Outcome of Salvage Therapy in Isolated Regional Recurrence in Head and Neck Squamous Cell Carcinoma

Roland Giger[1], MD; Raffael Fink[1], BMed; Marco Dematté[1,2], MD; Miranda Visini[1], MD; *Olgun Elicin[3], MD; *Lukas Anschuetz[1], MD

[1] Department of Otorhinolaryngology, Head and Neck Surgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[2] Department of Otorhinolaryngology, Head and Neck Surgery, Head and Neck and Sensory Organs Department, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

[3] Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

* Equally contributing last authors

Short Running Title

Isolated regional recurrences

Financial Disclosures

No funding is reported for the present study.

Conflict of Interest

The authors declare no conflict of interest.

Corresponding Author

Lukas Anschuetz, MD

Department of Otorhinolaryngology, Head & Neck Surgery, Inselspital, University Hospital, University of Bern, 3010 Bern, Switzerland

Email: anschuetz.lukas@gmail.com

Tel: +41316322654; Fax: +41316324872

Abstract

Objectives: Head and neck squamous cell carcinoma (HNSCC) has a high tendency for regional lymphatic spreading. Nevertheless, isolated regional lymph node (LN) recurrences are rare and only limited data regarding its management is available. The aim of this study is to describe treatment modalities, outcomes and to identify prognostic factors.

Methods: The records of all patients (n=498) with tumor persistence or recurrence after curatively intended treatment for HNSCC were retrospectively reviewed. Patients with synchronous secondary tumors at initial presentation, tumor persistence, local or locoregional recurrence and systemic metastases were excluded.

Results: A total of n=76 patients were included. The rate of occult additional metastasis in radiologically uninvolved neck compartments during salvage neck dissection was 25%. The salvaged patients showed a 37.5% 5-year recurrence-free survival (RFS). Multivariate analysis revealed initial stage IVA-B (HR: 4.16, $p<0.01$), extracapsular spread (HR: 3.71, $p=0.04$), higher involved/total lymph node ratio (HR: 6.79, $p<0.01$) and soft tissue infiltration (HR: 3.27, $p<0.01$) as independent adverse prognostic factors for RFS. Moreover, univariate data analysis identified recurrent

stage rcN2-3, clinical involvement of the neck levels IV, V and/or VI and smoking as adverse risk factors for RFS.

Conclusions: This study identifies initial stage IVA-B, extracapsular spread, higher involved/total lymph node ratio and soft tissue infiltration as independent adverse prognostic factors for RFS following isolated regional recurrences. The incidence of occult additional metastasis of radiologically uninvolved levels during salvage neck dissections was high (25%). Therefore, superselective or selective neck dissection would not have been the adequate type of salvage surgery.

Key words

Regional recurrence; head and neck squamous cell carcinoma; salvage therapy; outcome

Level of Evidence

4

Introduction

Head and neck squamous cell carcinoma (HNSCC) invades the neck lymph nodes, depending on the pattern of lymphatic spread based on anatomical tumor subsite.[1,2] The appearance of regional metastases correlates with the primary tumor's extension: up to 44% of patients with T1 tumors show clinical lymph node involvement, compared to 70% for patients with T4 cancer.[3] Due to their high tendency to spread to the lymph nodes, HNSCC generally require an elective treatment of the neck.[4]

Treatment failures most commonly lead to local or locoregional persistence or recurrence, whereas isolated regional recurrences remain an uncommon event.[5,6] Salvage neck dissection is the mostly adopted curative treatment modality for isolated regional relapse. However, patients with recurrent disease involving the prevertebral fascia, skull base or encasing the carotid artery most often do not qualify for salvage surgery. Selective salvage neck dissection seems to provide acceptable oncological control in patients with isolated regional recurrences, without causing extensive surgical morbidity.[7] Robbins et al. (2007) reported super-selective salvage neck dissection to be feasible in patients with persistent nodal disease initially treated with chemoradiation (CRT) and confined to one level.[8] Patients with isolated regional recurrences in advanced stage may benefit from adjuvant CRT, where applicable.[9]

There are several prognostic factors on the outcome of salvage surgery. The lack of disease-free interval (< 6 months), positive surgical margins and advanced initial and recurrent tumor stage lead to poor surgical outcomes.[10] Léon et al. (2017) reported the prognostic significance of extracapsular spread (ECS) in isolated regional recurrences in HNSCC.[9]

The aim of this study is to describe treatment modalities and associated outcomes for patients with isolated regional recurrence treated at our tertiary reference center, and to identify independent prognostic factors regarding the outcome.

Patients and Methods

Ethical considerations

The institutional and regional review board (Inselspital, University Hospital Bern, Bern, Switzerland, KEK-Nr. 2018-00989) granted approval to conduct the present study.

Patient selection

We defined isolated regional recurrence as the histologically or cytologically diagnosed reappearance of nodal squamous cell carcinoma in the neck after complete response with a minimal disease-free interval of 6 months after treatment. A disease-free interval of less than 6 months was defined as persistence and was an exclusion criterion. The records of all patients (n=498) with tumor persistence or recurrence after initially curatively intended treatment for HNSCC from 2003 to 2017 were retrospectively reviewed. Patients with concomitant secondary tumors at initial presentation were excluded from the study. Tumor persistence, local, locoregional or metastatic recurrences were excluded and only patients with isolated regional relapse were further investigated. The UICC TNM Classification 7th Edition (2010) was applied for the classification of the initial and recurrent tumor situation.

Statistical analysis

All time-to-event intervals were calculated based on the date of positive biopsy confirming the isolated regional recurrence. The follow-up time was not censored at a

predefined time point. Kaplan-Meier curves and log-rank test were used to depict and compare the variables regarding time-to event endpoints, respectively. Univariate Cox's proportional hazards regression was used to evaluate possible prognostic factors for recurrence-free survival (RFS). Variables yielding two-sided $p<0.1$ were used to build multivariate models. Backwards elimination was used to identify potential independent factors. Analyses were performed with JMP (version 14.0 - SAS Institute GmbH, Germany).

Results

The study cohort contained 76 patients with isolated regional recurrence of HNSCC, consisting of 54 men and 22 women, with a mean age of 63.9 years (+/- 14.6 years). The median follow-up was 45 months (range: 6-183) after recurrence. At the time of recurrence 32 patients were still active smokers and 21 patients with persistent alcohol abuse were identified.

Primary disease characteristics and treatment

The oral cavity was the most common subsite of the primary tumor, followed by the oropharynx as shown in **Table 1**. Initial treatment modalities were primary surgery (n= 24) or primary radiotherapy (n=17) or a multimodal approach (n=35) including a combination of surgery and CRT. The decision regarding the best suitable therapy was taken by the multidisciplinary tumor board.

Isolated regional recurrence characteristics and treatment

A mean interval of 18.1 months (standard deviation 20.4 months) between initial tumor treatment and histological/cytological diagnosis of the isolated regional recurrence was observed. Unilateral recurrence (97.4%) was the predominant

pattern (**Table 2**). A total of 11 patients were addressed for palliative chemotherapy or best supportive care. Among the curatively intended treatment the main modality was salvage neck dissection (n=58) of whom 20 patients underwent adjuvant radiotherapy and 24 adjuvant CRT. Six patients underwent salvage radiotherapy and one patient salvage CRT. Comparison between the treatment modalities (salvage surgery vs. salvage radiotherapy) by log-rank test revealed no statistical significance for RFS (p=0.47) and overall survival (OS) (p=0.52).

Salvage neck dissection

Among the 58 patients that underwent salvage neck dissection, the histological workup of the surgical resection detected ECS in 50 cases (86.2%). Soft tissue infiltration was found in 18 patients (31%) Occult additional metastases were defined as pathologically positive lymph nodes in any radiologically uninvolved neck levels on the clinically involved side and were observed in 14 neck dissection specimens (25%). False radiological positivity, defining a pathological nodal negativity compared to positive clinical staging, appeared in 7 neck dissection specimens (12.5%). Detailed results are shown in **Table 3**.

Univariate survival analysis

Patients undergoing curatively intended salvage therapy for isolated regional recurrences (n=65) were included in this analysis. The cohort showed a 5-year RFS and 5-year OS of 37.46% and 56.89%, respectively (**Figure 1**).

As summarized in **Table 4**, univariate data analysis demonstrated initial stage IVA-B (hazard ratio (HR): 2.16; 95% confidence interval (CI): 1.10-4.15; p=0.03) and recurrent stage rcN2-3 (HR: 2.03; CI: 1.03-4.25, p=0.04) as adverse risk factors for RFS. Initial stage IVA-B (HR: 3.34; CI: 1.53-7.44; p<0.01) had an additional negative

impact on OS. In patients with ECS we found a HR of 3.71 (CI: 1.08-23.31), p=0.04 on RFS, as well as clinical involvement of the neck levels IV, V and/or VI, we found a reduction in RFS (HR: 3.26, CI: 1.54-6.58, p<0.01) and OS (HR: 3.00; CI: 1.26-6.69; p=0.02). Additionally, ECS (HR: 4.68, CI :1.11-28.99; p<0.01), and soft tissue infiltration (HR: 3.27, CI: 1.47-7.19, p=0.02) were related to an impaired RFS. The involved/total lymph node ratio (LNR) was also found to be associated with poorer RFS (HR: 6.79, CI: 1.86-21.44, p<0.01).

Multivariate survival analysis

The initial stage IVA-B, higher involved/total resected lymph node ratio, the pathological detection of soft tissue infiltration and extracapsular spread at the time of appeared to be independent variables for impaired RFS (**Table 4**).

Discussion

This retrospective cohort study on patients with isolated regional recurrence after curatively treated HNSCC demonstrated that salvage treatment has an acceptable oncological outcome with a 5-year RFS of 37.46% and OS of 56.89%. Advanced initial stage IVA-B, histopathological ECS, higher involved/total lymph node ratio and presence of soft tissue infiltration were identified as independent risk factors for RFS. Moreover, the rate of occult additional metastasis in radiologically uninvolved neck levels was found in 14 out of 58 surgically treated patients (25%), which is relatively high.

Risk factors for prediction of survival

The isolated regional recurrence of HNSCC is a relatively uncommon event,[6] consequently a lack of detailed data is apparent regarding this topic. Leon et al.

(2017) retrospectively analyzed 123 patients with isolated regional recurrences and reported that the appearance of ECS in salvage neck dissections was significantly related to survival.[9] Patients with ECS showed a 5-year survival of 32%, compared to 77.2% for patients without ECS. Chung et al. (2015) confirmed the negative effect of ECS on OS conducting a retrospective study with 55 patients suffering from isolated regional failure of HNSCC.[10] Additionally, their results revealed early recurrence (<6 months), ECS, initial N2-3 classification, and in-field recurrence as significant adverse factors for OS. Similarly, our multivariate data analysis showed a significant adverse impact of ECS on RFS. Moreover, our multivariate analysis revealed soft tissue infiltration as an independent risk factor for RFS. In contrast to ECS, soft tissue infiltration lacks any nodal tissue in histopathological analysis associated to the regional recurrence. Whether the initially affected lymph node was completely consumed by the carcinoma or whether it is the result from a hematogenic spread cannot be differentiated from a histopathological point of view. As expected, initial tumor staging IVA-B independently predicts a decrease in RFS and OS. In our data analysis, we could not demonstrate a significant impact of recurrent nodal size (>3 cm) on OS. Grandi et al. (1993) investigated the results of salvage surgery in 113 patients with isolated regional recurrences of HNSCC, previously treated with surgery or radiotherapy and reported the size of the nodal recurrence (>3 cm) and the presence of mobility with respect to neighboring neck structures as prognostic factors for OS.[11] The univariate model additionally suggests an impact of involvement of lower neck nodes and persistent smoking on RFS.

Occult additional metastasis

In order to reduce postoperative complications associated with salvage neck dissection, a trend towards less invasive selective or super-selective neck

dissections is observed in the literature. Liu et al. (2019) analyzed the survival effect of comprehensive compared to selective neck dissections for the treatment of regional recurrence in 294 patients with nasopharyngeal carcinoma.[12] The authors conclude, that a selective neck dissection is not inferior to the comprehensive surgical approach when a similar radical dissection extent around the tumor is achieved. In our study, we only had one case of nasopharyngeal carcinoma, therefore this study is not fully comparable to ours.

Several other studies reported a frequent underestimation of nodal spread through clinical and radiological assessment. Massey et al. (2018) analyzed 39 studies assessing occult nodal metastasis in patients with T1 or T2 cN0 oral squamous cell carcinoma undergoing elective neck dissection.[13] They reported an overall rate of occult metastasis of 23%. Similarly, we evaluated the incidence of occult additional metastasis in the rcN+ neck by compartmentalization of the neck in its levels, which is especially useful for the planning of adjuvant salvage radiotherapy.[14] Occult additional metastases in radiologically uninvolved neck levels were observed in 25% of the patients treated with salvage neck dissection. Accordingly, occult metastasis appears to occur as often in isolated regional recurrences as it does in the electively treated previously treatment-naïve neck. Most frequently occult additional metastases were found in level IV, therefore selective or super-selective neck dissection as described by Liu et al.[12] and Robbins et al.[8] might have been inadequate in our cohort. Nevertheless, it is still a subject of question, whether the treatment of occult nodal metastases lead to a survival advantage in the salvage setting.[15]

Ding et al. (2019) investigated 149 patients with primary treatment for locally advanced oral squamous cell carcinoma and reported the LNR > 10% to be a robust

adverse prognostic factor for OS.[16] Our study similarly shows a statistically significant impact of the LNR found in the recurrent neck on RFS or OS.

Surgical and adjuvant treatment considerations

The choice of the most suitable treatment for patients with isolated regional recurrence requires a good balance between oncological radicalism and post-treatment related morbidity, such as wound infections, sepsis, or postoperative bleeding.[11] Regional disease control can be best obtained with surgical salvage combined with adjuvant radiotherapy. Adjuvant CRT provides a superior regional control, but also leads to a higher complication rate.[12,17] The feasibility and extent of the salvage therapy depends on the initial treatment, the extension of the regional recurrence, the overall health and performance status of the patient.[18] According to the high incidence of occult additional metastasis and the worsened outcome of regional recurrence affecting the caudal neck levels, we suggest the inclusion of these levels during the salvage neck dissection and to perform at least a selective neck dissection of the levels I to V in these patients at risk.

Limitations

Isolated regional recurrence is a relatively uncommon event, which makes it difficult to create a large cohort to obtain robust statistical results. Moreover, the results obtained in the present study only show associations, not causations, due to its retrospective nature.

Conclusion

This study identifies initial stage IVA-B, histopathological ECS, higher involved/total lymph node ratio and soft tissue infiltration as independent adverse prognostic

factors for post-salvage RFS following isolated regional recurrences of HNSCC. The incidence of occult additional metastasis of radiologically uninvolved neck levels during salvage neck dissections was considerable (25%). Therefore, only superselective or selective neck dissection would not have been the adequate type of salvage surgery in isolated regional recurrence. A quarter of the operated patients would have been undertreated.

References

1. Candela FC, Kothari K, Shah JP. Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. Head Neck 1990;12(3):197–203.
2. Candela FC, Shah J, Jaques DP, Shah JP. Patterns of cervical node metastases from squamous carcinoma of the larynx. Arch Otolaryngol Head Neck Surg 1990;116(4):432–5.
3. Bataini JP, Bernier J, Brugere J, Jaulerry C, Picco C, Brunin F. Natural history of neck disease in patients with squamous cell carcinoma of oropharynx and pharyngolarynx. Radiother Oncol 1985;3(3):245–55.
4. Clayman GL, Frank DK. Selective neck dissection of anatomically appropriate levels is as efficacious as modified radical neck dissection for elective treatment of the clinically negative neck in patients with squamous cell carcinoma of the upper respiratory and digestive tracts. Arch Otolaryngol Head Neck Surg 1998;124(3):348–52.
5. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24(14):2137–50.
6. Lambrecht M, Dirix P, Van den Bogaert W, Nuyts S. Incidence of isolated regional recurrence after definitive (chemo-) radiotherapy for head and neck squamous cell carcinoma. Radiother Oncol 2009;93(3):498–502.
7. Grabenbauer GG, Rödel C, Ernst-Stecken A, et al. Neck dissection following radiochemotherapy of advanced head and neck cancer--for selected cases only? Radiother Oncol 2003;66(1):57–63.
8. Robbins KT, Shannon K, Vieira F. Superselective neck dissection after

chemoradiation: feasibility based on clinical and pathologic comparisons. Arch Otolaryngol Head Neck Surg 2007;133(5):486–9.

9. León X, Rigó A, Farré N, et al. Prognostic significance of extracapsular spread in isolated neck recurrences in head and neck squamous cell carcinoma patients. Eur Arch Otorhinolaryngol 2017;274(1):527–33.
10. Chung E-J, Lee S-H, Baek S-H, Bae W-J, Chang Y-J, Rho Y-S. Clinical outcome and prognostic factors after salvage surgery for isolated regional squamous cell carcinoma recurrences. Head Neck 2015;37(11):1612–7.
11. Grandi C, Mingardo M, Guzzo M, Licitra L, Podrecca S, Molinari R. Salvage surgery of cervical recurrences after neck dissection or radiotherapy. Head Neck 1993;15(4):292–5.
12. Liu Y-P, Li H, You R, et al. Surgery for isolated regional failure in nasopharyngeal carcinoma after radiation: Selective or comprehensive neck dissection. Laryngoscope 2019;129(2):387–95.
13. Massey C, Dharmarajan A, Bannuru RR, Rebeiz E. Management of N0 neck in early oral squamous cell carcinoma: A systematic review and meta-analysis. Laryngoscope. 2019 Aug;129(8):E284-E298.
14. Elicin O, Putora PM, Siano M, et al. A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study—Part 2 (Radiation Oncology). Front. Oncol. 2019 9:1126. doi: 10.3389/fonc.2019.01126
15. Ward MC, Riaz N, Caudell JJ, Dunlap NE, Isrow D, Zakem SJ, et al. Refining Patient Selection for Reirradiation of Head and Neck Squamous Carcinoma in the IMRT Era: A Multi-institution Cohort Study by the MIRI Collaborative. Int J Radiat Oncol Biol Phys. 2018;100(3):586–94.
16. Ding D, Stokes W, Eguchi M, et al. Association Between Lymph Node Ratio

and Recurrence and Survival Outcomes in Patients With Oral Cavity Cancer. JAMA Otolaryngol Head Neck Surg 2019;145(1):53–61.

17. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350(19):1937–44.
18. Krol BJ, Righi PD, Paydarfar JA, et al. Factors related to outcome of salvage therapy for isolated cervical recurrence of squamous cell carcinoma in the previously treated neck: a multi-institutional study. Otolaryngol Head Neck Surg 2000;123(4):368–76.

Tables

Table 1: Patients' disease characteristics prior to initial curatively intended treatment.

Staging according to UICC TNM Classification 7th Edition (2010)

	n =76	%
Primary tumor localization		
Unknown primary	6	7.9
Oral cavity	33	43.3
Oropharynx	15	19.7
Hypopharynx	10	13.2
Larynx	6	7.9
Nasal cavity and paranasal sinuses	5	6.6
Nasopharynx	1	1.3
Clinical tumor classification		
cT0 (unknown primary)	6	7.9
cT1	23	30.3
cT2	24	31.6
cT3	9	11.8
cT4	14	18.4
Clinical nodal classification		
cN0	43	56.6
cN1	10	13.2
cN2	21	27.6
cN3	2	2.6
UICC Stage		
I-II	33	43.4
III-IVB	43	56.6
Initial treatment		
Surgery only	24	31.6
Surgery and adjuvant radiotherapy	18	23.7
Surgery and adjuvant chemoradiation	17	22.4
Chemoradiation	9	11.8
Radiotherapy only	8	10.5
Neck dissection during initial treatment		
Neck dissection ipsilateral	37	48.7
Neck dissection contralateral	10	13.2
Extracapsular spread	27	44.3

Abbreviations: UICC: Union for International Cancer Control

Table 2: Disease characteristics at the presentation of isolated nodal recurrences.

Staging Classifications according to UICC TNM Classification 7th Edition (2010)

	n = 76	**%**	
Neck localization			
Unilateral	74	97.4	
Bilateral	2	2.6	
Nodal classification (UICC stage)			
rcN1 (rIII)	27	35.5	
rcN2 (rIVA)	44	57.9	
rcN3 (rIVB)	5	6.6	
Radiological nodal recurrence per level*	**A***	**B* (%)**	**C* (%)**
I	23	15.8	30.7
IIa	40	27.4	53.3
IIb	37	25.3	49.3
III	20	13.7	26.7
IV	10	6.8	13.3
V	9	6.2	12
VI	2	1.4	2.7
VII (retropharyngeal and /or retrostyloid)	1	0.7	1.3
VIII (parotideal)	4	2.7	5.2
Therapy of nodal recurrence			
Salvage surgery	14	18.4	
Salvage surgery and adjuvant radiotherapy	20	26.3	
Salvage surgery and adjuvant chemoradiation	24	31.6	
Salvage radiotherapy	6	7.9	
Salvage chemoradiation	1	1.3	
Palliative chemotherapy	8	10.5	
Best supportive care	3	3.9	

Abbreviations: r: recurrent; UICC: Union for International Cancer Control

*: The information about the involvement of separate levels is missing in one patient. A: The number of patients who had the indicated level involved; B = A/146 (the sum of all involved levels: 146); C = A/75 (patients)

Table 3: Characteristics and analysis of salvage neck dissections. (n=58)

	n (%)	**n (%)**	
Type of salvage neck dissection	**Ipsilateral to primary tumor**	**Contralateral to primary tumor**	
Super-selective	4 (6.9)	4 (6.9)	
Selective	9 (16.1)	5 (8.6)	
Modified radical	25 (44.6)	11 (19)	
Radical	3 (5.4)	5 (8.6)	
Extended radical	2 (3.6)	-	
Histopathological examination			
Extracapsular spread	50 (86.2)		
False positivity for any level of the whole neck examined*	7 (12.5)		
False negativity (occult additional metastases) for any level of the whole neck examined*	14 (25)		
Level dissected (n)	**False Positive**	**False Negative**	
Level I (36)	0 (0)	3 (8.3)	
Level IIa (37)	3 (8.1)	1 (2.7)	
Level IIb (37)	3 (8.1)	4 (10.8)	
Level III (37)	1 (2.7)	8 (21.6)	
Level IV (38)	1 (2.6)	10 (26.3)	
Level V (37)	1 (2.7)	6 (16.2)	
Lymph nodes evaluation	**Mean**	**Median**	**SD**
Number of resected lymph nodes	31.2	25.5	27.1
Number of lymph nodes with metastasis	1.5	1	1.4
Involved / total lymph node ratio	17%	5.2%	28.9%
	n	**%**	
Largest involved node diameter[#]			
<3 cm	37	64.9	
3-6 cm	18	31.6	
>6 cm	2	3.5	
Soft tissue infiltration[+]	18	31	

Abbreviations: *: n=56 (2 missing values); SD: standard deviation; [#]: n=57 (1 missing value);
[+]: infiltrations of squamous cell carcinoma without identifiable lymph node structure in histopathological analysis

Table 4: Uni- and multivariate Cox proportional hazards models for recurrence-free survival after recurrence (non-curatively treated patients excluded).

	Univariate		Multivariate after backwards elimination	
Variable	HR (95% CI)	p value	HR (95% CI)	p value
Initial stage IVA-B	2.16 (1.10-4.15)	**0.026**	4.16 (1.84-9.24)	**<0.01**
Stage at recurrence IVA-B	2.03 (1.03-4.25)	**0.040**		
Extracapsular spread	4.68 (1.11-28.99)	**0.008**	3.71 (1.08-23.31)	**0.04**
Lack of disease-free interval prior to recurrence in months*	1.00 (0.98-1.01)	0.561		
Involvement of the caudal neck levels (IV, V, VI)	3.26 (1.54-6.58)	**0.003**		
Female vs. male sex	0.72 (0.34-1.43)	0.360		
Smoking in pack-years*	1.02 (1.01-1.04)	**0.007**		
Active alcohol abuse	1.66 (0.81-3.33)	0.162		
Involved / total lymph node ratio*	4.44 (1.37-12.02)	**0.016**	6.79 (1.86-21.44)	**<0.01**
Number of involved lymph nodes*	1.18 (0.93-1.40)	0.156		
Largest involved node diameter (ref: <3 cm)				
3-6 cm	1.31 (0.67-2.52)	0.422		
Soft tissue infiltration[+]	2.26 (1.13-4.37)	**0.023**	3.27 (1.47-7.19)	**<0.01**

Abbreviations: *: per unit change in regressor; CI: confidence interval; HR: hazard ratio

[+]: infiltrations of squamous cell carcinoma without identifiable lymph node structure in histopathological analysis

Figure Legend

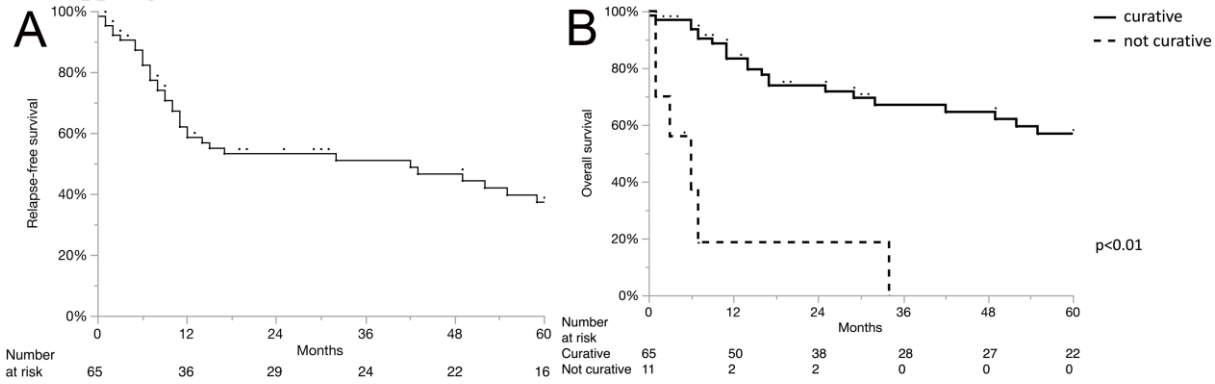

Figure 1 A: Recurrence-free survival in patients after any curatively intended salvage therapy; and **B**: overall survival after any curative salvage treatment vs. no curative treatment.