Locoregional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers. Version 2.2014. 2014; Available at: http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed September 30, 2015.	Review/Other-Tx	N/A	To provide NCCN practice guidelines on head and neck cancers.	N/A	4
2. Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2009;73(2):410-415.	Observational-Tx	122 patients	To determine the clinical predictors of severe long-term dysphagia in a heterogeneous population of locally advanced head-and-neck cancer patients treated with definitive RT.	A composite dysphagia outcome occurred in 38.5% of patients. The use of concurrent chemotherapy (P=0.01), primary site (P=0.02), and increasing age (P=0.02) remained significant on multivariate analysis. The addition of concurrent chemotherapy to RT for locally advanced head-and-neck cancer resulted in increased long-term dysphagia.	2
3. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiother Oncol.* 2009;90(2):189-195.	Observational-Tx	529 patients	Prospective study of HNSCC patients treated with curative RT. Purpose of study is to design a predictive model for swallowing dysfunction after curative RT or chemoradiation.	After univariate and multivariate logistic regression analyses, the following factors turned out to be independent prognostic factors for SWALL (6months): T3-T4, bilateral neck irradiation, weight loss prior to radiation, OP and nasopharyngeal tumors, accelerated RT and concomitant chemoradiation. By summation of the regression coefficients derived from the multivariate model, the Total Dysphagia Risk Score could be calculated. In the logistic regression model, the Total Dysphagia Risk Score was significantly associated with SWALL (6months) (P<0.001). Subsequently, the authors defined 3 risk groups based on the Total Dysphagia Risk Score. The rate of SWALL (6months) was 5%, 24% and 46% in case of low-, intermediate- and high-risk patients, respectively. These observed percentages were within the 95% CIs of the predicted values. The Total Dysphagia Risk Score risk group classification was also significantly associated with acute dysphagia (P<0.001 at all-time points) and with late swallowing dysfunction at 12, 18 and 24 months (P<0.001 at all-time points).	1

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4. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* 2008;26(21):3582-3589.	Observational-Tx	230 (99 patients with late toxicities and 131 controls)	To evaluate factors associated with severe late toxicity after CCRT for locally advanced head and neck cancer. Patients were analyzed from a subset of 3 previously reported Radiation Therapy Oncology Group (RTOG) trials.	43% of patients had a severe late toxicity. Severe late toxicity after CCRT is common. Older age, advanced T-stage, and larynx/hypopharynx primary site were strong independent risk factors. Neck dissection after CCRT was associated with an increased risk of these complications.	2
5. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol.* 2008;26(22):3770-3776.	Observational-Tx	425 disease-free patients	To investigate the impact of treatment-related toxicity on HRQoL among patients with HNSCC treated with RT either alone or in combination with chemotherapy or surgery.	Of the 6 RTOG scales investigated, 2 significantly affected self-reported HRQoL, salivary gland (RTOG (xerostomia)) and esophagus/pharynx (RTOG (swallowing)). Although RTOG(xerostomia) was reported most frequently, HRQoL was most affected by RTOG(swallowing), particularly in the first 18 months after completion of RT.	1
6. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol.* 2004;31(6):744-754.	Review/Other-Tx	N/A	Review role of HPV in the pathogenesis of a distinct subset of HNSCC.	Strong and consistent association between high-risk HPV types, specifically HPV16, a known human carcinogen, and distinctive OP cancers with molecular characteristics indicative of viral oncogene function.	4
7. Ernster JA, Sciotto CG, O'Brien MM, et al. Rising incidence of oropharyngeal cancer and the role of oncogenic human papilloma virus. *Laryngoscope.* 2007;117(12):2115-2128.	Review/Other-Tx	72 patients	Epidemiologic review and retrospective case series analysis to document the rising incidence of OP cancer and provide evidence that this increase is caused by oncogenic HPV.	OP cancer incidence is increasing in Colorado males and to a lesser extent in U.S. males. The HPV+ OP cancer cases were more frequent in the later years of the study. DSS was much better in the HPV+ patients, confirming that HPV testing defines a unique subset of patients. Findings suggest HPV oncogenesis accounts for the increase in average annual age-adjusted incidence of OP cancer.	4
8. Chien CY, Su CY, Fang FM, et al. Lower prevalence but favorable survival for human papillomavirus-related squamous cell carcinoma of tonsil in Taiwan. *Oral Oncol.* 2008;44(2):174-179.	Observational-Tx	111 patients	Retrospective study to investigate the prevalence and clinical significance of HPV in TSCC in Taiwan and examine its relationship with the clinicopathological parameters.	12.6% TSCC were HPV+. The favorable 5-year survival rate correlated significantly with HPV positivity (P=0.007), female (P=0.046), and early tumor (T) stage (P<0.001), but Cox's regression analysis revealed that only the status of HPV (P=0.04) and T stage (P=0.004) were independent prognostic factors for survival. Study concludes that the prevalence of HPV-related TSCC is much lower in Taiwan compared with the Western population, and the prognosis of HPV+ TSCC is better than that of HPV– TSCC.	2

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9. Fischer CA, Zlobec I, Green E, et al. Is the improved prognosis of p16 positive oropharyngeal squamous cell carcinoma dependent of the treatment modality? *Int J Cancer.* 2010;126(5):1256-1262.	Observational-Tx	365 patients	To analyze the impact of p16 expression status on the prognosis of OSCC treated by either RT or primary surgery.	p16 positivity correlated significantly with OP tumor localization (P<0.001). Patients with p16 positive OSCC exhibited a significantly better OS than those with p16 negative tumors (P=0.007).	2
10. Hannisdal K, Schjolberg A, De Angelis PM, Boysen M, Clausen OP. Human papillomavirus (HPV)-positive tonsillar carcinomas are frequent and have a favourable prognosis in males in Norway. *Acta Otolaryngol.* 2010;130(2):293-299.	Review/Other-Tx	137 patients	To evaluate the prevalence of HPV in patients with tonsillar carcinomas. The p53- and Ki-67-positive tumor cell fractions were measured and correlated with clinical variables.	HPV was found in 71/137; HPV-16 was the most frequent subtype (87%). HPV positivity did not correlate with gender, stage, T- and N categories, Ki-67 expression or p53 positivity. The HPV+ group had a significantly better survival (P<0.01) compared with the HPV– group in males.	4
11. Klozar J, Kratochvil V, Salakova M, et al. HPV status and regional metastasis in the prognosis of oral and oropharyngeal cancer. *Eur Arch Otorhinolaryngol.* 2008;265 Suppl 1:S75-82.	Observational-Tx	81 patients	To compare patients with HPV+ and HPV– tumors for survival and prevalence and type of regional metastasis, to identify prognostic factors and to test whether HPV presence is an independent factor of survival.	Overall, 64% of tumors were HPV+ with 80% in the tonsillar site. HPV+ patients had significantly better both OS (73% vs 35%) (P=0.0112) and DSS (79% vs 45%) (P=0.0015) rates than HPV– patients. HPV was the most significant prognostic factor in the group of patients with OP tumors (HR=0.27, 95% CI, 0.12–0.61) and possibly should be considered in treatment decisions.	2
12. Klussmann JP, Mooren JJ, Lehnen M, et al. Genetic signatures of HPV-related and unrelated oropharyngeal carcinoma and their prognostic implications. *Clin Cancer Res.* 2009;15(5):1779-1786.	Experimental-Tx	60 patients	Comparative genomic hybridization to identify critical genetic changes in 60 selected OSCC, 28 of which were associated with HPV-16 as determined by HPV-specific PCR and fluorescence in situ hybridization analysis and positive p16INK4a immunostaining. Results were correlated with HPV status and clinical data.	Two thirds of OSCC harbored gain at 3q26.3-qter irrespective of HPV status. Better DFS for HPV-related OSCC (P=0.02). Genetic signatures of HPV-related and HPV-unrelated OSCC are different and most likely underlie differences in tumor development and progression. Also, distinct chromosomal alterations have prognostic significance.	1
13. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol.* 2006;24(36):5630-5636.	Observational-Tx	90 consecutive patients	To clarify how the presence of high-risk - HPV, TP53, and p16INK4a status interact with clinical outcome, a retrospective series of OP cancer patients treated with surgery were examined.	Statistical analysis showed that HPV+ status significantly affects all investigated end points: OS (P=.0018), incidence of tumor relapse (P=.0371), and second tumor (P=.0152), whereas TP53 and p16INK4a status and p16 expression were not prognostic by themselves.	2
14. Straetmans JM, Olthof N, Mooren JJ, de Jong J, Speel EJ, Kremer B. Human papillomavirus reduces the prognostic value of nodal involvement in tonsillar squamous cell carcinomas. *Laryngoscope.* 2009;119(10):1951-1957.	Observational-Tx	81 patients	Retrospective 5-year survival analysis to assess the prognostic value of nodal status in relation to HPV status and the various treatment modalities in TSCC.	41% of TSCC were positive for HPV-16. The N status is an unreliable prognostic indicator in TSCC. HPV is only prognostically relevant in the total tumor population, but loses its value within patient groups receiving a single treatment modality.	2

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15. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol.* 2006;24(5):736-747.	Observational-Tx	79 tumors	To determine the prevalence of biologically relevant HPV in OSCC. Authors hypothesized that p16 overexpression in OSCC defines HPV-induced tumors with favorable prognosis. 77 tumors were classified into a three-class model: class I, HPV–, p16 low; class II, HPV+, p16 low; and class III, HPV+, p16 high.	OS was improved in class III (79%) compared with the other 2 classes (20% and 18%; *P*=.0095). DFS for the same class was 75% vs 15% and 13% (*P*=.0025). The 5-year local recurrence was 14% in class III vs 45% and 74% (*P*=.03). Only patients in class III had significantly lower p53 and Rb expression (*P*=.017 and .001, respectively). Multivariable survival analysis confirmed the prognostic value of the three-class model.	2
16. Settle K, Posner MR, Schumaker LM, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. *Cancer Prev Res (Phila).* 2009;2(9):776-781.	Observational-Tx	Retrospective cohort: 106 white and 95 black HNSCC patients; TAX 324 - 196 white and 28 black patients	Study first examined OS differences by OP and non-OP sites in a retrospective group of black and white patients with stage III and IV HNSCC and then analyzed patients from the multicenter randomized phase III TAX 324 trial for the presence of HPV-16 in pretreatment biopsy specimens.	Median OS in the retrospective cohort was 52.1 months (white) vs 23.7 months (black; *P*=0.009). In TAX 324, median OS was significantly worse for black patients (20.9 months) than for white patients (70.6 months; *P*=0.03) Overall, HPV positivity was 34% in white vs 4% in black patients (*P*=0.0004). Survival was similar for black and white HPV– patients (*P*=0.56).	2
17. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol.* 2008;26(19):3138-3146.	Observational-Tx	66 patients	To test IC followed by CCRT or surgery/RT for advanced OP cancer and to prospectively assess the effect of HPV on response and outcome.	54/66 patients (81%) had >50% response after IC. 4-year OS was 70.4%, and the DSS was 75.8% (median follow-up, 64.1 months). IC followed by CCRT is an effective treatment for OSCC, especially in patients with HPV+ tumors.	1
18. Kies MS, Holsinger FC, Lee JJ, et al. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. *J Clin Oncol.* 2010;28(1):8-14.	Experimental-Tx	47 patients	Phase II prospective trial to determine the potential efficacy of combining cetuximab with chemotherapy in patients with advanced nodal disease.	3-year PFS and OS rates were 87% (95% CI, 78%–97%) and 91% (95% CI, 84%–99%), respectively. HPV-16, found in 12 (46%) of 26 biopsies, was associated with improved PFS (*P*=.012) and OS (*P*=.046).	1

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19. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. *J Clin Oncol.* 2012;30(17):2102-2111.	Observational-Tx	2 trials - RTOG 9003 (n = 1,113) and RTOG 0129 (n = 743)	To investigate the impact of quantitative measures of tobacco smoking on survival outcomes in 2 trials: RTOG 9003 and RTOG 0129.	Prevalence of p16-positive cancer was 39.5% among patients in RTOG 9003 and 68.0% in RTOG 0129. Median pack-years of tobacco smoking were lower among p16-positive than p16-negative patients in both trials (RTOG 9003: 29 vs 45.9 pack-years; *P*=.02; RTOG 0129: 10 vs 40 pack-years; *P*<.001). After adjustment for p16 and other factors, risk of PFS or death (OS) increased by 1% per pack-year (for both, HR, 1.01; 95% CI, 1.00 to 1.01; *P*=.002) or 2% per year of smoking (for both, HR, 1.02; 95% CI, 1.01 to 1.03; *P*<.001) in both trials. In RTOG 9003, risk of death doubled (HR, 2.19; 95% CI, 1.46 to 3.28) among those who smoked during RT after accounting for pack-years and other factors, and risk of second primary tumors increased by 1.5% per pack-year (HR, 1.015; 95% CI, 1.005 to 1.026).	2
20. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol.* 2010;28(27):4142-4148.	Experimental-Tx	861 patients; 185 for p16 analysis	To determine the prognostic importance of p16 and HPV in patients with OP cancer treated on a phase III CCRT trial.	Slides were available for p16 assay in 206/465 patients, of which 185 were eligible, and p16 and HPV were evaluable in 172 patients. 106 (57%) of 185 were p16-positive, and in patients evaluable for both p16 and HPV, 88 (86%) of 102 p16-positive patients were also HPV+. Patients who were p16-positive had lower T and higher N categories and better Eastern Cooperative Oncology Group performance status. p16-positive tumors compared with p16-negative tumors were associated with better 2-year OS (91% vs 74%; HR, 0.36; 95% CI, 0.17 to 0.74; *P*=.004) and failure-free survival (87% vs 72%; HR, 0.39; 95% CI, 0.20 to 0.74; *P*=.003). p16 was a significant prognostic factor on multivariable analysis (HR, 0.45; 95% CI, 0.21 to 0.96; *P*=.04). p16-positive patients had lower rates of locoregional failure and deaths due to other causes. There was a trend favoring the tirapazamine arm for improved locoregional control in p16-negative patients (HR, 0.33; 95% CI, 0.09 to 1.24; *P*=.13).	1

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21. Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J. HPV-associated p16-expression and response to hypoxic modification of radiotherapy in head and neck cancer. *Radiother Oncol.* 2010;94(1):30-35.	Observational-Tx	331 patients	Retrospective analysis of the randomized Danish Head and Neck Cancer Group 5 trial. To assess the influence of p16-expression on the response to nimorazole in HNSCC using p16-status as a retrospective stratification parameter.	Patients treated with nimorazole had significantly better locoregional control than those given placebo. In the subgroup of patients with p16-negative tumors, locoregional failure was more frequent in the placebo group than in the nimorazole group (0.69 [0.50–0.95]). However, in the p16-positive group, patients treated with nimorazole had a locoregional control rate similar to patients given placebo. HPV-16-expression significantly improved outcome after RT in HNSCC. Hypoxic modification improved outcome in HPV-16-negative tumors but was of no significant benefit in HPV-16-positive tumors, suggesting that hypoxic radioresistance may not be clinically relevant in these tumors.	2
22. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008;100(4):261-269.	Experimental-Tx	96 patients	To prospectively evaluate the association of tumor HPV status with therapeutic response and survival among patients with stage III or IV HNSCC of the oropharynx or larynx who participated in a phase II trial and who received 2 cycles of IC with intravenous paclitaxel and carboplatin followed by concomitant weekly intravenous paclitaxel and standard fractionation RT.	Compared with HPV– tumors, patients with HPV+ tumors had higher response rates after IC (82% vs 55%, difference = 27%, 95% CI = 9.3% to 44.7%, *P*=.01) and after chemoradiation treatment (84% vs 57%, difference = 27%, 95% CI = 9.7% to 44.3%, *P*=.007). After a median follow-up of 39.1 months, patients with HPV+ tumors had improved OS (2-year OS = 95% [95% CI = 87% to 100%] vs 62% [95% CI = 49% to 74%], difference = 33%, 95% CI = 18.6% to 47.4%, *P*=.005, log-rank test). For patients with HNSCC of the oropharynx, tumor HPV status is strongly associated with therapeutic response and survival.	1

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23. Hafkamp HC, Manni JJ, Haesevoets A, et al. Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. *Int J Cancer.* 2008;122(12):2656-2664.	Observational-Tx	81 patients	Tissue sections of TSCC were analyzed by HPV 16-specific fluorescence in situ hybridization and p16INK4a-specific immunohistochemistry. Results were correlated with clinical and demographic data.	HPV-16 integration was detected by fluorescence in situ hybridization as punctate signals in 33/81 (41%) TSCC, 32 of which showed p16INK4a accumulation. Only 5/48 HPV– tumors showed p16INK4a immunostaining (P<0.0001). The presence of HPV correlates significantly with low tobacco (P=0.002) and alcohol intake (P=0.011), poor differentiation grade (P=0.019), small tumor size (P=0.024), presence of a local metastasis (P=0.001) and a decreased locoregional recurrence rate (P=0.039).	2
24. Maxwell JH, Kumar B, Feng FY, et al. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. *Clin Cancer Res.* 2010;16(4):1226-1235.	Experimental-Tx	124 patients	To examine the effect of tobacco use on disease recurrence (local/regional recurrence, distant metastasis, or second primary) among patients with HPV+ OSCC following a complete response to chemoradiation therapy.	102 patients (82.3%) had HPV+ tumors. Over two thirds (68%) of patients with HPV+ tumors were tobacco users. Among HPV+ patients, current tobacco users were at significantly higher risk of disease recurrence than never-tobacco users (HR, 5.2; CI, 1.1–24.4; P=0.038). 35% of HPV+ ever tobacco users recurred compared with only 6% of HPV+ never users and 50% of HPV– patients. All HPV– patients were tobacco users and had significantly shorter times to recurrence (P=0.002), and had reduced DSS (P=0.004) and OS (P<0.001) compared with HPV+ patients. Compared with HPV+ never-tobacco users, those with a tobacco history showed a trend for reduced DSS (P=0.064) but not OS (P=0.221).	1

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25. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol.* 2013;31(5):543-550.	Observational-Tx	505 patients	To define HPV+ OSCC suitable for treatment deintensification according to low risk of distant metastasis.	HPV status was ascertained in 505 (56%) of 899 consecutive OSCC. Median follow-up was 3.9 years. HPV+ patients (n = 382), compared with HPV– patients (n = 123), had higher local (94% vs 80%, respectively, at 3 years; *P*<.01) and regional control (95% vs 82%, respectively; *P*<.01) but similar distant control (90% vs 86%, respectively; *P*=.53). Multivariate analysis identified that HPV– (HR, 2.9; 95% CI, 2.0 to 5.0), N2b-N3 (HR, 2.9; 95% CI, 1.8 to 4.9), T4 (HR, 1.8; 95% CI, 1.2 to 2.9), and RT alone (HR, 1.8; 95% CI, 1.1 to 2.5) predicted a lower recurrence-free survival (all *P*<.01). Smoking pack-years >10 reduced OS (HR, 1.72; 95% CI, 1.1 to 2.7; *P*=.03) but did not impact recurrence-free survival (HR, 1.1; 95% CI, 0.7 to 1.9; *P*=.65). Recursive partitioning analysis segregated HPV+ patients into low (T1-3N0-2c; distant control, 93%) and high distant metastasis risk (N3 or T4; distant control, 76%) groups and HPV– patients into different low (T1-2N0-2c; distant control, 93%) and high distant metastasis risk (T3-4N3; distant control, 72%) groups. The distant control rates for HPV+, low-risk N0-2a or <10 pack-year N2b patients were similar for RT alone and CCRT, but the rate was lower in the N2c subset managed by RT alone (73% vs 92% for CCRT; *P*=.02).	2

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26. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363(1):24-35.	Observational-Tx	721 patients	To evaluate the effect of tumor HPV status on survival in patients with OSCC who were enrolled in a clinical trial of sufficient size to account for potentially confounding factors, including smoking status.	The median follow-up period was 4.8 years. The 3-year rate of OS was similar in the group receiving accelerated-fractionation RT and the group receiving standard-fractionation RT (70.3% vs 64.3%; P=0.18; HR for death with accelerated-fractionation RT, 0.90; 95% CI, 0.72 to 1.13), as were the rates of high-grade acute and late toxic events. A total of 63.8% of patients with OSCC (206/323) had HPV-positive tumors; these patients had better 3-year rates of OS (82.4%, vs 57.1% among patients with HPV-negative tumors; P<0.001 by the log-rank test) and, after adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment, had a 58% reduction in the risk of death (HR, 0.42; 95% CI, 0.27 to 0.66). The risk of death significantly increased with each additional pack-year of tobacco smoking. Using recursive-partitioning analysis, we classified our patients as having a low, intermediate, or high risk of death on the basis of 4 factors: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage.	2
27. Holsinger FC, McWhorter AJ, Menard M, Garcia D, Laccourreye O. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: I. Technique, complications, and functional results. *Arch Otolaryngol Head Neck Surg.* 2005;131(7):583-591.	Review/Other-Tx	191 patients	20-year retrospective case series review to describe the surgical technique for transoral lateral oropharyngectomy and its safety, postoperative management, complications, and functional outcomes.	Incidence of significant surgical complications from the oropharynx was 6.3%. Nasopharyngeal reflux and severe rhinolalia were the most common complications. Transoral lateral oropharyngectomy is a safe surgical approach for treating selected carcinoma of the tonsillar fossa. It is a reliable technique that should be considered for treatment of appropriate TSCC.	4
28. Moore EJ, Henstrom DK, Olsen KD, Kasperbauer JL, McGree ME. Transoral resection of tonsillar squamous cell carcinoma. *Laryngoscope.* 2009;119(3):508-515.	Observational-Tx	102 patients	To review oncologic and functional outcomes of patients with tonsillar carcinoma who underwent transoral tumor resection and neck dissection with or without postoperative RT or chemoradiotherapy.	Kaplan-Meier OS estimate was 92.2% at 2 years and 85% at 5 years. The 5-year local control estimate was 91.8%, and the 5-year Kaplan-Meier DSS estimate was 93.9%. Transoral resection of TSCC with or without postoperative adjuvant therapy provided excellent locoregional control and minimized treatment-related morbidity. Authors recommend transoral resection for patients with OSCC.	2

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29. Weinstein GS, Quon H, Newman HJ, et al. Transoral robotic surgery alone for oropharyngeal cancer: an analysis of local control. *Arch Otolaryngol Head Neck Surg.* 2012;138(7):628-634.	Observational-Tx	30 patients	To evaluate local control following transoral robotic surgery with the da Vinci Surgical System (Intuitive Surgical Inc.) as a single treatment modality for OSCC.	Follow-up duration was at least 18 months. At the time of diagnosis, 9 tumors were T1 (30%); 16 were T2 (53%); 4 were T3 (13%); and 1 was T4a (3%). The anatomic sites of these primary tumors were tonsil in 14 (47%), tongue base in 9 (30%), glossotonsillar sulcus in 3 (10%), soft palate in 3 (10%), and OP wall in 1 (3%). There was only 1 patient (3%) who had a positive margin after primary resection; further resection achieved a final negative margin. Perineural invasion was noted in 3 tumors (10%). No patient received postoperative adjuvant therapy. At a mean follow-up of 2.7 years (range, 1.5–5.1 years), there was 1 patient with local failure (3%).	3
30. Harrison LB, Zelefsky MJ, Pfister DG, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue. *Head Neck.* 1997;19(3):169-175.	Review/Other-Tx	36 patients	To evaluate the QoL patients treated with primary RT for cancer of the base of tongue.	Annual incomes were similar to those at initial examination at follow-up. 72% of those working full-time were still in full-time work, and 83% of those working part-time were still in part-time work. Most patients achieved excellent functional status and QoL.	4
31. Horwitz EM, Frazier AJ, Martinez AA, et al. Excellent functional outcome in patients with squamous cell carcinoma of the base of tongue treated with external irradiation and interstitial iodine 125 boost. *Cancer.* 1996;78(5):948-957.	Observational-Tx	20 patients	Analysis of local control, functional outcome, and complications in patients with carcinoma of the base of tongue to assess the impact of interstitial implant boost with I-125 seeds.	2 patients have failed within the tumor bed (T2 and T4) for a 5-year actuarial local control rate of 88%. The T2 patient was salvaged surgically, for an overall 5-year actuarial local control rate of 93%. The 5-year actuarial OS rate was 72%. Patients with cancer of the base of tongue can be treated effectively with an interstitial boost utilizing I-125 seeds.	2
32. Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiother Oncol.* 2007;85(1):64-73.	Observational-Tx	81 patients	Chart review of patients with OP cancers to assess the relationship between the RT dose received by the muscular components of the swallowing apparatus and dysphagia related QoL OP cancer.	Locoregional control of 84%, DFS of 78% and OS of 77% were observed at 3-years. Significant correlation was observed between the mean dose in the superior and middle constrictor muscle, and severe dysphagia complaints (univariate analysis). A steep dose-effect relationship, with an increase of the probability of dysphagia of 19% with every additional 10 Gy, was established. In the multivariate analysis, brachytherapy (dose) was the only significant factor.	2

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33. Pernot M, Hoffstetter S, Peiffert D, et al. Role of interstitial brachytherapy in oral and oropharyngeal carcinoma: reflection of a series of 1344 patients treated at the time of initial presentation. *Otolaryngol Head Neck Surg.* 1996;115(6):519-526.	Observational-Tx	1,344 patients	To examine the role of interstitial brachytherapy in oral and OP carcinoma. Study reports the experience of an institution that has been performing brachytherapy techniques with low-dose iridium 192 for about 20 years.	Authors insist on the efficacy of a brachytherapy boost in the treatment of primary tumors of the oral cavity and the oropharynx, in cases of positive or very narrow margins. These techniques enable delivery of significant doses to limited volumes with, in addition, a safety margin decreasing around the volume treated.	2
34. Petruson K, Mercke C, Lundberg LM, Silander E, Hammerlid E. Longitudinal evaluation of patients with cancer in the oral tongue, tonsils, or base of tongue--does interstitial radiation dose affect quality of life? *Brachytherapy.* 2005;4(4):271-277.	Observational-Tx	90 patients	Prospective longitudinal study to evaluate HRQoL in patients with oral tongue, tonsil, or base of tongue cancer and explore correlations between HRQoL scores and interstitial radiation dose, dose rate, and volume of implant.	HRQoL of all patients decreased during treatment. Most HRQoL scores returned to baseline values after 3 years; however, 60% of patients with oral tongue cancer and 80% with tonsil and base of tongue cancer reported problems with dry mouth and half of the patients with tonsil and base of tongue cancer reported problems with swallowing solid food at the 3-year follow-up. No correlations between brachytherapy quality indices and HRQoL scores were found.	1
35. 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;6:28.	Review/Other-Tx	32 trials with 10,225 patients	To carry out a new analysis using strict inclusion criteria about the addition of chemotherapy to RT and the use of hyperfractionated RT and accelerated RT in locally advanced squamous cell carcinoma of the head and neck.	32 trials with a total of 10,225 patients were included into 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-fluorouracil, 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 hyperfractionated RT compared to conventionally fractionated RT (both without chemotherapy).	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet.* 2006;368(9538):843-854.	Review/Other-Tx	15 trials with 6,515 patients	Meta-analysis was performed to assess whether unconventional fractionated RT in HNSCC could improve survival.	The median follow-up was 6 years. Tumors sites were mostly oropharynx and larynx; 5,221 (74%) patients had stage III-IV disease (International Union Against Cancer, 1987). There was a significant survival benefit with altered fractionated RT, corresponding to an absolute benefit of 3.4% at 5 years (HR 0.92, 95% CI, 0.86-0.97; *P*=0.003). The benefit was significantly higher with hyperfractionated RT (8% at 5 years) than with accelerated RT (2% with accelerated fractionation without total dose reduction and 1.7% with total dose reduction at 5 years, *P*=0.02). There was a benefit on locoregional control in favor of altered fractionation vs conventional RT (6.4% at 5 years; *P*<0.0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced. The benefit was significantly higher in the youngest patients (HR 0.78 [0.65–0.94] for under 50 year olds, 0.95 [0.83–1.09] for 51-60 year olds, 0.92 [0.81–1.06] for 61-70 year olds, and 1.08 [0.89–1.30] for over 70 year olds; test for trends *P*=0.007).	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2014;89(1):13-20.	Experimental-Tx	1,076 patients	To test whether altered radiation fractionation schemes (hyperfractionation, accelerated fractionation, continuous, and accelerated fractionation with split) improved local-regional control rates for patients with HNSCC when compared with standard fractionation of 70 Gy.	With patients censored for local-regional control at 5 years, only the comparison of hyperfractionation with standard fractionation was significantly different: hyperfractionation, HR 0.79 (95% CI, 0.62–1.00), *P*=.05; accelerated fractionation, continuous, 0.82 (95% CI, 0.65–1.05), *P*=.11. With patients censored at 5 years, hyperfractionation improved OS (HR 0.81, *P*=.05). Prevalence of any grade 3, 4, or 5 toxicity at 5 years; any feeding tube use after 180 days; or feeding tube use at 1-year did not differ significantly when the experimental arms were compared with standard fractionation. When 7-week treatments were compared with 6-week treatments, accelerated fractionation appeared to increase grade 3, 4 or 5 toxicity at 5 years (*P*=.06). When the worst toxicity per patient was considered by treatment only, the accelerated fractionation, continuous arm seemed to trend worse than the standard fractionation arm when grade 0-2 was compared with grade 3-5 toxicity (*P*=.09).	1
38. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys.* 2000;48(1):7-16.	Experimental-Tx	1,073 patients	Randomized trial was performed to test the efficacy of hyperfractionation and 2 types of accelerated fractionation individually against standard fractionation.	Patients treated with hyperfractionation and accelerated fractionation with concomitant boost had significantly better local-regional control (*P*=0.045 and *P*=0.050, respectively) than those treated with standard fractionation. There was also a trend toward improved DFS (*P*=0.067 and *P*=0.054, respectively) although the difference in OS was not significant. Patients treated with accelerated fractionation with split had similar outcome to those treated with standard fractionation. All 3 altered fractionation groups had significantly greater acute side effects compared to standard fractionation. However, there was no significant increase of late effects.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Lauve A, Morris M, Schmidt-Ullrich R, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II--clinical results. *Int J Radiat Oncol Biol Phys.* 2004;60(2):374-387.	Experimental-Tx	20 patients	Phase I radiation dose-escalation trial to determine the maximal tolerable dose deliverable to the gross tumor volume using an accelerated fractionation with simultaneous integrated boost IMRT regimen with parotid gland sparing as the sole therapy in the treatment of locally advanced HNSCC.	Dose level 2, 70.8 Gy in 30 fractions of 2.36 Gy, was defined as the maximal tolerable dose deliverable to the gross tumor volume. Adequate parotid sparing was achievable in most cases. Early toxicity, tumor control, and survival rates compared favorably with the outcomes after other accelerated regimens.	2
40. Mell LK, Mehrotra AK, Mundt AJ. Intensity-modulated radiation therapy use in the U.S., 2004. *Cancer.* 2005;104(6):1296-1303.	Review/Other-Tx	368 participants	To evaluate use of IMRT in the U.S. by conducting a survey. A random sample of radiation oncologists in the U.S., including a cohort of 441 physicians who were surveyed in 2002 was surveyed. Differences in responses between 2002 and 2004 were compared.	239 physicians of 368 evaluable participants responded. The proportion of respondents who used IMRT was 73.2% (175 physicians), compared with 32.0% in 2002. The adoption rate of IMRT among nonusers from 2002 to 2004 was 62.7%.	4
41. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys.* 2010;76(5):1333-1338.	Experimental-Tx	69 patients	To assess the results of a multi-institutional study of IMRT for early OP cancer.	At median follow-up for surviving patients (2.8 years), the 2-year estimated local-regional failure rate was 9%. 2/4 patients (50%) with major underdose deviations had local-regional failure compared with 3/49 (6%) without such deviations (P=0.04). All cases of local-regional failure, metastasis, or second primary cancer occurred among patients who were current/former smokers, and none among patients who never smoked. Maximal late toxicities Grade ≥2 were skin 12%, mucosa 24%, salivary 67%, esophagus 19%, osteoradionecrosis 6%. Longer follow-up revealed reduced late toxicity in all categories. Xerostomia Grade ≥2 was observed in 55% of patients at 6 months but reduced to 25% and 16% at 12 and 24 months, respectively. In contrast, salivary output did not recover over time.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Toledano I, Graff P, Serre A, et al. Intensity-modulated radiotherapy in head and neck cancer: results of the prospective study GORTEC 2004-03. *Radiother Oncol.* 2012;103(1):57-62.	Experimental-Tx	208 patients	To evaluate the results of IMRT before its routine use.	The median follow-up was 25.3 months (range: 0.4–72 months). There were 29 local-regional failures: 24 were in-field, 3 were marginal and 1 was out-field. The 2-year loco-regional control and OS were 86% and 86.7%, respectively. At 18 months, grade ≥2 xerostomia was 16.1%. A mean dose to the spared parotid below 28 Gy led to significantly less grade ≥ 2 xerostomia (8.5% vs 24%) with a relative risk of 1.2 [95% CI: 1.02–1.41, *P*=0.03]. Grade ≥2 xerostomia increased by approximately 3% per Gy of mean parotid dose up to 28 Gy then 7% per Gy above 33 Gy.	1
43. Eisbruch A, Ship JA, Dawson LA, et al. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. *World J Surg.* 2003;27(7):832-837.	Review/Other-Tx	15 patients treated with IMRT techniques	To facilitate sparing of the major salivary glands while adequately treating tumor targets in patients requiring comprehensive bilateral neck RT, and to assess the potential for improved xerostomia.	Xerostomia questionnaire scores suggested that xerostomia was significantly reduced in patients irradiated with bilateral neck, parotid-sparing RT, compared to patients with similar tumors treated with standard RT. Examination of locoregional tumor recurrence patterns revealed that the large majority of recurrences occurred inside targets, in areas that had been judged to be at high risk and that had received RT doses according to the perceived risk. Tangible gains in salivary gland sparing and target coverage are being achieved, and an improvement in some measures of QoL is suggested by our findings.	4
44. Lee N, Xia P, Fischbein NJ, Akazawa P, Akazawa C, Quivey JM. Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. *Int J Radiat Oncol Biol Phys.* 2003;57(1):49-60.	Experimental-Tx	150 patients	To examine the University of California-San Francisco (UCSF) experience of using IMRT to treat head-and-neck cancer focusing on the importance of target volume delineation and adequate target volume coverage.	2- and 3-year local freedom from progression rates was 97% and 95%. With a median follow-up of 17 months (range 8 to 56 months), 7 patients failed in the postoperative setting. The 2-year local freedom from progression rate was 83%. For the primary group, the average maximum, mean, and minimum doses delivered were 80 Gy, 74 Gy, 56 Gy to the gross target volume, and 80 Gy, 69 Gy, 33 Gy to the clinical target volume. For the postoperative group, the average maximum, mean, and minimum doses delivered were 79 Gy, 71 Gy, 37 Gy to the gross target volume and 79 Gy, 66 Gy, 21 Gy to the clinical target volume.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Saarilahti K, Kouri M, Collan J, et al. Intensity modulated radiotherapy for head and neck cancer: evidence for preserved salivary gland function. *Radiother Oncol*. 2005;74(3):251-258.	Experimental-Tx	17 patients	To examine the salivary gland function following IMRT for head and neck cancer.	Median basal saliva flow rate measured before RT was 0.13 mL/min, and at 6 and 12 months after the completion of IMRT 0.04 mL/min and 0.07 mL/min, respectively. The corresponding median stimulated saliva flow rates were 0.49 mL/min, 0.33 mL/min, and 0.45 mL, respectively. The D50 for an impaired stimulated parotid gland saliva flow rate was 25.5 Gy. Only 2 (12%) patients developed grade 3 and none grade 4 xerostomia during a median follow-up of 24 months (range, 12–40 months). No patients had locoregional cancer recurrence following IMRT.	1
46. Chao KS, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. *Int J Radiat Oncol Biol Phys*. 2001;49(4):907-916.	Experimental-Tx	41 patients	Prospective study to test the hypothesis that sparing the parotid glands may result in significant objective and subjective improvement of xerostomia in patients with head-and-neck cancers.	Correlation was observed between parotid mean dose and the fractional reduction of stimulated saliva output at 6 months after the completion of RT. Sparing of the parotid glands translates into objective and subjective improvement of both xerostomia and QoL scores in patients with head-and-neck cancers receiving RT. Modeling results suggest an exponential relationship between saliva flow reduction and mean parotid dose for each gland. Stimulated saliva flow at 6 months after treatment is reduced exponentially, for each gland independently, at a rate of approximately 4% per Gy of mean parotid dose.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. 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 nasopharyngeal carcinoma.	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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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol.* 2011;12(2):127-136.	Experimental-Tx	94 patients	To report results of the first multicenter randomized controlled trial to assess parotid-sparing IMRT in patients with HNSCC.	Median follow-up was 44.0 months (IQR 30.0–59.7). 6 patients from each group died before 12 months and 7 patients from the conventional RT and 2 from the IMRT group were not assessed at 12 months. At 12 months xerostomia side-effects were reported in 73/82 alive patients; grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional RT group (25 [74%; 95% CI, 56–87] of 34 patients given conventional RT vs 15 [38%; 23–55] of 39 given IMRT, P=0.0027). The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which was more prevalent in the IMRT group (18 [41%; 99% CI, 23–61] of 44 patients given conventional RT vs 35 [74%; 55–89] of 47 given IMRT, P=0.0015). At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional RT (20 [83%; 95% CI, 63–95] of 24 patients given conventional RT vs 9 [29%; 14–48] of 31 given IMRT; P<0.0001). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional RT, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomized groups in nonxerostomia late toxicities, locoregional control, or OS.	1
49. Gregoire V, De Neve W, Eisbruch A, Lee N, Van den Weyngaert D, Van Gestel D. Intensity-modulated radiation therapy for head and neck carcinoma. *Oncologist.* 2007;12(5):555-564.	Review/Other-Tx	N/A	Review clinical data supporting the use of IMRT for head and neck tumors.	Nonrandomized clinical series in paranasal sinuses and pharyngolaryngeal carcinoma have shown that IMRT was able to achieve a very high rate of locoregional control with less morbidity such as xerostomia.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. *J Clin Oncol.* 2006;24(17):2618-2623.	Review/Other-Tx	N/A	To review the role of IMRT in the standard management of patients with head and neck cancer.	IMRT may result in a dose distribution that is more conformal than that achieved with 3D conformal RT, allowing dose reduction to normal structures and thus decreasing toxicity and possibly enhancing locoregional control through dose escalation.	4
51. Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol.* 2010;28(18):2996-3001.	Observational-Tx	861 patients	To report the impact of RT quality on outcome in a large international phase III trial evaluating RT with concurrent cisplatin plus tirapazamine for advanced head and neck cancer.	At Trial Management Committee review, 25.4% of the patients had noncompliant plans but none in which Quality Assurance Review Center-recommended changes had been made. At secondary review, 47% of noncompliant plans (12% overall) had deficiencies with a predicted major adverse impact on tumor control. Major deficiencies were unrelated to tumor subsite or to T or N stage (if N+), but were highly correlated with number of patients enrolled at the treatment center (<5 patients, 29.8%; ≥20 patients, 5.4%; *P*<.001). In patients who received at least 60 Gy, those with major deficiencies in their treatment plans (n = 87) had a markedly inferior outcome compared with those whose treatment was initially protocol compliant (n = 502): -2 years OS, 50% vs 70%; HR, 1.99; *P*<.001; and 2 years freedom from locoregional failure, 54% vs 78%; HR, 2.37; *P*<.001, respectively.	2
52. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92(1):4-14.	Review/Other-Tx	87 randomized trials (16,485 patients)	Updated individual patient data meta-analysis which includes trials comparing locoregional treatment to locoregional treatment plus chemotherapy in HNSCC patients. Trial was conducted between 1965 and 2000.	The HR of death was 0.88 (*P*<0.0001) with an absolute benefit for chemotherapy of 4.5% at 5 years. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to IC. For the 50 concomitant trials, the HR was 0.81 (*P*<0.0001) and the absolute benefit 6.5% at 5 years. Study concludes that the benefit of concomitant chemotherapy was confirmed and was greater than the benefit of IC.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* 2003;21(1):92-98.	Experimental-Tx	295 patients	Phase III randomized trial to test the benefit of adding chemotherapy to radiation in patients with unresectable HNSCC. Patients were randomly assigned between Arm A (the control), single daily fractionated radiation (70 Gy at 2 Gy/d); Arm B, identical RT with concurrent bolus cisplatin, given on days 1, 22, and 43; Arm C, a split course of single daily fractionated radiation and 3 cycles of concurrent infusional fluorouracil and bolus cisplatin chemotherapy, 30 Gy given with the first cycle and 30 to 40 Gy given with the third cycle.	Grade 3 or worse toxicity occurred in 52% of patients in arm A, compared with 89% in arm B (P<.0001) and 77% in arm C (P<.001). 3-year projected OS for patients enrolled in arm A is 23%, compared with 37% for arm B (P=.014) and 27% for arm C (P=not significant). Addition of concurrent high-dose, single-agent cisplatin to conventional single daily fractionated radiation significantly improves survival, although it also increases toxicity.	1
54. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol.* 2004;22(1):69-76.	Experimental-Tx	226 patients	To report the 5-year survival and late toxicity results of a randomized clinical trial, which showed a 3-year improvement in OS and locoregional control of stage III or IV oropharynx carcinoma, using concomitant radiochemotherapy (arm B), compared with standard RT (arm A).	5-year OS, specific DFS, and locoregional control rates were 22% and 16% (log-rank P=.05), 27% and 15% (P=.01), and 48% and 25% (P=.002), in arm B and arm A, respectively. Stage IV, hemoglobin level lower than 125 g/L, and standard treatment were independent prognostic factors of short survival and locoregional failure by univariate and multivariate analysis. One or more grade 3 to 4 complications occurred in 56% of the patients in arm B, compared with 30% in arm A (P was not significant).	1
55. Rodriguez CP, Adelstein DJ, Rybicki LA, et al. Randomized phase III study of 2 cisplatin-based chemoradiation regimens in locally advanced head and neck squamous cell carcinoma: Impact of changing disease epidemiology on contemporary trial design. *Head Neck.* 2014:[E-pub ahead of print].	Experimental-Tx	69 patients	To compare the authors' institutional chemoradiotherapy regimen to the well-established standard of concurrent single-agent cisplatin and radiation.	Between February 2008 and October 2011, 69 patients were enrolled in this study. The study prematurely closed when a scheduled interim analysis showed superior outcomes in both arms and futility of continuation. 83% of patients had OP cancer, of these, 86% were HPV/p16+. The 3-year Kaplan-Meier outcome estimates (median follow-up, 41 months) for arms A and B were: relapse-free survival 87% vs 80% (P=.24), OS 97% vs 85% (P=.013), locoregional control 96% vs 94% (P=.52), and distant metastatic control 91% vs 87% (P=.9).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *Int J Radiat Oncol Biol Phys.* 2011;81(3):719-725.	Experimental-Tx	308 patients	Phase III randomized trial to determine whether the addition weekly cisplatin to daily RT would improve survival in patients with unresectable HNSCC.	Median follow-up was 62 months. The median failure-free survival was 6.5 and 7.2 months for the RT and RT + cisplatin groups, respectively (P=0.30). The p value for the treatment difference was P=0.096 in multivariate modeling of failure-free survival (compared to a P=0.30 in univariate analysis). Expected acute toxicities were significantly increased with the addition of cisplatin except for in-field RT toxicities. Late toxicities were not significantly different except for significantly more esophageal (9% vs 3%, P=0.03) and laryngeal (11% vs 4%, P=0.05) late toxicities in the RT + cisplatin group.	1
57. 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 nasopharyngeal carcinoma.	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
58. Chen Y, Liu MZ, Liang SB, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. *Int J Radiat Oncol Biol Phys.* 2008;71(5):1356-1364.	Experimental-Tx	316 patients	Prospective randomized phase III trial to evaluate the efficacy of concurrent chemotherapy and adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. Patients were randomly assigned to receive either RT alone or chemoradiotherapy concurrent with adjuvant chemotherapy.	CCRT group had more acute toxicity (62.6% vs 32%, *P*=0.000). 2-year OS rate, failure-free survival rate, distant failure-free survival rate, and locoregional failure-free survival rate for the CCRT and RT groups were 89.8% vs 79.7% (*P*=0.003), 84.6% vs 72.5% (*P*=0.001), 86.5% vs 78.7% (*P*=0.024), and 98.0% vs 91.9% (*P*=0.007), respectively.	1
59. Uygun K, Bilici A, Karagol H, et al. The comparison of weekly and three-weekly cisplatin chemotherapy concurrent with radiotherapy in patients with previously untreated inoperable non-metastatic squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol.* 2009;64(3):601-605.	Experimental-Tx	50 patients	To compare the efficacy and safety profile of RT and concurrent cisplatin chemotherapy given in 2 different schedules to patients with previously untreated inoperable nonmetastatic HNSCC. 30/50 (60%) patients received cisplatin 100 mg/m(2) on a 21-day schedule (group A). 20 (40%) patients received cisplatin 40 mg/m(2) on a 7-day schedule (group B).	Complete response rate was 50% in group A and 40% in group B (*P*>0.05). The objective response rate was 92% in group A and 90% in group B (*P*>0.05). All grade 3-4 toxic events were seen in 16 (53.3%) of group A patients and 8 (40%) of group B patients (*P*>0.05). Similar response rates and adverse event profile for 2 groups. Randomized phase III trial required.	1
60. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. *Acta Oncol.* 2008;47(8):1513-1518.	Observational-Tx	51 patients	Retrospective comparison to describe the differences in dose intensity, delays and toxicity between weekly cisplatin and 3-weekly cisplatin given concurrently to patients with locally advanced HNSCC.	Delivery of 100 mg/m(2) cisplatin 3-weekly with RT was less tolerated than 40 mg/m(2) weekly and resulted in less patients achieving cumulative dose beyond 200 mg/m(2), potentially lowering chemotherapy dose intensity.	2
61. Rades D, Fehlauer F, Sheikh-Sarraf M, et al. Toxicity of two cisplatin-based radiochemotherapy regimens for the treatment of patients with stage III/IV head and neck cancer. *Head Neck.* 2008;30(2):235-241.	Observational-Tx	128 patients	To compare 2 radiochemotherapy regimens for toxicity in patients with stage III/IV head and neck cancer. Patients received conventionally fractionated RT. Concurrent chemotherapy consisted of 3 courses cisplatin (group A) or 2 courses cisplatin (group B).	Acute toxicity was more severe in group A, especially nausea/vomiting (*P*=.002), nephrotoxicity (*P*=.001), ototoxicity (*P*=.034), and hematotoxicity (*P*=.049). 48% of group A and 10% of group B patients could not complete chemotherapy due to toxicity (*P*=.018). Late toxicity was similar (*P*=.99).	2
62. Beckmann GK, Hoppe F, Pfreundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. *Head Neck.* 2005;27(1):36-43.	Experimental-Tx	37 patients	To determine the feasibility and efficacy of hyperfractionated accelerated RT combined with simultaneous chemotherapy with weekly cisplatin in locally advanced inoperable head and neck cancer. Patients were treated in a prospective phase I/II trial.	2-year OS rate was 67%. Median OS and relapse-free survival times were 36 and 31 months, respectively. Hyperfractionated accelerated RT in combination with weekly cisplatin achieves a high rate of locoregional control and survival. 4 weekly cycles of 40 mg/m(2) cisplatin seem to be the dose limit for most patients.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Steinmann D, Cerny B, Karstens JH, Bremer M. Chemoradiotherapy with weekly cisplatin 40 mg/m(2) in 103 head-and-neck cancer patients: a cumulative dose-effect analysis. *Strahlenther Onkol.* 2009;185(10):682-688.	Observational-Tx	103 patients	Retrospective analysis of patients with HNSCC to examine feasibility and efficacy of a weekly cisplatin 40 mg/m(2) regimen.	12- and 18-month OS for patients with and without cumulative cisplatin dose of 200 mg/m(2) was 83.3% vs 72.1% (*P*=0.19) and 66.7% vs 67.2% (*P*=0.86), the 12- and 18-month locoregional control 66.7% vs 78.7% (*P*=0.325) and 59.5% vs 78.7% (*P*=0.109), respectively. Feasibility and efficacy of chemoradiotherapy with weekly cisplatin 40 mg/m(2) were suboptimal.	2
64. Traynor AM, Richards GM, Hartig GK, et al. Comprehensive IMRT plus weekly cisplatin for advanced head and neck cancer: the University of Wisconsin experience. *Head Neck.* 2010;32(5):599-606.	Observational-Tx	57 patients	To retrospectively examine the treatment efficacy and toxicity profile of IMRT plus concurrent weekly cisplatin chemotherapy in patients with locoregionally advanced HNSCC.	In-field tumor control at 2 years was 89.1%, locoregional control was 85.5%, and OS was 86.9%. The median radiation dose delivered was 70 Gy. The mean dose intensity of cisplatin administered was 25.7 mg/m(2)/week.	2
65. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol.* 2012;13(2):145-153.	Experimental-Tx	279 patients randomized to receive conventional chemoradiotherapy, 280 to accelerated RT-chemotherapy, and 281 to very accelerated RT	To assess the efficacy and safety of a combination of concomitant chemoradiotherapy and accelerated RT in patients with locally HNSCC.	Median follow-up was 5.2 years (IQR 4.9-6.2); rates of chemotherapy and RT compliance were good in all groups. Accelerated RT-chemotherapy offered no PFS benefit compared with conventional chemoradiotherapy (HR 1.02, 95% CI, 0.84–1.23; *P*=0.88) or very accelerated RT (0.83, 0.69–1.01; *P*=0.060); conventional chemoradiotherapy improved PFS compared with very accelerated RT (0.82, 0.67–0.99; *P*=0.041). 3-year PFS was 37.6% (95% CI, 32.1–43.4) after conventional chemoradiotherapy, 34.1% (28.7–39.8) after accelerated RT-chemotherapy, and 32.2% (27.0–37.9) after very accelerated RT. More patients in the very accelerated RT group had RTOG grade 3-4 acute mucosal toxicity (226 [84%] of 268 patients) compared with accelerated RT-chemotherapy (205 [76%] of 271 patients) or conventional chemoradiotherapy (180 [69%] of 262; *P*=0.0001). 158 (60%) of 265 patients in the conventional chemoradiotherapy group, 176 (64%) of 276 patients in the accelerated RT-chemotherapy group, and 190 (70%) of 272 patients in the very accelerated RT group were intubated with feeding tubes during treatment (*P*=0.045).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: altered fractionation regimens. *Lancet Oncol.* 2002;3(11):693-701.	Review/Other-Tx	N/A	Review results of clinical trials of various types of altered fractionation schedules in head and neck carcinomas.	Clinical investigations reveal improvement in locoregional disease control and consistent gain in survival have been achieved with combinations of RT and concurrent chemotherapy in patients with mostly stage IV carcinomas. Further data is needed before the combination of altered fractionation with chemotherapy can be recommended outside of a study setting.	4
67. Moreno-Jimenez M, Valero J, Lopez-Picazo JM, et al. Concomitant cisplatin, paclitaxel, and hyperfractionated radiotherapy in locally advanced head and neck cancer: comparison of two different schedules. *Am J Clin Oncol.* 2010;33(2):137-143.	Experimental-Tx	42 patients	To determine feasibility and efficacy of concurrent paclitaxel and cisplatin with definitive hyperfractionated RT in locally advanced HNSCC. Patients were enrolled in 2 consecutive prospective trials.	Overall, 93% of objective responses were observed (complete 76%, partial 17%). Pattern of recurrence was local 8%, distant 13%, and combined 3%. Acute toxicity grades 3 to 4 in studies 1 and 2 was 75% and 88%, respectively (P=ns). Globally, 5-year OS was 68%, with a median of 71 months (range: 50–91). Hyperfractionated RT combined with cisplatin and paclitaxel is very active but at the expense of severe toxicity.	1
68. Semrau R, Mueller RP, Stuetzer H, et al. Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: updated results of a randomized multicentric trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2006;64(5):1308-1316.	Experimental-Tx	240 patients	To prove an expected benefit of concurrent radiochemotherapy, a two-arm randomized multicentric study was performed. In a subgroup analysis the influence of pretherapeutical hemoglobin level on survival under locoregional control was tested.	After a median follow-up concurrent radiochemotherapy of 57 months, survival under locoregional control is significantly better in concurrent radiochemotherapy than in RT (P=0.01), with median survival under locoregional control of 17 months and 11 months, respectively. Also OS shows a benefit for concurrent radiochemotherapy (P=0.016), with a median survival of 23 months for concurrent radiochemotherapy and 16 months for RT. However, the benefit in survival under locoregional control and OS is not seen in hypopharyngeal carcinomas. In a multivariate analysis of OP cancer patients, pretherapeutical hemoglobin level levels lower than 12.7 g/dL resulted in lower survival under locoregional control compared with higher pretherapeutical hemoglobin level levels up to 13.8 g/dL. pretherapeutical hemoglobin level levels >13.8 g/dL did not further improve survival under locoregional control.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* 2010;11(1):21-28.	Experimental-Tx	424 patients	Report a 5-year survival data from a phase III randomized trial and investigate the relation between cetuximab-induced rash and survival. Patients with locoregionally advanced HNSCC of the oropharynx, hypopharynx, or larynx were randomized to receive either head and neck RT alone or RT plus weekly doses of cetuximab.	Updated median OS for patients treated with cetuximab and RT was 49 months (95% CI 32.8–69.5) vs 29.3 months (20.6–41.4) in the RT-alone group. 5-year OS was 45.6% in the cetuximab-plus-RT group and 36.4% in the RT-alone group. For patients with locoregionally advanced HNSCC, cetuximab plus RT improves OS at 5 years compared with RT alone. Cetuximab-treated patients with prominent cetuximab-induced rash (grade 2 or above) have better survival than patients with no or grade 1 rash.	1
70. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567-578.	Experimental-Tx	424 patients	Randomized multicenter phase III trial to compare RT alone with RT plus cetuximab in the treatment of locoregionally advanced HNSCC.	Median duration of OS was 49.0 months among patients treated with combined therapy and 29.3 months among those treated with RT alone (HR for death, 0.74; P=0.03). RT plus cetuximab significantly prolonged PFS. With the exception of acneiform rash and infusion reactions, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the 2 groups.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol.* 2014;32(27):2940-2950.	Experimental-Tx	891 patients	Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma.	Of 891 analyzed patients, 630 were alive at analysis (median follow-up, 3.8 years). Cetuximab plus cisplatin-radiation, vs cisplatin-radiation alone, resulted in more frequent interruptions in RT (26.9% vs 15.1%, respectively); similar cisplatin delivery (mean, 185.7 mg/m2 vs 191.1 mg/m2, respectively); and more grade 3 to 4 radiation mucositis (43.2% vs 33.3%, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity. No differences were found between arms A and B in 30-day mortality (1.8% vs 2.0%, respectively; *P*=.81), 3-year PFS (61.2% vs 58.9%, respectively; *P*=.76), 3-year OS (72.9% vs 75.8%, respectively; *P*=.32), locoregional failure (19.9% vs 25.9%, respectively; *P*=.97), or distant metastasis (13.0% vs 9.7%, respectively; *P*=.08). Patients with p16-positive OP carcinoma, compared with patients with p16-negative OP carcinoma, had better 3-year probability of PFS (72.8% vs 49.2%, respectively; *P*<.001) and OS (85.6% vs 60.1%, respectively; *P*<.001), but tumor epidermal growth factor receptor expression did not distinguish outcome.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol.* 2014;32(23):2486-2495.	Experimental-Tx	238 patients	To report results of a randomized phase II trial (RTOG-0234) examining CCRT and cetuximab in the postoperative treatment of patients with squamous cell carcinoma of the head and neck with high-risk pathologic features.	With a median follow-up of 4.4 years, 2-year OS was 69% for the cisplatin arm and 79% for the docetaxel arm; 2-year DFS was 57% and 66%, respectively. Patients with p16-positive oropharynx tumors showed markedly improved survival outcome relative to patients with p16-negative oropharynx tumors. Grade 3 to 4 myelosuppression was observed in 28% of patients in the cisplatin arm and 14% in the docetaxel arm; mucositis was observed in 56% and 54%, respectively. DFS in this study was compared with that in the chemoradiotherapy arm of the RTOG-9501 trial (Phase III Intergroup Trial of Surgery Followed by Radiotherapy Versus Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck), which had a HR of 0.76 for the cisplatin arm versus control (P=.05) and 0.69 for the docetaxel arm vs control (P=.01), reflecting absolute improvement in 2-year DFS of 2.5% and 11.1%, respectively.	1
73. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357(17):1705-1715.	Experimental-Tx	501 patients	Randomized multicenter phase III trial to compare 3 cycles of cisplatin and fluorouracil plus docetaxel IC with 3 cycles of cisplatin and fluorouracil IC; both regimens were followed by 7 weeks of chemoradiotherapy.	More patients survived in the cisplatin and fluorouracil plus docetaxel group than in the cisplatin and fluorouracil group. Estimates of OS at 3 years were 62% in the cisplatin and fluorouracil plus docetaxel group and 48% in the cisplatin and fluorouracil group; the median OS was 71 months and 30 months, respectively (P=0.006).	1
74. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357(17):1695-1704.	Experimental-Tx	358 patients	Randomized multicenter phase III trial to compare cisplatin and fluorouracil plus docetaxel with cisplatin and fluorouracil as IC in patients with locoregionally advanced, unresectable disease.	Median PFS was 11.0 months in the cisplatin and fluorouracil plus docetaxel group and 8.2 months in the cisplatin and fluorouracil group (HR for disease progression or death in the cisplatin and fluorouracil plus docetaxel group, 0.72; P=0.007). Treatment with cisplatin and fluorouracil plus docetaxel resulted in a reduction in the risk of death of 27% (P=0.02), with a median OS of 18.8 months, as compared with 14.5 months in the cisplatin and fluorouracil group.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
75. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst.* 2009;101(7):498-506.	Experimental-Tx	213 patients	To determine whether adding docetaxel to chemotherapy with cisplatin and 5-fluorouracil could increase the larynx preservation rate.	Baseline patient and tumor characteristics were well balanced between the docetaxel with cisplatin and fluorouracil (n = 110) and cisplatin and fluorouracil (n = 103) groups. With a median follow-up of 36 months, the 3-year actuarial larynx preservation rate was 70.3% with docetaxel with cisplatin and fluorouracil vs 57.5% with cisplatin and fluorouracil (difference = 12.8%; *P*=.03). Patients in the docetaxel with cisplatin and fluorouracil group had more grade 2 alopecia, grade 4 neutropenia, and febrile neutropenia, whereas patients in the cisplatin and fluorouracil group had more grade 3 and 4 stomatitis, thrombocytopenia, and grade 4 creatinine elevation. The overall response was 80.0% in the docetaxel with cisplatin and fluorouracil group vs 59.2% in the cisplatin and fluorouracil group (difference = 20.8%; *P*=.002).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
76. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol.* 2005;23(34):8636-8645.	Experimental-Tx	382 patients	To compare the antitumor activity and toxicity of the 2 IC treatments of paclitaxel, cisplatin, and fluorouracil vs standard cisplatin and FU, both followed by chemoradiotherapy, in locally advanced HNSCC.	382 eligible patients were randomly assigned to cisplatin and fluorouracil (n = 193) or paclitaxel, cisplatin, and fluorouracil (n = 189). The complete response rate was 14% in the cisplatin and fluorouracil arm vs 33% in the paclitaxel, cisplatin, and fluorouracil arm (P<.001). Median time to treatment failure was 12 months in the cisplatin and fluorouracil arm compared with 20 months in the paclitaxel, cisplatin, and fluorouracil arm (log-rank test, P=.006; Tarone-Ware, P=.003). Paclitaxel, cisplatin, and fluorouracil patients had a trend to longer OS (37 months in cisplatin and fluorouracil arm vs 43 months in paclitaxel, cisplatin, and fluorouracil arm; log-rank test, P=.06; Tarone-Ware, P=.03). This difference was more evident in patients with unresectable disease (OS: 26 months in cisplatin and fluorouracil arm vs 36 months in paclitaxel, cisplatin, and fluorouracil arm; log-rank test, P=.04; Tarone-Ware, P=.03). Cisplatin and fluorouracil patients had a higher occurrence of grade 2 to 4 mucositis than paclitaxel, cisplatin, and fluorouracil patients (53% vs 16%, respectively; P<.001).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Blanchard P, Bourhis J, Lacas B, et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. *J Clin Oncol.* 2013;31(23):2854-2860.	Review/Other-Tx	5 randomize control trials representing 1,772 patients	To study the efficacy and toxicity of taxane-cisplatin-fluorouracil and cisplatin and fluorouracil and identify differences in outcomes in subsets of patients.	Median follow-up was 4.9 years. The HR of death was 0.79 (95% CI, 0.70 to 0.89; *P*<.001; absolute benefit at 5 years: 7.4%) in favor of taxane-cisplatin-fluorouracil. Heterogeneity was significant (*P*=.08, I(2) = 51%) and related to 1 trial. There was no more heterogeneity after exclusion of this trial (*P*=.99, I(2) = 0%), and HR of death was 0.72 (95% CI, 0.63 to 0.83) in favor of taxane-cisplatin-fluorouracil. There was no interaction between treatment effect and the following patient covariates: age, sex, performance status, tumor stage, or site. Taxane-cisplatin-fluorouracil was associated with significant reductions of progression, locoregional failure, and distant failure compared with cisplatin and fluorouracil, with HRs of 0.78 (95% CI, 0.69 to 0.87; *P*<.001), 0.79 (95% CI, 0.66 to 0.94; *P*=.007), and 0.63 (95% CI, 0.45 to 0.89; *P*=.009) respectively.	4
78. Beitler JJ, Cooper JS. Seduction by induction? *J Clin Oncol.* 2009;27(1):9-10.	Review/Other-Tx	N/A	To review the value of induction therapy.	Induction therapy is an intriguing concept that currently needs to be explored in well-conducted prospective clinical trials.	4
79. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol.* 2014;32(25):2735-2743.	Experimental-Tx	285 patients	To determine whether IC before CRT further improves survival compared with CRT alone in patients with N2 or N3 disease.	The most common grade 3 to 4 toxicities during IC were febrile neutropenia (11%) and mucositis (9%); during CRT (both arms combined), they were mucositis (49%), dermatitis (21%), and leukopenia (18%). Serious adverse events were more common in the IC arm (47% vs 28%; *P*=.002). With a minimum follow-up of 30 months, there were no statistically significant differences in OS (HR, 0.91; 95% CI, 0.59 to 1.41), relapse-free survival, or DFS.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
80. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(3):257-264.	Experimental-Tx	145 patients	To compare 2 different treatments: IC followed by CCRT vs CCRT alone in patients with locally advanced, previously untreated, head and neck cancer.	145 patients were enrolled across 16 sites. After a median follow-up of 49 months (IQR 39–63), 41 patients had died-20 in the IC followed by chemoradiotherapy group and 21 in the chemoradiotherapy alone group. 3-year OS was 73% (95% CI, 60-82) in the induction therapy followed by chemoradiotherapy group and 78% (66-86) in the chemoradiotherapy alone group (HR 1.09, 95% CI 0.59–2.03; *P*=0.77). More patients had febrile neutropenia in the IC followed by chemoradiotherapy group (16 patients) than in the chemoradiotherapy alone group (1 patient).	1
81. Hitt R, Grau JJ, Lopez-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol.* 2014;25(1):216-225.	Experimental-Tx	439 patients	Randomized, open-label, phase III clinical trial to compare the efficacy between standard CCRT and 2 different IC regimens followed by CCRT.	In the intention-to-treat population (n = 439), the median PFS times were 14.6 (95% CI, 11.6–20.4), 14.3 (95% CI, 11.8–19.3) and 13.8 months (95% CI, 11.0–17.5) at docetaxel, cisplatin, and fluorouracil-CCRT, cisplatin and fluorouracil-CCRT and CCRT arms, respectively (log-rank *P*=0.56). The median time-to-treatment failure were 7.9 (95% CI, 5.9–11.8), 7.9 (95% CI, 6.5-11.8) and 8.2 months (95% CI, 6.7–12.6) for docetaxel, cisplatin, and fluorouracil-CCRT cisplatin and fluorouracil-CCRT and CCRT alone, respectively (log-rank *P*=0.90). There were no statistically significant differences for OS. Toxic effects from IC-CCRT were manageable.	1
82. Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. *Ann Oncol.* 2010;21(7):1515-1522.	Experimental-Tx	101 patients	To evaluate the efficacy of induction docetaxel, cisplatin, and fluorouracil before chemoradiotherapy vs chemoradiotherapy alone.	A total of 101 patients were randomly allocated to the study (51, arm A; 50, arm B). Complete response rates were 21.2% (arm A) vs 50% (arm B). Median PFS and OS were, respectively, 19.7 and 33.3 months (arm A) and 30.4 and 39.6 months (arm B). Hematologic and non-hematologic toxic effects during chemoradiotherapy were similar in the 2 arms.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
83. Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC. Carcinoma of the tongue base treated by transoral laser microsurgery, part one: Untreated tumors, a prospective analysis of oncologic and functional outcomes. *Laryngoscope.* 2006;116(12):2150-2155.	Observational-Tx	59 patients	Two center prospective case series analysis to report the oncologic and functional outcomes of TLM in the management of untreated primary carcinoma of the tongue base.	The 2 and 5-year Kaplan-Meier estimates were: local control, both 90%; locoregional control, both 88%; recurrence free survival, both 84% and OS 91% and 69% respectively.	3
84. Laccourreye O, Hans S, Menard M, Garcia D, Brasnu D, Holsinger FC. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. *Arch Otolaryngol Head Neck Surg.* 2005;131(7):592-599.	Observational-Tx	166 patients	Retrospective case series to determine the incidence of local and regional failure, distant metastasis, and OS following TLO and to determine factors associated with local recurrence.	The 1- and 5-year Kaplan-Meier local control estimates were 91.2% and 82.1%, respectively. The 1- and 5-year Kaplan-Meier local control estimates were 98.3% and 89.0% for T1, 88.9% and 81.7% for T2, and 78.9% and 62.7% for T3 lesions, respectively (P=.02). The 1-, 3-, and 5-year Kaplan-Meier survival estimates were 87.9%, 67.2%, and 57.7%, respectively. The Kaplan-Meier survival estimate was significantly reduced (P=.009) in patients with local failure.	2
85. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg.* 2003;129(1):36-43.	Observational-Tx	48 patients	Retrospective study to determine the role of TLM for base of tongue squamous cell carcinoma.	No local recurrence in T1 and T2 lesions, but there was a 20% local recurrence rate in T3 and T4 tumors. Kaplan-Meier 5-year recurrence-free and OS rates were 73% and 52%, respectively.	2
86. Weinstein GS, O'Malley BW, Jr., Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. *Arch Otolaryngol Head Neck Surg.* 2007;133(12):1220-1226.	Review/Other-Tx	27 patients	Prospective phase 1 clinical trial to describe and show the feasibility of a new surgical technique for transoral robotic surgery radical tonsillectomy.	Final margins negative for cancer were achieved in 25/27 patients (93%). Surgical complications included 1 case each of postoperative mucosal bleeding, delirium tremens, unplanned tracheotomy for temporary exacerbation of sleep apnea, and hypernasality and 2 cases of moderate trismus. 26/27 patients (96%) were swallowing without the use of a gastrostomy. Radical tonsillectomy using transoral robotic surgery is a new technique that offers excellent access for resection of carcinomas of the tonsil with acceptable acute morbidity.	4
87. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys.* 1993;26(1):3-11.	Experimental-Tx	302 patients	Prospective randomized trial to determine the optimal dose of conventionally fractionated postoperative RT for advanced head and neck cancer in relation to clinical and pathologic risk factors.	Overall crude and actuarial 2-year local-regional recurrence rates were 25.4% and 26%, respectively. Patients who received a dose of ≤54 Gy had a significantly higher primary failure rate than those receiving ≥57.6 Gy (P=0.02).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
88. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.	Experimental-Tx	334 patients	Randomized study to compare concomitant cisplatin and irradiation with RT alone as adjuvant treatment for stage III or IV head and neck cancer.	After a median follow-up of 60 months, the rate of PFS was significantly higher in the combined-therapy group than in the group given RT alone, with 5-year Kaplan-Meier estimates of PFS of 47% and 36%, respectively. The OS rate was also significantly higher in the combined-therapy group than in the RT group, with 5-year Kaplan-Meier estimates of OS of 53% and 40%, respectively.	1
89. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.	Experimental-Tx	459 patients; 231 randomized to receive RT alone and 228 to receive the identical treatment plus concurrent cisplatin	To test the hypothesis that concurrent postoperative administration of cisplatin and RT would improve the rate of local and regional control.	After a median follow-up of 45.9 months, the rate of local and regional control was significantly higher in the combined-therapy group than in the group given radiotherapy alone (hazard ratio for local or regional recurrence, 0.61; 95 percent confidence interval, 0.41 to 0.91; P=0.01). The estimated two-year rate of local and regional control was 82 percent in the combined-therapy group, as compared with 72 percent in the radiotherapy group. Disease-free survival was significantly longer in the combined-therapy group than in the radiotherapy group (hazard ratio for disease or death, 0.78; 95 percent confidence interval, 0.61 to 0.99; P=0.04), but overall survival was not (hazard ratio for death, 0.84; 95 percent confidence interval, 0.65 to 1.09; P=0.19). The incidence of acute adverse effects of grade 3 or greater was 34 percent in the radiotherapy group and 77 percent in the combined-therapy group (P<0.001). Four patients who received combined therapy died as a direct result of the treatment.	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
90. Marur S, Li S, Cmelak A, et al. E 1308: A phase II trial of induction chemotherapy (IC) followed by cetuximab with low dose versus standard dose IMRT in patients with human papilloma virus (HPV)-associated resectable squamous cell carcinoma of the oropharynx (OPSCC). *J Clin Oncol.* 2013;31:(suppl; abstr 6005).	Experimental-Tx	90 patients	A phase II trial of IC followed by cetuximab with low dose vs standard dose IMRT in patients with HPV-associated resectable OSCC.	From March 2010 to Oct 2011, 90 patients were enrolled (80 analyzable). Nodal stage: 39%–N2B, 29%–N2C, T stage: 23%–T1, 50%–T2, 16%–T3, 10%–T4. 96% received all 3 cycles of IC. Grade 3/4 toxicities included: rash (25%), neutropenia (11%). During chemoradiotherapy: oral mucositis (31%), dysphagia (17%), and radiation dermatitis (8%). Response: Biopsy at primary site post-baseline measurements rendered 7/80 patients unevaluable, 6/7 had investigator-reported chemoradiotherapy to IC. The centrally reviewed and investigator reported primary site chemoradiotherapy rate to IC was 63.8% (95% CI: 52.2%, 74.2%) and 71.3% (95% CI: 60.0%, 80.8%), respectively. Radiation: 73.8% (59/80 patients) received low dose IMRT/C to primary [54Gy (56), 52Gy (1), 40Gy (2)]. Best overall clinical response was 86% with 14% unevaluable. Rate of post-treatment neck dissection in low dose vs other RT group is 13.4% vs 22.2% (P=0.46), respectively. Median follow up is 11.8 months.	1

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

CCRT = Concurrent chemoradiotherapy

CI = Confidence interval

DFS = Disease-free survival

DSS = Disease-specific survival

HNSCC = Head and neck squamous cell carcinoma

HPV = Human papillomavirus

HR = Hazard ratio

HRQoL = Health-related quality of life

IC = Induction chemotherapy

IMRT = Intensity-modulated radiation therapy

OP = Oropharyngeal

OS = Overall survival

OSCC = Oropharyngeal squamous cell carcinoma

PFS = Progression-free survival

RT = Radiation therapy

TLM = Transoral laser microsurgery

TSCC = Tonsillar squamous cell carcinomas