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Oncological benefits of postoperative radiotherapy in node-negative early stage cancer of the oral cavity with isolated perineural invasion

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Abstract

Perineural invasion has been widely regarded as a poor prognostic factor in cancer of the oral cavity, but adjuvant treatment based only on this is still debatable. We have made an effort to address the question in a retrospective analysis of data from 2009–15 of patients with early node-negative cancers of the oral cavity. Patients with perineural invasion were divided into those who were treated with radiotherapy and those who were not. The records of a total of 169 patients were analysed, and 118 were given adjuvant radiotherapy and 51 were not. The median (range) duration of follow up was 45 (26–86) months. Of 169 patients, 47 (28%) developed recurrence, 28 in the treated, and 19 in the untreated, group. There was a significant disease-free survival benefit for adjuvant treatment ($p = 0.047$) but no overall survival benefit ($p = 0.54$).

We conclude that adjuvant radiotherapy should be considered for patients with perineural invasion, even in early cancers of the oral cavity.
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Keywords: perineural invasion; oral cavity cancer; adjuvant therapy; early oral cancer; radiation; disease free survival

Introduction

Head and neck cancer is the second leading cancer in the Indian subcontinent, and India contributes 7.8% of the global cases of cancer, and 8.3% of global deaths.[1] The most common site of head and neck cancer is the oral cavity, which accounts for 30% of all head and neck cancers in India, and the tongue is the second most common subsite.[2] Surgery is the main treatment for early-stage cancer of the oral cavity, while various treatments are required for most advanced cases.[3] About 20% of patients relapse or succumb to their disease despite apparently adequate treatment.

There has been a growing number of papers published in an attempt to identify the high-risk factors that contribute to an inferior outcome.[4] One such factor is perineural invasion, which has long been known to be a poor prognostic factor, but its role in deciding whether adjuvant radiotherapy is necessary is debatable. It is a unique route of tumour spread, and in cancers of the head and neck it is associated with increased locoregional recurrence. It is classified as an intermediate risk factor in terms of both overall and disease-free survival. Offering adjuvant treatment for isolated cases has been based

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on the European Organisation for Research and Treatment on Cancer 22931 and Radiation Therapy Oncology Group 9501 trials.[5,6] The combined analysis recommends postoperative radiotherapy for these cases, but it is largely an extrapolation of the data rather than direct results.[7] As the adjuvant treatment is associated with increased morbidity, selection of an appropriate regimen based only on known risk factors is of utmost importance.[4] The recent American Joint Committee on Cancer (AJCC) 8th edition acknowledges the fact that there is insufficient evidence for perineural invasion to be regarded as a prognostic variable, and so it is not included separately in the staging of cancers of the head and neck.[8] There is still no strong recommendation for or against adjuvant treatment for these cases.

We have therefore evaluated the role of adjuvant treatment in patients with isolated perineural invasion in node-negative early stage cancer of the oral cavity, and to our knowledge this is the largest series of such patients that has been analysed up to now.

Patients and methods

We reviewed our hospital database of patients with cancer of the head and neck from January 2009 to December 2015. We collected demographic and clinicopathological data, results of treatment, and survival in patients who satisfied the inclusion criteria. Only patients with a minimum of two years of follow up, or who were followed up until death, were included. The inclusion criteria were: patients with early-stage cancer of the oral cavity who were operated on for both the primary tumour and neck metastases, pathological stage T1–T2 (AJCC 7th edition) histopathologically node-negative, with perineural invasion, and an Eastern Cooperative Oncology Group performance status of 0–2. Exclusion criteria were: patients who had been treated elsewhere; had a histological diagnosis that was not squamous cell carcinoma (SCC); had invaded margins; whose tumour in the oral cavity was a second primary or a recurrence; and who had been lost to follow-up.

The definition of perineural invasion that we used was the finding of tumour cells within any of the layers (epineurium, perineurium, or endoneurium) of the nerve sheath, or invasion of cancer cells in, around, and through nerves. When the tumour cells were not found within the nerve sheath, perineural invasion was defined as at least a third of the circumference of the nerve surrounded by tumour cells. All patients had resection of the primary tumour with elective nodal dissection and were given an informed option of postoperative radiotherapy or close follow up.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean (SD) and median (range). Normality of data was tested by the Kolmogorov–Smirnov test. If the data were not normally distributed then a non-parametric test was used. The significance of differences in quantitative variables was compared using the independent *t* test, or the Mann–Whitney *U* test (when the data were not normally distributed). That in qualitative variables was assessed using the chi squared test or Fisher's exact test, as appropriate. Kaplan Meier survival analysis and the log-rank test were used to compare overall and disease-free survival. A p value of <0.05 was accepted as significant. The data were entered into an MS Excel spreadsheet and analysis was done using IBM SPSS Statistics for Windows (version 21.0, IBM Corp).

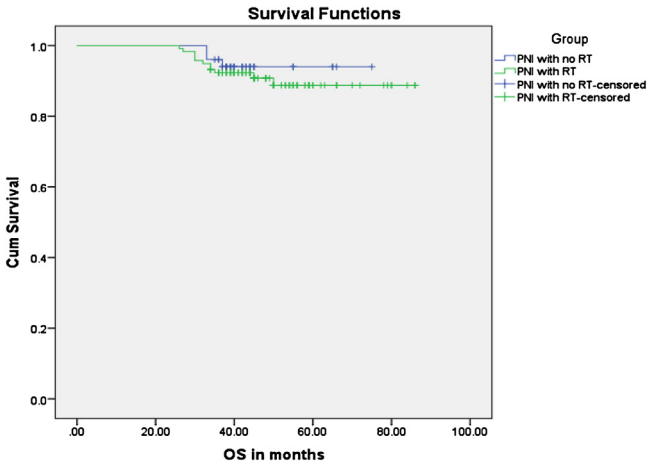

Fig. 1. Overall survival in patients with and without radiotherapy.

Results

Clinicopathological data

A total of 942 patients with head and neck cancer were analysed for this study, out of which 553 patients had early (T1, T2) node-negative tumours. Among the 553 patients, a total of 169 (31%) had perineural invasion with no other appreciable risk factors. Adjuvant radiotherapy was given to 118 of these patients, while 51 of them opted for close follow up. The most common histological grade seen was moderately differentiated SCC (91%). Patient's characteristics and their clinicopathological factors are shown in Table 1.

Oncological outcome

The median (range) duration of follow up was 45 (26–86) months. The distribution of recurrences is shown in Table 2. The difference in nodal recurrence between the two groups was significant (p = 0.013), while local, loco-regional, and overall recurrences were comparable (Figs. 1 and 2). Seven of the patients had salvage resections and the rest were referred for palliative chemoradiotherapy.

Table 1
Patients' characteristics and distribution of cases in the two arms of the study. Data are number (%) unless otherwise stated.

Factor	Postoperative RT (n = 118)	No RT (n = 51)	Total (n = 169)	p value
Clinicodemographic details:				
Mean (range) age (years)	48 (29–74)	47(27–78)	47 (27–78)	0.79
Sex M: F	95: 23	42: 9	137: 32	0.77
Percentage that smoked	22.03	23.52	22.48	0.83
Percentage that chewed tobacco	66.9	76.4	69.8	0.21
Pathological factor:				
pT stage (pathological T stage)				
Percentage T1	38.9	41.1	–	0.789
Percentage T2	61.01	58.8	–	
Grade				
1	7 (5.93)	0	7 (4.14)	
2	106 (89.83)	48 (94.12)	154 (91.2)	0.192
3	5 (4.24)	3(5.88)	8 (4.73)	
Depth of invasion (mm):				
<4	11 (9.32)	2 (3.90)	13 (7.6)	
4-10	72 (61.02)	35 (68.55)	107 (63.30)	0.087
>10	35 (29.66)	14 (27.45)	49 (28.99)	
Worst pattern of invasion:				
1-3	72 (61.02)	28 (54.9)	100 (59.17)	0.458
4-5	46 (38.98)	23 (45.10)	69 (40.83)	

RT = radiotherapy.

Table 2
Recurrence and survival details of the patients in the two groups.

Variable	Postoperative RT group	No RT group	Total	p value
Recurrence:				
Local	19	11	30	0.393
Nodal	8	10	8	0.013
Locoregional	27	21	48	0.121
Distant	4	3	7	0.432
Overall	28	19	47	0.072
Death	11	3	14	0.547
Survival:				
Median duration after locoregional recurrence (months)	12.3	12.2	12.2	–
Median duration overall recurrence (months)	11.2	11.4	11.3	–
Percentage disease-free survival at five years	75.63	62.74	–	0.047
Percentage overall survival at five years	88.76	93.9	–	0.549

RT = Radiotherapy.

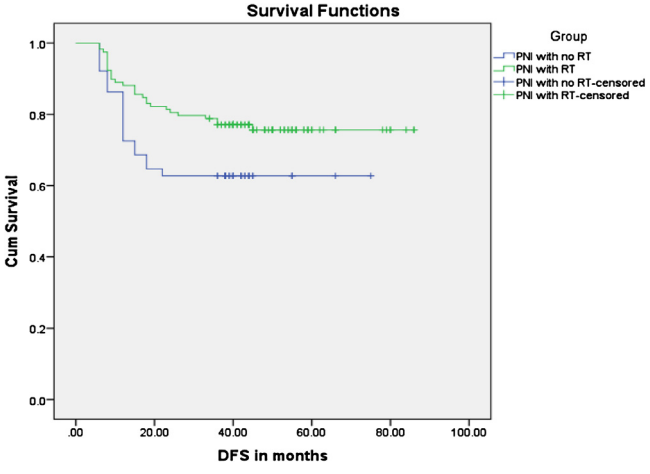

Fig. 2. Disease-free survival in patients with and without radiotherapy.

Discussion

The definition of perineural invasion has undergone various modifications as the understanding of it has improved over the years. Batsakis[9] described it as the finding of tumour cells within any of the layers of the nerve sheath (epineurium, perineurium, or endoneurium) or invasion of cancer cells in, around, and through nerves. However, Leibeg et al[10] suggested a modification of this, to cover for when tumour cells are not found within the nerve sheath. To differentiate it from focal abutment of tumour in the proximity of a nerve, it was defined objectively as at least a third of the circumference of the nerve surrounded by tumour cells.[10] The exact pathogenesis is not yet fully understood, and the previous theory of it being the path of least resistance has largely been discarded.

The most plausible mechanism is a complex interaction of three different cellular elements, including tumour cells,

nerve cells, and stromal cells, with possible involvement of autocrine and paracrine mechanisms. It is evident that it is an intermediate risk factor for locoregional recurrence.[4] It has been suggested that it is an indication for elective neck dissection and adjuvant radiotherapy for the treatment of patients with no other risk factors, but there is still a lot of controversy about the recommendation of adjuvant radiotherapy for isolated perineural invasion, particularly in early cancer of the oral cavity[5–7] Indeed, some papers have reported poorer outcomes in patients given adjuvant radiotherapy.[11] Postoperative radiotherapy is also not without complications, such as osteoradionecrosis, mucositis, and xerostomia. Relatively young age of onset and a good prognosis in early-stage cancer also brings the long-term complications of radiotherapy into the picture and hence, its judicious use is invaluable.

We have excluded all independent prognostic factors in relation to cancers of the head and neck that are obvious indications of adjuvant radiotherapy, such as patients who present with invaded nodes, T3/T4 tumours, or invaded margins. We have included the patients in whom neck dissection has been mentioned, to remove the confounding effect of not knowing the status of the neck.

Locoregional recurrence rates were comparable in both the arms of the study, although the nodal recurrence rate was higher in the group not given radiotherapy. The results are similar to most other reports, including the studies from Tai et al and Chinn et al.[12,13] Also more than 60% of the locoregional recurrences developed within the first year of follow up, the median duration of 12 months being similar to that of the series reported by Fagan et al.[14] They reported that perineural invasion was associated with an increased risk of local recurrence and decreased disease-specific survival in a series of 142 patients with SCC of the head and neck. Lanzer et al[15] also has reported that it was a prognostic factor for nodal metastases in both the ipsilateral and contralateral neck. However, neither series showed any benefit from adding radiotherapy in these patients.

Liao et al[16] retrospectively analysed the records of 460 patients with cT1–3, N0 oral cancers and failed to show a benefit either in disease-free or overall survival with postoperative radiotherapy in patients with perineural invasion in the absence of other risk factors. However, they stressed that the omission of neck dissection in these patients led to a poor local control rate.

The main drawback of this analysis, however, was that among the patients treated with radiotherapy 9/24 had T3 disease, which is itself an indication for radiotherapy, while only 9/44 had T3 disease among patients not given radiotherapy.

Chen et al,[17] in their analysis of early malignancies of the oral cavity, concluded that perineural invasion and lymphovascular space invasion were not important prognostic factors, and that the addition of adjuvant radiotherapy provided no additional benefit. An analysis by Chatzistefanou et al[18] concluded that perineural invasion is an important prognostic factor and an indicator for elective neck dissection, but adjuvant radiotherapy does not reduce the chances of recurrence. Tai et al[12] suggested that in patients with early T1–T2 oral malignancies routine elective neck dissection should be done in patients with perineural invasion, but they advised against adjuvant radiotherapy in those patients who had neck dissection.

Only a few series have shown any benefit from adding adjuvant radiotherapy in patients with perineural invasion. Katz et al[19] reported that it is an important prognostic factor and postoperative radiotherapy can improve survival, but they reported a small series of 48 patients only seven of whom were given adjuvant radiotherapy. In a study by Chinn et al,[13] 88 patients with early cancers of the oral cavity were analysed and they concluded that perineural invasion is an independent adverse risk factor in patients without nodal metastasis and extracapsular spread. They found a significant longer disease-free interval and locoregional control when patients were treated with adjuvant radiation. The drawback of this study was that the sample size was too small: 14 patients were given radiotherapy compared with six who were not.

The largest of the series showing survival benefits for radiotherapy is by Nair et al.[20] They reported an analysis of 1524 patients with cancer of the oral cavity, of whom 60 had early disease and 45 were given adjuvant radiation. They reported that addition of adjuvant radiotherapy was the only significant factor that affected overall survival in early cancer of the oral cavity. Ours is to our knowledge the largest study to show a significant survival benefit in patients with perineural invasion who were given adjuvant radiotherapy.

A few authors have tried to isolate the high-risk group further among patients with perineural invasion. Aivazian et al[21] showed that patients with multifocal invasion that was affecting larger nerves (>1 mm) had a significantly poorer prognosis. However, the significance was limited only to univariate analysis and the number of patients with involvement of larger nerves was too few to be properly analysed. Brandwein-Gensler et al[22] have reported similarly that involvement of larger nerves leads to higher locoregional recurrence. Miller et al[23] suggested that site and distance from the tumour are of prognostic importance, but this has not been reproduced in other series and warrants further validation.

As there seem to be few prospective series or randomised trials, evidence is largely decided on meta-analysis and systematic review. Bur et al[24] analysed eight series that assessed the role of adjuvant radiotherapy in patients with perineural invasion, and concluded that currently there is insufficient evidence for adjuvant radiotherapy when only perineural invasion is the indication, and informed decisions should be made individually after assessing the risk factors. A similar analysis by Chatzistefanou et al[25] also concluded that perineural invasion is an important prognostic factor for neck dissection, but the addition of adjuvant radiotherapy does not provide survival benefits. However, with these two new series (Nair et al[20] and the present paper), both from the Indian subcontinent, a randomised controlled trial may be the final answer (Table 3).

Table 3
Some important similar series and data for comparison.

First author, year, and reference	Cases PORT/No RT	Site	Percentage recurrence and p value PORT/No RT	Percentage disease-free survival and p value PORT/No RT	Percentage overall survival and p value PORT/ No RT
Liao *2008[16]	24/42	Oral cavity	25 /20.4 p- 0.876	p = 0.31	69.2/86.2 p = 0.093
Chinn 2013[13]	14/6	Oral cavity	NA	68/33 p = 0.014	p = 0.68
Chatzistefanou* 2014[18]	39	Oral cavity	NA	0.763	NA
Bajwa 2016[26]	27/13	Tongue	11.1/23	p = 0.365	NA
Nair 2018 [20]	45/15	Oral cavity	NA	NA	p = 0.02
Present series 2018	118/51	Oral cavity	16.1/21.56	75.63/62.74 p = 0.047	88.76/93.9 p = 0.549

PORT = postoperative radiotherapy; RT = radiotherapy; NA = not available. *T1 and T3 cases included.

The limitations of our study are its retrospective nature and its small sample size. The adjuvant radiation planned was based purely on the discussion of the treating physician and the patient. Another drawback of the study was that no distinction was made on whether perineural invasion was unifocal or multifocal. The results for overall survival failed to reach significance but this was expected as the study dealt with early stage disease with low mortality, and needed significantly higher numbers to power a study to assess overall survival.

Conclusion

Perineural invasion is a known risk factor for recurrence in cancer of the head and neck. However, adjuvant radiotherapy in otherwise low-risk patients is controversial. Our results suggest that postoperative radiotherapy in these patients with early cancers of the oral cavity had a significant impact on outcome in terms of disease-free survival, even in patients who have had elective neck dissections. Adjuvant radiotherapy should be considered in all patients with cancers of the oral cavity who present with perineural invasion.

Ethics statement/confirmation of patients' permission

This was a retrospective study and therefore exempt from the need for approval by the Institutional Review Board. No consent was required from patients.

Conflict of interest

We have no conflicts of interest.

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