13 ■ NASOPHARYNGEAL CANCER

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QUICK HIT ■ Nasopharyngeal Cancer (NPC) is rare in the United States, with high prevalence in endemic regions (South China, Southeast Asia, North Africa). The majority of U.S. cases (and nearly all cases in endemic areas) are related to EBV, and use of EBV DNA as a biomarker to guide therapy is under active investigation. Treatment is typically non-operative (Table 13.1).

Table 13.1 General Treatment Paradigm for Nasopharyngeal Cancer[1]

	Treatment Options
T1N0M0	Definitive IMRT (70 Gy/35 fx) + elective neck irradiation*
T1N1–3 and T2–4N0-3	Definitive concurrent chemoRT with adjuvant or induction CHT
M1	CHT ± locoregional RT (70 Gy) based on response

**If N0, treat RPNs and bilateral levels II to V; if node +, treat IB as well.*
Source: From NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers (Version 1). 2021. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

EPIDEMIOLOGY: A total of 3,200 cases per year in the United States (0.5–2 per 100,000). Endemic in South China, Hong Kong, Southeast Asia, and North Africa (rates as high as 25 per 100,000). Estimated 51,000 deaths worldwide. More common in males (2.3:1 ratio).[2] In endemic areas, incidence peaks at 50 to 59 years of age; otherwise, in low-risk populations incidence appears to increase with age.[3]

RISK FACTORS: EBV, salt-preserved fish, preserved foods, low fruit/vegetable diet, tobacco smoke, family history, HPV.[3]

ANATOMY: The nasopharynx is a cuboidal space bordered anteriorly by the choanae, posteriorly by the clivus and cervical vertebrae (C1–2), superiorly by the skull base (sphenoid sinus), and inferiorly by the soft palate. The lateral walls consist of the Eustachian tube orifice bounded by the torus tubarius, with the fossa of Rosenmüller located further posteriorly. Most NPCs arise from fossa of Rosenmüller.[4]

PATHOLOGY: WHO classification is divided into three groups: *keratinizing* squamous cell carcinoma, *nonkeratinizing* carcinoma (further subdivided into differentiated and undifferentiated subgroups), and *basaloid* squamous cell carcinoma (see Table 13.2).

Table 13.2 WHO Classification for Nasopharyngeal Cancer

WHO Classification[5]	U.S. Incidence	Endemic Incidence[6]	Notes[7]
Keratinizing	25%	1%	WHO type I (squamous cell carcinoma), associated with smoking and occasionally HPV
Nonkeratinizing • Differentiated	12%	3%	WHO type II (transitional cell carcinoma)
• Undifferentiated	63%	95%	WHO type III (lymphoepithelial carcinoma), endemic, associated with EBV, most favorable prognosis
Basaloid	–	<0.2%	Aggressive clinical course, poor survival

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SCREENING: Screening methods have been studied in endemic areas (e.g., IgA to EBV viral capsid antigen, circulating plasma EBV DNA), though currently no established screening protocols exist.[8]

CLINICAL PRESENTATION: Most common presentations are painless neck mass, nasal or ear symptoms, headache, diplopia, or facial numbness.[1] Diplopia occurs due to local invasion, with CN VI often compressed first. Jacod's triad of vision loss, ophthalmoplegia, and trigeminal neuralgia result from cavernous sinus invasion. Dysphagia, hoarseness, Horner's syndrome, and CN XI deficits can occur from lateral RPN compression on CNs IX to XII (Villaret's syndrome) or from invasion into jugular foramen (Vernet's syndrome). LN involvement is extremely common at diagnosis (75%–90%, bilateral in 50%). Five percent to 11% of patients have metastatic disease at the time of diagnosis. Most common sites for DM are bone, lung, and liver.[9–11]

WORKUP: H&P with attention to cranial nerves and neck adenopathy, nasopharyngoscopy. Dental, nutritional, speech and swallowing, and audiology exam as clinically indicated. Ophthalmologic and endocrine evaluation as clinically indicated. Smoking cessation should be advised.

Labs: Routine CBC, CMP, as well as EBV DNA testing. Pretreatment plasma EBV DNA levels are prognostic.[1]

Imaging: MRI and CT with contrast evaluating base of skull and regional node involvement. PET/CT for distant disease, especially for T3–4 or node-positive patients, as well as those with high EBV viral load.

PROGNOSTIC FACTORS: Performance status, stage, WHO classification (keratinizing worse, EBV-associated better), post-RT EBV DNA.[6]

STAGING (SEE TABLE 13.3):

Table 13.3 AJCC 8th ed. (2017): Staging for Nasopharynx Cancer

		cN0	cN1	cN2	cN3
T0	• No primary tumor, but EBV-positive cervical node (unknown primary)				
T1	• Confined to nasopharynx or extension to oropharynx/nasal cavity	**I**	**II**	**III**	**IVA**
T2	• Extension to parapharyngeal space and/or medial pterygoid, lateral pterygoid, prevertebral muscles				
T3	• Infiltration of bony structures[1]				
T4	• Extension[2]				
M1	• Distant metastasis	**IVB**			

Notes: Infiltration of bony structures[1] = Skull base, cervical vertebrae, pterygoid plates, paranasal sinuses. Extension[2] = Intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, soft tissue beyond lateral surface of lateral pterygoid muscle.
cN1, unilateral LNs and/or unilateral or bilateral metastasis in RPNs (≤6 cm), above caudal border of cricoid; cN2, bilateral LNs (≤6 cm), above caudal border of cricoid; cN3, unilateral or bilateral LNs (>6 cm) and/or LNs below caudal border of cricoid cartilage.

TREATMENT PARADIGM

Surgery: Surgery is not routine in up-front setting but rather reserved as salvage option in select patients. Persistent nodal disease after primary therapy or nodal recurrence may be treated with neck dissection.

Chemotherapy: Concurrent chemoradiation (chemoRT) with adjuvant CHT has historically been the standard treatment regimen in the United States for patients with stage II to stage IVB disease. However, induction CHT is a reasonable alternative to adjuvant (see Q&A section), with the advantage of potentially reducing RT volumes. Cisplatin is given concurrently with RT as 100 mg/m^2 bolus at weeks 1, 4, and 7 or 40 mg/m^2 weekly. Adjuvant CHT consists of cisplatin (80 mg/m^2) and 5-FU (1,000 mg/m^2 continuous infusion for 4 days) every 4 weeks for 3 cycles beginning 4 weeks after

completion of RT. Induction CHT consists of cisplatin (80 mg/m^2 day 1) and gemcitabine (1 gm/m^2 days 1 and 8) q3 weeks x 3 cycles; other induction regimens include TPF (docetaxel, cisplatin, and 5-FU) and cisplatin with 5-FU. Results from NPC 0501 suggest that it may be feasible to replace 5-FU with capecitabine.[12]

Radiation

Indications: Stage I disease (T1N0M0) is generally treated with RT alone. Stage II to stage IVB NPC are treated with concurrent chemoRT followed by adjuvant CHT, or induction CHT followed by concurrent chemoradiation.

Dose: Treat primary site to 70 Gy/35 fx or 69.96 Gy/33 fx. Elective nodal RT (bilateral in all) to RPNs, levels II to V. Treat level IB in node-positive patients or those with primary tumor extension to nasal cavity, hard palate or maxillary sinus. The following at-risk sites are also included in the elective volume: entirety of the nasopharynx, anterior one third of the clivus (the entire clivus if involved), foramen ovale, foramen rotundum, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus (entire sphenoid sinus if T3–4), posterior fourth of the nasal cavity and maxillary sinuses. Cavernous sinus can also be considered for T3–4 tumors.

Toxicity: Acute: xerostomia, dysphagia, odynophagia, nausea, weight loss. *Late*: Hearing loss, dental carries, trismus, brainstem necrosis, optic neuritis, endocrinopathy, cranial nerve palsies, stroke.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 4.[13]

■ EVIDENCE-BASED Q&A

■ What is the role of CHT in treatment of nasopharyngeal cancer?

Concurrent chemoRT followed by adjuvant CHT has been the standard of care in the United States. Historically, most patients were treated with RT alone, until the Intergroup Al-Sarraf trial demonstrated OS benefit to concurrent and adjuvant CHT compared to definitive RT alone in patients with stage III to stage IV NPC (AJCC, 4th edition). These results were initially controversial, particularly in Asia. Critics argued outcomes of definitive RT alone arm were worse than historical standards. In addition, high proportion of WHO type I patients (22%) may account for poor outcomes and need for CHT. WHO type I histology is more common in the United States compared to endemic regions. Since then, multiple randomized trials have defined benefit of concurrent CHT, and the MAC-NPC meta-analysis demonstrated absolute survival benefit of 6.3% at 5 years with concomitant CHT.[14] Recently, induction CHT followed by concurrent chemoRT has emerged as a new standard of care for select patients.

Al-Sarraf, Intergroup 0099 (*JCO* 1998, PMID 9552031): PRT of 193 patients with biopsy proven stage III to IV (M0) NPC. Note that *AJCC* 4th edition included N1 patients in stage III (now stage II). Randomized to RT alone vs. RT with concurrent cisplatin and adjuvant CHT with cisplatin and 5-FU (see Chemotherapy section). Study was closed early after interim analysis of 147 patients demonstrated OS benefit in experimental arm (see Table 13.4). Sixty-three percent completed all concurrent CHT, 55% completed all cycles of adjuvant. **Conclusion: Concurrent and adjuvant CHT with RT improves OS for stage III to stage IV (and N1, 7/8th edition stage II) nasopharyngeal cancer.**

Table 13.4 Results of Al-Sarraf INT 0099 Nasopharynx Trial

	5-Yr PFS*	5-Yr OS*
RT	29%	37%
ChemoRT + Adjuvant CHT	58%	67%

*$p < .001$

Blanchard, MAC-NPC Meta-analysis (*IJROBP* 2006, PMID 16377415; Update *Lancet Oncol* 2015, PMID 25957714): Update with 4,806 patients. MFU 7.7 years; addition of CHT to RT improved OS with absolute benefit of 6.3% at 5 years ($p < .0001$). Addition of CHT also improved PFS, LRC, distant control, and cancer mortality. Increase in OS was statistically significant for concomitant CHT (with and without adjuvant CHT), but not adjuvant CHT alone or induction CHT alone. **Conclusion: Concurrent CHT improves OS in locally advanced NPC.**

Is adjuvant CHT necessary?

This is an area of controversy (see Table 13.5). There has been one trial to directly address this question, detailed as follows. Although the trial was negative, it was heavily criticized (see the following comment). 2020 NCCN guidelines report concurrent chemoRT followed by adjuvant CHT a category 2A recommendation and concurrent chemoRT alone category a 2B recommendation.

Chen, Sun Yat-sen China (*Lancet Oncol* 2012, PMID 22154591): Multi-institution PRT involving institutions in China; 508 patients with stage III/IV (T3–4N0 excluded) randomized to concurrent chemoRT ± adjuvant CHT (cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2 for 120 hours q4 weeks x3 cycles). Primary endpoint was FFS. Two-year FFS rate was 84% in concurrent-only arm and 86% in concurrent + adjuvant arm (p = .13). **Conclusion: Adjuvant CHT did not improve FFS.** *Comment: Did not use noninferiority design, 18% randomized to adjuvant CHT did not receive it, nearly 60% did not complete concurrent CHT, 50% required RT dose reduction, and 70% had treatment delays.*

Table 13.5 Pros and Cons of Adjuvant CHT for NPC

Rationale for Eliminating Adjuvant CHT	Rationale for Employing Adjuvant CHT
• Historical trials investigating use of adjuvant CHT after definitive RT have been negative. • PRTs evaluating RT alone vs. chemoRT (w/o adjuvant) show survival benefit to concurrent CHT (Taiwan, Hong Kong, China). • Two meta-analyses investigating impact of CHT on outcomes have suggested that major driver of benefit is concurrent phase. The analysis of Baujat et al. found 18% reduction in HR of death with CHT overall, with 40% risk reduction with concurrent and 3% risk reduction with adjuvant.[15] The analysis of Langendijk et al. suggested 20% survival benefit at 5 years with concurrent CHT and no benefit to adjuvant.[16] • PRT from China randomized patients to chemoRT with weekly cisplatin ± 3 cycles adjuvant cisplatin/5-FU. While there were more failures in the arm without adjuvant CHT, they were not statistically different (p = .13).[17] • Compliance is poor; generally, only 50% to 60% of patients complete full course of adjuvant therapy on PRTs.	• Data from Taiwan suggest that for patients at high risk of distant failure, concurrent chemoRT is insufficient.[18] • Analysis of phase III Hong Kong data showed that concurrent cisplatin plus adjuvant cisplatin/5-FU was associated with improved distant control. In patients who received 0 to 1 cycles, 5-yr distant FFR was 68% vs. 78% for 2 to 3 cycles.[18] • Chinese PRT did not use noninferiority design; therefore, premature to suggest it should change practice. Additionally, 18% of patients in adjuvant arm did not receive it, 50% required RT dose reduction, and 70% had treatment delays. • In modern series using IMRT, LRC is excellent, and major pattern of failure is now distant.

Which patients benefit from CHT?

Patients with stage I NPC can be treated with definitive RT alone. Majority of clinical trials demonstrating benefit with addition of CHT to RT (including INT 0099) included patients with stage III to stage IV disease. Patients with stage II disease have been found to have worse outcomes compared to stage I with distant failure rates as high as 10% to 15% with N1 disease. RR from Taiwan suggested that addition of CHT in stage II patients resulted in similar outcomes to those found in stage I patients treated with RT alone.[19] This led to the following phase III trial in China.

Chen, Sun Yat-sen China (*JNCI* 2011, PMID 22056739): PRT of 230 patients with stage II NPC randomized to concurrent chemoRT with weekly cisplatin (30 mg/m^2) vs. RT alone. See Table 13.6. Concurrent CHT significantly improved OS (p = .007), PFS (p = .017), and DMFS (p = .007), at expense of worse acute toxicity (p = .001). OS advantage driven by improvement in DMFS; LRC unchanged. MVA showed that the number of CHT cycles delivered was the only factor associated with improved OS, PFS, and distant control. **Conclusion: Concurrent CHT improved survival for patients with stage II NPC.**

Table 13.6 Sun Yat-sen Trial (China) Investigating Concurrent ChemoRT for NPC

	5-Yr LRC	5-Yr PFS	5-Yr DMFS	5-Yr OS	Acute G3–4	Late G3–4
RT	91%	79%	84%	86%	40%	10%
ChemoRT	93%	88%	95%	95%	64%	14%

What is the role of induction CHT?

There has been significant interest in adding induction CHT to chemoRT due to the potential benefits of improved compliance (relative to adjuvant CHT) and downstaging to allow for reduced RT volumes. Note that RT volume reduction is particularly helpful for NPC due to proximity to serial structures such as optic structures and brainstem, in comparison to other H&N sites away from serial structures. Phase IIR trial from Hong Kong demonstrated 26.5% absolute improvement in 3-year OS by adding induction cisplatin and docetaxel to chemoRT with no compromise in ability to deliver full course of chemoRT afterward.[20] *However, phase IIR trial from Europe was negative.*[21] *NPC 0501 (six-arm trial investigating induction–concurrent sequence, use of capecitabine, and accelerated fractionation) found no difference in outcomes based on CHT sequence or RT acceleration; however, secondary analyses suggested improved efficacy of induction regimen.*[12]

Sun, China (*Lancet Oncol* 2016, PMID 27686945): Multicenter PRT involving 10 institutions in China, 480 patients, evaluating addition of induction CHT (TPF: cisplatin, 5-FU, docetaxel q3 weeks x 3 cycles) to concurrent chemoRT in locally advanced NPC. Eligibility criteria included stage III to IVB (except T3-4N0). Concurrent CHT was high-dose cisplatin. Primary endpoint FFS. MFU 45 months, 3-year FFS increased from 72% to 80% ($p = .034$) in favor of induction CHT. Induction CHT was associated with increased grade 3/4 toxicity: 42% vs. 17% neutropenia, 41% vs. 17% leukopenia, 41% vs. 35% stomatitis. **Conclusion: Induction CHT significantly improved 3-year FFS compared to concurrent chemoRT alone.**

Zhang, China (*NEJM* 2019, PMID 31150573): Multicenter PRT of 480 patients with stage III to stage IVB NPC with involved lymph nodes, randomized to induction cisplatin/gemcitabine followed by chemoRT vs. chemoRT alone. Induction CHT was cisplatin (80 mg/m^2 day 1) and gemcitabine (1 gm/m^2 days 1 and 8) q3 weeks x 3 cycles. Concurrent CHT was high-dose cisplatin. Induction CHT improved 3-year RFS (85.3% vs. 76.5%, HR 0.51, CI 0.34–0.77) and 3-year OS (94.6% vs. 90.3%, HR 0.43, CI 0.24–0.77). Vast majority of induction patients completed CHT (96.7%). G3 or higher acute toxicity increased with induction, 75.7% vs. 55.7%. Late G3 or higher toxicity was similar, 9.2% induction vs. 11.4% chemoRT alone. **Conclusion: Induction CHT with cisplatin and gemcitabine significantly improved RFS and OS over chemoRT alone. Comment: no adjuvant CHT used in comparison arm.**

What is the role of adaptive replanning?

Adaptive replanning should be strongly considered. NPC is radiosensitive tumor, and large anatomic changes are possible during treatment. Dosimetric studies have shown that replanning can improve coverage as well as reduce dose to surrounding critical structures. In a prospective study from China, 129 patients with M0 NPC were enrolled, 86 of whom were replanned before 25th fraction. Patients who were replanned were found to have superior 2-year LRC (97% vs. 92%) and reported improved global QOL, functional QOL, and symptoms (dyspnea, appetite loss, speech problems, dry mouth, etc.).[22]

What is the role of serum EBV DNA levels?

EBV is the primary etiologic agent in pathogenesis of NPC, and EBV levels both pre- and posttreatment are prognostic for survival. Patients with pre-treatment values ranging from <1,500 copies/mL to <4,000 copies/mL tend to have improved survival. Multiple studies have shown that detectable EBV after definitive RT is a poor prognostic marker.[23,24] *NRG HN001 is an ongoing phase II/III study of individualized treatment for NPC based on posttreatment EBV DNA. Undetectable patients are randomized to adjuvant CHT vs. observation, while detectable patients are randomized between cisplatin/5-FU and gemcitabine/paclitaxel.*[25]

Do metastatic patients benefit from locoregional RT?

A phase III trial showed an improvement in OS with the addition of locoregional RT in patients with metastatic nasopharyngeal cancer and initial response to CHT.[26] *See Chapter 71 for details.*

How is pediatric NPC treated?

In the United States, induction CHT is the standard treatment paradigm, illustrated by the following COG protocol, investigating dose-adapting RT based on response to CHT.

Rodriguez-Galindo, COG ARAR0331 (JCO 2019, PMID 31553639): Single-arm prospective study of 111 patients, median age 15, stage IIb to stage IV. Patients received 3 cycles induction cisplatin (80 mg/m^2 day 1) and 5-FU (1,000 mg/m^2/d continuous infusion days 1–4), every 3 weeks, followed by chemoRT with high-dose cisplatin. Dose was adapted from 61.2 Gy to 71.2 Gy based on response to induction CHT. After feasibility analysis, study was amended to reduce cisplatin from 3 to 2 cycles. Five-year EFS and OS were 84.3% and 89.2%, respectively. Five-year EFS for stage IV patients was 82.7%. Five-year local and distant failure were 3.7% and 8.7%, respectively. Patients treated with 3 cycles concurrent cisplatin had numerically higher 5-year EFS compared to those receiving 2 cycles (90.7% vs. 81.2%, $p = .14$). **Conclusion: Treatment with induction CHT resulted in excellent outcomes. Dose reduction is possible for patients with response to induction CHT. Three cycles of concurrent cisplatin may improve EFS compared to two cycles.**

REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers (Version 1). 2021. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359–E386. doi:10.1002/ijc.29210
3. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. C*ancer Epidemiol Biomarkers Prev.* 2006;15(10):1765–1777. doi:10.1158/1055-9965.EPI-06-0353
4. Halperin E, Perez C, Brady L. *Principles and Practice of Radiation Oncology.* 6th ed. Lippincott Williams & Wilkins; 2013.
5. Stelow EB, Wenig BM. Update from the 4th edition of the world health organization classification of head and neck tumours: nasopharynx. *Head Neck Pathol.* 2017;11(1):16–22. doi:10.1007/s12105-017-0787-0
6. Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet.* 2005;365(9476):2041–2054. doi:10.1016/S0140-6736(05)66698-6
7. Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual.* 8th ed. Springer International Publishing: American Joint Commission on Cancer; 2017.
8. Tabuchi K, Nakayama M, Nishimura B, et al. Early detection of nasopharyngeal carcinoma. *Int J Otolaryngol.* 2011;2011:638058. doi:10.1155/2011/638058
9. Vokes EE, Liebowitz DN, Weichselbaum RR. Nasopharyngeal carcinoma. *Lancet.* 1997;350(9084):1087–1091. doi:10.1016/S0140-6736(97)07269-3
10. Hsu MM, Tu SM. Nasopharyngeal carcinoma in Taiwan: clinical manifestations and results of therapy. *Cancer.* 1983;52(2):362–368. doi:10.1002/1097-0142(19830715)52:2<362::AID-CNCR2820520230>3.0.CO;2-V
11. Altun M, Fandi A, Dupuis O, et al. Undifferentiated nasopharyngeal cancer (UCNT): current diagnostic and therapeutic aspects. *Int J Radiat Oncol Biol Phys.* 1995;32(3):859–877. doi:10.1016/0360-3016(95)00516-2
12. Lee AWM, Ngan RKC, Ng WT, et al. NPC-0501 trial on the value of changing chemoradiotherapy sequence, replacing 5-fluorouracil with capecitabine, and altering fractionation for patients with advanced nasopharyngeal carcinoma. *Cancer.* 2020;126(16):3674–3688. doi:10.1002/cncr.32972
13. Videtic GMM, Vassil AD. *Handbook of Treatment Planning in Radiation Oncology,* 3rd ed. Demos Medical; 2020. doi:10.1891/9780826168429
14. Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol.* 2015;16(6):645–655. doi:10.1016/S1470-2045(15)70126-9
15. 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. doi:10.1016/j.ijrobp.2005.06.037
16. Langendijk JA, Leemans CR, Buter J, et al. 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. doi:10.1200/JCO.2004.10.074
17. 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. doi:10.1016/S1470-2045(11)70320-5
18. Lin JC, Liang WM, Jan JS, et al. Another way to estimate outcome of advanced nasopharyngeal carcinoma: is concurrent chemoradiotherapy adequate? *Int J Radiat Oncol Biol Phys.* 2004;60(1):156–164. doi:10.1016/j.ijrobp.2004.03.002
19. Cheng SH, Tsai SY, Yen KL, et al. Concomitant radiotherapy and chemotherapy for early-stage nasopharyngeal carcinoma. *J Clin Oncol.* 2000;18(10):2040–2045. doi:10.1200/JCO.2000.18.10.2040
20. 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. doi:10.1200/JCO.2008.18.1545
21. 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. doi:10.1093/annonc/mdr116

22. Yang H, Hu W, Wang W, et al. 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–e54. doi:10.1016/j.ijrobp.2012.09.033
23. 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. doi:10.1056/NEJMoa032260
24. Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. *J Clin Oncol*. 2006;24(34):5414–5418. doi:10.1200/JCO.2006.07.7982
25. Individualized Treatment in Treating Patients With Stage II-IVB Nasopharyngeal Cancer Based on EBV DNA. NRG Oncology. https://ClinicalTrials.gov/show/NCT02135042. Accessed June 9, 2021.
26. You R, Liu YP, Huang PY, et al. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyngeal carcinoma: a multicenter phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6(9):1345–1352. doi:10.1001/jamaoncol.2020.1808