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RADIOTHERAPY

Reirradiation of head and neck squamous cell carcinomas: a pragmatic approach—part I: prognostic factors and indications to treatment

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Abstract

Introduction Reirradiation (reRT) of locally recurrent/second primary tumors of the head and neck region is a potentially curative treatment for patients not candidate to salvage surgery. Aim of the present study is to summarize available literature on both prognostic factors and indications to curative reRT in this clinical setting.

Materials and methods A narrative review of the literature was performed on two topics: (1) patients' selection according to prognostic factors and (2) dosimetric feasibility of reRT. Postoperative reRT and palliative intent treatments were out of the scope of this work.

Results Patient-tumor and treatment-related prognostic factors were analyzed, together with dosimetric parameters concerning target volume and organs at risk. Based on available evidence, a stepwise approach has been proposed aiming to provide a useful tool to identify suitable candidates for curative reRT in clinical practice. This was then applied to two clinical cases, proposed at the end of this work.

Conclusion A second course of RT in head and neck recurrence/second primary tumors is a personalized approach that can be offered to selected patients only in centers with expertise and dedicated equipment following a multidisciplinary team discussion.

Keywords Reirradiation · Head and neck cancer · Squamous cell carcinoma · Prognostic factors · Treatment

Introduction

Squamous cell cancer of the head and neck (SCCHN) is the 6th most common malignancy and the 8th leading cause of cancer mortality worldwide [1]. While technological improvements in surgical and radiotherapy (RT) techniques have largely increased the therapeutic ratio of these therapeutic modalities [2], up to 50% of patients develop recurrent disease, with a predominance of locoregional failure [3]. In about 90% of cases, the recurrence occurs within the first three years after the end of the primary treatment. Additionally, long-term survivors with a smoking history have a

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higher risk of second primary tumors in the head and neck region, which can be as high as 20–25% in 10 years [4]. The treatment of recurrent/second primary (LRR)/SP SCCHN is challenging due to the overall dismal prognosis. Given the heterogeneity of R/M SCCHN, the main goal of any approach is balancing the chance of disease control and the burden of treatment-related toxicities on the patient's quality of life. The treatment may encompass salvage surgery (usually requiring post-operative re-irradiation), curative re-irradiation (reRT), palliative-intent systemic therapies, and best supportive care [5–8]. Surgery is considered the treatment of choice [9]. However, several factors as disease extent or morbidity associated with such an approach, make the surgical option available only in about 20% of the cases. If surgery is nor indicated or feasible, the only potentially curative therapeutic alternative reRT alone or combined with systemic therapy. In addition, a significant proportion of patients treated with salvage surgery necessitate post-operative radiation treatment due to histological high-risk features [10]. Clinical stage as well as other radiological signs (e.g., extracapsular extension) indicate the need for postoperative reRT since the baseline assessment. Therefore, management of such complex cases should always be managed by a multidisciplinary team. Historically, reRT of recurrent and second primary SCCHN within a previously irradiated field was discouraged due to concerns over excessive normal tissues damage [11]. Nevertheless, modern RT techniques such as Intensity Modulated Radiation Therapy (IMRT), Stereotactic Body Radiation Therapy (SBRT) and particle beam therapy (i.e., proton and heavy ion therapy) can offer at least comparable local control rates with fewer side effects than conventional 2D or 3D techniques [12–14]. Finally, favorable long-term survival outcomes are reported in some cases of R/M SCCHN treated with different modalities [15]. In summary, the therapeutic landscape in the locally recurrent SCCHN setting has evolved, thanks to the use of modern radiation treatment planning and delivery and the availability of proton- and heavy ion-based RT. Thus, our aim is to summarize available literature on the current status of RT in locally recurrent SCCHN, and to provide a pragmatic and useful tool for clinical practice.

Methods

A multidisciplinary group composed of Radiation Oncologists, Medical Oncologists and Radiologists dedicated to head and neck cancers proposed a workflow process to indicate reRT for locally recurrent cancer patients. Details on technical aspects of the reRT approach have been reported in a separate work focused on the same setting (Reirradiation of head and neck squamous cell carcinomas: a pragmatic approach. Part II: Radiation technique and fractionations). In the present work, technical aspects of the reRT approach have been presented with a focus on two topics: (1) patients' selection (prognostic and predictive factors) and (2) dosimetric feasibility. Postoperative reRT and palliative-intent irradiation were considered out of the scope of this work and were therefore not reviewed. A proposal of a pragmatic tool for daily clinical practice data through a stepwise approach which resumes literature data were then shared and discussed among all members. An initial search in the literature for full papers articles written in English, dating from 1995 to 2022 was performed. A combination of the terms "reirraidiation/re-irradiation," "head and neck radiotherapy," "prognostic factor," "patient selection," "dosimetric study," "treatment/indication to treatment" was queried. Finally, two clinical use-cases were provided for the application of the proposed approach.

Results

For unresectable recurrent/second primary head and neck tumors, full-dose reRT is the only potentially curative treatment. However, feasibility should be carefully assessed, based on clinical (e.g., patient- and tumor-related factors) and dosimetric factors (e.g., time interval from the primary RT course). Therefore, the analysis of the cost–benefit ratio includes several prognostic and predictive variables, including all previous oncologic treatments [16–20]. Schematically, such considerations can be articulated into three main steps, which are described below.

Accurate tumor staging

Radiological images have to accurately assess local tumor extent (to minimize the target volume that is most likely confined to gross-tumor volume [GTV] only). Staging through different imaging modalities (i.e., computed tomography -CT-, magnetic resonance -MR,—and fluorodeoxyglucose positron emission tomography-FDG-PET) is required to define tumor extension as well as the presence of nodal and/or distant metastases that cannot be detected by the sole physical examination [21–23]. Altogether, clinical staging is needed to define the proximity of the tumor to the surrounding healthy tissues (i.e., nervous structures, carotid arteries, skull base bones). Additionally, functional information conveyed by FDG-PET could also be correlated with prognosis, as for metabolic tumor volume (MTV), which has been identified as an independent prognostic factor by Velez et al. [24].

Additionally, biopsy of the suspected tumor recurrence is strongly recommended whenever feasible since surgical scars and/or radiation-related inflammation and fibrotic

processes could complicate the interpretation of both clinical findings and radiologic imaging.

Patient selection

Patient selection is the first fundamental step in the decision-making process to define the most appropriate treatment modality. However, factors that support the feasibility of a second RT course are not clearly defined yet. Consequently, decision often relies on the clinical judgment of the Radiation Oncologist within the multidisciplinary tumor board.

Several parameters have been associated with clinical outcome for recurrent and/or metastatic patients [25].

Of these, the most relevant is patient's prognosis. Indeed, prognosis not only determines indication to reRT, but also influences the choice of the irradiation technique and of the fractionation schedule. Patients with a long-life expectancy can be treated, when feasible, with a full-dose reRT course while patients with a short-life expectancy should rather be evaluated for a palliative reRT.

Additional prognostic and predictive factors have been identified and are summarized in Table 1. Feasibility of surgery was also considered in the analysis as a prognostic factor.

Overall, patients with good performance status, younger age and no or few comorbidities seem to be the best candidates for curative-intent reRT. Considering tumor characteristics, early stage tumor with no bulky disease/no organ dysfunction and location in the nasopharynx have been associated with better outcomes both in terms of overall survival (OS) and loco-regional control (LRC). Finally, among treatment-related factors, higher reRT doses (> 40 Gy) and longer interval between the two radiation courses (> 12 months), seem to be the most important factors associated with patients' outcomes. Finally, the presence of relevant radiation-related side effects such as osteo/chondroradionecrosis, carotid artery stenosis, soft-tissue injuries (e.g., severe fibrosis, fistulae), and myelopathies should be considered at least as relative contraindications for a second radiation course (Table 2).

Overall, the interpretation and clinical application of these data should be taken with caution due to their high heterogeneity, which also limits the possibility of a quantitative synthesis. Indeed, patients submitted to reRT still remain in a setting for which an extremely individualized approach has been offered cite (Table 3).

To date, some nomograms have been proposed and are briefly presented below. For instance, Tanvetyanon et al. [37] have presented a nomogram integrating several known prognostic factors (namely, comorbidity, organ dysfunction, isolated neck recurrence, tumor bulk and the time interval between the radiation courses) to predict death probability within 24 months after reRT. A recursive partitioning analysis that considered time interval between the two radiation courses, surgical resection and organ dysfunction allowed to identify three prognostic classes (62%, 40% and 17%, for class I, II and III, respectively) [27]. Similarly, Choe et al. found that previous chemoradiation, surgery before reRT, reRT dose > 60 Gy and reRT interval > 36 months may stratify patients into three risk groups according to their overall survival [51]. Riaz et al. proposed a nomogram to predict the 2 year locoregional control including tumor stage (I–III vs. IVA–B), tumor site (nasopharynx vs. oral cavity vs. other subsites), presence of organ dysfunction, presence of surgery prior reRT, RT dose > 50 Gy [34]. A summary of the abovementioned nomograms is provided in Suppl. S1.

A recent meta-analysis showed that IMRT improved both safety and survival as compared to pre-IMRT data [59]. Moreover, the operation rate (proportion of patients who underwent salvage surgery) was the best predictor of 2-year local control rate in patients treated with IMRT.

Other than oncologic outcomes, toxicity predictors have also been investigated. Takiar et al. reported an association between higher toxicity (grade ≥ 3), the volume of the recurrent tumor (> 50 cm^3) and the administration of concurrent chemotherapy [32]. Additionally, Lee et al. found that a shorter interval between the two radiation courses and larger tumor volume (> 100 cm^3) were independent predictors of severe dysphagia (mainly in terms of feeding tube-dependency). As a general rule, higher dose to different organs at risk have been correlated with higher risk of severe acute and late reRT-related side effects.

In conclusion, several prognostic and predictive factors have been associated to outcomes and toxicity in patients treated with a second RT course. These parameters should be considered to define the cost/benefit ratio for curative-intent reRT.

Dosimetric feasibility

A recently published review has summarized dose constraints for several organs, including nervous structures (i.e., spinal cord, brainstem, optic pathways, brachial plexus, brain), the mandible and carotid arteries [60]. For patients considered at high risk of severe late side effects, the balance between the expected toxicity profile and clinical outcome should be carefully evaluated. Of note, the risk of severe toxicity could be minimized through preventive strategies such as endovascular procedures (carotid artery occlusion and/or stenting) in patients with high risk of carotid blowout syndrome [61].

Therefore, dosimetric analysis is the last step in determining the feasibility of reRT (in terms of total dose and technique) and cost/benefit ratio (expected side effects/efficacy). The total dose of reRT mostly depends on the proximity of the recurrent tumors to organs at risk.

Table 1 Prognostic factors associated with outcomes in patients treated with re-irradiation for local/regional recurrent SCCHN

	Authors	Factors associated with better outcome	Outcome
Patient-related factors			
Performance status	May et al. [26], Ward et al. [27], Heron et al. [28]*	Higher KPS (as continuous variable or < vs > 80)	OS
	Seidl et al. [29]	ECOG 0–1	OS and LRC
	Lee et al. [30]	ECOG 0–1	OS
	Ohnleiter et al. [31]	ECOG 0–1	OS, LRFS, PFS
	Takiar et al. [32],	ECOG 0–1	OS, PFS
	Choi et al. [33]	ECOG 0–1	PFS
	Ward et al. [27], Riaz et al. [34]	KPS > 70	OS
Age	Lee et al. [35], Sulman et al. [14]	Younger Age (continuous variable)	OS
	Langlois D et al. [36]	Younger Age (continuous variable)	LRC
Gender	Sulman et al. [14]	Male	OS, LRC
Comorbidities	Tanvetyanon et al. [37]	CCI (no vs at last one comorb.) and ACE-27 (no/mild vs moderate/severe comorb.)	OS, PFS
Organ dysfunction	Lee et al. [38]	Absence of organ dysfunction	OS and LRFS
	Ward et al. [27], Orlandi et al. [39]	Absence of organ dysfunction	OS
	Riaz et al. [34]	Absence of organ dysfunction	OS, LRC
	Tanvetyanon et al. [37]	Absence of feeding tube	OS
Tumor-related factors			
Tumor site	Ward et al. [27], Heron et al. [28]*, Unger et al. [40], Mendenhall et al. [41]	Nasopharyngeal/base of skull tumor	OS
	Lee et al. [12]	Nasopharyngeal tumor	LRF
	Yamazaki et al. [42]*	Nasopharyngeal tumor	OS, LRC
	Takiar et al. [32]	Nasopharyngeal tumor	PFS
	Orlandi et al. [39]	Nasopharyngeal tumor	OS
	Platteaux et al. [43]	Nasopharyngeal and laryngeal tumor	LRC, DSS, DFS
	Riaz et al. [34]	Nasopharyngeal tumor	OS, LRC
	Duprez et al. [13]	Non hypopharyngeal	OS
Histology	Lee et al. [12], Unger et al. [40], Diao et al. [44]*	Non-squamous carcinoma	OS
rT-Stage	Duprez et al. [13]	T1–T3	OS, DSS
	Tanvetyanon et al. [37], Margalit et al. [45], Mendenhall et al. [41]	Early stage	OS
	Platteaux et al. [43]	T1–T3	LRC
	Riaz et al. [34]	T1–T3	LRC
N stage	Seidl et al. [29]	N0–1	OS and LRC
	Kawaguki et al. [46]	N0	OS
	Riaz et al. [34]	N0–1	LRC
Tumor volume at recurrence	Tanvetyanon et al. [37]	Tumor bulk	OS
	Kodani et al. [47]*	GTV < 15 cm^3	OS
	Diao et al. [44]*	GTV > 20 cm^3	OS
	Rwigema et al. [48]*	GTV < 25 cm^3	LC
	Vargo et al. [49]*	GTV < 25 cm^3	OS and LRC
	Orlandi et al. [39]	GTV < 36 cm^3	
	Huang et al. [50]*	GTV < 50 cm^3	OS, DSF
	Chen et al. [16]	PTV > 26.9 cm^3	LRC
	Yamazaki et al. [42]*	PTV < 40 cm^3	OS
	De Crevoisier et al. [11]	< 125 cm^3 and < 650 cm^3	OS
Ulceration	Yamazaki et al.[42]*	Absence	LRC
Setting	May et al. [26], Mendenhall et al. [41]	Second primary vs local recurrence	OS

Table 1 (continued)

	Authors	Factors associated with better outcome	Outcome
Treatment-related factors			
Primary treatment	Choe et al. [51]	No previous chemoradiation	OS
	Duprez et al. [52]	No previous chemoradiation	DSS
	Takiar et al. [32]	No previous chemoradiation	LRC
RT technique of previous RT	Ohnleiter et al. [31]	3D vs IMRT	OS
ReRT doses	Unger et al. [40]*	> 30 Gy	PFS, LRC
	Rwigema et al. [48]*	≥35 Gy	LC
	Sulman et al. [14]	Cumulative dose > 119.4 Gy	LRC
	Heron et al. [28]*	> 40 Gy	OS
	Lee et al. [12]	> 50 Gy	OS
	Riaz et al. [34]	> 50 Gy	OS, LRC
	Haraf et al. [53] Salama et al. [52]	> 58 Gy	OS, LRC
	Choe et al. [51]	> 60 Gy	OS
	Lee et al. [30]	> 60 Gy	OS, PFS
	Platteaux et al. [43]	> 60 Gy	2y DSS
	Caudell et al. [54], Choi [33]	> 66 Gy	OS
	De Crevoisier et al. [11]	> 60 Gy	OS
	Takiar et al. [32]	> 70 Gy	LRC
reRT technique	Lee et al. [12], Lee et al. [30]	IMRT instead of 3D	OS, 2y LRFS
Feasibility of salvage surgery	Lee et al. [12]	Surgery before reRT	OS, LRPFS
	Salama et al. [55]	Surgery before reRT	OS, PFS, LRC
	Ward et al. [27], Choe et al. [51], Duprez et al. [52], Kharofa et al. [56]	Surgery before reRT	OS
	Ohnleiter et al. [31]	Surgery before reRT	LRFS, PFS
	Platteaux et al. [43]	Surgery before reRT	DFS
	Lee et al. [30]	Surgery before reRT	OS, PFS
Surgical Margins	May et al. [26]	Positive surgical margins	OS
Interval between primary RT and reRT	Tanvetyanon et al. [37], Ohnleiter et al. [31],	Longer interval	OS
	Spencer et al. [57]	> 12 months	OS
	Huang et al. [50]*	> 12 months	OS, DSF
	Lee et al. [38]	> 20 months	LRFS
	Duprez et al. [13]	> 24 months	OS, DFS
	Kodani et al. [47]*, Kress et al. [58]*, Lee et al. [30], Ward et al [27]	> 24 months	OS
	Vargo et al. [49]*	> 24 months	LRC
	Choe et al. [51]	> 36 months	OS
ReRT duration	Vargo et al. [49]*	< 14 days	RFS
Response to IC	Takiar et al. [32]	Complete response	PFS, OS
Concurrent systemic treatment at reRT	Salama et al. [55]	Chemotherapy	DM
	Heron et al. [28]*	Cetuximab	OS, LRC
	Takiar et al. [32]	Chemotherapy	LRC
	Diao et al. [44]*	Not specified	LRC

ACE-27, Adult Comorbidity Evaluation-27; CCI, Charlson Comorbidity Index; AJCC, American Joint Committee on Cancer; Comorb., comorbidity; 3D, 3 dimensional; DFS, disease free survival; DM, distant metastases; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume; IC, Induction chemotherapy; OS, Overall Survival; KPS, Karnofsky performance status; IMRT, Intensity Modulated Radiotherapy; LRC, locoregional control; LRF, local relapse free survival; LRFS, local relapse free survival; PFS, progression free survival; PS, performance status; PTV, planning target volume; reRT, reirradiation; RT, radiotherapy

*The study refers to stereotactic body radiotherapy ** Nasopharyngeal tumors

Table 2 Literature data on risk factors correlated to toxicity in patients treated with a second course of RT in head and neck region

Toxicity	Authors	Risk factors	Dose constraints
Carotid blow out	Iseli et al. [62]	NR	Total dose > 58 Gy
	Kharofa et al. [56]	3D technique vs IMRT	NR
	Chen et al. [63]	Post-styloid space invasion (nasopharynx)	NR
	Yazici et al. [64]**	Every day SBRT > 180° carotid entrapment	Median dose > 34 Gy Cumulative dose > 100 Gy
	Buglione et al. [65], Garg et al. [66]	NR	> 120 Gy
	Guan et al. [67]	reRT alone vs concurrent chemo reRT	NR
	Margalit et al. [45]	Curative > postoperative	NR
	Popovtzer et al. [68]	Unresectable lymph node metastases	Cumulative dose > 140 Gy
	Xiao et al. [69]	Tumor volume > 22 cm^3	NR
	Guan et al. [67]	Nasopharynx	NR
	Ling et al. [70]^	NR	Dose < 47.6 Gy
Pharyngeal stenosis	Ohizumi et al. [71]	reRT neck (vs head) locoregional reRT (vs regional)	NR
Severe dysphagia	Spencer et al. [57]	NR	Median cumulative dose > 120 Gy
	Iseli et al. [62]	NR	Total dose > 58 Gy
	Chen et al. [63]*	Post-styloid space invasion	NR
	Lee et al. [38]	Short interval (< 20 months) and larger PTV (> 100 cm^3)	NR
	Phan et al. [72]	CTV volume > 50 cm^3	NR
	Takiar et al. [32]	CTV > 50 cm^3 and concurrent CTreRT	NR
	Margalit et al. [45]	Curative > postoperative	NR
Osteonecrosis	Kharofa et al. [56]	3D technique vs IMRT	NR
	Lee et al. [38]	Short interval (< 20 months) and larger PTV (> 100 cm^3)	NR
	Takiar et al. [32]	CTV > 50 cm^3 and concurrent CTreRT	NR
	Bots et al. [73]	Second primary and concurrent CTreRT	Median cumulative dose 114 Gy (range 90–130)
Mandibular necrosis	Bots et al. [73]	Second primary and concurrent CTreRT	Total dose > 104 Gy
Fistula	Kharofa et al. [56]	3D technique vs IMRT	NR
	Takiar et al. [32]	CTV > 50 cm^3 and concurrent CTreRT	NR
Cranial nerve palsy	Chen et al. [74]*	Post-styloid space invasion	NR
Brachial Plexus palsy	Chen et al. [16]	Low risk: time interval > 2 years and cumulative Dmax < 95 Gy	
		Inter. risk: time interval < 2 years and cumulative Dmax < 95 Gy time interval > 2 years and cumulative Dmax > 95 Gy	
		High risk: time interval < 2 years and cumulative Dmax > 95 Gy	
Nasopharyngeal necrosis	Chen et al. [74]*	Post-styloid space invasion	NR
Temporal Lobe necrosis	Chen et al. [74]*	Post-styloid space invasion	NR
	Chan et al. [75]	NR	Cumulative BED > 150 $Gy_{2.5}$
Mucosal necrosis	Tian et al. [76]	Tumor volume > 26 cm^3	NR
Soft-tissue necrosis	Buglione et al. [65]	NR	Total dose > 140 Gy
	Lee et al. [38]	Short interval (< 20 months) and larger PTV (> 100 cm^3)	NR
	Margalit et al. [45]	Curative > postoperative	NR
Trismus	Xu et al. [77]	Fractionated SBRT every other day	NR
	Lee et al. [38]	Short interval (< 20 months) and larger PTV (> 100 cm^3)	NR
	Guan et al. [67]	reRT alone vs concurrent chemo reRT	NR
	Takiar et al. [32]	CTV > 50 cm^3 and concurrent CTreRT	NR
Cord paralysis	Margalit et al. [45]	Curative > postoperative	NR
Spinal Cord Myelitis	Nieder et al. [78]	Cumulative BED ≤ 135.5 EQD2 (α/β 2 Gy spinal cord of the cervix and thorax, α/β 4 Gy spinal cord of the lumbar vertebrae and cauda) and interval > 6 months and BED of each RT ≤ 98 EQD2 (α/β 2 Gy spinal cord of the cervix and thorax, α/β 4 Gy spinal cord of the lumbar vertebrae and cauda)	
Brain stem injury	Chan et al. [75]	D1% ≤ 78 Gy	
Optic chiasm injury	Chan et al. [75]	78 Gy	

BED, biological equivalent dose; CT, chemotherapy; CTV, clinical target volume; IMRT, intensity modulated RT; PTV, planning target volume; RT, radiotherapy

*nasopharyngeal tumors

** SBRT administered with 30 Gy in 5–6 fractions

Table 3 Patients, tumor and treatment prognostic factors

Interval between two RT course	146 months
General Prognostic Features	Favorable: young age, good KPS, no toxicity from previous RT, no relevant comorbidities, no previous Chemotherapy concurrent to RT Unfavorable: Recurrent tumor, oropharyngeal location, advanced stage, mucosal ulceration
Prognostic score 2y OS	40% (Ward et al.), 70–80% (Tanetyanon et al.) < 10% (Choe et al.)
Prognostic score 2y LRC	~ 40% (Riaz et al.)
Prognostic score of late toxicity at 2 y	15–20% (Ward et al.)
PRANCIS score (only nasopharynx)	NA

RT, radiotherapy, KPS, Karnofsky performance status, CT/RT, chemoradiation, HPV, human papilloma virus, OS, overall survival, LRC, local recurrent control, y, year

Recently, international recommendations on dosimetric parameters for reRT for both SCCHN and nasopharyngeal cancers have been published [79, 80]. For patients with nasopharyngeal tumors, the PRANCIS (Predicting Radioresistant Nasopharyngeal Carcinoma Survival) prognostic score has also been reported (http://www.prancis.medlever.com/).

For an accurate dosimetric analysis, availability of Digital Imaging and COmmunications in Medicine (DICOM) files of the first radiation course is paramount. Uncertainties deriving from patient's positioning, altered anatomy and differences in dose calculation algorithms should be carefully considered when interpreting the obtained summed dosimetric profiles, and extra-caution in approving the final reRT plan must be taken accordingly.

The most frequent grade ≥ 3 late toxic effects included radionecrosis, feeding tube dependency and trismus. Mucosal necrosis and carotid blowout are both life-threatening adverse events. Notably, no largely recognized dosimetric constraints for the re-irradiated carotid arteries and mucosal tissues are available. Moreover, it is relevant to note that the dose limit of 120 Gy to the carotid artery suggested by some studies [66, 81] is below the therapeutic cumulative dose that should be given to the tumor for an effective reRT, considering a dose of 70 Gy EQD210 for the first course and a dose of 60–66 Gy for definitive reRT [54]. In this context, to ensure both tumor dose coverage and OARs preservation [72], other strategies such as pre–reRT stenting or embolization of the threatened artery could be evaluated. It is interesting to observe that, in the recent retrospective study by Bagley et al. [82] reviewing the outcomes of patients re-irradiated for oropharyngeal cancer, carotid stenting was performed in only 2/69 cases, and carotid endarterectomy was performed in 5/69 patients (7%). Three oropharyngeal hemorrhages from the lingual artery requiring embolization occurred as late grade ≥ 3 events. To reduce the likelihood of potentially fatal events resulting from major vessels damage, the authors suggest the use of specific avoidance structures during treatment planning. Specifically, the suggested constraints for the lingual vessel avoidance structure are a maximum dose less than 30 Gy to 0.3 cm^3 if the artery is outside the target volume (< 5 mm from the target), or to avoid hot spots if the artery is within the target volume.

The risk of soft-tissue necrosis should also be considered as a potential life-threatening adverse event after reRT; likewise, even in this scenario there are no clear dosimetric constraints to apply to the re-irradiated mucosa. Therefore, a careful evaluation of mucosal status pre reRT along with a strict follow-up imaging and SCCHN consultations with endoscopy for diagnosis and early treatment of soft-tissue is mandatory [83].

When using particle therapy, in consideration of the increased biological effectiveness of charged particles at the end of their range in tissues [84], special attention should be paid in treatment planning not to convey the beam distal fall-off toward serial critical structure such as carotid vessels, brainstem, mucosal tissue outside GTV [79].

Pragmatic approach to select patients for reRT

To summarize literature data and organize available information in a manageable tool, we propose a stepwise approach helping to define the best reRT candidate (Fig. 1).

Of note, given the existence of multiple clinical variables in the lack of well-defined cut-offs related to patients' prognosis, the definition of a "favorable" or "unfavorable" condition remains at the discretion of the referring Radiation Oncologist.

While reported time intervals between the two radiation courses ranged from 12 to 36 months, we proposed a cautionary threshold of 12 months. Moreover, it is worth reminding that this workflow should be shared and discussed with the patient, to fully understand their needs and expectations.

Below, two clinical cases are presented to provide the reader with a practical overview of how the proposed approach can be applied to real-life situations.

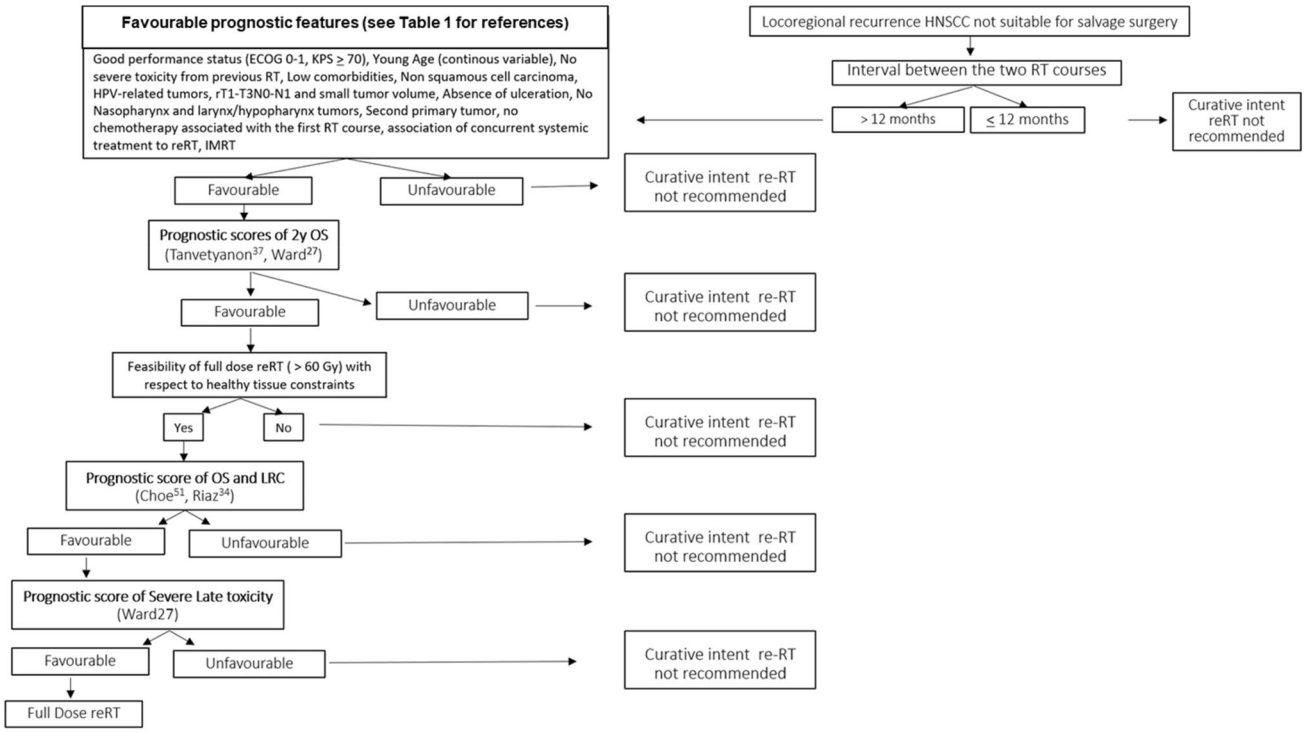

Fig. 1 A stepwise approach to help to define the best reRT candidate

Case 1

Patient: 50-year-old male. Comorbidities: gastritis and kidney stones.

Brief history: In 2007, the patient was diagnosed with a squamous cell carcinoma of the oral cavity (left mobile tongue) and treated with compartmental left hemiglossectomy and bilateral neck dissection. The resulting pathologic stage was pT4N0M0 (AJCC 7th Ed.) Postoperative RT was performed up to a total dose of 60 Gy (2 Gy/fraction) to the surgical tumor bed and 54 Gy to negative neck lymph nodes in February 2008. Three local recurrences occurred in 2009, 2012 and 2016: they were all considered as amenable to surgery, and were staged as rpT1, rpT4, and rpT3, respectively. Adopted approaches were transoral surgery of the amigdaloglossus region and reconstruction with a Bichat's flap, and hemimandibulectomy, respectively. The last recurrence was finally diagnosed in 2021, at the posterior margin of the pectoralis flap positioned in 2016.

Step 1) Diagnostic work up: Clinical Examination: KPS 90, no dysphagia, no dyspnea. No signs of bleeding. Slight headache responsive to paracetamol. Stable body weight (82 kg). No dysfunction from the previous radiation treatment (G1 subcutaneous fibrosis). Fibroscopy: presence of ulcer in the lateral oropharyngeal wall at the posterior edge of the oral cavity flap reaching the ipsilateral hypopharynx. MR: lesion of 16 mm of the left pharyngeal wall infiltrating the parapharyngeal space and the constrictor muscle up to the superior margin of the pyriform sinus. No infiltration of pre-vertebral muscles could be identified. FDG-PET: absence of pathological uptake other than the lesion in the parapharyngeal space. Resulting clinical stage was rcT4 rcN0 rcM0, with a volume of the recurrent tumor of 40 cm^3. A biopsy confirmed the histology of squamous cell carcinoma. The mass was judged not suitable for further surgery.

Step 2) Prognostic and Predictive Factors for patient's selection

Step 3) Dosimetric analysis

The dosimetric assessment showed that the current recurrence was partially included in the high dose area (60 Gy) of the first RT. Moreover, the ipsilateral carotid artery received the full dose from the previous treatment at the level of the last local recurrence. To maintain a cumulative dose < 120 Gy to the carotid artery, a full course of RT up to a total dose of 60 Gy by IMRT has been proposed. Table 4 summarizes risk factors for long-term toxicity considering the abovementioned characteristics.

Conclusion: both expected oncologic outcomes at 2 years and long-term toxicity profile seem to be quite favorable for the majority of considered prognosticators. Therefore,

Table 4 Risk factors for long-term toxicity. Red, yellow and green emojis stated whether a defined risk factor is present, is borderline or absent, respectively

Side effects	Risk factors from literature	Patient's risk factors
Carotid blow out	Previous total dose > 58 Gy, Curative > postoperative reRT, Tumor volume > 22 cm^3, Curative > postoperative reRT	☹
	3D conformal technique > IMRT, reRT alone vs concurrent chemo reRT, Unresectable node metastases, cumulative dose > 140 Gy, nasopharynx	☺
	Dose to carotid artery > 120 Gy	😐
	For nasopharyngeal tumor: post-styloid space invasion	NA
Pharyngeal stenosis	reRT neck (vs head) locoregional reRT (vs regional)	😐
NA Severe dysphagia	Previous total dose > 58 Gy, Curative > postoperative	☹
	Short interval (< 20 months) and larger PTV (> 100 cm^3), CTV volume > 50 cm^3, CTV > 50 cm^3 and concurrent CTreRT	☺
	Median cumulative dose > 120 Gy	😐
	For nasopharyngeal tumors: Post-styloid space invasion	NA
Osteonecrosis	3D technique vs IMRT, Short interval (< 20 months) and larger PTV (> 100 cm^3), CTV > 50 cm^3 and concurrent CTreRT	☺
Mandibular necrosis	Total dose > 104 Gy	☺
Fistula	3D technique vs IMRT, CTV > 50 cm^3 and concurrent CTreRT	☺
Cranial nerve palsy	Post-styloid space invasion (nasopharynx)	NA
Nasopharyngeal necrosis	Post-styloid space invasion (nasopharynx)	NA
Temporal Lobe necrosis	Cumulative BED > 150 $Gy_{2.5}$	NA
	For nasopharyngeal tumor: post-styloid space invasion	☺
Mucosal necrosis	Tumor volume > 26 cm^3	☹
Soft-tissue necrosis	Curative > postoperative	☹
	Total dose > 140 Gy, short interval (< 20 months) and larger PTV (> 100 cm^3)	☺
Trismus	Short interval (< 20 months) and larger PTV (> 100 cm^3), reRT alone vs concurrent chemo reRT, CTV > 50 cm^3 and concurrent CTreRT	☺
	Fractionated SBRT every other day	NA
Cord paralysis	Curative > postoperative	☹

NA = not applicable

based on the available data, it appears reasonable to propose a second RT course.

Case 2

Patient: 57-year-old male, with no reported comorbidities. Brief history: in June 2014 the patient was diagnosed with a non-keratinizing poorly differentiated nasopharyngeal carcinoma, staged as cT1cN1M0 (AJCC 7th Ed). Curative chemoradiation up to a total dose of 70 Gy (2 Gy/day) ended in June 2014. In October 2015 a retropharyngeal lymph node was detected at RM images during the follow-up. A biopsy was not feasible due to the tumor location.

Volume of the recurrent tumor was 20 cm^3.

The mass was judged not suitable for surgery.

Step 1) Diagnostic work up

Physical examination: KPS 100. No pain, no dysphagia, no respiratory distress. No dysfunction from the previous radiation treatment (xerostomia G2). Fibroscopy: no signs of local recurrence or mucosa ulcer. MR: pathologic lymph node 11 × 10 × 18 mm in the left parapharyn-

geal space (pre-styloid space), close to the carotid artery (< 180°). FDG-PET: no other pathologic uptake than in the left parapharyngeal space. Table 5 summarizes predictive and prognostic factor for patients' selection related to the analyzed case.
Step 2) Prognostic and Predictive Factors for patient's selection.
Step 3) Dosimetric analysis.

The dosimetric assessment showed that the recurrence fell within the high dose area (70 Gy) of the previous treatment. Moreover, carotid artery had received a full dose from the previous treatment at the level of the recent local recurrence. To maintain a cumulative dose < 120 Gy to the carotid artery, a full course of RT up to a total dose of 50 Gy has been proposed. Identified risk factors for long-term toxicity are summarized in Table 6.

Conclusion: overall both expected oncologic outcome at 2 years and long-term toxicity profile seems to be quite favorable for the majority of the considered prognosticators. Therefore, based on available data, it seems reasonable to propose a second course of RT up to a total dose of 50 Gy [12, 34].

Discussion

Several literature data have been provided during the last decades to guide reRT indications [18, 85–91]. The majority of these works were narrative reviews on several aspects that should be considered in locally recurrent cancers of the head and neck. Cacicedo et al. [18]: in their 2013 work reviewed prognostic and predictive factors for both clinical outcomes and toxicity and provided dosimetric information to estimate the risk of toxicity of a second course of RT in head and neck region. Nevertheless, during the last decades, several new clinical studies (i.e., on the use of particle beam therapy) and international recommendations have been published [79, 80]. Our work, therefore, summarizes current knowledge on the topic providing an updated pragmatic instrument to manage reRT in the setting of SCCHN.

We are aware of the several limitations of this work: (1) the majority of provided literature data derived from mono-institutional analysis and have limited sample sizes, (2) prognostic and predictive factors are often expressed in qualitative terms (e.g., "young" age), and derive from heterogenous populations treated with multiple reRT techniques and fractionation schedules. Indeed, there are no validated prognostic parameters for reRT. While the presence of HPV in RM SCCHN has been associated with improved overall and progression-free survival tumors [92], Nevertheless none of the available nomograms have incorporated this variable. This underlines the need of further studies in this clinical setting. (3) application of provided prognostic and predictive factors on cohorts that differ from the original ones, could produce differences in obtained results [39]. (4) Nomograms could provide different results for the same endpoint due to the different parameters used to build the final prognostic value. (5) Several potentially relevant factors (i.e., stage of the primary tumor, patients' compliance, supportive care network and logistic arrangements, psychological and rehabilitation aspects, individual tolerance to radiation etc.) have not been specifically reported but should be considered in real-life situations. (6) Not unique cut-off value has been found for several factors (i.e., tumor volume at recurrence, reRT dose, minimum interval between the two radiation courses) (7) the "favorable" vs "unfavorable" setting represented in Fig. 1 can be highly subjective as it was not possible to provide a cut-off to separate the two cohorts in each step of the process (8) the efficacy of the provided tool should be validated and adapted (if necessary) in prospectively enrolled in controlled clinical studies.

Moreover, the use of concurrent systemic treatments has not been detailed in this work. In particular, whether the association of concurrent systemic treatment could lead to dose de-escalation need further investigation.

Results reported in the present work were retrieved from a narrative review of the literature. We chose this approach as it allowed us either to report an overview

Table 5 Patients, tumor and treatment prognostic and predictive factors

Interval between two RT course	12 months
General Prognostic Features	Favorable: young age, high KPS, no toxicity from previous RT, no relevant comorbidities, no ulceration, early stage, no mucosa ulceration, nasopharynx Unfavorable: previous CT/RT, Squamous cell carcinoma, local recurrence, no association with concurrent chemotherapy
Prognostic score 2y OS	40% (Ward et al.), > 90% (Tanetyanon et al.) < 10% (Choe et al.)
Prognostic score OS and 2y LRC	~ 72% (Riaz et al.)
Prognostic score of severe late toxicity	< 10%
PRANCIS score (ony nasopharynx)	NA

Table 6 Risk factors for long-term toxicity

Side effects	Risk factors	Patient's characteristics
Carotid blow out	Previous total dose > 58 Gy, Curative > postoperative, Nasopharynx	☹
	3D technique vs IMRT, Post-styloid space invasion (nasopharynx), > 120 Gy, Tumor volume > 22 cm^3, reRT alone vs concurrent chemo reRT	☺
	Unresectable node metastases and cumulative dose > 140 Gy	😐
Pharyngeal stenosis	reRT neck (vs head) locoregional reRT (vs regional)	☹
Severe dysphagia	Previous total dose > 58 Gy, Curative > postoperative	☹
	Median cumulative dose > 120 Gy, -styloid space invasion (nasopharynx) CTV volume > 50 cm^3, CTV > 50 cm^3 and concurrent CTreRT	☺
	Short interval (< 20 months) and larger PTV (> 100 cm^3),	😐
Osteonecrosis	3D technique vs IMRT, CTV > 50 cm^3 and concurrent CTreRT	☺
	Short interval (< 20 months) and larger PTV (> 100 cm^3),	😐
Mandibular necrosis	Total dose > 104 Gy	☺
Fistula	3D technique vs IMRT, CTV > 50 cm^3 and concurrent CTreRT	☺
Cranial nerve palsy	Post-styloid space invasion (nasopharynx)	☺
Nasopharyngeal necrosis	Post-styloid space invasion (nasopharynx)	☺
Temporal Lobe necrosis	Post-styloid space invasion (nasopharynx), Cumulative BED > 150 $Gy_{2.5}$	☺
Mucosal necrosis	Tumor volume > 26 cm^3	☺
Soft-tissue necrosis	Curative > postoperative	☹
	Total dose > 140 Gy,	☺
	Short interval (< 20 months) and larger PTV (> 100 cm^3),	😐
Trismus	Fractionated SBRT every other day, reRT alone vs concurrent chemo reRT, CTV > 50 cm^3 and concurrent CTreRT	☺
	Short interval (< 20 months) and larger PTV (> 100 cm^3),	😐
Cord paralysis	Curative > postoperative	☹

of the available knowledge on the topic or to gather data provided by different authors. A systematic review generally provides a more robust evidence-based method, but considering the aim of our work as well as the nature of the vast majority of the studies focused on SCCHN reRT (retrospective monocentric analysis obtained from a low number of enrolled patients and with high heterogeneity of reported results) we preferred to proceed with a comprehensive and critical qualitative analysis of the current literature shreds of evidence. However, this approach is prone to criticism, and therefore all reported data need to be considered with caution when applied in daily clinical practice.

Despite the present work focuses on indication to a second course of full-dose RT, it is important to emphasize that a clear cut-off value for considering reRT as curative or cytoreductive intent has not yet been well established. Moreover, in the era of the high-precision RT (stereotactic body/intensity-modulated radiotherapy and hadrontherapy), the trade-off between prescription doses to the target volume and the ability to spare surrounding organs at risk should be carefully considered.

According to results of the present work, several factors should be considered in patients with recurrent/second primary head and neck tumors. However, most authors agree that a minimum interval of 6 months between two radiation courses, absence of severe radiation-related sequalae, limited volume of the recurrent tumor and the dosimetric feasibility should be minimum requirements to consider a patient for a full course reRT.

In conclusion, a reRT remains a personalized approach that can be offered to selected patients only in centers with expertise and dedicated equipment after a multidisciplinary discussion. Results of our work represent the first attempt to standardize the approach providing an evidence-based clinical tool for indication to reRT in SCCHN patients.

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Declarations

Conflict of interest The Division of Radiation Oncology of IEO received research funding from AIRC (Italian Association for Cancer Research), Fondazione IEO-CCM (Istituto Europeo di Oncologia-Centro Cardiologico Monzino) all outside the current project. BAJF received speakers fees from Roche, Bayer, Janssen, Carl Zeiss, Ipsen, Accuray, Astellas, Elekta, and IBA Astra Zeneca (all outside the current project). The remaining authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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