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Topic: State of the Art in the Management of Oral Squamous Cell Carcinoma

The role of radiotherapy in the treatment of oral cavity cancer

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ABSTRACT

Radiotherapy plays a critical role in the treatment of oral cavity squamous cell carcinoma as monotherapy in early stage cancer or combined with surgery and/or chemotherapy in advances ones. Recent developments in the imaging of cancer and radiation technology have allowed developing more precise delivery of treatment with recent data demonstrating improvement in survival and lessening of adverse toxics effects of radiation. This review will focus in the recent advances and current state-of-the-art in radiation oncology both external beam radiotherapy and brachytherapy. As complexity of cancer treatments increases a close coordination between head-neck surgeons and radiation oncologist is needed due to a significant proportion of patients will be treated with combined modality therapy.

Key words:

Radiotherapy; intensity modulated radiation therapy; high dose rate; low dose rate; head neck cancer; brachytherapy

INTRODUCTION

Although surgery is the recommended treatment for oral cavity squamos cell carcinoma (OCSCC),[1] radiotherapy (RT) plays a capital role in the treatment of OCSCC either exclusively or as adjuvant after surgery.

RT may be administered using two techniques, which, in turn, are likely to be combined together in the specific case of OCSCC: external beam radiotherapy (EBRT) and brachytherapy (BT). Usually patients with early stage disease are treated exclusively radical radiotherapy; however, patients with unresectable or advanced disease will receive radiotherapy plus chemotherapy or targeted therapy with monoclonal antibodies against epidermal growth factor receptor (EGFR) in order to enhance the cytotoxic effect of radiation.

The present manuscript is a revision of most important manuscripts concerning a large and extended bibliography has been performed in order to elucidate the current role of RT in the treatment of patients with squamous cell carcinoma of the oral cavity.

Access this article online	
Quick Response Code:	Website: http://www.parjournal.net
	DOI: 10.20517/2347-9264.2016.13

How to cite this article: Cabrera-Rodríguez JJ. The role of radiotherapy in the treatment of oral cavity cancer. Plast Aesthet Res 2016;3:158-66.

Received: *29-03-2016*; **Accepted:** *10-05-2016*

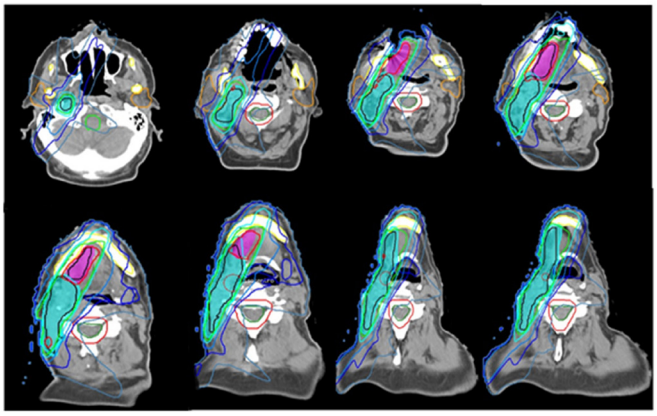

Figure 1: Postoperative intensity modulated radiation therapy plan for an oral tongue squamous cell carcinoma pT2 pN1 M0. High dose encompass risk volumes (blue: ipsilateral nodal bed. purple: tumor bed) while sparing healthy organ: parotids glands (orange) spinal cord (green) mandible and larynx (courtesy of Dr. Enrique Miragall from Fundación ERESA)

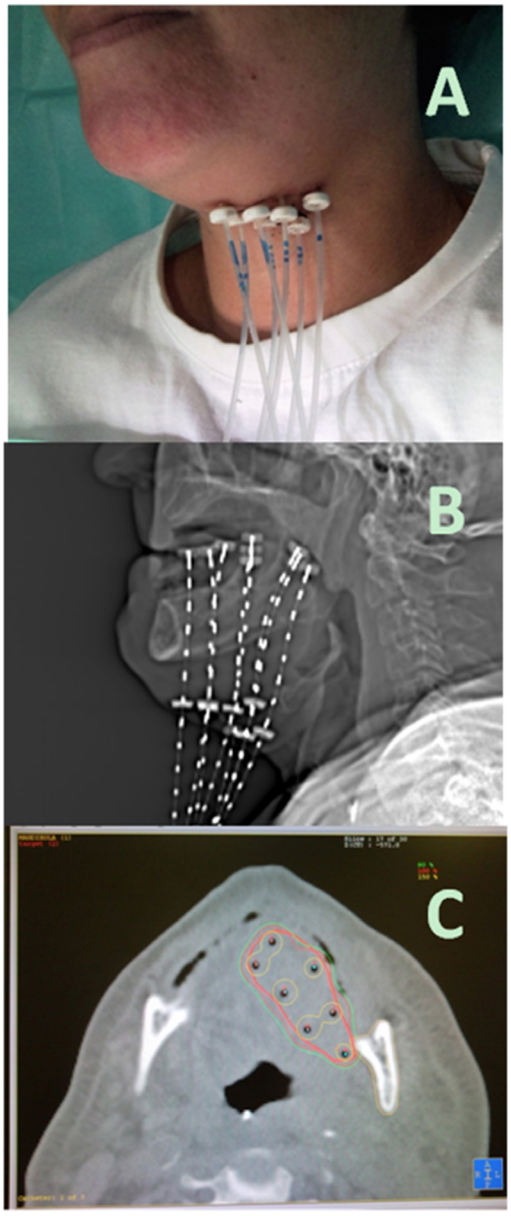

Figure 2: High dose rate brachytherapy for oral tongue carcinoma. (A) showing external outward apperance of percutnaeous catheters for afterloading technique; (B) digital radiographic reconstruction of the implant for planning purposes; (C) computed tomography axial view showing high isodoses lines covering tumor bed but sparing contralateral tongue, mandible and lips (courtesy of Dr. José Luis Guinot from Instituto Valenciano de Oncología)

RADIOTHERAPY TECHNIQUES OVERVIEW

Currently standard EBRT is based on the assessment of target volumes to irradiate and organs at risk to protect in 3D-computed tomography (CT) simulation plus multimodal images (e.g. positron emission tomography-CT, magnetic resonance imaging).[2-6] Delivery of treatment should be based on intensity modulated radiation therapy[7] (IMRT) which involves the use of multiple computer-aided beams of inhomogeneous radiation, allow dose shaping the spatial shape of treatment volume, improving the coverage of target area and the protection of healthy tissue [Figure 1]. When using IMRT different treatment volumes (e.g. macroscopic tumor *vs.* elective nodal levels) receive a different dosage during the same fraction, without increasing the number of RT sessions, so the intensity of treatment is adjusted to each volume of interest by dose gradients.[8] IMRT compared with traditional 2D-EBRT has been shown to improve toxicity[9] and survival[10] in patients with head neck cancer.

Traditionally BT implant has been performed with low dose rate (LDR) by inserting iridium needles (^{192}Ir) mainly; this technique has been gradually displaced by the so-called high dose rate (HDR) BT [Figure 2] due to its advantages of radiation protection of medical personnel, better dose distribution and shorter duration of treatment.[11] However, the accelerated treatment and high dose per fraction used in HDR could lead to a decrease in the therapeutic ratio because of the risk of complications in extreme cases.[12] Liu *et al*.[13] conducted a meta-analysis to compare HDR BT *vs.* LDR BT in the treatment of OCSCC. No statistically significant difference was found in the odds ratio (OR) between the group of patients treated with LDR or HDR in terms of local recurrence OR = 1.12, mortality OR = 1.01, and complications grade 3-4 OR = 0.86.

The equivalent fractionation and total dosing between LDR and HDR is unknown. Neither the Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO)[11] nor the American Brachytherapy Society[14] came to publish a consensus, although they recommended not to exceed a dose 6 Gy per fraction. In the comparative meta-analysis of Liu *et al*.,[13] the mean dose administered was 66.17 Gy in LDR group and 50.75 Gy in the HDR. Radiobiological studies suggest that the optimal dose for exclusive HDR is about 50 Gy[15,16] consistent with data from Liu *et al*.[13] GEC-ESTRO has published recommendations[17] for the calculation of equivalent doses between different protocols and BT techniques.

The main indication for combining EBRT and BT is the need to irradiate the cervical lymph node chains when the risk of involvement is significant due to the primary site,[18] tumor thickness greater than 4 mm[19] and stage cT2-T3.

Stages I-II

In treating early OCSCC the best results were obtained when BT is part of the treatment, either exclusively or as tumor overdose after EBRT.[11] Evidence supporting this practice is based entirely on retrospective series. Even with the advent of IMRT, BT administration is advantageous in terms of shaping and

Table 1: Radical brachytherapy for oral cavity squamos cell carcinoma only, not including other head and neck sites

Studies	No. of patients	Site	Technique	Radiotherapy schedule	5-year local control (%)	5-year survival (%)
Lau *et al*.[12] 1996	27	Tongue	HDR	BT only, 45.5 Gy @6.5 Gy	53	92
Leung *et al*.[22] 2002	19	Tongue	HDR	BT only, 45-63 Gy (median 55 Gy, ten fracions)	94.7 (4-year)	NS
Martínez-Monge *et al*.[23] 2009	8	Oral cavity	HDR	EBRT 45 + BT 16 Gy @4 Gy	86 (7-year)	52.3 (7-year)
Guinot *et al*.[24] 2010	33	Tongue	HDR	EBRT 55 + BT 18 Gy @3 Gy	79	74
	17	Tongue	HDR	BT only 44 Gy @4 Gy		
Inoue *et al*.[28] 2001	25	Tongue	HDR	BT only 60 Gy @6 Gy	87	
	26		LDR	BT only 70 Gy	84	
Yamazaki *et al*.[29] 2003	58	Tongue	HDR	BT only 60 Gy @6 Gy	84	
	341		LDR	BT only 70 Gy	80	
Yamazaki *et al*.[30] 2007	80	Tongue	HDR	EBRT 37 Gy + BT 36-60 Gy	85	
	217		LDR ^{226}Ra	EBRT 29 Gy + BT 59-94 Gy	74	
	351		LDR ^{192}Ir	EBRT 29 Gy + BT 59-94 Gy	72	
Kakimoto *et al*.[32] 2011	14	Tongue (T3)	HDR	EBRT 30 Gy + 60 Gy	71 (2-year)	
	61		LDR	EBRT 30 Gy + 72 Gy	62	
Akiyama *et al*.[33] 2012	17	Tongue	HDR	BT only 54 Gy @ 6 Gy	88	
	34			BT only 60 Gy @6 Gy	88	
Donath *et al*.[34] 1995	13	Oral cavity	HDR	BT only 45-50 Gy @4.5-5 Gy	92	
Inoue *et al*.[35] 1998	16	Floor or Mouth	HDR	EBRT 30-40 Gy + BT 36-48 Gy @6 Gy	94	
	41		LDR ^{198}Au	EBRT 30-40 Gy + BT 65-85 Gy	69	
Matsumoto *et al*.[36] 2013	67	Tongue	HDR	EBRT 20 Gy + BT 50 Gy	94	88.7
Khalilur *et al*.[37] 2011	125	Tongue	LDR	70 Gy	86	
Vedasoundaram *et al*.[38] 2014	33	Bucal mucosa	HDR	BT only 38.5 Gy @3.5 Gy EBRT 50 Gy + BT 21 Gy @3.5 Gy	92.3	
Lee *et al*.[39] 2014	16	Oral cavity	HDR	BT only 50 Gy @5 Gy EBRT 50 Gy +BT 35 Gy @5 Gy	84 (3-year)	70
Tuček *et al*.[40] 2014	20	Tongue	HDR	BT only 54 gy @3 Gy	85	75
Oota *et al*.[25] 2006	433	Tongue	LDR	BT only 70 Gy EBRT 35 Gy + BT 60 Gy	85.6	
Pernot *et al*.[41] 1996	552	Tongue	LDR	BT only 66 - 75 Gy	90.5	71.5
	207	FOM				
Lefebvre *et al*.[42] 1994	429	OC	LDR	BT only 66 Gy	90	
Mazeron *et al*.[43] 1991	279	Tongue & FOM	LDR	BT only 60-70 Gy	87-93	
Marsiglia *et al*.[44] 2002	160	FOM	LDR		88-93	76
Dearnaley *et al*.[45] 1991	149	Tongue & FOM	LDR	BT only	90	
Fujita *et al*.[46] 1999	207	Tongue	LDR	EBRT 30 Gy + BT 50-60 Gy BT only 65-70 Gy	82.2	
Bachaud *et al*.[27] 1994	94	Tongue & FOM	LDR	EBRT 48 Gy + BT 26 Gy BT only 66 Gy	61	
Ihara *et al*.[47] 2005	117	Tongue	LDR	EBRT 30 Gy + BT 65 Gy BT only 70 Gy	59.2	54

@: dose per fraction when HDR is used. LDR: low dose rate; HDR: high dose rate; EBRT: external beam radiotherapy; BT: brachytherapy; OC: oral cavity; FOM: floor of mouth; NS: no shown

uniformity of dose[20] and tumor control.[21] Table 1 summarizes the results of selected series of OCSCC patients treated with radical BT with or without EBRT.[12,22-47] In the case of floor of mouth stage cT1 local control is 93-95% and 72-88% for stage cT2. Local control in cancer of mobile tongue is achieved in 79-97% for stage I and 65-95% for stage II.

Stages III-IV

Usually the treatment of advanced cancer of OCSCC has been included in the group of "advanced head and neck cancer" (AHNC) because of this the indications, techniques and results from clinical trials are fully applicable.

Radiotherapy alone

Modification of EBRT fractionation allows to intensify radiation dose by means of two way: (a) increase in the total dose with hyperfractionation; and (b) shorten the duration of using accelerated fractionation radiotherapy.

Two meta-analyses of randomized trials[48,49] comparing conventional fractionation EBRT (CF-EBRT) against modified fractionation EBRT (MF-EBRT) were published. Bourhis *et al*.[48] analyzes all clinical trials for all locations of the head and neck (12.6% of cases OCSCC), however data are presented separately depending on location; Glenny *et al*.[49] examined trials for oral cavity and oropharynx cancer only.

Bourhis *et al*.[48] found a statistically significant benefit in terms of overall survival (OS) HR = 0.92 in favor of MF-EBRT as well as an improvement in locoregional control (LRC) HR = 0.82. Hyperfractionated EBRT was also significantly better in terms of OS than accelerated EBRT, with an absolute benefit of 8% at 5 years.

Table 2: Risk groups definition according multivariate analysis (recursive partitioning analysis) by Langendijk

		VUMC series		VUMC series	
RPA class	**Definition**	**LRC 5-year**	**OS 5-year**	**LRC 5-year**	**OS 5-year**
Class I (intermediate risk)	Free margins without ECE	92%	67%	82%	60%
Class II (high risk)	T1, T2, T4 tumors with close or positive surgical margins; One lymph node metastasis with ECE	78%	50%	82%	50%
Clase III (very high risk)	T3 tumors with close or positive surgical margins; Multiple lymph node metastases with extranodal spread; N3 neck	58%	37%	63%	36%

RPA: recursive partitioning analysis; LRC: locoregional control; OS: overall survival; ECE: extracapsular extension

Table 3: Adjuvant brachytherapy for oral cavity squamos cell carcinoma

Studies	No. of patients	Site	Technique	RT schedule	5-year local control (%)	5-year-overall survival (%)
Goineau *et al*.[89] 2015	112	Tongue	LDR	EBRT: 60-66 Gy + BT 50-55 Gy	76	56
Petera *et al*.[90] 2015	30	Tongue FOM	HDR	BT only 54 Gy @3 Gy	85.4 (3-year)	73 (3-year)
Lapeyre *et al*.[91] 2004	82	Tongue FOM	LDR	EBRT 48 Gy + BT 24 Gy BT only 60 Gy	81	80
Pernot *et al*.[92] 1995	97	Tongue FOM	LDR	NS	84	79
Fietkau *et al*.[93] 1991	50	Tongue FOM	LDR	EBRT 55 Gy + BT 24.5 Gy	94 (crude)	84 (crude)

@: dose per fraction when HDR is used. RT: radiotherapy; LDR: low dose rate; HDR: high dose rate; EBRT: external beam radiotherapy; BT: brachytherapy; FOM: floor of mouth; NS: not shown

Table 4: Postoperative intensity modulated radiation therapy for oral cancer

Studies	No. of patients	Site	RT schedule	Loco-regional control	Overall surivival
Chan *et al*.[94] 2013	180	Oral		83 (2-year)	65 (2-year)
Hoffman *et al*.[95] 2015	18	Oral cavity	66 Gy IMRT with SIB	78 (5-year)	77 (5-year)
Sher *et al*.[96] 2011	30	Oral	64.13 Gy IMRT secuencial boosting	91 (2-year)	85 (2-year)
Gomez *et al*.[97] 2011	35	Oral	60 Gy IMRT SIB	77 (3-year)	74 (3-year)
Chakraborty *et al*.[98] 2015	75	Oral	IMRT volumetric	88.9 (2-year)	80.5 (2-year)
Studer *et al*.[99] 2012	99 (R0-1) 17 (R2)	Oral (primary + recurrent)	70 Gy IMRT SIB	80 (4-year) 35 (4-year)	79 (4-year) 30 (4-year)
Collan *et al*.[100] 2010	40	Oral	58 Gy IMRT secuential boosting	87.5 (5-year)	75 (5-year)
Geretschläger *et al*.[101] 2012	53	Oral	66 Gy IMRT secuential boosting	79 (3-year)	73 (3-year)
Yao *et al*.[102] 2007	55 (5 p definitive RT)	Oral	66 Gy IMRT SIB	82 (3-year)	82 (3-year)
Daly *et al*.[103] 2011	37 (7 definitive RT)	Oral	66 Gy IMRT SIB	53 (3-year)	60 (3-year)

Most patients receive chemoirradiation. Only include studies about oral cancer or mixed head and neck tumors reporting oral cancer results separately. RT: radiotherapy; IMRT: intensity modulated radiation therapy; SIB: simultaneous integrated boost

Glenny *et al*.[49] reported that MF-EBRT, reduces overall mortality, HR = 0.86, and increased LRC HR = 0.79. Trials included as "purely hyperfractionated" also showed a significant gain in OS compared with the accelerated fractionation HR = 0.78.

Radiotherapy and chemotherapy combination

Pignon *et al*.[50] performed a meta-analysis on benefit of chemotherapy (CMT) added to EBRT in head and neck cancer (MACH-NC). Overall improvement in OS was demonstrated when chemotherapy is added to radiation. Maximum benefit was found when CMT is administered concurrently with EBRT: 5-year OS 8% improvement. The benefit of CRT is applicable to all locations of the head and neck.[51]

Two randomized trials have investigated whether the addition of chemotherapy to MF-EBRT is superior to CRT (CF-EBRT) or MF-EBRT alone.

The French Group of Radiation Oncology of Head and Neck Cancer (GORTEC)[52] randomized patients into three arms: accelerated EBRT alone, CF-EBRT plus CMT or accelerated EBRT plus CMT. No statistically significant difference was found between the treatment groups at 3-year OS: 32.2% *vs*. 37.6% *vs*. 34.1%, nor distant metastasis (DM). However, both locoregional failure (LCF) (49.9% *vs*. 41.7% *vs*. 45.4%) and progression-free survival (PFS) (32.2% *vs*. 37.6% *vs*. 34.1%) were significantly lower in the accelerated EBRT arm. Mucosal acute toxicity and the need for feeding tube were significantly higher in patients treated with MF-EBRT.

In the second study by the Radiation Therapy Oncology Group (RTOG)[53] patients were randomized to MF-EBRT alone or FM-EBRT plus CMT. No statistically significant difference was found in 8-year OS (48% in both arms) LRF (37% *vs*. 39%) PFS (42% *vs*. 41%) or DM (15% *vs*. 13 %) No statistically significant differences in toxicity were found

either. In conclusion, no advantage in combining MF-EBRT and CMT have been proved so far.

Target therapy

EGFR over expression leads to decreased survival and increased risk of local and regional recurrence in head and neck cancer.[54] The inhibition of EGFR by monoclonal antibodies (cetuximab) associated with EBRT in patients with non-operated AHNC showed an increase 5-year OS (46% *vs.* 36%) and LRC (47% *vs.* 34%) compared with EBRT alone.[55] Notably in this trial did not include patients with OCSCC therefore clinical benefit in this group of patients is presently unknown.

Nowadays, the standard of treatment for non-operable AHNC, including OCSCC, is EBRT plus CMT despite the fact that its benefit in OS and LRC probability equals of the hyperfractionated-EBRT. The reasons that have led to this situation are basically two: (1) logistics, due to the consumption of resources and the drawbacks associated with treating patients twice a day, for 7-8 weeks; and (2) the development of high conformation techniques as IMRT, which allow to exploit the different sensitivity to radiation of the tumor and healthy tissues using a single fraction per day with a shorter overall time of treatment, usually 5-6 weeks.

Postoperative radiation therapy

Adjuvant EBRT

The value of postoperative radiotherapy (PORT) for AHNC, was established by Fletcher and Evers[56] and Marcus *et al*.[57] in 1970's. The evidence that proves the usefulness of PORT has been based on retrospective studies of large groups of patients. Due to the inherent bias in such kind of studies the survival benefit of PORT is not fully confirmed, although there are no doubts about the gain in LRC.

Lundahl *et al*.[58] performed a retrospective, matched-pair analysis to compare surgery alone *vs.* surgery plus PORT. They found significant improvement in LRC and OS in the PORT group.

Lavaf *et al*.[59] and Kao *et al*.[60] analyzed patients with AHNC stage III-IV treated with surgery alone or surgery plus PORT from Surveillance Epidemiology End Results (SEER) data base. In multivariate analysis the survival benefit of PORT *vs.* surgery alone at 5-year was significant in both non-locally advanced tumors with lymph node metastasis (51.6% *vs.* 40.6%) as in the case of locally advanced tumors with lymph node metastasis (35.3 % *vs.* 25.2%). Overall PORT significantly improved OS by 11% and cancer-specific survival by 8.6%. They showed a greater reduction in the risk of death in stage N2b-N3 compared to N1-N2a (HR = 0.62, 0.78 and 0.82 respectively). The magnitude of the reduction was larger for tumors of the oropharynx, hypopharynx and larynx compared to oral cavity (HR = 0.72, 0.66 and 0.62 respectively) Patients with lymph node metastasis and any tumor sites, all benefited from the administration of PORT although the gain is greater in high-risk disease.

Whereas PORT is not routinely indicated in patients with HNSCC stage pT1-2 pN1[61] because there is not definitive data supporting that approach. Moergel *et al*.[62] published a meta-analysis of studies in order to elucidate the role of PORT in patients pN1 with oral cavity and oropharynx primaries. Any firm conclusions could be drawn due to the heterogeneity of the studies, although it was evident more mortality (not significant) in the group treated with PORT (44% *vs.* 34%). Shrime[63] analyzed the benefit of PORT in patients with OCSCC pT1-2 pN1. PORT improved OS at 5 years [41.4% *vs.* 54.2% ($P < 0.001$)] of note PORT improved OS in T2 tongue and floor of mouth subgroup [52.3% *vs.* 37.9% ($P = 0.002$) and 39.9% *vs.* 17.7% ($P = 0.003$), respectively] but not significantly in T1 subgroup.

The hypothesis that early nodal metastases may express a more aggressive biology supports adjuvant therapy in stage III.[64]

Risk factors for locoregional recurrence

Extracapsular extension (ECE) in cervical lymph node metastases and the involvement of surgical resection margins (ISRM) are the most important prognostic factors for risk of LRC and death.

RTOG[65] stratified patients treated with PORT into 3 risk groups according to the presence of ECE, 2 or more lymph nodes with metastasis or ISRM. Group I were those with no more than 2 nodes affected without ECE; group II included patients with more than 2 positive lymph nodes or ECE, negative margins; group III comprised patients with ISRM. Significant difference was found in the rate of loco-regional recurrence at 5 years between groups I, II and III of 17%, 27% and 67% respectively and median OS at 5.6 years, 2 years and 1.5 years, respectively.

Langendijk *et al*.[66] conducted a multivariate analysis to define different prognostic groups based on pathologic features a series of 801 patients with AHNC treated with PORT. The final model identified 6 prognostic factors and grouped the patients into 3 risk groups [Table 2]. This model was validated by the Dutch Head and Neck Oncology Cooperative Group (DHNOCG) in a multicenter study.[67]

Nowadays, there is consensus[68] to identify patients at high risk of recurrence after surgery who benefit from PORT: (1) major criteria: ECC or ISRM; and (2) minor criteria: inadequate surgical margins (< 5 mm), ≥ 2 lymph nodes metastases (N2b-N3), stage pT3-T4 even with negative margins, in primary oral cavity, metastases in levels IV and V, presence of PNI or LVI.

Perineural infiltration

One of most controversial point is the value of PORT when there is PNI but the absence of other factors associated with risk of recurrence. Neither in the analysis of Jonkman *et al*.[66] or its further validation,[67] PNI was found to be an independent prognostic factor. Bur *et al*.[69] after a systematic review on the potential benefit of PORT in patients with PNI concluded that there is insufficient evidence to recommend PORT routinely in these cases. The author suggests that in case of infiltration of cranial nerves or multiple PNI, PORT might be justified. PNI is associated with increased risk of nodal recurrence, therefore it is recommended to treat the neck in this scenario.

Time factor in PORT

Evidence exists suggesting that the risk of LRC is higher in patients with AHNC when receiving PORT more than 6 weeks

after surgery,[70] OR: 2.89. Further work[71] confirmed elevated RR 1.28 on LRC and decrease in OS (RR: 1.16) per month of delay. The waiting list to start radiotherapy has negative effect on the prognosis according to a Dutch national study.[72]

The accelerated repopulation during radiotherapy is a cause of treatment failure, that can be increased by the undue prolongation of radiation therapy.[73] González Ferreira *et al*.[74] found an loss in LRC of 1-1.2% per extra-day or 12-14% per extra-week. Prolongation of radiotherapy negatively interferes LRC and OS even in case of CRT.[74]

Finally, the overall treatment time (OTT) from the day of surgery to the end of PORT showed prognostic significance for the LRC and OS in a randomized trial when the entire duration of treatment was greater than 13 weeks.[75] No other randomized studies have been published that would confirm this finding, a retrospective series found no prognostic association in the OTT with LRC neither OS.[76]

Intensification of adjuvant treatment

The value of dose escalation with PORT as a function of risk of recurrence has been explored in 2 prospective randomized trials. Peters and Withers[77] showed the benefit of a dose of 63 Gy in 1.8 Gy fractions in patients with ECE, positive or inadequate surgical margins. Ang *et al*.[75] published the results of a multicenter trial that randomized 151 patients with high-risk criteria (ECE and 2 or more additional criteria) between accelerated concomitant boost radiotherapy 63 Gy in 5 weeks or the same dose in conventional fractionation in 7 weeks. The accelerated treatment showed significantly improvement in LRC and OS when the interval between surgery and the start of PORT was not stretched or if the duration of the whole treatment (surgery plus PORT) no exceeded 13 weeks. Role of accelerated PORT is not firmly established, a confirmatory phase III Dutch trial (POPART CKTO 2003-11) is currently in recruitment period.

A meta-analysis[78] on the benefit of postoperative CRT confirmed the reduction in RR of LRC (RR = 0.59) and death (RR = 0.80) and improvement in median survival (from 22-32 months to 40-72 months). The authors state that the patients included in those trials were under 70 years and with good performance status, so the impact of the CRT in patients aged 70 or older with associated co-morbidities is unknown.[50,78] A pooled analysis[79] of 2 phase III trials from RTOG[80] and the European Organization for Research and Treatment of Cancer (EORTC)[81] on the role of the postoperative CRT in adjuvant treatment of the SCCHN, confirmed that patients with ECE or ISMR were those who most benefit obtained with the administration of PORT chemoradiation in terms of risk reduction in LRC (48%) in time to progression (23%) and mortality (30%). Other pathological features commonly used to define patients at risk of relapse) were not so decisive influencing LRC, OS, neither benefit of CRT. However a updating of the RTOG 9501 trial[82] found no significant difference between patients treated with PORT alone and those treated CRT regarding LRC (28.8% *vs.* 22.3%, $P = 0.1$), DFS (19.1% *vs.* 20.1%, $P = 0.25$) or OS (27% *vs.* 29.1%, $P = 0.31$); an unplanned analysis on the subgroup of patients with ECE or ISMR showed that the combined treatment improved LRC (33.1% *vs.* 21%, $P = 0.02$) and DFS (12.3% *vs.* 18.4%, $P = 0.05$) but not OS (19.6% *vs.* 27.1%, $P = 0.07$).

On the technical aspects of PORT

PORT administration is a particular challenge from the point of view of the radiation oncologist. Anatomy distortion due to tumor resection, the presence of reconstruction flaps, prosthetic material and the position of scars may influence routes of dissemination and hamper assessing volumes at risk to irradiate. Due the narrow conformation of dose to the target volume by IMRT, failure to design an adequate treatment volume will leave untreated areas of unrecognized risk; on the contrary excessively large volumes lead to higher radiation exposure of healthy tissue regions with consequent toxicity.[83,84] Close collaboration between the radiation oncologist and head and neck surgeon is imperative when interpreting the pathological findings and surgical technique used; the engagement with radiologist and pathologist will be necessary in most cases. There is currently no international consensus on standard volumes for PORT irradiation in AHNC, but there are some guidelines published.[85-88].

Adjuvant brachytherapy

In the specific case of OCSCC, PORT can be performed in fully or partly by BT reaching an equivalent dose of 60-66 Gy (LDR or HDR) on the tumor bed when surgical margins are infiltrated (stages pT1-T3) EBRT is administered alone when cervical nodes are at risk or primary surgical bed is not amenable for BT. Adjuvant BT results are summarized in [Table 3].[89-93] While in early-stage OCSCC treated with radical RT adding BT plays a critical role in cure and local control, it is not the case of adjuvant setting (early nor advanced stage OCSCC) as either LRC and OS are equivalent between PORT-EBRT or PORT-BT. Table 4 shows recent published studies on patients with advanced OCSCC treated with PORT IMRT-based.[94-103]

Acknowledgments

The photographs illustrating in this article was kindly provided by Dr. Enrique Miragall from Fundación ERESA [Figure 1] and Dr. José Luis Guinot from Instituto Valenciano de Oncología [Figure 2].

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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