Received: 13 April 2020 | Revised: 28 August 2020 | Accepted: 21 September 2020

DOI: 10.1002/hed.26485

CLINICAL REVIEW

WILEY

Radical external beam re-irradiation in the treatment of recurrent head and neck cancer: Critical review

Michaela Svajdova MD[1,2] | Pavol Dubinsky MD, PhD[3,4] | Tomas Kazda MD, PhD[2,5,6]

[1]Clinic of Radiation and Clinical Oncology, Central Military Hospital—Teaching Hospital Ruzomberok, Slovakia

[2]Department of Radiation Oncology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

[3]Department of Radiation Oncology, East Slovakia Oncology Institute, Kosice, Slovakia

[4]Faculty of Health, Catholic University, Ruzomberok, Slovakia

[5]Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic

[6]Research Centre for Applied Molecular Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic

Correspondence
Michaela Svajdova, MD, Clinic of Radiation and Clinical Oncology, Central Military Hospital—Teaching Hospital Ruzomberok, Generala Milosa Vesela 21 034 26, Ruzomberok, Slovak Republic.
Email: svajdovam@uvn.sk

Funding information
Ministry of Health of the Czech Republic - Conceptual Development of Research Organization, Grant/Award Number: MMCI 00209805; National Oncology Institute Slovakia, Grant/Award Number: 20191111/SVKNOI/3

Abstract

Management of patients with recurrent head and neck cancer remains a challenge for the surgeon as well as the treating radiation oncologist. Even in the era of modern radiotherapy, the rate of severe toxicity remains high with unsatisfactory treatment results. Intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and heavy-ion irradiation have all emerged as highly conformal and precise techniques that offer many radiobiological advantages in various clinical situations. Although re-irradiation is now widespread in clinical practice, little is known about the differences in treatment response and toxicity using diverse re-irradiation techniques. In this review, we provide a comprehensive overview of the role of radiation therapy in recurrent or second primary head and neck cancer including patient selection, therapeutic outcome, and risk using different re-irradiation techniques. Critical review of published evidence on IMRT, SBRT, and heavy-ion full-dose re-irradiation is presented including data on locoregional control, overall survival, and toxicity.

KEYWORDS

head and neck cancer, radiotherapy, recurrence, re-irradiation, toxicity

1 | INTRODUCTION

Despite advances in multimodal cancer treatment, locoregional recurrence remains the major cause of mortality in long-term survivors with head and neck squamous cell carcinoma (HNSCC).[1-3] The incidence of relapses is reported in approximately 15% to 50% of patients.[4-6] In addition, survivors are at risk of developing a second primary malignancy (SPM) with the estimated reported risk at 15% to 40%.[7-9] Salvage surgery is the treatment of choice after the diagnosis of recurrent HNSCC (rHNSCC) or histology-proven SPM has been confirmed.[10] However, the majority of recurrences are inoperable given their infiltrative and multifocal nature, comorbidities or poor performance status of the pretreated patient; operable relapses represent only up to

20% of all cases. Re-irradiation (overlap of the new radiation fields with the prior full-dose radiation volume) is a therapeutic alternative for patients who are not candidates for surgical treatment and may offer long-term survival in carefully selected patients.[10-12] Unfortunately, almost all available evidence on the potential outcomes of re-irradiation comes from retrospective studies and is strongly biased by lack of control arms, which strictly limits the ability to clearly interpret the findings.

The aim of this critical review is to summarize the current evidence on feasibility, safety, and efficacy of radical external beam re-irradiation of recurrent or second primary malignancies of the head and neck using diverse radiotherapy techniques.

A comprehensive search was made of PubMed, Medline, Scopus, and UpToDate using the descriptors "re-irradiation," "head and neck cancer," and "recurrence." The abstracted literature was reviewed, as were references and related material. Only articles published in English that contained at least 20 patients treated with curative intent and papers that delivered at least 24 Gy using stereotactic body radiation therapy (SBRT), 59 Gy using intensity-modulated radiation therapy (IMRT), and 50 Gy using heavy-ion RT were included. Re-irradiation articles using brachytherapy, intraoperative radiotherapy, and palliative radiotherapy were excluded. Treatment parameters including histology, dose of re-irradiation, use of salvage surgery, and concurrent systemic therapy were abstracted and summarized.

2 | RATIONALE FOR RE-IRRADIATION

Because local recurrence is the major cause of death in patients with HNSCC,[1-3] re-irradiation could not only reduce the risk of further locoregional progression, but it could also favorably affect disease-free survival (DFS) and overall survival (OS). Retrospective analysis of 105 patients by Lee et al[13] brought evidence of significant improvement in 2-year OS in patients who achieved successful locoregional control (LRC) after re-irradiation compared to patients with further postradiotherapy locoregional failure (LRF) (2-year OS 56% vs 21%, $P < .001$). Achieving local control is crucial for improvement of survival in this group of patients. The major disadvantage of re-irradiation is the 29% estimated risk of severe (≥grade 3) toxicity despite the use of modern IMRT techniques.[14] Local growth of the tumor mass, apart from compression of surrounding healthy tissues, risk of perforation, and spread onto the skin surface with subsequent infections, can also have a critical impact on the individual's psychological functions and interpersonal relationships and usually results in quality of life (QoL) deterioration. Recurrent disease is also a common source of pain, body shape deformation and worsening of swallowing, chewing, voice, speech, and breathing functions. In addition to the positive impact on LRC, DFS, and OS, re-irradiation can also improve the patient's QoL.[15-18]

Hence, re-irradiation can potentially offer several major advantages to the patient. With careful selection, the patient can be given a second chance for a complete cure with long-term disease control. In addition, the potential improvement of QoL should be discussed with the patient in a shared decision-making approach, even in clinical situations where only short-term control in regard to disease extent is expected and the prognosis is poor.

3 | PATIENT SELECTION

Re-irradiation of head and neck malignancies is a controversial topic because many patients are potential candidates; however, only a small subset of them will truly achieve clinical benefit from it due to frequently radioresistant tumors and high risk of severe side effects. Yet the risk of progression or death is approximately 4 times higher than the risk of severe treatment-related toxicity in the era of IMRT.[19]

Most patients with rHNSCC or SPM have already received RT to a radical dose (≥60 Gy) and surrounding critical structures (spinal cord, brainstem, blood vessels, bone, and cartilage structures) called organs at risk (OaR) have already been exposed to a significant radiation dose. Patients with osteoradionecrosis (ORN) of the mandible, laryngeal chondronecrosis, carotid artery stenosis, pharyngocutaneous fistulae, RT-induced skin or mucosal ulcers, RT-induced myelopathy, or facial lymphedema are generally considered to be unfit for re-irradiation. Exposing the pretreated OaR to another course of full-dose RT imposes the risk of further severe and potentially fatal toxicity.[10,14,20]

Outcomes and expectations that may guide patient selection for IMRT-based re-irradiation were thoroughly investigated in a recursive partitioning analysis (RPA) of 412 patients with rHNSCC or SPM by Ward et al.[12] All patients in this study underwent full-dose re-irradiation using IMRT. Several factors with major impact on OS were identified and patients were subsequently stratified into three subgroups in which different but homogeneous OS values were observed. Group I included patients with a time interval > 2 years after completion of previous radical RT who underwent salvage surgery (regardless of resection margin status). Group II included patients

>2 years after previous full-dose RT with unresectable recurrence or ≤2 years after RT without organ dysfunction (percutaneous endoscopic gastrostomy or tracheostomy dependency). Group III included patients ≤2 years after RT with organ dysfunction. Twenty-three percent of patients in group II and 59% of patients in group III underwent salvage surgery with subsequent postoperative re-irradiation. Two-year OS was 61.9%, 40%, and 16.8% for groups I, II, and III, respectively ($P < .001$).[12]

Median OS in group III was 8.0 months, therefore indication of protracted course of conventionally fractionated RT (6-7 weeks) is highly debatable in these patients; a more rational treatment method may be a shortened, hypofractionated regimen with palliative intent.[16,18] Furthermore, a strongly negative impact on OS in recurrences localized in the oral cavity (HR 2.924, 95% CI 1.721-4.968, $P < .0001$) and oropharynx (HR 1.953, 95% CI 1.211-3.235, $P < .006$) was described on Cox proportional risk model. Worsened Karnofsky performance status (KPS) score was also a negative prognostic factor of OS (>70 vs ≤70, HR 0.652, 95% CI 0.448-0.948, $P < .025$). Age, smoking history, and concomitant systemic therapy had no significant impact on OS. A factor independently associated with improved OS on multivariate analysis was location of the recurrences in the nasopharynx or base of skull.[12]

Both the extent of recurrence and application of chemotherapy (CHT) in the past could serve as a guide for patient selection for an aggressive treatment approach. The disease extent was identified as a significant prognostic factor for cancer-specific survival in the study by Goodwin et al[21] with the anatomical site of recurrence having only marginal impact on survival. Median DFS in this study was 5.0 months for patients who had been previously treated with CHT and 24.5 months for patients who had not ($P < .001$).

Several authors recommend a ≥6 month interval from previous RT to recurrence as a basic selection criterion for re-irradiation[20,22,23] with the risk of severe toxicity decreasing and with the probability of local control increasing with time.[24] A trend toward better OS in the second primary compared to recurrent head and neck malignancies has been observed in several studies.[12,25,26] Patients with metachronous duplex lesions had significantly better survival rates compared to synchronous lesions.[27,28]

Another important re-irradiation selection criterion is the tumor volume.[29,30] In a study of Chen et al,[30] the planning target volume (PTV) was the only parameter predictive of local control. In a subgroup of patients with PTV <27 cm^3, the observed 2-year OS was 80%. Therefore, in the therapeutic consideration of re-irradiation of larger tumor deposits, particular attention should be placed on the potential benefit to the patient, again emphasizing high risk of severe toxic complications and ambiguous treatment outcome.

Considering appropriate patient selection, it may be concluded that proper indication will significantly affect treatment outcome. Patients with recurrent disease that occurs ≥2 years after previous full-dose RT, those with low-volume recurrences localized predominantly in the nasopharynx or base of skull, patients without comorbidities and with satisfactory KPS may achieve long-term survival. For these patients, the financially demanding techniques of particle re-irradiation may be considered as they could very likely lower the risk of acute treatment-related toxicity. On the contrary, in patients with a short DFS, with an early relapse ≤6 months after previous radical RT and with a high-volume disease, organ dysfunction, or comorbidities, only a short-term local effect can be expected and, most likely, these patients will not have any survival benefit from re-irradiation. In these patients, hypofractionated conventional EBRT techniques or SBRT should be considered, with the major goals residing in palliation of disease symptoms and reduction in overall treatment time.

3.1 | Re-irradiation following salvage surgery

Salvage surgery of recurrent head and neck malignancies, whenever feasible, has long been considered the standard of care. With this intervention, patients can achieve long-term disease control in 25% to 45% of cases.[31,32] Moreover, after complete resection of early recurrences of laryngeal cancer (T1, T2 classification), disease control may increase up to 80%.[21]

The indication of postoperative re-irradiation following salvage surgery is controversial mostly due to the cumulative risk of severe toxicity, yet it may be rational when there is high risk of further recurrence in the case of incomplete tumor removal (R1, R2 resection) and extracapsular extension (ECE) of nodal metastasis.[23,33-35] Furthermore, even in the case of successful salvage surgery with negative margins, the risk of another recurrence is up to 59%.[36] In several nonrandomized studies evaluating postoperative re-irradiation in high-risk patients, 3- and 4-year OS was observed in 48% and 43% of individuals who had undergone postoperative re-irradiation without the addition of concurrent CHT.[37,38] A prospective randomized phase III trial of the Groupe d'Etude des Tumeurs Tete et Cou (GETTEC) in collaboration with Groupe d'Oncologie Radiotherapie Tete et Cou (GORTEC) provided definitive evidence of the safety and efficacy of postoperative re-irradiation.[23] After resection of macroscopic disease and exclusion of patients

with gross residual disease, 130 patients were randomized into two arms.[23] In the first arm, observation was indicated and in the second arm patients underwent 3D conformal re-irradiation (median dose 60 Gy/30 fractions) combined with 5-fluorouracil (5-FU) and hydroxyurea. The PTV was limited only to the original extent of the recurrent disease without elective irradiation of the neck. Patients in the observation arm had significantly worse LRC (HR 2.73, 95% CI 1.66-4.51, $P < .0001$) and DFS (HR 1.68, 95% CI 1.13-2.50, $P < .01$). Remarkably, postoperative chemoradiotherapy (CRT) mostly had a local effect only; this evidence is strongly supported by the fact that the frequency of distant metastases was higher in the CRT arm (7.6%) than in the observation arm (1.5%) and the risk of regional failure was only slightly reduced in the CRT arm. Differences in OS did not reach statistical significance ($P = .50$). Two-year incidence of severe toxicity was 39% in the CRT arm compared to 10% in the observation arm ($P = .06$).[23]

In a meta-analysis of 16 studies by Merlotti et al, 522 patients with rHNSCC or SPM who had undergone postoperative re-irradiation were identified.[39] Variable values of 2-year OS (24%-81%) and 2-year LRC (21%-100%) were observed, which the authors justified by the heterogeneity of the evaluated patients and individual differences in their treatment. Modern IMRT techniques are recommended to reduce the risk of severe toxicity, yet the optimal fractionation regimen has not been identified so far. IMRT using image-guided RT (IGRT) technologies can help target the PTV more precisely and improve the sparing of critical organs.[13,30,40]

Re-irradiation dose in the postoperative setting is typically 60 Gy, and should take into account the presence of high-risk factors (R1 resection, ECE), dose of previous RT, dose-volume histograms (DVH) for OaR, and time interval from the previous RT. In a group of 115 patients with rHNSCC (42.6% underwent salvage surgery), Salama et al identified the dose of re-irradiation, operability, and CHT administration using a triplet of antineoplastic drugs (cisplatin, paclitaxel, gemcitabine) as independent prognostic factors of improved LRC, OS, and progression-free survival (PFS) wherein a cutoff value of 58 Gy was determined as the optimal dose of re-irradiation.[41] Some studies confirmed the hypothesis that increasing the dose to ≥60 Gy may offer benefit in terms of both LRC and OS.[34,42] In a retrospective analysis of 505 patients with rHNSCC or SPM (49.1% underwent salvage surgery), prophylactic re-irradiation of adjacent lymphatic nodes added no benefit to either 2-year OS or LRF regardless of the presence of lymph node (LN) metastases, on the contrary, this intervention increased severe acute toxicity.[42]

In conclusion, re-irradiation of the tumor bed to 58 to 60 Gy may be rational in clinical situations where high-risk factors (R1, ECE) are present. Adding CHT to re-irradiation is unlikely to reduce the risk of distant failure and it certainly will not improve OS. Given the rate of severe toxicity, which is approximately 3 to 4 times higher compared to observation, routine postoperative re-irradiation after complete tumor removal without high-risk features will not be an adequately justified intervention and cannot be recommended as a standard of care.

3.2 | Re-irradiation of inoperable recurrences

A relatively high percentage of rHNSCC or SPM are technically inoperable although the patient may present with a satisfactory KPS. Up to 65% of patients may present with unresectable recurrences and, in addition to anatomical contraindications, poor KPS, the presence of distant metastases, and patient disagreement all increase the total number of inoperable cases.[43] For this subgroup of patients, re-irradiation with or without concurrent systemic therapy may represent the only intervention with curative potential.[44]

The dose ≥66 Gy to the gross tumor volume (GTV) in inoperable recurrences in patients with satisfactory KPS is associated with improvement in both LRF and OS.[42] Dose escalation ≥66 Gy does not improve 2-year distant failure compared to 60 to 65.9 Gy (22.8% vs 24.3%, $P = .559$).[42]

Elective irradiation of uninvolved neck LN does not improve treatment outcome; on the contrary, this approach increases the rate of severe toxicity.[42] Therefore, it is strongly recommended to irradiate only the extent of well-visualized GTV with a 5 to 10 mm margin, (depending on the technique used, the accuracy of daily setup, and use of IGRT). When retrospectively evaluating the patterns of LRF in patients with unresectable rHNSCC irradiated with a median dose of 68 Gy, the majority (96%) of relapses were again located inside the GTV itself.[45]

Radical re-irradiation without concurrent systemic therapy yielded variable LRC, DFS, and OS, with acceptable toxicity in several studies.[46-50] Reported 1-, 2-, 3-, and 5-year OS were 39% to 51.1%, 27% to 33%, 22%, and 11%, respectively. Severe toxicity was observed in 18% to 75% of patients, which again emphasizes the need for careful selection of patients with uncertain treatment outcome.

Caution is needed in the interpretation of evidence provided by nonrandomized phase II studies as data derived from them are limited, biased by the small number of patients and their selection, and the fact that almost all of these studies lack control arms.

Furthermore, these studies include patients treated with both curative and palliative intent with highly variable doses (50-70 Gy) and, apart from that, a high percentage of the patients did not complete the course of full-dose re-irradiation due to high toxicity.[46-50]

Two prospective phase II RTOG studies investigated the effect of full-dose external beam re-irradiation combined with CHT. In RTOG 96-10, a combination of 5-FU and hydroxyurea was added to re-irradiation with the median survival reaching 8.5 months and 2-year OS in 15.2%.[25] In RTOG 99-11, cisplatin and paclitaxel were added to re-irradiation with a median survival of 12.1 months and 2-year OS in 25.9% and with severe (≥grade 3) toxicity in 78% of the cases.[22]

There is no evidence that re-irradiation with concurrent systemic therapy offers a survival advantage over palliative CHT.[51] Prospective randomized phase III trial RTOG 0421 designed to answer this question was terminated due to poor accrual.[52]

Conventional normofractionated re-irradiation of the GTV with 5 to 10 mm margin to a dose ≥66 Gy without elective LN irradiation is, in the absence of salvage surgery, an alternative treatment option with a potential long-term disease control. Administration of concurrent CHT is rational especially in patients who have not received it in the past with a combination of cisplatin and paclitaxel being the most effective known regimen. A doublet of antineoplastic drugs will very likely increase the risk of severe treatment-related toxicity; therefore, it is strongly recommended only for patients with satisfactory KPS without organ dysfunction.

4 | CHOICE OF TREATMENT TECHNIQUE

Currently, a number of treatment techniques can be used for radical external beam re-irradiation. Photon beam treatment techniques of EBRT (3D CRT, IMRT, volumetric-modulated arc therapy [VMAT], SBRT) and heavy ion techniques (protons, carbon ions) can all serve as effective forms of treatment, with each of them harboring a slightly different toxicity profile that must be taken into consideration in decision-making.

4.1 | Intensity-modulated radiation therapy

Modern IMRT techniques offer many advantages including higher conformality, improved dose distribution, and potential reduction in toxicity. To date, there is no evidence that IMRT could improve OS over the less conformal 3D CRT.[13,46,53] Lee et al compared the outcomes of re-irradiation using IMRT vs non-IMRT techniques in 105 consecutive patients who had previously received RT with a median dose of 62 Gy.[13] When multivariate analysis was used, patients that had undergone re-irradiation with IMRT had a significantly better locoregional progression-free survival (LRPFS) than patients irradiated with non-IMRT techniques (2-year LRPFS 52% for IMRT vs 20% for non-IMRT, HR 0.37, 95% CI 0.19-0.76, $P < .006$). Other available single-arm retrospective phase II studies using IMRT as re-irradiation technique report variable median survival of 15-28.6 months, 1-, 2-, and 5-year OS in 56% to 65%, 40% to 58%, and 22%, and severe (≥grade 3) acute and late toxicity in 6% to 57% and 15% to 48%, respectively[13,20,45,46,53-55] (Table 1). Re-irradiation using IMRT can be considered an effective treatment intervention with the potential to achieve long-term disease control both in the postoperative scenario and in the case of inoperable recurrence with an acceptable rate of treatment-related toxicity. Given the lower expected risk of toxicity compared to 3D CRT, IMRT should be the radiation technique of choice in the treatment of recurrent or second primary head and neck malignancies.

4.2 | Stereotactic body radiation therapy

SBRT is an attractive form of modern conformal high-precision EBRT that can provide various radiobiological benefits in many clinical situations.[56] The principle of stereotactic RT is the delivery of an ablative dose in several, typically ≤5 fractions, which enables reduction in overall treatment time compared to conventional EBRT techniques.[57] A steep dose gradient is created between the target and healthy tissues, which decreases the overall radiation dose to critical organs at close proximity to the target volume. The mechanism of action of stereotactic RT has not been elucidated yet. Published evidence suggests that tumor size reduction following ablative doses of RT could be largely dependent on T-cell response.[58] Activation of T-lymphocytes in regional lymphatics is dramatically increased in response to ablative doses of RT, resulting in eradication of tumor tissue in a CD8+ T-lymphocyte-dependent manner. The immune response induced by ablative doses of RT can be further potentiated by immunotherapy, which has become very attractive in recent clinical research. The ongoing randomized phase II trial "KEYSTROKE" (NCT03546582) is evaluating the treatment response by adding pembrolizumab to SBRT in patients with recurrent or second primary head and neck malignancies who had previously undergone radical RT.[59]

TABLE 1 Re-irradiation studies using IMRT w/wo systemic therapy

Study	No. of pts	Median dose, Gy	Histology of SCC, %	Salvage surgery, %	CHT, %	FU, mo	Response	Severe toxicity (≥grade 3), %
Biagioli et al[46]	41	60	85	42	100	14	2-y PFS: 38% 2-y OS: 48.7%	Acute: 31.7 Late: 14.6
Lee et al[13]	105	59.4	86	34	71.4	35	1-y OS: 56%	Acute: 23 Late: 15
Popovtzer et al[45]	66	68	90	61	71	42	2-y OS: 40% 5-y OS: 22%	Acute: 6 Late: 29
Sulman et al[53]	74	60	77	27	49	25.4	2-y LRC: 64% 2-y OS: 58%	: 20
Chen et al[20]	21	66	71.4	N/A	0%	20	1-y LRC: 72% 2-y LRC: 65% 1-y OS: 65% 2-y OS: 40%	Acute: 57
Curtis et al[54]	81	60	100	51.8	74.5	78.1	2-y OS postop: 53% 2-y OS inop: 48%	Late: 3.7
Takiar et al[55]	207	60	84	51	66	25.1	2-y LRC (SCC): 59% 2-y LRC (non-SCC): 90% 2-y OS (SCC) 51% 2-y OS (non-SCC): 85%	2-y: 32 5-y: 48

Abbreviations: FU, follow-up; IMRT, intensity-modulated radiation therapy; LRC, locoregional control; mo, months; N/A, not available; no., number; non-SCC, nonsquamous cell carcinoma; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

The exact position of SBRT in the treatment of recurrent head and neck malignancies is not easy to determine. Anatomically, the head and neck region is very complex with many radiosensitive structures in which the exact tolerance to high dose per fraction has not been defined yet. Conventional and cheaper EBRT techniques have demonstrated good efficacy in the treatment of recurrent head and neck malignancies and enable irradiation of high-risk elective LN at close proximity to the tumor lesion or tumor bed, albeit there is an increased risk of toxicity, which could be further enhanced with ablative doses of SBRT. The role of SBRT in the treatment of recurrent or second primary head and neck malignancies has been evaluated in several clinical trials[15,60-76,80-82] [15,60-76,80-82] (Table 2). These are all nonrandomized phase II trials with limited number of patients and with an administered average total dose of 18 to 44 Gy in 3 to 6 fractions. Reported median survival ranged from 10 to 12 months, values of 1-year OS 40% to 47.5%, 2-year OS 22% to 33%, and severe (≥grade 3) toxicity was variably reported in 6% to 50% of participants.

The available evidence on severe late toxicity in re-irradiation of recurrent or second primary head and neck malignancies using SBRT emphasizes the need for careful patient selection. Kodani et al[65] retrospectively reported toxicity ≥grade 4 in 28.6% of patients treated with SBRT with carotid artery blowout syndrome (CABS) occurring in 14%. All patients with CABS seen with regional nodal recurrences where the dose to carotid artery typically represented 30.7 to 31.7 Gy. In re-irradiation of 46 patients with unresectable previously irradiated recurrent head and neck malignancies with a median dose of 30 Gy, Cengiz et al[70] reported CABS in 17% of the patients. CABS typically occurred in cases where the tumor encircled >50% of vessel circumference and in cases where the carotid artery was irradiated to 100% of the prescribed dose. A simple strategy to reduce the incidence of CABS is to use SBRT 15 to 35 Gy in 4 to 6 fractions on alternating days.[71] Also, theories of carotid artery stabilization by flap reconstruction or insertion of endovascular stent prior to re-irradiation have been suggested, but these hypothetical interventions have not been verified yet.[72,73]

In a retrospective study of 291 patients treated with SBRT for recurrent or second primary head and neck malignancies, Ling et al[74] attempted to identify predictors

TABLE 2 Re-irradiation studies using SBRT w/wo systemic therapy

Study	No. of pts	FU, mo	Median dose Gy	Fractions	Systemic therapy, %	Response	Severe toxicity (≥grade 3), %
Voynov et al[60]	22	19	24	N/A	—	2-y LRC: 26% 2-y OS: 22%	Acute:4.5 Late: 0
Roh et al[61]	36	17.3	30	3–5	—	2-y OS: 30.9%	Acute: 6.1 Late: 8.3
Heron et al[75]	25	N/A	44	5	—	MS: 6 mo	Acute: 0 Late: 0
Siddiqui et al[62]	37	N/A	42	5–8	—	1-y LRC: 60.6%	N/A
Rwigema et al[63]	85	17.6	35	1–5	—	1-y LRC: 51.2% 2-y LRC: 30.7% 1-y OS: 48.5% 2-y OS: 16.1%	Acute:4.7
Unger et al[64]	65	16	30	2–5	50.7	2-y LRC: 30% 2-y OS: 41%	11%
Cengiz et al[70]	46	N/A	30	1–5	—	1-y OS: 46% 1-y PFS: 41%	13.3%
Heron et al[80]	35	24.8	N/A	N/A	100	MS: 24.5 months	0
Kodani et al[65]	34	16	30	3–8	—	1-y OS: 70.6% 2-y OS: 58.3%	Acute: 0 Late: 17.6
Ozyigit et al[66]	24	24	30	5	—	2-y LRC: 82%	Late: 21
Comet et al[81]	40	25.6	36	6	37.5	1-y OS: 58% 2-y OS: 24%	10
Lartigau et al[82]	60	11.4	36	6	93.3	1-y OS: 47.5%	30
Vargo et al[15]	50	18	42	5	100	1-y PFS: 33% 1-y OS: 40%	6

Abbreviations: FU, follow-up; Gy, Gray; LRC, locoregional control; mo, months; no., number; MS, median survival, N/A; not available; OS, overall survival; PFS, progression-free survival.

of severe acute and long-term toxicity. Patients treated with SBRT for isolated nodal recurrence had the lowest risk of long-term toxicity while patients with recurrences located in the hypopharynx or larynx had a 50% risk of severe toxicity. The cutoff limit at which the risk of severe toxicity increased significantly was >44 Gy.[74]

The optimal dose and fractionation scheme have not been defined yet.[75] An analysis by the American Association of Physicists in Medicine (AAPM) retrospectively evaluated the optimal dose in 300 patients from eight studies.[76] A dose of 35 to 45 Gy in 5 fractions was associated with significant improvement in both local control (LC) and OS compared to a dose <30 Gy. During the RT planning itself, co-registration with positron emission tomography-computed tomography (PET/CT) with precise delineation of GTV is recommended whenever SBRT is used. Several reports have provided evidence of significant reduction of GTV when co-registration with PET/CT was used.[77-79] Very likely, reduction of the irradiated volume could also decrease both acute toxicity and long-term toxicity.

Historically, the design of the first studies evaluating the role of SBRT in rHNSCC did not include concurrent systemic therapy. The current evidence already contains data on the safety and efficacy of cetuximab in this indication.[15,80-82] Heron et al[80] have demonstrated that adding cetuximab to SBRT can improve 2-year LC (49%) and OS (53%) compared to SBRT alone. An ongoing phase II trial is evaluating potential improvement of OS by adding docetaxel in patients with rHNSCC treated

with SBRT and concurrent cetuximab.[83] Another phase II study using pembrolizumab in combination with SBRT is ongoing to evaluate possible improvement in PFS in patients with recurrent or second primary head and neck malignancies.[59]

Hence, an ideal candidate for re-irradiation using SBRT would be a patient with an isolated neck recurrence with GTV <25 cm^3, especially in cases where the tumor does not directly invade the vessel wall or is located at a sufficient distance from major vessels. Conversely, a patient with a laryngeal recurrence is very unlikely to be an ideal candidate for SBRT even if the GTV is <25 cm^3 due to the high risk of severe toxicity in a patient with the potential for reaching long-term survival. An optimal fractionation scheme of 40 to 45 Gy in 5 fractions offers a similar treatment response compared to conventionally fractionated IMRT with the potential in overall treatment time reduction.

4.3 | IMRT vs SBRT

Vargo et al[67] retrospectively compared the efficacy of SBRT and IMRT in radical treatment of unresectable rHNSCC or SPM in 414 patients. Approximately half of the patients (52.4%) were retreated using IMRT and in 47.2%, SBRT was used. Median total treatment time was 43 days for IMRT and 10 days for SBRT ($P < .01$). Median OS was 13.3 months (95% CI 10.5-16.9) for patients treated with IMRT and 7.8 months (95% CI 6.8-9.8) for those treated with SBRT. When analyzing the data with implementation of Ward's RPA,[12] in group II (n = 353), clear benefit in OS was demonstrated for IMRT (2-year OS 39.1% for IMRT and 18.6% for SBRT, $P < .001$). In group III, a trend toward better OS was observed in the IMRT group (2-year OS 16.2% for IMRT and 3.6% for SBRT, $P = .042$). In a subgroup of patients with large tumor extent (T3, T4 classification or volume > 25 cm^3), a significant improvement in OS was observed in favor of IMRT compared to SBRT, regardless of whether SBRT dose was ≥35 Gy ($P < .001$) or <35 Gy ($P < .001$).[67] In another study, Vargo et al evaluated treatment response in re-irradiation with SBRT with a median dose of 40 Gy in 5 fractions in recurrent head and neck cancer with histological features other than SCC (non-SCC); a significant improvement in local control of tumors <25 cm^3 was observed.[15]

In the study by Vargo et al,[67] comparison of toxicities for both treatment techniques was especially important. Severe acute toxicity occurred in 16.6% of the patients treated with IMRT and in 11.7% of patients treated with SBRT; however, this difference did not reach statistical significance ($P = .15$). Acute toxicity ≥grade 4 was higher for IMRT than for SBRT (5.1% vs 0.5%, $P < .01$). The observed rate of severe late toxicity was without a significant difference for both techniques (12.4% for IMRT and 11.6% for SBRT, $P = .69$). Treatment-related deaths occurred in 1.8% using IMRT and in 0.5% when SBRT was used ($P = .42$). When rationally interpreting the obtained data, it should be noted that in patients treated with IMRT in this study, concurrent systemic therapy with a very different toxicity profile was administered; in 82% of the patients treated with IMRT, platinum-based CHT was used, while in 53.3% of the patients treated with SBRT the most common concurrent systemic agent was cetuximab, which could contribute to significant differences in toxicity profile for both subgroups.

In a definitive treatment technique, decision-making not only different radiobiological aspects but also logistic aspects may be crucial.[20,67] Conventionally fractionated or hyperfractionated IMRT is a protracted regimen that enables reparation of the adjacent healthy tissues during the course of treatment.[68] Conversely, SBRT is a technique that uses different radiobiological aspects in relation to tumor damage, particularly, direct damage to the blood vessel endothelium due to ablative doses of RT.[69] Hence, the decision-making in selecting the optimal radiation technique will be largely dependent not only on the availability and expertise within individual centers, but, due to differences in overall treatment time, it may also be driven by patient preference.

5 | RE-IRRADIATION USING HEAVY IONS

Re-irradiation using heavy particles (protons, carbon ions) is becoming increasingly popular among radiation oncologists who are trying to investigate if this type of treatment has lower toxicity than photon techniques. The ROCOCO in silico dosimetric study compared re-irradiation plans using VMAT, intensity-modulated proton therapy (IMPT) and intensity-modulated ion therapy (IMIT) in 25 patients with recurrent or second primary head and neck cancer.[84] IMPT and IMIT achieved a significant reduction in mean dose (Dmean) to OaR compared to VMAT. Dmean to OaR was reduced by 86% using IMPT and by 100% when IMIT was used, with significant dosimetric sparing of the contralateral organs (carotid artery, arytenoid, parotid, and submandibular glands), spinal cord, and brainstem.[84]

Particle re-irradiation could facilitate dose escalation in the tumor while sparing OaR, and with the expected reduction in long-term side effects of RT, it could also reduce the likelihood of normal tissue complication probability,[85] but any widespread recommendation on its

use in clinical practice is biased by short follow-up[86-92] (Table 3). Available evidence includes only retrospective phase II studies without control arms and with a limited number of patients. Reported median survival ranges from 16.5 to 26.1 months, 1- and 2-year OS was 65.2% to 95.9% and 32.7% to 65.2%, rate of severe (≥ grade 3) acute and late toxicity was variably reported in 3.1% to 30% and 8.7% to 37.5%, respectively (Table 3).

Although preliminary results of particle re-irradiation with regard to acute toxicity appear to be more favorable in comparison with photon techniques, the issue of long-term toxicity and the relatively high cost of these techniques impair wider implication of particle re-irradiation into standard clinical practice.

6 | CONCLUSION

Recurrent or second primary head and neck malignancies represent a therapeutic challenge for both surgeons and radiation oncologists. Salvage surgery, whenever technically feasible, is the preferred treatment method. In the case of positive resection margins or an extracapsular extension of nodal metastasis, the indication for postoperative re-irradiation is highly rational, and concurrent CHT should be considered especially in patients that have not received it in the past. In inoperable recurrences, re-irradiation is the only possible intervention with potentially curative intent. With careful patient selection, long-term survival is possible with re-

TABLE 3 Re-irradiation studies using particle therapy w/wo systemic therapy

Study	No. of pts	FU, mo	Histology of SCC, %	Salvage surgery, %	Median dose, (Gy, RBE) technique of RT	Systemic therapy, %	Response	Severe toxicity (≥grade 3), %
McDonald et al[86]	61	15.2	52.5	47.5	70 PT	27.9	MS: 16.5 months 2-y LF: 19.7% 2-y OS: 32.7%	Acute: 14.7 Late: 24.6
Phan et al[87]	60	13.6	66.7	58.3	61.5 PT	73	1-y LRC: 80.8% 2-y LRC: 72.8% 1-y PFS: 60.1% 2-y PFS: 48.2% 1-y OS: 81.3% 2-y OS: 69.0%	Acute: 30 Late: 16.7
Romesser et al[88]	92	13.3	56.5	39.1	60.6 PT	47.8	1-y LRF: 25.1% 1-y OS: 65.2%	Acute: 9.9 Late : 8.7
Gao[90]	141	14.7	75.3	16.3	60 CIT	0	1-y OS: 95.9%	7.1
Hayashi et al[91]	48	27.1	N/A	18.7	54 CIT	0	2-y LRC: 33.5% 2-y PFS: 29.4% 2-y OS: 59.6%	Acute: 10.4 Late: 37.5
Held et al[92]	229	28.5	26.2	17	51 CIT	0	MS: 26.1 months	Acute: 3.1 Late: 14.5

Abbreviations: CIT, carbon-ion therapy; Gy, Gray; FU, follow-up; LF, local failure; LRC, locoregional control; LRF, locoregional failure; mo, months; MS, median survival; no., number; OS, overall survival; PFS, progression-free survival; PT, proton therapy; RBE, relative biological effectiveness; SCC, squamous cell carcinoma.

irradiation following salvage surgery as well as in the case of inoperable recurrences. When choosing a proper external beam radiation technique, IMRT should always be preferred over 3D CRT. In a properly selected low-volume inoperable disease with excellent visualization of GTV that does not directly invade into major vessels of the neck, SBRT should be considered. Proton re-irradiation may be a technique of choice in relapses located in close proximity to critical structures, particularly in the nasopharynx or skull base with the intention of reducing acute severe toxicity in patients with a favorable prognosis. Potentiation of the therapeutic effect of re-irradiation by immunotherapy could improve treatment outcome in this difficult clinical scenario. Therefore, participation in similarly designed clinical trials should always be encouraged.

ACKNOWLEDGMENT

This work was partially supported by the National Oncology Institute (NOI) of the Slovak Republic (20191111/SVKNOI/3) and by the Ministry of Health of the Czech Republic—Conceptual Development of Research Organization (MMCI 00209805).

ORCID

Michaela Svajdova https://orcid.org/0000-0002-6372-3295

REFERENCES

1. 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.
2. Lambrecht M, Dirix P, Van den Bogaert W, Nuyts S. Incidence of isolated regional recurrence after definitive (chemo) radiotherapy for head and neck squamous cell carcinoma. *Radiother Oncol*. 2009;93:498-502.
3. Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer*. 2014;120:1507-1513.
4. Bourhis J, Le Maître A, Baujat B, et al. Individual patients' data meta-analyses in head and neck cancer. *Curr Opin Oncol*. 2007;19:188-194.
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. 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.
7. Lippman S, Hong W. Second malignant tumors in head and neck squamous carcinoma: the overshadowing threat for patients with early-stage disease. *Int J Radiat Oncol Biol Phys*. 1989;17:691-694.
8. Chao KS, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2003;55:312-321.
9. Leon X, Del Prado Venegas M, Orus C, et al. Metachronous second primary tumours in the aerodigestive tract in patients with early stage head and neck squamous cell carcinomas. *Eur Arch Otorhinolaryngol*. 2005;262:905-909.
10. McDonald MW, Lawson J, Garg MK, et al. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation expert panel on radiation oncology-head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2011;80:1292-1298.
11. Patel PR, Salama JK. Reirradiation for recurrent head and neck cancer. *Expert Rev Anticancer Ther*. 2012;12:1177-1189.
12. Ward MC, Riaz N, Caudell JJ, et al. Refining patient selection for reirradiation of head and neck squamous carcinoma in the IMRT era: a multi-institution cohort study by the MIRI collaborative. *Int J Radiat Oncol Biol Phys*. 2018;100:586-594.
13. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2007;68:731-740.
14. Dionisi F, Fiorica F, D'Angelo E, Maddalo M, Giacomelli I, Tornari E. Organs at risk's tolerance and dose limits for head and neck cancer re-irradiation: a literature review. *Oral Oncol*. 2019;98:35-47.
15. Vargo JA, Ferris RL, Ohr J, et al. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2015;91:480-488.
16. Lok BH, Jiang G, Gutiontov S, et al. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. *Oral Oncol*. 2015;51:957-962.
17. Ma J, Lok BH, Zong J, et al. Proton radiotherapy for recurrent or metastatic head and neck cancers with palliative Quad Shot. *Int J Part Ther*. 2018;4:10-19.
18. Corry J, Peters LJ, Costa ID, et al. The 'QUAD SHOT'—a phase II study of palliative radiotherapy for incurable head and neck cancer. *Radiother Oncol*. 2005;77:137-142.
19. Ward MC, Lee NY, Caudell JJ. A competing risk nomogram to predict severe late toxicity after modern reirradiation for squamous carcinoma of the head and neck. *Oral Oncol*. 2019;90:80-86.
20. Chen AM, Phillips TL, Lee NY. Practical considerations in the re-irradiation of recurrent and second primary head-and-neck cancer: who, why, how, and how much? *Int J Radiat Oncol Biol Phys*. 2011;81:1211-1219.
21. 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;110:1-18.
22. 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: 4800-4805.
23. 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;26:5518-5523.
24. Tanvetyanon T, Padhya T, McCaffrey J, et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. *J Clin Oncol*. 2009;27:1983-1991.
25. 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;30:281-288.
26. Spencer SA, Harris J, Wheeler RH, et al. RTOG 96-10: reirradiation with concurrent hydroxyurea and 5-fluorouracil in patients with squamous cell cancer of the head and neck. *Int J Radiat Oncol Biol Phys*. 2001;51:1299-1304.
27. Di Martino E, Sellhaus B, Hausmann R, et al. Survival in second primary malignancies of patients with head and neck cancer. *J Laryngol Otol*. 2002;116:831-838.
28. Rennemo E, Zätterström U, Boysen M. Impact of second primary tumors on survival in head and neck cancer: an analysis of 2,063 cases. *Laryngoscope*. 2008;118:1350-1356.
29. De Crevoisier R, Bourhis J, Domenge C, et al. Reirradiation for Unresectable head and neck carcinoma: experience at the Gustave-Roussy institute in a series of 169 patients. *J Clin Oncol*. 1998;11:3556-3562.
30. Chen AM, Farwell GD, Luu Q, et al. Prospective trial of high-dose reirradiation using daily image guidance with intensity-modulated radiotherapy for recurrent and second primary head-and-neck Cancer. *Int J Rad Oncol Biol Phys*. 2011;80: 669-676.
31. 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.
32. 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.
33. Milano MT, Vokes EE, Salama JK, et al. Twice-daily reirradiation for recurrent and second primary head-and-neck cancer with gemcitabine, paclitaxel, and 5-fluorouracil chemotherapy. *Int J Radiat Oncol Biol Phys*. 2005;61:1096-1106.
34. Langendijk JA, Bourhis J. Reirradiation in squamous cell head and neck cancer: recent developments and future directions. *Curr Opin Oncol*. 2007;19:202-209.
35. Salama JK, Vokes EE. Concurrent chemotherapy and reirradiation for locoregionally recurrent head and neck cancer. *Semin Oncol*. 2008;35:251-261.
36. 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.
37. 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;91:2071-2076.
38. Kasperts N, Slotman BJ, Leemans CR, De Bree RV, Doornaert P, Langendijk JA. Results of postoperative reirradiation for recurrent or second primary head and neck carcinoma. *Cancer*. 2006;106:1536-1547.
39. Merlotti A, Mazzola R, Alterio D, et al. What is the role of postoperative re-irradiation in recurrent and second primary squamous cell cancer of head and neck? A literature review according to PICO criteria. *Crit Rev Oncol Hematol*. 2017;111: 20-30.
40. Chen YJ, Kuo JV, Ramsinghani NS, al-Ghazi MSAL. Intensity modulated radiotherapy for previously irradiated recurrent head and neck cancer. *Med Dosim*. 2002;27:171-176.
41. 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;64:382-391.
42. Caudell JJ, Ward MC, Riaz N, et al. Volume, dose, and fractionation considerations for IMRT-based reirradiation in head and neck cancer: a multi-institution analysis. *Int J Radiat Oncol Biol Phys*. 2018;100:606-617.
43. 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.
44. Maddalo M, Bonomo P, Belgioia L, et al. Re-irradiation with curative intent in patients with squamous cell carcinoma of the head and neck: a national survey of usual practice on behalf of the Italian Association of Radiation Oncology (AIRO). *Eur Arch Otolaryngol*. 2018;275(2):561-567.
45. 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;74:1342-1347.
46. Biagioli MC, Harvey M, Roman E, et al. Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2007;69:1067-1073.
47. Dawson LA, Myers LL, Bradford CR, et al. Conformal reirradiation of recurrent and new primary head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;50:377-385.
48. Grimard L, Esche B, Lamothe A, Cygler J, Spaans J. Interstitial low-dose-rate brachytherapy in the treatment of recurrent head and neck malignancies. *Head Neck*. 2006;28:888-895.
49. 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; 78:306-312.
50. Goldstein DP, Karnell LH, Yao M, Chamberlin GP, Nguyen TX, Funk GF. Outcomes following reirradiation of patients with head and neck cancer. *Head Neck*. 2008;30: 765-770.
51. Creak AL, Harrington K, Nutting C. Treatment of recurrent head and neck cancer: re-irradiation or chemotherapy? *Clin Oncol (R Coll Radiol)*. 2005;17:138-147.
52. Wong SJ, Machtay M, Li Y. Locally recurrent, previously irradiated head and neck cancer: concurrent re-irradiation and chemotherapy, or chemotherapy alone? *J Clin Oncol*. 2006;24(17): 2653-2658.
53. 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;73:399-409.

54. Curtis KK, Ross HJ, Garrett AL, et al. Outcomes of patients with loco-regionally recurrent or new primary squamous cell carcinomas of the head and neck treated with curative intent reirradiation at Mayo clinic. *Radiat Oncol*. 2016;11:55.
55. Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys*. 2016;95(4): 1117-1131.
56. Baliga S, Kabarriti R, Ohri N, et al. Stereotactic body radiotherapy for recurrent head and neck cancer: a critical review. *Head Neck*. 2017;39:595-601.
57. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol*. 2014;32:2847-2854.
58. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood*. 2009;114:589-595.
59. https://clinicaltrials.gov/ct2/show/NCT03546582
60. Voynov G, Heron DE, Burton S, et al. Frameless stereotactic radiosurgery for recurrent head and neck carcinoma. *Technol Cancer Res Treat*. 2006;5:529-535.
61. Roh KW, Jang JS, Kim MS, et al. Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2009;74:1348-1355.
62. 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: 1047-1053.
63. 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;33:286-293.
64. Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2010;77:1411-1419.
65. Kodani N, Yamazaki H, Tsubokura T, et al. Stereotactic body radiation therapy for head and neck tumor: disease control and morbidity outcomes. *J Radiat Res*. 2011;52:24-31.
66. Ozyigit G, Cengiz M, Yazici G, et al. A retrospective comparison of robotic stereotactic body radiotherapy and three-dimensional conformal radiotherapy for the reirradiation of locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81:263-268.
67. Vargo JA, Ward MC, Caudell JJ, et al. A multi-institutional comparison of SBRT and IMRT for definitive reirradiation of recurrent or second primary head and neck Cancer. *Int J Radiat Oncol Biol Phys*. 2018;100:595-605.
68. Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2014;89(1):13-20.
69. Brown JM, Carlson DJ, Brenner DJ, et al. The tumor radiobiology of SRS and SBRT: are more than the 5 R's involved? *Int J Radiat Oncol Biol Phys*. 2014;88(2):254-262.
70. 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;81:104-109.
71. Yazici G, Sanli TY, Cengiz M, et al. A simple strategy to decrease fatal carotid blowout syndrome after stereotactic body reirradiation for recurrent head and neck cancers. *Radiat Oncol*. 2013;8:242.
72. Bates MC, Shamsham FM. Endovascular management of impending carotid rupture in a patient with advanced head and neck cancer. *J Endovasc Ther*. 2003;10:54-57.
73. Chmura SJ, Milano MT, Haraf DJ. Reirradiation of recurrent head and neck cancers with curative intent. *Semin Oncol*. 2004; 31:816-821.
74. Ling DC, Vargo JA, Ferris RL, et al. Risk of severe toxicity according to site of recurrence in patients treated with stereotactic body radiation therapy for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2016;95:973-980.
75. 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;75:1493-1500.
76. Vargo JA, Moiseenko V, Grimm J, et al. Head and neck tumor control probability: radiation dose-volume effects in stereotactic body radiation therapy for locally recurrent previously-irradiated head and neck cancer: report of the AAPM working group. *Int J Radiat Oncol Biol Phys*. 2018. https://doi.org/10.1016/j.ijrobp.2018.01.044.
77. Deantonio L, Beldi D, Gambaro G, et al. FDG-PET/CT imaging for staging and radiotherapy treatment planning of head and neck carcinoma. *Radiat Oncol*. 2008;3:29.
78. Moule RN, Kayani I, Moinuddin SA, et al. The potential advantages of (18) FDG PET/CT-based target volume delineation in radiotherapy planning of head and neck cancer. *Radiother Oncol*. 2010;97:189-193.
79. Wang K, Heron DE, Clump DA, et al. Target delineation in stereotactic body radiation therapy for recurrent head and neck cancer: a retrospective analysis of the impact of margins and automated PET-CT segmentation. *Radiother Oncol*. 2013;106(1):90-95.
80. 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;34:165-172.
81. Comet B, Kramar A, Faivre-Pierret M, et al. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head-and-neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys*. 2012;84:203-209.
82. Lartigau EF, Tresch E, Thariat J, et al. Multi institutional phase II study of concomitant stereotactic reirradiation and cetuximab for recurrent head and neck cancer. *Radiother Oncol*. 2013;109:281-285.
83. https://clinicaltrials.gov/ct2/show/NCT02057107
84. Eekers DBP, Roelofs E, Jelen U, et al. Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric in silico ROCOCO trial. *Radiother Oncol*. 2016; 121:387-394.
85. Cheng Q, Roelofs E, Ramaekers B, et al. EP-1480: development and validation of a proton decision support system comparing dose, toxicity and cost-effectiveness. *Radiother Oncol*. 2016;118 (2):281-285.
86. McDonald MW, Zolali-Meybodi O, Lehnert SJ, et al. Reirradiation of recurrent and second primary head and neck

cancer with proton therapy. *Int J Radiat Oncol Biol Phys*. 2016; 4:808-819.
87. Phan J, Sio TT, Nguyen TP, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys*. 2016;96:30-41.
88. Romesser PB, Cahlon O, Scher ED, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. *Int J Radiat Oncol Biol Phys*. 2016;95:386-395.
89. Verma V, Rwigema JM, Malyapa RS, et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiother Oncol*. 2017;125: 21-30.
90. Gao J, Hu J, Guan X, et al. Salvage carbon-ion radiation therapy for locoregionally recurrent head and neck malignancies. *Sci Rep*. 2019;9(1):4259.
91. Hayashi K, Koto M, Ikawa H, et al. Feasibility of re-irradiation using carbon ions for recurrent head and neck malignancies after carbon-ion radiotherapy. *Radiother Oncol*. 2019;136:148-153.
92. Held T, Windisch P, Akbaba S, et al. Carbon ion reirradiation for recurrent head and neck cancer: a single-institutional experience. *Int J Radiat Oncol Biol Phys*. 2019;105(4):803-811.

How to cite this article: Svajdova M, Dubinsky P, Kazda T. Radical external beam re-irradiation in the treatment of recurrent head and neck cancer: Critical review. *Head & Neck*. 2020; 1–13. https://doi.org/10.1002/hed.26485