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Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence

Cancer of the nasopharynx (NPC) is rare in Europe, with an annual crude incidence rate of 1.1 per 100 000. On the European scale, NPC accounts for 4760 new cases per year. Incidence is higher in men than women. [1, 2].

In Europe, the relative survival for NPC was 76% at 1 year and 50% at 5 years in adults. There were no survival differences between the sexes. The effect of age on survival is marked. Survival at 5 years was 72% for the youngest age group (15–45 years) and 36% in the oldest group of patients (65–74 years) [1, 2].

diagnosis

Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumor. The histological type should be classified according to World Health Organization (WHO) classification [3]. Since the first disease sign in patients is often the appearance of neck nodes it is not infrequent that patients undergo neck biopsy and/or neck nodal dissection. This procedure is not recommended since it may reduce cure probability and have an impact on late treatment sequelae.

staging and risk assessment

NPC is clinically staged according to the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) staging system (Table 1). Routine staging procedures include history, physical examination including cranial nerve examination, complete blood cell count, serum biochemistry (including liver function test), chest X-ray, nasopharyngoscopy, computed tomography (CT) scan or magnetic resonance imaging (MRI) of nasopharynx and base of skull and neck. Although MRI is generally preferred if available, each center will choose the best imaging technique according to their usual clinical practice and experience [III, B]. Imaging for distant metastases including isotope bone scan and CT scan of chest and upper abdomen could be considered for at-risk subsets (node positive, especially N3 stage) and for those patients with clinical or biochemical abnormalities detected [III, B]. The use of positron emission tomography CT scan can replace the traditional work-up for detection of distant metastatic disease since it has proved to be the most sensitive, specific and accurate diagnostic method. Both the pre-treatment and post-treatment plasma/serum load of Epstein-Barr viral DNA has been shown to be of prognostic value [III, B] [4–8].

treatment

The optimal treatment strategy of patients with advanced NPC should be discussed in a multidisciplinary team. Radiation therapy (RT) is the mainstay of treatment and is an essential component of curative-intent treatment of non-disseminated NPC. Stage I disease is treated by RT alone, while stage III, IVA, IVB disease are treated by RT with concurrent chemotherapy [I, A]. Concurrent chemotherapy is recommended for stage II disease [I, B] [9]. Patients should be treated by intensity-modulated radiation therapy (IMRT) [II, A] [10]. RT is targeted to the primary tumor and the adjacent regions considered at risk of microscopic spread from the tumor, and to both the sides of the neck (levels Ib–V, and retropharyngeal nodes). For patients with lower neck nodes, the supraclavicular fossa should be included as well. Elective nodal irradiation is recommended for N0 stage disease. The consensus is that a total dose of 70 Gy is needed for

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Table 1. The International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) staging system for NPC, seventh edition (2010)

Primary tumor (T)			
T1	Tumor confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension		
T2	Tumor with parapharyngeal extension		
T3	Tumor involves bony structures of skull base and/or paranasal sinuses		
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space		
Regional lymph nodes (N)			
N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, ≤6 cm, in greatest dimension		
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa		
N3	Metastasis in a lymph node(s) >6 cm and/or to supraclavicular fossa		
N3a	>6 cm in dimension		
N3b	Extension to the supraclavicular fossa		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

eradication of gross tumor and either 50–60 Gy or 46–60 Gy for elective treatment of potential risk sites. To minimize the risk of late toxicity (particularly, to adjacent neurological structures), fractional dose >2 Gy per daily fraction and excessive acceleration with multiple fractions >1.9 Gy/fraction should be avoided [III, E]. IMRT may offer improvement in local tumor control [II, A], and reduction in radiation xerostomia in early-stage disease [II, A]. The standard agent used in concurrent chemotherapy–RT is cisplatin [I, A]. This provides a benefit in terms of overall survival and on both locoregional and distant control [9, 11–15]. While three cycles of adjuvant cisplatin-5FU has been a standard part of many concurrent chemoradiotherapy regimens, its benefit is uncertain and toxic effect is substantial [16]. Cisplatinum-based induction chemotherapy has been shown to improve disease-free survival and may be considered in locally advanced disease although it is not seen as a standard treatment [II, B] [17]. In no case should induction chemotherapy negatively affect the optimal administration of concomitant chemoradiation.

follow-up

Documentation of complete remission in the nasopharynx and neck through clinical and endoscopic examination and/or imaging studies is important. MRI is often used to evaluate the response to RT or chemoradiotherapy, especially for T3 and T4 tumors, though distinction between post-irradiation changes and recurrent tumors may be difficult. Follow-up for patients includes periodic examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis. For T3 and T4 tumors, MRI might be used on a 6- to 12-month basis to evaluate the nasopharynx and the base of the skull at least for the first few years after treatment. Evaluation of thyroid function in patients with irradiation to the neck is recommended at 1, 2 and 5 years.

treatment of recurrent or metastatic disease

Small local recurrences are potentially curable and the main issue is the choice of the most appropriate therapeutic options, which include nasopharyngectomy, brachytherapy, radiosurgery, stereotactic RT, IMRT or a combination of surgery and RT, with or without concurrent chemotherapy. Treatment decisions are tailored to the specific situation of individual cases, taking into consideration the volume, location and extent of the recurrent tumor [III, A]. Regional recurrence is managed by radical neck dissection if resectable [III, A].

In metastatic NPC, palliative chemotherapy should be considered for patients with adequate performance status. Platinum combination regimens are commonly used as first-line therapy since cisplatin represents the most effective drug. Other active agents include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin and oxaliplatin, which can be used as single agents or in combination [III, B]. Polychemotherapy is more active than monotherapy. In this context treatment choice should be based on previous treatments and the expected toxicity [18].

Table 2 Summary of treatment recommendations for Cancer of the nasopharynx (NPC)

Early stage	Stage I	Radiation alone
Intermediate stage	Stage II	Concurrent chemoradiotherapy (I, B)
Advanced stage	Stage III, IVA, IVB	Concurrent chemoradiotherapy +/− adjuvant chemotherapy (I, A)
Problematic radiation therapy (RT) planning (e.g. tumor abutting chiasm)	Stage IVA, IVB	Induction chemotherapy followed by concurrent chemoradiotherapy (II, B)

notes

Levels of evidence [I–V] and grades of recommendation [A–E] adapted from the Infectious Diseases Society of American-United States Public Health Service Grading System are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts.

conflict of interest

Prof. Lefebvre has reported: lecturer and advisory board for Merck Serono and Sanofi-Aventis. Dr. Licitra has reported: advisory board of Bristol-Myers Squibb, GlaxoSmithKine, Lilly, Merck Serono and Amgen; institution has received clinical and research support from EISAI, Exelixis, Lilly, Merck-Serono, Amgen; and travel support from Merck Serono. Prof. Chan has reported receiving honoraria and research support from Merck-Serono, Amgen, Novartis, Roche, Pfizer and SanofiAventis. Dr. Felip has reported: consultancy/honoraria from Lilly, GlaxoSmithKline, Merck Serono, Roche, Boehringer Ingelheim. Dr. Hui has reported: consultancy and advisory board for Sanofi-Aventis and Pfizer. Prof. Grégoire has reported no conflicts of interest.

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