Author/s:
McDowell, LJ;Tan, TJ;Bressel, M;Estall, V;Kleid, S;Corry, J;Johnston, ML

Title:
Outcomes of cutaneous squamous cell carcinoma of the head and neck with parotid metastases

Date:
2016-10-01

Citation:
McDowell, L. J., Tan, T. J., Bressel, M., Estall, V., Kleid, S., Corry, J. & Johnston, M. L. (2016). Outcomes of cutaneous squamous cell carcinoma of the head and neck with parotid metastases. Journal of Medical Imaging and Radiation Oncology, 60 (5), pp.668-676. https://doi.org/10.1111/1754-9485.12484.

Persistent Link:
https://hdl.handle.net/11343/291432

Outcomes of Cutaneous Squamous Cell Carcinoma of the Head and Neck with Parotid Metastases.

Running Title: Outcomes of cSCC with parotid metastases

Authors

Lachlan J. McDowell FRANZCR [1]

TJ Tan MBBS [1]

Mathias Bressel MSc [2]

Vanessa Estall MD [1,3]

Stephen Kleid FRACS [4]

June Corry MD [1,3]

Meredith L. Johnston FRANZCR [1]

[1] Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre

[2] Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre.

[3] University of Melbourne, Parkville, Australia

[4] Division of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.

Corresponding Author: Dr Lachlan McDowell, William Buckland Radiotherapy Centre, Latrobe Hospital, Princes Highway, Traralgon, West Victoria, Australia, 3844. Email address: lachiemcd@hotmail.com

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1754-9485.12484

Received Date : 21-Dec-2015
Revised Date : 07-May-2016
Accepted Date : 13-May-2016
Article type : Radiation Oncology Original Article

Abstract

Introduction

Cutaneous squamous cell carcinoma of the head and neck (cHNSCC) metastatic to the parotid has a moderate risk of recurrence despite multimodality treatment. Immunosuppression is associated with lower rates of long term cure. Our aim was to review outcomes of current management in a tertiary centre with a view to targeting future strategies.

Methods

A retrospective review of clinico-pathological data and outcomes for patients with metastatic cHNSCC involving the parotid gland, undergoing radical surgery and adjuvant radiotherapy during 2000-14 was conducted. The Kaplan-Meier method was used to determine time-to-event outcomes.

Results

132 patients met the inclusion criteria. Median follow-up was 5.0 years. Five-year overall (OS), cancer-specific (CSS) and progression free survival (PFS) were 44% (95% Confidence Interval (CI) 34–53%), 64% (95% CI 52–74%) and 37% (95% CI 28-47%) respectively. Loco-regional control (LRC) was 67% (95% CI 55-77%) at five years. Immunosuppressed patients fared worse (compared with immune-competent) with five-year OS, CSS, and PFS of 14% versus 53% (HR = 3.19; 95% CI 1.91-5.34), 40% versus 71% (Hazard Ratio (HR) = 2.92; 95% CI 1.38-6.19) and 10% versus 46% (HR = 2.51; 95% CI 1.52-4.14) respectively. On multivariate analysis, immune status strongly predicted OS ($P < 0.001$), CSS ($P = 0.003$), DMFS ($P < 0.001$) and PFS ($P < 0.001$), but not LRC. Largest lymph node

size was the only significant factor predictive for LRC on multivariate analysis (P = 0.02).

Conclusions

Despite multimodality treatment metastatic cHNSCC involving the parotid shows moderate rates of recurrence. Immunosuppressed patients with this disease have a particularly poor prognosis, demonstrating lower rates of CSS with similar rates of LRC compared to their immunocompetent counterparts.

Keywords: Carcinoma, Squamous Cell; Immunosuppression; Parotid Neoplasms; radiotherapy; Skin Neoplasms;

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy in Australia, second only to cutaneous basal cell carcinomas.[1] Sun-exposed regions of the head and neck are most commonly involved and the majority of early cSCC are cured surgically with low morbidity and mortality. The overall risk of developing regional metastatic disease in cSCC is low at approximately 5%, but heralds a significant shift in morbidity and survival.[2] Clinicopathological features predicting an increased risk of regional spread include immunosuppression,[3] size and thickness of the index lesion,[4,5] tumour differentiation,[6,7] perineural and lymphovascular space invasion.[6,7] Local recurrence at the primary site has also been associated with an increased risk of regional relapse.[6]

Cutaneous squamous cell carcinoma arising within the head and neck region (cHNSCC), particularly certain anatomic subsites, are at increased risk of regional metastatic involvement.[7] The parotid gland is a common site for spread as it receives lymphatics from the ear, forehead, face, temple and scalp.[8] When parotid involvement is present, macroscopic or microscopic cervical metastases are frequently present.[9-12] Although at diagnosis clinical involvement of the neck is only seen in 17-24% of patients, this is a relatively insensitive assessment, as

pathologic involvement is found in 27-50% of patients undergoing neck dissection.[10-12]

The optimal management of patients presenting with parotid metastases from cHNSCC has not been defined by prospective studies and recommendations are predominantly based on retrospective data from single institutions. Surgical management of the parotid with preservation of facial nerve (where uninvolved), followed by adjuvant radiotherapy is recommended,[13] based on the high risk of relapse in the parotid with surgery alone,[14] and improved loco-regional control (LRC) and disease-specific survival (DSS) with adjuvant radiotherapy.[11,15,16] Controversy remains in defining the extent of parotidectomy required, as well as the role of neck dissection in the clinically-negative neck. The role of systemic therapies in this high-risk population is also undefined, and is the subject of a recent multi-institutional trial.[17]

This study defined a relatively homogeneous series of high-risk cHNSCC, presenting with parotid metastases to a tertiary oncology institution. All patients were treated with surgery and adjuvant radiotherapy with curative intent. We report on the clinico-pathological characteristics and treatment outcomes in this cohort. Our aim was to review contemporary outcomes in this patient cohort to inform on how to best target future management.

Methods and Materials

Data Extraction

The study was approved by the institutional ethics board. All patients with node-positive cHNSCC with parotid involvement who underwent radical treatment with surgical resection and adjuvant radiotherapy, treated at Peter MacCallum Cancer Centre from January 2000 to April 2014 were identified for this study from an electronic institutional database. Surgical pathology (from the parotid/neck dissection), radiology and clinical reports were reviewed in all cases. Patients with suspected local recurrence with direct parotid invasion (rather than metastatic nodal parotid disease) were excluded. Only patients who received a course of adjuvant radiotherapy biologically equivalent to at least

50Gy in 2Gy fractions were included. Patients were excluded if: the radiotherapy treatment course was not completed (unless it was ceased due to disease progression), a substantially hypofractionated radiotherapy regimen was used (i.e. > 3Gy/fraction; this was considered palliative), or patients were enrolled on a multi-institutional study (TROG 05.01 POST).[17]

Staging

Staging was in accordance with the American Joint Committee on Cancer Staging Manual, seventh edition.[18] Parotid and cervical nodes are both considered regional nodal metastases in this staging system. Histological factors (i.e. extranodal extension, lymphovascular invasion and differentiation) were scored as positive, negative or missing (if not specifically mentioned in the pathology report).

Treatment

All patients were presented at a multidisciplinary head and neck meeting. The extent of surgical resection was determined by the referring surgeon. Following surgery, all patients were assessed by a radiation oncologist. Institutional policy mandated elective neck irradiation in the absence of a neck dissection. Adjuvant radiation to the primary site was generally recommended if parotid recurrence occurred within 12 months, but remained at the discretion of the treating radiation oncologist. The decision to administer (off-study) concurrent chemotherapy was made on an individual basis.

Follow up

Patients underwent follow-up with the treating radiation or surgical oncologist. Follow-up was typically 3-monthly for at least two years post-treatment, however there was no standardized clinical or imaging follow-up schedule. Hospital records, correspondence from other oncologists and primary care physicians were used to obtain follow up information.

Statistical analysis

Survival analysis was performed using the Kaplan-Meier product-limit method, and annual survival rates with associated 95% confidence intervals (95% CI) were calculated for the time-to-event endpoints including overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), distant metastasis free survival (DMFS), freedom from loco-regional failure and freedom from local failure in patients treated with radical intent. In keeping with the definitions of local and regional disease in the current AJCC (7^{th} ed) classification, we defined local control as control at the index (primary) site, and regional control as control in the parotid or cervical nodal bed (combined). LRC was defined as control at both the primary site, as well as the regional sites including the parotid bed and the cervical lymph nodes. All time-to-event endpoints were calculated from the date of surgery to the date of the event. Univariable analysis using the logrank test (or exact logrank test for small group numbers) and likelihood ratio test with hazard ratios (HR) obtained from Cox proportional hazards models, was performed. Multivariable analysis was performed using bidirectional elimination until no further variable was removed or added to the model. Patient, disease and treatment factors analysed were sex, age, smoking, immunosuppression, tumour grade, size of largest lymph node, percentage of positive lymph nodes, nodal stage (N0-N3), extracapsular extension, perineural invasion, lymphovascular invasion, margin status and time from initial treatment of index lesion to parotidectomy. All statistical analyses were performed in R (version 3.1.1; R Development Core Team 2009).

Results

Patient, tumour and treatment characteristics

One hundred and thirty two patients met the inclusion criteria. Two patients who embarked on a course of radical treatment but did not complete treatment due to (1) excessive toxicity while on lenalidomide and (2) patient preference due to toxicity, were not included in this analysis. Patient and treatment characteristics are presented in *Table 1*. Computed Tomography imaging was performed in the majority of patients for staging; more recently patients were increasingly staged with Positron Emission Tomography (overall 38/132; 29%).

Most patients underwent a superficial parotidectomy (69%). The neck was managed surgically in 65% of patients. Radiotherapy practice evolved over the 14-year period from 2-dimensional and 3-dimensional conformal radiotherapy to Intensity-Modulated Radiotherapy (17% of patients). The most frequent adjuvant doses used were 60Gy (39% of patients) or 66Gy (31% of patients) in 2Gy fractions, and the majority of patients (73%) received at least 60Gy. Median time from surgery to commencing radiotherapy was 43 days (range 26-208 days). Median follow-up was 5.0 years (range 2 months to 11 years).

Time to failure outcomes

Data on the cumulative incidence of first failure is presented in *Table 2.* LRC at two and five years was 78% (95% CI 69-84%) and 68% (95% CI 55-77%) respectively (*Figure 3)*. Largest nodal size was the only significant factor on both univariate (HR = 1.02; 95% CI 1.01-1.04; $P = 0.02$) and multivariate analysis (HR = 1.02; 95% CI 1.01-1.04; $P = 0.02$) for LRC. As demonstrated in *Figure 3* and *Table 2* the majority of locoregional failures occurred with in the first two years following completion of treatment.

The two and five year DMFS was 58% (95% CI 48-66%) and 40% (95% CI 30-50%) respectively. On univariate analysis immunosuppression (HR = 2.80; 95% CI 1.68-4.67; $P < 0.001$) and largest lymph node size (HR = 1.02; 95% CI 1.00-1.03*;* P = 0.017) were the only significant factors for DMFS. On multivariate analysis immunosuppression (HR = 2.80; 95% CI 1.68-4.67; $P < 0.001$) was the only significant factor. Eighteen patients developed distant metastases (crude rate 14%) during the follow-up period, but not necessarily as the first site of failure.

Progression free survival

Two and five year PFS was 57% (95% CI 47–65%) and 37% (95% CI 28-47%) respectively. On univariate analysis, immunosuppression (HR = 2.51; 95% CI 1.52-4.14; $P < 0.001$) and the size of the largest node (HR = 1.02; 95% CI 1.00-1.03; $P = 0.023$) were significant factors. However, only immunosuppression

(HR = 2.51; 95% CI 1.52-4.14; $P < 0.001$) retained significance on multivariate analysis.

Cancer Specific Survival

The cause of death could not be determined for 23 cases (31% of all deaths, typically where patients had been discharged to external institutions and data was not provided) and CSS was determined in the remaining 109 patients. For the remaining 109 patients, the two and five year CSS rates were 74% (95% CI 63–82%) and 64% (95% CI 52–74%) respectively (*Figure 2)*. Immunosuppression (HR = 2.92; 95% CI 1.38-6.19; $P = 0.003$), largest node size (HR = 1.02; 95% CI 1.00-1.04; $P = 0.02$) and lymphovascular space invasion (HR = 2.87; 95% CI 1.03-7.97; $P = 0.035$) were significant factors on univariate analysis. On multivariate analysis, only immunosuppression (HR = 2.92; 95% CI 1.38-6.19; $P = 0.003$) remained significant, although lymphovascular space invasion trended to significance (HR = 2.68; 95%CI 0.97 – 7.44; $P = 0.053$).

Overall survival

Seventy-four patient deaths occurred during the follow-up period. The OS for the entire cohort and by immune status is presented in F*igure 1*. The two and five year OS rates were 65% (95% CI 55-73%) and 44% (95% CI 34-53%) respectively. On univariate analysis, age (HR = 1.02; 95% CI 1.00-1.05; P = 0.039), immunosuppression (HR = 3.09; 95% CI 1.85-5.16; $P < 0.001$) and largest node size (HR = 1.02; 95% CI 1.00-1.03; $P = 0.025$) were significant. On multivariate analysis age (HR = 1.03; 95% CI 1.00 - 1.05; $P = 0.033$) and immunosuppression (HR = 3.19; 95% CI 1.91 - 5.34; $P < 0.001$) remained significant.

Immunosuppression

Thirty-three patients (25%) were categorized as immune-compromised. The underlying cause was chronic lymphocytic leukaemia (18 cases), iatrogenic (solid organ transplant recipients, 4 cases; other medication-induced, 4 cases), chronic myeloproliferative disorders (4 cases) and a genetic immune dysregulation syndrome (1 case).

Immunosuppressed patients fared much worse than the immunocompetent. Comparative five-year survival outcomes were 14 versus 53% (HR = 3.19; 95% CI 1.91-5.34; $P < 0.001$) for OS, 40 versus 71% (HR = 2.92; 95% CI 1.38-6.19; $P = 0.003$] for CSS and 10 versus 46% (HR = 2.51; 95% CI 1.52-4.14; $P < 0.001$) for PFS. With respect to DMFS, the difference was 10 v 50% (HR = 2.75; 95% CI 1.65-4.58; $P < 0.001$). With respect to LRC, immune status was not statistically significant on univariate (HR = 1.96; 95% CI 0.91-4.19; P = 0.079 respectively) or multivariate analysis.

Chemotherapy

Twenty-seven patients (20%) received concurrent chemotherapy with adjuvant radiotherapy (off-trial). Chemotherapy regimens included weekly carboplatin (17 patients; 63%), cisplatin either high-dose or low-dose weekly (9 patients; 33%) and carboplatin-5 fluorouracil (1 patient; 4%). Younger patients ($P = 0.003$) and patients with higher nodal stage ($P = 0.024$) were significantly more likely to receive chemotherapy. Chemotherapy did not have a significant impact on any disease-related outcome, either on adjusted or unadjusted analysis.

Discussion

This study reports on a large and relatively homogenous series of patients with cHNSCC metastatic to the parotid. All patients underwent radical treatment defined by surgical management of the parotid (with or without neck dissection), followed by adjuvant radiotherapy. The five-year OS, CSS and LRC rates were 43, 64 and 67% respectively. Our outcomes are in line with other published series (*Table 3)*, though in the lower range, possibly due to the relatively high rate of adverse factors such as immunosuppression in our series, as will be discussed. *Table 3* (upper panel) comprises series which included those patients with parotid metastases (with or without cervical metastases), as well as "mixed" series (lower panel) which included patients with regional metastases (parotid, parotid and cervical or isolated cervical metastases), irrespective of parotid involvement.

Direct comparison is difficult as patient cohorts, staging systems, treatment variables and outcome measures differ between studies. The most recent edition of the AJCC staging system adopted the well-recognized head and neck mucosal nodal staging system and combines parotid and cervical disease into a single regional group, irrespective of the location of the metastases.[18] Other staging systems have been proposed, recognizing the distinction between behaviour of mucosal and cutaneous HNSCC, including those of O'Brien *et al.*,[11] and Forest *et al.*[19] However these proposed revised staging systems have not been uniformly validated.[20] Our study had fewer "clinically favourable" patients (solitary node <3cm) than in most other series. Although our results found only the size of the largest lymph node to be associated with decreasing LRC, other series have shown both the size and number of nodes to influence prognosis.[10]

Median time from surgery to commencement of adjuvant radiotherapy was 43 days in our study. While no high-level data is available to support the effect of overall treatment time on outcomes in cHNSCC, the effect in the post-operative mucosal setting is well documented, and we cannot exclude a potential role in the LRC rate seen in this cohort.[21]

Immunosuppression was confirmed as an important predictor for OS, CSS, DMFS and PFS in this cohort, consistent with others.[12,22-24] One-in-four patients in our study were immunosuppressed, a relatively high rate compared to other published series (*Table 3*). The AJCC staging system acknowledged the significance of immunosuppression in cSCC, but did not incorporate it into the TNM classification (which strictly precludes the incorporation of clinical risk factors). A recommendation was made to designate an "I" (indicating immunosuppression) to the stage where collection of this data is routine. Immune status should be regarded as essential information for improved risk stratification and tailored treatment approaches. However, this is an area which requires crucial further research in order to elaborate the underlying mechanism of interaction between immunosuppression and cSCC, and to identify more effective treatment strategies for these patients. Future directions include the exploration of therapeutic targets and the role of immunomodulation. Close

attention should be paid by clinicians to reduction or modification of iatrogenic immunosuppression, where possible, particularly in patients with a history of cutaneous malignancy.[25]

In patients with parotid metastases adjuvant radiotherapy has been recommended to reduce the high risk of recurrence following surgical resection alone. National Comprehensive Cancer Network guidelines suggest consideration of adjuvant radiotherapy even in the lowest risk disease (solitary node <3cm in size with no extranodal extension).[13] Reports of parotid control following surgical resection alone vary widely from 20-85%, but meet at a minimum the accepted threshold for recommending adjuvant radiotherapy.[14] The recommendation for adjuvant radiotherapy has arisen from multiple retrospective series, demonstrating an improvement in regional recurrence [11,15,16] and DSS.[15,16] Despite some reports, including a recent SEER database review reporting similar outcomes for patients treated with surgery alone versus the addition of adjuvant radiotherapy,[26] the data is confounded by the presence of higher-risk features in the group that received radiotherapy (extraparenchymal extension, cervical lymph node metastases). Furthermore, the latter study reported only DSS as an endpoint and fails to address the benefit of adjuvant treatment in reducing locoregional recurrence, which may be associated with substantial morbidity in the parotid region.

While most patients with cHNSCC involving the regional lymphatics suffer only moderate rates of recurrence, patients with extensive neck disease or immunosuppression are at considerably higher risk of recurrence. One strategy under investigation in an attempt to improve outcomes in high-risk cHNSCC is the use of concurrent systemic therapy. The recently-completed TROG 05.01 trial, tests the addition of weekly carboplatin to adjuvant radiotherapy in the setting of high-risk cHNSCC, and the results are awaited.[17] Our series did not demonstrate a benefit of concomitant chemotherapy compared to those treated with adjuvant radiotherapy alone, however interpretation of this is limited, due to selection bias and heterogeneity of treatment schedules, as expected in retrospective analysis.

The limitations of the present study are those inherent to any retrospective study, and difficulty in comparing retrospective data across various institutions highlights the need for prospective studies in this disease in order to provide crucial information to better inform treatment strategies. Significantly, we were unable to account for the cause in almost one-third of the overall deaths in this cohort. We also identified the lack of structured pathology reporting in cSCC, in both primary and regional specimens as an issue in this study, which hindered the evaluation of pathological risk features.

Conclusion

Regionally-metastatic cHNSCC involving the parotid is an aggressive disease with a moderate risk of locoregional failure despite radical multimodality treatment. Five-year OS and CSS was poor at 43% and 64%. Patients presenting with immunosuppression and metastatic cHNSCC involving the parotid represent a particularly poor prognostic group compared to their immunocompetent counterparts with a higher risk of death and development of distant metastases, and future research should be directed at better risk-stratification, as well as improved therapeutic strategies for these patients.

Acknowledgements

Mr Bernard Lyons (St. Vincent's Hospital), Mr Neil Vallance (Monash Medical Centre), Mr Sorway Chan (Western Health) and Mr Rod Mitchell (Bendigo Health).

References

1. Australian Institute of Health and Welfare. Non-melanoma skin cancer: general practice consultations, hospitalisations and mortality. Canberra. 2008.

2. Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. Dermatology. 1994;189(1):52-4.
3. Tomaszewski JM, Gavriel H, Link E, Boodhun S, Sizeland A, Corry J. Aggressive behavior of cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. Laryngoscope. 2014;124(9):2043-8.
4. Rowe DE, Carroll RJ, Day CL, Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol. 1992;26(6):976-90.
5. Kraus DH, Carew JF, Harrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 1998;124(5):582-7.
6. Moore BA, Weber RS, Prieto V*, et al.* Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. Laryngoscope. 2005;115(9):1561-7.
7. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J Surg Oncol. 2012;106(7):811-5.
8. Ebrahimi A, Moncrieff MD, Clark JR*, et al.* Predicting the pattern of regional metastases from cutaneous squamous cell carcinoma of the head and neck based on location of the primary. Head Neck. 2010;32(10):1288-94.
9. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS. Incidence of cervical node involvement in metastatic cutaneous malignancy involving the parotid gland. Head Neck. 2001;23(9):744-8.
10. Andruchow JL, Veness MJ, Morgan GJ*, et al.* Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicenter study of treatment outcomes. Cancer. 2006;106(5):1078-83.
11. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. Head Neck. 2002;24(5):417-22.

12. Palme CE, O'Brien CJ, Veness MJ, McNeil EB, Bron LP, Morgan GJ. Extent of parotid disease influences outcome in patients with metastatic cutaneous squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2003;129(7):750-3.
13. National Comprehensive Cancer Network. Squamous Cell Skin Cancer. 2015 [cited 2015 13 September]. Version 1.2015:[Available from: http://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf.
14. Mendenhall NP, Million RR, Cassisi NJ. Parotid area lymph node metastases from carcinoma of the skin. Int J Radiat Oncol Biol Phys. 1985;11(4):707-14.
15. Givi B, Andersen PE, Diggs BS, Wax MK, Gross ND. Outcome of patients treated surgically for lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2011;33(7):999-1004.
16. Ch'ng S, Maitra A, Allison RS*, et al.* Parotid and cervical nodal status predict prognosis for patients with head and neck metastatic cutaneous squamous cell carcinoma. J Surg Oncol. 2008;98(2):101-5.
17. Trans-Tasman Radiation Oncology Group. TROG 05.01 Post-operative Concurrent Chemo-radiotherapy Versus Post-operative Radiotherapy for Cancer of the Head and Neck 2016 [updated December 2015]. Available from: https://ClinicalTrials.gov/show/NCT00193895.
18. Edge SB. AJCC cancer staging manual. 7th ed. New York ; London: Springer; 2010. xiv, 648 p. p.
19. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers. Cancer. 2010;116(5):1298-304.
20. Hinerman RW, Indelicato DJ, Amdur RJ*, et al.* Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes. Laryngoscope. 2008;118(11):1989-96.
21. Ang KK, Trotti A, Brown BW*, et al.* Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):571-8.
22. Ebrahimi A, Clark JR, Ahmadi N, Palme CE, Morgan GJ, Veness MJ. Prognostic significance of disease-free interval in head and neck cutaneous

squamous cell carcinoma with nodal metastases. Head Neck. 2013;35(8):1138-43.
23. Schmidt C, Martin JM, Khoo E, Plank A, Grigg R. Outcomes of nodal metastatic cutaneous squamous cell carcinoma of the head and neck treated in a regional center. Head Neck. 2014.
24. Shao A, Wong DK, McIvor NP*, et al.* Parotid metastatic disease from cutaneous squamous cell carcinoma: prognostic role of facial nerve sacrifice, lateral temporal bone resection, immune status and P-stage. Head Neck. 2014;36(4):545-50.
25. Chockalingam R, Downing C, Tyring SK. Cutaneous Squamous Cell Carcinomas in Organ Transplant Recipients. J Clin Med. 2015;4(6):1229-39.
26. Chen MM, Roman SA, Sosa JA, Judson BL. Prognostic factors for squamous cell cancer of the parotid gland: an analysis of 2104 patients. Head Neck. 2015;37(1):1-7.
27. Chen AM, Grekin RC, Garcia J, Bucci MK, Margolis LW. Radiation therapy for cutaneous squamous cell carcinoma involving the parotid area lymph nodes: dose and volume considerations. Int J Radiat Oncol Biol Phys. 2007;69(5):1377-80.
28. Hong TS, Kriesel KJ, Hartig GK, Harari PM. Parotid area lymph node metastases from cutaneous squamous cell carcinoma: implications for diagnosis, treatment, and prognosis. Head Neck. 2005;27(10):851-6.

Figure 1A . Overall Survival for entire cohort.
Figure 1B. Overall Survival by immune status.
Figure 2A. Squamous cell carcinoma specific survival for entire cohort.
Figure 2B. Squamous cell carcinoma specific survival by immune status.
Figure 3. Locoregional control.

Table 1. Clinico-pathological features of parotid/neck dissection surgical specimens

Variable	Statistic	Patients (n=132)
Age	Median [range]	76 [27 - 98]
Gender	Female	11 (8%)
	Male	121 (92%)
Smoking	No	55 (49%)
(missing n=20)	Current	15 (13%)
	Ex-smoker	42 (38%)
Immunosuppression	No	99 (75%)
	Yes	33 (25%)
Differentiation	Poor	75 (63%)
(missing n=13)	Moderate	40 (34%)
	Well	4 (3%)
Largest node size (mm)	Median [range]	20 [1 - 92]
(missing n=9)		
Percent positive nodes	Median [range]	19 [2 - 100]
(missing n=7)		
Nodal stage	1	45 (34%)
(missing n=1)	2a	11 (8%)
	2b	70 (53%)
	2c	1 (1%)
	3	4 (3%)
Extranodal extension	No	15 (12%)
(missing n=4)	Yes	113 (88%)
Perineural invasion	No	52 (58%)
(missing n=42)	Yes	38 (42%)
Lymphovascular space invasion	No	51 (58%)
(missing n=44)	Yes	37 (42%)
Surgical margin status	Clear	40 (32%)
(missing n=8)	Close	49 (40%)
	Involved	35 (28%)
Parotidectomy	Deep	41 (31%)
	Superficial	91 (69%)

Extent of Lymph Node Dissection	Parotid Only	46 (35%)
	Modified radical	27 (20%)
	Radical	9 (7%)
	Selective	50 (38%)
Radiotherapy Technique	3DCRT	99 (75%)
	En-face electron	11 (8%)
	IMRT	22 (17%)
Chemotherapy	Yes	27 (20%)
	No	105 (80%)

3DCRT = 3-dimensional conformal radiotherapy; IMRT = Intensity-Modulated Radiotherapy

Table 2. Cumulative incidence of first failure.

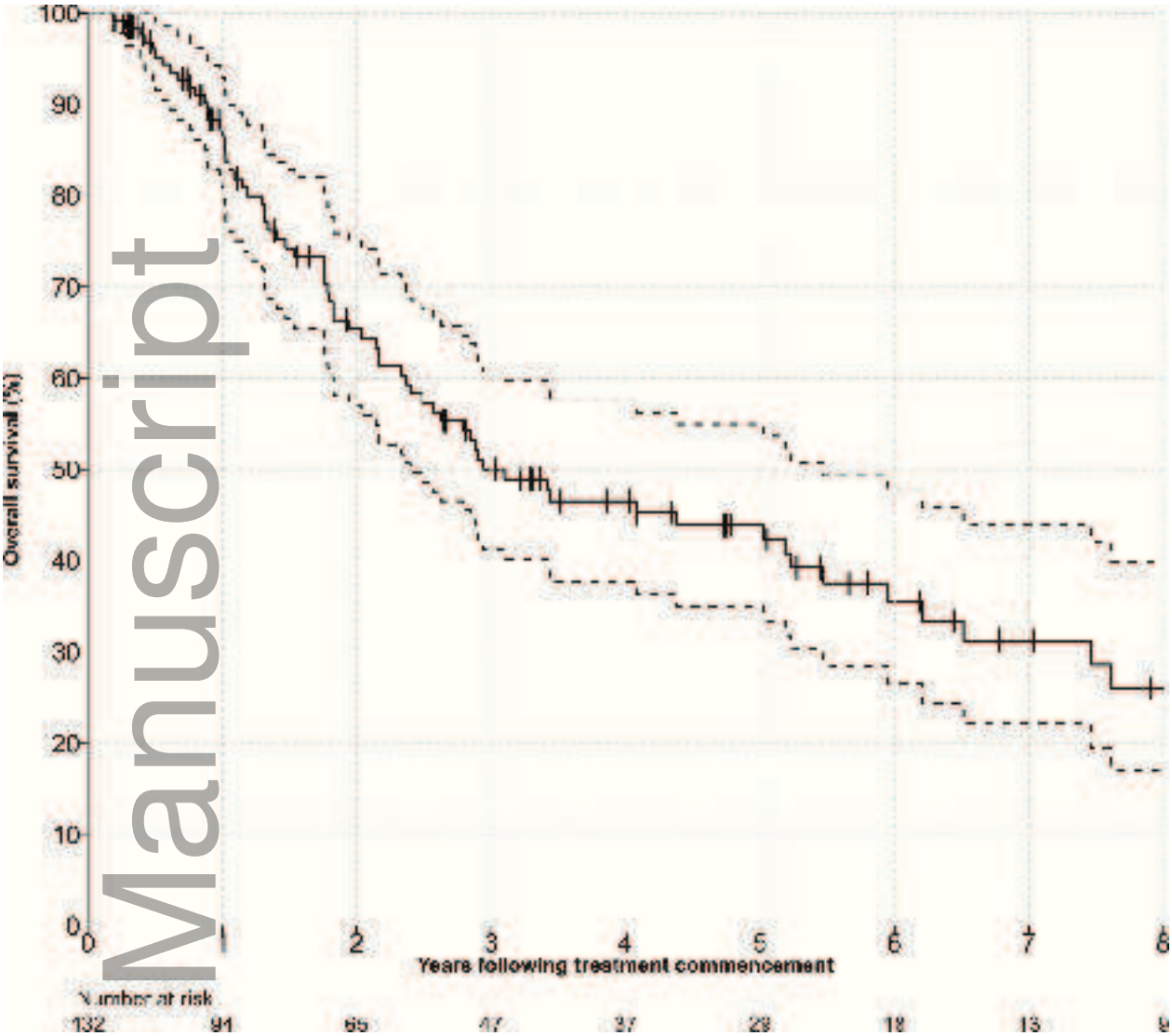
Year	Locoregional	Locoregional + Distant	Distant	Death
1	12.1	5	3.3	5.2
2	15	6	7.3	15
3	17.1	6	7.3	24.4
4	18.4	6	7.3	25.6
5	21.1	6	7.3	28.3

Table 3. Selected series reporting 5-year outcomes in series of metastatic parotid and/or cervical nodal squamous cell carcinoma

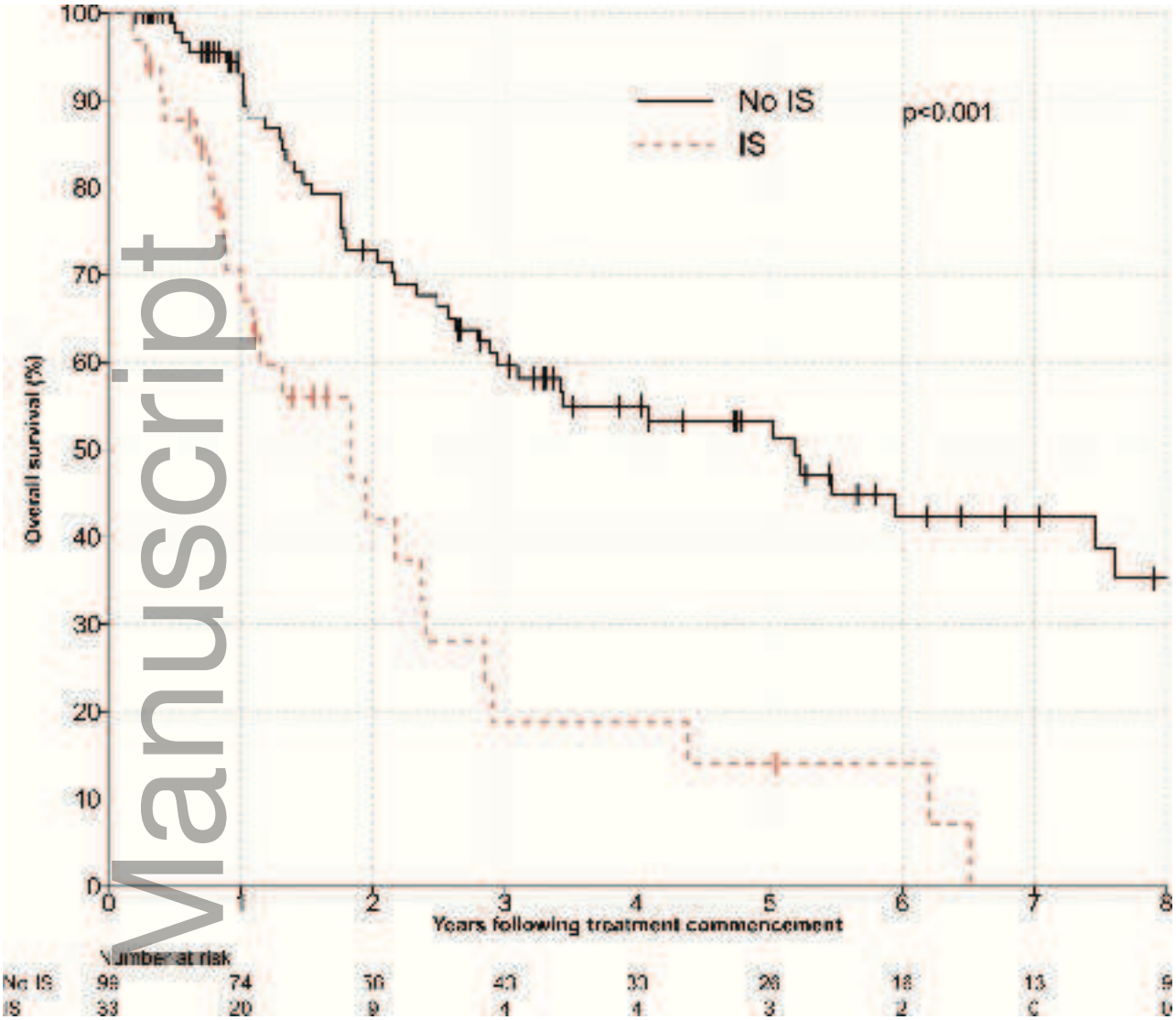
Study	N	Number parotid disease	Imm (%)	LND (%)	Stage N1 (%)	Adj. RT (%)	Def. RT (%)	5-year OS	5-year DSS	5-year LRC	Definition LRC
Studies including only parotid with or without cervical metastases											
Chen[26]	2104	2104	-	-	-	49	14	-	64	-	-
Shao[24]	160	160	18	100	30	80	0	48	77	83	ND
Hinerman[20]	120	120	-	-	41	86†	14	54	-	74	P + R
O'Brien[11]	87	87	-	75	38	86	0	-	63	76	P + R
Chen[27]	36	36	-	23	?	83	14	63	NR	67	P + R

Hong[28]	20	20	-	90	?	70	0	60	NR	85	P
Studies including parotid or cervical metastases or both											
Andruchow[10]	322	260	-	73	48	73	10	-	74	76	P + R
Forest[19]	215	198	-	77	47	81	0	69	77	73	ND
Ebrahimi[22]	229	135	8	91	37	88	0	NR	77	79	I + P + R
Ch'Ng[16]	170	120	-	94	35	77	0	48	69	64	I + P + R
Palme[12]	126	81	14	69	53	89	6	NR	68	73	P + R
Schmidt[23]	113	71	12	98	36	88	0	80	83	84	I + P + R
Givi[15]	51	33	22	88	-	71	0	30	-	-	-
Present Study	**132**	**132**	**25**	**65**	**34**	**100**	**0**	**43**	**64**	**67**	**I + P + R**

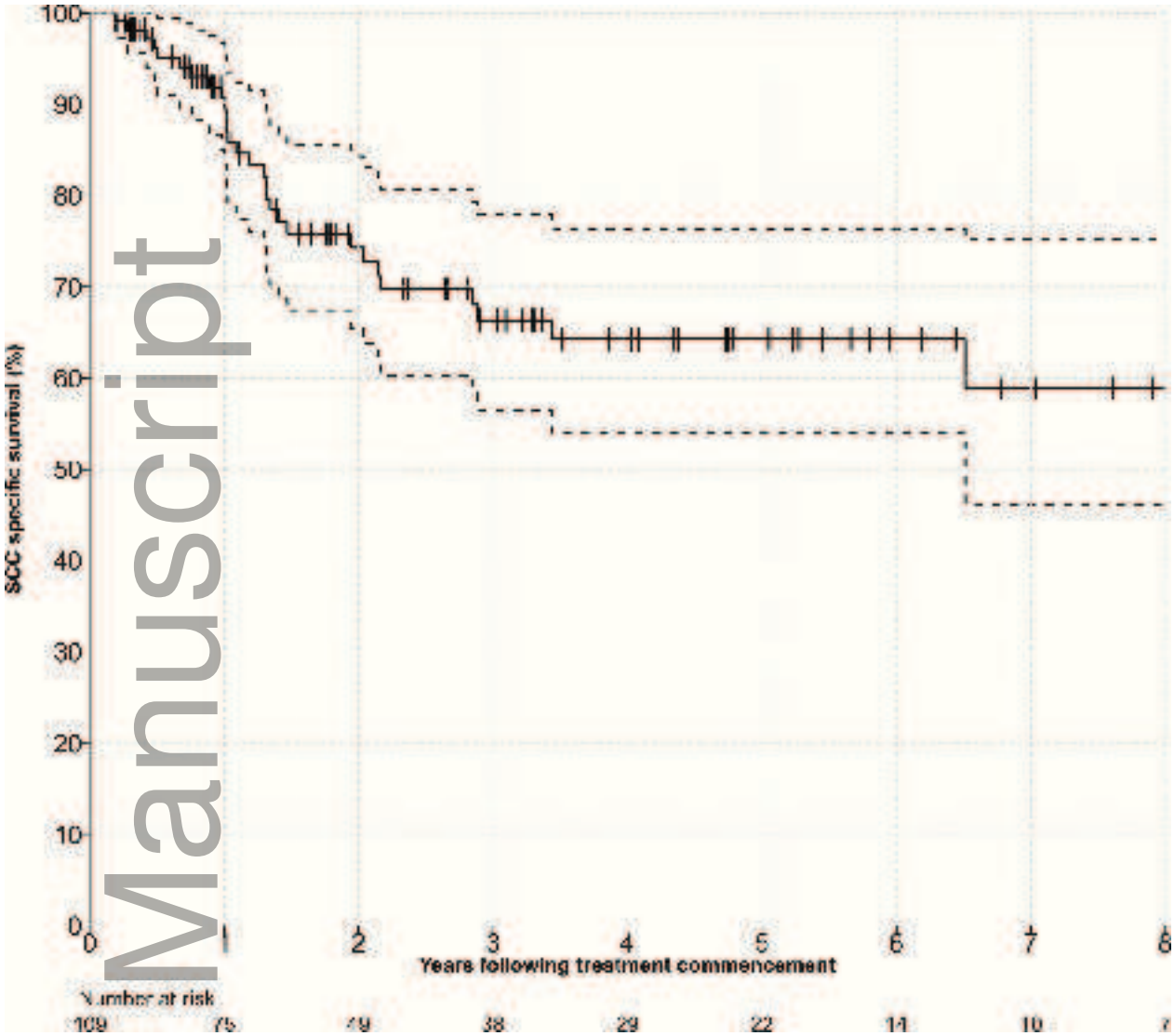
Imm = immunosuppressed; LND = Lymph Node Dissection; Adj = adjuvant; Def = definitive; OS = Overall Survival, DSS = Disease Specific Survival; LRC = locoregional control: ND = Not defined; I = index cutaneous lesion; P = parotid lymph nodes; R = Cervical lymph nodes; NR = not recorded;. † 17 patients (14% of all) received preoperative radiotherapy; ‡ 6 patients (8% of all) received preoperative radiotherapy



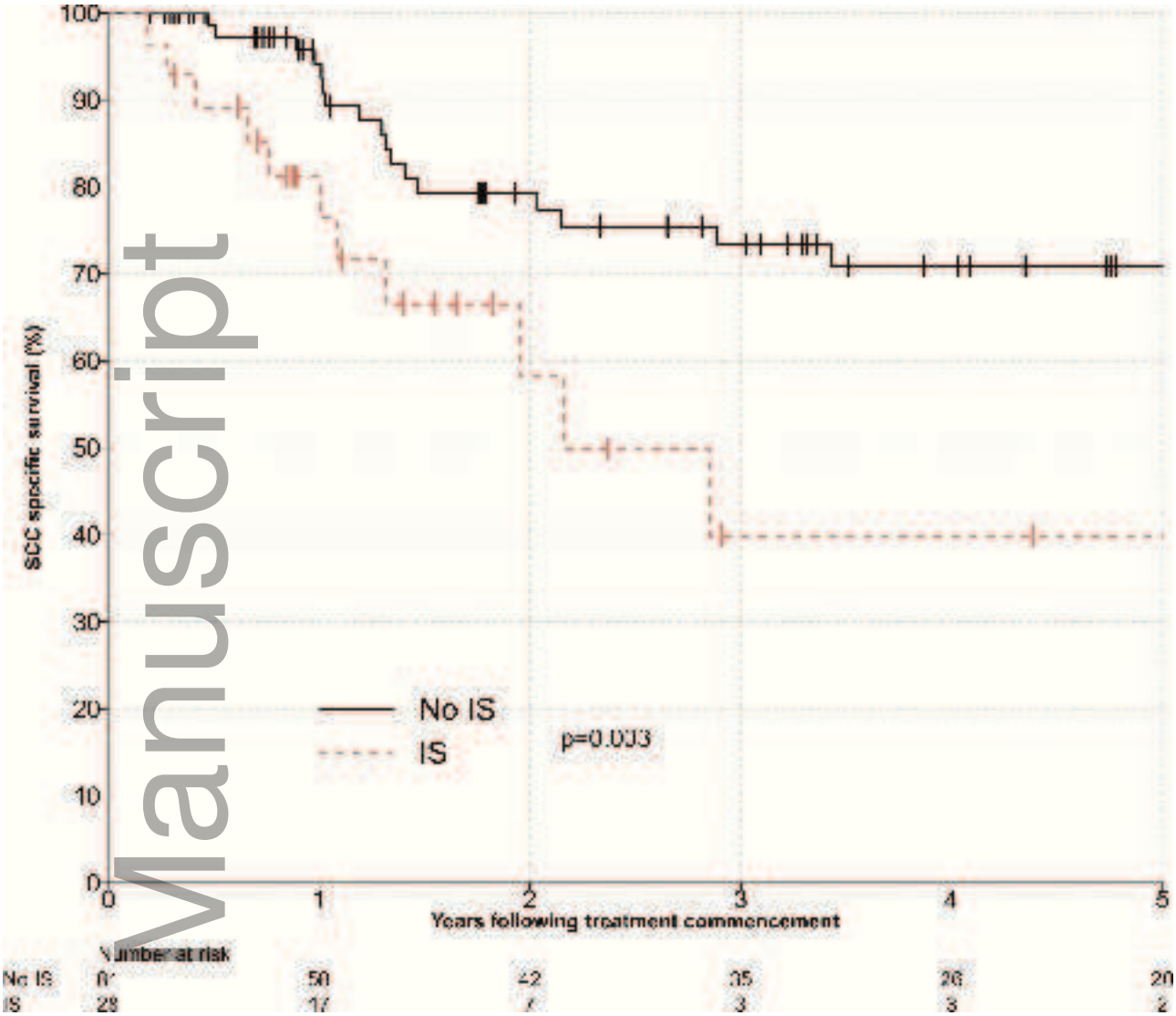
ara_12484_f1a.tiff



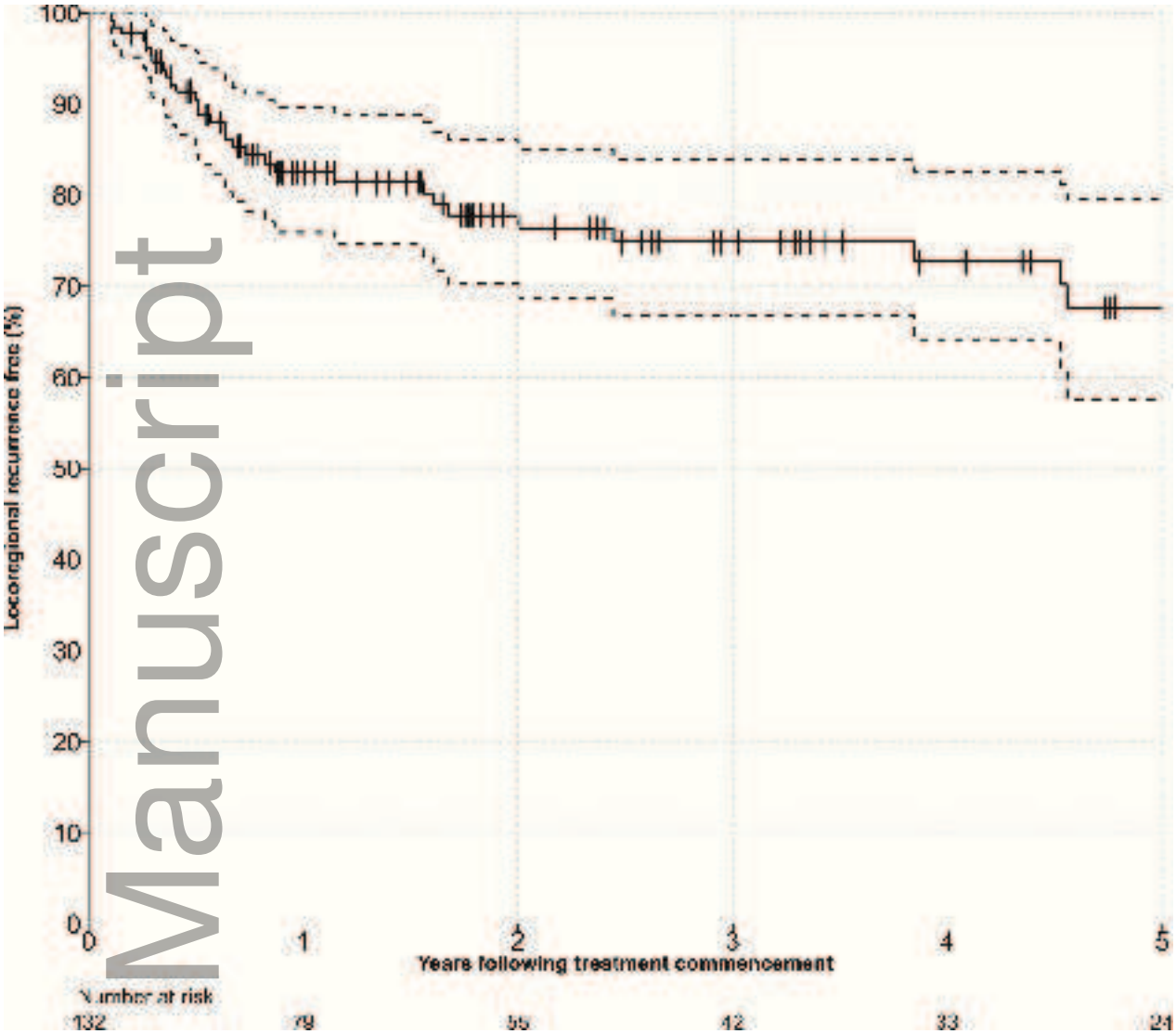
ara_12484_f1b.tiff



ara_12484_f2a.tiff



ara_12484_f2b.tiff



ara_12484_f3.tiff