**American College of Radiology**
**ACR Appropriateness Criteria®**

# RETREATMENT OF RECURRENT HEAD AND NECK CANCER
# AFTER PRIOR DEFINITIVE RADIATION

Expert Panel on Radiation Oncology–Head & Neck Cancer: Mark W. McDonald, MD[1]; Jonathan J. Beitler, MD, MBA[2]; Paul M. Busse, MD, PhD[3]; Jay S. Cooper, MD[4]; Shlomo Koyfman, MD[5]; Harry Quon, MD, MS[6]; John A. Ridge, MD, PhD[7]; Nabil F. Saba, MD[8]; Joseph K. Salama, MD[9]; Farzan Siddiqui, MD, PhD[10]; Richard V. Smith, MD[11]; Francis Worden, MD[12]; Min Yao, MD, PhD[13]; Sue S. Yom, MD, PhD.[14]

## Summary of Literature Review

### Introduction/Background

Despite treatment intensification for patients with head and neck squamous cell carcinoma (HNSCC), including altered radiation fractionation and the addition of chemotherapy to radiation, physicians and patients still face the challenge of recurrent or second tumors arising within or in close proximity to previously irradiated tissues. At 5 years after therapy, locoregional recurrences developed in 16%–25% of patients treated with definitive chemoradiation for larynx preservation [1] or with postoperative chemoradiation for high-risk HNSCC [2,3], and in 17%–52% of patients treated with definitive chemoradiation for locally advanced unresectable disease [4,5]. Locally recurrent tumors may arise from residual neoplastic cells that survive initial treatment, perhaps because of biological parameters and tumor molecular profiles [6] associated with radiosensitivity [7]. Insufficiencies in initial radiation treatment parameters, such as radiation dose, volume, fractionation, and treatment duration, were noted in a high percentage of patients enrolled on a small phase I trial of reirradiation [8] and are other potential sources of recurrence. Second cancers may arise from underlying field cancerization [9] as a radiation-induced malignancy or as a *de novo* process. A second HNSCC arising in the vicinity of the prior tumor may be indistinguishable from a local recurrence of the primary tumor [10]. Approximately 15% of patients have developed a second primary cancer within 5 years of radiation alone for HNSCC, and approximately one-quarter of these are in the head and neck [11].

### Rationale for Retreatment

Because locoregional tumor progression is the predominant cause of death in patients with head and neck cancer [12], achieving local control in patients with recurrent disease may impact survival. Indeed, results of a randomized trial in patients with recurrent HNSCC undergoing macroscopic complete salvage surgery found improved local control and disease-free survival in those receiving postoperative reirradiation with chemotherapy compared to observation [13]. In that trial, retrospective analysis of a single institution experience found improved overall survival when local tumor control was achieved in patients reirradiated for recurrent head and neck cancer [14].

In patients with recurrent or second primary tumors of the head and neck, local tumor growth is a potential source of great morbidity to include pain, disfigurement, bleeding, infection, and alteration of speech and swallowing. In a report of 150 patients reirradiated for head and neck cancer using stereotactic body radiotherapy (SBRT) with or without cetuximab, patient-reported quality of life, after an initial 1-month decline following reirradiation, noted progressive improvements in swallowing, speech, saliva, activity, and recreation, underlining the importance of local tumor control on patient quality of life [15].

[1]Principal Author, Indiana University School of Medicine, Indianapolis, Indiana. [2]Emory University School of Medicine, Atlanta, Georgia. [3]Massachusetts General Hospital, Boston, Massachusetts. [4]Maimonides Cancer Center, Brooklyn, New York. [5]Cleveland Clinic, Cleveland, Ohio. [6]Johns Hopkins University, Baltimore, Maryland. [7]Fox Chase Cancer Center, Philadelphia, Pennsylvania, American College of Surgeons. [8]Emory University, Atlanta, Georgia, American Society of Clinical Oncology. [9]Duke University, Durham, North Carolina. [10]Henry Ford Health System, Detroit, Michigan. [11]Montefiore Medical Center, Bronx, New York, American College of Surgeons. [12]University of Michigan, Ann Arbor, Michigan, American Society of Clinical Oncology. [13]University Hospitals Case Medical Center, Cleveland, Ohio. [14]Panel Chair, University of California San Francisco, San Francisco, California.

## Patient Evaluation and Selection for Retreatment

Patients presenting with recurrent or second primary tumors should undergo careful restaging evaluation prior to committing the patient to aggressive therapy with curative intent, be it surgery or reirradiation. In addition to the use of computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the extent of the recurrent tumor, positron emission tomography (PET)/CT or, at a minimum, chest CT, should be strongly considered to evaluate for metastatic disease [16]. In addition to documenting the extent of recurrent disease, the evaluation should include an assessment of the patient's comorbidities and life expectancy, performance status, speech and swallowing function, nutritional status, severity of current symptoms, expectations of retreatment, and documentation of sequelae of prior treatment, such as fibrosis, carotid stenosis, dysphagia, xerostomia, or osteoradionecrosis. Patients with metastatic disease, poor performance status, or severe toxicity from prior radiation are typically poor candidates for reirradiation. In addition to careful patient selection, the panel strongly recommends evaluation and treatment at care centers with an experienced head and neck oncology team equipped with the resources and experience to manage the complexities and toxicities of retreatment. (See Variant 1).

## Resectable Disease Recurrence

For patients with operable disease recurrence, surgical resection is considered the standard of care and may provide long-term disease control in 25%–45% of patients [17,18] and upwards of 80% in patients with small recurrent laryngeal tumors [19]. In multivariate analysis of pooled data from 9 phase I and II trials of reirradiation with chemotherapy for recurrent head and neck cancer, salvage surgical resection or debulking was associated with a lower hazard ratio (HR) for death (HR 0.52, $P$=.0006) [20]. In contrast, multivariate analysis of a large single institution experience found no statistically significant association between survival and salvage surgery, although increasing size of residual tumor after salvage surgery was associated with an increased risk of death (HR 1.12 per cm, $P$<.0001) [21]. These disparate findings likely highlight the inability of retrospective analyses to fully account for patient selection in therapeutic decision-making.

However, even patients who undergo complete resection of recurrent disease with uninvolved margins have a risk of local failure as high as 59% [22]. Single institution series have demonstrated the feasibility and efficacy of postoperative reirradiation alone [23] or with concurrent chemotherapy [24] in patients at significant risk of further local recurrence, including those with gross residual disease, involved margins, or extracapsular extension. A phase III multicenter trial conducted by the Groupe d'Etude des Tumeurs de la Tête et du Cou and the Groupe d'Oncologie et de Radiothérapie Tête Et Cou randomized the care of patients with recurrent HNSCC in previously irradiated tissue after macroscopic complete surgical resection to observation or reirradiation with chemotherapy [13]. Both local control and disease-free survival (the primary endpoint) were improved in patients receiving postoperative reirradiation and chemotherapy, with an HR of 1.68, although there was no apparent difference in overall survival compared with those observed after surgery. Grade 3 or 4 acute toxicity was seen in 28% of those reirradiated, and at 2 years late-grade 3 or 4 toxicity was as high as 40%, compared with 10% in those randomized to postoperative observation. Nearly half of the patients randomized to observation had a subsequent local recurrence, and half of those received salvage reirradiation with chemotherapy. (See Variant 2).

## Unresectable Disease Recurrence

Significant proportions of patients with recurrent disease have tumors that are technically unresectable, or the patients are medically unfit for surgery or refuse radical surgery [25]. In these patients, palliative chemotherapy has been considered the standard of care. Multiagent chemotherapy regimens may have a response rate near 35%, but results are rarely durable, and long-term survival is rare [26]. Incorporation of newer biological agents may improve outcomes [27]. Results from the phase III multicenter EXTREME trial in patients with recurrent or metastatic HNSCC found that the addition of cetuximab to platinum and fluorouracil chemotherapy improved median survival to 10.1 months compared with 7.4 months for those receiving platinum-fluorouracil alone [28]. All patients included in the trial had been deemed ineligible for further local therapy with surgery or radiation, and approximately half of the patients had only locoregional disease without evidence of distant metastatic spread.

For patients with unresectable disease, reirradiation is the only potentially curative treatment. The Radiation Therapy Oncology Group[®] (RTOG[®]) has completed 2 phase II studies using reirradiation and chemotherapy in this population. RTOG 96-10 [29] used concurrent hydroxyurea and 5-fluorouracil and achieved a median survival of 8.5 months and a 2-year survival rate of 15.2%, whereas RTOG 99-11 [30] employed concurrent cisplatin and paclitaxel with a median survival of 12.1 months and a 2-year survival rate of 25.9%. A 5-year

overall survival estimate of 14.3% was reported from pooled analysis of 9 prospective trials from a single institution, suggesting that reirradiation with chemotherapy is potentially curative in a small proportion of patients [20]. Acute toxicity reported in both RTOG studies was high. In RTOG 99-11, nearly half developed grade 3 toxicity, 23% for grade 4, and an additional 5% reached grade 5 toxicity (death). Although these 2-year survival outcomes appear superior to series of patients treated with chemotherapy alone, whether this apparent improvement is the result of selection bias is uncertain. A phase III trial randomizing patients with locally recurrent previously irradiated HNSCC to reirradiation with chemotherapy or chemotherapy alone was opened by the RTOG but closed secondary to poor accrual.

**Nodal Disease Relapse**

The prognosis for patients with recurrent neck disease after previous nodal irradiation is poor [25,31]. However, patients with cervical lymph node recurrence, alone or in combination with primary site recurrence, were included in the RTOG phase II studies [29,30], in institutional series of reirradiation [32,33], and in the randomized trial of reirradiation with chemotherapy following macroscopic complete resection [13]. Initial experience with CT-guided interstitial high dose-rate brachytherapy in a retrospective report of highly selected patients also reported favorable rates of local control and survival outcomes comparable to the RTOG trials of reirradiation and chemotherapy [34]. The Eastern Cooperative Oncology Group (ECOG) has an ongoing clinical trial (ECOG 1311) for patients at 6 to 16 weeks after completion of chemoradiation therapy for HNSCC and who undergo salvage neck dissection for persistent nodal disease. In ECOG 1311, patients are randomized to afatinib or placebo. (See Variant 3.)

**Nasopharynx**

Local failure, with or without recurrent nodal disease, may develop in 8%–10% of patients treated with chemoradiation for nasopharyngeal carcinoma [35,36]. A large retrospective analysis suggests patients undergoing reirradiation or nasopharyngectomy for recurrent disease have improved overall survival compared with those who receive chemotherapy alone or no salvage treatment, although selection bias exists and, in one series, the benefit appeared confined to patients with T1-T2 recurrence [37]. Patients with local-only recurrence have shown improved outcomes compared to those with local and nodal recurrence [38]. Experience with nasopharyngeal retreatment has included combinations of nasopharyngectomy, chemotherapy, external beam radiation therapy (EBRT), brachytherapy, intraoperative radiotherapy, hyperthermia, stereotactic radiosurgery, hypofractionated stereotactic radiotherapy (FSRT), and proton therapy [38]. Across these modalities, mortality with retreatment is <5% [37]. Advances in skull-base surgery have increased the feasibility of salvage nasopharyngectomy. Long-term local control after salvage nasopharyngectomy has been reported in 58% of patients with recurrent T1 disease and in 28% in patients with recurrent T2 disease, with approximately 40% of patients receiving postoperative reirradiation as well, usually because of involved margins [39]. Superior results were seen in a series of patients in whom endoscopic en-bloc resections were achieved [40]. Brachytherapy alone appears to be very successful in salvaging limited-volume recurrent disease (recurrent T1 or minimal T2) with long-term local control approaching 90% [41].

A small institutional study of reirradiation with chemotherapy for recurrent T1-T4 nasopharynx disease found no difference in local control or survival for patients treated with EBRT or those treated with combined EBRT and brachytherapy, but grade 3 or worse late toxicity was 8% when treatment incorporated brachytherapy, versus 73% with EBRT alone, although there were more advanced recurrent T-stage patients among those treated with EBRT alone [42]. Multivariate analysis in a larger series found that only the recurrent T stage predicted central nervous system complications [43]. When EBRT alone is used, disease control appears superior when reirradiation doses of ≥60 Gy are employed [37]. In addition to the published experience with intensity modulated radiation therapy (IMRT) for primary treatment of nasopharyngeal carcinoma, this technique has demonstrated its feasibility for retreatment of locally recurrent disease as well [14,44,45]. FSRT outcomes have been reported in small institutional series. Three to 5-year local failure-free survival rates of 75%–79% have been reported, with crude rates of serious toxicity reported at 16%–25%, including nasopharyngeal necrosis and hemorrhage [46,47]. (See Variant 4.)

**Radiation Technique, Volume, Fractionation, Dose, and Constraints**

Patients with recurrent HNSCC following prior radiation are a heterogeneous group. Differences in the location and extent of recurrent tumor, initial radiation treatment parameters, elapsed time since prior treatment, extent of normal tissue sequelae, and relatively sparse data on acute and late normal tissue recovery from prior treatment

and tolerance to reirradiation [48] pose a significant challenge to the formulation of widely applicable schemata for reirradiation.

The optimal treatment volume for reirradiation is uncertain. The RTOG phase II studies of reirradiation with chemotherapy targeted a volume created from a 2-cm expansion around the recurrent gross tumor volume. In an effort to limit the toxicity of retreatment, many reported experiences with reirradiation have targeted the recurrent gross disease with limited margin and not added elective nodal reirradiation. In a series of patients undergoing salvage surgery for local recurrence after initially irradiated clinically node-negative HNSCC, 29 of 30 patients undergoing elective node dissection were free of lymph node metastases [49], suggesting that lymphatic spread to a previously irradiated neck is uncommon. In patients who presented with initial neck disease or who have larger, inoperable local recurrences, the risk of recurrent nodal disease is unclear. Pattern of failure analysis in a series of 66 patients with unresectable recurrent HNSCC reirradiated with curative intent using a 0.5-cm margin around recurrent gross disease found that 45 of 47 patients (96%) who suffered a second local failure experienced recurrence within the retreatment volume [50]. Other patterns of failure analysis also suggest that limited reirradiation volumes that omit elective reirradiation of nodal areas are sufficient [51].

In terms of the dose delivered in the second treatment course, institutional data suggest a greater likelihood of local control with administration of at least 50 to 60 Gy in reirradiation [21,33,37,52]. Both RTOG phase II studies used an accelerated hyperfractionated regimen delivering 1.5 Gy twice daily in 4 week-on week-off cycles to a total dose of 60 Gy, a schedule previously developed at the University of Chicago [33]. Although this regimen appears to facilitate intensification of concurrent chemotherapy, it prolongs overall treatment time by introducing multiple planned radiation treatment breaks, which are necessary to manage toxicity but may be radiobiologically deleterious to local control [53]. In a phase I trial, researchers at University of Alabama were able to eliminate planned treatment breaks and deliver continuous course radiation with a delayed concomitant boost after making some dose reductions in concurrent 5-fluorouracil and hydroxyurea [54]. Multiple single institution reports of reirradiation have used once daily standard fractionation in a planned continuous treatment course with acute treatment-related deaths of 0%–1% [14,45,52,55] compared with the 5%–10% rate of acute grade 5 toxicity reported in studies using the accelerated hyperfractionated weekly cycle regimen [29,30,33,56]. Differences in study design, patient selection, and chemotherapy regimens make it difficult to discern what independent effect, if any, differences in radiation fractionation may have on the risk of acute grade 5 toxicity.

In an effort to improve dose conformality and minimize reirradiation of non-target tissues, many recently published institutional series of reirradiation have utilized IMRT [45]. In one retrospective series, reirradiation with IMRT was associated with improved local control compared to conventional radiation techniques [14]. This apparent improvement may stem from advantages in dose distribution with potentially better coverage of retreatment targets in close proximity to previously irradiated critical normal structures but may also reflect unmeasured biases such as improvements in patient staging, imaging, and increasing expertise with reirradiation. Proton therapy, a radiation modality with a finite range and no exit dose, has also been reported in reirradiation of nasopharyngeal cancer [57]. In light of the risk of significant toxicity to normal tissues with reirradiation, highly conformal techniques that limit the volume of reirradiation are preferred.

SBRT is a highly conformal, precisely targeted radiation technique that delivers a high dose of radiation to a limited volume in 1 to 5 fractions. An early institutional retrospective report [58] of SBRT in primary, recurrent, or metastatic HNSCC reported a 1-year tumor control rate of 60% for those with recurrent tumors and a median survival of 7 months. There was no apparent difference in results between those treated with one or 2–5 fractions. In a phase I dose-escalation trial of SBRT in reirradiation of head and neck cancer, a dose of 44 Gy in 5 fractions was delivered without reaching acute dose-limiting toxicity [59]. An institutional experience of 85 patients receiving SBRT (median 35 Gy in 5 fractions) for recurrent, previously irradiated head and neck cancer reported a 2-year local control of 31%, median overall survival of 11.5 months, and no grade 4 or 5 treatment-related toxicities. Treatment to doses of 35–44 Gy in 5 fractions was associated with improved local control compared to those receiving total doses <35 Gy in 5 fractions, with no discernible increase in acute or late toxicity [60]. In contrast, another institutional series reported a carotid blowout rate of 17% after reirradiation with SBRT (median 30 Gy in 5 fractions) [61]. A retrospective matched cohort study of SBRT (median 40 Gy in 5 fractions) with or without cetuximab suggests that the addition of concurrent cetuximab to SBRT improves both local control (49% at 2 years) and overall survival (53% at 2 years) compared to SBRT alone [62].

Normal tissue tolerances to reirradiation are poorly defined, and there are numerous potential contributing factors including patient comorbidities, interval from prior therapy, and the effect of partial volume dose. There are scant

data to guide expectations on risks or formulate dose constraints for soft tissues, bone, and neurovascular structures after reirradiation [48], especially with the large-dose fractions given with SBRT. Given the poor survival in patients with recurrent HNSCC, many patients may not survive long enough to see potential late normal tissue complications from reirradiation. Carotid blowout is an uncommon but usually fatal complication of salvage therapy that may occur in approximately 3% of patients receiving reirradiation based on a review of published series [63]. Spinal cord myelopathy is particularly feared as portions of the cervical spinal cord have typically already received 45–50 Gy, the conventional recommended tolerance dose, from the initial radiation treatment. Animal experiments in rhesus monkeys suggest substantial recovery of the cervical and upper thoracic spinal cord from initial radiation after just one year, with a low risk of myelopathy after reirradiation despite cumulative doses >100 Gy [64]. Human data include the apparent tolerance of full-dose reirradiation in children with recurrent intracranial ependymoma, suggesting that significant spinal cord and brainstem recovery occur [65]. Additional clinical data suggest that the risk of spinal cord myelopathy is rare when the interval between radiation courses is at least 6 months and when the cumulative biologically effective dose to the spinal cord (assuming an alpha/beta ratio of 2) is kept below 135.5 $Gy_2$ [66]. The RTOG phase II studies of reirradiation [29,30] and several institutional experiences [33,55,56] limited the cumulative spinal cord dose to 50 Gy; others to 60 Gy [67]; and others have allowed for normal tissue recovery of up to 50% of prior dose and delivered somewhat higher cumulative spinal cord doses [45], all with a reported risk of myelopathy of <1%. (See Variant 5.)

## Summary

- As in the management of initial disease, multidisciplinary evaluation and treatment of patients with recurrent or second primary head and neck cancer is critical.

- Surgical salvage is considered the standard of care for patients with technically resectable disease who are medically fit for surgery. Randomized data support the role of postoperative reirradiation with chemotherapy to improve local control and disease-free survival.

- Patient selection for reirradiation is critical. Additional data are needed to determine which patient subsets will most likely benefit from reirradiation. Patients with metastatic disease, poor performance status, or severe toxicity from prior radiation are typically poor candidates for reirradiation.

- For patients treated with curative intent, reirradiation with chemotherapy (including biologic agents) is preferred over reirradiation alone.

- For patients treated with curative intent, reirradiation to doses of 60 Gy or greater to the recurrent disease are recommended, and elective nodal reirradiation does not appear to be warranted. Conventional fractionation or hyperfractionation with a minimum 6-hour interval are favored.

- Highly conformal radiation techniques such as IMRT are recommended over less conformal modalities.

- Newer conformal radiation modalities, including stereotactic body radiation therapy and proton therapy, may be appropriate in select cases. Additional data are needed to determine which patient subsets will most likely benefit from these modalities.

## Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

## References

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.
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.
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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

40. Chen MY, Wen WP, Guo X, et al. Endoscopic nasopharyngectomy for locally recurrent nasopharyngeal carcinoma. *Laryngoscope.* 2009;119(3):516-522.

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.

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.

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.

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.

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.

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.

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.

48. Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. *Semin Radiat Oncol.* 2000;10(3):200-209.

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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.

**Clinical Condition:** Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation

**Variant 1:** 68-year-old man with T3N2bM0 pyriform sinus squamous cell carcinoma status/post concurrent chemoradiation (70 Gy gross disease/54 Gy uninvolved neck plus 3 cycles of cisplatin 100mg/m$^2$ q 21 days). Post-treatment follow-up is sparse, and one year after treatment, his family brings him for evaluation because of pain and significant weight loss. He has bulky, biopsy-proven recurrent disease in the hypopharynx with extensive prevertebral fascia involvement on imaging, in addition to bilateral neck lymphadenopathy. There is no evidence of distant disease on restaging. KPS is 50 (requires considerable assistance and frequent care).

| Treatment | Rating | Comments |
|---|---|---|
| Best supportive care/hospice | 9 | |
| Chemotherapy (including biologic agents) alone | 5 | |
| Reirradiation with palliative intent | 5 | |
| Reirradiation alone to the recurrent disease (primary and necks) with curative intent | 1 | |
| Reirradiation with chemotherapy with curative intent | 1 | |
| **Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | |

**Variant 2:** 60-year-old man with T3N2aM0 supraglottic squamous cell carcinoma status/post concurrent chemoradiation (70 Gy gross disease/54 Gy uninvolved neck plus 3 cycles of cisplatin 100mg/m$^2$ q 21 days). One year after treatment, he has biopsy-proven squamous cell carcinoma in the base of tongue, clinical T2, without evidence of distant or regional disease on restaging. Conservative resection at the base of tongue is performed with positive margins. There are no major complications in postoperative healing. KPS is 70 (cares for self, unable to carry on normal activity). Further surgical resection would require a total glossectomy, which the patient declines.

| Treatment | Rating | Comments |
|---|---|---|
| Reirradiation (using preferred technique) with chemotherapy with curative intent | 8 | |
| Reirradiation alone (using preferred technique) curative intent | 5 | |
| Close observation | 4 | |
| Chemotherapy (including biologic agents) alone | 3 | |
| **Reirradiation Technique** | | |
| External beam radiation | 6 | |
| Brachytherapy | 6 | |
| Combined external beam and brachytherapy | 6 | |
| **Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | |

**Clinical Condition:**   **Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation**

**Variant 3:**   **55-year-old man with pT4apN2bM0 glottic squamous cell carcinoma status/post total laryngectomy and postoperative concurrent chemoradiation (60 Gy postoperative bed and bilateral neck plus 3 cycles of cisplatin 100mg/m$^2$ q 21 days). One year after treatment, he has a 4-cm level III mass in his initially involved neck, which is squamous cell carcinoma on fine-needle aspiration. There is no evidence of distant disease on restaging. An ipsilateral salvage neck dissection is performed. There is extracapsular extension at the nodal mass; 16 additional lymph nodes are negative. There are no major complications in postoperative healing. KPS is 70.**

| Treatment | Rating | Comments |
|---|---|---|
| Reirradiation (using preferred technique) with chemotherapy with curative intent | 8 | |
| Close observation | 5 | |
| Reirradiation alone (using preferred technique) curative intent | 5 | |
| Chemotherapy (including biologic agents) alone | 3 | |
| **Reirradiation Technique** | | |
| External beam radiation | 8 | |
| Brachytherapy (assumes catheters placed at surgery) | 8 | |
| External beam plus brachytherapy or intraoperative | 8 | |
| Intraoperative radiation | 7 | |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

**Clinical Condition:** **Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation**

**Variant 4:** **53-year-old woman with T3N2 WHO grade 3 nasopharyngeal carcinoma treated 26 months ago with definitive chemoradiation (69.96 Gy to gross disease, 59.4 Gy elective volumes plus 3 cycles cisplatin 100mg/m$^2$ q 21 days and adjuvant cisplatin/5FU) presents with imaging consistent with T2-recurrence extending into the parapharyngeal space, which is confirmed on endoscopy and biopsy. Examination and imaging find no evidence of regional or distant disease. She tolerated initial treatment well and has chronic xerostomia but no evidence of CNS late toxicities. She has a KPS of 80 (normal activity with effort, some symptoms).**

| Treatment | Rating | Comments |
|---|---|---|
| Reirradiation (using preferred technique) with chemotherapy with curative intent | 7 | |
| Reirradiation alone (using preferred technique) curative intent | 6 | |
| Chemotherapy (including biologic agents) alone | 3 | |
| Nasopharyngectomy | 3 | This treatment may be more appropriate for smaller volume recurrence. Parapharyngeal extension is not generally amenable to complete surgical resection. |
| Best supportive care/hospice | 1 | |
| **Reirradiation Technique** | | |
| External beam alone to dose ≥60 Gy | 7 | |
| External beam plus stereotactic radiation boost | 6 | |
| External beam plus brachytherapy boost | 4 | This treatment may be more appropriate for smaller volume recurrence. Intracavitary brachytherapy cannot adequately cover parapharyngeal extension. |
| Stereotactic radiation therapy alone | 4 | |
| Brachytherapy alone | 2 | This treatment may be more appropriate for smaller volume recurrence. Intracavitary brachytherapy cannot adequately cover parapharyngeal extension. |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

**Clinical Condition:**     Retreatment of Recurrent Head and Neck Cancer after Prior Definitive Radiation

**Variant 5:**     57-year-old woman with T2N2b tonsillar squamous cell carcinoma treated with definitive chemoradiation (70 Gy gross disease/54 Gy uninvolved neck plus 3 cycles of cisplatin 100mg/m$^2$ q 21 days) is found to have recurrent, unresectable disease in the infratemporal fossa, eroding the clivus and extending to foramen ovale 6 months after treatment, which is biopsy-proven recurrent squamous cell carcinoma. Review of her prior treatment records shows that the recurrent disease is within an intermediate-dose region, which received approximately 50 Gy. She tolerated initial treatment well, has mild neck fibrosis, mild xerostomia, and a KPS of 80. She consents to reirradiation with curative intent with concurrent chemotherapy.

| Treatment | Rating | Comments |
|---|---|---|
| **Volume** | | |
| Reirradiation to recurrent tumor volume with limited margin (0.5–2 cm) | 8 | |
| Reirradiation to recurrent tumor volume and limited elective nodal reirradiation | 3 | |
| **Technique** | | |
| 3-D CRT | 3 | |
| IMRT | 8 | |
| Proton therapy | 6 | |
| SBRT | 3 | The large volume and proximity of the target to critical neural structures, in addition to the short interval from prior radiation, suggest that aggressively hypofractionated treatment is not as appropriate as fractionated therapy. |
| **Dose to Recurrent Disease (if not SBRT)** | | |
| Reirradiation <50 Gy | 3 | |
| Reirradiation 50–59 Gy | 4 | |
| Reirradiation 60 Gy or more | 8 | |
| **Fractionation (if not SBRT)** | | |
| Once daily fractionation, 1.8–2 Gy, planned continuous course | 8 | |
| Twice daily fractionation, 1.2 Gy, planned continuous course | 7 | |
| Twice daily fractionation, 1.5 Gy, planned split course or weekly cycles | 4 | |
| Once daily fractionation, 1.8–2 Gy, planned split course | 1 | |
| **Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | |