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RETREATMENT OF RECURRENT HEAD AND NECK CANCER AFTER PRIOR DEFINITIVE RADIATION

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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].

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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

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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**		