Critical Reviews in Oncology / Hematology 143 (2019) 67–75

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

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

Postoperative radiotherapy (PORT) for early oral cavity cancer (pT1-2,N0-1): A review

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ARTICLE INFO

Keywords:
Early stage oral cavity cancer
Postoperative radiotherapy
Adverse pathological feature

ABSTRACT

Early stage (T1-2, N0-1) oral squamous cell carcinoma (OSCC) has a generally favorable prognostic outcome. However, locoregional recurrences can occur in up to 30–35% of patients, and 20% will eventually die of disease. National and international treatment guidelines do not recommend the use of postoperative radiotherapy (PORT) in a setting of early OSCC, and highlight surgery alone as the standard single modality treatment. Notwithstanding, the negative prognostic impact of some adverse pathological features, such as perineural and lymphovascular invasion, poor differentiation, depth of invasion > 4 mm, and presence of nodal metastasis, is well known. The advantages of PORT in such scenarios are still debated. The aim of this study was to review the more recent literature to provide evidence on the benefits of PORT in the context of early stage OSCC.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common neoplasm worldwide (Bessell et al., 2011). Among head and neck cancers, it represents a major cause of morbidity and mortality, with a 5-year overall survival of 60% (Chinn and Myers, 2015; Sieegel et al., 2014). In the 8th American Joint Committee on Cancer (AJCC) TNM classification system, pT1-2 N0-1 OSCC is considered to be an early (Stage I-II) disease thanks to its favorable prognostic outcome (Amin et al., 2017). However, locoregional recurrences can occur in up to 30–35% of patients (Ganly et al., 2012), and around 20% will eventually die of the disease. This is mainly due to the heterogeneous biologic behavior of these tumors, demonstrating different patterns of invasion and prognostic outcomes in otherwise similar neoplasms (Bhargava et al., 2010; Tsantoulis et al., 2007).This factor, along with the well-known tendency for precocious locoregional progression explains the extremely low salvage rate of recurrent tumors. Nevertheless, numerous reports, and especially the 2018 National Comprehensive Cancer Network treatment guidelines, do not recommend the use of postoperative radiotherapy (PORT) in OSCC patients with pT1-2 N0-1 disease (NCCN, 2018), and highlight the use of surgery alone as the standard single modality treatment.

In locally-advanced head and neck squamous cell carcinoma (HNSCC), the decision to complement surgery with radiotherapy (RT) is usually based on final pathological assessment, which includes an analysis of tumor differentiation (grade), pattern of invasion, presence of lymphovascular (LVI) and perineural invasion (PNI), surgical margins, and nodal status (in case of concomitant neck dissection). In such a clinical setting, the indications for PORT arise from the results of several retrospective studies and 3 randomized trials with small cohorts (only one specific for OSCC) (Kokal et al., 1998; Rodrigo et al., 2004; Mishra et al., 1996). On the other hand, indications for PORT with

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https://doi.org/10.1016/j.critrevonc.2019.08.003
Received 27 July 2018; Received in revised form 20 June 2019; Accepted 12 August 2019

concomitant chemotherapy (CHT) were derived from 2 large randomized trials (Peters et al., 1993; Cooper et al., 2004). Overall, one or more major (M) adverse pathological features (APFs) [i.e., positive surgical margins and extranodal extension (ENE)], as well as minor (m) APFs (i.e., LVI and PNI) have been found to negatively impact survival outcomes. This led to the indication of PORT alone in the presence of mAPFs, and a combination of RT and CHT in the presence of at least one MAPF (Peters et al., 1993; Cooper et al., 2004). Thus, in locally-advanced OSCC, PORT is recommended for patients with locally advanced primary tumors (T3-4), close or positive surgical margins, and evidence of PNI, LVI, multiple positive nodes, or ENE (Brown et al., 2012).

On the other hand, the beneficial role of PORT in preventing recurrence and/or increasing survival in pT1-2 lesions with negative neck or single positive node without ENE, and in the presence of LVI and/or PNI, is much debated. In addition, in this clinical scenario, other mAPFs are also called into question [i.e., poor differentiation and depth of invasion (DOI) > 4 mm]. In fact, a potential prognostic role for these pathological features has been reported by several authors with conflicting results (Brown et al., 2012). The reason for the conflicting evidencemay be attributed to the heterogeneity of OSCCs. Moreover, the prognostic implications of APFs in various subsites and stages of oral cancer have not been clearly determined (Subramaniam et al., 2017). Thus, so far, it is very challenging to identify “high-risk” early oral cancers. As a result, to date, there is no consensus regarding adjuvant treatment when the tumor exhibits these features, or whether RT should be only focused on the primary tumor or both the primary and the neck (Katz et al., 2017). In particular, all decisions in this regard are based on institutional policies, expertise of the multidisciplinary team, and patient preference.

In a previous review on this issue, including 10 studies on early stage OSCC published between 1996 and 2010, the benefit of PORT was supported only by a low level of contradictory evidence (Brown et al., 2012). In addition, the prevalent RT technique used in those studies was two-dimensional or conformal RT, and only a small percentage of patients received postoperative intensity modulated radiotherapy (IMRT). Over the last years, IMRT has been widely implemented into routine clinical practice, in particular in the definitive setting. The capability of IMRT to deliver non-uniform photon fluency from any given position to the treatment beam allows more precise isodose shaping, allowing improved target conformality while partially sparing normal tissues. Data regarding outcomes using IMRT in the postoperative setting, and specifically for the treatment of locally-advanced OSCC, are gradually growing, demonstrating better toxicity profiles without a compromise in disease control compared to previously used RT techniques (Quinlan-Davidson et al., 2017; Studer et al., 2012; Bednarek et al., 2017; Hoffmann et al., 2015; Hsieh et al., 2016).

Therefore, our aim was to perform a review of the most recent literature to get an overall picture of the role of PORT in determining the outcomes of early stage OSCC, possibly finding a common ground in terms of its indications. Finally, we focused our attention on technique, RT dose, and target volumes to provide specific recommendations on these technical aspects.

2. Materials and methods

This review was designed and developed according to the PRISMA guidelines (Liberati et al., 2009).

2.1. Search strategy

We formulated a key issue reflecting the participants, interventions, comparators, outcomes and study design (PICOS) approach (see Table 1), and made it the subject of our literature search. We queried the Medline database, for all entries up to April 2018, for the period 2010–2018. The key entries for research were: 1) early oral cavity cancer AND radiotherapy; 2) oral cavity AND postoperative radiotherapy; 3) adjuvant radiotherapy AND early oral cavity cancer; 4) radiotherapy AND oral cavity cancer T1-2; and 5) treatment of early oral cavity cancer.

Table 1
Key issues according to the PICOS approach.

Participants	Early OSCC patients undergoing surgery (pT1-2)
Interventions	PORT
Comparators	No PORT
Outcomes	Local/locoregional control or overall survival or disease free/specific survivals
Study designs	Retrospective studies

Once we identified the relevant studies through title and abstract, the publications were screened in 2 steps using specific exclusion and inclusion criteria. The aim of the first step was to exclude any title and abstract that was clearly not relevant, while retaining those that were possibly relevant to the research question. For inclusion in the study sample, full-text screening was performed on retained articles, and publications were included if they met all of the following criteria: 1) full-text publication in English; 2) prospective or retrospective study comparing surgery alone and surgery plus PORT (both cohort studies and matched pair case-control studies); 3) participant selection limited to clinical or pathological early stage OSCC, with or without pN1 category; 4) study evaluating at least one mAPF with or without MAPFs; 5) study outcomes including patient survival or recurrence. Studies featuring Stages other than I and II were considered only if the early stage cohort was subject to a separate subgroup analysis. We did not consider those papers focusing on the impact of APFs without any comparison between surgery and surgery plus PORT or that provided no details about total RT dose. Additionally, in cases of multiple publications from the same group, only studies that reported data from non-overlapping time periods were included.

2.2. Data collection process

Two authors collected data independently by using a data extraction template, with a third serving as a tiebreaker when consensus was not reached. For each study, the information collected included observation period, number of OSCC patients, site, type of APFs, treatment (with particular attention given to the radiation technique, dose, and field applied), clinical outcome in terms of overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), local (LC), loco-regional (LRC), and regional control (RC).

3. Results

3.1. Literature search

The primary search retrieved 5958 articles. Once we identified the relevant studies through title and abstract information and removed duplicates, 73 studies were selected for full-text evaluation. Of these, 15 met the requirements and were included in the systematic review. We considered evaluable two papers by the same group since a different study population was included and a different analysis performed (Barry et al., 2015, 2017). The PRISMA search flow diagram is presented in Fig. 1.

All papers were retrospective in nature. The overall study period ranged from 1983 to 2015. The majority of these were cohort studies and only one included case-matched patients (Ganly et al., 2012). Thus, while we did not rigorously assess and report on the risk of bias and methodological quality of included studies, they were all considered to be at high-risk of bias. Of these, 4 papers were limited to oral tongue cancer, whereas the other 11 examined OSCC at all oral cavity sites. Twelve studies were limited to patients with early (Stages I-II) disease and the remaining 3 also included patients with advanced lesions. The

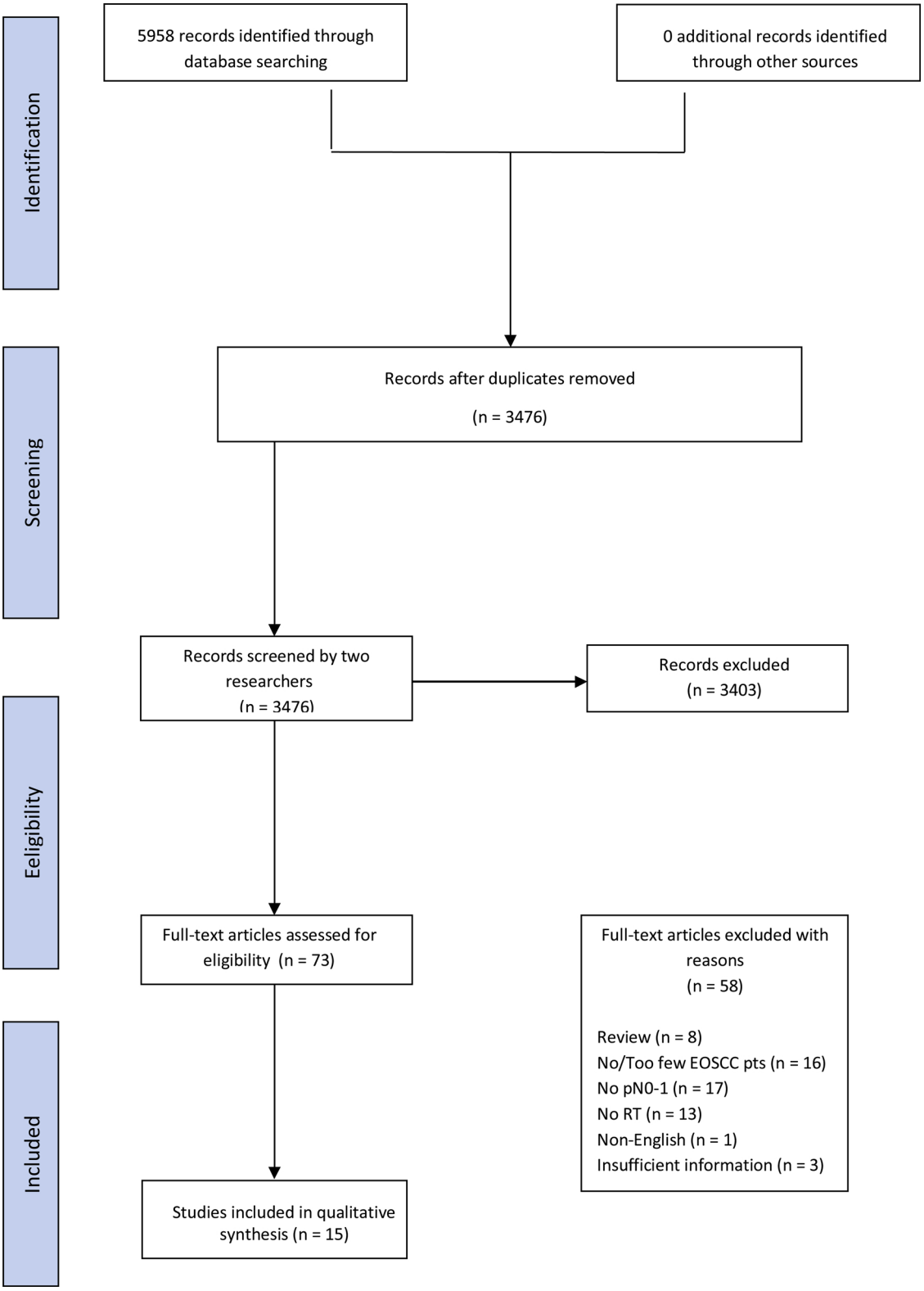

Fig. 1. Study flow diagram.

majority of patients underwent primary tumor resection and concomitant neck dissection. With regards to RT, few studies specifically reported on technique, fields, and radiation dose. There was a wide variability in the criteria used to administer adjuvant RT. The most frequent were PNI/LVI, close/positive margins, and N1 lesions. Median follow up ranged from 24 to 70 months.

The main characteristics and intervention details of the selected studies are reported in Table 2.

3.2. APFs: impact on the outcome

3.2.1. Multiple APFs

Three studies compared patients with different APFs who received PORT and those with APFs who were treated by surgery alone. In a

Table 2
Characteristics and intervention details of the selected studies (N = 15).

	Authors	Type of study	Period	N. of patients	c/pTN stage	Site	Risk Factors Included	Type of Surgery	Radiotherapy technique	RT dose	Radiotherapy fields
1	Katz et al. (2016)	Retrospective	1997-2012	48 (12 S + PORT 36 S)	pT1/T2, N0	Tongue	PNI, close margins, DOI > 5 mm, poor differentiation	T + N	IMRT	54-60 Gy	T and/or N
2	Chatzistefanou et al. (2014)	Retrospective	2005-2011	78 (30 S + PORT 48 S)	pT1/T4, N0/1	Oral cavity	PNI	T +/- N	n.a.	50-70 Gy	n.a.
3	Singareddy et al. (2016)	Retrospective	2012-2014	40 (27 S + PORT 13 S)	pT1/T2, N0	Tongue	PNI	T + N	3D CRT or IMRT	60 Gy	n.a.
4	Tai et al. (2012)	Retrospective	2001-2009	307 (62 S + PORT 245 S)	cT1/T2, N0/+	Oral cavity	PNI	T +/- N	n.a.	62 + -2.83-62.8 + - 3.55Gy	T and/or N
5	Chen et al. (2013)	Retrospective	2004-2009	442 (16 S + PORT 426 S)	pT1/T2, N0	Tongue, buccal mucosa, oral areas	PNI, LVI	T + N	n.a.	n.a.	n.a.
6	Gokavarapu et al. (2015)	Retrospective	2010-2012	103 (62 S + PORT 41 S)	pT1/T2, N0	Tongue	DOI 4 mm or greater, Margin status, PNI, Grade, Tobacco	T + N	n.a.	50 Gy	N
7	Dik et al (2014)	Retrospective	2004-2010	200 (39 S + PORT 161 S)	pT1/T2, Nx	Tongue, floor of mouth, cheek	Margins Status	T +/- N	n.a.	66 Gy	n.a.
8	Barry et al. (2015)	Retrospective	1998-2010	295 (114 S + PORT 181 S)	pT1/T2, N+/-	Tongue, FOM, buccal mucosa, maxilla and mandibular gingival, hard palate	Margins Status	T + N	n.a.	n.a.	n.a.
9	Jang et al. (2017)	Retrospective	1996-2012	325 –	pT1/T4, N+/-	Tongue, floor of mouth	Margins Status	T + N	3D CRT or IMRT	n.a.	n.a.
10	Shrime et al. (2010)	Retrospective	1983-2004	1539 (1209 S + PORT 330 S)	pT1/T2, N1	Tongue, floor of mouth, other	pN1	T + N	n.a.	n.a.	n.a.
11	Chen et al. (2016)	Retrospective	2004-2013	1467 OC (740 S + PORT 727 S) 790 OP	pT1/ T2,N1	Oral cavity, oropharyngeal	pN1	T + N	n.a.	n.a.	n.a.
12	Barry et al. (2017)	Retrospective (case-matched study)	1998-2013	318 (57 S + PORT 261 S)	pT1/T2, N1	Oral cavity	pN1, PNI, LVI	T + N	2D or 3D CRT or IMRT	54-64 Gy	T and N
13	Fridman et al (2018)	Retrospective	1970-2011	1257 (355 S + PORT 902 S)	pT1/T2, N0	Oral cavity	Margins Status	T + N	n.a.	40-70 Gy	n.a.
14	Shim et al (2010)	Retrospective	2000-2006	86 (14 S + PORT 72 S)	pT1/ T2,N0/N1	Tongue	Poor tumor differentiation, DOI > 0.5 cm	T +/- N	3D CRT or IMRT	60-65 Gy T 45.6-57.1 Gy N	T and/or N
15	Nair et al (2018)	Retrospective	2012-2015	1524 (1172 S + PORT 352 S)	cT1/T4, N+/-	Oral cavity	PNI	T +/- N	n.a.	n.a.	n.a.

Abbreviations: Ssurgery; PORTpostoperative radiotherapy; IMRTintensity modulated radiotherapy; 3D CRT3D conformal radiotherapy; ppathological; cclinical; PNIperineural invasion; LVIlymphovascular invasion; DOIdepth of invasion; n.a., not available.

study by Katz et al., focusing on tongue carcinoma, there was significant improvement in DFS among 12 patients (25% of the cohort study) with APFs (i.e., PNI, PVI, poor degree of differentiation, DOI > 5 mm, surgical margin < 1 mm) treated by surgery plus PORT compared to surgery alone (complete resection of the tumor and elective ipsilateral supraomohyoid neck dissection). In addition, no locoregional failure occurred among patients with APFs who received PORT that included both the primary site and the neck (Katz et al., 2017).

3.2.2. PNI

Four studies investigated the role of PORT in patients with PNI. Chatzistefanou at al., in a large retrospective study, observed that PNI-positive patients (without other APFs or lymph node involvement) who underwent neck dissection did not benefit from PORT. In fact, PORT did not significantly alter the incidence of local (p = 0.763) or regional recurrence (p = 0.319) in patients with PNI-positive early OSCC (Chatzistefanou et al., 2014). Similar results were reported in the study by Singareddy et al., who also evaluated the role of PORT in pT1-2 N0 oral tongue SCC with isolated PNI. LRC was 88.9% in patients receiving PORT and 76.9% in those treated by surgery alone. Furthermore, no significant differences in DFS were observed between the two cohorts (p = 0.365) (Singareddy et al., 2016). Tai et al. confirmed that PNI remained an independent predictor for nodal metastasis, neck recurrence, and worse 5-year DSS. However, cN0 PNI positive patients who underwent neck dissection did not show improved results with PORT (5-year DSS PORT, 81.3% vs. no PORT, 88.5%; 5-year OS PORT, 71.3% vs. no PORT, 83.8%) (Tai et al., 2012).

On the contrary, Nair et al. found that the addition of adjuvant RT to patients with early node-negative cancer and PNI was associated with a significant improvement in OS (p = 0.022), even though patients treated by PORT had thicker tumors compared to those managed by surgery alone. Therefore, these authors concluded that it may be beneficial to add adjuvant RT in patients with early node-negative cancer with PNI (Nair et al., 2018).

3.2.3. PNI/LVI

A further study demonstrated that PNI/LVI was not a significant risk factor for disease control and OS in early-stage OSCC patients. PORT did not provide any additional benefit to disease control and OS for Stages I-II OSCC patients, pN0, having only these risk factors. Between PNI and/or LVI positive patients with and without PORT, there was no significant difference in either DFS (61.4% vs. 73.3%, p = 0.71) or OS (88.9% vs. 90%, p = 0.96) (Chen et al., 2013). Finally, in the only case-matched study by Barry et al., PORT did not improve LRC for patients with PNI/LVI (p = 0.965).

3.2.4. Close surgical margins

The distance between tumor and surgical margins was also evaluated in 3 studies. Dik et al. analyzed the results of re-resection, PORT, or watchful waiting in the treatment of early stage OSCC in the presence of close or involved margins. No conclusive evidence was found to suggest local adjuvant treatment in case of close margins (≥3 mm) with ≤2 APFs (overall recurrence rate PORT, 13% vs. re-resection, 3% vs. watchful waiting, 2%) (Dick et al., 2014).

Other authors evaluated the impact of surgical margins on local recurrence and reported that close surgical margins (< 5 mm) were not a significant risk factor for local recurrence. PORT did not significantly improve LRC in early-stage OSCC with close margins (surgery alone vs. surgery plus RT; p = 0.259). In particular, close margins did not affect the LC rate in T1 tumors, while they significantly decreased LRC in T2-4 tumors (Jang et al., 2017). Finally, in a very recent international collaborative group including 1257 patients, multivariate analysis showed that PORT significantly improved the outcomes of patients with close/positive margins (OS p = 0.002 and LRC p = 0.03) (Fridman et al., 2018).

3.2.5. DOI

A study investigating the impact of PORT in 103 pT1-2 N0 oral tongue SCC patients with DOI ≥ 4 mm suggested similar locoregional recurrence (OR 4.34 vs. 1.00, p = 0.078) and survival (p = 0.338) rates between patients who received PORT and those who did not (Gokavarapu et al., 2015). A risk group sub-analysis performed by Shim et al. on 57 oral tongue cancer patients with DOI > 5 mm or moderate/poor grade who underwent surgery at the primary site and neck, demonstrated that, although there was no significant difference in local, regional, or distant recurrence rates between the two groups, there was no local failure in patients receiving PORT (Shim et al., 2010).

3.2.6. Single positive lymph node

A significant impact of PORT in patients with early-stage OSCC was found by some authors specifically evaluating patients with a single positive lymph node (pT1-2 N1). In particular, Shrime et al. concluded that PORT was associated with significant improvement in OS in patients with T2 disease (48.8% vs. 32.5%), with the most significant improvement in cancers of the oral tongue (52.3% vs. 37.9%) and floor of mouth (39.9% vs. 17.7%). Improvements in DSS were also seen in patients with T2 disease in the same subsites (Shrime et al., 2010). Finally, Chen et al. examined the outcomes of patients with pT1-2 N1 oropharyngeal squamous cell carcinoma and OSCC without other APFs. They found that PORT was associated with improved survival in this low-risk patient population (HR 0.76, p = 0.004), especially those younger than 70 years (HR 0.77) and those with pT2 disease (HR 0.64, p = 0.003) (Chen et al., 2016).

Clinical results for the selected series are shown in Table 3.

3.3. Radiotherapy technical aspects

Few data were available about the technical aspects of radiation treatment, with scarce specifics on delivered doses, target volumes, and adopted techniques. The most frequently reported parameter was the total radiation dose which, in the majority of cases, was approximately 60 Gy. With regards to the radiation technique, when reported, conformal techniques, including IMRT, were the most frequently adopted. Only one study stated that RT fields included both the primary surgical bed and nodal stations (Barry et al., 2017), while another referred only to nodal areas (Gokavarapu et al., 2015).

4. Discussion

We conducted a review of the most recent literature with the aim of providing evidence on the benefits of PORT in the context of early stage OSCC. The retrospective nature of the majority of selected studies, a large variation in the indications for adjuvant treatment, and a wide heterogeneity in outcome endpoints considered within clinical studies make the role of PORT in such a clinical scenario still conflicting, especially when one or more mAPFs are present. However, starting from these limiting assumptions, still some considerations can be drawn to guide clinicians in an evidence-based management of this group of patients in the postoperative setting.

In patients operated for OSCCs and documented ENE, combined postoperative systemic therapy and RT is the recommended treatment (Peters et al., 1993; Cooper et al., 2004), with level 1 evidence. This has been determined by high-quality data showing that ENE is the leading independent variable influencing LRC in HNC patients, demonstrating a survival benefit with increasing RT doses and concomitant chemo-radiation.

Another essential prognostic factor is, undoubtedly, the positivity of surgical margins. In fact, inadequate surgical resection margins can contribute to increased local recurrence and decreased survival (Hinni et al., 2013). However, when considering patients with positive margins, the indications are less straightforward and should be carefully evaluated according to the individual patient profile. The preferred

recommendation is re-resection, with the aim of completing tumor excision by achieving clear surgical margins. In this view, early OSCC presents the ideal characteristics: 1) in most cases, tumor resection has been performed through a purely transoral approach, leading to easy access to the primary excision site without adjunctive surgical morbidity; 2) a complex reconstruction is seldom needed, since the surgical wound can be frequently closed primarily or left to heal by secondary intention. Therefore, re-resection can be accomplished without the need to remove any sort of tissue transfer potentially hiding the primary surgical field. Of note, PORT with or without systemic therapy should also be considered in patients where re-resection is not feasible, cannot give reliable results, or can lead to significant morbidity.

In case of intermediate-risk features, options may vary according to the specific clinical scenario and include RT with or without systemic therapy (NCCN, 2018). The main adjunctive mAPFs usually considered in such a context are PNI and close margins. PNI has been the most investigated prognosticator in early OSCC. When identified concomitantly to nodal metastases and ENE, the addition of adjuvant therapies is a well-established practice of treatment (Peters et al., 1993; Cooper et al., 2004). On the other hand, decision-making becomes more challenging in case of a pathologically negative neck with clear evidence of PNI at the primary site. Only one study reported on the beneficial effects of PORT on isolated PNI in early OSCC patients (Nair et al., 2018). The largest study available to date still included only 60 patients, 15 of whom were treated by surgery alone and 45 by surgery plus PORT. Patients receiving PORT experienced better OS despite their less favorable risk profile (Nair et al., 2018). The other 3 published studies did not find any positive impact of adding PORT to patients with PNI. Reasons for this lack of efficacy could be found in the advantage already obtained by elective neck dissection in this series, reaching satisfactory LRC and survival and without any negative impact from PNI. The reason why, in the majority of papers, isolated PNI in pN0 patients did not show a negative prognostic impact is proposed by Tai et al.: the elective neck dissection reduces the risk of regional recurrence in PNI positive early OSCC, given that PNI is an independent risk factor for neck recurrence. So, PORT is not indicated in view of the satisfactory LRC and survival.

Finally, a quantitative characterization of the degree of PNI may help in identifying high-risk patients that may benefit from PORT.

Cracchiolo et al reported a local recurrence HR of 4.07 when comparing patients with PNI foci density positive and negative, while regional recurrence HR was 4.32. The risk of distant recurrence was increased 19.40 times when PNI foci density was present (Cracchiolo et al., 2018). In particular, Cracchiolo et al. demonstrated that a high density of PNI foci was predictive of a significantly poorer DSS in a subgroup analysis of T1-2 tumors (n = 336), in both univariate and multivariate analysis. There is even less data assessing the influence of PORT in LVI-positive patients with a negative neck. In fact, LVI is often considered in conjunction with other APFs, making it difficult to isolate the impact of PORT on this particular variable. LVI has a well-known prognostic significance, as recently underlined by Cassidy et al. (2017). The authors found that the presence of LVI in patients with node-negative oral tongue cancer was associated with worse LC and LRC. Furthermore, PNI and LVI frequently arise along with other high-risk features in OSCC, making it difficult to separate the impact of each variable (Jardim et al., 2015; Adel et al., 2015). However, even when they are taken together in pathologically neck negative patients, no benefit from PORT has been reported.

With regards to close surgical margins, extensive data on their prognostic role have been published in the literature on OSCC (Zelefsky et al., 1993; Larsen et al., 2009; Binahmed et al., 2007). Current guidelines define as adequate a margin which is more than 5 mm from the tumor front (Amit et al., 2016). However, some evidence may suggest the use of a reduced cut-off value to adequately differentiate high- and low-risk patients. In fact, a comprehensive analysis by Zanoni et al. (Zanoni et al., 2017) showed comparable results in patients with margin distance between 2.2 and 5 mm, and those with clear margins (> 5 mm). This is aligned with what was also reported by Dik et al. (2014). Most studies are burdened by the methodological variability and subjective nature of margin evaluation, resulting in heterogeneous outcomes and unclear indications. However, it is worth mentioning that the most extensive study on this subject (1257 patients affected by early OSCC) suggested that patients with positive/close margins have poor long-term outcomes. Furthermore, their results showed that adjuvant treatment may be associated with improved survival. In this view, close margins should be considered as an indicator of a less predictable disease extension, thus identifying a category of intermediate-high risk patients needing PORT at least. However, like in case of positive margins, the possibility of re-resection should always be considered.

With regards to DOI, its impact on survival is well-established. Liao and others (Liao et al., 2012) carried out a study on over 1250 patients treated by primary excision and neck dissection that showed a DOI > 4 mm led to worse outcomes and hypothesized that such patients may benefit from PORT. Ebrahimi and coworkers (Ebrahimi et al., 2014) developed new staging models incorporating DOI in the overall tumor categorization. This new paradigm is evident in the last AJCC Cancer Staging Manual which classifies oral cavity tumors as T1 (DOI < 5 mm), T2 (DOI between 5–10 mm), and T3 (DOI > 10 mm) (Amin et al., 2017). This further reinforces the need to find an adequate cut-off value aimed at identifying tumors that may benefit from PORT. However, to date, there is no clear evidence on this matter and DOI should be considered in conjunction with other APFs on a patient by patient basis.

A single positive neck node without ENE and without other adverse features could be an indication to PORT, with benefit found particularly in pT2, oral tongue and floor of mouth subsites, and younger patients (< 70 years old). However, the presence of small T categories and pN1 without any adjunctive risk factor are very rare conditions. A meta-analysis by Moergel et al., also including oropharyngeal cancer patients, was quite inconclusive in that it lacked valid and homogeneous outcome data (Moergel et al., 2011). A European trial designed in 2009 to evaluate the effectiveness of PORT in pT1-2 pN1 OSCC and oropharyngeal cancers with clear resection margins is still unpublished (Moergel et al., 2009). In addition, other nodal-related factors should be taken into consideration in early stage OSCC disease. Among these, lymph node ratio [LNR, number of pathological positive LN (pN +)/total number of excised LNs] has been suggested as a potent prognosticator in OSCC (Patel et al., 2013; Hosni et al., 2017).

According to what was already mentioned, a single isolated mAPF is not sufficient to prescribe adjuvant RT. Importantly, data from Katz and Shim (Katz et al., 2017; Shim et al., 2010) suggest that patients with multiple mAPFs are more likely to have poorer outcomes and to benefit from PORT. A number of other predictive models have been designed for aggressive tumor patterns in early stage OSCC potentially needing PORT. In particular, Almangush et al. proposed a simple histopathological model for the prognostication of survival in patients with early oral tongue SCC based on tumor budding (TB) and DOI (Almangush et al., 2015). TB was defined as the presence of a single cancer cell, small clusters of a single cancer cell, or small clusters of < 5 cancer cells at the tumor invasive front. The cut-off for TB was set at 5 buds (low-risk < 5; high-risk > 5) and for DOI at 4 mm (low-risk < 4 mm; high-risk > 4 mm). The scores of TB and DOI merged into one predictive model. On multivariate analysis, a high-risk score correlated significantly with loco-regional recurrence ($p = 0.033$) and death ($p < 0.001$) in early stage OSCC (Almangush et al., 2015). The authors concluded that this could be a valuable tool to identify patients who require aggressive multimodality treatment.

Similarly, Brandwein Gensler and others collected a number of histological features for a risk-assessment score based on 3 variables: PNI, lymphocytic infiltration at the tumor interface, and worst pattern of invasion at the interface, with a respective score of 0, 1, and 3. This resulted in patients falling into 3 categories: low-risk (0), intermediate-

Table 3
Outcome results of the selected studies (N = 15).

Authors	APFs	Median Follow-up (mos) (range, mos)	Outcome endpoint assessed (S vs PORT)
Katz et al. (2016)	PNI, LVI, close margins, DOI > 5 mm, poor differentiation	70	2 -year DFS 60% vs 100% (p = 0.01).
Chatzistefanou et al. (2014)	PNI	42.7 (24 - 96)	PORT not significantly alter the incidence of local (p = 0.763, OR = 3.387) or regional recurrence (p = 0.319, OR = 4.741) Among patients who did not receive PORT, no statistical significant difference between patient with or without PNI, regarding local (26.3% vs 27.5%, p = 0.923) or regional (10.5% vs 5.2%, p = 0.322) recurrence
Singareddy et al. (2016)	PNI	25 (15 - 32)	LRC 76.9% vs 88.9%. No significant difference in DFS between two groups (p = 0.365)
Tai et al. (2012)	PNI	49.1 (16 - 116)	5 -year DFS 88.5% vs 81.3% (p < 0.0001) 5 -year OS 83.8% vs 71.3% (p < 0.0001)
Chen et al. (2013)	PNI, LVI	46 (4 - 105)	5-years DFS 73.3% vs 61.4% (p = 0.71) 5-years DFS 90.0% vs 88.9% (p = 0.96) LC 13.43% vs 20% (p = 0.69) RC 10.45% vs 6.67% (p = 1)
Gokavarapu et al. (2015)	DOI 4 mm or greater, Margin status, PNI, Grade, Tobacco	41.3	No significant difference in LRR (p = 0.078, OR = 4.34) and survival (p = 0.339).
Dik et al (2014)	Margins Status	60	Total recurrence 2% vs 13%
Barry et al. (2015)	Margins Status	24	PORT is one of the strongest factors predictive of LR (5.5% vs 15.8%, p = 0.004)
Jang et al. (2017)	Margins Status	39 (1 - 184)	PORT did not improve the 5-years LRC in patients with close margins (p = 0.628)
Shrime et al. (2010)	pN1	n.a.	5-years OS 41.4% vs 54.2% (p < 0.001) OS T2 tumors 32.5% vs 48.8% (p < 0.001) OS T1 tumors 56.5% vs 63.4% (p = 0.25) OS oral tongue 37.9% vs 52.3% (p = 0.002) OS floor of mouth 17.7% vs 39.9% (p = 0.003) 5-years DSS 64.3% vs 72.1% (p = 0.12) DSS T2 tumors 57% vs 69.5% (p = 0.03) DSS T1 tumors 76.6% vs 75.3%, (p = 0.35) 5-years DSS T2 tongue cancer 54.3% vs 69.5% (p = 0.32) 5-years DSS T2 floor of mouth cancer 65.6% vs 66.8% (p = 0.36)
Chen et al. (2016)	pN1	62.4 (range: 38.4 - 86.4)	5-years OS 54.4% vs 58.8% (p = 0.007)
Barry et al. (2017)	pN1, PNI, LVI	44.4	LRC 60% vs 84% (p = 0.039), concentrated in the pN1 subgroup (p = 0.036) No difference in OS (p = 0.129) and DSS (p = 0.534)
Fridman et al (2018)	Margins Status	56	Among patients with close or positive margins OS 46.6% vs 61.8% (p < 0.0001); DSS 52.2% vs 64.6% (p < 0.0001); DFS 47.2% vs 51.9% (p < 0.0001); LC 55.5% vs 67.2% (p < 0.0001)
Shim et al (2010)	Poor tumor differentiation, DOI > 0.5 cm	45 m (range: 4 – 99)	There was no statistically significant difference among the recurrence rates (LR 18.% vs 0%, p = 0.107; RR 29% vs 15%, p = 0.252).
Nair et al (2018)	PNI	24	PORT showed improvement in survival (p = 0.022).

APF = adverse pathologic features; S = surgery; PORT = post operative radiotherapy; m = months; LR = local recurrence; RR = regional recurrence ; LC = local control; RC = regional control; OS = overall survival; DFS = disease free survival; DSS = disease specific survival; OR = Odds Ratio ; PNI, perineural invasion; LVI; lymphovascular invasion.

risk (1–2), and high-risk (3–9). PORT was deemed to be effective on LRC only in the high-risk group (Brandwein-Gensler et al., 2005). All these observations underline the need for a more precise definition of the risk level in patients with early stage OSCC undergoing surgical intervention.

Three other issues should be finally discussed. First, PORT is associated with local toxicity that may impact the patients' quality of life (Brown et al., 2007). Thus, patient characteristics should be carefully considered to quantify the expected risk/benefit ratio. Patient age, comorbidities, previous treatments, and risk of second tumors play an important role in the choice of treatment. Second, no biological or genetic stratification is used to guide adjuvant treatment in resected early OSCC. Future treatment approaches as in other non-SCC tumors should be focused on genomic and molecular factors. Several biomarkers have been studied in this disease, but none has been validated; further research in this field is eagerly awaited.

Finally, we found scanty details as for technical aspects, even though we herein support the use of IMRT technique, as reported in national and international guidelines (NCCN, 2018; Merlotti et al., 2014), in order to reduce RT-related toxicity and potentially improve the patients' quality of life. It is important to mention that, even today, an alternative to IMRT or in association with it, is already available, namely interstitial brachitherapy (BRT). This can be offered in T1-3 with close or positive resection margins or LVI. A retrospective study of local tumor excision followed by postoperative BRT with and without external RT has shown excellent LRC (Grabenbauer et al., 2001). However, this technique presents a number of limitations in connection with the radiation primary site to be targeted (i.e., early and superficial well-defined tumor located more than 5 mm from the mandible) and the need of infrastructures and hospitalization within highly specialized centers.

Over the last few years, stereotactic RT (SRT) has gained momentum in the management of selected head and neck cancer scenarios (i.e., re-irradiation and sequential boost in the first course of RT). In both situations the target volumes are small and highly conformal RT doses needed. This may be the case of PORT in early stage OSCC: currently, a GORTEC phase II study is ongoing (2017-039 PHRC-K-16-164), investigating postoperative SRT (36 Gy in 6 consecutive fractions) in early stage oropharyngeal and OSCC with high-risk margins. The first aim of the study was to document severe toxicity (Biau et al., 2017).

Given the debatable indications of PORT in pT1-2 OSCC, there are no formal guidelines for selection and delineation of RT target volumes and prescribed doses. Therefore, recommendations can come from the literature on PORT for HNC. In pN0 patients, we suggest to treat the surgical tumor bed in the presence of PNI without other adverse tumor features. We also suggest to irradiate the primary surgical bed in the

presence of at least two mAPFs. In addition, no RT on nodal levels should be planned when an adequate neck dissection has been performed. In pN1 patients, an ipsilateral nodal volume could be defined including at least lymph nodes of levels IA, IB, IIA, and IIB only for well-lateralized OSCC. A total dose of 66 Gy and 54–60 Gy with conventional fractionation can be administered in presence of M and mAPFs, respectively.

5. Conclusion

No high-quality data can clearly guide the indications for PORT in early stage OSCC. Current evidence prompts the design of dedicated trials aimed at further refining the management of this disease. However, both tumor and patient characteristics should always be assessed in a personalized manner, in order to provide the ideal balance between treatment toxicity and survival outcomes for each individual case. In this view, the development of a more precise biologic classification of early OSCC may help in identifying high-risk patients needing more aggressive treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could constitute a potential conflict of interest.

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