



SEOM–TTCC clinical guideline for nasopharyngeal carcinoma (update 2025)

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Received: 19 January 2026 / Accepted: 21 January 2026 / Published online: 17 February 2026
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Abstract

Nasopharyngeal carcinoma is distinct from other cancers of the head and neck in biology, epidemiology, histology, natural history, and response to treatment. Radiotherapy is the cornerstone of locoregional treatment of non-disseminated disease and, in combination with chemotherapy, improves survival rates. In the case of metastatic disease stages, treatment requires platinum/gemcitabine-based chemotherapy, and patients may achieve a long survival time. In these guidelines (updated in 2025), we summarize current evidence and available therapies for the medical management of advanced nasopharyngeal carcinoma.

Keywords Nasopharyngeal cancer · Clinical practice guidelines · Diagnosis · Treatment · Follow-up

Introduction

Nasopharyngeal carcinoma (NPC) differs from other head and neck squamous cell carcinomas in epidemiology, histology, natural history, and treatment response [1, 2]. It

also displays a distinct racial and geographic distribution, which is reflective of its multifactorial etiology [2]. While NPC is endemic in Southeast Asia, it is relatively rare in Europe (83.5% and 4.4% of prevalent cases, respectively, in 2022) [3, 4]. Well-known risk factors for these tumors

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include Epstein–Barr virus (EBV), host genetics, and environmental factors such as smoke, alcohol, and wood dust-related occupations [5].

There were 120,434 new cases of NPC reported in 2022 [3]. These were mainly in endemic areas, with only about 4500 cases of NPC reported in Europe [3]. In Spain, in 2022, the incidence of NPC was 0.54 cases/100,000/year, with a total number of diagnosed cases of 417 [3]. The age distribution of NPC differs in areas of low versus high incidence [6]. The incidence of NPC in low-incidence areas increases with age, with bimodal peaks in adolescents/young adults and 65 + years, whereas the incidence in endemic areas increases after 30 years of age, peaking at 40–59 years and then decreasing thereafter [6].

NPC survival is closely associated with disease stage at diagnosis, with 5-year overall survival (OS) rates of 82%, 72%, and 49% reported for stage I, II, and IV disease, respectively [7]. There is also a marked effect of age on survival, with 5-year survival rates of 72% in patients with NPC aged 15–45 years and 36% in those aged 65–74 years [8]. In addition, the incidence of NPC is twofold to threefold higher in males than in females, and prognosis is better in female versus male patients [2].

Methods

These Clinical Practice Guidelines have been produced by oncologists from the Spanish Group for the Treatment of Head and Neck Tumors (TTCC) and the Spanish Society for Medical Oncology (SEOM) with the objective of establishing standard diagnostic and treatment guidelines useful for clinical practice. The guidelines include the most recent scientific evidence for the diagnosis, treatment, and follow-up of patients with NPC, within the context of currently approved indications in Spain. Recommended interventions are intended to correspond to the ‘standard’ approach, according to current consensus among the experts that conceived and wrote the guidelines.

The updated recommendations in these guidelines (July 2025) reflect the results of clinical trials released since the publication of the previous version of these guidelines (2021) [9], and some minor corrections to the wording of the original guidelines; a summary of the changes is provided in Table 1. The relevant literature has been selected by the expert authors, and the updated version of these guidelines has been approved by all of the authors. Levels of evidence and grades of recommendation have been applied using The Infectious Diseases Society of America grading system (Table 2) [10].

Diagnosis

Endoscopic-guided biopsy of the primary nasopharyngeal tumor is used to provide definitive diagnosis of NPC [II, A]. Where no clinical primary tumor is visible at endoscopy, it is suggested that nasopharyngeal tissue positive at magnetic resonance imaging (MRI) or positron emission tomography (PET) be biopsied [6, 11].

Since the appearance of neck nodes is often the first sign of NPC, patients frequently undergo neck biopsy and/or neck nodal dissection. However, node dissection is not recommended due to the reduced probability of cure and increased risk of late morbidity. If unavoidable, for example in cases where the primary tumor is not visible, node dissection without capsular effraction or ultrasonography-guided transcuteaneous Tru-cut biopsy are the preferred options, while node surgical biopsy should be avoided. Subsequent determination of EBV on the histological sample by in situ hybridization (ISH) is indicated in all cases.

Pathological diagnosis

The histological type should be classified according to the 5th edition of the World Health Organization (WHO) classification (Table 3) [12]. There are three pathological subtypes of NPC: keratinizing squamous, non-keratinizing, and basaloid squamous. Non-keratinizing NPC can be further divided into differentiated and undifferentiated tumors.

The keratinizing subtype constitutes < 25% of cases worldwide, being relatively rarer in endemic areas (~ 2–5%) where non-keratinizing NPC (mostly undifferentiated) account for the majority of cases (> 94%) [13–15]. In addition, the non-keratinizing subtype is predominantly associated, even if not sufficiently causative, with EBV infection [14], whereas the role of EBV in keratinizing cancer is less pronounced. EBV is identified by ISH, which determines the presence of EBV-encoded RNA (EBER) in NPC tissue [16].

Added to the WHO classification in 2005, basaloid squamous cell carcinoma is a rarely reported NPC subtype notable for its aggressive clinical course and poor survival [6, 17, 18].

Changing NPC histology in European populations suggests modification of the natural history of the disease [15]. In Europe, the decreasing incidence of keratinizing NPC (WHO type I), which is smoking-related and has a worse prognosis than non-keratinizing NPC, may have influenced the increase in survival observed over recent years [15].

We suggest obtaining pretreatment plasma EBV DNA levels as part of the diagnostic and staging evaluation. Pretreatment plasma EBV DNA levels are prognostic and have been associated with survival outcomes [19].

Table 1 Summary of changes made in the 2025 guidelines

2021 recommendation	New or changed 2025 recommendation
Methodology	
Table 2	
Strength of recommendation A–E; quality of evidence graded I–III	The definitions of the strength of recommendation and quality evidence have been reworded, and two further lower levels of quality of evidence (IV [evidence from retrospective cohort studies or case–control studies] and V [evidence from studies without control group, case reports, or expert opinions]) have been added
Diagnostic and staging evaluation	
Table 4	
Determination of EBV on the histological specimen by ISH is indicated [III, B]	Histology must be performed according to the WHO criteria [12]. Determination of EBV on the histological specimen by ISH is indicated [II, A]
Analysis of EBV DNA in plasma is useful for screening at-risk populations for nasopharyngeal carcinoma. It can detect the cancer at an early stage with a superior treatment outcome compared with the unscreened population [III, A]	Deleted
For the initial diagnostic evaluation of nasopharyngeal carcinoma, we suggest endoscopically guided biopsy of the primary tumor and magnetic resonance imaging (MRI) of the nasopharynx, skull base, and neck to assess locoregional disease extent [III, B]	Deleted
For patients with advanced nodal stage (N3) or clinical or biochemical evidence of distant metastases, we offer additional imaging with positron emission tomography (PET) or integrated PET/computed tomography (CT) imaging if available. Otherwise, bone scan and CT of the chest and abdomen may be obtained [III, B]	Deleted
We suggest obtaining pretreatment plasma EBV DNA levels for their prognostic significance. There is emerging evidence supporting serial measurement of plasma EBV DNA levels to assess treatment response or monitor for recurrence	Deleted
N/A	ECOG performance status, complete physical examination, geriatric and nutritional evaluation should be assessed. Blood analysis, including hemogram and renal panel, CT scan or MRI of the nasopharynx and base of the skull and neck (MRI preferred) must be performed. When ordering an MRI, it is important to specifically request cranial nerve imaging, as a standard brain MRI does not provide adequate detail
N/A	18F-FDG-PET/CT is indicated for patients with advanced nodal disease (stage N3), clinical evidence suggesting distant metastases, or an EBV DNA load ≥ 4000 copies/mL, since these patients are at high risk for distant metastases
N/A	NPC is clinically staged according to the AJCC staging classification 8th Edition [21]
N/A	The addition of pretreatment plasma EBV DNA to the 8th edition of the AJCC TNM staging system [21] has improved its prognostic performance. Patients with advanced locoregional disease and an EBV DNA load ≥ 4000 copies/mL are at increased risk of distant metastases
Introduction	
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 European where it declined over time [3, 4]	NPC survival is closely associated with disease stage at diagnosis, with 5-year overall survival (OS) rates of 82%, 72%, and 49% reported for stage I, II, and IV disease, respectively [7]
Pathological diagnosis	
The histological type should be classified according to the 4th edition of the World Health Organization (WHO) classification (Table 3) [7]	The histological type should be classified according to the 5th edition of the World Health Organization (WHO) classification (Table 3) [12]

Table 1 (continued)

2021 recommendation	New or changed 2025 recommendation
Induction chemotherapy Recently, two Asian trials have been reported that obtain a benefit in recurrence-free survival (RFS) with adjuvant capecitabine after CRT in high-risk locally advanced NPC [42, 43] Recommendations for locoregional treatment <i>Management of locoregional recurrences and metastatic disease</i> Preliminary results with proton and carbon ion therapy are promising Immunotherapy with immune-checkpoint inhibitors (specifically toripalimab and camrelizumab) combined with chemotherapy has shown an improvement in PFS in preliminary results reported in Asian population [55, 56]. Final results are awaited Immunotherapy with immune-checkpoint inhibitors has shown promising activity too [57–59] [III, B]. Nivolumab, pembrolizumab, and camrelizumab showed 20–34% of response rate in different phase I/II trials. Phase III trials are ongoing to elucidate the role of immunotherapy	Also, two Asian trials have reported a benefit in RFS and OS with adjuvant capecitabine after CRT in high-risk locally advanced NPC [54–56]. The benefit in OS was confirmed upon meta-analysis [57] While initial results with proton and carbon ion therapy appeared promising, these approaches remain experimental due to restricted availability and high costs [65–67] Also, while not funded by the Spanish public health system, addition of an anti-programmed cell death protein 1 (PD-1) drug to cisplatin–gemcitabine should be considered [IA]. Three randomized phase III trials have demonstrated improved outcomes with addition of an anti-PD-1 antibody (toripalimab, camrelizumab, tislelizumab) to first-line gemcitabine–cisplatin in recurrent/metastatic nasopharyngeal carcinoma [70–72]. All three studies (JUPITER-02, CAPTAIN-1st, and RATIONALE-309, respectively) showed improved PFS versus cisplatin–gemcitabine alone, with JUPITER-02 reporting a statistically significant OS benefit with longer follow-up (median not reached vs 33.7 months; HR 0.63; 95% CI 0.45–0.89; $p=0.008$) [70–72] Immunotherapy with immune-checkpoint inhibitors has shown promising activity too [III, B], with nivolumab, pembrolizumab, and camrelizumab showing response rates of 20–34% in various phase I/II trials [73–75]. To date, Phase III data are available for pembrolizumab, with the KEYNOTE-122 study failing to show a statistically significant OS benefit with pembrolizumab versus chemotherapy (i.e., capecitabine, gemcitabine, or docetaxel), with median OS of 17.2 versus 15.3 months (HR 0.90; 95% CI 0.67–1.19; $p=0.2262$) [76]. Results of ongoing Phase III trials of immunotherapy will help further elucidate its role in this setting
Figure 2 N/A	Addition of a footnote to the recommendation of cisplatin–gemcitabine for the first-line treatment of patients with primary metastatic disease (no previous CRT): *Addition of an anti-PD-1 drug (not funded by the Spanish public health system) to cisplatin–gemcitabine should be considered [I, A]
Locoregional recurrence and metastatic disease There is no strong evidence to choose between re-irradiation and surgery [59] rT1–3 tumors might benefit more from endoscopic nasopharyngectomy than from IMRT [83] Immunotherapy with immune-checkpoint inhibitors (specifically toripalimab and camrelizumab) combined with chemotherapy has shown an improvement in PFS in preliminary results reported in Asian population [55, 56]. Final results are awaited	A randomized study has shown that endoscopic nasopharyngectomy increases survival and reduces local sequelae compared to re-irradiation with IMRT in highly selected patients with small local recurrences, rT1-2 rN0-1 [65] Based on recent phase III randomized trials, the combination of cisplatin–gemcitabine plus an anti-programmed cell death protein 1 (PD-1) antibody is currently considered the standard of care in the first-line treatment of recurrent or metastatic NPC [I, A]. Three randomized phase III studies (JUPITER-02, CAPTAIN-1st, and RATIONALE-309) have consistently demonstrated a significant improvement in PFS with the addition of toripalimab, camrelizumab, or tislelizumab, respectively, to gemcitabine–cisplatin compared with chemotherapy alone [70–72]. With longer follow-up, the JUPITER-02 trial also showed a statistically significant OS benefit (median not reached vs 33.7 months; HR 0.63; 95% CI 0.45–0.89; $p=0.008$) [70–72]. However, despite the level I evidence supporting this approach, anti-PD-1 antibodies in combination with cisplatin–gemcitabine are not currently funded by the Spanish National Health System, which limits their routine use in clinical practice in Spain. In Spain, although toripalimab and tislelizumab have received EMA approval and national authorization, public reimbursement was not available at the time of guideline publication

Table 1 (continued)

2021 recommendation	New or changed 2025 recommendation
Follow-up, long-term implications, and survivorship (Table 7)	
Final assessment (2–3 months after the end of treatment)	Final assessment (2–3 months after the end of treatment)
- Local and regional exam plus nasopharyngeal fibroscopy - FDG-PET/CT and/or MRI [II, B]	- Local and regional exam plus nasopharyngeal fibroscopy - FDG-PET/CT and/or MRI [II, B] - Plasma EBV DNA (every year)* [V, B]
First year	First year
- Local and regional exam plus nasopharyngeal fibroscopy (every 3 to 4 months) - CT/MRI (every 6 months) - Chest X-ray, thyroid function test (yearly) [V, B]	- Local and regional exam plus nasopharyngeal fibroscopy (every 3 to 4 months) - CT/MRI (every 6 months) - Chest X-ray, thyroid function test (yearly) [V, B] - Plasma EBV DNA (every year)* [V, B]
2–3 years	2–3 years
- Local and regional exam plus nasopharyngeal fibroscopy (every 6 months) - CT/MRI (every 6 months) - Chest X-ray, thyroid function test (yearly) [V, B]	- Local and regional exam plus nasopharyngeal fibroscopy (every 6 months) - CT/MRI (every 6 months) - Chest X-ray, thyroid function test (yearly) [V, B] - Plasma EBV DNA (every year)* [V, B]
4–5 years	4–5 years
- Local and regional exam plus nasopharyngeal fibroscopy (every 6 months) - Chest X-ray, thyroid function test, CT/MRI (yearly) [V, B]	- Local and regional exam plus nasopharyngeal fibroscopy (every 6 months) - Chest X-ray, thyroid function test, CT/MRI (yearly) [V, B] - Plasma EBV DNA (every year)* [V, B]

AJCC American Joint Committee on Cancer; *CI* confidence interval; *CT*: computed tomography; *DNA* deoxyribose nucleic acid; *EBV* Epstein–Barr virus; *ECOG* Eastern Cooperative Oncology Group; *FDG* fluorodeoxyglucose; *HR* hazard ratio; *ISH* in situ hybridization; *MRI* magnetic resonance imaging; *N/A* not applicable; *NPC* nasopharyngeal carcinoma; *OS* overall survival; *PD-1* programmed cell death protein 1; *PET* positron emission tomography; *PFS* progression-free survival; *TNM* tumor, node, metastasis; *WHO* World Health Organization

*Plasma EBV DNA is a promising marker for the diagnosis of recurrence [II, B]

Table 2 Strength of recommendation and quality of evidence score

Category, grade	Definition
Strength of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Evidence from small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Evidence from prospective cohort studies
IV	Evidence from retrospective cohort studies or case–control studies
V	Evidence from studies without a control group, case reports, or expert opinions

Screening

In endemic regions, plasma screening of EBV DNA in patients with NPC, utilizing a primer/probe assay targeting the BamHI-W region of the EBV genome (in duplicate ≥ 4 weeks apart) in combination with endoscopic

examination and MRI, showed a sensitivity and specificity of 97.1% and 98.6%, respectively [20]. Also, the number of individuals needed to be screened to detect one case was determined to be 593. Therefore, the use of this method is only recommended for detecting early asymptomatic NPC in endemic regions in higher risk individuals (i.e., males

Table 3 World Health Organization classification of nasopharyngeal carcinomas [12]

Type of nasopharyngeal carcinoma	World Health Organization classification
Keratinizing squamous cell carcinoma	WHO type I
Non-keratinizing carcinoma	
Differentiated type	WHO type II
Undifferentiated type	WHO type III
Basaloid squamous cell carcinoma	

aged 40–62 years) [III, A]. While OS data for a screened population are unavailable, 3-year progression-free survival (PFS) has been shown to be significantly improved versus a matched historical cohort diagnosed with NPC without screening (97% vs 70%; hazard ratio [HR] 0.10; 95% confidence interval [CI] 0.05–0.18; $p < 0.001$) [20].

Diagnostic evaluation and staging

In line with the current European guidelines [6], diagnostic work-up should include:

1. A complete medical history and physical examination.
2. Full exploration of the head and neck area (including endoscopic examination and cranial nerves evaluation). A definitive diagnosis is made with the aid of endoscope-guided biopsy of the primary tumor. Incisional neck biopsy or nodal dissection should be avoided as this procedure will negatively impact subsequent treatment.

3. CT scan or MRI of the nasopharynx and base of the skull and neck (MRI preferred). When ordering an MRI, it is important to specifically request cranial nerve imaging, as a standard brain MRI does not provide adequate detail.
4. General blood count and serum biochemistry, including liver function tests and alkaline phosphatase.
5. Tumor biopsy (EBER by ISH).
6. Baseline audiometric testing, dental examination, nutritional status evaluation, ophthalmological and endocrine evaluation.
7. Plasma EBV DNA. The addition of pretreatment plasma EBV DNA to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system has improved its prognostic performance [21].
8. 18F-FDG-PET/CT is indicated for patients with advanced nodal disease (stage N3), clinical evidence suggesting distant metastases, or an EBV DNA load ≥ 4000 copies/mL, since these patients are at high risk for distant metastases. Metastatic lymph nodes and bone lesions are better detected by 18F-FDG-PET/CT.

Levels of evidence and grades of recommendation applied for recommendations for diagnostic and staging evaluation are shown in Table 4.

NPC is clinically staged according to the American Joint Committee on Cancer (AJCC) staging classification 8th edition [21] (Table 5). This staging system provides important prognostic information and guidance for choosing the appropriate treatment for patients with NPC (Table 6).

Table 4 Recommendations for diagnostic and staging evaluation

Diagnosis and staging	Level of evidence
A definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumor. Incisional neck biopsy or nodal dissection should be avoided as this procedure will negatively impact the subsequent treatment	II, A
Histology must be performed according to the WHO criteria [12]. Determination of EBV on the histological specimen by ISH is indicated	II, A
ECOG performance status, complete physical examination, geriatric and nutritional evaluation should be assessed. Blood analysis, including hemogram and renal panel, CT scan or MRI of the nasopharynx and base of the skull and neck (MRI preferred) must be performed. When ordering an MRI, it is important to specifically request cranial nerve imaging, as a standard brain MRI does not provide adequate detail	III, B
18F-FDG-PET/CT is indicated for patients with advanced nodal disease (stage N3), clinical evidence suggesting distant metastases, or an EBV DNA load ≥ 4000 copies/mL, since these patients are at high risk for distant metastases	III, B
NPC is clinically staged according to the AJCC staging classification 8th Edition [21]	V, B
The addition of pretreatment plasma EBV DNA to the 8th edition of the AJCC TNM staging system [21] has improved its prognostic performance. Patients with advanced locoregional disease and an EBV DNA load ≥ 4000 copies/mL are at increased risk of distant metastases	III, B

18F-FDG-PET/CT: 2-deoxy-2- [18F]fluoro-D-glucose positron emission tomography/computed tomography; AJCC American Joint Committee on Cancer; CT computed tomography; EBV Epstein–Barr virus; ECOG Eastern Cooperative Oncology Group; ISH in situ hybridization; MRI: magnetic resonance imaging; NPC nasopharyngeal carcinoma; TNM tumor, node, metastasis; WHO World Health Organization

Table 5 Nasopharyngeal carcinoma TNM staging per AJCC UICC 8th edition [21]

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Tumor in situ
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC American Joint Committee on Cancer; EBV Epstein–Barr virus; TNM tumor, node, metastasis; UICC Union for International Cancer Control

Table 6 Prognostic stage groups per AJCC UICC 8th edition [21]

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1, T2	N0, N1	M0
Stage III	T0, T1, T2, T3	N2, N0, N1, N2	M0, M0
Stage IVA	T4, Any T	N0, N1, N2, N3	M0, M0
Stage IVB	Any T	Any N	M1

AJCC American Joint Committee on Cancer; M metastasis; N node; T tumor; UICC Union for International Cancer Control

Treatment

The optimal treatment strategy for patients with NPC should be discussed within a multidisciplinary team. Treatment of patients in high-volume facilities is recommended.

Management of local/locoregional disease

Radiotherapy (RT) is the cornerstone of locoregional treatment for NPC. Intensity-modulated radiotherapy (IMRT) has shown the best results with fewer late effects than conventional RT, with a 5-year disease-specific survival rate of 92–94% [22–25]. In addition to the primary tumor and pathological nodes, both sides of the neck (levels II–V) and the retropharyngeal nodes should be included due to the high incidence of occult neck node involvement [26]. The dose should be 70 Gy in 33–35 fractions (2.0–2.12 Gy per fraction) delivered over 7 weeks (once daily, five fractions per week) in the primary tumor and affected lymph node areas and 50–60 Gy for the treatment of potential at-risk sites [I, A]. Both sequential boost and simultaneous integrated boost radiotherapy may be offered [27] [II, B].

Early stages (I and II)

The treatment for stage I and II tumors is RT alone, except for some special situations that suggest increased risk of

recurrence. Administration of concomitant chemotherapy with RT (CRT) in patients with stage II disease remains poorly defined. The use of CRT with cisplatin 30 mg/m² weekly + conventional RT demonstrated benefit versus RT alone in OS, PFS, and distant metastases-free survival, but not in locoregional relapse-free survival [28] [II, B]. Also, there were no statistically significant differences between CRT and RT treatment groups when the RT used was IMRT [28–30]. Considering that specific subgroups of patients with stage II disease have differing risks of distant metastases, use of CRT may be considered in patients with N1 or bulky T2 disease, or in those with high EBV DNA levels (> 4000 copies per mL) [II, B].

Locally advanced stages (III and IV A/B)

Concurrent chemoradiotherapy

Concurrent CRT with cisplatin 100 mg/m² every 3 weeks is the standard treatment for locoregionally advanced NPC carcinoma, and it substantially improves OS, locoregional and distant control compared with RT alone [31, 32] [I, A]. Weekly cisplatin [33, 34] or carboplatin [32] can be considered if standard treatment is contraindicated [II A, II B].

Since distant metastasis is the main cause of relapse and death despite this treatment [35], different strategies have been developed to improve these results.

Induction chemotherapy

Various randomized trials [36–38] and meta-analyses [39–44] have demonstrated that addition of induction chemotherapy (IC) carries a benefit in distant relapse-free survival (DRFS) compared with standard CRT in patients with locally advanced NPC at high risk of developing metastases (non-keratinizing histology, significant lymph node involvement, very fast-growing tumors) and, as a consequence, in OS [I, A]. Most of these studies used platinum + 5-fluorouracil or docetaxel + cisplatin + 5-fluorouracil, and patients with T3–4N0 disease were excluded.

It is important to take into account the characteristics of the patient and the toxicity associated with IC when selecting this strategy, so that it does not compromise compliance with CRT. IC with cisplatin and gemcitabine (cisplatin–gemcitabine) followed by CRT has demonstrated greater efficacy than CRT alone in terms of recurrence-free survival (RFS), DRFS, and OS with greater acute hematologic and gastrointestinal toxicity, but without increasing late toxicity and with acceptable compliance of treatment [45] [I, A].

Although there is no head-to-head comparison between IC–CRT and CRT plus adjuvant chemotherapy (AC), results from various analyses suggest that IC achieves superior efficacy results due to better distant disease control [32, 46, 47].

Adjuvant chemotherapy

The addition of AC to CRT remains controversial [II, B]. In addition, accurate selection of patients is critical due to toxicity and compliance of AC after CRT [48].

Most randomized studies and meta-analyses have failed to demonstrate an OS benefit of AC when added to CRT utilizing IMRT [49–51], even a trial that randomized patients to receive AC with cisplatin–gemcitabine based on detectable plasma EBV DNA after CRT [52]. However, the Inter-group-0099 trial established CRT followed by AC with platinum + 5-fluorouracil as the standard treatment of locoregionally advanced (stage III–IVA) NPC, given the superior OS over conventional RT alone [53]. Also, two Asian trials have reported a benefit in RFS and OS with adjuvant capecitabine after CRT in high-risk locally advanced NPC [54–56]. The benefit in OS was confirmed upon meta-analysis [57].

Recommendations for locoregional treatment

Treatment options (with strength of recommendation and quality of evidence) for early (stages I and II) and locally advanced (stages III–IVA) NPC are shown in Fig. 1.

Management of locoregional recurrences and metastatic disease

Given that locoregional recurrences may be curable [58], local treatment is often recommended [II, B], albeit with significant sequelae. The main therapeutic options include surgery (open or endoscopic nasopharyngectomy [59]) and/or re-irradiation (IMRT), brachytherapy, radiosurgery (SRS), and stereotactic body RT (SBRT) with or without concurrent chemotherapy [60]. Recurrence volume, disease-free interval, performance status, and comorbidities are important decision factors [58, 60, 61].

For the evaluation of surgery, referral of the patient to a high-volume center would be desirable. Prognostic factors for surgery are rT and rN stage [62], surgical approach, feasibility of adjuvant re-irradiation [63], and pretreatment circulating EBV DNA [64] (as in metastatic disease). Lymphatic recurrences in the neck can be treated with radical or selective neck dissection [III, A]. A randomized study has shown that endoscopic nasopharyngectomy increases survival and reduces local sequelae compared to re-irradiation with IMRT in highly selected patients with small local recurrences (rT1–2 rN0–1) [65]. Nasopharyngectomy is contraindicated in the presence of carotid invasion or intracranial invasion [II, E].

Patient selection for re-irradiation is essential due to the very high incidence of complications [III, B]. Prognostic factors for re-irradiation are: recurrence volume, age, prior RT toxicity, advanced rT stage, and higher re-IMRT dose

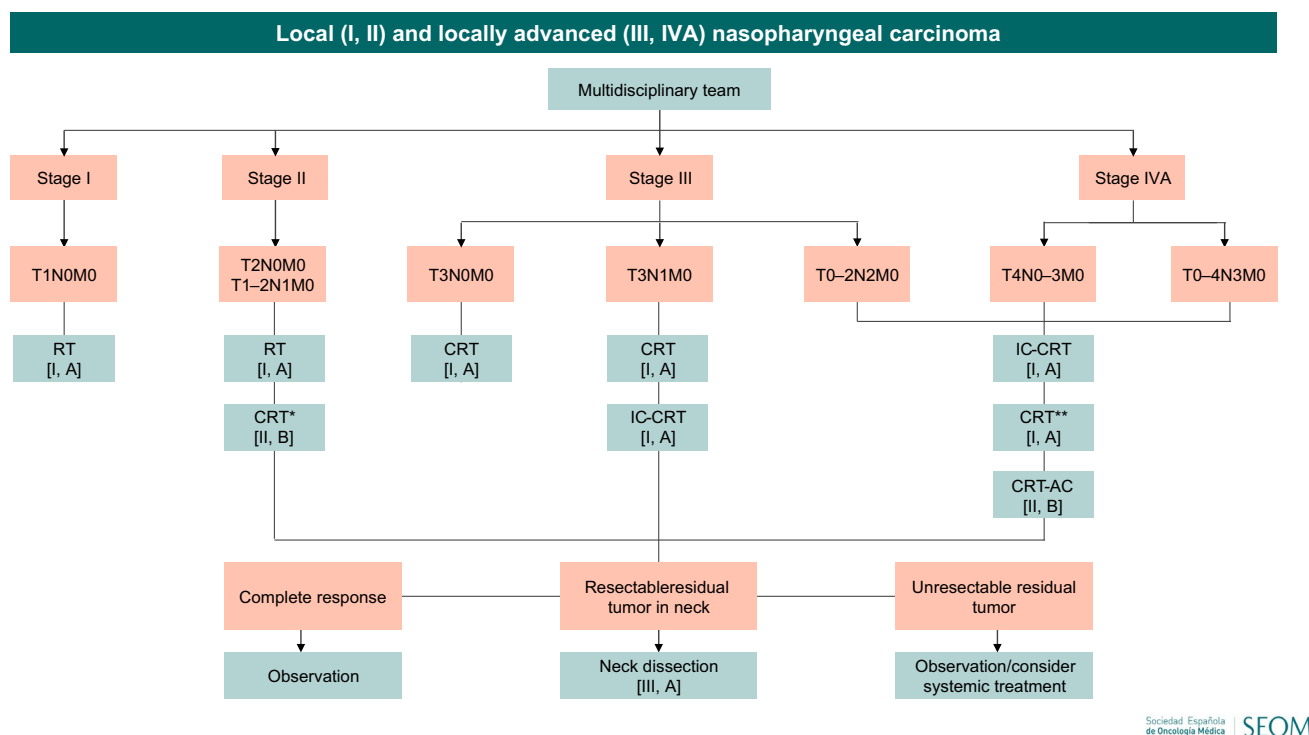


Fig. 1 Treatment options in early and locally advanced nasopharyngeal carcinoma. Adjuvant chemotherapy (AC): capecitabine (metronomic or standard dose) in high-risk locoregionally advanced NPC [II, B]; radiotherapy (RT): mandatory; chemoradiotherapy (CRT): cisplatin 100 mg/m² every 3 weeks (or carboplatin) plus RT; EBV

Epstein–Barr virus; induction chemotherapy (IC): cisplatin and gemcitabine; IMRT intensity-modulated radiation therapy. *Consider initial CRT in N1, bulky tumors or high EBV DNA. **Consider initial CRT in T4N0

[66]. While initial results with proton and carbon ion therapy appeared promising, these approaches remain experimental due to restricted availability and high costs [67–69].

Platinum-based chemotherapy is the backbone of first-line treatment in patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) not amenable to curative therapy. Cisplatin–gemcitabine has historically been established as the standard chemotherapy regimen after a phase III trial demonstrated superior efficacy compared with cisplatin plus 5-fluorouracil administered every 3 weeks [68]. This study included 362 Asian patients, predominantly with non-keratinizing undifferentiated NPC (type III, 83%), and showed a significant improvement in progression-free survival (PFS) (median 7 months [IQR 4.4–10.9] vs 5.6 months [IQR 3–7]; HR 0.55; 95% CI 0.44–0.68; $p < 0.0001$), as well as overall survival (OS) (median 29.1 months [IQR 12–31.5] vs 20.9 months [IQR 0.45–0.84]) [68]. The objective response rate was higher with cisplatin–gemcitabine (64% vs 42%), with a different toxicity profile: increased hematologic toxicity with cisplatin–gemcitabine and higher rates of mucositis with cisplatin plus 5-fluorouracil [I, A]. In patients with contraindications to cisplatin or gemcitabine, cisplatin/carboplatin plus 5-fluorouracil may be considered as an alternative regimen. In patients with newly diagnosed metastatic NPC

who have achieved a response with first-line chemotherapy, the addition of locoregional radiotherapy improves OS [70]. A phase III trial randomized 126 patients to receive cisplatin + 5-fluorouracil chemotherapy with or without locoregional IMRT 70 Gy [70]. The 24-month OS rate was 76.4% in the combination arm versus 54.5% in the chemotherapy only arm (HR 0.42; 95% CI 0.23–0.57) [69]. Non-significant differences in toxicity were observed [II, A].

Based on recent phase III randomized trials, the combination of cisplatin–gemcitabine plus an anti-programmed cell death protein 1 (PD-1) antibody is currently considered the standard of care in the first-line treatment of recurrent or metastatic NPC [I, A]. Three randomized phase III studies (JUPITER-02, CAPTAIN-1st, and RATIONALE-309) have consistently demonstrated a significant improvement in PFS with the addition of toripalimab, camrelizumab, or tislelizumab, respectively, to gemcitabine–cisplatin compared with chemotherapy alone [70–72]. With longer follow-up, the JUPITER-02 trial also showed a statistically significant OS benefit (median not reached vs 33.7 months; HR 0.63; 95% CI 0.45–0.89; $p = 0.008$) [70–72]. However, despite the level I evidence supporting this approach, anti-PD-1 antibodies in combination with cisplatin–gemcitabine are not currently funded by the Spanish National Health System,

which limits their routine use in clinical practice in Spain. In Spain, although toripalimab and tislelizumab have received EMA approval and national authorization, public reimbursement was not available at the time of guideline publication. No standard second-line therapy has been established, although some agents have proven activity (paclitaxel, docetaxel, 5-fluorouracil, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, oxaliplatin, and cetuximab) [III, B]. Immunotherapy with immune-checkpoint inhibitors has shown promising activity too [III, B], with nivolumab, pembrolizumab, and camrelizumab showing response rates of 20–34% in various phase I/II trials [71–73]. To date, Phase III data are available for pembrolizumab, with the KEY-NOTE-122 study failing to show a statistically significant OS benefit with pembrolizumab versus chemotherapy (i.e., capecitabine, gemcitabine, or docetaxel), with median OS of 17.2 versus 15.3 months (HR 0.90; 95% CI 0.67–1.19; $p=0.2262$) [74]. The role of immunotherapy in platinum-refractory patients or after progression to anti-PD1 in the first line needs to be elucidated.

Oligometastatic patients may benefit from local treatment of the metastatic sites after a favorable course with chemotherapy [75] [II, B].

Treatment recommendations for locoregional recurrences and metastatic disease are shown in Fig. 2.

Follow-up, long-term implications, and survivorship

Evaluation of clinical response in the nasopharynx and neck should be performed using clinical and endoscopic examination and imaging studies, with the first assessment suggested to take place 3 months after the completion of treatment. While MRI and PET have similar sensitivity [II, B], the higher specificity of PET helps to differentiate between post-irradiation changes and recurrent tumors [76]. Thereafter, periodic follow-up of patients is recommended (i.e., every 3 months in the first year, every 6 months in the second and third years, then annually for the first 5 years), with endoscopic examination of the nasopharynx, and evaluation of neck, cranial nerve function, and systemic complaints to identify distant metastasis [V, B] (Table 7). For T2–T4 tumors, 6-monthly MRI can be used for evaluation of the nasopharynx and the base of the skull for the first few years after treatment [V, B].

Since plasma EBV DNA has been shown to be a promising marker for the diagnosis of recurrence [II, B], annual testing (at minimum) is recommended [77] [V, B]. Also, annual evaluation of thyroid function (in patients who have received RT to the neck) and annual thoracic imaging are recommended [V, B].

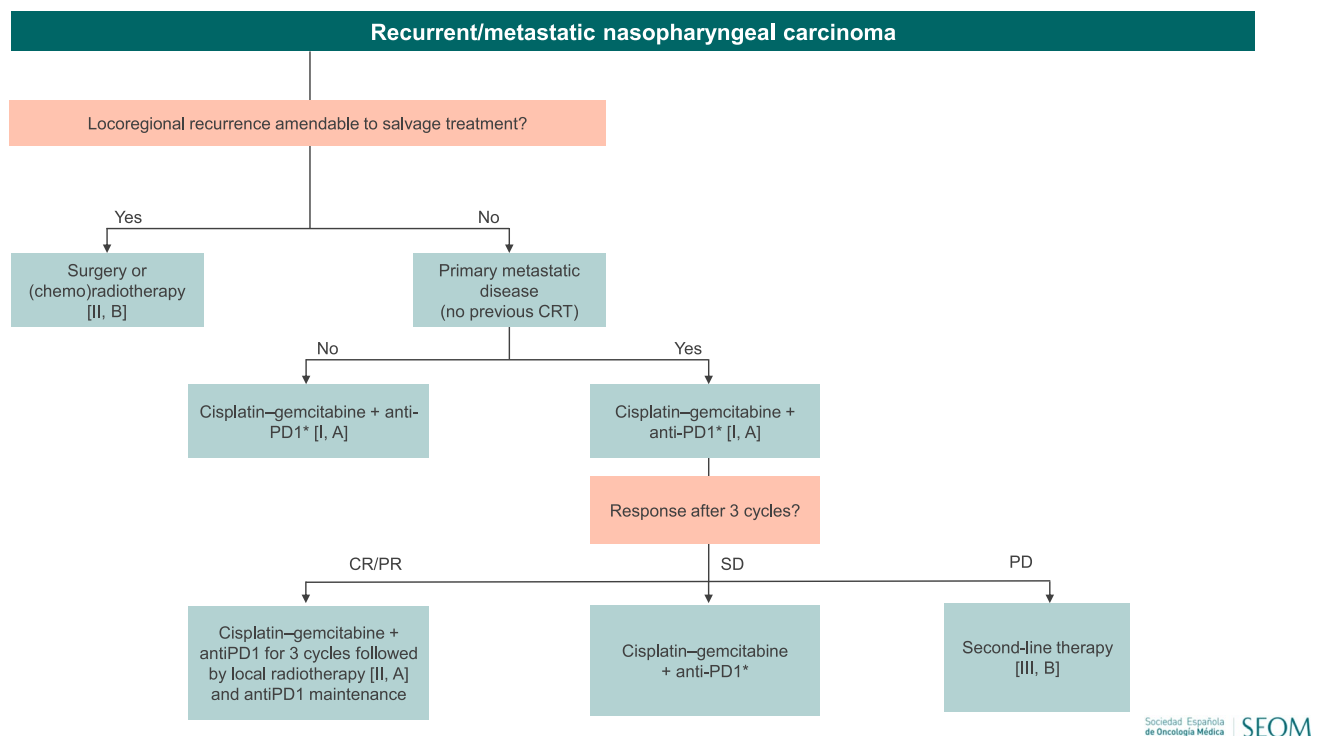


Fig. 2 Treatment options in locoregional recurrences and metastatic nasopharyngeal carcinoma. *CR* complete response; *CRT* chemoradiotherapy; *PD-1* programmed cell death protein 1; *PD*: progressive

disease; *PR* partial response; *SD* stable disease. *Addition of an anti-PD-1 drug (not funded by the Spanish public health system) to cisplatin-gemcitabine should be considered [I, A]

Table 7 Follow-up recommendations for nasopharyngeal carcinoma

Final assessment (2–3 months after the end of treatment)	• Local and regional exam plus nasopharyngeal fibroscopy • FDG-PET/CT and/or MRI [II, B] • Plasma EBV DNA (every year)* [V, B]
First year	• Local and regional exam plus nasopharyngeal fibroscopy (every 3 to 4 months) • CT/MRI (every 6 months) • Chest X-ray, thyroid function test (yearly) [V, B] • Plasma EBV DNA (every year)* [V, B]
2–3 years	• Local and regional exam plus nasopharyngeal fibroscopy (every 6 months) • CT/MRI (every 6 months) • Chest X-ray, thyroid function test (yearly) [V, B] • Plasma EBV DNA (every year)* [V, B]
4–5 years	• Local and regional exam plus nasopharyngeal fibroscopy (every 6 months) • Chest X-ray, thyroid function test, CT/MRI (yearly) [V, B] • Plasma EBV DNA (every year)* [V, B]

CT computed tomography; EBV Epstein–Barr virus; FDG fluorodeoxyglucose; MRI magnetic resonance imaging; PET positron emission tomography

*Plasma EBV DNA is a promising marker for the diagnosis of recurrence [II, B]

Importantly, patients should also be followed for late toxicities, paying special attention to the recognition of late treatment-related toxicities (e.g., xerostomia, trismus, hearing impairment, temporal lobe necrosis [TLN], cognitive impairment, cranial nerve injuries). The use of IMRT instead of 2-dimensional RT has substantially reduced these late events, with the exception of TLN. The risk is higher depending on disease stage, the addition of chemotherapy, and the total dose of RT to the temporal lobe [78, 79]

Patients with NPC have a lower risk of second neoplasms than other tobacco-related head and neck cancers [80, 81]; therefore, long-term follow-up should not overly focus on the detection of second neoplasms [III, B]. Even so, the risk of bone cancer in irradiated areas must be taken into account [82].

Acknowledgements We would like to thank Andrea Bothwell and Bernadette Pfang who provided editorial assistance in developing the first draft of this updated manuscript on behalf of Springer Health+.

Author contributions The Spanish Society of Medical Oncology (SEOM) was responsible for the article conception. All authors were equally responsible for this work; all authors performed the literature search and data analysis, drafted and/or critically revised the manuscript, and approved the final version.

Funding This work was funded by the Spanish Society of Medical Oncology (SEOM).

Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest Antonio Rueda Domínguez has received speaker fees and attended advisory boards for BMS, MSD, Merck, Roche, and Takeda; and has attended an advisory board for Gilead. Beatriz Cirauqui has received speaker fees and attended an advisory board for

BMS, MSD, Merck, and Leo Pharma; and has received other fees from BMS, MSD, and Merck. Leticia Iglesias Rey has received speaker fees from Novartis, Roche, and Pfizer; and has received speaker fees and attended an advisory board for BMS. Virginia Arrazubi has attended an advisory boards for BMS and MSD; has received speaker fees from Organon, Astellas, AstraZeneca, BiOne, MSD; and has received non-financial support from Merck. Ricard Mesía has received speaker fees and attended advisory boards for Merck and MSD; has attended an advisory boards for Bayer, Roche, Nanobiotix, and Seagen; and has received speaker fees from BMS. Almudena García Castaño, Ruth Alvarez Cabellos, Alberto Carral Maseda, Beatriz Castelo Fernández, and Jordi Rubió-Casadevall have nothing to disclose.

Ethical approval and informed consent Not applicable. The manuscript does not contain clinical studies or patient data.

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