National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Survivorship

Version 3.2017 — February 16, 2018

NCCN.org

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NCCN Guidelines Version 3.2017 Panel Members Survivorship

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‡ Hematology/Hematology oncology
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Ψ Neurology/Neuro-oncology

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Nursing
≅ Nutrition science/Dietitian
¥ Patient advocacy
€ Pediatric oncology
θ Psychiatry, psychology, including health behavior
£ Supportive care including palliative, pain management, pastoral care, and oncology social work
¶ Surgery/Surgical oncology
ω Urology
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NCCN Guidelines Version 3.2017 Sub-Committees Survivorship

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines Version 3.2017 Updates Survivorship

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Updates in Version 3.2017 of the NCCN Guidelines for Survivorship from Version 2.2017 include:

GENERAL SURVIVORSHIP PRINCIPLES

Survivorship Assessment (Patient Version)

SURV-A

- **"Lymphedema" was added to the list of "Survivorship Concerns" and the following corresponding questions were included:**
  - **Did your cancer treatment include radiation or surgery to the lymph nodes in your armpit, groin, abdomen, or neck (including sentinel lymph node biopsy)? Yes/No/Don't know**
  - **Since your cancer treatment, have you had any swelling, fatigue, heaviness, or fullness on the same side as your treatment that has not gone away? Yes/No**

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Lymphedema

- **A new algorithm that provides recommendations for symptom assessment, workup, treatment, and surveillance of lymphedema in survivors was added. (SLYMPH-1)**
- **A new section was added to the Discussion text to correspond to the new lymphedema algorithm. (MS-1)**

Pain

SPAIN-2

- **Cancer Pain Syndromes: The recommendations for lymphedema were deleted and moved to the new lymphedema algorithm. A link to SLYMPH-1 was added.**

PREVENTIVE HEALTH

Physical Activity

SPA-3

- **Footnote regarding lymphedema was deleted: "Lymphedema is not a contraindication for physical activity. Moderate activity is safe for most survivors. Lymphedema patients are considered high risk if performing resistance/strength training exercise of the affected limb. They are not considered high risk if participating in cardiovascular/aerobic exercise or strength training of unaffected limbs. Patient education about the risk of lymphedema is recommended. Consider referral to lymphedema specialist for evaluation prior to starting physical activity program that involves strength or resistance training of the affected limb." A link to the new lymphedema algorithm was added.**

SPA-A Considerations for Specific Populations

- **The recommendations for lymphedema were deleted. A link to the new lymphedema algorithm was added.**
- **The following bullets were added:**
  - **For workup and treatment of lymphedema (See SLYMPH-3)**
  - **For considerations regarding phyisical activity in survivors with or at risk for lymphedema (See SLYMPH-B)**

SPA-C Guidance For Resistance Training Recommendations

- **Last bullet revised: "Survivors at risk for or with lymphedema *(See SLYMPH-B)* ~~should utilize compression garments when engaging in resistance training~~"**

Updates in Version 2.2017 of the NCCN Guidelines for Survivorship from Version 1.2017 include:
- **The Discussion text for all sections was updated to reflect the changes in the algorithm. (MS-1)**

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Menopause-Related Symptoms

SMP-1
- **This page was extensively revised and became a separate section for "Principles of Menopause Management in *Female Survivors*." Previously, it contained recommendations for both females and males.**

SMP-2
- **This section was extensively revised and renamed "*Principles of Menopausal Symptoms In Male Survivors*." Formerly it was entitled "Male Menopause-related Symptoms Due to Androgen Deprivation Therapy (ADT)"**

SMP-3
- **Treatment: The symptoms list for treatment was divided into "Females," "Males," and "Females and Males."**
- **Gynecomastia" and "Anemia" were added to the list of symptoms to treat for males.**
- **Footnote "g" is new: *"ADT-associated anemia is generally responsive to blood transfusions and erythropoietin and should be treated as per the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia."***

SMP-6
- **First column:**
  - **Header revised, "~~Menopause~~ *ADT-Related* Symptoms."**
  - **A new pathway and treatment options were added for "Gynecomastia."**
- **Treatment bullets for vasomotor symptoms were reorganized and the following revisions were made:**
  - **"*Modification to ADT (See NCCN Guidelines for Prostate Cancer)*" added.**
  - **Revised "~~Non-hormona~~l Pharmacologic Treatments", with sub-bullets of "*Hormonal therapy*" and "*Non-hormonal therapies*" added.**
  - ***Medroxyprogesterone, Cyproterone acetate, and Estrogen (eg, diethylstilbestrol)* added as hormone therapies.**
  - ***Venlafaxine* and *Gabapentin* added as non-hormonal therapies.**
  - **Categories of non-hormonal pharmacologic treatments were removed: low-dose antidepressants, anti-convulsants, neuropathic pain relievers, and certain anti-hypertensives.**

PREVENTIVE HEALTH

Immunizations and Infections

SIMIN-2

- Footnote g revised: "Safe pet care tips include washing hands with soap and running water after handling animal~~s and their~~ feces. If possible, survivors *at high risk for immune suppression* should avoid direct contact with animal feces *and other bodily secretions. Survivors with elevated risk of infection and those who are immunocompromised are at higher risk for zoonoses and should use extra caution*."
- Footnote j revised: "*For dosing and schedule*, See General Principles..."

SIMIN-3

- Treatment: "Pneumococcal vaccine" was removed from the "Recommended for all cancer survivors" pathway and added to the "Recommended if some special circumstance or risk factor is present" pathway.
- Footnote o was revised: "PCV-13 and PPSV-23 are recommended for adults ~~with immunocompromising conditions~~ *65 years or older and for younger adults who are immunocompromised* (ie, HCT and functional or anatomic asplenia)." and reference was updated.

SIMIN-A

- Vaccines Contraindicated Or To Be Used With Caution in Actively Immunocompromised Survivors; Live attenuated vaccines: "Influenza: live, attenuated influenza vaccine (LAIV)" was removed from the list of vaccines.
- Revised section heading: "*Live* Vaccines That Can Be Used With Caution..."
  - "Influenza: live, attenuated influenza vaccine (LAIV)" was removed from the list of vaccines.
- Footnote "4" is new: "*Live oral polio vaccine should not be administered to close contacts of immunocompromised survivors.*"

SIMIN-B General Principles of Vaccines in Cancer Survivors

- 1 of 3 (Vaccination in Non-Transplant Survivors)
  - ◊ Pneumococcal vaccine; New bullets added
    - *Recommended for adults 65 years or older and for younger adults who are immunocompromised.*
    - *A second dose of PPSV23 is recommended 5 years after the first dose for immunocompromised survivors and those with functional or anatomic asplenia.*
  - Tetanus, diphtheria, pertussis vaccine (Td/Tdap): "*Consider administering a Tdap booster every 5 years*" added.
  - Revised "Consider human papillomavirus (HPV) vaccine in survivors ~~11–26 years of~~ *through age 26 years. For dosing and schedules, see* *https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html*"
    - ◊ "Female 3 doses" and "Male 3 doses" removed.
  - References for footnotes 1 and 2 revised.
- 2 of 3 (Vaccination in Hematopoietic Cell Transplant (HCT) Survivors)
  - Under "Consider human papillomavirus vaccine": Revised "Consider administration of 3 doses of HPV vaccine 6–12 months after HCT for ~~female patients aged 11–26 years and HPV vaccine for males aged 11–26 years~~ for survivors through age 26 years."
- 3 of 3 Vaccines Considered Safe for Cancer and Transplant Survivors and Close Contacts
  - Footnote 9 regarding the influenza vaccine was revised: "~~This vaccine is recommended for patients with egg allergies.~~ *Administration of the flu vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138.*"
    Change also made for SIMIN-C for footnote 3.

SIMIN-C Principles of Influenza Vaccine(s)

- Fourth bullet revised: "Influenza vaccines can be inactivated *or* recombinant ~~or live-attenuated~~. They may contain..."
- Footnote removed, "IIV influenza vaccine recommended except for patients with severe egg allergies."

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Updates in Version 1.2017 of the NCCN Guidelines for Survivorship from Version 2.2016 include:

GENERAL SURVIVORSHIP PRINCIPLES

SURV-1

- Definition of Survivorship: Revised, "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also ~~impacted~~ *affected by cancer*."
- Standards for Survivorship Care: Bullets under "Develop a survivorship care plan that includes:" were revised.
- References from the American Society of Clinical Oncology and Commission on Cancer were added.

SURV-3 Screening for Second Cancers

- New bullet added: "*Regular updating of family cancer history is recommended to reassess hereditary risk, based on recent family diagnoses and on any new evidence in the field of cancer genetics that expands the basis for assessing inherited risk.*"
- Seventh bullet revised: "...a potential increased risk for second malignancies based on genetic profile. *Appropriate candidates include survivors with a cancer diagnosis at a young age or with multiple primary cancers*."

SURV-4 Assessment by Health Care Provider

- New bullet added: "*Assess weight and health behaviors that can modify cancer risk.*"

SURV-A 1 of 2 Survivorship Assessment (Patient Version)

- Instructions revised: " Please answer the following questions ~~regarding possible symptoms that you may have experienced~~:"
- Sleep Disorder: "Are you having problems falling asleep, staying asleep*, or waking up too early*?"
- Healthy Lifestyle: "Do you engage in regular physical activity or exercise, such as brisk walking, jogging, *weight/resistance training*, bicycling, swimming, etc.?"

SURV-A 2 of 2 Survivorship Assessment (Provider Key)

Instructions revised, "~~Please answer the following questions regarding possible symptoms that you may have experienced~~
Based on the survivor's answers to the assessment questions, refer to the detailed recommendations indicated below:"

SURV-B Survivorship Resources

- New resources were added under "General online information, Help Lines, Nutrition and Weight Management, Integrative Therapies, and Smoking Cessation."

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Anthracycline-Induced Cardiac Toxicity

SCARDIO-1-- Principles of Anthracycline-Induced Cardiac Toxicity

- Third bullet revised, "Survivors may have risk factors that predispose them to heart failure ~~(such survivors are considered to have Stage A heart failure)~~ or may have structural heart disease (such survivors are considered to have Stage B heart failure) even if they have no actual symptoms. A history of anthracycline exposure is a risk factor that ~~classifies a survivor as having Stage A heart failure~~ *predisposes survivors to cardiac disease.*"
- New reference added: "*Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.*"

SCARDIO-2

- Initial Clinical Assessment
  - Second bullet; Sixth sub-bullet revised: " High cumulative anthracycline dose (ie, cumulative doxorubicin dose at or higher than ~~300~~ *250* mg/m^2 or equivalent)."
  - Third bullet revised, "Review medications, *alcohol use, and other substance use*"
  - "Alcoholism" was removed from "Evaluate for presence of heart failure risk factors."

SCARDIO-3

- New footnote "i" added: "*For a list of potentially cardiotoxic chemotherapy agents see Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Eng J Med 2016;375:1457-1467.*"

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Anxiety, Depression, and Distress

SANXDE-1 General Principles

- First bullet revised, "... that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment." *The NCCN Guidelines for Survivorship complement the NCCN Guidelines for Distress Management.*"
- Second bullet revised, "Survivors of cancer treatment are at ~~high~~ *elevated* risk for *mental health issues such as* fear of recurrence, distress, anxiety, and depression ~~due to the multiple challenges they face~~ *that may persist many years after diagnosis*."

SANXDE-2 Screening: Anxiety and Depression

- Bullets revised
  - "In the past two weeks, *on more days than not* have you:"
  - Nervous/anxious: "...had worries or fears related to your cancer *on more days than not*?
  - Sad/depressed: "...felt sad or depressed *on more days than not*?

SANXDE-5

- First column; Seventh bullet revised: "Feeling worthless~~ness~~ or *having* excessive guilt"

SANXDE-7 Evaluation

- Medical Factors: Under "General Review", new bullet added "*Other medical factors incldng cognitive function.*"
- Psychiatric/Emotional Factors: Under "Consider other major psychiatric disorders," the following examples were removed "Schizophrenia, bipolar disorder, personality disorder, obsessive compulsive disorder."

SANXDE-8 Management and Treatment

- Nonpharmacologic interventions for adjustment disorder..."
  - ◊ Revised: "Psychological or social factors interfering with ~~adherence~~ *prescribed care.*"

SANXDE-A

- First column; Safety Evaluation; Danger to self or others...: "*Perceives self as a burden*" was added as a risk factor to consider.
- Last column; Acute Interventions: Under, "Develop safey plan with survivor
  - Third bullet revised: "Have survivor agree to contact a health care provider*, call 911, or go to the nearest emergency room* if suicidal thoughts increase or change
  - New bullet added: "*For suicide hotline information (See SURV-B)*"

SANXDE-C Principles of Pharmacologic Interventions

- Caveats; Fifth bullet revised: "Avoid psychotropics with cytochrome P_{450} interactions in patients taking tamoxifen~~, or with complicated medical problems or high likelihood for recurrence~~
  - Fluvoxamine and Nefazodone were added to the list of psychotropics.
  - New footnote added: "*Pure SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6 and should be used with caution for women on tamoxifen.*"

Cognitive Function

SCF-1 General Principles

- Second bullet revised: "~~Studies using neurologic~~ *Neuropsychological* testing and brain imaging ~~provide objective evidence of cognitive dysfunction~~ *have demonstrated abnormalities in patients who have had chemotherapy* following cancer treatment."
- Fourth bullet revised: "There is limited evidence to guide management of this condition~~, especially for cancers other than breast~~."
- New bullet added: "*These guidelines address cognitive function of survivors with non-central nervous system (CNS) malignancies who did not have CNS-directed therapies.*"

SCF-3 Cognitive Function Assessment

- General strategies; Sixth bullet revised: "Consider meditation, yoga, mindfulness-based stress reduction, *and cognitive training (ie, brain games).*"
- New footnote "b" added: "*Cognitive dysfunction may be progressive in survivors of CNS cancers or those who had CNS-directed therapies.*"

SCF-4

- Second-Line Interventions: Revised, "Consider *trial* use of psychostimulants..."
- New footnote "e" added; "*Overall the evidence for psychostimulants is lacking, but they may be of some benefit.*"

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Fatigue

SFAT-3

- First column; Assessement of treatable contributing factors; sub-bullet revised: "*Prescribed or OTC* medications"
- Third column;Other diagnostic testing: Second bullet revised, "... other VEGF- or HER2-targeted therapy, *or other therapy known to cause cardiac dysfunction*."
- New footnote "c" added: "*Refer to a pulmonologist for pulmonary complaints*."

SFAT-5

- Physical activity; Third bullet revised: "Make use of local resources to help patients increase exercise *(eg, aerobics, strength training, yoga)."*
- Third column heading revised: "Other ~~Behavioral~~ Interventions."
  - Acupuncture added.

Menopause-Related Symptoms

SMP-1

- Revised header: "Treatment Options for ~~Menopausal~~ *Vasomotor* Symptoms."
  - Non-hormonal options (females and males): "*Lifestyle modifications (See HL-1)*" was added.
  - Hormonal therapies...; Females:
    - Bullet revised: "~~Selective estrogen receptor modulators (SERMs) and~~ Tissue selective estrogen complexes (TSECs)"
    - "*Custom-compounded bioidentical hormone therapy*" added.
    - Hormonal therapies removed: Vaginal hormonal therapies, bioidentical hormones, androgens.
- Footnote "a" added: "*Novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen creating a tissue selective estrogen complex (TSEC)*."
- Footnote removed: "Supplemental calcium, vitamin D may be used for prevention of fractures and skeletal-related events."

SMP-4

- Treatment for vasomoter symptoms in females
  - The following nonpharmacolgic treatments were added:
    - *Weight loss if overweight or obese (See SNWM-1)"*
    - *Integrative therapies including cognitive behavioral therapy (CBT), yoga, and hypnosis*
- New footnote "d" regarding "Compounds with limited evidence of safety and efficacy" was added. Previously "Phytoestrogens, botanicals, melatonin, and dietary supplements" were listed under "Nonpharmacologic treatments."
- Footnote "f" revised: "~~Recommend avoidance of red wine.~~ *Drinking alcohol may cause hot flashes in males/females. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake*."

SMP-5

- Treatment for vasomoter symptoms in males
  - Nonpharmacologic treatments: "*Weight loss if overweight or obese (See SNWM-1)*" was added.
- New footnote "i" regarding "Compounds with limited evidence of safety and efficacy" was added. Previously "Phytoestrogens, botanicals, melatonin, and dietary supplements" were listed under "Nonpharmacologic treatments."
- Footnote "f" added.

SMP-6

- Vaginal dryness; Treatment:
  - Local estrogen treatment sub-bullet revised: "Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories and therefore i*f estrogen based treatment is warranted, rings and suppositories* are preferred over creams for survivors with hormonally sensitive tumors."
  - Revised: "Other topical prescriptions (ie, ~~androgens~~ *testosterone*,~~ vaginal DHEA~~)."

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Menopause-Related Symptoms---continued

SMP-A Non-Homonal Pharmacologic Treatments and Dosing

- Lowest dose possible was specified for all drugs.

SMP-B Principles of Menopausal Hormone Therapy (Females)

- Second bullet
  - Second sub-bullet revised: " ~~The SERM ospemifene and~~ The TSEC conjugated estrogens/bazedoxifene ~~are~~ is FDA approved..."
  - Third sub-bullet revised: "*Custom-compounded* bioidentical hormone *therapy*."
    - ◊ Revised: "There is a lack of data supporting claims that *custom-compounded* bioidentical hormones..."
- Sixth bullet:
  - "Caution in survivors with heart disease *or hypertension*"
  - *Current smokers* added as a caution.

Pain

SPAIN-1 General Principles of Pain Management

- Sixth bullet revised: "Physical modalities (heat, cold, massage, physical therapy, *or occupational therapy*) are useful..."

SPAIN-4 Chronic Pain Syndrome

- "Consider mirror therapy" was added as an optionfor post-amputation syndrome. Previously it was listed in a footnote.

SPAIN-6 Skeletal Pain

- General measures for vertebral compression: Recommendation revised, "Bisphosphonates *or other antiresorptive medications if appropriate"*
- For avascular necrosis: "*Core decompression*" was added.

SPAIN-7 Myofascial pain

- This section was extensively reorganized.
- Footnote "i" is new: "*For muscle cramps or spasms, check electrolytes, calcium and magnesium levels, and hydration status."* Previously these recommnedations were in the algorithm above.

SPAIN-A Principles of Opioid Use in Long-term Survivors

- New bullet added, "*The panel endorses the* ASCO Policy Statement on Opioid Therapy: Protecting Access to Treatment for Cancer-Related Pain (2016)*, particularly as it relates to weighing the risks/benefits of opioid treatment.*"

Sexual Function (Female and Male)

SSF-1

- After "Screening questions indicate an issue....": "*Re-evaluate and discusss potential impact of treatment on sexual function at future visits*" was added as an option.

SSF-2

- Treatment:
  - Symptoms of menopause, vaginal dryness...:
    - ◊ Recommendations were removed and pathway is redirected to the Menopausal-Related Symptoms algorithm (SMP-5)
    - ◊ Ospemifene removed as an option.
  - Symptoms of pain with sexual activity: Prasterone added as a treatment option.
  - Low or lack of desire, libido, or intimacy: Bupropion and buspirone added as treatment options.
- New footnote "f" added: "Bupropion and buspirone may be considered as off-label treatments for hypoactive sexual desire disorder, despite limited safety and efficacy data."
- Footnote "g" revised: "There is a lack of data showing a benefit of sildenafil in women or of flibanserin *and androgens* in cancer survivors. *In addition there is a lack of safety data for the use of androgen based therapy in survivors of hormonally mediated cancers.*"

Sleep Disorders

SSD-1

- Screening question revised: "Are you having problems falling asleep, staying asleep, *or waking up too early*?
- Third column:
  - "Assessment of treatable *or modifiable* contributing factors"
  - Comorbidities revised: "Neurologic disorders *including chemotherapy-induced peripheral neuropathy*"
- Fourth column revised: "Insomnia symptoms (difficulty falling asleep ~~and/or maintaining sleep~~, staying asleep, *or waking up too early*)"

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Sleep Disorders---continued

SSD-2

- Third column: "*Environmental and Sleep hygiene*" added as secondary causes to evaluate.
- Sleep hygiene education added as a treatment for circadian rhythmn disorder.
- Footnote "i" revised: "Sleep hygiene alone has not been shown to be effective, but should be part of the initial treatment of all ~~patients~~ *survivors with sleep disorders* and as a prevention."

SSD-3

- Associated with uncomfortable sensation; Testing: "*History and physical exam (See SSD-D) and evaluate for iron defficiency*" added. "Ferritin level <45 ng per mL" removed.
- New footnote "n" added: "*The following tools may be used to assess sleep apneas: STOP Questionnaire (Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812-821.) and Berlin Questionnaire* (http://sleepapnea.org/wp-content/uploads/2017/02/berlin-questionnaire.pdf)"

SSD-A General Sleep Hygiene Measures

- Fifth bullet revised: "Avoid alcohol~~, caffeine,~~ and nicotine too close to bedtime."
- New bullet added: "*Limit caffeine consumption and avoid caffeine consumption at least 4 hours before bedtime.*"
- Eleventh bullet revised: "*If necessary,* limit to 1 short nap per day *in the afternoon* (no longer than 30 min)."

SSD-B Cognitive Behavioral Treatments

- Sleep restriction: "Maintaining a regular sleep schedule *by keeping a standard bedtime and wake time every day.*"
- Relaxation training: " Techniques include progressive muscular relaxation, *deep breathing,* ~~transcendental~~ meditation, yoga, and biofeedback."
- New footnote "2" added: "*Match total amount of time spent in bed to the actual amount of time spent sleeping (no less than 5 hours).*"
- New footnote "3" added: "*Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior "therapy for insomnia (CBT-I) in cancer survivors. Sleep Med Rev 2016;27:20-28.*"

PREVENTIVE HEALTH

Sleep Disorders---continued

SSD-C

- Fourth column in table revised: "Indicated for Sleep ~~Onset~~ *Initiation* and Maintenance."

SSD-D

- A new section was added for "Iron Deficiency and RLS."

Healthy Lifestyles

HL-1 General Principles of Healthy Lifestyles

- Edits made to the following sections:
  - "For a healthy lifestyle, all survivors should be encouraged to:
    - ◊ Achieve and maintain a normal body mass index (BMI) *and strive for metabolic health.*
    - ◊ Weigh oneself *daily if goal is weight loss and if not, weigh oneself* at least weekly to monitor weight ~~gain/loss~~.
    - ◊ Engage in physical activity regularly (preferably daily): New bullet added "*Strive to participate in strength or resistance training at least twice a week.*"
    - ◊ Maintain a healthy diet high in vegetables, fruits, and whole grains and low in ~~red and processed meats,~~ sugars and fats ~~in order to promote weight control and avoid obesity~~"
      - *– New sub-bullet added: "Limit red meat and avoid processed meat."*
- Minimize alcohol intake: "Limit intake to *no more than* one drink per day for a woman and two drinks per day for a man.
- Avoid tobacco products: "~~Attempt tobacco cessation~~ *Stop smoking* if currently smoking or using smokeless tobacco."
- New bullet added: "*Clinicians should assess individual and community-level barriers to meeting the healthy lifestyle recommendations and support patients in developing strategies to overcome challenges.*"
- New footnote "b" added: "*There are some cancers for which survivors should abstain from alcohol. These include liver, esophageal, kidney, and head and neck cancers.*"

PREVENTIVE HEALTH

Physical Activity

SPA-1 General Principles of Physical Activity

- Second bullet; Third sub-bullet revised: "Stretch major muscle groups ~~on a routine basis~~ at least two days per week"

SPA-3 Risk Assessment for Physical Activity-Induced Adverse Events

- First column; Third pathway; Fourth bullet revised: "~~Extreme~~ *Severe* fatigue."
- Second column; Third pathway revised: "Medical *evaluation and* clearance by physician *prior to initiation of exercise program*."
- Footnote "f" revised: "Trained personnel can include physical a*nd occupational* therapists, certified ~~trainers~~ *exercise professionals,* ~~cancer~~ and rehabilitation specialists~~, pulmonary or cardiac rehabilitation specialist, or exercise specialists~~. Specialized training in ~~cancer exercise is available through the~~ *working with survivors is available for both physical therapists and exercise professionals* (American College of Sports Medicine [ACSM] [*http://acsm.org/certification*]; *American Physical Therapy Association [APTA] Oncology section* http://oncologypt.org/home-page.cfm.*)* ~~Patients should be encouraged to use an ACSM-certified trainer when available~~"

SPA-4 Implementation of Recommendations

- Second column; Bottom pathway revised: "Not meeting Guideline recommendations ~~and/or patients with comorbidities~~"
- Third column; Bottom pathway sub-bullet revised: "Type: ~~Brisk~~ *Aerobic activity (ie,* walking) and/or resistance prescription"

SPA-C Guidance for Resistance Training Recommendations

- Resistance training sub-bullet revised: "Frequency: 2–3 times/week. "*Survivors should wait at least 48 hours between resistance training sessions*."

Nutrition and Weight Management

SNWM-1 General Princples of Nutrition

- First bullet revised: "Assess *dietary pattern for* daily intake of fruits, vegetables, and *unrefined grains,* as well as *red and* processed meats, alcohol, and *processed* foods or beverages with added fats and/or sugars."
- Second bullet revised: "Assess eating habits, including portion size, night grazing, snacking habits, frequency of eating out *and use of added fats and/or sugars to foods or beverages*."

Nutrition and Weight Management--continued

SNWM-2 General Principles of Weight Management

- Fourth bullet "Principle of weight loss":
  - Under monitor weight daily, new sub-bullet added, "*Recommend weight loss of no more than 2 pounds per week and no more than 1 pound per week in survivors over 64 years.*"
  - New sub-bullet added: "*Incorporate physical activity, particularly strength training, to assure optimal lean body mass*."
- New bullet added: "*In conjunction with primary care, survivors should be assessed for metabolic health and body composition independently of body mass index (BMI).*"

SNWM-3

- "*Psychosocial distress and fear*" were added to the list of treatment effects and medical issues to asses.
- Footnote "g" revised: The body mass index (BMI) chart was removed from the algorithm and replaced with a link to the BMI calculator from the Centers for Disease Control Prevention http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html.

SNWM-4

- Interventions
  - "*Manage contributing treatment effects and risk factors as clinically indicated*" was added to the "Overweight/Obese; Normal weight; and Underweight" pathways.
  - Overweight/Obese: "*Contributing pyschosocial factors*" added.
  - Underweight: This section was reorganized.

Supplement Use

SSUP-1 General Principles of Supplement Use

- New bullet added "*Refer survivors using multiple and/or or unfamiliar supplements to a registered nutritionist/dietitian, preferably one with oncology credentials*."

Immunizations and Infections

- The 2017 algorithm update is in progress (SIMIN-1)

General Survivorship Principles

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

DEFINITION OF SURVIVORSHIP

- **An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also affected by cancer.[a]**
- **These guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer have on the adult survivor. This includes the potential impact on health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.**

STANDARDS FOR SURVIVORSHIP CARE[b]

Care of the cancer survivor should include:

1. **Prevention of new and recurrent cancers and other late effects**
2. **Surveillance for cancer spread, recurrence, or second cancers[c]**
3. **Assessment of late psychosocial and physical effects**
4. **Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns)**
5. **Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met**
6. **Survivorship care planning:[d,e]**
   - ◊ **Develop a survivorship care plan that includes:**
     - **– Summary of treatment received**
     - **– Information regarding follow-up care and surveillance recommendations**
     - **– Information on post-treatment needs, including information regarding treatment-related effects and health risks when possible (See NCCN Disease-Specific Guidelines)**
     - **– Delineation regarding roles of oncologists and primary care physician and timing of transfer of care if appropriate**
     - **– Healthy behavior recommendations (See HL-1)**

[a]Adapted with permission from the National Coalition for Cancer Survivorship as shown in the National Cancer Institute's Office of Cancer Survivorship Definitions web page available at http://cancercontrol.cancer.gov/ocs/statistics/definitions.html.

[b]From Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council 2006. Available at: http://www.nap.edu/catalog/11468.html.

[c]Surveillance testing (eg, labwork, imaging, other studies) should be based on cancer diagnosis and individualized patient risk. A small excess risk of cancer has been linked to frequent radiographic imaging. Surveillance testing should be performed as per disease-specific NCCN Guidelines. Additional labwork, imaging, or other studies to evaluate for recurrence should be based on clinical presentation and judgment.

[d]Mayer DK, Nekhlyudov L, Snyder CF, et al. American society of clinical oncology clinical expert statement on cancer survivorship care planning. J Oncol Pract 2014;10:345-351.

[e]Commission on Cancer: Cancer Standards Program (2016 edition): https://www.facs.org/quality-programs/cancer/coc/standards

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GENERAL PRINCIPLES OF THE SURVIVORSHIP GUIDELINES

- These guidelines are focused on survivors after the completion of cancer treatment and in clinical remission.
- These guidelines are designed to provide a framework for the general survivorship care and management of potential long-term and/or late effects of cancer and its treatment that survivors may experience.
- The NCCN Guidelines for Survivorship should be used as a supplement to the follow-up recommendations within the disease-specific guidelines. See the NCCN Guidelines for Treatment of Cancer by Site and NCCN Guidelines for Palliative Care for recommendations regarding metastatic disease.
- The panel does not assume that all survivorship issues will be addressed at every visit. The panel recommends periodic screening assessments and appropriate follow-up care as clinically indicated.
- These guidelines provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment, and are intended for health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in both the oncology and primary care practices.
- These guidelines, with the appropriate disease-specific guideline, provide a framework for the coordination of care between the survivor's health care providers to insure that needs are appropriately addressed.
- The topics, assessments, and interventions may also be applicable to those survivors living with metastatic disease, as clinically appropriate. (Also see the NCCN Guidelines for Supportive Care Table of Contents).
- For survivorship issues related to younger populations, also see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology and the Children's Oncology Group Childhood Survivorship guidelines (www.survivorshipguidelines.org).

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SCREENING FOR SECOND CANCERS

- Subsequent malignant neoplasms may occur in survivors, due to genetic susceptibilities (ex, cancer syndromes), shared etiologic exposures (ex, smoking, environmental exposures), and mutagenic effects of cancer treatment.
- The overall cancer rate in survivors is higher than in the general population.
- Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.
- Screening for second primary cancers should be a shared responsibility between primary and oncology care physicians (See the NCCN Guidelines for Detection, Prevention, and Risk Reduction Table of Contents).
- Evidence suggests that excess radiation exposure from CT imaging may be associated with an increased risk of developing a radiation-associated cancer. Use of radiologic studies to screen for recurrent cancer should be based on diagnosis and evidence that early detection of recurrence will improve cancer-related outcomes.
- Regular updating of family cancer history is recommended to reassess hereditary risk, based on recent family diagnoses and on any new evidence in the field of cancer genetics that expands the basis for assessing inherited risk.
- Referral to genetic risk assessment and/or testing should be considered for appropriate survivors to identify those with a potential increased risk for second malignancies based on genetic profile. Appropriate candidates include survivors with a cancer diagnosis at a young age or with multiple primary cancers.
- Management recommendations for patients with known germline mutations linked to an increased risk for cancer can be found in the following NCCN Guidelines:
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - NCCN Guidelines for Gastric Cancer
  - NCCN Guidelines for Neuroendocrine Tumors
  - NCCN Guidelines for Thyroid Cancer

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ASSESSMENT BY HEALTH CARE PROVIDER (ONCOLOGY OR PRIMARY CARE) AT REGULAR INTERVALS

- **A periodic assessment at least annually is recommended for all survivors to determine any needs and necessary interventions. For sample assessment, see SURV-A.[d]**
- **Shared coordinated care between the oncology provider and primary care provider is encouraged.**
- **Assess weight and health behaviors that can modify cancer risk.**
- **Care providers are also encouraged to assess the following at regular intervals to determine whether reversible or contributing causes for symptoms exist:**

1. **Current disease status**
2. **Functional/performance status**
3. **Medication (including over-the-counter [OTC] medications and supplements)**
4. **Comorbidities (including weight and tobacco/alcohol use)**
5. **Prior cancer treatment history and modalities used**
6. **Family history**
7. **Psychosocial factors**
8. **See NCCN Guidelines for Treatment of Cancer by Site for disease-specific recommendations for surveillance/follow-up**

[d]This is a sample assessment tool. While this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment. Validation of the best way to assess survivorship issues is ongoing.

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SURVIVORSHIP ASSESSMENT (Patient Version)

Please answer the following questions:

Survivorship Concerns	Survivorship Care Survey
Cardiac Toxicity	1. Did you receive anthracycline therapy (eg, doxorubicin, epirubicin, daunorubicin, AC [doxorubicin + cyclophosphamide])? Yes/No 2. Do you have shortness of breath or chest pain after daily activities (eg, walking up stairs) or exercise? Yes/No 3. Do you have shortness of breath when lying flat, wake up at night needing to get air, or have persistent leg swelling? Yes/No
Anxiety, Depression, and Distress	4. Have you been bothered more than half the days by little interest or pleasure in doing things? Yes/No 5. Have you been bothered more than half the days by feeling down, depressed, or hopeless? Yes/No 6. Have you been bothered more than half the days by not being able to stop or control worrying, or have you felt nervous or on edge? Yes/No
Cognitive Function	7. Do you have difficulties with multitasking or paying attention? Yes/No 8. Do you have difficulties with remembering things? Yes/No 9. Does your thinking seem slow? Yes/No
Fatigue	10. Do you feel persistent fatigue despite a good night's sleep? Yes/No 11. Does fatigue interfere with your usual activities? Yes/No 12. How would you rate your fatigue on a scale of 0 (none) to 10 (extreme) over the past month? 0–10
Lymphedema	13. Did your cancer treatment include radiation or surgery to the lymph nodes in your armpit, groin, abdomen, or neck (including sentinel lymph node biopsy)? Yes/No/Don't know 14. Since your cancer treatment, have you had any swelling, fatigue, heaviness, or fullness on the same side as your treatment that has not gone away? Yes/No
Menopause	15. Have you been bothered by hot flashes/night sweats? Yes/No 16. Have you been bothered by other menopause-related symptoms (ex, vaginal dryness, incontinence)? Yes/No
Pain	17. Are you having any pain? Yes/No 18. How would you rate your pain on a scale of 0 (none) to 10 (extreme) over the past month? 0–10
Sexual Function	19. Do you have any concerns regarding your sexual function, sexual activity, sexual relationships, or sex life? Yes/No 20. Are these concerns causing you distress? Yes/No
Sleep Disorder	21. Are you having problems falling asleep, staying asleep, or waking up too early? Yes/No 22. Are you experiencing excessive sleepiness (ie, sleepiness or falling asleep in inappropriate situations or sleeping more during a 24-hour period than in the past)? Yes/No 23. Have you been told that you snore frequently or that you stop breathing during sleep? Yes/No
Healthy Lifestyle	24. Do you engage in regular physical activity or exercise, such as brisk walking, jogging, weight/resistance training, bicycling, swimming, etc.? Yes/No ▸ 24a. If you answered "Yes," how often? 25. Excluding white potatoes, do you eat at least 2½ cups of fruits and/or vegetables each day? Yes/No 26. Do you have concerns about your weight? Yes/No 27. Do you take vitamins or supplements? Yes/No
Immunizations and Infections	28. Have you received your flu vaccine this flu season? Yes/No 29. Are you up to date on your vaccines? Yes/No/Don't know

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SURVIVORSHIP ASSESSMENT*
(Provider Key)

Based on the survivor's answers to the assessment questions, refer to the detailed recommendations indicated below:

Survivorship Concerns	Survivorship Care Survey	Provider Key
Cardiac Toxicity	Questions 1–3	If received anthracycline therapy or YES to any question, refer to SCARDIO-1
Anxiety, Depression, and Distress	Questions 4–6	If YES to any question, refer to SANXDE-1
Cognitive Function	Questions 7–9	If YES to any question, refer to SCF-1
Fatigue	Questions 10–12	If YES to either question 10 or 11, or a rating of >3 to question 12, refer to SFAT-1
Lymphedema	Questions 13–14	If YES to any question or Don't know to question 13, refer to SLYMPH-1
Menopause	Questions 15–16	If YES to any question, refer to SMP-1
Pain	Questions 17–18	If YES to question 15 and a rating of >4 to question 16, refer to SPAIN-1
Sexual Function	Questions 19–20	If YES to any question, refer to SSF-1
Sleep Disorder	Questions 21–23	If YES to any question, refer to SSD-1
Healthy Lifestyle	Questions 24–27	If NO to question 24 or 25, or YES to question 26, OR if question 24a is less than 3 times per week, OR if BMI not in the healthy range, refer to HL-1 If YES to question 27, refer SSUP-1
Immunizations and Infections	Questions 28–29	If NO to question 28, or No or Don't know to question 29, refer to SIMIN-1

*This is a sample assessment tool. While this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment. Validation of the best way to assess survivorship issues is ongoing.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS*

General Online Information	
National Coalition for Cancer Survivorship (NCCS)	http://www.canceradvocacy.org/
American Association for Cancer Research (AACR) • A six-part podcast series about survivorship in partnership with CR Magazine and The Wellness Community:	http://www.aacr.org/ http://www.crmagazine.org/archive/Crpodcasts/Pages/SurvivingThriving.aspx
American Cancer Society (ACS) • Survivorship information • Cancer Survivors Network • National Cancer Survivorship Resource Center • Physical Side Effects information, including sexual function	http://www.cancer.org/index http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index http://csn.cancer.org/ http://www.cancer.org/SurvivorshipCenter http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/index
American Institute for Cancer Research (AICR): Survivorship information • Survivorship information • Nutrition, physical activity, weight management	http://www.aicr.org/patients-survivors/after-cancer-treatment.html
American Society of Clinical Oncology (ASCO) • Survivorship information for patients • Tools and resources for oncology providers	http://www.cancer.net/survivorship https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/survivorship/survivorship-compendium
Cancer Care: Free, professional support services for anyone affected by cancer	www.cancercare.org
Centers for Disease Control and Prevention: Survivorship information	http://www.cdc.gov/cancer/survivorship/index.htm
Leukemia & Lymphoma Society: Survivorship information	http://www.lls.org/diseaseinformation/managingyourcancer/survivorship/
LIVESTRONG	http://www.livestrong.org/
National Cancer Institute: Cancer Survivorship Research • Facing Forward series, designed to educate cancer survivors, family members, and health care providers about the challenges associated with life after cancer treatment	http://survivorship.cancer.gov http://cancercontrol.cancer.gov/ocs/resources/ffseries.html
National Comprehensive Cancer Network (NCCN) • Life After Cancer: Patient and Caregiver Resources and Information	http://www.nccn.org/index.asp http://www.nccn.org/patients/resources/life_after_cancer/
MedlinePlus: Current accurate information by cancer site	http://www.nlm.nih.gov/medlineplus/cancers.html
Oncology Nursing Society: Putting Evidence Into Practice	https://www.ons.org/practice-resources/pep
Help Lines	
American Cancer Society	1.800.227.2345 http://www.cancer.org
American Psychosocial Oncology Society	1.866.276.7443 http://apos-society.org/
Cancer Support Community	1.888.793.9355 http://www.cancersupportcommunity.org/
LIVESTRONG SurvivorCare	1.855.220.7777
National Cancer Institute's Cancer Information Service	1.800.4.CANCER
National Suicide Prevention Lifeline	1-800-273-TALK http://suicidepreventionlifeline.org

*There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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Continued

SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS* (continued)

Other Survivorship Guidelines	
Children's Oncology Group: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers	http://www.survivorshipguidelines.org/
Survivorship Care Planning	
ASCO Cancer Treatment Summaries	http://www.cancer.net/survivorship/follow-care-after-cancer-treatment/asco-cancer-treatment-and-survivorship-care-plans
Journey Forward: Resources for survivorship care planning	http://www.journeyforward.org/
Integrative Therapies	
Memorial Sloan Kettering Cancer Center's Herbs website	https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs
National Center for Complementary and Integrative Resources for Healtchcare Providers	https://nccih.nih.gov/health/providers
Legal and Employment Issues	
Cancer and Careers: Patient information about working and dealing with cancer	http://www.cancerandcareers.org/en
National Coalition for Cancer Survivorship (NCCS) Employment Rights, "Working It Out" Publication	http://www.canceradvocacy.org/resources/employment-rights/
National Coalition for Cancer Survivorship (NCCS) "What Cancer Survivors Need To Know About Health Insurance" Publication	http://www.canceradvocacy.org/resources/health-insurance/
ACS: Understanding Health Insurance	https://www.cancer.org/treatment/finding-and-paying-for-treatment/understanding-health-insurance.html
Physical Activity	
American Cancer Society • Nutrition and Physical Activity Guidelines for Cancer Survivors, Patient Page • "Physical Activity and the Cancer Patient" guide	http://onlinelibrary.wiley.com/doi/10.3322/caac.21146/pdf http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingactive/physical-activity-and-the-cancer-patient
American College of Sports Medicine: ACSM ProFinder: Search for Certified Professionals	https://certification.acsm.org/pro-finder
Cancer Supportive and Survivorship Care: Exercise: A Cancer Survivor's Tool For Wellness	http://www.cancersupportivecare.com/whyexercise.html
LIVESTRONG at the YMCA	http://www.livestrong.org/YMCA
SilverSneakers: A program that helps older adults live healthy, active lifestyles	https://www.silversneakers.com/

*There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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Continued

SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS* (continued)

Nutrition and Weight Management	
ASCO Obesity and Cancer Toolkit	https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/obesity-cancer
Cancer Nutrition Consortium: Nutritional Guidance & Support	http://www.cancernutritionconsortium.org/
LIVESTRONG MyPlate Calorie Tracker	http://www.livestrong.com/myplate
National Heart, Lung, and Blood Institute • Guideline for the Management of Overweight and Obesity in Adults • 3 Steps to Initiate Discussion About Weight Management With Your Patients	http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/obesity-evidence-review http://www.nhlbi.nih.gov/health/prof/heart/obesity/aim_kit/steps.pdf
National Institute of Diabetes and Digestive Kidney Diseases Body Weight Planner	https://www.niddk.nih.gov/health-information/health-topics/weight-control/body-weight-planner/Pages/bwp.aspx/Pages/default.aspx
Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics	http://www.oncologynutrition.org/
Cardiovascular Health	
American Heart Association/American Stroke Association Tools	http://millionhearts.hhs.gov/resources/tools.html
Oral and Dental Health	
National Institute of Dental and Craniofacial Research: Oral Complications of Cancer Treatment	http://www.nidcr.nih.gov/oralhealth/Topics/CancerTreatment/OralComplicationsCancerOral.htm
Smoking Cessation	
American Cancer Society: Smoking cessation support	http://www.cancer.org/healthy/stayawayfromtobacco/index
ASCO: Tobacco Cessation and Control Resources	https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control
North American Quitline Consortium	http://map.naquitline.org/
U.S. Federal Government: Smoking cessation support	http://www.smokefree.gov/

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Late Effects/Long-Term Psychosocial and Physical Problems

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PRINCIPLES OF ANTHRACYCLINE-INDUCED CARDIAC TOXICITY

- **Cancer treatments can result in diverse cardiovascular issues. These guidelines focus specifically on heart failure or cardiomyopathy that may arise from anthracycline therapy. Other systemic therapies may also cause cardiomyopathy (eg, HER2-targeted therapies), and some of the concepts presented in these recommendations may apply to these other cardiomyopathies.**
- **Anthracycline-induced heart failure may take years or even decades to manifest. Data suggest that signs of cardiac dysfunction can be seen prior to the development of symptoms. If detected early, anthracycline-induced heart failure may be responsive to cardioprotective medications, although prospective studies evaluating these medications are lacking.**
- **Survivors may have risk factors that predispose them to heart failure or may have structural heart disease (such survivors are considered to have Stage B heart failure) even if they have no actual symptoms. A history of anthracycline exposure is a risk factor that predisposes survivors to cardiac disease* (See SCARDIO-3).**
- **Having a history of anthracycline exposure plus additional cardiovascular risk factors increases the risk of developing cardiomyopathy and heart failure. It is encouraged that such survivors should have heart failure risk factors, including hypertension, dyslipidemia, and diabetes addressed in coordination with primary care.**
- **The risk for cardiovascular problems varies greatly depending on the type of anthracycline used and the cumulative dose received.**
- **For these guidelines, the panel has placed an emphasis on early recognition and prevention of clinical heart failure, as well as early treatment of patients at risk with appropriate cardioprotective medications to prevent cardiac remodeling over time. Therefore, for high-risk survivors, the panel emphasizes the need for a thorough clinical screening for heart failure within one year after completion of anthracycline therapy.**

*Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.

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INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical
  - Assess for signs and symptoms of heart failure[a,d]
  - Assess patient's ability to perform routine and desired activities of daily living
  - Look for signs of volume overload
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - High cumulative anthracycline dose (ie, cumulative doxorubicin dose at or higher than 250 mg/m^2 or equivalent)
  - Low-normal LVEF (50%–54%) at baseline
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], baseline evidence of structural heart disease)
  - Smoking
  - Obesity
- Review medications, alcohol use, and other substance use
- Review oncologic history
  - Review total cumulative dose of anthracycline
  - Other systemic therapy[b] and/or chest radiation therapy

→ Cardiovascular risk factor management[c]
• Consider two-dimensional echocardiogram (ECHO) with doppler flow study for survivors with one or more risk factors within 1 year after completion of anthracycline therapy[d,e]

→ No evidence of structural heart disease, but symptomatic[a]
→ • Workup for other causes of symptoms
• Referral to other specialties (eg, pulmonology or cardiology)

→ No evidence of structural heart disease and asymptomatic
or
No ECHO performed and asymptomatic
→ See Stage A (SCARDIO-3)

→ Evidence of structural heart disease (asymptomatic or symptomatic[a]):
• Evidence of left ventricular (LV) dysfunction
• Evidence of LV hypertrophy
• Valvular disease
→ Determine stage of cardiomyopathy (heart failure) (See SCARDIO-3)

[a]Signs and symptoms of heart failure include: Shortness of breath or chest pain after physical activity or exercise, shortness of breath when sleeping, waking up at night due to shortness of breath, and swelling in the legs.
[b]Trastuzumab, pertuzumab (other HER2-targeted therapy), VEGF signaling pathway (VSP) inhibitors, taxanes in combination with anthracyclines.
[c]Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[d]Patients with symptoms of heart failure should undergo an echocardiogram.
[e]Referral to cardiologist/cardio-oncologist if there are echocardiographic abnormalities.

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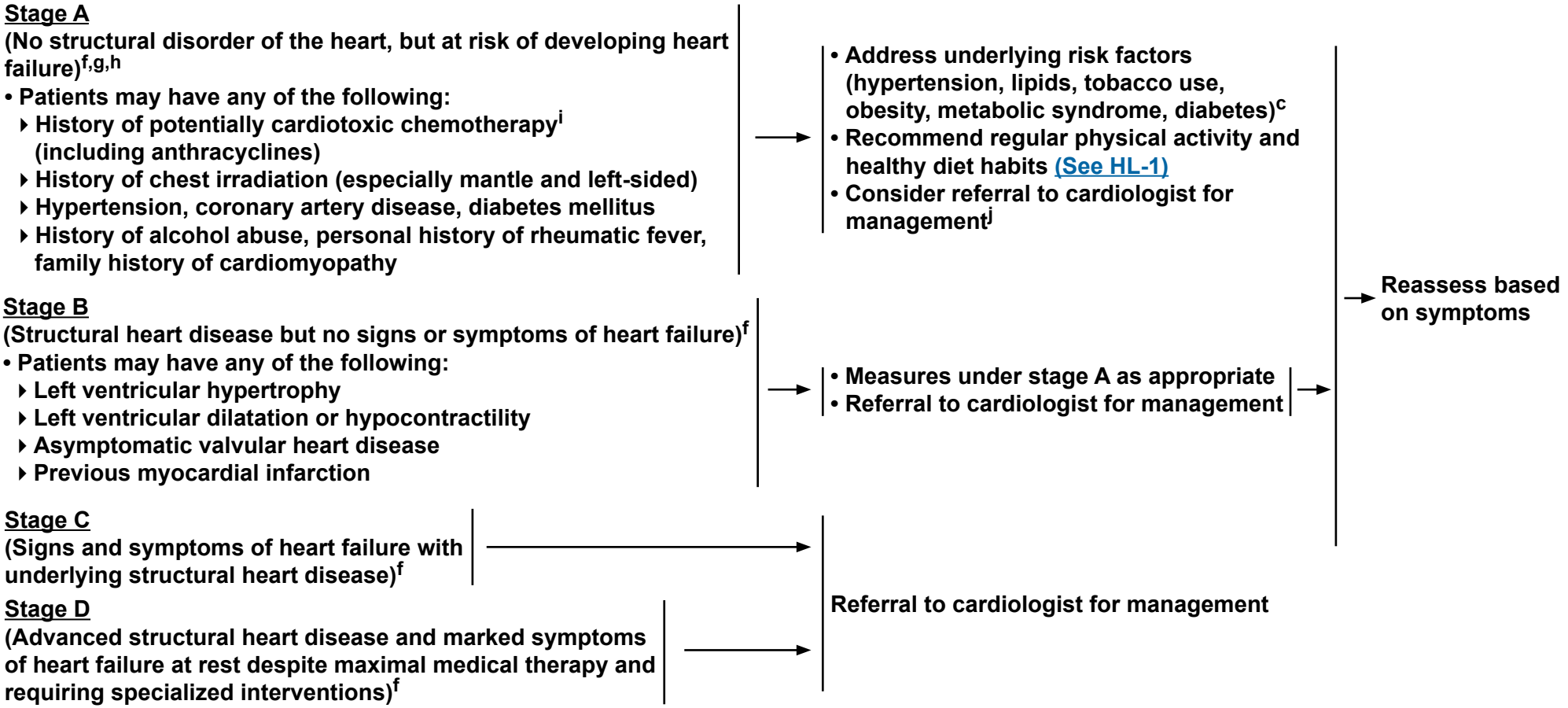

[c]Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[f]Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the Amercian College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240-e327.
[g]The use of biomarkers should be considered in select patients at high risk for heart failure (Stage A).
[h]Any patient who has received potentially cardiotoxic chemotherapy and/or chest radiation (and specifically anthracycline-based chemotherapy) should be considered Stage A cardiomyopathy.
[i]For a list of potentially cardiotoxic chemotherapy agents see Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Eng J Med 2016;375:1457-1467.
[j]Consider referral to a cardiologist, especially if additional anthracycline therapy or other cardiotoxic treatment is needed.

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GENERAL PRINCIPLES OF ANXIETY, DEPRESSION, AND DISTRESS

- **The NCCN Guidelines for Distress Management define distress as "a multifactorial unpleasant emotional experience of a psychological (ie, cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment." The NCCN Guidelines for Survivorship complement the NCCN Guidelines for Distress Management.**
- **Survivors of cancer treatment are at elevated risk for mental health issues such as fear of recurrence, distress, anxiety, and depression that may persist many years after diagnosis.***
  - **Fear of recurrence can lead to increased symptoms when surveillance testing or follow-up appointments are scheduled and increased anxiety when physical symptoms occur that may or may not be similar to those experienced during the cancer diagnosis.**
  - **Medical, psychosocial, environmental, and psychiatric health factors may affect the mood of cancer survivors and need to be considered when screening for distress, anxiety, and depression in survivors and deciding on treatment. (See SANXDE-6)**
  - **Recurrent worry, fear, thoughts, or images related to cancer events should be distinguished from obsessive compulsive disorders. Repetitive, persisting thoughts, images, or behaviors or mental acts that a person is compelled to perform, aimed at reducing intense anxiety or preventing a dreaded event require psychiatric referral for evaluation and treatment.**
  - **Monitor distress, especially at times of transitions in care, cancer surveillance, significant loss, other major life events, and with social isolation.**
    - ◊ **Patients may not appear to be distressed and should be encouraged to inform their health care provider when they are feeling increased distress, anxiety, or depression. See DIS-B from the NCCN Guidelines for Distress Management.**

- **This algorithm is intended for oncologists and other health care providers to screen for distress, anxiety, and depression in cancer survivors, to provide steps for addressing these concerns with survivors, and to facilitate decisions about referral to specialists.**
  - **The algorithm is not intended as a psychiatric diagnosis and treatment tool.**
  - **The algorithm focuses on more common mood disorders after cancer; it does not screen or address treatment for psychiatric conditions such as bipolar disorders, schizophrenia, personality disorders, or obsessive compulsive disorders.**

- **Decisions about treatment and referral will depend on the acuteness of onset of symptoms, their intensity, and safety of the survivor and others. (See SANXDE-6 and SANXDE-A)**

*Lu D, Andersson TM, Fall K, et al. Clinical diagnosis of mental disorders immediately before and after cancer diagnosis: a nationwide matched cohort study in sweden. JAMA Oncol 2016;1188-1196.

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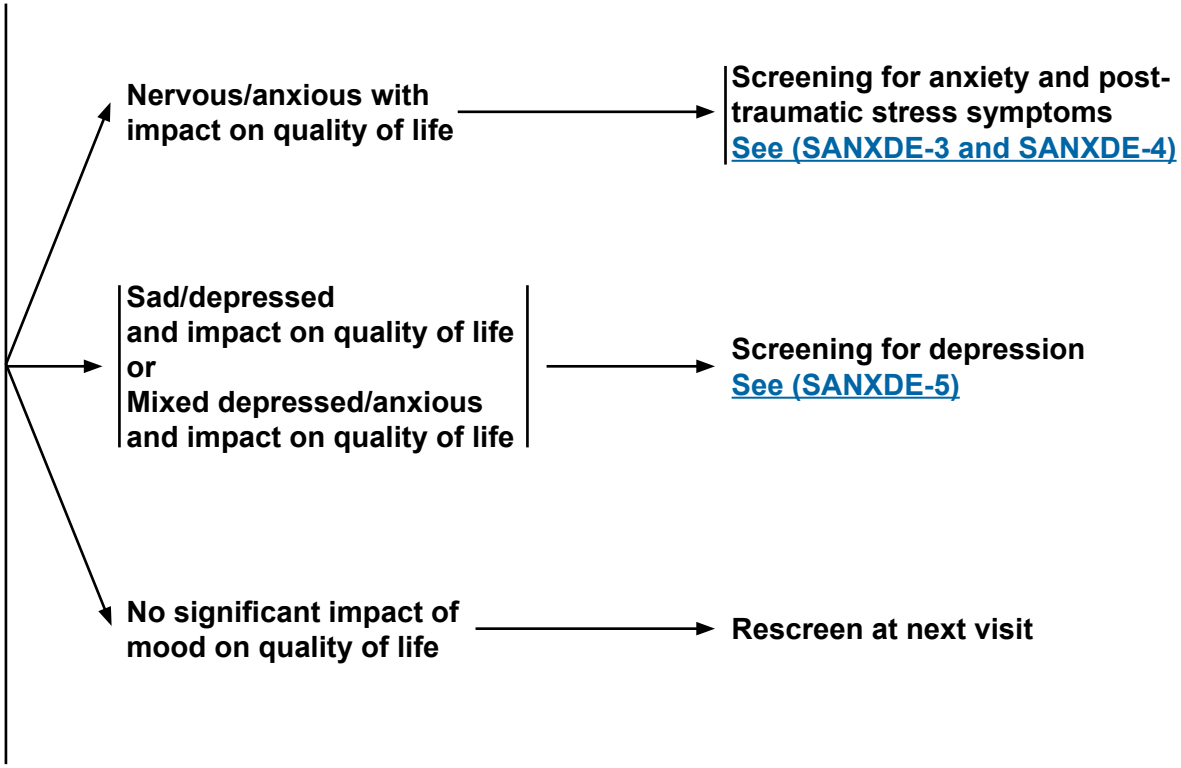
SCREENING: ANXIETY AND DEPRESSION

Screening questions[a] to be asked at regular intervals, especially when there is a change in clinical status or treatment, or patient presents with multiple somatic complaints:[b]

- **In the past two weeks, on more days than not have you:**
  - **Nervous/anxious**
    - ◊ **had worries or fears related to your cancer?**
    - ◊ **felt nervous, or worried about other things?**
    - ◊ **had trouble controlling your worry?**
  - **Sad/depressed**
    - ◊ **had less interest or enjoyment in activities than usual?**
    - ◊ **felt sad or depressed?**
- **Additional screening for impact of mood on quality of life if "Yes" to any of the above:**
  - **had difficulty performing daily activities because of these (above mentioned) feelings or problems?**
  - **had trouble sleeping (eg, staying asleep, falling asleep, too much sleep)?[a]**
  - **had difficulty concentrating?[a]**



[a]A positive response to any of the questions should result in further assessment. However, if a patient has an isolated problem with sleep or concentration in the absence of other symptoms, refer to the Sleep Disorders Guidelines (SSD-1) or Cognitive Function Guidelines (SCF-1).
[b]If the NCCN Distress Thermometer is used as a primary screening tool, these questions would follow for those survivors with an elevated level of distress.

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SCREENING: ANXIETY AND PANIC[c]

Anxiety
Excessive anxiety and worry that is difficult to control and ≥3 of the following:
- **Restless or on edge**
- **Easily fatigued**
- **Difficulty concentrating or mind going blank**
- **Irritability**
- **Muscle tension**
- **Sleep disturbance**

Panic
Sudden intense fear or discomfort that peaks within minutes and ≥4 of the following:[d]
- **Palpitations, pounding heart**
- **Sweating**
- **Trembling or shaking**
- **Sensations of shortness of breath or smothering**
- **Chest pain or discomfort**
- **Nausea or abdominal distress**
- **Feeling dizzy, lightheaded, unsteady**
- **Chills or heat sensations**
- **Paresthesias (numbness or tingling)**
- **Feelings of unreality or being detached from oneself**
- **Fear of losing control**
- **Fear of dying**

DIAGNOSIS

≥3 symptoms and persisting more than 6 months: General anxiety disorder → **Safety evaluation[f]** → **See Evaluation (SANXDE-7) or Refer to mental health services for evaluation and treatment[g]**

<3 symptoms and/or persisting less than 6 months: Adjustment disorder[e] with anxious or mixed mood or Other anxiety disorder → **See Screening (SANXDE-6)**

Panic disorder → **Safety evaluation[f]** → **See Evaluation (SANXDE-7) or Refer to mental health services for evaluation and treatment[g]**

[c]The following additional tools may be used for individual intensive screening for a specific problem: Anxiety: GAD7; Panic: Brief Patient Health Questionnaire, item 2 a-e. Both tools can be found at http://www.phqscreeners.com.
[d]Consideration should be taken for evaluation of other medical causes to rule out alternative etiologies.
[e]Development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). (American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.)
[f]See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[g]Psychiatrist, psychologist, advanced practice clinicians, and/or social worker.

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SCREENING: POST-TRAUMATIC STRESS DISORDER (PTSD) -RELATED SYMPTOMS[h,i,j]

DIAGNOSIS OF PTSD REQUIRES SYMPTOMS FROM EACH OF THE FOLLOWING 4 CATEGORIES

Exposure to traumatic events (eg, cancer diagnosis, treatment)[k] and the following symptoms that cause clinically significant distress or impairment in social interactions, capacity to work, or other functioning for more than 1 month:

- **Re-experiencing: repeated, disturbing memories, dreams, or flashbacks (minimum 1 symptom)**
- **Persistent avoidance: avoidance of distressing memories, thoughts, feelings, or external reminders of the cancer experience (minimum 1 symptom)**
- **Negative alterations in mood or cognition: exaggerated negative beliefs about oneself or the world, feeling detached or estranged from others, lack of positive emotions, feelings of fear, horror, anger, guilt, or shame (minimum 2 symptoms)**
- **Arousal: aggressive, risky or self-destructive behavior, sleep disturbance, hypervigilance (being super-alert or watchful or on guard), difficulty concentrating (minimum 2 symptoms)**

→

DIAGNOSIS

- **Post-traumatic stress symptoms impacting quality of life**
- **Consider PTSD[j]**
- **Consider adjustment disorder/distress (see SANXDE-6)**

→ **Safety evaluation[f]** →

See Evaluation (SANXDE-7)
or
Refer to mental health services for evaluation and treatment[g]

[f] See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[g] Psychiatrist, psychologist, advanced practice clinicians, and/or social worker
[h] For a complete list of screening symptoms review the American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
[i] The following additional tools may be used for screening: Primary Care PTSD Screen (PC-PTSD), 4 items, http://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp; or full screening with the 20-item PTSD Checklist for DSM-5 (PCL-5), intended for use by qualified health professionals with advanced graduate training in psychological diagnostic assessment: http://www.ptsd.va.gov/professional/assessment/documents/ptsd_trauma_assessments.asp.
[j] See Risk Factors for PTSD (SANXDE-B).
[k] Person may directly experience the traumatic event, witness the event, learn of the event occurring to a close family member or friend, or experience repeated or extreme exposure to aversive details of the trauma. Life-threatening illness or cancer or debilitating medical condition is not necessarily considered a traumatic event, but may be. A history of PTSD prior to a cancer diagnosis increases risk for symptoms of PTSD to be associated with cancer treatment if experiences remind the survivor of a prior traumatic event.

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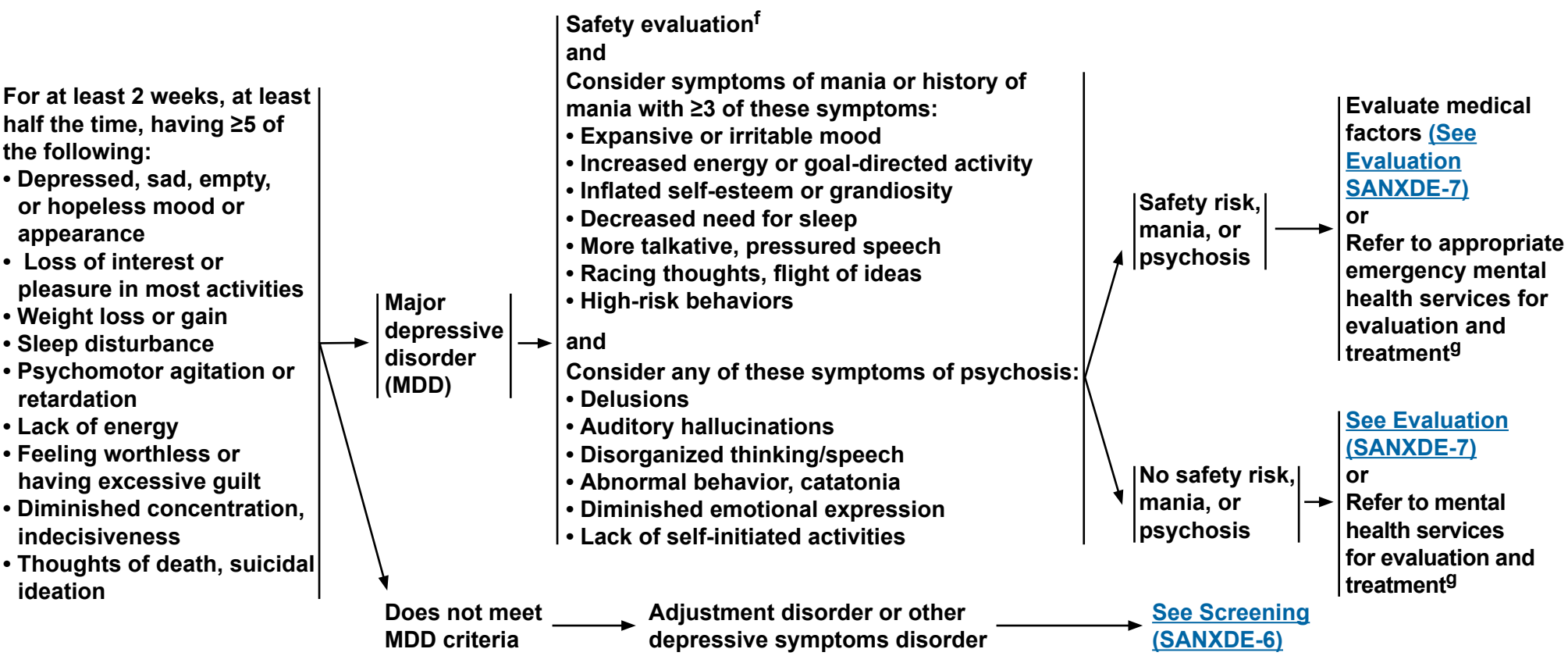

[f] See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[g] Psychiatrist, psychologist, advanced practice clinicians, and/or social worker.
[h] For a complete list of screening symptoms review the American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
[l] The following additional tools may be used for individual intensive screening for a specific problem: Screening Tools: PHQ-9 or PHQ-2. The PHQ-2 is comprised of the first two items of the PHQ-9 and can be used as an initial depression screening. If the patient responds affirmatively to either of these two items, the remaining 7 items are asked. (Available at: www.phqscreeners.com and http://www.commonwealthfund.org/usr_doc/PHQ2.pdf).
[m] When screening, also take into consideration a survivor's cultural differences at presentation (eg, somatization as expression of emotional distress).

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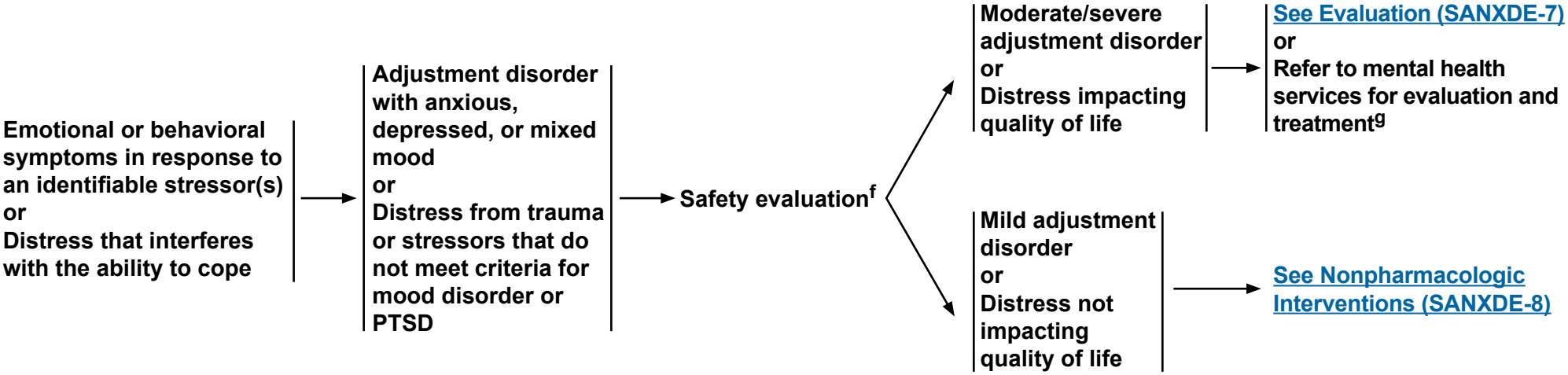
SCREENING: ADJUSTMENT DISORDER/DISTRESS[h,n]

DIAGNOSIS



[f] See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[g] Psychiatrist, psychologist, advanced practice clinicians, and/or social worker.
[h] For a complete list of screening symptoms review the American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
[n] The following additional tool may be used for screening distress level: NCCN Distress Thermometer Screening Tool [DIS-A]. A score of ≥4 indicates moderate/severe distress: "On a scale of 0–10 how much distress have you been experiencing in the past week, including today with 0 = No Distress and 10 = Extreme Distress?"

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EVALUATION: ANXIETY, DEPRESSION, AND DISTRESS[o]

Medical Factors (H&P Exam)

- **General review:**
  - Illness status/progression
  - Medication changes/side effects
  - Presence of new or poorly controlled symptoms (ie, pain, nausea, constipation)
  - Status of coexisiting medical conditions
  - Substance abuse
  - History of prior major depression, anxiety disorder, or suicide attempt
  - Fatigue level (See SFAT-1)
  - Functional status
  - Current coping strategies
  - Sexual function (See SSF-1)
  - Infertility
  - Other medical factors including cognitive function (See SCF-1)
- **Laboratory studies to consider:**
  - Metabolic studies
  - Infection workup
  - Anemia with underlying deficiencies
  - Endocrine/hormonal status
- **Other studies as clinically indicated:**
  - Neurologic:
    - ◊ CNS imaging
    - ◊ Neuropsychological testing
  - Cardiac: electrocardiogram (EKG), ECHO, stress test (See SCARDIO-1)
  - Pulmonary function tests
  - Sleep evaluation (See SSD-1)

→

Psychiatric/Emotional Factors

- Symptom review based on the Survivorship Anxiety and Depression screening recommendations (See SANXDE-2 through SANXDE-6); evaluate for anticipation/fear of recurrence in the setting of:
  - Active surveillance by oncology team
  - New symptoms or findings suggestive of recurrence
  - Transitions in surveillance and care
- Consider other major psychiatric disorders

→

Social/External Factors

- Environmental stressors and non-cancer-related factors:
  - Social isolation, living alone
  - Family and caregiver conflicts, roles, and responsibilities
  - Spouse, intimate partner relationship
  - Financial problems and limited insurance coverage
  - Employment concerns
  - Limited access to medical care
  - Younger age, survivors of childhood cancers, lack of peers
  - History of abuse (emotional, physical, sexual)
  - Spiritual, religious, or existential concerns
  - Other stresses

→

Management and Treatment (See SANXDE-8)
or
For mania, psychosis, extensive psychiatric history, or moderate to high safety risk
- **Refer for psychiatric evaluation and treatment**

[o]These are general factors/principles that effect anxiety, depression, distress, and adjustment and that need to be considered when evaluating survivors.

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ANXIETY, DEPRESSION, DISTRESS: MANAGEMENT AND TREATMENT

NONPHARMACOLOGIC INTERVENTIONS

- **FOR ALL SURVIVORS**
  - Address treatable contributing factors
    - ◊ Pain, sleep disturbance, fatigue, toxic metabolic/endocrine/other medical comorbidities, substance abuse
  - Provide reassurance that symptoms of worry, stress, anxiety, and depression are common problems among cancer survivors and that these symptoms can be treated
  - Provide support and education to patient and family regarding normal recovery phases after treatment, common stresses, distress and fears, and strategies for managing uncertainty and distress
  - Provide resources for social support networks and specific social, emotional, spiritual, intimacy, and practical problem needs (See SURV-B)
  - Develop a plan for regular physical activity and healthy nutrition (See HL-1)

- **FOR ADJUSTMENT DISORDER OR DISTRESS WITHOUT SAFETY RISK, MANIA, OR PSYCHOSIS:**
  - Refer for therapy (social work, psychologist, psychiatrist, licensed therapist):
    - ◊ Psychological or social factors interfering with prescribed care
    - ◊ Social work for complex social factors
    - ◊ Supportive normalizing of survivor's experience
    - ◊ Cognitive behavioral therapy (CBT)
    - ◊ Existential therapy related to values, meaning, purpose in life
  - Refer to chaplain for spiritual support for religious conflict, concerns about death and afterlife, guilt, grief, meaning and purpose in life
  - Consider integrative therapies (ie, mindfulness meditation, imagery/hypnosis, yoga)
  - Refer for couples, family, caregiver, or relationship counseling/support

- **FOR MODERATE TO SEVERE INTENSITY MAJOR DEPRESSION, GENERALIZED ANXIETY, PANIC, OR PTSD SYMPTOMS**
  - Refer for evaluation and treatment by a mental health professional[g]
  - Consider pharmacologic and/or nonpharmacologic treatments

- **FOR SUBSTANCE ABUSE**
  - Safety Evaluation (SANXDE-A)
  - See DIS-21 from the NCCN Guidelines for Distress Management
  - Refer to substance abuse specialist

- Reevaluate symptoms and function at next visit
- Revise referrals and interventions if symptoms are persistent or increased

Consider pharmacologic interventions (See SANXDE-9)

[g]Psychiatrist, psychologist, advanced practice clinicians, and/or social worker.

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ANXIETY, DEPRESSION, DISTRESS: MANAGEMENT AND TREATMENT

PHARMACOLOGIC INTERVENTIONS[p]

- **First-line treatment:**
  - **Selective serotonin reuptake inhibitors (SSRIs)**
  - **Serotonin-norepinephrine reuptake inhibitors (SNRIs):**
    - ◊ **Consider for concomitant pain**
    - ◊ **Consider for concomitant hot flashes**
  - **Monitor for potential side effects.**
  - **Counsel survivor that it may take up to 2 to 6 weeks at a therapeutic dose for SSRIs and SNRIs to take effect.**
  - **Benzodiazepines (BZD) (ie, clonazepam, lorazepam):**
    - ◊ **For acute anxiety relief or while waiting for antidepressant to take effect**
    - ◊ **Adjust dose once SSRIs or SNRIs are fully effective and symptoms are partially or completely abated.**
  - **Counsel survivor that symptoms of withdrawal may occur should any of the above-mentioned medications be abruptly discontinued.**
- **Consider referral to mental health professional[g] for medication failure if inadequate response to first-line treatment**

→

- **Reevaluate distress and function at next visit**
- **Revise referrals and interventions if distress is persistent or increased**

[g]Psychiatrist, psychologist, advanced practice clinicians, and/or social worker.
[p]See Principles of Pharmacologic Interventions (SANXDE-C).

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SAFETY EVALUATION

DANGER TO SELF OR OTHERS, OR INABILITY TO CARE FOR SELF

Consider at elevated risk if survivor:

Has an organized plan for suicide or homicide

OR

Has suicidal or homicidal thoughts and, based on clinical judgment, the survivor is at imminent risk of harm to self or others

- **Consider the following risk factors:**
  - **Previous attempts at suicide**
  - **Family history or other exposure to suicide**
  - **Male**
  - **Age (late teens, >55)**
  - **No spouse or live-in partner**
  - **Isolation**
  - **Recent loss of important person or relationship breakdown**
  - **Chronic illness or recent change in health status**
  - **Alcohol or other substance abuse**
  - **Depression**
  - **Loss of rational thinking**
  - **Feeling hopeless**
  - **Access to firearms/weapons, potentially lethal medications (opioids, BZD, antidepressants)**
  - **Perceives self as a burden**

ACUTE (URGENT/EMERGENT) INTERVENTIONS

Lower risk based on:
- **Suicidal ideation with no plan, no thoughts of danger to others**
- **Few of the risk factors**
- **Clinical judgment**

→

Develop safety plan with survivor
- **Immediate referral for mental health evaluation based on urgency**
- **Regular follow-up and monitoring until psychiatric care is in place**
- **Have survivor agree to contact a health care provider, call 911, or go to the nearest emergency room if suicidal thoughts increase or change**
- **For suicide hotline information (See SURV-B)**

Elevated risk of danger to self or others based on:
- **Suicidal or homicidal thoughts with plan and/or with multiple other risk factors or**
- **Clinical judgment**
- **Inability to care for self**

→

Emergency intervention:
- **Evaluate availability of firearms/weapons and arrange to have them secured**
- **If offsite and threat is to others or patient is agitated or threatening:**
  - **Call 911 and/or identify caregiver who is with patient to take to emergency room or call 911 or follow state mental health emergency plan**
- **If onsite and patient becomes agitated or threatening:**
  - **Involve other staff/security, keep door open, call 911**
  - **Refer to emergency psychiatric evaluation procedures onsite**
  - **Identify and follow any state reporting or other requirements**

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SAFETY EVALUATION	ACUTE (URGENT/EMERGENT) INTERVENTIONS
DANGER FOR ABUSE OR NEGLECT OF VULNERABLE PERSON (CHILD, ELDERLY, PERSON UNABLE TO CARE FOR SELF): • Self-report or observation of risk for or actual physical, sexual, health care, or financial abuse	→ Determine acuity, involve social work or emergency services, follow mandatory reporting requirements • Refer to urgent social work or emergency room for full evaluation of risks and options • Follow state laws for reporting abuse
SUBSTANCE ABUSE/DEPENDENCE • Self-report, caregiver/family report, or observation of misuse of medications or of altered mental status potentially related to drug or alcohol use	→ See Substance-Related and Addictive Disorders (DIS-21) section in the NCCN Guidelines for Distress Management

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RISK FACTORS FOR PTSD

- **Physical**
  - **Recurrence of cancer**
  - **Intensive treatment (eg, bone marrow/stem cell transplant)**
  - **Advanced disease**
  - **Younger age**
- **Psychosocial**
  - **Exposure to previous trauma (eg, combat, sexual assault, major loss)**
  - **History of mental health issues prior to cancer**
  - **Poor coping skills (eg, using avoidance)**
  - **Lower income and/or less education**
  - **Less social support**

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PRINCIPLES OF PHARMACOLOGIC INTERVENTIONS

Special Pharmacologic Considerations for Concomitant Problems:

- Substance abuse
  - Minimize use of benzodiazepines
  - Alternatives for sedation and acute anxiety are low-dose atypical neuroleptics (ie, olanzapine, quetiapine) or gabapentin
- Pain syndromes (eg, neuropathy) (See SPAIN-1)
  - Seratonin-norepinephrine reuptake inhibitors (SNRIs)
  - Tricyclic antidepressants (TCAs)
    - ◊ Amitriptyline has sedating properties that may or may not be desirable
    - ◊ Nortriptyline and desipramine have the fewest side effects
- Fatigue (See SFAT-1)
  - Bupropion may have less sedating side effect
  - Evidence for psychostimulant effects for depression and fatigue are limited and mixed (See SFAT-5)
- Insomnia
  - See Sleep Disorders (See SSD-1)

Caveats:

- Review side effects with patient, noting that some may be beneficial (sedation, arousal, or weight gain and appetite stimulation)
- Monitor QT interval on electrocardiogram at initiation and dose increases with neuroleptics and citalopram
- Blood pressure should be monitored with venlafaxine and treated appropriately
- Refer to specialist if first-line treatment fails or if there are complicating factors such as chronic pain or substance abuse
- Avoid psychotropics with cytochrome P_{450} interactions in patients taking tamoxifen
  - Fluoxetine*
  - Paroxetine*
  - Sertraline*
  - Bupropion
  - Fluvoxamine
  - Nefazodone

*Pure SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6 and should be used with caution for women on tamoxifen.

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COGNITIVE FUNCTION FOLLOWING CANCER TREATMENT

General Principles

- **Growing evidence supports the validity of the patient-reported experience of cognitive dysfunction associated with cancer treatment.**
- **Neuropsychological testing and brain imaging have demonstrated abnormalities in patients who have had chemotherapy following cancer treatment.**
- **There is modest correlation between patient reports of cognitive dysfunction and objective deficits with testing.**
- **There is limited evidence to guide management of this condition.**
- **Patients benefit from validation of their symptom experience, a thorough evaluation of this concern and related issues, and education.**
- **Imaging studies may not be helpful, except to rule out structural abnormalities as indicated by high-risk illness, or focal neurologic deficits or comorbidities.**
- **Patients who report cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, such as depression, sleep disturbance, and fatigue.**
- **Currently no effective brief screening tool for cancer-associated cognitive dysfunction has been identified. The Mini-Mental State Examination (MMSE®)[a] and similar screening tools lack adequate sensitivity for subtle decline in cognitive performance.**
- **These guidelines address cognitive function of survivors with non-central nervous system (CNS) malignancies who did not have CNS-directed therapies.**

[a]Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

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COGNITIVE FUNCTION ASSESSMENT

Focused history:

- Focal neurologic deficits
- High risk or known metastatic disease/brain primary
- Onset, temporality
- Age (a risk factor for developing cognitive deficiency)
- Trajectory over time
- Cancer treatment history
- Prescription medications/OTC medications and supplements
- Education attainment
- Caregiver assessment of cognitive function
- Nature of impairments per patient; clarifying questions may include:
  - Do you have difficulty paying attention? Multitasking?
  - Do you frequently leave tasks incomplete?
  - Do you have difficulty finding words?
  - Do you have difficulty remembering things?
  - Do you need to use more prompts like notes or reminders than you used to?
  - Does it take you longer to think through problems; does your thinking seem slower?
  - Do you notice an impact on functional performance? Job performance?
- Assessment of medical history that may impact cognitive function

Assessment of contributing factors:

- Medications/side effects
- Emotional distress
  - Depression/anxiety (See SANXDE-1 and NCCN Guidelines for Distress Management)
- Symptom burden
  - Pain (See SPAIN-1)
  - Fatigue (See SFAT-1)
  - Sleep disturbance (See SSD-1)
- Comorbidities
- Use of alcohol and other agents that alter cognition

SPECIALIZED EVALUATION

Neuroimaging

See Cancer-associated Cognitive Dysfunction Interventions (SCF-3)

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CANCER-ASSOCIATED COGNITIVE DYSFUNCTION INTERVENTIONS

Patient/Family Education and Counseling
- Validation of experience of cognitive dysfunction associated with cancer diagnosis and treatment
- Reassurance that cancer-associated cognitive dysfunction is often not a progressive neurologic disorder like progressive dementias[b]
- Support self-management and coping strategies

→

General Strategies for Management of Cancer-Associated Cognitive Dysfunction
- Teach enhanced organizational strategies (ie, using memory aids like notebooks and planners, keeping items in the same place, using reminder notes, smart phone technology)
- Encourage patients to do the most cognitively demanding tasks at the time of day when energy levels are highest
- Provide information about relaxation or stress management skills for daily use
- Recommend routine physical activity (See HL-1)
- Recommend limiting use of alcohol and other agents that alter cognition and sleep
- Consider meditation, yoga, mindfulness-based stress reduction, and cognitive training (ie, brain games)
- For older adults also see the cognitive function section of the NCCN Guidelines for Older Adult Oncology (OAO-E)
- Optimize management of:
  - Depression or emotional distress (See appropriate survivorship guidelines or NCCN Guidelines for Distress Management)
  - Sleep disturbance (See SSD-1)
  - Fatigue (See SFAT-1)
  - Contributing symptoms such as pain (See SPAIN-1)
  - Medical comorbidities

→ See Specific Interventions (SCF-4)

[b]Cognitive dysfunction may be progressive in survivors of CNS cancers or those who had CNS-directed therapies.

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CANCER-ASSOCIATED COGNITIVE DYSFUNCTION SPECIFIC INTERVENTIONS

FIRST-LINE INTERVENTIONS

- **Neuropsychological evaluation and recommendations[c]**
- **Cognitive rehabilitation**
  - **Occupational therapy[d]**
  - **Speech therapy**
  - **Neuropsychology**
- **Recommend routine physical activity** **(See HL-1)**

SECOND-LINE INTERVENTIONS

Consider trial use of psychostimulants (methylphenidate or modafinil)[e]

[c]Neuropsychological evaluation and intervention may be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.

[d]Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for an individual who notes the impact of specific functional limitations (ie, word finding, comprehension or task completion, quality-of-life or role expectations).

[e]Overall the evidence for psychostimulants is lacking, but they may be of some benefit.

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DEFINITION OF CANCER-RELATED FATIGUE

- **Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.**

CONSIDERATIONS FOR FATIGUE IN CANCER SURVIVORS

- **Fatigue is a common complaint in individuals undergoing cancer therapy and can be a persistent problem for some cancer survivors in the months and years after cancer diagnosis.**
  - **Receipt of chemotherapy and radiation are both predisposing factors for cancer-related fatigue, but it can be seen in some patients who are treated with surgery alone.**
  - **The time-course of fatigue is unique to the survivor and his or her treatment plan, but some general principles apply: Mild to moderate fatigue is common in cancer survivors who undergo chemotherapy and/or radiation; mild to moderate fatigue lasting up to one year can occur in a proportion of cancer survivors.**
  - **Fatigue that initially presents months after the completion of adjuvant therapy or fatigue that worsens over this period warrants additional evaluation.**

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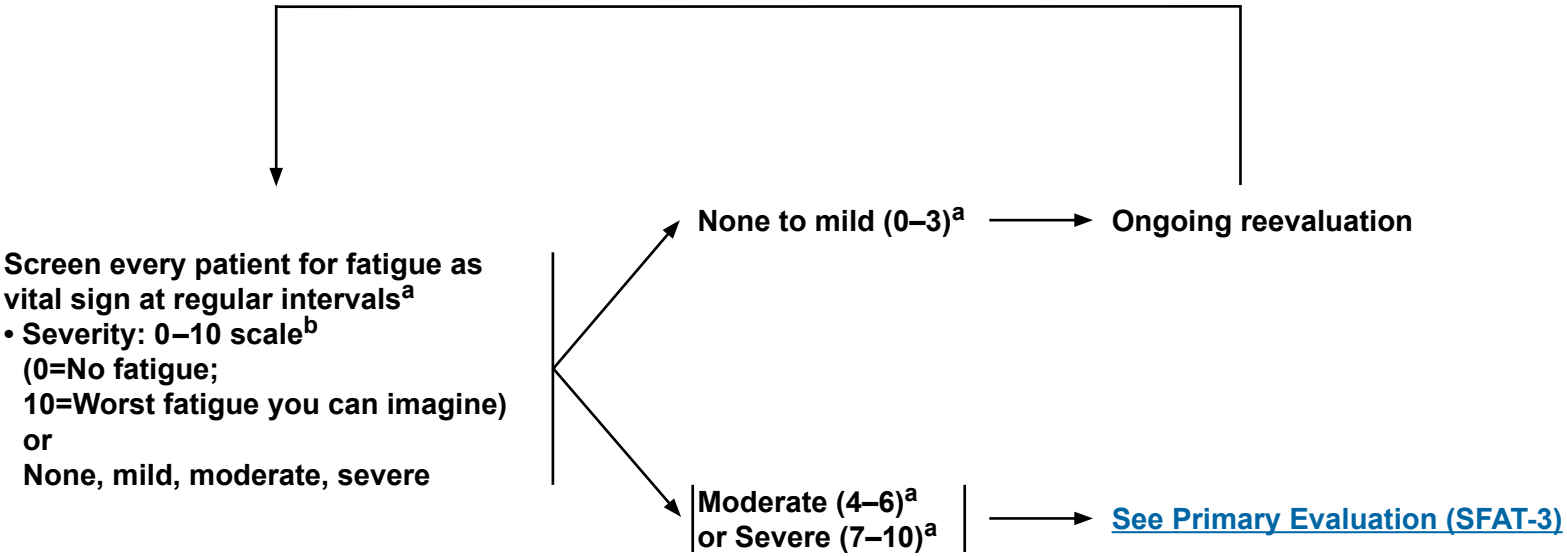
SCREENING



[a]Recommended screen and re-evaluation: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?"
[b]Butt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. J Pain Symptom Manage 2008;35:20-30.

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PRIMARY EVALUATION FATIGUE SCORE: MODERATE OR SEVERE (4–10)

H&P:

- Focused fatigue history
  - Onset, pattern, duration
  - Change over time
  - Associated or alleviating factors
  - Interference with function
- Evaluate disease status
  - Evaluate risk of recurrence based on stage, pathologic factors, and treatment history
  - Perform review of systems to determine if other symptoms substantiate suspicion for recurrence
- Assessment of treatable contributing factors:
  - Comorbidities
    - ◊ Alcohol/substance abuse
    - ◊ Cardiac dysfunction
    - ◊ Endocrine dysfunction (eg, hypothyroidism, hypogonadism, adrenal insufficiency)
    - ◊ Pulmonary dysfunction
    - ◊ Renal dysfunction
    - ◊ Anemia
    - ◊ Arthritis
  - Prescribed or OTC medications (eg, sleep aids, pain medications, antiemetics)
  - Emotional distress- screen for anxiety and depression (See SANXDE-1)
  - Sleep disturbance (eg, insomnia, sleep apnea, vasomotor symptoms, restless legs syndrome [RLS]) (See SSD-1)
  - Pain (See SPAIN-1)
  - Nutritional issues
    - ◊ Weight/caloric intake changes
  - Deconditioning/loss of muscle mass

→

EVALUATION

Laboratory Evaluation:

- Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of fatigue
  - CBC with differential
    - ◊ Compare end-of-treatment hemoglobin/hematocrit with current values
    - ◊ Assess other cell lines (WBC and platelets)
  - Comprehensive metabolic panel
    - ◊ Assess electrolytes
    - ◊ Assess hepatic and renal function
  - Endocrine evaluation
    - ◊ TSH, especially in patients who have received prior head/neck, torso, or breast radiation
    - ◊ Consider more comprehensive evaluation or referral to specialist if other symptoms present
    - ◊ Cortisol stimulation test, if history of prolonged steroid use

→

Other Diagnostic Testing:

- Consider radiologic assessment only if high risk of disease recurrence OR if accompanying signs and symptoms suggest presence of metastatic disease
- Consider cardiac testing (ECHO) for patients treated with an anthracycline (See SCARDIO-1), trastuzumab, bevacizumab, other VEGF- or HER2-targeted therapy, or other therapy known to cause cardiac dysfunction
- Chest x-ray and oxygen saturation testing for pulmonary complaints[c]

→ See Treatment of Contributing Factors (SFAT-4)

[c]Refer to a pulmonologist for pulmonary complaints.

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TREATMENT OF CONTRIBUTING FACTORS

- **Treat contributing factors:**
  - **Medications/side effects**
  - **Pain** (See SPAIN-1)
  - **Emotional distress** (See SANXDE-1) **and** NCCN Guidelines for Distress Management
  - **Anemia**
    - ◊ **Treat iron, B_{12}, folate deficiency, if present**
    - ◊ **Consider referral/further evaluation for anemia or cytopenias**
  - **Sleep disturbance** (See SSD-1)
  - **Nutritional deficit/imbalance**
  - **Comorbidities**

→ See Interventions for Cancer Survivors (SFAT-5)

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INTERVENTIONS FOR CANCER SURVIVORS

Patient/Family Education and Counseling

- Provide information about patterns of fatigue during and after treatment
- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities
  - Pace
  - Schedule activities at times of peak energy

→

Physical Activity

- Maintain adequate levels of physical activity (category 1) (See SPA-1 and SPA-4)
- Survivors at higher risk of injury (eg, those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy or other comorbidities) should be referred to a physical therapist or exercise specialist
- Make use of local resources to help patients increase exercise (eg, aerobics, strength training, yoga)
  - Exercise classes at cancer centers
  - Community programs focused on cancer survivors
  - Exercise professional certified by the American College of Sports Medicine
  - For patients with fatigue interfering with function, consider referral to a physical therapist or physiatrist

→

Other Interventions[c]

- Psychosocial interventions (category 1)
  - Cognitive behavioral therapy[d]/Behavioral therapy (category 1)
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies (category 1)[e]
- Nutrition consultation
- Cognitive behavioral therapy[d] for sleep (category 1) (See SSD-1)
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene
- Acupuncture

→

Pharmacologic[f]

Consider psychostimulants[g] (methylphenidate[h]) after ruling out other causes of fatigue and failure of other interventions

[c]Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.
[d]A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment.
[e]Supportive expressive therapies (such as support groups, counseling, and journal writing) facilitate expression of emotion and foster support from one or more people.
[f]Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients.
[g]Psychostimulants are at times used to treat cancer-related fatigue. A number of studies have evaluated their efficacy in the setting of active treatment and results have been mixed. There are extremely limited data regarding the use of these agents in the post-treatment setting.
[h]Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in patients with cancer.

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DEFINITION AND STAGES OF LYMPHEDEMA[a-c]

- **Definition: Lymphedema occurs when lymph fluid accumulates in the interstitial tissue, causing swelling of the limb or other areas such as the neck, trunk, or genitals. It is a common side effect of cancer treatment, occurring on the same side of the body as the cancer treatment, as a result of dysfunction of the lymphatic system.**
- **Stage 0 (latent/subclinical): Lymphatic dysfunction without swelling; subtle symptoms, such as a feeling of heaviness or fatigue in the limb, may be present.**
- **Stage 1 (spontaneously reversible): Accumulation of fluid and protein causing swelling; pitting edema may be evident; increased girth, heaviness, and/or stiffness of affected area. For the limbs, swelling is relieved with elevation.**
- **Stage 2 (irreversible): Spongy tissue consistency, with pitting edema that becomes less evident as swelling increases; tissue fibrosis causing hardness and increase in size. For the limbs, swelling is not relieved with elevation.**
- **Stage 3 (lymphostatic elephantiasis): Severe dry, scaly, thickened skin; increased swelling and girth of affected area; can be debilitating. In the limbs, fluid leakage and blisters are common.**

[a]National Cancer Institute Lymphedema (PDQ®)–Health Professional Version. https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq.
[b]International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology 2013;46:1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23930436.
[c]National Lymphedema Network: https://www.lymphnet.org/le-faqs/what-is-lymphedema/signs-and-symptoms.

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PRINCIPLES OF LYMPHEDEMA

- **Lymphedema is a potential side effect after the treatment of cancer resulting from damage to the lymphatic system. Lymphedema is most often diagnosed within 18 months of treatment; however, it can develop anytime in the life of the survivor. Depending on stage of diagnosis, lymphedema can be an acute or chronic condition.**
- **Swelling on the same side as the cancer treatment is a universal symptom of lymphedema. Additional initial symptoms may include sensation of heaviness, fatigue, fullness or tightness in the skin, or pain. Symptoms including decreased range of motion or strength and thickening of the skin may occur in later stages.[a]**
- **Survivors who had surgery or radiation to the axillary, supraclavicular, cervical, or inguinal lymph node system are at risk for the development of lymphedema. Sentinel node biopsy also increases the risk of lymphedema, although it poses less risk than complete dissection or radiation to the nodal group.**
- **Obesity (BMI >30 kg/m^2), localized infection, increased number of nodes removed, and higher initial extent of disease raise the risk of lymphedema development.**
- **Pretreatment limb measurement of both sides should be performed as a baseline for survivors with treatment-related or individual risk factors, preferably by a trained lymphedema specialist.**
- **Early detection/diagnosis is key for optimal lymphedema management because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment. Therefore, survivors should be told to inform their medical provider if subtle swelling or any other symptoms (eg, fullness, tightness, heaviness, pain) on the treated side are noted.**
- **Lymphedema may cause or exacerbate psychological distress (See SANXDE-1).**
- **Survivors at risk for lymphedema and those with lymphedema are at a higher risk of localized infection in the affected area. These infections can require hospitalization for IV antibiotics. Therefore, survivors with or at risk for lymphedema should be educated to inform their medical provider immediately for signs of infection in the affected area.**
- **Progressive weight training under supervision and physical activity are not associated with exacerbation or development of lymphedema.[d,e,f]**
- **Observational studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[g,h] In the absence of high-level data, however, the panel recommends that medical procedures such as venipuncture and blood pressure measurements be done on the non–at-risk arm/limb if possible.[i] If necessary, procedures may be done using the at-risk arm/limb. More research is needed to determine the effect of these procedures on the risk of lymphedema.**

[a]National Cancer Institute Lymphedema (PDQ®)–Health Professional Version https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-pdq.
[d]Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine.American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426.
[e]Irwin M, ed. ACSM's Guide to Exercise and Cancer Survivorship. Champaign, IL: The American College of Sports Medicine; 2012.
[f]National Lymphedema Network. Position Paper: Exercise 2013. https://www.lymphnet.org/resources/position-paper-exercise
[g]Asdourian MS, Skolny MN, Brunelle C, et al. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. Lancet Oncol. 2016;17:e392-405.
[h]Ahn S, Port ER. Lymphedema Precautions: Time to Abandon Old Practices? J Clin Oncol 2016;34:655-658.
[i]National Lymphedema Network. Position Paper: Lymphedema Risk Reduction Practices 2012 https://www.lymphnet.org/pdfDocs/position.papers/Risk.Reduction.pdf.

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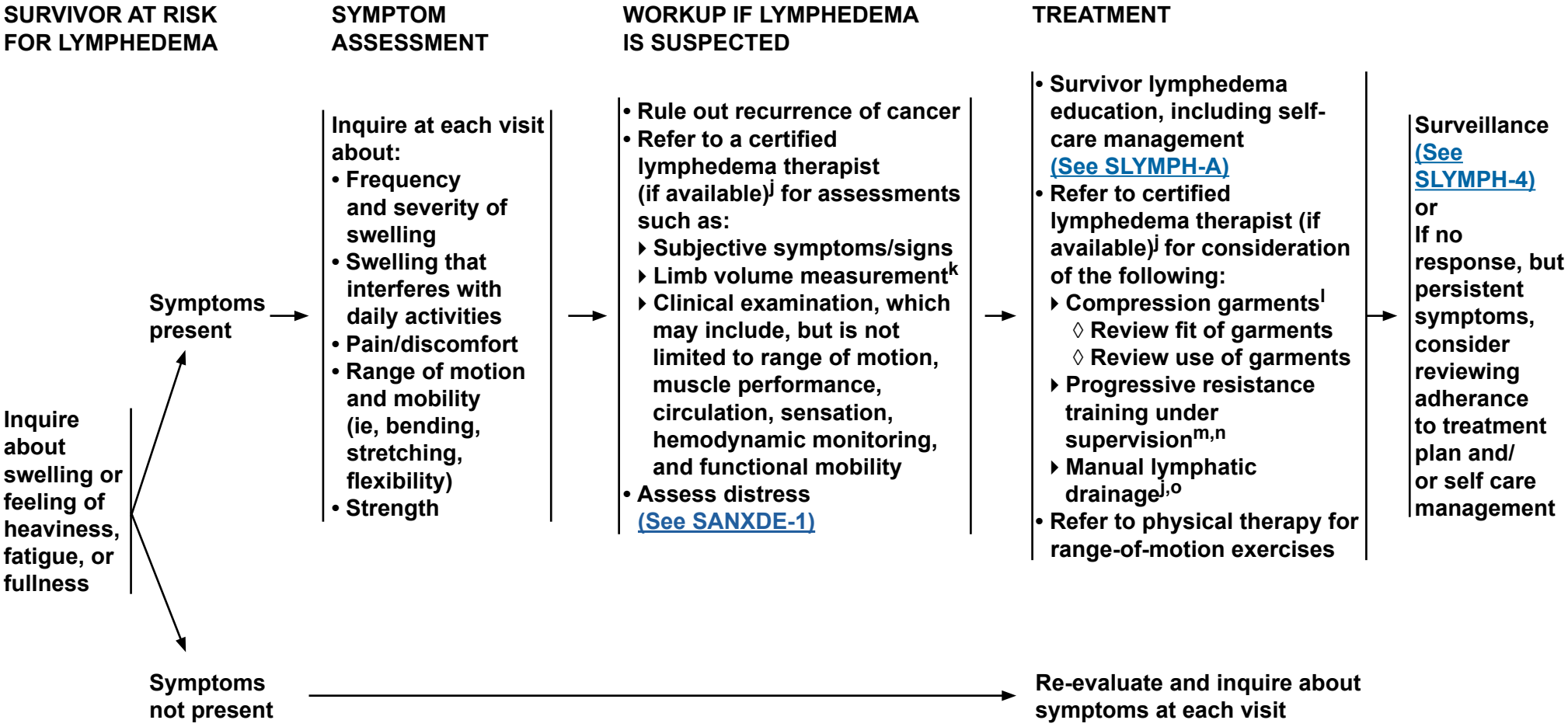

[j]Certified lymphedema therapists can be located using the following resource: https://www.clt-lana.org/search/therapists/.
[k]If baseline measurement is not available, measure unaffected contralateral limb as a reference.
[l]Compression garments should be prescribed. Optimally, they should be fitted and measured by a certified lymphedema therapist.
[m]If a certified therapist is not available, survivors with lymphedema can perform resistance training with a professional trainer who has knowledge of cancer-related physical activity principles. Weights should be slowly progressed as tolerated, and lymphedema should be evaluated periodically.
[n]See Principles of Physical Activity for Survivors with or At Risk for Lymphedema (SLYMPH-B).
[o]If a certified lymphedema therapist is not available, consider referral to appropriate provider for treatment.

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SURVEILLANCE

Follow-up with treatment team as clinically indicated

- **Inquire about fit and age of compression garments**
- **Replace compression garments as clinically indicated**
- **Check range of motion**
- **Inquire about performance of prescribed exercises**
- **Inquire about self-care management**
- **Continue survivor lymphedema education (See SLYMPH-A)**
- **Continue treatment as clinically indicated (See SLYMPH-3)**
- **Assess for distress (See SANXDE-1)**

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SURVIVOR LYMPHEDEMA EDUCATION

- **Survivors should be educated regarding:**
  - **Signs and symptoms of lymphedema and the importance of rapid reporting to the treatment team.**
  - **Signs and symptoms of infection (eg, redness, pain, skin streaking/warm to touch) in the affected area and the importance of rapid reporting to the treatment team.**
  - **Self-care management: Infection prevention measures,[1] risk reduction strategies,[2] maintenance of skin integrity on the affected side**
- **Survivors should also be informed that:**
  - **Progressive weight training under supervision and physical activity are not associated with exacerbation or development of lymphedema.[3,4,5]**
    - ◊ **Progressive resistance training under supervision may improve lymphedema symptoms. However, caution is advised in this population, and survivors with or at risk for lymphedema should discuss physical activity plans with a lymphedema specialist before starting a program that involves strength or resistance training.**
  - **Studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[6,7] However, medical procedures such as venipuncture and blood pressure measurements should be done on the non–at-risk arm/limb if possible.[8] If necessary, procedures may be done using the at-risk arm/limb.**

[1]Risk of infections can be reduced by safe pet care and gardening techniques (See SIMIN-2).
[2]For a complete list of lymphedema risk reduction practices, see the Position Statement from the National Lymphedema Network: https://www.lymphnet.org/pdfDocs/position.papers/Risk.Reduction.pdf.
[3]Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine.American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426.
[4]Irwin M, ed. ACSM's Guide to Exercise and Cancer Survivorship. Champaign, IL: The American College of Sports Medicine; 2012.
[5]National Lymphedema Network. Position Paper: Exercise 2013. https://www.lymphnet.org/pdfDocs/position.papers/Exercise.pdf
[6]Asdourian MS, Skolny MN, Brunelle C, et al. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. Lancet Oncol. 2016;17:e392-405.
[7]Ahn S, Port ER. Lymphedema Precautions: Time to Abandon Old Practices? J Clin Oncol 2016;34:655-658.
[8]National Lymphedema Network. Position Paper: Lymphedema Risk Reduction Practices 2012 https://www.lymphnet.org/pdfDocs/position.papers/Risk.Reduction.pdf.

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PRINCIPLES OF PHYSICAL ACTIVITY FOR SURVIVORS WITH OR AT-RISK FOR LYMPHEDEMA

- **Lymphedema is not a contraindication for physical activity, and no special precautions are required if participating in cardiovascular/aerobic exercise or strength training of unaffected limbs.**
- **Continued full use of the extremity and range-of-motion exercises are encouraged to maintain strength and range of motion even in the presence of lymphedema.**
- **Progressive resistance training/weight lifting: Gradually increase resistance by smallest increment possible with monitoring.[1]**
- **Consider referral to lymphedema specialist for evaluation prior to starting a physical activity program that involves strength or progressive resistance training of the affected or at-risk limb.**
- **Survivors with lymphedema should initiate strength training exercise involving affected body part only if lymphedema specialist or other appropriate health care provider determines that lymphedema is stable. Factors that may be considered include:**
  - **No need for lymphedema therapy within past 3 months**
  - **No recent limb infections requiring antibiotics**
  - **No change in limb circumference >10%**
  - **No change in ability to perform activities of daily living**
- **Survivors with or at-risk for lymphedema should work with trained exercise professionals for weight training or progressive resistance training.[2]**
- **Compression garments may be required during resistance training.**
- **Survivors should undergo baseline and periodic evaluation for development or exacerbation of lymphedema.**
- **Survivors should stop exercise and see a lymphedema specialist if exacerbation of lymphedema occurs.**

[1]In progressive resistance training/weight lifting, resistance is gradually increased by smallest increment possible with monitoring.

[2]Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://acsm.org/certification] or American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

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NCCN Guidelines Version 3.2017
Menopause-Related Symptoms (Females)

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PRINCIPLES OF MENOPAUSE MANAGEMENT IN FEMALE SURVIVORS

Menopause

- Menopause is defined as no menses for one year in the absence of prior chemotherapy or tamoxifen use, or no menses after surgical removal of all ovarian tissue.
- Many survivors may experience symptoms without meeting the definition of menopause.
- In female survivors with prior chemotherapy or pelvic radiation exposure or survivors on tamoxifen, serial estradiol levels may be useful to confirm post-menopausal status.

Menopausal Signs and Symptoms

- Vasomotor symptoms (ie, hot flashes/night sweats)
- Vaginal dryness
- Urogenital complaints
- Sexual dysfunction
- Sleep disturbance
- Mood disturbance and depression
- Cognitive dysfunction
- Arthralgias/myalgias
- Fatigue

Menopause-Related Health Risks

- Osteoporosis/bone fractures
- Cardiovascular disease

Treatment Options for Vasomotor Symptoms (See SMP-4)

- Non-hormonal options
  - Prescription alternatives (See SMP-A)
  - Over-the-counter (OTC) options
  - Integrative therapies
  - Lifestyle modifications (See HL-1)
- Hormonal therapies (contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk) (See SMP-B)
  - Combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus)
  - Tissue selective estrogen complexes (TSECs)[a]
  - Custom-compounded bioidentical hormone therapy

[a]Novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen creating a tissue selective estrogen complex (TSEC).

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PRINCIPLES OF MANAGEMENT OF MENOPAUSAL SYMPTOMS IN MALE SURVIVORS

- **Male survivors who have received radiation therapy, chemotherapy, or surgery for non-prostate malignancies may have hypogonadism and should be screened and treated with testosterone for menopausal symptoms.**
- **Androgen deprivation therapy (ADT) is the main therapeutic approach to metastatic prostate cancer, and may be used as adjuvant or neoadjuvant therapy in the initial treatment of prostate cancer.**
- **Male survivors who have received or are receiving ADT may experience menopausal symptoms and sexual dysfunction. These patients should not receive androgens (eg, testosterone).**
- **ADT-related symptoms and health risks**
  - **Acute kidney injury**
  - **Anemia**
  - **Arthralgias/myalgias**
  - **Cardiovascular disease[b]**
    - ◊ **Prolongation of QT/QTc interval**
  - **Cognitive dysfunction**
  - **Decreased muscle (sarcopenia) and increased body fat**
  - **Decreased penile size**
  - **Mood disturbance and depression**
  - **Diabetes mellitus (new onset)**
    - ◊ **Reduced insulin sensitivity**
  - **Fatigue**
  - **Gynecomastia**
  - **Osteoporosis/bone fractures**
  - **Sexual dysfunction[c]**
  - **Sleep disturbance**
  - **Testicle atrophy**
  - **Thinning body hair[d]**
  - **Vasomotor symptoms (ie, hot flashes/night sweats)[e]**
  - **Venous thromboembolic disease**

Treatment Options for Vasomotor Symptoms (See SMP-6)

- **Non-hormonal options**
  - **Prescription alternatives (See SMP-A)**
  - **Over-the-counter (OTC) options**
  - **Integrative therapies**
  - **Lifestyle modifications (See HL-1)**
- **Hormonal therapies (contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk)**
  - **Androgens (eg, testosterone)**
    - ◊ **Contraindicated in males with carcinoma of the breast or known or suspected prostate cancer**
  - **Medroxyprogesterone acetate (a progestin)**
  - **Cyproterone acetate (an antiandrogen)**
  - **Estrogen (eg, diethylstilbestrol)**

[b]In males, androgen deprivation therapy (ADT) may increase cardiovascular morbidity and mortality, notably in the first 6 months of therapy and in men with two or more prior cardiovascular events. An increase in serum LDL-cholesterol, HDL-cholesterol and triglycerides may also be seen.
[c]ADT-related sexual dysfunction includes loss of libido, loss of nocturnal and morning erections and varying degrees of erectile dysfunction.
[d]Although facial and body hair decrease, some bald men may have some regrowth of scalp hair.
[e]Hot flashes may be associated with nausea, sweating and may occur during sleep.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 3.2017
Menopause-Related Symptoms (Females and Males)

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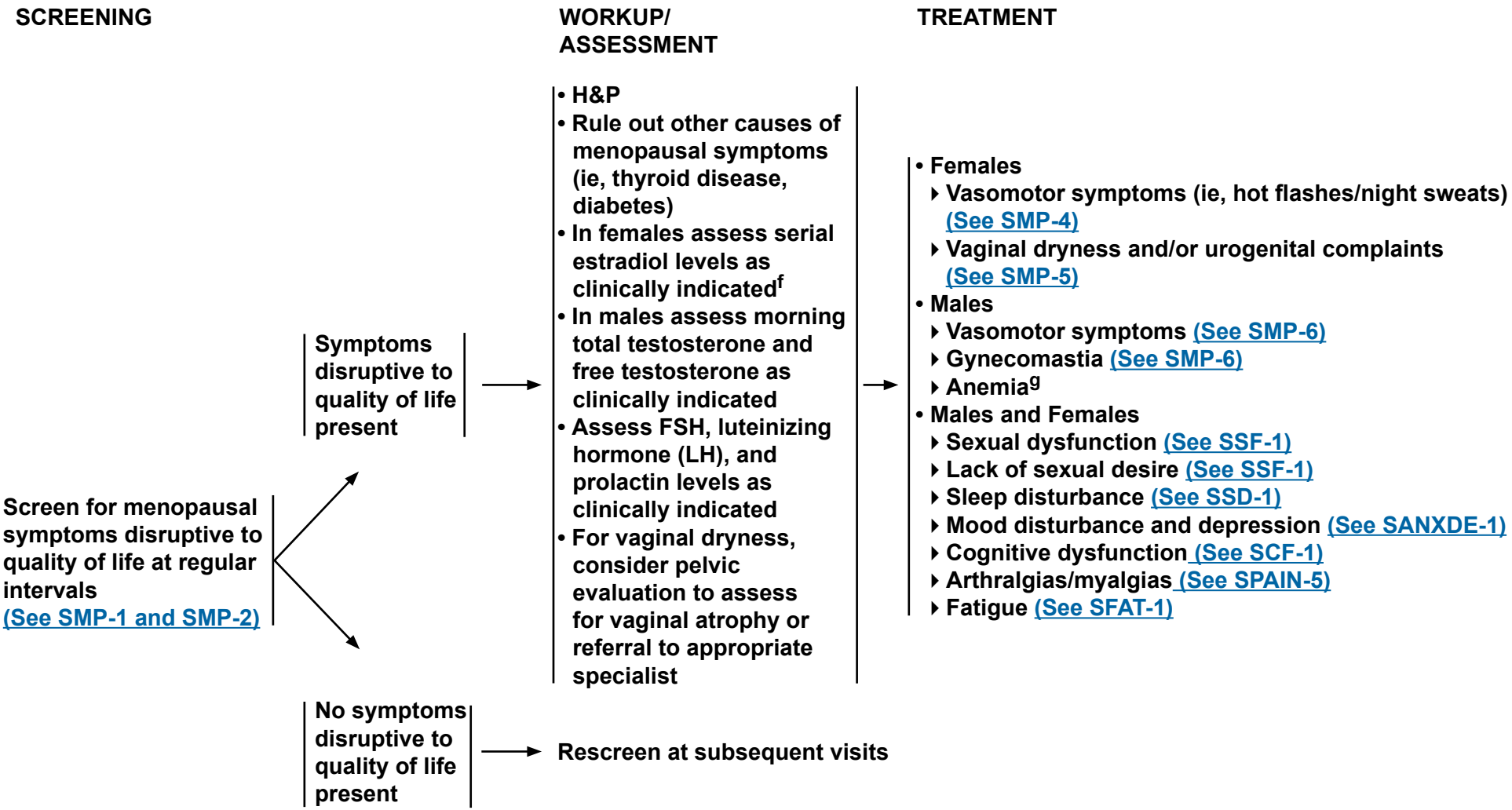

[f]For peri- or pre-menopausal female survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), and inhibin may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or those on tamoxifen, but alone are not reliable to ensure menopausal status.

[g]ADT-associated anemia is generally responsive to blood transfusions and erythropoietin and should be treated as per the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MENOPAUSE SYMPTOM	TREATMENT
Vasomotor symptoms (ie, hot flashes/night sweats) disruptive to quality of life in females	**• Non-hormonal pharmacologic treatments[h]** **▸ Categories include low-dose antidepressants, anti-convulsants, neuropathic pain relievers, and certain anti-hypertensives** **• Non-pharmacologic treatments[i]** **▸ Acupuncture** **▸ Exercise/physical activity (See SPA-1)** **▸ Lifestyle modifications[k] (See HL-1)** **▸ Weight loss if overweight or obese (See SNWM-1)** **▸ Integrative therapies including cognitive behavioral therapy (CBT), yoga, and hypnosis** **• Menopausal hormone therapy (MHT) or other hormonal therapies in appropriate candidates[l,m] with referral to appropriate specialist for MHT dosing and management**

[i]Compounds with limited evidence of safety and efficacy (all category 2B)[j]
- Phytoestrogens
- Botanicals
- Dietary supplements
  - Limited data show a possible benefit of black cohosh for vasomotor symptoms in the general population; however, randomized data in breast cancer survivors show no benefit. www.ncbi.nlm.nih.gov/pubmed/16782922

[h]See Non-Hormonal Treatments and Dosing (SMP-A).
[j]Data are mixed or limited on the effectiveness and safety of these nonpharmacologic treatments in survivors of some cancers.
[k]Drinking alcohol may cause hot flashes in males/females. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake.
[l]See Principles of Menopausal Hormone Therapy (MHT) Use In Survivors (Females) (SMP-B).
[m]MHT is contraindicated in survivors of hormonally-mediated cancers.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 3.2017
Menopause-Related Symptoms (Females)

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MENOPAUSE SYMPTOM	TREATMENT

Vaginal dryness	• Non-hormonal treatments
	  ▸ Vaginal moisturizers, vaginal gels, oils, topical vitamin D or E (category 2B)
	  ▸ Lubricants for sexual activity
	• Local estrogen treatment[n] (rings, suppositories, creams) (category 2B)
	  ▸ Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories. Therefore, if estrogen based treatment is warranted, rings and suppositories are preferred over creams for survivors of hormonally sensitive tumors.
	• Other topical prescriptions (ie, testosterone)
	• Consider referral to appropriate specialist for management

Urogenital complaints (females)	• Local estrogen treatment[n] • Referral to appropriate specialist for management

[n]Vaginal estrogen preparations can be used in managing vaginal atrophy, but safety has not been established for use in patients with or survivors of breast cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADT-RELATED SYMPTOMS	TREATMENT
Vasomotor symptoms (ie, hot flashes/night sweats) disruptive to quality of life in males	• Modification to ADT (See NCCN Guidelines for Prostate Cancer) • Pharmacologic treatments ▸ Hormonal therapy in appropriate candidates[o] with referral to appropriate specialist for dosing and management ◊ Medroxyprogesterone ◊ Cyproterone acetate ◊ Estrogen (eg, diethylstilbestrol) ▸ Non-hormonal therapies[h] ◊ Venlafaxine ◊ Gabapentin • Non-pharmacologic treatments[p] ▸ Acupuncture ▸ Exercise/physical activity (See SPA-1) ▸ Lifestyle modifications[k] (See HL-1) ▸ Cognitive behavior therapy ▸ Weight loss if overweight or obese (See SNWM-1)
Gynecomastia	• Prophylactic radiation (must be delivered prior to development of breast tissues) • Tamoxifen • Reduction mammoplasty

[p]Compounds with limited evidence of safety and efficacy (all category 2B)[j]
- Phytoestrogens
- Botanicals
- Vitamin E
- Dietary supplements

[h]See Non-Hormonal Treatments and Dosing (SMP-A).
[k]Drinking alcohol may cause hot flashes in males/females. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake.
[j]Data are mixed or limited on the effectiveness and safety of these nonpharmacologic treatments in survivors of some cancers.
[o]Testosterone is contraindicated in males with carcinoma of the breast or known or suspected prostate cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NON-HORMONAL PHARMACOLOGIC TREATMENTS AND DOSING[1]

Class	Drug	Commonly used daily dose for managment of vasomotor symptoms	Comments
Antidepressants[2]	Venlafaxine[3] (SNRI)	75 mg	Start at lowest dose possible (25 mg or 37.5 mg) and increase as tolerated
	Desvenlaxafine (SNRI)	100 mg	Start at lowest dose possible (25 mg or 50 mg) and increase as tolerated
	Paroxetine (SSRI)[4]	Low-dose 7.5 mg or Standard paroxetine short acting up to 20 mg, controlled release up to 25 mg	• Low-dose (7.5 mg) paroxetine is the only FDA-approved alternative to hormones for hot flashes • Use with caution for women on tamoxifen
	Escitalopram (SSRI)	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Use with caution for women on tamoxifen
	Citalopram (SSRI)	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Use with caution for women on tamoxifen
	Fluoxetine (SSRI)[4]	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Limited data on effectiveness • Use with caution for women on tamoxifen
	Sertraline (SSRI)[4]	50 mg	• Start at lowest dose possible (25 mg) and increase as tolerated • Limited data on effectiveness • Use with caution for women on tamoxifen
Anti-convulsant	Gabapentin[3]	900 mg (typically 300 mg 3 times a day)	• Start at lowest dose possible (100 mg or 300 mg) and increase as tolerated • Consider starting at night time as this drug tends to cause sedation
	Pregabalin	150–300 mg	Start at lowest dose possible (25 mg) and increase as tolerated
Alpha-agonist hypertensive	Clonidine	0.1 mg (oral or transdermal)	Transdermal preparations may have fewer side effects

[1] For long-term care or maintenance and/or if lack of response, consider referral to appropriate health care specialist. A gradual tapering of dose rather than an abrupt discontinuation of drug is recommended when discontinuing these treatments.
[2] Anticipated clinical response of SSRIs/SNRIs for menopausal symptoms tends to be more rapid than the typical response for depression.
[3] Venlafaxine and gabapentin have been studied for the treatment of menopause symptoms in males, but data are limited. The other therapies have been used but not tested in males.
[4] Pure SSRIs and in particular paroxetine block conversion of tamoxifen to active metabolites through CYP2D6 and should be used with caution for women on tamoxifen.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF MENOPAUSAL HORMONE THERAPY (MHT) USE IN SURVIVORS (FEMALES)

- **MHT is the most effective therapy for management of vasomotor symptoms.**
- **General recommendations are to use the lowest dose possible to control symptoms.**
  - **Combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus)**
    - ◊ **Formulations of hormones include oral, transdermal, vaginal ring, and intrauterine device**
  - **The TSEC conjugated estrogens/bazedoxifene is FDA approved for treating menopausal symptoms in healthy post-menopausal women.**
    - ◊ **These drugs are contraindicated in survivors of hormonally dependent cancers.**
  - **Custom-compounded bioidentical hormone therapy**
    - ◊ **There is a lack of data supporting claims that custom-compounded bioidentical hormones are a safer and more effective alternative to standard hormone therapies.**
- **If MHT is used, refer to appropriate specialist for MHT dosing and management.**
- **For young cancer survivors experiencing menopause at an early age, consider oral contraceptives or MHT for symptom relief and potential cardiac and bone benefits as long as not contraindicated.**

- **Contraindications for MHT in cancer survivors mirror those for the general population and include:**
  - **History of hormonally mediated cancers**
  - **History of abnormal vaginal bleeding**
  - **Active or recent history of thromboembolic event**
  - **Pregnancy**
  - **Active liver disease**
- **Caution in:**
  - **Survivors with coronary heart disease or hypertension**
  - **Survivors at increased genetic risk for cancers**
  - **Current smokers**

- **Approach to treatment should be individualized based on risks and benefits.**

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENERAL PRINCIPLES OF PAIN MANAGEMENT

- Comprehensive pain assessment should be done to determine the etiology of the pain.
  - If the pain is new and acute, differential diagnosis should include cancer recurrence.
  - If the pain is chronic, a specific cancer pain syndrome should be identified if possible.
- Conduct a discussion with the patient and family regarding realistic treatment goals, including improvement in functionality as well as pain relief.
- Opioid treatment is sometimes necessary, and the lowest appropriate dose should be used for the shortest amount of time, if possible. Adjuvant medications should be used in addition to the opioids if indicated.
- Non-opioids are appropriate as primary therapy for many pain syndromes.
- Non-pharmacologic interventions can be used as the sole treatment for pain, or as adjuncts to pharmacologic therapy.
- Physical modalities (heat, cold, massage, physical therapy, or occupational therapy) are useful and should be considered for some pain syndromes.
- Use a multimodality approach to pain management if warranted, and if those resources are available.
- Psychological support of the survivor with chronic pain is necessary, and referral to psychosocial services should be considered for survivors in distress. (See SANXDE-1)
- Consider referral to a specialist for patients who might benefit from further pain interventions. This could include referral to anesthesia pain, physical medicine and rehabilitation, palliative care, urology, gynecology, orthopedic surgery, gastroenterology, or other appropriate consultants.

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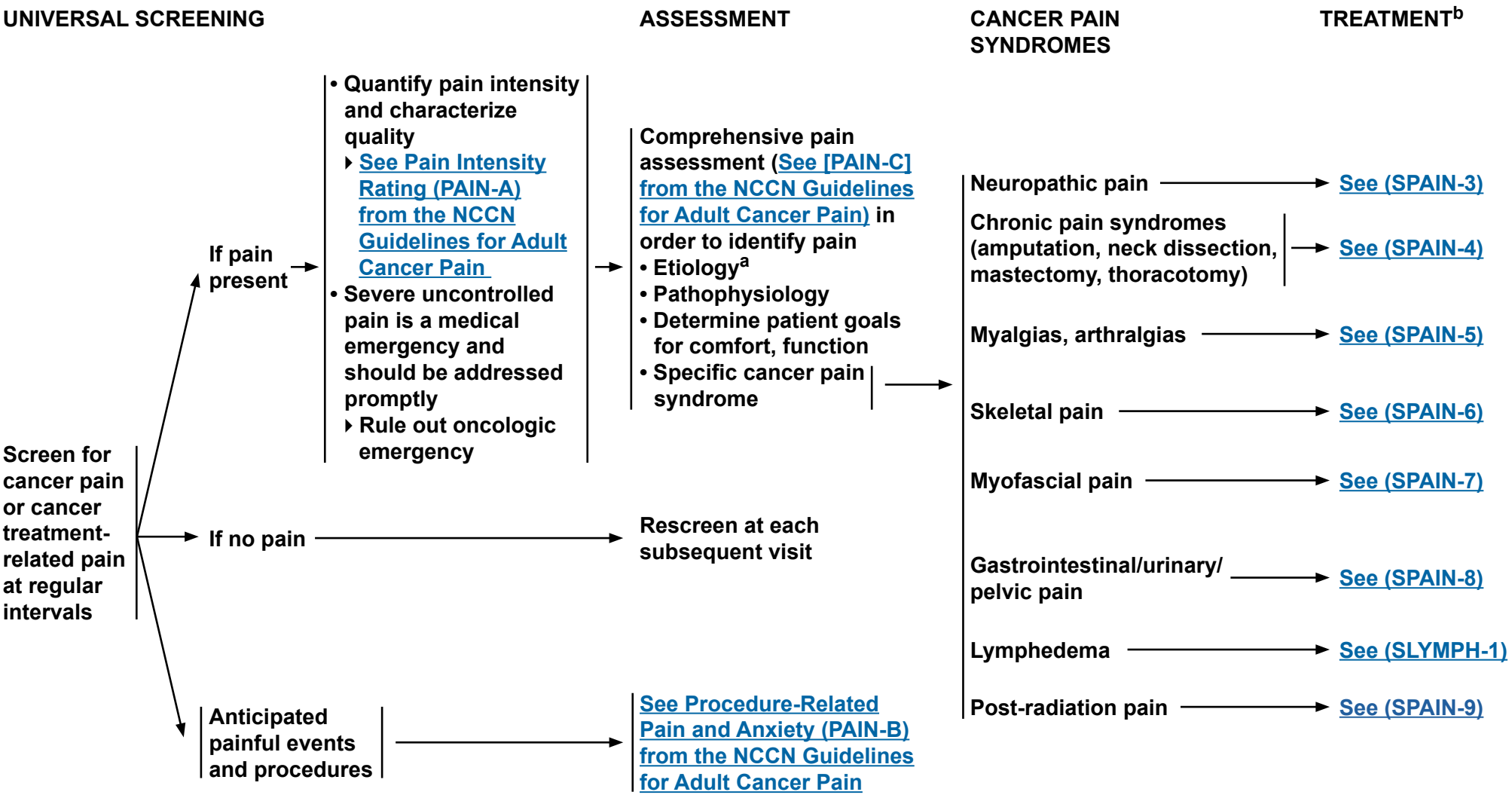
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[a]Referral to primary care physician for non-cancer treatment-related workup and pain management (ie, rheumatoid arthritis) and consider the possibility of pain due to cancer recurrence.

[b]See General Principles of Pain Management (SPAIN-1).

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CANCER PAIN SYNDROME	TREATMENT
Neuropathic pain[c] • Paresthesias (tingling or prickling) • Shooting, "electrical" • Numbness	• General measures: ▸ Adjuvant analgesics (See [PAIN-G] from the NCCN Guidelines for Adult Cancer Pain) ◊ Antidepressants ◊ Anticonvulsants ▸ Opioids[d] See (PAIN-3, PAIN-4, and PAIN-5) from the NCCN Guidelines for Adult Cancer Pain ▸ Cognitive behavioral therapy and psychosocial support (See [PAIN-H] from the NCCN Guidelines for Adult Cancer Pain) ◊ Consider hypnosis ▸ Local therapies ◊ Pharmacologic therapies – Topical patches (lidoderm, capsaicin) – Creams (ketamine and amitriptyline combined) ◊ Non-pharmacologic therapies – Heat – Ice – Acupuncture • For refractory pain, consider referral to pain management services, interventional specialist, physical therapy, physical medicine, palliative care, and/or rehabilitation ▸ Neurotomy with radiofrequency ablation ▸ Consider transcutaneous electrical nerve stimulation (TENS) unit ▸ Consider dorsal column stimulation

[c]For recommendations regarding peripheral neuropathy, see Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:1941-1967.
[d]See Principles of Opioid Use in Long-Term Survivors (SPAIN-A).

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CANCER PAIN SYNDROME	TREATMENT		TREATMENT
Chronic pain syndrome (amputation, neck dissection, mastectomy, thoracotomy) →	• General measures: ▸ Adjuvant analgesics See (PAIN-G) from the NCCN Guidelines for Adult Cancer Pain ▸ Psychosocial support and behavioral interventions See (PAIN-H) from the NCCN Guidelines for Adult Cancer Pain ▸ Opioids[d] See (PAIN-3, PAIN-4, and PAIN-5) from the NCCN Guidelines for Adult Cancer Pain • For refractory pain, consider referral to pain management services, interventional specialist, physical therapy, physical medicine, palliative care, and/or rehabilitation for services such as: ▸ TENS unit ▸ Dorsal column stimulation ▸ Neurotomy with radiofrequency ablation	→ Specific chronic pain syndromes[e] →	• For post-amputation syndrome: ▸ Physical therapy for desensitization ◊ Consider mirror therapy ▸ Cognitive therapy ▸ Upper extremities: ◊ Consider stellate ganglion block ▸ Lower extremities: ◊ Consider lumbar sympathetic block ▸ Neuromas: ◊ Consider phenol/alcohol block • For post-radical neck dissection syndrome: ▸ Physical therapy for stretching, range of motion ▸ Myofascial release ▸ Soft tissue massage ▸ Trigger point injections ▸ Possible botulinum toxin injection • For post-mastectomy or post-thoracotomy syndrome: ▸ Intercostal nerve block ▸ TENS unit

[d] See Principles of Opioid Use in Long-Term Survivors (SPAIN-A).
[e] There are other postoperative pain syndromes and many treatment measures can be used across syndromes. Also consider referral to appropriate specialist.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER PAIN SYNDROME	TREATMENT
Myalgias, Arthralgias	• Nonpharmacologic ▸ Physical activity ▸ Heat (paraffin wax, hot pack) ▸ Cold pack ▸ Aquatic therapy ▸ Ultrasonic stimulation[f] ▸ Massage ▸ Acupuncture ▸ Yoga • Pharmacologic[g] ▸ Nonsteroidal anti-inflammatory drugs (NSAIDs) ▸ Muscle relaxants ▸ Anticonvulsant drugs (gabapentin, pregabalin) ▸ SNRIs ▸ Tricyclic antidepressants (TCAs) ▸ Acetaminophen ▸ COX-2 inhibitors • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, palliative care, and/or rehabilitation

[f]Ultrasonic stimulation is a type of heat treatment that can penetrate directly to the bone and should be used with caution. It is not recommended for patients with multiple myeloma or bone metastases.
[g]Consider switching to an alternative aromatase inhibitor (AI) or tamoxifen for AI-induced arthralgia.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER PAIN SYNDROME	TREATMENT
Skeletal pain[h] →	• For vertebral compression: ▸ General measures: ◊ Bisphosphonates or other antiresorptive medications if appropriate ◊ NSAIDs ◊ Muscle relaxants ◊ Consider vertebral augmentation (vertebroplasty, kyphoplasty) ◊ Acetaminophen ◊ COX-2 inhibitors ▸ Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, palliative care, and/or rehabilitation ▸ For acute vertebral compression: ◊ Opioids[d] ◊ Bracing (thoracolumbar sacral orthosis [TLSO], Jewett brace) ◊ Limited bedrest ◊ Weight-bearing exercises when pain improves ◊ Physical therapy ▸ For chronic vertebral compression: ◊ Weight-bearing exercises ◊ Physical therapy – thoracic and lumbar stabilization exercises • For avascular necrosis: ▸ Physical therapy – based on weight-bearing and range-of-motion restrictions ▸ Opioids[d] ▸ Muscle relaxants if myofascial component ▸ Core decompression • For osteonecrosis of the jaw: ▸ Referral to oral surgeon ▸ Anti-convulsants ▸ SNRIs ▸ Opioids[d]

[d] See Principles of Opioid Use in Long-Term Survivors (SPAIN-A).

[h] For skeletal metastases and/or bone pain, see (PAIN-D) from the NCCN Guidelines for Adult Cancer Pain. Consider orthopedic/surgical referral.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER PAIN SYNDROME	TREATMENT
Myofascial pain[i]	• Nonpharmacologic ▸ Physical activity ▸ Range-of-motion exercises ▸ Strengthening exercises ▸ Soft tissue/myofascial release massage ▸ Ultrasonic stimulation[f] ▸ Acupuncture or acupressure • Pharmacologic ▸ Topical ointments (ketamine) and patches (lidocaine, capsaicin) ▸ NSAIDs ▸ Anticonvulsant drugs ▸ SNRIs ▸ Acetaminophen ▸ COX-2 inhibitors • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, palliative care, and/or rehabilitation for services such as trigger point injections

[f]Ultrasonic stimulation is a type of heat treatment that can penetrate directly to the bone and should be used with caution. It is not recommended for patients with multiple myeloma or bone metastases.

[i]For muscle cramps or spasms, check electrolytes, calcium and magnesium levels, and hydration status.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER PAIN SYNDROME	TREATMENT
Gastrointestinal/urinary/pelvic pain →	• For gastrointestinal pain: ▸ Consider referral to gastroenterologist • For chronic pelvic pain:[j] ▸ Consider referral to specialist in pelvic floor pain such as urologist, gynecologist, or physical medicine and rehabilitation (PM&R) ▸ Consider physical therapy for pelvic floor exercises ▸ Proper hydration ▸ Bowel regimen ▸ Dorsal column stimulation for chronic cystitis and chronic pelvic pain • For dyspareunia: ▸ (See SSF-2) ▸ Consider referral to gynecologist or sexual health specialist • For refractory gastrointestinal/urinary/pelvic pain: ▸ Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, palliative care, and/or rehabilitation

[j]Multidisciplinary treatment for chronic pelvic pain is preferred if available.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER PAIN SYNDROME	TREATMENT
Post-radiation pain • Pain may be acute or appear months or years after radiation • Radiation may lead to scarring, adhesions, or fibrosis ▸ Differentiate fibrosis from recurrent tumor • Radiation to a localized area of the body may cause a chronic pain syndrome in that area	→ • Treat according to specific cancer pain syndrome guidelines, if appropriate (See SPAIN-2 for list of cancer pain syndromes) • Physical therapy • Pain medication (appropriate to the etiology) • Surgical lysis of adhesions may be indicated in extreme circumstances

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF OPIOID USE IN LONG-TERM SURVIVORS

- When opioids are appropriate and necessary, establish treatment goals with survivors and caregivers and use the lowest effective opioid dose for the shortest period of time possible.
- Functional outcomes are important measures for patients on opioid therapy. The expected outcome (ie, improvement in function and/or pain) should be clearly discussed with survivors and caregivers, agreed upon, and documented upon initiation and continuation of chronic therapy.
- Re-evaluate the effectiveness and necessity of opioids on a regular basis
  - If the expected outcome is not achieved, other treatment alternatives should be considered. If opioids are no longer appropriate, recommend gradual tapering of opioids to help avoid symptoms of withdrawal.
  - Discussion of gradual tapering should be routine
- Consider establishing pain treatment agreements (See PAIN-L of the NCCN Guidelines for Adult Cancer Pain)
- Address medical-related issues due to chronic or high-dose opioids
  - Endocrine/hypopituitary abnormalities
    - ◊ Testosterone deficiency
- Monitor for aberrant drug-taking behaviors (See PAIN-E 3 of 11 of the NCCN Guidelines for Adult Cancer Pain)
- The panel endorses the ASCO Policy Statement on Opioid Therapy: Protecting Access to Treatment for Cancer-Related Pain (2016), particularly as it relates to weighing the risks/benefits of opioid treatment.

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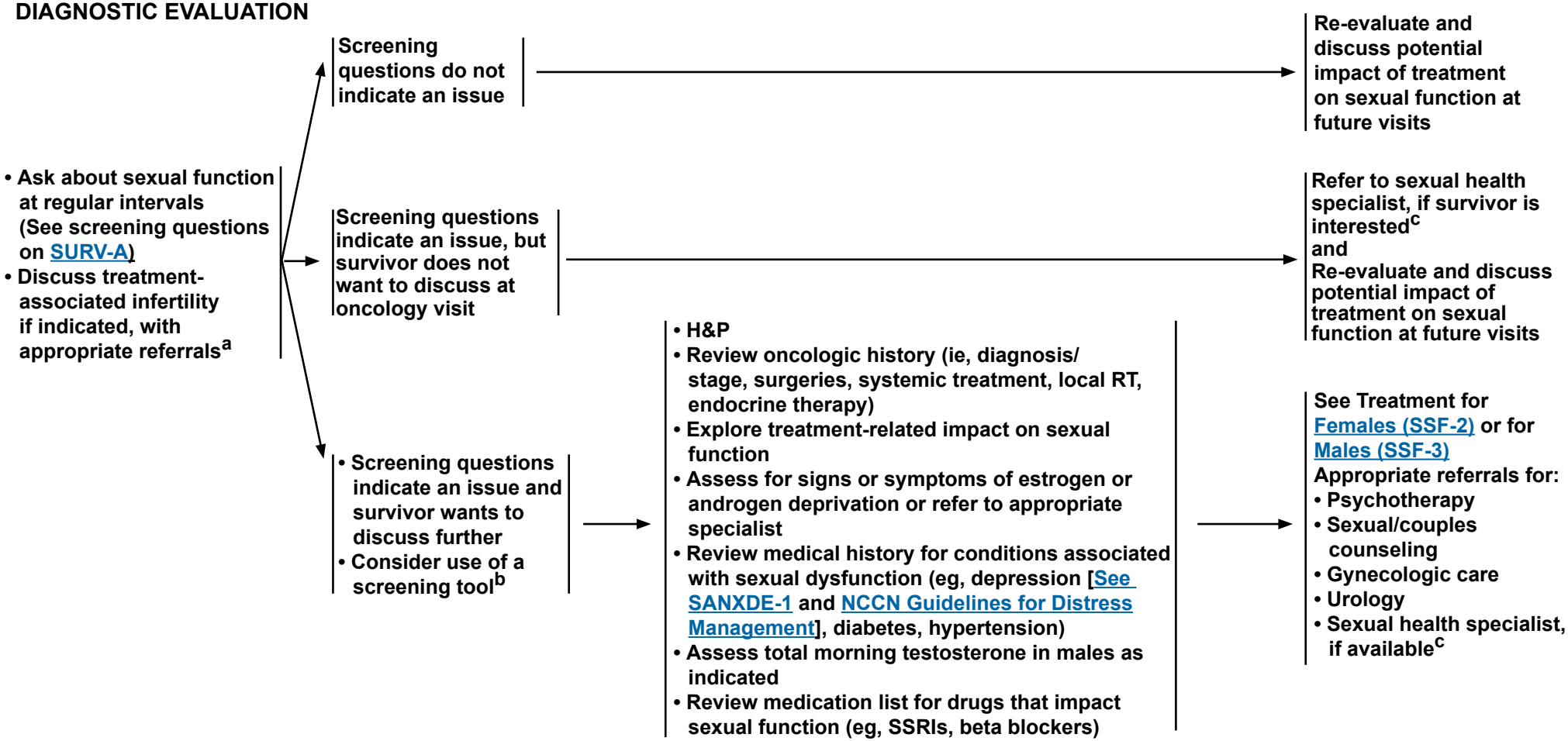
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

DIAGNOSTIC EVALUATION



[a]For information regarding fertility preservation for patients with cancer, see Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:2500-2510. http://www.ncbi.nlm.nih.gov/pubmed/23715580

[b]Several Screening tools are available for both men and women. For women, options include the Brief Sexual Symptom Checklist for Women (SSF-A), Arizona Sexual Experience Scale (http://dx.doi.org/10.1080/009262300278623), and the Female Sexual Function Index (http://www.fsfiquestionnaire.com/). For men, the Sexual Health Inventory for Men (SHIM) (SSF-B), Sexual-Quality of Life-Men (http://dx.doi.org/10.1111/j.1743-6109.2007.00749.x), and the PROMIS Brief Function Profile-Male (http://www.assessmentcenter.net/) are examples.

[c]Sexual health specialists may come from a range of backgrounds, including primary care, gynecology, urology, oncology, psychology, and/or rehabilitation medicine. Whenever possible, survivor should be referred to an appropriate local resource for further sexual health evaluation.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 3.2017
Sexual Function (Female)

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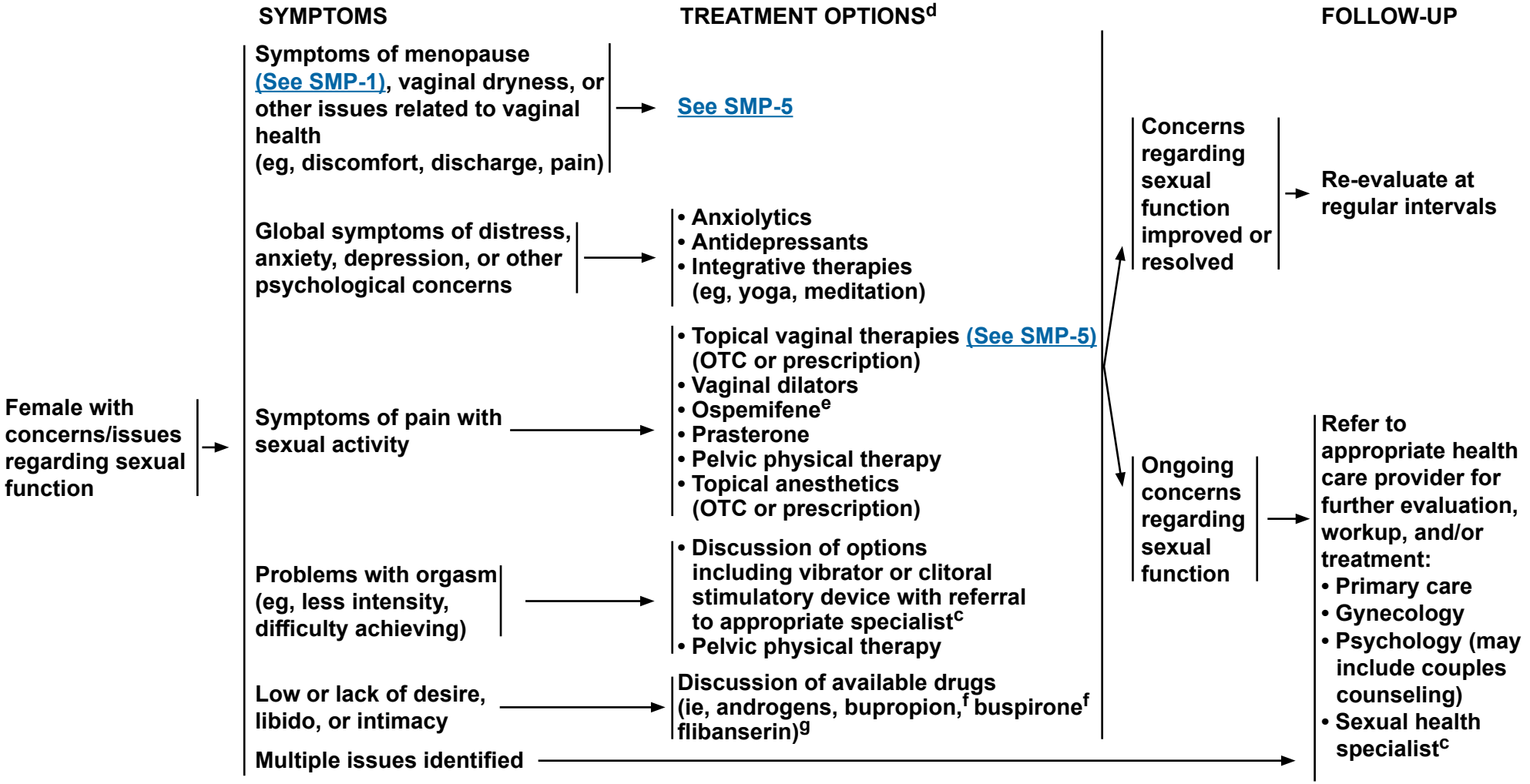

[c]Sexual health specialists may come from a range of backgrounds, including primary care, gynecology, urology, oncology, psychology, and/or rehabilitation medicine. Whenever possible, survivor should be referred to an appropriate local resource for further sexual health evaluation.
[d]Discuss risk/benefits of prescription medications if not contraindicated for cancer type or refer to appropriate health care provider (eg, sexual health specialist) for prescription and/or treatment as necessary.
[e]Currently ospemifene is contraindicated in survivors with a history of estrogen-dependent cancers.
[f]Bupropion and buspirone may be considered as off-label treatments for hypoactive sexual desire disorder, despite limited safety and efficacy data.
[g]There is a lack of data showing a benefit of sildenafil in women or of flibanserin and androgens in cancer survivors. In addition there is a lack of safety data for the use of androgen based therapy in survivors of hormonally mediated cancers.

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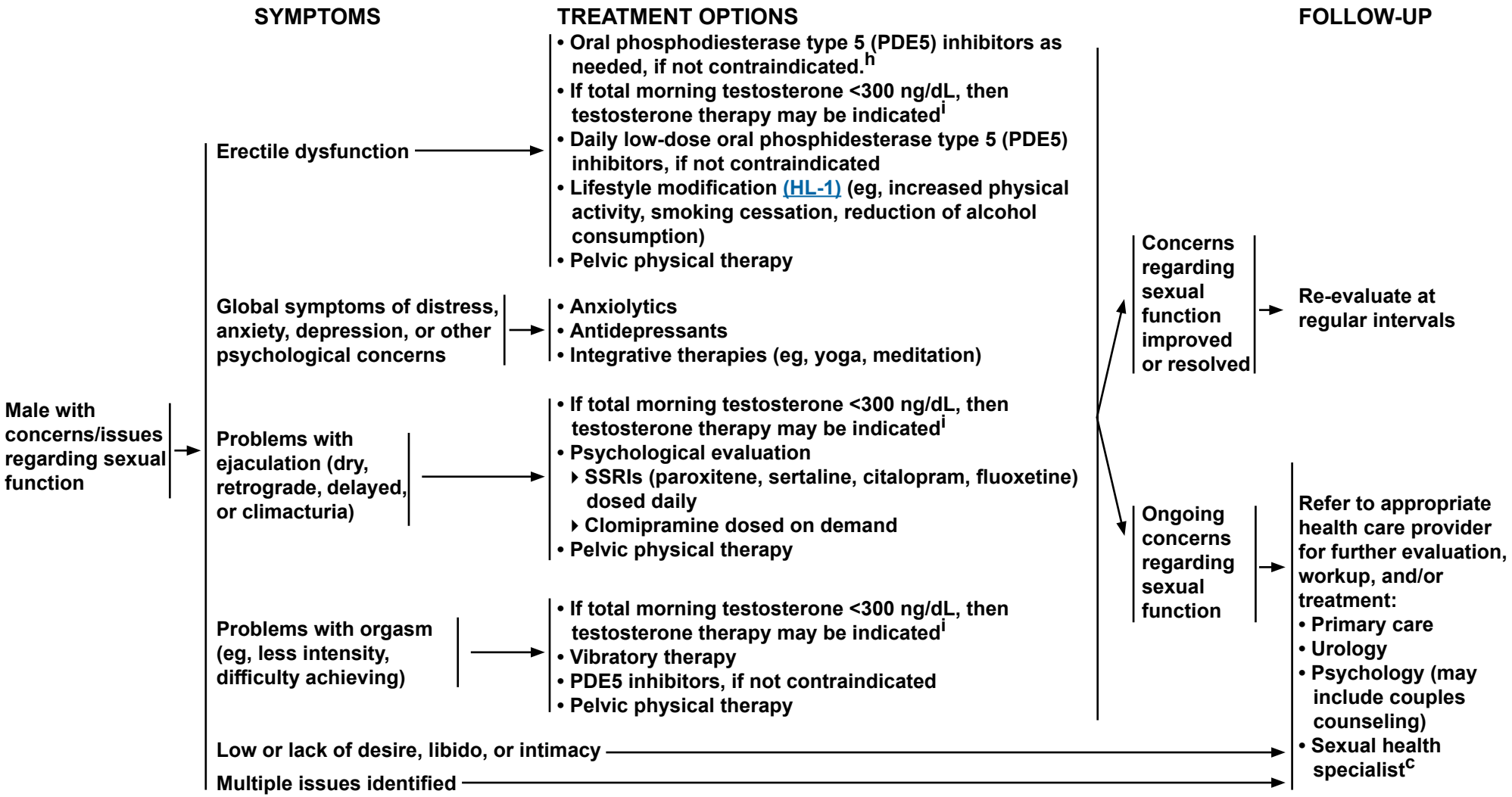

[c]Sexual health specialists may come from a range of backgrounds, including primary care, gynecology, urology, oncology, psychology, and/or rehabilitation medicine. Whenever possible, survivor should be referred to an appropriate local resource for further sexual health evaluation.

[h]Dosing should be titrated to optimal effect.

[i]Testosterone therapy should only be used if not contraindicated by primary oncologic diagnosis (eg, prostate cancer on active surveillance, prostate cancer under therapy with androgen deprivation).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BRIEF SEXUAL SYMPTOM CHECKLIST FOR WOMEN[1]

Please answer the following questions about your overall sexual function:

1. Are you satisfied with your sexual function?

__ Yes __No

If no, please continue.

2. How long have you been dissatisfied with your sexual function?

3a. The problem(s) with your sexual function is:
(mark one or more)

__1 Problem with little or no interest in sex

__2 Problem with decreased genital sensation (feeling)

__3 Problem with decreased vaginal lubrication (dryness)

__4 Problem reaching orgasm

__5 Problem with pain during sex

__6 Other:

3b. Which problem is most bothersome? (circle)
1 2 3 4 5 6

4. Would you like to talk about it with your doctor?
__Yes __No

[1]Reprinted with permission from Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)[1]

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that best describes your own situation.

Please be sure that you select one and only one response for each question.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)	No Sexual Activity	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half The Time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half The Time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half The Time)	Almost Always or Always
	0	1	2	3	4	5

PROVIDER KEY: Add the numbers corresponding to questions 1-5. **TOTAL: _____**

The SHIM further classifies ED severity with the following breakpoints: 1-7: Severe ED 8-11: Moderate ED 12-16: Mild to Moderate ED 17-21 Mild ED

[1]Reproduced and modified with permission from Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. Int J Impot Res 2005;17:307-319.

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SCREENING

Screening/assessment questions[a] to be asked at regular intervals, especially when there is a change in clinical status or treatment:

- **Are you having problems falling asleep, staying asleep, or waking up too early?**
- **Are you experiencing excessive sleepiness (sleepiness or falling asleep in inappropriate situations or sleeping more during a 24-hour period than in the past?)**
- **Have you been told that you snore frequently or stop breathing during sleep?**

No concerns for sleep disorder/disturbance → **Re-evaluate at subsequent visits/post therapy**

Concerns for sleep disorder/disturbance[b] →

H&P

- **Assessment of treatable or modifiable contributing factors:**
  - **Comorbidities**
    - ◊ **Alcohol and/or substance abuse**
    - ◊ **Obesity**
    - ◊ **Cardiac dysfunction**
    - ◊ **Respiratory disorders**
    - ◊ **Endocrine dysfunction (eg, hypothyroidism)**
    - ◊ **Anemia**
      - **Iron and ferritin levels**
    - ◊ **Emotional distress: screen for anxiety and depression (See SANXDE-1 and NCCN Guidelines for Distress Management)**
    - ◊ **Neurologic disorders including chemotherapy-induced peripheral neuropathy**
    - ◊ **Psychiatric disorders**
  - **Medications[c]**
  - **Hot flashes**
  - **Review sleep/wake timing and/or sleep log/diary if available**
  - **Review caffeine intake**
  - **Review history of cancer treatments**
  - **Pain (See SPAIN-1)**
  - **Fatigue (See SFAT-1)**
  - **Shift work**
  - **Current coping strategies (eg, relaxation techniques, meditation)**

→ **Insomnia symptoms (difficulty falling asleep staying asleep, or waking up too early):[d]**
- **Duration >4 weeks**
- **Occurring at least 3 times per week**

→ **See SSD-2**

→ **Sleep disturbance and/or excessive sleepiness[d]**
- **Hypersomnias**
- **Obstructive sleep apnea[e]**
- **Restless leg syndrome (RLS)[e,f]**

→ **See SSD-3**

[a] The following additional tools may be used for individual intensive screening to assess sleep quality: PSQI https://outcometracker.org/library/PSQI.pdf and PROMIS SLEEP http://www.rehabmeasures.org/Lists/RehabMeasures/Attachments/1112/PROMIS%20SF%20v1.0%20-%20Sleep%20Disturbance-SF8a.pdf.

[b] Patients may have more than one sleep disorder.

[c] Consider persistent use of sleep aids, pain medications, antiemetics, stimulants, antidepressants, anti-psychotics, sedative/hypnotics, opioids, over-the-counter sleep aids, or antihistamines.

[d] In the differential diagnosis of insomnia or excessive sleepiness symptoms, consider parasomnia or circadian rhythm sleep disorders and referral to a sleep specialist.

[e] Note that obstructive sleep apnea, restless legs syndrome (RLS), circadian rhythm sleep disorders, and parasomnia may also present with symptoms of insomnia.

[f] RLS is also known as Willis-Ekbom disease.

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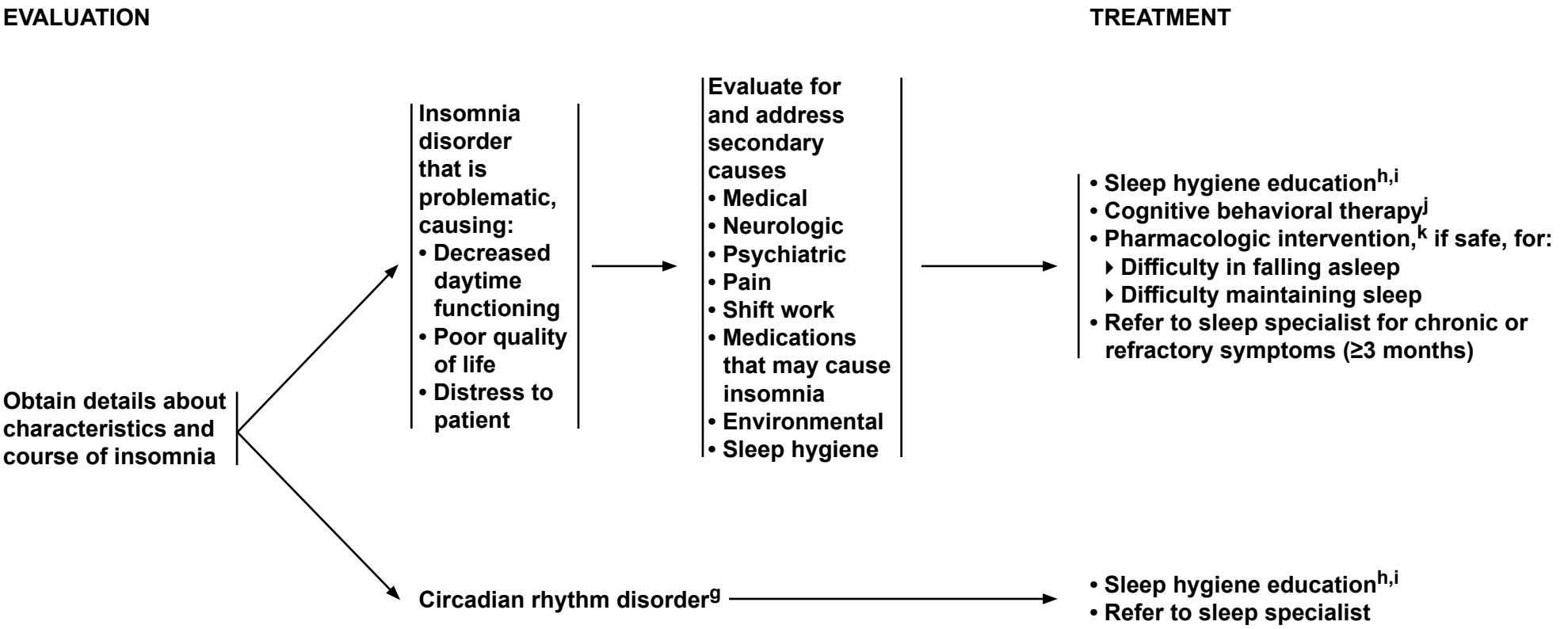

[g]Circadian rhythm disorder: A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to an alteration of the circadian timing system or to a misalignment with the sleep-wake schedule required by an individual's physical environment or social/work schedules.
[h]See General Sleep Hygiene Measures (SSD-A).
[i]Sleep hygiene alone has not been shown to be effective, but should be part of the initial treatment of all survivors with sleep disorders and as a prevention strategy for insomnia disorder.Sleep hygiene alone is not the recommended treatment for insomnia, but should be used in conjunction with other treatments such as CBT-I and/or pharmacotherapy.
[j]See Cognitive Behavioral Treatments (SSD-B).
[k]See Principles for Choosing an FDA-Approved Hypnotic (SSD-C).

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Sleep Disorders

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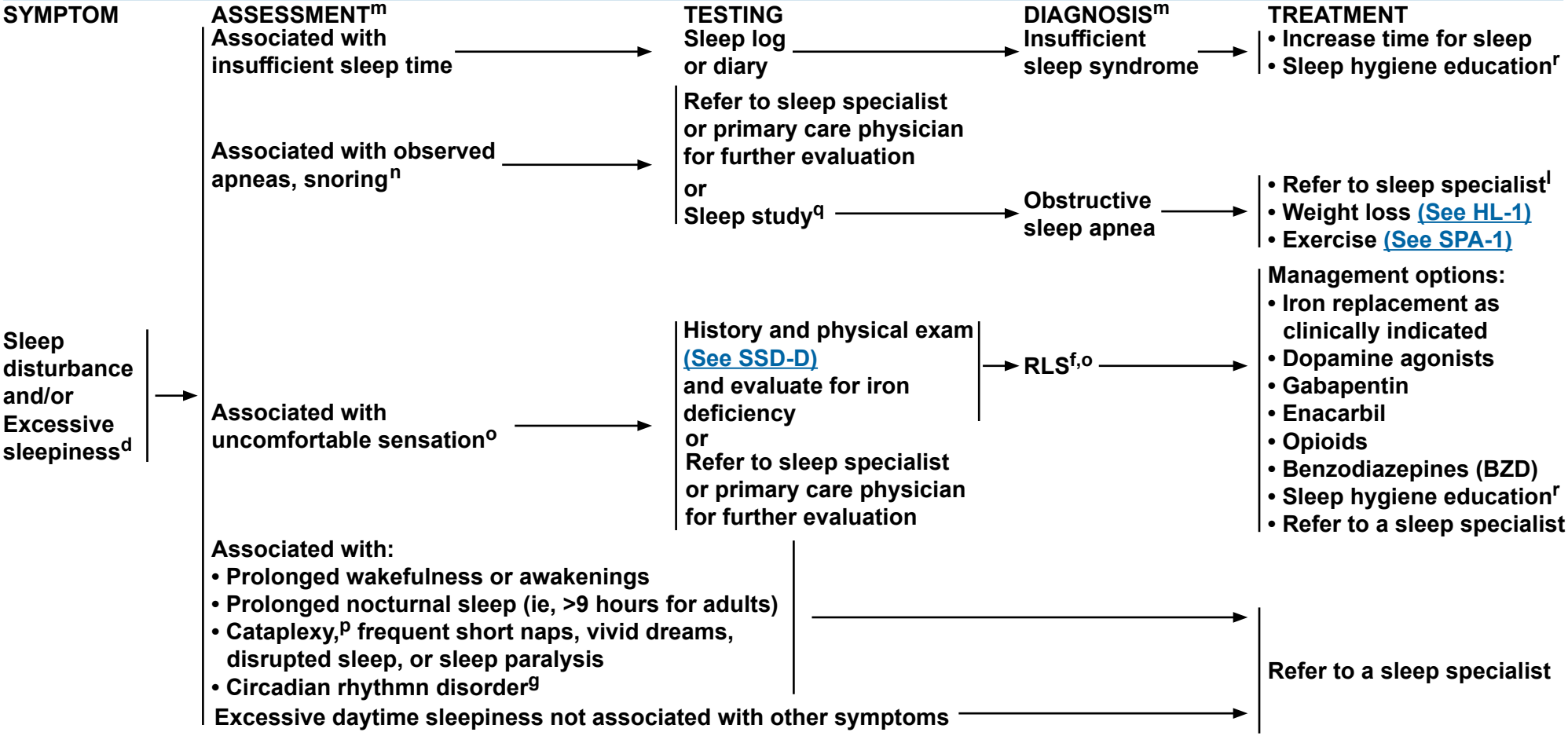

[d] In the differential diagnosis of insomnia or excessive sleepiness symptoms, consider parasomnia or circadian rhythm sleep disorders and referral to a sleep specialist.
[f] RLS is also known as Willis-Ekbom disease.
[g] Circadian rhythm disorder: A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to an alteration of the circadian timing system or to a misalignment with the sleep-wake schedule required by an individual's physical environment or social/work schedules.
[l] The most common medical treatment for obstructive sleep apnea is continuous positive airway pressure (CPAP).
[m] For other less frequent syndromes, refer to a sleep specialist.
[n] The following tools may be used to assess sleep apneas: STOP Questionnaire (Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812-821.) and Berlin Questionnaire (http://sleepapnea.org/wp-content/uploads/2017/02/berlin-questionnaire.pdf)
[o] See Essential Diagnostic Criteria for Restless Legs Syndrome (SSD-D).
[p] Cataplexy: Sudden loss of muscle tone, typically triggered by strong emotions, such as laughter or anger. Cataplexy is the most specific diagnostic feature of narcolepsy.
[q] Sleep studies can be done as laboratory PSG or as home sleep study. However, survivors with known cardiac disease or neurologic disease, who have used opiates for cancer-related pain, may not be good candidates for some home sleep tests.
[r] See General Sleep Hygiene Measures (SSD-A).

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GENERAL SLEEP HYGIENE MEASURES[1,2,3]

- Regular physical activity in the morning and/or afternoon (See SPA-1). Avoid moderate to strenous physical activity within 3 hours of bed time
- Increase exposure to bright light during the day
- Reduce exposure to bright light (ie, computer, phone screens, light sources close to the eye) within a few hours before bedtime and during the night
- Avoid heavy meals and limit fluid intake within 3 hours of bed time
- Avoid alcohol and nicotine too close to bedtime
- Limit caffeine consumption and avoid caffeine consumption at least 4 hours before bedtime.
- Enhance sleep environment (dark, quiet room; comfortable temperature)
- Set aside a worry time before bedtime
- Avoid looking at the clock when awake during the night
- Maintain a regular bedtime and waketime every day
- If necessary, limit to 1 short nap per day in the afternoon (no longer than 30 min)
- Turn off electronics and light-emitting sources at bedtime

[1]National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. 1998. NIH Publication. 98-4088.
[2]Kupfer DJ and Reynolds CF. Management of insomnia. N Engl J Med. 1997;336:341-346.
[3]Lippmann S, Mazour I, Shahab H. Insomnia: therapeutic approach. South Med J. 2001;94:866-873.

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COGNITIVE BEHAVIORAL TREATMENTS[1]

Strategy	Goal
Stimulus control	**Associate the bed/bedroom as a place for sleep or sexual activity only**
Sleep restriction	**Improve sleep continuity by:** **• Limiting time spent in bed[2]** **• Maintaining a regular sleep schedule by keeping a standard bedtime and wake time every day**
Cognitive therapy[3]	**Challenge patient's dysfunctional beliefs and misconceptions about sleep disturbances**
Relaxation training	**• Reduce physiologic and cognitive arousal at bedtime** **• Techniques include progressive muscular relaxation, deep breathing, meditation, yoga, and biofeedback**

[1]Data from Bootzin RR and Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992;53(suppl):37-41.
[2]Match total amount of time spent in bed to the actual amount of time spent sleeping (no less than 5 hours).
[3]Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep Med Rev 2016;27:20-28.

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PRINCIPLES FOR CHOOSING AN FDA-APPROVED HYPNOTIC:[1,2,3,4]

- **Does the patient have difficulty initiating or maintaining sleep?**
- **Does the patient have both sleep onset and sleep maintenance difficulty?**

AGENT	HELPS WITH SLEEP INITIATION	INCREASES TOTAL SLEEP TIME	INDICATED FOR SLEEP INITIATION AND MAINTENANCE
Zolpidem	+	+	–
Zolpidem CR	+	+	+
Zaleplon	+	–	–
Eszopiclone	+	+	+
Ramelteon	+	+/–	–
Temazepam	+	+	+
Doxepin (3–6 mg)	–	+	+
Suvorexant	+	+	+

[1]Data from the Physicians' Desk Reference (ed 66). Montvale, NJ: PDR Network, LLC; 2012.
[2]Inform patients that taking hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating).
[3]Other commonly used medications for insomnia include sedating medications such as antidepressants (ex, trazodone), antihistamines, atypical anti-pyschotics, other benzodiazepine receptor agonists, and nutritional/herbal supplements (ex, melatonin). They do not have an FDA-approved indication for the treatment of insomnia, and do not have enough data to be recommended for routine use.
[4]Most of these agents, with the exception of ramelteon, doxepin, and suvorexant, are benzodiazepine receptor agonists and can be associated with dependence, abuse, and withdrawal. Assessment for the continued need of hypnotics is recommended every 1–3 months.

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ESSENTIAL DIAGNOSTIC CRITERIA FOR RESTLESS LEGS SYNDROME[1]

- **An urge to move the legs usually accompanied by uncomfortable and unpleasant sensations in the legs, and sometimes the arms or other body parts.**
- **The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.**
- **The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.**
- **The symptoms are more pronounced in the evening or night or may only occur in the evening or night.**

IRON DEFICIENCY AND RESTLESS LEG SYNDROME

- **Iron deficiency is a secondary cause of RLS and can also exacerbate symptoms.**
- **Treatment with iron replacement in survivors with documented iron deficiency can improve symptoms.**

[1]Reproduced with permission from Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-119.

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Preventive Health

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GENERAL PRINCIPLES OF HEALTHY LIFESTYLES

- All survivors should be encouraged to achieve and maintain a healthy lifestyle with attention to physical activity (SPA-1), healthy dietary habits (SNWM-1), and weight management (SNWM-2).
- Healthy lifestyle habits have been associated with improved overall health and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.
- For a healthy lifestyle, all survivors should be encouraged to:
  - Achieve and maintain a healthy body weight throughout life (SNWM-2).
    - ◊ Pay attention to calories consumed versus calories expended via diet and physical activity.
    - ◊ Achieve and maintain a normal body mass index (BMI) and strive for metabolic health.
    - ◊ Weigh oneself daily if goal is weight loss and if not, weigh oneself at least weekly to monitor weight.
  - Engage in physical activity regularly (preferably daily) (SPA-1).
    - ◊ Engage in general physical activity daily (eg, taking the stairs, parking in the back of parking lot).
    - ◊ Strive for at least 150 minutes of moderate or 75 minutes of vigorous activity per week, spread out over the course of the week.[a]
    - ◊ Strive to participate in strength or resistance training at least twice a week.
    - ◊ Avoid prolonged sedentary behavior (eg, sitting for long periods).
  - Maintain a healthy diet high in vegetables, fruits, and whole grains and low in sugars and fats (SNWM-1).
    - ◊ Limit red meat and avoid processed meat.
  - Minimize alcohol intake.
    - ◊ Limit intake to no more than one drink per day for a woman and two drinks per day for a man.[a,b]
  - Avoid tobacco products. (See NCCN Guidelines for Smoking Cessation)
    - ◊ Stop smoking if currently smoking or using smokeless tobacco.
  - Practice sun safety.
    - ◊ Utilize a sunscreen with an SPF of at least 30 that protects against UVA and UVB rays and is water resistant.
    - ◊ Apply sunscreen generously and reapply every two hours or after swimming/excessive sweating.
    - ◊ Consider using physical barriers whenever possible (ie, hats, shirts with sleeves, avoiding direct sun during peak hours).
    - ◊ Avoid tanning beds
  - Follow up with primary care physician regularly.
    - ◊ Adhere to age-appropriate health screening, preventive measures (SIMIN-1), and cancer screening recommendations (See NCCN Guidelines for Detection, Prevention, and Early Detection).
- Routine use of dietary supplements is not recommended for the purposes of cancer control. Nutrients should be obtained from food sources rather than relying on dietary supplements (SSUP-1).
- Survivors should work with primary care to set incremental goals for diet, physical activity, and weight management.
- Clinicians should assess individual and community-level barriers to meeting the healthy lifestyle recommendations and support patients in developing strategies to overcome challenges.

[a]Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full.

[b]There are some cancers for which survivors should abstain from alcohol. These include liver, esophageal, kidney, and head and neck cancers.

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GENERAL PRINCIPLES OF PHYSICAL ACTIVITY

- **Physical activity and exercise recommendations should be tailored to individual survivor's abilities and preferences**
- **Physical activity for cancer survivors:[a]**
  - **Overall volume of weekly activity should be at least 150 minutes of moderate-intensity[b] activity or 75 minutes of vigorous-intensity[b] activity or equivalent combination**
  - **Two to three sessions per week of strength training that include major muscle groups**
  - **Stretch major muscle groups at least two days per week**
- **Engage in general physical activity daily (eg, taking the stairs, parking in the back of parking lot)**
  - **Physical activity includes exercise, daily routine activities, and recreational activities**
  - **Avoid prolonged sedentary behavior (eg, sitting for long periods)**

[a]Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full and Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine & Science in Sports & Exercise 2010;42:1409-1426. Available at: http://journals.lww.com/acsm-msse/Fulltext/2010/07000/American_College_of_Sports_Medicine_Roundtable_on.23.aspx.

[b]Light exercise: No noticeable change in breathing pattern; Moderate exercise: Can talk, but not sing; Vigorous exercise: Can say a few words without stopping to catch a breath (See Examples of Exercise [SPA-B]).

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PHYSICAL ACTIVITY ASSESSMENT

Ask about prior and current participation in physical activity and assess level of current physical activity at regular intervals

→

Focused clinical evaluation
- Weight/BMI
- Blood pressure
- Functional status/performance status
- Assess baseline level of activity prior to diagnosis and current level of activity[c]
- Barriers to physical activity as assessed by survivor
  - Environmental (home, gym access, outdoor space)
  - Financial
  - Physical limits
  - Time/competing demands
  - Social support
  - Stress
- Review of systems
- Disease status
- Nutritional status

Assessment of treatable contributing factors
- Pain
- Fatigue
- Emotional distress
- Nutritional deficits/imbalance
- Medications/side effects

→

Assessment of comorbidities and treatment effects as appropriate:
- Cardiovascular disease (including cardiomyopathy)
- Pulmonary disease
- Arthritis/musculoskeletal issues
- Lymphedema
- Peripheral neuropathy
- Bone health/bone strength (including presence of bone metastases)
- Incontinence
- Presence of stoma or ostomy
- Fall risk assessment
- Need for assistive devices (cane, walker, brace, etc.)
- History or presence of anemia/thrombocytopenia
- Steroid myopathy

→

Determine risk level for exercise-induced adverse events
(See SPA-3)

[c]Ask patient about duration, intensity, and frequency of activity. For example, see Godin G and Shepard RJ. Godin Leisure-Time Exercise questionnaire. Medicine and Science in Sports and Exercise 1997; 29 June Supplement: S36-S38. (http://healthandfitnessjournalofcanada.com/index.php/html/article/viewFile/82/49)

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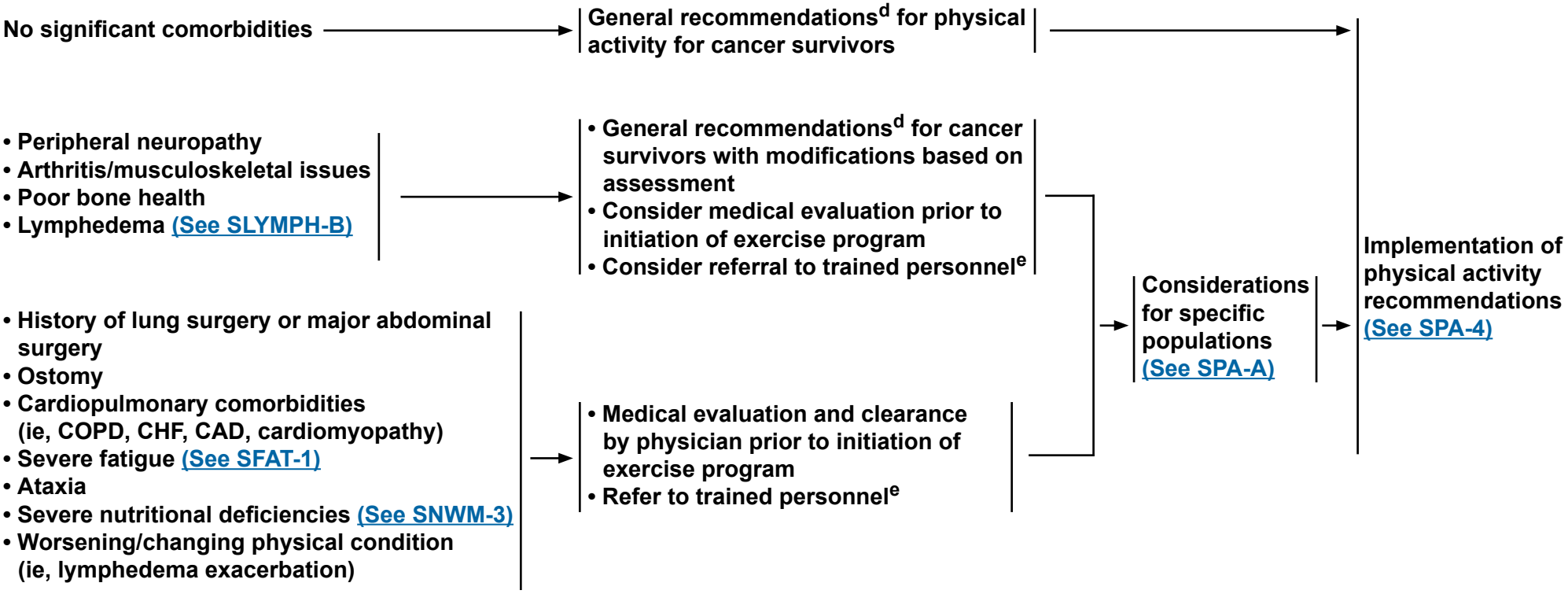
RISK ASSESSMENT FOR PHYSICAL ACTIVITY-INDUCED ADVERSE EVENTS



[d] See General Principles of Physical Activity (SPA-1).

[e] Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://acsm.org/certification] and American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org/home-page.cfm]).

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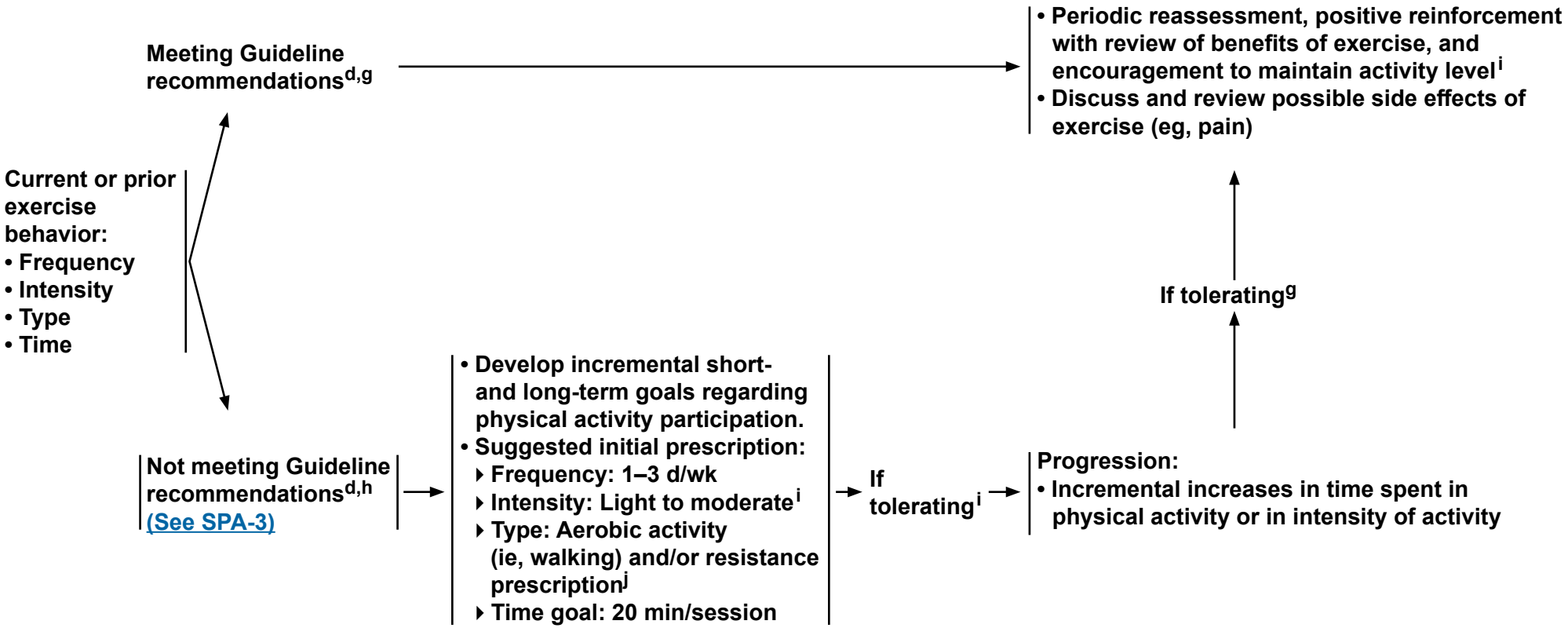
IMPLEMENTATION OF RECOMMENDATIONS[g]



[d] See General Principles of Physical Activity (SPA-1).

[f] Reproduced and adapted with permission from Jones L, Eves ND, Pepperorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol 2010;11:914-916.

[g] If tolerating minimum guideline recommendations, consider encouragement of variation within exercise program or physical activities.

[h] Patients with comorbidities may need additional evaluation before doing more rigorous activity.

[i] See Examples of Physical Activity and Strategies to Increase Physical Activity (SPA-B).

[j] See Guidance For Resistance Training Recommendations (SPA-C).

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CONSIDERATIONS FOR SPECIFIC POPULATIONS[1]

- **Lymphedema:**
  - For workup and treatment of lymphedema (See SLYMPH-3)
  - For considerations regarding phyisical activity in survivors with or at risk for lymphedema (See SLYMPH-B)
- **Stem cell transplant:**
  - Initiate physical activity as tolerated, with clearance by transplant provider
  - Survivors with indwelling catheters should avoid swimming until catheter is removed
  - Public gym use should not be discouraged because the benefits of exercise outweigh the risk of exposure
- **Ostomy:**
  - Empty ostomy bag before engaging in exercise
  - Weight lifting/resistance exercises should start with low resistance and progress slowly under the guidance of trained exercise professionals[2]
  - Avoid contact sports and exercises that result in excessive intra-abdominal pressure
  - Infection precautions recommended
- **Peripheral neuropathy:**
  - Stability, balance, and gait should be assessed before engaging in exercise; consider balance training as indicated
  - Consider alternative aerobic exercise (stationary biking, water aerobics) rather than walking if neuropathy affects stability
  - Resistance training recommendations:
    - ◊ Monitor discomfort in hands when using hand-held weights.
    - ◊ Consider using dumbbells with soft/rubber coating, and/or wear padded gloves (eg, cycling gloves)
    - ◊ Consider resistance training machines
- **Poor bone health:**
  - Survivors with osteoporosis should have fracture risk and/or bone density assessed before initiation of exercise program as clinically indicated
  - Consider balance assessment and training as indicated for patients at risk for falls

[1]When possible, survivors in these populations should initiate exercise program under supervision by trained personnel.
[2]Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://acsm.org/certification] or American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

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EXAMPLES OF PHYSICAL ACTIVITY

Light Exercise[1] (No noticeable change in breathing pattern)	Moderate Exercise[2] (Can talk, but not sing)	Vigorous Exercise[2] (Can say a few words without stopping to catch a breath)
• Leisurely biking at 5 miles/hour or less • Activity-promoting video game • Light housework (light sweeping, dusting) • Bowling • Playing catch • Slow walking • Child care • Yoga • Tai chi	• Ballroom/line dancing • Biking on level ground or with few hills • General gardening • Baseball, softball, volleyball • Doubles tennis • Using a manual wheelchair • Brisk walking • Water aerobics • Yoga	• Aerobic/Fast dancing • Biking faster than 10 miles/hour • Heavy gardening • Hiking uphill • Jumping rope • Martial arts • Race walking, jogging, running • Running sports (basketball, hockey, soccer) • Swimming (fast pace or laps) • Singles tennis • Stair climbing • High intensity yoga

STRATEGIES TO INCREASE PHYSICAL ACTIVITY

- Physician and/or fitness expert recommendation
- Supervised exercise program or classes
- Telephone counseling
- Motivational counseling
- Evaluate readiness to change, importance of change, self-efficacy
- Cancer survivor-specific print materials (See SURV-B 2 of 2)
- Set short- and long-term goals
- Consider use of pedometer or wearable fitness tracker to monitor activity goals (eg, obtain 10,000 steps per day)
- Encourage social support (exercise buddy, group)

[1]From the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/phy_act.htm) and the Compendium of Physical Activities (https://sites.google.com/site/compendiumofphysicalactivities).

[2]Reproduced and adapted from U.S. Department of Health and Human Services. Be Active Your Way: A Fact Sheet for Adults. Washington, DC: U.S. Department of Health and Human Services; 2008. http://www.health.gov/PAGuidelines/factSheetAdults.aspx. Accessed July 21, 2017.

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GUIDANCE FOR RESISTANCE TRAINING RECOMMENDATIONS

- Health benefits of resistance training include improvement in muscle strength and endurance, improvements in functional status, and maintenance/improvement in bone density
- Multi-joint exercises are recommended over exercises focused on a single joint
- All major muscle groups (chest, shoulders, arms, back, abdomen, and legs) should be incorporated into a resistance training program
- Larger muscle groups (legs, back, and chest) should be worked before smaller muscle groups (arms and shoulders)
- Resistance training prescription
  - Frequency: 2–3 times/week. Survivors should wait at least 48 hours between resistance training sessions.
  - Intensity: 2–3 sets of 10–15 repetitions per set; consider increasing weight amount as tolerated when 3 sets of 10–15 repetitions becomes easy
  - Time: 20 minutes per session
  - Rest: 2- to 3-minute rest period between sets and exercises
  - For survivors who do not currently do resistance training: Start with one set of each exercise and progress up to 2–3 sets as tolerated
- Utilize weight amount that would allow for performance of 10–15 repetitions
- Survivors at risk for or with lymphedema (See SLYMPH-B)

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GENERAL PRINCIPLES OF NUTRITION

- **Assess dietary pattern for daily intake of fruits, vegetables, and unrefined grains, as well as red and processed meats, alcohol, and processed foods or beverages with added fats and/or sugars**
- **Assess eating habits, including portion size, night grazing, snacking habits, frequency of eating out and use of added fats and/or sugars to foods or beverages**
- **Encourage informed choices about food to ensure variety and adequate nutrient intake**
- **Recommend plant-based diet with the majority of food being vegetables, fruit, and whole grains with limited amounts of refined sugars and red or processed meat[a,b,c]**
- **Recommended sources of dietary components:**
  - **Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and fatty fish[d]**
  - **Carbohydrates: fruits, vegetables, whole grains, and legumes**
  - **Protein: poultry, fish, legumes, low-fat dairy foods, and nuts**
- **Currently there is no consensus either refuting or supporting the role of soy foods in cancer control. Thus, moderate consumption (3 or fewer servings per day) of soy foods is considered prudent.**

[a]Recommendation for healthy food portion sizes can be found on the American Institute of Cancer Research (AICR) website (http://www.aicr.org/new-american-plate/reduce_diet_new_american_plate_portion.html) as well as the USDA "Choose My Plate" website www.choosemyplate.gov.

[b]Encourage the use of healthy recipes from resources such as the American Cancer Society's "Find Healthy Recipes" website: http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/maindishes/index.

[c]For patients desiring further recommendations for dietary guidelines, the USDA approximate food plate volumes (www.choosemyplate.gov) are:

- Vegetables and fruits should comprise half the volume of food on the plate
  - Vegetables 30% of plate; Fruits 20% of plate
- Whole grains: 30% of plate
- Protein: 20% of plate

[d]These foods are high in calories and should be limited if weight control is an issue.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENERAL PRINCIPLES OF WEIGHT MANAGEMENT

- **Weight management should be a priority for all cancer survivors.**
  - **Weight gain should be a priority for underweight survivors.**
  - **Maintenance of weight should be encouraged for normal weight survivors.**
  - **Weight loss should be a priority for overweight/obese survivors.**
- **Weight gain after cancer diagnosis and treatment is common; providers should discuss strategies to prevent weight gain for normal weight and overweight/obese survivors.**
- **Weight gain can exacerbate risk for functional decline, comorbidity, and possibly cancer recurrence or death, and can reduce quality of life.**
- **Principles of weight loss:**
  - **Limit foods that are high in calories, particularly those that provide relatively few nutrients such as sugar-sweetened beverages and foods with high amounts of fats and sugars (ie, many desserts, fried foods, fast foods).**
  - **Substitute high-calorie foods with low-calorie, nutrient-dense foods such as water-rich vegetables, fruits, soups, and whole grains.**
  - **Practice portion control by using smaller plates and restricting intake to one serving.**
  - **Make informed food choices through routine evaluation of food labels.**
  - **Monitor weight daily**
    - ◊ **Recommend weight loss of no more than 2 pounds per week and no more than 1 pound per week in survivors over 64 years.**
  - **Incorporate physical activity, particularly strength training, to assure optimal lean body mass (SPA-1)**
  - **Track diet, calories, and physical activity routines**
- **In conjunction with primary care, survivors should be assessed for metabolic health and body composition independently of body mass index (BMI).**
- **Referrals to registered dietitians, especially those who are Certified Specialists in Oncology Nutrition (CSO) and members of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics, should be considered.[e]**
- **There is no current evidence to support the use of weight loss supplements in cancer survivors.**

[e]Many hospitals employ CSOs and those in private practice can be accessed via the Academy of Nutrition and Dietetics locator at www.eatright.org.

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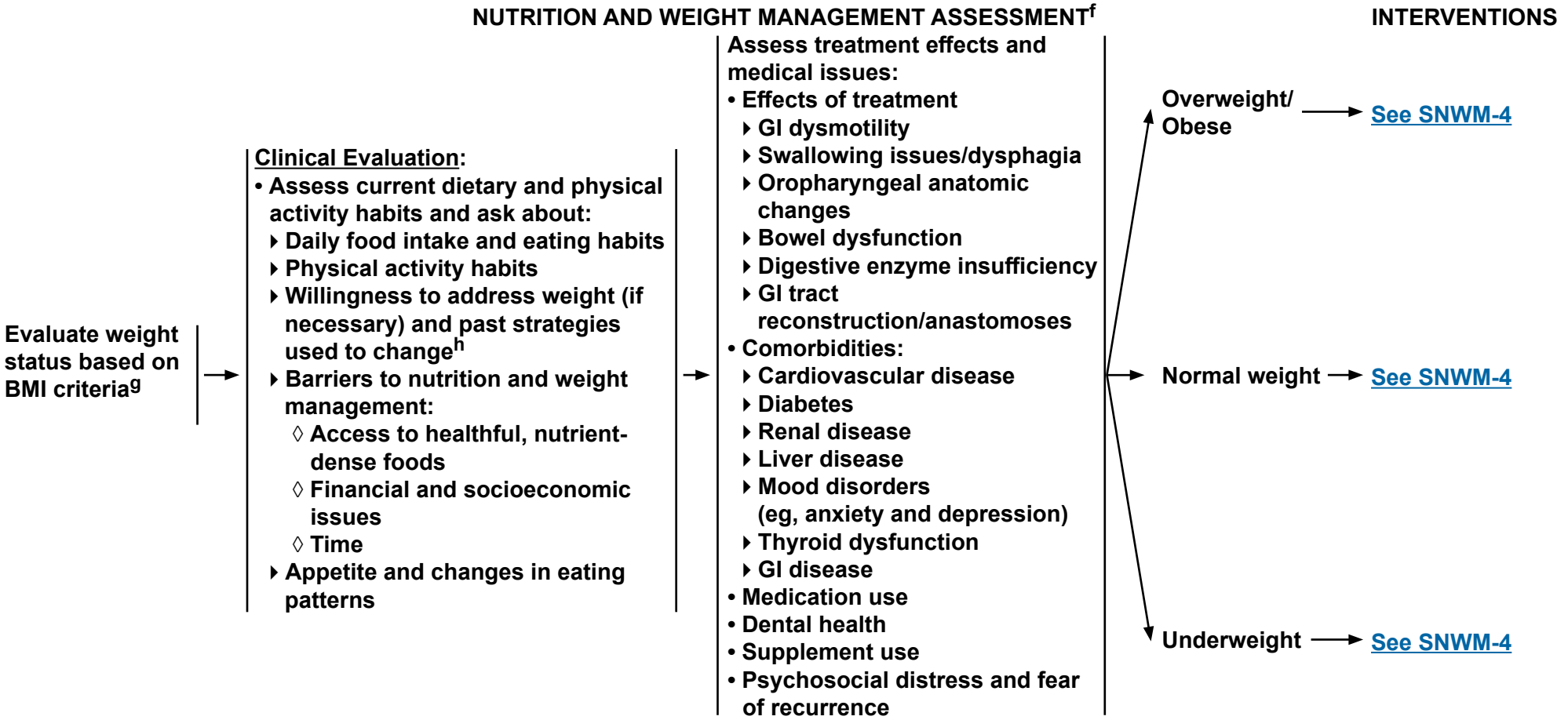

[f]Coordination with primary care physicians and other involved providers is recommended.

[g]The following BMI calculator from the Centers for Disease Control and Prevention may be used: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html.
BMI is calculated using the following formula: weight in pounds (lbs) X 703 / height in inches squared. The weight categories are as follows:
- Underweight (BMI <18.5 kg/m^2)
- Normal weight (BMI 18.5–24.9 kg/m^2)
- Overweight (BMI 25–29.9 kg/m^2)
- Obese (BMI ≥30 kg/m^2)

[h]For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/obesity-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.

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NUTRITION AND WEIGHT MANAGEMENT INTERVENTIONS[f,h]

Overweight/ Obese →

- Discuss “General Principles of Nutrition” (See SNWM-1)
- Discuss “General Principles of Weight Management” (See SNWM-2)
- Discuss “General Principles of Physical Activity” (See SPA-1)
- Discuss portion control[i]
- Manage contributing treatment effects and risk factors as clinically indicated
  - Contributing psychosocial factors, including depression (See SANXDE-1)
- Refer to community resources
- Refer to dietitian or weight management programs for individualized help as needed[j]
- Consider evaluation for bariatric surgery or pharmacologic therapy[k] as appropriate (if obese or morbidly obese)

Normal weight →

- Discuss “General Principles of Nutrition” (See SNWM-1)
- Discuss “General Principles of Physical Activity” (See SPA-1)
- Reinforce maintenance of normal body weight throughout lifetime
- Manage treatment effects and risk factors as clinically indicated
- Discuss "General Principles of Weight Management" (See SNWM-2)

Underweight →

- Discuss “General Principles of Nutrition” (See SNWM-1)
- Discuss increasing frequency of feeding[i]
- Discuss avoiding fluid intake with meals
- Manage contributing treatment effects and risk factors as clinically indicated
  - Dental health and risk factors for poor oral intake
  - Swallowing disorder, taste/smell disorders, and GI motility as appropriate
  - Offer smoking cessation assistance as appropriate (See NCCN Guidelines for Smoking Cessation)
  - Contributing psychosocial factors (See SANXDE-1)
- Consider referral to dietitian for individualized counseling
- Discuss "General Principles of Weight Management" (See SNWM-2)

[f]Coordination with primary care physicians and other involved providers is recommended.
[h]For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/obesity-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.
[i]Modification of diet and dietary components should be done on an individual basis.
[j]Strongly consider for survivors with negligible weight loss from diet and exercise interventions.
[k]The safety and efficacy of these drugs in cancer survivors is unknown. Lifestyle modifications are preferred over pharmacologic therapy.

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GENERAL PRINCIPLES OF SUPPLEMENT USE

- **Supplement use is not recommended for most survivors, except in instances of documented deficiencies, inadequate diet, or comorbid indications (eg, osteoporosis, ophthamologic disorders, cirrhosis).**
- **Little data exist to support the use of vitamins or other dietary supplements for the purposes of cancer control, recurrence, or prevention.**
- **Taking vitamin supplements does not replace the need for adhering to a healthy diet. All efforts should be made to obtain nutrients from dietary intake.[a]**
- **Providers should assess supplement use at regular intervals. Ask about reasons for supplement use and supplement ingredients.[b]**
- **Refer survivors using multiple and/or or unfamiliar supplements to a registered nutritionist/dietitian, preferably one with oncology credentials.**
- **Survivors of certain cancers are at risk for vitamin deficiencies based on their cancer treatment. Deficiencies should be assessed and repleted as needed (For example, See GAST-6 from the NCCN Guidelines for Gastric Cancer).**

[a]Referral to registered dietitians, especially those who are Certified Specialists in Oncology Nutrition (CSO) should be considered for guidance in supplement use, if deemed necessary.
[b]Consider use of available resources for information on supplements (See SURV-B 2 of 3).

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GENERAL PRINCIPLES OF IMMUNIZATIONS

- **These principles apply to cancer survivors, including those with hematologic or solid tumor malignancies and those post transplant.**
- **Clinicians should consider and encourage the administration of inactivated vaccines (eg, influenza), vaccines made of purified antigens (eg, pneumococcus), bacterial components (eg, diphtheria-tetanus-pertussis), or genetically engineered recombinant antigens (eg, hepatitis B) in all cancer and transplant survivors. In the absence of known harm, administration of inactivated vaccines with the hope of achieving some protection may be worthwhile. The usual doses and schedules are recommended.[a,b,c]**
  - **Recommended Adult Immunization Schedule for Adults Aged 19 Years or Older — United States, 2017 https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf**
- **Vaccines as a strategy to prevent infection represents a unique challenge in cancer and transplant survivors. Vaccines may not trigger protective immune responses in actively immunocompromised individuals or in survivors with residual immune deficits. In addition, certain vaccines such as those that are live attenuated (eg, zoster, MMR) are contraindicated in actively immunosuppressed individuals because of a proven or theoretical increased risk of prolonged shedding and disease from the live organism present in the vaccine; other live attenuated vaccines might also be contraindicated in survivors' close contacts (eg, oral polio vaccine). Live viral vaccines[d] should be avoided in survivors with lymphomas, other malignant neoplasms affecting the bone marrow or lymphatic system, or history of cellular immunodeficiency.**
- **Ideally, clinicians should have administered all indicated vaccines to patients before initiation of cancer treatment (if possible, at least two weeks before cancer treatment).[e]**
  - **Inactivated or recombinant vaccines should be administered 2 or more weeks before cancer treatment and 3 or more months after cancer chemotherapy. While this schedule is preferred, the inactivated influenza vaccine can be administered during cancer treatment.**
  - **Live viral vaccines[d] can be administered 4 or more weeks before cancer treatment or 3 or more months after cancer chemotherapy, but consultation with an infectious disease specialist or physician familiar with vaccination in survivors and/or patients with cancer is recommended.**
- **In survivors who received anti-B cell antibody therapy, vaccination should be delayed for at least 6 months after chemotherapy and the last dose of such therapy.**

[a]National Center for Immunization and Respiratory Diseases. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21293327.

[b]Also see: Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138.

[c]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-18.

[d]See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors/Live Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors (SIMIN-A).

[e]Cancer treatment includes chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, and splenectomy.

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RISK ASSESSMENT AND SCREENING

Risk factors for infections:
- Underlying disease
- Post-splenectomy
- Prior chemotherapy
- Monoclonal antibodies (eg, rituximab, alemtuzumab)
- Prior radiation
- Corticosteroids
- Prior hematopoietic cell transplantation (HCT)[f]
- Prior/current exposure to endemic infections or epidemics
- Blood transfusion history

→

INTERVENTIONS

- Education on infection prevention practices
  - Safe pet care/avoidance of zoonosis[g]
  - Travel precautions[h]
  - Gardening precautions[i]
- Vaccines[d,j]
  - Assess overall immune system viability and history of allergic reactions to vaccines
    - ◊ Baseline WBC should be adequate before starting vaccinations, unless elevated due to disease status
    - ◊ Patient should not be on immunosuppressive drugs[k] or chemotherapy
    - ◊ Ongoing infection should not be present
- Antimicrobial prophylaxis (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)

→ See SIMIN-3

[d] See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors/Live Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors (SIMIN-A).

[f] HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

[g] Safe pet care tips include washing hands with soap and running water after handling animal feces. If possible, survivors at high risk for immune suppression should avoid direct contact with animal feces and other bodily secretions. Survivors with elevated risk of infection and those who are immunocompromised are at higher risk for zoonoses and should use extra caution.

[h] Travel precautions include education on the need for pre-travel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections. Travelers may find useful information at http://wwwnc.cdc.gov/travel/yellowbook/2016/advising-travelers-with-specific-needs/immunocompromised-travelers or by consulting a travel clinic.

[i] Examples of gardening precautions include:
- Wearing gloves to avoid skin cuts/punctures that could have delayed healing and to avoid thorns that can have fungus or staphylococcus/streptococcus.
- Wearing a protective mask to avoid spores. (For guidelines on physical activity, see [SPA-1])

[j] For dosing and schedule, See General Principles of Vaccines in Cancer Survivors (SIMIN-B).

[k] Patients should not be on immunosuppressive drugs including ≥0.5 mg/kg of prednisone or equivalent, or greater than a combination of two immunosuppressive medications given concurrently.

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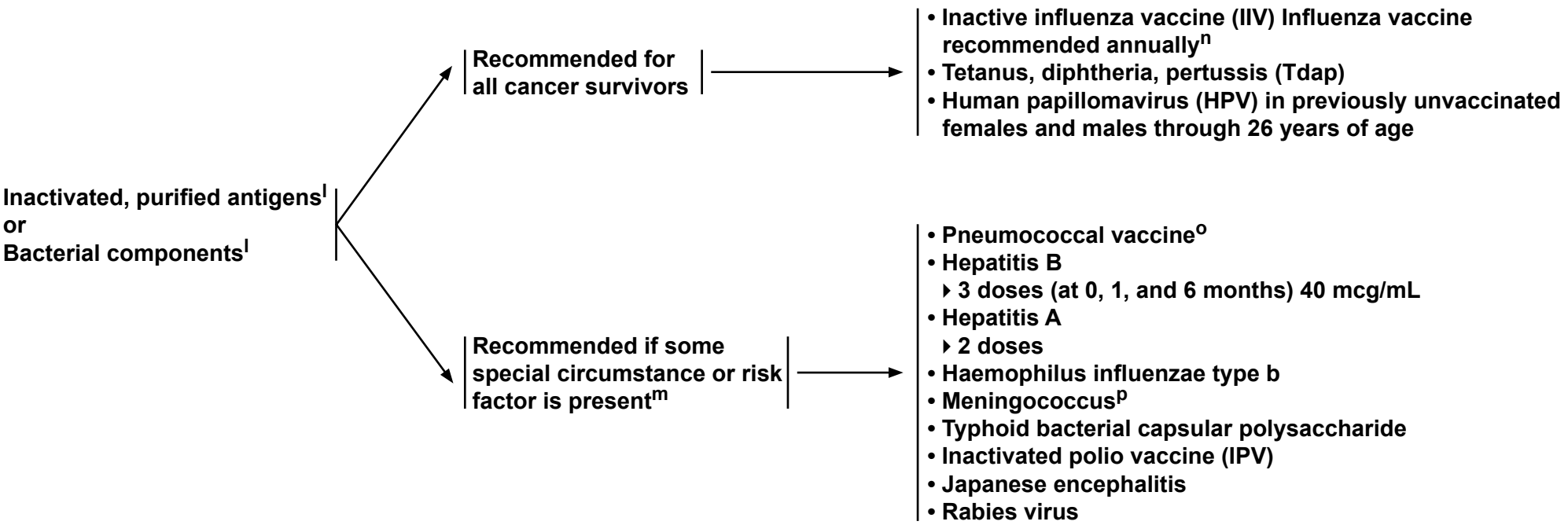

[d] See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors/Live Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors (SIMIN-A).

[j] For dosing and schedule, See General Principles of Vaccines in Cancer Survivors (SIMIN-B).

[l] Inactivated or purified antigens or bacterial components should be administered beginning at least 3 months after chemotherapy or radiation therapy and 6 months after hematopoietic cell transplantation (HCT) (a dose of inactivated influenza vaccine can be given as early as 4 months after HCT, but a second dose should be considered in this situation).

[m] These vaccines should be considered if there are unique circumstances such as functional or anatomic asplenia or in patient's lifestyle, upcoming travel, or local epidemic or risks that merit their use. Please consult with an infectious disease or travel medicine specialist.

[n] See Principles of Influenza Vaccine(s) (SIMIN-C).

[o] PCV-13 and PPSV-23 are recommended for adults 65 years or older and for younger adults who are immunocompromised (ie, HCT and functional or anatomic asplenia). Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep September 3, 2010;9(34):1102-1106 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5934a3.htm#tab

[p] Recommended in high-risk patients or those with functional or anatomic asplenia. Committee On Infectious Diseases. Recommendations for serogroup B meningococcal vaccine for persons 10 years and older. Pediatrics 2016;138.

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VACCINES CONTRAINDICATED OR TO BE USED WITH CAUTION IN ACTIVELY IMMUNOCOMPROMISED SURVIVORS

Live attenuated vaccines[1]

- **Measles, mumps, rubella (MMR)**
- **Varicella (VAR)**[2,3]
- **Zoster (ZOS)**[2,3]
- **Oral typhoid**
- **Yellow fever**
- **Rotavirus**
- **Oral polio**[4]

LIVE VACCINES THAT CAN BE USED WITH CAUTION IN CLOSE CONTACTS OF IMMUNOCOMPROMISED SURVIVORS[5,6]

- **Measles, mumps, and rubella (MMR)**
- **Varicella (VAR)**[2,3]
- **Zoster (ZOS)**[2,3]
- **Oral typhoid**
- **Yellow fever**
- **Rotavirus**[5]

[1]Severe complications have followed vaccination with live attenuated vaccines among immunocompromised patients. They should not be offered to an actively immunocompromised or transplant survivor or their close contacts, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist. If a live attenuated vaccine is inadvertently administered to a survivor's close contact, close contact with the survivor should be avoided for 2 to 6 weeks following vaccination depending on the type of administered vaccine.
[2]For additional recommendations regarding Zoster vaccine, see Principles of Zoster (Shingles) Vaccine Use in Cancer or Transplant Survivors (SIMIN-D).
[3]Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of varicella or zoster vaccine, until the lesions clear.
[4]Live oral polio vaccine should not be administered to close contacts of immunocompromised survivors.
[5]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA Clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[6]Immunocompromised survivors should avoid handling diapers of children who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Non-Transplant Survivors[1,2]

- **These principles apply to survivors of hematologic or solid tumor malignancies except those receiving anti-B-cell antibodies.[3]**

- **The following vaccines can be administered to cancer survivors:**
  - **Influenza vaccine annually (See Principles of Influenza Vaccine(s) SIMIN-C)**
  - **Pneumococcal vaccine**
    - ◊ **Recommended for adults 65 years or older and for younger adults who are immunocompromised[1]**
    - ◊ **13-valent pneumococcal conjugate vaccine (PCV13) x 1 dose if never vaccinated against pneumococcus**
    - ◊ **23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks after the indicated dose(s) of PCV13**
    - ◊ **For those who received PPSV23, PCV13 should be administered ≥1 year after the last PPSV23 dose**
    - ◊ **A second dose of PPSV23 is recommended 5 years after the first dose for immunocompromised survivors and those with functional or anatomic asplenia.**
  - **Tetanus, diphtheria, pertussis vaccine (Td/Tdap):**
    - ◊ **Administer a one-time dose of Tdap to adults younger than age 65 years who have not received Tdap previously or for whom vaccine status is unknown to replace one of the 10-year Td boosters (substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years). Otherwise Td booster every 10 years.**
    - ◊ **Consider administering a Tdap booster every 5 years**
  - **Consider human papillomavirus (HPV) vaccine in survivors through age 26 years. For dosing and schedules see https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html**

[1]Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb Mortal Wkly Rep 2010;59:1102-1106. https://www.ncbi.nlm.nih.gov/pubmed/20814406

[2] Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138.

[3]In survivors who received anti-B cell antibody therapy, the above vaccines can be given, but should be delayed for at least 6 months after chemotherapy and the last dose of such therapy.

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Hematopoietic Cell Transplant (HCT) Survivors[4,5]

- Influenza vaccine annually
  (See Principles of Influenza Vaccine(s) SIMIN-C)
  - One dose should be administered annually to all cancer survivors starting 6 months after HCT and starting 4 months after if there is a community outbreak of influenza as defined by the local health department.
- Pneumococcal vaccine
  - Three doses (1 month apart) of PCV13 should be administered 3–6 months after HCT.
  - At 12 months after HCT, 1 dose of PPSV23 should be given provided the patient does not have chronic graft-versus-host disease (GVHD).
  - For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HCT.
- Haemophilus influenzae type b (Hib) vaccine
  - Three doses of Hib vaccine should be administered 6–12 months after HCT.
- Meningococcal conjugate vaccine quadrivalent (MCV4)
  - The MCV4 vaccine may be considered in outbreak situations or in endemic areas.
- Tetanus, diphtheria, pertussis (Td/Tdap) vaccine
  - Three doses of tetanus/diphtheria–containing vaccine should be administered 6 months after HCT (administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second). This three-dose-regimen should be followed by Td boosters every 10 years.
  - Administration of 3 doses of Tdap should be considered (can replace second and third dose by Td).
- Hepatitis B vaccine
  - Three doses of HepB vaccine should be administered 6–12 months after HCT.
  - If a postvaccination anti-Hepatitis B surface antigen (anti-HBs) concentration of ≥10 mIU/mL is not obtained, a second 3-dose series of HepB vaccine is recommended.
  - 1st dose of HepB vaccine (after which anti-HBs is tested) using high dose (40 µg) should be administered.
- Inactivated Polio Vaccine (IPV)
  - Three doses of IPV vaccine should be administered 6–12 months after HCT
- Consider human papillomavirus (HPV) vaccine
  - Consider administration of 3 doses of HPV vaccine 6–12 months after HCT for for survivors through age 26 years.
- Live viral vaccines should not be administered to HCT survivors with active GVHD or ongoing immunosuppression. They should only be administered to HCT survivors without active GVHD or ongoing immunosuppression following consultation with an infectious diseases specialist.
  - Measles, mumps, rubella (MMR) vaccine
    - ◊ MMR vaccine should be avoided within 4 weeks before HCT.
    - ◊ A 2-dose series of MMR vaccine should be administered to measles-seronegative adolescents and adults 24 months after HCT in patients with neither chronic GVHD nor ongoing immunosuppression and 8–11 months after the last dose of immune globulin intravenous (IGIV).
  - Zoster vaccine (VAR)
    - ◊ A 2-dose series of VAR should be administered 24 months after HCT to varicella-seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of IGIV.

[4]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309-18. http://www.ncbi.nlm.nih.gov/pubmed/24421306.

[5]HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccines Considered Safe For Cancer And Transplant Survivors And Close Contacts[6]

Inactivated or purified antigens or bacterial components[7]

- **Influenza: inactivated influenza virus vaccine[9]**
  - **Trivalent (IIV3), Standard Dose**
  - **Trivalent (IIV3), High Dose**
  - **Quadrivalent (IIV4), Standard Dose**
- **Pneumococcus:**
  - **Pneumococcal conjugate vaccine (PCV)**
  - **PPSV**
- **Meningococcus:**
  - **Quadrivalent meningococcal conjugate vaccine (MCV4: serotypes A, C, W, Y)**
  - **Meningococcal vaccine (serotype B)[8]**
- **Tetanus, diphtheria, pertussis (Td/Tdap)**
- **Hepatitis A**
- **Haemophilus influenzae type b**

Recombinant viral antigens

- **Hepatitis B**
- **Human papillomavirus (HPV) female and HPV male**
- **Recombinant trivalent influenza vaccine (RIV3)[9]**

[6]Ideally, clinicians should have administered all indicated vaccines to patients at least 2 weeks before initiation of cancer treatment (ie, chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, splenectomy).

[7]For patients traveling to endemic countries, vaccines such as typhoid bacterial capsular polysaccharide, inactivated polio vaccine (IPV), Japanese encephalitis, and rabies virus are recommended by the Centers for Disease Control and Prevention (www.cdc.gov).

[8]Folaranmi T, Rubin L, Martin SW, Patel M, MacNeil JR; Centers for Disease Control (CDC). Use of serogroup B meningococcal vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep 2015 Jun 12;64(22):608-12.

[9]Administration of the flu vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138.

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PRINCIPLES OF INFLUENZA VACCINE(S)[1,2]

- **Annual influenza vaccination is recommended[2] for all cancer and transplant survivors. Live attenuated influenza vaccines should be avoided in these individuals unless they have been cleared to do so by an infectious disease specialist or physician familiar with vaccination in this population.**
- **For a summary of recommendations for prevention and control of influenza with vaccines see: https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm**
- **Components of the influenza vaccine are determined each year by the World Health Organization (WHO) according to reports of the most common influenza viruses that are likely to circulate that year.**
- **Influenza vaccines can be inactivated or recombinant. They may contain standard or higher doses of the antigen. They can be trivalent or quadrivalent.**

Preferred Vaccines

- **Inactivated influenza vaccine**
  - **Trivalent (IIV3), Standard Dose**
  - **Trivalent (IIV3), High Dose**
  - **Quadrivalent (IIV4), Standard Dose**
- **Recombinant influenza vaccine[3]**
  - **Trivalent (RIV3)**

To date, there is no evidence that one vaccine is superior to any other vaccine. Health care providers should primarily choose one of the inactivated or recombinant vaccines and avoid giving the live-attenuated virus vaccine to cancer and transplant survivors.

[1]Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138.
[2]Davlin SL, Blanton L, Kniss K, et al. Influenza activity - United States, 2015-16 season and composition of the 2016-17 influenza vaccine. MMWR Morb Mortal Wkly Rep 2016;65:567-575.
[3]Administration of the flu vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138.

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PRINCIPLES OF ZOSTER (SHINGLES) VACCINE USE IN CANCER OR TRANSPLANT SURVIVORS[1,2]

- **Zoster vaccine may be considered in survivors with a history of solid tumors or leukemia whose disease is in remission, who have restored their immunocompetence, and who have not received chemotherapy or radiation for at least 3 months.**
- **If zoster vaccine is given prior to starting therapy, it should be administered at least 4 weeks prior to the first dose of immunosuppressive therapy.[2]**
- **The vaccine can be administered to select immunocompetent survivors regardless of whether they report a prior episode of herpes zoster.[3]**
- **Licensed antiviral medications active against members of the herpes virus family (eg, acyclovir, famciclovir, valacyclovir, valganciclovir) might interfere with replication of the live, varicella zoster virus (VZV)-based zoster vaccine.[4]**

- **A single dose of zoster vaccine is recommended for cancer or transplant survivors 60 years of age and older assuming that active or ongoing immunodeficiency is not present and that there is no history of cellular immunodeficiency.**
  - **For survivors age 50–59 years, zoster vaccination should be considered in those with a history of varicella or zoster infection or VZV seropositive with no previous doses of varicella vaccine.**

- **Zoster vaccine should be avoided:**
  - **in patients with lymphomas, other malignant neoplasms affecting the bone marrow or lymphatic system, or a history of cellular immunodeficiency;**
  - **in patients on immunosuppressive therapy, including high-dose corticosteroids (>20 mg/d of prednisone or equivalent) lasting two or more weeks; and**
  - **in patients undergoing or with history of HCT. The experience of HCT recipients with VZV-containing vaccines (eg, zoster vaccine) is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation in patients without active graft-versus-host disease (GVHD) or enhanced immunosuppression.**

[1]Hales CM, Harpaz R, Ortega-Sanchez I. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly 2014;22:63:729-731.
[2]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[3]Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing postherpetic neuralgia (PHN, a common complication of zoster that results in chronic, often debilitating pain that can last months or even years), or to treat ongoing PHN. Before routine administration of zoster vaccine, it is not necessary to ask patients about their history of varicella (chickenpox) or to conduct serologic testing for varicella immunity. Hales CM, Harpaz R, Ortega-Sanchez I. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly 2014;22:63:729-731.
[4]Survivors taking chronic acyclovir, famciclovir, valacyclovir, or valganciclovir should discontinue these medications at least 24 hours before administration of zoster vaccine. These medications should not be used for at least 2 weeks after vaccination, by which time the immunologic effect should be established.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Overview

A report issued by the U.S. Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI) and data from the American Cancer Society (ACS) estimate that the number of cancer survivors in the United States increased from approximately 3 million in 1971 to nearly 15.5 million in 2016.[1-3] These numbers are predicted to reach more than 20 million by 2026.[2] This striking increase is generally attributed to rising cancer incidence rates (mainly resulting from an aging population), earlier detection, and better treatment.

An analysis of the SEER database showed that approximately 62% of survivors were 65 years of age or older in 2016.[1] Only 5% are younger than 40 years, and survivors of childhood cancer constitute between 0.5% and 3.0% of the survivor population.[4,5] In fact, an estimated 1 of every 5 persons older than 65 years is a cancer survivor. The most common cancer sites in the survivor population are breast, prostate, colon/rectum, and melanoma, together accounting for approximately 58% of survivors.[4] Approximately 64% of survivors were diagnosed 5 or more years ago, whereas 15% of survivors were diagnosed 20 or more years ago, and approximately 5% have survived 30 years or longer.[4]

Unfortunately, many of these cancer survivors experience physical and/or psychosocial late and/or long-term effects of cancer and its treatment, which can be severe, debilitating, and sometimes permanent. Survivors may be discharged from the care of their oncologist and feel isolated and scared. Furthermore, their primary care physicians (PCPs), who may now be responsible for their care, often do not know how best to care for the specific concerns and needs of cancer survivors.[6] ASCO's recent statement, "Achieving High-Quality Cancer Survivorship Care," cites a need for standardized, evidence-based practice guidelines for the management of treatment effects and health promotion of survivors.[7] ASCO, NCCN, ACS, and other groups that are working in parallel hope to provide this guidance.[8-10]

The NCCN Survivorship Panel is comprised of a multidisciplinary panel of experts that includes at least one oncologist, bone marrow transplant clinician, gynecologist, urologist, infectious disease specialist, cardiologist, PCP, psychologist, exercise physiologist, nutrition scientist, nurse, epidemiologist, and patient advocate. The panel defined general principles of cancer survivorship to help guide the recommendations that form the basis for these guidelines.[11]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Survivorship, an electronic search of the PubMed database was performed to obtain key literature in the field of cancer survivorship published between October 1, 2015 and October 1, 2016, using the following search terms: ((“neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “cancer”[All Fields]) AND (“survivors”[MeSH Terms] OR “survivors”[All Fields] OR “survivor”[All Fields])) OR ((“neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “cancer”[All Fields]) AND (“survivorship”[All Fields])). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[12]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 112 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

General Principles of These Guidelines

These NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The recommendations in these guidelines therefore pertain to patients who may be in remission and those who are cured. The guideline recommendations may also be applicable to those survivors for whom cancer has become a chronic condition and are living with metastatic disease. These guidelines are designed to provide a framework for the management of long-term and/or late effects of cancer and its treatment. The guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer can have on the adult survivor's health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.

These guidelines should be used as a supplement to the follow-up recommendations within the disease-specific guidelines (see NCCN Guidelines for Treatment of Cancer by Site, available at www.NCCN.org) and should provide a framework for the coordination of care between the survivor's health care providers to ensure that needs are appropriately addressed. Although these guidelines are focused on survivors who are in clinical remission after the completion of cancer treatment, the topics, assessments, and interventions may also be applicable to survivors living with metastatic disease, as clinically appropriate (also see NCCN Guidelines for Supportive Care, available at www.NCCN.org).

These guidelines are not intended to provide guidance for the care of survivors of childhood cancer (detailed guidelines for the care of childhood cancer survivors are available from the Children's Oncology Group at http://www.survivorshipguidelines.org/). For survivorship issues related to younger populations, please also see the NCCN Guidelines for Adolescent and Young Adults (available at www.NCCN.org).

For this version of the NCCN Guidelines for Survivorship, the panel focused on several common issues of survivors: 1) anxiety and depression; 2) anthracycline-induced cardiac toxicity; 3) cognitive decline; 4) fatigue; 5) lymphedema; 6) menopause-related symptoms; 7) pain; 8) female and male sexual dysfunction; and 9) sleep disorders. They also focused on the preventive health issues of immunizations and prevention of infections and healthy lifestyle behaviors. Additional topics will be addressed in subsequent updates.

Cancer Survivors

The NCCN Survivorship Panel supports the NCI's definition of a cancer survivor: "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also affected by the survivorship experience and are therefore included in this definition."[13] Throughout these

guidelines, however, “survivor” refers to an individual with a history of cancer; family, friends, and caregivers are not currently addressed.

The Effects of Cancer and Its Treatment

For some survivors, the consequences of cancer are minimal; these patients can return to a normal life after the completion of treatment. In fact, most cancer survivors report being in good general health and experience good to excellent quality of life.[14,15] Also, a recent survey of 659 survivors of breast, colorectal, and prostate cancers found that a majority do not suffer from psychologic morbidity or have a large number of unmet supportive care needs.[16] Other studies have similarly found that most survivors enjoy a high quality of life without a large number of cancer-related symptoms.[17,18]

However, many survivors do experience physical and/or psychosocial effects of cancer and its treatment.[19-21] Some sequelae become evident during anticancer treatment (long-term effects), whereas others may not manifest for months or years after active therapy (late effects). The problems can range from mild to severe, debilitating, or even life-threatening. Some problems are temporary or improve with time, whereas other problems are progressive or permanent. This topic has been well reviewed.[15,22]

A recent review suggests that at least 50% of survivors experience some late effects of cancer treatment.[22] The most common problems in cancer survivors are depression, pain, and fatigue.[23] The exact prevalence of various effects of cancer and its treatment are hard to quantify, because few studies have addressed these issues in a longitudinal fashion, comparing patients with and without a history of cancer to differentiate between the effects of cancer and the effects of aging.[15] In general, the prevalence of late effects in cancer survivors is believed to have increased over time, likely because anticancer interventions have become more complex and intense with combinations of surgery, radiation, chemotherapy, hormone therapy, and targeted biologics.[24]

Physical Effects

Physical problems in cancer survivors include pain, musculoskeletal issues, fatigue, lack of stamina, urinary/bowel problems, lymphedema, premature menopause, cognitive deficits, and sexual dysfunction.[15,25-27] The effects of cancer treatment on the heart and bone are also well known.[28-31] The type of physical problems depends mainly on the treatment. For example, radiation to the pelvis can be associated with bowel, urinary, and sexual dysfunction and increased risk for second primary malignancies.[32,33] The ACS Study of Cancer Survivors II found that 38% of survivors reported at least one unmet need in the physical domain (eg, pain, sexual dysfunction).[20]

Second Primary Cancers

Importantly, the overall incidence of second primary cancers in survivors is higher than in the general population because of genetic susceptibilities (eg, cancer syndromes), shared causative factors (eg, smoking, obesity, environmental exposures), and/or the mutagenic effects of cancer treatment.[34-43] Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.[44-50] These secondary malignancies are especially well studied in long-term survivors of childhood cancers.[51-54] Studies by individual cancer type show that the incidence of subsequent unrelated cancers ranges from 2% in survivors of malignant lymphoma to 30% in survivors of small cell lung cancer.[22] Another study of over 2 million cancer survivors in the SEER database identified the highest risk for second primary cancers in survivors of bladder cancer (34% at 20 years).[55]

Overall, this study found that 8.1% of survivors of cancers diagnosed after age 18 years develop a subsequent malignancy within a mean follow-up of 7.1 years, with 55% of these survivors dying as a result of the second cancer.

Screening for second primary cancers should be a shared responsibility between primary and oncology care physicians (see the NCCN Guidelines for Detection, Prevention, and Risk Reduction, available at www.NCCN.org). In addition, lifestyle modifications that reduce the risk of second primary cancers (eg, smoking cessation, physical activity, weight loss) should be encouraged.[56] Finally, referral to genetic risk assessment and/or testing should be considered for appropriate survivors, such as those with a cancer diagnosis at a young age or with multiple primary cancers, to identify those with a potential increased risk for second malignancies based on genetic profile.[57] Family cancer history should be regularly updated to reassess hereditary risk based on recent family diagnoses and on any new evidence in the field of cancer genetics that expands the basis for assessing inherited risk. Several NCCN Guidelines (available at www.NCCN.org) include management recommendations for patients with known germline mutations linked to an increased risk for cancer, as listed above in these guidelines.

Psychosocial Effects

Cancer can have positive effects on a significant portion of individuals, including strengthened relationships, a sense of gratitude or empowerment, and an increased appreciation for life.[58-63] Many survivors, however, experience psychologic distress after active treatment, and some experience a combination of positive and negative psychologic effects. Distress can result from the fear of recurrence or death or secondary to physical, social, or practical problems.[58,61,64] In fact, as many as 19% of survivors meet the criteria for post-traumatic stress disorder (PTSD).[58,61,65-67] Practical and social problems of survivors include issues surrounding employment, finances, and health and life insurance.[58,68-71]

Fear of Recurrence

As many as 70% of post-treatment cancer survivors report high levels of fear of cancer recurrence, which can cause significant and enduring distress.[61,72-75] In addition, caregivers report distress from fear of cancer recurrence in their loved one.[76] These fears and their associated distress may cause patients and their caregivers to either avoid appropriate surveillance or to demand more intense surveillance than evidence supports.[75] In addition, survivors with high levels of fear of recurrence are more likely to be depressed and have a lower quality of life.[77]

Employment Issues and Return to Work

Cancer and its treatment often have an adverse effect on work status, performance, and satisfaction.[78] Survivors often take long breaks from or even leave their jobs during treatment, and returning to work after cancer treatment can be critical to restoring normalcy to the lives of survivors. However, survivors may be left with disabilities or late/long-term effects that decrease their employment prospects or ability to perform at their previous levels. Several studies have shown that unemployment rates for survivors are higher than for the general population.[78-81] Furthermore, those survivors who do return to work often encounter difficulties, such as physical or cognitive limitations, fatigue, depression, anxiety, and perceived or real discrimination.[78,82,83]

Several studies have addressed factors that predict a delayed return to work.[84-89] For example, a French population-based study revealed that clinical factors, such as severity of the cancer, receipt of chemotherapy, or the experience of adverse effects, were associated with a delay in

return to work.[88] In addition, a systematic review of cohort studies found that survivors who were older, had a lower education level, or had a lower income were less likely to return to work.[89] Another systematic review identified factors related to the person (eg, symptoms, coping, motivation), environmental supports (eg, family, workplace), and occupation (eg, type of work, job flexibility) that impacted successful return to work after cancer treatment.[90]

Some interventions to enhance return-to-work in cancer survivors have been studied (eg, psycho-education, physical training, vocational counselling).[91] Multidisciplinary interventions that combine vocational counselling with other elements (eg, patient education, patient counselling, behavioral training, physical exercises) may increase rates of return-to-work compared to usual care.

Financial Burden

The LIVESTRONG 2012 Survey found that approximately 33% of working-age survivors went into debt and 3% had filed for bankruptcy.[92] The ACS Study of Cancer Survivors II found that 20% of survivors reported unmet financial needs.[20] A study in Washington state found that patients with cancer have a 2.6-fold increased risk of bankruptcy.[93] In another study, 38% of patients with stage III colon cancer reported financial hardship resulting from cancer treatment, defined as accruing debt, selling or refinancing a home, borrowing money from friends or family, or experiencing a ≥20% decline in annual income.[94] Another recent study found that, in addition to the average >$16,000 excess economic burden that patients feel in the early phases of cancer treatment, survivors (>1 year from diagnosis) have an average annual excess economic burden that exceeds $4,000.[95] Much of this excess burden was because of excess medical expenditures.

Clearly, with lost wages and increased expenses, the financial burden on many cancer survivors is great. Recent data suggest that patients belonging to racial and ethnic minorities are more likely to suffer financial hardship after cancer treatment.[96] Furthermore, the financial burden associated with cancer treatment and survivorship can lower health-related quality of life, increase psychologic distress, and impact adherence to prescribed medications.[97-99]

Standards for Survivorship Care

In 2005, the Institute of Medicine (IOM) and the National Research Council compiled a report entitled, “From Cancer Patient to Cancer Survivor: Lost in Transition.”[24] According to this report, the essential components of survivorship care are:

1. Prevention of new and recurrent cancers and other late effects
2. Surveillance for cancer spread, recurrence, or second cancers
3. Assessment of late psychosocial and physical effects
4. Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns)
5. Coordination of care between primary care providers and specialists to ensure that all of the survivor’s health needs are met.

In addition, the IOM report discusses the importance of policies that ensure access to and health insurance coverage for all aspects of survivorship care, including psychosocial services. Cancer survivors with untreated distress have poorer compliance with surveillance screenings and are less likely to exercise and quit smoking.[100] A 2008 IOM report, “Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs,”[101] concluded that psychosocial screening and care should be a part of the new standard for quality cancer care and should

be integrated into routine care across the trajectory of cancer, which includes the period after active treatment. See the NCCN Guidelines for Distress Management (available online at www.NCCN.org) and *Anxiety and Depression* below for recommendations on screening for and treating distress.

In September 2011, the LIVESTRONG Foundation convened a meeting of experts and stakeholders in the survivorship field to define essential elements of survivorship care. After 2 days of consensus building, the group agreed on the following elements that all medical settings must provide for cancer survivors, either directly or through referral (http://images.livestrong.org/downloads/flatfiles/what-we-do/our-approach/reports/ee/EssentialElementsBrief.pdf):

1. Survivorship care plan, psychosocial care plan, and treatment summary
2. Screening for new cancers and surveillance for recurrence
3. Care coordination strategy that addresses care coordination with PCPs and primary oncologists
4. Health promotion education
5. Symptom management and palliative care

The 2016 Commission on Cancer (CoC) of the American College of Surgeons' accreditation standards for hospital cancer programs (https://www.facs.org/quality-programs/cancer/coc/standards) has a patient-centered focus that includes the development and dissemination of a survivorship care plan for all patients completing primary therapy.

Implementation of these standards for survivorship care has been challenging, and reasons for the difficulties have been described.[102] To move toward the goal of all cancer survivors receiving all essential components of care, advances must be made in: 1) survivorship research; 2) education of health care providers; 3) education and empowerment of survivors; and 4) policies that address reimbursement and resource allocation issues.

Models of Survivorship Care and the Role of Primary Care Providers

Various models have been proposed to facilitate the implementation of all the essential components of survivorship care for the growing population of post-treatment cancer survivors. These include survivorship clinics within academic or community cancer centers, community survivorship clinics run by primary care clinicians, and survivorship care in the primary care setting.[103-106] In each case, survivorship care is delivered by either physicians or by advanced practice clinicians such as nurse practitioners.[107] Each model has advantages and disadvantages, and no one model is clearly the best for all situations.

With the population of cancer survivors growing at a rapid pace, the demand for follow-up care is expected to increase. An increasing proportion of this care will likely be performed by primary care teams. In fact, a systematic review identified specific needs of cancer survivors in the primary care setting, including psychosocial needs, cancer/survivor information needs, and medical needs.[108] Because studies have shown that primary care providers often do not know how best to care for the specific concerns and needs of cancer survivors,[6,109-112] education for primary health care providers regarding appropriate survivorship care will be increasingly important.

A study in the Netherlands found that patients with cancer 2 to 5 years after diagnosis increased their number of consultations with primary care compared with age- and sex-matched controls without cancer by 15% for colorectal cancer ($P < .05$), 24% for breast cancer ($P < .001$), and 33% for prostate cancer ($P < .001$).[113] These survivors also had

more chronic conditions than controls. Although an American study using the SEER-Medicare database showed a smaller increase in primary care use by breast cancer survivors (10% increase in year 4 after diagnosis; $P < .05$),[114] these results show that PCPs are providing a substantial amount of survivorship care. In fact, according to IOM analyses of the 2001 and 2002 National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, approximately one-third of the more than 36 million cancer-related visits to physicians' offices were made to primary care.[24] Furthermore, a nationally representative survey by NCI and the ACS found that >50% of PCPs provide survivors with cancer-related follow-up care, often with co-management by oncologists.[115]

However, in a survey of survivors regarding their preferences for follow-up care, most participants said that the PCP should only provide care if the responsibility was shared with the oncologist.[116] One of the reasons commonly cited for this preference was that survivors believe their PCPs lack the needed expertise to deal with their specific issues. In addition, survivors cited a desire for continuity of care. Additional surveys of survivors of breast cancer in the United States and of survivors of breast, colorectal, and prostate cancer in the United Kingdom found similar preferences for oncologist-driven follow-up care over PCP follow-up care.[117,118] Importantly, however, two randomized trials comparing survivorship care administered by PCPs (provided guidelines outlining appropriate follow-up care) versus oncologists found no difference in disease-related outcomes, including survival.[119,120]

Survivorship Care Plans

Because primary care offices are in fact already caring for cancer survivors, it is critical for information to be shared between oncology and primary care teams. Good communication at the oncology/primary care interface may allow survivors to feel they have the continuity of care they desire. The CoC accreditation standards include the provision of a survivorship care plan at the completion of treatment, as recommended in the IOM report.[24,121] According to the report, the plan should include a personalized treatment summary, information on possible late and long-term effects, information on signs of recurrence, guidelines for follow-up care, identification of providers, recommendations for healthy living, and identification of supportive care resources.

Some data suggest that treatment summaries lead to improvements in outcomes for survivors such as having fewer emotional concerns and more often reporting that their needs have been met.[122] However, a randomized controlled trial of 408 survivors of breast cancer that assessed the effects of survivorship care plans found no differences on patient-reported outcomes, including cancer-specific distress, between patients who received a discharge visit and a care plan and those who received only a discharge visit.[123,124] Criticisms of this trial, including the relevance of its outcome measures, have been published.[125-127] Another trial randomized 221 survivors of stage I-III colorectal cancer to usual care or usual care plus a supportive care package that included a survivorship care plan, educational materials, a needs assessment, an end-of-treatment session, and three follow-up telephone calls.[128] No effects on distress, supportive care needs, or quality of life were seen, although survivors in the care plan group were more satisfied with their care. In addition, a trial in which 12 hospitals were randomized to usual care or to patient-tailored, automated survivorship care plans found that the receipt of a care plan was associated with an increase in symptoms, concern about illness, and emotional impact.[129] No differences in satisfaction with information or care were evident.

A more recent randomized controlled trial tested the role of survivorship care plans in 212 low-income, predominantly Latina survivors of stage 0-III breast cancer.[130] Survivors in the intervention group received the care plan with a treatment summary and a 1-hour counseling session with a trained, bilingual, bicultural nurse who encouraged patient empowerment; the care plan and treatment summary were also delivered to the health care providers of survivors in the intervention group. Patient-reported physician implementation of recommended survivorship care (eg, for depression, hot flashes), the primary trial outcome, was greater in the intervention group than in the usual care group (P = .003). Patient adherence to recommended survivorship care, the secondary outcome, was also greater for the intervention group, but did not reach statistical significance (P = .07). Whereas this trial provides support for the benefits of survivorship care plans, it is impossible to separate the effects of the care plan and the intensive counseling session, and the applicability of the findings to other populations is unknown.

Thus, definitive data supporting the benefits of survivorship care plans are clearly lacking.[131-133] Furthermore, providing a survivorship care plan is time-consuming and resource-intensive and could have unforeseen harms.[127,134]

A survey that included a nationally representative sample of 1130 oncologists found that fewer than 5% of them provide a written survivorship care plan to survivors.[135] The survey also included 1020 PCPs, who were 9 times more likely (95% CI, 5.74–14.82) to have survivorship discussions with survivors if they received a written care plan. A more recent survey reported that 35% of survivors received a written follow-up care plan and 40% received a written treatment summary.[136]

ASCO released a clinical expert statement on cancer survivorship care planning in 2014.[137] The group of experts identified barriers to the successful implementation of survivorship care planning (including the time it takes to complete one, the lack of reimbursement for doing so, and the uncertainty as to whose responsibility it is to prepare the plan) and revised the ASCO survivorship care plan template to help address some of these barriers. In addition, a recent pilot study assessed the use of electronic health records (EHRs) to reduce the time and effort involved with creating care plans.[138] Although many plan elements required manual entry by the oncologist, the median time to complete the plans was only 3 minutes (range 2–12 minutes). Another group reported on a similar initiative to facilitate generation of care plans using EHRs.[139] Care plan creation took a mean 12 minutes (range 10–15 minutes). However, a study in which EHR-based treatment summaries were abstracted and cross-checked revealed that 30% contained ≥1 omissions and 10% contained ≥1 errors, indicating that autopopulation systems will require manual double-checking to insure accuracy.[140]

Although definitive evidence that survivorship care plans improve outcomes is lacking, the NCCN Survivorship Panel currently recommends the use of survivorship care plans if appropriate resources are available. The survivorship care plan should include:

- Summary of treatment received
- Information regarding follow-up care and surveillance recommendations
- Information on post-treatment needs, including information regarding treatment-related effects and health risks when possible (See NCCN Disease-Specific Guidelines)
- Delineation regarding roles of oncologists and PCP and timing of transfer of care if appropriate
- Healthy behavior recommendations

Data from ongoing trials will help inform future recommendations.

Surveillance for Cancer Recurrence

Screening for cancer recurrence is an important aspect of survivorship care. In general, this surveillance is performed by the oncology team. When surveillance is overseen by the primary care team, the oncologist should provide evidence-based recommendations based on currently available guidelines. Specific recommendations for surveillance testing vary between cancer site and stage and individualized patient risk and are not addressed in these guidelines. Please see individual NCCN Guidelines for Treatment of Cancer by Site (available online at www.NCCN.org) for disease-specific surveillance recommendations. Additional lab work, imaging studies, or other studies to evaluate for recurrence should be based on clinical presentation and judgment. The use of radiologic imaging studies (ie, CT) should be based on evidence that early detection of recurrence will improve cancer-related outcomes, because evidence suggests that excess radiation exposure associated with CT imaging may be associated with an increased risk of developing a radiation-associated cancer.[141,142]

Assessment for Effects of Cancer and Its Treatment

All survivors should be assessed at least annually for symptoms related to cancer and prior cancer treatment, with appropriate follow-up care as clinically indicated. This assessment can be done by the oncologist or primary care clinician. Shared, coordinated care between the oncology provider and primary care provider is encouraged. The panel does not assume that all survivorship issues will be addressed at every visit.

Some tools that screen for long-term and late physical and psychosocial effects of cancer and its treatment in survivors have been validated.[143-148] In addition, the NCCN Survivorship Panel created a sample screening instrument that is guideline-specific and can be self-administered or administered by an interviewer. This assessment tool was developed specifically for use in combination with the NCCN Guidelines for Survivorship to help providers deliver necessary and comprehensive survivorship care. Although this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment via validated tools and/or clinical evaluation.

In addition to screening by history and physical examination, care providers should assess the following to determine whether reversible or contributing causes for symptoms exist:

1. Current disease status
2. Functional/performance status
3. Current medications, including over-the-counter medications and supplements
4. Comorbidities, including weight and tobacco/alcohol use
5. Prior cancer treatment history and modalities used
6. Family history
7. Psychosocial factors
8. Disease-specific recommendations for surveillance/follow-up (see NCCN Guidelines for Treatment of Cancer by Site, at www.NCCN.org)

Weight and health behaviors that can modify cancer risk should also be assessed.

This information can also inform about the patient's risk for specific late or long-term effects, including risks for second primary cancers and comorbidities. For example, patients who received pelvic irradiation or surgery are at risk for sexual dysfunction; patients with a history of brain metastasis or cranial irradiation have an elevated risk for cognitive

dysfunction. In general, those who underwent more intensive therapy are at higher risk for multiple late and/or long-term effects. Survivors undergoing certain treatments, such as mantle radiation or certain systemic therapies, may be at increased risk for secondary malignancies. Those survivors who continue to smoke are at increased risk for smoking-related comorbidities and second primary cancers.

Reassessment

Survivors should be followed and reassessed at regular intervals, depending on the nature and severity of late and long-term effects being treated. At each time point, assessment of disease status and ongoing effects of cancer and its treatment should be addressed. In addition, survivors should be periodically rescreened for the development of new late and long-term effects of cancer and its treatment. The outcomes of any interventions for ongoing effects of cancer and its treatment should be evaluated regularly based on best practices and available resources. Outcome assessment may include survivor satisfaction with the effectiveness of the intervention in reducing symptom burden, adequate pain control, receipt of recommended immunizations and preventive care, and improved adherence to guideline recommendations for health behaviors.

Survivorship Research

The IOM survivorship report cites a paucity of longitudinal cohort studies linking specific cancer types or treatments with specific late effects, making it difficult to predict risk for individual patients.[24] Research is needed to increase understanding of the prevalence of, mechanisms of, and risks factors for late and long-term effects of cancer and its treatment. In addition, research is needed to better define interventions that relieve symptoms, restore function, and improve the quality of life of survivors.[149] Finally, research can help better define optimal follow-up and surveillance schedules for cancer survivors after treatment.[150,151]

A recent report highlighted several key gaps in current survivorship research.[152] For instance, more research pertaining to survivors >65 years of age, to survivors of cancers other than breast, and to long-term survivors (>5 years) is needed. In addition, research focused on patterns and quality of survivorship care is lacking.

In June 2012, the ACS, the CDC, the LIVESTRONG Foundation, and NCI held a joint meeting and created an action plan to facilitate the translation of survivorship research into survivorship care.[153] The plan is driven by collaboration between researchers, survivors, clinicians, and public health professionals; the use of technology, such as EHRs; analysis of information from the viewpoints of multiple stakeholders; and the integration and synthesis of knowledge using systematic reviews and meta-analyses.

Recommendations for Specific Effects of Cancer and Its Treatment

Randomized controlled trials have provided evidence for the effectiveness of interventions for cancer survivors to lessen symptoms such as depression, fatigue, pain, sleep disorders, and sexual dysfunction.[151] The NCCN Survivorship Panel used such evidence as the basis for the recommendations in these guidelines. When evidence in survivorship populations was lacking, extrapolation from other populations was used as deemed appropriate. The panel also evaluated existing guidelines from other organizations as appropriate when making recommendations. Otherwise, expert opinion and panel consensus was used to form recommendations. These recommendations and their evidence base are discussed below.

Anthracycline-Induced Cardiac Toxicity

Many cancer treatments, including chemotherapeutics, targeted agents, hormonal therapies, and radiation, are associated with cardiovascular toxicities.[154-159] Cardiovascular sequelae can include arrhythmias, pericardial disease, hypertension, thrombosis, cardiomyopathy/heart failure, and vascular and metabolic issues. Survivors of some cancer types have a markedly increased risk of developing cardiovascular disease compared with non-cancer populations.[160] As a result, a new field, called “Cardio-Oncology,” focused on the cardiovascular health of patients with cancer and survivors has become established.[161,162]

Anthracyclines (eg, doxorubicin, epirubicin, daunorubicin) are used to treat many cancer types, including lymphoma, sarcoma, and breast cancer, and are among the best studied and most common causes of cancer treatment-induced cardiac injury.[163-165] The mechanism by which anthracyclines cause cardiomyopathy is not fully understood, but likely involves the formation of reactive oxygen species (ROS), oxidative injury, and the subsequent induction of apoptosis in cardiac cells.[166] Recently, a role for topoisomerase-IIβ in cardiomyocytes in the production of ROS in response to anthracyclines has been suggested.[167]

Studies suggest that the incidence of clinical congestive heart failure (CHF) after anthracycline-based therapy for adult-onset cancer is <5%.[168-171] For instance, in the NSABP B-31 trial of patients with breast cancer, the rates of symptomatic heart failure after 7 years were 4% in patients treated with anthracycline-based chemotherapy and trastuzumab and 1.3% in those treated with anthracycline-based chemotherapy alone.[170] However, a significantly higher percentage of patients have evidence of subclinical heart failure with reports of asymptomatic left ventricular ejection fraction (LVEF) decline being 9% to 50% in various studies.[168,172-174]

The panel focused specifically on anthracycline-induced cardiac toxicity for this version of the guidelines. Other systemic therapies (eg, HER2-targeted agents, angiogenesis inhibitors, immunotherapies) may cause cardiomyopathy or other myopathies like myocarditis,[155,175] and the panel acknowledges that some of the concepts presented in these recommendations may apply to these other cardiomyopathies. However, it is important to note that less data are available on the cardiomyopathies associated with non-anthracycline systemic therapies and that these cardiomyopathies may differ in nature from those induced by anthracyclines.[155] More research is needed to understand the specific mechanisms of cardiomyopathies associated with newer agents. In addition, the panel emphasizes that the approach to cardiomyopathy may be different than the approach to other cardiac diseases such as coronary artery disease (CAD), which could occur, for example, as a result of radiation therapy.[176]

Panel Considerations Regarding Anthracycline-Induced Cardiac Toxicity

Anthracycline-induced heart failure may take years or decades to manifest. Previous dogma has suggested that anthracycline-induced heart failure portends poor prognosis and is not responsive to therapy. However, emerging data in heart failure due to other types of cardiac injury suggest that signs of cardiac dysfunction can be seen early, prior to the development of symptoms.[177] Additionally, data from these other types of cardiac injury suggest that early intervention with cardioprotective medications results in better long-term cardiac function.[178,179] It is possible that if anthracycline-induced cardiac dysfunction is detected early, it may also be responsive to cardioprotective medications.[155,177-180] In fact, data from a prospective

study that followed 2625 patients who received anthracycline-containing therapy through the survivorship phase suggest that early initiation of heart failure therapy may allow for at least partial recovery of LVEF in this population.[172] In this study, survivors were started on treatment when LVEF decreased by >10 absolute points and was <50%. A full recovery was observed in 11% of treated survivors (LVEF increased to the baseline value), and 71% had partial recovery (LVEF increased by >5 absolute points and reached >50%). In addition, a growing body of preclinical, observational, and pilot research suggests that lifestyle changes, such as weight control,[181-183] dietary modification (either through correcting dietary deficiencies or increasing intakes of various nutrients),[184] and exercise,[185-189] may also be helpful at these early stages, prior to the onset of heart failure symptoms, although more research is necessary.[190,191]

These emerging issues in anthracycline-induced cardiomyopathy are consistent with the changes in the cardiology community's approach to heart failure at large. Clinical heart failure has established risk factors, and the earliest signs of heart failure begin with the accumulation of these risk factors over time, ultimately resulting in structural cardiac abnormalities and later symptomatic heart failure. As a result, more than a decade ago, this evolutionary and progressive nature of heart failure was recognized by cardiologists and incorporated into the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Evaluation and Management of Heart Failure.[192] In 2001, the AHA/ACC guidelines proposed a new classification for heart failure.[192] Traditional classifications only recognized heart failure when patients presented with clinical signs and symptoms. The 2001 classification scheme, in contrast, introduced stages of heart failure beginning before the patient is symptomatic, and emphasized the importance of prevention in heart failure management.

The panel believes that this revised AHA/ACC classification is particularly relevant to cardio-oncology populations. Therefore, in formulating the present recommendations for screening, evaluation, and treatment of cardiac dysfunction in survivors who received anthracyclines during their cancer treatment, the panel took into consideration the updated AHA/ACC classification and guidelines for management of heart failure. For these NCCN Guidelines for Survivorship, the panel emphasized early recognition of cardiac toxicity with the goal of preventing the development of clinical, symptomatic heart failure by addressing other known risk factors for heart failure. In particular, appropriate use of cardioprotective medications, such as neurohormonal antagonists (ie, angiotensin-converting enzyme [ACE] inhibitors, beta blockers), can be considered with the goal of preventing cardiac remodeling over time in some patients. In this respect, the panel emphasizes a thorough clinical screen for heart failure for all survivors with exposure to anthracyclines after completion of therapy, with the additional consideration of an echocardiographic screen in high-risk survivors, as discussed in more detail below. The panel also believes that early involvement of a cardio-oncologist or cardiologist in the care of the cancer survivor is important. Therefore, there should be a low threshold for referral to a cardio-oncologist or cardiologist. In addition, symptoms of heart failure may mimic other conditions such as pulmonary issues and/or cardiac ischemia; therefore, a global approach may be necessary when assessing survivors with decreased cardiorespiratory fitness.[193]

Classification of the Stages of Heart Failure

The revised AHA/ACC classification identifies patients who do not have symptoms associated with heart failure but are either at risk for heart failure (Stage A) or have structural abnormalities of the heart (Stage B).[192] This revised classification has both diagnostic and therapeutic utility, because evidence suggests that treatments prescribed in the

absence of structural heart abnormalities or symptoms can reduce the morbidity and mortality of heart failure in the general population.[155,172,177-180] Left untreated, however, the accumulation of cardiac risk factors leads to injury or stress on the myocardium and generates a cascade of signaling events in the heart. The subsequent change in the geometry and structure of the left ventricle, often referred to as cardiac remodeling (Stage B), may manifest as cardiac hypertrophy or chamber dilatation. In other cases, the result may be decreased cardiac contractility, which can result in decreased LVEF (also Stage B). Cardiac remodeling generally precedes the development of symptoms (by months or even years), continues after symptoms become evident, and contributes substantially to symptom progression and mortality despite treatment. Individuals are considered to have Stage C heart failure when clinical signs and symptoms accompany structural changes to the heart. Stage D is the most advanced stage, with patients showing advanced structural heart disease and significant heart failure symptoms at rest that are refractory to medical therapy; these patients require specialized interventions.

The panel also considered the New York Heart Association's functional classification of heart failure.[194] In this system, which is based on limitations to physical activity and the effect of physical activity on heart failure symptoms, Stage I is similar to AHA/ACC Stage B, while Stages II and III would be considered AHA/ACC Stage C and Stage IV is similar to AHA/ACC Stage D.

Assessment for Anthracycline-Induced Cardiac Toxicity

The panel recognizes a lack of high-quality data to inform the benefits of screening for heart failure among patients treated with anthracyclines. However, the panel believes that all survivors who have completed anthracycline therapy should undergo a clinical evaluation to assess for signs and symptoms of heart failure. The lack of data is illustrated in a 2007 clinical evidence review by ASCO, which concluded that no studies had systematically addressed the benefits of screening adult cancer survivors with a history of anthracyclines for cardiotoxicity.[195] The review also found no direct evidence showing the effectiveness of cardiac treatment on outcomes of asymptomatic survivors.[195] A 2008 multidisciplinary task force from the Children's Oncology Group came to largely similar conclusions regarding screening for cardiotoxicity in survivors of pediatric cancers.[196] Some reasons for the lack of data on screening survivors for cardiotoxicity have been discussed,[197] and, unfortunately, high-quality data have not been forthcoming since ASCO's 2007 review.

In the absence of data, the Children's Oncology Group relied on the collective clinical experience of its panel members and recommended echocardiograms or multiple-gated acquisition (MUGA) scans for survivors of pediatric cancer at the conclusion of treatment and then every 1 to 5 years for life depending on age at treatment, anthracycline dose, and chest irradiation (http://www.survivorshipguidelines.org). An international collaborative supports lifelong echocardiographic surveillance at least every 5 years in survivors of childhood cancer treated with anthracyclines.[198] Although the frequency of cardiac assessment using echocardiograms or MUGA scans in this population has been a matter of debate, there is general support for at least one assessment in children who have completed anthracycline therapy.[199,200]

A 2014 joint expert consensus statement from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommends yearly cardiovascular assessment of adult survivors after the completion of potentially cardiotoxic therapy to look for early signs and symptoms of cardiovascular disease, with cardiac imaging used at the discretion of the clinician.[201] The groups

recommend echocardiogram as the preferred imaging modality, when imaging is performed. The report also acknowledged the limited data available to inform their recommendations.

In 2017, ASCO released a clinical practice guideline for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers.[202] The ASCO panel gave a moderate-strength recommendation (as based on evidence and the balance between harms and benefits) that echocardiogram can be performed for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction at 6 to 12 months after treatment, including survivors with a history of anthracycline therapy. Insufficient evidence prevented the ASCO panel from making a recommendation regarding the frequency and duration of additional surveillance of survivors who are asymptomatic and who showed no signs of cardiac dysfunction on initial assessment.

The NCCN Survivorship Panel defined its screening recommendations based largely on consensus and on the idea that early recognition and treatment of cardiotoxicity can allow for earlier interventions that may improve prognosis (discussed below).

Assessment for Symptoms of Heart Failure

According to the 2013 AHA/ACC guidelines, the cardinal manifestations of clinical heart failure (Stage C) include dyspnea and fatigue (which may lead to limited exercise tolerance) or fluid retention (which may lead to pulmonary and peripheral edema).[203] These symptoms can lead to decreased functional capacity and affect quality of life. Heart failure symptoms associated with fluid retention may also include orthopnea or paroxysmal nocturnal dyspnea. Therefore, the panel recommends a history and physical to look for these symptoms to help identify survivors who might already be symptomatic. These survivors should undergo evaluation with an echocardiogram. If no evidence of structural heart disease is seen, then a workup for other causes of the symptoms is warranted with referral to other specialties (eg, pulmonology or cardiology) as needed. Symptomatic survivors with evidence of structural heart disease require immediate referral to a cardio-oncologist or cardiologist.

Assessment of Comorbidities and Cardiovascular Risk Factors

The panel recommends assessment of comorbidities and other traditional risk factors for heart disease. Furthermore, the oncologic history of the survivor should be reviewed. Chest radiation can increase the risk of ischemic cardiac disease, which can contribute to heart failure.[154,161,204,205] The addition of other cardiotoxic therapies (eg, HER2-targeted agents) to anthracyclines can further increase the risk of heart failure over that seen with the use of anthracyclines alone.[206] Older survivors, those with a higher cumulative anthracycline dose (cumulative doxorubicin dose of 250 mg/m^2 or equivalent), those with underlying cardiovascular disease or risk factors, and those who had a low-normal (50%–54%) baseline ejection fraction are also at increased risk for the development of heart failure. Recent data also showed that being overweight or obese is a risk factor for cardiotoxicity from anthracyclines in breast cancer survivors.[207]

Imaging

When developing these imaging guidelines for screening for cardiac toxicity in survivors with a history of anthracycline exposure, the panel considered several questions: 1) Is the prevalence of structural heart disease high enough to warrant screening of anthracycline-treated survivors?; 2) Is an abnormal echocardiogram post-anthracycline therapy associated with an increased risk for the future development of symptomatic heart failure?; and 3) Does the recognition of cardiac abnormalities and treatment of cardiac risk factors post-anthracycline therapy affect outcomes?

As for the prevalence of structural heart disease in patients treated with anthracyclines, a study of 2625 patients with cancer (mostly breast cancer or non-Hodgkin's lymphoma) assessed LVEF before, every 3 months during anthracycline chemotherapy and during the following year, every 6 months for the next 4 years, and annual after that.[172] Cardiotoxicity, defined as LVEF <50% and decreased by >10 absolute points, was observed in 9% of the study population. In the large randomized controlled NSABP B-31 trial, cardiac function was assessed by cardiac imaging in patients after initial anthracycline-based therapy as a requirement for further treatment with trastuzumab.[208] Over 7% of patients experienced cardiac symptoms and/or a decrease in LVEF of >15% after receiving anthracyclines, thus excluding them from being considered for trastuzumab. It is important to note that this was a clinical trial patient population without significant cardiac risk factors or history of cardiac disease. In a non-clinical trial population of patients with cancer, many may already have cardiac risk factors or actual cardiomyopathy prior to treatment, thus elevating the risk of developing heart failure. Together, these results indicate that a significant proportion of survivors with early-onset Stage B or greater heart failure can be identified with appropriate imaging after therapy. However, it is not clear that these declines in LVEF after anthracycline therapy were associated with an increased risk of developing subsequent heart failure.

Regarding the second question, little is known regarding the natural history of heart failure in survivors with Stage B heart failure post-anthracycline therapy, and the long-term prognosis of survivors with cardiac structural abnormalities following anthracycline exposure is not known. However, regarding the final question, limited evidence suggests that further remodeling of the heart may be able to be mitigated by initiation of cardioprotective medications. A number of observational and retrospective studies have suggested that early intervention with cardioprotective medication may decrease the rate of cardiac remodeling and progression to heart failure. A randomized controlled trial of 135 survivors of pediatric cancer with ≥1 cardiac abnormality found that the ACE inhibitor enalapril reduced left ventricular end-systolic wall stress compared to placebo (P = .03).[180] The authors concluded that any theoretical benefit of reduced left ventricular end-systolic wall stress must be weighed against the side effects of treatment; dizziness or hypotension was observed in 22% of the treatment group versus 3% of those receiving placebo (P = .0003), and fatigue was observed in 10% versus 0% (P = .013) of participants. More recently, a review of 247 patients with cancer and declines in LVEF at the Stanford cardiology clinic found that mean LVEF increased after treatment (most often with ACE inhibitors and beta-blockers) and rose to ≥50% in 77% of patients.[179] In addition, a study of 201 adult patients with cancer, who were treated with anthracyclines and had an LVEF of ≤45%, found that earlier initiation of enalapril (and sometimes the beta-blocker carvedilol) was associated with a higher likelihood of LVEF recovery.[177] In addition, in the larger study by this group (2625 patients), heart failure therapy was initiated in all patients with LVEF <50% that had decreased by >10 absolute points, and 82% of patients experienced a full or partial recovery.[172] In the noncancer setting, a randomized controlled trial of >4200 participants found that treatment of patients with asymptomatic left ventricular dysfunction (ejection fraction ≤35%) with enalapril reduced the incidence of heart failure compared with placebo (20.7% vs. 30.2%; P < .001).[178]

Considering these data, the panel believes that survivors with one or more risk factors who have completed anthracycline therapy can be considered for assessment for structural heart disease with appropriate cardiac imaging within 12 months of the last anthracycline dose.

Approximately 98% of cases of cardiotoxicity are observed within the first year after treatment.[172] Risk factors to consider include age >65 years, a high cumulative anthracycline dose, underlying cardiovascular disease/risk factors, or a low-normal baseline LVEF.[165]

The panel recommends two-dimensional echocardiogram, coupled with Doppler flow studies, as the cardiac imaging modality of choice when imaging is performed. This technique is widely available and inexpensive, gives no radiation exposure, and is the most useful diagnostic test in the evaluation of patients with possible heart failure.[209,210] It can recognize early stages of heart failure by revealing abnormalities of the pericardium, myocardium, and heart valves.[203] While radionuclide ventriculography (also called radionuclide angiography or MUGA scan) can provide accurate measurements of left ventricular size and function and assessment of ventricular enlargement, it cannot assess valvular abnormalities or cardiac hypertrophy and exposes patients to radiation. Other imaging modalities for the assessment of heart failure have been reviewed elsewhere.[209,211]

In agreement with these guidelines, ASCO's guidelines that address monitoring of cardiac toxicity after treatment in survivors of adult-onset cancer indicate that echocardiogram can be considered for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction, including survivors with a history of anthracycline therapy.[202]

Biomarkers

The panel recognizes the growing body of literature suggesting the possible utility of cardiac biomarkers (specifically troponin) as a non-invasive marker of cardiotoxicity. The panel believes that more prospective, multi-institutional studies are needed to make definite recommendations. The optimal timing of troponin assessment in relation to completion of chemotherapy is currently unclear, the cut-off point for a positive test is undefined, and the optimal assay platform remains to be determined. In addition, the sensitivity and specificity of troponin I levels for predicting cardiotoxicity are fairly low, reported at 48% (95% CI, 0.27–0.69) and 73% (95% CI, 0.59–0.84), respectively.[212] A systematic review of the role of post-treatment cardiac troponins as predictive markers of anthracycline-induced left ventricular dysfunction revealed few studies and inconsistent data.[213] The utility of other potential cardiac biomarkers have been reviewed elsewhere.[211]

Treatment of Anthracycline-Induced Cardiac Toxicity

Progression of heart failure is accelerated with accumulation of risk factors. Injury or stress on the myocardium (such as during and after treatment with anthracyclines) can lead to activation of endogenous neurohormonal systems, which play a critical role in cardiac remodeling and therefore progression to Stage B heart failure.

The panel recommends that heart failure risk factors, including hypertension, obesity, metabolic syndrome, and diabetes, be addressed in all survivors who have completed anthracycline therapy. In addition, survivors with a history of anthracycline therapy should be advised to engage in regular physical activity, eat a healthy diet, and avoid behaviors that may increase the risk of heart failure or cardiovascular disease (eg, tobacco or illicit drug use). Physical activity has been shown to improve control of hypertension and to slow cardiac remodeling in patients with heart failure.[214] Involvement of the survivor's primary care provider in managing risk factors is encouraged.

The panel recommends that a low threshold be established for referral to a cardio-oncologist or cardiologist for all patients previously treated with an anthracycline. Additional recommendations for each stage of heart failure are discussed below.

Treatment of Stage A Heart Failure

Stage A heart failure recognizes several well-established risk factors, each of which contribute to early stages of heart failure. These include hypertension, CAD, diabetes mellitus, a family history of heart failure, or a history of cardiotoxins such as anthracyclines. Therefore, all survivors with exposure to anthracyclines have, by definition, at least one risk factor that predisposes them to cardiac disease and should be treated as appropriate. Other anti-cancer systemic therapies are potentially cardiotoxic and may increase the risk of cardiac disease.[157] Involvement of the survivor's PCP in the management of survivors with cardiac risk factors is encouraged. Management can include addressing underlying risk factors, recommending physical activity and healthy dietary habits, and referral to a cardiologist.

Treatment of Stages B, C, and D Heart Failure

The panel recommends referral to a cardiologist for all survivors with Stages B, C, or D heart failure. The sooner that treatment is initiated, the more likely it is to be successful.[177]

Anxiety, Depression, and Distress

Cancer survivors are at elevated risk for anxiety, depression, and other forms of psychosocial distress and mental health issues. A large nationwide matched cohort study in Sweden found that mental health disorders can persist in survivors for as long as 10 years post-diagnosis.[215] Unfortunately, the majority of community-based physicians report insufficient psycho-oncology services and difficulty in the referral process, such that psycho-oncology needs often do not receive the attention they need.[216]

Many cancer survivors may not have psychiatric clinical diagnoses but still have symptoms that can have a negative impact on quality of life and require further evaluation and intervention. Such survivors have what the NCCN Guidelines for Distress Management (available at www.NCCN.org) define as distress: "a multifactorial unpleasant experience of a psychological (ie, cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment." Distress, often related to fear of recurrence, is common in survivors and can negatively impact quality of life.[16,61,217-219] Survivors with untreated, uncontrolled emotional distress are less likely to adhere to recommended surveillance and are less likely to engage in health-promoting activities, such as exercise and smoking cessation.[100] Sometimes these individuals develop thoughts of ending their lives; the incidence of completed suicide among patients with cancer and survivors in the United States is about twice that of the general population.[220-225]

Risk factors for psychosocial distress in cancer survivors include persistent problems with physical health; enduring physical signs of cancer/negative body image; a tendency towards self-criticism; non-white race; low educational, financial, or social support; financial concerns; being unmarried; and having survived multiple primary cancers.[226]

Fear of recurrence, with persisting worry and distress sometimes reaching levels of clinical anxiety, is common, occurring in up to 80% of cancer survivors.[226] This fear can increase at times of routine cancer surveillance testing or with physical symptoms that may or may not be related to the cancer diagnosis.[16,61,217-219,227] Anxiety and/or depression can also occur in survivors secondary to physical compromise, social isolation, or work and financial problems that result from cancer treatment.[58,61,64,219,228] These challenges are underscored by the inevitable decreased medical and interpersonal support following completion of treatment and transition to the surveillance stage.[151]

Anxiety and/or depression affect up to 29% of survivors.[58,61,65-67,229,230] Studies also show that 17% to 38% of survivors have PTSD symptoms while 5% to 12% meet full criteria.[226] A meta-analysis determined the log odds ratio for a PTSD diagnosis in cancer survivors compared with non-cancer controls to be 1.66 (95% CI, 1.09–2.53).[231] In one longitudinal study, 12% of survivors reported that their PTSD symptoms resolved over 5 years, whereas 37% reported that their symptoms persisted or worsened during that time.[66] PTSD symptoms in survivors can fluctuate over time, because of other events or trauma occurring in the survivor's life.

The panel's recommendations for the management of anxiety, depression, and distress in survivors adhere to the following general structure: screen regularly, refer those with needs beyond the clinician's scope of expertise, and ensure the safety of the survivor. Referral to mental health services may include a psychiatrist, psychologist, advanced practice clinicians, and/or social worker, or management with oncology or primary-care support and/or online, telephone-based, or community support resources.

For additional information regarding anxiety, depression, and distress in patients with cancer, please see the NCCN Guidelines for Distress Management (available at www.NCCN.org). The NCCN Guidelines for Survivorship complement the NCCN Guidelines for Distress Management. These guidelines may be modified to accommodate the individual circumstances of cancer survivors.

Screening for Anxiety, Depression, and Distress

Psychosocial problems are pervasive in survivors and many distressed survivors may not appear distressed. Therefore, all survivors should be screened for anxiety, depression, and distress, especially at times of disease transition, surveillance, significant loss, major life events, and social isolation. Survivors who present with multiple somatic complaints should also be screened as part of their overall work-up.

The panel lists questions that can be asked of survivors to determine if they have been feeling nervous/anxious or sad/depressed and whether these moods are impacting quality of life. The panel does not recommend use of the NCCN Distress Thermometer (DT) as an initial screening tool in survivors, because studies generally find that it lacks sufficient sensitivity and specificity in this population.[232-239] For example, a study of 120 survivors of adult-onset cancer found that the DT had a sensitivity of 47.6% and 51.7%, using cutoff values of 5 and 4, respectively.[237] The panel therefore recommends supplemental screening when the DT is used as an initial screening tool. Survivors with an elevated level of distress by the DT should still be asked the initial screening questions provided in these guidelines. These more specific questions allow the clinician to determine what particular psychological symptoms are affecting the survivor and may provide more sensitivity and specificity than the DT in identifying distressed survivors who need treatment or additional resources.

Diagnosis of Anxiety, Depression, and Distress

Oncologists and PCPs generally do not feel comfortable diagnosing major psychiatric disorders, nor should they be doing so. Therefore, these guidelines do not specify the full diagnostic criteria for depression, anxiety, PTSD, etc. Instead, the guidelines list the essential criteria for screening psychiatric diagnoses that are most common in survivors and some key symptoms from the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5[240]). The panel's intent is to provide information to facilitate initial steps in providing care and decisions about referrals rather than to provide guidelines for psychiatric diagnosis and extended treatment.

Safety Evaluation

Cancer survivors with anxiety, depression, PTSD, or other psychiatric disorder that is impacting their quality of life should undergo a safety evaluation to assess whether they are a danger to themselves or others. Risk factors to assess include previous attempts at suicide, a family history or other exposure to suicide, not having a spouse or live-in partner, social isolation, perceiving self as a burden, recent loss of an important person, a relationship breakdown, chronic illness or recent change in health status, alcohol or other substance abuse, loss of rational thinking, feeling hopeless, and access to firearms/weapons or potentially lethal medications (opioids, benzodiazepines [BZDs], antidepressants). Males and those in their late teens or older than age 55 years are also at elevated safety risk.

Survivors with suicidal or homicidal thoughts or a plan and/or with multiple other risk factors are at an elevated risk of danger to self or others. In addition, clinical judgment or the inability of the survivor to care for his- or herself may also indicate an elevated safety risk. These survivors require an emergency intervention that includes arranging to have weapons secured, possibly calling 911, and following state mental health emergency plans or referring to emergency psychiatric evaluation procedures onsite.

Survivors with intermittent suicidal ideation or thoughts that they might be better off dead, but no plan to harm themselves nor thoughts of endangering others, are at lower safety risk, as are those with fewer risk factors. A safety plan should be developed with these survivors and should include immediate referral for mental health evaluation based on urgency, regular follow-up and monitoring until psychiatric care is in place, and having the survivor agree to contact a health care provider, call 911, or go to an emergency room if suicidal thoughts increase or change.

Management of Anxiety, Depression, and Distress

Survivors with suspected major psychiatric diagnoses, including mania or psychosis, those with an extensive psychiatric history, and those with a moderate to high safety risk should be referred for psychiatric evaluation and treatment. Survivors with substance abuse issues should be referred to a substance abuse specialist. Survivors with moderate to severe intensity major depression, generalized anxiety, panic, or PTSD should also be referred for evaluation and treatment by a mental health professional; however, pharmacologic and/or nonpharmacologic treatments, as described below, can also be considered for these survivors.

All survivors should have treatable contributing factors (eg, pain, sleep disturbance, fatigue, metabolic/endocrine problems, other medical comorbidities) addressed. Reassurance should be given that symptoms of worry, stress, anxiety, and depression are common problems among cancer survivors and that these symptoms can be treated. In addition, support and education should be provided to the survivor and family regarding normal recovery phases after treatment, common stresses, distress, and fears, and strategies for managing uncertainty and distress. Finally, resources should be provided for social support networks and specific social, emotional, spiritual, intimacy, and practical needs. Additional treatment options are described below.

Nonpharmacologic Treatments

Treatment recommendations for managing depression, anxiety, and distress include a strong recommendation for regular physical activity, which has been shown in clinical trials and meta-analyses to have significant effects in reducing symptoms of anxiety and depression among survivors.[241,242] In fact, evidence suggests that exercise and antidepressants (discussed below) may be equally effective in the treatment of depression.[243]

Psychotherapy, and in particular cognitive behavioral therapy (CBT) and problem-solving therapy, have been shown to be effective at treating depression, anxiety, and PTSD in the general population.[244-248] Therapy, including CBT, has also been shown to be effective at reducing anxiety, depression, and distress in the survivorship population.[151,249-255] One study found a psychoeducation program that included 3 telephone-based psychotherapy sessions reduced the severity of fear of recurrence in melanoma survivors.[256]

Other alternative treatments (eg, yoga, tai chi, mindfulness) may also be helpful to survivors suffering from distress, although data showing their effectiveness are limited.[257-260] Mindfulness is possibly the best-studied alternative treatment for psychological problems in cancer survivors.[261-265] For example, a randomized controlled trial of 322 survivors of breast cancer found that a 6-week mindfulness-based stress reduction (MBSR) program reduced anxiety and fear of recurrence and also improved fatigue.[265] In non-cancer settings, weight loss interventions have improved depression in obese individuals,[266] although evidence in cancer or survivor populations is lacking.

Pharmacologic Treatments

Cancer survivors use medication for anxiety and depression at a rate about twice that of the general population.[267] Antidepressants and antianxiety drugs have been shown to be beneficial for the treatment of depression and anxiety in patients with cancer.[268-275] Evidence of these effects is lacking in cancer survivors, although these drugs have been studied in this population for their effects on vasomotor symptoms (see *Menopause-Related Symptoms*). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can therefore be used in survivors with moderate to severe intensity major depression, generalized anxiety, panic, or PTSD. SNRIs should be considered for concomitant pain or concomitant hot flashes (also see *Menopause-Related Symptoms*). Psychotropics with cytochrome P450 interactions (ie, fluoxetine, paroxetine, sertraline, bupropion, fluvoxamine, nefazodone) should be avoided in survivors taking tamoxifen. Pure SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6 and should be used with caution for women on tamoxifen (see *Menopause-Related Symptoms* for a discussion of psychotropics and cytochrome P450 interactions).[276]

Survivors should be counseled that it may take up to 2 to 6 weeks at a therapeutic dose for SSRIs and SNRIs to take effect, and that a trial of several different drugs may be needed to find the best option for an individual. BZDs (ie, clonazepam, lorazepam) can be used for acute anxiety relief or while waiting for antidepressants to take effect. The BZD dose should be adjusted once SSRIs or SNRIs are fully effective and symptoms are partially or completely abated. Survivors should be also counseled that symptoms of withdrawal may occur should any of the above-mentioned medications be abruptly discontinued. Referral to a mental health professional should be considered if the response to first-line treatment is inadequate.

Cognitive Dysfunction

Cognitive impairment is a common complaint among cancer survivors and may be a consequence of the tumors themselves or of the direct effects of cancer-related treatment (eg, chemotherapy, radiation therapy). This symptom may be especially prominent in survivors of primary central nervous system (CNS) cancers or those with brain metastases, but survivors who never had brain involvement may also report difficulties in cognition.[277] For some survivors, symptoms persist long-term.[278] When severe, the presence of cognitive dysfunction can impact quality of life and function. Cognitive dysfunction is most

commonly connected with chemotherapy (sometimes referred to as "chemobrain"), but evidence suggests that therapies other than chemotherapy, such as endocrine therapy, radiation, and surgery may be associated with cognitive impairments.[279-286] A national cross-sectional study found that a history of cancer is independently associated with a 40% increase in the likelihood of self-reported memory problems.[287]

Cancer-related cognitive changes have primarily been studied in patients with CNS cancer, breast cancer, and lymphoma, and those who have undergone hematopoietic stem cell transplant (HSCT), with a reported incidence ranging widely from 19% to 78%.[278,288-302] In the 2010 LIVESTRONG survey of 3108 post-treatment survivors of a variety of cancer types, approximately 46% of respondents perceived cognitive deficits.[303] Deficits commonly occur in the domains of executive function, learning and memory, attention, and processing speed.[278,301]

Growing evidence supports the patient experience of cognitive dysfunction associated with cancer and its treatment.[304-306] In one meta-analysis of 17 studies, women treated with chemotherapy for breast cancer 6 or more months previously (n = 807) had lower functional abilities than those not treated with chemotherapy (n = 291).[292] These deficits were limited to verbal (eg, word-finding) and visuospatial (eg, copying complex images) abilities. However, when compared with their pre-chemotherapy baseline, no differences were noted among patients complaining of cognitive dysfunction. In another study, cognitive function was compared among 196 long-term survivors of breast cancer treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) who were, on average, 21 years out from diagnosis, and 1509 control patients with no history of cancer.[307] The chemotherapy group did significantly worse on several neuropsychological tests (eg, immediate and delayed verbal memory, executive functioning, psychomotor speed). Another study compared 101 patients who underwent an HSCT with 82 patients treated with a non-myeloablative therapy; both groups showed mild cognitive impairments at baseline.[308] Although no significant differences in cognitive dysfunction were identified at 2-year follow-up, patients who underwent HSCT had poorer performances in several areas, including executive and psychomotor functions and attention.

The correlation between patient reports of cognitive decline and results of neuropsychological testing has not been consistently demonstrated, possibly because of various definitions of cognitive dysfunction and differences in the statistical analyses across studies.[301] However, a study of 189 breast cancer survivors found that memory and executive function complaints, present in approximately 20% of the cohort, showed a statistically significant association with results of domain-specific neuropsychological tests.[309] A study that included 291 participants with stage I-III colorectal cancer before or after surgery and healthy controls found that 45% of patients with cancer had cognitive impairment versus 15% of the control group (odds ratio, 4.51; $P < .001$), with the largest effects seen in complex processing speed, attention/working memory, and verbal learning efficiency.[284] Results of this study suggest that the cancer diagnosis itself and/or the surgical intervention contribute to cognitive dysfunction because these patients had not received chemotherapy at the time of neurocognitive testing.

Brain imaging has demonstrated abnormalities in patients who have had chemotherapy following cancer treatment,[278,281,291,310,311] and functional MRI studies show that changes in brain activity accompany cognitive complaints or cognitive deficits in survivors.[311-313]

The underlying mechanisms that might increase the risk for cancer-related cognitive changes are not known. Studies have reported elevated levels of cytokines or DNA damage as some of the possible mechanisms.[314] Structural studies have supported the hypothesis that neurotoxicity resulting in damage to white matter of the brain may play an important role in cognitive deficits after chemotherapy treatment.[278,281,291,310,311] In addition, fatigue and depression, common in cancer survivors, may negatively influence cognitive function, although several studies have found that cognitive dysfunction does not correlate with mood.[307,315] Psychosomatic effects can also contribute, as evidenced by a study of patients to be treated with chemotherapy that found that those who were informed of the possible cognitive side effects were more likely to report cognitive dysfunction and perform worse on neuropsychological testing than uninformed patients.[316] A better understanding of the mechanisms that cause cancer-related cognitive impairment is essential for the development of treatments to improve cognitive function and quality of life in patients with cancer and survivors.[277,317,318]

In October 2006, the International Cognition and Cancer Task Force (ICCTF) was formed, comprising a multidisciplinary group of health professionals and health advocates. The mission of ICCTF is to advance understanding of the impact of treatment-related cognitive and behavioral functioning in patients with non-CNS cancers.[319] The group published recommendations regarding neuropsychological testing, defining cognitive impairment/changes, and future study design.[318]

These guidelines address cognitive function of survivors with non-CNS malignancies who did not have CNS-directed therapies.

Assessment and Evaluation for Cognitive Dysfunction

Patients who report cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, including depression, pain, fatigue, and sleep disturbance. Some medications can also contribute to cognitive impairment. Therefore, current medications, including over-the-counter medications and supplements, should be reviewed.

For those who present with concomitant focal neurologic deficits and those whose symptoms evolve to include these findings, imaging is indicated to rule out structural abnormalities (ie, brain or CNS disease). In addition, imaging in the absence of focal findings may be appropriate for patients deemed to be at high risk for recurrence or metastatic disease involving the CNS.

Unfortunately, no effective brief screening tool for cancer-associated cognitive dysfunction in the asymptomatic cancer survivor currently exists. The Mini-Mental State Examination (MMSE[320]) and similar screening tools lack adequate sensitivity to detect a subtle decline in cognitive performance. Instead, the panel listed several questions that can help clarify the nature of the impairment, including inquiries about the ability to pay attention, find words, remember things, think clearly, and perform functions. The time of onset and the trajectory over time should also be assessed.

Management of Cognitive Dysfunction

Survivors benefit from validation of their symptom experience and should be reassured that, in most survivors, cognitive dysfunction does not worsen over time. In fact, data from breast cancer survivors suggest that symptoms may improve over time.[280] The panel recommends the use of nonpharmacologic interventions whenever possible, with pharmacologic interventions as a last line of therapy in survivors for

whom other interventions have been insufficient, as discussed in the following sections. Additional recommendations for cognitive dysfunction in older adults can be found in the cognitive function section of the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org).

Nonpharmacologic Interventions for Cognitive Dysfunction
Prospective data to inform the use or potential benefits of non-pharmacologic interventions for cancer survivors who complain of cognitive dysfunction are limited. Practical suggestions include instruction in self-management and coping strategies (eg, using planners, reminder notes, and/or smart phone technology; keeping items in the same place), which the panel believes can be very helpful to patients. Discontinuation or limitation of use of medications known to cause or contribute to cognitive impairment should be attempted. Management of depression/emotional distress, pain, sleep disturbances, and fatigue should be provided. In fact, a recent study showed that CBT for fatigue was effective at reducing self-reported cognitive disability and concentration problems in 98 severely fatigued cancer survivors.[321]

CBT for cognitive dysfunction may also help some survivors. In one small study, CBT was evaluated in 40 breast cancer survivors using a waitlist control trial design.[322] Although overall quality of life improved with the intervention, statistically significant improvement was noted only with verbal memory, not with self-reports of daily cognitive complaints. Another study of 98 severely fatigued survivors randomized to CBT or wait-list found that CBT decreased self-report of cognitive disability.[321] However, no difference in neuropsychological test performance was observed. Finally, a study of CBT delivered by video conference in 47 survivors of breast cancer found that CBT led to improvements in self-reported cognitive impairment and in neuropsychological processing speed compared with supportive therapy.[323]

Routine physical activity should be encouraged. Substantial evidence shows that physical activity enhances cognitive function in elderly people in general, although only few studies specific to cancer survivors have been reported.[324-327]

Cognitive training (ie, brain games) can also be considered. Cognitive training has demonstrated benefits in self-reported and objectively assessed cognitive function, including memory, executive function, and verbal function.[325,328] One study randomized 157 breast cancer survivors to web-based cognitive training with telephone support or to waitlist control.[329] Verbal learning and results on a working memory test showed statistically significant improvement in the cognitive training group, but no improvements were seen for an objective measure of working memory and a measure of perceived cognitive functioning. Another study used a 5-session, small-group intervention of psychoeducation and cognitive exercises in 48 breast cancer survivors.[330] Compared to survivors randomized to a waitlist control group, survivors in the intervention arm experienced improvements in self-reported cognitive complaints and memory functioning on neurocognitive testing. A larger study of 242 survivors with self-reported, persistent cognitive symptoms after chemotherapy for non-CNS cancers found that survivors randomized to a web-based cognitive training program had statistically significant improvements in perceived cognitive impairment immediately and 6 months after the intervention.[331] Improvements in anxiety, depression, fatigue, and stress were also seen after the intervention, which used adaptive exercises that targeted cognitive domains, such as visual precision, working memory, and visual processing speed.

Relaxation, stress management, meditation, and yoga can also be considered. A small pilot randomized controlled trial of 71 fatigued survivors showed that MBSR improved some domains of cognitive function.[332] A larger study also found improvements in cognitive symptoms after a mindfulness-based approach.[263] Two studies have assessed the effects of yoga on cognition in survivors.[333,334] Both reported improvements in patient-reported cognitive dysfunction.

Cognitive rehabilitation, including occupational therapy and speech therapy, may also be useful. Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for individuals who note the impact of specific functional limitations, such as word finding, comprehension, and task completion, on work performance, quality of life, or role expectations.[335]

Finally, neuropsychological evaluation can be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.

Pharmacologic Interventions for Cognitive Dysfunction

If nonpharmacologic interventions have been insufficient, consideration of a trial of psychostimulants such as methylphenidate or modafinil is reasonable, although data informing the efficacy of these agents are lacking. Trials assessing the effects of methylphenidate have reported mixed results.[336] For example, a randomized, placebo-controlled, double-blind trial found that d-methylphenidate had no effect on neuropsychological test scores.[337] In contrast, a randomized, double-blind, crossover trial of child survivors of acute lymphoblastic leukemia or brain tumors showed that methylphenidate was more effective than placebo at improving attention, cognitive flexibility, and processing speed.[338]

Results of studies on modafinil are more consistent. A randomized controlled trial assessing the efficacy of modafinil for fatigue and cognitive function in breast cancer survivors found significantly greater improvement in memory and attention among patients receiving modafinil than in the placebo group.[339] Similarly, a double-blind, randomized, cross-over trial also in breast cancer survivors found that participants receiving modafinil performed significantly better on cognitive tests of attention and psychomotor speed.[340] Benefits with treatment were also noted among patients with primary brain tumors.[341]

Fatigue

Note: The Discussion text regarding fatigue in survivors has been adapted from the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org).

NCCN defines cancer-related fatigue as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”[342] Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.[343-345] According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[346,347] Cancer survivors report that fatigue continues to be a disruptive symptom after treatment ends,[348-356] with studies showing that 17% to 29% of cancer survivors experience persistent fatigue for years after the completion of active therapy.[357-359] In fact, one study of 6011 long-term cancer survivors found that 39% to 51% (depending on tumor type) were classified as fatigued after completion of the Fatigue

Assessment Scale compared with 21% of a representative normal population.[360]

Persistent cancer-related fatigue affects quality of life, because individuals become too tired to fully participate in the roles and activities that make life meaningful.[350,361] In fact, severe fatigue in survivors of Hodgkin lymphoma is associated with a decreased likelihood of employment.[362] Disability-related issues are also relevant for cancer survivors, because obtaining or retaining disability benefits from insurers is often difficult for patients with cancer-related fatigue. Identification and management of fatigue remains an unmet need for many cancer survivors.

The specific mechanisms involved in the pathophysiology of cancer-related fatigue are unknown. Proposed mechanisms include pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation.[363-368] Several studies have focused on the cause of fatigue, especially in cancer survivors with no evidence of active disease, and have suggested that persistent immune system activation and chronic inflammatory processes may be involved.[348,369-371] Evidence supporting these mechanisms is limited.

Screening for Fatigue

All survivors should be screened for fatigue to ensure that those with moderate to severe fatigue are identified and treated promptly and effectively. Because fatigue is a subjective experience, clinicians must rely on patients' descriptions of their fatigue level. The panel recommends the use of a severity scale, with survivors being asked, "How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?" Alternately, screening can be performed with patients asked to rate their fatigue as none, mild, moderate, or severe. Scores of 0 to 3 or none to mild fatigue require no further assessment or interventions; these patients should be rescreened at regular intervals. Patients with scores of 4 or greater or indicating moderate or severe fatigue should be evaluated further. Studies in patients with cancer have revealed a marked decrease in physical functioning at a reported fatigue level of 7 or higher on the 0 to 10 scale.[372,373]

Evaluation for Moderate to Severe Fatigue

When fatigue is rated as moderate to severe, with a score of 4 to 10, a more focused history and physical examination should be conducted. A thorough history is warranted, because the recommended workup for fatigue differs according to the timing of fatigue onset in relation to the completion of active therapy and the presence of predisposing factors and other symptoms. Fatigue has a variable natural history, with some patients complaining of only mild levels of fatigue even during active therapy and others experiencing severe fatigue for years after treatment completion.

In general, mild to moderate levels of fatigue that persist for 6 to 12 months after the completion of therapy do not warrant an extensive workup, unless other symptoms are present. Conversely, when moderate to severe fatigue begins after or worsens during this period, or when other symptoms are present, such as pain, pulmonary complaints, or unintentional weight loss, a more extensive workup is warranted to screen for the presence of metastatic disease or other comorbidities. Referral to a pulmonologist should be made for pulmonary complaints.

Regardless of fatigue onset, it is always relevant to screen for common contributing factors such as emotional distress, sleep disturbance, pain, and the use of prescriptions or over-the-counter medications or supplements. Possible medical causes of fatigue, including cardiac

disease and hypothyroidism, should also be assessed. Disease and treatment considerations also affect recommendations for screening, such as the inclusion of echocardiograms for patients who received cardiotoxic treatments and thyroid screening for patients who received radiation to the neck or thorax or agents such as immunotherapies or small molecule tyrosine kinase inhibitors.

Management of Fatigue

Several interventions and strategies have been shown to help alleviate fatigue and reduce distress caused by this symptom in patients with cancer and survivors; recommended strategies and interventions are described herein. For additional information about fatigue in survivors and patients with cancer, please see the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org). These guidelines may be modified to fit the individual survivor's circumstances.

Treatment of Contributing Factors

Management of fatigue in survivors first includes the treatment of contributing factors such as pain, distress, anemia, and sleep disturbances (more information on the treatment of pain, anxiety/depression, and sleep disorders in survivors can be found throughout these guidelines). In a recent randomized controlled trial of 152 fatigued patients with advanced cancer, treatment of accompanying physical symptoms, including pain, nausea, vomiting, and shortness of breath, resulted in a significantly higher impact on general fatigue, activity, and motivation than usual care.[374]

Patient and Family Education and Counseling

Education and counseling can be beneficial in helping patients cope with fatigue. Understanding typical patterns of fatigue during and after treatment can help patients set reasonable expectations regarding improvements in energy after the completion of cancer therapy and can help allay concerns that persistent fatigue after the completion of therapy is evidence of disease recurrence. Counseling can help patients develop strategies for self-monitoring of fatigue and techniques such as energy conservation that may be helpful in the immediate post-treatment period.[375]

Physical Activity

Activity enhancement is a category 1 recommendation for the management of fatigue in survivors. Improving strength, energy, and fitness through regular exercise, even a moderate walking exercise program, has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase tolerance for physical activity. Therefore, survivors with moderate to severe fatigue should be encouraged to maintain adequate levels of physical activity (category 1). Robust data support the efficacy of increased physical activity for reducing fatigue in patients with cancer and survivors.[258,376-387] A recent meta-analysis of randomized controlled trials found that cancer survivors who participated in exercise interventions, either during or after treatment for cancer, experienced significant improvements in fatigue compared with patients randomized to the control group.[388] Another meta-analysis of 44 studies, including 3254 cancer survivors, concluded that moderate-intensity resistance exercise among older cancer survivors reduced fatigue.[377] Finally, a meta-analysis of randomized clinical trials in adults with cancer found that exercise is effective at reducing cancer-related fatigue during and after treatment.[386]

Survivors at a higher risk of injury should be referred to a physical therapist or exercise specialist (also see *Healthy Lifestyles*, below).

Psychosocial and Other Interventions

Psychosocial interventions, such as CBT, psycho-educational therapy, and supportive expressive therapy, including support groups, counseling, and journal writing (all category 1 recommendations), have also been shown to reduce fatigue in cancer survivors, although data are not entirely consistent.[265,389-394] Several meta-analyses have evaluated the role of psychosocial interventions in reducing fatigue.[386,389,393,395] For example, Kangas et al[393] reported a weighted pooled mean effect of −0.31 for psychosocial interventions on fatigue in an analysis of 3620 patients with cancer from 41 studies. Jacobsen et al[395] analyzed 30 randomized controlled trials and found a significant effect size (dw) for psychological interventions (dw, 0.10; 95% CI, 0.02–0.18) but not for activity-based programs (dw, 0.05; 95% CI, −0.08–0.19). A meta-analysis by Duijts et al[389] reported that, like exercise programs, behavioral techniques, including cognitive therapy, relaxation techniques, counseling, social support, hypnosis, and biofeedback, are beneficial in improving fatigue among patients with breast cancer during and after treatment (standardized mean difference [SMD], −0.16).

Several published studies support the conclusion that CBT interventions designed to optimize sleep quality in patients with cancer may also improve fatigue.[396-399] Two randomized clinical trials of patients who reported chronic insomnia in the survivorship phase demonstrated improvements in both sleep and fatigue after 4 to 5 weekly behavioral therapy sessions.[390,391,400] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[396,398] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[399,401] The American Academy of Sleep Medicine (AASM) has recommended 3 specific therapies for chronic insomnia in healthy individuals: relaxation training, CBT, and stimulus control therapy.[402]

Acupuncture and acupressure have been studied for the treatment of fatigue in patients with cancer and survivors.[403-410] A pilot study in 30 breast cancer survivors found that acupuncture resulted in a significant reduction in fatigue after 2 weeks.[408] In addition, a phase 3 randomized, single-blind clinical trial in 424 breast cancer survivors found that self-administered relaxing acupressure reduced persistent fatigue and improved sleep quality and quality of life.[410] Although results of studies are mixed and many compared acupuncture to usual care rather than sham acupuncture or another active comparator, the panel believes acupuncture is an acceptable option that may improve symptoms for survivors with moderate to severe fatigue.

Pharmacologic Interventions

Psychostimulants, such as methylphenidate, are also used to treat fatigue, although data regarding their use to treat fatigue in cancer survivors are very limited. A 54% response rate to methylphenidate was reported in a phase II trial of 37 breast cancer survivors.[411] A randomized trial in 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the dexmethylphenidate arm.[412] A recent meta-analysis of 5 randomized controlled trials of patients with cancer found limited evidence for the efficacy of 4 or more weeks of methylphenidate treatment for cancer-related fatigue (mean difference, −3.70; 95% CI, −7.03 to −0.37; P = .03).[413] However, another meta-analysis identified 7 trials of methylphenidate and concluded that it was superior to placebo for the treatment of cancer-related fatigue.[414] A Cochrane review found that methylphenidate was likely effective for cancer-related fatigue and warrants further study.[415] However, a second comprehensive meta-analysis did not support this finding, nor did it support the use of pharmacologic interventions for the treatment of cancer-related fatigue.[386]

Other drugs, including modafinil, have also been studied for post-treatment fatigue.[416,417] In particular, a large phase III trial of 631 patients receiving chemotherapy suggested that modafinil is beneficial in patients with severe fatigue.[417] However, a placebo-controlled, double-blind randomized controlled trial in 208 patients with non-small cell lung cancer (NSCLC) showed no effect of modafinil on cancer-related fatigue.[418] In addition, a meta-analysis identified 3 studies evaluating modafinil for fatigue in patients with cancer and found that the drug was not better than placebo.[414] Recommendations for modafinil have therefore been removed from both the NCCN Guidelines for Cancer-Related Fatigue and the NCCN Guidelines for Survivorship. Both guidelines continue to recommend that methylphenidate may be considered after ruling out other causes of fatigue and failure of other interventions, although they acknowledge the limited data supporting the use of this agent in this setting, especially in cancer survivors.

Small pilot studies and one recent randomized controlled trial have evaluated the impact of supplements, including ginseng and vitamin D, for cancer-related fatigue.[419] The evidence to date is inconsistent, and the panel currently does not recommend the use of supplements for the treatment of fatigue.

Lymphedema

Lymphedema is a common side effect of cancer treatment, occurring on the same side of the body as the cancer treatment, resulting from damage to the lymphatic system. It occurs when lymph fluid accumulates in the interstitial tissue, causing swelling of the limb or other areas such as the neck, trunk, or genitals. Lymphedema is most often diagnosed within 18 months of treatment; however, it can develop any time in the life of the survivor.

More than 20% of cancer survivors reported lymphedema as a physical concern in a survey of almost 14 million survivors in the United States in a 2010 LIVESTRONG study.[19] The incidence of lymphedema varies by disease site. In one study, 41% of almost 1000 breast cancer survivors developed lymphedema by 10-year follow-up.[420] In a study of survivors of gynecologic cancers, the incidence of lymphedema 2 years after surgery was 37%.[421] In one study of 431 survivors of melanoma who had been treated with complete lymph node dissection and/or wide local excision and axillary or inguinal sentinel lymph node surgery, the reported incidence of lymphedema was 25%.[422]

Lymphedema may cause or exacerbate psychological distress.[423,424] In one study that included 692 breast cancer survivors with lymphedema, almost half reported moderate to extreme distress related to their lymphedema.[425] Lymphedema can also affect social roles, employment, physical function, and quality of life and cause disability.[426-428] Unfortunately, only 55% of cancer survivors with self-reported lymphedema in the LIVESTRONG study said that they received care for lymphedema.[19]

Risk Factors for Lymphedema

Survivors whose cancer treatment included surgery and/or radiation to the axillary, supraclavicular, cervical, or inguinal lymph node system are at risk for the development of lymphedema.[429-432] Sentinel lymph node biopsy also appears to increase the risk of lymphedema, although it poses less risk than complete dissection or radiation to the nodal group, and data are not completely consistent.[430,433-437] Other treatment-related factors that have been associated with an increased risk of lymphedema are receipt of chemotherapy or radiation, and the extent of lymph node dissection.[420,421,429-432,435,437-439] Overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2), localized infection, and higher initial stage

of disease also raise the risk of lymphedema development.[420,421,429,430,432,437,439-441]

Assessment and Workup for Lymphedema

Survivors with a history of radiation or surgery to the lymph nodes should be asked about swelling or feeling of heaviness, fatigue, or fullness at each visit. Early detection and diagnosis is key for optimal lymphedema management, because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment (see *Definition and Stages of Lymphedema* in the algorithm). Swelling on the same side as the cancer treatment is a universal symptom of lymphedema. Additional initial symptoms may include pain or discomfort and/or sensations of heaviness, fatigue, fullness, and/or tightness in the skin. Symptoms including decreased range of motion or strength and thickening of the skin may occur in later stages. If symptoms are present, survivors should be asked about the frequency and severity of swelling, pain and/or discomfort, any issues with strength or range of motion and mobility (ie, bending, stretching, flexibility), and whether symptoms interfere with daily activities.

If lymphedema symptoms are present, a recurrence of cancer should be ruled out. The survivor should then be referred to a certified lymphedema therapist, if available, for additional assessments. These assessments can include subjective signs and symptoms of lymphedema and limb volume measurements. Ideally, pretreatment limb measurement of both sides should be performed as a baseline prior to initiation of any therapy for those with treatment-related or individual risk factors. If not, the contralateral limb can be used for comparison in the post-treatment setting. Clinical examination by a lymphedema therapist may include range of motion, muscle performance, circulation, sensation, hemodynamic monitoring, and functional mobility.

Survivors with lymphedema should also be assessed for distress (see *Anxiety, Depression, and Distress*, above).

Treatment of Lymphedema

High-level evidence supporting treatments for lymphedema are lacking, and most studies have been performed in breast cancer survivors.[26,442-444] Most of the recommendations made by the panel are thus based on lower-level evidence, clinical experience, and expert consensus.

The oncology team can provide education regarding self-care management, including infection prevention measures, risk reduction strategies, and maintenance of skin integrity on the affected side (see *Survivor Lymphedema Education*, below). Distress should be treated if present (see *Anxiety, Depression, and Distress*, above). Referral should be made to a certified lymphedema therapist, if available, for prescription and fitting of compression garments, performance of manual lymphatic drainage, and direction of supervised progressive resistance training. If a certified lymphedema therapist is not available, referral to an appropriate alternative provider for treatment should be considered.

Compression garments have been shown to reduce limb volume, and are often used with other modalities such as manual lymphatic drainage.[444,445] Manual lymphatic drainage is performed by a specific massage technique designed to encourage lymph fluid to drain from the affected limb. Systematic reviews and meta-analyses have assessed the efficacy of manual lymphatic drainage in breast cancer survivors with lymphedema and found that it can provide additional benefit when added to standard therapy.[446,447] In particular, compression bandaging alone leads to limb volume reductions of 30% to 39%, and manual lymphatic drainage appears to increase that reduction by an additional 7%.

Progressive resistance/weight training under supervision is recommended for survivors with lymphedema. Progressive resistance training and physical activity are not associated with exacerbation or development of lymphedema, and may improve lymphedema symptoms.[448-456] However, caution is advised in this population,[457] and survivors with or at risk for lymphedema should consider discussing physical activity plans with a lymphedema specialist before starting a program that involves strength or resistance training. Survivors with lymphedema should initiate strength training exercise involving the affected body part only if lymphedema is stable (ie, no need for lymphedema therapy within the past 3 months, no recent limb infections requiring antibiotics, no change in limb circumference >10%, no change in the ability to perform activities of daily living). Survivors should undergo baseline and periodic evaluation for development or exacerbation of lymphedema, and should stop exercise and see a lymphedema specialist if exacerbation of lymphedema occurs. If a certified therapist is not available for supervision, survivors with lymphedema can perform resistance training with a professional trainer who has knowledge of cancer-related physical activity principles. Weights should be slowly progressed as tolerated, and lymphedema should be evaluated periodically. Most survivors with or at risk for lymphedema require compression garments during resistance training. The National Lymphedema Network has published a position statement with additional guidance for exercise in individuals with lymphedema.[455]

Survivor Lymphedema Education

Early detection and diagnosis is key for optimal lymphedema management because earlier stages are reversible. Therefore, survivors should be educated about the signs and symptoms of lymphedema and the importance of rapid reporting to the treatment team. Survivors should be told to inform their medical provider if subtle swelling or any other symptoms (eg, fullness, tightness, heaviness, pain) on the treated side are noted.

Survivors at risk for lymphedema and those with lymphedema are at a higher risk of localized infection in the affected area. These infections can require hospitalization for IV antibiotics. Therefore, survivors with or at risk for lymphedema should be educated to inform their medical provider immediately for signs of infection in the affected area. Risk of infections can be reduced by safe pet care and gardening techniques (See *Immunizations and Prevention of Infections*, below). Survivors should also be educated on how to maintain skin integrity with meticulous skin care of the affected area that includes avoidance of cuts, burns, skin irritants and allergens, insect bites, and pet scratches.[458,459] The use of moisturizing soaps and over-the-counter, fragrance-free emollients may also be helpful.[459]

Observational studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[429,431,440,441,460-463] For instance, in one study of 632 women with breast cancer prospectively screened for lymphedema with 3041 arm volume measurements, no association was found between the development of lymphedema and blood draws, injections, or air travel.[441] In the absence of high-level data, however, the panel recommends that medical procedures such as venipuncture and blood pressure measurements be done on the non–at-risk arm/limb if possible.[464] If necessary, procedures may be done using the at-risk arm/limb. More research is needed to determine the effect of these procedures on the risk of lymphedema.

Survivors should be informed that lymphedema is not a contraindication for physical activity and that no special precautions are required for

cardiovascular/aerobic exercise or strength training of unaffected limbs.[448-450,452,453,457] In addition, continued full use of the involved extremity and range-of-motion exercises should be encouraged to maintain strength and range of motion even in the presence of lymphedema. Progressive resistance/weight training under supervision is recommended for patients with lymphedema, as discussed above (see *Treatment of Lymphedema*). Exercise and physical therapy may also help prevent lymphedema symptoms. In the randomized controlled Lymphedema Education and Prevention study (CALGB 70305), women randomized to the education plus exercise arm self-reported greater range of motion at 12 months after lymph node dissection (a pre-specified secondary outcome) compared with women in the education only arm (left, 91% vs 84%; *P* =.16; right, 90% vs 83%; *P* = .02).[465]

Surveillance of Survivors with Lymphedema

Survivors with lymphedema should have follow-up with the treatment team as clinically indicated. Clinicians should check range of motion, inquire about the fit and age of compression garments, replace compression garments if needed, and inquire about the performance of prescribed exercises and self-care management. Assessment for distress should also be performed as part of routine surveillance.

Menopause-Related Symptoms

The NCCN Guidelines for Survivorship define menopause as no menses for one year in the absence of prior chemotherapy or tamoxifen use or no menses after surgical removal of all ovarian tissue. Healthy women reach menopause at a mean age of 51 years, with 95% of women reaching menopause between 45 and 55 years of age.[466] Many cancer survivors experience menopausal symptoms without meeting the definition of menopause, including female survivors on aromatase inhibitors or with a history of oophorectomy or chemotherapy and male survivors who received or are receiving androgen ablative therapies (ie, androgen deprivation therapy [ADT]). These symptoms can include hot flashes/night sweats, vaginal dryness, urinary complaints, sexual dysfunction, sleep disturbance, mood disturbance, depression, cognitive dysfunction, arthralgias/myalgias, and fatigue. These menopausal symptoms can occur in both men and women. Males may also experience gynecomastia, decreased testicle size, and thinning of body hair. Menopausal symptoms can have a profound impact on quality of life.[467,468]

Menopausal symptoms in cancer survivors have been most extensively studied in female survivors after treatment of breast cancer. Hot flashes are reported to occur in about 46% to 73% of breast cancer survivors.[467,469-471] In one study of breast cancer survivors diagnosed at age 40 years or younger, 46% of women reported hot flashes, 51% reported vaginal dryness, and 39% reported dyspareunia.[471] Similarly, about 50% to 80% of men on ADT experience hot flashes, which can persist after treatment.[472-477] The incidence of gynecomastia in men on ADT varies with the method of ADT used and can be as high as 80% in men on estrogen therapy.[474,478]

Premenopausal cancer survivors who have received chemotherapy may experience transient or permanent menopause.[479-481] If appropriate and desired, referral for fertility preservation should be considered before chemotherapy, because studies report that 33% to 73% of premenopausal women treated for breast cancer become peri- or postmenopausal after treatment.[467] Younger survivors with irregular menses may have primary ovarian insufficiency and may develop menopausal symptoms.[482] These women may or may not be fertile, and should be counseled about the possibility of pregnancy despite amenorrhea.

Assessment and Evaluation for Menopausal Symptoms

Survivors with menopausal symptoms disruptive to quality of life should be assessed and treated for medical causes of menopausal symptoms such as thyroid disease and diabetes. Lab evaluation includes estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, as clinically indicated. FSH is not a reliable marker of menopausal status in female survivors with prior chemotherapy or pelvic radiation exposure or in female survivors on tamoxifen. In male survivors, morning total testosterone and free testosterone may also be checked if hypogonadism is suspected.[483] For women with complaints of vaginal dryness, a pelvic evaluation should be done to assess for vaginal atrophy and can be accomplished by referral to an appropriate specialist.

For peri- or pre-menopausal female survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including FSH, anti-Müllerian hormone (AMH), and inhibin may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or those on tamoxifen, but alone are not reliable to ensure menopausal status.[484,485]

Management of Menopausal Symptoms in Female Survivors

Management of sexual dysfunction, lack of sexual desire, sleep disturbance, mood disturbance, depression, cognitive dysfunction, fatigue, and arthralgias/myalgias is described in other sections of these guidelines. Management of hot flashes, vaginal dryness, and urogenital complaints associated with menopause are described herein. The panel prefers the use of non-hormonal options as first-line therapy for survivors with menopausal symptoms disruptive to quality of life, but hormonal therapies can also be used after consideration of the risks and benefits to an individual survivor.

Non-Hormonal Pharmacologic Treatment of Hot Flashes

For the management of hot flashes, non-hormonal pharmacologic options include low-dose antidepressants, anti-convulsants, neuropathic pain relievers, and certain anti-hypertensives.[486-489]

SSRIs and SNRIs have been shown to improve vasomotor symptoms in the general population, although the degree of symptom reduction may be smaller than with hormonal treatments.[490-492] A randomized clinical trial in healthy post-menopausal women showed that low-dose paroxetine reduces the frequency and severity of hot flashes.[492] Small studies have shown that SSRIs and SNRIs also reduce the severity and frequency of hot flashes in female cancer and survivor populations.[493-502] One of these studies was a randomized, double-blind, placebo-controlled study in 80 survivors of gynecologic cancers.[494] Results showed that 7.5 mg daily of paroxetine reduced the frequency and severity of vasomotor symptoms and the number of resultant nighttime awakenings.

However, pure SSRIs, and in particular paroxetine, should be used with caution in women on tamoxifen, because these drugs block the conversion of tamoxifen to active metabolites through inhibition of cytochrome P450 2D6 (CYP2D6).[503] However, an analysis of a large database that included almost 17,000 breast cancer survivors found no evidence of an increase in cancer recurrence in women on concurrent tamoxifen and antidepressants, including paroxetine.[504] In contrast, a study of 2430 breast cancer survivors found an increased risk of cancer death in those taking tamoxifen and an SSRI.[505] The panel recommends alternative therapy if available, although no definitive conclusion regarding the impact of the interaction between pure SSRIs and tamoxifen can be drawn. Doses of antidepressants required for improvements in vasomotor symptoms are typically much lower than those needed for depression, and the response is typically faster. Side

effects include dry mouth, decreased appetite, fatigue, nausea, constipation, and possible sexual dysfunction. Upon discontinuation, SNRIs and SSRIs should be gradually tapered to minimize withdrawal symptoms.

The anticonvulsants gabapentin and pregabalin have also been shown to improve menopause-related vasomotor symptoms in the general population and in female cancer survivors.[506-511] For example, one trial of 420 survivors of breast cancer experiencing ≥2 hot flashes/day found that 900 mg/day gabapentin decreased the hot flash severity score by 46% at 8 weeks compared with a 15% reduction in the placebo group.[510] As with antidepressants, the doses of anticonvulsants used in this setting are lower than in other settings. Side effects of anticonvulsants include somnolence, so they may be particularly useful when given at bedtime in patients with hot flashes disturbing sleep.

Small studies provide evidence that the alpha agonist anti-hypertensive clonidine can reduce hot flashes in some healthy post-menopausal women.[512,513] Randomized controlled trials in breast cancer survivors also show that clonidine can reduce hot flash frequency and severity in postmenopausal women taking tamoxifen.[514,515] Side effects include sleep difficulties, dry mouth, fatigue, dizziness, and nausea.

Several studies have compared non-hormonal pharmacologic treatments. For example, venlafaxine has been compared with clonidine in breast cancer survivors.[516-518] Results of these studies varied, but it appears that venlafaxine may have a faster effect but is less well tolerated than clonidine. A randomized, crossover study compared venlafaxine with gabapentin in breast cancer survivors.[511] Whereas both treatments resulted in similar reductions in hot flash severity, 68% of participants indicated a preference for venlafaxine compared with 32% who preferred gabapentin.

Non-Pharmacologic Treatment of Hot Flashes

Non-pharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss if overweight or obese, hypnosis, and CBT may help survivors manage hot flashes.[486,488,489,519-524] Phytoestrogens, botanicals, and dietary supplements can also be tried (category 2B for all); however, data are mixed or limited on the effectiveness and safety of these particular treatments in the general menopausal population and in survivors.[487,525-532] Vitamin E has been thought to have marginal improvement in vasomotor symptoms in both general menopause and patients with breast cancer, but data are limited and have shown mixed results.[533] Limited data show a possible benefit of black cohosh for vasomotor symptoms in the general population.[534-536] However, randomized data in breast cancer survivors show no benefit.[537]

Acupuncture is used as a treatment for hot flashes in the general population, although evidence supporting its benefit is limited in the non-cancer setting.[538,539] Several studies in women with cancer or female survivors have shown acupuncture to be a safe and effective option for managing vasomotor symptoms.[540-543] In fact, three of these studies compared acupuncture with either venlafaxine or gabapentin and found acupuncture to be equivalent to or better than drug treatment.[540,542,543]

Yoga may also help survivors manage hot flashes. A randomized trial in 355 healthy peri- and postmenopausal women found that yoga improved quality of life associated with menopause, including an improvement in the vasomotor symptom domain.[544] Another randomized controlled trial showed yoga improved sleep but did not affect the frequency of symptomatic burden of vasomotor symptoms.[545]

Evidence that exercise/physical activity helps manage hot flashes in postmenopausal women is inconclusive.[486,544,546-552] In fact, a randomized controlled trial of 261 perimenopausal and postmenopausal women found no difference in the frequency of hot flashes between those randomized to an exercise intervention and the control group.[547] A similar trial involving 248 women also found that physical activity did not improve vasomotor symptoms.[550] Studies in the survivorship and cancer populations are limited and also do not support a role for the use of physical activity specifically to improve hot flash symptoms.[553] Despite the lack of data suggesting a benefit for vasomotor symptoms, the panel believes that physical activity should be recommended in menopausal cancer survivors given the many beneficial effects on overall health.

Other lifestyle modifications may also help minimize vasomotor symptoms. In the Women's Health Initiative (WHI) Dietary Modification trial of 17,473 postmenopausal women who were not taking menopausal hormone therapy (MHT), those who lost ≥10% of their body weight were more likely to eliminate hot flash symptoms than those who maintained their body weight.[521] Data in breast cancer survivors also suggest that weight loss may help alleviate hot flashes in this population.[522,524] A longitudinal study in 761 women showed that those who quit smoking saw improvements in the frequency and severity of hot flashes compared to women who continued to smoke.[554] Although studies of this sort have not been done in survivor populations, data suggest that survivors who are current smokers are more likely to experience hot flashes.[555] Individual vasomotor responses to alcohol vary.[556] If alcohol triggers hot flashes in an individual survivor, limiting intake should be recommended.

Evidence suggests that CBT may reduce vasomotor symptoms in the general population.[557,558] CBT has also been studied for the management of vasomotor symptoms in cancer and survivor populations. In one trial, patients with breast cancer were randomized to receive CBT, CBT plus an exercise intervention, or a control group.[553] Results suggested that CBT lessened the perceived burden of hot flashes. Another study randomized 96 women with menopausal symptoms after breast cancer treatment to a group CBT intervention or a usual care group.[559] The hot flashes and night sweats problem rating was significantly reduced in the CBT arm.

Hormonal Treatment of Hot Flashes

MHT is the most effective treatment for the management of vasomotor symptoms in post-menopausal women.[466,560-564] However, the use of long-term MHT is controversial because for many women the health risks associated with MHT are thought to outweigh the potential benefits. In the past, MHT was typically given to post-menopausal women not only to treat vasomotor symptoms, but with the thought that MHT was effective at preventing heart disease. The best data looking at health benefits and risks came from the large WHI study that showed that estrogen alone in postmenopausal women with prior hysterectomy was associated with an increased risk of stroke, a decreased risk of hip fracture, and had no effect on coronary heart disease or breast cancer incidence.[565] In the WHI, estrogen plus progestin in postmenopausal women with a uterus was associated with a decreased risk of colorectal cancer and hip fracture, and an increased risk of stroke, pulmonary embolism, and invasive breast cancer.[566] The women in these trials also had a higher rate of death from lung cancer during the intervention and were diagnosed with more advanced stages of colorectal cancer during the intervention and follow-up than women who received placebo.[567-569] MHT was also associated with an increase in breast cancer incidence and the cancers were more likely to be lymph node positive.[570,571] However, the absolute numbers of trial participants diagnosed with

breast cancer were small, and the absolute risk was low. A systematic review of randomized double-blinded studies of MHT versus placebo found no evidence that MHT affects the incidence of colorectal cancer, but found that MHT increases the risk of breast cancer and death from lung cancer in post-menopausal women taking estrogen and progestins combined.[572]

Data from retrospective studies and an incomplete randomized controlled trial suggest that MHT is safe to use in survivors of early-stage endometrial cancer.[573-577] In survivors of breast cancer, the data are inconclusive, because the only 2 randomized controlled trials of MHT in breast cancer survivors had conflicting results. The HABITS trial found an increased risk of breast cancer recurrence with the use of MHT; the cumulative incidence at 5 years was 22.2% in the MHT arm and 8.0% in the control arm.[578] In the Stockholm trial, no difference was seen in breast cancer recurrence after 10.8 years of follow-up.[579]

Overall, based on these data, the panel believes that MHT can be used in appropriate female cancer survivors. Alternatives to MHT should typically be tried first and patients should be referred to an appropriate specialist for dosing and management of MHT. MHT is contraindicated in survivors with a history of hormonally mediated cancers. Other contraindications for survivors mirror those for the general population, and include a history of abnormal vaginal bleeding, active or recent history of thromboembolic event, pregnancy, and active liver disease. In addition, MHT should be used with caution in survivors with coronary heart disease or hypertension, in current smokers, and in those with increased genetic cancer risk. In general, the lowest dose possible to control symptoms should be used, and treatment should be individualized based on risks.

Hormonal treatments for the relief of hot flashes in women include combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus). There are different local and systemic formulations of hormones including oral, transdermal, vaginal ring, and an intrauterine device. Estrogen transdermal formulations may be preferred over other formulations due to lower rates of venous thromboembolism (VTE) and stroke.[580] Micronized progestin may be preferred over medroxyprogesterone acetate (MPA) due to lower rates of VTE and breast cancer risk. Other hormonal options for treating hot flashes include novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen, creating a tissue-selective estrogen complex (TSEC). One of these TSECs contains a conjugated estrogen and the SERM bazedoxifene,[581]and is FDA-approved for treating menopausal symptoms in healthy post-menopausal women. Custom compounded bioidentical hormones are not recommended, because data supporting claims that they are safer and more effective than standard hormones are lacking.[582,583] Young cancer survivors experiencing menopause at an early age can consider oral contraceptives or MHT for symptom relief and potential cardiac and bone benefits as long as not contraindicated.

Treatment of Vaginal Dryness

Vaginal dryness can be treated with over-the-counter vaginal moisturizers, gels, oils, and topicals for comfort and topical vitamin D or E.[584,585] Lubricants can be used for sexual activity.[586,587] Local hormonal treatments can also be used,[566,588-592] although some controversy exists regarding their safety in survivors of hormone-dependent cancers.[593] However, evidence suggests that local estrogen does not increase the risk of breast cancer recurrence.[594] Vaginal estrogen preparations include rings, suppositories, and creams and have been shown to be

effective for managing symptoms of vaginal dryness in menopausal women.[592,595] Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories, and they are therefore preferred for survivors with hormonally sensitive tumors if estrogen-based treatment is warranted.[593,596] Other topical hormone prescriptions (ie, testosterone) can also be considered, but data regarding safety or effectiveness are limited. One randomized controlled trial of 441 survivors of breast or gynecologic cancer showed that vaginal DHEA led to significant improvements in sexual desire, arousal, pain, and overall sexual function.[597] In this trial, clinically important systemic estrogenic activity was not evident, and the treatment was safe and well tolerated.

Overall, the decision to use local hormones should be individualized with a discussion of the possible risks and benefits. Referral to an appropriate specialist for management can also be considered.

Treatment of Urogenital Complaints

Women sometimes present with urogenital complaints associated with menopause, such as urogenital atrophy and urinary incontinence. The panel recommends treatment with local vaginal estrogen and referral to an appropriate specialist.[595,598] See *Treatment of Vaginal Dryness*, above, for a discussion on the safety of vaginal estrogen.

Management of ADT-Related Symptoms in Male Survivors

Survivors of prostate cancer may be on ADT for 2 to 3 years without evidence of disease (see the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org), and may experience many symptoms, including hot flashes, gynecomastia, and anemia.

Vasomotor Symptoms

For vasomotor symptoms disruptive to quality of life in men, alternative ADT options, such as intermittent ADT or antiandrogen monotherapy, can be tried if deemed appropriate by the oncologist (see the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org).

Androgens (eg, testosterone) are used as MHT for the relief of hot flashes in men who have hypogonadism and are cured of prostate cancer or who have hypogonadism from chemotherapy or radiation for other malignancies. However, androgens are contraindicated in men with advanced prostate malignancy on ADT. Hormonal options for the relief of hot flashes in survivors on ADT include MPA, estrogen, and cyproterone acetate.[599-602]

Non-hormonal options include the SSRIs venlafaxine and the anti-convulsant gabapentin. Gabapentin has been shown to be safe and moderately effective at controlling hot flashes in men with prostate cancer in two randomized controlled trials.[603-605] Case reports and small pilot studies have shown that venlafaxine may improve hot flash symptoms in men with prostate cancer undergoing ADT.[606]

As in female cancer survivors, men with ADT-related symptoms can try non-pharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss if overweight or obese, hypnosis, and CBT. Small studies in prostate cancer survivors with a history of ADT have also found that acupuncture is effective at controlling hot flashes in this population.[607,608] A study of 68 patients with prostate cancer on ADT also found that CBT reduced the perceived burden of hot flashes compared with usual care.[609]

Also as in women with vasomotor symptoms, phytoestrogens, botanicals, and dietary supplements are often used in males (category

2B for all). However, data are very limited on the effectiveness and safety of these nonpharmacologic treatments in survivors on ADT.[610] Furthermore, there are concerns that supplemental vitamin E may increase the risk for prostate cancer.[611,612]

Gynecomastia

Gynecomastia and breast pain can be treated in men on ADT by prophylactic radiation (must be delivered prior to development of breast tissue), tamoxifen, or reduction mammoplasty.[478,613,614]

Anemia

Anemia in men on ADT is generally responsive to erythropoietin (EPO), blood transfusion. These men can be treated as per the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia (available at www.NCCN.org).

Pain

More than one-third of post-treatment cancer survivors experience chronic pain, which often leads to psychological distress; decreased activity, motivation, and personal interactions; and an overall poor quality of life.[615-619] Pain in survivors is often ineffectively managed. Barriers to optimal pain management in cancer survivors include health care providers' lack of training, fear of side effects and addiction, and reimbursement issues.[620]

Pain has 2 predominant mechanisms: nociceptive and neuropathic.[621,622] Injury to somatic and visceral structures and the resulting activation of nociceptors present in skin, viscera, muscles, and connective tissues cause nociceptive pain. Somatic nociceptive pain is often described as sharp, throbbing, or pressure-like, and often occurs after surgical procedures. Visceral nociceptive pain is often diffuse and described as aching or cramping. Neuropathic pain is caused by injury to the peripheral or CNS and might be described as numbness or as burning, sharp, tingling, prickling, electrical, or shooting. Neuropathic pain often occurs as a side effect of chemotherapy or radiation therapy or is caused by surgical injury to the nerves.

The incidence of chronic pain after surgical treatment varies with the type of procedure and is as high as 60% in patients treated with breast surgery and 50% in those treated with lung surgery.[615] Arthralgias, characterized by joint pain and stiffness, occur in roughly half of women taking aromatase inhibitors as adjuvant therapy for breast cancer.[623] Pelvic pain often occurs after pelvic radiation, resulting from fractures, fistulae, proctitis, cystitis, dyspareunia, or enteritis.[615]

These NCCN Guidelines for Survivorship make recommendations for the management of 7 categories of cancer pain syndromes: neuropathic pain, chronic pain syndromes (ie, pain syndromes after amputation, neck dissection, mastectomy, thoracotomy), myalgias/arthralgias, skeletal pain, myofascial pain, gastrointestinal/urinary/pelvic pain, and postradiation pain. Neuropathic pain commonly results from certain systemic anticancer agents.[615] Recommendations for the prevention and management of chemotherapy-induced peripheral neuropathy (CIPN) in survivors can be found in ASCO's clinical practice guideline.[624] ASCO also has clinical practice guidelines for the management of chronic pain in survivors of adult cancers.[625]

Screening for and Assessment of Pain

All cancer survivors should be screened for pain at regular intervals. If pain is present, the intensity should be quantified by the survivor. Because pain is inherently subjective, self-report of pain is the current standard of care for assessment. Intensity of pain should be quantified using a 0 to 10 numeric rating scale, a categorical scale, or a pictorial scale (eg, Wong-Baker FACES Pain Rating Scale).[626-629] In addition, the

survivor should be asked to describe the characteristics of the pain (eg, aching, burning). Severe uncontrolled pain is a medical emergency and should be addressed promptly. In addition, an oncologic emergency should also be ruled out in these cases.

A comprehensive evaluation, as outlined in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org), is essential to ensure proper pain management. The survivor's goals for comfort and function should be determined, and the cause and pathophysiology of the pain should be identified to determine the optimal therapeutic strategy. If the pain is new and acute, the possibility of pain due to cancer recurrence should be considered. If the pain is chronic, a specific cancer pain syndrome should be identified if possible. Referral to a PCP can be made for non-cancer or non-cancer-treatment–related workup and pain management (ie, rheumatoid arthritis).

Management of Pain

The goals of pain management are to increase comfort, maximize function, and improve quality of life. A multidisciplinary approach, which may include a combination of pharmacologic treatments, psychosocial and behavioral interventions, physical therapy and physical activity, occupational therapy, local therapies, and interventional procedures, is recommended.[616,630,631] These approaches are discussed in more detail below. For survivors with refractory pain and/or those who might benefit from further pain interventions, referral to a specialist (ie, pain management services, interventional specialist, physical therapy, physical medicine, palliative care, rehabilitation, anesthesia pain, urology, gynecology, orthopedic surgery, gastroenterology, other appropriate consultants) can also be considered. Finally, psychological support for survivors with chronic pain is necessary, and referral to psychosocial services should be considered for survivors in distress.

For more information about the management of cancer-related pain, please see the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). These guidelines include information on opioid use and pain treatment agreements for patients at risk for medication misuse or diversion; adjuvant analgesics; and psychosocial support and behavioral interventions that may be modified to fit the individual survivor's circumstances.

Pharmacologic Interventions

Pharmacologic measures are the foundation of treatment of many of the common pain syndromes in survivors. Pharmacologic recommendations in these guidelines vary depending on the pain syndrome and include opioids, adjuvant analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants.[616,632-634] Topical medications are discussed in *Local Therapies*, below.

Opioids: Opioids may be recommended for the treatment of neuropathic pain, skeletal pain, and chronic pain syndromes. Data on the long-term use of opioids in survivors are lacking.[631,633,635] In fact, data on the long-term safety and effectiveness of opioids in the non-cancer setting are scarce as well.[636]

In March 2016, the CDC released guidelines for prescribing opioids for chronic pain.[637] In May 2016, ASCO released a policy statement, describing principles to help balance concerns for the abuse and misuse of opioids with concerns for appropriate access of opioids for pain management in patients with cancer and survivors.[638] The NCCN Survivorship Panel shares these concerns and supports ASCO's statement.

The NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org) recommend screening survivors for risk factors of

aberrant opioid use or diversion of pain medication, using a detailed patient evaluation and/or tools such as the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) or Opioid Risk Tool (ORT) before prescribing.[639-643] In addition, if opioids are deemed necessary for any survivor (regardless of aberrant use risk level), the NCCN Survivorship Panel recommends using the lowest dose possible for the shortest period of time possible and reevaluating the effectiveness and necessity of opioids on a regular basis. Pain treatment agreements can also be considered.[644]

Adjuvant Analgesics: Adjuvant analgesics include antidepressants (eg, SNRIs, tricyclic antidepressants) and anticonvulsants (eg, gabapentin, pregabalin). These are recommended for the treatment of survivors with neuropathic pain, post-radiation pain, chronic pain syndromes, myalgias, and arthralgias. The term adjuvant refers to the fact that they are often coadministered with an opioid to enhance analgesia or reduce the opioid requirement, but they may also be used as the sole pain treatment. A recent systematic review found that antidepressants, anticonvulsants, other adjuvant analgesics, and opioids were all effective at reducing neuropathic pain in patients with cancer.[633] Another review found that antidepressants and anticonvulsants may provide additional neuropathic pain relief when added to opioids in patients with cancer.[645]

Tricyclic antidepressants have been shown to relieve neuropathic pain in the noncancer setting.[646,647] In addition, the SNRI duloxetine was recently shown to effectively reduce pain in a multi-institutional, randomized, double-blind, placebo-controlled, crossover trial of 231 patients with painful CIPN.[648] The ASCO clinical practice guideline for the prevention and management of CIPN in survivors of adult cancers recommend duloxetine in this setting.[624]

The most commonly used anticonvulsant drugs for the treatment of cancer-related pain are gabapentin and pregabalin. They are recommended in these guidelines for the treatment of myalgias and arthralgias.[649] Both drugs have also demonstrated efficacy in diabetic and postherpetic neuropathy,[650-652] but have not been well-studied in the cancer or survivorship settings.[624] One randomized, placebo-controlled, cross-over trial in 115 survivors found that gabapentin did not effectively treat CIPN.[653] However, because high-level evidence is limited to this one trial, ASCO's CIPN panel believes that extrapolation from other neuropathic pain conditions is reasonable and that gabapentin can be offered to select survivors with CIPN after informing them about the inconclusiveness of the evidence and of potential harms, benefits, and costs.[624]

Corticosteroids are not recommended for the management of pain in cancer survivors. A recent randomized, placebo-controlled, double-blind trial of adult patients with advanced cancer receiving opioids found that methylprednisolone did not provide additional analgesia over that provided by the opioids.[654]

Nonsteroidal Anti-Inflammatory Drugs: NSAIDs, including COX-2 inhibitors, and acetaminophen are recommended for the treatment of myofascial and skeletal pain, post-radiation pain, and for myalgias and arthralgias. NSAIDs are nonopioid analgesics that block the biosynthesis of prostaglandins, which are inflammatory mediators that initiate, cause, intensify, or maintain pain. A recent systematic review found that data supporting the use of NSAIDs for control of pain in patients with advanced cancer are limited and weak, but suggest some efficacy at reducing pain and opioid dose requirement.[655]

A discussion of contraindications and safety precautions that should be considered before prescribing NSAIDs is provided in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org).

Muscle Relaxants: Muscle relaxants (eg, diazepam, lorazepam, metaxalone) reduce muscle spasm and are recommended for the treatment of skeletal pain, myalgias, and arthralgias. Evidence for their efficacy in providing pain relief in the noncancer settings is limited.[656,657] No data could be found in the setting of cancer-related pain.

Psychosocial Support and Behavioral Interventions

Cognitive interventions are aimed at enhancing a sense of control over the pain or its underlying cause. Breathing exercises, relaxation, imagery or hypnosis, and other behavioral therapies can be very useful.[617,658-663] A randomized controlled trial of 129 breast cancer survivors with pain found that an 8-week mindfulness-based cognitive therapy program reduced pain intensity and nonprescription pain medication use compared with a waitlist control group.[664] Quality of life was also improved in the intervention arm, but distress was not reduced.

Psychosocial support and education should also be provided.[665] Some studies in patients with cancer suggest that psychosocial and behavioral interventions such as skills training, education, relaxation training, supportive–expressive therapy, and CBT may be effective at reducing pain.[660,666] Hypnosis can also be considered for treatment of neuropathic pain. Overall, data support the benefit of hypnosis for controlling pain in cancer and other settings, but are lacking in the survivorship population.[667]

Mirror therapy, if available, can be considered for the treatment of chronic “phantom limb” pain after amputation. In mirror therapy, the survivor views a reflected image of their intact limb in a mirror while trying to move the amputated limb. In a small randomized trial, mirror therapy reduced pain in 6 of 6 patients and in 8 of 9 patients who switched to mirror therapy from the control conditions (covered mirror or mental visualization).[668] One case report suggests that this therapy can be effective in survivors.[669]

In general, studies regarding psychosocial support and behavioral interventions for reducing pain in survivors are limited. A recent systematic review and meta-analysis assessed the efficacy of psychosocial interventions for treating pain in patients with breast cancer and survivors.[670] Although results suggest an effect, more studies are clearly needed in the survivorship population.

Physical Therapy and Physical Activity

Physical therapy and general physical activity may also be effective for the treatment of pain in survivors, with the main goal of increasing mobility.[382,617,630,671] Several randomized controlled trials have reported a reduction of neck and shoulder pain associated with exercise or therapy programs.[672-674] In one study, 52 survivors of head and neck cancer were randomized to a progressive resistance exercise training (PRET) program or standard therapeutic exercise for 12 weeks.[674] Pain scores decreased more dramatically in the PRET group (P = .001). In another study of 66 survivors of breast cancer, those randomized to an 8-week water exercise program experienced a greater reduction of neck and shoulder pain than those randomized to usual care.[672] A more recent randomized trial showed that breast cancer survivors with aromatase-inhibitor-induced arthralgia randomized to an exercise arm (150 min/wk of aerobic exercise plus supervised strength training twice per week) experienced greater improvements in worst joint pain scores, pain severity, and pain interference than those in the usual care arm (all P < .001).[675]

In addition, group exercise in the community with trainers specifically trained to work with cancer survivors has been shown to reduce pain and other symptoms.[676] Yoga may also be helpful for pain management in cancer survivors. In a randomized controlled trial of 167 breast cancer survivors on aromatase inhibitors or tamoxifen, yoga reduced musculoskeletal pain symptoms.[677]

Local Therapies

Local therapies, including heat, cold packs, massage, and medicated creams, ointments, and patches, are recommended for the treatment of myalgias, arthralgias, and neuropathic pain.[617] Specifically, topical lidocaine, capsaicin, ketamine, and amitriptyline are recommended for treatment of some of the various cancer pain syndromes. Data are limited on the effectiveness of ketamine and amitriptyline,[678-683] but the evidence for the effectiveness of lidocaine and capsaicin is stronger.[678,680-682] Lidocaine has been shown to reduce the severity of postherpetic neuropathy and cancer-related pain.[684,685] In a randomized trial of 35 patients with non–cancer-related postherpetic, postoperative, or diabetes-related neuropathic pain, pain intensity was reduced with topical lidocaine but not with topical amitriptyline when compared with placebo.[681] A larger trial with a similar population of 92 patients found no effect of topical amitriptyline, ketamine, or a combination of the two.[686] Another study found that a higher dose of amitriptyline had some efficacy in reducing peripheral neuropathy, but also showed systemic effects.[687] More recently, results of a multicenter, phase III, randomized, double-blind, placebo-controlled trial of 462 survivors with CIPN found that ketamine/amitriptyline cream had no effect.[688]

Interventional Procedures

Referral to pain management services for consideration of interventional procedures, including transcutaneous electrical nerve stimulation (TENS), intercostal nerve blocks, neurotomy with radiofrequency ablation, and dorsal column stimulation, is recommended for refractory pain in survivors. Data on the efficacy of these interventions are mainly from patients with active cancer or from the noncancer setting.[617,689] TENS is a noninvasive procedure with electrodes placed in or around the painful area.[617] A recent systematic review found that data supporting the efficacy of TENS for reducing cancer-related pain are inconclusive.[690] The goal of invasive interventions, such as an intercostal nerve block, is to interrupt nerve conduction by either destroying nerves or interfering with their function.[617] The data on these interventions are also limited.[617]

Acupuncture

Acupuncture is recommended as a possible option for the treatment of myofascial or neuropathic pain in survivors. Evidence supporting the efficacy of this technique for reducing cancer-related pain is extremely limited.[691-693] A small randomized controlled trial compared electro-acupuncture (EA) to WLC and sham acupuncture in 67 postmenopausal women with breast cancer and aromatase inhibitor-associated arthralgia.[694] Pain severity was improved in both the EA and sham acupuncture arms compared with the control arm (mean reduction in pain severity in the EA vs. WLC groups at week 8, -2.2 vs. -0.2; P = .0004). While this small trial suggests some effect of acupuncture for pain relief, larger studies in the cancer survivorship population are clearly needed.

Sexual Dysfunction

Cancer treatment, especially hormonal therapy and therapy directed towards the pelvis, can often impair sexual function. In addition, depression and anxiety, which are common in survivors, can contribute to sexual problems. Thus, sexual dysfunction is common in survivors and can cause increased distress and have a significant negative

impact on quality of life.[695-700] Nonetheless, sexual function is often not discussed with survivors.[701-705] Reasons for this include a lack of training of health care professionals, discomfort of providers and/or survivors with the topic, survivors' perception of discomfort from the provider, and insufficient time during visits for discussion.[695] However, effective strategies for treating both female and male sexual dysfunction exist, making these discussions a critical part of survivorship care.

Female Sexual Dysfunction

Female sexual problems relate to issues in sexual desire, arousal, orgasm, and pain.[706-708] Sexual dysfunction after cancer treatment is common in female survivors.[25,699,709-714] A survey of 221 survivors of vaginal and cervical cancer found that the prevalence of sexual problems was significantly higher among survivors than among age- and race-matched controls from the National Health and Social Life Survey (mean number of problems 2.6 vs 1.1; $P < .001$).[713] A survey of survivors of ovarian germ cell tumors and age- and race- and education-matched controls found that survivors reported a significant decrease in sexual pleasure.[715]

Female sexual dysfunction varies with cancer site and treatment modalities.[710,711] For example, survivors of cervical cancer who were treated with radiotherapy had worse sexual functioning scores (for arousal, lubrication, orgasm, pain, and satisfaction) than those treated with surgery, whose sexual functioning was similar to that of age- and race-matched noncancer controls.[710] A systematic review of sexual functioning in cervical cancer survivors found similar results, except that no differences in orgasm/satisfaction were observed.[716] Chemotherapy seems to be linked to female sexual dysfunction in breast cancer survivors,[711] possibly related to the prevalence of chemotherapy-induced menopause in this population.[707] Furthermore, body-image changes related to breast cancer surgery and reconstruction can affect women's sexual health and well-being.[717] In addition, survivors with a history of HSCT may have multiple types of sexual dysfunction even 5 to 10 years after diagnosis.[718-720] Some of the sexual dysfunction associated with HSCT is related to graft-versus-host disease (GVHD), which can result in vaginal fibrosis, stenosis, mucosal changes, vaginal irritation, bleeding, and increased sensitivity of genital tissues.[719,721] In addition, high-dose corticosteroids used for chronic GVHD can increase emotional lability and depression, affecting feelings of attractiveness, sexual activity, and quality of sexual life.

Male Sexual Dysfunction

The NIH Consensus Conference on Impotence defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[722] In fact, impotence and erectile dysfunction (ED) are not synonymous. Impotence can involve problems of sexual desire, orgasm, or ejaculation, which are not necessarily linked with achieving or maintaining an erection.[723]

ED occurs frequently in the general population and increases with age.[724] In one community-based study, 33% of men aged ≥75 years reported moderate ED or worse.[725] ED is also very common in male cancer survivors. Anticancer treatment modalities used in a variety of cancers have the potential to damage blood vessels, leading to a reduction in blood circulation to the penis and/or damage to the autonomic nervous system. Thus, higher rates of ED are seen in cancer survivors than in the general population. The prevalence of ED in male survivors of colorectal cancer has been reported to range from 45% to 75%,[696,726,727] and it has been reported in up to 90% of survivors of prostate cancer.[728-732]

Male cancer survivors exposed to radiation or chemotherapy often experience hypogonadism – usually primary hypogonadism. Hypogonadism in men refers to a decrease in the production of sperm and/or testosterone. Primary hypogonadism is the result of testicular failure. In these men testosterone levels and sperm counts are below normal, and serum LH and FSH are above normal. Secondary hypogonadism is a disease of the pituitary or hypothalamus. In men with secondary hypogonadism, serum testosterone levels and sperm counts are subnormal, and the serum LH and FSH levels are normal or reduced. Adult-onset hypogonadism is characterized by a deficiency of testosterone and a failure of the body to produce an adequate compensatory response. In these men, low testosterone levels are associated with normal or low levels of gonadotropins, suggesting physiologic failure of both the testicles and hypothalamic-pituitary system.

Evaluation and Assessment for Sexual Function

All adult cancer survivors, regardless of gender identity and sexual orientation, should be asked about their sexual function at regular intervals, by inquiring about any concerns or distress regarding sexual function, sexual activity, sexual relationships, or sex life. Cancer survivors who report distress should be evaluated further. Inquiries into treatment-related infertility should be made if indicated, with referrals as appropriate. ASCO's recently updated clinical practice guidelines on fertility preservation for patients with cancer have more information on the topic.[733] It is important for providers to be aware that fertility issues can be addressed in the survivorship phase, whether or not they were addressed prior to treatment.[734-736] A discussion regarding the need for contraception may also be helpful in some cases, because the incidence of unplanned pregnancies is approximately 3 times higher in cancer survivors than in the general population.[737]

Survivors for whom screening does not indicate an issue with sexual function should be rescreened at subsequent visits. For survivors with sexual function concerns who do not wish to discuss them at the current visit, referral can be made to a sexual health specialist if the survivor is interested. These survivors should also be re-evaluated and engaged in discussions about the potential impact of treatment on sexual function at future visits.

For survivors who want to discuss their sexual function further, screening tools can be considered. Several screening tools are available for both men and women. For women, options include the Brief Sexual Symptom Checklist for Women, the Arizona Sexual Experience Scale (ASEX), the Female Sexual Function Index (FSFI), and a breast cancer-specific adaptation of the FSFI (FSFI-BC).[738-741] For men, the Sexual Health Inventory for Men (SHIM), the Sexual Quality of Life Questionnaire-Men, and the PROMIS Brief Function Profile-Male are examples.[724,742,743] The FSFI has been validated in patients with cancer and cancer survivors.[744,745] The FSFI and ASEX were also identified in a systematic review as tools that have acceptable psychometric properties in patients with breast cancer.[746] The other tools have not been validated in cancer or survivor populations.

Survivors with concerns about their sexual function should undergo a more thorough evaluation, including screening for possible psychosocial problems or mental health issues (ie, anxiety, depression, relationship issues, body image concerns, drug or alcohol use) that can contribute to sexual dysfunction. It is also important to identify prescription and over-the-counter medications (especially hormone therapy, narcotics, beta blockers, and SSRIs) that could be a contributing factor. Traditional risk factors for sexual dysfunction, such as cardiovascular disease, diabetes, obesity, smoking, and alcohol abuse, should also be assessed, as should the patient's oncologic and treatment history. In

addition, the impact of cancer and cancer treatment on sexual function should be explored further. Finally, for men, total morning testosterone should be measured, if indicated by concerns regarding hypogonadism.[483]

Interventions for Female Sexual Dysfunction

Female sexual dysfunction is often multifactorial in nature. Therefore, treatment of sexual dysfunction often requires a multidimensional treatment plan that addresses the underlying issues, which can be physiologic (eg, menopause, illness), disease-induced, medication-induced, psychologic (eg, anxiety, depression), and interpersonal. Informed patient and physician decision-making is the standard for guiding treatment decisions for treatment of female sexual dysfunction. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, gynecologic care, sexual health specialist) should be made if appropriate and available.

Overall, the evidence base for interventions to treat female sexual dysfunction in survivors is weak and high-quality studies are needed.[747,748] Based on evidence from other populations, evidence from survivors when available, recommendations from the American College of Obstetricians and Gynecologists (ACOG),[706] and consensus among NCCN Survivorship Panel members, the panel made recommendations for treatment of female sexual dysfunction in survivors. The panel recommends that treatment be guided by the specific type of problem. Treatments depend on the type of sexual dysfunction and may include both over-the-counter and prescription options, as well as pelvic physical therapy and integrative therapies. When prescription medications are being considered, the risks and benefits should be discussed or the survivor should be referred to an appropriate health care provider (eg, sexual health specialist) for prescription and/or treatment. The evidence base for each recommendation is described herein.

Integrative therapies, including yoga and meditation, may be helpful for female survivors with sexual dysfunction.[544,749] In addition, CBT has been shown to be effective at improving sexual functioning in breast cancer survivors.[750]

Vaginal moisturizers, vaginal gels, oils, and topical vitamin D or E can help alleviate symptoms such as vaginal dryness and sexual pain,[585,751] although data on these over-the-counter products are limited in the general population. In one study of breast cancer survivors, the control group used a non-hormonal moisturizer and saw a transient improvement in vaginal symptoms.[584] Topical anesthetics may help with vaginal pain as shown in a study in 46 breast cancer survivors that found that application of lidocaine to the vulvar vestibule before vaginal penetration improved dyspareunia.[752]

Pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual pain, arousal, lubrication, orgasm, and satisfaction. A small study of 34 survivors of gynecologic cancers found that pelvic floor training significantly improved sexual function.[753]

Vaginal dilators are an option for survivors with pain during sexual activity. In addition, vaginal dilators are used for survivors with vaginal stenosis from pelvic radiation. However, evidence for the effectiveness of dilators is limited.[754]

Several topical prescription medications can also be considered for female survivors with sexual dysfunction. For example, vaginal estrogen (pills, rings, or creams) has been shown to be effective in treating vaginal dryness, itching, discomfort, and painful intercourse in postmenopausal women.[566,588-592] A study in 76 post-menopausal breast

cancer survivors on aromatase inhibitor therapy found that intravaginal testosterone cream or an estradiol-releasing vaginal ring were safe and improved vaginal atrophy and sexual function.[755]

Vaginal androgens (ie, DHEA; also known as prasterone) can be considered for vaginal dryness or pain with sexual activity. Prasterone received FDA approval in 2016. Several studies have shown prasterone to be effective at reducing dyspareunia in postmenopausal women.[756-760] However, a systematic review and meta-analysis published in 2015 concluded that it is uncertain whether prasterone improves menopausal symptoms.[761] A randomized controlled trial of 441 survivors of breast or gynecologic cancer showed that vaginal DHEA led to significant improvements in sexual desire, arousal, pain, and overall sexual function.[597] In this trial, clinically important systemic estrogenic activity was not evident, and the treatment was safe and well tolerated. Overall, data for safety data for the use of androgen-based therapy in survivors of hormonally mediated cancers are limited. The FDA label for prasterone warns that exogenous estrogens are contraindicated in women with a history of breast cancer.[762]

The FDA approved the SERM ospemifene for treating moderate to severe dyspareunia in postmenopausal women without known or suspected breast cancer and without a history of breast cancer in 2013.[763] Ospemifene has been studied in several large trials of women with postmenopausal vulvar and vaginal atrophy and was found to effectively treat vaginal dryness and dyspareunia.[764-766] No data in the survivor population are available. The panel recommends consideration of ospemifene for dyspareunia in survivors of cancers that are not hormonally sensitive.

In August 2015, the FDA approved flibanserin to treat acquired, generalized hypoactive sexual desire disorder in premenopausal women.[767] Meta-analyses have shown that flibanserin resulted in approximately 1 additional satisfying sexual event every 2 months in premenopausal women.[768,769] This drug has not been studied in patients with cancer or survivors, but it is a reasonable option to discuss with premenopausal survivors with low or lack of desire, libido, or intimacy.

Other options for survivors with low or lack of desire, libido, or intimacy include bupropion and buspirone.[770] These drugs have been studied in a few trials involving non-cancer populations.[771-773] Despite limited safety and efficacy data, these drugs may be considered as options for hypoactive sexual desire disorder.

Currently, the panel does not recommend the use of oral phosphodiesterase type 5 inhibitors (PDE5i) for female sexual dysfunction because of the lack of data regarding their effectiveness in women. Although thought to increase pelvic blood flow to the clitoris and vagina,[774,775] PDE5i showed contradictory results in randomized clinical trials of various non-cancer populations of women being treated for sexual arousal disorder.[776-781] More research is needed before a recommendation can be made regarding the use of sildenafil for the treatment of female sexual dysfunction.

Interventions for Male Sexual Dysfunction

Using a consensus-based approach, the NCCN Survivorship Panel concluded that: 1) informed patient and physician decision-making is the standard for guiding treatment decisions for treatment of male sexual dysfunction; and 2) a psychological overlay frequently exists in patients with sexual dysfunction and may be even more pronounced in the face of cancer survivorship. Thus, treatment of male sexual dysfunction may require a multidimensional treatment plan that addresses the underlying issues. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, urology, sexual health

specialist) should be made if appropriate and available. Treatment of sexual dysfunction in male survivors should be guided by the specific type of problem.

Treatment for male sexual dysfunction should include modification of risk factors, such as smoking cessation, weight loss, increasing physical activity, and avoiding excess alcohol consumption. Several trials have shown that such lifestyle modifications can improve sexual function in men.[782-785] In fact, one study found that PDE5i treatment with an aerobic activity program was more effective than PDE5i treatment alone in 60 men with ED.[786] Evidence for these effects in patients with cancer and survivors is lacking.

In addition, treatment of psychosocial problems, with referral to sex and couples therapy as appropriate, can often alleviate symptoms of male sexual dysfunction.[787-791] Small studies in survivors of prostate cancer suggest that these approaches can be helpful in the survivorship population as well.[792,793] Therapy is often offered in conjunction with medical therapy.

PDE5i treatment has been shown to improve the symptoms of ED and be well tolerated.[794,795] These drugs can also be used for problems with male orgasms (eg, less intensity, difficulty achieving). Many studies have also shown the efficacy and tolerability of PDE5i for treating ED in patients with cancer and survivors.[796,797] Importantly, PDE5i are contraindicated in patients taking oral nitrates, because together they can lead to a dangerous decrease in blood pressure.[798,799] The timing and dose of on-demand PDE5i should be started conservatively, and it should be titrated to maximum dose if needed.[723] The patient should be monitored periodically for efficacy, side effects, and any significant change in health status. In addition to on-demand PDE5i treatment, studies have shown that daily, low-dose treatment with these drugs can be effective.[800-803]

If total morning testosterone is <300 ng/dL, then hypogonadism is diagnosed and testosterone therapy may relieve symptoms of ED, problems with ejaculation, or problems with orgasm.[804] A randomized controlled trial in 470 men older than 65 years of age with testosterone levels <275 ng/dL found that testosterone gel led to improvements in sexual function, desire, and activity.[805,806] Other studies have shown that the addition of testosterone to PDE5i therapy in men with low serum testosterone levels helps improve ED.[807-812] Testosterone therapy should not be used if contraindicated by the primary oncologic diagnosis (eg, prostate cancer on active surveillance, prostate cancer on ADT).

Other treatments may help with ED and with ejaculation and orgasm issues. Although evidence in the general population is lacking,[813] studies in prostate cancer survivors suggest that pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual function in this population.[814,815] Vibratory therapy may reduce problems with orgasm.[816] Finally, SSRIs (paroxetine, sertraline, citalopram, fluoxetine) dosed daily or clomipramine dosed on demand may relieve problems with ejaculation (dry, retrograde, delayed, or climacturia).[817-820]

Sleep Disorders

Sleep disturbances include insomnia (trouble falling or staying asleep resulting in daytime dysfunction), excessive sleepiness (which can result from insufficient sleep opportunity, insomnia, or other sleep disorders), and sleep-related movement or breathing disorders.[821] Sleep disturbances are common, affecting 30% to 50% of patients with cancer and survivors, often in combination with pain, fatigue, anxiety, and/or depression.[821-831] Improvements in sleep quality lead to improvements in

fatigue, mood, and overall quality of life.[400] Most clinicians, however, do not know how best to evaluate and treat sleep disorders.[821]

Sleep disorders are common in patients with cancer as a result of multiple factors, including disease- or treatment-related biologic changes in sleep and wake regulation, the stress of diagnosis and treatment, and side effects of therapy (eg, pain, fatigue).[832] In addition, evidence suggests that changes in inflammatory processes from cancer and its treatment play a role in sleep disorders. These sleep disturbances can be perpetuated in the survivorship phase by chronic side effects, anxiety, depression, medications, and maladaptive behaviors such as shifting sleep times, excessive time in bed because of fatigue, and unplanned naps.[832]

Additional information about sleep disorders in patients with cancer can be found in the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org). These guidelines may be modified to fit the individual survivor's circumstances.

Screening for and Assessment of Sleep Disorders

Survivors should be screened for possible sleep disorders at regular intervals, especially when they experience a change in clinical status or treatment. The panel lists screening questions that can help determine whether concerns about sleep disorders or disturbances warrant further assessment. Other tools to screen for sleep problems have also been validated and may be used for individual intensive screening to assess sleep quality.[833-836] It is important to note that survivors may have more than 1 sleep disorder simultaneously.

The panel recommends that sleep/wake timing and/or sleep logs or diaries be reviewed. Many survivors may be using wearable devices to track sleep. However, studies have shown that these devices do not accurately measure sleep when compared to results of polysomnography.[837-842] Results from wearable devices may be useful for tracking sleep patterns, but should not be used for diagnosis or clinical decision making.

If concerns regarding sleep quality are significant, the panel recommends that treatable or modifiable contributing factors be assessed and managed. Comorbidities that can contribute to sleep problems include alcohol and substance abuse, obesity, cardiac dysfunction, endocrine dysfunction, respiratory disorders, anemia, neurologic disorders (including CIPN), pain, fatigue, and emotional distress. Screening for common sleep disorders such as obstructive sleep apnea (OSA), restless legs syndrome (RLS, also known as Willis-Ekbom disease), and circadian rhythm sleep wake disorders (such as shift work) can help identify specific therapies for these conditions that may be helpful. In addition, some medications, both prescription and over-the-counter, can contribute to sleep issues. For instance, pain medication, antiemetics, antihistamines, antidepressants, and antipsychotics can all contribute to sleep disturbance, as can the persistent use of sleep aids.

Diagnosis of Sleep Disorders

The panel divided sleep disorders into 2 general categories: 1) insomnia and 2) sleep disturbance and/or excessive sleepiness. Insomnia is diagnosed when patients have difficulty falling asleep, staying asleep, or waking up too early at least 3 times per week for at least 4 weeks. These categories were based on the most common types of symptoms that patients with sleep disturbances are likely to report.

Diagnosing patients with excessive sleepiness can be challenging, because it can be caused by a variety of factors. When excessive

sleepiness is associated with observed apneas or snoring, the STOP questionnaire can be used as a screening tool to determine the risk of OSA.[843] Other screening tools for OSA risk have also been validated.[844,845] Sleep studies can confirm the diagnosis of OSA; alternatively, referral can be made to a sleep specialist or PCP for further evaluation. Narcolepsy should be considered when excessive sleepiness is accompanied by cataplexy. Parasomnias (eg, sleep walking, sleep paralysis, periodic limb movement disorder) and circadian rhythm disorders (eg, shift work sleep disorder, advanced or delayed sleep phase disorders) should also be considered; survivors with these types of sleep disturbances may also present with symptoms of insomnia.

Excessive sleepiness can also be associated with uncomfortable sensations or an urge to move the legs (and sometimes the arms or other body parts). These symptoms are usually worse at night and with inactivity, may be improved or relieved with movement such as walking or stretching, and indicate RLS. In these individuals, a history and physical exam should be performed, with evaluation for iron deficiency if RLS is diagnosed.[846,847] Alternatively, referral can be made to a sleep specialist or PCP for further evaluation.

Evaluation for Insomnia

If insomnia is diagnosed, details should be obtained regarding the course of insomnia, including the duration of symptoms. Insomnia is considered to be chronic if symptoms have been ongoing for ≥3 months. It should also be determined whether or not the insomnia symptoms are causing distress, impacting daytime functioning, or affecting the survivor's quality of life.

Management of Sleep Disorders

In all cases, comorbidities that may be contributing to the sleep disorder should be addressed. Survivors should also be advised that sleepiness can increase the risk of accidents, including while operating a motor vehicle. In addition, several types of interventions are recommended, as described below.[402,821,848] Referral to a sleep specialist can be considered in most cases, especially for OSA, RLS, parasomnias, circadian rhythm disorders, narcolepsy, and chronic or refractory insomnia.

Sleep Hygiene Education

Educating survivors about general sleep hygiene is recommended, especially for the treatment of circadian rhythm disorders, insomnia, and excessive sleepiness associated with insufficient sleep time.[849-851] Key points are listed in the guidelines and include regular morning or afternoon physical activity; daytime exposure to bright light; keeping the sleep environment dark, quiet, and comfortable; and avoiding heavy meals, moderate to strenuous physical activity, alcohol, and nicotine near bedtime. However, sleep hygiene alone is insufficient for the effective management of sleep disorders.

Physical Activity

Physical activity can improve sleep in middle-aged and older individuals in non-cancer settings.[852-854] Physical activity may also improve sleep in patients with cancer and survivors.[382,855-860] One randomized controlled trial compared a standardized yoga intervention plus standard care with standard care alone in 410 survivors (75% breast cancer; 96% women) with moderate to severe sleep disruption.[857] Participants in the yoga arm experienced greater improvements in global and subjective sleep quality, daytime functioning, and sleep efficiency (all $P \leq .05$). In addition, the use of sleep medication declined in the intervention arm ($P \leq .05$). However, a 2013 systematic review concluded that the evidence

that yoga programs aimed at cancer survivors improve insomnia or sleep quality is very limited.[861]

A 2012 meta-analysis of randomized controlled trials in patients who had completed active cancer treatment showed that physical activity improved sleep at a 12-week follow-up.[382] Overall, however, data supporting improvement in sleep with physical activity are limited in the survivorship population.

Psychosocial Interventions

Psychosocial interventions such as CBT for insomnia (CBT-I), psychoeducational therapy, and supportive expressive therapy are recommended to treat sleep disturbances in survivors.[862]

In particular, several randomized controlled trials have shown that CBT improves sleep in the survivor population.[390-392,399,863-865] For example, a randomized controlled trial in 150 survivors (58% breast cancer; 23% prostate cancer; 16% bowel cancer; 69% women) found that a series of 5 weekly group CBT sessions was associated with a reduction in mean wakefulness of almost 1 hour per night, whereas usual care (in which physicians could treat insomnia as they would in normal clinical practice) had no effect on wakefulness.[390] Another trial randomized 96 survivors (68% breast cancer; 87% female) to a 7-week intervention of CBT, armodafinil, CBT plus armodafinil, or placebo.[865] CBT resulted in significant improvements in insomnia symptoms and sleep quality at 0 and 3 months after the intervention, but armodafinil had no effect. A recent meta-analysis identified 8 studies, including 752 cancer survivors, and found large effect sizes for self-reported insomnia severity (d = .77) following CBT.[866] Further, a meta-analysis of randomized controlled trials in cancer survivors found strong evidence that CBT- I can produce large and durable effects on insomnia severity.[866] In fact, the American College of Physicians recommends that CBT be the initial treatment for all adults with chronic insomnia disorder.[867]

A small randomized controlled trial of 57 survivors (54% breast cancer; 75% women) found that mind–body interventions (mindfulness meditation or mind-body bridging), decreased sleep disturbance more than sleep hygiene education did.[868] A preliminary report of a subset of participants in a larger randomized controlled trial of breast cancer survivors showed MBSR improved objective sleep parameters including sleep efficiency and percent of sleep time.[869]

A randomized, partially blinded, noninferiority trial compared CBT with MBSR in 111 patients with cancer.[870] Both groups experienced improvements in sleep diary-measured sleep onset latency, wake after sleep onset, total sleep time, stress, and mood disturbance. MBSR was inferior to CBT for improving insomnia severity immediately following the intervention, but was noninferior at 5 months. These results have not been replicated in survivors, and the relative efficacy of these strategies is not established in this population. Another randomized study compared Tai Chi Chih, a mindful movement meditation, with CBT-I in 90 breast cancer survivors and found it to be non-inferior for improving insomnia symptoms at 3, 6, and 15 months after the intervention.[871]

Pharmacologic Interventions

Many pharmacologic treatments for sleep disturbances are available, including hypnotics for insomnia (eg, zolpidem, ramelteon).[872,873] Many of the FDA-approved hypnotics are BZD receptor agonists and can be associated with dependence, abuse, and withdrawal. The panel therefore recommends that survivors taking these medications be assessed every 1 to 3 months to determine if they are still needed. In

addition, survivors should be informed that hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating).

In addition, antidepressants, antihistamines, atypical antipsychotics, other BZD receptor agonists, and nutritional/herbal supplements (eg, melatonin) are often used off-label for the treatment of insomnia, even though limited to no efficacy or effectiveness data are available for this use. The panel noted that these medications are associated with significant risks and should be used with caution. One small, open-label study found that the antidepressant mirtazapine increased the total amount of nighttime sleep in patients with cancer.[874] A recent randomized, double-blind, placebo-controlled study of 95 postmenopausal breast cancer survivors found that melatonin subjectively improved sleep quality after 4 months of treatment (mean change in Pittsburgh Sleep Quality Index (PSQI) score, -0.1 for placebo and -1.9 for melatonin; $P < .001$).[532] Overall, however, data on pharmacologic interventions aimed at improving sleep in patients with cancer and survivors are lacking.[831]

Treatment of Obstructive Sleep Apnea

Weight loss should be recommended to survivors with OSA, because studies have shown weight loss to be associated with reduced hypoxia and excessive sleepiness in patients with OSA.[875] Small randomized studies have also shown that physical activity can improve OSA symptoms independent of weight loss.[876,877] In addition, survivors with OSA should be referred to a sleep specialist. The most common medical treatment for OSA is continuous positive airway pressure (CPAP).[878]

Treatment of Restless Legs Syndrome

For RLS associated with iron deficiency, iron replacement can improve symptoms. RLS is also treated with dopamine agonists, BZDs, gabapentin, and/or opioids.[879-887] Two separate recent meta-analyses found dopamine agonists and calcium channel alpha-2-delta ligands (eg, gabapentin) to be helpful for reducing RLS symptoms and improving sleep in the noncancer setting.[887,888] Referral to a sleep specialist is also an appropriate option for survivors with RLS. In addition, certain mind-body interventions and dietary supplementation may benefit some patients with RLS, although data are limited.[889]

Recommendations for Preventive Health

Analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS) indicates that a large proportion of cancer survivors have significant comorbidities, smoke, are obese, and/or do not engage in physical activity.[890] Analysis of data from other studies, including the National Health Interview Survey, showed similar results.[891-893] Separate surveys by the ACS and the CDC found that 9.3% and 17% of survivors smoke, respectively.[893,894]

In addition, many survivors forego recommended cancer screenings (ie, colorectal and cervical screening) and follow-up surveillance[895-897] or demand more intense surveillance than evidence supports.[75]

Healthy Lifestyles

Healthy lifestyle habits, such as engaging in routine physical activity, maintaining a healthy diet and weight, and avoiding tobacco use, have been associated with improved health outcomes and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.[898-904] Therefore, survivors should be encouraged to achieve and maintain a healthy lifestyle, including attention to weight management, physical activity, metabolic health, and dietary habits. Survivors should be advised to limit alcohol intake and avoid tobacco products, with emphasis on tobacco cessation if the

survivor is a current smoker or user of smokeless tobacco (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[905] Clinicians should also advise survivors to practice sun safety habits as appropriate, such as using a broad-spectrum sunscreen, avoiding peak sun hours, and using physical barriers. Finally, survivors should be encouraged to see a PCP regularly and adhere to age-appropriate health screenings, preventive measures (eg, immunizations), and cancer screening recommendations.

The panel made specific recommendations regarding physical activity, weight management, nutrition, and supplement use, which are discussed herein. Although achieving all of these healthy lifestyle goals may be difficult for many survivors, even small reductions in weight among overweight or obese survivors or small increases in physical activity among sedentary individuals are thought to yield meaningful improvements in cancer-specific outcomes and overall health.[906] Clinicians should assess individual and community-level barriers to meeting the healthy lifestyle recommendations and support patients in developing strategies to overcome challenges.

Physical Activity

During cancer treatment, many survivors become deconditioned and can develop impaired cardiovascular fitness because of the direct and secondary effects of therapy.[907] Randomized trials have shown that exercise training is safe, tolerable, and effective for most survivors. Structured aerobic and resistance training programs after treatment can improve cardiovascular fitness and strength and can have positive effects on balance, body composition, fatigue, emotional well-being, and quality of life.[377,382,387,454,908-915] The effectiveness of exercise is especially well studied in women with early-stage breast cancer. Survivors of breast cancer who exercise have improved cardiovascular fitness and therefore an increased capacity to perform daily life functions, resulting in a better quality of life.[378,384,387,454,916] Furthermore, a recent study of adult survivors of childhood Hodgkin lymphoma found that vigorous exercise was associated with a reduction in the risk of major cardiovascular events after a median follow-up of 11.9 years.[188] In fact, the finding was dose-dependent, and survivors who reported ≥9 metabolic equivalent (MET) h/wk experienced a 51% reduction in risk compared with those reporting <9 MET h/wk (P = .002). A similar study in patients with breast cancer found a similar reduction in the risk of cardiovascular events with ≥9 MET h/wk.[189]

In addition, observational studies have consistently found that physical activity is linked to decreased cancer incidence and recurrence and increased survival for certain tumor types.[912,917-932] For example, one meta-analysis of 6 studies including more than 12,000 survivors of breast cancer found that post-diagnosis physical activity reduced all-cause mortality by 41% (P < .00001) and disease recurrence by 24% (P = .00001).[921] Data from other meta-analyses primarily consisting of observational studies of survivors of colorectal, ovarian, non-small cell lung, brain, prostate, and breast cancers show that physical activity is associated with decreased all-cause mortality and/or cancer-specific mortality.[919,922,930,933] In fact, analyses of data from 986 survivors of breast cancer from the National Runners' and Walkers' Health Studies found that mortality decreased with increased rates of energy expenditure.[931] Evidence in other disease sites is less robust, but also suggests survival benefits associated with exercise in survivors after treatment.[933]

Data also support the idea that inactivity/sedentary behavior is a risk factor for cancer incidence and mortality and impacts mood and quality of life in survivors, independent of the level of an individual's recreational or occupational physical activity.[898,934-940] For example, in a cohort of more than 2000 survivors of nonmetastatic colorectal cancer,

those who spent more leisure time sitting had a higher mortality than those who spent more time in recreational activity.[898]

Evaluation and Assessment for Physical Activity

Survivors should be asked about readiness for participation in and their current level of physical activity at regular intervals. The Godin Leisure-Time Exercise Questionnaire is one tool that can be used to assess a survivor's exercise behavior, with a modified version also able to assess daily time in moderate-to-vigorous activity.[941,942]

For survivors who are not meeting the guideline recommendations (see later discussion), barriers to physical activity should be discussed and addressed, if possible. Common barriers include not having enough time to exercise, not having access to an acceptable exercise environment, uncertainty about safety of exercise post-treatment, lack of knowledge regarding appropriate activities, and physical limitations.[943] Alleviation of pain, fatigue, distress, or nutritional deficits can facilitate the initiation of an exercise program.

Risk Assessment for Exercise-Induced Adverse Events

Exercise is considered safe for most survivors.[387,454,944] However, a significant portion of survivors may have comorbid conditions or risk factors that make them unable to safely exercise without trained supervision.[945] Therefore, a risk assessment is required for all survivors before prescribing a specific exercise program.[454,946] The type of cancer, treatment modalities received, and the number and severity of comorbidities determine risk levels.[944] Thus, disease and treatment history, late and long-term effects, and comorbidities should be assessed. A standardized pre-participation screening questionnaire, such as the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+),[947] can also be considered to identify patients for whom unsupervised physical activity is likely safe versus those for whom it may pose undue risk.

Survivors with peripheral neuropathy, poor bone health, arthritis, or musculoskeletal issues are considered at moderate risk for exercise-induced adverse events. Stability, balance, and gait should be assessed in survivors with peripheral neuropathy and possibly in survivors with poor bone health before they engage in exercise, and exercise choice should be made based on the results (ie, stationary bike or water aerobics for survivors with poor balance). In addition, balance training can be recommended for patients at risk for falls. Survivors with osteoporosis should have fracture risk and/or bone density assessed as clinically indicated before initiating an exercise program. Moderate-risk survivors can often follow the general recommendations for physical activity; however, medical clearance and/or referrals to trained personnel such as a physical or occupational therapist, certified exercise professional, or rehabilitation specialist can also be considered. Specialized training in working with survivors is available for both physical therapists and exercise professionals through the American College of Sports Medicine (ACSM; http://www.acsm.org/get-certified) and the American Physical Therapy Association (APTA) Oncology section (http://oncologypt.org/home-page.cfm). Survivors should be encouraged to use an ACSM- or APTA-certified trainer when available.

Lymphedema is not a contraindication for physical activity, and no special precautions are required for cardiovascular/aerobic exercise or strength training of unaffected limbs (see *Survivor Lymphedema Education,* above).[448-450,452,453,457] Progressive resistance training under supervision is recommended as part of treatment for survivors with lymphedema (see *Treatment of Lymphedema,* above).

Survivors at high risk for exercise-associated adverse events include those with a history of lung surgery or major abdominal surgery, an ostomy, cardiopulmonary comorbidities (eg, chronic obstructive pulmonary disease [COPD], CHF, CAD, cardiomyopathy), ataxia, severe nutritional deficiencies, severe fatigue, or worsening/changing physical condition (eg, lymphedema exacerbation). These survivors should receive medical evaluation and clearance prior to initiation of an exercise program and referral to trained personnel for a supervised exercise program.[944] In general, exercise should be individualized to the participant based on current exercise level and medical factors and should be increased in terms of intensity, duration, and frequency as tolerated.

Physical Activity Recommendations for Survivors

Both the ACS and the ACSM have made physical activity recommendations for cancer survivors.[454,914] The panel supports these recommendations and has adapted them as follows:

1. Physical activity and exercise recommendations should be tailored to individual survivors' abilities and preferences.
2. Survivors who are able should be encouraged to engage in daily physical activity, including exercise, routine activities, and recreational activities.
3. All survivors should be encouraged to avoid prolonged sedentary behavior (eg, sitting for long periods) and return to daily activities as soon as possible.
4. Physical activity for cancer survivors:
    - Overall volume of weekly activity should be at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity, or an equivalent combination
    - Individuals should engage in 2 to 3 sessions per week of strength training (see *Resistance and Strength Training*, below) that include major muscle groups; and
    - Major muscle groups should be stretched at least two days per week.

The panel acknowledges that most survivors do not meet these exercise recommendations, and a significant portion reports that they perform no leisure-time activity.[890,948] However, the evidence suggests that even light-intensity physical activity can improve physical functioning in survivors.[949] For survivors who are inactive, clinicians should not advise the immediate initiation of a high-intensity, high-frequency program.[950,951] Instead, the panel suggests that clinicians provide sufficient information to encourage survivors to avoid a sedentary lifestyle.[946] Survivors and providers should work together to develop incremental short- and long-term physical activity goals. These goals may include incremental increases in time spent in physical activity or in intensity of activity over time. The panel suggested a possible initial physical activity prescription (starting inactive survivors with 1 to 3 light-/moderate-intensity sessions of 20-minute or more per week), with progression based on tolerance.[950] For survivors tolerating the minimum guideline recommendations, clinicians should consider encouraging incremental increases in time spent in physical activity or in intensity of activity. Walking and using a stationary bike are safe for virtually all survivors.

Resistance and Strength Training

The health benefits of resistance training include improvement in muscle strength and endurance, improvements in functional status, and maintenance/improvement in bone density. Studies in survivors have shown improvements in lean body mass, muscular function, and upper

body strength, and a slowing of physical function deterioration.[952-957] A recent systematic review of 15 studies of resistance training interventions during and/or after cancer treatment concluded that meaningful improvements in physiologic and quality-of-life outcomes can be achieved.[954] A similar review of 11 randomized controlled trials came to similar conclusions.[957] One recent study that included 2863 cancer survivors found resistance exercise to be associated with a 33% lower risk of all-cause mortality (95% CI, 0.45–0.99), independent of aerobic exercise.[958]

Multi-joint exercises (eg, chest press, shoulder press, squats, lunges, pushups) are recommended over exercises focused on a single joint, and all major muscle groups (chest, shoulders, arms, back, abdomen, and legs) should be incorporated into a resistance training program. For survivors who do not currently engage in resistance training, clinicians should recommend starting with 1 set of each exercise and progress up to 2 to 3 sets as tolerated. A weight that would allow the performance of 10 to 15 repetitions is recommended; however, individualizing recommendations for resistance and strength training is important. Survivors can consider increasing the weight when 3 sets of 10 to 15 repetitions become easy.

Interventions to Increase Physical Activity

Dozens of studies have looked at the efficacy of a variety of behavioral and exercise interventions for increasing exercise behavior in cancer survivors.[454,913,959-961] However, data comparing different interventions are limited, and there is currently no “best” physical activity program for cancer survivors.[962-965] Several studies have examined the physical activity and counseling preferences of survivors, with the goal of informing possible strategies to best encourage increased activity in this population.[966-968]

The panel suggests several strategies to help increase physical activity. These strategies include a simple recommendation from a physician, physical therapist, and/or certified exercise physiologist.[969-971] In addition, participation in supervised exercise programs or classes or enlisting the support of an exercise group or buddy may be helpful for survivors.[676,972-974] In addition, setting short- and long-term goals and considering the use of a pedometer or wearable activity tracker to monitor these goals (eg, achieving 10,000 steps per day) can be helpful in overweight or obese adults.[975-981] Print materials, telephone counseling, motivational counseling, and theory-based behavioral approaches (discussed in *Health Behavioral Change*, below) are other strategies that may be effective for increasing physical activity in the survivor population.[973,979,982-987] Combination approaches (eg, oncologist recommendation plus exercise DVDs, pedometers, exercise diaries, exercise education sessions) may also increase exercise participation in survivors.[988]

Nutrition and Weight Management

Weight gain after cancer diagnosis and treatment is common, and the prevalence of obesity in the survivor population is greater than in the general population and has increased at a faster rate.[522,989,990] The vast majority of studies on weight and weight gain in survivors have been performed in survivors of breast cancer, but some studies have also been done in survivors of other cancers. Weight gain or being overweight or obese can exacerbate a survivor’s risk for functional decline, comorbidity, and cancer recurrence or death, and can reduce quality of life.[522,991-998] For example, a systematic review and meta-analysis of studies in survivors of breast cancer found a correlation between higher body mass index (BMI) and higher risk of total and breast-cancer-specific mortality.[993] Additionally, a recent meta-analysis demonstrated that this risk for increased breast cancer mortality is predominantly confined to the pre- and perimenopausal, hormone-

receptor-positive population.[999] A retrospective study of survivors of stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that survivors with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[899,903] In addition, some evidence suggests that weight loss or gain increases mortality risk in survivors, suggesting that weight maintenance is optimal.[1000]

ASCO recently published a position statement on obesity and cancer.[1001] The ASCO panel established an initiative to reduce the impact of obesity on cancer through education, tools, and resources for clinicians by promoting research (eg, in health behavioral change) and advocating for policies that can help patients with cancer manage their weight.

Nutrition and Weight Management Assessment

The BMI of survivors should be evaluated at regular intervals. A BMI of 18.5 to 24.9 kg/m^2 is considered ideal. It is important to inform patients of their weight status, particularly if they are underweight (BMI <18.5), overweight (BMI = 25–29.9), or obese (BMI ≥30), and discuss the importance of interventions to attain a normal body weight. The panel notes, however, that BMI should be considered in context of body composition. For more muscular survivors, waist circumference may be a better measure of overall disease risk. A waist circumference of >35 inches for women and >40 inches for men increases risk for diabetes, hypertension, and cardiovascular disease.[1002]

Current dietary and physical activity habits and potential barriers to physical activity or a healthful diet of those in high-risk groups should be ascertained either by the oncologist or other appropriate allied health personnel (eg, nurses, dietitians). In addition, effects of cancer treatment and other medical issues, including psychosocial distress and fear of recurrence, should be assessed and addressed as necessary.

Weight Management for Survivors

Providers should discuss strategies to prevent weight gain for normal and overweight/obese survivors. Clinicians should reinforce the importance of maintaining a normal body weight throughout life and stress that weight management should be a priority for all cancer survivors. In conjunction with primary care, survivors should be assessed for metabolic health, body composition, and BMI. Regardless of BMI, all survivors should be advised about nutrition (see *Nutrition in Survivors*, below) and physical activity recommendations (see *Physical Activity*, above). Contributing treatment effects and risk factors should be managed as clinically indicated. For additional resources, see the ASCO Tool Kit on Obesity and Cancer (https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/obesity-cancer) and the LIVESTRONG MyPlate Calorie Tracker (http://www.livestrong.com/myplate/).

Recommendations for Normal Weight Survivors

In addition to discussing nutrition (see *Nutrition in Survivors*, below) and physical activity (see *Physical Activity*, above), clinicians should reinforce the importance of maintaining a normal weight throughout life in survivors with a BMI in the normal range.

Recommendations for Overweight/Obese Survivors

Survivors with a BMI in the overweight or obese range should be engaged in discussions about nutrition, weight management, and physical activity, as outlined in these guidelines. In addition, clinicians should specifically discuss portion control; substituting high-calorie foods with low-calorie, healthful, nutrient-dense foods; and tracking diet, calories, and physical activity. Clinicians should also refer overweight/obese survivors to appropriate hospital-based or community resources. Furthermore, contributing psychosocial factors should be

assessed and addressed. Referrals can also be made to a registered dietitian, especially those who are Certified Specialists in Oncology Nutrition (CSO) or members of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics. Diet, exercise, and behavioral modification are the cornerstones of weight management; however, in cases of morbid obesity, pharmacologic agents or bariatric surgery can be considered with appropriate referral to primary care and other providers. Of note, the safety and efficacy of weight loss drugs or bariatric surgery in cancer survivors is currently unknown.

Randomized trials have shown that intensive behavioral weight loss interventions can lead to weight loss in overweight/obese cancer survivors.[1003-1008] For example, the ENERGY trial used a group-based behavioral intervention with telephone counseling and newsletters and achieved a 6.0% weight loss compared with 1.5% weight loss in the control group at 12 months.[1008] In general, however, these trials see some weight re-gained in survivors at the end of the intervention; maintenance of weight loss remains a challenge in this population.[1003]

Recommendations for Underweight Survivors

Survivors with a BMI in the underweight range should be engaged in discussions about nutrition (see below), and contributing psychosocial factors should be assessed and addressed. In addition, advising underweight survivors to increase their frequency of eating and to avoid fluid intake with meals may help with weight gain. Furthermore, smoking status, dental health, swallowing and taste/smell disorders, and gastrointestinal motility should be assessed and addressed as appropriate. Consideration can also be given to referral to a registered dietitian for individualized counseling.

Nutrition in Survivors

Systematic reviews and meta-analyses of observational studies have shown that healthy dietary patterns are associated with a decreased risk of primary cancer development.[1009-1012] A population study in England with >65,000 participants found that consumption of ≥7 servings daily of fruit and vegetables reduced cancer incidence by 25% (HR, 0.75; 95% CI, 0.59–0.96).[1013] In addition, results of a randomized controlled trial, in which 4282 women were randomly assigned to a Mediterranean diet with olive oil, a Mediterranean diet with mixed nuts, or a control low-fat diet, suggest that the olive oil/Mediterranean diet reduced the risk of invasive breast cancer (HR, 0.32; 95% CI, 0.13–0.79).[1014]

Data also suggest that healthy dietary patterns (as characterized by plant-based diets that have ample amounts of fruits, vegetables, and whole grains, with limited quantities of red and processed meats and refined grains and sugars) are associated with a decrease in cancer recurrence and improved outcomes in survivors.[914,1015,1016] In survivors of stage III colon cancer, a diet consisting of more fruits, vegetables, whole grains, poultry, and fish, and less red meat, refined grains, and concentrated sweets was found to be associated with an improved outcome in terms of cancer recurrence and death, as well as overall survival.[1017] Higher dietary glycemic load (associated with high intakes of refined starches and sugars) was associated with an increased risk of recurrence and mortality in this same population.[1018] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intakes of red and processed meat had a higher risk of colorectal cancer-specific mortality than those with low intakes (RR, 1.79; 95% CI, 1.11–2.89).[1019] For survivors of non-colorectal cancers,

the evidence linking a healthy diet with better outcomes is less robust. A study of 1901 survivors of early-stage breast cancer found that a diet higher in fruits, vegetables, whole grains, and poultry and lower in red and processed meats and refined grains resulted in a decreased risk of overall death and death from non-breast cancer causes, but was not associated with risk of breast cancer recurrence or death from breast cancer.[1020]

Unfortunately, a national survey of 1533 adult cancer survivors and 3075 matched controls found that cancer survivors had worse dietary patterns.[1021] All survivors should be encouraged to make informed choices about food to ensure variety and an adequate nutrient intake. Recommendations for food sources in a healthy diet are included in the guidelines. In general, a healthy diet is rich in plant sources, such as vegetables, fruits, whole grains, legumes, olive or canola oil, avocados, seeds, and nuts. Fish and poultry are recommended, while red and processed meats should be limited. Processed foods and foods and beverages with high amounts of sugars and/or fats should also be limited.

In addition, survivors should be advised to limit alcohol intake to one drink per day for a woman and two drinks per day for a man.[914] An exception is for survivors of liver, esophageal, kidney, and head and neck cancers, who should refrain from alcohol due to an increased risk of mortality with alcohol consumption.[1016,1022,1023] Survivors of breast cancer do not need to be advised to refrain completely from alcohol consumption, because it has no proven impact on outcomes, but should adhere to general population recommendations.[1016,1024,1025]

Currently, no consensus regarding the role of soy foods in cancer control exists. Several large studies have found no adverse effects on breast cancer recurrence or total mortality related to the intake of soy food.[1026-1030] In fact, trends towards decreased recurrence and mortality were observed. The panel therefore considers moderate consumption of soy foods (≤3 servings a day) to be prudent.

The NCCN Survivorship Panel supports a plant-based diet with the majority of food being vegetables, fruits, and whole grains.

1. Recommended food volumes
    - Vegetables and fruits should comprise half the volume of food on the plate (30% vegetables; 20% fruit)
    - Whole grains should comprise 30% of the plate
    - Protein should comprise 20% of the plate
2. Sources of dietary components
    - Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and fatty fish
    - Carbohydrates: vegetables, fruits, whole grains, and legumes
    - Protein: poultry, fish, legumes, low-fat dairy foods, and nuts
3. Limit intake of red meat and refined sugars
4. Avoid processed meat.

The use of healthy recipes, such as those found in resources such as the ACS's "Find Healthy Recipes" website: http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/index, should be encouraged.

Supplement Use in Survivors

Numerous systematic reviews and meta-analyses have assessed the role of various vitamins or other dietary supplements for the purposes of primary cancer prevention, cancer control, or preventing cancer recurrence.[1031-1043] No clear evidence supports an effect of dietary supplements for cancer prevention, control, or recurrence, although a

few exceptions may warrant further studies.[1044,1045] In fact, a prospective cohort study of 2,118 postmenopausal cancer survivors found that postdiagnosis dietary supplement use was associated with a trend towards higher mortality among those with a poor diet.[1046]

Furthermore, although the FDA regulates dietary supplement products under the Dietary Supplement Health and Education Act of 1994 (DSHEA),[1047] analyses of dietary supplements from multiple manufacturers have found that many products do not contain the purported active ingredient and can contain unlisted ingredients such as cheap fillers (eg, rice, house plants) or banned pharmaceutical ingredients.[1048,1049] Furthermore, dietary supplements may remain available to consumers even following FDA class I drug recalls.[1048]

Despite the lack of data supporting supplement use and the lack of assurance regarding supplement quality, as many as 79% to 85% of survivors take some vitamin or mineral dietary supplements, often without disclosing this information to their physicians.[1046,1050,1051] Thus, the panel recommends that providers ask survivors about supplement use at regular intervals. The panel notes that supplement use is not recommended for most survivors, except in instances of documented deficiencies (eg, survivors of gastric cancer), inadequate diet, or comorbid indications (eg, osteoporosis,[1052] ophthalmologic disorders,[1053] cirrhosis[1054,1055]). Survivors should be advised that taking vitamin supplements does not replace the need for adhering to a healthy diet. If deemed necessary (eg, for survivors taking multiple and/or or unfamiliar supplements), referral to a registered dietitian, especially a CSO, should be considered for guidance in supplement use.

Health Behavioral Change

Lifestyle behaviors are one area survivors can control if they are encouraged to change and are aware of resources to help them. Ambivalence about changing behavior is common in the general population, but among cancer survivors levels of motivation are often heightened, especially close to the time of diagnosis.[908,969,1056]

Data suggest that recommendations from the oncologist can carry significant weight for patients with cancer, yet many providers do not discuss healthy lifestyle changes with survivors.[969-971] Print materials and telephone counseling are other strategies that may be effective for improving healthy behavior in the survivor population, and several trials show support for these strategies.[973,979,984-987,1004,1057] In fact, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer.[985,1058] Moreover, results of the recently completed Reach Out to Enhance Wellness (RENEW) trial showed that an intervention of telephone counseling and mailed materials in 641 older, obese, and overweight survivors of breast, prostate, and colorectal cancers not only resulted in improved diet quality, weight loss, and physical activity but also had a long-lasting effect that was sustained a year after the intervention was complete.[973] The Exercise and Nutrition Routine Improving Cancer Health (ENRICH) intervention, which includes 6 theory-based 2-hour sessions, has also shown a positive effect on physical activity, diet, weight, and BMI.[1059]

Another strategy, motivational counseling, may be an effective technique for increasing physical activity and other healthy behaviors in cancer survivors.[982,983] Motivational counseling focuses on exploring the survivor's thoughts, wants, and feelings and is directed at moving ambivalence so survivors choose to change their behavior.[1060] Other behavioral strategies may also be useful, such as improving self-efficacy (ie, the belief that one can perform the actions of new activity and maintain this practice by addressing barriers and planning for behavior change) and self-monitoring.[1061,1062]

Immunizations and Prevention of Infections

Cancer survivors are at elevated risk for infection because of immune suppression associated with previous cancer treatments, such as chemotherapy, radiation, corticosteroids, certain surgeries, and stem cell transplantation. In fact, antibody titers to vaccine-preventable diseases decrease after anti-cancer treatment.[1063,1064] In addition, survivors are at increased risk of complications from vaccine-preventable diseases, such as those caused by human papillomavirus (HPV) and influenza viruses.[1064,1065]

Many infections in survivors can be prevented by the use of vaccines. However, data from the BRFSS found that 42% of survivors did not receive an influenza vaccination in 2009, and 52% reported never receiving a pneumococcal vaccination.[890] Analysis of the SEER-Medicare database showed that survivors of breast cancer, aged 65 years or older, were less likely to receive an influenza vaccination than matched non-cancer controls.[114] A separate analysis of the SEER-Medicare database by another group found similar results.[1066]

Vaccines represent a unique challenge in cancer and transplant survivors because they may or may not trigger the desired protective immune responses due to possible residual immune deficits.[1067-1069] In addition, certain vaccines, such as those that are live attenuated (eg, zoster; measles, mumps, rubella [MMR]), are contraindicated in actively immunosuppressed survivors because of an increased risk of developing the disease and/or prolonged shedding of the live organism given in the vaccine.

Risk Assessment and Screening for Immunizations and Prevention of Infections

Survivors are at elevated risk for infections if their cancer treatment included chemotherapy, monoclonal antibodies (eg, rituximab, alemtuzumab), radiation, corticosteroids, splenectomy, and/or hematopoietic cell transplantation (HCT; which includes peripheral blood stem cell transplantation, bone marrow transplantation, and cord blood transplantation). Risk is also elevated if the survivor has prior or current exposure to endemic infections or epidemics, or has a history of blood transfusion.

Interventions for Prevention of Infections

Infection in survivors can be prevented by education, antimicrobial prophylaxis, and the judicious use of vaccines. For information regarding antimicrobial prophylaxis, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available online at www.NCCN.org).

Education

Survivors should be educated about safe pet care, the avoidance of zoonosis, travel precautions, and gardening precautions.[1070-1075] Contact with pets did not increase the risk of fever, bacteremia, pneumonia, and gastroenteritis in children with acute myeloid leukemia,[1076] and the panel believes that contact with pets is generally safe for most survivors. However, survivors should wash hands with soap and running water after handling animal feces. If possible, survivors at high risk for immune suppression should avoid direct contact with animal feces and other bodily secretions. Survivors with elevated risk of infection and those who are immunocompromised are at higher risk for zoonoses and should use extra caution. Travel precautions include education on the need for pre-travel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections.[1077] Travelers may find useful information at http://wwwnc.cdc.gov/travel/yellowbook/2016/advising-travelers-with-specific-needs/immunocompromised-travelers or by consulting a travel clinic. Gardening precautions include wearing gloves

to avoid cuts and punctures that could be delayed in healing or become infected with fungus or staphylococcus/streptococcus that may be present on thorns, and wearing a protective mask to avoid inhalation of spores.

Immunizations

Vaccination, or "active immunization," involves administration of all or part of a microorganism or a modified product of a microorganism (eg, a toxoid, a purified antigen, or an antigen produced by genetic engineering) to produce an immunologic response that mimics that of natural infection but usually presents little or no risk to the recipient. The use of vaccines that do not contain live organisms should be considered and encouraged in all cancer and transplant survivors who have completed immune-suppressive therapy (ie, chemotherapy or antibody-based therapy) at least 3 months prior to planned vaccination. Patients receiving anti-estrogen or other hormone-modulating therapy do not have to delay vaccination for the completion of therapy. In general, the usual doses and schedules are recommended, as outlined by the Advisory Committee on Immunization Practices (ACIP).[1078] The Infectious Diseases Society of America (IDSA) has outlined guidance for vaccination in immunocompromised patients, including those with cancer and those post-HCT.[1079] The NCCN Survivorship Panel outlined immunization guidelines specific to survivors of hematologic malignancies and solid tumors, with separate guidelines for survivors who have received HCT. In survivors who received anti–B-cell antibody therapy, vaccination should be delayed for at least 6 months after chemotherapy or the last dose of such therapy to allow for reconstitution of the B-cell population. More details are available in the guidelines.

Before vaccination, immune system viability and history of allergic reactions to vaccines should be assessed. Baseline WBC counts should be in the normal range or within reasonable limits before starting vaccinations, unless they are elevated because of disease status. The survivor should not be on immunosuppressive drugs or chemotherapy, and ongoing infection should not be present.

The following vaccines should be considered and encouraged for all survivors, administered according to the usual doses and schedules: influenza vaccine (only inactivated or recombinant); tetanus, diphtheria, pertussis (Tdap); and HPV (in previously unvaccinated female survivors through age 26 years and male survivors through age 21).[1078] These vaccines do not contain live organisms; instead they contain inactivated organisms, purified antigens, bacterial components, or genetically engineered recombinant antigens. Whereas the effectiveness of these vaccinations might be suboptimal because of lingering immune suppression,[1069] their administration is likely worthwhile to achieve some protection in the absence of known harm.

Pneumococcal vaccine (PPSV-23/PCV-13) is recommended for all adults age 65 years or older and those at any age with immunocompromising conditions.[1080] Other vaccines, as listed in the guidelines, should be considered in consultation with an infectious disease or travel medicine specialist if unique circumstances in the survivor's lifestyle, upcoming travel, functional or anatomic asplenia, or local epidemic/risks merit their use.

Influenza Vaccines

Annual influenza vaccination is recommended for all cancer and transplant survivors.[1081] Live attenuated influenza vaccines, which are no longer recommended for the general population because of low effectiveness, should be avoided in this population.[1078] Preferred vaccines include inactivated influenza vaccines (ie, trivalent [IIV3] standard-dose, trivalent [IIV3] high-dose, and quadrivalent [IIV4] standard-dose) or recombinant influenza vaccine (ie, trivalent

[RIV3]).[1078,1082] Recent evidence suggests that the high-dose IIV3 vaccine may provide better protection than standard-dose IIV3 in individuals 65 years or older.[1083] No studies have addressed the superiority of any influenza vaccine in the cancer survivor population specifically. Administration of the influenza vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions, as currently recommended for all individuals.[1078]

Live Viral Vaccines

Vaccines that contain live attenuated organisms (eg, live-attenuated influenza vaccine; MMR; oral polio vaccine [OPV]) are contraindicated in actively immunocompromised survivors because of a proven or theoretical increased risk of disease and prolonged shedding of the live organism present in the vaccine. They should not be offered to actively immunocompromised survivors, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist. Live viral vaccines should be avoided in survivors of lymphomas or other malignant neoplasms affecting the bone marrow or lymphatic system and in those with a history of cellular immunodeficiency.

Live viral vaccines can be administered, however, to immunocompetent survivors 3 or more months after treatment, although consultation with an infectious disease specialist or clinician familiar with vaccination in patients with cancer is recommended.

Healthy immunocompetent individuals who live in a household with immunocompromised survivors can receive the following live vaccines with caution: MMR, varicella (VAR), zoster, yellow fever, rotavirus, and oral typhoid vaccines.[1079] Live OPV should not be administered to individuals who live in a household with immunocompromised survivors. Immunocompromised survivors should avoid contact with persons who develop skin lesions after receipt of VAR or zoster vaccine until the lesions clear. In addition, immunocompromised survivors should avoid handling diapers of children who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.

Zoster (Shingles) Vaccine

A single dose of zoster (shingles) vaccine is recommended for survivors aged 60 years or older without active or ongoing immunodeficiency, no history of cellular immunodeficiency or HCT, and who have not received chemotherapy or radiation within the past 3 months, or it can be given at least 4 weeks before initiation of chemotherapy or immunosuppressive drugs.[1079,1084] Zoster vaccination should also be considered for survivors aged 50 to 59 years with a history of varicella zoster virus (VZV) infection or VZV seropositivity with no previous doses of VAR vaccine. The zoster vaccine should be avoided in immunocompromised survivors, but can be considered in transplant survivors without active GVHD or enhanced immunosuppression 24 or more months after transplantation.

Summary

With improved diagnostic and treatment modalities, the population of cancer survivors is rapidly growing. Many survivors will experience late and/or long-term effects of cancer and its treatment that can include physical and/or psychosocial problems. These issues need to be addressed in a regular and systematic manner. Unfortunately, many of these effects are not addressed until discharge from the oncologist, and interventions may be left to health care providers who may not have much experience treating the concerns of cancer survivors. The NCCN Survivorship Panel hopes that these guidelines can help both oncologic and primary health care professionals lessen the burden left on

survivors by their cancer experience so they can transition back to a rewarding life.

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