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Title

Positive survival trend in metastatic head and neck cutaneous squamous cell carcinoma over four-decades: a multicenter study

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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: [10.1002/hed.25912](https://doi.org/10.1002/hed.25912)

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Financial disclosure:

None of the authors has a financial interest in any of the products, devices or drugs
mentioned in this manuscript.

Acknowledgement:

All the authors confirm that the presented manuscript conforms to the Declaration of Helsinki.

Presented at:

Not present at any meeting to date.

Short running head:

Metastatic cutaneous squamous cell carcinoma survival trend in Australia

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head and neck; carcinoma; surgery; chemoradiation; survival

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The authors have no conflicts of interest relevant to this article to disclose

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ABSTRACT

Word count 148

Background

This study assessed changes over time of survival of head and neck cutaneous squamous cell carcinoma (HNcSCC) with lymph node metastases.

Methods

Multicentre analysis of 1301 patients with metastatic HNcSCC treated between 1980-2017. Differences in disease-specific (DSS) and overall survival (OS) by decade were assessed using multivariate Cox regression.

Results

Over the study period, we noted an increase in the proportion of patients aged over 80 years (3.9% to 31.7%; $P<.001$) and immunosuppression (1.9% to 9.9%; $P=.034$). After adjusting for number and size of metastatic nodes, extranodal extension, perineural invasion, immunosuppression, treatment and institution, there was a reduction in risk of cancer-related mortality from 0.47 in 1990-1999 ($P=.036$) to 0.30 in 2000-2009 ($P<.001$) when compared to 1980-1989. This remained stable at 0.30 in 2010-2017 ($P=.001$). Overall survival remained stable after 1990.

Conclusion

Despite an aging and more frequently immunosuppressed population, fewer patients are dying from metastatic HNcSCC.

Introduction

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Cutaneous squamous cell carcinoma (cSCC) accounts for approximately 20% of all nonmelanoma skin cancer which is the most common malignancy worldwide¹. Australia has the highest rate of cSCC secondary to excess sun exposure in a largely fair-skinned population². Whilst less than 5% of head and neck cSCC (HNcSCC) metastasize³, lymph node metastases in the parotid and/or neck are potentially lethal and require morbid multimodal regional therapy with surgery and adjuvant radiotherapy (RT)⁴. Although the fundamental treatment approach has remained largely unchanged, there have been several advances which may impact survival.

In Australia, the age-standardised mortality rate from mucosal head and neck cancer has steadily decreased over time⁵. Similarly, in the United States there was reported improvement in survival for most forms of head and neck cancer between 1973-2006^{6,7}. However, there have been very few studies examining trends in survival of HNcSCC, particularly metastatic HNcSCC^{8,9}. Gnanasekaran *et al*¹⁰ recently examined the trends in prognosis of patients with metastatic HNcSCC over the last 30 years within a single Australian institution. The authors reported improved cancer-specific survival over time despite treating increasing numbers of elderly patients and more aggressive cancers.

The present study aims to provide further insight into this issue using a large multicentre Australian cohort. The study further investigates changes over time in other characteristics such as adverse clinicopathological features and treatment approaches.

Methods

Study Population

Data was extracted from clinicopathological databases at four Australian cancer centres, including prospective databases at Westmead Hospital and Chris O'Brien Lifehouse/Royal Prince Alfred Hospital and retrospective databases at Liverpool Hospital and Peter MacCallum Cancer Centre after approval by the Royal Prince Alfred Hospital Ethics Review Committee (X16-0096 & HREC/17/RPAH/602) as well as site specific approvals from each institution. Patients with HNCSCC metastatic to parotid and/or cervical nodes treated with surgery $\pm$ adjuvant therapy with curative intent were included. After excluding cases with distant metastases at presentation, peri-operative mortality, or lack of follow-up data, the final study population consisted of 1301 patients treated between 1980-2017. Demographic, clinicopathological, treatment and follow-up details were retrieved for all patients. Tumor staging was performed using the eighth edition of the American Joint Committee on Cancer staging manual (AJCC8)¹¹.

Statistical analysis

Data were divided into four-decade brackets: 1980-1989, 1990-1999, 2000-2009 and 2010-2017. The data was analysed for differences in disease-specific survival (DSS) and overall survival (OS) over time using univariate and multivariate Cox proportional hazards models. Shared frailty models were used to account for presumed heterogeneity between institutions. Survival curves were generated using the Kaplan-Meier method where appropriate. OS was calculated from the date of surgery to the date of last follow-up or death and for DSS patients who died from other causes were censored at the time of death. Sensitivity analyses were performed to ensure the results were robust when immunosuppressed patients, those treated with surgery alone and patients without extranodal extension (ENE) were excluded from the

analysis. Statistical analysis was performed using Stata version 12.0 SE (StataCorp LLC, 2011). All statistics were two-sided and P -values $<.05$ were deemed statistically significant.

Results

Study Population

There were a total of 1301 patients with metastatic HNSCC with a median age of 73 years (range: 18-100) and median follow-up of 3.2 years. The majority were male (85%) and most (80%) had AJCC8 TNM Stage IV disease. In total, 250 (19.2%) patients underwent surgery alone, 972 (74.7%) had surgery and adjuvant radiotherapy (RT), whilst 79 (6.1%) had surgery and adjuvant chemoradiation therapy (CRT). The time period of treatment consisted of 52 (4.0%) patients treated between 1980-1989; 220 (16.9%) between 1990-1999; 562 (43.2%) between 2000-2009 and 467 (35.9%) between 2010-2017. Table 1 summarises patient demographic, staging and treatment data.

Changes over time

Table 2 summarizes changes in clinicopathological and treatment data over the time period of the study. The proportion of patients aged over 80 years increased from 3.9% in the first decade to 31.7% in the last ($P < .001$). The proportion of male patients remained stable at approximately 85% ($P = .40$). The rate of immunosuppression increased from 1.9% to 9.9% ($P = .034$). Haematological malignancy was the most common form of immunosuppression (49 out of 114 cases) followed by solid organ transplantation (19) and use of immunosuppressive medications (13). The presence of perineural invasion (PNI) was reported more frequently (11.5% to 33.6%, $P < .001$). The remaining adverse risk factors

remained unchanged including tumour differentiation ($P = .260$), presence of ENE ($P = .49$), surgical margin status ($P = .705$), number of involved lymph nodes (≥ 3 versus < 3 metastatic nodes; $P = .652$), nodal size ($\geq 3\text{cm}$ versus $< 3\text{cm}$; $P = .54$), pathological N category ($P = .77$) and TNM stage ($P = .86$). The use of concurrent neck dissection with parotidectomy increased from 25% to 68% ($P < .001$) and when performed, neck dissections were more frequently selective rather than comprehensive (44% versus 78%; $P < .001$). Over time, the use of adjuvant CRT increased from 1.9% in the first decade to 7.7% in the final decade ($P < .001$), however, the proportion receiving some form of adjuvant therapy remained relatively stable.

Prognosis

The median OS of the study cohort was 5.7 years. A total of 596 (46%) deaths occurred, of which 226 (17%) were from HNSCC. After adjusting for the number and size of metastatic lymph nodes, ENE, PNI, immunosuppression and treatment on multivariate analysis, there was a progressive reduction in hazard of disease-specific death from 0.47 in 1990-1999 ($P = .036$) to 0.30 in 2000-2009 ($P < .001$) when compared to the baseline cohort treated between 1980-1989. The hazard reduction remained stable at 0.30 for the period 2010-2017. The hazard reduction in DSS from the year 2000 onwards compared to 1990-1999 reduced to 0.66 ($P = .05$). Multivariate analysis of OS was also performed adding age into the full regression model. An improvement in OS was noted from 1990 onwards and appeared stable over time as shown in Table 3 but failed to reach statistical significance based on a global p value ($P = .10$). There was however some improvement in overall survival noted after 1990. Adjusted survival curves are shown in Figure 1.

There was no effect modification based on an interaction term between treatment decade and institution ($P=0.994$). Sensitivity analyses confirmed that the improvement in DSS over time was consistent after excluding Liverpool Hospital and Peter MacCallum Cancer Centre since neither institution had data for patients treated before the year 2000 ($P = .001$). Similarly, the results were robust to exclusion of immunosuppressed patients ($P = .004$), those treated with surgery alone ($P = .017$), or patients without ENE ($P = .040$). In the subset of 250 patients treated with surgery alone, the reduction in risk over time (HR 0.42) was not statistically significant ($P = .52$).

Discussion

Australia has the highest incidence of cSCC in the world, with more than 387 cases per 100,000 per year¹². This analysis of 1301 patients from four Australian centres spanning over four decades showed that DSS from HNSCC with lymph node metastases has improved over time despite an increasingly elderly and more frequently immunosuppressed patient population. The present multicentre study, to our knowledge, is the largest examining time trends in prognosis of metastatic HNSCC.

Population-based studies in the United States^{6,13} and several Northern European nations^{8,14} examining trends in survival from non-melanoma skin cancer indicate improved prognosis over time. However, these studies included other non-melanoma skin cancers, non-head and neck sites, and very few patients with lymph node metastases, who have a vastly different prognosis. It is not possible to perform population-based studies on cSCC in Australia because cSCC is at epidemic rates and not routinely recorded by cancer registries. Recently

however Gananasekaran *et al*¹⁰ reported a 5-year DSS improvement from 57% during 1987–1996 to 88% during 2007–2016 in the first study specifically examining the prognosis of metastatic HNCSCC over time. Despite an aging and more frequently immunosuppressed patient population, we confirmed that death from metastatic HNCSCC has decreased over time in the present study, with disease-specific survival rates plateauing after the year 2000. Despite this, rates of OS have remained relatively stable, particularly post 1990. Presumably this is a consequence of an increasingly elderly patient cohort dying from age-related non-cancer comorbidities.

Gananasekaran and colleagues¹⁰ found an increase in the incidence of metastatic HNCSCC which this study demonstrates as well. Over the last four decades Australian population has risen from 14.7 million to 24 million with the proportion aged over 65 increasing by from 9% to 15%^{15,16}. Over the same period ultraviolet radiation exposure in Australia has progressively increased¹⁷. The growing incidence is further explained by better capture of patients with increasing number of specialised centres. The authors also found an increase in the rates of observed adverse prognostic features including the number and size of metastatic nodes. However, no evidence for this was found in the present study. PNI was a significant predictor of both DSS ($P = 0.001$) and OS ($P < .001$) on multivariate analysis as were the number and size of metastatic nodes. Increasing rates of PNI however likely reflects reporting bias with routine implementation of synoptic reporting as has been described for nodal yield²⁴. There was also no evidence to suggest that patients were presenting at an earlier stage to explain the improved prognosis. In fact, the proportion of immunosuppressed patients

increased over time suggesting that improvements in survival may be related to improved management of metastatic HNCSCC.

Management has improved in several ways, including advances in imaging¹⁸ leading to more accurate preoperative staging, subspecialisation in surgery, radiation oncology, and pathology with a better understanding of prognostic factors¹⁹⁻²³ to allow appropriate selection of patients that may benefit from treatment intensification²⁴. The routine use of higher quality pre-operative imaging, such as PET scans, may have led to improved detection of incurable disease and exclusion of these cases over time. In addition, high quality imaging may ensure that both surgery and radiotherapy fields encompass all disease in patients with regional metastases in atypical locations. Technological advancements have led to the delivery of conformal RT that more accurately treats target volumes at risk yet minimises collateral normal tissue damage without compromising disease control²⁵. The implementation of synoptic pathological reporting²⁶ also impacts treatment. For example, the presence of PNI may alter RT target volumes to include the course of the facial or auriculotemporal (V3) nerves that may also include intracranial neural pathways. Finally, multidisciplinary team (MDT) meetings have enabled effective implementation of these advances through coordinated care²⁷. Whilst there is a lack of robust evidence to show that multidisciplinary care improves survival in early stage head and neck cancer, Friedland *et al*²⁷ documented improved survival in TNM Stage IV disease for patients managed by a MDT compared to those managed by individual disciplines (HR = 0.690, $P = .004$).

Whilst the fundamentals of surgery have not changed over this time period, there has been a move towards more frequent implementation of concurrent neck dissection with

parotidectomy to address microscopic occult disease, and a more selective approach to neck dissection, particularly over the last two decades^{2,28,29}. Metastatic HNCSCC rarely presents with concurrent primary and nodal disease (20-30%)³⁰. In up to a quarter of metastatic cases the primary index lesion remains indeterminate or several primaries co-exist². As a result most parotidectomy and neck dissections are done beyond the time of primary excision. Surgery is more often performed by subspecialised head and neck surgeons and reconstructive surgery may facilitate more radical resections when indicated. Gananasekaran *et al*¹⁰ reported DSS with surgery alone improved from 60% during 1987-1996 to 92% in 2007-2016 ($P = .017$), although no such improvement was observed in the present study. Interestingly however, between 2000-2009 and 2010-2017, the proportion of patients treated by surgery alone increased by 10% while DSS remained relatively stable suggesting that the discrepancy probably reflects institutional differences regarding which patients are selected for single modality therapy.

The lack of further improvement in disease-specific survival beyond the year 2000 suggests locoregional therapy with surgery and RT may have reached the limit of effectiveness to cure patients. Without effective systemic therapy, further improvements are unlikely to be achieved as has been shown in Stage IV colorectal cancer with the introduction of chemotherapy around 2000³¹. In this context, the recent negative results of the randomised multicentre postoperative chemoradiation study in regionally metastatic HNCSCC were disappointing³². However, recent studies evaluating immunotherapy demonstrate that cSCC has a high response rate to PD-1/PD-L1 blockade and this treatment option may also be better suited to an aging population than platinum-based chemotherapy³³. It is very likely that the

next generation of adjuvant trials in HNSCC will incorporate PD-1/PD-L1 immunotherapy in conjunction with adjuvant RT.

Several limitations of this study need to be acknowledged. There is likely heterogeneity between institutions, however, we believe this strengthens the generalisability of the study and we accounted for this using shared frailty models. Also, the results may be confounded by patient co-morbidities, which are particularly important in an elderly cohort, but we were unable to include these in the study due to its retrospective nature. It is also possible that the more elderly population treated later in the study period may be dying from competing risks due to age-related comorbidities and hence not experiencing death from HNSCC. It is important to recognise that when analysing cancer outcomes over periods of time that prognosis may improve by means of redistributing patients to different stages without affecting outcomes for individual patients. This paradox, referred to as the Will Rogers phenomenon, often results from enhanced detection of cancer by newer technology³⁵.

Conclusion

Although the fundamentals of treatment have not changed, relatively fewer patients are dying from metastatic HNSCC despite treating an increasingly elderly and immunosuppressed patient population. The improved prognosis has been most marked between 1980 and 2000, with stable disease-specific survival since. The lack of sustained gains suggests that we have reached the limits of what high quality surgery and postoperative RT can achieve, and effective systemic therapies need to be developed.

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Tables

TABLE 1. Patient demographic and treatment factors.

Variable	No. of patients (%)
Age, years	
≤60	222 (17.1)
60-80	742 (57)
>80	337 (25.9)
Gender	
Male	1107 (85.1)
Female	194 (14.9)
Treatment decade	
1980-1989	52 (4)
1990-1999	220 (16.9)
2000-2009	562 (43.2)
2010-2017	467 (35.9)
Institution	
Liverpool Hospital	100 (7.7)
Chris O'Brien Lifehouse	577 (44.4)
Westmead Hospital	419 (32.2)
Peter MacCallum Cancer Centre	205 (15.7)
Pathological nodal stage	
pNx	155 (11.9)
pN1	114 (8.8)
pN2a	363 (27.9)
pN2b	74 (5.7)
pN2c	8 (0.6)
pN3a	4 (0.3)
pN3b	583 (44.8)

TNM stage*	
Stage III	111 (8.5)
Stage IV	1035 (79.6)
Treatment modality	
Surgery alone	250 (19.2)
Surgery + RT	972 (74.7)
Surgery + CRT	79 (6.1)
Surgery	
Parotidectomy alone	198 (15.2)
Parotidectomy + SND	550 (42.3)
Parotidectomy + CND	269 (20.7)
SND alone	172 (13.2)
CND alone	99 (7.6)
Other	13 (1.0)

* TNM Stage was missing in 155 patients due to missing data on pathological nodal stage.

Abbreviations: RT = radiotherapy; CRT = chemoradiation therapy; SND = selective neck dissection; CND = comprehensive neck dissection

TABLE 2. Distribution of patient demographic, clinicopathological findings and treatment over time.

Variable	Time period, (%)				<i>p</i> value
	1980-1989	1990-1999	2000-2009	2010-2017	
Patient features					
Age >80 years	3.9	14.6	27.5	31.7	<.001
Male	86.5	88.2	85.2	83.3	.402
Immunosuppressed	1.9	5.0	9.9	9.9	.034
Nodal features					
Nodal size <3cm	76.7	65.9	71.2	68.2	.537
Extranodal extension	74.5	76.7	80.6	80.8	.490
≥3 Nodal metastases	23.5	22.6	26.5	27.0	.652
pN3 Category	43.5	45.6	51.4	54.6	.765
Perineural invasion	11.5	21.4	25.1	33.6	<.001
Clear margins	53.5	58.9	55.4	58.8	.705
TNM Stage IV	87.0	91.2	90.3	90.3	.858
Treatment modality					
Surgery alone	23.1	14.1	15.5	25.7	<.001
Surgery + RT	75	85	77.4	66.6	
Surgery + CRT	1.9	0.9	7.1	7.7	

Abbreviations: pN = pathological nodal; RT = radiotherapy; CRT = chemoradiation therapy.

TABLE 3. Multivariate analysis of changes in disease-specific and overall survival over time.

Time period	Disease-Specific Survival*		Overall Survival[†]	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
1980-1989	Reference		Reference	
1990-1999	0.47 (0.23-0.95)	.036	0.56 (0.33-0.96)	.035
2000-2009	0.30 (0.15-0.58)	<.001	0.55 (0.33-0.92)	.024
2010-2017	0.30 (0.15-0.60)	.001	0.50 (0.29-0.87)	.013

* Multivariate analysis adjusted for number and size of nodal metastases, extranodal extension, perineural invasion, immunosuppression and treatment (surgery; surgery and radiotherapy; surgery and chemoradiotherapy)

[†] Multivariate analysis adjusted for age, number and size of nodal metastases, extranodal extension, perineural invasion, immunosuppression and treatment (surgery; surgery and radiotherapy; surgery and chemoradiotherapy)

ABSTRACT

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Background

This study assessed changes over time of survival of head and neck cutaneous squamous cell carcinoma (HNCSCC) with lymph node metastases.

Methods

Multicentre analysis of 1301 patients with metastatic HNCSCC treated between 1980-2017. Differences in disease-specific (DSS) and overall survival (OS) by decade were assessed using multivariate Cox regression.

Results

Over the study period, we noted an increase in the proportion of patients aged over 80 years (3.9% to 31.7%; $P<.001$) and immunosuppression (1.9% to 9.9%; $P=.034$). After adjusting for number and size of metastatic nodes, extranodal extension, perineural invasion, immunosuppression, treatment and institution, there was a reduction in risk of cancer-related mortality from 0.47 in 1990-1999 ($P=.036$) to 0.30 in 2000-2009 ($P<.001$) when compared to 1980-1989. This remained stable at 0.30 in 2010-2017 ($P=.001$). Overall survival remained stable after 1990.

Conclusion

Despite an aging and more frequently immunosuppressed population, fewer patients are dying from metastatic HNCSCC.

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Tables

TABLE 1. Patient demographic and treatment factors.

Variable	No. of patients (%)
Age, years	
≤60	222 (17.1)
60-80	742 (57)
>80	337 (25.9)
Gender	
Male	1107 (85.1)
Female	194 (14.9)
Treatment decade	
1980-1989	52 (4)
1990-1999	220 (16.9)
2000-2009	562 (43.2)
2010-2017	467 (35.9)
Institution	
Liverpool Hospital	100 (7.7)
Chris O'Brien Lifehouse	577 (44.4)
Westmead Hospital	419 (32.2)
Peter MacCallum Cancer Centre	205 (15.7)
Pathological nodal stage	
pNx	155 (11.9)
pN1	114 (8.8)
pN2a	363 (27.9)
pN2b	74 (5.7)
pN2c	8 (0.6)
pN3a	4 (0.3)
pN3b	583 (44.8)
TNM stage*	
Stage III	111 (8.5)
Stage IV	1035 (79.6)
Treatment modality	

Surgery alone	250 (19.2)
Surgery + RT	972 (74.7)
Surgery + CRT	79 (6.1)
<hr/>	
Surgery	
Parotidectomy alone	198 (15.2)
Parotidectomy + SND	550 (42.3)
Parotidectomy + CND	269 (20.7)
SND alone	172 (13.2)
CND alone	99 (7.6)
Other	13 (1.0)

* *TNM Stage was missing in 155 patients due to missing data on pathological nodal stage.*

Abbreviations: RT = radiotherapy; CRT = chemoradiation therapy; SND = selective neck dissection; CND = comprehensive neck dissection

TABLE 2. Distribution of patient demographic, clinicopathological findings and treatment over time.

Variable	Time period, (%)				<i>p</i> value
	1980-1989	1990-1999	2000-2009	2010-2017	
Patient features					
Age >80 years	3.9	14.6	27.5	31.7	<.001
Male	86.5	88.2	85.2	83.3	.402
Immunosuppressed	1.9	5.0	9.9	9.9	.034
Nodal features					
Nodal size <3cm	76.7	65.9	71.2	68.2	.537
Extranodal extension	74.5	76.7	80.6	80.8	.490
≥3 Nodal metastases	23.5	22.6	26.5	27.0	.652
pN3 Category	43.5	45.6	51.4	54.6	.765
Perineural invasion	11.5	21.4	25.1	33.6	<.001
Clear margins	53.5	58.9	55.4	58.8	.705
TNM Stage IV	87.0	91.2	90.3	90.3	.858
Treatment modality					
Surgery alone	23.1	14.1	15.5	25.7	<.001
Surgery + RT	75	85	77.4	66.6	
Surgery + CRT	1.9	0.9	7.1	7.7	

Abbreviations: pN = pathological nodal; RT = radiotherapy; CRT = chemoradiation therapy.

TABLE 3. Multivariate analysis of changes in disease-specific and overall survival over time.

Time period	Disease-Specific Survival*		Overall Survival [†]	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
1980-1989	Reference		Reference	
1990-1999	0.47 (0.23-0.95)	.036	0.56 (0.33-0.96)	.035
2000-2009	0.30 (0.15-0.58)	<.001	0.55 (0.33-0.92)	.024
2010-2017	0.30 (0.15-0.60)	.001	0.50 (0.29-0.87)	.013

* Multivariate analysis adjusted for number and size of nodal metastases, extranodal extension, perineural invasion, immunosuppression and treatment (surgery; surgery and radiotherapy; surgery and chemoradiotherapy)

[†] Multivariate analysis adjusted for age, number and size of nodal metastases, extranodal extension, perineural invasion, immunosuppression and treatment (surgery; surgery and radiotherapy; surgery and chemoradiotherapy)

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Title:

Positive survival trend in metastatic head and neck cutaneous squamous cell carcinoma over four-decades: Multicenter study

Date:

2019-11-01

Citation:

Hasmat, S., Ebrahimi, A., Luk, P. P., Low, T. -H. H., McDowell, L., Magarey, M. J. R., Veness, M., Gupta, R. & Clark, J. (2019). Positive survival trend in metastatic head and neck cutaneous squamous cell carcinoma over four-decades: Multicenter study. HEAD AND NECK-JOURNAL FOR THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK, 41 (11), pp.3826-3832. <https://doi.org/10.1002/hed.25912>.

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