Recurrent and second primary squamous cell carcinoma of the head and neck: When and how to reirradiate

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ABSTRACT: *Background.* Local and/or regional recurrence and metachronous primary tumor arising in a previously irradiated area are rather frequent events in patients with head and neck squamous cell carcinoma (HNSCC). Re-treatment is associated with an increased risk of serious toxicity and impaired quality of life (QOL) with an uncertain survival advantage.

Methods. We analyzed the literature on the efficacy and toxicity of photon/electron-based external beam reirradiation for previously irradiated patients with HNSCC of non-nasopharyngeal origin. Studies were grouped according to the radiotherapy technique used for reirradiation. Patient selection criteria, target volume identification method, tumor dose, fractionation schedule, systemic therapy administration, and toxicities were reviewed.

Results. In addition to disease-related factors, current comorbidities and preexisting organ dysfunction must be considered when selecting patients for reirradiation. As morbidity from re-treatment may be considerable and differ depending on which mode of re-treatment is used, it is important to give patients information on potential morbidity outcomes so that an informed choice can be made within a shared decision-making context. With improved dose distribution and adequate imaging support, including positron emission tomography-CT, modern radiotherapy techniques may improve local control and reduce toxicity of reirradiation. A reirradiation dose of $\geq$60 Gy and a volume encompassing the gross tumor with up to a 5-mm margin are recommended. Concomitant administration of systemic therapeutics and reirradiation is likely to be of similar benefit as observed in large randomized studies of upfront therapy.

Conclusion. Reirradiation, administered either with or without concurrent systemic therapy, is feasible and tolerable in properly selected patients with recurrent or a new primary tumor in a previously irradiated area of the head and neck, offering a meaningful survival (in the range of 10% to 30% at 2 years). Whenever feasible, salvage surgery is the method of choice for curative intent; patients at high-risk for local recurrence should be advised that postoperative reirradiation is expected to increase locoregional control at the expense of higher toxicity and without survival advantage compared to salvage surgery without reirradiation. © 2014 Wiley Periodicals, Inc. *Head Neck* **37**: 134–150, 2015

KEY WORDS: head and neck cancer, squamous cell carcinoma, recurrence, second primary cancer, reirradiation, salvage surgery, systemic therapy

INTRODUCTION

Initial multimodality treatments for locally advanced head and neck squamous cell carcinoma (HNSCC) can be unsuccessful, resulting in persistent or recurrent disease, and the past and current lifestyle choices of many patients increase their risk for new primary cancers even if the initial tumor was cured. Recurrent and second primary HNSCC in previously radiated regions pose a unique challenge to clinicians dealing with this disease. As multidisciplinary management is common in head and neck oncology, most of these patients already have received considerable intensified prior

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treatment consisting of surgery, radiotherapy (RT), and/or chemotherapy.

In the present study, we reviewed the efficacy and toxicity of photon/electron-based external beam reirradiation as salvage treatment of HNSCC for patients previously irradiated for HNSCC primary tumors of non-nasopharyngeal origin. Reports using brachytherapy as the main reirradiation procedure were not included in the present analysis.[1]

MATERIALS AND METHODS

A systematic review of the English-language literature was conducted using the PubMed database with the following search terms: reirradiation, re-treatment, and head and neck cancer. The content of publications identified in the search results was reviewed for possible inclusion, and references were checked for additional relevant reports. Only studies fulfilling the following criteria were included: (1) published as a full article in peer-reviewed journals; (2) the majority of patients had non-nasopharyngeal primaries and the prevailing histology was squamous cell carcinoma; (3) results for different RT techniques were reported separately; and (4) overall survival (OS) data was reported or could be estimated from the Kaplan–Meier plot.

Depending on the RT technique used in a particular study, salvage treatments were divided into 4 groups: (1) salvage surgery performed with curative intent in combination with reirradiation using conventional techniques; (2) reirradiation for unresectable disease using conventional techniques; (3) reirradiation using intensity modulated radiotherapy (IMRT); and (4) reirradiation using stereotactic body radiotherapy (SBRT). In addition, the quantitative aspect and other issues specifically related to reirradiation (target volume definition, tumor dose, regimen, and tolerance of reirradiated tissues) were reviewed and discussed together with systemic drugs used in conjunction with reirradiation and criteria for the selection of patients who are likely to benefit from aggressive reirradiation programs.

RESULTS

Extent of the problem

By definition, HNSCC is largely a locoregional problem, with the distribution of most recurrences after primary, curative-intent RT regimens occurring within the treatment field. According to the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) data from 50 concomitant chemotherapy-RT trials and 30 induction chemotherapy trials, the rates of local and/or regional recurrence at 5 years were 50.8% and 47.5% in the experimental arms, respectively, and 60.1% and 46.5% in the control arms (ie, RT alone) of the trials, respectively.[2] The corresponding rates of distant metastasis were below 20%. Although patients with locoregional tumor recurrence can be considered salvageable with surgical and/or reirradiation-based therapies, considering the health status and preferences of patients with recurrence, morbidity after previous therapies and the extent of the disease, approximately half or less were amenable to salvage surgery or other curative intent treatment strategies.[3–6]

Another indication for re-treatment in a previously irradiated area of the head and neck is metachronous HNSCCs. Their appearance relates to a lengthy exposure of the upper aerodigestive tract mucosa to the immoderate use of tobacco and alcohol, resulting in a "field cancerization" effect, and genetic predisposition.[7,8] Analyzing the Radiation Therapy Oncology Group (RTOG) registry with 2066 patients prospectively entered with HNSCC, Cooper et al[9] identified 601 patients without prior/coincident of another malignant tumor who were treated with RT alone and were free of disease at 6 months posttherapy. The estimated risk of developing a second malignant tumor in these patients at 3, 5, and 8 years (plus 6 months) from the start of RT was 9%, 14%, and 23%, respectively, and the proportion of new primary tumors arising in the head and neck was 18%. A study presenting the University of Florida experience on 1112 patients with HNSCC treated with curative RT and followed for at least 2 years was reported by Erkal et al.[10] Among these patients, there were 9% who developed a new HNSCC at 0.6 to 21.7 years after RT, and the rates of occurrence of a second primary HNSCC at 5 years by the site of the initial malignancy were 11%, 12%, and 3% for patients with carcinoma of the oropharynx, hypopharynx, and supraglottic larynx, respectively. In the series from the MD Anderson Cancer Center, 3.4% of 1292 patients with HNSCC who completed different treatment programs developed a second HNSCC, corresponding to 36.7% of all second primary tumors diagnosed in this cohort.[8]

Re-treatment strategies

Patients who present with a locoregional recurrence or a second primary HNSCC are frequently heavily pretreated with surgery and RT, with or without chemotherapy, or both. Surgical salvage has proven to be the most effective curative-intent treatment and is the treatment of choice for all patients with resectable tumors and sufficiently good health status. According to a meta-analysis of 32 studies with a total of 1080 patients reported by Goodwin,[11] a survival rate of 39% can be expected at 5 years after salvage surgery. The best chance for cure has been reported for patients with early-stage recurrent tumors, whereas those with rT3-classified and rT4-classified recurrent disease should be considered poor candidates to undergo salvage surgery.[3,11,12] The efficacy of salvage surgery also correlated with the site of recurrent cancer, and the outcome tended to be better in recurrent cancer of the larynx as compared to other tumor sites. However, the impact of the treated site was found to be less important than recurrence stage.[11]

The role of chemotherapy as a single therapeutic modality in such patients is palliative. A phase III clinical trial has shown that the median survival of patients with recurrent, unresectable HNSCC can be improved from 7.4 to 10.1 months (hazard ratio [HR], 0.80; $p = .04$) with the addition of cetuximab to platinum/5-fluorouracil (FU) systemic therapy.[13] However, it is known from earlier randomized trials in recurrent/metastatic HNSCC that, with platinum-based combination chemotherapy, only 3.6% of patients are still alive after 5 years.[14]

In recurrent, unresectable head and neck cancer, decision analysis models informed by results from systematic reviews and expert panel-generated utility values showed that concurrent chemotherapy and reirradiation offers an improvement in quality of life (QOL)-years of approximately 5 weeks compared to best supportive care.[15]

Reirradiation (using conventional techniques) and combinations with other treatment modalities: a review of effectiveness. In the era of conventional RT techniques, several retrospective reports, but only a few prospective studies, have been published using reirradiation as a salvage modality in locoregional recurrence and/or second primary HNSCC. There have been only 2 prospective phase III studies exploring the efficacy of conventional reirradiation, and one of them was underpowered because of slow accrual resulting in premature closure.

Reirradiation after salvage surgery. In 2008, the Groupe d'Etude des Tumeurs de la Tête Ed du Cou and Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) groups reported on a phase III randomized trial of postoperative reirradiation combined with chemotherapy compared with salvage surgery alone.[16] Between 1999 and 2005, a total of 130 patients from 16 French and Belgian centers were randomized to the trial arms. Surgical resection encompassed a lymph node dissection in 84% of patients, although two-thirds had cN0 disease. Histopathological examination of the resected specimens revealed positive/close margins, extracapsular rupture, or >1 invaded nodes in 49% of the patients. In the experimental arm, patients were to receive 6 cycles of 5 × 2 Gy/fraction (fx) reirradiation, concomitantly with hydroxyurea/5FU, with a 9-day rest period between cycles. The tumor bed with a 1- to 2-cm margin and the first adjacent metastasis-free nodal area were irradiated. Significant improvements in locoregional control (LRC; HR, 4.51; $p < .0001$) and disease-free survival (DFS; HR, 1.68; $p = .01$) were observed in the reirradiation arm, but OS (45% at 2 years in the reirradiation arm) did not differ between the 2 arms because of more treatment-related deaths, distant metastases, and second primary tumors among the reirradiated patients. An increase in serious (grade 3 or 4) late toxicities was associated with adjuvant therapy (39% vs 10% at 2 years; $p = .06$), and 5 treatment-related deaths were recorded in this group.

Several smaller prospective or retrospective series have been reported in the literature, and the main characteristics and results from these reports are presented in Table 1.[16–25] Conclusions drawn from these studies might include the following: (1) only patients with high-risk features found at histopathological examination of the resected specimen should be considered for postoperative reirradiation (eg, close or involved surgical margins and extracapsular tumor extension); (2) grade 3 or 4 late toxicities occur in greater than a third of the patients; (3) up to 8% of patients will die because of causes related to retreatment; (4) OS rates in the range of 40% to 50% at 2 years are achievable (in a selected population of fit patients with smaller tumor volumes than in those not amenable to salvage surgery); and (5) compared to salvage surgery alone, adjuvant reirradiation (with or without concomitant chemotherapy) improves LRC and DFS but has no effect on OS. It is not clear whether the addition of concurrent chemotherapy to reirradiation improves treatment efficacy.

The morbidity and mortality associated with adjuvant reirradiation cannot be understated. Some have suggested that the introduction of vascularized tissue in the form of a muscle flap may help to protect the vascular structures and the overlying skin from radiation injury. Suh et al[24] retrospectively evaluated 12 patients who received microvascular free flap reconstruction for recurrent or second primary head and neck cancer in a previously irradiated field. All free flaps were inset directly into the field of previous radiation and were exposed to reirradiation. The authors compared their results with the published complication rate and they found that microvascular free flaps allow for maximal resection and reliable reconstruction of previously irradiated cancers before high-dose reirradiation and may reduce the incidence of severe late complications and treatment-related mortality. In those patients who are undergoing salvage surgery with the intent on reirradiation, the introduction of vascularized tissue may reduce the rate of skin sloughing, spontaneous fistula, and great vessel rupture.

Reirradiation for unresectable disease. The only trial with randomized design was conducted by the French Head and Neck Oncology Radiotherapy Group (GORTEC 98-03) during 1999 to 2005 and was closed prematurely.[26] Only 57 patients (of a planned 160 patients), unsuitable for any curative salvage therapy, were randomized between weekly single agent methotrexate (until disease progression or toxicity, 27 patients) or 6 cycles of reirradiation (5 × 2 Gy/fx/cycle) and concurrent hydroxyurea/5FU (30 patients), with a 9-day intercycle rest period. The irradiated volume encompassed the gross tumor volume (GTV) with ≥2-cm margin and the first adjacent nodal station. With more rT3-4 tumors in the reirradiation arm (88% vs 60%), 4 patients from this group experienced a complete response (but none in the methotrexate arm), although no differences in OS was found between the 2 approaches (1-year survival, 22% vs 23%; $p = .6$). The reirradiation arm proved to be more toxic compared to the methotrexate arm with regard to treatment-related deaths (3 vs 1) and grade 3/4 late toxicities (11 vs 5).

In 2004, the RTOG launched a phase III randomized trial (RTOG 04-21) comparing concomitant chemotherapy and reirradiation (the same regimen as in the RTOG 9911, see below) and 3 cisplatin-based standard chemotherapy regimens. As in the case of the GORTEC 98-03 trial, it was closed prematurely because of poor accrual, and results have not been reported.

However, the RTOG designed and successfully conducted 2 multi-institutional prospective phase II trials. In the RTOG 9610 trial (1996–1999), a total of 86 patients were recruited and treated with 4 weekly cycles of chemotherapy and reirradiation (1.5 Gy/fx b.i.d., concurrently with hydroxyurea/5FU, days 1–5), separated by 1 week of rest.[27] Only the gross disease was irradiated with a margin of ≥2 cm. Of 79 analyzable patients, all 4 chemotherapy cycles and >54.6 Gy were received by 73.4% and 77.2% patients, respectively. In the acute phase of the protocol, there were 6 treatment-related deaths (7.6%);

TABLE 1. Salvage surgery and adjuvant reirradiation (using conventional techniques).

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	Therapy			Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
			Post-surgical status	Reirradiation	Chemotherapy		
Emami et al, 1987[17] (1967–1985)	48, retrospective	N.S.	N.S.	N.S. Reirradiation volume: N.S. ± ELN-RT	No	N.S.	OS, 46%†
Benchalal et al, 1997[18] (1980–1992)	14, prospective	30 (9–15)	R_+/ECE, 100%	TD_{median} 60 Gy, 1.2 Gy/fx b.i.d. Reirradiation volume: N.S.	No	50% TRD, 0%	LC, 27%† OS, 36%
Nag et al, 1998[19] (1992–1997)	38, retrospective	N.S.	$R_{1/close\ margins}$, 92% R_2, 8%	Intraoperative electron beam: TD 15–20 Gy (90% isodose) Reirradiation volume: TB	No	13% TRD, 3%	LC, 13% LRC, 4% OS, 21%
De Crevoisier et al, 2001[20] (1991–2001)	25, prospective	23 (5–137)	R_+/ECE	TD_{median} 60 Gy, 2 Gy/fx (d 1–5 → 9-d break) Reirradiation volume: TB + ≥15–20 mm	HU + 5FU	N.S. TRD, 0	OS, 48%†
Machtay et al, 2004[21] (1998–2001)	16, prospective	23.5 (7–156)	R_2, 13%	TD_{median} 60 Gy, 1.5 Gy/fx b.i.d. (30 Gy → 1-wk break) Reirradiation volume: TB + ≥20 mm ± ELN-RT	CDDP + 5FU amisfostine	38% TRD, 6%	LRC, 100% OS, 81%
Kasperts et al, 2006[22] (1997–2003)	39, prospective	36 (11–156)	$R_{1/close\ margins}$, 49% ECE, 49% Perineural growth, 20%	TD 60–66 Gy, 2 Gy/fx $CTV = GTV_{preop}$ + 5 mm ± ELN-RT	No	N.S. TRD, 0%	LRC, 74%† OS, 67%†
Salama et al, 2006[23] (1986–2001)	49, prospective	N.S.	N.S.	TD 60–74 Gy, 2 Gy/fx or 1.5 Gy/fx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: TB + 10 mm ± ELN-RT	HU + 5FU, other agents	N.S.	3-y LRC, 68% 3-y OS, 39%
Suh et al, 2008[24] (1996–2007)	12‡, retrospective	15.5 (8–516)	$R_{1/2}$, 17% ECE, 8% Perineural growth, 25%	TD_{median} 50.5 Gy Reirradiation volume: N.S.	Yes, 42%	33% TRD, 0%	OS, 52%†
Janot et al, 2008[16] (1999–2005)	65§, randomized phase III	43 (6–366)	$R_{1/close\ margins}$, 22% ECE, 29% Vascular emboli/ perineural growth/ diffuse infiltration, 54%	TD_{median} 60 Gy, 2 Gy/fx (d 1–5 → 9-d break) Reirradiation volume: TB + 10–20 mm + ELN-RT	HU + 5FU	39% (of 18 patients, at 2 y) TRD, 8%	LRC, 56%† OS, 48%†
Janssen et al, 2010[25] (1987–2008)	20, retrospective	19 (5–199)	N.S.	TD_{mean} 46 Gy Reirradiation volume: TB + "safety margin"	Yes, 35%	N.S.	LRC, 21% OS, 24%

Abbreviations: N.S., not specified; ELN-RT, elective lymph node radiotherapy; OS, overall survival; R+, positive margin; ECE, extracapsular extension; TD, tumor dose; fx, fraction; TRD, treatment-related death; LC, local control; TB, tumor bed; LRC, locoregional control; HU, hydroxyurea; 5FU, 5-fluorouracil; CDDP, cisplatin; CTV, clinical target volume; GTVpreop, preoperative gross tumor volume.

* Median (range), in months.

† Estimated from Kaplan–Meier plot.

‡ Proton therapy in 3 patients, intensity-modulated radiotherapy in 1 patient.

§ Postoperative reirradiation combined with chemotherapy arm of the trial.

69.6% of patients had a feeding tube at the last follow-up, and the estimated cumulative incidence of late grade 3/4 toxicities at 2 and 5 years was 9.4%. Death was related to the index cancer in 72.7% of the patients, and OS was 15.2% at 2 years. The second study (RTOG 9911) was conducted during 2000 to 2003 and included 105 patients who were treated according to the same reirradiation protocol (IMRT was allowed and used at the discretion of the investigator) but with a different chemotherapy regimen (cisplatin/paclitaxel, concurrently with reirradiation, days 1–5) and granulocyte colony-stimulating factor support (days 6–13, every other week).[28] All 4 chemotherapy cycles were completed in 74% of 99 analyzable patients, and 76% of patients received >52.5 Gy. The incidence of grade 3/4 late adverse effects was 33.8%, and the incidence of treatment-related deaths was 8% (early 5, late 3). At 2 years, progression-free survival and OS were 15.8% and 25.9%, respectively, with 71% of deaths recognized as cancer-related. Comparing the outcome results from RTOG 9610 and RTOG 9911, the OS rate seems superior in the latter trial ($p = .0444$).

The studies using reirradiation in patients with unresectable tumors are listed in Table 2.[17,23,25–51] The review of the reported results shows that at 2 years, one quarter to one third of the patients will be free of locoregional tumor; OS rates in the 10% to 30% range can be expected at 2 years of follow-up, although long-term survivors are rare. Late toxicities of grade 3/4 severity may occur in up to 40% of reirradiated patients, and nearly 10% of patients will have treatment-related deaths. Obviously, the outcomes differ considerably across these studies and depend primarily on the selection criteria for re-treatment and intensity of the applied therapies. Moreover, there are still questions regarding the most effective reirradiation regimen (split-course vs continuous-course; once-daily fractionation vs hyperfractionation) and on the added value of concurrent chemotherapy that remain unanswered. To date, no randomized comparison of reirradiation treatment schemes has been conducted, and the wide diversity in patient populations and in tumor-related and treatment-related parameters across the reported studies prevents any meaningful conclusions.

There are several reasons why the treatment results in the reirradiation series dealing with unresectable disease are inferior when compared to the adjuvant (postoperative) reirradiation series. First, patients referred for salvage surgery have, by definition, operable, lower-volume tumors, compared with those referred for reirradiation, implying, per se, a higher probability for cure in such cases. Furthermore, in surgical candidates, the processes of tissue scarring, initiated during the previous course of RT, are expected to be less prominent and, consequently, involved tissues are likely less hypoxic. After salvage surgery, tumor burden is considerably reduced, and less compromised vasculature and better oxygenation in the treated area make residual tumor cells more sensitive to subsequent RT and better exposed to systemic drugs than is probably the case in patients not amenable for salvage surgery. Last, only patients with good performance status are suitable for general anesthesia and a major surgical procedure, which is a prerequisite for a successful completion of the planned therapy and subsequent rehabilitation.

How to irradiate

Experiences with re-treatment of patients with head and neck cancer gained during the last decades provide a solid ground for refinement of the existing reirradiation strategies. Moreover, given the enormous progress in RT technology and targeted drug development, several exciting novel paradigms bring new optimism to these patients with traditionally poor prognosis.

Reirradiation volumes. The main challenge in a reirradiation setting is the extent of the clinical target volume (CTV), expanding around the recurrent primary tumor or regional lymph nodes, and whether to electively irradiate the neighboring noninvolved nodal area(s). In this respect, several observations should be taken into account. First, after performing contrast-enhanced CT of the neck in the post-RT setting, the negative predictive value for regional metastases is >94%.[52] Second, differences in the pattern of metastases (the incidence and/or geographic distribution of metastases) can be expected after previous RT. Changes in nodal size and the caliber of lymphatic vessels have been observed in the irradiated lymphatic tissue, with marked hyalinization and fibrotic changes found in lymph nodes irradiated with doses of >40 Gy.[53–55] Also, lymphoscintigraphy performed as part of the sentinel node procedure in early oral cancer showed an unexpected lymph drainage pattern in 67% of the patients with a previously treated neck.[56] Third, high rates of local failures and systemic metastases reported in patients after local and/or regional salvage treatment markedly reduce the potential therapeutic gain that would be expected from elective RT.[57] Locoregional recurrence and second primary tumors have been identified as high-risk factors for the development of distant metastases.[58]

Considering only recent reirradiation series with a more consistent utilization of contemporary imaging for target determination and computer-assisted three-dimensional (3D) RT planning,[57,59–69] it seems that, at the site of recurrence, the reirradiation CTV should include the GTV/tumor bed with no or only a narrow margin (≤0.5 cm) of the normal-appearing surrounding tissue. The margin is intended to cover potential microscopic tumor extensions and/or compensate for geographic uncertainties originating from an imperfect visualization of the tumor/normal-tissue border, as well as differences in the appearance of the GTV resulting from the implementation of various imaging modalities.[70]

The need for any "safety" margin around GTV was questioned by Popovtzer et al.[57] They expanded GTV by 0.5 cm to form a planning target volume (PTV): 45 to 47 (96%) of local failures in their series occurred within the high-dose reirradiation volume. Moreover, using SBRT, Wang et al[71] used no margin at all around the visually delineated GTV (GTV = CTV = PTV). In the non-positron emission tomography-CT (non-PET-CT) planning group, 25 of 44 patients (57%) had a local recurrence: 11 of 25 recurrences (36%) occurred "in field" (≥20% of the recurrent tumor inside the GTV), whereas 14 of 25 recurrences (64%) were declared as marginal (<20% inside the GTV, but with the

TABLE 2. Salvage reirradiation in unresectable tumors (using conventional techniques).

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	Therapy		Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
			Reirradiation	Chemotherapy		
Skołyszewski et al, 1980[29] (1968–1974)	20, retrospective	26 (5–94)	TD 34–75 Gy, 2 Gy/fx Reirradiation volume: GTV + "very narrow margin"	No	20% TRD, 0%	70% patients survived 3 y after reirradiation
Langlois et al, 1985[30] (1973–1981)	35‡, retrospective	40 (4–19)	TD_{median} 60–69 Gy, 2 Gy/fx Reirradiation volume: N.S.	No	29% TRD, 9%	LC, 24% OS, 19%
Emami et al, 1987[17] (1967–1985)	40, retrospective	N.S.	N.S.	No	N.S.	OS, 33%†
Levendag et al, 1992[31] (1970–1980)	55‡, retrospective	N.S.	TD_{mean} 46 Gy§, 2 Gy/fx Reirradiation volume: N.S.	Yes, 49%	N.S.	OS, 26%†
Wang and McIntyre, 1993[32] (−1992)	20‖, retrospective	N.S.	TD_{median} 67 Gy, q.d. or b.i.d. Reirradiation volume: 5 × 5 or 5 × 4.5 cm	No	N.S.	5-y LC, 61% 5-y OS, 92%
Tercilla et al, 1993[33] (1985–1988)	10, prospective	73 (0–336)	TD 30–45 Gy§, 1.4–1.6 Gy/fx b.i.d. Reirradiation volume: GTV + 10 mm	No	50% TRD, 0%	50% patients alive ≥34 mo after reirradiation
Stevens et al, 1994[34] (1964–1991)	100, retrospective	N.S.	$TD_{planned}$ ≥50 Gy, 1.8–2 Gy/fx Reirradiation volume: N.S.	No	9% TRD, 4%	SPT: OS, 59% RT: OS, 27%
Hartsell et al, 1994[35] (1981–1989)	21, prospective	25 (9–133)	TD_{median} 40 Gy, 2 Gy/fx (d 1–5 → 9-d break) Reirradiation volume: N.S.	CDDP + 5FU	N.S. TRD, 10%	LRC, 24% OS, 19%
De Crevoisier et al, 1998[36] (1980–1996)	Group 1, 27 (retrospective) Group 2, 106 (phase II) Group 3, 36 (phase I/II)	33 (N.S.) 40 (N.S.) 23 (N.S.)	TD_{median} 65 Gy, 2 Gy/fx D_{median} 60 Gy, 2 Gy/fx (d 1–5 → 9-d break) TD_{median} 60 Gy, 1.5 Gy/fx b.i.d., (wk 1–2 → 2-wk break) Reirradiation volume, all: GTV + 15–20 mm	No HU + 5FU MMC + 5FU + CDDP	N.S. TRD, 3.5%	Group 1: OS, 25% Group 2: OS, 24% Group 3: OS, 10%
Spencer et al, 1999[37] (1989–1991)	35, prospective	24 (7–144)	TD 40–60 Gy, 2 Gy/fx q.d. or 1.2–1.5 Gy/fx b.i.d. (wk 1, 3, 5, 7) Reirradiation volume: GTV + ≥20 mm ± ELN-RT	HU + 5FU	12% TRD, 11%	OS, 20%†
Schaefer et al, 2000[38] (1995–1998)	32, prospective	17 (5–134)	TD_{median} 50 Gy, 2 Gy/fx 8 (d 1–5 → 9-d break) Reirradiation volume: GTV + 20 mm	HU + 5FU	12% (of 26 patients with FUP ≥3 mo) TRD, 6%	OS, 5%†
Dawson et al, 2001[39] (1983–1999)	40‡, retrospective	21 (0.5–227)	TD_{median}.60 Gy, 1.8–2 Gy/fx q.d. or 1.2 Gy/fx b.i.d. Reirradiation volume: PTV = GTV + 5–20 mm	Yes, 33% CDDP/carboplatin	18% TRD, 0%	LRC, 19.5% OS, 32.6%

TABLE 2. *Continued*

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	Therapy		Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
			Reirradiation	Chemotherapy		
Ohizumi et al, 2002[40] (1984–1997)	44, retrospective	13.5 (1–134)	TD_{median} 53 Gy, 1.9–2 Gy/fx q.d. or 1.2–1.4 Gy/fx b.i.d. Reirradiation volume: GTV + 10–20 mm	Yes, 23% CDDP, Bleo, PM, 5FU, tegafur	12% (of 33 patients with FUP ≥3 mo) TRD, 0%	OS, 10%
Spencer et al, 2003[41] (1992–1999)	52, prospective (phase I)	N.S.	TD 50–60 Gy, 2 Gy/fx q.d. and 1.5 Gy/fx b.i.d. Reirradiation volume: GTV + 20 mm	5FU + HU	8% TRD, 0%	OS, 15%
Nagar et al, 2004[42] (1991–1999)	29, retrospective	13 (3–90)	TD_{median} 34 Gy, 1.8–2 Gy/fx Reirradiation volume: GTV + 15–20 mm	CDDP ± 5FU	N.S. TRD, 0%	OS, 12%
Kramer et al, 2005[43] (1996–2002)	38, prospective (phase I/II)	N.S.	TD 51–60 Gy, 1.2–1.5 Gy/fx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + 20 mm	CDDP + paclitaxel	N.S. TRD, 3%	OS, 35%
Langendijk et al, 2006[44] (1997–2003)	34, prospective	90 (12–233)	TD 60–66 Gy, 2 Gy/fx CTV = GTV + 5 mm ± ELN-RT Reirradiation volume: PTV = CTV +5 mm	No	N.S. TRD, 0%	LRC, 27% OS, 38%
Salama et al, 2006[23] (1986–2001)	66, prospective	N.S.	TD 66–67 Gy, 2 Gy/fx q.d. or 1.5 Gy/fx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + 10 mm ± ELN-RT	HU + 5FU, CDDP, gemcitabine, paclitaxel, irinotecan	N.S.	3-y LRC, 36% 3-y OS, 11%
Langer et al, 2007[28] (2000–2003)	99, prospective RTOG 9911	40 (6–318)	TD_{median} 60 Gy, 1.5 Gy/fx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + ≥20 mm	CDDP + paclitaxel	N.S. TRD, 8%	OS, 25.9%
Cohen et al, 2007[45] (2001–2003)	25, prospective (phase I)	32 (11–198)	TD_{median} 72 Gy, 1.8 Gy/fx (CB with 1.5 Gy 2nd fx for last 12 d) Reirradiation volume: GTV + 15 mm + ELN-RT	CDDP + tirapazamine	8% TRD, 8%	OS, 27%
Spencer et al, 2008[27] (1996–1999)	79, prospective RTOG 9610	30 (7–238)	TD 60 Gy, 1.5 Gy/fx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + ≥20 mm	HU + 5FU	At 2–5 y, 9.4% TRD, 7.6%	OS, 25.9%
Seiwert et al, 2008[46] (2001–2004)	29, prospective (phase I)	18 (4–362)	TD_{median} 70 Gy, 1.8–2 Gy/fx (d 1–5 → 9-d break) Reirradiation volume: GTV + 10–15 mm	HU + 5FU + bevacizumab	34% TRD, 14%	OS, 17.2%
Watkins et al, 2009[47] (1997–2007)	39‡, retrospective	28 (6–228)	TD_{median} 60 Gy, 1.5 Gy/fx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: PTV = GTV + 3–5 mm	HU + 5FU *or* CDDP + paclitaxel	N.S. TRD, 10%	OS, 45.1%

TABLE 2. *Continued*

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	Therapy		Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
			Reirradiation	Chemotherapy		
Janssen et al, 2010[25] (1987–2008)	55, retrospective	19 (5–199)	TD_{mean} 46 Gy Reirradiation volume: GTV + "safety margin"	Yes, 47% CDDP, 5FU, CMb carboplatin, taxol, gemcitabine	N.S.	Reirradiation: LRC, 13% Reirradiation: OS, 16% Reirradiation + chemotherapy: LRC, 51% Reirradiation + chemotherapy: OS, 30%
Berger et al, 2010[48] (1997–2007)	57‡, prospective	16 (7.5–188)	TD 40 Gy, 2 Gy/fx (wk 2 + 3, 5 + 6) *or* TD 49.6 Gy, 2 Gy/fx (wk 2 + 3, 5 + 6, CB with 1.6 Gy 2nd fx after 28 Gy) Reirradiation volume: PTV = GTV + 10 mm	CDDP + docetaxel	40% TRD, 7%	40 Gy group: OS, 16%† 49.6 Gy group: OS, 31%
Tortochaux et al, 2011[26] (1999–2005)	30¶, randomized GORTEC 98-03	N.S.	TD_{median} 60 Gy, 2 Gy/fx, (d 1–5 → 9-d break) Reirradiation volume: GTV + ≥2 cm + ELN-RT	HU + 5FU	37% TRD, 7%	OS, 8%†
Platteaux et al, 2011[49] (2000–2009)	51‡, retrospective	60.5 (3–324)	TD_{median} 60 Gy, 1.8–2 Gy/fx Reirradiation volume: PTV = GTV + 5–20 mm	Yes, 31% CDDP, carboplatin, 5FU, CMb, docetaxel	35.3% TRD, 0%	LRC, 32% OS, 30%
Balermpas et al, 2012[50] (2008–2010)	18, prospective	21 (5–109)	TD_{median} 50.4 Gy, 1.8 Gy/fx Reirradiation volume: PTV = GTV + 10–15 mm	CMb	N.S. TRD, 0%	LC, 26%† OS, 19%
Vormittag et al, 2012[51] (N.R.)	31, prospective	15 (N.S.)	TD_{median} 50 Gy, 2 Gy/fx Reirradiation volume: PTV = GTV + 10 mm	Capecitabine	N.S. TRD, 0%	OS, 10%

Abbreviations: TD, tumor dose; fx, fraction; GTV, gross tumor volume; TRD, treatment-related death; N.S., not specified; LC, local control; OS, overall survival; q.d., once per daily; b.i.d., twice per day; SPT, second primary tumor; RT, recurrent tumor; 5FU, 5-fluorouracil; LRC, locoregional control; HU, hydroxyurea; MMC, mitomycin C; CDDP, cisplatin; ELN-RT, elective lymph node radiotherapy; FUP, follow-up; PTV, planning target volume; PM, pepleomycin; CTV, clinical target volume; RTOG, Radiation Therapy Oncology Group; CB, concomitant boost; CMb, cetuximab; GORTEC, Groupe d'Oncologie Radiothérapie Tête et Cou; N.R., not reported.

* Median (range), in months.

† Estimated from Kaplan–Meier plot.

‡ Salvage surgery in 34%[29], 20%[30], 10%[38], 23%[46], 11%[47], and 27.5%[48] of the patients.

§ Brachytherapy boost in 18%[30], 30%[32], 18%[33], and 10%[38] of the patients.

‖ Early-stage glottis or supraglottis carcinoma (T1–2N0) in 95% of the patients.

¶ Only results of reirradiation + chemotherapy arm are reported.

closest edge within 1 cm of the GTV). In the PET-CT planning group (45 patients with 16 local recurrences), there were only 6 of 16 marginal failures (38%). After retrospectively adding margins of 1 to 5 mm to the GTVs, a median coverage of recurrence volumes, as measured by the GTV-recurrence volume overlap, increased from 11.7% (GTV +0 mm) to 48.2% (GTV +5 mm) in non-PET-CT patients and from 45% to 93.6% in PET-CT–planned patients. The authors concluded that margins of up to 5 mm around the GTV may effectively reduce failures but could possibly increase toxicity. The similarity of GTV size and disparity of outcome between the 2 types of planning suggests that PET-CT planning may alter GTV location rather than volume. With PET-CT planning, near-miss failures can be effectively reduced with a smaller increase in GTV size.

With regard to elective reirradiation of the regional lymphatics, 3 clinical scenarios must be considered. First, in patients with isolated local recurrence and clinically and radiographically N0 necks who were originally treated with elective RT to cN0 necks, the risk of occult neck disease is generally low, usually not justifying elective treatment to the neck. Dagan et al[72] reported on 57 such patients who underwent salvage surgery of recurrent primary with or without neck dissection. Occult metastases were found in 4 of 46 dissected specimens (9%; in 4 of 40 patients; 10%), and only 1 of the observed patients had neck recurrence. None of these patients had an isolated neck recurrence. By adding neck dissection, no improvement in LRC, cause-specific survival, or OS was found, whereas the likelihood of adverse events was increased. Summarizing the results from 6 recent literature series dealing with patients surgically salvaged for isolated locally recurrent HNSCC[72–77] after (chemo)-RT for initially staged cN0 HNSCC, the rate of pathologically involved nodes was 10% among a total of 274 patents. A comparably low rate of occult nodal metastasis (8%) was found in 13 patients diagnosed with a second node-negative primary HNSCC who had already received elective neck RT.[78] In patients with recurrent supraglottic/hypopharyngeal tumors or rT3-4 tumors, however, the risk of occult metastases in the neck lymphatics seems higher, and these patients may benefit from elective (re)treatment of the neck.[73,75,79]

The second scenario includes patients with an isolated local recurrence who were initially treated for node-positive disease. In this group, elective treatment of regional lymphatics might be indicated. Solares et al[80] reported on 69 patients who underwent 96 selective neck dissections and found histologically positive nodes in 25% of the patients (23% of the operated hemi-necks). There were no recurrences in salvaged necks when the primary site was controlled, and the pattern of lymphatic spread was found unaffected by previous RT. In the recent series of Amit et al,[79] elective dissection revealed occult nodal metastases in 4 of 8 patients (50%) and 2 of 26 patients (8%) who received RT to the neck at initial treatment for N+ and N0 disease, respectively. In the group previously irradiated for early-stage (T1–2N0) glottic (12 cases) or supraglottic (2 cases) primaries but having no elective neck RT, the rate of occult metastases was 14% (2 of 17 neck specimens; 12%), whereas the risk of metastases in the contralateral neck was 0% (0 of 9). Recently, Lee et al[81] also found a significant advantage for elective neck dissection during salvage surgery in node-positive patients at initial treatment and recurrent cases that developed within 1 year.

The third scenario consisted of patients with isolated regional recurrence. In line with the surgical experiences and differences related to the use of previous neck RT, the CTV in adjuvant reirradiation should include only the involved nodal levels, whereas for unresectable neck tumor, the CTV should encompass the GTV with a margin, adapted to a geographic distribution of high-dose areas created during previous RT to the neck.[82]

Radiotherapy regimen and normal tissue tolerance to reirradiation. No objective comparison of various reirradiation regimens has been conducted to date. Experiences collected from irradiation of RT-naive patients with HNSCC suggest hyperfractionated regimens with proven capacity for sparing late-reacting normal tissues in the vicinity of the target to be the most effective.[83] A rather high fraction dose of 1.5 Gy delivered twice daily in "1-week-on/1-week-off" or similar fashion was tested by the RTOG and in some others studies.[21,23,27,28,36,37,43,47] No apparent advantage of these prolonged regimens was seen with regard to treatment efficacy or toxicity compared to similar split-course regimens using 1 daily fraction[16,20,23,35–38,46,48] or continuous course regimens with either hyperfractionation or conventional fractionation of 1.8 to 2 Gy/day.[18,22,29–34,36,39–42,44,45,49–51]

In the majority of reirradiation studies, the reported profile of acute toxicity remains within the limits of those observed during the initial course of RT or it was less intensive, probably because of smaller target volumes used in reirradiated patients. Specifically, hematologic toxicity depends primarily upon the intensity of systemic component of the re-treatment regimen and is usually not affected by prior therapy. Conversely, this is not the case with late radiation-induced morbidity. In a cohort of 103 patients treated between 1998 and 2008, late toxicities of grade $\geq$3 occurred in 47.5%[84] and, in another study using different RT techniques, they were found more frequent in patients treated with 3D-conformal RT than in patients treated with IMRT (44% vs 7%; $p < .05$).[69] Even though there is usually a window, albeit narrow, to burden pre-irradiated late-reacting tissues with an additional dose, including the spinal cord as the most critical among these structures, the need for reducing the extra dose as much as possible is obvious.

Ang et al[85] demonstrated a significant capacity of the spinal cord to recover from occult radiation injury. Modeling clinical data from reirradiation experiments performed on monkeys previously irradiated to 44 Gy in a 2.2-Gy per daily fraction, recovery estimates of 76%, 85%, and 101% of the initial dose, after 1, 2, and 3 years, respectively, at the 5% incidence level for myoparesis, were done. Recently, Kirkpatrick et al[86] summarized the existing knowledge on this issue and concluded that a partial repair of subclinical damage in the cord produced by conventionally fractionated RT of the full cord cross-section becomes evident about 6 months post-RT (ie, reirradiation at 2 Gy/day: increase in cord tolerance of at

least 25%) and increases over the next 2 years. For partial cord RT using SBRT, a maximum cord dose of 13 Gy/1 fx or 20 Gy/3 fx seems associated with a <1% risk of injury. In routine practice, Sulman et al[63] assumed, using this background data, a 50% dose tolerance recovery of central nervous system structures, if the posttreatment interval is ≥12 months. Also, Nieder et al[87] suggested that the spinal cord might tolerate significant reirradiation doses (eg, 25 Gy in 30 fractions after previous exposure of 45 Gy in 35 fractions). Several studies reported on the methods for an accurate assessment of the delivered dose on different spinal cord sections and planning techniques to spare doses to the spinal cord and brainstem, which could be of considerable importance in a reirradiation setting.[88,89]

A pooled analysis of published data on carotid blowout, another dreaded complication of reirradiation, determined a rate of 2.6% at a median of 7.5 months post-reirradiation; 76% of events were fatal.[90] No impact of previous salvage surgery or administration of concurrent chemotherapy was established. A lower rate of carotid blowout was found among patients treated in a continuous course with conventional fractionation or hyperfractionation compared to accelerated hyperfractionation regimens (1.3% vs 4.5%; $p = .002$), although a heterogeneous patient population and treatment parameters preclude definitive conclusions about the impact of fractionation.

The estimated incidences of other late radiation-induced toxicities are less systematic and accurate. Swallowing impairment seems to be the most common toxicity, reported in up to 50% or more of treated patients.[27,48,67,91] However, dysphagia is still less frequent than expected, particularly when the baseline functional status resulting from the first RT course is taken into account.[27,44,48] Because of the same reason, sparing of parotid glands during reirradiation planning is of minor importance. The rates of mandibular osteoradionecrosis reported in larger reirradiation series using predominantly conventional RT techniques were up to 10%,[36,84,91] and did not correlate with any of the RT/reirradiation parameters.[36] Because of more precise planning and targeting, reirradiation with modern RT techniques (IMRT, SBRT) resulted in a significantly reduced rate of mandibular necrosis, ranging from 0% to 7% (median 0%).[57,59–69,92–101] Obviously, options offered with reconstructive surgery as a necrosis-rescuing procedure or preventative swallowing exercise programs cannot outweigh the importance of precise RT planning and dose delivery.[102] Besides the mandibular bone, other tissues, like the laryngeal cartilages and brain, are also sensitive to radiation. Consequently, the localization of the tumor influences the type of radiation-induced toxicity.

Tumor regrowth is thought to result from repopulation of radioresistant clonogens that survive the first course of RT, which are likely to be more difficult to control with a repeated course of RT. From this perspective, high RT doses seem mandatory, although, in a reirradiation scenario, one must consider the tradeoff for the efficacy and morbidity of high-dose RT. A dose-effect relationship was established in several reirradiation studies.[17,23,25,29,30,33–36,38,40,47–49,51,59,60,63,84,91–93] In different studies, the cut-point dose suggesting an improved outcome is usually set at around 60 Gy. By increasing the dose above this level, extreme caution is warranted, as the aim to cure does not always justify excessive morbidity and deterioration in the patient's QOL. Thus, when deciding on the reirradiation dose, one must take into account the volume of the tissue to be reirradiated (GTV with margin, eventually neighboring lymph node stations), the level of precision of the RT technique used, and the latency period from the first RT course. There was a strong relationship established between treatment-related morbidity and reirradiation volume,[36,39,40,57,64,84,93] RT technique (see below) and RT-reirradiation time interval.[27–30,34,37,38,43,64,84,85,91,94]

New irradiation techniques. Capability to deliver nonuniform photon fluency from any given position to the treatment beam allows a more precise isodose shaping (according to the 3D shape of the target), whereas the increased implementation of modern imaging and stereotactic principle in RT practice resulted in improved disease targeting. Both modulation of beam intensity and image guidance were widely adopted in RT practice because of their potential to significantly change the toxicity profile and/or treatment efficacy compared with conventional RT techniques.[102–104]

Reports on the use of IMRT and SBRT are presented in Tables 3 and 4.[57,59–69,92–101] In general, the numbers of patients treated in individual series are low and a wide heterogeneity can be observed with regard to RT details and implementation of salvage surgery and/or systemic therapy across these studies. Compared to conventional techniques, no obvious survival advantage can be observed with IMRT or SBRT. However, improvement in local tumor control can be seen, despite the fact that the treated volumes seem smaller when new RT techniques are used. No conclusions can be drawn with regard to toxicity and treatment-related deaths, presumably because of a less systematic collection of pertinent data in older series.

Lee et al[60] retrospectively evaluated the efficacy and toxicity data of 105 patients who underwent reirradiation with curative intent between 1996 and 2005 with either conventional RT techniques (31 patients) or IMRT (74 patients). The IMRT approach yielded a significantly better locoregional recurrence-free survival over non-IMRT techniques at 2 years (52% vs 20%; $p < .001$) and was also recognized as an independent prognosticator in the multivariate analysis (HR, 0.37). For OS, the advantage of the IMRT technique was only observed by univariate analysis, implying that an improvement in LRC did not transfer to improve the OS. No separate data on toxicity was presented for the 2 treatment groups. For locally recurrent nasopharyngeal carcinoma, 3D-conformal RT (27 patients) and robotic SBRT (24 patients) were compared by Ozyigit et al.[105] No apparent difference in tumor dose, volume, and time interval between the first RT and reirradiation was found between the groups; in 3D-conformal RT patients, larger margins were used (PTV = GTV +5–10 mm vs PTV = GTV), and the cumulative nasopharyngeal dose was lower (128.2 Gy vs 132.6 Gy; $p = .1$). At 2 years, local control rates were similar in the 2 groups (80% vs 82%), with no significant difference in cancer-specific survival (47% vs 64%). However,

TABLE 3. Intensity-modulated radiotherapy reirradiation.

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	IMRT	Other therapy	Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
Chen et al, 2002[59] (1997–1999)	12, retrospective	15.5 (4–55)	TD_{median} 60 Gy, d/fx_{median} 2 Gy Reirradiation volume: N.S.	Surgery, 25%‡ Chemotherapy, 42%	N.S. TRD, 8%	8 patients alive at 3–16 mo post-reirradiation
Lee et al, 2007[60] (1996–2005)	74, retrospective	38 (5–380)	TD_{median} 59.4 Gy, 1.8–2 Gy/fx Reirradiation volume: PTV = GTV/TB + 10–20 mm	Surgery, N.S. Chemotherapy, N.S.	N.S.	LRC, 52%
Biagioli et al, 2007[61] (2001–2006)	41, retrospective	25 (6–240)	1.8–2 Gy/fx/week → 9-d break, to TD_{median} 60 Gy Reirradiation volume: PTV = GTV/TB + 5–20 mm	Surgery, 41.5% Induction chemotherapy, 31.7% Concomitant chemotherapy, 100%	10% TRD, 5%	OS, 48.7%
Goldstein et al, 2008[62] (1998–2003)	41‡, retrospective	N.S.	TD_{mean} 54.5 Gy (palliative) and 61.1 Gy (curative), 1.8–2 Gy/fx Reirradiation volume: GTV/TB +"high-risk areas"	Surgery, 39%	N.S.	All: OS, 19.5% Curative: OS, 28.6% Palliative: OS, 0%
Sulman et al, 2009[63] (1999–2004)	74, retrospective	46 (23–445)	TD_{median} 60 Gy, 1.8.−2 Gy/fx CTV = GTV/TB + 1–2 cm, ± ELN-RT Reirradiation volume: PTV = CTV + 3–5 mm	Surgery, 27% Chemotherapy, 49%	20% TRD, 1.4%	LRC, 64% OS, 58%
Duprez et al, 2009[64] (1997–2008)	84, retrospective	49.5 (5–298)	TD_{median} 69 Gy, 2–2.5 Gy/fx Reirradiation volume: CTV = TB *or* GTV + 5–15 mm ELN-RT, 43% PTV = CTV + 3 mm	Surgery, 23% Chemotherapy, 20%	21% (of 52 patients with FUP ≥ 6 mo) TRD, 2%	LRC, 48% OS, 35%
Popovtzer et al, 2009[57] (1994–2007)	66, retrospective	37 (6–184)	TD_{median} 68 Gy, 2 Gy/fx or 1.25 Gy/fx b.i.d. Reirradiation volume: PTV = GTV/TB + 5 mm	Surgery, 33% Concurrent chemotherapy, 71%	29% TRD, 2%	LRC, 27% OS, 42%
Sher et al, 2010[65] (2004–2008)	35, retrospective	30	TD_{median} 60 Gy, 1.8–2 Gy/fx CTV = GTV + 1–1.5 cm Reirradiation volume: PTV = CTV + 5 mm	Surgery, 49% Induction chemotherapy, 28% Concomitant chemotherapy, 100%	46% TRD, 11%	LRC, 67% OS, 48%
Zwicker et al, 2011[66] (2000–2008)	38, retrospective	43	TD_{median} 49 Gy, 1.8–2 Gy/fx CTV = GTV + 0.5–1 cm Reirradiation volume: PTV = CTV + "safety margin"	Surgery, 34% Concurrent chemotherapy, 50%	20% TRD, 3%	LC, 53% LRC, 45% OS, 34%

TABLE 3. *Continued*

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	IMRT	Other therapy	Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
Chen et al, 2011[67] (2006–2009)	21, retrospective	14 (6–132)	TD_{median} 66 Gy Reirradiation volume: CTV = GTV + 5 mm PTV = CTV + 3 mm	No	N.S. TRD, 0%	LC, 65% LRC, 77% OS, 40%
Zygogianni et al, 2012[68] (2007–2012)	15, retrospective	52 (24–228)	TD_{median} 66 Gy CTV = GTV/TB + 1.5 cm, + ELN-RT Reirradiation volume: PTV = CTV + 3–5 mm	Surgery, 33%	47% TRD, 0%	OS, 95%†
Kharofa et al, 2012[69] (2001–2009)	38‡, retrospective	28 (3–228)	TD_{median} 60 Gy, 2 Gy/fx Reirradiation volume: PTV = GTV/TB + 10–20 mm	Surgery, 34% Concomitant chemotherapy, 100%	16% (IMRT: 7%) TRD, 0%	OS, 40%

Abbreviations: IMRT, intensity-modulated radiotherapy; TD, tumor dose; d/fx_{median}, median dose/fraction; N.S., not specified; TRD, treatment-related death; PTV, planning target volume; GTV, gross tumor volume; TB, tumor bed; LRC, locoregional control; OS, overall survival; CTV, clinical target volume; ELN-RT, elective lymph node-radiotherapy; FUP, follow-up; b.i.d., twice per day; LC, local control.
* Median (range), in months.
† Estimated from Kaplan–Meier plot.
‡ IMRT was used in 78%[61] and 76%[68] of the patients.

serious late complications were more frequent with 3D-conformal RT (48% vs 21%; $p = .04$), but the incidence of fatal complications was comparable (14.8% vs 12.5%), and no correlation was found between the cumulative nasopharyngeal dose and the rate of serious late adverse events.

Combinations with systemic agents. Whether the addition of systemic agents to RT improves the effectiveness of reirradiation is not known. There have been no head-to-head comparisons of reirradiation versus combined modality therapy, and the results of selective studies implementing reirradiation alone compete favorably with those of chemotherapy reirradiation series. For example, in a definitive and postoperative setting, excellent LRC and OS were reported using only a well-defined RT protocol without any chemotherapy.[22,44] The explanation may lay in the refinement of RT procedures that can counterbalance the addition of systemic drugs, although a reduced effectiveness of systemic agents in a reirradiation setting could not be excluded. On the other hand, presented results are based on small and mainly retrospective studies: taking into account the fact that in large randomized studies of upfront RT vs chemotherapy-RT the survival benefit is about 6%, there is simply no chance to detect a potential benefit of concomitant chemotherapy in these retrospective series.[2] One may hypothesize that the benefit of concurrent chemotherapy, and also cetuximab, in a reirradiation setting is likely to be similar to their respective benefits in large randomized studies of upfront therapy.

Considering the report from the MACH-NC, concomitant administration of systemic drugs with reirradiation would be expected to increase treatment intensity and result in an improved outcome compared to reirradiation alone.[2] Few studies reported on an improved outcome with an increase in the intensity of the chemotherapy component of re-treatment regimens.[28,47,48] In this respect, an intriguing finding was reported by Choe et al,[91] who analyzed the treatment results and survival of 166 previously irradiated patients with nonmetastatic HNSCC from 9 consecutive phase I and II protocols on concurrent chemotherapy and reirradiation. Half of the cohort (48.8%) underwent salvage surgery or debulking before reirradiation, with a median dose of 66 Gy. After dividing the patients with respect to previous use of chemotherapy, significantly better OS (at 2 years: 28.4% vs 10.8%; $p = .0043$) and DFS ($p = .0008$) rates were recorded in chemotherapy naive patients. A similar observation was reported by Nagar et al.[42] Patients who had initial RT did significantly better (DFS, $p = .01$; OS, $p = .008$) compared with those who were initially treated by concomitant chemo-RT. One can hypothesize that previous intensive chemotherapy-RT regimens resulted in a more pronounced proliferation of fibrous tissue in the treated area, and when ineffective, it is likely that recurrence consisted of surviving highly RT-resistant tumor clonogens. In poorly vascularized, fibrotic regions, drug delivery is compromised and RT-resistant hypoxic areas are more extensive. Consequently, subsequent treatment may not be as effective as expected.

Several different chemotherapy regimens have been utilized concurrently with reirradiation, most frequently

TABLE 4. Stereotactic body radiotherapy reirradiation.

Author, y, reference no. (recruitment period)	No. of patients, study type	Interval to reirradiation*	SBRT	Other therapy	Late toxicity (grade 3/4, serious)	Outcome (at 2 y)
Siddiqui et al, 2009[94] (2002–2006)	21, retrospective	19 (3–200)	Single-fx, 16 Gy or 18 Gy Fractionated, 36 Gy/6 fx *or* 48 Gy/6 fx Reirradiation volume: PTV = GTV	No	24% TRD, 0%	LC, 40.4% OS, 14.3%
Roh et al, 2009[95] (2004–2006)	36, retrospective	24 (3–253)	TD_{median} 30 Gy/3–5 fx PTV = GTV + 2–3 mm	Adjuvant chemotherapy, 17%	8% TRD, 3%	LC, 52.2% OS, 30.9%
Heron et al, 2009[96] (2005–2007)	25, prospective (phase I)	13 (5–94)	TD 25–44 Gy/5 fx Reirradiation volume: PTV = GTV	No	N.S.	1-y OS, 16%†
Unger et al, 2010[92] (2002–2008)	65‡, retrospective	26 (2–318)	TD_{median} 30 Gy/5 fx Reirradiation volume: PTV = GTV + 2–10 mm ELN-RT in 34%	Surgery, 29% Chemotherapy, 54%	9% TRD, 1.5%	LRC, 30% OS, 41%
Heron et al, 2011[97] (2003–2008)	98, retrospective Group 1, 64% Group 2, 36%	Group 1, 18 (8–312) Group 2, 19 (4–270)	TD_{median} 40 Gy/5 fx Reirradiation volume: N.S.	Group 1: no Group 2: concurrent CMb	Group 1: N.S. Group 2: 6% TRD, 0%	Group 1: LC, 33%†, OS, 13%† Group 2: LC, 49.2%, OS, 53.3%
Cengiz et al, 2011[93] (2007–2009)	46, retrospective	38 (4–306)	TD_{median} 30 Gy/5 fx Reirradiation volume: PTV = GTV	No	13.3% TRD, 15.6%	1-y OS, 47%
Kodani et al, 2011[98] (2005–2008)	21, retrospective	51 (2–360)	TD_{median} 30 Gy/5 fx Reirradiation volume: PTV = GTV	No	19% TRD, 10%	OS, 50%†
Comet et al, 2012[99] (2007–2010)	40, prospective	32 (8–263)	36 Gy/6 fx Reirradiation volume: CTV = GTV + 5 mm PTV = CTV + 1 mm	Concurrent CMb, 37.5% Concurrent CP, 2.5%	7.5% TRD, 0%	OS, 24%
Iwata et al, 2012[100] (2005–2010)	51, retrospective	18 (3–132)	Single fx, 20 Gy Fractionated, 30 Gy/3 fx *or* 35 Gy/5 fx reirradiation volume: PTV = GTV + 0–5 mm	Adjuvant chemotherapy, 33%	23% TRD, 0%	LC, 40%† OS, 40%†
Shikama et al, 2013[101] (2007–2011)	28§, retrospective	9 (3–40)	TD_{median} 30 Gy/1–7 fx Reirradiation volume: N.S., no ELN-RT	Concurrent chemotherapy, 11%	4% TRD, 10.7%	OS, 21.7%

Abbreviations: SBRT, stereotactic body radiotherapy; fx, fraction; PTV, planning target volume; GTV, gross tumor volume; TRD, treatment-related death; LC, local control; OS, overall survival; TD, tumor dose; N.S., not specified; ELN-RT, elective lymph node radiotherapy; LRC, locoregional control; CMb, cetuximab; CTV, clinical target volume; CP, cisplatin.

* Median (range), in months.

† Estimated from Kaplan–Meier plot.

‡ Thirty-eight patients were treated with definitive intent, and 27 patients were treated with palliative intent.

§ Six (14%) patients were treated with conventional external beam radiotherapy.

platinum-based and those consisting of 5FU-hydroxyurea platform invented and extensively tested at the University of Chicago.[23,91] However, no comparison of their efficacy is possible, mainly because of the retrospective nature of the reports and heterogeneity of different study parameters. Furthermore, the toxicity reporting seems inconsistent in many of these studies, not allowing any reliable assessment of the tolerance and safety of the tested regimens. Several combinations of reirradiation and other/new drugs were tested in phase I settings: bendamustine, an alkylating agent,[106] the hypoxia-targeting agent tirapazamine,[45] the proteasome inhibitor bortezomib,[107] the epidermal growth factor receptor inhibitor erlotinib, alone or in combination with cyclooxygenase-2 inhibitor celecoxib,[108,109] antivascular endothelial growth factor agent bevacizumab,[46] and the paclitaxel-cisplatin combination.[110] No apparent advantage in the efficacy or toxicity profile was observed in these studies compared to more frequently used chemotherapy and reirradiation combinations.

More information is available on reirradiation with cetuximab, which proved effective in combination with RT, with acceptable toxicity in therapy-naive patients.[111] Moreover, the toxicity profile differed significantly from that associated with the platinum-based and other chemotherapy regimens usually used in patients with HNSCC. In addition to small retrospective and pilot-study reports,[25,49,50,66,99] there are 2 larger series on the use of cetuximab and reirradiation.[97,112] Heron et al[97] used standard-dose cetuximab concurrently with SBRT (5×8 Gy delivered every other day) in 35 patients with recurrent HNSCC, who were matched with 35 patients re-treated with SBRT alone. Patients were matched by age, sex, performance status, year of treatment, and prior therapy, including radiation dose, interval to recurrence, as well as recurrent disease characteristics (site, size, and presence of systemic metastases). At 2 years, the local control rates were 33.6% for the SBRT-alone group and 49.2% for the cetuximab-SBRT group (HR for local progression, 0.37; $p = .009$), respectively, with 2-year OS rates of 21.1% and 53.3% (HR for death, 0.59; $p = .031$). A survival advantage was also observed in patients who received cetuximab during the first course of RT and were re-treated with cetuximab-SBRT combination. On multivariate analysis, performance status, nasopharynx primary, SBRT dose, and cetuximab predicted for improved survival. There were no grade ≥ 4 acute toxicities, no difference in the acute or late toxicity profile between the 2 groups, and the incidence of grade 3 late adverse effects were 3% and 6%, respectively.

In another report, Vargo et al[112] compared the patient-reported QOL after SBRT with (51 patients) or without (57 patients) concurrent cetuximab, using the University of Washington Quality-of-Life Revised Questionnaire. SBRT consisted of 40 to 50 Gy in 5 fractions, and cetuximab was administered in standard doses; 24% of patients had salivary gland/paranasal recurrences, mostly of nonsquamous histology. Overall and health-related patient-reported QOL and select domains commonly affected by reirradiation (ie, swallowing, speech, and saliva) progressively showed significant improvements to baseline. The addition of cetuximab to SBRT had no influence on the observed improvements in QOL. However, the baseline overall QOL was a significant predictor of OS, with patients denoting the overall QOL as "poor" or "very poor" (corresponding to an assigned value of ≤ 20) showing statistically inferior OS at 1 year (23%) compared to patients reporting "fair" (value >20) baseline QOL (1 year, 48%; $p = .014$).

Outside of a clinical trial, cetuximab should be administered as a single agent during reirradiation. Given the individual radiosensitizing effects of cetuximab and cytotoxic chemotherapies, as well as the potency of cetuximab administered with platinum-based chemotherapy in incurable settings, combining the 2 approaches (cetuximab plus cisplatin) with RT initially seemed intuitive and promising. However, the RTOG 0522 phase III trial in previously untreated patients failed to demonstrate improved outcomes of the cisplatin/cetuximab combination over cisplatin alone, suggesting no further enhancement effect above that reached with cisplatin, but yet leading to more toxicity.[113]

When to irradiate

Appropriate patient selection is crucial when deciding on reirradiation to avoid unnecessary morbidity in those with a short life expectancy. Several risk factors for OS and adverse events were identified in different studies, which were recently extensively elaborated by Yamazaki et al.[114] However, low patient numbers, selection bias, inconsistency in reporting on treatment details and toxicity, and inadequate follow-up make the findings from these studies questionable.

In 2011, Choe et al[91] reviewed their experience with 166 patients with recurrent and second primary HNSCC, representing the largest reirradiation cohort analyzed so far, with a median follow-up of 53 months. For OS, salvage surgery (before reirradiation, HR = 0.52; $p = .0006$), previous chemo-RT (HR, 1.83; $p = .0043$), RT dose ≥ 60 Gy (HR, 0.35; $p < .0001$), and the time interval from previous RT of ≥ 36 months (HR, 0.64; $p = .0259$) were significant independent prognostic variables. After stratifying the patients according to the number of prognostic factors present, the OS differed significantly among the risk groups ($p < .0001$) with the rate of 30% at 5 years (estimated from the Kaplan–Meier plot) in the most favorable risk group (0–1 adverse prognostic factors). All those with 3 to 4 unfavorable risk factors had died before that time. Patient-related factors had no influence on the survival in this cohort, most probably because 80% of the patients were Eastern Cooperative Oncology Group performance status 0 to 1.

A detailed analysis of the potential prognostic factors for survival, including comorbidity and preexisting organ dysfunction, was conducted by Tanvetyanon et al[84] on a group of 103 patients with HNSCC treated with reirradiation during 1998 to 2008. Comorbidity was assessed by Charlson index and Adult Comorbidity Evaluation-27 (ACE-27) grading, whereas organ dysfunction was defined as feeding tube dependency, functioning tracheostomy, or soft-tissue defect. On multivariate analysis, in addition to disease-related variables (interval since last RT, rT-classification, tumor bulk after salvage surgery) and treatment-related variables (reirradiation dose), organ dysfunction and comorbidity (measured either by Charlson index or ACE-27 comorbidity grading) also

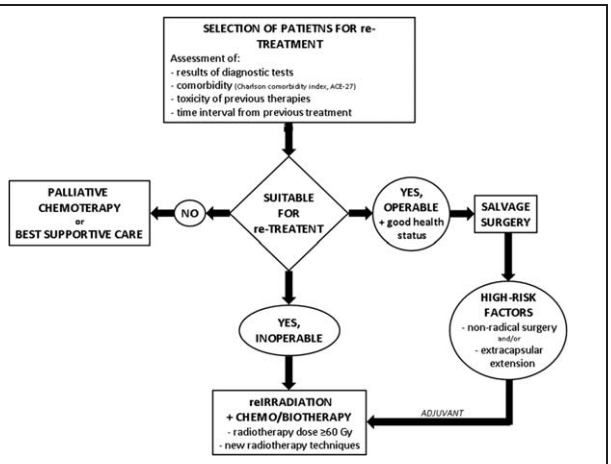

FIGURE 1. Reirradiation: management algorithm.

exhibited the ability to independently predict survival. If both comorbidity and organ dysfunction were present, no long-term survivors were observed (median survival 5.5 months vs 59.6 months in patients with neither of the 2 predictors). Using significant prognostic factors, a nomogram was created to predict the probability of death within 24 months after reirradiation, taking into account their contribution to the accuracy of prediction. A good agreement between the predicted and the observed outcomes was found with this nomogram (concordance index 0.75), showing a negligible chance of survival at 2 years after reirradiation for most patients with organ dysfunction and comorbidity and those who did not have an isolated nodal recurrence. The nomogram has already been successfully tested by entering data of 28 patients reported by Shikama et al.[101]

CONCLUSIONS

The following principles and recommendations based on prospective and retrospective data analyses should be considered when planning a treatment strategy for patients with locoregional recurrence or new primary cancer in a previously irradiated area (Figure 1). First, proper selection of patients for reirradiation is crucial. Only those with no or insignificant comorbidity and toxicity of previous RT should be considered candidates for re-treatment. If possible, the functional status of the patient should be assessed by using standardized measures (ie, the Charlson comorbidity index or ACE-27 grading). Other predictors that should be taken into account are presence of isolated neck recurrence, tumor bulk, and the time interval from previous RT, preferably in the context of the published nomogram.[84] Second, salvage surgery offers the best chance for cure and should be performed whenever possible. Patients at high risk for local recurrence after surgery (eg, positive margins, extracapsular tumor spread) should be advised that adjuvant reirradiation is expected to increase LRC at the expense of higher toxicity and without survival advantage as compared to no postoperative reirradiation.[15] Thrid, new RT techniques are recommended for patients undergoing reirradiation. Although there was no significant effect of IMRT or SBRT on the OS, improved dose distribution with high isodose conformity and a steep dose gradient at the target's margin limits injury to the neighboring tissues and may improve RT outcomes in terms of local control and toxicity. Fourth, significant repair of subclinical damage produced by previous RT can occur in the spinal cord. For reirradiation of the full cord cross-section at 2 Gy per day, at least 25% increase in cord tolerance 6 months after prior conventionally fractionated RT can be considered[86] or 50% dose tolerance recovery if the posttreatment interval is $\geq$12 months.[63] Fifth, a radiation dose in the range of $\geq$60 Gy is recommended, delivered by using conventional fractionation (1.8–2 Gy/fx), hyperfractionation, or hypofractionation (in case of SBRT). With adequate imaging support, preferably implementing PET-CT for target volume determination, GTV with a margin of up to 5 mm to create CTV should be irradiated, with no intention to electively treat the adjacent regions in a majority of patients. Sixth, the benefit of concurrent chemotherapy (or cetuximab) and reirradiation is expected to be similar to their respective benefits observed in large randomized studies of upfront therapy. Seventh, for patients with poor prognostic factors who are not candidates for surgery or aggressive reirradiation with or without concomitant systemic therapy, palliative systemic therapy and best supportive care remain appropriate options. Eighth, when available, all patients should be considered for participation in clinical trials. At the moment, the key knowledge gaps that should be addressed in future multi-institutional reirradiation clinical trials or comparative effectiveness research seem to be the refinement of selection criteria for aggressive reirradiation and comparison of different RT techniques (IMRT vs SBRT) and concomitant systemic therapies.

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