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TITLE PAGE

Title: **Contralateral neck failure in oral tongue cancer: outcomes from two centres using pre-defined treatment criteria.**

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Brief running title: Contralateral neck failure in oral tongue cancer

Keywords: oral tongue squamous cell carcinoma, head and neck cancer, contralateral lymph node metastasis, radiation therapy, surgery

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Abstract

Background

The objective was to determine the incidence of, and factors associated with contralateral neck failure (CNF) in oral tongue squamous cell carcinoma (OTSCC).

Methods

Consecutive OTSCC patients between 2007-2016 were included. The predefined policy of the contralateral neck included neck dissection (ND) where: (1) the primary tumour extended/ crossed midline or the contralateral neck was involved; and elective nodal irradiation (ENI) where the primary tumour was ≤1cm from midline/2cm from tip.

Results

This study included 258 patients. ND was ipsilateral 169 (66%) and bilateral 33 (13%). Fifty-five patients (21%) received ENI to the undissected contralateral neck. CNF occurred in 19 patients (7%) and was similar by treatment received. Utilising this approach, we observed higher rates of CNF with increasing N classification, perineural invasion, extracapsular extension and depth of invasion ≥ 6mm.

Conclusions

Using our institutional policy of treatment to the contralateral neck a low rate of CNF (≤10%) was observed.

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Introduction

Worldwide, there are over 350,000 new cases of oral cavity cancer each year.[1] Oral tongue is the most common site of oral cavity cancer.[2]. Oral tongue cancer has been shown to have a particularly poor outlook compared to other oral cavity and non-oral cavity head and neck cancer (HNC) sites.[2] The five-year relative survival for oral tongue cancer is approximately 67%.[3]

Treatment of oral tongue tumours includes wide local excision with or without neck dissection. In the cN0 setting an ipsilateral elective neck dissection has become the standard of care following the prospective study by D'Cruz et al. that demonstrated a significant survival benefit compared to delayed management of the neck.[4] However, there is still no clear evidence regarding the optimal management of the contralateral neck.[5] Although not always pathologically involved, a contralateral sentinel lymph node has been identified in as many as 12.4% of lateralised oral cancer patients.[6] Occult contralateral lymph node involvement has been identified in 11% of cN0 oral cavity tumours when bilateral neck dissection has been performed.[7] Rates of contralateral neck failure (CNF) have been reported to be 3-17% in multiple case series.[8-11]

American Society of Clinical Oncology (ASCO) guidelines recommend consideration of contralateral neck dissection (CND) or irradiation in contralateral cN0/pNX patients who have advanced T classification tumours (T3/4) or where the tumour approaches midline. They also recommend considering tumour thickness (TT) in the context of other adverse pathological factors.[12] Whilst NCCN guidelines similarly advocate CND for comparable patients, there is no clarity regarding contralateral neck irradiation. Additionally, there is a lack of consensus about what constitutes "approaching midline", including how to factor in the tumours'

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proximity to the tip or base of tongue where contralateral lymphatic flow is more likely, and also how to factor in additional adverse features, such as TT or depth of invasion (DOI) when determining management of the contralateral neck. It is also interesting to observe that while many advocate elective nodal irradiation (ENI) to treat microscopic disease in the contralateral neck where a contralateral elective neck dissection (END) has been omitted, this approach is not generally endorsed for managing microscopic disease in the ipsilateral neck. However, bilateral neck irradiation is not without its consequences and has been shown to negatively impact toxicity and quality of life (QoL).[13]

The objective of our study was to evaluate the contralateral neck failure (CNF) in our cohort of oral tongue squamous cell carcinoma (OTSCC) patients using our predefined institutional approaches and identify factors which may predict for an increased risk of CNF.

Materials and Methods

Patients undergoing surgical resection for oral tongue SCC at the Royal Melbourne Hospital (RMH) or the Peter MacCallum Cancer Centre (PMCC) between 2006-2017 were eligible for inclusion. Multisite ethics approval was obtained for this study (HREC/17/PMCC/220). Eligible patients were identified from two separate institutional databases, one of which was prospectively collected, and was retrospectively analysed. Patients were excluded if they were aged less than 18 years or had a prior history of head and neck cancer (HNC). PMCC provides the large majority of adjuvant treatment for patients treated surgically at both centres, and only cases where adjuvant treatment was delivered at PMCC were included. This was to ensure treatment was delivered at a high volume radiation oncology HNC centre using the subsequently mentioned predefined treatment policy with an established radiotherapy

quality assurance program.[14] All cases were discussed pre- and post-operatively at a multi-disciplinary tumour meeting. Pre-operative staging generally included computed topography (CT) and selected patients underwent magnetic resonance imaging (MRI) or (18F)-fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) imaging.

Surgical excision of the primary was undertaken to obtain clear margins. If feasible, re-resection was performed for positive margins. Neck dissection was performed where there was clinical involvement of the neck or electively in the cN0 neck where the DOI was assessed as being ≥4mm, the role of dissection for DOI between 2mm and 4mm was resolved within the MDM on an individual case basis. The policy of both institutions was to prophylactically dissect the contralateral neck if the primary tumour reached or crossed the midline, or if there was clinical involvement of the contralateral neck.

Postoperative radiotherapy (PORT) was indicated in suitably fit patients in the setting of adverse pathological features, including T3/4 tumour, close/positive margin, lymphovascular space invasion (LVSI), perineural invasion (PNI), DOI≥7mm and any nodal disease (>N1). Contralateral neck PORT was delivered if the neck was pathologically involved or if it was dissected but pathologically negative, but to a lower dose. Elective irradiation (ENI) of the contralateral neck was dictated by a predefined institutional protocol, which included tumour extension to within 1cm of the midline or 2cm to the tongue tip or if there was extensive base of tongue involvement. Distance to midline or the tip was determined from clinical and radiological findings. Standard dose fractionation schedules were 66Gy in 33 fractions for positive margins or extracapsular extension (ECE) and 60Gy in 30 fractions for all other patients. Dissected but pathologically uninvolved neck levels were treated to an equivalent dose of 54Gy. Over the study period we transitioned from 3D conformal radiotherapy to intensity modulated radiotherapy (IMRT) in the adjuvant setting. In suitably fit patients,

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concomitant chemotherapy was recommended in patients with a positive margin or ECE. Unless contraindicated, weekly cisplatin was the recommended chemotherapy regimen. Patients were followed up at least 3 monthly for the first 2 years and at least 6 monthly for the next 3 years.

Patient medical records were accessed for demographic and tumour factors and primary, adjuvant and salvage treatment details. Patients were staged in accordance with the American Joint Committee on Cancer (AJCC) 7th edition.[15] Time to event outcomes included freedom from locoregional failure (FFLRF), freedom from contralateral neck failure (CNF), distant-metastasis free survival (DMFS), disease-specific survival (DSS) and overall survival (OS). Local, regional or distant failure was defined as radiological or pathological recurrence. Time to event outcomes were measured from the date of surgery to the date of the event. Other causes of death were censoring events for DSS and patients with unknown cause of death were not included in the DSS estimates. Any CNF was recorded, even if not isolated.

Statistical Analysis

Baseline characteristics were summarised using descriptive statistics. The Kaplan-Meier method was used to estimate the time-to-event curves. Estimates and associated 95% confidence intervals at key time points were reported. No imputation of missing values was performed. All statistical analyses were performed in R version 3.6.1.[16]

Results

We identified 258 eligible patients. Baseline demographic, pathologic and treatment characteristics are shown in **Table 1**. The median age at time of surgery was 61.4 years old

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(range 21.8-95.0) with an equal gender distribution (50%). Approximately half had a documented smoking history, including current (28%) or ex-smokers (26%).

Adjuvant treatment was indicated in 135/258 patients (52.4%), including 68 patients (26.4%) who received PORT alone and 67 (26.0%) who received both PORT and adjuvant chemotherapy. For the 67 patients undergoing adjuvant chemotherapy, cisplatin was the most common regimen (n=51, 76.1%).

The median follow-up was 4.8 years (range 0-11.6). FFLF, DMFS, OS and DSS Kaplan-Meier curves are presented in **Supplementary Figure 1**. Five-year freedom from locoregional failure was 75% (95% CI 68-80%); DSS and OS was 80% (95 % CI 73-85%) and 69% (95% CI 62-75%), respectively.

Contralateral neck management and outcomes

Of the 258 patients, 202 (78.3%) underwent an ipsilateral neck dissection and 33 of those patients (12.8% overall) also underwent a CND (Figure 1). Of these 33 patients, only five (15.2%) had pathological involvement of the contralateral neck (pN2c). Contralateral neck dissection included level 1 only (n=4), levels 1-2 (n=2), levels 1-3 (n=7), levels 1-4 (n=15) and levels 1-5 (n=5).

Of the 135 patients who received adjuvant radiotherapy, all received radiotherapy to the ipsilateral neck and 73 of these patients also received contralateral neck irradiation (5 pathologically involved, 13 pathologically negative, 55 elective). Radiotherapy was delivered via 3DCRT for 64 patients (47%) and IMRT for 71 patients (53%).

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The contralateral neck was observed in 170 patients (65.9%). Eighteen patients (7.0%) received CND and PORT, 15 patients (5.8%) underwent CND alone and 55 patients (21.3%) received ENI.

Freedom from CNF is represented in **Figure 2**. A total of 19 patients (7.4%) in our cohort developed CNF. Nine patients had an isolated CNF, while synchronous CNF was observed in five cases of local and ipsilateral neck failures, one case of a local failure and four with an ipsilateral neck failure. Eight patients who had CNF developed distant failure at some point during follow up. The three-year freedom from CNF was 91% (95% CI 87-95%). Of these 19 patients with CNF, 13 (68.4%) had no initial treatment of the contralateral neck (either CND or ENI), one patient underwent CND alone, four patients received contralateral ENI alone and one patient underwent both CND and contralateral PORT.

There was no difference in outcomes between different contralateral neck management approaches (Figure 2). The three-year freedom from CNF was 93% (95% CI 61-99%) for CND alone, 92% (95% CI 80-97%) for contralateral PORT alone, 92% (95% CI 57-99) for CND/contralateral PORT and 91% (95% CI 85-95%) for no contralateral neck treatment.

Table 2 outlines rates of CNF for multiple factors. In particular, we observed increased rates of CNF with increasing N classification, DOI≥6mm, ECE and PNI.

Discussion

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In the present study, we report the freedom from CNF based on a predefined multi-institutional protocol in a large cohort of 258 patients treated for oral tongue SCC over a ten year period. This series was primarily composed of early stage (T1-2) primary tumours and our overall oncological outcomes, including locoregional free failure (75% at five years), distant-metastasis free (67%) and overall survival (80%) are comparable to other reports.[17, 18] CNF occurred in 19 patients (7.4%) and was the only site of failure in nine, with a three-year CNF rate of 9%. The majority of events (13/19) occurred in patients who had no contralateral neck treatment; which was the most frequent contralateral neck management in our series (170/258). With our management approach, the rates of failure did not differ by treatment, the three-year freedom from CNF was high across all treatment groups (91-93%). For patients with pathological features such as ECE, PNI, increasing N classification and increased DOI, higher rates of CNF were observed. This suggests that when present, deviating from our current contralateral neck policy may lead to less optimal outcomes.

There are several strengths to our study. First, our contralateral neck treatment protocol was consistent across the ten-year study period. Second, both institutions included were high-volume surgical centres, a factor shown to correlate with improved survival [19, 20]. Adjuvant therapy was delivered at a single high-volume HNC institution with strict quality assurance [14] which has also been shown to reduce the rate of non-compliant radiotherapy plans.[21] Third, although this study was conducted across two different institutions, there was a consistent surgical and radiotherapy policy to managing the contralateral neck. It is also worth noting that our study period is relatively recent, especially compared to other series, with the earliest resection in 2006. Therefore, our paper represents outcomes of current contemporary work up and management, including imaging such as MRI and FDG PET/CT in a proportion of

patients. One of the most significant differences over this time period was a protocol transition from using 3DCRT to using IMRT (71/135 irradiated patients; 52.6%).

Multiple studies have reported their experience of contralateral neck management in OTSCC (Table 3).[8, 9, 11, 22] Two included only patients with T1-2N0 OTSCC[8, 11] and three excluded patients with OTSCC crossing the midline.[9, 11, 22] Each study reported their different contralateral neck treatment policies which included dissection alone[8, 22], dissection and irradiation[11] or neither.[9] Rates of overall CNF ranged from 0-6.9% (7.4% in the present study) while the isolated CNF rate ranged from 0-3.7% (3.4% in the present study). Our contralateral neck outcomes using our institutional management policy are comparable, despite including patients with more advanced nodal disease and midline proximity.

In our cohort, increased rates of CNF were observed in patients with increasing N classification, PNI and ECE (Table 2). Ganly et al reported that TT ≥4mm was the only variable significantly associated with regional neck failure (two-year regional recurrence 24% vs 5.7%, p=0.02) and 39% of the regional recurrences were contralateral.[8] Similarly in our series, we observed higher CNF with increasing DOI and TT, particularly ≥6mm. Some patients had only DOI or TT reported and others had both. None of the 72 patients (35% of the DOI cohort) with a DOI<6mm had a CNF whilst only one of the 45 patients (29% of the TT cohort) with a TT<6mm had a CNF.

Whilst contralateral ENI is routinely performed, this practice has not been consistently advocated for the management of the ipsilateral neck. A prospective study by our centre in cT1-2N0 OTSCC was undertaken to determine if single modality management of the ipsilateral neck (PORT alone or neck dissection alone) could be achieved.[25] However, a high rate of

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locoregional recurrence (23%) was observed and the study was closed early. Of these recurrences, only 3/18 patients (17%) treated with elective radiation to the ipsilateral neck failed and 1 was successfully salvaged. While surgery is the standard option for managing microscopic disease in the neck, the practice of contralateral ENI in OTSCC seems counterintuitive given that it is not standard practice for the ipsilateral neck. Although most of the factors associated with CNF when our institutional policy was used were factors that would only be identified or confirmed at pathological analysis, in borderline cases where a tumour approximates our midline criteria with pre-operative features of deep invasion or multiple neck nodes and/or ECE, it may be worth considering an elective contralateral neck dissection. However, where unexpected findings are found on pathological examination, ENI appears a reasonable option.

Survivors of HNC experience significant disease and treatment-related side effects and there is significant interest in risk adapting treatment policies to minimise morbidity while maintaining disease control. In oral cavity cancers, omitting the contralateral ENI is an appealing strategy offering improved QoL and decreased toxicity. However, this needs to be done cautiously, balanced against the risk of recurrence. Patients meeting the criteria for contralateral neck treatment based on our institutional policy and who have either PNI, DOI, N2b and ECE may not be a reasonable group to offer reduced contralateral treatment. Regional recurrences in oral cavity cancers are often morbid and salvage rates are only modest. Despite monitoring patients with serial neck ultrasound, D'Cruz et al. reported that many in the watch-and-wait arm presented with extensive neck recurrences, including 17.5% who were surgically inoperable. Even where operable, almost all had ECE (93%) necessitating intensified adjuvant treatment.[4] Ganly et al reported that patients who did not receive adjuvant radiotherapy and who developed a neck recurrence experienced significantly

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decreased disease-specific survival).[8] Of 13 patients with CNF in the paper by Habib et al, only 2 were successfully salvaged.[9] Of the 19 CNF in our series, 15 patients died from OTSCC, one patient died of an unknown cause and only three were alive at last follow-up.

Our study has several limitations. First, there are the inherent limitations of a retrospective study. It is also impossible to definitively conclude whether a CNF occurring at, or around the time of a local or ipsilateral neck failure is a consequence of residual microscopic disease from the original episode, or whether it has resulted from a new seeding event. However, we acknowledge that our data represents a worst-case scenario. A more conservative estimate may have been to report the 9 isolated CNF. Compared to other published series, we reported an increased proportion of females and non-smokers in our contemporary cohort, an observation which echoes a recent report suggesting a similar demographic shift in OTSCC patients.[34] We also had no patients with N3 disease so we cannot extrapolate our findings to this clinical scenario. This is not entirely unexpected as other large multicentre studies have also reported rates <1% when using AJCC 7th Edition Staging.[15,35] A central review of pathology specimens may have increased the consistency of reporting in our study, especially where DOI and TT were concerned. We provided both outcomes where reported, but focused on DOI given it was more commonly reported (only 21% not available) and has been incorporated into AJCC 8th Edition Staging due to its improved prognostic value.[36] Due to the low number of CNF, we were unable to perform multivariable analysis. .. We are planning a prospective study incorporating findings from this study and protocolised imaging interpretation including radiological proximity to midline.

Conclusion

In conclusion, contralateral neck recurrence in OTSCC occurs in less than 10% based on our institutional approach to management of the contralateral neck.

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References

1. Yamada K, Murakami M, Okamoto Y, et al. Treatment results of radiotherapy for carcinoma of the cervical esophagus. Acta oncologica 2006;45(8):1120-5.
2. Rusthoven K, Ballonoff A, Raben D, Chen C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. Cancer 2008;112(2):345-51.
3. National Cancer Institute. Cancer Stat Facts: Tongue Cancer. [August 3, 2020]; Available from: https://seer.cancer.gov/statfacts/html/tongue.html.
4. D'Cruz AK, Vaish R, Kapre N, et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. The New England journal of medicine 2015;373(6):521-9.
5. National Comprehensive Cancer Network. Head and Neck Cancers (Verson 2.2020). [August 3, 2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
6. Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. European journal of cancer (Oxford, England : 1990) 2015;51(18):2777-84.
7. Koo BS, Lim YC, Lee JS, Choi EC. Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head & neck 2006;28(10):896-901.
8. Ganly I, Goldstein D, Carlson DL, et al. Long-term regional control and survival in patients with "low-risk," early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumor thickness. Cancer 2013;119(6):1168-76.
9. Habib M, Murgasen J, Gao K, et al. Contralateral neck failure in lateralized oral squamous cell carcinoma. ANZ J Surg 2016;86(3):188-92.
10. Kowalski LP, Bagietto R, Lara JR, Santos RL, Tagawa EK, Santos IR. Factors influencing contralateral lymph node metastasis from oral carcinoma. Head & neck 1999;21(2):104-10.
11. Lim YC, Lee JS, Koo BS, Kim SH, Kim YH, Choi EC. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. The Laryngoscope 2006;116(3):461-5.
12. Koyfman SA, Ismaila N, Holsinger FC. Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline Summary. Journal of Oncology Practice 2019;15(5):273-278.
13. Chin RI, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. Cancer 2017;123(23):4594-4607.
14. Amarasena I, Herschtal A, D'Costa I, et al. Outcomes of Routine Intensity Modulated Radiation Therapy Quality Assurance in a Large Head and Neck Cancer Center. Int J Radiat Oncol Biol Phys 2017;98(3):541-546.
15. Edge SB, American Joint Committee on C. AJCC cancer staging manual. New York: Springer; 2011.
16. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
17. Liao CT, Chang JT, Wang HM, et al. Survival in squamous cell carcinoma of the oral cavity: differences between pT4 N0 and other stage IVA categories. Cancer 2007;110(3):564-71.
18. Chan AK, Huang SH, Le LW, et al. Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure. Oral oncology 2013;49(3):255-60.
19. Farquhar DR, Masood MM, Lenze NR, et al. Academic Affiliation and Surgical Volume Predict Survival in Head and Neck Cancer Patients Receiving Surgery. Laryngoscope 2020.
20. Torabi SJ, Benchetrit L, Kuo Yu P, et al. Prognostic Case Volume Thresholds in Patients With Head and Neck Squamous Cell Carcinoma. JAMA otolaryngology-- head & neck surgery 2019.

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21. Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. J Clin Oncol 2010;28(18):2996-3001.
22. O'Steen L, Amdur RJ, Morris CG, Hitchcock KE, Mendenhall WM. Challenging the Requirement to Treat the Contralateral Neck in Cases With >4 mm Tumor Thickness in Patients Receiving Postoperative Radiation Therapy for Squamous Cell Carcinoma of the Oral Tongue or Floor of Mouth. American journal of clinical oncology 2019;42(1):89-91.
23. Kurita H, Koike T, Narikawa JN, et al. Clinical predictors for contralateral neck lymph node metastasis from unilateral squamous cell carcinoma in the oral cavity. Oral oncology 2004;40(9):898-903.
24. Gonzalez-Garcia R, Naval-Gias L, Sastre-Perez J, et al. Contralateral lymph neck node metastasis of primary squamous cell carcinoma of the tongue: a retrospective analytic study of 203 patients. International journal of oral and maxillofacial surgery 2007;36(6):507-13.
25. Brennan S, Corry J, Kleid S, et al. Prospective trial to evaluate staged neck dissection or elective neck radiotherapy in patients with CT-staged T1-2 N0 squamous cell carcinoma of the oral tongue. Head & neck 2010;32(2):191-8.
26. Deschuymer S, Nevens D, Duprez F, et al. Randomized clinical trial on reduction of radiotherapy dose to the elective neck in head and neck squamous cell carcinoma; update of the long-term tumor outcome. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2020;143:24-29.
27. Contreras JA, Spencer C, DeWees T, et al. Eliminating Postoperative Radiation to the Pathologically Node-Negative Neck: Long-Term Results of a Prospective Phase II Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2019;37(28):2548-2555.
28. de Veij Mestdagh PD, Schreuder WH, Vogel WV, et al. Mapping of sentinel lymph node drainage using SPECT/CT to tailor elective nodal irradiation in head and neck cancer patients (SUSPECT-2): a single-center prospective trial. BMC Cancer 2019;19(1):1110.
29. Leeman JE, Romesser PB, Zhou Y, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. The Lancet Oncology 2017;18(5):e254-e265.
30. Hawkins PG, Lee JY, Mao Y, et al. Sparing all salivary glands with IMRT for head and neck cancer: Longitudinal study of patient-reported xerostomia and head-and-neck quality of life. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2018;126(1):68-74.
31. Steenbakkers R, Stokman M, Kierkels RGJ, et al. Stem Cell Sparing IMRT for Head and Neck Cancer Patients: A Double-Blind Randomized Controlled Trial. International Journal of Radiation Oncology*Biology*Physics 2019;105(1):S16-S17.
32. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. The New England journal of medicine 2016;375(19):1856-1867.
33. Mroz EA, Patel KB, Rocco JW. Intratumor heterogeneity could inform the use and type of postoperative adjuvant therapy in patients with head and neck squamous cell carcinoma. Cancer 2020;126(9):1895-1904.
34. Satgunaseelan L, Allanson BM, Asher R, et al. The incidence of squamous cell carcinoma of the oral tongue is rising in young non-smoking women: An international multi-institutional analysis. Oral oncology 2020;110:104875.
35. Ebrahimi A, Gil Z, Amit M, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA otolaryngology-- head & neck surgery 2014;140(12):1138-48.
36. Edge SB, American Joint Committee on C. AJCC cancer staging manual; 2017.

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Table 1: Baseline demographic, pathological and treatment characteristics

Characteristic	Total (N=258)
Follow up, years [range]	**4.8 [0-11.6]**
Age at time of surgery, years	
Median [range]	61.4 [21.8 - 95.0]
Interquartile range	49.8 - 72.4
Sex, n (%)	
Female	128 (50%)
Male	130 (50%)
Smoking, n (%)	
Current smoker	73 (28%)
Ex-smoker	68 (26%)
Non smoker	117 (45%)
Packs/year history	
Mean (SD)	34.0 (17.0)
Median [range]	35.0 [5.0 - 80.0]
Interquartile range	20.0 - 45.0
Missing	27
pT classification, n (%)	
1	136 (53%)
2	91 (35%)
3	22 (9%)
4	9 (3%)
pN classification	
0	117 (45%)
1	32 (12%)
2a	1 (0%)
2b	47 (18%)
2c	5 (2%)
X	56 (22%)
Margin, n (%)	
0	21 (8%)
0.1-0.9	16 (6%)
1-4.9	76 (29%)
<5	3 (1%)
5	18 (7%)
>5	19 (7%)
5-10	70 (27%)
>10	35 (14%)
DOI, mm	
Mean (SD)	9.5 (7.6)
Median [range]	8.0 [0.3 - 45.0]
Interquartile range	4.0 - 13.0
Missing	55
Tumour thickness , mm	
Mean (SD)	10.3 (8.2)
Median [range]	9.0 [0.4 - 45.0]

Characteristic	Total (N=258)
Interquartile range	5.0 - 13.2
Missing	102
PNI, n (%)	
No	193 (78%)
Yes	54 (22%)
Missing	11
LVSI, n (%)	
No	216 (87%)
Yes	32 (13%)
Missing	10
ECE, n (%)	
Yes	36 (14%)
No	222 (86%)
Type of adjuvant treatment, n (%)	
No adjuvant treatment	123 (48%)
Adjuvant RT	68 (26%)
Adjuvant CRT	67 (26%)
Radiotherapy Technique, n (%)	
3DCRT	64 (47%)
IMRT	71 (53%)

Abbreviations: DOI= depth of invasion; PNI= perineural invasion; LVSI= lymphovascular space invasion; ECE= extracapsular extension; 3DCRT= three-dimensional conformal radiation therapy; IMRT= intensity-modulated radiation therapy

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Table 2: Kaplan Meier estimates % (95% CI) of freedom from contralateral neck failure by demographic, treatment and pathological factors

Variable	Level	N	Events	FFCNF at 3 years (95% CI)
Age at time of surgery	<50 years old	65	9	85 (73-92)
	≥50 years old	193	10	94 (89-97)
Sex	Female	128	11	90 (83-95)
	Male	130	8	93 (86-96)
T classification	1	136	9	93 (86-96)
	2	91	9	88 (78-94)
	3	22	1	93 (61-99)
	4	9	0	-
N classification	0	117	3	98 (92- 99)
	1	32	3	90 (73- 97)
	2a	1	0	-
	2b	47	8	74 (54- 86)
	2c	5	1	-
	X	56	4	90 (75- 96)
DOI (n=203)*	<6mm	72	0	100%
	≥6mm	131	13	88 (80-93)
PNI	No	193	11	94 (89-97)
	Yes	54	7	85 (70-92)
LVSI	No	216	15	92 (88-95)
	Yes	32	2	91 (67-98)
ECE	No	222	12	94 (89-97)
	Yes	36	7	73 (50-86)
Type of adjuvant treatment	No adj tmt	123	7	94 (87-97)
	Adj RT	68	3	94 (84-98)
	Adj CRT	67	9	84 (71-91)

Abbreviations: DOI= depth of invasion; PNI= perineural invasion; LVSI= lymphovascular space invasion; ECE= extracapsular extension; Adj = adjuvant; Tmt = treatment; RT= radiotherapy; CRT= chemoradiotherapy

*Histopathology reports included either: a) DOI or tumour thickness; b) both

Table 3: Comparison to other similar published cohorts

Study	N	Stage	Crossing midline	Contralateral Neck Management*	Overall CNF	Isolated CNF
Present study	258 2006-2016	T1-4N1-2c	Included	Dissection, Irradiation	7.4%	3.4%
Ganly et al	164 1985-2005	T1-2N0	Included	Dissection	6.9%	NR
Lim et al	54 1992-2003	T1-2N0	Excluded	Dissection, Irradiation: NR	0%	0%

O'Steen et al	32 1998-2014	T1-4N1-2b	Excluded	Dissection	NR	0%
Habib et al	242 1985-2012	T1-4N1-3	Excluded	Excluded	NR	3.7%
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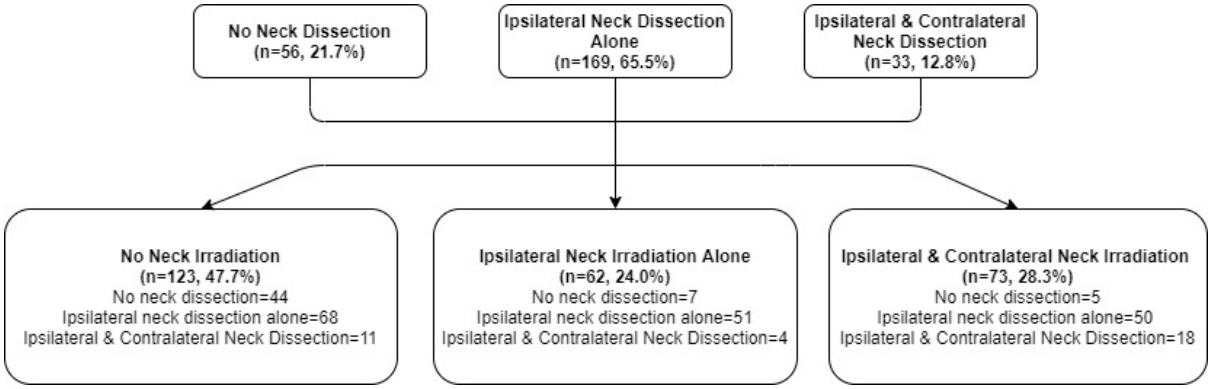

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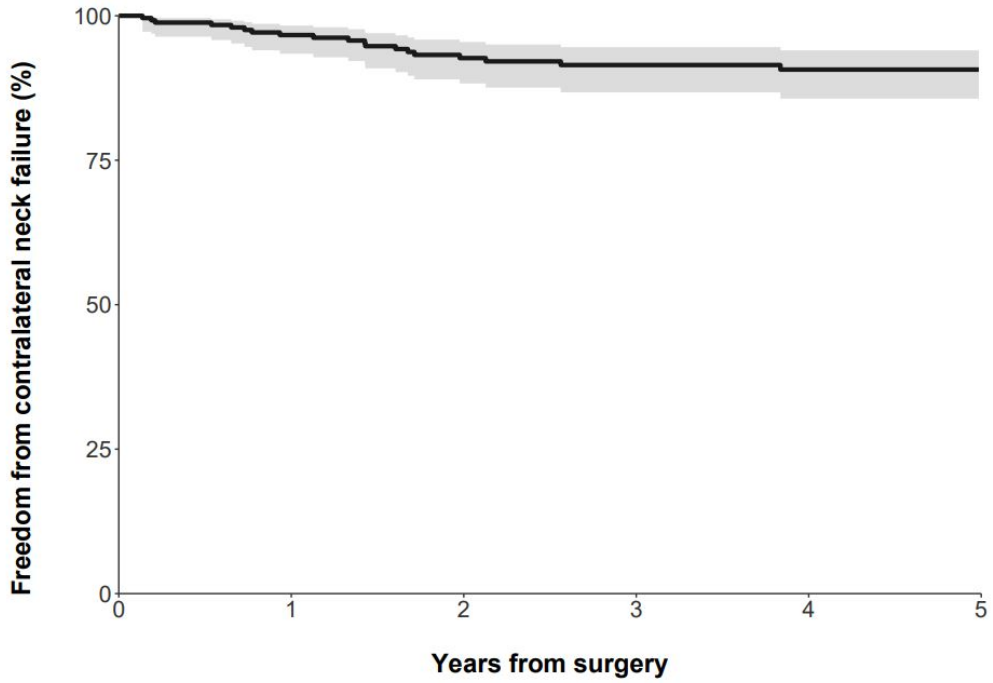
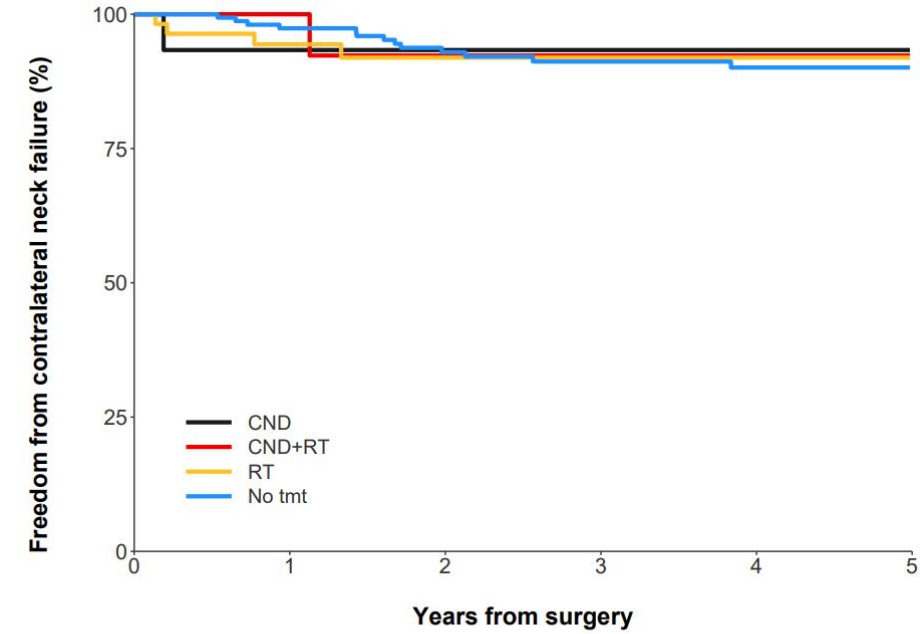
Figure 2: Freedom from contralateral neck failure; a) overall, b) by treatment

Abbreviations: CND= contralateral neck dissection; CND+RT= contralateral neck dissection and contralateral neck radiotherapy; RT= contralateral neck radiotherapy; RT= radiotherapy



No. at risk (No. censored)

All	258 (0)	212 (38)	168 (74)	137 (103)	113 (126)	78 (161)



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CND	15 (0)	13 (1)	10 (4)	7 (7)	5 (9)	3 (11)
CND+RT	18 (0)	13 (5)	10 (7)	8 (9)	7 (10)	6 (11)
RT	55 (0)	42 (10)	33 (18)	28 (23)	22 (29)	16 (35)
No tmt	170 (0)	144 (22)	115 (45)	94 (64)	79 (78)	53 (104)

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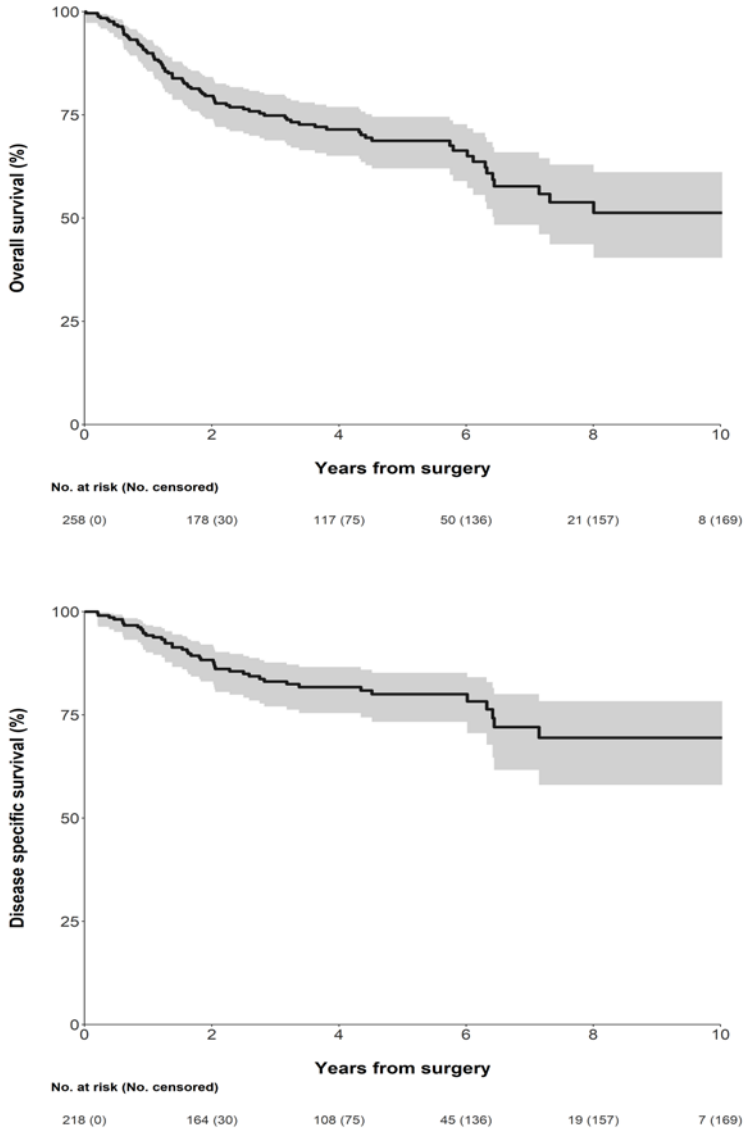
Supplementary Material

Supplementary Material Figure 1: Time to event outcomes; a) Overall Survival, b) Disease Specific Survival, c) Locoregional Failure, d) Distant Metastasis Free Survival



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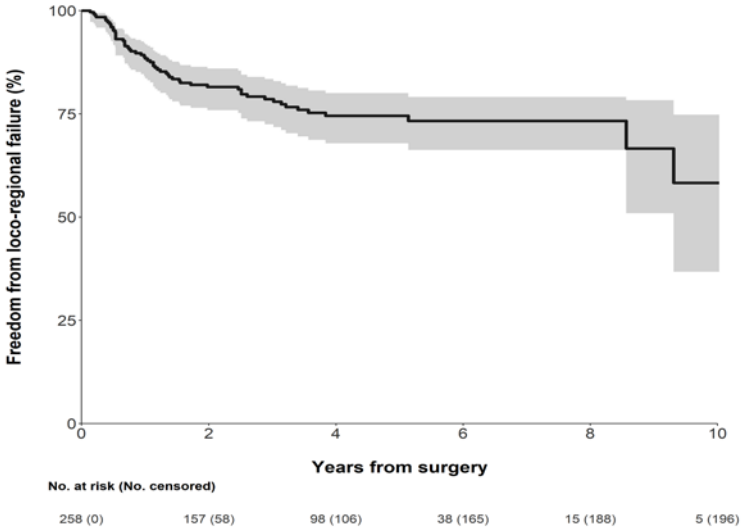

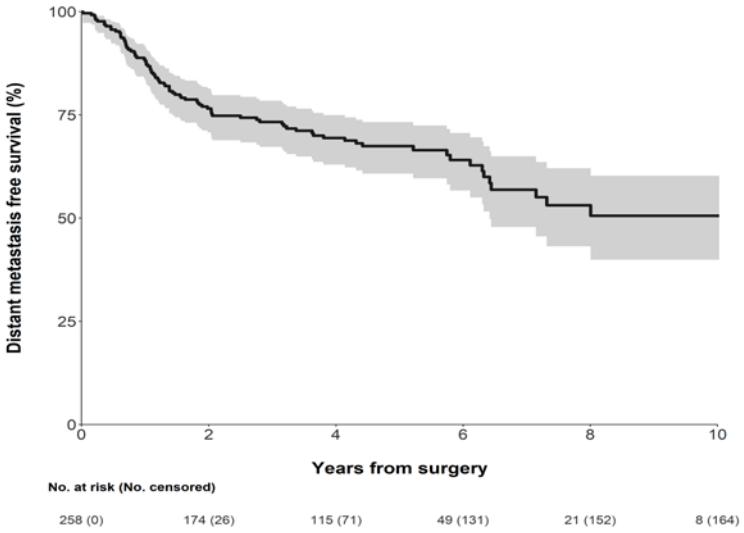

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Table 1: Baseline demographic, pathological and treatment characteristics

Characteristic	Total (N=258)
Follow up, years [range]	**4.8 [0-11.6]**
Age at time of surgery, years	
Median [range]	61.4 [21.8 - 95.0]
Interquartile range	49.8 - 72.4
Sex, n (%)	
Female	128 (50%)
Male	130 (50%)
Smoking, n (%)	
Current smoker	73 (28%)
Ex-smoker	68 (26%)
Non smoker	117 (45%)
Packs/year history	
Mean (SD)	34.0 (17.0)
Median [range]	35.0 [5.0 - 80.0]
Interquartile range	20.0 - 45.0
Missing	27
pT classification, n (%)	
1	136 (53%)
2	91 (35%)
3	22 (9%)
4	9 (3%)
pN classification	
0	117 (45%)
1	32 (12%)
2a	1 (0%)
2b	47 (18%)
2c	5 (2%)
X	56 (22%)
Margin, n (%)	
0	21 (8%)
0.1-0.9	16 (6%)
1-4.9	76 (29%)
<5	3 (1%)
5	18 (7%)
>5	19 (7%)
5-10	70 (27%)
>10	35 (14%)
DOI, mm	
Mean (SD)	9.5 (7.6)
Median [range]	8.0 [0.3 - 45.0]
Interquartile range	4.0 - 13.0
Missing	55
Tumour thickness , mm	
Mean (SD)	10.3 (8.2)
Median [range]	9.0 [0.4 - 45.0]

Characteristic	Total (N=258)
Interquartile range	5.0 - 13.2
Missing	102
PNI, n (%)	
No	193 (78%)
Yes	54 (22%)
Missing	11
LVSI, n (%)	
No	216 (87%)
Yes	32 (13%)
Missing	10
ECE, n (%)	
Yes	36 (14%)
No	222 (86%)
Type of adjuvant treatment, n (%)	
No adjuvant treatment	123 (48%)
Adjuvant RT	68 (26%)
Adjuvant CRT	67 (26%)
Radiotherapy Technique, n (%)	
3DCRT	64 (47%)
IMRT	71 (53%)

Abbreviations: DOI= depth of invasion; PNI= perineural invasion; LVSI= lymphovascular space invasion; ECE= extracapsular extension; 3DCRT= three-dimensional conformal radiation therapy; IMRT= intensity-modulated radiation therapy

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Table 2: Kaplan Meier estimates % (95% CI) of freedom from contralateral neck failure by demographic, treatment and pathological factors

Variable	Level	N	Events	FFCNF at 3 years (95% CI)
Age at time of surgery	<50 years old	65	9	85 (73-92)
	≥50 years old	193	10	94 (89-97)
Sex	Female	128	11	90 (83-95)
	Male	130	8	93 (86-96)
T classification	1	136	9	93 (86-96)
	2	91	9	88 (78-94)
	3	22	1	93 (61-99)
	4	9	0	-
N classification	0	117	3	98 (92- 99)
	1	32	3	90 (73- 97)
	2a	1	0	-
	2b	47	8	74 (54- 86)
	2c	5	1	-
	X	56	4	90 (75- 96)
DOI (n=203)*	<6mm	72	0	100%
	≥6mm	131	13	88 (80-93)
PNI	No	193	11	94 (89-97)
	Yes	54	7	85 (70-92)
LVSI	No	216	15	92 (88-95)
	Yes	32	2	91 (67-98)
ECE	No	222	12	94 (89-97)
	Yes	36	7	73 (50-86)
Type of adjuvant treatment	No adj tmt	123	7	94 (87-97)
	Adj RT	68	3	94 (84-98)
	Adj CRT	67	9	84 (71-91)

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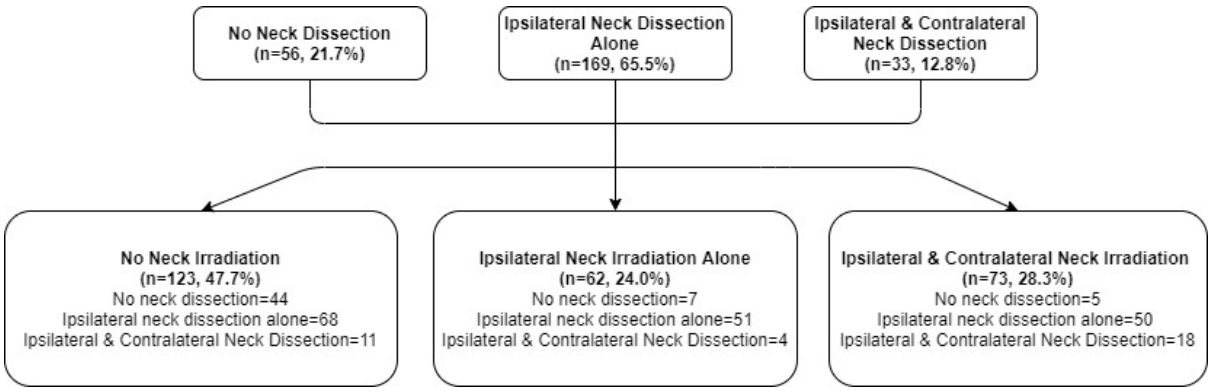

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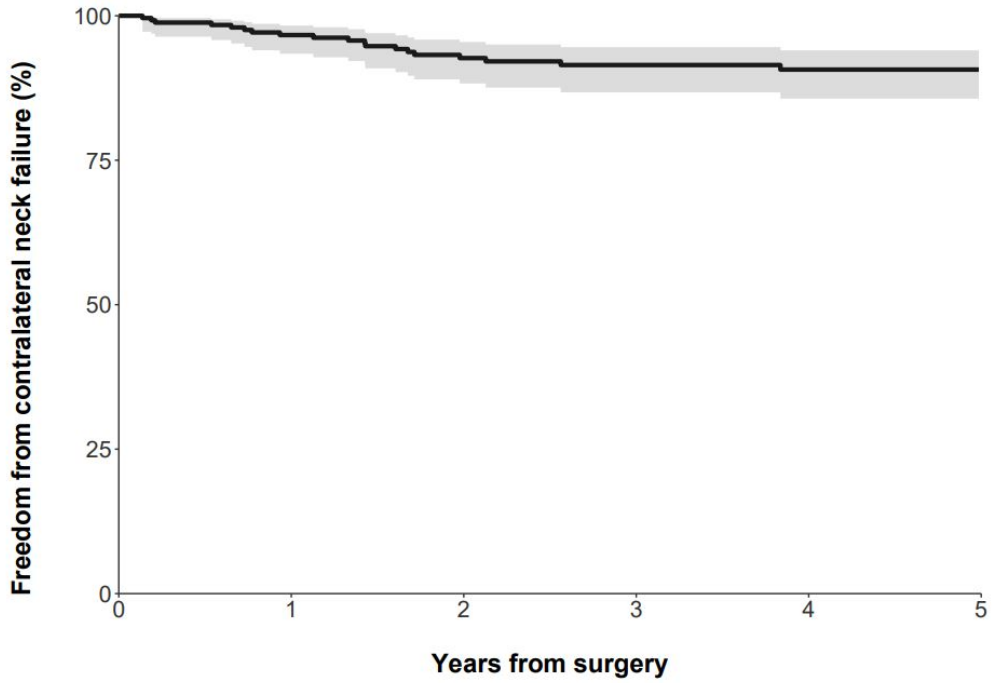

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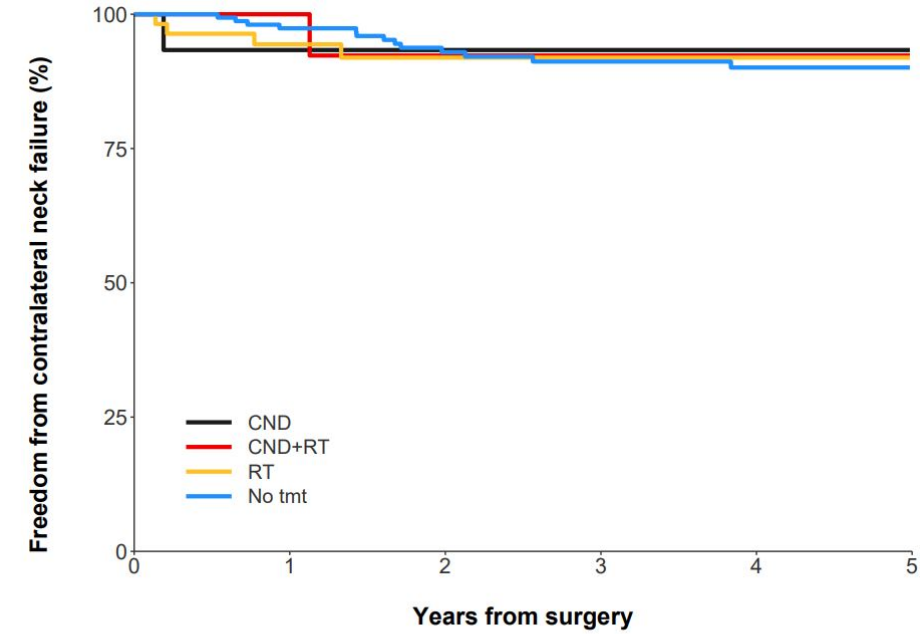

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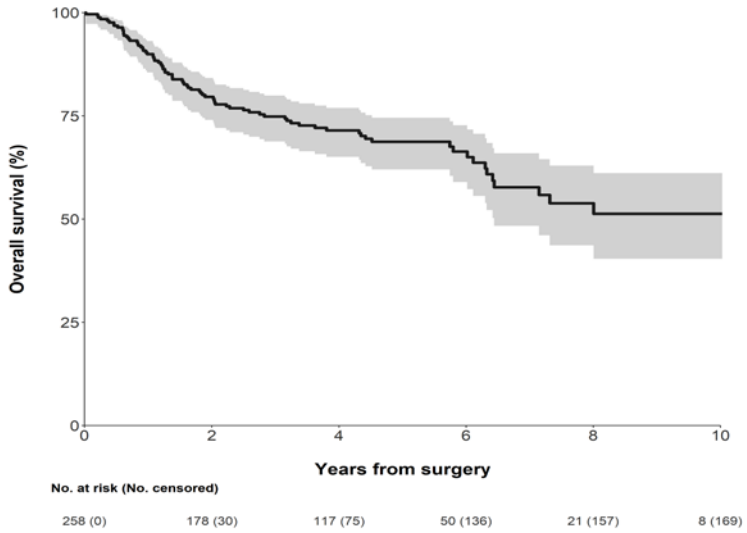

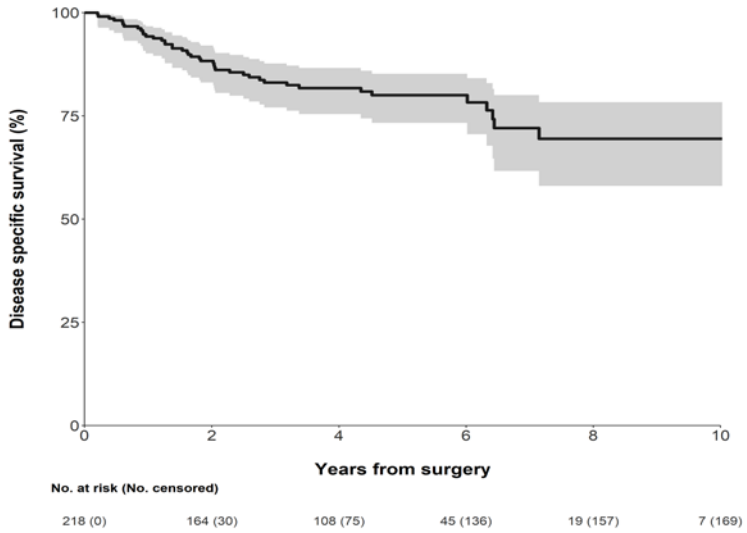

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