Author/s:
Toppi, J;Tham, YS;Webb, A;Henderson, MA;Rischin, D;Magarey, MJR

Title:
Surgical management of recurrent cutaneous squamous cell carcinoma of the head and neck after definitive surgery and radiotherapy

Date:
2020-07-01

Citation:
Toppi, J., Tham, Y. S., Webb, A., Henderson, M. A., Rischin, D. & Magarey, M. J. R. (2020). Surgical management of recurrent cutaneous squamous cell carcinoma of the head and neck after definitive surgery and radiotherapy. ANZ Journal of Surgery, 90 (7-8), pp.1391-1395. https://doi.org/10.1111/ans.16095.

Henderson Michael A (Orcid ID: 0000-0002-2496-8572)
Magarey Matthew (Orcid ID: 0000-0002-0296-4060)
Toppi Jason (Orcid ID: 0000-0002-4363-6960)

Surgical management of recurrent cutaneous squamous cell carcinoma of the head and neck after definitive surgery and radiotherapy

Short title: Management of recurrent head & neck cSCC

Jason Toppi[1], Yik Seng Tham[1], Angela Webb[1], Michael A Henderson[1,2], Danny Rischin[2,3], Matthew J R Magarey[1, 4]

[1]Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[2]Sir Peter MacCallum Department of Oncology, University of Melbourne

[3]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[4]Department of Medical Education, University of Melbourne

The authors have no conflicts of interest to declare. This research was presented at the RACS annual scientific congress in Bangkok, Thailand on 8th May 2019.

Abstract word count: 162

Manuscript word count: 2776

Figures and tables: 4

Supplementary figures: 2

Supplementary tables: 1

Total word count: 3938

Corresponding author and address for reprints:

Dr. Jason Toppi

Department of Surgical Oncology, Peter MacCallum Cancer Centre

305 Grattan St, Melbourne, Victoria 3000

jttoppi1@gmail.com

Abstract

Backgrounds

Surgery is the primary treatment for patients with recurrent head and neck cutaneous squamous cell carcinoma (cSCC) who have previously been treated by definitive surgery and radiotherapy. There is limited published data to direct management and the role of immunotherapy is currently under evaluation.

Methods

This was a retrospective study of patients with at least stage III recurrent head and neck cSCC previously managed by definitive surgery and radiotherapy.

Results

30 patients met the inclusion criteria. 87% were male and the median age at the time of surgery was 79 years. After salvage surgery, 7% developed local recurrence and 43% regional or distant failure. The 2-year overall survival and disease-free survival were 45% (95% CI:24-64) and 11% (95% CI:1-34), respectively. Advanced age was associated with a higher risk of overall mortality ($P<0.05$).

Conclusion

Patients with recurrent head and neck cSCC in the setting of previous radiotherapy have high recurrence rates with poor survival justifying consideration for treatment with anti-PD-1 immunotherapy strategies.

Key Words: SCC, squamous cell carcinoma, immunotherapy, salvage surgery

Introduction

Non-melanoma skin cancer (NMSC) is the most common type of cancer worldwide (1). Cutaneous squamous cell carcinoma (cSCC) represents the second most common type of NMSC and mostly arises in sun exposed areas of the head and neck (2). It is prevalent amongst Caucasian populations and particularly those with fair complexion (1). Resection is the definitive treatment of choice and adjuvant radiotherapy has been shown to improve outcomes in cases of advanced primary disease or where there is regional lymph node involvement (3).

The rate of local recurrence of cSCC ranges from 0.5-75% depending on tumour stage (4). In a population of patients with head and neck cSCC with predominantly advanced regional disease, the 5-year disease-free survival rate was 67% (5). For patients with recurrent disease, surgical approaches may be necessary but often present technical challenges and will vary depending on the site and extent of disease (6). Salvage surgery is associated with a high risk of complication and should only be offered if the tumour is completely resectable (4, 6). Major reconstruction is frequently required as part of a multidisciplinary approach. Regional recurrence in the setting of previous lymphadenectomy requires careful evaluation of the potential for further surgery (7).

There is limited data describing the management of these patients. We describe our experience highlighting patient outcomes as increasingly effective systemic therapies for recurrent and metastatic cSCC, specifically anti-PD-1 immunotherapy, become available. This study aimed to investigate demographics, treatment and outcomes in patients who had previously received radiotherapy and underwent salvage surgery for recurrent cSCC of the head and neck.

Methods

Participants

This was a retrospective review of all patients who underwent salvage surgery for at least T3N0M0 or at least T0N1M0 (AJCC 8th edition) recurrent cSCC of the head and neck between July 2014 and July 2017 (supplementary figure 1) (8). Patients were identified from the master patient index and Division of Radiation Oncology database. Only patients who were managed with curative intent were eligible. All patients were adults (aged 18 years or older) and met the following eligibility criteria 1) cSCC of the head and neck; 2) previous post-operative radiotherapy to the head and neck region; 3) surgically resectable stage III or IV disease without evidence of distant metastases based on preoperative positron emission tomography (PET) scan. The mean potential follow-up (I.e mean follow-up of those who survived) was 21-months. Ethics approval was obtained from the Peter MacCallum Cancer Centre Human Research Ethics Committee (17/203R).

Procedures

Patient demographics included: age, gender, length of hospital stay, type of recurrence (local, regional or both) and immunosuppression. Patients with a documented haematological malignancy, pharmacological immunosuppression, organ transplant or human immunodeficiency virus (HIV) were defined as being immunosuppressed. Tumour characteristics included: pathology characteristics, closest margin, the presence of perineural invasion (PNI) or lymphovascular invasion (LVI), tumour thickness and diameter, grade and the presence of satellite lesions. The number of neck levels dissected, the presence of extra capsular extension (ECE), the number of positive nodes and in-hospital post-operative complication rates were also collected. Complication data included wound breakdown, bleeding, infection, perioperative venous thromboembolism, return to theatre or death. All complications were then reclassified based on the Clavien-Dindo scale (9). Treatment and outcomes included type of salvage surgery, use of post-operative radiotherapy, overall survival and recurrence rates after salvage surgery.

Data analysis

Patient data was summarised using standard descriptive statistics. For categorical variables, frequencies and percentages were reported. For continuous variables, mean and standard deviation (SD) or median and interquartile ranges (IQR) were provided. Kaplan Meier Survival curves were calculated for overall survival (time from salvage surgery to death) and disease free-survival (time from salvage surgery to local, regional or distant recurrence or death). Kaplan Meier Survival curves were compared with the log-rank test and a P-value of ≤0.05 was considered significant. All analyses were performed using Stata (version 13).

Results

Patient demographics

A total of 30 patients underwent salvage surgery for recurrent cSCC of the head and neck (table 1 and supplementary figure 2). The common sites of disease were the scalp (17%), ear (17%), peri-orbita (10%) and cheek (10%). Other sites included the mandible, nose, brow/forehead and parotid region.

Treatment

The commonest procedure performed was salvage neck dissection/parotidectomy (40%) or both local excision and neck dissection/parotidectomy (37%) (table 2). Among the patients who underwent local resection only (23%), over half (58%) had an involved margin (table 2). Whilst elective neck dissections were offered in some patients with N0 disease each patient was assessed on a case-by-case basis with all surgical plans discussed at a multidisciplinary team meeting (MDM). For the seven patients who underwent local excision without elective neck dissection, all were free of neck disease on pre-operative PET scan and were deemed to be low risk for occult metastasis based on previous tumour pathology and primary tumour site; thus elective neck dissections were not performed on these patients (10). Of the five patients with both local and regional recurrence none had an involved margin.

Post-operative care and outcomes

The median length of hospital stay after salvage surgery was 5 days and most patients (63%) had further radiotherapy after salvage surgery (table 3). .Patients were discussed at our centre's MDM and previous radiotherapy doses/fields reviewed in conjunction with post-operative pathology. Radiotherapy would be offered in cases where further treatment was indicated and deemed feasible. Overall there were five patients who sustained a post-operative complication (17%). Two patients (7%) died as result of a post-operative complications; one due to an in-hospital cardiovascular complication in the context of pneumonia 12 days after surgery and the other due to a tension pneumocephalus secondary to an iatrogenic anterior cranial fossa defect. The 2-year overall survival and disease-free survival were 45% (95% CI:24-64) and 11% (95% CI:1-34), respectively. The median overall survival was 21 months and median disease free-survival 11 months (figure 1). Factors associated with overall survival are summarized in supplementary table 1. Increased age significantly increased the risk of overall mortality however gender, involved surgical margins, PNI, disease stage, further radiotherapy and immunosuppression showed no significant associations (supplementary table 1).

Discussion

This study provides a comprehensive analysis of patients who have undergone salvage surgery for recurrent cSCC of the head and neck. This study which describes patient experience in an era when there is no effective systemic therapies for recurrent cSCC confirms the poor survival of these patients with significant perioperative morbidity and

mortality. We were unable to address the functional and cosmetic morbidity of salvage treatment but anecdotally it is known to be significant.

Other relevant studies

Although there is extensive literature about treatment outcomes in patients with recurrent mucosal head and neck SCC, there is limited data about recurrent cSCC (11, 12).

Dean et al investigated a cohort of 72 patients with stage III or IV recurrent cSCC of the head and neck, although these included patients without a history of radiotherapy. The mean age (71 years) and proportion of males (85%) were similar to those in our study, although our cohort included more patients with stage IV disease; 30% in this study vs. 11% in their study (2). Our study also had a higher proportion of immunosuppressed patients (30% vs. 14%). Dean et al found a two-year disease-free survival of 62% and there were non-significant trends towards worse outcome in patients with age greater than 65 (p=0.34), male gender (0.06), immunosuppression (p=0.22) and previous radiation (p=0.4). Clear surgical margins, post-operative radiotherapy and PNI had no significant impact on mortality (2). Sun et al reported a median survival of 26-months for nine patients who underwent salvage surgery for recurrent cSCC in the setting of previous radiotherapy of the head and neck (13). These findings reinforce the notion that outcomes after salvage surgery are markedly worse when compared with those after treatment for primary disease.

It is well established that outcomes in patients with advanced cSCC of the head and neck are significantly improved with multimodal treatment in the form of surgery and adjuvant

radiotherapy (14, 15). However, in most cases of recurrent cSCC further radiotherapy may not be an option. In our study, 63% of patients were able to have further radiotherapy, which is similar to previously published rates for patients undergoing surgery for clinically advanced recurrent disease (2). However, these recurrent tumours already display a degree of radio-resistance, which may explain the poor outcomes after radiotherapy in our cohort. Rates of adjuvant treatment for primary cases of head and neck SCC are usually much higher. In a retrospective study of 167 patients by Veness et al with cSCC of the head and neck involving regional lymph nodes, 87% had adjuvant radiotherapy (14). Of the patients from this study that did have multimodal treatment, freedom from locoregional relapse and 5-year overall survival rates were 80% and 50%, respectively (median follow-up of 64 months) (14). Porceddu et al also demonstrated similar results in their study with a 2-year freedom from locoregional relapse rate of 88% in a cohort of 157 patients who underwent local resection and post-operative radiotherapy for high risk cSCC of the head and neck. The 2-year overall survival rate was 88% (5).

Implications for treatment and future research

It is likely that the reasons behind poorer outcomes in patients who undergo salvage surgery are multifactorial. More advanced disease at presentation, radio-resistance, higher rates of post-operative complication and a reduced capacity for further high dose radiotherapy are all likely contributors. Previous studies in patients with recurrent cSCC have demonstrated a greater proportion of larger tumours with deeper invasion and greater likelihood of PNI or

LVI suggesting radiotherapy is less likely to work with increasing tumour burden (2, 16, 17). Extensive surgery is also often required with complex reconstruction techniques and longer operating times, which is at least partly responsible for the high complication rates. These issues are also exacerbated by the fact that these patients tended to be elderly (2, 16, 17).

The demonstration of practice changing results for immune checkpoint inhibitor therapy in solid tumours, and its association with immunosuppression and a high mutational burden prompted investigation in cSCC (18, 19). In a phase I study and subsequent phase II trial of the anti-PD-1 agent cemiplimab in cSCC in immunocompetent patients, durable responses were observed in approximately half the patients (20). In a subsequent report of 78 patients with locally advanced disease (no regional or distant metastases), the investigator determined objective response rate was 53% and by central review 44%. 63% had durable disease control defined as no evidence of progression $\geq$105 days. Median overall survival and progression free survival had not yet been reached at a median follow-up of 9.3 months (range 0.8 – 27.9), with estimated 12-month progression-free probability of 58% and overall survival of 93%. Interestingly the response rate appeared to be lower in patients who had $\geq$2 surgical procedures in the same location. Moderately severe immune mediated adverse events (grade 3 and higher) were seen in 10% patients (21). Based on this data anti-PD-1 therapy should be strongly considered for immunocompetent patients with recurrent local and/or regional cSCC which may be unresectable or where salvage surgery is deemed unlikely to be curative. In addition, promising results have been reported with neoadjuvant

therapy (22). The incorporation of immune checkpoint inhibitors into the management of locoregionally advanced recurrent cSCC is likely to change treatment paradigms for immunocompetent patients. However, there remains a significant unmet need for immunocompromised patients with advanced SCC. The efficacy and tolerability of anti-PD1 therapy in immunocompromised patients with SCC is unproven, although trials are underway (NCT04242173). Current and future trials will help further define the optimal use of immune checkpoint inhibitors in recurrent cSCC.

Limitations

The limitations of this retrospective study were primarily related to the rarity of this condition and the heterogenous nature of recurrent cSCC in the head and neck. Whilst all eligible patients were included in our study, cases of advanced stage recurrent cSCC in the setting of previous radiotherapy were infrequent. This impacted the ability to perform direct comparisons of patient groups and identify risk factors for mortality and recurrence. Nevertheless, cSCC is a significant problem in Australia with a combination of high ambient ultraviolet levels, outdoor lifestyle and a genetically susceptible Caucasian population. There is a potential for referral bias in this study, but these cases are complex and require multidisciplinary input from a variety of health practitioners leading to centralisation of referral and management.

Conclusion

This paper provides a descriptive analysis of demographics and outcomes after salvage surgery for advanced recurrent cSCC of the head and neck. It highlights the over representation of older males in this patient population, as well as high mortality and recurrence rates despite radical surgery. Given these poor outcomes, immunotherapy should be considered as a treatment option in immunocompetent patients and future research should aim to evaluate the role of evolving therapies, including anti-PD-1 therapy, and how they may be integrated into the care of these patients.

References

1. Gurudutt VV, Genden EM. Cutaneous squamous cell carcinoma of the head and neck. J Skin Cancer. 2011;2011:502723.

2. Dean NR, Sweeny L, Magnuson JS, Carroll WR, Robinson D, Desmond RA, et al. Outcomes of recurrent head and neck cutaneous squamous cell carcinoma. J Skin Cancer. 2011;2011:972497.

3. McGuire JF, Ge NN, Dyson S. Nonmelanoma skin cancer of the head and neck I: histopathology and clinical behavior. Am J Otolaryngol. 2009;30(2):121-33.

4. Paleri V, Kelly CG. Re-irradiation with concurrent chemotherapy in recurrent head and neck cancer: a decision analysis model based on a systematic review. Clin Otolaryngol. 2008;33(4):331-7.

5. Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM, et al. Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial. J Clin Oncol. 2018;36(13):1275-83.

6. Paleri V, Urbano TG, Mehanna H, Repanos C, Lancaster J, Roques T, et al. Management of neck metastases in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S161-S9.

7. Ferlito A, Rinaldo A, Robbins KT, Silver CE. Neck dissection: past, present and future? The Journal of laryngology and otology. 2006;120(2):87-92.

8. Amin MB, Edge, S., Greene, F., Byrd, D.R., Brookland, R.K., Washington, M.K., et al. AJCC Cancer Staging Manual (8th edition): Springer International Publishing; 2017.

9. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

10. Martinez JC, Cook JL. High-risk cutaneous squamous cell carcinoma without palpable lymphadenopathy: is there a therapeutic role for elective neck dissection? Dermatol Surg. 2007;33(4):410-20.

11. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567-78.

12. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med. 2008;359(11):1143-54.

13. Sun L, Chin RI, Gastman B, Thorstad W, Yom SS, Reddy CA, et al. Association of Disease Recurrence With Survival Outcomes in Patients With Cutaneous Squamous Cell Carcinoma of the Head and Neck Treated With Multimodality Therapy. JAMA Dermatol. 2019;155(4):442-7.

14. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. Laryngoscope. 2005;115(5):870-5.

15. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. Cancer. 2006;106(11):2389-96.

16. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck. 2007;29(7):621-31.

17. Clayman GL, Lee JJ, Holsinger FC, Zhou X, Duvic M, El-Naggar AK, et al. Mortality risk from squamous cell skin cancer. J Clin Oncol. 2005;23(4):759-65.

18. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003;348(17):1681-91.

19. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 2017;9(1):34.

20. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2018;379(4):341-51.

21. Migden MR, Khushalani NI, Chang ALS, Lewis KD, Schmults CD, Hernandez-Aya L, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol. 2020;21(2):294-305.

22. N. Gross RF, P. Nagarajan, D. Bell, A. El-Naggar, J.M. Johnson, Y. Yuan, B.S. et al. Phase II Study of Neoadjuvant Cemiplimab Prior to Surgery in Patients with Stage III/IV (M0) Cutaneous Squamous Cell Carcinoma of the Head and Neck. Annals of Oncology. 2019;30(suppl_5):v851-v934.

Acknowledgements

We would like to thank Mathias Bressel for his valuable comments and suggestions.

Disclosures

All authors are in agreement with the content of the manuscript and have no conflicts of interest to declare

Figure legend

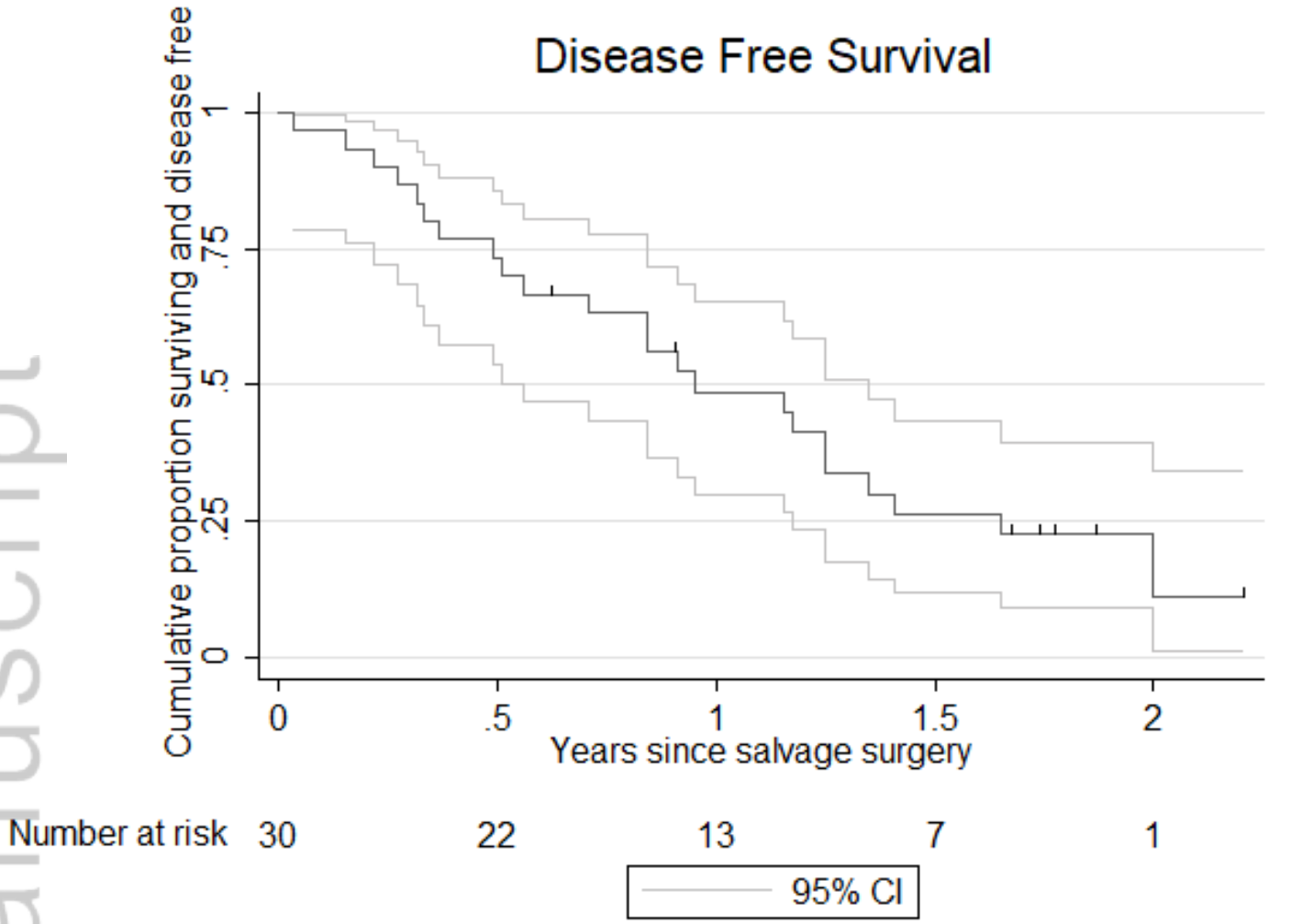
Figure 1: Disease free and overall survival

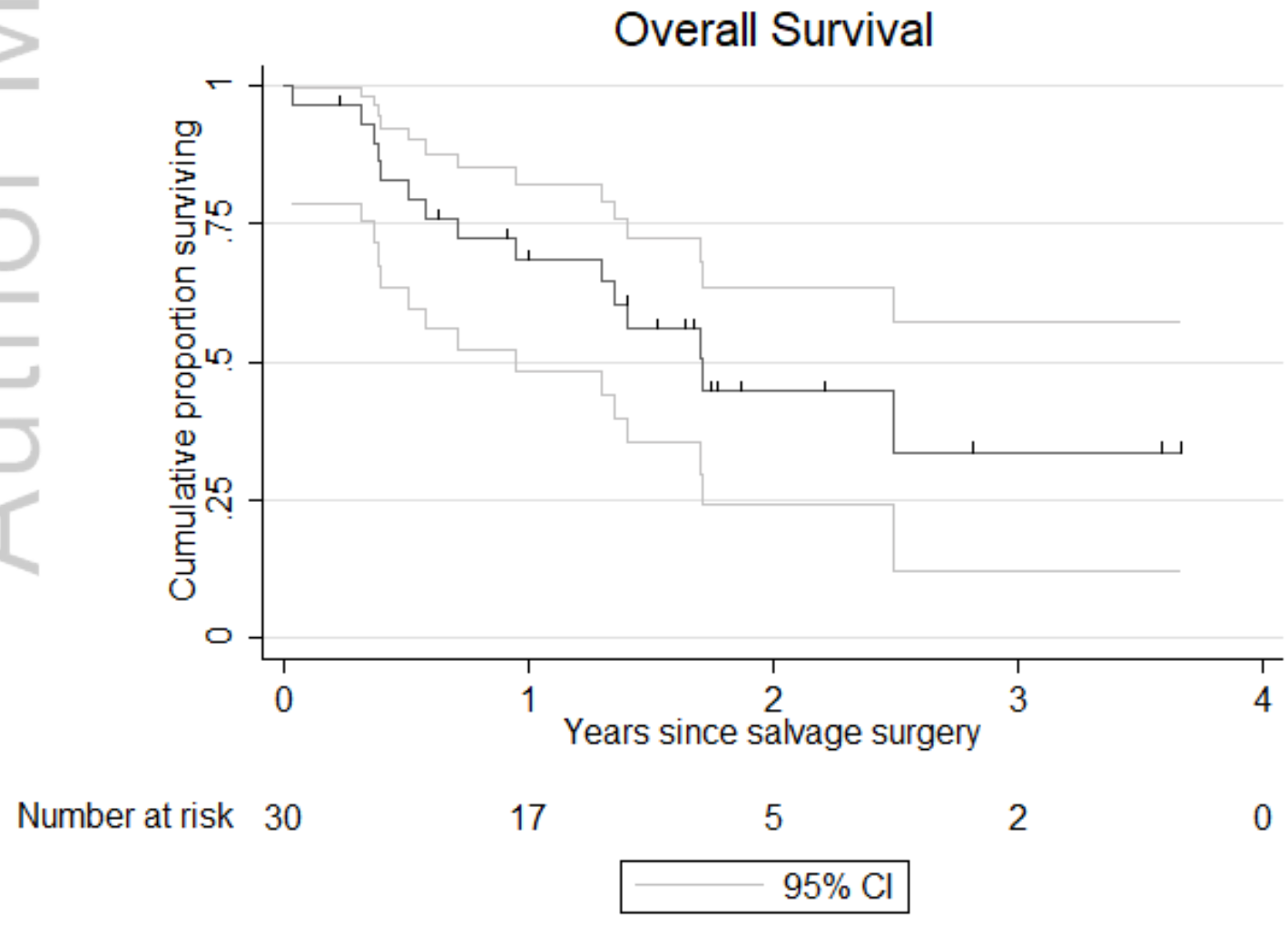
Supplementary figures and tables

Figure S1: AJCC Cancer Staging (8th edition)

Figure S2: Consort diagram

Table S1: Factors associated with overall survival and locoregional or distant failure





ANS_16095_Figure 1 graph FINAL.png

Table 1. Demographics

Characteristics	All patients (n= 30)
Gender	
Male	26 (86.7%)
Female	4 (13.3%)
Age	
Median (IQR)- years	79 (72, 85)
Mean potential follow-up‡	
Mean (±SD)- months	21.2 (11.8)
Type of recurrence at presentation	
Local recurrence only	12 (40.0%)
Regional recurrence only	13 (43.3%)
Local and regional recurrence	5 (16.7%)
Stage of disease at presentation	
III	21 (70.0%)
IV	9 (30.0%)
Immunosuppression†	
Yes	9 (30%)
Previous radiotherapy‡	
Median dose (IQR)- Gy	55 (50, 60)

†Documented haematological disease, pharmacological immunosuppression, organ transplant or HIV ‡Missing data for n= 4 ‡Includes patients who survived only (n=15)

Table 2. Treatment

Characteristics	All patients (n= 30)
Surgery type	
Local excision only	7 (23.3%)
Neck dissection or parotidectomy alone	12 (40.0%)
Local excision + neck dissection/parotidectomy	11 (36.7%)
Closest tumour resection margin†	
Involved	7 (58.3%)
Not involved (≥0.1mm)	5 (41.7%)
Tumour thickness†	
Median (IQR)- mm	20.0 (10.0, 25.0)
Mean (±SD)- mm	18.9 (±10.1)
Extra Nodal Extension (ENE)‡	
Yes	7 (38.9%)
Number of nodes dissected§	
Median (IQR)	17.5 (14, 31)
Number of positive nodes§	
Median (IQR)	0.5 (0, 1)
Perineural invasion (PNI)	
Yes	11 (36.7%)
Lymphovascular invasion (LVI)	
Yes	8 (26.7%)
Differentiation	
Well	0
Moderately	10 (35.7%)
Poorly	18 (64.3%)

†Local recurrence cases only (n= 12), ‡Locoregional and regional recurrence cases only (n= 18 cases), §Locoregional and regional recurrence cases and 4 local recurrence only cases that underwent elective neck dissection (n=22)

Table 3. Post-operative care and outcomes

Characteristics	All patients (n= 30)
Adjuvant treatment†	
Further radiotherapy	17 (63.0%)
Chemotherapy	3 (12.5%)
Length of stay	
Median (IQR)- days	5 (4, 7)
Mean (±SD)- days	8 (±8)
Post-operative complication	
Clavien-Dindo grade IIIb	3 (10.0%)
Clavien-Dindo grade V	2 (6.7%)
Recurrence after salvage surgery	
Any recurrence‡	15 (50%)
Locoregional recurrence only	12 (40%)
Distant recurrence only	3 (10%)
Deceased	
Yes	15 (50.0%)

†data missing for n=3 (radiotherapy) and n= 6 (chemotherapy), ‡Local, regional and/or distant failure after salvage surgery