Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol.* 2013;31(7):845-852.	Experimental-Tx	520 patients	To report the long-term results of the Intergroup Radiation Therapy Oncology Group 91-11 study evaluating the contribution of chemotherapy added to radiation therapy (RT) for larynx preservation.	Median follow-up for surviving patients is 10.8 years. Both chemotherapy regimens significantly improved laryngectomy-free survival compared with RT alone (induction chemotherapy vs RT alone: HR, 0.75; 95% CI, 0.59 to 0.95; P=.02; concomitant chemotherapy vs RT alone: HR, 0.78; 95% CI, 0.78 to 0.98; P=.03). OS did not differ significantly, although there was a possibility of worse outcome with concomitant relative to induction chemotherapy (HR, 1.25; 95% CI, 0.98 to 1.61; P=.08). Concomitant cisplatin/RT significantly improved the larynx preservation rate over induction cisplatin/fluorouracil followed by RT (HR, 0.58; 95% CI, 0.37 to 0.89; P=.0050) and over RT alone (P<.001), whereas induction cisplatin/fluorouracil followed by RT was not better than treatment with RT alone (HR, 1.26; 95% CI, 0.88 to 1.82; P=.35). No difference in late effects was detected, but deaths not attributed to larynx cancer or treatment was higher with concomitant chemotherapy (30.8% vs 20.8% with induction chemotherapy and 16.9% with RT alone).	1
2. 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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
3. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1198-1205.	Experimental-Tx	410 patients	To look at the long-term outcome of RTOG 9501.	At 10 years, the local-regional failure rates were 28.8% vs 22.3% (P=.10), DFS was 19.1% vs 20.1% (P=.25), and OS was 27.0% vs 29.1% (P=.31) for patients treated by RT vs RT + chemotherapy, respectively. In the unplanned subset analysis limited to patients who had microscopically involved resection margins and/or extracapsular spread of disease, local-regional failure occurred in 33.1% vs 21.0% (P=.02), DFS was 12.3% vs 18.4% (P=.05), and OS was 19.6% vs 27.1% (P=.07), respectively.	1
4. 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	Phase III multicenter randomized trial comparing RT alone with concomitant radiochemotherapy in advanced stage oropharynx carcinoma.	5-year OS, specific DFS, and LR 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 LR 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
5. Brockstein B, Haraf DJ, Rademaker AW, et al. Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multi-institutional experience. *Ann Oncol.* 2004;15(8):1179-1186.	Review/Other-Tx	337 patients	Prospective, multicenter phase II trial to assess changes in patterns of failure, prognostic factors for recurrence, and overall outcome, using two different strategies of chemoradiotherapy.	The pattern of failure varied greatly between study types 1 and 2 (5-year LR failure of 31% and 17% for study types 1 and 2, respectively, P=0.01; 5-year distant failure rate of 13% and 22% for study types 1 and 2, P=0.03). Combined 5-year OS was 47% and PFS was 60%. Both treatment strategies yielded similar survival rates. Poor OS and distant recurrence were best predicted by advanced nodal stage. Randomized trials of induction chemotherapy needed.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Suwinski R, Jaworska M, Nikiel B, et al. Predicting the effect of accelerated fractionation in postoperative radiotherapy for head and neck cancer based on molecular marker profiles: data from a randomized clinical trial. *Int J Radiat Oncol Biol Phys.* 2010;77(2):438-446.	Review/Other-Tx	148 patients	To determine the prognostic and predictive values of molecular marker expression profiles based on data from a randomized clinical trial of postoperative conventional fractionation therapy vs 7-day-per-week postoperative continuous accelerated irradiation therapy for HNSCC.	Patients who had tumors with low Ki-67, low p-53, and high EGFR expression levels and oral cavity/oropharyngeal primary cancer sites tended to benefit from postoperative continuous accelerated irradiation. A joint score for the gain in locoregional tumor control from postoperative continuous accelerated irradiation based of these features was used to separate the patients into 2 groups: those who benefited significantly from postoperative continuous accelerated irradiation with respect to locoregional tumor control (n = 49 patients; 5-year locoregional tumor control of 28% vs 68%; P=0.01) and those who did not benefit from postoperative continuous accelerated irradiation (n = 99 patients; 5-year locoregional tumor control of 72% vs 66%; P=0.38). The nm23 expression level appeared useful as a prognostic factor but not as a predictor of fractionation effect.	4
7. Hedman M, Bjork-Eriksson T, Mercke C, West C, Hesselius P, Brodin O. Comparison of predicted and clinical response to radiotherapy: a radiobiology modelling study. *Acta Oncol.* 2009;48(4):584-590.	Observational-Tx	46 patients	To evaluate the value of a model that incorporates the following individually measured radiobiology parameters: intrinsic radiosensitivity, proliferation and number of clonogenic cells. The hypothesis underlying the study was that the incorporation of individually measured tumor parameters in a model would increase its reliability in predicting treatment outcome compared with the use of average population derived data.	4/18 patients had a >95% calculated probability of cure and none developed a local recurrence resulting in a NPV of 100% (compared with 67% for population-derived data). The sensitivity of the model in predicting local recurrence was 75% (compared with 38% for population-derived data).	2
8. Kao J, Genden EM, Chen CT, et al. Phase 1 trial of concurrent erlotinib, celecoxib, and reirradiation for recurrent head and neck cancer. *Cancer.* 2011;117(14):3173-3181.	Observational-Tx	14 patients	To determine the maximum tolerated dose and efficacy of concurrent erlotinib and celecoxib as a radiosensitizing regimen.	The recommended phase 2 dose of celecoxib was 400 mg. Three dose-limiting toxicities included late in-field orocutaneous fistula (Dose Level 2), osteonecrosis (Dose Level 3), and trismus (Dose Level 3). Acute grade ≥3 toxicities were uncommon and included mucositis (21%) and dermatitis (14%). At a median follow-up of 11 months, the 1-year LR control, PFS, and OS rates were 60%, 37%, and 55%, respectively.	1

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9. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer.* 1953;6(5):963-968.	Review/Other-Tx	N/A	To review field cancerization in oral stratified squamous epithelium.	Oral squamous-cell carcinomas in 783 patients have been reviewed from the gross and microscopic standpoint. 88 instances of independent mu1tiple tumors were found, an incidence of 11.2%, which is far beyond the statistical possibility of chance occurrence. Microscopic evidence of multicentric origin was demonstrated by serial section in all excised tumors <1 cm in diameter. Abnormal and hyperplastic, often atypical, epithelium was found to surround all oral cancers for varying distances. Multicentric origin through a process of field cancerization would seem to be an important factor in the persistence or recurrence of epidermoid carcinoma following therapy.	4
10. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res.* 2003;63(8):1727-1730.	Review/Other-Tx	N/A	Review Slaughter's concept of field cancerization.	Development of an expanding preneoplastic field appears to be a critical step in epithelial carcinogenesis with important clinical consequences. Diagnosis and treatment of epithelial cancers should not only be focused on the tumor but also on the field from which it developed.	4
11. Cooper JS, Pajak TF, Rubin P, et al. Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. *Int J Radiat Oncol Biol Phys.* 1989;17(3):449-456.	Review/Other-Tx	928 patients	Review the Radiation Therapy Oncology Group's (RTOG) prospectively collected registry of all head and neck patients to examine second malignancies and its effect on survival and implications.	Estimated risk of developing a second tumor within 3 years of RT was 10%, within 5 years 15%, and within 8 years 23%. Second malignant tumors influenced subsequent survival adversely. Analysis of the database also revealed that the extent of the primary tumor influenced the risk of a second; most occurred in patients who presented with the smallest primary tumors because of their better survival. Data indicate that preventive medicine should have its greatest impact in those patients who are treated for an early stage primary tumor.	4
12. Coatesworth AP, Tsikoudas A, MacLennan K. The cause of death in patients with head and neck squamous cell carcinoma. *J Laryngol Otol.* 2002;116(4):269-271.	Review/Other-Tx	106 patients	Review the cause of death in patients with HNSCC.	Data on 106 patients diagnosed with HNSCC that subsequently died is reported. The literature related to this topic is discussed, and recommendations are made for data collection.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. *J Clin Oncol.* 2008;26(34):5518-5523.	Experimental-Tx	130 patients	Randomized trial of postoperative reirradiation combined with chemotherapy (RT arm) after salvage surgery compared with salvage surgery alone in head and neck carcinoma.	The most serious acute toxicity in the RT arm was mucositis, attaining grade 3 or 4 in 28% of patients. At 2 years, 39% of patients in the RT arm and 10% in the "wait and see" approach experienced grade 3 or 4 late toxicity. DFS was significantly improved in the RT arm, with a HR of 1.68 (95% CI, 1.13 to 2.50; P=.01), but OS was not statistically different.	1
14. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2007;68(3):731-740.	Observational-Tx	105 patients	Retrospective review of treatment outcomes for recurrent head and neck cancer patients treated with re-irradiation at a single medical center.	The 2-year LR PFS and OS rates were 42% and 37%, respectively. Patients who underwent IMRT, compared to those who did not, had a better 2-year LR PFS (52% vs 20%, P<0.001). On multivariate analysis, non-nasopharynx and non-IMRT were associated with an increased risk of LR failure. Patients with LR progression-free disease had better 2-year OS vs those with LR failure (56% vs 21%, P<0.001).	2
15. Vargo JA, Heron DE, Ferris RL, et al. Prospective evaluation of patient-reported quality-of-life outcomes following SBRT +/- cetuximab for locally-recurrent, previously-irradiated head and neck cancer. *Radiother Oncol.* 2012;104(1):91-95.	Observational-Tx	150 patients	To report the first prospective evaluation of patient-reported quality-of-life following re-irradiation with SBRT +/- cetuximab for recurrent HNSCC.	Overall patient-reported quality-of-life, health-related patient-reported quality-of-life, and select domains commonly affected by re-irradiation progressively increase following an initial 1-month decline with statistically significant improvements noted in swallowing (P=0.025), speech (P=0.017), saliva (P=0.041), activity (P=0.032) and recreation (P=0.039).	1

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16. Gourin CG, Watts T, Williams HT, Patel VS, Bilodeau PA, Coleman TA. Identification of distant metastases with PET-CT in patients with suspected recurrent head and neck cancer. *Laryngoscope.* 2009;119(4):703-706.	Observational-Dx	64 consecutive patients	To investigate the utility of PET-CT in identifying distant metastatic disease in patients with suspected recurrent HNSCC.	The majority of patients (81%) had TNM stage III or IV disease. PET-CT was suspicious for pulmonary malignancy in 14 patients (22%) and indeterminate in 6 patients (9%). Pulmonary metastases or a new lung primary were present in 10 patients (16%): 7/14 patients with positive PET-CT scans (50%) and 3/50 patients with negative or indeterminate PET-CT scans (6%). Including nonpulmonary sites, the overall incidence of distant disease was 23% (15/64) with 20% (13/64) unsuspected prior to PET-CT. The sensitivity and specificity of PET-CT in predicting distant malignancy was 86% and 84%, respectively, with a positive predictive value of 60% and a NPV of 95%. There was a significant correlation between SUV on PET-CT and positive histology, with a mean SUV of 8.5 (range, 4.7-16.2) in patients with distant metastases compared with a mean SUV of 2.9 (range, 1.9-4.2) in patients with benign pathology ($r = 0.87$, $P<.0001$).	3
17. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Salvage surgery following radiation failure in squamous cell carcinoma of the supraglottic larynx. *Int J Radiat Oncol Biol Phys.* 1995;32(3):605-609.	Review/Other-Tx	206 patients	To analyze the clinical course of patients who developed local (primary) recurrence following high-dose irradiation of squamous cell carcinoma of the supraglottic larynx.	50% of patients who underwent surgery had successful salvage. The overall rate of postsurgical complications was 37%. The 5-year survival rate for all 46 patients, calculated from the date of irradiation failure, was 20%, while the 5-year survival rate after salvage surgery for the 30 patients who underwent the procedure was 29%.	4
18. Bachar GY, Goh C, Goldstein DP, O'Sullivan B, Irish JC. Long-term outcome analysis after surgical salvage for recurrent tonsil carcinoma following radical radiotherapy. *Eur Arch Otorhinolaryngol.* 2010;267(2):295-301.	Observational-Tx	175 patients	Retrospective review to report the long-term outcomes of salvage surgery following local and/or regional failure of tonsillar carcinoma treated with standard fractionation RT.	5-year OS rate was 23%. The 5-year cause-specific survival was 40%. The probability of death due to disease was higher than the probability of death due to other causes. Both N-classification and T-classification were found to be significant predictors of time to death. Study shows the poor prognosis of recurrent disease. Despite the poor prognosis, 20% of patients will be alive at 5 years and therefore salvage surgery should be considered when possible.	2

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19. Goodwin WJ, Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *Laryngoscope.* 2000;110(3 Pt 2 Suppl 93):1-18.	Review/Other-Tx	32 published reports; meta-analysis 109 patients; observational study	Meta-analysis and prospective observational study to assess the value of salvage surgical procedures in the treatment of local and regional recurrence.	The weighted average of 5-year survival in the meta-analysis was 39%. In the prospective study, median DFS was 17.9 months in 109 patients, and this correlated strongly with recurrent stage, weakly with recurrent site, and not at all with time to presalvage recurrence.	4
20. Choe KS, Haraf DJ, Solanki A, et al. Prior chemoradiotherapy adversely impacts outcomes of recurrent and second primary head and neck cancer treated with concurrent chemotherapy and reirradiation. *Cancer.* 2011;117(20):4671-4678.	Observational-Tx	160 patients	To examine potential prognostic factors associated with survival by retrospectively reviewing the outcomes of patients who received chemotherapy and reirradiation.	166 patients were identified, including 81 patients who underwent surgical resection or debulking before enrollment. The median reirradiation dose was 66 gray. After a median follow-up of 53 months among surviving patients, the median OS was 10.3 months. The 2-year rates for OS, DFS, LR control, and freedom from distant metastasis were 24.8%, 19.9%, 50.7%, and 61.4%, respectively. 33 patients (19.9%) died of treatment-related toxicity. In subgroup analysis, survival was significantly reduced in patients who received previous concurrent chemoradiotherapy compared with patients who were naive to chemoradiotherapy (2-year OS rate, 10.8% vs 28.4%; P=.0043). In multivariable analysis, prior chemoradiotherapy was associated independently with OS along with surgery before protocol treatment, full-dose reirradiation, and RT interval.	2
21. Tanvetyanon T, Padhya T, McCaffrey J, et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. *J Clin Oncol.* 2009;27(12):1983-1991.	Review/Other-Tx	103 patients	Review records of patients treated with reirradiation to examine potential prognostic factors, including comorbidity and pre-existing organ dysfunction, for survival after reirradiation.	Comorbidity and pre-existing organ dysfunction are among several important prognostic factors for patients undergoing reirradiation. For those with both comorbidity and organ dysfunction, reirradiation largely serves as a palliative therapy.	4

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22. Zafereo ME, Hanasono MM, Rosenthal DI, et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer.* 2009;115(24):5723-5733.	Observational-Tx	168 patients	Retrospectively review OS, functional outcomes, and prognostic factors in patients who underwent salvage surgery for locally recurrent squamous cell carcinoma of the oropharynx after initial RT.	3-year OS rate for patients who underwent salvage surgery or received reirradiation, palliative chemotherapy, or supportive care were 48.7%, 31.6%, 3.7%, and 5.1%, respectively. For patients who underwent salvage surgery, older age (P=.03), the absence of a disease-free interval (P<.01), and advanced recurrent tumor stage (P=.07) were associated with lower OS. Patients with recurrent neck disease (P=.01) and positive surgical margins (P=.04) had higher rates of recurrence after salvage surgery.	2
23. Kasperts N, Slotman BJ, Leemans CR, de Bree R, Doornaert P, Langendijk JA. Results of postoperative reirradiation for recurrent or second primary head and neck carcinoma. *Cancer.* 2006;106(7):1536-1547.	Observational-Tx	39 patients	Prospective study to examine the effects of a second course of postoperative RT on LR control, survival, toxicity, and quality of life in patients who underwent resection of a second primary or LR recurrent head and neck tumor in a previously irradiated area.	The LR control rate after 3 years in the retreated with postoperative RT group was 74%, and the 3-year OS rate was 44%. Retreated with postoperative RT after surgery for recurrent LR tumors and/or second primary tumors should be considered in patients who have high-risk histopathologic features.	1
24. De Crevoisier R, Domenge C, Wibault P, et al. Full dose reirradiation combined with chemotherapy after salvage surgery in head and neck carcinoma. *Cancer.* 2001;91(11):2071-2076.	Observational-Tx	25 patients	Prospective study to analyze the tolerance and efficacy of full dose reirradiation combined with chemotherapy in patients with head and neck carcinoma with a high risk of recurrence after salvage surgery.	During the reirradiation course, grade 3 and 4 mucositis were observed in 40% and 12%, respectively. Analysis of late effects (>6 months after reirradiation) showed that 16% of the patients had osteoradionecrosis and 40% had grade 2-3 cervical fibrosis. The patterns of failure were as follows: local only (n = 9), lymph node only (n = 2), local and lymph node only (n = 1), and metastatic (n = 4). The 4-year survival rate after reirradiation was 43%.	1
25. Mabanta SR, Mendenhall WM, Stringer SP, Cassisi NJ. Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. *Head Neck.* 1999;21(7):591-594.	Observational-Tx	51 patients	To analyze the likelihood of salvage treatment for patients with recurrence in the neck after RT.	Recurrence was in the neck alone in 10 patients (55%); neck and distant sites in 3 patients (17%); neck, primary site, and distant sites in 2 patients (11%); and with distant metastasis alone in 3 patients (17%). Control of neck disease at 5 years was 9% for the 18 patients who underwent a salvage attempt, as well as for all 51 patients. For the overall group, absolute and cause-specific survival rates were both 10% at 5 years.	3

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26. Forastiere AA, Leong T, Rowinsky E, et al. Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. *J Clin Oncol.* 2001;19(4):1088-1095.	Experimental-Tx	210 patients	Randomized phase III trial to determine dose-response effects and the activity of paclitaxel combined with cisplatin in patients with incurable HNSCC. Patients with locally advanced, recurrent, or metastatic disease were randomly placed in either Arm A, paclitaxel 200 mg/m(2) (24-hour infusion) + cisplatin 75 mg/m(2) + granulocyte colony-stimulating factor, or Arm B, paclitaxel 135 mg/m(2) (24-hour infusion) + cisplatin 75 mg/m(2).	Estimated median survival was 7.3 months. The 1-year survival rate was 29%, and event-free survival was 4.0 months. The objective response rate (complete response plus partial response) was 35% for the high-dose patients and 36% for the low-dose patients. Myelosuppression was the most frequent toxicity: grade 3 or 4 granulocytopenia, 70% of patients in Arm A and 78% in Arm B; febrile neutropenia, 27% of patients in Arm A and 39% in Arm B. Grade 5 toxicities occurred in 22 patients (10.5%).	1
27. Seiwert TY, Jagadeeswaran R, Faoro L, et al. The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. *Cancer Res.* 2009;69(7):3021-3031.	Observational-Tx	121 tissues (HNSCC/normal) and 20 HNSCC cell lines	To examine the MET receptor tyrosine kinase as a novel target for the treatment of HNSCC. The effects of MET inhibition using small interfering RNA/two small-molecule inhibitors (SU11274/PF-2341066) on signaling, migration, viability, and angiogenesis were determined.	Mutational analysis of 66 tumor tissues and 8 cell lines identified novel mutations in the semaphorin (T230M/E168D/N375S), juxtamembrane (T1010I/R988C), and tyrosine kinase (T1275I/V1333I) domains (incidence: 13.5%). Increased MET gene copy number was present with >10 copies in 3/23 (13%) tumor tissues. MET is functionally important in HNSCC with prominent overexpression, increased gene copy number, and mutations. MET is a promising, novel target for HNSCC.	2
28. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359(11):1116-1127.	Experimental-Tx	442 patients	Randomized phase III trial to examine the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic HNSCC.	Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum-fluorouracil) significantly prolonged the median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab. The addition of cetuximab prolonged the median PFS time from 3.3 to 5.6 months and increased the response rate from 20% to 36% (P<0.001). As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum-fluorouracil chemotherapy improved OS when given as first-line treatment.	1

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29. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. *Head Neck.* 2008;30(3):281-288.	Observational-Tx	86 patients	Prospective multi-center trial to determine the incidence of acute and late toxicities and to estimate the 2-year OS for patients treated with reirradiation and chemotherapy for unresectable HNSCC.	79/86 patients enrolled were analyzable. The worst acute toxicity was grade 4 in 17.7% and grade 5 in 7.6%. Grade 3 and 4 late toxicities were found in 19.4% and 3.0%, respectively. The estimated cumulative incidence of grade 3 to 4 late effects occurring at >1 year was 9.4% at 2 and 5 years. The 2- and 5-year cumulative incidence for grade 4 toxicity was 3.1%. The estimated 2- and 5-year survival rates were 15.2% and 3.8%, respectively. Patients who entered the study at >1 year from initial RT had better survival than did those who were <1 year from prior RT (median survival, 9.8 months vs 5.8 months; P=.036). No correlation was detected between dose received and OS.	1
30. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *J Clin Oncol.* 2007;25(30):4800-4805.	Observational-Tx	105 patients	Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent HNSCC (RTOG Protocol 9911).	Grade 4 or worse acute toxicity occurred in 28%, grade 4 or worse acute hematologic toxicity in 21%. 8 treatment-related deaths (8%) occurred: 5 in the acute setting, 3 late (including two carotid hemorrhages). Median survival time was 12.1 months, with estimated 1- and 2-year OS rates of 50.2% and 25.9%. Despite a high incidence of grade 5 toxicity, 1- and 2-year OS rates for split-course bid RT and concurrent cisplatin/paclitaxel exceed results generally seen with chemotherapy alone.	1
31. Bernier J, Bataini JP. Regional outcome in oropharyngeal and pharyngolaryngeal cancer treated with high dose per fraction radiotherapy. Analysis of neck disease response in 1646 cases. *Radiother Oncol.* 1986;6(2):87-103.	Review/Other-Tx	1,646 patients	To examine high dose per fraction RT in oropharyngeal and pharyngolaryngeal cancer. Neck disease response in 1,646 cases is analyzed.	The actuarial 3-year nodal control rate using the American Joint Committee for Cancer Staging and End Results Recording (AJC) classification was: N0 98%, N1 90%, N2 88%, N3 71% when the primary was controlled. The regional outcome is influenced by clinical features such as nodal size, multiplicity and fixity. Cervical recurrence frequency is higher for pharyngolaryngeal carcinoma than for oropharyngeal cancer.	4

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32. Iseli TA, Iseli CE, Rosenthal EL, et al. Postoperative reirradiation for mucosal head and neck squamous cell carcinomas. *Arch Otolaryngol Head Neck Surg.* 2009;135(11):1158-1164.	Observational-Tx	87 patients	Retrospective review to compare toxic effects and functional outcomes of reirradiation with and without salvage surgery for nonnasopharyngeal mucosal HNSCC.	Compared with reirradiation without surgery, postoperative reirradiation was associated with increased early grade 3 to grade 5 toxic effects (50% [19/38] vs 29% [14/49], P=.04) and with longer median survival (17.3 vs 8.9 months, P<.001). Free-flap reconstruction decreased early toxic effects in the surgical cohort by 16% (from 60% [9/15] to 43% [10/23], P=.32). The median survival for curative patients was 12.5 months. The estimated 2-year survival was 25%, and the estimated 5-year survival was 8%.	2
33. Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;64(2):382-391.	Observational-Tx	115 patients	To define favorable pretreatment characteristics for OS, PFS, LR control, and freedom from distant metastasis for patients with recurrent and second primary head-and-neck cancer treated with concomitant chemotherapy and reirradiation.	Median OS and PFS was 11 and 7 months, respectively. 3-year OS, PFS, LR control, and freedom from distant metastasis rate was 22%, 33%, 51%, and 61%, respectively. Multivariate analysis identified reirradiation dose, triple agent (cisplatin-, paclitaxel-, or gemcitabine-containing chemotherapy), and surgery before protocol treatment as independently prognostic for OS, PFS, and LR control. For recurrent and second primary head-and-neck cancer, trimodality therapy with surgery, concurrent chemotherapy, and reirradiation for a full second dose offers potential for long-term survival.	2
34. Kolotas C, Tselis N, Sommerlad M, et al. Reirradiation for recurrent neck metastases of head-and-neck tumors using CT-guided interstitial 192Ir HDR brachytherapy. *Strahlenther Onkol.* 2007;183(2):69-75.	Observational-Tx	49 patients	To report the therapeutic results obtained with CT-guided interstitial high-dose-rate brachytherapy as exclusive treatment for recurrent neck metastases of head-and-neck tumors.	Response rate was 83% with complete remission in 20% (10/49) and partial remission in 63% (31/49) of the implanted tumor sites at a minimum 6-week follow-up. After 19 months of median follow-up, the local control rate was 69% and 30% experienced local disease progression. Of these, 18% had LR progression and 12% progression within the treated volume. The OS rate was 52% at 1 year, 31% at 2 years, and 6% at 3 years.	2

Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol.* 2005;23(27):6730-6738.	Experimental-Tx	221 patients	Randomized trial to confirm the findings of the Intergroup 00-99 Trial and its applicability to patients with endemic nasopharyngeal cancer. Patients were randomly assigned to receive RT alone (n=110) or chemoradiotherapy (n=111).	Distant metastasis occurred in 38 patients on RT alone and 18 patients on chemotherapy. The 2- and 3-year OS rates were 78% and 85% and 65% and 80% for RT alone and chemoradiotherapy, respectively. Report confirms the findings of the Intergroup 00-99 Trial and demonstrates its applicability to endemic nasopharyngeal cancer. This study also confirms that chemotherapy improves the distant metastasis control rate in nasopharyngeal cancer.	1
36. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol.* 1998;16(4):1310-1317.	Experimental-Tx	147 patients – primary analysis; 185 patients – secondary analysis	Randomized phase III trial to compare chemoradiotherapy with RT alone in patients with nasopharyngeal cancers.	3-year PFS rate was 24% vs 69%, respectively (P<.001). The median survival time was 34 months for the RT group and not reached for the chemoradiotherapy group, and the 3-year survival rate was 47% vs 78%, respectively (P=.005). 185 patients were included in a secondary analysis for survival. The 3-year survival rate for patients randomized to RT was 46%, and for the chemoradiotherapy group was 76% (P<.001). Chemoradiotherapy is superior to RT alone for patients with advanced nasopharyngeal cancers with respect to PFS and OS.	1
37. Yu KH, Leung SF, Tung SY, et al. Survival outcome of patients with nasopharyngeal carcinoma with first local failure: a study by the Hong Kong Nasopharyngeal Carcinoma Study Group. *Head Neck.* 2005;27(5):397-405.	Observational-Tx	2915 patients	To report the OS outcome of patients with nasopharyngeal carcinoma with local failure who received salvage treatment and to identify prognostic factors for OS.	3-year actuarial OS for patients with isolated local failure was 74%. On multivariate analysis, advanced initial T classification and the use of salvage treatment were independent prognostic factors. For the subgroups of patients who had the same recurrent and initial T classification, salvage treatment was associated with improved OS only in the subgroup with T1 to T2 local failure (n=127; P=0.0446), but not in the subgroups with T3 (n=48) or T4 (n=54) disease. Salvage treatment is feasible in most of the patients with clinically isolated local failure. Patients who had early initial T classification have a more favorable prognosis. Subgroup analysis suggests that salvage treatment only prolongs survival in patients with T1 to T2 recurrent disease.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Hwang JM, Fu KK, Phillips TL. Results and prognostic factors in the retreatment of locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 1998;41(5):1099-1111.	Observational-Tx	74 patients	To review the results and evaluate the prognostic factors in the retreatment of locally recurrent nasopharyngeal carcinoma.	3-, 5-, and 10-year actuarial OS following retreatment were 49%, 37%, and 18%, respectively. 3-, 5-, and 10-year local-regional progression-free rates were 52%, 40%, and 38%, respectively. Histologic type, interval to recurrence, and treatment modality for early-stage disease was significant prognostic factors for OS, with age being marginally significant. For LR progression-free rate, only histology was significant. On multivariate analysis, age, histology, and interval to recurrence were significant for OS, and only histology and presence of complications were significant for LR progression-free rate.	2
39. Hao SP, Tsang NM, Chang KP, Hsu YS, Chen CK, Fang KH. Nasopharyngectomy for recurrent nasopharyngeal carcinoma: a review of 53 patients and prognostic factors. *Acta Otolaryngol.* 2008;128(4):473-481.	Observational-Tx	53 consecutive patients	Retrospective review to report the local control and OS outcome of patients with nasopharyngeal carcinoma with local failure who received salvage nasopharyngectomy and to identify prognostic factors.	5-year local control rates were T1, 58.3%; T2, 27.8%; T3, 53.3%; T4, 75.0%; and all stages, 53.6%. The 5-year OS rates were stage I, 64.8%; stage II, 38.1%; stage III, 25.9%; stage IV, 46.9%; and all stages, 48.7%. Multivariate analysis revealed that gender, margin status, adjuvant treatment type and parapharyngeal space involvement were significant impact factors of local control, whereas dura or brain involvement, local recurrence and adjuvant treatment type were significant impact factors of survival.	2
40. Chen MY, Wen WP, Guo X, et al. Endoscopic nasopharyngectomy for locally recurrent nasopharyngeal carcinoma. *Laryngoscope.* 2009;119(3):516-522.	Observational-Tx	37 patients	To examine the use of endoscopic nasopharyngectomy for locally recurrent nasopharyngeal carcinoma.	2-year OS rate, local relapse-free survival rate, and PFS rate were 84.2%, 86.3%, and 82.6%, respectively. Appropriate endoscopic nasopharyngectomy is a minimally invasive, safe, and promising surgical modality for the en bloc excision of recurrent nasopharyngeal carcinoma with encouraging short-term outcome.	2
41. Law SC, Lam WK, Ng MF, Au SK, Mak WT, Lau WH. Reirradiation of nasopharyngeal carcinoma with intracavitary mold brachytherapy: an effective means of local salvage. *Int J Radiat Oncol Biol Phys.* 2002;54(4):1095-1113.	Observational-Tx	118 consecutive patients	Retrospective review to assess the role of intracavitary mold brachytherapy in salvaging local failure of nasopharyngeal carcinoma.	Overall complete remission rate was 97%. The rates of 5-year local control, relapse-free survival, disease-specific survival, OS, and major complication were 85%, 68.3%, 74.8%, 61.3%, and 46.9%, respectively. Intracavitary mold brachytherapy was effective in salvaging nasopharyngeal carcinoma with early-stage local persistence or first recurrence.	2

Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Koutcher L, Lee N, Zelefsky M, et al. Reirradiation of locally recurrent nasopharynx cancer with external beam radiotherapy with or without brachytherapy. *Int J Radiat Oncol Biol Phys.* 2010;76(1):130-137.	Observational-Tx	29 patients	To determine survival rates of patients with locally recurrent nasopharynx cancer treated with modern therapeutic modalities.	5-year actuarial local control, event-free survival, and OS rates were 52%, 44%, and 60%, respectively. No difference was observed between patients treated with EBRT or combined-modality treatment. OS was better in patients who achieved local control. The incidence of late grade ≥3 events in patients re-treated with EBRT alone was significantly increased compared with those receiving combined-modality treatment (73% vs 8%; P=0.005).	2
43. Leung TW, Tung SY, Sze WK, et al. Salvage radiation therapy for locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1331-1338.	Observational-Tx	91 patients	Retrospective analysis to examine the treatment outcome in patients with locally recurrent nasopharyngeal carcinoma and to explore whether a combination of high-dose-rate intracavitary brachytherapy and EBRT could improve the therapeutic ratio.	Multivariate analyses showed the rT stage was significant for predicting the occurrence of major (P=0.004) and central nervous system complications (P=0.04). For rT1-2 local recurrences, combined-modality treatment with at least 60 Gy total equivalent dose is recommended.	2
44. Lu TX, Mai WY, Teh BS, et al. Initial experience using intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2004;58(3):682-687.	Observational-Tx	49 patients	To report the feasibility, toxicity, and tumor control using IMRT for retreatment of recurrent nasopharyngeal carcinoma.	LR control rate was 100% at a median follow-up of 9 months (range 3-13). The improvement in tumor target coverage and significant sparing of adjacent critical structures allow the feasibility of IMRT as a retreatment option for recurrent nasopharyngeal carcinoma. after initial conventional RT.	2
45. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer-disease control and morbidity outcomes. *Int J Radiat Oncol Biol Phys.* 2009;73(2):399-409.	Observational-Tx	78 consecutive patients	Retrospectively review the medical records of patients who received IMRT reirradiation for either locoregionally recurrent or in-field second primary disease.	2-year OS and LR control rates were 58% and 64%, respectively. Severe reirradiation related toxicity occurred in 15 patients (20%); one treatment-related death was observed. The use of IMRT for reirradiation of recurrent or second primary head and neck cancers resulted in encouraging local control and survival.	2
46. Seo Y, Yoo H, Yoo S, et al. Robotic system-based fractionated stereotactic radiotherapy in locally recurrent nasopharyngeal carcinoma. *Radiother Oncol.* 2009;93(3):570-574.	Observational-Tx	35 patients	To review survival, local control, and toxicity in patients with locally recurrent nasopharyngeal carcinoma who had been treated with FSRT.	The OS rate, local failure-free survival rate, and disease PFS rate at 5 years were 60%, 79%, and 74%, respectively. 23 patients achieved complete response after FSRT. Only T stage at recurrence was an independent prognostic factor for OS and disease PFS. 5 patients exhibited severe late toxicity (Grade 4 or 5).	2

Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Wu SX, Chua DT, Deng ML, et al. Outcome of fractionated stereotactic radiotherapy for 90 patients with locally persistent and recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2007;69(3):761-769.	Observational-Tx	90 patients	To review the treatment outcome after FSRT for nasopharyngeal carcinoma.	Complete response rate after FSRT was 66% for Group 1 and 63% for Group 2. 1-, 2-, and 3-year disease-specific survival and PFS rates for all patients were 82.6%, 74.8%, 57.5%, and 72.9%, 60.4%, 54.5%, respectively. 3-year local failure-free survival, disease-specific survival, and PFS rates were 89.4%, 80.7%, and 72.3% for Group 1, and 75.1%, 45.9%, and 42.9% for Group 2, respectively. Multivariate analysis showed that recurrent disease and large tumor volume were independent factors that predicted poorer disease-specific survival and PFS. 17 patients developed late complications, including 2 with fatal hemorrhage.	2
48. Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. *Semin Radiat Oncol.* 2000;10(3):200-209.	Review/Other-Tx	N/A	Article summarizes available experimental and clinical data on reirradiation tolerance of various tissues.	Data show that generally, acutely responding tissues recover radiation injury within a few months and, therefore, can tolerate another full course of radiation. For late toxicity endpoints, however, tissues vary considerably in their capacity to recover from occult radiation damage.	4
49. Temam S, Koka V, Mamelle G, et al. Treatment of the N0 neck during salvage surgery after radiotherapy of head and neck squamous cell carcinoma. *Head Neck.* 2005;27(8):653-658.	Review/Other-Tx	30 patients	To determine the rate of occult neck node metastasis and the surgical morbidity of patients after salvage surgery for local relapse after definitive RT.	Risk of neck node metastasis during salvage surgery for local recurrence in patients treated initially with radiation for N0 HNSCC is low. Neck dissection should be performed in only limited area, depending on the surgical procedure used for tumor resection.	4
50. Popovtzer A, Gluck I, Chepeha DB, et al. The pattern of failure after reirradiation of recurrent squamous cell head and neck cancer: implications for defining the targets. *Int J Radiat Oncol Biol Phys.* 2009;74(5):1342-1347.	Observational-Tx	66 patients	Retrospective review of patients who underwent curative-intent reirradiation for nonresectable recurrent or second primary mucosal HNSCC.	At a median follow-up of 42 months, 16 (23%) were alive and disease-free. 50 patients (77%) had a third recurrence or persistent disease, including 47 LR failures. All LR failures occurred within the recurrent gross tumor volume except for two (4%). 19 patients (29%) had grade ≥3 late complications, mostly dysphagia (12 patients).	2

Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Hoebers F, Heemsbergen W, Moor S, et al. Reirradiation for head-and-neck cancer: delicate balance between effectiveness and toxicity. *Int J Radiat Oncol Biol Phys.* 2011;81(3):e111-118.	Observational-Tx	58 patients	To analyze the effectiveness and toxicity of reirradiation for head-and-neck cancer.	Median follow-up was 57 months (range, 9-140). LR control was 50% at 2 and 5 years. The 2-year and 5-year OS was 42% and 34%. The following factors were associated with improved OS: postoperative reirradiation (vs primary reirradiation), treatment with RT only (vs chemoradiotherapy) and interval >3 years between previous RT and reirradiation. For patients treated with postoperative reirradiation and definitive reirradiation, the 5-year OS was 49% and 20%, respectively. Patients treated with chemoradiotherapy had a 5-year OS of 13%. Serious (late) toxicity ≥Grade 3 was observed in 20/47 evaluable patients (43%). 3 cases of treatment-related death were recorded. The 2- and 5-year serious toxicity-free interval was 59% and 55%, respectively. Associated with increased risk of serious toxicity were chemoradiotherapy and higher reirradiation dose. The event-free survival rates at 2 and 5 years were 34% and 31%, respectively.	2
52. Stevens KR, Jr., Britsch A, Moss WT. High-dose reirradiation of head and neck cancer with curative intent. *Int J Radiat Oncol Biol Phys.* 1994;29(4):687-698.	Observational-Tx	100 patients	To evaluate the response of new or recurrent head and neck cancers and the response of associated normal tissues to high dose reirradiation with curative intent.	5-year survival was 37% for patients with new second primary cancers and 17% for patients with recurrent cancers. LR tumor control was achieved in 60% of the patients with new tumors and in 27% of the patients with recurrent tumors.	3
53. 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 phase III trial to examine the efficacy of hyperfractionation and two 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.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. Spencer S, Wheeler R, Peters G, et al. Phase 1 trial of combined chemotherapy and reirradiation for recurrent unresectable head and neck cancer. *Head Neck.* 2003;25(2):118-122.	Observational-Tx	52 patients	Phase I trial of combined chemotherapy and reirradiation for recurrent unresectable head and neck cancer. Purpose is to determine the maximum tolerated dose of infusional 5-flourouracil, hydroxyurea, and reirradiation.	The median survival was 10.2 months and the 1-year survival was 41%. The median survival for the entire group was 9.4 months, with a 1- and 2-year survival of 39% and 15%, respectively. Reirradiation can be given in a continuous fashion with concurrent 5-flourouracil and hydroxyurea.	1
55. Dawson LA, Myers LL, Bradford CR, et al. Conformal re-irradiation of recurrent and new primary head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;50(2):377-385.	Observational-Tx	40 patients	To review the outcome of head-and-neck cancer patients reirradiated using conformal radiation.	Median survival following completion of reirradiation was 12.5 months. The 1- and 2-year actuarial survival rates were 51.1% and 32.6%, respectively. On multivariate analysis, palliative intent of treatment, tumor bulk, and tumor site other than nasopharynx or larynx were associated with worse survival.	2
56. Watkins JM, Shirai KS, Wahlquist AE, et al. Toxicity and survival outcomes of hyperfractionated split-course reirradiation and daily concurrent chemotherapy in locoregionally recurrent, previously irradiated head and neck cancers. *Head Neck.* 2009;31(4):493-502.	Observational-Tx	39 patients	Retrospective cohort analysis of toxicity and survival outcomes in locoregionally recurrent, previously irradiated patients with head/neck cancer treated with hyperfractionated split-course RT and concurrent chemotherapy.	At median survivor follow-up of 24.5 months (range, 3-63.9), 10 patients are alive without evidence of disease. Median survival is 19.0 months, with estimated 1-, 2-, and 3-year OSs of 60.1%, 45.1%, and 22.7%, respectively. LR failure was the predominant site of postreirradiation recurrence. Male sex, total RT dose, cycles of chemotherapy completed, and clinical response were associated with improved OS.	2
57. Lin R, Slater JD, Yonemoto LT, et al. Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy--dose-volume histogram analysis. *Radiology.* 1999;213(2):489-494.	Observational-Tx	16 patients	To analyze control, survival, and complication rates of conformal proton radiation for recurrent nasopharyngeal carcinoma.	24-month actuarial overall and local-regional PFS rates were both 50%. The 24-month actuarial OS rates for patients with "optimal" dose-volume histogram coverage vs "suboptimal" coverage were 83% and 17%, respectively (P=.006). Doses to critical structures were low (0-22.0 Gy); no central nervous system side effects supervened.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Siddiqui F, Patel M, Khan M, et al. Stereotactic body radiation therapy for primary, recurrent, and metastatic tumors in the head-and-neck region. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1047-1053.	Observational-Tx	44 patients	To determine the feasibility, safety, and efficacy of SBRT, also known as radiosurgery, in patients with head-and-neck cancers.	55 lesions were treated in 44 patients (25 men, 19 women). There were 3 groups of patients: those with primary (n = 10), recurrent (n = 21), and metastatic tumors (n = 13). The predominant histologic type was squamous cell carcinoma (n = 33). The majority of lesions were treated using SBRT (n = 37). Based on radiographic and clinical assessment, a 77% (complete + partial response) response rate was noted. Percentage of reduction in tumor volume was 52% +/- 38% based on follow-up scans in 24 patients. Tumor control rates at 1 year were 83.3% and 60.6% in the primary and recurrent groups, respectively. Median OS was 28.7, 6.7, and 5.6 months for the primary, recurrent, and metastatic groups, respectively. RTOG Grade 1-2 mucositis was noted in all patients treated for oropharyngeal or laryngeal lesions.	2
59. Heron DE, Ferris RL, Karamouzis M, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. *Int J Radiat Oncol Biol Phys.* 2009;75(5):1493-1500.	Observational-Tx	25 patients	To evaluate the safety and efficacy of SBRT in previously irradiated patients with HNSCC.	No Grade 3/4 or dose-limiting toxicities occurred. 4 patients had Grade 1/2 acute toxicities. 4 objective responses were observed, for a response rate of 17% (95% CI, 2%-33%). The maximum duration of response was 4 months. 12 patients had stable disease. Median time to disease progression was 4 months, and median OS was 6 months. Self-reported quality of life was not significantly affected by treatment. Fluorodeoxyglucose PET was a more sensitive early-measure response to treatment than CT volume changes.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Rwigema JC, Heron DE, Ferris RL, et al. Fractionated stereotactic body radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma: updated report of the University of Pittsburgh experience. *Am J Clin Oncol.* 2010;33(3):286-293.	Observational-Tx	85 patients	To assess the safety and outcome of SBRT in patients with recurrent previously irradiated HNSCC.	The median follow-up of all patients was 6 months (range: 1.3-39 months). For those patients who were alive at last follow-up (40%) the median follow-up was 17.6 months. The mean total dose of prior radiation to the primary site was 74 Gy (range: 32-170 Gy). Those patients who received SBRT <35 Gy had significantly lower local control than those with ≥35 Gy at 6 months the median follow-up time (P=0.014). Tumor responses were 34% complete response, 34% partial response, 20% stable disease, and 12% progressive disease. Among those with an initial tumor response followed by progression (58 patients), there was a median interval of 5.5 months for time-to-progression. The 1-year and 2-year local control and OS rates for all patients were 51.2% and 30.7%, and 48.5% and 16.1%, respectively. Overall, the median survival for all patients was 11.5 months (range: 3-51). Treatment was well-tolerated with no grade 4 or 5 treatment-related toxicities.	2
61. Cengiz M, Ozyigit G, Yazici G, et al. Salvage reirradiaton with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. *Int J Radiat Oncol Biol Phys.* 2011;81(1):104-109.	Observational-Tx	46 patients	To present our results of reirradiation of locally recurrent head-and-neck cancer with image-guided, fractionated, frameless SBRT technique.	Of 37 patients whose response to therapy was evaluated, 10 patients (27%) had complete tumor regression, 11 (29.8%) had partial response, and 10 (27%) had stable disease. Ultimate local disease control was achieved in 31 patients (83.8%). The OS was 11.93 months in median (ranged, 11.4-17.4 months), and the median PFS was 10.5 months. 1-year PFS and OS were 41% and 46%, respectively. Grade II or greater long-term complications were observed in 6 (13.3%) patients. On follow-up, 8 (17.3%) patients had carotid blow-out syndrome, and 7 (15.2%) patients died of bleeding from carotid arteries. We discovered that this fatal syndrome occurred only in patients with tumor surrounding carotid arteries and carotid arteries receiving all prescribed dose.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Heron DE, Rwigema JC, Gibson MK, Burton SA, Quinn AE, Ferris RL. Concurrent cetuximab with stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: a single institution matched case-control study. *Am J Clin Oncol.* 2011;34(2):165-172.	Observational-Tx	70 patients	To compare SBRT alone with combination therapy, using concomitant cetuximab with SBRT, to enhance clinical efficacy while minimizing toxicity.	The median follow-ups for patients alive at last contact were 21.3 months and 24.8 months for SBRT only (n=13) and SBRT plus cetuximab (n=22), respectively. Our results indicate that cetuximab conferred an OS advantage (24.5 vs 14.8 months) when compared with the SBRT alone arm, without a significant increase in grade 3/4 toxicities. This survival advantage was also observed in the subgroup that had received cetuximab therapy during their prior therapeutic regimen.	2
63. McDonald MW, Moore MG, Johnstone PA. Risk of carotid blowout after reirradiation of the head and neck: a systematic review. *Int J Radiat Oncol Biol Phys.* 2012;82(3):1083-1089.	Review/Other-Tx	27 published articles on head and neck reirradiation involving 1,554 patients	To determine the reported rate of carotid blowout in patients receiving salvage reirradiation for head and neck cancer.	Among 1,554 patients receiving salvage head and neck reirradiation, there were 41 reported carotid blowouts, for a rate of 2.6%; 76% were fatal. In patients treated in a continuous course with 1.8–2 Gy daily fractions or 1.2 Gy twice-daily fractions, 36% of whom received concurrent chemotherapy, the rate of carotid blowout was 1.3%, compared with 4.5% in patients treated with 1.5 Gy twice daily in alternating weeks or with delayed accelerated hyperfractionation, all of whom received concurrent chemotherapy (P=0.002). There was no statistically significant difference in the rate of carotid blowout between patients treated with or without concurrent chemotherapy, or between patients treated with or without salvage surgery before reirradiation.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. Ang KK, Jiang GL, Feng Y, Stephens LC, Tucker SL, Price RE. Extent and kinetics of recovery of occult spinal cord injury. *Int J Radiat Oncol Biol Phys.* 2001;50(4):1013-1020.	Observational-Tx	56 rhesus monkeys	To obtain clinically useful quantitative data on the extent and kinetics of recovery of occult radiation injury in primate spinal cord, after a commonly administered elective radiation dose of 44 Gy, given in about 2 Gy per fraction.	Only 4/45 monkeys completing the required observation period (2–2.5 years after reirradiation, 3–5.5 years total) developed myeloparesis. The data revealed a substantial recovery of occult injury induced by 44 Gy within the first year, and suggested additional recovery between 1 and 3 years. Fitting the data with a model, assuming that all (single course and reirradiation) dose-response curves were parallel, yielded recovery estimates of 33.6 Gy (76%), 37.6 Gy (85%), and 44.6 Gy (101%) of the initial dose, after 1, 2, and 3 years, respectively, at the 5% incidence (D(5)) level. The most conservative estimate, using a model in which it was assumed that there was no recovery between 1 and 3 years following initial irradiation and that the combined reirradiation curve was not necessarily parallel to the single-course curve, still showed an overall recovery equivalent to 26.8 Gy (61%). The spinal cords of symptomatic monkeys consistently revealed a mixture of white matter necrosis and vascular injury, but the majority of spinal cords of asymptomatic animals did not exhibit overt lesions detectable by light microscopy.	2
65. Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. *Int J Radiat Oncol Biol Phys.* 2008;71(1):87-97.	Observational-Tx	38 pediatric patients	Retrospective study to report disease control for patients with recurrent ependymoma treated with surgery and a second course of RT.	Radiosurgery resulted in significant brainstem toxicity and one death (median dose, 18 Gy). PFS ratio was greater than unity for 4/6 patients; there was one long-term survivor. 4-year event-free survival rate was 53% +/- 20% for 12 patients with metastatic failure treated with craniospinal irradiation. Failure after craniospinal irradiation was observed in 1/3 patients with a history of local failure and 3/4 patients with a history of combined failure.	2

Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Nieder C, Grosu AL, Andratschke NH, Molls M. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. *Int J Radiat Oncol Biol Phys*. 2006;66(5):1446-1449.	Review/Other-Tx	38 patients	To update a combined analysis of all published clinical data.	The 2005 risk score based on 3 variables (cumulative BED, highest BED of all treatment series in a particular individual, and interval), which discriminate 3 different risk groups, does not require modification. The low-risk group now contains 1 case of radiation myelopathy after hypofractionated stereotactic reirradiation. Therefore, the rate increased from 0% to 3%. Intermediate-risk patients developed radiation myelopathy in 25%, and high-risk patients in 90%. When the interval between the 2 treatment courses is not shorter than 6 months and the dose of each course is ≤98 Gy(2), the cumulative BED where no case of radiation myelopathy has yet been reported is 120 Gy(2).	4
67. Langendijk JA, Kasperts N, Leemans CR, Doornaert P, Slotman BJ. A phase II study of primary reirradiation in squamous cell carcinoma of head and neck. *Radiother Oncol.* 2006;78(3):306-312.	Observational-Tx	34 patients	Prospective study to examine the effect of a second course of primary RT on LR control, survival and toxicity in patients who underwent a second course of high dose irradiation for second primary or LR recurrent HNSCC in a previously irradiated area.	The LR control rate after 2 years was 27%. The 3-year OS was 22%. The most frequently reported acute side-effect was acute mucositis resulting in swallowing complaints. Pharyngeal and oesophageal late morbidity was also the most important late side-effect.	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.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

BED = Biologically effective dose

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

EBRT = External-beam radiation therapy

FSRT = Fractionated stereotactic radiotherapy

HNSCC = Head and neck squamous cell carcinoma

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

LR = Locoregional

NPV = Negative predictive value

OS = Overall survival

PET = Positron emission tomography

PFS = Progression-free survival

RT = Radiotherapy

SBRT = Stereotactic body radiotherapy

SUV = Standardized uptake value