Oral Oncology 98 (2019) 35–47

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Organs at risk's tolerance and dose limits for head and neck cancer re-irradiation: A literature review

F. Dionisi[a,*], F. Fiorica[b,1], E. D'Angelo[c,1], M. Maddalo[d], I. Giacomelli[a], E. Tornari[e], A. Rosca[f], F. Vigo[f], D. Romanello[g], M. Cianchetti[a], F. Tommasino[h], M. Massaccesi[i], E. Orlandi[j]

[a] Proton Therapy Unit, Azienda Provinciale Per i Serivizi Sanitari, Trento, Italy
[b] Department of Radiation Oncology, University Hospital Ferrara, Italy
[c] Radiotherapy Unit, Department of Oncology, University Hospital of Modena, Italy,
[d] Radiation Oncology Department, University of Brescia-Spedali Civili, Italy
[e] University of Genova- Radiotherapy Unit, Genova, Italy
[f] Radiotherapy Unit, Reggio Emilia, Italy
[g] Univeristy of Milan, Italy
[h] Department of Physics, University of Trento, Trento Institute for Fundamental Physics and Applications (TIFPA), Italy
[i] Radiation Oncology Department, Gemelli-ART , Università Cattolica S. Cuore, Rome, Italy
[j] Radiation Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Italy

ARTICLE INFO

Keywords:
Head and neck cancer
Re-irradiation dose limits
Tolerance of organs at risk
Carotid blowout
Temporal lobe radionecrosis

ABSTRACT

Re-irradiation is becoming an established treatment option for recurrent or second primary head and neck cancer(HNC). However, acute and long-term RT-related toxicities could dramatically impact patients' quality of life. Due to the sparse literature regarding HNC re-irradiation, data on tolerance doses for various organs at risk (OARs) are scarce. Our aim was to systematically review the clinical literature regarding HNC re-irradiation, focusing on treatment toxicity, OARs tolerance, and dose limit recommendations. Thirty-nine studies (three randomized, five prospective, 31 retrospective) including 3766 patients were selected. The median interval time between the first course and re-irradiation was 28 months (range, 6–90). In 1043 (27.6%) patients, post-operative re-irradiation was performed. Re-irradiation doses ranged from 30 Gy in 3 fractions using stereotactic technique to 72 Gy in conventional fractionation using intensity-modulated radiotherapy. Pooled acute and late toxicityrates ≥G3 were 32% and 29.3%, respectively. The most common grade 3–4 toxic effects were radio-necrosis, dysphagia requiring feeding tube placement and trismus. In 156 (4.1%) patients, carotid blowout was reported. Recommendations for limiting toxicity included the time interval between radiation treatments, the fractionation schedules, and the re-irradiation treatment volumes. Cumulative dose limit suggestions were found and discussed for the carotid arteries, temporal lobes, and mandible.

Introduction

Radiation therapy (RT) represents a cornerstone in the treatment of head and neck cancer (HNC) patients, both in the definitive and the adjuvant settings in combination with systemic therapy in loco-regionally advanced cases. However, loco-regional relapses still affect about 15–50% of patients, representing the first cause of death in spite of the improved treatment options available nowadays [1,2]. Furthermore, there is a risk(up to 40%) of secondary primary HNCs among survivors, due to an “in-field cancerization” of the upper aero-digestive tract [3]. These clinical situations are very challenging from the perspective of a radiation oncologist.

Surgery still remains the first treatment choice for either second primary HNCs or recurrent tumors, albeit applicable to few patients due to tumor burden and site and because of patient-related clinical conditions [4]. In this scenario, postoperative re-irradiation can optimize the surgical outcomes in terms of durable disease control in a defined subset of patients [5]; moreover, re-irradiation as a definitive treatment can improve outcome and cure rates in specific clinical scenarios such as nasopharyngeal recurrent tumors [6].

However, acute and long-term RT-related toxicities could dramatically impact patients’ quality of life [7,8]. The risk of severe life-

* Corresponding author at: Proton therapy Unit, Azienda Provinciale per i Serivizi Sanitari, Via al Desert, 14, 38123 Trento, Italy.
E-mail address: francesco.dionisi@apss.tn.it (F. Dionisi).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.oraloncology.2019.08.017
Received 11 April 2019; Received in revised form 18 August 2019; Accepted 25 August 2019
Available online 16 September 2019
1368-8375/

threatening sequelae indeed could outweigh the benefits of re-treatment. Thus, an appropriate patient selection for re-RT is crucial to improve the therapeutic ratio.

Although modern RT techniques, such as intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), image-guided radiotherapy (IGRT) and protons allow a better sparing of normal tissues due to their improved conformity and precision, re-irradiation side effects are still a matter of concern as a result of the lower tolerance of healthy tissue to a second RT course. In particular, these include extensive fibrosis, soft tissue necrosis, osteoradionecrosis, myelopathy and carotid artery blowout.

Due to the sparse literature regarding HNC re-irradiation studying usually small sample sizes with different and heterogeneous treatment schemes, data on tolerance doses for various organs at risk (OARs) are scarce.

Our aim, on behalf of the Italian Association of Radiation Oncology re-irradiation study group, was to perform a critical review of the most recent literature in order to get a clearer picture of re-irradiation-induced toxicities with a focus on OARs tolerance. Data on survival and local control are also reported, aiming at clarifying whether state-of-the-art re-irradiation techniques translate into a more favorable therapeutic ratio.

Methods

Selection of studies

A computerized search of the literature was performed using the MEDLINE, EMBASE, OVID and Cochrane databases from the time of inception to 2017. Recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9] were followed.

The search strategy included terms related to re-irradiation and head and neck cancers. The computer search was supplemented with hand searches of reference lists for all available review articles, primary studies, meetings, abstracts, and bibliographies of books to identify additional studies not found in the computer search. The final inclusion of articles was determined by consensus between two authors (F.F. and F.D.), discrepancies among reviewers were infrequent (overall inter-observer variations < 10%) and were solved by discussion.

Criteria for inclusion and exclusion

Only the studies analyzing outcomes of re-treated patients in which irradiation involved overlap with previous radiotherapy were taken into consideration. Each study included in the reviewanalyzed at least 30 patients. Abstracts, letters, proceedings from scientific meetings, editorials, expert opinions, reviews without original data, case reports, repetitive data, non-English language papers and animal studies were excluded. Decisions on which studies to include were made blindly by two reviewers (F.D. and F.F.). Disagreements were solved by discussion. When the results of a single study were reported in more than one publication, only the most recent and complete data were included.

Review of the studies

Studies were first reviewed using a list of predefined, pertinent aspects concerning the characteristics of patients and treatments. The methodological quality of studies was assessed with a checklist for quality appraisal of case series studies produced by the Institute of Health Economics (IHE) and modified to improve applicability [10]. The following items were evaluated for each study: a clearly stated aim, prospective data collection, multicentric study, consecutive patients, characteristics of patients, clearly stated eligibility criteria, described intervention, reported lost to follow-up and adverse events, and conclusions of the study supported by the results. To improve the comparability of the different re-irradiation regimens and to assess the relationship between radiation dose and toxicity, when not reported in the study, an equivalent dose in 2 Gy fractions (EQD2) was calculatedaccording to $D \times (D/n + \alpha/\beta)/(2 + \alpha/\beta)$, derived from the linear-quadratic model. Moreover, we calculated the cumulative dose for acute responding tissue and for late responding tissue, neglecting repair effects between irradiations [11].We have hypothesized that OARs near recurrences received a cumulative dose calculated for acute and late responding tissue. To determine the pooled grade ≥ 3 late toxicities rate, overall survival and local recurrence-free survival, a meta-analysis technique over a single arm study was performed. For this purpose, we calculated the estimated population proportion of late toxicity, local control and overall survival with 95% confidence intervals (CI) for every separate study [12]. Pooled effect size aided the general evaluation of re-irradiation risk and effect. Heterogeneity across studies was examined by the Cochran Q chi-square test and the I^2 statistics. Studies with an I^2 statistic of 25%–50%, 50%–75% and > 75% were deemed to have low, moderate and high heterogeneity, respectively [13].We used random-effects models because there was great subjectivity given the lack of related control groups in the non-comparative studies and a tendency toward high heterogeneity.

Results

The search of the literature yielded 66 sources. Of these, 39 studies met the inclusion criteria (Fig. 1). The main features of the studies included in this systematic review are shown in Table 1. These studies were published between 2002 and 2019 in 11 countries. Three trials were randomized [5,14,15] and another five studies were prospective trials [8,16-19]. The analyzed population of each study varied greatly, ranging from 31 [20] to 505 [21] patients. Overall, the 39 studies included 3766 patients who were re-irradiated within the head and neck region. Treatment intent (i.e., palliation versus cure) was generally not well described. Median follow-up from re-irradiation in studies specifically examining re-irradiated patients was 18.5 months (range, 8–78).

Re-irradiation treatment details

Head and neck re-irradiation was reported for local disease recurrence, lymph node recurrences and new primary tumors arising in the head and neck. The degree of overlap between the former and re-irradiation plans was not well described. In all cases, the reported locations of re-irradiated lesions indicated that the re-irradiation volumes were likely to have been contained within at least the 50% isodose of the previous radiotherapy plan, and most often, wholly or partly, within the high dose region. Previous radiotherapy was delivered with a median dose of 65.7 Gy (range, from 56 to 71) using a conventional fractionation in all studies. The mean time elapsed since previous irradiation ranged from 6 to 90 months, and the median interval time was 28 months. IMRT was generally used to re-irradiate patients in all studies, excluding five [16,18,22-24] in which a conventional 3D radiotherapy approach was applied, two [25,26] in which proton therapy was used, three [20,27,28] using SBRT, and one study [19] in which brachytherapy was applied. Re-irradiation prescription doses were variable, ranging from 30 Gy in 3 fractions [28] to 72 Gy with IMRT and SBRT [29,30]. Chemotherapy was a part of the re-treatment program in 2373 patients (63%). In 1043 patients (27.6%) re-irradiation was delivered after surgery.

Toxicity and radiation tolerance of organs at risk

All studies reported OARs constraints either as maximum point doses or as cumulative doses from the previous irradiation and the re-irradiation. Data on acute toxicity were analyzed in 38 studies: grade ≥ 3 acute toxicity was observed in 1193 patients (32%). There was no difference in grade ≥ 3 acute toxicity rate with respect to different

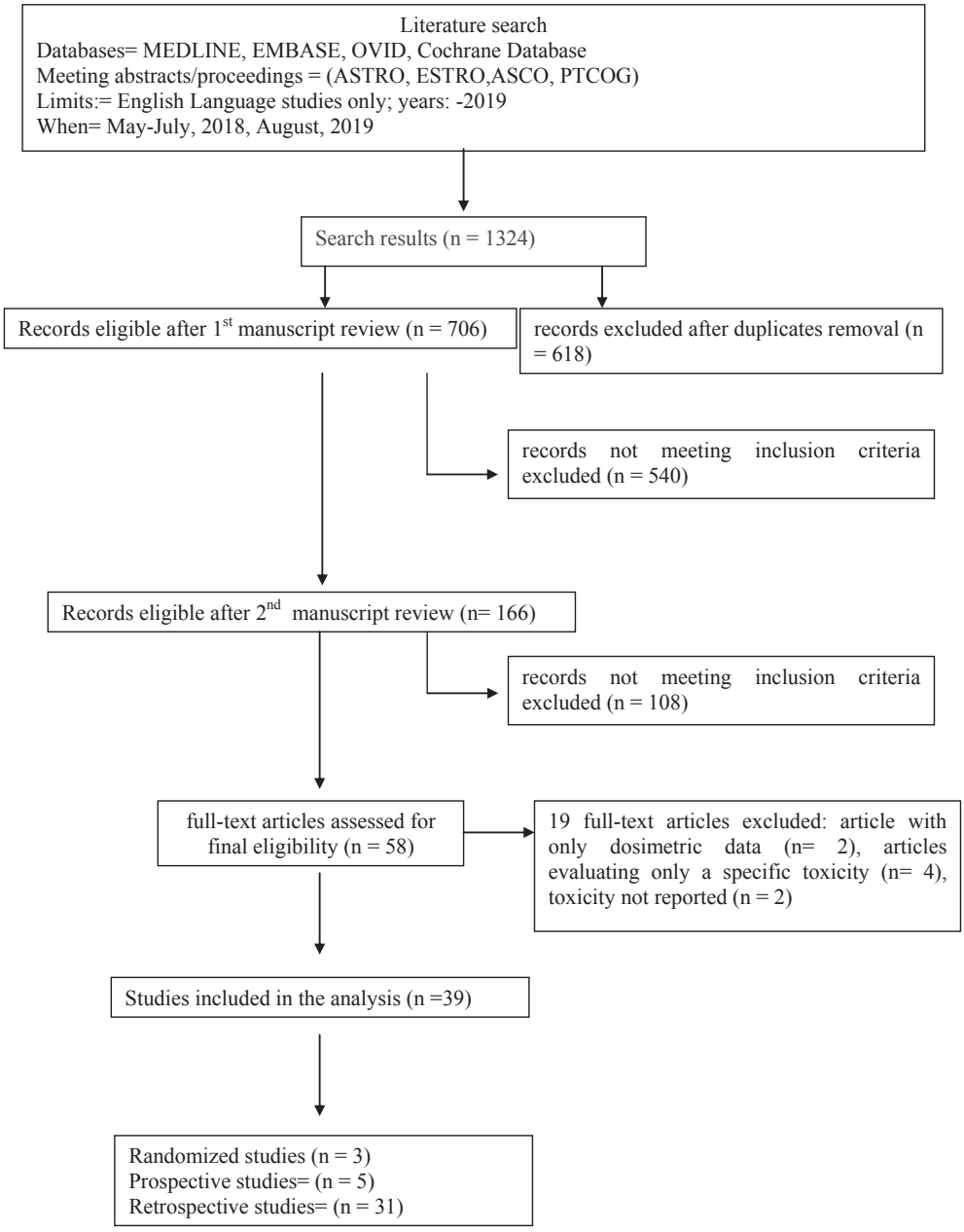

Fig. 1. Flow chart of the studies screened, excluded, and selected for analysis. ASCO = American Society of Clinical Oncology, ESTRO = European Society for Radiotherapy and Oncology PTCOG = Particle Therapy Cooperative Group.

radiation techniques, cumulative dose and re-irradiation total dose and fractionation. Thirty-seven patients (0.9%) died from acute treatment toxicities: neutropenia, fatal hemorrhages (bleeding as a result of rapid tumor regression in an area of compromised vasculature) and aspiration pneumonia were described.

Patients in a re-irradiation program had a grade ≥3 late toxicity rate of 29.3% (95% CI: 23.5–36.4%) with high heterogeneity (I^2 = 195.4, P < 0.001) (Fig. 2). The most common grade 3–4 toxic effects were radionecrosis, dysphagia requiring feeding tube placement, and trismus (Table 2). In 156 (4.1%) patients, carotid blowout was reported, as listed in Table 3. After omitting studieswith a cumulative dose ≥125 Gy, the pooled grade ≥3 late toxicity rate was 26.5% (95% CI: 18.8%–37.3%) with no reduction in heterogeneity (I^2 = 94.6%, P < 0.001).

Outcomes

All studies reported the 2-year OS rate. The pooled 2-year OS rate was 41.3% (95% CI: 37.3%–45.7%) with high heterogeneity (I^2 = 86.9%, P < 0.001) (Fig. 3).

No difference in heterogeneity was evidenced after omitting studies not using IMRT [16,18-20,22-28] and after omitting studies with a cumulative dose ≥ 120 Gy. All studies but six [17,18,20,27,31,32]reported the 2-year local recurrence-free survival. The pooled 2-year local recurrence-free survival rate was 48.8% (95% CI: 43.7%–54.5%) with high heterogeneity (I^2 = 82.7%, P < 0.0001) (Fig. 4). This heterogeneity was not modified by excluding studies not using IMRT [16,18-20,22-28] and studies with a cumulative dose ≥120 Gy.

Discussion

The ultimate goal of radiotherapy lies in finding the best

Table 1
Main characteristics of the selected studies.

First author, year of publication	Patient number	Accrual period	Previoustotal dose	Time elapsed since previous irradiation	Re-RT total dose/fractionation	Re-RT technique
Ohizumi 2002	91	1984–1997	mean 59 Gy (range, 20–85 Gy)	22 mo (1–175)	55 Gy (range, 17–78)	3DCRT
Spencer 2002	52	1992–1999	≤55 Gy (5 pts) 55–70 Gy (33pts) > 70 Gy (13 pts) 1 unknown	at least 6 mo	2 Gy once daily for weeks 1 and 2, then 1.5 Gy twice daily for weeks 4 and 5, all for a total dose of 50–60 Gy'.	3DCRT
Kramer 2005	38	1996–2002	median 64.2 Gy (range, 15–74 Gy)	na	Phase I (42 Gy total dose,1.5 Gy twice daily week n°1, then 1.2 Gy daily) Phase II (60 Gy, 1.5 Gy twice daily)	3DCRT
Langendijk 2006	34	1997–2003	n/a	90 mo (12–233)	60–66 Gy/30-33fr	IMRT
Spencer 2007	79	1996–1999	median 65.2 Gy (range, 45–73.8)	median 60 mo (range, 5–234.6)	60 Gy at 1.5 Gy twice-daily fractions	3DCRT
Langer 2007	105	2000–2003	Median 65.4 (range, 45.0–75.0)	39.6 m (range, 6.1–317.9)	1.5 Gy per fraction bid 5 days every 2 weeks 4	IMRT
Lee 2007	105	1996–2005	62 Gy (range, 28–78)	38 months (range, 5–380)	59.4 Gy (30–70) 1.8–2.0 Gy	IMRT
Biagioli 2007	41	2001–2006	Not reported, cumulative dose: 121.2 (range, 102.0–132.0)	25 m (range, 6–240)	60 (range, 38.0–60.57) 2 Gy per fraction (range, 1.8–2.0)	IMRT
Janot 2008	65	1999–2005	Not reported (≥45 Gy)	3.5 years (range, 0.5–30.5 years)	60 Gy (range, 5–60 Gy)	na
Iseli 2009	87	1992–2007	cumulative dose < > 58 Gy	n/a	cumulative dose < > 120 Gy	na
Watkins 2009	39	1997–2007	66.8 (range, 54–76)	2.3 years (range, 0.5–19)	60 Gy (range, 20–68.4) 1.5 Gy twice daily	3DCRT
Popovtzer 2009	66	1994–2007	64 Gy (range, 46–76.8 Gy).	37 months (range, 6–184)	68 Gy (range, 15–79.6 Gy) conventional/hyperfractionated	IMRT
Sulman 2009	74	1999–2004	60 (16–75)	46 (3–445)	60 (range, 15–70)	IMRT
Sher 2010	35	2004–2008	67.5 Gy(IQR 63–70 Gy)	30 mo	60 Gy (IQR 60–64 Gy): 26 pts 200 cGy once daily, 8 pts 180 cGy once daily, 1 pt 120 cGy twice daily	IMRT-3DCRT
Pletteaux 2011	51	2000–2009	median 66 Gy (range, 26–72 Gy)	60.5 mo (3–324)	60 Gy (range, 37.5–72 Gy)/2 Gy (32 pts)/1.8 Gy (11 pts)/2 Gy and 1.8 Gy combined (1 pt)/hyperfractionation(4 pts)/ hypofractionation (3 pts)	3DCRT/IMRT/ BRT
Gaztañaga2012	40	2000–2008	n/a	n/a	32 Gy/8 fxbid for R0; 40 Gy/10 fxbid for R1	BRT
Kharofa 2012	38	2001–2009	median 68 Gy(range, 54–70 Gy)	median 28 mo (range, 3–228)	median 60 (22–70)/most cases 60 Gy in 2 Gyfract	IMRT
Garg 2013	50	n/a	64 Gy (range, 37–70.2)	median 28 mo (range, 6–356)	60 Gy (range, 37–72.6)/2 Gy (range, 1.1–3)	IMRT/3DCRT
Chen 2013	54	2005–2012	n/a	< 24 mo = 37%, > 24 mo < 60 mo = 29.6%, > 60 mo = 33.3%	68.5 Gy (range, 49.8–76.8)	IMRT
Yazici 2013	75	2007–2011	Group I 65 (range, 30–77.4), Group II 64 (38–78)	Group I median 35 mo (range, 9–232) Group II median 36 mo(range, 10–300)	Group I 30 Gy in 5 (range, 25–35 in 3–5 fr) Group II 30 Gy in 5 (range, 15–35 in 4–6)	SBRT
Tian 2014	117	2003–2007	Group A median 70 Gy (range, 68–86 Gy) Group B median 70 Gy (range, 68–82 Gy)	Group A median 25 mo (range, 9–188) Group B median 26.5 mo (range, 10–190)	Group A median CTV dose 60.2 Gy (range, 55.1–64.2 Gy) Group B median CTV dose 63.1 Gy (range, 58.2–66.6 Gy)	IMRT
Duprez 2014	60	1997–2011	66 Gy (range, 50–71)	median 27 mo (range, 6–240)	70 Gy/35 fr (up to 2004); 69.12/32 fr (thereafter)	IMRT
Buglione 2015	75	2005–2013	median 66 (range, 40–70) in curative setting, 60 (range, 50–70) in postoperative	median 28 mo (range, 3–173) for recurrences, 144 (range, 35–446) for second primary tumors	29–84 Gy BED (a/b10) for non-SBRT/26 standard fractionation, 24 hyperfractionation once or twice a day, 6 moderate once-a-day hypofractionation; SBRT: 25 Gy/5 fx (5 pts, BED 37.50 Gy), 30 Gy/6 fx (11 pts, BED 48 Gy), 35 Gy/7 fx (3 pts, BED 59.50)	3D-CRT/ IMRT/SBRT
Kress 2015	85	2002–2011	median 68 (range, 36–120)	median 32 mo	median 30 Gy (range, 16–41 Gy), median 5 fractions (range, 3–5 fractions)	SBRT
Xiao 2015	291	2001–2012	≤70 Gy = 61.5% > 70 Gy = 39.5%	Median 26 mo (range, 6–265)	Prescribed dose = 60–70 Gy to the GTV, 50–54 Gy to the CTV, other data n/a	IMRT
Xu 2015	31	2004–2013	64 Gy (range, 24–75.6 Gy)	n/a	44 Gy (range, 15–50 Gy)/ IN 1–5 fractions (median 44 in 5)	SBRT
Curtis 2016	81	2003–2011	definitive: 66 Gy (range, 26.4–79.2 Gy); post-operative: 66 Gy (range, 50–72 Gy)	n/a	radical 60 Gy (range, 12–70); adjuvant 69.96 Gy (range, 48–76.8)	IMRT
Lee 2016	66	2008–2015	median > 56 Gy	median of 37.5 mo	median 70 (50–74 Gy)	IMRT
Phan 2016	60	2011–2015	median 60 Gy	47.1 mo (7.3–438.2)	61.5 Gy(range, 50–70 adjuvant), 66 (range, 50–70 definitive)	PT
Romesser 2016	92	2011–2014	61.4 Gy (range, 54.0–69.9)	median 34.4 mo (14.2–92.5)	60.6 GyRBE (50.0–66.1)/2.0 Gy	PT
Guan 2016	69	2002–2008	Group I median 70 Gy (range,66–78) Group II median 72 Gy (range, 68–86)	Group I median 26.5 mo (range, 12–121) Group II median 30 mo (range, 9–72)	60 Gy in 27 fr (range, 39.6–60)	IMRT

(*continued on next page*)

Table 1 (*continued*)

First author, year of publication	Patient number	Accrual period	Previoustotal dose	Time elapsed since previous irradiation	Re-RT total dose/fractionation	Re-RT technique
Takiar 2016	227	1999–2014	median 65 Gy (range, 30–79)	SCC median 36.1 mo, non-SCC 74 mo	median 66 Gy (range, 50–70) 2 Gy daily/13 pts 60 Gy in 40 fractions twice daily + CT	IMRT
Ahlawat 2016	51	2006–2015	66.6	41.88 mo	radical 66 Gy/33 fr; adjuvant 60 Gy/30 fr	IMRT
Bots 2017	137	1986–2013	68–70 (radical); 64–66 (post-operative)	12 mo	60–66/30–33 fr	2D/3D-CRT/IMRT
Chan 2017	38	2005–2013	n/a	n/a	64.8 Gy/1.2 Gy bid (13 pts), 50–60 Gy/2 Gy per day (25)	IMRT
Margalit 2017	75	2004–2013	median 70 Gy (range, 45–80 Gy)	28 mo (1.6–315)	median 60 Gy, range, 59.4–70 Gy/30 fractions	IMRT
Vargo 2018	414	n/a	IMRT 66.4 (range, 41.4–80)SBRT 70 (range, 40–170.7)	IMRT 36.8 mo (range, 1.6–40.8) SBRT 13.6 mo (range, 0.8–420)	IMRT 60 (40–72)once-daily fractionation (79%) or twice-daily hyperfractionation (20%), SBRT 40 (16–50) every other day	IMRT/SBRT
Choy 2018	73	2006–2015	median 66 Gy(range, 42–74)	median 31 mo (range, 3–204)	median 60 Gy(range, 48–78)	IMRT
Ward 2019	505	1998–2015	median 66 Gy(range, 40–80)	median 21.5 mo (range, 0–128.1)	median 60 Gy(range, 39.6–79.2)	IMRT

Abbreviations: RE-RT, re-irradiation; mo, months; qd, once daily; bid, twice daily; n/a, not available; PT, proton therapy; SBRT, stereotactic body radiation therapy; 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; CTV, clinical target volume; GTV, gross tumor volume; IQR, interquartile range; BRT, brachytherapy; CT, chemotherapy.

compromise between delivering the maximum dose to the tumor while maintaining OARs dose at an acceptable level in terms of treatment toxic effects. In the setting of the first course of radiotherapy, robust clinical and dosimetric data along with world-renowned guidelines exist regarding OARs tolerance to radiation [33].

On the other hand, re-irradiation represents a challenging clinical scenario in which the therapeutic window for a safe and effective treatment is narrowed by the radiation dose previously delivered to healthy tissues. Moreover, literature data regarding OARs tolerance to re-irradiation are scarce, and no guidelines currently exist. In this context, most of the existing literature has focused on neurological structures [34]. However, even in the pivotal studies by Nieder regarding spinal cord re-irradiation, data from a limited number of only 78 patients were analyzed [35,36]. In the present work, we reviewed data from 39 HNC re-irradiation studies, most of them retrospective, including almost 3800 patients. Our primary focus was to systematically explore data regarding OARs tolerance to re-irradiation in search of consistent clinical and dosimetric recommendations for a safe and effective re-irradiation treatment course.

Taken globally, the results of our analysis of such a significant number of patients confirmed that HNC re-irradiation is feasible at the cost of severe late toxicity in about one-third of patients.

Several factors can determine OARs tolerance to re-irradiation, including stem cell depletion in the tissue, the interval between the two courses of RT (influencing tissue regeneration), the volume of the tissue/organ undergoing re-irradiation, the re-irradiation technique adopted, the concomitant addition of chemotherapy, patient-related factors such as age, comorbidities, organ dysfunctions and the fractionation schedule used in the initial course of RT. Concerning the latter point, data indicate that higher doses per fraction are related to more severe late effects and, consequently, to less tolerance for repeated courses of RT [37].

Knowledge of residual OARs tolerance is hence of pivotal importance when planning re-irradiation.

In light of this, some recommendations and hints can be derived from our work:

- Re-treatment volume is a strong predictor of toxicity, independently by the generally accepted rule of avoiding elective nodal treatment during re-irradiation [38]. In the study of Phan et al. [25] regarding 60 HNC patients undergoing re-irradiation with proton therapy (PT), a clinical target volume > 50 cc was significantly associated with both acute and late grade ≥3 toxicities. Similarly, in the analysis of Lee et al. [39] of 66 HNC patients re-irradiated with modern IMRT between 2008 and 2015, smaller re-irradiated volumes (PTV ≤100 cc) significantly reduced the risk of severe toxicities at 2 years (14% vs. 36%). In the study of Xiao et al. [40], which analyzed 291 consecutive patients with locally recurrent, nonmetastatic nasopharyngeal carcinoma undergoing IMRT re-irradiation, tumor volume (TV) was found as a significant predictor of late toxicity. Of note, in patients with TV ≥22 cc, radiation-induced injuries represented the leading cause of death. In the study of Tian et al. [15], TV > 26 cc) was also found to be a significant independent negative prognostic factor for massive hemorrhage and mucosal necrosis.
- The time interval between radiation treatment courses is correlated with the risk of developing severe toxicity. In the already mentioned work of Lee et al., 80% of patients with a longer interval (≥20 months) to re-irradiation remained free of severe toxicities at 2 years compared with 47% of patients with a shorter interval.
- As for the association between the addition of chemotherapy and the risk of toxicity, in the study of Takiar et al. [41], which retrospectively reviewed the records of 227 HNC patients who received IMRT re-irradiation, the receipt of any chemotherapy and the receipt of concurrent chemotherapy were significantly associated with grade ≥3 toxicity on univariate analysis. On multivariate analysis,

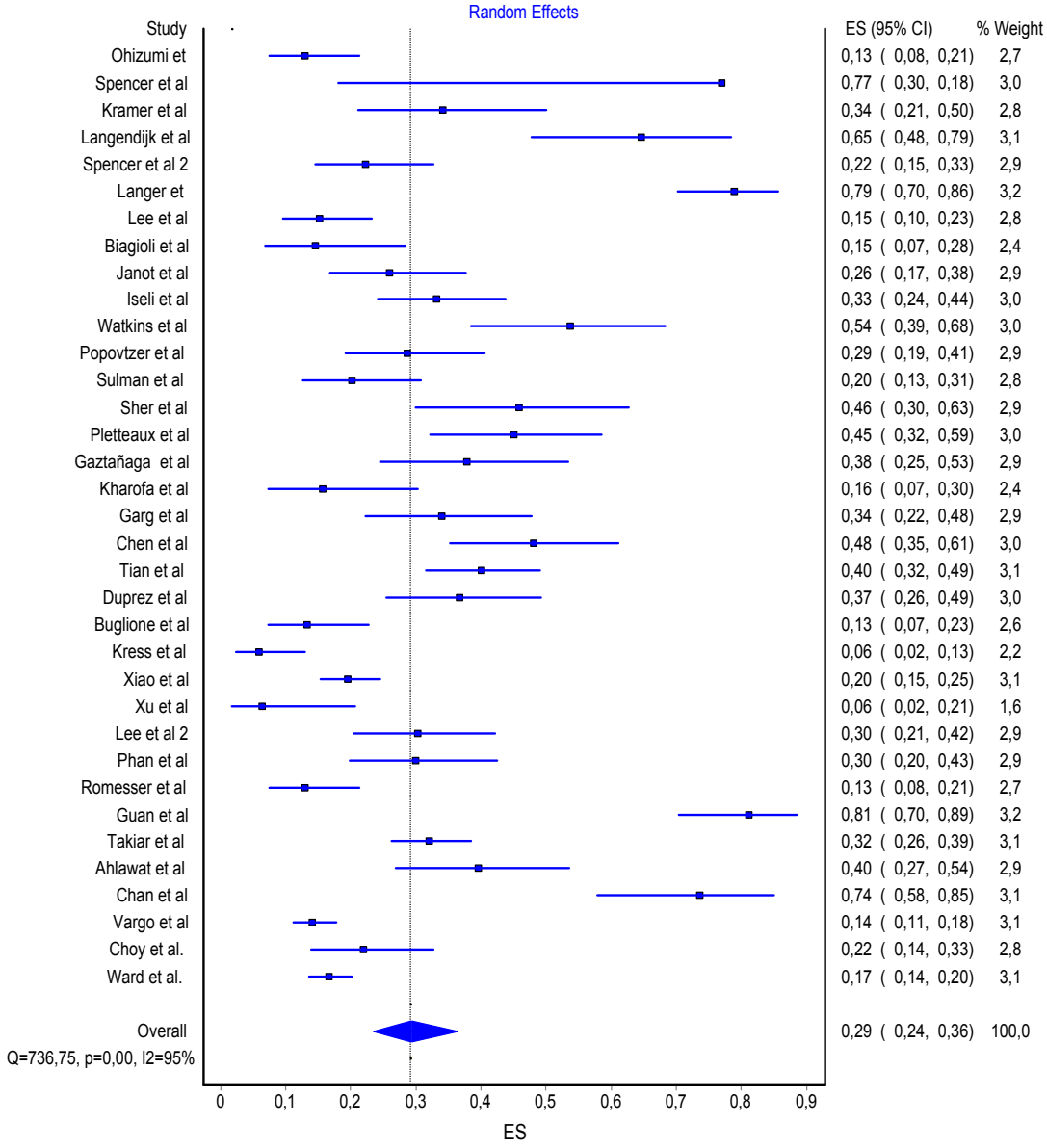

Fig. 2. Pooled rate of ≥G3 late toxicity in re-irradiated patients for included studies. Abbreviations: Q: cochran's *Q*-statistic, I2: *I2*-statistic (both are used to evaluate heterogeneity across studies), ES: Effect Size.

patients who received concurrent chemotherapy were more likely to experience grade 4 toxicity. In the phase II randomized study of Guan et al. [14] comparing intensity-modulated radiotherapy with or without weekly cisplatin for the treatment of locally recurrent nasopharyngeal carcinoma, conflicting results were found: the incidence of grade 3 and grade 4 acute toxicities was higher in the concomitant chemotherapy group (17.6%) than in the radiotherapy alone group (8.6%). Serious late toxicities were similar between the two groups. Interestingly, the incidence of nasopharyngeal massive hemorrhage was significantly lower in the concomitant chemotherapy group than in the radiotherapy alone group. The authors hypothesized that chemoradiotherapy might be able to shrink the tumor faster and accelerate the blood supply to the surrounding tissues, thus reducing the probability of mucosal necrosis.

- The impact of the re-irradiation technique on the risk of toxicity was reported by a limited number of studies. The study of Kharofa et al. [42] reported a significantly higher rate of late toxicities in patients treated with three-dimensional conformal RT than in patients treated with IMRT (44% and 7%, respectively). Conversely, in the study of Bots et al. [43], late complication rates did not differ between patients treated with IMRT and patients treated with conventional RT.
- Among the above cited patient-related factors which could influence re-irradiation toxicity, the patient's age was the only reported factor which was associated with OARs tolerance in some of the retrieved studies, with controversial results. In the study of Ohizumi et al. [22], age greater than 80 years was significantly associated with acute complications. In the study of Margalit et al. [44], a trend toward major severe toxicity with increasing age was also noted. Conversely, in the already cited study of Bots et al. [43], patients aged 65 years or younger at re-irradiation experienced more complications (41% vs. 2%; $P = 0.02$). Age was one of the six clinical factors (along with first RT dose, organ dysfunction, surgery, tumor site, recurrence vs. second primary) included in the nomogram developed by Ward et al. [21] to predict severe late toxicity after IMRT re-irradiation. Increasing age was protective for late toxicity in the model, suggesting that because elderly patients are at increased risk of death, the risk of developing late toxicity is reduced.

Table 2
Most relevant late toxicities occurring in the selected studies.

First author, year of publication	Late grade ≥ 3 toxicity (%)	Additional data-possible related factors-dose limit recommendation
Ohizumi 2002	Pharyngeal stenosis (1.1) Laryngeal edema (4.4) Esophageal stenosis (2.2)	Irradiation to the neck (vs. head) and locoregional irradiation (vs. local) significantly associated with higher risk of late complications
Spencer 2002	Soft tissue necrosis (3.8) Osteonecrosis (1.9) Trismus (1.9)	
Kramer 2005	Osteonecrosis (5.2) Carotid blowout (CB) (5.2) Fistula (5.2)	Hyperfractionated split-course re-irradiation study with concurrent chemotherapy
Langendijk 2006	G-tube dependency (11.7) Osteonecrosis (2.6)	
Spencer 2007	G-tube dependency (75) Dysphagia (10.1)	All 3 patients that experienced grade ≥3 toxicity beyond 1 year received > median cumulative RT dose of 120 Gy
Langer 2007	CB (1.9) Osteonecrosis (4.8) Fistula (0.8)	In the first 2 years, an estimated 84.9% of patients experienced grade 3 to 5 toxicity, whereas an estimated 31.8% experienced grade 4 non-hematologic or grade 5 toxicity
Lee 2007	Trimus (2.8) Temporal lobe necrosis (2.8) Unilateral blindness (0.9)	4% grade 4 late toxicity rate
Biagioli 2007	CB (2.3) Fistula (4.6) G-tube dependency (4.6) Esophageal stenosis (2.3)	Concurrent chemotherapy with IMRT given every other week
Janot 2008	Osteonecrosis (17) Pharyngeal stenosis (5.5) Trismus (28)	Randomized trial of postoperative re-irradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone: at 2 years, 39% of patients in the RT arm and 10% in the surgery arm experienced grade 3 or 4 late toxicity($P = 0.06$)
Iseli 2009	CB (6) G-tube dependency (70)	Re-irradiation doses exceeding 58 Gy were associated with a higher rate of late toxic effects (25% vs. 43%, $P = 0.08$)
Watkins 2009	Trismus (12.8) Osteonecrosis (10.2) Esophagealstenosis (10.2)	All five treatment-related deaths occurred in patients treated with concomitant CDDP-paclitaxel chemotherapy
Popovtzer 2009	CB (3) G-tube dependency (18) Laryngeal chondronecrosis (3) Temporal lobe necrosis (1.5) Pharyngeal stenosis (3)	Insignificant associations between late complications and the radiation doses or concurrent chemotherapy
Sulman 2009	Osteonecrosis (5.1) Dysphagia (7.7) Temporallobenecrosis (1.3) Fistula (1.3) Panhypopituitarism (1.3)	Cumulative spinal cord and other central neural structures doses ≤50 Gy
Sher 2010	Osteonecrosis (6) Soft tissue necrosis (6) Trismus (11) Laryngeal edema (9) Esophageal stenosis (49)	Insignificant correlation betweenprior disease-free interval, surgical resection, disease site, treatment time, induction chemotherapy and grade 5 toxicity
Pletteaux 2011	Dysphagia (33.3) Fistula (9.8) Temporal lobe necrosis (1.9) Optic neuropathy (1.9) Osteonecrosis (1.9)	The median/mean Dmax spinal cord at primary treatment was 40/32.4 Gy (range 0–51) and at retreatment was 9/17.8 Gy (range 0–51.9)
Kharofa 2012	Osteonecrosis (7.9) Fistula (5.3) Lingual artery hemorrhage(2.6) G-tube dependency (68)	Late toxicity was more frequent in patients treated with3DCRT than in patients treated with IMRT (44% and 7% respectively, $P < 0.05$)
Garg 2013	Trismus (10) CB (2) G-tube dependency (10) Esophageal stenosis (8)	Patients with toxicity events had composite DVHs that fell at or above the third quartile when compared with all other analyzed patients
Chen 2013	Cranial nerve palsy (3.7) Necrosis of nasopharynx (30.8) Dysphagia(17.3) Temporal lobe necrosis(17.3) Massive hemorrhage (11.5)	In the multivariate analysis, post-styloid space invasion was the only independent predictive factor for the occurrence of severe late toxicity
Yazici 2013	CB (14.6)	Every day SBRT median dose > 34 Gy > 180° carotid entrapment
Tian 2014	Xerostomia Group A (13.5), Group B (10.3) Hearing loss Group A (15.2), Group B (12.1) Mucosal necrosis Group A (28.8), Group B (50) Hemorrhage Group A (18.6), Group B (31) Trismus Group A (13.5), Group B (18.9) Temporal lobe necrosis Group A (20.3), Group B (22.4) Cranial nerve palsy Group A (13.5), Group B (12.1)	The incidence of mucosal necrosis among patients with a tumor volume > 26 cc was53.1%, which was significantly greater than that noted among patients with a tumor volume ≤26 cc, at 22.6%

(*continued on next page*)

Table 2 (*continued*)

First author, year of publication	Late grade ≥ 3 toxicity (%)	Additional data-possible related factors-dose limit recommendation
Duprez2014	Dysphagia (3.3) Osteonecrosis (1.6) CB (3.3) Soft tissue necrosis (6.6) Ocular (3.3) Aspiration pneumonia (1.6)	Correlation not found between the occurrence of late grade 3 toxicity and concomitant chemotherapy nor age > 65 or > 70 years. More late grade 3 toxicity was seen in operated patients (55% vs. 25%, $P = 0.022$)
Buglione 2015	CB (5.3) Thromboembolic event (1.3) Soft tissue necrosis (1.3)	Lifetime dose of radiation for carotid blowout: 126 Gy, 120 Gy, 120 Gy;lifetime dose of radiation for soft tissue necrosis: 140 Gy
Kress 2015	Soft tissue necrosis (1.2)	SBRT study: the maximum doses to the spinal cord, brainstem, and optic nerve were 21 Gy, 37 Gy, and 34 Gy, respectively
Xiao 2015	Ulcer/necrosis of the nasopharyngeal mucosa (33.7) Trismus (30.2) Temporal lobe necrosis (30) Massive hemorrhage (17.2) Hearing deficit (24) Headache (19.2) Dysphagia (5.5) Difficulty in speaking (5.1) Vision deficit (4.5)	Tumor volume (TV)was a significant predictive factor for the occurrence of severe late toxicity.In patients with TV ≥ 22 cc, radiation-induced injuries became the leading cause of death
Xu 2015	Trismus (20)	Fractionated SBRT every other day could lead to lower toxicity compared to single fraction SBRT
Curtis 2016	CB (2) G-tube dependency (3.7) Osteonecrosis (2.4) Esophageal stenosis (2.4) Fistula (1.2)	
Lee 2016	Dysphagia (18) Osteonecrosis (1.5) Soft tissue necrosis (6) Trismus (3)	Shorter intervals to re-irradiation (< 20 months) and larger re-irradiated PTVs (> 100 cc) were independent predictors of developing severe long-term toxicity
Phan 2016	Osteonecrosis (3) G-tube dependency (10)	CTV volume > 50 cc associated with grade 3 acute and late toxicities and G-tube dependency
Romesser 2016	Dysphagia (7.1) CB (2.9)	Both patients experiencing CB were without evidence of disease on PET imaging
Guan 2016	Massive hemorrhage CCRT group(8.8), RT group (34.3) Mucosal necrosis CCRT group(23.5), RT group (37.1) Radiation encephalopathy CCRT group(11.8), RT group (14.3) Trismus CCRT group (0), RT group (14.3) Cranial nerve palsy CCRT group(5.8), RT group (11.4)	The incidences of nasopharyngeal hemorrhage and trismus were significantly lower in the concomitant chemoradiotherapy group than in the radiotherapy alone group
Takiar 2016	Osteonecrosis (5.7) Trismus (1.4) G-tube dependency (5.7) Fistula (1.8)	Patients with CTV retreatment volume ≥ 50 cc were more likely to experience grade 3 toxicity; those who received concurrent chemotherapy were more likely to experience grade 4 toxicity
Ahlawat 2016	Dysphagia (22.9) Trismus (18.7) Pharyngeal stenosis (10.4) Osteonecrosis (6.2)	Accepted PRV spine and PRV brainstem cumulative doses = 50 and 54 Gy, respectively Cumulative dose to carotid arteries was kept below 120 Gy
Bots 2017	Osteonecrosis (5.8) CB (2.2)	The median cumulative radiation dose to the late complication sites was 114 Gy (range 94–130 Gy) In the 5 patients who developed mandibular ORN, the dose range was 104–128 Gy The actuarial 5-year mandibular necrosis rate for patients receiving ≥ 100 Gy to the mandible group was 27%
Chan 2017	Dysphagia (26.3) Trismus (7.9) Soft tissue necrosis (21) Hearing loss (44.7)	An inverse relationship between cumulative BED to the temporal lobe and the time of TLN manifestation was observed;no TLN was registered with a cumulative BED < $150\ Gy_{2.5}$
Margalit 2017	Cord paralysis (18) CB (9.3) G-tube dependency (69) Soft tissue necrosis (19)	Postoperative re-irradiationafter surgical salvage was statistically significantly associated with a decreased risk of serious toxicity; trend for increased toxicity in hypopharynx/larynx
Vargo 2018	CB (1)	The 2-year cumulative incidence of grade ≥3 late toxicity was12.4% in the IMRT cohort compared with 11.6% in the SBRT cohort (P = NS)
Choy 2018	Dysphagia (6.3) Trismus (3.2) Soft tissue necrosis (3.2) Hearing impairment (3.2)	Of 63 evaluable patients, 14 (22%) showed clinically significant late toxicity;no grade 5 toxicity was observed and no association with severe late toxicity was identified

(*continued on next page*)

Table 2 (*continued*)

First author, year of publication	Late grade ≥ 3 toxicity (%)	Additional data-possible related factors-dose limit recommendation
Ward 2019	Esophageal Stricture (4.6) Feeding tube dependence (new and persistent) (4.3) Osteoradionecrosis (3) Aspiration (2.8) CB (1) Fistula (0.4)	A multivariable competing-risk model was fit to the actuarial risk of late toxicity with progression or death as the competing risk;the final model included six clinical factors (first RT dose, organ dysfunction, surgery, tumor site, age, recurrence vs. second primary);dose, volume and fractionation did not significantly impact toxicity

Abbreviations: CB,carotid blowout; PT, proton therapy; SBRT, stereotactic body radiation therapy; 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; CCRT, concomitant radiochemotherapy; RT, radiotherapy; CTV, clinical target volume; PRV, planning at-risk volume; TLN, temporal lobe necrosis; BED, biological equivalent dose; NS, insignificant.

- Re-irradiation fractionation schedules are not standardized, and various schemes (conventional fractionation, hyperfractionation, SBRT, brachytherapy) were reported in the retrieved studies. A superiority between treatment fractionation in terms of reduction of severe toxicity could not be found; however, in the pivotal American series, the first to provide a toolkit toidentify prognostic categories for patients receiving re-irradiation with both SBRT and IMRT [29], grade ≥4 acute toxicity was greater in the IMRT group than in the SBRT group (5.1% vs. 0.5%, $P < 0.01$), with no significant difference in late toxicity. On the other hand, IMRT was associated with improved OS ($P < 0.001$) for patients > 2 years from the first treatment with unresected tumors or < 2 years from the first treatment and without organ dysfunction (Class II patients, those with an interval between radiation treatments < 2 years and without feeding tube or tracheostomy dependence).
- Extreme caution should be taken when proposing re-irradiation with SBRT if recurrences are located very close to critical structures. Indeed, SBRT delivers highly precise doses to (small) high-risk volumes, thus normal tissues embedded within the targets or adjacent to them are assumed to receive similar ablative doses to those received by the tumor. It is also well known that the fraction size represents the main factor in determining late effects, impairing sublethal damage repair processes [45]. As recommended by Roman et al. [46], who recently developed an algorithm to help the

Table 3
Studies reporting carotid blowout events.

First author, year of publication	CB incidence (%)	Time interval between the end of re-irradiation and CB	Additional data-possible related factors-dose limit recommendation
Kramer 2005	2 (5.2)	16, 18 mo	/
Langer 2007	2 (1.9)	9, 14 mo	/
Biagioli 2007	1 (2.4)	6 mo	/
Janot 2008	1 (1.6)	1 mo	/
Iseli 2009	5 (6)	7.2 mo	1 grade 5,three carotid ruptures followed surgery and re-irradiation;two carotid ruptures followed re-irradiation without salvage surgery
Watkins 2009	3 (7.6)	54 days, 17 mo	Site of re-irradiation (1 patient): larynx
Popovtzer 2009	2 (3)	Not reported	Patients had unresectable neck nodal metastases and received a cumulative RT dose of 140 Gy to the carotid artery
Garg 2013	1 (2)	6 mo	Tumor encased the carotid artery and tumor-related injury cannot be ruled out as a cause of this complication
Chen 2013	6 (11.5)	Not reported	Site of re-irradiation: nasopharynx All patients experienced mucosal necrosis
Yazici 2013	11 (14.6)	Not reported	Every-day SBRT median dose > 34 Gy > 180° carotid entrapment
Tian 2014	Group A 11 (18.6) Group B 18 (31)	Not reported	Site of re-irradiation: nasopharynx Group A = patients received 60 Gy in 27 fractions Group B = patients received 68 Gy in 34 fractions
Duprez2014	2 (3.3)	≥6 mo	125 and 129 maximum cumulative dose
Buglione 2015	4 (5.3)	3 acute, 1 at7 mo	120,126,120,140 lifetime dose
Xiao 2015	50 (17.2)	Not reported	Site of re-irradiation: nasopharynx Mucosal necrosis or massive hemorrhage represented the cause of death in 8 (10%) and 49(23%) patients with tumor volume < and ≥ 22 cc, respectively
Curtis 2016	1 (2)	Not reported	Nonfatal carotid artery bleeding aneurysm, successfully treated with embolization
Romesser 2016	2 (2.9)	Not reported	PT study, both patients experiencing CB were without evidence of disease on PET imaging
Guan 2016	CCRT group 3 (8.8) RT group 12 (34.3)	Not reported	Site of re-irradiation: nasopharynx The incidence of nasopharyngeal hemorrhage was significantly lower in the concomitant chemoradiotherapy group than in the radiotherapy alone group
Bots 2017	3 (2.2)	Not reported (late)	128–130 maximum cumulative dose
Margalit 2017	7 (9.3)	8.3 mo	4 grade 5, 2 patients were without evidence of disease
Vargo 2018	4 (1)	> 3 mo	2 in the IMRT cohort and 2 in the SBRT cohort
Ward 2019	5 (1)	Not reported	/

Abbreviations: CB, carotid blowout; PT, proton therapy; SBRT, stereotactic body radiation therapy; IMRT, intensity modulated radiotherapy; CCRT, concomitant radiochemotherapy; RT = radiotherapy.

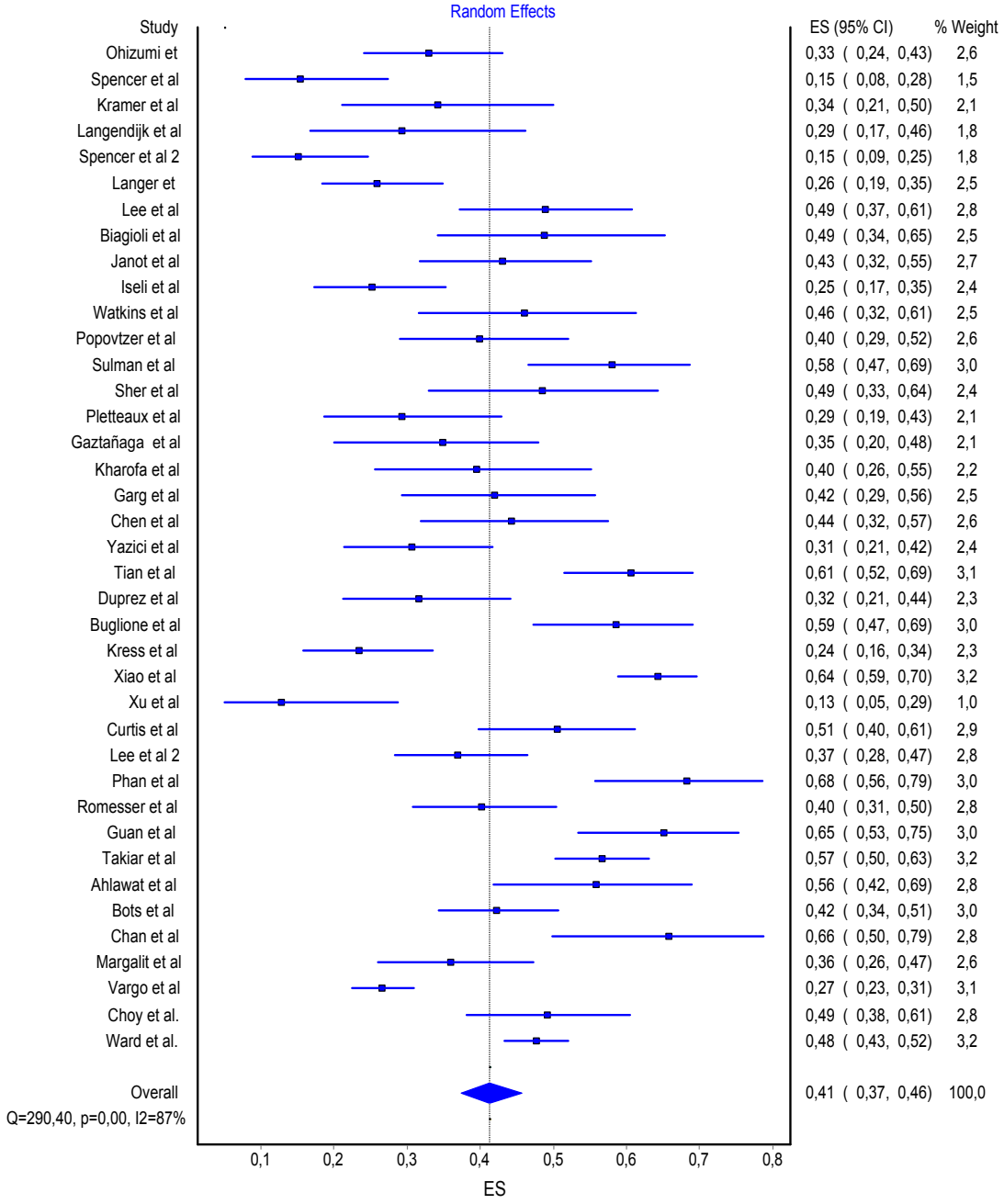

Fig. 3. Pooled objective 2 y overall survival in re-irradiated patients for included studies. Abbreviations: Q: cochran's *Q*-statistic, I2: *I2*-statistic (both are used to evaluate heterogeneity across studies), ES: Effect Size.

radiation oncologist community in choosing a local RT approach in recurrent HNC patients, IMRT rather than SBRT should be adopted with tumors located in the vicinity of neurological structures or a carotid artery. Similar suggestions came from the work of Yazici et al. [27], who recommended using IMRT instead of SBRT if the dose to the carotid artery exceeded 34 Gy, or if the tumor invaded more than 180° of the carotid artery. Regarding SBRT fractionation, the same author reported a reduced risk of severe toxicity by shifting from sequential SBRT to an every-other-day protocol.

In the selected studies, the most common grade 3–4 late toxic effects were radionecrosis, dysphagia requiring feeding tube placement and trismus.

For such events, specific suggestions regarding OARs tolerance and re-irradiation recommendations could be retrieved from some of the selected studies. In the study of Chan et al. [47] regarding recurrent nasopharyngeal cancer patients, the actuarial rate of temporal lobe necrosis (TLN) ≥ grade 3 at 3 years was 24.2%. An inverse relationship between TL 1 cc lifetime biological equivalent dose (BED) and the time of TLN occurrence was noted. Of note, no TLN was observed with lifetime 1 cc BED < 150 $Gy_{2.5}$.

In the study of Bots et al. [43], 8 patients (5.8%) developed osteoradionecrosis (ORN) following re-irradiation, with a median cumulative dose of 114 Gy (range, 94–130 Gy). The dose range to the mandible for the 5 patients developing mandibular ORN was 104–128 Gy.

Garg et al. [48] examined dosimetric characteristics of HNC patients treated with re-irradiation. No clear relationship was found between composite dose to the constrictor muscles and the risk of severe dysphagia requiring a feeding tube. On the other hand, composite doses of

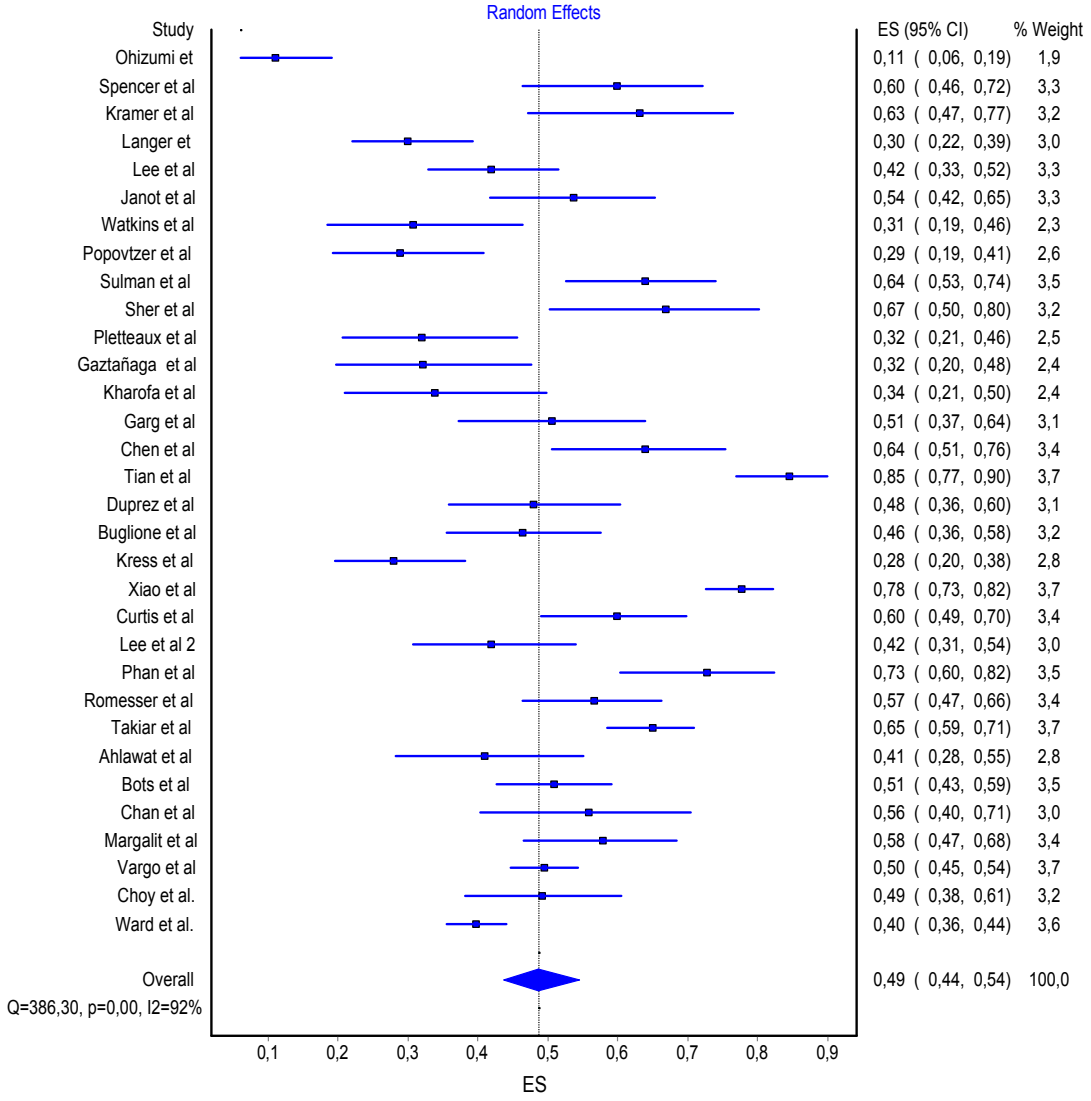

Fig. 4. Pooled objective 2-year local-recurrence-free survivalin re-irradiated patients for included studies. Abbreviations: Q: cochran's *Q*-statistic, I2: *I2*-statistic (both are used to evaluate heterogeneity across studies), ES: Effect Size.

patients experiencing esophageal strictures were all above the third quartile compared with others in the patient population.

Death related to re-irradiation toxicity can also occur; in our analysis, a low risk (< 5%) of grade 5 toxicity was detected. Most of the deaths were caused by fatal hemorrhage caused by carotid blowout (CB). CB indeed represents a catastrophic and life-threatening potential consequence of HN re-irradiation, with limited salvage treatment options and high rates of mortality [49].

Currently, there is a lack of dosimetric constraints to apply to re-irradiated carotid arteries in order to reduce the risk of CB. The majority of the studies analyzed in the present work did not apply constraints to the carotid arteries, considering the risk of these toxicities "unavoidable".

In our analysis, 21 out of the 39 studies reported at least one event of fatal arterial bleeding; the global incidence of blowout in these studies was around 6%. Although clear dosimetric constraints to avoid the risk of CB could not be retrieved, some interesting recommendations could be discussed (Table 3):

- In our analysis, 107 out of the 156 bleeding events (68.5%) occurred in re-irradiated nasopharyngeal cancer patients. The risk of bleeding after nasopharyngeal re-irradiation is higher than the overall low rate reported when considering all HN subsites [50]. This finding could have several explanations, such as the close proximity of the internal carotid artery to the nasopharyngeal mucosa, the existing association between skull base osteoradionecrosis and the risk of blowout [51], the curative intent of re-irradiation with the use of high doses, and the longer life expectancy (and the consequent higher risk of developing late toxicity) of re-irradiated NPC patients compared with other HN subsites [41].
- The study of Yazici et al. [27] regarding the use of SBRT for inoperable recurrent HNC reported a CB rate of 14.6% (11/75). CB did not occur with a maximum carotid dose < 34 Gy in 5–6 fractions. CB was also not observed in patients with lesions entrapping < 180° of the carotid arteries.
- As for conventional fractional studies, Tian et al. [15] randomized a total of 117 patients with locally recurrent nasopharyngeal carcinoma to two different models of total dose and fraction size (Group A, 60 Gy in 27 fractions vs. Group B, 68 Gy in 34 fractions). The incidence of massive hemorrhage in Group B patients was significantly higher than in Group A patients. In the study by Garg et al. [48], the authors reported the chances of developing a carotid blowout at a maximum dose of < 120 Gy and > 120 Gy as 4.6%. 13.3% at 6 months and 5.9%. 25% at 12 months, respectively. Of

note, the power of this finding is limited by the paucity of events (one case of CB in which a tumor-related injury could not be ruled out as the cause of the complication) and the small sample size. In the other studies, no specific dosimetric constraints were suggested. Of note, in the selected studies with conventional fractionation, the median lifetime doses for patients who died from fatal bleeding was 126 Gy [30,43,48,52]. The value of 126 Gy is below the therapeutic cumulative dose that should be given to the tumor for an effective re-irradiation treatment, considering a dose of 70 Gy $EQD2_{10}$ for the first course and a dose of 60–66 Gy for definitive re-irradiation [53].

In this context, in the absence of clear dosimetric criteria, or with the inability to ensure both tumor dose coverage and OARs preservation due to tumor-OARs proximity, even with the most advanced radiation technologies [25], and with the goal of decreasing radiation-induced life-threatening injuries (thus increasing cure rates), other therapeutic strategies such as pre–re-irradiation stenting or even occlusion of the threatened artery could be evaluated.

In terms of outcome, the pooled 2-year OS rate of the retrieved studies was 38.5% (95% CI: 34.2–43.5%) and the grade ≥3 late toxicity rate was 28.6% (95% CI: 22.6–36.3%). In our analysis we did not focus on the risk of toxicity at the same 2 year interval. Many patients experienced tumor progression or death before experiencing severe sequelae. Ward et al. [21] analyzed data from 505 re-irradiated patients from nine institutions in order to build a multivariable competing-risk model to assess whether the actuarial risk of late toxicities outweighs the risk of progression or death. They reported that the 2-year incidence of grade ≥3 late toxicities was 16.7% (95% CI 13.2–20.2%), whereas for progression or death it was 64.2% (95% CI 59.7–68.8%). They concluded that, after re-irradiation, the risk of progression or death is approximately four times higher than the risk of radiation-related severe late toxicities.

The advancements in radiation technology and their widespread adoption has allowed an increasing use of re-irradiation for HNC, as demonstrated by the significant population of patients considered in our analysis. Taken together with the high risk of re-irradiation severe toxicity, this suggests the urgent need to improve our knowledge regarding HN OARs tolerance to re-irradiation in order to deliver a safer and potentially more effective treatment.

Our work contributed positively to this need by deeply exploring the HNC re-irradiation literature, focusing on OARs tolerance to find possible recommendations to reduce the risk of complications.

As is already known, in addition to the OARs delivered dose, various patient-related factors such as comorbidities, smoking status and genetic features may act as modifiers of the dose-response curve [54] and therefore could be investigated and placed into multivariable models to predict the risk of a certain toxicity.

The way toward a comprehensive analysis of normal tissue complications in the setting of HNC re-irradiation (a sort of HNC re-irradiation QUANTEC) is open.

Declaration of Competing Interest

No conflict of interest to declare.

References

[1] Lambrecht M, Dirix P, Van den Bogaert W, Nuyts S. Incidence of isolated regional recurrence after definitive (chemo-) radiotherapy for head and neck squamous cell carcinoma. Radiother Oncol 2009;93:498–502. https://doi.org/10.1016/j.radonc.2009.08.038.

[2] Langendijk JA, Bourhis J. Reirradiation in squamous cell head and neck cancer: recent developments and future directions. Curr Opin Oncol 2007;19:202–9. https://doi.org/10.1097/CCO.0b013e3280f00ff8.

[3] Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol 2011;29:739–46. https://doi.org/10.1200/JCO.2010.31.8311.

[4] Maddalo M, Bonomo P, Belgioia L, Bacigalupo A, Donato V, Alterio D, et al. Re-irradiation with curative intent in patients with squamous cell carcinoma of the head and neck: a national survey of usual practice on behalf of the Italian Association of Radiation Oncology (AIRO). Eur Arch Oto-Rhino-Laryngol 2018;275:561–7. https://doi.org/10.1007/s00405-017-4853-8.

[5] Janot F, de Raucourt D, Benhamou E, Ferron C, Dolivet G, Bensadoun R-J, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol 2008;26:5518–23. https://doi.org/10.1200/JCO.2007.15.0102.

[6] Yu KH, Leung SF, Tung SY, Zee B, Chua DTT, Sze WM, et al. Survival outcome of patients with nasopharyngeal carcinoma with first local failure: a study by the Hong Kong Nasopharyngeal Carcinoma Study Group. Head Neck 2005;27:397–405. https://doi.org/10.1002/hed.20161.

[7] Spencer SA, Harris J, Wheeler RH, Machtay M, Schultz C, Spanos W, et al. RTOG 96–10: reirradiation with concurrent hydroxyurea and 5-fluorouracil in patients with squamous cell cancer of the head and neck. Int J Radiat Oncol Biol Phys 2001;51:1299–304.

[8] Langer CJ, Harris J, Horwitz EM, Nicolaou N, Kies M, Curran W, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol 2007;25:4800–5. https://doi.org/10.1200/JCO.2006.07.9194.

[9] Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement - Journal of Clinical Epidemiology n.d. < https://www.jclinepi.com/article/S0895-4356(09)00179-6/fulltext > (accessed May 11, 2018).

[10] Institute of Health Economics|About Methodology Development n.d. < https://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about > (accessed May 11, 2018).

[11] Basic Clinical Radiobiology: International Journal of Radiation Biology: Vol 86, No 11 n.d. < https://www.tandfonline.com/doi/full/10.3109/09553002.2010.496030 > (accessed May 12, 2018).

[12] Julious SA. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe, Statistics in Medicine 1998; 17:857-872. Stat Med 2005;24:3383–4. doi:10.1002/sim.2164.

[13] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.

[14] Guan Y, Liu S, Wang H-Y, Guo Y, Xiao W-W, Chen C-Y, et al. Long-term outcomes of a phase II randomized controlled trial comparing intensity-modulated radiotherapy with or without weekly cisplatin for the treatment of locally recurrent nasopharyngeal carcinoma. Chin J Cancer 2016;35:20. https://doi.org/10.1186/s40880-016-0081-7.

[15] Tian Y-M, Zhao C, Guo Y, Huang Y, Huang S-M, Deng X-W, et al. Effect of total dose and fraction size on survival of patients with locally recurrent nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: a phase 2, single-center, randomized controlled trial. Cancer 2014;120:3502–9. https://doi.org/10.1002/cncr.28934.

[16] Kramer NM, Horwitz EM, Cheng J, Ridge JA, Feigenberg SJ, Cohen RB, et al. Toxicity and outcome analysis of patients with recurrent head and neck cancer treated with hyperfractionated split-course reirradiation and concurrent cisplatin and paclitaxel chemotherapy from two prospective phase I and II studies. Head Neck 2005;27:406–14. https://doi.org/10.1002/hed.20163.

[17] Langendijk JA, Kasperts N, Leemans CR, Doornaert P, Slotman BJ. A phase II study of primary reirradiation in squamous cell carcinoma of head and neck. Radiother Oncol 2006;78:306–12. https://doi.org/10.1016/j.radonc.2006.02.003.

[18] Spencer SA, Harris J, Wheeler RH, Machtay M, Schultz C, Spanos W, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck 2008;30:281–8. https://doi.org/10.1002/hed.20697.

[19] Gaztañaga M, Pagola M, Cambeiro M, Ruiz MER, Aristu J, Montesdeoca N, et al. Comparison of limited-volume perioperative high-dose-rate brachytherapy and wide-field external irradiation in resected head and neck cancer. Head Neck 2012;34:1081–8. https://doi.org/10.1002/hed.21874.

[20] Xu KM, Quan K, Clump DA, Ferris RL, Heron DE. Stereotactic ablative radiosurgery for locally advanced or recurrent skull base malignancies with prior external beam radiation therapy. Front Oncol 2015;5. https://doi.org/10.3389/fonc.2015.00065.

[21] Ward MC, Lee NY, Caudell JJ, Zajichek A, Awan MJ, Koyfman SA, et al. A competing risk nomogram to predict severe late toxicity after modern re-irradiation for squamous carcinoma of the head and neck. Oral Oncol 2019;90:80–6. https://doi.org/10.1016/j.oraloncology.2019.01.022.

[22] Ohizumi Y, Tamai Y, Imamiya S, Akiba T. Complications following re-irradiation for head and neck cancer. Am J Otolaryngol 2002;23:215–21. https://doi.org/10.1053/ajot.2002.124540.

[23] Spencer S, Wheeler R, Peters G, Meredith R, Beenken S, Nabel L, et al. Phase 1 trial of combined chemotherapy and reirradiation for recurrent unresectable head and neck cancer. Head Neck 2003;25:118–22. https://doi.org/10.1002/hed.10178.

[24] Watkins JM, Shirai KS, Wahlquist AE, Stuart RK, Chaudhary UB, Garrett-Mayer E, et al. Toxicity and survival outcomes of hyperfractionated split-course reirradiation and daily concurrent chemotherapy in locoregionally recurrent, previously irradiated head and neck cancers. Head Neck 2009;31:493–502. https://doi.org/10.1002/hed.20986.

[25] Phan J, Sio TT, Nguyen TP, Takiar V, Gunn GB, Garden AS, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;96:30–41. https://doi.org/10.1016/j.ijrobp.2016.03.053.

[26] Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. Int J Radiat Oncol Biol Phys 2016;95:386–95.

https://doi.org/10.1016/j.ijrobp.2016.02.036.
[27] Yazici G, Sanlı TY, Cengiz M, Yuce D, Gultekin M, Hurmuz P, et al. A simple strategy to decrease fatal carotid blowout syndrome after stereotactic body reirradiaton for recurrent head and neck cancers. Radiat Oncol 2013;8:242. https://doi.org/10.1186/1748-717X-8-242.
[28] Kress M-AS, Sen N, Unger KR, Lominska CE, Deeken JF, Davidson BJ, et al. Safety and efficacy of hypofractionated stereotactic body reirradiation in head and neck cancer: Long-term follow-up of a large series: Stereotactic reirradiation in head and neck cancer. Head Neck 2015;37:1403–9. https://doi.org/10.1002/hed.23763.
[29] Vargo JA, Ward MC, Caudell JJ, Riaz N, Dunlap NE, Isrow D, et al. A multi-institutional comparison of SBRT and IMRT for definitive reirradiation of recurrent or second primary head and neck cancer. Int J Radiat Oncol Biol Phys 2018;100:595–605. https://doi.org/10.1016/j.ijrobp.2017.04.017.
[30] Buglione M, Maddalo M, Mazzeo E, Bonomo P, Spiazzi L, Bruni A, et al. Reirradiation in head and neck recurrent or second primary tumor: efficacy, safety, and prognostic factors. Tumori 2015;101:585–92. https://doi.org/10.5301/tj.5000368.
[31] Biagioli MC, Harvey M, Roman E, Raez LE, Wolfson AH, Mutyala S, et al. Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated, recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:1067–73. https://doi.org/10.1016/j.ijrobp.2007.04.057.
[32] Iseli TA, Iseli CE, Rosenthal EL, Caudell JJ, Spencer SA, Magnuson JS, et al. Postoperative reirradiation for mucosal head and neck squamous cell carcinomas. Arch Otolaryngol Neck Surg 2009;135:1158. https://doi.org/10.1001/archoto.2009.161.
[33] Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys 2010;76:S3–9. https://doi.org/10.1016/j.ijrobp.2009.09.040.
[34] Grosu A-L, Andratschke N, Nieder C, Molls M. Retreatment of the spinal cord with palliative radiotherapy. Int J Radiat Oncol Biol Phys 2002;52:1288–92.
[35] Nieder C, Grosu AL, Andratschke NH, Molls M. Proposal of human spinal cord reirradiation dose based on collection of data from 40 patients. Int J Radiat Oncol Biol Phys 2005;61:851–5. https://doi.org/10.1016/j.ijrobp.2004.06.016.
[36] Nieder C, Grosu AL, Andratschke NH, Molls M. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 2006;66:1446–9. https://doi.org/10.1016/j.ijrobp.2006.07.1383.
[37] Das S, Patro KC, Mukherji A. Recovery and tolerance of the organs at risk during reirradiation. J Curr Oncol 2018;1:23. https://doi.org/10.4103/jco.jco_2_17.
[38] McDonald MW, Lawson J, Garg MK, Quon H, Ridge JA, Saba N, et al. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation expert panel on radiation oncology-head and neck cancer. Int J Radiat Oncol Biol Phys 2011;80:1292–8. https://doi.org/10.1016/j.ijrobp.2011.02.014.
[39] Lee JY, Suresh K, Nguyen R, Sapir E, Dow JS, Arnould GS, et al. Predictors of severe long-term toxicity after re-irradiation for head and neck cancer. Oral Oncol 2016;60:32–40. https://doi.org/10.1016/j.oraloncology.2016.06.017.
[40] Xiao W, Liu S, Tian Y, Guan Y, Huang S, Lin C, et al. Prognostic significance of tumor volume in locally recurrent nasopharyngeal carcinoma treated with salvage intensity-modulated radiotherapy. PLoS ONE 2015;10:e0125351https://doi.org/10.1371/journal.pone.0125351.
[41] Takiar V, Garden AS, Ma D, Morrison WH, Edson M, Zafereo ME, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117–31. https://doi.org/10.1016/j.ijrobp.2016.03.015.
[42] Kharofa J, Choong N, Wang D, Firat S, Schultz C, Sadasiwan C, et al. Continuous-course reirradiation with concurrent carboplatin and paclitaxel for locally recurrent, nonmetastatic squamous cell carcinoma of the head-and-neck. Int J Radiat Oncol Biol Phys 2012;83:690–5. https://doi.org/10.1016/j.ijrobp.2011.06.2010.
[43] Bots WTC, van den Bosch S, Zwijnenburg EM, Dijkema T, van den Broek GB, Weijs WLJ, et al. Reirradiation of head and neck cancer: Long-term disease control and toxicity. Head Neck 2017;39:1122–30. https://doi.org/10.1002/hed.24733.
[44] Margalit DN, Schoenfeld JD, Rawal B, Haddad RI, Catalano PJ, Goguen LA, et al. Patient-oriented toxicity endpoints after head and neck reirradiation with intensity modulated radiation therapy. Oral Oncol 2017;73:160–5. https://doi.org/10.1016/j.oraloncology.2017.08.012.
[45] Fowler JF. Dose response curves for organ function or cell survival. Br J Radiol 1983;56:497–500. https://doi.org/10.1259/0007-1285-56-667-497.
[46] Román AA, Jodar C, Perez-Rozos A, Lupiañez-Perez Y, Medina JA, Gomez-Millan J. The role of stereotactic body radiotherapy in reirradiation of head and neck cancer recurrence. Crit Rev Oncol Hematol 2018;122:194–201. https://doi.org/10.1016/j.critrevonc.2017.12.007.
[47] Chan OSH, Sze HCK, Lee MCH, Chan LLK, Chang ATY, Lee SWM, et al. Reirradiation with intensity-modulated radiotherapy for locally recurrent T3 to T4 nasopharyngeal carcinoma. Head Neck 2017;39:533–40. https://doi.org/10.1002/hed.24645.
[48] Garg S, Kilburn JM, Lucas JT, Randolph D, Urbanic JJ, Hinson WH, et al. Reirradiation for second primary or recurrent cancers of the head and neck: Dosimetric and outcome analysis. Head Neck 2016;38(Suppl 1):E961–9. https://doi.org/10.1002/hed.24136.
[49] Chaloupka JC, Putman CM, Citardi MJ, Ross DA, Sasaki CT. Endovascular therapy for the carotid blowout syndrome in head and neck surgical patients: diagnostic and managerial considerations. Am J Neuroradiol 1996;17:843–52.
[50] McDonald MW, Moore MG, Johnstone PAS. Risk of carotid blowout after re-irradiation of the head and neck: a systematic review. Int J Radiat Oncol Biol Phys 2012;82:1083–9. https://doi.org/10.1016/j.ijrobp.2010.08.029.
[51] Chen K-C, Yen T-T, Hsieh Y-L, Chen H-C, Jiang R-S, Chen W-H, et al. Postirradiated carotid blowout syndrome in patients with nasopharyngeal carcinoma: a case-control study. Head Neck 2015;37:794–9. https://doi.org/10.1002/hed.23671.
[52] Duprez F, Berwouts D, Madani I, Bonte K, Boterberg T, De Gersem W, et al. High-dose reirradiation with intensity-modulated radiotherapy for recurrent head-and-neck cancer: disease control, survival and toxicity. Radiother Oncol 2014;111:388–92. https://doi.org/10.1016/j.radonc.2014.04.018.
[53] Caudell JJ, Ward MC, Riaz N, Zakem SJ, Awan MJ, Dunlap NE, et al. Volume, dose, and fractionation considerations for IMRT-based reirradiation in head and neck cancer: a multi-institution analysis. Int J Radiat Oncol Biol Phys 2018;100:606–17. https://doi.org/10.1016/j.ijrobp.2017.11.036.
[54] Orlandi E, Iacovelli NA, Rancati T, Cicchetti A, Bossi P, Pignoli E, et al. Multivariable model for predicting acute oral mucositis during combined IMRT and chemotherapy for locally advanced nasopharyngeal cancer patients. Oral Oncol 2018;86:266–72. https://doi.org/10.1016/j.oraloncology.2018.10.006.