Nasopharyngeal Carcinoma
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1765-1777.	Review/Other-Tx	N/A	To summarize the current knowledge regarding the epidemiology of NPC and to propose new avenues of research that could help illuminate the causes and ultimately the prevention of this remarkable disease.	No results stated in abstract.	4
2. Liebowitz D. Nasopharyngeal carcinoma: the Epstein-Barr virus association. *Semin Oncol.* 1994;21(3):376-381.	Review/Other-Tx	N/A	To describe the etiology of NPC including its virological, genetic, and environmental factors.	NPC provides a model system for understanding the interactions of genetic, infectious, and environmental factors involved in oncogenic transformation. Recent developments in organoculture systems and transgenic animal technology should allow dissection at the molecular level of the specific mechanisms involved in this process.	4
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.	Review/Other-Tx	133 cases; 212 controls	To investigate whether NPC risk was altered by the consumption of foods containing antioxidants including vitamin C and carotenoids, which have been associated with a reduced risk of both NPC and other epithelial tumors of the head and neck.	Cases (n = 133) identified at 5 population-based cancer registries and controls (n = 212) identified through random digit dialing completed a telephone interview and self-administered food frequency questionnaire. Dietary exposures were expressed as quartiles of intake, and ORs calculated using the lowest quartile of intake as the reference category. Risk of nonkeratinizing and undifferentiated tumors of the nasopharynx was increased in frequent consumers of preserved meats, which contain high levels of added nitrites. ORs in the 2nd, 3rd and highest quartile were 1.99, 4.35 and 4.59, although 95% CIs did not exclude 1.0. Risk of differentiated squamous cell carcinoma, but not other histologic types, was significantly reduced in individuals with vitamin C intake above the lowest quartile (ORs 0.30, 0.33 and 0.30 in the 2nd, 3rd and highest quartiles, respectively). This association was markedly stronger among nonsmokers and former smokers than among current smokers. Finally, individuals who reported consuming supplemental vitamins were at an approximately 50% reduced risk of NPC.	4

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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.	Review/Other-Tx	935 NPC patients and 1,032 community controls	A population-based case-control study was conducted in Shanghai, China, to investigate the association between dietary factors and risk of NPC.	Exposures to salted fish and other protein-containing preserved food were associated with increased risk of NPC. Individuals who ate salted fish at least once a week had an 80% increase in risk of NPC relative to those who ate salted fish less than once a month (P=0.07). Compared with those in the lowest quartile of protein-containing preserved foods, subjects in the highest quartile of intake experienced a statistically significant 78% increase in risk of NPC [OR = 1.78, 95% CI = 1.37–2.31], with a dose-dependent relationship (P for linear trend <0.001). A similar association between intake of preserved vegetables and NPC risk was observed (OR = 1.39, P for linear trend =0.003). In contrast, high intake of oranges/tangerines was associated with a statistically significant reduction in risk of NPC (OR = 0.55, P for linear trend <0.001). When the joint effect of preserved food and oranges/tangerines were examined on risk of NPC, subjects in the highest tertile of preserved food and the lowest tertile of orange/tangerine intake had a 3-fold increase in risk (95% CI = 2.08–4.91) compared with those in the lowest tertile of preserved food and the highest tertile of orange/tangerine intake.	4

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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.	Review/Other-Tx	231 cases and 246 controls	To study a low-incidence population to determine whether tobacco use, alcohol consumption, and certain medical conditions and treatments are related to NPC and to examine variations in risk by histology.	There was a strong dose-response relationship between cigarette smoking and risk of differentiated squamous cell carcinoma (test for trend, $P<0.001$). The highest risk [OR, 6.5; 95% CI, 2.0–21.3] occurred among current smokers with a history of more than 60 pack-years. In contrast, there was no evidence that undifferentiated or nonkeratinizing carcinomas were associated with cigarette smoking. Similarly, a significant increase in risk was observed for the heaviest alcohol consumers (21 or more drinks/week) only for differentiated squamous cell carcinomas (OR, 2.9; 95% CI, 1.2–6.9). The associations with cigarettes and alcohol appeared to be stronger among persons 50 years or older. There was a suggestion that diagnosis with infectious mononucleosis (a marker of late infection with EBV) is linked with decreased NPC risk (OR, 0.4; 95% CI, 0.1–1.1).	4
6. Wang Y, Zhang Y, Ma S. Racial differences in nasopharyngeal carcinoma in the United States. *Cancer Epidemiol.* 2013;37(6):793-802.	Review/Other-Tx	5,868 patients	To provide a comprehensive description of racial differences among NPC patients in the U.S. in terms of patients' characteristics, clinical-pathologic features, incidence, treatment strategy, and survival rates by analyzing the SEER database.	Patient characteristics that were significantly different across races included age at diagnosis, histologic type, in situ/malignant tumors in lifetime, stage, grade, and regional nodes positive. Incidence and mortality rates were significantly different across races, with Asians having the highest rates overall and stratified by age and/or histologic type. Asians also had the highest rate of receiving radiation only. The racial differences in treatment were significant in the multivariate stratified analysis. When stratified by stage and histologic type, Asians had the best 5-year survival rates. The survival experience of other races depended on stage and type. In the multivariate analysis, the racial differences were significant.	4
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.	Review/Other-Dx	N/A	Book chapter.	N/A.	4

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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.	Review/Other-Tx	79 frozen biopsy samples	To review the role of HPV and EBV in epithelial carcinomas of the upper aerodigestive tract.	HPV DNA was detected in 13 samples (16.5%) by Southern blot hybridization under low stringency conditions and in 3 samples (3.8%) by polymerase chain reaction using general primers targeting the HPV L1 region. HPV seemed to have affinity for labial carcinomas: 4 of the 6 samples (66.7%) were HPV DNA positive. The detection rate of HPV diminished from the labial and oral epithelium towards the laryngeal region. In Southern blot hybridization, EBV DNA was not found in any of the biopsy samples.	4
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.	Review/Other-Tx	11 biopsy samples	To screen nasopharyngeal-biopsy samples for preinvasive lesions, including dysplasia and carcinoma in situ to determine whether EBV infection is an early, initiating event in the development of nasopharyngeal carcinoma.	Evidence of EBV infection was detected in all 11 tissue samples with dysplasia or carcinoma in situ. EBV-encoded RNAs were identified in all 8 samples tested, and LMP-1 was detected in all 6 of the tested samples. 6 of the 7 samples tested for the EBV termini contained clonal EBV DNA: Transcription of the latent EBV gene products, EBV nuclear antigen 1, LMP-1, LMP-2A, and the BamHI-A fragment, was detected in most of the samples. Viral proteins characteristic of lytic lesions were not detected.	4
10. Muller E, Beleites E. The basaloid squamous cell carcinoma of the nasopharynx. *Rhinology.* 2000;38(4):208-211.	Review/Other-Tx	1 case	To report a new case of basaloid squamous cell carcinoma located in the nasopharynx, considering, in particular, the clinical aspects.	No results stated in abstract.	4
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.	Review/Other-Tx	13 studies with 2,920 NPC cases	To study the pattern and probability of nodal metastasis through a meta-analysis of published evidences, with an aim to establish an evidence-based guideline for selecting and delineation of clinical target volume of neck lymphatics for conformation radiation for NPC.	85% of NPC cases presented with lymphadenopathy. The most commonly involved regions include retropharyngeal (69%) and level II lymph nodes (70%). The overall probability of levels III, IV, and V nodal involvement are 45%, 11%, and 27%, respectively. Low-risk node groups included the supraclavicular, levels IA/IB and VI nodes, and parotid nodes with involvement rates at 3%, 0%, 3%, 0%, and 1%, respectively. Nodal metastases followed an orderly pattern and the probability of "skip" metastasis between levels varied between 0.5%–7.9%.	4

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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.	Observational-Tx	5,037 patients	To present the characteristics of our patients, their patterns of failure, and survival rates.	The stage distribution according to Ho's classification was 9% stage I, 13% II, 50% III, 22% IV, and 6% stage V. Only 4,488 (89%) patients had a full course of megavoltage RT. The median equivalent dose to the nasopharyngeal region was 65 Gy and cervical region in node-positive patients 53 Gy. 70% (906/1290) of the node-negative patients had no prophylactic neck irradiation. The overall actuarial 10-year survival rate was 43% and the corresponding failure-free survival rate 34%. Altogether, 4,157 (83%) patients achieved complete remission lasting more than 6 months, but 53% (2,205/4,157) of them relapsed after a median interval of 1.4 years. The 10-year actuarial local, regional, and distant FFRs were 61%, 64%, and 59%, respectively. 38% (338/891) of all patients with local recurrence achieved second local remission. The local complete remission rate with aggressive re-irradiation alone was 47% (333/706). But 37% (124/338) of the responders recurred the second time. The incidence of distant failure correlated significantly with both the N-stage and the T-stage, with the highest (57%) occurring in patients with N3 disease. The incidence of nodal relapse in node-negative patients was 11% (44/384) among those given prophylactic neck irradiation, but 40% (362/906) among those without. Therapeutic irradiation achieved a complete regional remission rate of 90% (306/339). However, despite successful salvage, these patients had a significantly higher distant failure rate than those without nodal relapse, even if they remained local-failure-free (21% vs 6%).	2

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13. Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec.* 2001;63(4):214-216.	Review/Other-Tx	N/A	To review distant metastases from NPC.	Literature reports up to 11% distant metastases at presentation and up to 87% at autoptic studies. Pretreatment workup should include: personal history, clinical and fiberscopic examination, magnetic resonance imaging or computed tomography scan of the base of the skull and neck, histology of the primary and cytology of neck lumps, bone marrow aspiration and biopsy, and EBV serological profile. Clinical and pathological factors predicting possible distant spread are primary tumor and node extension, and treatment failure. Up to now no reliable predictive biological markers have been identified. After treatment, distant metastases are found in about 30% of patients within 5 years and generally have a bad prognosis. Metastatic nodes above the clavicle, in absence of locoregional failure, aggressively treated with chemoradiotherapy, have a DFS longer than 5 years.	4

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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.	Observational-Tx	99 patients	To investigate whether the plasma EBV DNA load, measured by real-time quantitative polymerase chain reaction, correlates with the response to treatment and the likelihood of relapse and survival among patients with NPC.	Plasma EBV DNA was detectable before treatment in 94/99 patients, but not in 40 healthy controls or 20 cured patients. The median concentrations of plasma EBV DNA were 681 copies per mL among 25 patients with stage III disease, 1,703 copies per mL among 74 patients with stage IV disease, and 291,940 copies per mL among 19 control patients with distant metastasis ($P<0.001$). Patients with relapse had a significantly higher plasma EBV DNA concentration before treatment than those who did not have a relapse (median, 3,035 vs 1,202 copies per mL; $P=0.02$). The consistent genotyping of EBV DNA between paired samples of plasma and primary tumor suggested that the circulating cell-free EBV DNA may originate from the primary tumor. Unlike the rebound of plasma EBV DNA concentrations in the patients who had a relapse, the plasma EBV DNA concentration was persistently low or undetectable in patients with a complete clinical remission. OS ($P<0.001$) and relapse-free survival ($P=0.02$) were significantly lower among patients with pretreatment plasma EBV DNA concentrations of at least 1,500 copies per mL than among those with concentrations of <1,500 copies per mL. Patients with persistently detectable plasma EBV DNA had significantly worse OS ($P<0.001$) and relapse-free survival ($P<0.001$) than patients with undetectable EBV DNA 1 week after the completion of RT.	1

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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.	Observational-Tx	170 NPC patients	To investigate the value of plasma EBV DNA as a prognostic factor for NPC.	99% of patients achieved complete clinical remission. Levels of post-treatment EBV DNA dominated the effect of levels of pretreatment EBV DNA for PFS. The risk ratios for NPC recurrence was 11.9 (95% CI = 5.53 to 25.43) for patients with higher post-treatment EBV DNA and 2.5 (95% CI = 1.14 to 5.70) for patients with higher pretreatment EBV DNA. Higher levels of post-treatment EBV DNA were statistically significantly associated with OS (P<.001; risk ratios for NPC recurrence = 8.6, 95% CI = 3.69 to 19.97). The positive and negative predictive values for NPC recurrence for a higher level of post-treatment EBV DNA were 87% (95% CI = 58% to 98%) and 83% (95% CI = 76% to 89%), respectively.	2
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.	Experimental-Tx	51 patients	To compare directly the effect of IMRT vs conventional RT on salivary flow and QoL in patients with early-stage NPC.	46 patients (88%) were in disease remission 12 months after RT. At 12 months post-RT, 12 (50.0%) and 20 patients (83.3%) in the IMRT group had recovered at least 25% of pre-RT stimulated whole saliva and stimulated parotid saliva flow respectively, compared with 1 (4.8%) and 2 patients (9.5%), respectively, in the conventional RT group. Global health scores showed continuous improvement in QoL after both treatments (P<0.001). However, after 12 months subscale scores for role-physical, bodily pain, and physical function were significantly higher in the IMRT group, indicating a better condition (P<0.05). Dry mouth and sticky saliva were problems in both groups 2 months after treatment. In the IMRT group, there was consistent improvement over time with xerostomia-related symptoms significantly less common than in the conventional RT group at 12 months post-RT.	1

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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.	Experimental-Tx	60 patients	A randomized trial to compare the rates of delayed xerostomia between 2D-RT and IMRT in the treatment of early-stage NPC.	At 1 year after treatment, patients in IMRT arm had lower incidence of observer-rated severe xerostomia than patients in the 2D-RT arm (39.3% vs 82.1%; *P*=.001), parallel with a higher fractional stimulated parotid flow rate (0.90 vs 0.05; *P*<.0001), and higher fractional stimulated whole saliva flow rate (0.41 vs 0.20; *P*=.001). As for patient's subjective feeling, although a trend of improvement in patient-reported outcome was observed after IMRT, recovery was incomplete and there was no significant difference in patient-reported outcome between the 2 arms.	1
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.	Review/Other-Tx	N/A	An editorial to summarize the background of the current revision and outlines the major issues on TNM.	No results stated in abstract.	4
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.	Observational-Tx	8 patients	To investigate the potential advantages of intensity-modulated proton therapy compared with IMRT in NPC.	Both treatment techniques were equal in terms of averaged mean dose to target volumes. Intensity-modulated proton therapy plans significantly improved the tumor coverage and conformation (*P*<0.05) and they reduced the averaged mean dose to several organs at risk by a factor of 2-3. The low-to-medium dose volumes (0.33–13.2 GyE) were more than doubled by IMRT plans.	2

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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.	Observational-Tx	2,687 consecutive patients	To analyze the treatment results achievable for NPC in the modern era to identify the key failures for future improvement and to provide an updated baseline for future trials.	The 5-year local, nodal, and distant FFRs were 85%, 94%, and 81%, respectively; patients with local failure had significantly higher risk of nodal and distant failures. The 5-year PFS, OS, and cancer-specific survival rates were 63%, 75%, and 80%, respectively. The presenting stage was the most important prognostic factor for all endpoints: with OS decreasing from 90% for stage I to 58% for stage IVA-B. The results achieved by the 2,070 patients treated by RT alone were almost identical to that of the whole series, the distant FFR among patients with locoregional control was 89% for stage I-II and 75% for stage III-IVB. The 860 patients (32%) staged with magnetic resonance imaging achieved significantly better results than those staged by computed tomography, the OS being 93% vs 83% for stages I-II, and 72% vs 63% for stages III-IVB (P=0.001).	2
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.	Review/Other-Tx	N/A	To provide practice guidelines for diagnosis, treatment and follow-up of NPC.	No results stated in abstract.	4

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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.	Experimental-Tx	114 patients received RT and 116 patients received CCRT	To determine the OS benefits for patients with Chinese 1992 stage II NPC with the addition of concurrent, weekly cisplatin-based (30 mg/m2) CRT and to compare the tumor response, PFS, distant metastasis-free survival, locoregional relapse-free survival, and acute and late toxic effects of patients between the 2 treatment arms.	With a median follow-up of 60 months, adding chemotherapy statistically significantly improved the 5-year OS rate (94.5% vs 85.8%; HR of death = 0.30, 95% CI = 0.12 to 0.76; *P*=.007), PFS (87.9% vs 77.8%; HR of progression = 0.45, 95% CI = 0.23 to 0.88; *P*=.017), and distant metastasis-free survival (94.8% vs 83.9%; HR of distant relapse = 0.27, 95% CI = 0.10 to 0.74; *P*=.007); however, there was no statistically significant difference in the 5-year locoregional relapse-free survival rate (93.0% vs 91.1%; HR of locoregional relapse = 0.61, 95% CI = 0.25 to 1.51; *P*=.29). Multivariable analysis showed that the number of chemotherapy cycles was the only independent factor that was associated with OS, PFS, and distant control in stage II NPC. The CCRT arm experienced statistically significantly more acute toxic effects (*P*=.001), although the rate of late toxic effects did not increase statistically significantly.	1
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.	Observational-Tx	69 patients	To evaluate the clinical outcomes for early-stage NPC in northwest China.	Median follow-up was 34 months. World Health Organization type II was the predominant histology (71%). All treatment failures occurred in T2N1 NPCs (14.5%), with metastasis the major reason. The 3-year OS, local recurrence-free survival, and distant metastasis-free survival were 93.3%, 94.1%, and 94.8% respectively. The 3-year survival rate for T2N1 and IMRT alone group were both significantly poorer than the T1N0, T2N0, and T1N1 groups and the chemoradiation group, respectively (*P*<.05). N1 classification, T2N1 classification, and addition of chemoradiation were significant independent predictors (*P*<.05). No grade IV toxicities were observed.	2

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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.	Review/Other-Tx	2 trials with 334 and 456 patients each	To evaluate the effect of induction chemotherapy in NPC further, we performed subgroup analysis of 2 phase III trials according to the T and N stage.	No significant differences in OS, locoregional failure-free, or distant metastasis-free rates were observed between the combined and RT arms in Groups 2 to 4. Significant differences in the OS and distant metastasis-free rates were observed only in Group 1, favoring the combined chemotherapy and RT arm. The 5-year OS rate was 79% in the combined arm and 67% in the RT-alone arm (P=0.048). The corresponding 5-year distant metastasis-free rates were 86% and 74% (P=0.0053).	4
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.	Experimental-Tx	147 patients	To compare chemoradiotherapy vs RT alone in patients with NPCs.	Of 193 patients registered, 147 (69 RT and 78 chemoradiotherapy) were eligible for primary analysis for survival and toxicity. The median PFS time was 15 months for eligible patients on the RT arm and was not reached for the chemoradiotherapy group. The 3-year PFS rate was 24% vs 69%, respectively (P<.001). The median survival time was 34 months for the RT group and not reached for the chemoradiotherapy group, and the 3-year survival rate was 47% vs 78%, respectively (P=.005). 185 patients were included in a secondary analysis for survival. The 3-year survival rate for patients randomized to RT was 46%, and for the chemoradiotherapy group was 76% (P<.001).	1
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.	Experimental-Tx	221 patients	To confirm the findings of the 00-99 trial and its applicability to patients with endemic NPC.	Distant metastasis occurred in 38 patients on RT alone and 18 patients on CRT. The difference in 2-year cumulative incidence was 17% (95% CI, 14% to 20%; P=.0029). The HR for DFS was 0.57 (95% CI, 0.38 to 0.87; P=.0093). The 2- and 3-year OS rates were 78% and 85% and 65% and 80% for RT alone and CRT, respectively. The HR for OS was 0.51 (95% CI, 0.31 to 0.81; P=.0061).	1

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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.	Review/Other-Tx	8 trials with 1,753 patients	To study the effect of adding chemotherapy to RT on OS and event-free survival for patients with NPC.	8 trials with 1,753 patients were included. One trial with a 2 x 2 design was counted twice in the analysis. The analysis included 11 comparisons using the data from 1975 patients. The median follow-up was 6 years. The pooled HR of death was 0.82 (95% CI, 0.71–0.94; *P*=0.006), corresponding to an absolute survival benefit of 6% at 5 years from the addition of chemotherapy (from 56% to 62%). The pooled HR of tumor failure or death was 0.76 (95% CI, 0.67–0.86; *P*<0.0001), corresponding to an absolute event-free survival benefit of 10% at 5 years from the addition of chemotherapy (from 42% to 52%). A significant interaction was observed between the timing of chemotherapy and OS (*P*=0.005), explaining the heterogeneity observed in the treatment effect (*P*=0.03), with the highest benefit resulting from concomitant chemotherapy.	4
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.	Review/Other-Tx	10 randomized clinical studies including 2,450 patients	To determine the additional value of neoadjuvant, concurrent, and/or adjuvant chemotherapy to radiation in the treatment of locally advanced NPC with regard to the OS and the incidence of local-regional recurrences and distant metastases.	10 randomized clinical studies were identified, including 2,450 patients. The pooled HR of death for all studies was 0.82 (95% CI, 0.71 to 0.95; *P*=.01) corresponding to an absolute survival benefit of 4% after 5 years. 3 categories of trials were defined according to the sequence of chemotherapy, including neoadjuvant chemotherapy, at least concomitant chemoradiotherapy, and adjuvant chemotherapy. A significant interaction term (*P*=.02) was found among these 3 categories. The largest effect was found for concomitant chemotherapy, with a pooled HR of 0.48 (95% CI, 0.32 to 0.72), which corresponds to a survival benefit of 20% after 5 years. Comparable results were found for the incidence of local-regional recurrences and distant metastases.	4

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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.	Review/Other-Tx	2 trials with 348 and 93 patients each	To provide more comprehensive data to evaluate the efficacy of the Intergroup-0099 regimen and the contributing factors.	Comparison by intention-to-treat showed that the CRT(i) group achieved significant improvement in overall FFR, locoregional-FFR and cancer-specific survival ($P \leq 0.019$); but the improvements for distant-FFR and OS were statistically insignificant ($P \geq 0.14$). Further exploratory studies based on actual treatment showed that an additional improvement achieved was a significant gain in OS (CRT(a) vs RT(a) group: 72% vs 63% at 5-year, $P=0.037$). Multivariate analyses showed that the dose of cisplatin during the concurrent phase had significant impact on locoregional-FFR and OS, while that of 5-FU during the adjuvant phase was significant for distant-FFR. The 5-year locoregional-FFR for patients who received 0–1, 2 and 3 concurrent cycles were 79%, 88% and 88%, respectively; the corresponding distant-FFR by adjuvant cycles were 68%, 78% and 77%, respectively.	4
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.	Experimental-Tx	284 patients	To compare CCRT vs RT alone in patients with advanced NPC.	Baseline patient characteristics were comparable in both arms. After a median follow-up of 65 months, 26.2% (37/141) and 46.2% (66/143) of patients developed tumor relapse in the CCRT and RT-alone groups, respectively. The 5-year OS rates were 72.3% for the CCRT arm and 54.2% for the RT-only arm ($P=.0022$). The 5-year PFS rates were 71.6% for the CCRT group compared with 53.0% for the RT-only group ($P=.0012$). Although significantly more toxicity was noted in the CCRT arm, including leukopenia and emesis, compliance with the combined treatment was good. The second cycle of concurrent chemotherapy was refused by 9 patients and was delayed for ≥1 week for another 9 patients. There were no treatment-related deaths in either arm.	1

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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.	Experimental-Tx	50 patients	To achieve improvement in locoregional control, disease-free interval and OS using induction chemotherapy and to compare conventional fractionation with an accelerated hyperfractionation regimen.	50 patients were treated (5 AJCC stage III, 45 stage IV) with induction chemotherapy consisting of 2 cycles of cisplatin and 5-FU. Patients were then randomized between conventional fractionation and accelerated hyperfractionation therapy. A clinical response to induction chemotherapy was reported in 86% of patients prior to RT (44% complete response, 42% partial response). Patients with complete or major partial responses to induction chemotherapy had a significantly better 5-year OS (60%) and disease-free interval (59%) than those with no response or minor partial response (15% and 18% *P*=0.009 and 0.0009). Acute radiation reactions were more pronounced in the accelerated hyperfractionation group (*P*=0.0002), and the incidence of late normal tissue injury was more frequent (*P*=0.08). At 5 years, the locoregional control rate was higher in the accelerated hyperfractionation arm (76%) than in the conventional fractionation group (54%), but the difference was not significant (HR, 0.52; 95% Cl, 0.15–2.83; *P*=0.186). With a median follow-up period of 55 months (range 4–120), the 5-year disease-free interval and OS rates were more favorable in the accelerated hyperfractionation group than in the conventional fractionation group, but the differences were not significant (59% and 54% vs 34% and 36%, respectively, HR for disease-free interval = 0.71; 95% CI, 0.27–1.88; *P*=0.198 and HR for OS = 0.81; 95% CI, 0.37–1.78; *P*=0.433). The overall treatment failure rate was 48%. Locoregional failures occurred in 12 patients (24%) and the incidence of distant metastases reached 30%.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	49 consecutive patients	To report patients with NPC who were treated by IMRT combined with simultaneous but not adjuvant chemotherapy.	The median follow-up for the entire cohort was 48 months. RT was completed without interruption in all patients and 76% of the patients received at least 80% of the scheduled adjuvant chemotherapy. 4 local recurrences have been observed, transferring into 1-, 3-, and 5-year local control rates of 98%, 90% and 90%. One patient developed an isolated regional nodal recurrence, resulting in 1-, 3-, and 5-year regional control rates of 98%. All locoregional failures were located inside the radiation fields. Distant metastases were found in 6 patients, transferring into 1-, 3, and 5-year distant control rates of 92%, 86% and 86%. PFS rates after 1, 3 and 5 years were 86%, 70% and 69% and 1-, 3- and 5-year OS rates were 96%, 82% and 79%. Acute toxicity ≥ grade III mainly consisted of dysphagia (32%), leukopenia (24%), stomatitis (16%), infection (8%) and nausea (8%). Severe late toxicity (grade III) was documented in 18% of the patients, mainly as xerostomia (10%).	2
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.	Observational-Tx	822 patients	To compare 5 cisplatin-based regimens including cisplatin + 5-FU, paclitaxel + cisplatin, gemcitabine + cisplatin, paclitaxel + cisplatin + 5-FU, and bleomycin + cisplatin + 5-FU regimen most frequently used as the first-line protocols for metastatic NPC retrospectively.	The higher response rates in gemcitabine + cisplatin and paclitaxel + cisplatin + 5-FU regimens comparing to cisplatin + 5-FU regimen were achieved (Chi (2) = 4.57, P=0.033; Chi (2) = 7.04, P=0.008), as well as in paclitaxel + cisplatin + 5-FU regimen comparing to paclitaxel + cisplatin regimen (Chi (2) = 5.579, P=0.018). The occurrence rate of the major III-IV grade toxicity was significantly different between the 5 groups. However, no statistically significant difference was observed in PFS (PFS; P=0.247) and OS (P=0.127) among the 5 groups. Cox multivariate analysis identified the following independent prognostic factors: liver metastases, plasma EBV-DNA level, cycles of chemotherapy, and second-line chemotherapy.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	206 patients	To compare CCRT with carboplatin vs standard CCRT with cisplatin in patients with locoregionally advanced NPC.	With a median follow-up of 26.3 months (range 3–74.6 months), 59% of patients in the cisplatin arm completed the planned CCRT treatment, compared to 73% in the carboplatin arm. 42% of cisplatin patients completed the 3 cycles of adjuvant therapy compared to 70% in the carboplatin group. There were more renal toxicity, leucopenia, and anemia in the cisplatin group, and more thrombocytopenia in the carboplatin arm. The 3 year DFS rates were 63.4% for the cisplatin group and 60.9% for the carboplatin group (P=0.9613) (HR 0.70, 95% CI: 0.50–0.98). The 3 year OS rates were 77.7% and 79.2% for cisplatin and carboplatin groups, respectively (P=0.9884) (HR 0.83, 95% CI: 0.63–1.010).	1
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.	Experimental-Tx	350 patients	An analysis to compare concurrent cisplatin-RT with RT alone in patients with locoregionally advanced NPC.	350 eligible patients were randomized. Baseline patient characteristics were comparable in both arms. There were significantly more toxicities, including mucositis, myelosuppression, and weight loss in the cisplatin-RT arm. There were no treatment-related deaths in the cisplatin-RT arm, and 1 patient died during treatment in the RT-alone arm. At a median follow-up of 2.71 years, the 2-year PFS was 76% in the cisplatin-RT arm and 69% in the RT-alone arm (P=.10) with a HR of 1.367 (95% CI, 0.93 to 2.00). The treatment effect had a significant covariate interaction with tumor stage, and a subgroup analysis demonstrated a highly significant difference in favor of the cisplatin-RT arm in Ho's stage T3 (P=.0075) with a HR of 2.328 (95% CI, 1.26 to 4.28). For T3 stage, the time to first distant failure was statistically significantly different in favor of the cisplatin-RT arm (P=.016).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	350 patients	To compare concurrent cisplatin-RT vs RT alone in patients with locoregionally advanced NPC.	The primary endpoint was OS, and the median follow-up was 5.5 years. The 5-year OS was 58.6% (95% CI = 50.9% to 66.2%) for the RT arm and 70.3% (95% CI = 63.4% to 77.3%) for the cisplatin-RT arm. In Cox regression analysis adjusted for T stage, age, and overall stage, the difference in OS was statistically significantly in favor of concurrent cisplatin-RT (*P*=.049, HR = 0.71 [95% CI = 0.5 to 1.0]). Subgroup analysis demonstrated that there was no difference between OS in the arms for T1/T2 stage (*P*=.74, HR = 0.93 [95% CI = 0.59 to 1.4]), whereas there was a difference between the arms for T3/T4 stage (*P*=.013, HR = 0.51 [95% CI = 0.3 to 0.88]), favoring the cisplatin-RT arm.	1
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.	Experimental-Tx	144 patients	To compare induction chemotherapy with 3 cycles of CEP followed by CCRT with CCRT alone.	62 patients (86%) received 3 cycles of induction chemotherapy. No difference between the arms was observed in the number of patients who completed RT (61 vs 64, *P*=018). Overall and complete response rates were very similar in the 2 arms and so were 3-year PFS and OS rates. Grade III or IV toxic effects from induction chemotherapy were infrequent, apart of alopecia. Mucositis, weight loss and leukopenia were the most prominent side-effects from CCRT.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	284 patients	To evaluate a simple risk grouping system and determine whether CCRT is adequate for patients with advanced NPC.	According to the 1992 AJCC staging system, 80.3% (228/284) of NPC patients are Stage IV, whereas only 19.7% are Stage III. Most patients are downstaged by the 1997 AJCC staging system with 28.5% (81/284) Stage IV and 71.5% (203/284) Stage III/II. Our risk criteria stratify more even patient distribution, because 119 patients (41.9%) are assigned to the high-risk group and 165 patients (58.1%) to the low-risk group. Log-rank test of Kaplan-Meier survival curves, multivariate comparison of the Cox proportional hazards model, and 3 goodness-of-fit indices validated that our risk grouping system seemed to be at least as efficacious as, or slightly superior to, the 1992 and 1997 AJCC systems. The 5-year nasopharynx disease free (95.1% vs 76.8%, P=0.0012), neck disease free (100% vs 95.7%, P=0.0974), distant metastasis disease free (90.5% vs 78.1%, P=0.0282), OS (83.2% vs 59.7%, P=0.0041), and PFS (87.3% vs 61.5%, P=0.0003) were significantly better in patients receiving CCRT than RT alone for the low-risk group. However, the corresponding survival rates between CCRT and RT for high-risk patients were 74.9% vs 67.6% (P=0.2545) for nasopharynx disease free, 92.1% vs 86.8% P=0.4744) for neck disease free, 59.7% vs 60.0% (P=0.5537) for distant metastasis disease free, 55.8% vs 46.3% (P=0.1761) for OS, and 44.5% vs 43.1% (P=0.3911) for PFS, respectively.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	251 patients in the CCRT plus adjuvant chemotherapy group and 257 patients in the CCRT group	To assess the contribution of adjuvant chemotherapy to CCRT vs CCRT alone.	After a median follow-up of 37.8 months (range 1.3–61.0), the estimated 2 year failure-free survival rate was 86% (95% CI, 81–90) in the CCRT plus adjuvant chemotherapy group and 84% (78–88) in CCRT only group (HR 0.74, 95% CI, 0.49–1.10; *P*=0.13). Stomatitis was the most commonly reported grade 3 or 4 adverse event during both RT (76/249 patients in the CCRT plus adjuvant chemotherapy group and 82/254 in the CCRT alone group) and adjuvant chemotherapy (43 [21%] of 205 patients treated with adjuvant chemotherapy).	1
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.	Observational-Tx	127 patients	To test the prognostic implication of plasma EBV DNA level in metastatic/recurrent NPC patients treated with palliative chemotherapy.	Patients with a low pre-treatment plasma EBV DNA level (<median) had significantly better survival than those with a high pre-treatment plasma EBV DNA level (≥median). Patients with a post-treatment plasma EBV DNA decline to an undetectable level had better survival and better tumor response compared with those with a sustained detectable post-treatment plasma EBV DNA level. The early decrease of post-treatment plasma EBV DNA to an undetectable level after 1 cycle of chemotherapy was associated with significantly increased survival. Patients with low pre-treatment plasma EBV DNA level and undetectable post-treatment plasma EBV DNA showed a favorable prognosis (5-year overall and PFS of 50.6% and 21.7%, respectively).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Dx	40 samples	To harmonize the method between 4 centers with expertise in EBV DNA quantitation.	The initial intraclass correlations for the first 40 samples between each center and the index center were 0.62 [95% CI: 0.39–0.78], 0.70 (0.50–0.83), and 0.59 (0.35–0.76). The largest variability was the use of different PCR master mixes and calibrators. Standardization improved intraclass correlations to 0.83 (0.5–0.95), 0.95 (0.83–0.99) and 0.96 (0.86–0.99), respectively, for 10 archival frozen samples. For fresh plasma with spiked-in EBV DNA, correlations were more than 0.99 between the centers. At 5 EBV DNA copies per reaction or above, the coefficient of variance was less than 10% for the cycle threshold among all centers, suggesting this concentration can be reliably used as a cutoff for defining the presence of detectable EBV DNA.	2
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.	Experimental-Tx	65 patients	To compare the toxicities, tumor control, survival, and QoL of NPC patients treated with sequential neoadjuvant chemotherapy followed by concurrent cisplatin-RT or cisplatin-RT alone.	From November 2002 to November 2004, 65 eligible patients were randomly assigned to neoadjuvant chemotherapy followed by cisplatin-RT (n = 34) or cisplatin-RT alone (n = 31). There was a high rate of grade 3/4 neutropenia (97%) but not neutropenic fever (12%) during neoadjuvant chemotherapy. No significant differences in rates of acute toxicities were observed between the 2 arms during cisplatin-RT. Dose intensities of concurrent cisplatin, late RT toxicities and QoL scores were comparable in both arms. The 3-year PFS for neoadjuvant vs control arm was 88.2% and 59.5% (HR = 0.49; 95% CI, 0.20 to 1.19; *P*=.12). The 3-year OS for neoadjuvant vs control arm was 94.1% and 67.7% (HR = 0.24; 95% CI, 0.078 to 0.73; *P*=.012).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	172 patients	To compare survival, tumor control, toxicities, and QoL of patients with locally advanced NPC treated with induction chemotherapy and CCRT, against CCRT alone.	Between September 2004 and August 2012, 180 patients were accrued, and 172 (GCP 86, control 86) were analyzed by intention to treat. There was no significant difference in OS (3-year OS 94.3% [GCP] vs 92.3% [control]; HR 1.05; 1-sided *P*=.494]), DFS (HR 0.77, 95% CI, 0.44-1.35, *P*=.362), and distant metastases-free survival (HR 0.80, 95% CI, 0.38-1.67, *P*=.547) between the 2 arms. Treatment compliance in the induction phase was good, but the relative dose intensity for concurrent cisplatin was significantly lower in the GCP arm. Overall, the GCP arm had higher rates of grades 3 and 4 leukopenia (52% vs 37%) and neutropenia (24% vs 12%), but grade 3 and 4 acute radiation toxicities were not statistically different between the 2 arms. The global QoL scores were comparable in both arms.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	706 patients	To evaluate the potential therapeutic benefit from changing to an induction-concurrent chemotherapy sequence, replacing fluorouracil with oral capecitabine, and/or using accelerated rather than CRT fractionation.	In total, 803 patients were accrued, and 706 patients were randomly allocated to all 6 treatment arms. Comparisons of induction cisplatin and fluorouracil vs adjuvant cisplatin and fluorouracil did not indicate a significant improvement. Unadjusted comparisons of induction cisplatin and capecitabine vs adjuvant cisplatin and fluorouracil indicated a favorable trend in PFS for the conventional fractionation arm (P=.045); analyses that were adjusted for other significant factors and fractionation reflected a significant reduction in the hazards of disease progression (HR, 0.54; 95% CI, 0.36–0.80) and death (HR, 0.42; 95% CI, 0.25–0.70). Unadjusted comparisons of induction sequences vs adjuvant sequences did not reach statistical significance, but adjusted comparisons indicated favorable improvements by induction sequence. Comparisons of induction cisplatin and capecitabine vs induction cisplatin and fluorouracil revealed fewer toxicities (neutropenia and electrolyte disturbance), unadjusted comparisons of efficacy were statistically insignificant, but adjusted analyses indicated that induction cisplatin and capecitabine had a lower hazard of death (HR, 0.57; 95% CI, 0.34–0.97). Changing the fractionation from conventional to accelerated did not achieve any benefit but incurred higher toxicities (acute mucositis and dehydration).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	32 trials	To perform a meta-analysis based on randomized trials fulfilling strictly defined entry criteria that tested concurrent or alternating chemoradiation vs RT alone.	32 trials with a total of 10,225 patients were included in the meta-analysis. An OS benefit of 12.0 months was observed for the addition of simultaneous chemotherapy to either conventionally fractionated-RT or hyperfractionated-RT/ accelerated-RT (P<0.001). Separate analyses by cytostatic drug indicate a prolongation of survival of 24.0 months, 16.8 months, 6.7 months, and 4.0 months, respectively, for the simultaneous administration of 5-FU, cisplatin-based, carboplatin-based, and mitomycin C-based chemotherapy to RT (each P<0.01). Whereas no significant gain in OS was observed for accelerated-RT in comparison to conventionally fractionated-RT, a substantial prolongation of median survival (14.2 months, P<0.001) was seen for HFRT compared to conventionally fractionated-RT (both without chemotherapy).	4
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.	Experimental-Tx	189 patients	To evaluate the therapeutic benefits by adding chemotherapy and/or accelerated-fractionation for patients with T3-4N0-1M0 NPC.	The accelerated-fractionation + chemotherapy group achieved significantly higher FFR (88% at 5-year) than the conventionally fractionated group (63%; P=0.013), the accelerated-fractionation group (56%; P=0.001) and the conventionally fractionated + chemotherapy group (65%; P=0.027). As compared with conventionally fractionated alone, the increase in late toxicity was statistically insignificant (36% vs 20%; P=0.25). Deaths due to cancer progression decreased (7% vs 33%; P=0.011) but deaths due to incidental causes increased (9% vs 2%; P=0.62). Improvement in OS reached borderline significance (85% vs 66%; P=0.058).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	154 patients	To evaluate the impact of a split course bifractionated RT regimen in a phase III randomized trial.	Patients were well balanced between the 2 arms. The complete remission rate was 91% in CRT arm and 93% in bifractionated RT arm (P=0.3). There was more grade II-III skin fibrosis in experimental arm with a 5 year actuarial probability of 66% vs 52% (P=0.04). Locoregional and distant relapses occurred in 34% of cases in conventional arm and 38% in experimental arm (P=0.28). With a median follow-up of 56 months, the 5 year OS and the DFS rates were, respectively (71% and 61%), in conventional arm and (62% and 60%) in bifractionated arm, the difference being statistically nonsignificant.	1
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.	Experimental-Tx	159 patients	To compare the survival, local control and complications of conventional/accelerated-hyperfractionated RT and CRT in nonmetastatic NPC.	With comparable distribution among the T stages between the 2 arms, the free from local failure rate at 5 years after RT was not significantly different between the 2 arms (85.3%; 95% CI, 77.2%–93.4% for Arm I; and 88.9%; 95% CI, 81.7%–96.2% for Arm II). The 2 arms were also comparable in OS, relapse-free survival, and rates of distant metastasis and regional relapse. Conventional/accelerated-hyperfractionated RT was associated with significantly increased radiation-induced damage to the central nervous system (including temporal lobe, cranial nerves, optic nerve/chiasma, and brainstem/spinal cord) in Arm II. Although insignificant, radiation-induced cranial nerve(s) palsy (typically involving VIII-XII), trismus, neck soft tissue fibrosis, and hypopituiturism and hypothyroidism occurred more often in Arm II. In addition, the complications occurred at significantly shorter intervals after RT in Arm II.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	67 patients	To update our experience with IMRT in the treatment of NPC.	With a median follow-up of 31 months (range 7 to 72 months), there has been 1 local recurrence at the primary site. One patient failed in the neck. 17 patients developed distant metastases; 5 of these patients have died. The 4-year estimates of local progression-free, local-regional progression-free, and distant metastases-free rates were 97%, 98%, and 66% respectively. The 4-year estimate of OS was 88%. The worst acute toxicity documented was as follows: Grade 1 or 2 in 51 patients, Grade 3 in 15 patients, and Grade 4 in 1 patient. The worst late toxicity was Grade 1 in 20 patients, Grade 2 in 15 patients, Grade 3 in 7 patients, and Grade 4 in 1 patient. At 3 months after IMRT, 64% of the patients had Grade 2, 28% had Grade 1, and 8% had Grade 0 xerostomia. Xerostomia decreased with time. At 24 months, only one of the 41 evaluable patients had Grade 2, 32% had Grade 1, and 66% had Grade 0 or no xerostomia. Analysis of the dose-volume histograms showed that the average maximum, mean, and minimum dose delivered were 79.3 Gy, 74.5 Gy, and 49.4 Gy to the gross tumor volume, and 78.9 Gy, 68.7 Gy, and 36.8 Gy to the clinical tumor volume. An average of only 3% of the gross tumor volume and 3% of the clinical tumor volume received <95% of the prescribed dose.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	1,571 patients	To compare clinical outcomes of patients with unknown primary melanoma and known primary melanoma with regional nodal metastases.	Multivariate analysis of data from 1,571 study patients identified 4 significant covariates associated with worse prognosis: age ≥60 years (HR = 1.294; *P*=.0017), male sex (HR = 1.335; *P*=.0004), nodal tumor burden ≥1 (HR = 1.256; *P*<.0001), and known primary (HR = 1.507; 95% CI, 1.220 to 1.862; *P*=.0001). 5-year OS was significantly higher for 262 patients with unknown primary melanoma than for 1,309 patients with known primary melanoma (55% +/- 6% vs 44% +/- 3%; *P*=.0021). Computerized matching of unknown primary melanoma and known primary melanoma by 4 significant covariates (age, sex, nodal tumor burden, and decade of diagnosis) yielded 221 matched pairs. Median and 5-year OS rates were 165 months and 58% +/- 7%, respectively, for unknown primary melanoma as compared with 34 months and 40% +/- 7%, respectively, for known primary melanoma (*P*=.0006).	2
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.	Experimental-Tx	129 patients	To evaluate the effects of replanning on QoL and clinical outcomes during the course of IMRT for NPC patients.	IMRT replanning had a profound impact on the QoL of NPC patients, as determined by statistically significant changes in global QoL and other QoL scales. Additionally, the clinical outcome comparison indicates that replanning during IMRT for NPC significantly improved 2-year local regional control (97.2% vs 92.4%, respectively, *P*=.040) but did not improve 2-year OS (89.8% vs 82.2%, respectively, *P*=.475).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	92 patients	To evaluate the efficacy and safety of a paclitaxel, cisplatin and 5-FU combination in metastatic and/or recurrent NPC.	A total of 95 patients were enrolled; 92 patients were evaluable for response. The overall response and disease control rates were 78.9% and 93.6%, respectively. At a median follow-up of 24.8 months, the respective median OS and PFS were 22.7 months (95 % CI, 18.6-26.9 months) and 8.6 months (95 % CI, 7.7-9.5 months). Toxicities were moderate and manageable. Grade 3/4 toxicities included leucopenia (14.7%), neutropenia (17.9%), anemia (3.2%), thrombocytopenia (6.4%), nausea (4.2%), vomiting (9.5%), stomatitis (9.5%), diarrhea (3.2%), aminotransferase (2.2%) and sensory neuropathy (3.2%).	1
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.	Experimental-Tx	442 patients	To investigate the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.	Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum-fluorouracil) significantly prolonged the median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (HR for death, 0.80; 95% CI, 0.64 to 0.99; P=0.04). The addition of cetuximab prolonged the median PFS time from 3.3 to 5.6 months (HR for progression, 0.54; P<0.001) and increased the response rate from 20% to 36% (P<0.001). The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19% and 13%, respectively), neutropenia (23% and 22%), and thrombocytopenia (11% in both groups). Sepsis occurred in 9 patients in the cetuximab group and in 1 patient in the chemotherapy-alone group (P=0.02). Of 219 patients receiving cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	101 patients	To evaluate whether DNA repair gene polymorphisms had an effect on clinical outcomes in metastatic/recurrent NPC patients treated with cisplatin-based chemotherapy.	The ERCC1 C8092A polymorphism was an independent predictor of PFS in Chinese NPC patients treated with cisplatin-based chemotherapy. Compared to the patients carrying the C/C genotype, the patients with the C/A or A/A genotype had an increased risk of disease progression on cisplatin-based chemotherapy (7.9 vs 9.3 months; HR 1.61; 95 % CI, 1.08–2.61; *P*=0.047). However, no association between the other polymorphisms, response rate, disease progression and survival was detected in metastatic/recurrent NPC patients.	1
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.	Experimental-Tx	17 patients	To evaluate the efficacy and toxicity of capecitabine as a salvage chemotherapy regimen in Chinese patients with recurrent or metastatic NPC previously treated with platinum-based chemotherapy.	7 patients had local recurrence, 7 had distant metastases, 1 had loco-regional recurrence, and 2 had both local/regional recurrence and distant metastases. Patients received a median number of 3 cycles of capecitabine (range: 1–6). The median follow-up was 7.5 months (range: 3–25.3). All patients were included in the efficacy and adverse events analysis. 3 patients (17.6%) achieved partial response and 1 patient (5.9%) achieved complete response, with an overall response rate of 23.5% (95% CI, 7%–50%). The duration of responses were 4.2, 5, 6+, and 23.1+ months. 9 patients (52.9%) had stable disease whereas 4 (23.5%) had progressive disease. The median time to progression was 4.9 months. The median survival was 7.6 months. 5 patients are still alive with an estimated 1-year survival rate of 35%. Treatment-related adverse events were generally mild except hand-foot syndrome which occurred in 58.8% of patients.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	27 patients	Two parallel phase II trials in chemonaive and previously treated patients with metastatic NPC to evaluate the tumor response, PFS and OS, and toxicity of gemcitabine.	25 chemonaive and 27 previously treated patients were enrolled. The overall response rate was 28% [95% CI 14% to 48%] for the chemonaive and 48% (95% CI 31% to 66%) for previously treated patients. Toxicities ≥grade 3 occurred in 15 (60%) chemonaive and 13 (48%) previously treated patients. Neutropenia was uncommon in chemonaive patients, but occurred in 37% of previously treated patients. The median time to progression was 3.6 months (range 0.9–7.9) for chemonaive and 5.1 months (0.9–13.1) for previously treated patients. Median OS time was 7.2 months (1.4–15.6) and 10.5 months (2.4–15.0) for chemonaive and previously treated patients, respectively.	1
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.	Experimental-Tx	28 patients	To evaluate the efficacy and safety of irinotecan in patients with advanced NPC.	28 patients were evaluable for toxicity and response. Patient characteristics were as follows: The median age was 46.5 years (range, 40.3–71.6 years), the median number of prior lines of chemotherapy was 2 (range, 1–9), the majority of patients (89%) had good Eastern Cooperative Oncology Group performance status (0–1), and the majority of patients (82.1%) had ≥2 sites of distant metastases. A total of 79 cycles of irinotecan with a median of 3 cycles per patient were administered. Toxicity >Grade 3 included neutropenia in 5 patients (17%), anemia in 5 patients (17%), and diarrhea in 4 patients (14%). The best response outcomes were 4 patients (14%) who achieved partial responses and 1 patient (4%) who achieved stable disease. Global QoL scores were stable during treatment. Using the Kaplan-Meier method, the median PFS was 3.9 months, and the median OS was 11.4 months. The partial responders had a durable response (range, 5.7–12.2 months).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	30 patients	To evaluate the efficacy and toxicity of single-agent docetaxel (Taxotere) as therapy in patients with disseminated NPC.	30 patients were assessable for toxicity and response. The median age of the patients was 47 years (range 25–68 years) and the majority of patients had good performance status (Eastern Cooperative Oncology Group 0–1). Grade 3 or 4 toxicity included fatigue (13%), anemia (10%) and diarrhea (3%) of patients. 11 (37%) and 4 (13.3%) patients achieved partial response and stable disease, respectively. The median PFS was 5.3 months and median OS of 12.8 months. The partial responders had a mean duration of response of 4.1 months. Docetaxel caused a significant decline in QoL scores during treatment of patients responding or progressing with the treatment.	2
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.	Experimental-Tx	33 patients	To hypothesize that pazopanib would have antiangiogenic activity in NPC in a single arm monotherapy study of pazopanib in patients with WHO type II/III NPC who had metastatic/recurrent disease and failed at least one line of chemotherapy.	33 patients were accrued. Patients were ECOG 0–1 with median age of 50 years (range 36–68). There were 2 (6.1%) partial responses, 16 (48.5%) stable disease, 11 (33.3%) progressive disease, 4 (12.1%) were not evaluable for response. The clinical benefit rate was 54.5% (95% CI: 38.0–70.2). 10 patients (30.3%) received more than 6 cycles (4 months) of treatment and 7 (21.2%) had partial response/SD that lasted at least 6 months. One patient each died from epistaxis and myocardial infarction. Common grade 3/4 toxicities included fatigue (15.2%), hand-foot syndrome (15.2%), anorexia (9.1%), diarrhea (6.1%), and vomiting (6.1%). Serial dynamic contrast-enhanced computed tomography scans show significant reductions in tumor blood flow, permeability surface area product, and fractional intravascular blood volume.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	54 patients	To investigate the efficacy and tolerability of sorafenib combined with cisplatin and 5-FU in patients with recurrent or metastatic NPC.	In total, 54 patients were enrolled. The objective response rate reached 77.8%, including 1 complete response and 41 partial responses. The median PFS was 7.2 months (95% CI 6.8-8.4 months), and the median OS was 11.8 months (95% CI 10.6-18.7 months). Major toxic effects included hand-foot skin reaction, myelosuppression, and gastrointestinal reaction. The incidence of hemorrhage was 22.2%, and 1 patient with liver metastases died of gastrointestinal bleeding. Contrast-enhanced ultrasonography was carried out in a subset of patients with liver metastases.	2
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.	Experimental-Tx	13 patients	To evaluate the safety and efficacy of single-agent sunitinib in NPC.	13 patients were enrolled. Recruitment was stopped after 2 patients died of hemorrhagic events. All patients had previously received curative RT to nasopharynx/neck (including 9 patients who had chemoradiotherapy). Patients received a median of 3 cycles of sunitinib. One patient was still on sunitinib with stable disease after 24 cycles. Hemorrhagic events occurred in 9 patients (64%), including epistaxis in 6, hemoptyses in 3 and hematemesis in 2 patients. Prior RT to thorax was significantly associated with hemoptyses (P=0.03). 2 patients with local tumor invasion into the carotid sheath developed fatal epistaxis/hematemesis within the first cycle of sunitinib, likely due to internal carotid blowout after tumor shrinkage.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To discuss the different options for salvage of locally recurrent NPC.	Retreatment of locally recurrent NPC using RT, alone or in combination with other treatment modalities, as well as surgery, can result in long-term local control and survival in a substantial proportion of patients. For small-volume recurrent tumors (T1-T2) treated with external RT, brachytherapy or stereotactic radiosurgery, comparable results to those obtained with surgery have been reported. In contrast, treatment results of advanced-stage locally recurrent NPC are generally more satisfactory with surgery (with or without postoperative RT) than with reirradiation.	4
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.	Observational-Tx	268 patients	To investigate the prognostic factors for salvage nasopharyngectomy.	The median follow-up duration was 52 months. Among the 268 patients, 79.1% had clear resection margins. The 5-year actuarial local tumor control and OS was 74% and 62.1%, respectively. On multivariate analysis, tumor size, resection margin status, and gross tumor in the sphenoid sinus were independent prognostic factors for local tumor control. For OS, resection margin status, synchronous cervical nodal recurrence, and cavernous sinus invasion had a negative influence on OS after surgery.	2
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.	Observational-Tx	73 patients	To address the efficacy and toxicity profile of IMRT for a cohort of patients with locally recurrent NPC.	The median dose to the recurrent tumor was 70 Gy (range, 50–77.4 Gy). 65 patients received the planned RT; 5 patients received between 50 and 60 Gy because of acute side effects. With a median follow-up time of 25 months, the rates of 2-year locoregional recurrence-free survival, DFS, and OS were 65.8%, 65.8%, and 67.4%, respectively. Moderate to severe late toxicities were noted in 25 patients (35.7%). 11 patients (15.7%) had posterior nasal space ulceration, 17 (24.3%) experienced cranial nerve palsies, 12 (17.1%) had trismus, and 12 (17.1%) experienced deafness. Extended disease-free interval (relative risk 2.049) and advanced T classification (relative risk 3.895) at presentation were adverse prognostic factors.	2

Nasopharyngeal Carcinoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	654 patients	To identify factors for maximizing local salvage and minimizing damages by reirradiation for recurrent NPC.	The 5-year actuarial local salvage and complication-free rates were 23% and 52%, respectively. Multivariate analyses showed that the extensiveness of local recurrence was the most significant factor affecting local salvage, while T-stage of primary tumor also influenced prognosis. Choice of method for reirradiation and fractional effect during both courses affected the risk of late complications. For patients treated by teletherapy alone, the hazard of local failure decreased by 1.7% per Biological Effective Dose (assuming alpha/beta ratio = 10) of the second course, while radiation factors during primary RT had no significant effect. On the other hand, the risk of late complications was predominantly affected by the primary treatment: the hazard increased by 4.2% per Biological Effective Dose (assuming alpha/beta ratio = 3) of the first course, while the corresponding impact of reirradiation failed to reach statistical significance. Length of the gap between the two courses did not affect the outcome.	2
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.	Observational-Tx	136 NPC patients	To evaluate the efficacy and toxicity of fractionated stereotactic in patients with residual NPC.	5-year local failure-free survival, freedom from distant metastasis, OS, and DFS rates for all patients were 92.5%, 77.0%, 76.2%, and 73.6%, respectively. No statistical significant differences were found in local failure-free survival, DFS and OS in patients with stage I/II vs stage III/ IV diseases. 19 patients exhibited late toxicity. T stage at diagnosis was a significant prognostic factor for OS and DFS. Age was a prognostic factor for OS.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	410 patients	To review the applicability and efficacy of endoscopic nasopharyngectomy and IMRT, and to identify the most effective treatment modality.	The 5-year OS and distant metastasis-free survival were significantly higher in endoscopic nasopharyngectomy and IMRT groups than in 2D conventional RT group both in the entire series and in the subgroup of patients with recurrent T1 to 2 NPC (*P*<.05), except in the subgroup of recurrent T3 to 4 stratifications (IMRT vs 2D conventional RT; 28.8% vs 16.8%; p = .351). Furthermore, endoscopic nasopharyngectomy was associated with better OS than IMRT in the recurrent T1 to 2 subgroup (79.2% vs 62.1%; *P*=.007). Multivariate analysis indicated therapeutic modality was an independent predictor of OS and distant metastasis-free survival (*P*<.001).	2
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.	Review/Other-Tx	N/A	To provide recommendations for brachytherapy for head and neck squamous cell carcinomas.	N/A	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	33 patients	To evaluate the treatment outcome and major late complications of all patients with recurrent NPC treated with intracavitary brachytherapy in Hospital Kuala Lumpur.	33 patients were eligible for this study. The median age at recurrence was 56 years with a median time to initial local recurrence of 27 months. Majority of patients were staged as rT1-2 (94%) or rN0 (82%). The proportion of patients categorized as stage III-IV at first local recurrence was only 9%. 21 patients received a combination of intracavitary brachytherapy and external beam RT while 12 patients were treated with intracavitary brachytherapy alone. Median interval of recurrence post re-irradiation was 32 months (range: 4–110 months). The median local recurrence free survival, DFS and OS were 30 months, 29 months and 36 months respectively. The 5 year local recurrence free survival, DFS and OS were 44.7%, 38.8% and 28.1% respectively. The N stage at recurrence was found to be a significant prognostic factor for local recurrence free survival and DFS after multivariate analysis. Major late complications occurred in 34.9% of our patients.	2

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

5-FU = 5-fluorouracil

CCRT = Concurrent chemoradiotherapy

CI = Confidence interval

CRT = Conventional radiotherapy

DFS = Disease-free survival

EBV = Epstein-Barr virus

FFR = Failure-free rate

HPV = Human papillomavirus

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

NPC = Nasopharyngeal carcinoma

OR = Odds ratio

OS = Overall survival

PFS = Progression-free survival

QoL = Quality of life

RT = Radiotherapy