Choice of Levels in Selective Neck Dissection and Its Impact On Regional Control and Survival in 661 Patients With Head and Neck Squamous Cell Carcinoma

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Research Article

Keywords: Selective Neck Dissection, Head & Neck Squamous Cell Carcinoma

Posted Date: September 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-667635/v1>

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Abstract

Background: Selective Neck Dissection (SND) is the surgical treatment of choice in suspected or manifest nodal positive squamous cell carcinoma of the head and neck (HNSCC). For SND to be successful, treated levels should be selected accordingly. Aim of this study was to identify neck dissection levels that had an impact on the individual prognosis.

Methods: We conducted a retrospective review of SND as part of primary treatment of HNSCC. Overall survival (OS) and regional control rates (RCR) were calculated for all patients.

Results: 661 patients with HNSCC were included, 644 underwent ipsilateral and 319 contralateral SND. Average follow up was 78.9 ± 106.4 months. 67 (10.1%) patients eventually developed nodal recurrence. Tumor sites were oral cavity (135), oropharynx (179), hypopharynx (118) and larynx (229). Tumor categories pT1 – pT4a, and all clinical and pathological nodal categories were included. Multivariate analysis indicated improved OS rates for patients undergoing SND in ipsilateral levels I and V as well as level III contralaterally. Analysis for tumor origin showed that SND in ipsilateral level I showed a significantly improved OS in HNSCC of the oral cavity.

Conclusion: In HNSCC of the oral cavity, ipsilateral level I needs to be included when performing SND.

Introduction

Clinical and pathological presence of lymph node metastasis is – apart from distant metastasis – the most important prognostic factor in patients suffering from squamous cell carcinoma of the head and neck (HNSCC).(1) It has been reported that only one affected lymph node may decrease overall survival rates by as much as 50%.(2) Consequently, adequate treatment of the lymphatic regions is paramount to obtain an adequate oncologic result.

Generally speaking, the neck is commonly treated in the same manner as the primary tumor – i.e. if the tumor was treated surgically, so is the neck, with or without postoperative radio-(chemo-)therapy. In turn, if a tumor is treated by definitive chemoradiation, the neck is commonly radiated as well. If the neck is treated surgically, selective neck dissection (SND) is the treatment of choice,(3) except in cases where non-lymphatic structures are involved by tumor spread and have to be removed by radical or modified radical neck dissection. Neck Dissection is the surgical treatment of choice in lymphatic affection in HNSCC and should be performed even in early and clinically inapparent stages.(4)

While RND has been the treatment of choice for the past, focus in neck dissection has shifted to less invasive techniques in the past decade.(5, 6) In selective neck dissection (SND), many structures that are usually removed are preserved, including muscles, nerves and vascular structures. Moreover, one or several lymph node levels of the ipsi- or contralateral side are regularly spared. The assumption behind this approach is that the metastatic behavior of the primary tumor follows a predictable pattern, depending on where the tumor originated, and the treated regions are selected accordingly. The concept

of predictable sequential regional spread in HNSCC has recently been confirmed for oral cavity scc by a comprehensive meta-analysis.(7) This makes neck dissection significantly less invasive and causes less short- and long-term side effects.

SND is to this day the surgical treatment of choice in patients with both likely nodal spread(8) as well as patients with clinically positive neck status(9). However, decision making is still difficult when it comes to selective neck dissection. Hence, we conducted a retrospective analysis of factors influencing the outcomes of neck dissection in a large collective at a tertiary referral center.

Materials And Methods

Ethics

The study at hand was conducted in accordance with the Declaration of Helsinki in its current form (seventh revision, 2013). The study was approved by the ethics committee at the University Medical Center of the Georg-August University Göttingen (Niedersachsen, Federal Republic of Germany) on January 10th 2017 under the File No. DOK_200_2016. All study participants consented in written form to the analysis of medical data before treatment at the study center.

Data acquisition

For data acquisition, the tumor database of the Department of Otorhinolaryngology of the University of Göttingen, established in 1986 by Wolfgang Steiner and coworkers, was used. This is a prospective Database in which all patients that had been primarily treated for HNSCC in the otolaryngology department and individual follow-ups were recorded. The database was used to extract patient information that included age, gender, tumor location, size, clinical TNM category, pathological TNM status, whether a neck dissection was performed, which levels were operated and the subsequent follow-up. Whenever the tumor database provided insufficient information on a specific case, individual patient files were consulted. TNM-Stages were given according to the 6th edition from 2002.

Inclusion and exclusion criteria

Patients with primary diagnosis of head and neck squamous cell carcinoma and surgical therapy in curative intention were considered for this analysis. Included were only patients with neck dissection as part of the initial therapy sequence. Exclusion criteria were cT4b stadium, distant metastasis when the tumor was initially diagnosed, patient that did not undergo surgical therapy of the tumor and patients that suffered from a synchronous secondary malignant disease. Also, patients that developed a local recurrence during follow-up were excluded from the analysis.

Surgical approach

All patients that were included in this study underwent transoral laser microsurgery (TLM) as primary treatment as has been established by Steiner and coworkers(10–12) with concomitant neck dissection. The dominance of TLM is particular for the local philosophy for management of HNSCC. Generally

speaking, patients underwent SND of the ipsilateral levels II and III. If the primary tumor site was in the oral cavity, ipsilateral level I was included as well. In supraglottic laryngeal and hypopharyngeal tumor sites, levels II and III were treated on both sides. If tumor size was cT3 or cT4a of the oropharynx, hypopharynx or larynx, SND was performed in levels II, III and IV, respectively. If a cT3 or cT4a tumor was located in the oral cavity, levels I-IV were treated bilaterally. If any level showed suspicious lymph nodes, that regions was included in the SND as well. Patients that underwent SND in other levels than stated previously were still included in the analysis.

Calculation of Overall survival and regional control rates

When calculating overall survival (OS), death from any cause was counted as an event. When calculating regional control rates (RCR), tumor associated death or lymph node recurrence were counted as an event; patient that died from any cause apart from tumor associated death were considered as censored.

Statistics

Statistics were carried out using Project R for Mac (Build 3.4.1 for El Capitan, The R Project for Statistical Computing, <http://www.r-project.org/>) To estimate 5 and 10 year OS and RCR Kaplan-Meier-estimates were used. To assess the influence of individual parameters on OS or RCR, COX-Regressions were used. To detect interactions of the effects between tumor site and side, additional COX-Regressions were performed. If $p < 0.05$, the results were considered to be statistically significant.

Results

Overall, 1608 patients were in the database. Out of these, 661 patients met inclusion criteria. Average age at time of diagnosis was 56.8 ± 10.1 years, with 558 (84.4%) being male and 103 (15.6%) being female. Mean follow-up time was 78.9 ± 106.4 months. Out of the 661 patients that were included, 67 patients (10.1%) eventually had lymphatic recurrence of the tumor. 135 (20.4) patients had their primary tumor site in the oral cavity, 179 (27.1%) in the oropharynx, 118 (17.8%) in the hypopharynx and 229 (34.6%) in the larynx. In terms of sides, 158 (23.9%) were situated bilaterally, 23 (3.5%) in the midline, 255 (38.6%) on the right and 225 (34.0%) on the left side. In terms of clinical lymph node category, 261 (39.4%) patients were classified as inapparent/cN0, 111 (16.8%) as N1, 246 (37.2%) as N2 and 5 (0.8%) as N3; in 38 (5.7%) patients, there was no information on clinical lymph node status (cNx). After pathological examination, 302 (45.7%) were classified as pN0, 119 (18.0%) were classified as pN1, and 240 (36.3%) as pN2. 105 (15.6%) patients developed systemic metastasis during follow up, while 558 (84.4%) did not. 291 (44.1%) patients underwent adjuvant radio-(chemo-)therapy after initial surgical tumor therapy, while 370 (55.9%) did not. (Table 1) Respective Kaplan-Meier-diagrams can be found in Fig. 1.

Table 1
– Basic patient, tumor and surgery characteristics of all patients included in the study

Characteristic	No. of Patients (n = 661)
Age (years)	56.8 ± 10.1 [15.7–91.6]
Gender (male/female)	558 (84.4%) / 103 (15.6%)
Follow up (months)	78,9 ± 106.4 [0.3–263.3]
Origin	
Tumor Origin: Oral cavity	135 (20.4%)
Tumor Origin: Oropharynx	179 (27.1%)
Tumor Origin: Hypopharynx	118 (17.8%)
Tumor Origin: Larynx	229 (34.6%)
Side	
Tumor side: bilateral	158 (23.9%)
Tumor side: midline	23 (3.5%)
Tumor side: right	255 (38.6%)
Tumor side: left	225 (34.0%)
Tumor Stage	
pT1	86 (13.0%)
pT2	208 (31.5%)
pT3	239 (36.2%)
pT4	128 (19.4%)
Lymph Node Status	
cN0	261 (39.4%)
cN1	111 (16.8%)
cN2	246 (37.2%)
cN3	5 (0.8%)
cNx	38 (5.7%)
pN0	302 (45.7%)
pN1	119 (18.0%)

Characteristic	No. of Patients (n = 661)
pN2	240 (36.3%)
Development of distant metastasis during follow-up	
M0	558 (84.4%)
M1	103 (15.6%)
Postoperative (chemo-)radiotherapy	
No adjuvant therapy	370 (55.9%)
Postoperative (chemo-)radiotherapy	291 (44.1%)
Levels Treated in Neck Dissection	
Ipsilateral ND	644 (97.4%)
Level I ipsilateral	120 (18.2%)
Level II ipsilateral	613 (92.7%)
Level III ipsilateral	605 (91.5%)
Level IV ipsilateral	140 (21.2%)
Level V ipsilateral	26 (3.9%)
Contralateral ND	319 (48.3%)
Level I contralateral	54 (8.2%)
Level II contralateral	313 (47.4%)
Level III contralateral	309 (46.7%)
Level IV contralateral	55 (8.3%)
Level V contralateral	7 (1.1%)

Out of these patients, 644 (97.4%) underwent ipsilateral and 319 (48.3%) underwent contralateral neck dissection. On the ipsilateral side, Level I was operated on in 120 (18.2%) patients, Level II in 613 (92.7%), Level III in 605 (91.5%), Level IV in 140 (21.2%) and Level V in 26 (3.9%) patients. On the contralateral side, Level I was operated in 54 (8.2%) patients, Level II in 313 (47.4%), Level III in 398 (46.7%), Level IV in 55 (8.3%) and Level V in 7 (1.1%) patients (Table 1).

The exact comparisons between the groups in terms of OS and RCR can be found in Table 2. Univariate testing found significant differences in RCR between hypopharynx and larynx as well as hypopharynx and oropharynx, showing lower hazard of regional recurrence for primaries located in the oropharynx (HR 0.6 [0.4–1.0]) and larynx (HR 0.4 [0.2–0.7]). In terms of OS, only the difference between larynx and hypopharynx was significant, demonstrating a better prognosis for laryngeal cancer (HR 0.4 [0.2–0.7]).

However, multivariate testing showed a significant influence of the tumor site on both RCR and OS. In terms of pathological tumor category, there was no uni- or multivariate influence on RCR. In terms of OS, pT4a compared to all other categories showed significant differences in univariate testing. Multivariate testing showed a significant influence of pathological tumor category on OS.

Table 2

– Univariate and multivariate testing of tumor and surgery characteristics and their respective influence on OS and RCR

Stage	Hazard Ratio	p (univariate)	p (multiple)	Hazard Ratio	p (univariate)	p (multiple)
Regional Control Rate				Overall Survival		
Tumor Origin		< 0.01	< 0.01		0.02	0.01
Larynx vs. Hypopharynx	0.4 [0.2–0.7]	< 0.01		0.4 [0.2–0.7]	< 0.01	
Oral Cavity vs. Hypopharynx	0.6 [0.4–1.1]	0.12		0.6 [0.4–1.1]	0.12	
Oropharynx vs. Hypopharynx	0.6 [0.4–1.0]	0.05		0.7 [0.4–1.2]	0.16	
Oral Cavity vs. Larynx	1.7 [1.0–3.1]	0.06		1.5 [0.9–2.8]	0.15	
Oropharynx vs. Oral Cavity	0.9 [0.5–1.6]	0.78		1.1 [0.6–1.9]	0.80	
Oropharynx vs. Larynx	1.5 [0.6–1.5]	0.12		1.6 [0.9–2.8]	0.08	
Pathological Tumor Category		0.13	0.07		< 0.01	< 0.01
pT2 vs. pT1	1.6 [0.8–3.2]			1.7 [0.8–3.6]	0.16	
pT3 vs. pT1	1.1 [0.5–2.1]			1.2 [0.6–2.7]	0.57	
pT4 vs. pT1	1.7 [0.8–3.4]			3.1 [1.5–6.5]	< 0.01	
pT3 vs. pT2	0.6 [0.4–1.0]			0.7 [0.4–1.2]	0.25	
pT4 vs. pT3	0.6 [0.4–1.0]			2.5 [1.5–4.2]	< 0.01	

Stage	Hazard Ratio	p (univariate)	p (multiple)	Hazard Ratio	p (univariate)	p (multiple)
pT4 vs. pT2	1.0 [0.6–1.7]			1.8 [1.1–3.0]	0.01	
Clinical Lymph Node Category		< 0.01	< 0.01		< 0.01	< 0.01
cN1 vs. cN0	1.9 [1.1–3.4]	0.03		1.8 [1.0–3.4]	0.06	
cN2 vs. cN0	2.4 [1.5–3.8]	< 0.01		3.0 [1.8–4.9]	< 0.01	
cN3 vs. cN0	5.4 [1.3–22.7]	0.02		9.4 [2.2–40.0]	< 0.01	
cN2 vs. cN1	1.3 [0.7–2.1]	0.40		1.6 [0.9–2.8]	0.09	
cN3 vs. cN1	2.6 [0.6–11.2]	0.20		4.9 [1.1–22.2]	0.04	
cN3 vs. cN2	2.3 [0.6–9.6]	0.24		3.0 [0.7–12.3]	0.13	
Pathological Lymph Node Category		< 0.01	< 0.01		< 0.01	< 0.01
pN1 vs. pN0	1.9 [1.0–3.5]	0.05		2.6 [1.4–5.0]	< 0.01	
pN2 vs. pN0	4.0 [2.5–6.4]	< 0.01		5.2 [3.1–8.7]	< 0.01	
pN2 vs. pN1	2.1 [1.3–3.7]	< 0.01		2.0 [1.2–3.3]	0.01	
Development of distant metastasis	6.6, [4.5–9.6]	< 0.01	0.25	9.8 [6.5–14.6]	< 0.01	< 0.01
Postoperative (Chemo-) radiation	0.9, [0.6–1.3]	0.51	< 0.01	0.5 [0.3–0.8]	< 0.01	0.13

Stage	Hazard Ratio	p (univariate)	p (multiple)	Hazard Ratio	p (univariate)	p (multiple)
Neck Dissection ipsilateral	0.7 [0.3–2.0]	0.56	0.37	0.9 [0.3–3.0]	0.93	0.64
Level I ipsilateral	1.3 [0.8–2.0]	0.30	0.25	1.0 [0.6–1.7]	0.96	0.68
Level II ipsilateral	0.5 [0.3–0.9]	0.01	0.72	0.5 [0.3–0.9]	0.02	0.83
Level III ipsilateral	0.6 [0.3–1.1]	0.07	0.18	0.6 [0.3–1.0]	0.05	0.96
Level IV ipsilateral	1.1 [0.7–1.8]	0.62	0.44	1.2 [0.8–1.9]	0.42	0.61
Level V ipsilateral	0.8 [0.2–2.5]	0.68	0.44	0.7 [0.2–2.9]	0.63	0.27
Neck Dissection contralateral	1.0 [0.7–1.4]	0.93	0.40	1.3 [0.9–2.0]	0.14	0.79
Level I contralateral	1.6 [0.9–2.9]	0.10	0.17	1.8 [1.0–3.3]	0.04	0.07
Level II contralateral	1.0 [0.7–1.4]	0.89	0.88	1.3 [0.9–1.9]	0.23	0.21
Level III contralateral	1.0 [0.7–1.4]	0.96	0.70	1.3 [0.9–1.9]	0.20	0.83
Level IV contralateral	1.2 [0.7–2.4]	0.50	0.48	1.6 [0.8–2.9]	0.16	0.86
Level V contralateral	0.0 [0.0 - ∞]	0.15	0.23	0.0 [0 - ∞]	0.20	0.30

Clinical lymph node status showed a significant effect on RCR in any stage compared with cN0 in univariate analysis, demonstrating a higher hazard ratio of regional recurrence in cN + disease. For overall survival this was only the case for cN2 and compared to cN1. Multivariate testing showed a significant influence both for RCR and OS (Table 2).

Pathological lymph node status showed a significant influence on RCR and OS both in univariate and multivariate testing. Development of distant metastasis showed a significant influence on OS both in uni- and multivariate testing and a significant influence on RCR in univariate testing. Adjuvant (chemo)radiotherapy showed a significant impact on RCR in multivariate and a significant impact on OS in univariate testing. Treated levels during SND showed a significant influence on RCR if ipsilateral Level II was treated in univariate testing. In terms of OS, ipsilateral regions II and III as well as contralateral level I showed a significant influence in univariate testing.

To test whether the observed impact on OS and RCR was dependent on the tumor origin, COX-regression models were fitted that considered the interactions of the tumor origin. These models found a significant influence of surgical treatment of levels I and V ipsilateral and level III contralateral on OS. None of the fitted models revealed a significant influence of any level treated on RCR. (Table 3) Significant findings in these levels indicated that treatment or omission of treatment of these regions may influence overall survival dependent of tumor origin.

Table 3
– COX-Regression Models of Operated Regions dependent and independent of tumor origin

	Overall Survival p (multiple)	Regional Control Rates p (multiple)
Region	0.02	< 0.01
Level I Ipsilateral	0.93	0.36
Level II Ipsilateral	0.08	0.04
Level III Ipsilateral	0.69	0.10
Level IV Ipsilateral	0.58	0.79
Level V Ipsilateral	0.54	0.68
Level I Contralateral	0.02	0.25
Level II Contralateral	0.39	0.80
Level III Contralateral	0.65	0.87
Level IV Contralateral	0.45	0.50
Level V Contralateral	0.20	0.16
Models with Tumor Origin Interaction		
Level I Ipsilateral	0.03	0.81
Level II Ipsilateral	0.19	0.07
Level III Ipsilateral	0.43	1.00
Level IV Ipsilateral	0.47	0.95
Level V Ipsilateral	0.02	0.16
Level I Contralateral	0.66	0.14
Level II Contralateral	0.98	0.99
Level III Contralateral	< 0.01	0.13
Level IV Contralateral	0.60	0.68
Level V Contralateral	1.00	1.00

Subsequently, we fitted COX-regression models for each tumor region. (Table 4) Treatment of level V ipsilateral or level III contralateral showed no significant influence on OS in any tumor origin. Treatment of level I ipsilateral showed a significant influence on OS when the tumor originated in the oral cavity. The

hazard ratio calculated was 0.4 with a confidence interval of 0.2–0.9. This indicated a favorable effect of SND in level I in HNSCC of the oral cavity.

Table 4
– Influence of Neck Dissection Levels for each Tumor Origin

Parameter	Region			
	Hypopharynx	Larynx	Oral Cavity	Oropharynx
Level I Ipsilateral	4.0 [0.9–17.2] p = 0.06	3.7 [0.5–27.3] p = 0.21	0.4 [0.2–0.9] p = 0.02	1.9 [0.8–4.7] p = 0.17
Level V Ipsilateral	0.0 [0.0 - ∞] p = 0.16	0.0 [0.0 - ∞] p = 0.24	0.0 [0.0 - ∞] p = 0.26	3.0 [0.7–13.1] p = 0.14
Level III Contralateral	1.7 [0.7–3.7] p = 0.22	1.2 [0.5–2.8] p = 0.68	1.7 [0.7–4.0] p = 0.21	1.4 [0.7–2.9] p = 0.38

Discussion

Synopsis of key findings

This retrospective analysis of data basing on prospective documentation of consecutive cases of head and neck cancer identified factors for regional failure and general outcome. Firstly, we found that the tumor site has both a significant effect on regional control rates as well as overall survival. Moreover, both clinical and pathological lymph node status shows a significant impact on both overall survival and regional control rates. Tumor size, as indicated by the pT-categories, showed a significant impact on OS but not RCR. Finally, the value of ipsilateral dissection of level I in oral cavity cancer was emphasized.

Strengths and Limitations

A strength of this work is a high number of 661 cases and a considerably long follow-up-time of 78.9 ± 106.4 months. Other recent studies report 84 to 123 patients (13–15) with 12 to 30 months of follow-up. (13, 15)

However, due to the at least partially retrospective nature of this analysis, this study is subject to probably systematic lack of data and various kinds of bias. Clinical decisions, for example regarding the inclusion or omission of a particular neck level into a neck dissection might have been due to factors that cannot be deducted from the available data in retrospect.

Comparison to other studies

It has been established that SND is the appropriate treatment for regional spread in HNSCC. D’Cruz and colleagues found in a randomized, prospective study that elective SND in early HNSCC of the oral cavity

is superior to a wait-and see approach and subsequent SND in the case of positive lymph nodes.(16)An influence of tumor site on regional control and overall survival is mainly due to the fact that laryngeal and oropharyngeal HNSCC are showing a significant impact on OS and RCR. This is not surprising as hypopharyngeal carcinomas have a very poor overall prognosis; commonly they are diagnosed in a late stage and with advanced nodal stage.(17) Moreover, they often show a tendency for more dedifferentiated carcinomas and occult cervical metastasis.(18) These factors make surgical management of hypopharyngeal carcinoma significantly more demanding, with a distinct possibility of occult tumor cells remaining on site, impairing both RCR as well as OS.A heavy influence of clinical and pathological lymph node status is not surprising, given that the greater the load of tumor cells in the neck, the greater the probability of cells not being reached by surgery and eventually creating the foundation for recurrence of cancer. Subsequently, this observation is very much in line with literature addressing this topic: Layland and colleagues found in over 3.800 patients that advanced neck stages are associated with poorer OS in all tumor sites.(18) Ambrosch and colleague found in a very similar collective to that at hand that advanced nodal stage as well as extracapsular extension are associated with a greater probability for regional recurrences.(19)While the impact of tumor size on OS is not surprising and has been evaluated in large-scale studies,(20) the missing correlation between tumor size and RCR in our sample is somewhat surprising. We believe that this observation may be explained by the (relatively) effective removal of the primary tumor by TLM.(21–23) When considering the individual neck dissection levels that were included during surgery, we found in the models that included an interaction with the tumor site that levels I and V ipsilaterally as well as level III contralaterally showed an influence on overall survival upon closer examination. When correcting those models for the tumor site, we only found a significant impact on overall survival on ipsilateral neck dissection in contralateral level I in HNSCC of the oral cavity. Fittingly, the respective level has been included in the prospective study by D’Cruz and colleagues that found elective neck dissection to be superior to a wait-and-see approach.(16) The recommendation for elective and therapeutic surgical treatment of level I in oral cavity SCC has already been given in a comprehensive clinical practice guideline.(24) While those models that did correct for tumor origin did not indicate a statistically significant influence on OS, it is our conviction that inclusion of these levels in primary SND may still be beneficiary and should be considered by surgeons. Fittingly, Frohwitter and colleagues found that affection of ipsilateral levels IV and V considerably decreases overall survival in HNSCC of the oral cavity.(14)

Conclusion

In conclusion, we found clear evidence that SND is effective both in preventing nodal relapse in clinically inapparent necks as well as treating clinically positive necks. The study at hand is – to the best of the authors knowledge – the largest study to comprehensively analyze the treated levels in SND dependent on tumor size and origin. Consequently, we found evidence that when performing surgery on the neck on HNSCC of the oral cavity, dissection of ipsilateral level I should be included.

Abbreviations

HNSCC Head and Neck Squamous Cell Carcinoma

OS Overall Survival

RCR Regional Control Rate

RND Radical Neck Dissection

SND Selective Neck Dissection

TLM Transoral Laser Microsurgery

Declarations

Ethics approval and consent to participate

The study at hand was conducted in accordance with the Declaration of Helsinki in its current form (seventh revision, 2013). The study was approved by the ethics committee at the University Medical Center of the Georg-August University Göttingen (Niedersachsen, Federal Republic of Germany) on January 10th 2017 under the File No. DOK_200_2016. All study participants consented in written form to the analysis of medical data before treatment at the study center.

Dataset

The authors of this manuscript declare that the data at hand have not been published, submitted or used in any other manuscript elsewhere.

Consent for publication

Not Applicable.

Availability of data and materials

The dataset generated and analysed during the current study is not publicly available, since the local ethics committee explicitly discouraged the publication of individual data in its statement due to data privacy. The corresponding author will provide an anonymized dataset on reasonable request.

Competing interests

The authors declare no relevant conflict of interest.

Funding

This work was partially funded by a grant to FI by the German Federal Ministry of Education and Health (BMBF) (grant number 01 EO 0901).

Authors' contributions

Study concept: FI

Study design: MB, FH, MC

Data acquisition: NZ, BGW, JLS

Quality control of data and algorithms: MB, SF, BGW, FI

Data Analysis and Interpretation: MB, SF, BGW, FH, FI, JLS

Statistical analysis: SF

Manuscript Preparation; MB, NZ, JLS

Manuscript editing: BGW, FH, FI

Manuscript Review: SF, MC

All authors have read and approved the manuscript.

Acknowledgements

The authors are indebted to Professor Wolfgang Steiner for his inspiring work in head and neck surgery and for clinical, surgical, as well as scientific guidance. The authors want to thank Brigitte Bruhse for excellent support in the documentation of tumor cases throughout many years.

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Figures

Figure 1

Kaplan Meier Curves: (A) Overall Survival of all patients dependent of tumor site (B) Regional control rate of all patients dependent of tumor site (C) Overall survival of all patients dependent on clinical lymph node category (D) Regional control rate of all patients dependent on clinical lymph node category (E) Overall survival of all patients dependent on pathological lymph node category (F) Regional Control Rate of all patients dependent on pathological lymph node stage (G) Overall survival of all patients dependent

on whether they underwent postoperative radio-(chemo-)therapy (H) Regional control rate of all patients dependent on whether they underwent postoperative Radio-(chemo-)therapy (I) Overall survival of all patients dependent on whether they developed distant metastasis (J) Regional control rate of all patients dependent on whether they developed distant metastasis