Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Johnson JT, Barnes EL, Myers EN, Schramm VL, Jr., Borochovitz D, Sigler BA. The extracapsular spread of tumors in cervical node metastasis. *Arch Otolaryngol* 1981; 107(12):725-729.	15	177 radical neck dissections	To test the validity of the assumption that nodes <3 cm in diameter do not have ECS; specimens were reviewed retrospectively with regard to ECS.	65% of nodes ≤2.9 cm in diameter were found to demonstrate ECS. No substantial difference was found in the number of patients who had no histologic disease in their necks when compared with a second group of patients who had metastasis confined to the lymph node. The patients whose lesions had ECS had statistically significantly reduced numbers of survivors. Other factors, eg, tumor differentiation and the number of malignant nodes, had no prognostic importance.	3
2. Snow GB, Annyas AA, van Slooten EA, Bartelink H, Hart AA. Prognostic factors of neck node metastasis. *Clin Otolaryngol Allied Sci* 1982; 7(3):185-192.	15	405 patients with SCC of the head and neck had 484 radical neck dissections	Retrospective clinico-pathological study in a series of patients with SCC of the head and neck who had neck dissections.	Recurrence rate in the neck in 327 patients who had histological positive nodes was 21.1%. Histological factors such as extra-nodal spread and the number of histological positive nodes have been shown to be of much more prognostic importance than clinical parameters. When corrections are made for interdependencies between variables, histological extra-nodal spread proved to be the most important single prognostic factor (P<10).	3

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
3. Tupchong L, Scott CB, Blitzer PH, et al. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. *Int J Radiat Oncol Biol Phys* 1991; 20(1):21-28.	1	277 patients 141 PORT patients 136 reoperative RT patients	A report of a 10-year median follow-up of a randomized, prospective study investigating the optimal sequencing of RT in relation to surgery for operable advanced head and neck cancer.	• Loco-regional control was significantly better for PORT patients than for preoperative RT patients (P=0.04), but absolute survival was not affected (P=0.15). • When the analysis was restricted to supraglottic larynx primaries (60 PORT patients vs 58 preoperative RT patients), the difference for loco-regional control was highly significant (P=.007), but not for survival (P=0.18). • In considering only supraglottic larynx, 78% of loco-regional failures occurred in the first 2 years. 31% (18/58) of preoperative patients failed locally within 2 years vs 18% (11/60) of postoperative patients. • After 2 years, distant metastases and second primaries became the predominant failure pattern, especially in PORT patients. • Because of an increased incidence of late distant metastases and secondary primaries, additional therapeutic intervention is required beyond surgery and PORT to impact significantly upon survival.	1

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
4. 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.	1	334 total patients 167 patients randomized to receive RT alone (66 Gy over a period of 6 1/2 weeks) 167 to receive the same RT regimen combined with 100 mg of cisplatin per square meter of body-surface area on days 1, 22, and 43 of the RT regimen	Randomized controlled trial to determine whether the addition of cisplatin to high-dose RT after radical surgery increases PFS in patients at high-risk for recurrent cancer. Concomitant cisplatin and irradiation was compared 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 (P=0.04 by the log-rank test; HR for disease progression, 0.75; 95 % CI, 0.56 to 0.99), 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 (P=0.02 by the log-rank test; HR for death, 0.70; 95 % CI, 0.52 to 0.95), with 5-year Kaplan-Meier estimates of OS of 53% and 40%, respectively. • The cumulative incidence of local or regional relapses was significantly lower in the combined-therapy group (P=0.007). The estimated 5-year cumulative incidence of local or regional relapses (considering death from other causes as a competing risk) was 31% after RT and 18% after combined therapy. Severe (grade 3 or higher) adverse effects were more frequent after combined therapy (41%) than after RT (21%, P=0.001); the types of severe mucosal adverse effects were similar in the two groups, as was the incidence of late adverse effects. • Postoperative concurrent administration of high-dose cisplatin with RT is more efficacious than RT alone in patients with locally advanced head and neck cancer and does not cause an undue number of late complications.	1

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
5. 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.	1	459 total patients 231 randomly assigned to receive RT alone (60-66 Gy in 30-33 fractions over a period of 6 to 6.6 weeks) 228 patients to receive the identical treatment plus concurrent cisplatin (100 mg/m^2 of body-surface area intravenously on days 1, 22, and 43)	Randomized trial to determine whether concurrent cisplatin therapy and PORT improve the rates of local and regional control among patients who have high-risk operable HNSCC.	• 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 RT alone (HR for local or regional recurrence, 0.61; 95 % CI, 0.41 to 0.91; P=0.01). • The estimated 2-year rate of local and regional control was 82% in the combined-therapy group, as compared with 72% in the RT group. • DFS was significantly longer in the combined-therapy group than in the RT group (HR for disease or death, 0.78; 95% CI, 0.61 to 0.99; P=0.04), but OS was not (HR for death, 0.84; 95% CI, 0.65 to 1.09; P=0.19). • The incidence of acute adverse effects of grade 3 or greater was 34% in the RT group and 77% in the combined-therapy group (P<0.001). Four patients who received combined therapy died as a direct result of the treatment. • Among high-risk patients with resected HNSCC, concurrent postoperative chemotherapy and RT significantly improve the rates of local and regional control and DFS. However, the combined treatment is associated with a substantial increase in adverse effects.	1
6. Maccomb WS, Fletcher GH. Planned combination of surgery and radiation in treatment of advanced primary head and neck cancers. *Am J Roentgenol Radium Ther Nucl Med* 1957; 77(3):397-414.	5	Case reports of patients	To demonstrate the systematic use of planned combination of surgery and radiation in treatment of advanced primary head and neck cancers. Case reports demonstrating results obtained with combined treatment were mentioned.	Group of cases presented shows the effectiveness with which surgery and RT can be used, the one augmenting the other in patients presenting malignant tumors in advanced stages or in sites offering but little hope of control by one modality alone.	4

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
7. Lavaf A, Genden EM, Cesaretti JA, Packer S, Kao J. Adjuvant radiotherapy improves overall survival for patients with lymph node-positive head and neck squamous cell carcinoma. *Cancer* 2008; 112(3):535-543.	3a	8,795 patients	Retrospective review of high-quality, population-based data to examine the frequency and effect of adjuvant RT on OS in patients with resected lymph node-positive HNSCC.	• Adjuvant RT was utilized in 84% of patients. Adjuvant RT improved the 5-year OS (43.2%, 95% CI, 41.9-44.4] for surgery + RT vs 33.4% [95% CI, 30.7-36.0] for surgery alone; P<.001) and cancer-specific survival (50.9% for surgery + RT vs 42.1% for surgery) on univariate analysis. • On multivariate analysis, adjuvant RT (HR of 0.78; 95% CI, 0.71-0.86 [P<.001]) remained a significant predictor of improved survival. The significant benefit of RT on OS was noted for lymph node-positive patients with both primary tumors localized to the involved organ (HR of 0.81; 95% CI, 0.71-0.94 [P=.007]) and more locally invasive primary tumors (HR of 0.77; 95% CI, 0.68-0.87 [P<.001]). • Despite combined surgery and adjuvant RT, outcomes in this high-risk population remain suboptimal, emphasizing the need for continued investigation of innovative treatment approaches.	2

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
8. Kao J, Lavaf A, Teng MS, Huang D, Genden EM. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. *Int J Radiat Oncol Biol Phys* 2008; 71(2):362-370.	3a	5,297 patients with node-positive (N1 to N3) HN cancer	Retrospective review of high-quality population-based dataset to determine the impact of adjuvant radiation on cancer-specific and OS in various subgroups of patients with node-positive head-and-neck cancer.	• Adjuvant RT significantly improved 5-year OS (46.3%: 95% CI, 44.7-48.0 for surgery + RT, vs 35.2%: 95% CI, 32.0%-38.5% for surgery alone, P<0.001) and cancer-specific survival (54.8%: 95% CI, 53.2-56.4 for surgery + RT, vs 46.2% for surgery alone 95% CI, 42.4-50.0, P<0.05). • Adjuvant RT remained a significant predictor of survival on multivariable analysis (HR, 0.75; 95% CI, 0.68-0.83; P<0.001). • Subset analyses demonstrated that adjuvant RT was associated with significantly improved survival for N1 (HR, 0.78; 95% CI; 0.67-0.90; P=0.001), N2a (HR, 0.82; 95% CI, 0.67-0.99, P= 0.048) and N2b to N3 nodal disease (HR, 0.62; 95% CI, 0.51-0.75; P<0.001). • Adjuvant RT increased OS for node-positive patients with oropharynx (HR, 0.72; 95% CI, 0.57-0.90; P=0.004), hypopharynx (HR, 0.66; 95% CI, 0.49 to 0.88; P=0.004), larynx (HR, 0.66; 95% CI, 0.52-0.84; P=0.001), and oral cavity (HR, 0.84; 95% CI, 0.73-0.98; P=0.025) primary tumors.	2

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
9. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001; 51(3):571-578.	1	213 total patients 31 patients no PORT for low-risk group 31 patients 57.6 Gy during 6.5 weeks, intermediate-risk group 76 patients 63 Gy during 5 weeks 75 patients 7 weeks for the high-risk group	Multicenter, prospective, randomized trial undertaken in patients with advanced HNSCC to address: 1. the validity of using pathologic risk features, established from a previous study, to determine the need for, and dose of PORT; 2. the impact of accelerating PORT using a concomitant boost schedule; and 3. the importance of the overall combined treatment duration on the treatment outcome.	• Patients with low or intermediate risks had significantly higher loco regional control and survival rates than those with high-risk features (P=0.003 and P= 0.0001, respectively), despite receiving no PORT or lower dose PORT, respectively. • For high-risk patients, a trend toward higher loco regional control and survival rates was noted when PORT was delivered in 5 rather than 7 weeks. • A prolonged interval between surgery and PORT in the 7-week schedule was associated with significantly lower loco regional control (P= 0.03) and survival (P=0.01) rates. • Consequently, the cumulative duration of combined therapy had a significant impact on the loco regional control (P=0.005) and survival (P=0.03) rates. A 2-week reduction in the PORT duration by using the concomitant boost technique did not increase the late treatment toxicity.	1
10. Mishra RC, Singh DN, Mishra TK. Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. *Eur J Surg Oncol* 1996; 22(5):502-504.	1	140 total patients 80 PORT arm 60 no further treatment following surgery	Randomized trial to determine the role of PORT in enhancing DFS. Patients with stages III and IV cancer of the buccal mucosa potentially curable by surgery were randomized to surgery only or PORT.	DFS at the end of the study was 38% and 68% (P<0.005), respectively. PORT was thus seen to improve DFS in SCC of the buccal mucosa.	2
11. 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.	1	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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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
12. Cooper JS, Pajak TF, Forastiere A, et al. Precisely defining high-risk operable head and neck tumors based on rtog #85-03 and #88-24: Targets for postoperative radiochemotherapy? *Head & Neck* 1998; 20(7):588-594.	7	N/A	Review data derived from Radiation Therapy Oncology Group (RTOG) protocols #85-03 and #88-24 to identify characteristics of tumors that predicted local-regional recurrence of disease following surgery and PORT.	The presence of tumor in two or more lymph nodes, and/or ECS of nodal disease, and/or microscopic-size tumor involvement of the surgical margins of resection impart a high risk of local-regional relapse. Data also support the hypothesis that, following surgery, the concurrent addition of chemotherapy to RT may increase the likelihood of local-regional control of disease for patients who have these high-risk characteristics. A prospective trial of surgery followed by concurrent RT and chemotherapy is warranted for patients who have high-risk characteristics found at surgery.	3
13. Schiff PB, Harrison LB, Strong EW, et al. Impact of the time interval between surgery and postoperative radiation therapy on locoregional control in advanced head and neck cancer. *J Surg Oncol* 1990; 43(4):203-208.	3a	111 patients with AJCC stages III and IV	To evaluate the impact of the time interval between surgery and PORT on locoregional control in advanced head and neck cancer.	The current analysis suggests that a prolonged delay in PORT in itself does not have a negative impact on locoregional control as long as appropriate tumorcidal doses of more than 60 Gy are employed.	2
14. Vikram B, Strong EW, Shah J, Spiro RH. Elective postoperative radiation therapy in stages III and IV epidermoid carcinoma of the head and neck. *Am J Surg* 1980; 140(4):580-584.	3a	105 patients	To evaluate elective PORT in stages III and IV epidermoid carcinoma of the head and neck.	• Follow-up periods range from 16 to 66 months. • 19 patients (18%) have had recurrence in the head and neck area. • When RT was started no later than 6 weeks after surgery, only 3/54 patients (5.5%) had local recurrence, but when there was a longer delay 16/51 patients (31.5%) had recurrence. • These results suggest that elective PORT improves local control in patients with advanced head and neck cancer, but that it should be delivered soon after surgery for maximum effectiveness.	2

Adjuvant Therapy for Resected Squamous Cell Carcinoma of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. Rosenthal DI, Harris J, Forastiere AA, et al. Early postoperative paclitaxel followed by paclitaxel and cisplatin concurrent with radiation therapy (RT) (phase II trial RTOG H-0024) is well tolerated for patients with resected, high-risk squamous carcinoma of the head and neck (HNSCC). *International journal of radiation oncology, biology, physics* 2004; 60(1):S322.	2	64 total patients 45 had nodal risk 19 had positive margins	To test a regimen of early postoperative chemotherapy followed by concurrent chemoradiation. This approach was designed to combat the regenerative response of sub-clinical tumor clones persisting in a growth factor-rich postoperative tumor bed in patients receiving PORT for high-risk HNSCC.	Primary tumor sites included: oropharynx 21 (33%), oral cavity 23 (36%), larynx 15 (23%), and hypopharynx 5 (8%). Primary tumor T-stages were: T4: 26 (41%), T3: 11 (17%), T2: 18 (28%), and T1: 5 (8%), Tis 2 (3%), and unknown 2 (3%). Fifty-five (86%) had N2, 6 (9%) had N1, and 2 (3%) had N0 disease; the nodal status of one was unknown. The estimated compliance rate is 71.9% [95% CI, (59.2%, 82.4%)]. There was one treatment-related death from myocardial ischemia. Six additional patients experienced grade 4 nonhematologic toxicities. There was one fistula, and no serious wound infections were reported. Early postoperative induction chemotherapy followed by concurrent chemoradiation therapy is safe and well tolerated.	2
16. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005; 27(10):843-850.	7	Data from 2 trials	Comparative analysis of concurrent PORT plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501) to define risk levels in locally advanced head and neck cancers.	Data suggest that in locally advanced head and neck cancer, microscopically involved resection margins and ECS of tumor from neck nodes are the most significant prognostic factors for poor outcome. The addition of concomitant cisplatin to PORT improves outcome in patients with one or both of these risk factors who are medically fit to receive chemotherapy.	3
17. Woolgar JA, Triantafyllou A. A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection specimens. *Oral Oncol* 2005; 41(10):1034-1043.	4	301 consecutive radical resections	Study of routine diagnostic material to describe the frequency, type and morphological features of involved margins, and assess the influence of tumor site and pathological T and N stage.	• 70 resections (23%) had involved margins. • The frequency was related to primary tumor site, and pathological T and N stage. • Mucosal involvement was evident in 11 resections, bone in 10, and deep soft tissue in 61. • 12 resections had multiple category involvement. • Both anatomical factors and histological "markers" of tumor characteristics influence the status of surgical resection margins.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
18. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. *Head Neck* 1997; 19(4):281-286.	4	10 mongrel dogs	To quantify the change in size of mucosal and muscle surgical margins following excision, formalin fixation, and slide preparation of tongue and labiobuccal tissue in a canine model.	• The mean shrinkage from initial resection to final microscopic assessment of the lingual surface mucosal margins was 30.7% (P<0.0001). • The deep tongue margin shrank 34.5% (P<0.0001). • The mean shrinkage of the labiobuccal mucosal margin was 47.3% (P<0.0001). • In all cases, the greatest proportion of shrinkage occurred immediately upon resection. • From the in-situ measurement by the surgeon to final pathologic evaluation on the microscope slide, the measured dimensions of oral cavity mucosal and tongue muscle margins shrink significantly. To obtain 5 mm of pathologically clear margin an in-situ margin of resection of at least 8 to 10 mm needs to be taken. Studies reporting clinical correlation of recurrence and survival information with surgical margin status should include a detailed description of the technique used to determine the reported surgical margin status.	4
19. Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. *Int J Radiat Oncol Biol Phys* 1989; 16(1):25-36.	4	134 patients	Retrospective analysis of the results of PORT for HNSCC.	Two factors were found to significantly increase the probability of death due to cancer: a) neck stage (N0-1 vs N2-3); b) extension of tumor from the primary site into the skin or soft-tissues of the neck. Overall, 7% of patients experienced a severe complication of combined therapy.	2
20. Looser KG, Shah JP, Strong EW. The significance of "positive" margins in surgically resected epidermoid carcinomas. *Head Neck Surg* 1978; 1(2):107-111.	7	62 patients	To determine the incidence of local recurrence, the subsequent clinical course, and survival in patients with epidermoid carcinomas of the head and neck. A review of the literature is presented, and recommendations are made for this clinical setting.	Four histologic findings are classified as positive margins: 1) margin closeness (tumor within 0.5 cm), 2) premalignant change in the margin, 3) in-situ cancer in the margin, and 4) invasive microscopic cancer at the margin. Patients with these variants showed a significant increase in local recurrence and in mortality when compared to those with negative margins.	3

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
21. Meier JD, Oliver DA, Varvares MA. Surgical margin determination in head and neck oncology: current clinical practice. The results of an International American Head and Neck Society Member Survey. *Head Neck* 2005; 27(11):952-958.	15	476 completed surveys	To examine ways in which surgeons who perform head and neck ablative procedures on a regular basis define margins, how they use frozen sections to evaluate margins, and the effect of chemoradiation on determining tumor margins.	No uniform criteria to define a clear surgical margin exist among practicing head and neck surgeons. Most head and neck surgeons consider margins clear if resection completed after an initial positive frozen section margin reveals negative margins, but this view is not shared by all. Most surgeons take frozen sections from the surgical bed; however, error may occur when identifying the positive margin within the surgical bed. The definition of a clear tumor margin after chemoradiation is unclear. These questions could be addressed in a multicenter prospective trial.	4
22. Sawair FA, Irwin CR, Gordon DJ, Leonard AG, Stephenson M, Napier SS. Invasive front grading: reliability and usefulness in the management of oral squamous cell carcinoma. *J Oral Pathol Med* 2003; 32(1):1-9.	4	102 cases of intraoral SCC from Northern Ireland	To examine the value of histological grading with emphasis on reliability of assessment.	• Intraobserver agreement was acceptable but interobserver agreement was not satisfactory. The degree of keratinisation was assessed most consistently while nuclear polymorphism was the least reliable feature. • Multivariate survival analysis showed that the total grading score was associated with OS while the pattern of tumor invasion was the most valuable feature in estimating regional lymph node involvement. • The number of positive lymph nodes was strongly associated with regional relapse, while the treatment modality and status of the surgical margins correlated with local relapse. • Grading of selected features in oral SCC is reliable and can facilitate treatment planning.	2
23. Harrison D. The questionable value of total glossectomy. *Head Neck Surg* 1983; 6(2):632-638.	4	104 patients	To evaluate the value of total glossectomy.	The high rate of local recurrence that occurred when partial glossectomy followed curative RT suggests that in selected patients total glossectomy is of value. Patients with more extensive tumors requiring total laryngectomy are rarely cured and the procedure entails serious rehabilitation problems.	3

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
24. Batsakis JG. Surgical excision margins: a pathologist's perspective. *Adv Anat Pathol* 1999; 6(3):140-148.	7	N/A	Review on the current applications and the clinical implications of surgical margins for the removal of SCC in these tracts.	Specific points addressed in this article are: 1) postremoval (artifactual) changes in measurements; 2) the impact of margin status, as currently assessed, on recurrence and patient outcome; 3) margins and conservation surgery of the larynx; 4) margins and bone (mandible) invasion; and 5) molecular (p53 and eIF4E) margins.	4
25. Chao KS, Emami B, Akhileswaran R, Simpson J, Spector G, Sessions D. The impact of surgical margin status and use of an interstitial implant on T1, T2 oral tongue cancers after surgery. *Int J Radiat Oncol Biol Phys* 1996; 36(5):1039-1043.	4	55 patients	To determine whether positive surgical margin remains a poor prognostic factor after RT, and the contribution of interstitial implants to disease control.	• At 2 and 5 years, the OS for all patients were 82% and 68%. • The DFS was 82% and 70%, respectively. • There was no significant difference in the pattern of failure and DFS when stratified by the status of surgical margins and the type of the surgical procedure. • Local control was achieved in 15/18 patients when surgical margins were involved by tumor and in 29/37 patients without tumor involving margins (P>0.05). 10/18 (56%) patients with tumor involving resection margins were treated with interstitial implant, whereas only 3/33 (9%) of those with negative margins received interstitial implant • Local control was achieved in 32/39 patients treated with EBRT alone, and 13/16 patients who received interstitial implant (P>0.05). • Four patients treated with interstitial implant developed persistent soft tissue ulceration and mandibular bone exposures.	3
26. Beitler JJ, Smith RV, Silver CE, et al. Close or positive margins after surgical resection for the head and neck cancer patient: the addition of brachytherapy improves local control. *Int J Radiat Oncol Biol Phys* 1998; 40(2):313-317.	3a	29 patients	To demonstrate improved local control in head and neck cancer patients who had a resection with curative intent, and had unexpected, microscopically positive or close surgical margins.	29 patients were followed for a median of 26 months (range 5-86 months). 2-year actuarial local control was 92%. 125I, after EBRT, is an excellent method to improve local control in the subset of patients with unexpectedly unsatisfactory margins.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
27. Fujita M, Hirokawa Y, Kashiwado K, et al. Interstitial brachytherapy for stage I and II squamous cell carcinoma of the oral tongue: factors influencing local control and soft tissue complications. *Int J Radiat Oncol Biol Phys* 1999; 44(4):767-775.	3a	207 total stage I and II SCC of the oral tongue 127 treated by interstitial brachytherapy alone 80 combination using EBRT	To study the treatment parameters that influence local control and soft tissue complications in a series between 1980 and 1993.	• The 5-year local recurrence-free rate for T1, T2a, and T2b was 92.9%, 81.9%, and 71.8%, respectively (P<0.05). • The 5-year crude survival rate for T1, T2a, and T2b was 83.4%, 66.0%, and 70.9%, respectively. • To achieve better local control and fewer soft tissue complications, the following relationships between dose and dose rate are recommended. In brachytherapy alone, dose rate should be maintained at < 0.6 Gy/h with a preferable brachytherapy dose 65-70 Gy. • In the combined treatment, total dose, brachytherapy dose and dose rate should be kept between >85 Gy and ≤100 Gy, between >55 Gy and ≤70 Gy, and <0.55 Gy/h, respectively. • It is also recommended to have longer follow-up periods; more than 5 years might be necessary for late local recurrences and for secondary cancers.	2
28. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys* 1996; 36(5):999-1004.	1	83 total patients 44 patients treated by RT only (RT group) 39 by RT with chemotherapy	To report the final results of a prospective randomized trial that aimed to evaluate efficacy and toxicity of concomitant PORT and Cisplatin infusion in patients with stage III or IV HNSCC and histological evidence of ECS of tumor in lymph node metastases.	The RT group displayed a higher rate of loco-regional failures as compared to chemotherapy group (41 vs 23%; P=0.08). The OS, the survival corrected for deaths by intercurrent disease, and the DFS were better in chemotherapy group as compared to RT group with statistically significant differences. Survival without loco-regional treatment failure was better in the chemotherapy group, the difference being close to the level of significance (P=0.05). Survival without distant metastases was comparable in the two therapeutic groups. Ten severe late complications were observed, four in the RT group (17%) and six in the chemotherapy group (22%). Cox univariate analysis confirmed the importance of the therapeutic modality in predicting the OS, the survival corrected for deaths by intercurrent disease, and the DFS.	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
29. Fietkau R, Lautenschlager C, Sauer R, et al. Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: Results of the German phase III trial ARO 96-3. *J Clin Oncol (Meeting Abstracts)* 2006; 24(18_suppl):5507.	1	440 total patients with high-risk HNSCC 214 randomized to RT (66 Gy/33 Fx/6.6 weeks) 226 to identical RT plus Cisplatin (20 mg/m^2 on day 1–5, 29–33) and 5-FU (600 mg/m^2 on day 1–5, 29–33)	Postoperatively radiochemotherapy with Cisplatin/5-FU vs RT alone was compared in a prospective randomized phase III trial.	The 5 year local-regional control rate is 72.2 ± 3.7% following RT and 88.6 ± 2.4% for the radiochemotherapy group (P=0.00259; 5-year progression free survival 50.1 ± 4.0% and 62.4 ± 4.4% (P=0.024) and 5-year OS 48.6 ± 4.4% vs 58.1 ± 4.6% (P=0.11). There was no difference in the 5 year incidence of distant metastases (19.3 ± 3.6% vs 25.5 ± 4.6%; P=0.45). The incidence of grade 3+ acute toxicity was higher during RCT: mucositis 12.6% vs 20.8% (P=0.04), leucopenia 0% vs 4.4% (P=0.007). Acute toxicity is increased to an acceptable level by radiochemotherapy. Postoperative radiochemotherapy compared to RT improves locoregional control and progression free survival; thus survival as a trend is improved by 10% after 5 years.	1

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

5-FU = Fluorouracil

CI = Confidence interval

DFS = Disease-free survival

EBRT = External-beam radiation therapy

ECS = Extracapsular spread

HNSCC = Head and neck squamous-cell carcinoma

HR = Hazard ratio

OS = Overall survival

PFS = Progression-free survival

PORT = Postoperative radiotherapy

RT = Radiation therapy

SCC = Squamous cell carcinoma