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Neck Failure Following A Pathologically Staged Negative Neck Dissection (pN0) in Oral Squamous Cell Carcinoma (OSCC). A Systematic Review

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Abstract

Background

Due to the risk of occult cervical metastasis, elective neck dissection (END) is recommended in the management of patients with early oral cancer. Despite maximal surgical treatment some patients relapse in the neck. This paper presents systematic review and meta-analysis of studies that recorded isolated regional recurrence (RR) in the pN0 neck following END in order to quantify the failure rate.

Materials and Methods

NCBI and Ovid databases were systematically searched for articles published between January 2009 and January 2019. Studies reporting RR following END in patients with OSCC who had no pathological evidence of lymph node metastasis to the neck were eligible for inclusion in

this meta-analysis. In addition, selected large head and neck units were invited to submit unpublished data which met the criteria of this study.

Results

Search criteria produced a list of 5448 papers of which 18 studies met the inclusion criteria. Three institutions also contributed unpublished data. This included a total of 4824 patients. 8 datasets included patients staged T1-T4 with RR 17.3%, 13 datasets included patients staged T1-T2 with RR 7.5%. Overall across all 21 studies, isolated neck recurrence was identified in 627 cases giving a mean RR of 13.0%. Further data analysed included study design, primary tumour site, treatment protocol, follow-up period and follow-up protocol.

Conclusions

Mean regional recurrence after pN0 neck dissection was 13%. Recurrence was higher amongst studies of T1-T4 as compared with T1-T2. This should be considered when offering END and evaluating other methods of managing cN0 neck.

Word count 249/250

Key words

Elective neck dissection
Oral cancer
Neck recurrence
Sentinel node biopsy

Introduction

Oral squamous cell carcinoma (OSCC) is one of the few cancers that continues to increase in incidence in the developed and developing world (1). It is an aggressive cancer with high recurrence and mortality, even in patients who initially present with early local disease and no detectable metastasis (2). The current gold standard is to complete an elective neck dissection (END) on patients with early oral cancer (3-5).

END involves the removal of lymph node levels with the highest incidence of metastasis. Removal of these levels gives the highest probability of identifying patients with occult metastasis and removal of pathological nodes. Multiple studies have shown an occult metastasis rate of up to 30% in clinically node negative patients (6, 7). Multiple studies have examined the improved sensitivity and specificity of neck dissection in identifying neck disease compared with imaging modalities. D'Cruz et al (6) and Hutchinson et al (7) showed an improvement in overall survival and disease-free survival in patients who underwent END compared with clinical surveillance hazard ratio for death of 0.64 and 0.71 resepectively.

Sentinel node biopsy is an alternative method of identifying occult metastasis. It has not been directly compared with END in a trial setting. The Sentinel European Node Trial (SENT) showed a disease specific survival (94%) and overall survival (88%) similar to that reported for END (8).

Currently we do not have a clear standard for the expected nodal relapse rate following END, particularly when the neck dissection has been staged N0. The establishment of a standard would allow comparison of outcomes, comparison with other techniques and allow calculation of the numbers needed to power randomised studies.

In this study we examined isolated regional recurrence (RR) following a pathologically staged N0 END as the primary outcome. We defined RR as nodal recurrence without recurrence at the primary site at any time following tumour resection and END (by definition in a clinically negative neck). The secondary outcomes in this study included location and timing of RR.

Method

Systematic review was carried out according to PRISMA guidelines (ref). The National Centre for Biotechnology Information (NCBI) Pubmed (www.ncbi.nlm.nih.gov) and Ovid MEDLINE (U.S national library of medicine) databases were searched for articles published between January 2009 and January 2019. The key terms used were oral, mouth, tongue, cancer, recurrence, metastasis, failure, neck, cervical, lymph*, nod*. The asterix denotes terms used with open suffix. Only full texts, in English language, relating to human species were included. All controlled clinical trials, prospective and retrospective cohorts, case-control studies, and case series were included. Repeat articles were removed using EndNote software (www.myendnoteweb.com). The reference list was manually checked to identify studies which met the study criteria [Figure 1].

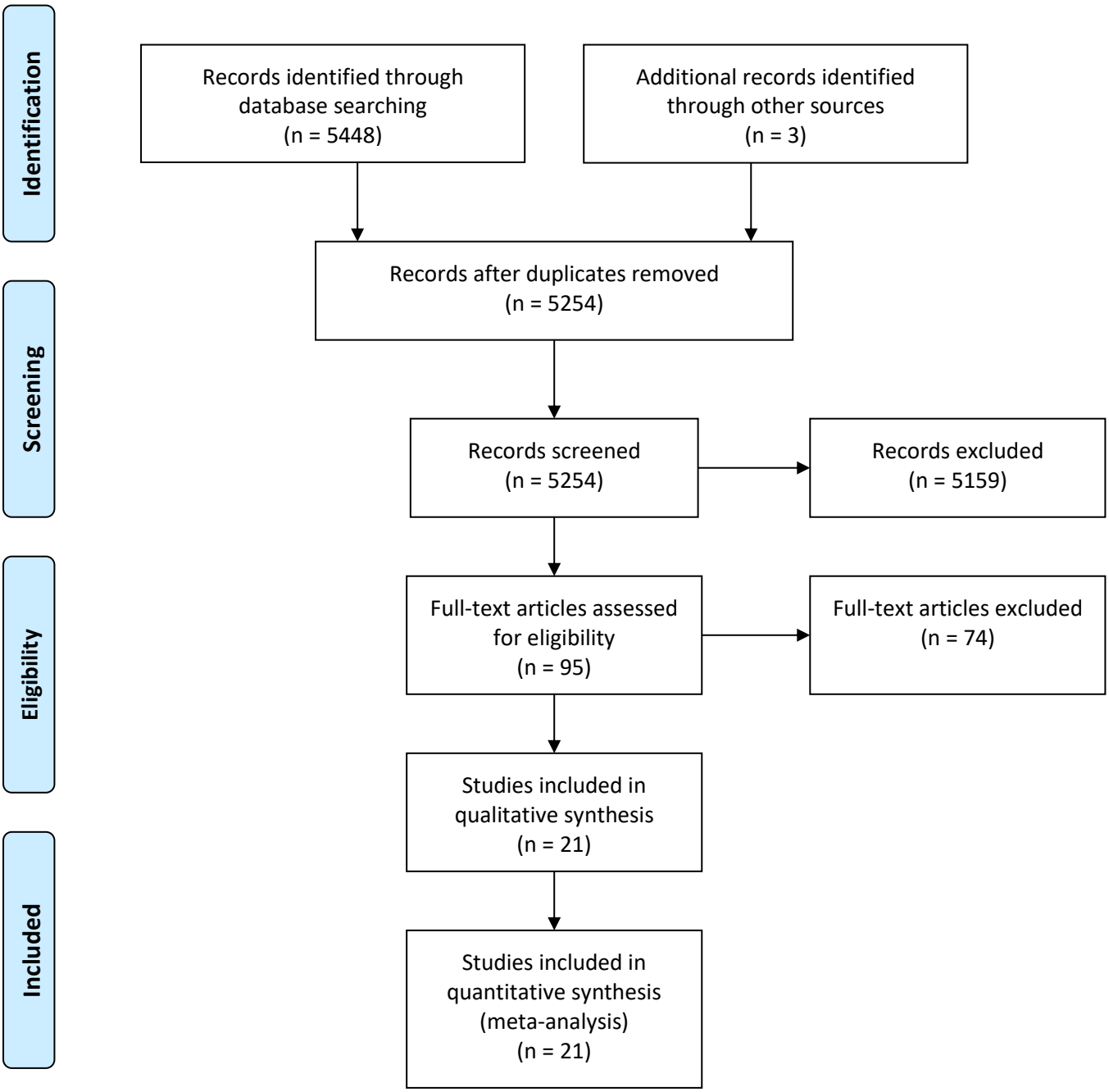
Database search was first carried out by the first author and thereafter independently by a second investigator. A standard proforma was used to collect data on study design, primary tumour site and T stage, number of patients included, number of patients with isolated regional recurrence, treatment protocol, follow-up period and follow-up protocol.

Few studies reported RR as a primary outcome. Papers were included that reported the isolated regional recurrence (neck metastasis) of patients with OSCC who underwent END, staged pathological with no neck metastasis (pN0), in the absence of recurrence at the primary site.
Many studies were excluded because they did not publish a breakdown of regional recurrence based on pathological neck status. Most commonly, studies reported a combined recurrence rate for all patients following neck dissection (positive and negative pathological neck stage). Corresponding authors of studies where this had occurred were contacted and invited to submit breakdown of the data for the pN0 cohort of patients. This produced a further 3 studies which are included in the results below. All patients who had concurrent local recurrence were excluded.

It was expected that RR would be influenced by the T staging. For this reason, the data was divided into two cohorts according to the range of T stage included in the study; T1-T2 or T1-T4.

Some studies stated RR as a percentage. This percentage was calculated for the other studies from the incidence of RR and the total number of pN0 cases. Boxplot was used to graphically represent the range of RR in each cohort.

Figure 1 Study selection for the meta-analysis



Results

Of 5254 papers identified by the initial search, 18 met the inclusion criteria (3833 patients). All but one study was retrospective. Seven studies included T1-T4 primary tumours (n=2441) the remaining 11 studies focussed on T1-T2 tumours only (n=1392). Study design inclusion and exclusion criteria are showing in Table 1 (T1-T4) and Table 2 (T1-T2). In addition three units submitted retrospective anonymised data derived from institutional audit databases (Leeds n=589, Amrita n=270, Virgen de las nieves n=132 cases).

A total of 4824 patients with pN0 disease were thus available for analysis. Across the combined 21 datasets, isolated neck recurrence was identified in 627 cases giving a mean neck recurrence rate (RR) of 13.0%.

Table 1 Study characteristics and isolated regional recurrence reported in studies of T1-T4 primary tumours

First author year country (reference)	Study Design	Squamous Carcinoma Site	pN0 Patient Number	Indications for post-operative radiotherapy (PORT) and chemoradiotherapy (CRT)	Isolated Regional Recurrence (%)	Follow-up (months)	Follow-up Protocol
Kang 2011 Taiwan (9)	Retrospective	Oral	149	PORT if pT4 or margin ≤4mm	6.0	Median 78	Unspecified
Poeschl 2012 Austria (10)	Retrospective	Maxillary alveolar or gingival, palatal	33	PORT if involved margins	18.2	Median 42.4, range 6-130	Unspecified
Amit 2014 International (11)	Retrospective	Oral	1913	Indications for PORT/CRT not specified	23.0	Median 68	Unspecified
Givi 2016 USA (12)	Retrospective	Maxillary alveolus and hard palate	30	Indications for PORT not specified	3.0	Median 52.5, range 0.6-261	unspecified

Shimamoto 2017 Japan (13)	Retrospective	Oral	156	PORT or CRT not administered to pN0 group	2.6	Median 75.3	1st year monthly, thereafter 2 monthly. CT or PETCT 6 monthly for 2 years
Troeltzsch 2018 Germany (14)	Retrospective	Oral	86	PORT/CRT indications as per German national guidelines (4)	5.8	Median 46	1st and 2nd year 3 monthly with CT 6 monthly. Thereafter seen upto 5 years.
So 2018 S. Korea (15)	Retrospective	Oral tongue	74	Indications for PORT not specified	5.4	Median 46.9, range 3-179	Unspecified
Amrita Institute of Medical Sciences India *	Retrospective	Oral tongue and floor of mouth	270	Indications for PORT not specified	5.6	Median 31.5	Unspecified
Total			2711				

*unpublished data requested directly from unit

Table 2: Study characteristics and isolated regional recurrence reported in studies of T1-T2 primary tumours

First author year country (reference)	Study Design	Squamous Carcinoma Site	pN0 Patient Number	Indications for post-operative radiotherapy (PORT) and chemoradiotherapy (CRT)	Isolated Regional Recurrence (%)	Follow-up (months)	Follow-up Protocol
Huang 2010 Taiwan (16)	Retrospective	Oral	89	No adjuvant therapy	3.4	Median 40, range 1-80	unspecified
Lin 2011 Australia (17)	Retrospective	Oral tongue	23	Indications for PORT/CRT not specified	8.6	Median 34, range 4-132	Unspecified
Liao 2012 Taiwan (18)	Retrospective	Oral	387	No adjuvant therapy	8.0	Median 66, range 8-167	Unspecified
Tai 2012 Taiwan (19)	Retrospective	Oral tongue	142	CRT administered if inadequate surgical margin	9.9	Median 42.4, range 7-112	1st year monthly, second year 2 monthly, thereafter 3 monthly
Ganly 2013	Retrospective	Oral tongue	164	No adjuvant therapy (therefore excluded	14.0	Unspecified	Unspecified

USA (20)				close margins, PNI, LVI)			
Feng 2014 China (21)	Retrospective	Oral	116	No adjuvant therapy	9.5	Median 58	Clinic or telephone: 1st year 2monthly, 2nd year 3 monthly, 3rd-5th year 6 monthly, Thereafter 6-12 monthly
Kelner 2014 Brazil (22)	Retrospective	Oral tongue and floor of mouth	128	PORT administered if margin ≤ 0.5cm, PNI	5.5	Median 68.7, range 6-282	Unspecified
Yeh 2014 Taiwan (23)	Retrospective	Oral	137	Post-operative radiotherapy: Positive margin	5.8	Median 61.9, range 24-130	1st year 1 monthly, Second year 2 monthly Thereafter 3 monthly
Low 2016 Australia (24)	Retrospective	Oral tongue and floor of mouth	36	Indications for PORT not specified	7.0	Median 38.4, range 5-180	Unspecified
Hussain 2016	Retrospective	Oral tongue	133	PORT administered if LVI**, PNI**.	1.5	Median 46	Unspecified

Pakistan (25)				CRT administered if positive margins			
Hernando 2016 Spain (26)	Prospective	Oral	37	PORT administered if positive margins	13.5	Mean 48.2, range 7-70	Unspecified
Leeds General Infirmary UK*	Retrospective	Oral	589	No adjuvant therapy	6.8	Unspecified	Unspecified
Hospital Universitario Virgen de las nieves Spain*	Retrospective	Oral	132	Unspecified	7.6	Unspecified	Unspecified
Total			2113				

*unpublished data requested directly from centre

** perineural invasion (PNI), lymphovascular invasion (LVI)

T1-T4 cohort

Across eight studies of T1-T4, 468 RR occurred in 2711 pN0 cases [table 1]. This gives calculated mean RR of 17.3%.

Individually, the T1-T4 studies reported a RR ranging between 2.6% and 23.0%. The average reported RR across these studies is 8.7% with a standard deviation (SD) 7.1. Studies by Poeschl et al (RR18.2%), Amit et al (RR23.0%), Shimamoto et al (RR2.6%) and Givi (RR3.0%) reported RR more than 2.5SD from this mean (10-13).

Poeschl et al studied maxillary SCC only, all recurrences in pN0 cases were from pT4 tumours (10). Givi et al also studied maxillary alveolus and hard palate OSCC. The majority of their pN0 patients were staged pT1-2 (21 of 30 patients) (12). Amit et al. contributed the largest number of patients for analysis with cases collected from 11 cancer centres across the world. Of note 32% of these cases were T4 stage, overall positive margin was 11% and mean surgical nodal harvest was 25. Nevertheless, large patient databases often have wide variation in local protocol (11). Shimamoto et al was the only study which specified routine imaging during the follow-up protocol. They describe a 6 monthly CT or PETCT regimen for the first 2 years in follow-up. Otherwise their overall patient group was predominantly pT2 and patients received a level I-III END (13).

T1-T2 cohort

Across 13 studies including T1-T2 cases only, 158 RR occurred in 2113 pN0 cases [table 2]. This gives a calculated mean RR of 7.5%.

These studies reported a RR between 1.5% and 14.0%. The mean reported RR across these studies was 7.8% with a SD 3.5. Studies by Huang et al (RR3.4%), Ganly et al (RR14.0%), Hussain et al (RR1.5%) and Hernando (RR13.5%) reported RR more than 2.5SD from this mean (16, 20, 25, 26).

Huang et al recognised that the RR did not statistically differ between patients who had END and those who did not (p=0.44)
82% cases had well differentiated tumour with 92% negative lymphovascular invasion and 94% negative perineural invasion (16). Ganly et al reported a higher proportion of unfavourable markers in their patient cohort. This includes 32% well differentiated tumour, and 76% negative perineural invasion. They found a statistical association between tumour depth and RR. 89% of their patient cohort had tumour depth >4mm (20). Hussain et al described the

administration of adjuvant therapy to all tumours with perineural or lymphovascular invasion. In their study, 66% of patients received adjuvant radiotherapy or chemoradiotherapy (25).

Time to recurrence

Time to recurrence was reported in one published paper and one invited dataset. Amrita Institute of Medical Sciences had a mean time to RR of 14.9 months (range 5-29 months). This value was specific to patients staged pN0 and developed isolated RR. Ganly et al reported a shorter time to RR of 7.5 months (range 2.3-29 months) in the ipsilateral neck and 8.9 months (range 5-58 months) in the contralateral neck (20).

Location of recurrence

Six datasets commented on the location of the recurrence (table 3). This represented data from 466 patients of which 44 had isolated regional recurrence (9.4%). Of these cases, 12 patients developed RR in the contralateral neck (27% of cases with RR). These recurrences occurred outside the field of END. In addition a further 10 cases where specified as occurring in the ipsilateral neck but outside the field of END.

Table 3 Study characteristics and isolated regional recurrence reporting on location and number of nodal recurrence

Author year country (reference)	**T stage**	**Number of pN0 patients**	**Number of pN0 patients with Isolated Regional Recurrence**	**Location and number of nodal recurrence**
Poeschl 2012 Austria (10)	T1-T4	30	6	Ipsilateral: 5 in levels IV and V Contralateral: 1

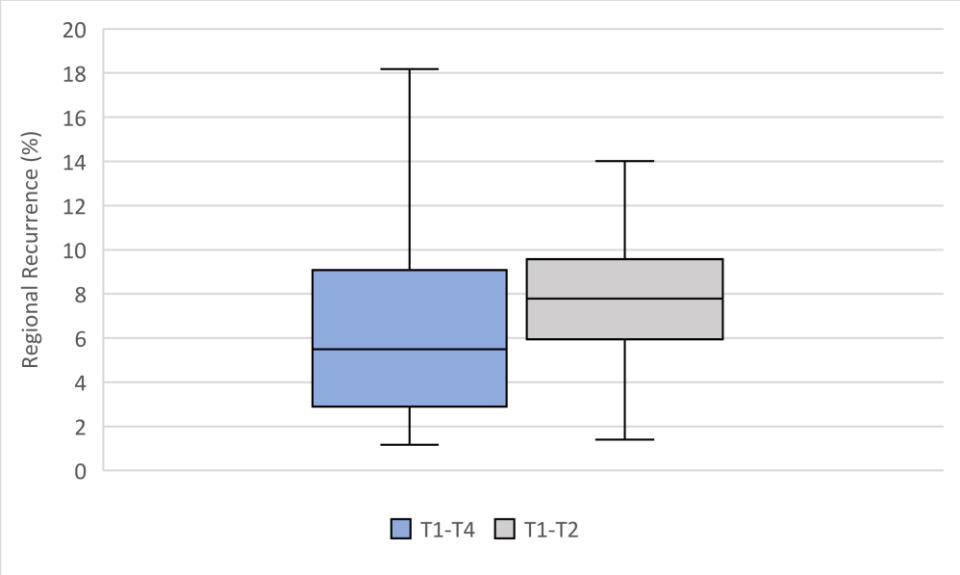
Shimamoto 2017 Japan (13)	T1-T4	156	4	Ipsilateral: 2 level IV Contralateral: 2 level I and III All beyond field of ND
Troeltzsch 2018 Germany (14)	T1-T4	86	5	Ipsilateral: 1 level I, 1 level III and 2 multiple levels Contralateral: 0
So 2018 S. Korea (15)	T1-T4	74	4	Ipsilateral: 1 in field of ND and 3 outside field of ND Contralateral: 0
Lin 2011 Australia (17)	T1-T2	23	2	Ipsilateral: 2 Contralateral: 0
Ganly 2013 USA (20)	T1-T2	164	23	Ipsilateral: 14 Contralateral: 9

Variables in management

The follow-up regimen was not specified in most studies (n=15). Five studies reporting follow up showed a wide variation in clinical and imaging protocol. It should be noted that the follow-up listed refers to the whole study population and not the pN0 subgroup in isolation. The minimum median follow-up time was 34 months (2.8 years).

The indications for post-operative radiotherapy (PORT) or Chemoradiotherapy (CRT) were reported in most studies, however the number of patients in the group of interest (pN0) receiving adjuvant therapy was not reported. In six studies adjuvant therapy was not offered to any patients. This represents a minimum of 847 patients in T1-T2 cohort (n=2204) and 156 patients in T1-T4 cohort (n=2825) who did not receive adjuvant therapy.

Figure 2. Boxplot showing pooled regional recurrence data for two cohorts of pN0 patients; T1-T2 vs T1-T4



Discussion

The principle aim of this study was to identify the isolated neck recurrence following pN0 END in the literature and unpublished data. This has been shown to be 13% overall, 7.5% in T1-T2 studies and 23% in T1-T4 studies.

END is commonly offered to patients with OSCC who are staged as cN0. Clinical staging is based on the absence of lymphadenopathy on preoperative clinical and radiological examination. Studies have shown a survival advantage when patients undergo END alongside tumour excision (6, 7) compared with surveillance alone. This has since been incorporated in treatment guidelines (3, 4, 27).

The aim of the END is to remove potentially metastatic lymph nodes from the neck, allowing identification of occult metastasis providing prognostic information and risk stratifying patients for adjuvant treatment. Some authors use the nodal harvest to assess quality of END. However, this does not account for the anatomic variation in the number and location of lymph nodes between patients. In this study we have used isolated neck recurrence following pN0 neck dissection as the endpoint to assess quality.

Isolated regional recurrence (RR) was selected as the end point to reduce the inclusion of 'new' neck metastasis. Isolated regional recurrence is likely to represent a true failure of the END to identify metastasis in the neck. Primary recurrence or a second primary can produce new metastasis since the END. This would not represent failure of the END as the nodes would not have been present at the time of END.

Patients staged as pN0 will have undergone an END and no occult metastasis has been identified. If the END is effective, these patients should truly have no malignant disease in the neck. Therefore a subsequent isolated neck recurrence would represent a failure of the END.

Whilst many studies report disease free survival, few were found with a breakdown of recurrence according to location, type or pathological staging. To boost the results, multiple units were invited to submit their unpublished data.

The data was divided into studies reporting T1-T2pN0 and T1-T4pN0 cases. T stage has a recognised association with recurrence (28). This division was made to better allow comparison of outcomes. There is an overlap mean between the two cohorts. This is to be expected given that T1-T4 cohort will include patients with T1-T2 primary tumours. This was shown in these results. The T1-T4 group had an over-all RR of 17.3% whilst the T1-T2 group had an over-all RR of 7.5%.

The secondary outcomes of the study reported on time and location of the RR. This was only reported in 2 studies. The invited study reported a time to recurrence of 14.9 months. The second study reported 7.5 months (range 2.3-29 months) in the ipsilateral neck and 8.9 months (range 5-58 months) in the contralateral neck. The short time to an isolated regional recurrence suggests this is disease missed from the END. This is comparable to the recurrence time quoted in the SENT trial of 9-12 months (unpublished data).

The location of the RR includes contralateral levels and level IV and V. These would likely be beyond the field of END for a cN0 case. It is known that the traditional END levels I-III will incorprorate the most likely affected nodes (29) but not all. RR in these levels may represent skip metastases. This may explain the failure rate of END recorded in this study. The SENT study found 2.4% of lateralised tumours drained exclusively to the contralateral neck(8).

Reported confounding variables included follow-up protocol and adjuvant therapy received. In patients undergoing END followed by adjuvant therapy, it is difficult to dissect the impact of each treatment modality on the neck recurrence. The majority of studies included patients with adjuvant therapy. This and the indications were included in the data collection. Adjuvent therapy is a variable which was aimed to reduce. To this end, patients who where staged postoperatively as pN+ where excluded. The majority of these patients would receive adjuvant therapy. Therefore the number of patients included in the metanalysis who received adjuvant therapy is believed to be very small. This is in particular the case in the T1-T2 group.

Other variables such as seniority of surgeon, patient characteristic, margin clearance and tumour characteristic was not reliably reported and therefore not recorded in this study. It is accepted that these variables would influence the RR.

Assuming a low incidence of 'new' metastasis showing up as RR, the failure of the END can only be hypothesised. The hypothesis would have to include causes leading to inadequate nodal clearance, in-transit metastases at the time of operating, skip metastasis to unoperated neck levels or underreporting of the pathological specimen.

One of the mostly likely sources of error is in the under-reporting of pathological specimens. The large node yield of END precludes the routine use of serial section to analyse each node due to temporal and financial constraints. It is likely that many reported pN0 necks contain occult metastasis that cannot be detected during bisection and H&E alone. Two studies have reported on re-examination of END specimen by serial section. This resulted in 13.4% and 15% upstaging respectively in the Ganly et al and Amit et al studies (11, 20). In these cases the upstaging by more intensive pathology may have made the patient eligible for adjuvant treatment and improved the survival outcome.

Conclusion

This is the first study to examine the failure rate following pN0 END. There has been no incentive to question the value of END when there was no real alternative management. This systematic review has shown a surprising isolated regional recurrence rate following END in pN0 staged patients. The review is using historical data but the results are reasonably

consistent. It could be argued that the higher recurrence rate in T3-4 tumours may be due to aberrant drainage and so explain some of their failures but applies to T1-2 lesions with a recurrence rate of 7.5%.

Word count /6000

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