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NASOPHARYNGEAL CARCINOMA

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Summary of Literature Review

Epidemiology and Risk Factors of Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a rare disease in the Western world, with an incidence in the United States of 0.5–2 per 100,000 [1]. However, the incidence of NPC is significantly higher in southern China, southeast Asia, and the Middle East/North Africa, where it is one of the most common cancers [1]. This geographic variation suggests interactions of different factors such as Epstein-Barr virus (EBV) infection [2], genetic predisposition, and environmental factors including diet [3,4], which are more likely to be found in combination in endemic regions. In the Western world, some of the incidence may be driven by classic risk factors common to most head and neck cancers, such as tobacco use or alcohol consumption [5], but the highest incidence rates are still found in Asian immigrant populations [6]. The incidence of NPC peaks around ages 50 to 59 and then declines [7]. However, an increased incidence of NPC in younger individuals in endemic regions suggests that affected individuals may carry a genetic predisposition towards EBV infection early in life, leading to an increased predisposition to NPC. NPC cells express EBV latent proteins, such as EBNA-1, LMP-1, and LMP-2, as well as BamHI, a fragment of the EBV genome [8]. It is thought that viral proteins may induce epithelial cellular growth following exposure to EBV [9], with secondary genetic alterations occurring with exposure to environmental carcinogens later in life [3].

Clinical Presentation and Evaluation

NPC patients commonly present with headache, cranial nerve involvement, nasal obstruction, or a neck mass due to nodal metastases. However, patients may remain asymptomatic for a long time, given the often clinically occult site of presentation. When a patient is suspected of having NPC, endoscopic visualization of the primary tumor should be the initial step. Most tumors arise in the lateral nasopharyngeal wall in the fossa of Rosenmüller. Endoscopic biopsy should be performed. In the most recently modified World Health Organization (WHO) classification, the category of squamous cell carcinoma subtype (keratinizing squamous cell carcinoma) was retained, while the other 2 subtypes were combined under a single category of "nonkeratinizing carcinoma," which was further subdivided as being "differentiated" or "undifferentiated." In addition, lymphoepithelioma-like carcinoma was considered a morphologic variant of undifferentiated carcinoma. The use of numerical designations of WHO types 1, 2, and 3 was also eliminated in the most recent classification, and the subtype of basaloid squamous cell carcinoma was added [7,10]. NPC is clinically staged according to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). To assess the locoregional extent of disease, imaging for NPC patients usually should include magnetic resonance imaging (MRI) of the nasopharynx, skull base, and neck. The upper mediastinum should also be imaged if there are low neck nodal metastases. Although computed tomography (CT) can detect mass lesions in the nasopharynx, MRI is superior at detecting the extent of osseous, cranial nerve, and intracranial involvement, which is critical given the propensity for skull base invasion and intracranial spread. As NPC tends to metastasize early, with distant metastases having

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a reported frequency of up to 11% [11], additional imaging with positron emission tomography (PET) may be helpful. In a case where a PET scan is not available, a bone scan and CT scan of the chest and abdomen is recommended [12,13]. In light of the evidence supporting measurement of baseline and post-treatment plasma EBV DNA levels to monitor response and recurrence, a pretreatment and post-treatment EBV DNA level may be appropriate; the value in guiding therapy is the subject of an ongoing NRG protocol [14,15].

General Treatment for Nasopharyngeal Carcinoma

Given that most patients present with locoregionally advanced disease not amenable to definitive surgical resection as well as the inherent morbidity of surgical resection in the nasopharynx, most patients with NPC are treated with radiation with or without chemotherapy. Surgery is typically reserved for salvage of post-radiation therapy recurrences and can be combined with brachytherapy or other forms of reirradiation. Interestingly, in the United States, Asians have the highest rate of receiving radiation only [6], which was significant in the multivariate stratified analysis; it is unclear if this is due to an unfit or elderly age distribution in this population or a cultural or socioeconomic factor resulting in higher levels of guideline-discordant care.

Treatment of Stage I (Early) Disease

NPC is a radiosensitive tumor, and early-stage disease (T1N0) is usually treated with radiation therapy (RT) only. Traditionally, 3-D conformal radiation therapy (3D-CRT) has been used for treating early-stage NPC, but recent randomized studies point to the benefits of intensity-modulated radiation therapy (IMRT) in avoiding late toxicities such as xerostomia [16,17]. In 1 randomized study comparing 3D-CRT with IMRT for early-stage NPC patients, the European Organisation for the Research and Treatment of Cancer (EORTC) core questionnaire and EORTC quality-of-life module for head and neck cancer (QLQ-H&N35) were completed at baseline and 2, 6, and 12 months after RT to assess for differences in toxicity based on radiation technique. At 12 months post-RT, more patients had recovered at least 25% of pre-RT stimulated whole saliva, 12 (50.0%) in the IMRT group compared to 1 (4.8%) in the 3D-CRT group. Furthermore, recovery of 25% of pre-RT stimulated parotid saliva flow was seen in 20 patients (83.3%) in the IMRT group and 2 patients (9.5%) in the 3D-CRT group. This study confirms that IMRT was superior to 3D-CRT in terms of parotid sparing and improved quality of life for early-stage disease [16]. In a second study of 60 patients with stages T1–2bN0–1M0 [18], patients were randomized to either IMRT or 2D-CRT. At 1 year after treatment, patients in the IMRT arm had a lower incidence of severe xerostomia based on the Radiation Therapy Oncology Group®/EORTC late radiation morbidity scoring criteria compared to patients receiving 2D-CRT therapy (39.3% versus 82.1%; *P*=0.001) [17]. Regarding intensity-modulated proton therapy in NPC, mature clinical data is lacking, although some institutions have started performing comparative studies between the 2 modalities [19]; in the main, it remains a largely experimental approach.

Early-stage NPC is curable with RT alone, with a 5-year overall survival (OS) of close to 90% for stage I disease [18,20]. Even though a noted improvement in outcome in recent years can be attributable to better staging modalities and stage migration, an improvement in radiation planning and delivery techniques likely explains at least some of this improvement [12,20]. It is unclear if adjuvant or neoadjuvant systemic therapy would offer any benefit to patients with early-stage NPC, as very few patients with stage I or early stage II disease have been included in clinical trials examining this question.

Treatment of Stage II (Intermediate) Disease

Patients with stage II NPC (T1N1, T2N0-1), especially those with node-positive disease, have a substantial rate of distant metastases, and therefore concurrent chemotherapy and radiation therapy is recommended [21]. In a study involving 230 stage II (Chinese staging of 1992) NPC patients (T1-2N1 or T2N0 with parapharyngeal space involvement), participants were randomized to RT alone (n =114) or RT with concurrent cisplatin (n =116) (CCRT). Patients on the CCRT arm received cisplatin (30 mg/m^2 weekly during CRT) and had a statistically significant improvement in the 5-year OS rate (94.5% versus 85.8%, *P*=0.007), progression-free survival (PFS) rate (87.9% versus 77.8%, *P*=0.017), and distant metastasis–free survival rate (94.8% versus 83.9%, *P*=0.007). There was, however, no difference noted in the 5-year locoregional relapse–free survival rate (93.0% versus 91.1%, *P*=0.29) [22]. The main contributor to the improvement in OS was the significant reduction in the rate of distant metastases. Furthermore, on multivariable analysis the only independent factor associated with OS, PFS, and distant control was the number of chemotherapy cycles administered. As one might expect, chemotherapy leading to improvements in outcome also resulted in increased acute toxicity. Fortunately, no clear increase in chronic toxicities was observed. These findings support concurrent chemoradiotherapy as the treatment of choice

for patients with stage II NPC [22]. As patients with T2N1 disease appear to have a higher distant metastasis risk compared to patients with T2N0 and T1N1 disease, the use of systemic therapy for patients with T2N1 disease is more justifiable [23,24].

Treatment of Stage III or IV (Advanced) Disease

Concurrent Chemoradiotherapy

Concurrent chemotherapy and radiation is the backbone of treatment of locally advanced NPC. One of the early trials comparing radiation alone to concurrent chemoradiotherapy was the phase III Intergroup 0099 study randomizing patients to RT only (1.8 to 2.0 Gy per day for 35 to 39 fractions, for a total dose of 70 Gy) versus RT plus chemotherapy. Of note, the RT was delivered using opposed lateral beams, not IMRT. The chemotherapy regimen consisted of cisplatin 100 mg/m^2 on days 1, 22, and 43 during RT, followed by cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil (5-FU) 1000 mg/m^2/day on days 1 to 4, administered every 4 weeks for 3 cycles after RT. Although only 63% of patients completed 3 cycles of concurrent therapy and only 55% completed adjuvant chemotherapy, by intention-to-treat analysis, the use of concurrent chemotherapy dramatically improved both PFS and OS. The median PFS time was 15 months for eligible patients on the RT arm and was not reached for the chemoradiotherapy group. Furthermore, the 3-year PFS rates were 24% and 69%, respectively (P<0.001). The median survival time was 34 months for the RT arm and was not reached for the chemoradiotherapy arm, and the 3-year survival rates were 47% versus 78%, respectively (P=0.005) [25].

Other studies have confirmed the basic findings of the Intergroup 0099 study, demonstrating its applicability to endemic NPC regions and confirming the essential role of concurrent therapy [26-30]. However, the difficulty of administering a concurrent and adjuvant chemotherapy regimen remains a challenge due to acute and late toxicities. This has led to an increased interest in investigating the efficacy of alternative cisplatin dosing schedules or alternative systemic agents combined with radiation therapy. A single-center noninferiority trial compared carboplatin 100 mg/m^2/day [7,19,31,32] with cisplatin 100 mg/m^2/day [17,33] in the concurrent setting. Following the completion of chemoradiation, those assigned to the carboplatin arm received carboplatin at area under the curve dose 5 intravenously and 5-FU infusion at 1000 mg/m^2/day by 96-hour infusion every 4 weeks for a total of 3 cycles, and those in the cisplatin arm received cisplatin 80 mg/m^2 intravenously and 5-FU infusion at 1000 mg/m^2/d by 96-hour infusion every 4 weeks for a total of 3 cycles, both beginning 4 weeks after the end of RT. The efficacy of the 2 regimens was equivalent, with carboplatin better tolerated, with less renal toxicity, nausea, vomiting, and anemia. Confirmation trials are needed, as the confidence intervals for survival in this trial were rather wide [34]. Additionally, as RT with weekly cisplatin has been found to be superior to radiation alone in randomized trials conducted in endemic regions, many Asian centers have adopted weekly concurrent cisplatin as a standard clinical practice, although the weekly regimen has not been compared head to head against the standard of 100 mg/m^2 cisplatin every 3 weeks [35,36].

Sequencing of Additional Chemotherapy With Chemoradiotherapy

Although meta-analysis results in the wake of Intergroup 0099 confirm the positive effects of concurrent chemoradiotherapy, the role of chemotherapy in the neoadjuvant or adjuvant setting remains a topic of debate [37-39]. Adjuvant systemic therapy following concurrent chemoradiotherapy was assessed in a study from China in which a total of 251 patients were assigned to concurrent chemoradiotherapy followed by adjuvant chemotherapy, and another 257 patients were assigned to chemoradiotherapy only. Approximately 20% of the patients in the adjuvant arm did not receive chemotherapy per protocol. After a median follow-up of 37.8 months, the 2-year failure-free survival rate was 86% in the concurrent-adjuvant group versus 84% in the concurrent group (P=0.13) [39]. Although the data suggest that adjuvant chemotherapy may not be beneficial, it must be noted that this study was not designed as a noninferiority study against the standard. Hence, it is difficult to draw definitive conclusions. Given the fact that plasma EBV DNA levels have prognostic value in patients with recurrent metastatic NPC [40], there is increasing interest in stratifying the care of patients based on the detectability of EBV after definitive concurrent therapy [15]. NRG HN 001 randomizes patients with undetectable EBV after their definitive chemoradiotherapy to either chemotherapy with cisplatin and 5-FU versus observation. On the other hand, patients with detectable EBV will be randomized to cisplatin/5-FU versus gemcitabine/paclitaxel. The study will enroll patients in North America as well as Asia and may help answer the question of whether adjuvant chemotherapy can be omitted, at least for a selected group of patients with undetectable EBV. The study could better define the role of EBV titers in determining the most appropriate therapeutic choices after chemoradiotherapy; however, 1 issue remains: the need for harmonization of the PCR assays for detection of EBV [41] (see Variant 1).

As adjuvant chemotherapy on Intergroup 0099 was poorly tolerated and may not be the main factor in the improved survival seen in this study, chemotherapy given prior to chemoradiotherapy, also called neoadjuvant or induction therapy, has been proposed as a possible alternative.

Several phase II studies have attempted the induction approach with acceptable outcomes and toxicity profiles. A randomized phase II trial comparing induction chemotherapy followed by concurrent therapy to concurrent therapy only provided encouraging results, with a possible positive impact on survival. However, this requires confirmation in the phase III setting [42]. In a trial investigating a radiation fractionation question, 50 patients with stage III and IV disease were treated with an induction chemotherapy approach, with response to induction being strongly predictive for locoregional control, disease-free interval, and OS [31]. In a randomized phase II study completed in Hong Kong, induction docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were administered every 3 weeks for 2 cycles, followed by cisplatin at 40 mg/m^2/week given concurrently with RT; this was compared to concurrent therapy only. The 3-year PFS rates for the induction versus concurrent-only arms were 88.2% versus 59.5% (hazard ratio [HR] =0.49; 95% confidence interval [CI], 0.20–1.19; *P*=0.12), and the 3-year OS rates were 94.1% versus 67.7% (HR =0.24; 95% CI, 0.078–0.73; *P*=0.012), favoring the induction arm [42]. GORTEC is completing a multicenter phase III trial comparing induction chemotherapy with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiotherapy to concurrent chemoradiotherapy alone for patients with T2b, T3, or T4 NPC with lymph node involvement (≥N1). The results of a recently completed randomized trial of induction therapy with gemcitabine, carboplatin, and paclitaxel failed to show an advantage to induction therapy [43]. Another recently reported trial (NPC-0501) failed to show a benefit in changing the sequence of therapy from a concurrent-adjuvant to an induction-concurrent approach [44] (see Variant 2).

Alternative Radiation Schedules

The current standard radiation schedule for NPC is 70 Gy in 2 Gy fractions given daily. Although meta-analyses have suggested improved outcomes with accelerated or hyperfractionated regimens for head and neck cancers in general, these have not been widely adopted in NPC [45]. The role of accelerated fractionation in patients with NPC was investigated in a 4-arm randomized trial and appeared to offer an advantage in the concurrent-adjuvant chemotherapy arm with accelerated radiation, achieving a reduction in local failure and cancer-specific deaths [46]. NPC-0501 investigated the role of accelerated fractionation in addition to systemic therapy and concluded that acceleration is not recommended in locoregionally advanced NPC [44]. Despite these findings, other studies have revealed increased toxicity, especially to the central nervous system and skin, without a clear benefit in outcome when using accelerated approaches [47,48]. Many studies have reported excellent locoregional control with the use of IMRT [49,50], with reduced xerostomia establishing this as a standard modality in NPC. Of note, most centers employ IMRT using a simultaneous integrated boost technique, which typically enacts a mild acceleration of the radiation dose to gross disease volumes. In addition, replanning during IMRT can improve the quality of life for patients with NPC [51].

Treatment of Recurrent and Metastatic Disease

As NPC is a chemosensitive disease with a response rate approaching 80%, systemic chemotherapy is considered the standard of care for patients who have metastatic disease as well as those with locoregionally recurrent disease who are not candidates for further locoregional therapy. In general, combination therapies that include a platinum agent have been noted to produce superior benefits compared to single-agent therapies [52]. Despite the fact that the results of the EXTREME regimen revealed a survival advantage by adding cetuximab to a platinum-based regimen in squamous cell carcinoma of the head and neck, this is not a recommended approach in NPC, given that this trial did not include patients with this disease [53]. However, no randomized trials have established a standard regimen for patients with recurrent metastatic NPC. In a large single-institution retrospective study, several regimens were compared, including cisplatin + 5-FU, paclitaxel + cisplatin, gemcitabine + cisplatin, paclitaxel + cisplatin + 5-FU, and bleomycin + cisplatin + 5-FU. No statistically significant differences were observed in PFS (*P*=0.247) or OS (*P*=0.127) among the different groups in this retrospective analysis [33]. Recent evidence suggests that ERCC1 C8092A polymorphism can predict PFS in metastatic/recurrent NPC treated with cisplatin [54]. The performance status of patients and their history of previous chemotherapy play a significant role in deciding which chemotherapy regimen would be most appropriate and whether single- or double-agent regimens would be more suitable. Of note is that plasma EBV DNA levels have been shown to have prognostic value in patients with recurrent or metastatic NPC and can be used as a prognostic tool when obtained serially at time points prior to therapy initiation as well as at follow-up visits [40] (see Variant 3 and Variant 4). For patients with known metastatic disease to the bone, the use of bisphosphonates is advocated.

Second-line chemotherapy can be considered for patients with progression of disease following first-line therapy, as several agents have been shown to have activity in metastatic NPC. Potential choices include taxanes, gemcitabine, capecitabine, methotrexate, irinotecan, and vinorelbine [55-58].

Tyrosine kinase inhibitors (TKIs) have also been shown to have clinical activity in recurrent disease, but none of these agents have been approved for this indication. The overall response rate, if the outcome of stable disease is included, has been reported as high as 54% [59]. The use of TKIs in NPC remains largely within the clinical trial setting [59,60]. TKIs have also been used in combination with cytotoxic chemotherapy in the recurrent or metastatic setting [60], but this combination approach should similarly not be considered outside of a clinical trial. The high incidence of hemorrhage observed in some studies using antivascular agents has precluded the further development of these drugs for recurrent or metastatic NPC [61].

Local recurrence is a major cause of mortality and morbidity, despite advances in treating locally advanced disease. The best salvage treatment for locally recurrent NPC is unclear and should be determined on a case-by-case basis. Options for salvage include brachytherapy, external radiation therapy, stereotactic radiation therapy (SRT), and nasopharyngectomy. Reirradiation of the primary site or salvage surgery, if technically feasible, should be considered for treatment of local or regional recurrences, and these have been performed for selected patients with recurrent T1 or T2 disease [62] (see Variant 5). A nasopharyngectomy via a maxillary swing approach has been investigated and can be considered if carefully tailored to individual cases [63].

Reirradiation should be performed in selected centers with expertise [62]. Recent studies suggested that reirradiation with IMRT may offer long-term control, with a 2-year locoregional recurrence–free survival rate close to 65%. This was at the price of moderate to severe late toxicities in up to 35.7% of reirradiated patients [64]. The decision to proceed with reirradiation has to be weighed very carefully against potential toxicity and ought to be done in centers with technical and supportive care expertise. Factors affecting the decision to reirradiate include performance status, prior RT dose, and the expected remaining tolerance of normal tissues [65]. Even though IMRT has been used in this setting, there is no clearly adopted standard of radiation technique used to treat the recurrent disease. Fractionated SRT may provide excellent local control, although toxicities have always been a concern. The rate of long-term toxicity may be as low as 5.3% in selected patients treated at experienced centers [66]. However, there is no clear consensus on what constitutes an optimal fractionation regimen [66]. In a recent large retrospective report, the 5-year OS and distant metastasis–free survival rates were significantly higher when a program of endoscopic nasopharyngectomy and IMRT was compared to conventional 2-D RT [67]. Brachytherapy for recurrent node-negative T1 or T2 disease has been effective in salvaging a selected group of patients. A high rate of local control with low morbidity is possible if rigorous selection processes are applied. No randomized trials have been performed in this clinical setting, and there are few recommendations [68]. Major late complication rates as high as 35% have been reported in some retreatment series, stressing the need to restrict these approaches to a very select patient population treated in centers with expertise [69] (see Variant 6).

Summary of Recommendations

- Patients with locally advanced NPC who had poor tolerance to initial concurrent therapy can either omit adjuvant chemotherapy or receive it, provided it can be administered in a timely manner and they have a good recovery from their toxicity.
- Patients with locally advanced and bulky, invasive NPC are almost always treated with concurrent chemoradiation, although sequential or adjuvant approaches are also acceptable modalities.
- Patients with NPC presenting with an isolated bone focus of metastatic disease may achieve lengthy progression-free survival when treated with definitive concurrent chemoradiation to the primary site as well as definitive radiation (or SBRT) to the metastatic bone disease.
- A platinum doublet is the most accepted standard systemic regimen for recurrent or metastatic NPC.
- Nasopharyngectomy, SRT, IMRT alone, or IMRT with concurrent chemotherapy are all acceptable modalities in the management of locally recurrent NPC in the absence of distant disease.

Summary of Evidence

Of the 69 references cited in the *ACR Appropriateness Criteria® Nasopharyngeal Carcinoma* document, 67 are categorized as therapeutic references including 25 well designed studies, and 22 good quality studies.

Additionally, 2 references are categorized as diagnostic references including 1 good quality study. There are 21 references that may not be useful as primary evidence.

The 69 references cited in the *ACR Appropriateness Criteria® Nasopharyngeal Carcinoma* document were published from 1992-2015.

While there are references that report on studies with design limitations, 48 well designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2006;15(10):1765-1777.
2. Liebowitz D. Nasopharyngeal carcinoma: the Epstein-Barr virus association. *Semin Oncol.* 1994;21(3):376-381.
3. Farrow DC, Vaughan TL, Berwick M, Lynch CF, Swanson GM, Lyon JL. Diet and nasopharyngeal cancer in a low-risk population. *Int J Cancer.* 1998;78(6):675-679.
4. Yuan JM, Wang XL, Xiang YB, Gao YT, Ross RK, Yu MC. Preserved foods in relation to risk of nasopharyngeal carcinoma in Shanghai, China. *Int J Cancer.* 2000;85(3):358-363.
5. Vaughan TL, Shapiro JA, Burt RD, et al. Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. *Cancer Epidemiol Biomarkers Prev.* 1996;5(8):587-593.
6. Wang Y, Zhang Y, Ma S. Racial differences in nasopharyngeal carcinoma in the United States. *Cancer Epidemiol.* 2013;37(6):793-802.
7. World Health Organization Classification of Tumours. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *Pathology and Genetics of Head and Neck Tumours*. IARC Press, Lyon 2005.
8. Atula S, Auvinen E, Grenman R, Syrjanen S. Human papillomavirus and Epstein-Barr virus in epithelial carcinomas of the head and neck region. *Anticancer Res.* 1997;17(6D):4427-4433.
9. Pathmanathan R, Prasad U, Sadler R, Flynn K, Raab-Traub N. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. *N Engl J Med.* 1995;333(11):693-698.
10. Muller E, Beleites E. The basaloid squamous cell carcinoma of the nasopharynx. *Rhinology.* 2000;38(4):208-211.
11. Ho FC, Tham IW, Earnest A, Lee KM, Lu JJ. Patterns of regional lymph node metastasis of nasopharyngeal carcinoma: a meta-analysis of clinical evidence. *BMC Cancer.* 2012;12:98.
12. Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys.* 1992;23(2):261-270.
13. Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec.* 2001;63(4):214-216.
14. Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med.* 2004;350(24):2461-2470.
15. Chan AT, Lo YM, Zee B, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2002;94(21):1614-1619.
16. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys.* 2006;66(4):981-991.
17. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol.* 2007;25(31):4873-4879.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17(6):1471-1474.
19. Taheri-Kadkhoda Z, Bjork-Eriksson T, Nill S, et al. Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. *Radiat Oncol.* 2008;3(4):4.

20. Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys.* 2005;61(4):1107-1116.
21. Chan AT, Gregoire V, Lefebvre JL, Licitra L, Felip E. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21 Suppl 5(suppl 5):v187-189.
22. Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Natl Cancer Inst.* 2011;103(23):1761-1770.
23. Luo S, Zhao L, Wang J, et al. Clinical outcomes for early-stage nasopharyngeal carcinoma with predominantly WHO II histology treated by intensity-modulated radiation therapy with or without chemotherapy in nonendemic region of China. *Head Neck.* 2014;36(6):841-847.
24. Chua DT, Ma J, Sham JS, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: Subgroup analysis of two Phase III trials. *Int J Radiat Oncol Biol Phys.* 2006;65(5):1300-1306.
25. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol.* 1998;16(4):1310-1317.
26. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol.* 2005;23(27):6730-6738.
27. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys.* 2006;64(1):47-56.
28. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J Clin Oncol.* 2004;22(22):4604-4612.
29. Lee AW, Tung SY, Ngan RK, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 Trials. *Eur J Cancer.* 2011;47(5):656-666.
30. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol.* 2003;21(4):631-637.
31. El-Weshi A, Khafaga Y, Allam A, et al. Neoadjuvant chemotherapy plus conventional radiotherapy or accelerated hyperfractionation in stage III and IV nasopharyngeal carcinoma--a phase II study. *Acta Oncol.* 2001;40(5):574-581.
32. Saleh-Ebrahimi L, Zwicker F, Muenter MW, et al. Intensity modulated radiotherapy (IMRT) combined with concurrent but not adjuvant chemotherapy in primary nasopharyngeal cancer - a retrospective single center analysis. *Radiat Oncol.* 2013;8:20.
33. Jin Y, Cai XY, Shi YX, et al. Comparison of five cisplatin-based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma. *J Cancer Res Clin Oncol.* 2012;138(10):1717-1725.
34. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *Eur J Cancer.* 2007;43(9):1399-1406.
35. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol.* 2002;20(8):2038-2044.
36. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2005;97(7):536-539.
37. Fountzilas G, Ciuleanu E, Bobos M, et al. Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Ann Oncol.* 2012;23(2):427-435.
38. Lin JC, Liang WM, Jan JS, Jiang RS, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma--is concurrent chemoradiotherapy adequate? *Int J Radiat Oncol Biol Phys.* 2004;60(1):156-164.

39. Chen L, Hu CS, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol.* 2012;13(2):163-171.
40. An X, Wang FH, Ding PR, et al. Plasma Epstein-Barr virus DNA level strongly predicts survival in metastatic/recurrent nasopharyngeal carcinoma treated with palliative chemotherapy. *Cancer.* 2011;117(16):3750-3757.
41. Le QT, Zhang Q, Cao H, et al. An international collaboration to harmonize the quantitative plasma Epstein-Barr virus DNA assay for future biomarker-guided trials in nasopharyngeal carcinoma. *Clin Cancer Res.* 2013;19(8):2208-2215.
42. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol.* 2009;27(2):242-249.
43. Tan T, Lim WT, Fong KW, et al. Concurrent chemo-radiation with or without induction gemcitabine, Carboplatin, and Paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2015;91(5):952-960.
44. Lee AW, Ngan RK, Tung SY, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer.* 2015;121(8):1328-1338.
45. Budach W, Hehr T, Budach V, Belka C, Dietz K. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. *BMC Cancer.* 2006;6(6):28.
46. Lee AW, Tung SY, Chan AT, et al. A randomized trial on addition of concurrent-adjuvant chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. *Radiother Oncol.* 2011;98(1):15-22.
47. Daoud J, Toumi N, Siala W, Ghorbel A, Drira MM, Frikha M. Results of a prospective randomised trial comparing conventional radiotherapy to split course bifractionated radiation therapy in patients with nasopharyngeal carcinoma. *Radiother Oncol.* 2007;85(1):17-23.
48. Teo PM, Leung SF, Chan AT, et al. Final report of a randomized trial on altered-fractionated radiotherapy in nasopharyngeal carcinoma prematurely terminated by significant increase in neurologic complications. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1311-1322.
49. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys.* 2002;53(1):12-22.
50. Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. *J Clin Oncol.* 2008;26(4):535-541.
51. Yang H, Hu W, Wang W, Chen P, Ding W, Luo W. Replanning during intensity modulated radiation therapy improved quality of life in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2013;85(1):e47-54.
52. Chen C, Wang FH, An X, et al. Triplet combination with paclitaxel, cisplatin and 5-FU is effective in metastatic and/or recurrent nasopharyngeal carcinoma. *Cancer Chemother Pharmacol.* 2013;71(2):371-378.
53. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359(11):1116-1127.
54. Chen C, Wang F, Wang Z, et al. Polymorphisms in ERCC1 C8092A predict progression-free survival in metastatic/recurrent nasopharyngeal carcinoma treated with cisplatin-based chemotherapy. *Cancer Chemother Pharmacol.* 2013;72(2):315-322.
55. Chua DT, Sham JS, Au GK. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol.* 2003;39(4):361-366.
56. Foo KF, Tan EH, Leong SS, et al. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol.* 2002;13(1):150-156.
57. Poon D, Chowbay B, Cheung YB, Leong SS, Tan EH. Phase II study of irinotecan (CPT-11) as salvage therapy for advanced nasopharyngeal carcinoma. *Cancer.* 2005;103(3):576-581.
58. Ngeow J, Lim WT, Leong SS, et al. Docetaxel is effective in heavily pretreated patients with disseminated nasopharyngeal carcinoma. *Ann Oncol.* 2011;22(3):718-722.
59. Lim WT, Ng QS, Ivy P, et al. A Phase II study of pazopanib in Asian patients with recurrent/metastatic nasopharyngeal carcinoma. *Clin Cancer Res.* 2011;17(16):5481-5489.

60. Xue C, Huang Y, Huang PY, et al. Phase II study of sorafenib in combination with cisplatin and 5-fluorouracil to treat recurrent or metastatic nasopharyngeal carcinoma. *Ann Oncol.* 2013;24(4):1055-1061.
61. Hui EP, Ma BB, King AD, et al. Hemorrhagic complications in a phase II study of sunitinib in patients of nasopharyngeal carcinoma who has previously received high-dose radiation. *Ann Oncol.* 2011;22(6):1280-1287.
62. Suarez C, Rodrigo JP, Rinaldo A, Langendijk JA, Shaha AR, Ferlito A. Current treatment options for recurrent nasopharyngeal cancer. *Eur Arch Otorhinolaryngol.* 2010;267(12):1811-1824.
63. Chan JY, To VS, Chow VL, Wong ST, Wei WI. Multivariate analysis of prognostic factors for salvage nasopharyngectomy via the maxillary swing approach. *Head Neck.* 2014;36(7):1013-1017.
64. Qiu S, Lin S, Tham IW, Pan J, Lu J, Lu JJ. Intensity-modulated radiation therapy in the salvage of locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2012;83(2):676-683.
65. Lee AW, Foo W, Law SC, et al. Reirradiation for recurrent nasopharyngeal carcinoma: factors affecting the therapeutic ratio and ways for improvement. *Int J Radiat Oncol Biol Phys.* 1997;38(1):43-52.
66. Liu F, Xiao JP, Xu GZ, et al. Fractionated stereotactic radiotherapy for 136 patients with locally residual nasopharyngeal carcinoma. *Radiat Oncol.* 2013;8:157.
67. Zou X, Han F, Ma WJ, et al. Salvage endoscopic nasopharyngectomy and intensity-modulated radiotherapy versus conventional radiotherapy in treating locally recurrent nasopharyngeal carcinoma. *Head Neck.* 2015;37(8):1108-1115.
68. Mazeron JJ, Ardiet JM, Haie-Meder C, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. *Radiother Oncol.* 2009;91(2):150-156.
69. Cheah SK, Lau FN, Yusof MM, Phua VC. Treatment outcome with brachytherapy for recurrent nasopharyngeal carcinoma. *Asian Pac J Cancer Prev.* 2013;14(11):6513-6518.

Clinical Condition: **Nasopharyngeal Carcinoma**

Variant 1: **A 70-year-old man presents with a T3N2M0 EBV-positive nonkeratinizing nasopharyngeal carcinoma. He completes a definitive course of IMRT to a prescribed dose of 6996 cGy in combination with concurrent cisplatin (100 mg/m^2 for 3 doses) but requires 2 dose reductions and experiences 1 brief hospitalization near the end of treatment due to severe mucositis, dehydration, and need for feeding tube placement.**

Treatment	Rating	Comments
No further therapy	6	
Testing of EBV DNA level and recommendation for adjuvant therapy if test is positive	5	See reference [41]. NRG HN001 is testing this, but until the result of this trial is available, standard treatment is still 3 cycles of adjuvant chemotherapy. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Adjuvant cisplatin/5-FU × 3 cycles	5	See reference [25]. A large proportion of patients could not complete adjuvant chemotherapy. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Break for 3 months, then adjuvant cisplatin/5-FU × 3 cycles	3	
SRT to boost the skull base	3	See reference [66]. Toxicities were considerable.
Adjuvant therapy with paclitaxel and carboplatin	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2: **A 35-year-old woman presents with worsening otitis and a bulky right-sided neck mass extending into the supraclavicular fossa. Endoscopy of the nasopharynx reveals a 3-cm infiltrative-appearing tumor centered in the right fossa of Rosenmüller, and biopsy shows undifferentiated carcinoma of the nasopharynx that is EBV positive. MRI shows that the primary tumor is invading into the parapharyngeal space and there are bilateral 1-cm retropharyngeal nodes, 2-cm adenopathy on the left, and 5-cm adenopathy on the right (T2N3bM0, stage IVB). There is no evidence of distant disease on CT of the chest and bone scan. Karnofsky Performance Status (KPS) is 90%.**

Treatment	Rating	Comments
Cisplatin/5-FU followed by concurrent cisplatin-based chemoradiation	5	See reference [42]. This procedure requires confirmation through a phase III trial.
Docetaxel/platinum/5-FU followed by concurrent cisplatin-based chemoradiation	4	See reference [42]. This procedure requires confirmation through a phase III trial.
Concurrent cisplatin-based chemoradiation	5	See references [25,27,28], which favor the concurrent approach but do not negate the induction or adjuvant approaches. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Concurrent cisplatin-based chemoradiation followed by adjuvant chemotherapy	8	See reference [25].
Definitive RT alone	1	See references [25-27], which negate the validity of radiation alone.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Nasopharyngeal Carcinoma**

Variant 3: **A 38-year-old man presents with nasal congestion and left-sided otitis. Endoscopy shows a tumor centered in the left fossa of Rosenmüller, and the biopsy is read as undifferentiated nasopharyngeal carcinoma, EBV positive. An MRI shows erosion of the sphenoid sinus but no intracranial involvement, with 2-cm left retropharyngeal adenopathy and bilateral enlarged jugulodigastric nodes. The chest CT shows no pulmonary parenchymal metastasis, but a bone scan shows an isolated 2-cm lesion that is biopsy-proven metastatic disease in the lumbar spine with no compression (T3N2M1). He does not complain of back pain and his neurologic examination is normal. He is not interested in a clinical trial.**

Treatment	Rating	Comments
Definitive chemoradiation therapy to the nasopharynx and neck, followed by adjuvant chemotherapy	4	The first logical step, however, is a biopsy to prove the metastatic nature of the spine lesion. The ratings, therefore, reflect the presumed positivity.
Chemotherapy followed by definitive RT to the nasopharynx and neck and palliative RT to the spine	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Emergent palliative RT to the spine followed by chemotherapy	3	
Chemotherapy only	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Chemotherapy followed by palliative-dose RT to the nasopharynx, neck, and spine	5	
Definitive chemoradiation therapy to the nasopharynx and neck, followed by chemotherapy as well as definitive radiation to the spinal lesion	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Definitive chemoradiation therapy to the nasopharynx and neck as well as definitive radiation to the spinal lesion	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Nasopharyngeal Carcinoma**

Variant 4: **A 22-year-old man is admitted to the hospital because of a 30-pound weight loss in a period of 3 months, with mild constant headaches. CT scan of the head reveals a nasopharyngeal lesion. MRI of the brain and orbits shows an infiltrating mass with extra-axial intracranial and extracranial extension. There is involvement along the dura, multiple cranial nerves, orbits, adjacent osseous structures, nasopharynx, and nasal cavity, with bilateral cervical lymphadenopathy. His tumor biopsy reveals an EBV-positive undifferentiated NPC. He undergoes 3 cycles of cisplatin with concurrent RT and has an excellent response, with resolution of symptoms. On a follow-up scan 6 months after completion of therapy, he does not have evidence of local progression, but there are 2 lung metastases as well as mediastinal nodal disease. He is asymptomatic and has an excellent PS.**

Treatment	Rating	Comments
Platinum doublet	5	See references [35,52]. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Cisplatin, 5-FU and cetuximab (the EXTREME regimen)	3	See reference [53]. Nasopharyngeal patients were excluded from the EXTREME study.
Single-agent gemcitabine	4	See reference [56]. The first choice is a platinum doublet, not a single agent.
Single-agent paclitaxel	4	See reference [58]. The first choice is a platinum doublet, not a single agent.
Single-agent multitargeted TKI	4	See references [59-61].
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 5: **A 45-year-old man is diagnosed with T3N1M0 keratizing carcinoma of the nasopharynx. He is treated with definitive chemoradiation to a maximum prescribed dose of 70 Gy to the nasopharynx, given in conventional fractionation with 3D-CRT, with concurrent cisplatin at 100 mg/m(2) for 3 cycles, followed by 3 cycles of adjuvant cisplatin/5-FU. At 14 months after finishing his RT, the patient complains of worsening numbness in his face. MRI reveals an infiltrative tumor causing mild erosion of the clivus and an enlarging area of bone erosion at the right foramen ovale, with enhancement suggestive of perineural recurrence.**

Treatment	Rating	Comments
IMRT	6	See references [64,67].
IMRT with concurrent chemotherapy	7	
Induction chemotherapy followed by IMRT	3	See references [64,66,67].
SRT	6	See reference [66].
Intracavitary brachytherapy	1	See references [68,69].
Nasopharyngectomy	2	See reference [62].
Chemotherapy only	5	See references [35,52]. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Nasopharyngeal Carcinoma**

Variant 6: **A 22-year-old woman presents with severe headaches and left-sided diplopia. MRI reveals a large skull base tumor originating from the nasopharynx, with abutment against the posterior aspect of the bilateral optic nerves and partial engulfment of the optic chiasm. There is bilateral cavernous sinus involvement, worse on the left. There are bilateral 1–2 cm jugulodigastric lymph nodes that are FDG-avid on PET/CT scan (T4N2M0, stage IVB). Nasopharyngeal biopsy reveals keratinizing carcinoma. KPS is 80%. She is started on dexamethasone, with partial improvement of her symptoms.**

Treatment	Rating	Comments
Concurrent chemoradiation followed by adjuvant chemotherapy	7	See reference [25].
Induction chemotherapy followed by concurrent chemoradiation	6	See reference [42]. This procedure requires confirmation through a phase III trial.
Definitive conventionally fractionated RT with SRT boost	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		