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Impact of postoperative radiotherapy on survival and loco-regional control in node-negative oral cavity tumours classified as T3 using the AJCC Cancer Staging Manual eighth edition

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N. Subramaniam, D. Balasubramanian, S. Murthy, P. Rathod, S. Vidhyadharan, K. Thankappan, S. Iyer: Impact of postoperative radiotherapy on survival and loco-regional control in node-negative oral cavity tumours classified as T3 using the AJCC Cancer Staging Manual eighth edition. Int. J. Oral Maxillofac. Surg. 2019; 48: 152–156.

Abstract. According to the eighth edition of the AJCC Cancer Staging Manual (AJCC8), a depth of invasion (DOI) >10 mm is classified as pT3, representing a locally advanced tumour requiring postoperative radiotherapy (PORT). When node-negative, however, evidence regarding whether PORT improves loco-regional control or survival is unclear. To clarify this, two cohorts of patients were studied: (1) patients classified as pT3N0 by the seventh edition of the AJCC manual (AJCC7), with DOI >10 mm and a tumour diameter >4 cm (17 patients who received PORT), and (2) patients classified as pT1N0 and pT2N0 by AJCC7, with DOI >10 mm and a tumour diameter <4 cm (55 patients who did not receive PORT). Loco-regional control and survival were analysed. PORT was found not to impact overall survival or disease-free survival. It was also found not to impact local, regional, or distant recurrence. Although the two subsets of patients considered here (DOI >10 mm with tumour diameter below or above 4 cm) were previously distinct, they are both considered pT3 in AJCC8. Data from this study indicate that the routine administration of PORT to patients with a DOI >10 mm may not be warranted in the absence of other risk features such as nodal disease or close margins.

Key words: oral cancer; AJCC 8th edition; radiotherapy.

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The eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (AJCC8), planned for implementation from 2018, is the first to incorporate depth of invasion (DOI) in the T-staging of oral squamous cell carcinoma (OSCC)[1]. Tumours are classified as pT1 when the diameter is <2 cm and DOI is ≤5 mm, as pT2 when the diameter is 2–4 cm and DOI is ≤10 mm or the diameter is <2 cm and DOI is 5–10 mm, and as pT3 when the diameter is >4 cm or DOI is >10 mm. This was based on the work of Spiro et al.[2], who showed DOI to be a predictor of nodal metastasis[3,4]. DOI was also later shown to be a better predictor of disease-specific survival than tumour diameter in a large multi-institutional cohort study[5]. This helped address a major limitation of the previous AJCC TNM staging system – to distinguish between thin exophytic and thick indurative tumours having similar external diameters but significant differences in DOI and behaviour[6].

As a result, tumours with a DOI >10 mm will now be re-classified as pT3 (locally advanced) even if their external diameter is <4 cm, and routine postoperative radiotherapy (PORT) would be indicated in such cases. When these tumours are pathologically node-positive, even if N1, PORT is likely to improve survival[7,8]. However, it remains unclear whether PORT improves survival in node-negative patients. Given the lack of prospective evidence and the paradigm shift in T-staging, it is unclear whether DOI alone is an adequate indication for PORT in the absence of other risk features, such as close margins and nodal spread.

The purpose of this study was to determine whether PORT confers any benefit on survival or loco-regional control in patients classified as T3N0 by AJCC8. To determine this, two cohorts of patients were studied: (1) patients classified as pT3N0 by the seventh edition of the AJCC manual (AJCC7)[9], with DOI >10 mm and a tumour diameter >4 cm (who received PORT), and (2) patients classified as pT1N0 and pT2N0 by AJCC7, with DOI >10 mm and a diameter <4 cm (who did not receive PORT) and who would have been classified as pT3N0 by AJCC8. Loco-regional control and survival were analysed.

Materials and methods

Patients with pT1–3N0 OSCC (tongue, buccal mucosa, and floor of mouth tumours) classified according to AJCC7[9], with DOI >10 mm, were identified in a prospectively maintained database of patients treated at Amrita Institute of Medical Sciences, Kochi, India. Only those who underwent treatment with curative intent (surgical resection with or without adjuvant radiotherapy) at the study institution and who had adequate surgical margins (≥5 mm) were included. Preoperative assessment included cross-sectional imaging (contrast-enhanced computed tomography or magnetic resonance imaging of the head and neck). The surgery performed was wide local excision with selective neck dissection (levels I–IV). The radiotherapy employed was conformal or intensity-modulated radiotherapy, with a total dose of 60 Gy in 30 fractions, delivered over 5 days a week for 6 weeks. Seventy-two patients were included in the final analysis.

Recurrent disease was defined as any proven local, regional, or distant disease occurring at least 3 months after the date of surgery. Overall survival (OS) was defined as the time from initial surgery to the date of death or last follow-up evaluation. Disease-free survival (DFS) was defined as the time from initial surgery to the date of first recurrence or last follow-up evaluation.

The statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) and Excel version 2010 (Microsoft Corp., Redmond, WA, USA). The endpoint for analysis was OS. Survival curves were generated using the Kaplan–Meier method, and univariate analysis was performed using the log rank test. All statistics were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient, disease, and treatment characteristics

The final analysis included 72 patients (Table 1), of whom 56 (78%) were male. The subsites included were the tongue ($n = 54$, 75%), buccal mucosa ($n = 3$, 4%), and floor of the mouth ($n = 15$, 21%). Almost half of the patients (49%) had a history of tobacco usage. The tumour was well-differentiated in 52%, moderately differentiated in 44%, and poorly differentiated in 4%. Perineural invasion was seen in 25% and lymphovascular invasion in 13%. Local recurrence occurred in 33%, nodal recurrence in 11%, and distant recurrence in 3%. PORT was administered in 17 (24%); only those with a tumour diameter >4 cm received PORT, as they were classified as pT3 by AJCC7.

Determinants of overall and disease-free survival

The univariate analysis performed for predictors of OS and DFS is shown in Table 2. Lymphovascular invasion, perineural

Table 1. Patient, disease, and treatment characteristics.

Patient and tumour characteristics		Number (%)
Sex	Male	56 (78%)
	Female	16 (22%)
Subsite	Tongue	54 (75%)
	Buccal mucosa	3 (4%)
	Floor of mouth	15 (21%)
Tumour staging[a]	pT1	20 (28%)
	pT2	35 (48%)
	pT3	17 (24%)
Histological grade	Well-differentiated	37 (52%)
	Moderately differentiated	32 (44%)
	Poorly differentiated	3 (4%)
Smoking	Yes	35 (49%)
	No	37 (51%)
Perineural invasion	Yes	18 (25%)
	No	54 (75%)
Lymphovascular invasion	Yes	9 (13%)
	No	63 (87%)
Local recurrences	Yes	24 (33%)
	No	48 (67%)
Nodal recurrences	Yes	8 (11%)
	No	64 (89%)
Distant recurrence	Yes	2 (3%)
	No	70 (97%)
Postoperative radiotherapy	Yes	17 (24%)
	No	55 (76%)

[a] According to the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.

Table 2. Univariate analysis for predictors of overall survival (OS) and disease-free survival (DFS).

Variable	Number of patients	5-year OS %	*P*-value	5-year DFS %	*P*-value
Lymphovascular invasion					
Yes	9	84%	0.920	60%	0.708
No	63	64%		58%	
Perineural invasion					
Yes	18	83%	0.540	60%	0.974
No	54	82%		58%	
Histological grade					
Well-differentiated	37	90%	0.657	58%	0.637
Moderate or poorly differentiated	35	78%		57%	
Management					
Surgery	55	90%	0.616	60%	0.867
Surgery + PORT	17	77%		59%	

PORT, postoperative radiotherapy.

invasion, histological grade, and PORT were considered in this analysis, and none of these impacted OS or DFS. The use of PORT in this cohort did not significantly improve OS (Fig. 1) or DFS (Fig. 2).

Determinants of local, regional, and distant control

The univariate analysis performed for predictors of local recurrence-free survival (LRFS), nodal recurrence-free survival (NRFS), and distant recurrence-free survival (DRFS) is shown in Table 3. Of the adverse pathological features, only differentiation showed a trend towards significance for LRFS; those with well-differentiated tumours had a better 5-year LRFS than those with moderately or poorly differentiated tumours (70% vs. 50%, $P = 0.063$). PORT did not impact local, regional, or distant control rates.

Discussion

Overall, the outcomes were good in this cohort of pT3N0 OSCC, with the 5-year OS and 5-year DFS in those treated with surgery alone being 90% and 60%, respectively. In this cohort, 24% of patients received PORT; this was used when the maximum tumour diameter was >4 cm. PORT failed to improve loco-regional control or survival ($P > 0.05$). A limitation of this study is that tongue, floor of mouth, and buccal cancers were included, which may have introduced heterogeneity into the study cohort, since the DOI is likely to be more significant for nodal metastasis in tongue and floor of mouth tumours than buccal tumours. However it was felt that since AJCC8 applies to all subsites of the oral cavity and only pathologically node-negative tumours were included, the study findings may also apply to buccal cancers.

PORT is an integral part of the treatment of OSCC; however it may cause significant morbidity to the patient due to local effects such as xerostomia, skin and mucosal complications, and osteoradionecrosis. It is hence vital to advise the use of PORT only in situations where it is likely to improve loco-regional control or survival.

Although the two subsets of patients considered here (DOI >10 mm with tumour diameter below or above 4 cm) were previously distinct, they are both considered pT3 in AJCC8. The purpose of this study was two-fold: firstly, to determine whether PORT confers any benefit on loco-regional control or survival, and secondly, to determine factors affecting recurrence and survival. A univariate analysis of the entire cohort was performed to identify factors associated with recurrence or mortality that may benefit from PORT, but none could be identified.

Although T3N0 is stage III and is likely to merit PORT according to the National Comprehensive Cancer Network (NCCN) guidelines[10] (which are yet to be updated to reflect AJCC8), some groups have argued that T3 disease in the absence of nodal spread is still a minor risk factor and does not merit routine administration[11]. Studies that have shown a DOI >10 mm to portend a poor prognosis have also considered it a minor adverse feature and have not advised PORT in the absence of other risk features[12]. Although DOI is a robust indicator of disease-specific survival, it is important to examine it as an independent adverse feature and to weigh the evidence in considering it an indication for

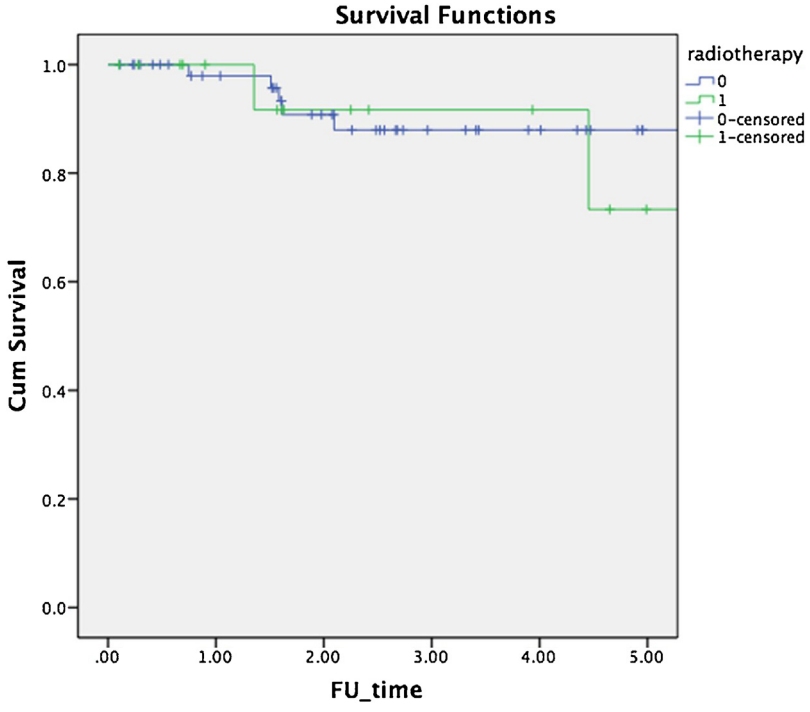

Fig. 1. Kaplan–Meier curve showing overall survival in pT3N0 patients receiving postoperative radiotherapy (1) versus those who did not (0).

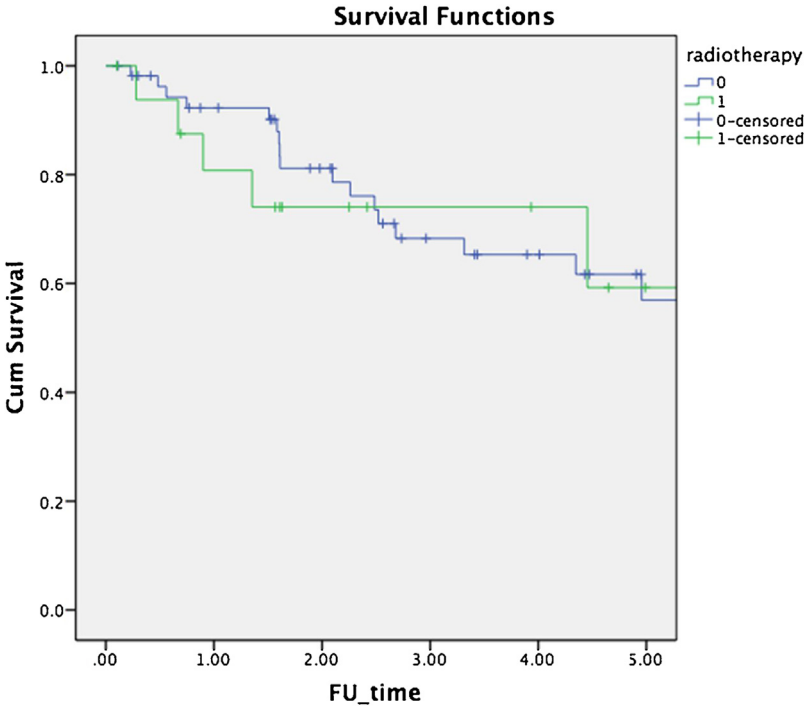

Fig. 2. Kaplan–Meier curve showing disease-free survival in pT3N0 patients receiving postoperative radiotherapy (1) versus those who did not (0).

Table 3. Univariate analysis for predictors of local recurrence-free survival (LRFS), nodal recurrence-free survival (NRFS), and distant recurrence-free survival (DRFS).

Variable	Number of patients	5-year LRFS %	*P*-value	5-year NRFS %	*P*-value	5-year DRFS %	*P*-value
Lymphovascular invasion							
Yes	9	60%	0.564	84%	0.793	85%	0.135
No	63	69%		98%		97%	
Perineural invasion							
Yes	18	63%	0.517	83%	0.878	95%	0.406
No	54	57%		93%		93%	
Histological grade							
Well-differentiated	37	70%	0.063	93%	0.890	100%	0.247
Moderate or poorly differentiated	35	50%		83%		92%	
Management							
Surgery	55	59%	0.692	84%	0.828	97%	0.331
Surgery + PORT	17	59%		92%		95%	

PORT, postoperative radiotherapy.

PORT in the subsequent NCCN guidelines. This was the intention of the present study: this study is novel in examining the impact of PORT on outcomes in pT3N0 OSCC classified by AJCC8 in order to determine whether a DOI >10 mm is an adequate risk factor in isolation to warrant PORT.

Given the modest sample size of this study, caution is advised in the generalization of the results. However the data suggest that a DOI >10 mm as an isolated risk feature is insufficient to warrant PORT in the absence of other associated risk features. Further prospective studies are required to improve outcomes.

In conclusion, the administration of PORT showed no loco-regional control or survival benefit in patients classified by AJCC8 as pT3N0. The DOI is a known predictor of nodal metastases; however, routine administration of PORT in patients with a DOI >10 mm may not be warranted in the absence of other risk features such as nodal disease or close margins.

Funding

None.

Competing interests

None.

Ethical approval

An ethical exemption was sought and given in view of the retrospective nature of the study and no patient interaction.

Patient consent

Not required.

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