Postoperative radiotherapy for patients with oral squamous cell carcinoma with intermediate risk of recurrence: a case match study

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Abstract:

Background: The purpose of this study was to determine the effect of postoperative radiotherapy (PORT) on recurrence and survival in patients with oral squamous cell carcinoma (OSCC) of intermediate risk of recurrence.
Methods: Intermediate risk patients, defined as pT1, pT2, pN0 or pN1 with at least one adverse pathological feature, were identified form the head and neck databases of Liverpool Head and Neck Cancer Unit and Sydney Head and Neck Cancer Institute. Patients who had received surgery and PORT were case matched with patients who were treated by surgery alone based on pN, pT, margins and pathological features.
Results: Of 1029 pT1T2 OSCC patients, 308 met the inclusion criteria and 90 were matched into 45 pairs. There was a significant improvement in locoregional control with PORT (p=0.039), which was concentrated in the pN1 subgroup (p=0.036), but not the pN0 subgroup (p=0.331).
Conclusions: PORT significantly improves locoregional control for intermediate risk OSCC in the presence of nodal metastases.

Introduction:

Oral squamous cell carcinoma (OSCC) is usually treated by primary surgery.[1] The need for adjuvant therapy, in particular postoperative radiotherapy (PORT), is based on a synthesis of several clinical and pathological adverse features that increase the risk of locoregional failure. Patients at low risk of recurrence, where PORT can be safely omitted, are those with completely excised primary tumours less than 4cm in diameter (T1/T2) without adverse pathological features or nodal metastases. Locoregionally advanced tumours, particularly those with multiple nodal metastases, extracapsular spread (ECS) or positive margins have a high risk of recurrence and adjuvant therapy is essential. The remaining patients generally fall into an intermediate risk group. The decisions regarding the need for adjuvant therapy are based on institutional preferences, clinical acumen and patient preference and are supported only by low level contradictory evidence.[2] This group includes node negative patients with close margins or adverse pathological features at the primary site, and patients with a single positive node without ECS.[3] There is no consensus as to which of these patients will benefit from PORT[4] and the potential for reduced recurrence must be balanced against the significant local toxicity[5-7].

A systematic review of the literature by the senior author (JSB) has highlighted how weak the evidence is for prescribing PORT for intermediate risk patients.[2] The issue is further confounded by the prescription bias associated with retrospective cohort studies comparing outcomes for patients

who have been treated with surgery followed by PORT and those treated by surgery alone. Patients treated by surgery and PORT often have worse outcomes than those treated by surgery alone[2] reflecting the fact that patients who receive PORT generally have higher stage disease and more adverse pathological features.

The prescription bias could be eliminated with a randomized trial but there would almost certainly be difficulties with recruitment. In the absence of data from a trial, we have attempted to minimize bias by case matching patients with intermediate risk who have received PORT with those treated by surgery alone.

Methods:

Patients with newly diagnosed OSCC between 1998 and 2013 were identified from the head and neck cancer databases of Liverpool Head and Neck Unit and the Sydney Head and Neck Cancer Institute (SHNCI). Patients fulfilling the following criteria were included: (1) OSCC treated by primary surgery including neck dissection; (2) pT1 or pT2; (3) pN0 or pN1 without ECS; (4) detailed pathological examination of the resection and neck specimens with deep and mucosal margin size recorded in mm; (5) at least one adverse pathological feature; (6) at least 1 year follow up. The exclusion criteria were (1) previously treated OSCC; (2) patients who did not have a neck dissection and therefore whose pN status was unknown; (3) patients with tumour reaching <1mm from the inked margin on histological examination; (4) patients with multiple positive nodes or ECS; (5) sites other than oral cavity SCC; (6) synchronous primary tumours; (7) patients treated with primary radiotherapy or neoadjuvant chemotherapy. Clinicopathological data was retrieved from the case notes and pathology reports.

Patients who were treated by surgery and PORT were precisely case matched with patients treated by surgery alone. Lymphovascular invasion (LVI) and perineural invasion (PNI) were considered together to aid the matching process.

The hierarchy of matching was as follows:

1. pN category

2. pT category
3. Margin status
4. Presence of PNI or LVI
5. Tumour subsite
6. Age of the patient
7. Tumour differentiation

For example, a 50 - 55 year old patient with pT2 pN0 tongue cancer with close margins, moderate differentiation and perineural invasion who was treated by surgery alone would be matched with a 50 – 55 yr old patient with a pT2 pN0 tongue cancer with close margins, moderate differentiation and PNI and/or LVI who was treated by surgery and PORT. The investigator who performed the matching was blinded to outcome.

Margins were categorised as involved (<1mm); close (1-4.9mm) or clear (5mm or greater), as per Royal College of Pathologists (RCPath) guidelines[8]. Survival was calculated from the date of surgery to death taken from death certificate information tracked through the Office of National Statistics to 1st July 2015 for Liverpool patients and clinician follow up data for Sydney patients. Differences in survival and locoregional control were analysed using the log-rank test and p values of less than 0.05 were considered statistically significant.

Results

Of the 520 pT1T2 OSCC patients in the Liverpool Head and Neck Cancer database, 193 (117 males and 76 females) met the inclusion criteria. There were 27 patients treated by surgery and PORT (60Gy in 30 fractions), and 166 were treated by surgery alone. Of these, 42 patients were successfully matched into 21 pairs. Of 509 pT1T2 OSCC patients in the SHNCI database, 115 (66 males and 59 females) patients met the inclusion criteria. There were 30 patients treated with surgery and PORT (60Gy in 30 fractions), and the remaining 95 were treated by surgery alone. Of these, 48 patients were matched into 24 pairs.

In total, 45 matched pairs (90 patients) were included. The median age was 60 (22.5-84.4) years. The median age of the Surgery and PORT group was 58 (range 29.9-84.4) years and the median age for the Surgery alone group was 61 (range 22.5-84.4) years. There were 60 pN0 patients and 30 pN1 patients. 77 patients had close margins and 35 had PNI/LVI. The mean number of matched criteria per matched pair was 5 (median 6; range 4-7). pN status and presence of PNI/LVI were matched in every case. pT status was matched in 43 of 45 cases. In the two cases were a pT1 was matched with a pT2, the matches were accepted on the basis that there was otherwise complete concordance (6 of 7 criteria). In one case a patient with a close margin (3mm) was matched with a patient with a clear margin. This match also otherwise had complete concordance of criteria. The characteristics of

the patient cohort are shown in Table 1 and the characteristics of the matched pairs are shown in Table 2.

Locoregional failure occurred in 22 patients (24.4%). This comprised 7 (7.8%) patients in the surgery and PORT group and 15 (16.7%) patients in the surgery alone group (p=0.039), shown in Figure 1. There was no difference in overall survival between the two groups (p=0.129) as shown in Figure 2. Of patients that recurred, salvage was attempted in 3 of 7 from the PORT group and 9 of 15 from the surgery alone group. Successful salvage was achieved in 2 (28.6%) surgery and PORT patients compared with 7 (46.7%) of surgery alone patients.

The cohort was stratified by nodal stage (pN0 or pN1), and the presence of PNI/LVI. PORT was associated with improved locoregional control for the pN1 group (p=0.036) as shown in Figure 3, but did not influence recurrence in the pN0 subgroup (p=0.331) as shown in Figure 4. PORT did not improve locoregional control for patients with PNI/LVI (p=0.965).

The number of patients needed to be treated (NNT) with PORT in order to avoid one locoregional failure was 5.7, but this reduced to 3.0 for the pN1 subgroup.

Discussion:

This study examines the effect of PORT on locoregional control and survival in patients with intermediate risk OSCC after primary surgery. The results show that PORT significantly improves locoregional control (p=0.039) over those treated by surgery alone. However, this benefit does not appear to translate directly into improved overall survival (p=0.129) and the effect was principally observed in patients with nodal involvement (pN1). The inability to demonstrate a survival difference may be in part due to the higher proportion of patients with recurrence successfully salvaged in the surgery alone group (7 of 15 compared with 2 of 7 in the surgery and PORT group).

To our knowledge, this is the only case match study comparing outcomes for patients treated by primary surgery and PORT with those treated by primary surgery alone. The results are strengthened by the strict matching criteria and the utilization of two large head and neck databases from which to recruit patients. The Sydney Head and Neck Cancer Institute and the Liverpool Head and Cancer Unit have adopted very similar treatment paradigms in their approaches to intermediate risk OSCC with a preference for withholding PORT wherever possible. This is reflected in the small proportion of eligible patients who had received PORT (18.5%, 57/308). All specimens were reported by dedicated Head and Neck pathologists adhering to RCPath guidelines[7] for processing and reporting oral cavity specimens. Patients treated prior to the introduction of these guidelines in 1998 were excluded. The inclusion only of patients who had a neck dissection allows us to

accurately match patients based on their pathological nodal status and exclude high-risk patients with multiple nodes and/or ECS.

We have attempted to eliminate the prescription bias associated with cohort studies comparing outcomes for patients receiving surgery and PORT with those treated by surgery alone by applying rigid matching criteria but must accept the reduced size of the final cohort associated with this.

There is a paucity of high level evidence to base recommendations for prescription of PORT for OSCC[6]. Despite the widespread use of PORT since its introduction by Maccomb[9] in 1957, only 3 randomised trials exist in the literature. All 3 examined the benefits of PORT in stage III/IV head and neck SCC but only one study was restricted to oral cavity disease[10]. The trials by Kokal[11] and Rodrigo[12] have conflicting results, and multiple weaknesses including mixed head and neck cohorts and small cohort size, limiting the relevance of their findings. The trial by Mishra was restricted to Stage III/IV buccal SCC and found improved overall and disease-free survival (p=0.005) for patients treated with surgery and PORT. This study is remarkable for the reported 3 year overall survival rates of 94% (surgery and PORT) and 84% (surgery alone), for stage III/IV buccal SCC which is often associated with poor prognosis[13,14].

Our findings conflict with previously published data from our units. Brown et al[3] compared outcomes for unmatched cohorts of intermediate risk patients treated by surgery and PORT with those treated by surgery alone and found improved locoregional recurrence and survival (p=0.002) for patients in whom

PORT was withheld. This data is confounded by the prescription bias associated with an unmatched comparative study of this nature. The patients in the PORT group are likely to have more advanced stage disease and more adverse pathological features[15], explaining their poor outcome. Our results are consistent with those of Shrime et al[16], who reported a survival advantage ($p<0.001$) for patients receiving PORT in a similar cohort (T1-2N1).

The negative impact of the local toxicity associated with PORT on HRQOL is well documented[3-5]. Overall HRQOL declines during and after treatment but appears to recover to baseline levels after a year. However, physical function scores, especially those related to saliva and swallowing, remain persistently low[4]. This effect is worse for conventional radiotherapy compared with intensity-modulated radiotherapy (IMRT)[17]. Balancing the merits and toxicity of radiotherapy within an individual is critical to patient care. In this study approximately 6 patients would endure the side effects of radiotherapy in order to prevent one locoregional failure if the results were indiscriminately applied to all intermediate risk patients. Although this can be halved by only prescribing PORT to patients with nodal disease, other pathological features need to be carefully considered along with the patient's preference. While the study did not demonstrate a difference in disease control for patients with PNI/LVI treated by surgery and those treated with surgery and PORT, it was not specifically designed to test this and the subgroup is too small to have confidence in the findings.

Limitations

While minimized, the prescription bias cannot be completely eliminated. Medical comorbidity strongly influences overall survival but quantifying and matching patients' performance status would be very difficult. We have attempted to match the patients' age as a surrogate for comorbidity but accept the limitations of this approach. Even within the rigid confines of our inclusion criteria, the intermediate risk patients are not a homogenous group, rather they are a heterogeneous group of patients with a gradation of recurrence risk. The potential for locoregional failure is certainly greater for a patient with a pT2N1 tumour with close margins and perineural spread than a pT1N0 patient whose risk factor is close margins. Therefore some caution must be exercised in generalisation of the results.

Conclusion

PORT is associated with improved locoregional control in intermediate risk OSCCC patients. Despite this, it appears to reduce the chances of successful salvage, thereby negating any expected survival benefit. The positive affect appears to be concentrated in the pN1 patients and is much less clear for node negative patients. This study supports the use of PORT for node positive OSCC patients.

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Table 1: Cohort characteriestics: Number (percentage)

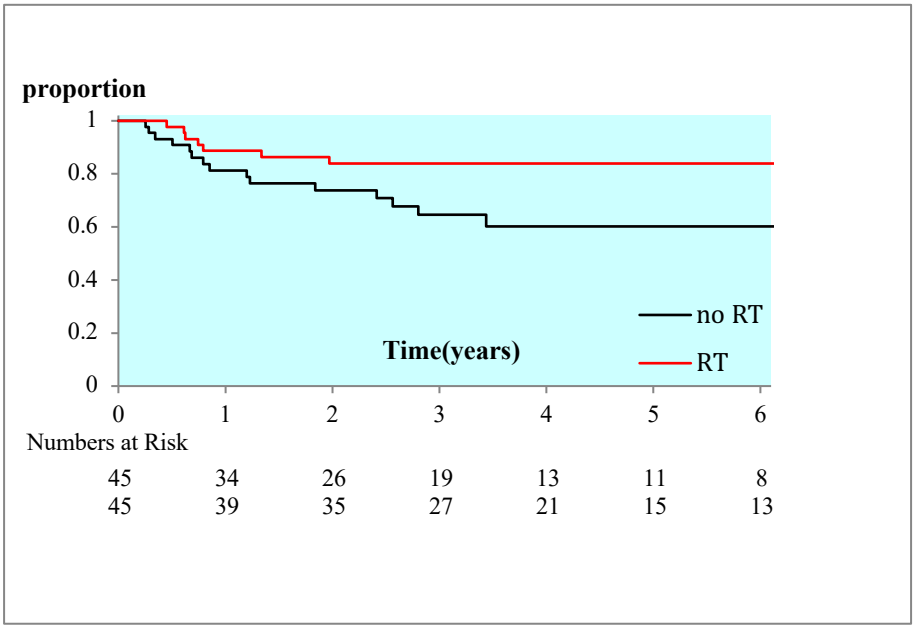
	Overall	Surgery + PORT	Surgery alone
Mean age:	60.0	58.0	61.0
Gender:			
Male	54 (60%)	29 (32.2%)	25 (27.8%)
Female	36 (40%)	16 (17.8)	20 (22.2%)
Length of follow up (yrs):	3.7	4.1	3.2
Site:			
Tongue	56 (62.2%)	28 (31.1%)	28 (31.1%)
Floor of mouth	19 (21.1%)	9 (10.0%)	10 (11.1%)
Buccal mucosa	12 (13.3%)	6 (6.65%)	6 (6.65%)
Hard palate or RMT	3 (3.3%)	2 (2.2%)	1 (1.1%)
pT stage			
pT1	24 (26.6%)	11 (12.2%)	13 (14.4%)
pT2	66 (73.4%)	34 (37.8%)	32 (35.6%)
pN stage			
pN0	60 (66.7)	30 (33.35%)	30 (33.35%)
pN1	30 (33.3)	15 (16.65%)	15 (16.65%)
Margins:			
Clear	13 (14.4%)	7 (7.8%)	6 (6.6%)
Close	77 (85.5%)	38 (42.2%)	39 (43.3%)

PNI	30 (33.3%)	15 (16.65%)	15 (16.65%)
LVI	9 (10.0%)	4 (4.4%)	5 (5.6%)
PNI or LVI or both	35 (38.9%)	17 (18.9%)	18 (20.0%)
Tumour differentiation:			
Well	15 (16.6%)	6 (6.6%)	9 (10.0%)
Moderate	57 (63.3%)	28 (31.1%)	29 (32.2%)
Poor	13 (14.4%)	8 (8.89%)	5 (5.55%)
Unknown	5 (5.55%)	3 (3.33%)	2 (2.22%)

Table 2: Characteristics of matched pairs

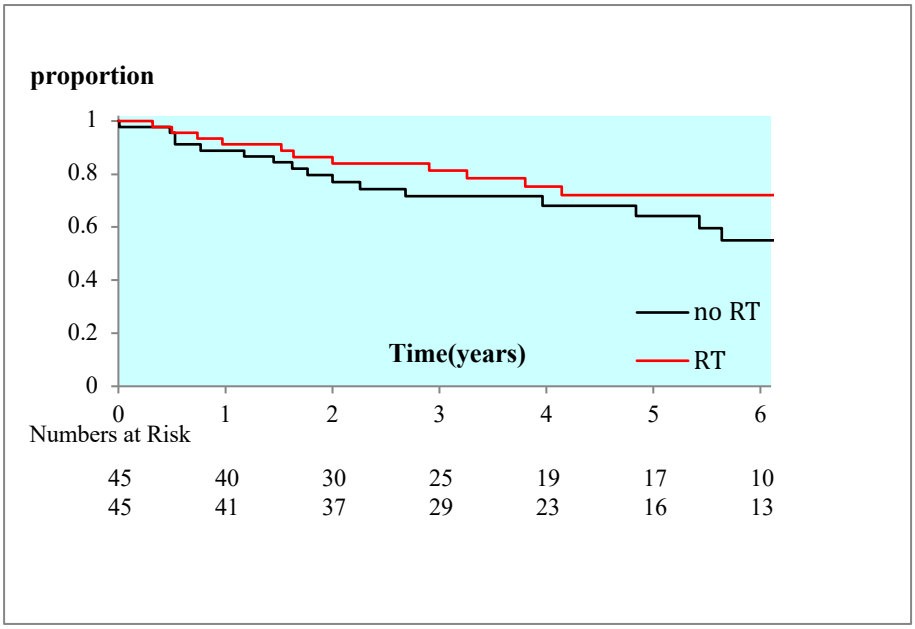
Characteristics:	No. of matched pairs (Number of patients)
pT1pN0, close margins, No PNI/LVI	5 (10)
pT1pN0, close margins, PNI/LVI	2 (4)
pT1/T2pN0, close margins, PNI/LVI	2 (4)
pT2pN0, clear margins, No PNI/LVI	1 (2)
pT2pN0, clear margins, PNI/LVI	2 (4)
pT2pN0, clear/close margins, PNI/LVI	1 (2)
pT2pN0, close margins, No PNI/LVI	10 (20)
pT2pN0, close margins, PNI/LVI	7 (14)
pT1pN1, clear margins, PNI/LVI	1 (2)
pT1pN1, close margins, No PNI/LVI	3 (6)
pT2pN1, clear margins, No PNI/LVI	1 (2)
pT2pN1, clear margins, PNI/LVI	1 (2)
pT2pN1, close margins, No PNI/LVI	7 (14)
pT2pN1, close margins, PNI/LVI	2 (4)
TOTAL:	45 (90)

Figure 1: Kaplan Meier curve of locoregional recurrence:



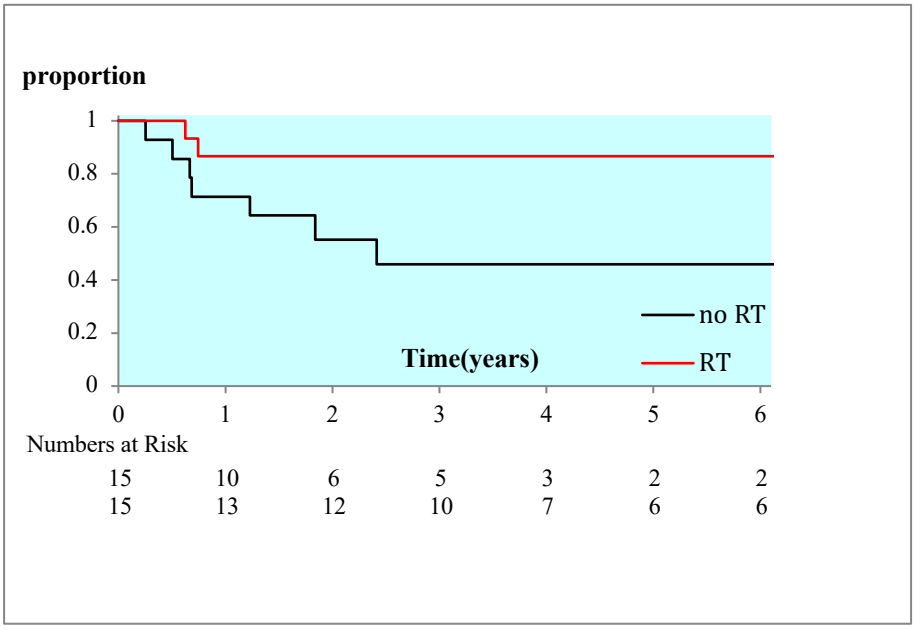
p=0.039

Figure 2: Kaplan Meier curves of overall survival:



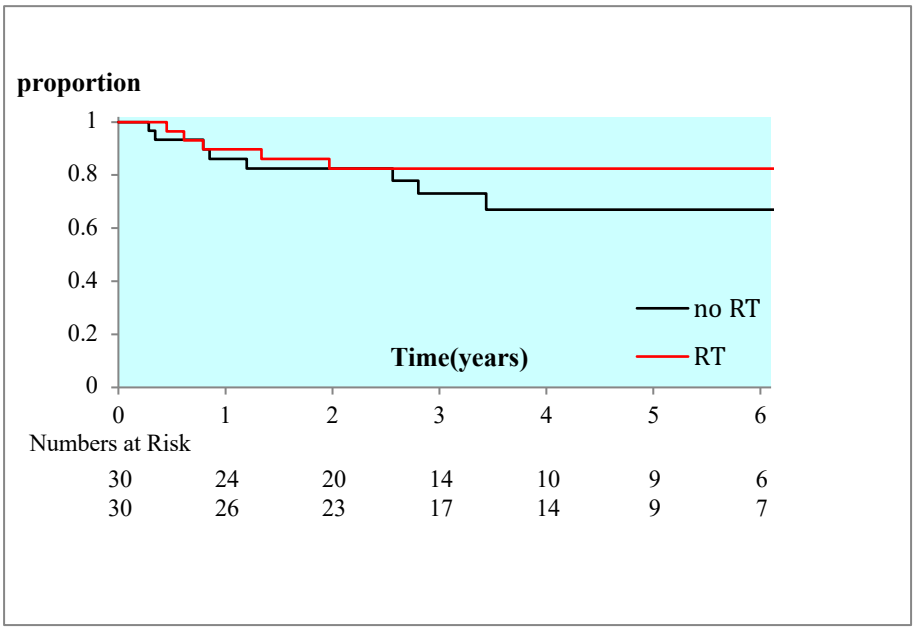
p=0.129

Figure 3: Kaplan Meier curves of locoregional control for pN1 disease



p=0.036

Figure 4: Kaplan Meier curves of locoregional control for pN0 disease



P=0.331