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Surgery Remains the Treatment of Choice for Retromolar Trigone Carcinomas

Robert I Smee[1,2,3], Janet R Williams[1,2*], Damian P Kotevski[1]

[1]Department of Radiation Oncology, The Prince of Wales Cancer Centre, Randwick, Australia

[2]Prince of Wales Clinical School, The University of New South Wales, Randwick, Australia

[3]Department of Radiation Oncology, Tamworth Base Hospital, Tamworth, Australia

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[*]**Corresponding author:** Janet R Williams, Department of Radiation Oncology, The Prince of Wales Cancer Centre, Level 1, Nelune Comprehensive Cancer Centre, High Street, Randwick, Australia

ABSTRACT

Purpose: To evaluate whether radiotherapy can be substituted for surgery in the management of squamous cell carcinoma (SqCC) arising in the retromolar trigone (RMT) anatomical site.

Materials and Methods: This ethics approved study evaluated patients diagnosed with a RMT SqCC and treated at the Prince of Wales Cancer Centre (POWCC) between 1974 and 2017, with minimum two-year follow-up. Analysis was performed using the Kaplan-Meier method and log-rank test to describe any time-to-event data.

Objectives: Endpoints which were evaluated include local and ultimate local control, nodal and ultimate nodal control, cancer-specific and overall survival, and time to development of a second malignancy.

Results: There were 53 patients meeting all the eligibility criteria, with a definite smoking and alcohol consumption association. There were 16 (30%) patients having surgery as the only treatment and combined with radiotherapy in 16 (30%) patients, and 19 (36%) patients had radiotherapy alone, with two (4%) patients treated with chemotherapy only. Of the radiotherapy group, 8 (42%) patients failed locally. With surgical salvage, ultimate local control for this group was 69% at 5 years. Ultimate local control was 75% for patients treated initially with surgery alone, and 73% for combined treatment at 5 years (p=0.823). There is a high probability of developing another smoking related malignancy.

Conclusions: Although surgical salvage can be considered, radiotherapy as the only treatment has an inferior outcome to surgery (± radiotherapy). Surgery remains the best way to address RMT SqCC where the patient is fit enough for the operation.

Keywords: Head and Neck Cancer; Retromolar Trigone; Radiotherapy; Surgery; Survival

INTRODUCTION

The retromolar trigone (RMT) anatomically defines, as the name implies, a triangular patch of mucosa located posterior to the last molar tooth with the base inferiorly, and the apex superiorly. The mucosa overlays the ascending ramus of the mandible. More typically, the carcinomas arising at this site are squamous cell

carcinomas (SqCC), infrequent in incidence (1.4% of all oral cavity carcinomas in Japan, and 6-7% in non-Asian countries),[1,2] but usually locally advanced with bone involvement given the thin layer of mucosa in contact with bone.[3] It is a smoking related malignancy,[2,4] and although close anatomically to the oropharynx, it is not associated with human papilloma virus (HPV) related infection.[5] Presentation is usually on the basis of oral pain, trismus, and/or otalgia.[4,6]

Management decisions are orientated towards surgery as the main modality,[6-8] with imaging necessary to define the presence,[9] and then the extent of bone involvement. Limited bone involvement allows for a marginal mandibular resection as a preference to segmental resection.[6,10] Reconstruction currently would make use of a free flap allowing a larger mucosal resection particularly since there can be centrifugal expansion onto the adjacent buccal and soft palate mucosa.[11] Early stage disease, although less common, may be considered for robotic resection.[12] Local control (LC) figures where surgery is utilised for advanced disease, with added radiotherapy, typically reach 80% at three years of follow-up.[3,10] By contrast, LC figures for radiotherapy alone have a 40-50% rate.[13]

Many publications record patient numbers of 30-80, with mega data series such as the Surveillance, Epidemiology, and End Results (SEER) database, the only source of large patient numbers.[14] Whilst providing very useful information, important patient related data such as the impact of cigarette smoking, disease data, the site and extent of nodal disease, are missing. This review will focus on a well-documented population of patients presenting with a carcinoma taking origin in the RMT anatomical region, in the context of being managed within Australia.

MATERIAL AND METHODS

Study design

Data for this Ethics approved study South Eastern Local Health District (10/040) was evaluated retrospectively from prospectively collected information, with written informed patient consent. This data has been stored in our facility's Head and Neck Cancer Database (HNCD), which was audited for patients with a carcinoma diagnosis, and origin in the RMT region. Dates covered by this review extend from 30 April 1974 to 15 July 2017. Eligibility criteria were: definitive management at our centre, SqCC histology (including in situ disease), age ≥18 years, and a minimum of two-year follow-up period. TNM staging was via the 7th edition Union for International Cancer Control classification manual (published in 2009), which does not require documentation on imaging of extra-nodal spread. Patients were excluded if referred for management of recurrence/progressive disease, or had distant metastatic disease at presentation.

Treatment

All patients were presented in a Multidisciplinary Head and Neck Cancer clinic with subsequent recommended treatment. Note was made and recorded of relevant patient and disease factors, and then included in the patients file with subsequent translation into the HNCD.

Surgery was performed by experienced head and neck surgeons, with reconstruction by equally competent reconstruction surgeons. Attention was paid, where relevant, to functional aspects and oncological outcomes. Fitness for surgery using a modified Charlson Comorbidity Index scale was applied, and consequently and

consistently recorded. Radiotherapy was delivered using 4-6 MeV Linear Accelerator (Linac) directed photons, with head fixation and regular assessment of the patient set up. Daily dose delivery was 2-2.25 gray (Gy) per fraction with appropriate designation of spinal cord tolerance, and treating all fields daily. Progressive modification of treatment planning systems occurred with intensity-modulated radiotherapy (IMRT) used in recent years.

Data collection and follow-up

Data inputted into the HNCD was grouped into three sections: patient, disease, and treatment related information, for each specific anatomical subsite. This data originated from the hospital notes including pathology, referring specialist's correspondence, and imaging reports. All patients had a follow-up regimen of every 3-4 months during the first two years, then every 6-12 months thereafter. The cut-off date for follow-up was December 30, 2019. Follow-up information, particularly targeting sites of recurrence/progression, was collected via medical records, referring clinicians, including General Practitioners, the NSW Registry of Births, Deaths and Marriages, the National Death Index, managed by the Australian Institute of Health and Welfare (E02017/5/392), and the Ryerson Index website (public domain).

Endpoints

The main endpoint was time to local failure and corresponding time to ultimate local failure. Local failure was defined as persistent disease within the radiotherapy and surgery field after initial definitive treatment, or local recurrence after achieving complete clearance of the disease. Ultimate local failure was apparent when there was a local failure and salvage treatment was not attempted, or salvage treatment was performed but local malignancy recurred.

Cancer-specific survival (CSS) was designated as the secondary endpoint, the definition being those patients who either survived or those who died without HNC. Death with HNC was defined as those patients who still had cancer at the time of death.

The tertiary endpoint relates to whether a second malignancy developed, consequent to the aetiological factor (smoking) for this malignancy.

Statistical analysis

Statistical analysis was performed using SPSS statistics 26.0 (IBM, Armonk, New York). The Shapiro-Wilk test determined data distribution for continuous variables. The mean (standard deviation) and median (interquartile range (IQR)) values were reported for normally and non-normally distributed data respectively. Time-to-event analysis on primary outcomes was performed using the Kaplan-Meier method. The log rank test assessed differences between curves when present, the Mann-Whitney U test identified the difference between two groups, for all groups. The level of significance for all tests was set to $P<0.05$ and all P-values are two-sided.

RESULTS

Over the timeframe of the review (1974 to 2017), there were 53 patients who met the eligibility criteria, with a median follow-up period of 6.7 years. There was a perception in the 1980s that chemotherapy could be used to cure patients with an oral cavity primary. Thus, two patients commenced this as their definitive treatment and

were included in the analysis. The eligibility criteria covered those who had definitive treatment at this facility, without specifying which treatment was delivered. All dates were measured from the initial date of treatment.

Patient

Patient demographics are listed in table 1, noting that only two (4%) patients were never smokers, and six (11%) had no history of alcohol consumption. Consistent with these features is that most patients were males with an age range of 43 to 87 years. A prior HNC was recorded in 10 (19%) patients, 48 (91%) patients were fit for surgery, and only two (4%) patients had inoperable cancer. Twenty-three (43%) patients were treated pre-1990, and 30 (57%) beyond this time point.

Tumour

T stage was T1-2 in 36 (68%) patients, thus T3-4 in 17 (32%) patients (Table 1). The majority were N0 (38 patients, 72%), with sites of nodal involvement depicted in Figure 1. The median largest nodal size was 23 mm (interquartile range (IQR) 20-57 mm). Stage III-IV disease was present in 27 (50%) patients.

Table 1: Patient demographics and tumour features

	Total population N=53 (%)[c]	**Surgery only N=16 (%)**	**Radiotherapy only N=19 (%)**	**Surgery + radiotherapy N=16 (%)**	**P-value**
Age at presentation, years, mean (SD)	62 (10)	62 (12)	63 (10)	60 (8)	1
Gender					
Male	41 (77%)	11 (69%)	16 (84%)	14 (87%)	0.451[a]
Female	12 (23%)	5 (31%)	3 (16%)	2 (13%)	
Previous tumour[b]					
Head and neck	10 (19%)	7 (44%)	1 (5%)	2 (13%)	**0.015**[a]
Lung	1 (2%)	0	1 (5%)	0	1.000[a]
Other	3 (6%)	0	1 (5%)	2 (13%)	0.504[a]
Comorbidities[b]					
Diabetes	2 (4%)	0	1 (5%)	1 (6%)	1.000[a]
Hypertension	15 (28%)	2 (13%)	7 (37%)	5 (31%)	0.328[a]
Hypothyroidism	1 (2%)	1 (6%)	0	0	0.627[a]
Tobacco use					
Never smoked	2 (4%)	1 (6%)	0	1 (6%)	0.432[a]
Ex-smoker, not for two years	16 (30%)	7 (44%)	4 (21%)	4 (25%)	
Current/recent smoker	34 (64%)	8 (50%)	14 (74%)	11 (69%)	
Unknown	1 (2%)	0	1 (5%)	0	
Alcohol consumption					
Nil	6 (11%)	3 (19%)	0	2 (13%)	**0.022**[a]
Social only	12 (23%)	5 (31%)	6 (32%)	1 (6%)	
Daily drinker	28 (53%)	5 (31%)	10 (53%)	13 (81%)	
Unknown	7 (13%)	3 (19%)	3 (15%)	0	
Cancer operable	51 (96%)	16 (100%)	17 (90%)	16 (100%)	0.322[a]
Fit for operation	48 (91%)	16 (100%)	16 (84%)	15 (94%)	0.369[a]
Performance (ECOG) status					
0 - Normal	18 (34%)	5 (31%)	4 (21%)	8 (50%)	0.116[a]
1 - Symptoms/self-care	20 (38%)	5 (31%)	8 (42%)	7 (44%)	
2 - Ambulatory <50%	3 (6%)	0	3 (16%)	0	

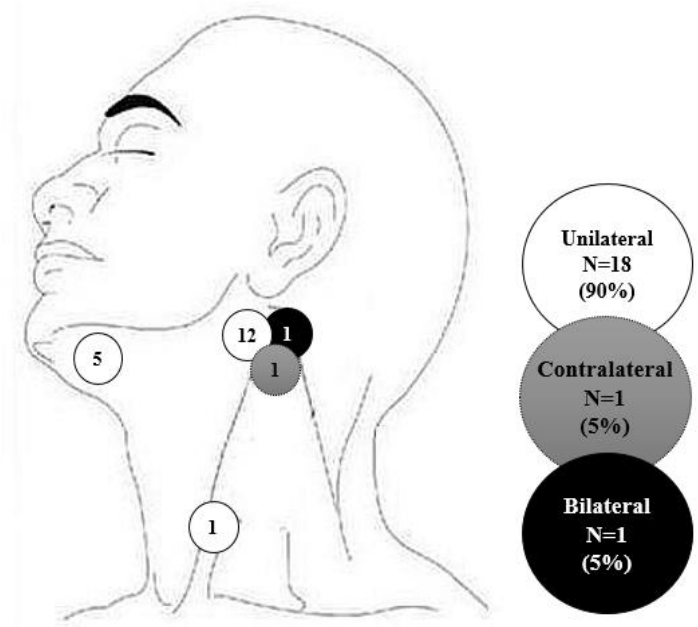
3 - Ambulatory >50%	0	0	0	0	
4 - Bedridden	0	0	0	0	
Unknown	12 (22%)	6 (38%)	4 (21%)	1 (6%)	
Tumour grade					
Well differentiated	7 (13%)	3 (19%)	1 (5%)	3 (19%)	0.595[a]
Moderately-well differentiated	33 (62%)	12 (75%)	8 (42%)	12 (75%)	
Poorly differentiated	4 (8%)	0	2 (11%)	1 (6%)	
Unknown	9 (17%)	1 (6%)	8 (42%)	0	
T stage (7th edition)					
T1	14 (26%)	10 (62%)	1 (5%)	2 (12%)	**0.004**[a]
T2	22 (42%)	3 (19%)	12 (63%)	7 (44%)	
T3	8 (15%)	2 (13%)	2 (11%)	3 (19%)	
T4	9 (17%)	1 (6%)	4 (21%)	4 (25%)	
N stage (7th edition)					
N0	38 (72%)	14 (88%)	13 (68%)	9 (56%)	0.565[a]
N1	7 (13%)	1 (6%)	2 (11%)	4 (25%)	
N2	6 (11%)	1 (6%)	3 (16%)	2 (13%)	
N3	2 (4%)	0	1 (5%)	1 (6%)	
Clinical stage (7th edition)					
I	13 (25%)	10 (61%)	1 (5%)	1 (6%)	**0.004**[a]
II	13 (25%)	2 (13%)	7 (37%)	4 (25%)	
III	11 (20%)	2 (13%)	4 (21%)	4 (25%)	
IV	16 (30%)	2 (13%)	7 (37%)	7 (44%)	

ECOG: Eastern Cooperative Oncology Group, NC: not calculable, SD: standard deviation

[a]Fisher's Exact test used when >20% of cells have an expected cell count less than 5, otherwise Pearson's Chi-square is used

[b]Not mutually exclusive, patients may have multiple previous tumours or comorbidities

[c]Includes two patients treated with chemotherapy only



Retromolar Trigone Neck Node Distribution by Level I-V (15 patients)

Level I	Level II	Level III	Level IV	Level V	Total Nodes
5 (25%)	14 (70%)	0	1 (5%)	0	20

Figure 1: Neck node distribution by level.

Treatment

The majority of patients (n=32) had surgery (Table 2) with 16 (30%) having surgery only, 19 (36%) having radiotherapy only, and 16 (30%) having combined treatment. Of note was that two patients had chemotherapy only as their initial treatment. Surgery took place to the primary in 31 patients, with one patient having neck dissection only, no primary surgery. A neck dissection was performed in 23 patients, all unilateral.

Radiotherapy was given to 35 patients, as definitive treatment to 19 patients with a median dose of 66 Gy (IQR 60-68 Gy), fraction number of 33, (IQR 31-35 fractions), and a treatment duration of 44 days (IQR 41-54 days), with only one patient having a treatment interruption of greater than one week. Radiotherapy was coupled with surgery in 16 patients for a median dose of 56 Gy (IQR 55-62 Gy), over 29 fractions (IQR 28-31 fractions), with a treatment duration of 41 days (IQR 38-44 days), and also only one patient having a treatment interruption of greater than one week.

The 23 patients treated prior to 1990 had 2D conformal planning, with median dose of 60 Gy (IQR 53-64 Gy) and fraction number of 30 (IQR 28-33 fractions). Subsequently, 30 patients treated after 1990 were predominantly managed with 3D planning and median dose of 66 (IQR 56-68 Gy) and 33 (IQR 28-34) fractions. From the 2000s onwards, IMRT was increasingly used but VMAT was not available during this timeframe.

Toxicity data was not a consistently recorded feature, hence, not available to be addressed for this population. The majority of patients were treated prior to the evidence of benefit of concurrent chemotherapy with radiotherapy for patients aged less than 70 years. Hence this factor was not included in the evaluation.

Table 2: Treatment details

	Total population N=53 (%)
Treatment modality	
Surgery	16 (30%)
Radiotherapy	19 (36%)
Surgery + radiotherapy[a]	16 (30%)
Chemotherapy	2 (4%)
Conventional radiotherapy details (radiotherapy only)	**19**
Dose, gray, median (IQR)	66 (60-68)
Fractions, median (IQR)	33 (31-35)
Treatment length, days, median (IQR)	44 (41-54)
Treatment interruptions >1 week	1 (5%)
Conventional radiotherapy details (+ surgery)	**16**
Dose, gray, median (IQR)	56 (55-62)
Fractions, median (IQR)	29 (28-31)
Treatment length, days, median (IQR)	41 (38-44)
Treatment interruptions >1 week	1 (6%)
Surgical treatment (± radiotherapy)	**32**
Surgery to primary site	31 (97%)
Neck dissection only	1 (3%)
Depth of invasion, mm, median (IQR)	7 (6-7)
Reconstruction to primary	**31**
Nil	1 (3%)
Pectoralis major	6 (20%)
Primary closure	5 (16%)

Radial forearm	5 (16%)
Buccal	3 (10%)
Jejunal	2 (7%)
Deltoid pectoralis	1 (3%)
Tongue	1 (3%)
Nasolabial	1 (3%)
Other	1 (3%)
Unknown	5 (16%)

IQR; Interquartile Range, MM; Millimetres

[a]Includes one patient treated with radiotherapy + surgery

Pathology

The median depth of infiltration of the primary was 7 mm, with clear surgical margins of at least 5 mm achieved in 10 patients. Positive margins were present in two patients, with in-situ disease at the margin in two patients, and 13 patients had disease within 5 mm of the margin. Only four were unknown margins. Twenty-three patients had a neck dissection with no tumour found in 13 (56%). Intracapsular disease was present in 5 patients, with extracapsular disease in two patients, gross extracapsular disease in one patient, and unknown disease in two patients. The type of reconstruction used in the 31 patients having surgery to the primary is indicated in Table 2, with many different types.

Outcomes

The median follow-up interval was 6.7 years (IQR 1.2-10.8 years). A complete response to all treatment was achieved in 46 (87%) patients (Table 3), with a local failure evident in 19 (36%) patients. The median time to local failure being evident was 9.8 months (supplement Table 1), greater (14.8 months) for those patients having surgery only, possibly reflecting earlier stage disease. The number of patients at-risk of disease failure or death are presented in supplement Table 2. There were four patients who were salvaged by surgery, thus ultimate local control (ULC) was achieved in 39 (74%) patients. By modality, there were four (25%) failures in patients having surgery alone (16 patients), 8 failures in 19 (42%) patients treated by radiotherapy alone, and 6 of 16 (38%) patients managed by the combined approach of surgery plus radiotherapy. This is graphically represented in Figure 2A, with a 5-year LC rate of 75% for surgery, 49% for radiotherapy, and 60% for combined treatment (p=0.262). With salvage included, the 5-year ULC rate was 75% for surgery alone, 69% for radiotherapy alone, and 73% for combined treatment (p=0.823) (figure 2B). Salvage was achieved by further surgery, although these figures were not statistically different, there was a strong clinical trend.

Nodal control (NC) was evident in 45 (85%) patients; the median time to nodal failure was 5.9 months (Table 3). Nodal failure was more likely in ipsilateral lymph nodes. A nodal recurrence occurred in 5 patients, with three having persistent nodal disease. By treatment modality, the 5-year NC rate was 93% for surgery only, 72% for radiotherapy only, and 100% for combined treatment (p=0.076) (Figure 2C). Salvage treatment to address the nodal failure was effective in 6 patients, for ultimate nodal control (UNC) in 51 (96%) patients. Patients treated with surgery (± radiotherapy) had a 5-year UNC rate of 100%, while patients treated with radiotherapy only had a 90% rate (p=0.177) (Figure 2D).

Five-year CSS demonstrates the survival decline progressively from T1-2 to T3-4 (T1 77%, T2 72%, T3 57%, T4 56%, p=0.578) (Figure 2E), also evident is the change from stage I-II to III-IV (stage I 76%, stage II 92%, stage III 40%, stage IV 60%, p=0.029) (Figure 2F). Not unexpectedly, N0 vs N1-3 also led to decline in CSS

(72% vs 47% respectively, p=0.178) (Figure 2G). When age was considered as a binary point of greater or less than 70 years, CSS was worse for patients aged >70 years (74% vs 47% respectively, p=0.029) (Figure 2H). Five-year overall survival (OS) depicts similar features with T3-4 and stages III-IV, having poorer survival compared to T1-2 (T1 86%, T2 63%, T3 38%, T4 33%, p=0.117) (Figure 2I), and stage I-II (stage I 85%, stage II 85%, stage III 36%, stage IV 38%, p=0.018) (Figure 2J), this being statistically significant. Patients who were N1-3 also had a worse OS than patients who were N0 (47% vs 65% respectively, p=0.319) (Figure 2K). Comparably, patients aged >70 years old had worse OS than those patients aged <70 years old (50% vs 63% respectively, p=0.004) (Figure 2L). Of interest is that one of the two patients having chemotherapy only as definitive treatment required no further treatment, and was a long term survivor. The numbers become small, however, there is no difference in ULC and CSS for those patients treated by radiotherapy pre-1990 versus post-1990.

A new primary developed in 18 (34%) patients, of median time 4.6 years (Table 3). In 10 patients, this was a new head and neck (H&N) primary, and in four patients a lung carcinoma. The median time to a new H&N primary was 5.2 years, and 4.9 years for a new lung primary. This is in addition to the cancers diagnosed prior to treatment (H&N in 10 patients, lung in one patient, and other in three patients, of which one had multiple other primaries) (Figure S1). Notable is that the likelihood of having a second primary increased with time since treatment.

Table 3: Treatment outcomes

	Total population N=53 (%)[e]	**Surgery only N=16 (%)**	**Radiotherapy only N=19 (%)**	**Surgery + radiotherapy N=16 (%)**	**P-value**
Treatment response					
Complete response	46 (87%)	16 (100%)	13 (68%)	15 (94%)	0.123[a]
Partial response	2 (4%)	0	2 (11%)	0	
Stable disease	1 (2%)	0	1 (5%)	0	
Progressive disease	4 (7%)	0	3 (16%)	1 (6%)	
Local recurrence					
No	34 (64%)	12 (75%)	11 (58%)	10 (63%)	0.380[a]
Yes	13 (25%)	4 (25%)	4 (21%)	5 (31%)	
Persistent disease	6 (11%)	0	4 (21%)	1 (6%)	
Time to local failure[b], months, median (IQR)	9.8 (4.3-19.2)	14.8 (8.0-32.1)	6.3 (0-25.9)	8.4 (3.2-17.6)	0.365
Site for local recurrence	**13**	**4**	**4**	**5**	
Surgical area	4 (31%)	4 (100%)	0	0	**<0.001**[a]
Radiation area	5 (38%)	0	4 (100%)	1 (20%)	
Surgical and radiation area	4 (31%)	0	0	4 (80%)	
Time to local recurrence, months, median (IQR)	10.3 (6.8-33.9)	14.8 (8.0-32.1)	20.5 (7.3-41.0)	10.3 (5.4-24.0)	0.804
Site for persistent disease	**6**	**0**	**4**	**1**	
Radiation area	5 (83%)	0	4 (100%)	1 (100%)	NC
Initial observation area	1 (17%)	0	0	0	
Time to persistent disease, days, median (IQR)	2.5 (0-240)	NC	2.5 (0-139)	0	0.8
Nodal recurrence					

No	45 (85%)	15 (94%)	14 (74%)	15 (94%)	0.336[a]
Yes	5 (9%)	1 (6%)	2 (10%)	1 (6%)	
Persistent disease	3 (6%)	0	3 (16%)	0	
Time to nodal failure[b], months, median (IQR)	5.9 (2.8-12.2)	13.1 (13.1-13.1)	3.1 (1.4-5.9)	6.7 (6.7-6.7)	0.145
Site for nodal recurrence	**5**	**1**	**2**	**1**	
Ipsilateral node	4 (80%)	1 (100%)	1 (50%)	1 (100%)	1.000[a]
Contralateral node	1 (20%)	0	1 (50%)	0	
Bilateral node	0	0	0	0	
Time to nodal recurrence, months, median (IQR)	9.7 (3.1-46.5)	13.1 (13.1-13.1)	3.1 (2.7-3.1)	6.7 (6.7-6.7)	0.259
Site for persistent disease	**3**	**0**	**3**	**0**	
Ipsilateral node	3 (100%)	0	3 (100%)	0	NC
Contralateral node	0	0	0	0	
Bilateral node	0	0	0	0	
Time to persistent disease, days, median (IQR)	95 (5.0-95.0)	NC	95 (5.0-95.0)	NC	NC
Nodal failure					
Nodal control	45 (85%)	15 (94%)	14 (74%)	15 (94%)	0.193[a]
Nodal fail	8 (15%)	1 (6%)	5 (26%)	1 (6%)	
Metastasis					
No	47 (89%)	15 (94%)	17 (89%)	14 (87%)	1.000[a]
Yes	6 (11%)	1 (6%)	2 (11%)	2 (13%)	
Time to metastasis, years, median (IQR)	3 (1.1-4.8)	5 (5.0-5.0)	1 (0.5-1.0)	3 (1.3-3.0)	0.301
Site of metastasis	**10**	**1**	**2**	**2**	
Lung	1 (17%)	0	0	0	NC
Liver	0	0	0	0	NC
Bone	4 (66%)	1 (100%)	2 (100%)	1 (50%)	1.000[a]
Other	1 (17%)	0	0	1 (50%)	1.000[a]
New primary					
No	35 (66%)	9 (56%)	14 (74%)	10 (62%)	0.547
Yes	18 (34%)	7 (44%)	5 (26%)	6 (38%)	
Time to new primary, years, median (IQR)	4.6 (2.8-6.4)	4 (2.8-5.1)	5.7 (1.2-8.1)	6.5 (3.1-13.3)	0.471
Site of new primary[d]	**18**	**7**	**5**	**6**	
Head and neck	10 (56%)	6 (86%)	0	4 (67%)	**0.013**[a]
Lung	4 (22%)	1 (14%)	3 (60%)	0	0.060[a]
Other	7 (39%)	2 (29%)	3 (60%)	2 (33%)	0.593[a]
Time to new head and neck primary, years, median (IQR)	5.2 (3.9-8.7)	4.1 (3.2-5.3)	NC	9.9 (5.9-15.7)	**0.019**
Time to new lung primary, years, median (IQR)	4.9 (1.8-9.1)	4 (4.0-4.0)	5.7 (1.1-5.7)	NC	0.655
Time to new other primary, years, median (IQR)	2.8 (1.1-4.2)	3.5 (2.8-3.5)	1.4 (1.1-1.4)	2.4 (1.1-2.4)	0.651
Ultimate local failure					
Ultimate local control	39 (74%)	12 (75%)	14 (74%)	11 (69%)	1.000[a]
Ultimate local fail	14 (26%)	4 (25%)	5 (26%)	5 (31%)	
Time to ultimate local failure[c], years, median	1 (0.5-2.4)	1.5 (0.9-4.2)	0.6 (0.4-1.3)	1 (0.5-4.9)	0.406

(IQR)					

IQR: Interquartile Range, NC: Not Calculable

[a]Fisher's Exact test used when >20% of cells have an expected cell count less than 5, otherwise Pearson's Chi-square is used

[b]Local failure and nodal failure include patients with recurrence and persistent disease at first local and nodal sites respectively

[c]Ultimate local and nodal failure include recurrence/persistent disease at second local and nodal sites respectively, and those patients who did not receive treatment for first local and/or nodal recurrence respectively

[d]Not mutually exclusive, patients may have multiple new primaries

[e]Includes two patients treated with chemotherapy only

Supplement Table 1: Treatment for recurrence and follow up.

	Total population N=53 (%)[f]	**Surgery only N=16 (%)**	**Radiotherapy only N=19 (%)**	**Surgery + radiotherapy N=16 (%)**	**P-value**
Local failure	**53**	**16**	**19**	**16**	
Local control	34 (64%)	12 (75%)	11 (58%)	10 (62%)	0.559
Local fail	19 (36%)	4 (25%)	8 (42%)	6 (38%)	
Recurrent treatment[b]	**23**	**5**	**11**	**6**	
No treatment	5 (22%)	1 (20%)	3 (27%)	1 (17%)	0.351[a]
Surgery	12 (52%)	3 (60%)	7 (64%)	2 (33%)	
Radiotherapy	2 (9%)	0	0	2 (33%)	
Surgery + radiotherapy	1 (4%)	0	0	0	
Chemotherapy	2 (9%)	1 (20%)	0	1 (17%)	
Unknown	1 (4%)	0	1 (9%)	0	
Response to recurrent treatment	**17**	**4**	**7**	**5**	
Complete response	11 (65%)	2 (50%)	6 (86%)	2 (40%)	0.575[a]
Partial response	2 (12%)	1 (25%)	0	1 (20%)	
Stable disease	1 (6%)	0	0	1 (20%)	
Progressive disease	3 (17%)	1 (25%)	1 (14%)	1 (20%)	
Second local recurrence	**17**	**4**	**7**	**5**	
No	8 (47%)	1 (25%)	5 (71%)	1 (20%)	0.203[a]
Yes	3 (18%)	2 (50%)	0	1 (20%)	
Persistent disease	6 (35%)	1 (25%)	2 (29%)	3 (60%)	
Time to second local recurrence, years, median (IQR)	5 (2.1-5.0)	3.5 (2.1-3.5)	NC	6.7 (6.7-6.7)	0.221
Time to second persistent disease, years, median (IQR)	1 (0.5-1.6)	0.9 (0.9-0.9)	0.8 (0.5-0.8)	1 (0.6-1.0)	0.807
Second nodal recurrence	**17**	**4**	**7**	**5**	
No	17 (100%)	4 (100%)	7 (100%)	5 (100%)	NC
Yes	0	0	0	0	
Persistent disease	0	0	0	0	
Ultimate nodal failure					
Ultimate nodal control	51 (96%)	16 (100%)	17 (89%)	16 (100%)	0.322[a]
Ultimate nodal fail	2 (4%)	0	2 (11%)	0	
Time to ultimate nodal failure[c], years, median	0.3 (0.3-0.3)	NC	0.3 (0.3-0.3)	NC	NC

(IQR)					
Disease free[d]					
No	19 (36%)	5 (31%)	8 (42%)	5 (31%)	0.735
Yes	34 (64%)	11 (69%)	11 (58%)	11 (69%)	
Follow up status					
Alive	6 (11%)	1 (6%)	3 (16%)	2 (13%)	0.602[a]
Dead, not with head and neck cancer	32 (61%)	12 (75%)	9 (47%)	9 (56%)	
Dead, with head and neck cancer	15 (28%)	3 (19%)	7 (37%)	5 (31%)	
Follow up interval, years, median (IQR)	6.7 (1.2-10.8)	8.5 (5.2-16.1)	2 (0.6-8.6)	6 (1.3-14.8)	0.072
Survival interval, years, median (IQR)[e]	7.1 (4.4-14.0)	5.2 (5.2-5.2)	7.4 (6.8-7.4)	13 (1.8-13.0)	0.651

IQR; interquartile range

[a]Fisher's Exact test used when >20% of cells have an expected cell count less than 5, otherwise Pearson's Chi-square is used

[b]Treatment for first local and/or nodal recurrence, including persistent disease (n=23 patients)

[c]Ultimate local and nodal failure include recurrence/persistent disease at second local and nodal sites respectively, and those patients who did not receive treatment for first local and/or nodal recurrence respectively

[d]Disease free is defined in patients who did not have ultimate local and nodal failure, no distant metastasis, and did not die from their head and neck cancer

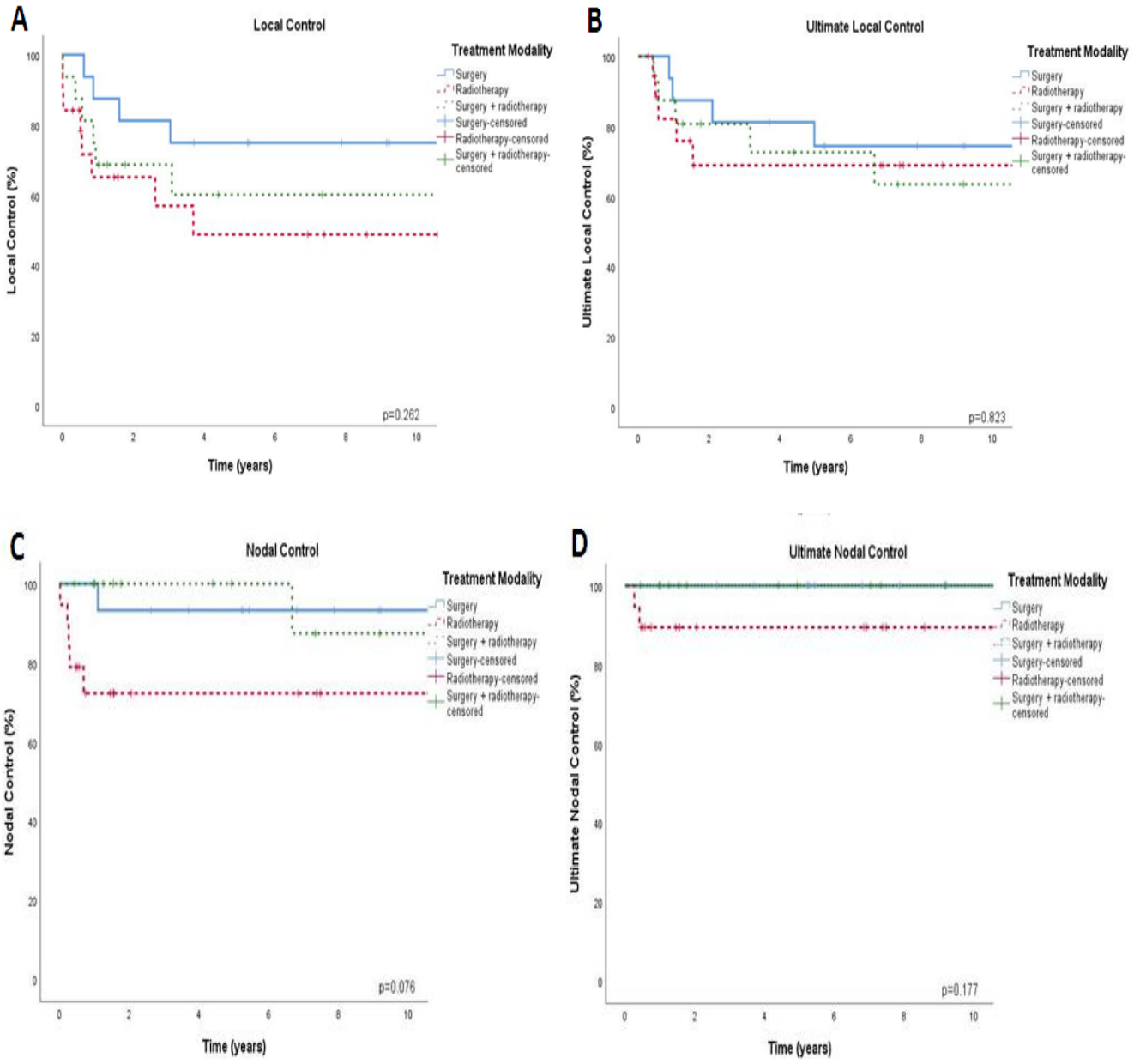
[e]Survival interval for alive patients only

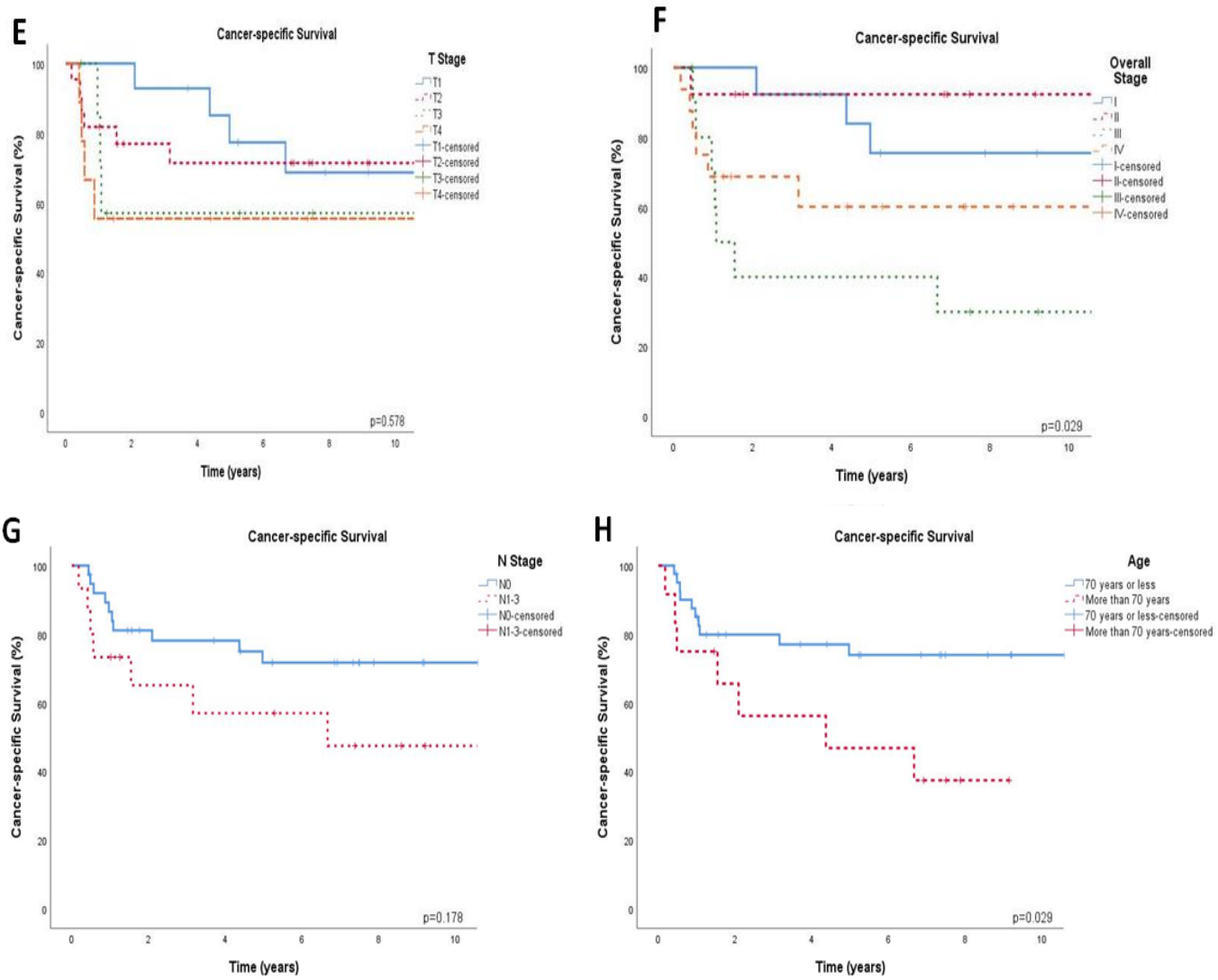
[f]Includes two patients treated with chemotherapy only

Supplement Table 2: Number of patients at-risk of disease failure or death.

		Number of patients					
Figure	**Variable**	**0 years**	**2 years**	**4 years**	**6 years**	**8 years**	**10 years**
2A	Surgery	16	13	11	9	8	6
	Radiotherapy	19	8	6	6	4	3
	Surgery + radiotherapy	16	8	7	6	5	5
2B	Surgery	16	14	12	9	8	6
	Radiotherapy	19	9	9	9	5	4
	Surgery + radiotherapy	16	10	9	8	6	5
2C	Surgery	16	14	12	9	7	5
	Radiotherapy	19	7	6	6	3	3
	Surgery + radiotherapy	16	10	10	8	6	5
2D	Surgery	16	15	13	10	8	6
	Radiotherapy	19	10	9	9	5	4
	Surgery + radiotherapy	16	10	10	8	6	5
2E	T1 stage	14	14	13	10	7	6
	T2 stage	22	14	14	13	9	6
	T3 stage	8	4	3	2	1	1
	T4 stage	9	5	4	3	2	2
2F	Stage I	13	13	12	9	7	6
	Stage II	13	10	10	10	7	6
	Stage III	11	5	4	4	2	1
	Stage IV	16	9	8	5	3	2
2G	N0	38	29	26	22	15	13
	N1-3	15	8	8	6	4	2
2H	≤70 years	41	30	27	22	18	15

	>70 years	12	7	7	6	1	0
2I	T1 stage	14	14	13	10	7	6
	T2 stage	22	14	14	13	9	6
	T3 stage	8	4	3	2	1	1
	T4 stage	9	5	4	3	2	2
2J	Stage I	13	13	12	9	7	6
	Stage II	13	10	10	10	7	6
	Stage III	11	5	4	4	2	1
	Stage IV	16	9	8	5	3	2
2K	N0	38	29	26	22	15	13
	N1-3	15	8	8	6	4	2
2L	≤70 years	41	30	27	22	18	15
	>70 years	12	7	7	6	1	0




E
Cancer-specific Survival
T Stage
T1
T2
T3
T4
T1-censored
T2-censored
T3-censored
T4-censored
Cancer-specific Survival (%)
p=0.578
Time (years)
F
Cancer-specific Survival
Overall Stage
I
II
III
IV
I-censored
II-censored
III-censored
IV-censored
Cancer-specific Survival (%)
p=0.029
Time (years)
G
Cancer-specific Survival
N Stage
N0
N1-3
N0-censored
N1-3-censored
Cancer-specific Survival (%)
p=0.178
Time (years)
H
Cancer-specific Survival
Age
70 years or less
More than 70 years
70 years or less-censored
More than 70 years-censored
Cancer-specific Survival (%)
p=0.029
Time (years)

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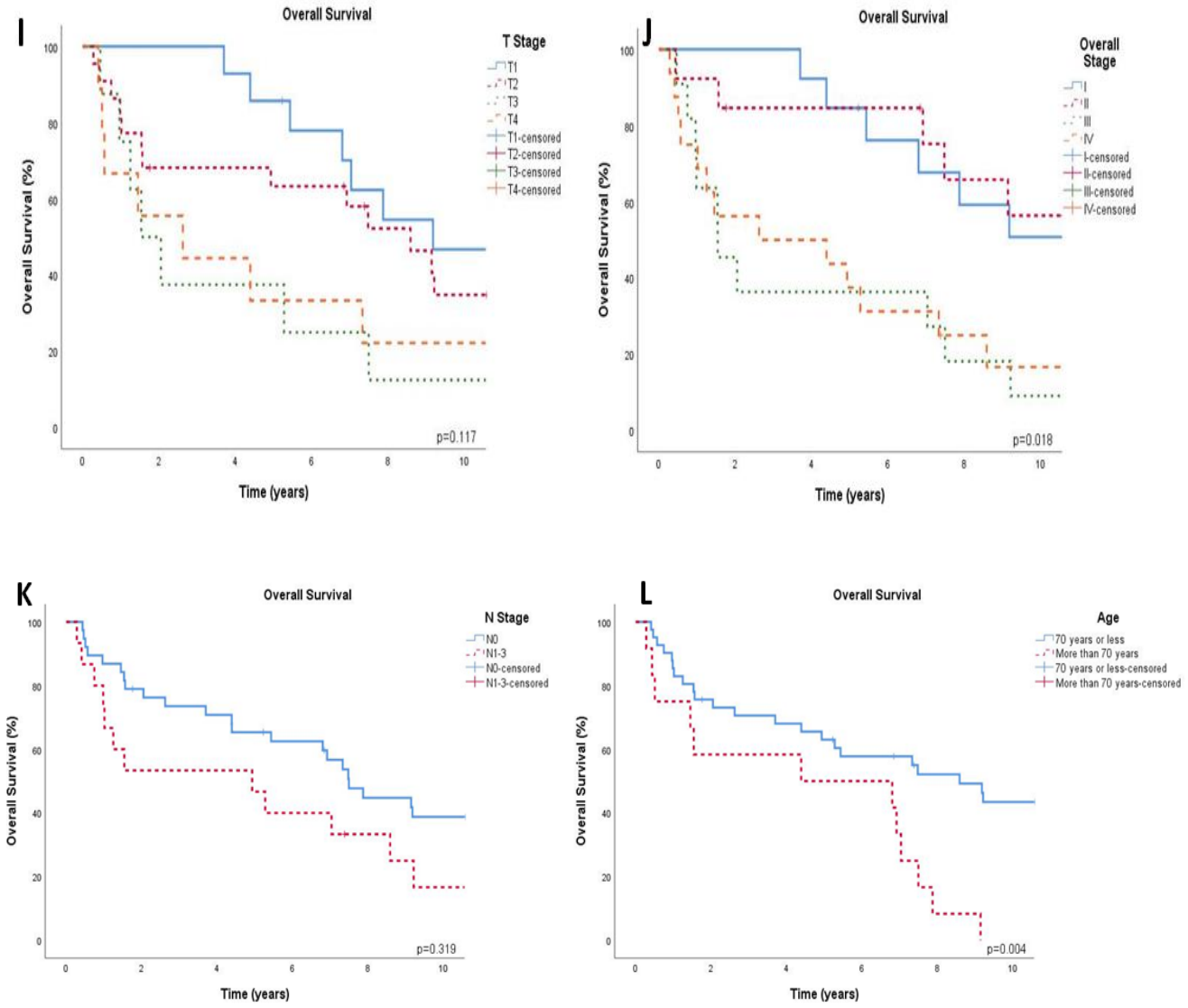
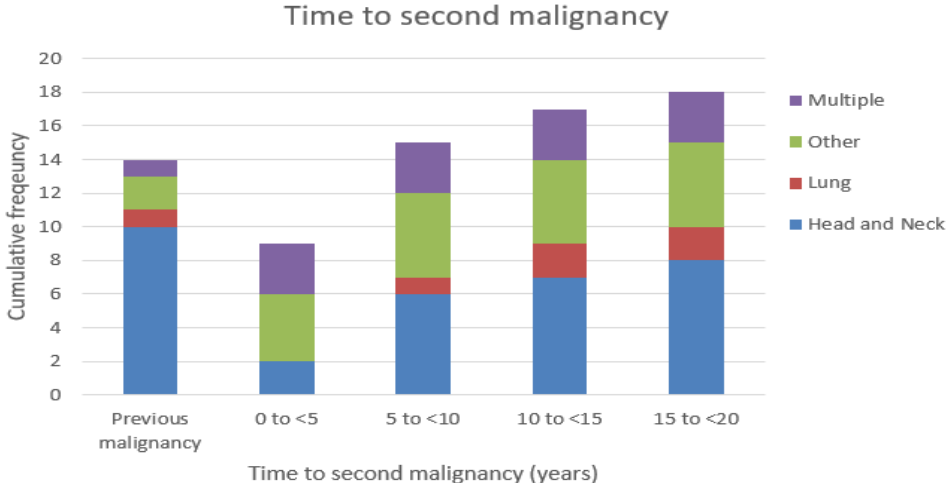


Figure 2: Impact of treatment modality on a) local control, b) ultimate local control, c) nodal control, and d) ultimate nodal control (surgery=16, radiotherapy=19, surgery plus radiotherapy=16), cancer-specific survival by e) T stage (T1=14, T2=22, T3=8, T4=9), f) overall stage (I=13, II=13, III=11, IV=16), g) N stage (N0=38, N1-3=15), and h) age (≤70 years=41, >70 years=12), and overall survival by i) T stage (T1=14, T2=22, T3=8, T4=9), j) overall stage (I=13, II=13, III=11, IV=16), k) N stage (N0=38, N1-3=15), and l) age (≤70 years=41, >70 years=12).



Supplement Figure 1. Time to second malignancy

DISCUSSION

Squamous cell carcinomas originating in the RMT are uncommon.[10,11] The numbers presented in this review seem small, however, consistent with the literature. Horta, in a review of the management of this anatomically defined carcinoma, reported on the outcomes for seven series with only one having more than 100 patients in their review.[2] Rizvi described those patients included in the SEER database from 1973 to 2012, where 4022 patients were defined.[3,14] Nishi indicated that it represented only 1.4% of all oral cancers in Japan.[6] As in this series, most patients have a smoking and alcohol consumption background.[11]Its proximity to the oropharynx raises the interesting point as to whether there can be a HPV related association,[5] to date this has not been established.

Given the thin mucosal coverage overlying the bony ramus of the mandible, presentation with locally advanced disease is not unexpectedly common.[15] Modern imaging techniques allow for better demonstration of the extent of bone involvement.[9] Horta describes the various types of mandibular resections which can be performed, dependent upon the extent of disease,[2] with various modes of reconstruction.[11] Despite this extent of resection, clear margins are only evident in the minority,[15] in this series in only 10 of 31 (32%) patients having surgery. Deo reported that negative margin resections could be achieved in 42 (93%) patients,[16] and for Faisal, it was only 54%.[10] Kerker indicated that close or positive margins are more likely to occur in the RMT compared to other oral cavity sites.[15] Smaller size, whilst allowing for robotic resection,[12] does not necessarily denote a more favourable prognosis where bone invasion is evident.[17] Ellis advised this may not be as significant a factor where surgery is performed by high volume surgeons.[18]

Radiotherapy, as a definitive treatment, is less commonly used.[19] Scher, using a chemoradiotherapy approach, records a loco-regional failure rate of 41% for a population of patients with oral cavity primaries.[13] Hitchcock notes loco-regional control rate of 52% for stage I-III, and 46% for stage IV.[19] This series records 8 of 19 patients treated initially by definitive radiotherapy as failing locally. There were some patients surgically salvaged so that the 5-year ULC rate for patients initially treated with radiotherapy is 69%. Whilst the ULC for the radiotherapy only patients ends up being reasonable, this is in the context that a considerable number of these patients required two procedures to achieve this end point, compared to one procedure for the majority of those patients having surgery as the initial treatment. The necessity for two procedures to achieve ULC is, if not statistically significant, clinically very important with durable effect upon survivorship.

Surgery (± radiotherapy) is more consistently reported as demonstrating improved outcomes. Hitchcock recorded 5-year CSS rates of 82% for surgery versus 52% for radiotherapy for stage I-III, although there are comparable outcomes for stage IV disease (surgery 45% versus radiotherapy 43%).[19] In the SEER database, on multivariate analysis, there was improved OS and disease-specific survival (DSS) for surgery.[14] This large database also records a better cancer-specific mortality rate for RMT than for other sites in the oral cavity.

This series reports better CSS and OS for lower T stage (T1-2 vs T3-4), low overall stage (stage I-II vs stage III-IV), low N stage (N0 vs N1-3) and age (<70 years versus >70 years). The same perspective is evident for these factors when considered for OS. Early stage disease carries a more favourable outlook as depicted here, and in the SEER database,[14] where the addition of radiotherapy to surgery is defined as conveying a better result.

The tertiary event in this audit was to investigate the incidence of second malignancy, both prior too, and subsequent to treatment. There is a high likelihood of this occurring, reflective of the strong prevalence of smoking and alcohol use,[20,21] apparent across other HNC sites (floor of mouth and larynx).[21,22]

The limiting feature is the time frame during which these patients were treated, a feature which is common with other case series. It should be noted that all staging is clinical with consistency in the management approach at the HNC clinic. The only missing information which would have relevance is the decision statements defining the rationale for surgery versus radiotherapy.

CONCLUSIONS

Carcinomas arising in the RMT present a therapeutic challenge. Many can present with advanced disease with bone involvement, apparent both clinically, and with better imaging procedures, which then defines the process and outcome of management. Surgical resection with appropriate reconstruction, and where needed with added radiotherapy, ensures a more favourable outcome, at least as initial upfront treatment, readily apparent here in Australia and around the world.

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