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What is the role of postoperative re-irradiation in recurrent and second primary squamous cell cancer of head and neck? A literature review according to PICO criteria

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ABSTRACT

Re-irradiation has been increasingly offered as a potential effective treatment for head and neck squamous cell carcinoma (HNSCC) loco-regional recurrence as well as second primary tumor in previously irradiated area. This review focused on the role of postoperative re-irradiation (POreRT) in terms of feasibility, toxicity and long-term outcomes in HNSCC patients. The key issue for the research was formulated in two questions according to the PICO (population, intervention, control, and outcomes) criteria. A total of 16 publications met the inclusion criteria for a total of 919 patients; in 522 patients POreRT was performed. POreRT in recurrent and second primary HNSCC seems to be feasible in highly selected patients with

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the intent to guarantee an acceptable LC compared to surgery alone. The optimal RT schedule remains unclear due to the heterogeneity of literature data.

1. Introduction

Loco-regional recurrences frequently occur up to 42% at three years (Lambrecht et al., 2009) in head and neck squamous cell cancer (HNSCC) patients, specifically, in patients with initial locally advanced HNSCC (stages III–IV) (Ang and Sturgis, 2012). After a primary course of curative treatment, two main conditions affect the prognosis and result of challenging management in clinical practice: 1) loco-regional relapses (predominantly occurring within the first two years (Lambrecht et al., 2009); 2) secondary metachronous HNSCC due to an "in field cancerization" of the upper aero-digestive tract (Bosetti et al., 2011; Morris et al., 2011).

In the majority of cases, this clinical scenario occurs within the previous high radiation dose area ("in field" recurrence) (Chao et al., 2003; Eisbruch et al., 2004; Studer et al., 2007) placing clinicians to face an enigmatic question: *to treat or not to treat*? Surgery is considered the standard of care for patients with operable recurrence and good performance status (PS), providing a local control estimated in 25–45% of patients (Parsons et al., 1995; Bachar et al., 2010).

Postoperative re-irradiation (POreRT) could optimize the surgical outcomes in terms of durable disease control. Obviously, acute and long-term RT-related toxicities could dramatically impact on patient's quality of life (Janot et al., 2008; Spencer et al., 2001; Langer et al., 2007).

Over the last years, re-irradiation has been increasingly proposed in highly selected patients with local recurrence/second primary HNSCC. A possible explanation could be related to advances in RT planning and delivery, including the routinely adoption of Intensity Modulated RT (IMRT), Stereotactic body RT (SBRT), Image Guided RT (IGRT). These recent tools allowed Radiation Oncologists to achieve a higher dose conformation on the target volumes and better organs at risk sparing compared to traditional 2D/3D RT delivery. Although, available guidelines (NCCN, 2016; McDonald et al., 2011; Gregoire et al., 2010) suggest the re-irradiation option after salvage surgery for local recurrence/second primary HNSCC, a clear consensus in terms of patients selection, doses prescription and technique is lacking.

Aim of the present literature analysis is to provide a review on efficacy and safety of patients treated with POreRT for locally recurrent and second primary HNSCC.

2. Methods

2.1. Search strategy

The key issue was formulated in two questions according to the PICO (population, intervention, control, and outcomes) criteria (Aslam and Emmanuel, 2010). These questions (see Table 1) have been the subject of a literature search in the following databases and online trial registry from January 1995 to May 2016: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register. Reference lists of retrieved studies were also searched. Titles and abstracts were screened independently by three authors (AM, DA, RM) to determine relevant references to include for full-text review. Search strategy is shown in Table 2.

2.2. Selection criteria for full-text article review

Publications were eligible for inclusion in the full text review if the following criteria were satisfied: (1) published as a full article in peer-reviewed journals; (2) SCC-histology; (3) photon external beam RT techniques with or without concurrent CHT; (4) follow-up of at least one year; (5) at least one of the considered outcomes (efficacy and/or safety) reported; (6) articles written in English language; (7) articles with patients treated radically or postoperatively. The following studies were included: interventional, observational, prospective, retrospective. Exclusion criteria were: (1) Re-irradiation with other modalities than external beam photon RT (brachytherapy, intraoperative RT, hadron therapy) and non-squamous cell cancer; (2) studies with induction CHT prior to surgery and POreRT. A total of 16 publications met the inclusion criteria for a total of 919 patients; in 522 patients POreRT was performed.

2.3. Risk of bias

For each selected study, the risk of bias was independently assessed by two investigators (AM, DA) according to Cochrane Handbook for Systematic Reviews of Interventions (Reeves et al., 2008; Higgins et al., 2011; Higgins et al., 2013).

2.4. Data collection

Data extraction form was validated by the researchers AM and EO. Data were independently extracted by the two researchers.

3. Results

The selected studies analyzed in the present review are shown in Table 3. Key characteristics and description of these studies are summarized in Table 4. The assessment of risk bias is reported in Table 5. One out of 15 selected studies was a Randomized Controlled Trial (RCT) (Janot et al., 2008). Several studies, here analyzed, were methodologically limited by a high degree of selection and detection biases. On the contrary the bias of attrition was less relevant because of the small number of patients enrolled in the selected studies with a low incidence of data lost during the follow-up. Given the large number of events (toxicities and second relapses) in a limited period of follow up, the duration of follow-up did not worsen attrition. The considered outcomes reported in the selected studies are summarized in Table 6.

3.1. Patient population

POreRT was performed in 495 patients. The majority of cases were recurrent HNSCC and non-nasopharyngeal cancers. One hundred ninety-three patients had good Performance Status (ECOG ≤ 2 or was KPS ≥ 70), whereas this information was not available for the remaining patients. In 48% of cases it was clearly reported the absence of late G3 sequelae (according to RTOG scale) after the first course of treatment, in absence of specifics regarding the skin, the soft tissues or the upper aero-digestive tract. The time between salvage surgery and re-irradiation was not specified for the majority of series. The average RT dose received during the first course

Table 1
Research questions according to PICO criteria.

#Query	Population	Intervention	Comparison	Outcomes
#1	Previously irradiated patients with resected local recurrence or second primary SCCHN	Postoperative re-irradiation (+/− chemotherapy)	none	Local/loco-regional control and Overall survival
#2	Previously irradiated patients with resected local recurrence or second primary SCCHN	Postoperative re-irradiation (+/− chemotherapy)	none	Acute and late toxicity Quality of life (assessed using a quality of life instrument)

Table 2
Search strategy: identification of citation to submit for inclusion criteria.

Database	Date searched	#	Search terms	Citations
Embase + Medline	1995- 2016	1	'head and neck cancer'/exp OR 'ent cancer' OR 'orl cancer' OR 'cancer, head and neck' OR 'cervicofacial cancer' OR 'ear nose throat cancer' OR 'head and neck cancer' OR 'head neck cancer' OR 'otorhinolaryngeal cancer' OR 'otorhinolaryngologic cancer' OR 'otorhinolaryngological cancer' OR 'relapse'/exp OR 'relapse' OR 'second cancer'/exp OR 'neoplasms, second primary' OR 'second cancer' OR 'second cancers' OR 'second malignancies' OR 'second malignancy' OR 'second primary cancer' OR 'second primary cancers' OR 'second primary malignancies' OR 'second primary malignancy' OR 'second primary tumor' OR 'second primary tumors' OR 'second primary tumor' OR 'second primary tumors'	301.209
		2	'reirradiation'/exp OR 're-irradiation' OR 'reirradiation'	1.945
		#1 AND #2		712
		4	#3 AND (1995:py OR 1996:py OR 1997:py OR 1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py)	659
Cochrane Library/Cochrane Central Register of Controlled Trials	1995- 2016	#1	'head neck cancer'	4.147
		#2	#1 and 'reirradiation' (filter Publication Year from 1995 to 2016)	5
Manual search				5
Total number of unduplicated citation				667

Table 3
Search results: abstracts screened for eligibility and inclusion of full papers.

Records after duplicates removal: n = 667	
Records screened on title/abstract: n = 64	Records excluded: n = 39
Full text articles assessed for eligibility: n = 25	Full text articles excluded n = 10 (1 wrong population, 9 outcome not differentiated between operated and not operated patients)

Studies included in qualitative synthesis: n = 16.

of treatment was ≥ 60 Gy, with a minimum RT dose delivered of 45 Gy.

In 3 studies the criteria for postoperative re-irradiation were not clarified (Janssen et al., 2010; Salama et al., 2006; Machtay et al., 2004). In the majority of cases, re-irradiation was proposed in case of: i) positive margins (R +), ii) close margins (Vargo et al., 2014; Kasperts et al., 2006; Sulman et al., 2009; Lee et al., 2007; Curtis et al., 2016; Biagioli et al., 2007; Takiar et al., 2016; Benchalal et al., 1995; De Crevoisier et al., 2001; Suh et al., 2008), iii) extracapsular extension (ECE) (Vargo et al., 2014; Kasperts et al., 2006; Curtis et al., 2016; Iseli et al., 2009; Takiar et al., 2016; Benchalal et al., 1995; De Crevoisier et al., 2001; Suh et al., 2008), iv) rT4 stage for laryngeal cancer (Janot et al., 2008), v) bone infiltration and deep infiltration in oral cavity cancer (Janot et al., 2008; Takiar et al., 2016), vi) nodal recurrence exceeding 3 cm (Janot et al., 2008), vii) deep perineural invasion (Kasperts et al., 2006; Curtis et al., 2016; Takiar et al., 2016; Suh et al., 2008).

3.2. Intervention

Sixty percent of patients were treated with 2D or 3D technique (Janot et al., 2008; Janssen et al., 2010; Salama et al., 2006; Kasperts et al., 2006; Iseli et al., 2009; Benchalal et al., 1995; De Crevoisier et al., 2001; Suh et al., 2008), 35% with IMRT (Sulman et al., 2009; Lee et al., 2007; Curtis et al., 2016; Biagioli et al., 2007), the remaining 5% with SBRT (Vargo et al., 2014). In case of POreRT the median total dose was 60 Gy (range, 40–60 Gy). Several RT schedules were adopted: conventional fractionation, conventional fractionation with split, conventional fractionation a week on a week off, conventional fractionation 5 days and 9 days rest, altered fractionation with or without split, SBRT every other day. The median overall treatment time was 6 weeks (range, 1–11 weeks). In sixty-two percent of patients CHT was administered with different drugs and schedules. In the majority of patients the treated volume included the tumor surgical bed with a margin of 1–2 cm, while in 17% of patients margins were not added to the tumor bed (Vargo et al., 2014) or accounting only for the set-up uncertainties (Janssen et al., 2010; Kasperts et al., 2006).

3.3. Comparison

Only one study was a RCT (Janot et al., 2008). This study randomized previously irradiated patients with recurrent HNSCC to receive a wait-and-see approach (WS) or POreRT with concomitant CHT after salvage surgery. In the WS arm, around 50% of patients with a second recurrent (n = 16) were subsequently treated with POreRT concomitantly to CHT. Kasperts at al. (Kasperts et al., 2006) compared the toxicity profile and the quality of life (QoL) of HNSCC patients enrolled in their study with a group treated with POreRT

Table 4
Key characteristics and description of studies included.

Study		Population			Intervention		
			Patients characteristics	Time from first RT and POreRT	Schedule	POreRT total dose	Technique
Janot et al. (2008)	Phase III multicentric trial	130 pts between 1999–2005 (65 re-RT arm, 65 wait and see arm). 60 actually re-irradiated (58 also with cht).	KPS ≥80, Median age not detailed, no pts with ongoing G3 tox fron FCoT	All > 6 months between first RT and re-irradiation	6 cycles with 9-day rest between each cycle (2 Gy day + hydroxyurea 1.5 g/day and 5–fluoruracil 800 mg/m2/day).	60 Gy (range 5–60)	4–6 MV photons, 2D/3D RT
Machtay et al. (2004)	Pilot study	16 pts between 1998–2001 (one pediatric)	KPS ≥70, Median age 58 (7–66), no pts with ongoing G3 tox fron FCoT	All > 6 months between first RT and re-irradiation	Amifostine 500 mg ev every day of RT + accelerated hyperfractionated RT 1.5 b.i.d (6 h interval) to 30 Gy, 1 week split, to total dose 54–60 Gy + Cisplatin 25 mg/m2 days 1–3 of week 1 and 5, 5-Fluoruracil 500 mg/m2 days 1–4 of weeks 1 and 5.	60 Gy (range 54–66 Gy)	No details on RT technique
Benchalal et al. (1995)	Pilot study	19 pts between 1988–1992, 14 had radical surgery, 5 with response > 80% after cht with cisplatin and 5-fluoruracil.	PS ≤ 2. Median age of the 14 operated pts 55 (27–74). Not stated exclusion for pts with sequelae from FCoT.	All > 9 months between first RT and re-irradiation	hyperfractionated 1.2 Gy b.i.d (6–8 h interval)	60 Gy (range 45.6–60 Gy)	Cobalt 60 or Linac photons. 2D RT
De Crevoisier et al. (2001)	Pilot study	25 pts between 1991–1996	84% PS < 2. Median age 58 (35–71), no pts with ongoing G4 tox fron FCoT	91% 6 months between first RT and re-irradiation	6 cycles with 7-day rest between each cycle (2 Gy day + hydroxyurea 1.5 g/day and 5–fluoruracil 800 mg/m2/day)	60 Gy (range 50–70 Gy)	Cobalt 60. 2D/3D RT
Kasperts et al. (2006)	Prospective study	39 pts between 1997–2003	PS non stated. Median age 63 y (44–81), no pts with ongoing G3 (RTOG) tox fron FCoT. 51% recurrent disease, 49% SPC	1y between first RT and re-irradiation for SPT pts, 2y for recurrent pts	conventional fx	60–66 Gy. Median cumulative dose 113 Gy (92 Gy–130 Gy)	Linac photons 6 MV. 3D RT
Salama et al. (2006)	Population study, retrospective	49 pts (tot = 115 including resected and unresected patients) between 1986 and 2001	not separately analyzed	non stated	14-day cycles. cht-RT on days 1–5, 9 days rest. 4–7 cycles.2 Gy die + HU + 5FU+/− third agent or hyperfractionated RT 1.5 gy b.i.d + HU + 5FU +/− third agent	64.8 Gy median (range 7.2–75.2 Gy).	Linac photons 4–6 MV. 2D/3D
Janssen et al. (2010)	Retrospective analysis	20 pts (tot = 75 including resected and unresected patients) between 1987–2009	not separately analyzed	mean time interval 19.4 mo (range 4.8–198.9)	conventional fx +/− cht	Mean 46 Gy (range 20–75 Gy)	Linac photons. 3D RT
Iseli et al. (2009)	Retrospective analysis	38 pts (tot = 87 including resected and unresected patients) between 1992–2007	PS not stated. Mean age 59.6, no patients with ongoing G3 tox from FCoT. 63% recurrent disease, 29% SPC, 8% only neck	All > 6 months between first RT and re-irradiation	split-course altered fractionation with concurrent HU + 5FU or platin. From 2000 more use of platinum-based cht and IMRT.	not stated	3D/IMRT

Table 4 (*Continued*)

Study		Population			Intervention		
			Patients characteristics	Time from first RT and POreRT	Schedule	POreRT total dose	Technique
Biagioli et al. (2007)	Retrospective analysis	17 pts (tot = 41including resected and unresected patients) between 2001–2006. Not differentiated recurrence and SPC.	PS not stated. Median age 63 (range 19–82). Not stated exclusion for pts with sequelae from FCoT.	mean time interval 25 mo (range 6–240)	conventional fx 1 week on, 1 week off with cht	Mean 60 Gy (range 38–60.57)	6 MV photons. IMRT
Curtis et al. (2016)	Retrospective analysis	42 pts (tot = 81 including resected and unresected patients), between 2003–2011. SPC not included	PS not stated. Median age 61 (34–83). Not stated exclusion for pts with sequelae from FCoT.	mean time interval > 12 mo	hyperfractionated RT +/− cht in the majority of cases	74% at least 60 Gy	86% IMRT
Lee et al. (2007)	Retrospective analysis	36 pts (tot = 105 including resected and unresected patients. SCCHN non-nasopharyngeal = 71) between 1996–2005.All rescurrent disease	KPS >/ = 70. Median age 58 (31–84). Not stated exclusion for pts with sequelae from FCoT.	mean time interval 38 mo (range 5–380)	Various schedule. Majority once-a-day RT +/−cht	Median 59.4 Gy (range 30–70)	70% IMRT
Vargo et al. (2014)	Retrospective analysis	28 pts, between 2005–2011. 93% recurrent disease	PS not stated. Median age 66 y (range 42–88). Not stated exclusion for pts with sequelae from FCoT.	median interval 25 mo (range 6–156)	SBRT every other day +/− cetuximab	Median dose 40 Gy (range 25–44)	SBRT
Sulman et al. (2009)	Retrospective analysis	20 pts (tot = 74 including resected and unresected patients), between 1999–2004. Majority SCCHN, majority recurrent disease.	PS not stated. Median age 61.8 y (19.6–84) whole population. Good functional status/physical reserve.	median interval 46 mo (range 2.8–445.3)	conventional fx (cht in only 1 pt)	Median dose 60 Gy (50.8–70)	IMRT
Suh et al. (2008)	Retrospective analysis	12 pts (from a surgical database of patients who received microvascular free flap reconstruction), 3 with protons, between 1996–2007	PS not stated. Median age 64 (range 30–79). Not stated exclusion for pts with sequelae from FCoT.	median interval 16 mo (range 8–140)	mostly conventional fx RT	Median dose 50.5	75% linac photons (3D RT mostly), 25% proton,
Takiar et al. (2016)	Retrospective analysis	80 pts (tot = 173 including resected and unresected patients), between 1999–2014. Majority SCCHN, majority recurrent disease.	73% PS < 2. Median age 60 (range 27–84). Not stated exclusion for pts with sequelae from FCoT.	median time interval 27.4 mo (range 5–388.7)	conventional fx +/− cht	Mean dose 60 Gy	IMRT
Hoebers et al. (2011)	Retrospective analysis	27 pts between 1998–2009 Majority SCCHN, majority recurrent disease.	Median age 60 (range 27–84). Good functional status/physical reserve.	median time interval 3.0 years (range, 0.3–43)	conventional fx +/− cht	Elective areas: 46 Gy, followed by a boost of 14–20 Gy to the high-risk area	IMRT

Abbreviarions: Pts = patients, KPS = Karnofsky performance status, SCCHN = Squamous Cell Carcinoma of the Head and Neck, RT = radiotherapy, FCoT = first course of treatment, mo = months, tox = toxicity, y = years, PNI = perineural invasion, cht = chemotherapy, IMRT = intensity modulated radiotherapy, SBRT = stereotactic body radiotherapy, SPT = s primary tumor, conventional fx = conventional fractionation (2 Gy die), OC = oral cavity, OP = oropharynx.

Table 5
Risk of bias assessment.

Study	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study free of other problems that could put it at a high risk of bias?	Summary assessement
Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Janot et al. (2008)	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Unclear risk of bias
Machtay et al. (2004)	High risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
Benchalal et al. (1995)	High risk of bias	Low risk of bias	High risk of bias	High risk of bias	Unclear risk of bias	High risk of bias
De Crevoisier et al. (2001)	High risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	High risk of bias
Kasperts et al. (2006)	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Salama et al. (2006)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Janssen et al. (2010)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Iseli et al. (2009)	High risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Biagioli et al. (2007)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Curtis et al. (2016)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Lee et al. (2007)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Vargo et al. (2014)	High risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Sulman et al. (2009)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Suh et al. (2008)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Takiar et al. (2016)	High risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	High risk of bias
Hoebers et al. (2011)	High risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	High risk of bias

in the same period but using a different RT schedule. For some endpoints eight further studies (Janssen et al., 2010; Salama et al., 2006; Sulman et al., 2009; Lee et al., 2007; Curtis et al., 2016; Biagioli et al., 2007; Iseli et al., 2009; Takiar et al., 2016) compared patients treated with POreRT with patients submitted to re-irradiation (+/− CHT) without salvage surgery.

3.4. Clinical outcome

The median follow-up was 33 months (range, 12–60 months). Among the considered studies, endpoints (LC and OS) were calculated using different criteria (from the first day of RT, from the end of RT, from the day of surgery, from the day of randomization). Data on LC at 2 years were available in nine studies (Janot et al., 2008; Janssen et al., 2010; Machtay et al., 2004; Vargo et al., 2014; Kasperts et al., 2006; Sulman et al., 2009; Lee et al., 2007; Curtis et al., 2016; Benchalal et al., 1995) (representing around 66% of patients analyzed in the present review) and ranged from 21% to 100% (median 55%). One study (Salama et al., 2006) reported a LC rate of 68% at 3 years (corresponding to 12% of patients analyzed in the current review). In the RCT a statistically significant better LC was found in POreRT patients compared to the control group (Janot et al., 2008).

Five studies (Janssen et al., 2010; Salama et al., 2006; Sulman et al., 2009; Lee et al., 2007; Takiar et al., 2016) compared patients submitted to POreRT with patients treated with re-irradiation alone. Only 2 studies (Salama et al., 2006; Lee et al., 2007) found a statistically significant better LC in resected patients whereas in the other studies (Janssen et al., 2010; Sulman et al., 2009; Takiar et al., 2016) the differences were not significant.

Data on disease free survival (DFS) or progression free survival (PFS) at 2 years were available in 7 studies (51% of patients) (Janot et al., 2008; Salama et al., 2006; Machtay et al., 2004; Vargo et al., 2014; Sulman et al., 2009; De Crevoisier et al., 2001) and ranged between 21% and 81% (median 41%). The median 2-years OS was 48% (range, 24–81%). One study reported a 5-years-OS of 57% (Takiar et al., 2016). In the RCT by Janot et al. (Janot et al., 2008) OS was not improved with the addition of adjuvant CHT/Re-RT but the study was not powered for OS. Data on 2-years OS for patients not surgically treated were available in six studies (Janssen et al., 2010; Vargo et al., 2014; Lee et al., 2007; Curtis et al., 2016; Biagioli et al., 2007; Iseli et al., 2009) and ranging between 8 and 58% (median 37%). One study (Salama et al., 2006) reported a 3-years-OS of 39% in resected patients versus 11% in the not resected group. Only two studies (Salama et al., 2006; Lee et al., 2007) (considering only non-nasopharyngeal SCC) showed a statistically significant better OS in resected and re-irradiated patients (+/− CHT) compared to patients treated with re-irradiation (+/− CHT) without salvage surgery.

Distant metastasis free survival (DMFS) rate was reported in four studies (Janssen et al., 2010; Salama et al., 2006; Vargo et al., 2014; Sulman et al., 2009) ranging between 80 and 92% at 2-years and between 68 and 75% at 3-years, without differences when CHT or Cetuximab were added to POreRT.

Three studies (Kasperts et al., 2006; Curtis et al., 2016; Benchalal et al., 1995) analyzed the spatial correlation between irradiated volumes of POreRT and location of the second recurrence showing an in-field recurrence respectively in 78%, 53% and 100% of cases, respectively.

In the context or re-irradiation, image fusion (rigid or deformable) to better assess the "real" accumulative dose (the contribution of both RT courses in the anatomic region of interest) represents a crucial tool in the decision-making strategy in these patients. Further progress in this field is advocated.

Table 6
Outcomes.

Study	Outcome									
	mean follow-up	End points calculation	LRC	DFS/PFS	OS	DMFS	pattern of failure correlation with re-irradiated volumes	Acute tox/scale	Late tox/scale	QoL
Janot et al. (2008)	33 mo	End points calculated from the date of randomization.	LRC 2y 55% (vs 20% in not POreRT)	DFS 2y 32% (vs 12% in not POreRT)	OS 2y 42% (vs 40% in not POreRT)	not available	not analyzed	28% G3-4 mucositis/pharyngitis, 5% G5 (RTOG scale)	3% G5, 6% G3-4 mucositis, 22% G3-4 fibrosis, 28% G3-4 trismus, 17% osteoradionecrosis, 5.5% pharingeal stenosis, 48% feeding tube. Late tox 2y 40% re-RT arm G3-4 tox vs 10% WS arm (RTOG scale)	not analyzed
Machtay et al. (2004)	35 mo	End points calculated from the first day of RT	LRC 2y 100%, 3y 81%	DFS 2y 81%, 3y 50%	OS 2y 81%, 3y 63%	not available	not analyzed	44% G3 mucositis/pharyngitis (scale CTC.2)	38% G3-4 dysphagia, 31% G3 fibrosis, 12.5% G4 vascular events, 6% G5 fatal stroke (RTOG scale)	not analyzed
Benchalal et al. (1995)	17 mo (range 3–45)	End points calculated from the end of RT	LRC 2Y 43%	DFS 2y 21%	OS 2y 36%	not available	79% in-field.	47% G3 mucositis (author'scale)	16% G3-4 pharynx, 29% G4 fibrosis (moderate to severe tox according to author's scale)	not analyzed
De Crevoisier et al. (2001)	66 mo	End points calculated from the first day of RT	not available	DFS at 2y 36%, at 5y 26%	OS 2y 43%, 5y 36%	not available	not analyzed	52% G3-4 mucositis, 42% G4 dysphagia, 12% G3 dermatitis (WHO scale)	44% G2-3 fibrosis, 20% G4 mucositis, 24% G2-3 trismus, 16% osteoradionecrosis (RTOG scale)	not analyzed
Kasperts et al. (2006)	32 mo (range 3–84)	End points calculated from the day of surgery	LRC 2 y 74%, LRC 3y 74%	not available	OS 2y 75%, OS 3y 65%	DMFS 3y 75%	100% in-field	100% G2 mucositis (RTOG scale)	31% G3-4 fibrosis, 8% G3-4 larynx, 8% G3-4 bone, 3% G3-4 mucosae, 13% feeding tube, 36% G3-4 pharynx/esophagus (RTOG scale)	Qol (EORT QLQ-H&N35, EORT QLQ-C30) no differences in global QoL
Salama et al. (2006)	67 m (range 18.5–158.7)	not stated	LRC 3y 68% (vs 36% in not resected patients)	PFS 3y 51% (vs 19% in not resected patients)	OS 3y 39% (vs 11% in not resected patients)	DMFS 3y 68% (vs 52% in not resected patients)	not analyzed	not separately analyzed	not separately analyzed. None of the 6 carotid blowout were in POreRT patients	not analyzed
Janssen et al. (2010)	8.7 m (range 0.03–94)	End points calculated from the end of RT	LRC 2y 21% (vs 43% in not resected patients)	not available	OS 2y 24% (vs 48% in not resected patients)	DMFS 2y 80% (82% in not resected patients)	not analyzed	not separately analyzed	not separately analyzed.	not analyzed
Iseli et al. (2009)	5 years (range 3.7–8)	End points calculated from the first day of RT	not available	not available	OS 2y 25%, OS 5y 8%	not available	not analyzed	G3-5 acute tox 50% in surgical salvage patients vs 29% in reRt alone (p 0.04). (RTOG/EORTC scale)	70% feeding tube, 33% G4 tracheostomy, 8% carotid rupture, 7% G5. (RTOG/EORTC scale)	not analyzed

Biagioli et al. (2007)	14 mo (range 1–53)	End points calculated from the end of RT	not available	not available	OS 2y 57%, 3y 37% (vs 37% and 25% in not resected patients)	not available	not analyzed	not separately analyzed	not separately analyzed	not analyzed
Curtis et al. (2016)	78.1 mo (range 56–96.8)	End points calculated from the end of RT	LRC 2y 76% LRC 3y 66% (vs 50% and 40% in not resected patients)	not available	OS 2y 53% (vs 48% in not resected patients) (inferior OR fo dose < 60 Gy)	not available	not analyzed	not separately analyzed	2% G4 non-fatal carotid bleeding, 2% feeding tube, 2% G4 bone, 2% G3-4 fibrosis, 2% G4 tracheoesophageal fistula (scale not specified)	not analyzed
Lee et al. (2007)	35 mo (range 2.4–80)	not stated	LRPFS 2y 45% (vs 19% in not resected patients)	not available	OS 2y 36% (vs 12% in not resected patients)	not available	not analyzed	not separately analyzed	not separately analysis	not analyzed
Vargo et al. (2014)	14 mo (range 2–69)	not stated	LRC 2y 42%, LRC 3y 37%	DFS 2y 41%	OS 2y 48%	DC 2y 82%	not analyzed	0% ≥ G3 (scale not stated)	8% ≥ G3 dysphagia (scale not stated)	56% improved/stable overall QoL (validate questionnaire, objective and PR)
Sulman et al. (2009)	25.4 mo (range 0.86)	End points calculated from the end of RT	LRC 2Y 76% (vs 56% in not resected patients)	PFS 2y 68%. PFS 3y 62% (vs 57% and 52% in not resected patients)	OS 2y 68%. OS 3y 62% (vs 58% and 49% in not resected patients)	DMFS 2y 93% (vs 87% in not resected patients)	not analyzed	not separately analyzed	G5 5% (three point author's scale)	not analyzed
Suh et al. (2008)	not stated	not stated	not available	not available	OS 2y 52%	not available	not analyzed	11% G3 dysphagia (RTOG/EORTC scale)	33% G3-4 (RTOG/EORTC scale) glaucoma, dysphagia, osteoradionecrosis, soft tissue necrosis.	not analyzed
Takiar et al. (2016)	22.9 mo (range 0.1–115.4)	Survival endpoints calculated from date of recurrent or second primary diagnosis. Locoregional control calculated from end of RT	LRC 2y 52% OC/OP, LRC 2-year LRC 83% after neck retreatments	not available	OS 5y 57% for SCC	not available	Not analyzed	not separately analyzed	not separately analyzed	Not analyzed
Hoebers et al. (2011)	17 months (range, 0.5–140) for all patients	Event-free survival (EFS), which was defined as survival without disease recurrence and without serious toxicity (CTC superior or equal Grade 3).	LC was 50% at 2 and 5 years.	The DFS was 36% at 2 years and 34% at 5 years.	OS was 42% at 2 years and 34% at 5 years	not available	Loco-regional in 65% of cases,	not separately analyzed	not separately analyzed	Not analyzed

Abbreviations: Pts = patients, RT = radiotherapy, tox = toxicity.

3.5. Toxicity

Acute and late toxicities were reported using different scales: Radiation Therapy Oncology Group (RTOG) (Cox et al., 1995), Common Toxicity Criteria version 2.0 (CTCAE 2.0) (Arbuck et al., 2017), World Health Organization (WHO) (WHO, 1979). Five studies included patients treated both with POreRT and definitive re-irradiation and toxicities-related data were not separately analyzed (Janssen et al., 2010; Salama et al., 2006; Sulman et al., 2009; Lee et al., 2007; Biagioli et al., 2007). Therefore, acute toxicity data were available only for the remaining studies. The rate of severe mucositis and/or dysphagia/pharyngitis (G3-4 according RTOG or CTCAE 2.0) was between 11 and 52% (median 44%).

In the RCT by Janot et al. (Janot et al., 2008) acute treatment-related death was estimated in 5%. In the study by Iseli et al. (Iseli et al., 2009) acute toxic death was 6% for the entire population analyzed.

The most frequent G3-4 late toxicity was fibrosis (range 2–44%) (Janot et al., 2008; Machtay et al., 2004; Kasperts et al., 2006; Curtis et al., 2016; De Crevoisier et al., 2001) and pharynx dysfunction (feeding-tube dependency or stenosis) experienced by 2–70% of patients (Machtay et al., 2004; Vargo et al., 2014; Kasperts et al., 2006; Curtis et al., 2016; Benchalal et al., 1995). In the RCT by Janot et al. (Janot et al., 2008) 48% of patients required enteral nutrition (with feeding tube) at 2-years. Not lethal vascular events occurred in 2–12% of patients (Machtay et al., 2004; Curtis et al., 2016; Iseli et al., 2009). Osteoradionecrosis occurred in 2–17% of patients (Janot et al., 2008; Kasperts et al., 2006; Curtis et al., 2016; De Crevoisier et al., 2001). Late treatment-related death was reported between 3 and 5% (Janot et al., 2008; Machtay et al., 2004; Sulman et al., 2009; Iseli et al., 2009).

Only two studies reported data on QoL (Vargo et al., 2014; Kasperts et al., 2006). Kaspert et al. found that the more general dimension of QoL was similar between the two analyzed groups (re-irradiated versus POreRT patients) although there was a tendency towards an higher incidence of late toxicity and head and neck symptoms in re-irradiated patients. Vargo et al. (Vargo et al., 2014) compared baseline versus post-treatment QoL in 28 patients treated with SBRT POreRT +/− cetuximab. Results showed an improved or stable overall QoL in 56% of cases.

4. Discussion

In regards to the research questions investigated in the present review for POreRT, according to PICO criteria (*see* Table 1), it emerges that: (Query #1) LC ranged from 21% to 100% while median 2-years OS was 48% (range, 24–81%); (Query #2) the most common severe toxicities were mucositis and/or dysphagia/pharyngitis (range, 11–52%), late fibrosis (range, 2–44%) and pharynx dysfunction (range, 2–70%). Quality of life was assessed in the experience by Vargo et al. (Vargo et al., 2014) with an improved or stable overall QoL in 56% of cases.

Several limitations of the studies here analyzed does not permit to obtain further definitive data due to the heterogeneity of patients, treatment characteristics and biases analysis. Nevertheless several considerations and suggestions can be proposed. Patient-, disease- and treatment-related factors (both related to the first course of RT and re-irradiation) are of crucial importance to propose a POreRT to patients with a recurrent or second primary in the head and neck region as emphasized in the available international guidelines, consensus and previous published reviews (NCCN, 2016; McDonald et al., 2011; Ho et al., 2014; Cacicedo et al., 2014; Strojan et al., 2015). Concerning the patient population to candidate a second course of RT, in the majority of the analyzed studies the patient's performance status was considered the main selection criteria for re-irradiation. Concerning the disease related characteristics, few studies reported cancer stages and tumor size at the beginning of the salvage therapy. For definitive re-irradiation it has been reported that patients with smaller carcinoma volume have better prognosis. Additionally, it is recognized that radical surgery compared to a debulking approach is related to better oncologic outcomes (De Crevoisier et al., 1998; Leung et al., 2000). However, in the analysis by Choe KS et al. (Choe et al., 2011), no significant survival difference was found between patients submitted to radical surgery or debulking approach. Another important consideration is that the majority of studies here analyzed were not able to distinguish the outcomes of patients with recurrence and second primary tumor. The criteria for classifying a tumor as a second primary malignancy were first reported by Warren and Gates (Warren Shields, 1932) and, later, modified by the National Cancer Institute (Curtis et al., 2006).

Some authors stated that second primary tumors can have better prognoses than patients with local recurrences probably related to less radiation-resistant clones (Ho et al., 2014; Choe et al., 2011). In order to obtained more information on tumor radio-resistance, detailed data on biological patients' characteristics, such as Human papilloma Virus (HPV status) are of crucial importance. Fakhry and colleagues (Fakhry et al., 2014) stated that tumor HPV status was a strong and independent predictor of OS after disease progression suggesting it to be considered a stratification factor for clinical trials for patients with recurrent or metastatic oropharyngeal cancer. However, in the recent paper by Sweeny et al. (Sweeny et al., 2016) there was no difference in overall survival rates when oropharyngeal recurrent patients submitted to salvage surgery were stratified by HPV status. Additionally, other biological markers, Ki 67, E-cadherin, p53, EGFR, inflammatory infiltrate should be investigated in order to better predict the probability of tumor response to re-irradiation (Hoffmann et al., 2008; Ow et al., 2015; Nguyen et al., 2016).

Villaflor et al. (2011) evaluated the possibility to select patients with potentially curable recurrent or secondary SCCHN through the use of induction CHT. This approach (induction CHT followed by salvage surgery and POreRT) could further increase the acute and late toxicities of re-treatment and, for this reason, it remains investigational.

Two other points need to be discussed: 1) the interval after the previous course of RT, 2) the interval between surgery and POreRT. All the considered studies included patients with at least six months between the two course of RT-treatments. Disease-free interval is a good surrogate of tumor aggressiveness, but its predictive value both for OS and for LC was not confirmed in the analyzed studies (Janssen et al., 2010; Sulman et al., 2009; Curtis et al., 2016; Iseli et al., 2009).

Nevertheless, with longer interval time between the two RT-courses, there is a lower probability to develop severe sequelae (Wong and Spencer, 2008; Hoebers et al., 2011; Chen et al., 2011). In the primary course of RT, it is recognized that POreRT should start within 6–8 weeks after surgery according to the risk profile and any delay have been demonstrated to have a relevant negative impact on clinical outcome (Ang et al., 2001). This parameter (time interval between salvage surgery and POreRT) was not available in the selected studies of the present review and its impact on this subset of patients is therefore unclear. Thus, we suggest to take into account this aspect in future studies on POreRT.

With regard to the first RT-course, total RT dose superior to 60 Gy was administrated only in 54% of the analyzed patients and, except for three studies (Biagioli et al., 2007; Takiar et al., 2016; De Crevoisier et al., 2001) no details on the first course of therapy were available. Therefore, it is unclear whether the patients included in this review reflect the current clinical practice because the curative

treatments for HNSCC have intensified over the years both in terms of delivered RT doses and association with systemic treatments.

The radiation techniques used in these studies can be considered quite outdated today. Globally, it is well recognized that IMRT allowed to obtain an acceptable toxicity profile in HNSCC (Nutting et al., 2011; Mazzola et al., 2014; Mazzola et al., 2016; Mazzola et al., 2015). In the setting of POreRT here analyzed only six studies used IMRT (Sulman et al., 2009; Lee et al., 2007; Curtis et al., 2016; Biagioli et al., 2007; Iseli et al., 2009; Takiar et al., 2016). In one study (Iseli et al., 2009) IMRT allowed to obtained a lower rate of late toxicity compared to previously published studies. Another crucial point is that the analyzing data support the avoidance of large margins to the surgical tumor bed and the prophylactic nodal irradiation, but also suggest that extreme reduction of margins may lead to a higher risk of marginal-miss. Also, the POreRT dose required remains unclear as a dose range of 45–70 Gy was delivered. A trend for better OS, not statistically significant, has been reported with doses superior to 60 Gy (Curtis et al., 2016).

Although brachytherapy have not been included in the current search, we consider this modality could be taken into account in the setting of perioperative re-irradiation (Martínez-Monge et al., 2006).

Finally, the role of CHT associated with POreRT remains unclear, however, the potential advantage of CHT addiction should be weighed against the risk of higher toxicity.

5. Conclusions

Despite the limitations and given the difficulty in performing prospective randomized studies, the available data here discussed for POreRT, allow us to state that: i) after salvage surgery, POreRT should be proposed to highly selected patients with high risk features (i.e. R+, ECE); ii) irradiation should be performed with highly conformal techniques and only when a dose > 50 Gy can be delivered. In regards to the queries investigated according to PICO criteria, it can be concluded that: #1) LC varied from 21% to 100% with 2-years-OS of 48% (range, 24–81%); #2) the most represented adverse events were mucositis and/or dysphagia/pharyngitis (range, 11–52%), late fibrosis (range, 2–44%) and pharynx dysfunction (range, 2–70%). Toxicity should not be underestimated, considering that in some studies death may occur in up to 6,8% of the cases.

Future studies to assess the optimal schedule using advanced radiation techniques and association with CHT or targeted therapies as well as their impact on LC, OS and toxicity and patient's QoL are advocated.

Disclosures

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6.2. Conflict of interest

None.

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