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SPECIAL ARTICLE

Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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INCIDENCE AND EPIDEMIOLOGY

Nasopharyngeal carcinoma (NPC) is a disease with unique epidemiological features. The distribution of the disease demonstrates a clear regional, racial and gender prevalence. In 2018, the global age-standardised incidence rates (ASIRs) varied from 2.1 to 0.4 per 100 000 in Asia and Europe, respectively.[1] The highest ASIRs per 100 000 were in East and South East Asia (e.g. seven in Singapore, the Maldives and Indonesia; six in Malaysia and Vietnam; three in China). There were more than 129 000 new cases of NPC reported in 2018, including more than 5000 in Europe.[1] In recent decades (1970-2007), the incidence of NPC has declined worldwide, with substantial reductions in South and East Asia, North America and the Nordic countries.[2]

NPC has several features that differ according to geographic area. For example, age distribution differs in low-incidence areas compared with endemic areas. In low-incidence areas, the incidence of NPC increases with age and has a bimodal peak: the first in adolescents and young adults and the second after 65 years of age, whereas in endemic areas, the incidence increases after 30 years of age, peaks at 40-59 years and decreases thereafter. The male–female incidence ratio is 2.75.[3]

In Europe, during the period of 2000-2007, the 5-year survival rate for adults with NPC was 49% (www.rarecarenet.eu). Survival rates increased during 1999-2007 in Europe, except in Eastern Europe where it declined over time.[4]

In the USA, during the period of 2009-2015, the 5-year relative survival rate was 60%, with differences seen across ethnic groups.[5] Asians seem to have a disease-specific survival advantage independent of gender, age at diagnosis, grade, TNM (tumour–node–metastasis) staging and treatment.[6] In addition, the hazard rate patterns for NPC-related mortality appear significantly different between histological subtypes.[7]

The effect of age on survival is marked. Five-year survival rates were 72% in the youngest age group (15-45 years) and 36% in the oldest group of patients (65-74 years).[8]

In general, the prognosis is better for women than men.[9,10]

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis

Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumour [II, A]. In case of no clinical primary tumour visible at endoscopy, biopsy of nasopharyngeal tissue positive at magnetic resonance imaging (MRI) or positron emission tomography (PET) is suggested.[11] Since the first sign of disease is often the

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appearance of neck nodes, it is frequent that patients undergo neck biopsy and/or neck nodal dissection. This procedure is not recommended since it may reduce the probability of cure and have an impact on late treatment sequelae. Nevertheless, if carried out (for example, if the primary tumour is not visible), node dissection without capsular effraction or ultrasonography-guided, transcutaneous tru-cut biopsy are the best options; node surgical biopsy should be avoided. Determination of Epstein-Barr virus (EBV) on the histological sample by *in situ* hybridisation (ISH) is indicated.

Pathology/molecular biology

The histological type should be classified according to the 4th edition of the World Health Organization (WHO) classification (Table 1).[12] The term 'nasopharyngeal carcinoma' refers to all squamous cell cancers which are categorised into keratinising, non-keratinising (subdivided into differentiated and undifferentiated) and basaloid carcinoma subtypes. Keratinising cancer is more frequent in non-endemic than endemic areas, whereas non-keratinising cancer comprises the vast majority of cases and is linked to EBV infection.

EBV expression. EBV is considered in 'Group 1' by the International Agency for Research on Cancer (IARC) in respect to NPC, i.e. a virus for which there is sufficient evidence of carcinogenicity in humans.[13,14] EBV is identified by ISH by the presence of EBV-encoded RNAs in NPC tissue.

Latent EBV has been found in high-grade dysplasia and NPC cells but not in normal epithelium or low-grade dysplasia.[15] EBV has also been identified in a clonal pattern in pre-invasive lesions of the nasopharynx that contain EBV RNAs characteristic of latent infection. EBV-infected cells express several latent proteins, both as EB nuclear antigens [EBNAs 1, 2, 3A, 3B and 3C and EBNA-leader proteins (LPs)] and as latent membrane proteins (LMPs 1, 2A and 2B).[16] However, the EBV latent-gene expression in NPC is predominantly restricted to EBNA1, LMP2A and LMP2B. These viral proteins are considered as poorly immunogenic, partially explaining the way in which NPC may elude immune recognition.

The role of EBV genomic variants on NPC development has not been completely clarified; however, whole genome sequencing of EBV has revealed a high variability in many genomic regions of NPC biopsy specimens.[17]

EBV is almost always a necessary, even if not sufficiently causative, factor for non-keratinising NPC; its role in keratinising cancer is less pronounced.

Human papillomavirus expression. In regions where NPC is endemic, p16 positivity and human papillomavirus (HPV) expression (screened using RNA probes to detect 13 high-risk and 5 low-risk HPV types) is reported in up to 8% of non-keratinising undifferentiated carcinoma, and carries a better prognosis than its EBV counterpart.[18] In non-endemic areas, the presence of HPV data are limited, with a higher frequency seen in keratinising cancer; however, an association with prognosis is not as clear.[19] Whether HPV is involved in carcinogenesis and disease progression has yet to be established.

Table 1. WHO classification of nasopharyngeal carcinomas

	ICD-O code
Non-keratinising squamous cell carcinoma	8072/3
Keratinising squamous cell carcinoma	8071/3
Basaloid squamous cell carcinoma	8083/3

ICD-O, International Classification of Diseases for Oncology; WHO, World Health Organization.

Molecular analysis. Although no actionable mutations in NPC have been identified, a role for gene signature discovery is increasing. Molecular deciphering is beyond the scope of this guideline. However, gene expression analysis may be useful in identifying patients at higher risk of developing distant metastases.[20] In addition, mutational signatures relevant to DNA repair pathways show prognostic value with potential clinical implications.[21]

Other risk factors. Genetic susceptibility plays a clear role in the development of NPC, as witnessed by the discovery of susceptibility loci and candidate genes in NPC patients or high-risk individuals.[22] Environmental factors are also causal agents, mainly related to the consumption of salted fish, while there is less evidence to support other agents or dietary products.[23]

Screening

In regions where NPC is endemic, the use of plasma EBV DNA with a primer/probe assay targeting the BamHI-W region of the EBV genome, carried out in duplicate (at least 4 weeks apart) and coupled with endoscopic examination and MRI, showed a sensitivity and specificity in screening NPC of 97.1% and 98.6%, respectively.[24] The number of subjects needed to be screened to detect one case was 593. Its use can therefore only be recommended for detecting early asymptomatic NPC in endemic areas and is limited to those considered at higher risk (i.e. males aged 40-62 years) [III, A]. Although overall survival (OS) data for the screened population are not available, the 3-year progression-free survival (PFS) was significantly improved compared with a matched historical cohort [97% versus 70%; hazard ratio (HR) 0.10; 95% confidence interval (CI) 0.05-0.18]. One of the issues related to plasma EBV DNA is the poor standardisation between the different assays used.

Recommendations

- Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumour [II, A]; diagnostic neck biopsy and/or neck nodal dissection should be avoided.
- Determination of EBV on the histological specimen by ISH is indicated [III, B].

- In regions where NPC is endemic, the use of plasma EBV DNA, coupled with endoscopic examination and MRI, can be recommended for detecting early, asymptomatic NPC [III, A].

STAGING AND RISK ASSESSMENT

NPC is clinically staged according to the American Joint Committee on Cancer (AJCC) staging classification 8th edition (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.12.007).[25] Compared with the previous edition, the new classification better delineates the T2 stage to also include prevertebral muscle and medial or lateral pterygoid involvement, and the T4 stage now includes parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle, thus eliminating other ambiguous terminology. Nodal extension to the supraclavicular fossa has been substituted by the limit of the caudal border of the cricoid cartilage and so better delineates the 'lower neck' extension; N3 definition includes both the previous N3a and N3b groups. Moreover, EBV-positive cervical nodes in cancer of unknown primary are staged according to the NPC classification.

Routine staging procedures (Table 2) include a medical history, physical examination (including cranial nerve examination), complete blood count (CBC), serum biochemistry [including liver and renal function tests and lactate dehydrogenase (LDH)], nasopharyngoscopy, computed tomography (CT) scan or MRI of the nasopharynx and base of the skull and neck (up to the clavicle) and ^{18}F-fluorodeoxyglucose (FDG)-PET/CT imaging. MRI is the most accurate way of defining local tumour staging as it is sensitive in depicting small mucosal thickening, parapharyngeal and masticatory space involvement and skull base and cranial nerve infiltration, and it should therefore be preferred whenever available and according to the centre's expertise [III, B]. Accuracy of nodal involvement detection is higher with MRI compared with CT; FDG-PET adds further accuracy in nodal staging [III, B]. The best imaging for detecting distant metastases is FDG-PET in terms of sensitivity and specificity, and it is recommended at least in locally advanced disease [III, B].[26] Moreover, a systematic review and meta-analysis showed that baseline metabolic values of FDG-PET were able to predict survival outcomes for NPC patients.[27]

Baseline audiometric testing, dental examination, nutritional status evaluation and ophthalmological and endocrine evaluation should be carried out as appropriate. Pre-treatment quality of life (QoL) scales [e.g. the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ)-C30], mainly physical functioning, have been found to be a more accurate predictor of OS than performance status (PS).[28] Their application in clinical practice may better delineate the individual risk and prompt medical or physical support before the start of treatment [III, B].

Due to the variability in assessments between laboratories, EBV DNA measurement needs further harmonisation.[29] Both the pre- and post-treatment plasma/serum load of EBV DNA with a primer/probe set targeting the BamHI-W region of the EBV genome has shown prognostic value [III, B]. A pre-treatment cut-off value of between 1500 and 4000 copies/ml has been proposed in endemic areas.[30,31] The prognostic role of pre-treatment EBV DNA has also been reported in non-endemic areas using PCR, which amplifies the gene coding for the EBNA-1 protein [IV, B].[32] Incorporation of plasma EBV DNA both in the pre- and post-treatment setting may improve the prognostic capacity of the TNM staging system.[33,34] At this time, however, plasma EBV DNA detection has no impact on treatment strategy.

Biomolecular signatures with gene expression and microRNA have been shown to add prognostic value to clinical and radiological staging.[35,36] Several nomograms have also been proposed to better stratify patient prognosis in endemic regions using factors such as T and N stage, age, gender, body mass index, haemoglobin, LDH, plasma EBV DNA and C-reactive protein. They may help to determine prognosis, but data are limited to support their use in choosing a treatment strategy [IV, C]. No data in this regard exist for non-endemic areas.

Table 2. Diagnostic work-up

1. Medical history and physical examination
2. CBC, serum biochemistry
3. Nasopharyngoscopy
4. Tumour biopsy (EBER by ISH [III, B])
5. CT scan or MRI of the nasopharynx and base of the skull and neck (to the clavicle) (MRI preferred [III, B])
6. ^{18}F-FDG-PET/CT imaging [III, B]
7. Baseline audiometric testing, dental examination, nutritional status evaluation, ophthalmological and endocrine evaluation
8. Plasma EBV DNA [III, B]
9. QoL assessment (e.g. EORTC QLQ-C30) [III, B]

^{18}F-FDG, ^{18}F-fluorodeoxyglucose; CBC, complete blood count; CT, computed tomography; EBER, Epstein-Barr virus-encoded RNA; EBV, Epstein-Barr virus; EORTC, European Organisation for Research and Treatment of Cancer; ISH, *in situ* hybridisation; MRI, magnetic resonance imaging; PET, positron emission tomography; QLQ, quality of life questionnaire; QoL, quality of life.

Recommendations

- Routine staging procedures include a medical history, physical examination with cranial nerve examination, CBC, serum biochemistry (including liver and renal function tests and LDH), nasopharyngoscopy and radiological imaging.
- MRI is the most accurate way of defining local and nodal tumour staging and it should be preferred whenever available and according to the centre's expertise [III, B].
- FDG-PET adds further accuracy in nodal staging, is the best imaging method for detecting distant metastases and is recommended at least in locally advanced disease [III, B].
- Baseline audiometric testing, dental examination, nutritional status evaluation and ophthalmological and endocrine evaluation should be carried out as appropriate.

- Pre-treatment QoL scales may be suggested to better delineate the individual risk and to prompt medical or physical support before the start of treatment [III, B].
- Pre- and post-treatment plasma/serum load of EBV DNA has prognostic value [III, B].

TREATMENT

Management of local/locoregional disease

Efficacy data and consequent recommendations described here are derived largely from studies in the endemic setting, where non-keratinising, EBV-related carcinomas constitute most cases. Where the evidence is lower, these data will still be considered for non-endemic carcinomas.

The optimal treatment strategy for patients with advanced NPC should be discussed within a multidisciplinary team (MDT). Treatment of patients in high-volume facilities is recommended as this was reported as an independent prognostic factor for improved survival, at least in areas where the disease is endemic [IV, B].[37]

A proposed treatment algorithm for local and locoregional NPC is shown in Figure 1. Radiotherapy (RT) is the mainstay of treatment and is an essential component of curative-intent treatment of non-disseminated NPC. Intensity-modulated RT (IMRT) is an important milestone in the management of NPC, providing enhanced outcomes and less severe late effects compared with previous RT techniques [conventional two-dimensional (2D) and three-dimensional (3D) by parallel improved dosimetric parameters]. Indeed, a meta-analysis showed a significant improvement in 5-year OS and 5-year local control (LC) favouring IMRT over other techniques [II, A].[38]

Regarding late effects, a significant reduction in late xerostomia, trismus and temporal lobe injury was reported in favour of IMRT compared with older RT techniques [II, A].[38] The largest Asiatic series reported that 5.1% of patients had cranial nerve palsies, 7.1% had severe hearing loss, 3% had dysphagia requiring long-term tube feeding and 0.9% had symptomatic temporal lobe necrosis (TLN) at a median follow-up of 80 months [IV, A].[39] In addition, IMRT improved QoL for long-term survivors over time compared

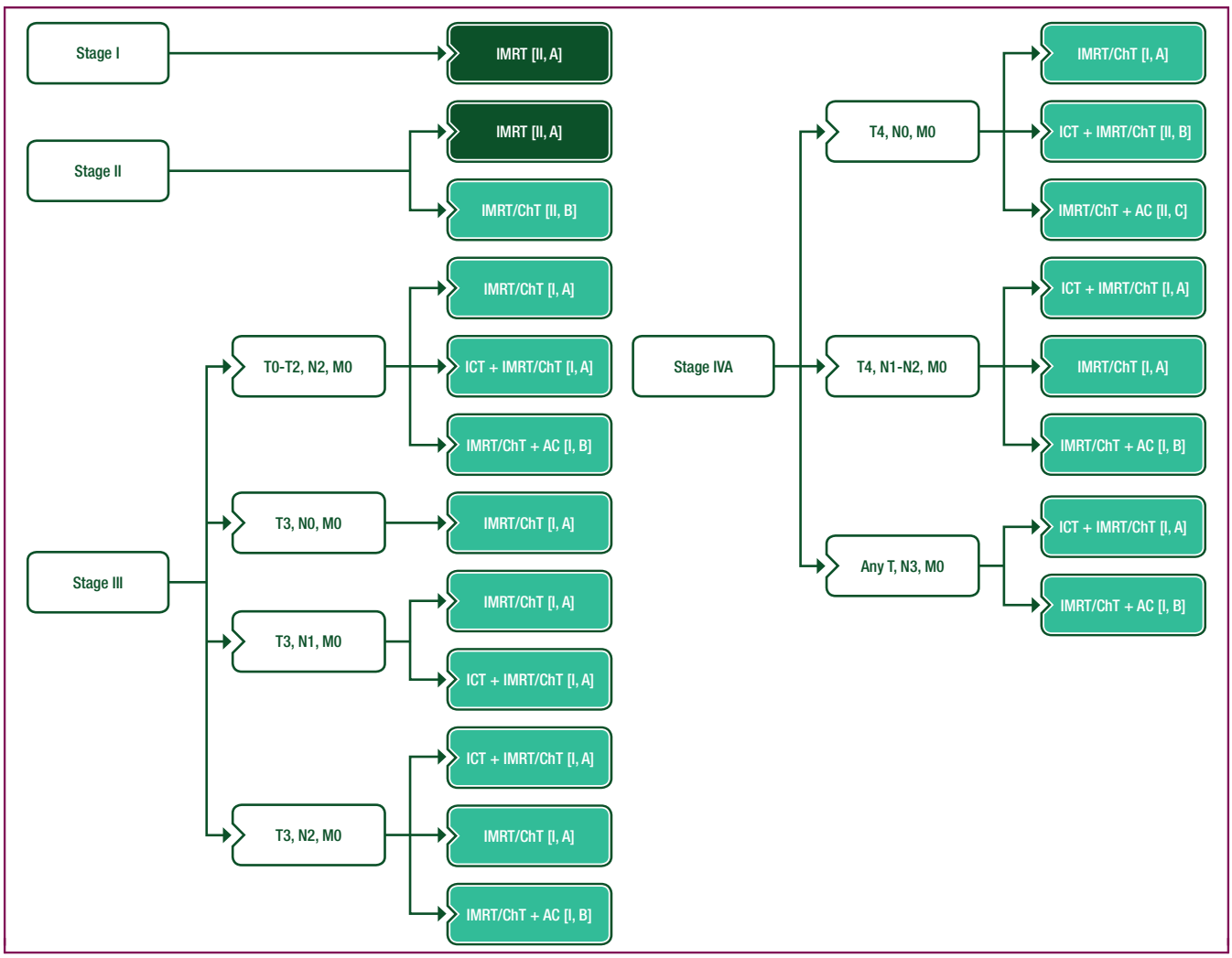

Figure 1. Treatment algorithm for stage I-IVA NPC.
AC, adjuvant chemotherapy; ChT, chemotherapy; ICT, induction chemotherapy; IMRT, intensity-modulated radiotherapy; M, metastasis; N, node; NPC, nasopharyngeal cancer; T, tumour.

with older techniques both in endemic and non-endemic regions [IV, A].[40,41]

Although IMRT represents the current standard RT technique for NPC, particle therapy, including protons and carbon ions, is gaining popularity based on its physical and biological proprieties. In particular, to maintain a high RT dose and avoid neurological structures, proton therapy represents a promising approach for patients with locally advanced NPC. A few small studies with a relatively short follow-up have shown a benefit in terms of clinical outcome when proton therapy was added as a boost for locally advanced disease [III, C].[42-44] In particular, significantly lower rates of severe (grade 3) mucositis and salivary dysfunctions were reported in NPC patients receiving IMRT followed by proton therapy boost (55.6% of whom had T4-stage disease) compared with patients receiving a full course of IMRT only (41.2% of whom had T4-stage disease).[42]

Target volume definition represents a major issue during IMRT planning for NPC, as witnessed by the need for international guidelines for appropriate target contouring.[45] Overall, RT is targeted according to the primary tumour and pathological nodes, but also to the adjacent regions considered at risk of microscopic spread from the tumour and generally to both sides of the neck (levels II-V and retropharyngeal nodes) because of the high incidence of occult neck node involvement.[45] A total dose of 70 Gy is needed for the eradication of macroscopic disease and 50-60 Gy for the treatment of potential at-risk sites, usually by conventional or moderately accelerated RT.[46] IMRT may be applied using either a sequential boost or a simultaneous integrated boost (SIB). A recent randomised trial comparing these two techniques found no difference in terms of clinical outcome and toxicities. Due to the convenience of an SIB strategy, this approach can be considered the technique of choice for NPC treatment [II, B].[47]

Recently, many trials have investigated the opportunity to reduce the extension of target volumes in order to reduce the toxicity burden. In node-negative NPC, upper versus whole-neck prophylactic RT led to a similar lower neck control rate, suggesting that a reduced nodal volume approach may be feasible [II, B].[48]

When obtaining tumour shrinkage with induction chemotherapy (ICT), the strategy of planning IMRT with reduced primary gross tumour volume (GTV) based on post-chemotherapy (ChT) MRI scan volumes may be adopted. This approach—tested on a limited number of patients—appears not to show any detrimental effect on LC and survival if the pre-induction tumour areas received at least an intermediate dose (64 Gy); an improvement in QoL score was shown compared with planning of GTV based on pre-ChT MRI scans [II, B].[49,50]

Planning optimisation in terms of prioritisation and dose constraints for target and radiosensitive structures is fundamental in order to avoid missing tumour coverage while maintaining organs at risk at their tolerance dose levels. International guidelines on dose prioritisation and acceptance criteria with IMRT for NPC have been recently established.[51]

Target volume definitions are shown in Table 3. IMRT dose prescription to target volumes and fractionation schemes are shown in Table 4. In most cases, conventional or moderate hypofractionation regimens are used to a total dose of 70 Gy in 33-35 fractions. A scheme used in a dose-escalation trial with a total dose to macroscopic primary disease of 76 Gy is also reported.[52] However, extreme caution should be exercised when increasing the total dose due to the high risk of developing late toxicities (e.g. osteoradionecrosis, carotid pseudoaneurysm and neurological toxicities).

Stage I disease is treated by RT alone, whereas patients with stage II NPC benefit from concurrent chemoradiotherapy (CRT) with cisplatin 30 mg/m^2/week when 2D-RT is used [II, B][53]; a non-significant difference in survival outcomes was shown for CRT versus RT alone when IMRT was adopted [II, B].[54]

Stage III and IVA disease are treated by CRT [I, A]. The standard agent used is cisplatin [I, A].[55] This provides a benefit in terms of OS and both locoregional and distant control. The most commonly used regimen is cisplatin 100 mg/m^2 every 3 weeks with concomitant RT [I, A].[56] Weekly cisplatin (40 mg/m^2/week) has also been shown to improve OS [II, A].[57] The optimal cumulative total dose of concurrent cisplatin should be higher than 200 mg/m^2 [IV, B].[58] Concurrent nedaplatin was found to be non-inferior to cisplatin in one randomised trial [II, B].[59] Concurrent carboplatin is considered an available option but the evidence is conflicting [II, C].[60,61] The addition of bevacizumab to platinum-based ChT concurrently with RT showed a substantial rate of high-grade toxicities and is not recommended [III, D][62]; the role of anti-epidermal growth factor receptor (EGFR) agents (such as nimotuzumab) concurrently with RT, in addition to or instead of ChT, requires further clarification as there are no unequivocal data in this setting.

The propensity of NPC to develop distant metastases is a major cause of treatment failure and death.[63] Intensification of the systemic treatment is therefore needed for stage III-IVA non-keratinising NPC. Adjuvant ChT (AC) is generally difficult to complete, with only ~60% of patients completing the planned treatment cycles and half of patients require a dose reduction.[64] In contrast, ICT offers the possibility of delivering an adequate dose intensity of ChT. However, as a prerequisite, ICT added to CRT should not hinder the subsequent delivery of full-dose CRT, and the time between the end of ICT and the start of RT should be kept as short as possible. Recently, a phase III trial comparing ICT with cisplatin and gemcitabine followed by CRT versus CRT alone in patients with stage III/IVB (according to AJCC 7th edition) NPC showed a benefit in favour of ICT in recurrence-free survival (RFS), OS and distant RFS, with higher acute but not late toxicities [I, A].[65] Importantly, 96.7% of patients randomised to the ICT arm completed the 3 cycles of cisplatin/gemcitabine and 92% received at least 2 cycles of cisplatin 100 mg/m^2 concomitantly with RT. In this study, patients with T3-4 N0 disease were excluded. Long-term results of a randomised trial of ICT with cisplatin and 5-fluorouracil (5-FU) followed by CRT versus CRT alone

Table 3. CTV delineation and anatomic boundaries according to International Guidelines[45,102,103]

CTV definition			CTV delineation and anatomic boundaries
Primary tumour	High-risk volume (full therapeutic dose)	CTVp1	GTVp + 5mm (± whole NP) GTVp + 1 mm if tumour in close proximity to brainstem and spinal cord
Node(s)	High-risk volume (full therapeutic dose)	CTVn1	GTVn + 5 mm (consider 10 mm if nodal ECE)
Primary tumour	Intermediate-risk volume (prophylactic dose)	CTVp2	GTVp + 10 mm + whole NP GTVp + 2 mm if tumour in close proximity to brainstem and spinal cord ***Nasal cavity – posterior part*:** at least 5 mm from choana ***Posterior maxillary sinuses:*** at least 5 mm from posterior wall (to ensure pterygopalatine fossae) coverage ***Posterior ethmoid sinus*:** include vomer ***Base of skull:*** cover foramina ovale, rotundum, lacerum and petrous tip ***Cavernous sinus*:** if T3/T4 (only involved side) ***Parapharyngeal spaces:*** full coverage ***Sphenoid sinus:*** inferior 1/2 if T1-2; whole if T3-4 ***Clivus*:** anterior 1/3 if no invasion; whole if invasion
Node(s)	Intermediate-risk volume (prophylactic dose)	CTVn2	Lymph nodes bilaterally: RP, II, III, VA, (IV, VB) for all T and N categories plus at least ipsilateral one level below the involved node levels ***Ipsilateral coverage of ipsilateral IB if:*** • IB level positive (include whole level) • Structures that drain to level IB as the first echelon site (oral cavity, anterior half of nasal cavity) • Involvement of submandibular gland • Ipsilateral level IIA LNs with ECE • Consider if ipsilateral level IIA LNs with maximum nodal axial diameter greater than 2 cm
Nodes	Low-risk volume (prophylactic dose)-optional	CTVn3	***Levels IV and VB down to clavicle if VB:*** • If nodal involvement is confined to level II nodes only • Possible omission if N0 or N1 based solely on RP positivity

CTV, clinical target volume; CTVn, nodal clinical target volume; CTVp, primary tumour clinical target volume; ECE, extracapsular extension; GTVn, nodal gross target volume; GTVp, primary tumour gross target volume; LN, lymph node; NP, nasopharynx; RP, retropharyngeal.

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confirmed the benefit of ICT on survival outcomes and the comparable late toxicities.[66] Moreover, a recent update of an individual patient data network meta-analysis (NMA) showed that ICT with taxanes followed by concomitant CRT ranked as the best treatment in terms of OS versus concurrent CRT alone or with AC.[67] Long-term data from a multicentre, randomised, factorial trial showed that shifting from the concurrent-adjuvant to the induction-concurrent sequence achieved significant improvements in PFS and marginal improvements in OS without an adverse impact on late toxicity [II, B].[68]

The selection of patients to receive more ChT or immunotherapy in addition to CRT in the form of either ICT or AC is a therapeutic area that is being explored in ongoing randomised, controlled trials (see later for individualised risk assessment).

Two NMAs have analysed the impact of different ChT regimens added to RT, although they do not include the most recent data from induction trials.[69,70] In the first NMA, AC added to CRT proved to be the best approach for all clinical endpoints except distant control, where ICT followed by CRT was superior. In the second NMA, which was limited to studies with IMRT, ICT followed by CRT was superior for all clinical endpoints except locoregional RFS, where AC achieved better results.

Evaluating the risk profile of each patient is a key issue. Advanced nodal and primary stage, as well as high basal EBV DNA, have been proposed as a means to select patients

Table 4. Selected IMRT dose fractionation schedules

	High-risk CTV Td/df/nf (Gy)	Intermediate-risk CTV Td/df/nf (Gy)	Low-risk CTV-optional Td/df/nf (Gy)
International guidelines[51]	70/2/35 69.96/2.12/33	63-60/1.8-1.7/35 63-59.4/1.9-1.8/33	56/1.6/35 54/1.63/33
RTOG[62]	69.96/2.12/33	59.4/1.8/33	54.12/1.64/33 50/2/25
PYNEH[46]	70/2.12/33 70/2/35	59.4/1.8/33 61.25/1.75/35	52.5/1.75/30
DAHANCA[104]	66/2/33	60/1.82/33	50/1.52/33
PWH[52]	70-76/2-2.17/35	60/2/35	NS
INT[105]	69.96/2.12/33	59.4/1.8/33	56.1/1.7/33

CTV, clinical target volume; DAHANCA, Danish Head and Neck Cancer Group; df, dose per fraction; IMRT, intensity-modulated radiotherapy; INT, National Cancer Institute, Milan; nf, number of fractions; NS, not specified; PWH, Prince of Wales Hospital; PYNEH, Pamela Youde Nethersole Eastern Hospital; RTOG, Radiation Therapy Oncology Group; Td, total dose.

for ICT in order to improve the therapeutic ratio.[71] Persistent EBV DNA at 6-8 weeks after completion of RT or CRT is a negative prognostic factor that has been used as an inclusion criterion for a randomised trial of AC versus observation. No improvement in RFS or OS has been seen with adjuvant cisplatin and gemcitabine in this high-risk population; therefore, this approach is not recommended in clinical practice [I, E].[72] In case of persistent, high EBV DNA values after definitive treatment, a personalised approach with non-cross-resistant drugs or participation in a clinical trial is suggested [V, C].

Elderly patients have been under-represented in clinical trials testing the addition of ChT to RT. In the cited meta-analysis, unlike data from other non-nasopharyngeal subsites, no interaction was observed between treatment effect on OS and patient age, whereas for PFS, the benefit was dependent on the age range (HR 0.72; 95% CI 0.65-0.80 for patients $<$50 years and HR 0.84; 95% CI 0.70-1.01 for patients $\geq$60 years).[55] However, as a general principle, concurrent ChT is not tolerated as well in elderly patients compared with younger patients and consequently dose intensity is reduced; thus, patient selection is crucial.

Management of advanced/metastatic disease

Treatment of locoregional recurrences. Small local recurrences are potentially curable.[73] The main therapeutic options include nasopharyngectomy, brachytherapy, radiosurgery, stereotactic RT (SRT), IMRT or a combination of surgery and RT, with or without concurrent ChT. No comparative trials have been carried out to compare re-irradiation versus a surgical approach. Treatment decisions are tailored to the specific situation of each individual case, taking into consideration the volume, location/extent of the recurrent tumour, previous treatments, disease-free interval (DFI), comorbidities and any pre-existing organ dysfunction [III, A].

A proposed treatment algorithm for recurrent and/or metastatic NPC is shown in Figure 2. For surgical salvage treatments, prognostic factors include T and N stage at recurrence, surgical approach (with a better outcome reported for endoscopic surgery) and feasibility of adjuvant re-irradiation [II, B].[74]

Patients with local recurrences not invading the carotid artery and not extending intracranially are candidates for nasopharyngectomy; local recurrence stage rT1-rT3, might benefit more from endoscopic nasopharyngectomy than from IMRT [IV, B].[75]

Lymphatic recurrences in the neck can be treated with neck dissection [III, A]. The extent of neck dissection depends on the nature of the recurrence (N stage and extracapsular extension) and can range from selective to radical neck dissection.

Pre-treatment circulating EBV DNA has been shown to be a prognostic factor for distant metastasis in candidates for surgery.[76]

For re-irradiation, patient selection is crucial due to the high incidence of major late complications, even with modern RT

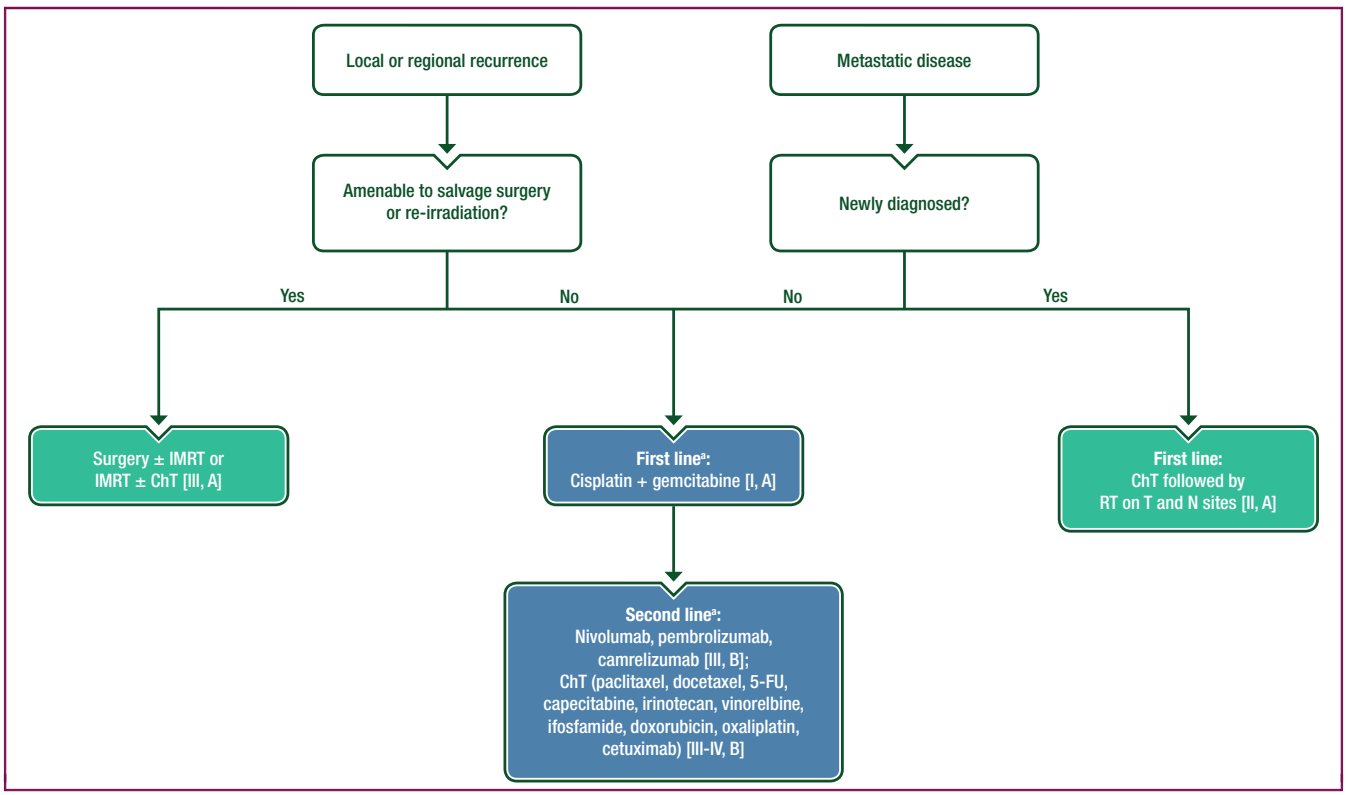

Figure 2. Treatment algorithm for recurrent and/or metastatic NPC.
5-FU, 5-fluorouracil; ChT, chemotherapy; IMRT, intensity-modulated radiotherapy; N, node; NPC, nasopharyngeal cancer; RT, radiotherapy; T, tumour.
[a] Consider RT [III, B] or surgery [IV, C] on metastatic sites.

techniques. Disease- and treatment-related prognostic factors for re-irradiated patients are: T and N stage at recurrence, tumour volume, DFI, dosimetry calculations (recurrence within the previous fields of radiation or outside), dose to target and fractionation schedule, window dose for organs at risk and RT technique (IMRT, SRT) [IV, B].[77-79]

Preliminary results have shown activity and limited toxicity with proton and carbon ion therapy for locally recurrent NPC [IV, C].[80,81]

Treatment of metastatic disease or locoregional recurrences not amenable to curative approaches. In metastatic NPC, palliative ChT should be considered for patients with an adequate PS. A treatment combination of cisplatin and gemcitabine is the first-line choice and improves OS [I, A].[82] In patients with newly diagnosed metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and ultimately OS [II, A].[83]

No standard second-line treatment exists. Active agents include paclitaxel, docetaxel, 5-FU, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, oxaliplatin and cetuximab, which can be used as single agents or in selected combinations [III, B].[84] Poly-ChT is more active than monotherapy [overall response rate (ORR) of 64% versus 24%] at a cost of increased and cumulative toxicities. The estimated PFS and OS with second-line therapy are around 5 and 12 months, respectively.[84] In this context, treatment choice should be based on previous treatments, patient symptoms, PS, patient preference and the expected toxicity.

Immunotherapy represents a promising strategy in this disease, especially because of the causal role of EBV and the possibility to elicit a response against its antigens. To-date, no phase III trials have been published in NPC and available evidence is derived from phase II studies, mainly with checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1), or adoptive immunotherapy. Nivolumab, pembrolizumab and camrelizumab have been shown to be safe and active as monotherapy for recurrent and/or metastatic NPC, with ORRs of 20%, 25% and 34%, respectively, with most of the best responses occurring at first radiological evaluation. However, their therapeutic positioning is still to be defined [III, B].[85-87] Cytotoxic T-cell lymphocyte (CTL) adoptive immunotherapy has demonstrated activity in highly pretreated patients [III, B].[88,89]

Oligometastatic patients may achieve long-term survival after aggressive treatment, including ChT, surgery or definitive RT to the metastases [III, B].[90,91]

Pre-treatment plasma EBV DNA and clearance rates are prognostic factors in metastatic patients treated with first-line ChT [III, B].[92]

Recommendations

- The optimal treatment strategy for patients with advanced NPC should be discussed in an MDT. Patients should be treated at high-volume facilities [IV, B].
- IMRT is the mainstay of treatment [II, A].
- Overall, RT is targeted according to the primary tumour, pathological nodes and adjacent regions considered at risk of microscopic spread from the tumour, and generally to both sides of the neck (levels II-V and retropharyngeal nodes).
- A total dose of 70 Gy is needed for the eradication of macroscopic disease and 50-60 Gy for the treatment of potential at-risk sites.
- Planning optimisation in terms of prioritisation and dose constraints for target and radiosensitive structures is fundamental.
- Stage I-II disease is treated by RT alone; for stage II disease, this approach is only used when IMRT is adopted [II, B].
- Stage III and IVA disease are treated by CRT [I, A]. The standard agent used is cisplatin [I, A].
- The most commonly used regimen is cisplatin 100 mg/m^2 every 3 weeks concomitantly to RT [I, A]. Weekly cisplatin (40 mg/m^2/week) has also been shown to improve OS [II, A]. The optimal cumulative total dose of concurrent cisplatin should be higher than 200 mg/m^2 [IV, B].
- Concurrent nedaplatin was found to be non-inferior to concurrent cisplatin [II, B].
- Concurrent carboplatin is an available option but the evidence is conflicting [II, C].
- Intensification of the systemic treatment is needed for stage III-IVA non-keratinising NPC.
- ICT with cisplatin and gemcitabine followed by CRT for locally advanced NPC is associated with a benefit in RFS, OS and distant RFS, with more acute but not late toxicities versus CRT alone [I, A].
- The selection of patients to receive more ChT in addition to CRT in the form of either ICT or AC is a therapeutic area that is being explored in ongoing randomised, controlled trials.
- In cases of persistent, high EBV DNA values after definitive treatment, a personalised approach with non-cross-resistant drugs or participation in a clinical trial is suggested [V, C].
- Small, local recurrences are potentially curable. The main therapeutic options include nasopharyngectomy, brachytherapy, radiosurgery, SRT, IMRT or a combination of surgery and RT, with or without concurrent ChT [III, A].
- Patients with local recurrences not invading the carotid artery or extending intracranially are candidates for nasopharyngectomy; local recurrence stage rT1-rT3 might benefit more from endoscopic nasopharyngectomy than IMRT [IV, B].
- Lymphatic recurrences in the neck can be treated with neck dissection [III, A].
- In metastatic NPC, palliative ChT should be considered for patients with an adequate PS. A treatment combination of cisplatin and gemcitabine is the first-line choice and improves OS [I, A].
- In patients with newly diagnosed, metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and ultimately OS [II, A].

- No standard second-line treatment exists. Active agents include paclitaxel, docetaxel, 5-FU, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, oxaliplatin and cetuximab, which can be used as single agents or in selected combinations [III, B].
- Immunotherapy represents a promising strategy in this setting but its therapeutic positioning is still to be defined [III, B].
- CTL adoptive immunotherapy has demonstrated activity in highly pre-treated patients [III, B].
- Oligometastatic patients may achieve long-term survival after aggressive treatment, including ChT, surgery or definitive RT to the metastases [III, B].

PERSONALISED MEDICINE

EBV infection is strongly associated with NPC. Plasma EBV DNA can be used to facilitate early diagnosis and recurrence monitoring and also has prognostic value, both before and just after the end of treatment (Table 5). However, more research is needed to refine the role of plasma EBV DNA in the management of NPC and to identify additional molecular markers which could lead to advances in personalised medicine in NPC.

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

A proposed algorithm for follow-up after completion of curative treatment of NPC is shown in Figure 3.

Documentation of complete remission in the nasopharynx and neck through clinical and endoscopic examination and/or imaging studies is important. The first radiological imaging is suggested 3 months after treatment completion. Sensitivity of MRI and metabolic imaging (i.e. PET) are similar [II, B], whereas the specificity of PET is higher and so helps to differentiate between post-irradiation changes and recurrent tumours [II, B].[93] However, the cost and availability of PET should be taken into account and could prevent its widespread use. Delayed clinical complete responses to IMRT at 6-9 months do not jeopardise the patient's prognosis.[94]

Risk of recurrence in the era of IMRT seems to have a bimodal behaviour: one after ~1.5 years following the end of treatment (mainly in cases of T3, T4 and N2, N3 diseases) and one after 3.5 years (for all T stages and N2, N3 diseases).[95]

Further follow-up for patients includes periodic (every 3 months in the first year, every 6 months in the second and third year and annually thereafter for the first 5 years) examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis [V, B]. For T2-T4 tumours, MRI might be used on a 6-monthly basis to evaluate the nasopharynx and the base of the skull at least for the first 3 years after treatment [V, B]. PET imaging may be used in cases of equivocal imaging results. Plasma EBV DNA is a promising marker for the diagnosis of recurrence [II, B][96] and should be evaluated at least every year [V, B]. Evaluation of thyroid function in patients who have received RT to the neck is recommended annually; pituitary function should also be evaluated periodically or in case of signs and/or symptoms [V, B].

Attention should be paid to the recognition of late treatment-related toxicities, mainly consisting of xerostomia, trismus, hearing impairment, TLN, cognitive impairment, cranial nerve injuries and second primary tumours possibly related to RT. The employment of IMRT instead of 2D-RT has substantially reduced these late events with the exception of TLN; significant factors affecting the risk of TLN include T stage, the addition of ChT and the maximal RT dose to the temporal lobe.[97]

Long-term survivors after IMRT may experience a decline in cognitive function and in NPC-specific domains of QoL.[98]

More specific considerations on survivorship care planning for head and neck cancer patients can be found in the American Society of Clinical Oncology Clinical Practice Guideline, which also endorsed the American Cancer Society Guideline.[99] In the future, adopting a risk-based follow-up could improve the early detection of relapse and allow for optimisation of resources.[100]

Recommendations

- The first radiological imaging is suggested 3 months after completion of curative treatment. Sensitivity of MRI and PET are similar, whereas the specificity of PET is higher and so helps to differentiate between post-irradiation changes and recurrent tumours [II, B].

Table 5. Personalised medicine synopsis

Biomarker	Methodology	Use	LoE, GoR
Plasma EBV DNA	PCR	Prognostic before curative treatment	III, B (IV, B[a])
		Prognostic role of clearance during ICT and CRT	IV, B
		Prognostic 1-4 weeks after RT	II, B
		Early diagnosis of recurrence during follow-up	V, B
		Prognostic in recurrent and/or metastatic disease	III, B

CRT, chemoradiotherapy; EBV, Epstein-Barr virus; GoR, grade of recommendation; ICT, induction chemotherapy; LoE, level of evidence; RT, radiotherapy.
[a] In non-endemic areas.

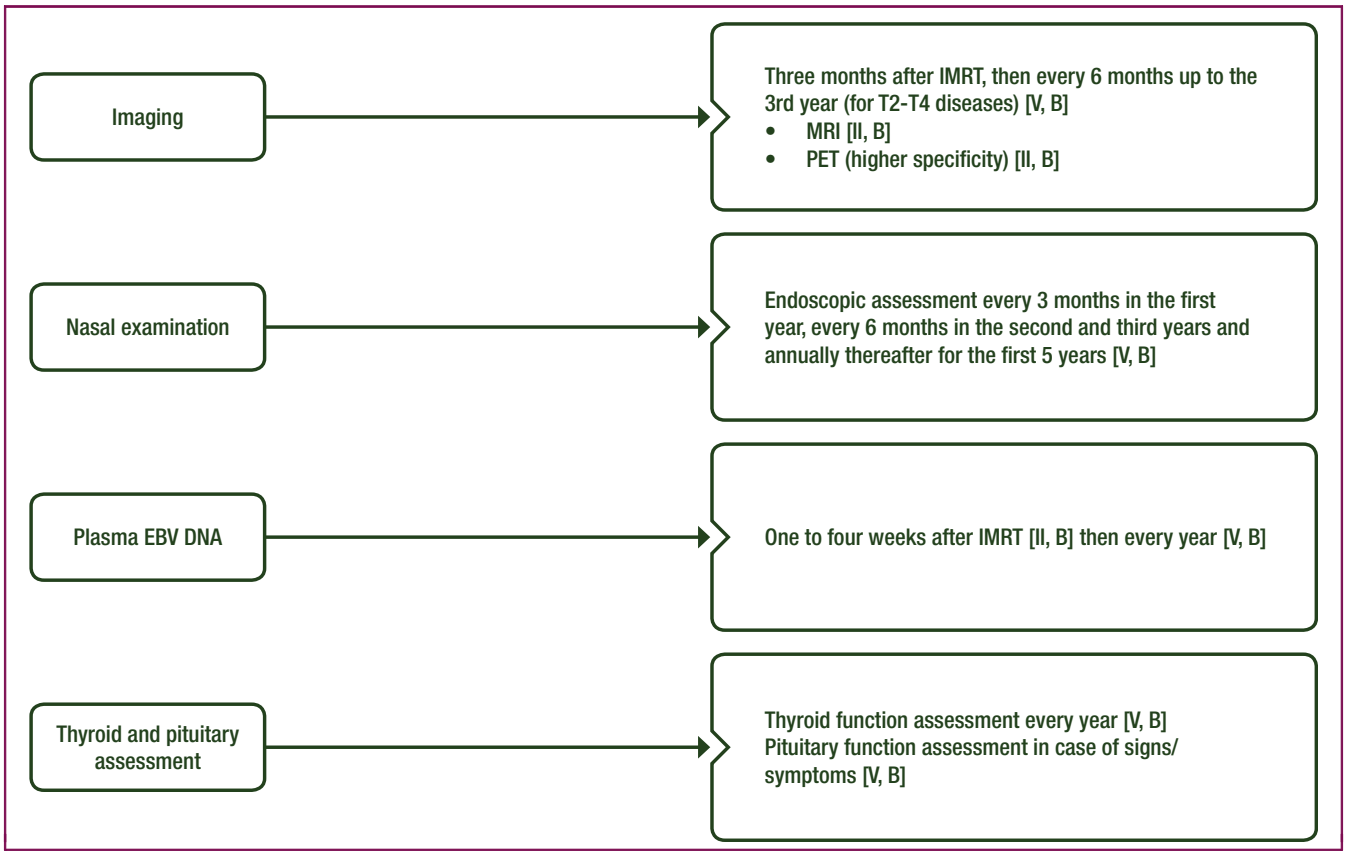

Figure 3. Follow-up algorithm after completion of curative treatment of NPC.
EBV, Epstein-Barr virus; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; NPC, nasopharyngeal cancer; PET, positron emission tomography.

- Further follow-up for patients includes periodic examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis [V, B]. For T2-T4 tumours, MRI might be used on a 6-monthly basis for at least the first 3 years after treatment [V, B].
- Plasma EBV DNA is a promising marker for the diagnosis of recurrence [II, B] and should be evaluated at least every year [V, B].
- Evaluation of thyroid function in patients who have received RT to the neck is recommended annually; pituitary function should also be evaluated according to signs/symptoms [V, B].

METHODOLOGY

These Clinical Practice Guidelines have been produced by the European Society for Medical Oncology (ESMO) in partnership with EURACAN, the European Reference Network for rare adult solid cancers. These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). They are conceived to provide a standard approach to diagnosis, treatment and survivorship of NPC. Recommended interventions are intended to correspond to the 'standard' approaches, according to current consensus among the European multidisciplinary NPC community of experts. These are represented by the members of the ESMO NPC Faculty and experts appointed by all institutions belonging to the NPC domain of EURACAN. Experimental interventions considered to be beneficial are labelled as 'investigational'. Other non-standard approaches may be proposed to the single patient as 'options' for a shared patient-physician decision in conditions of uncertainty, as long as some supporting evidence (though not conclusive) is available. Algorithms accompany the text, covering the main typical presentations of disease, and are meant to guide the user throughout the text.

The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.12.007.[101] Statements without grading were considered justified standard clinical practice by the experts.

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