J Cancer Res Clin Oncol (2017) 143:1605–1612
DOI 10.1007/s00432-017-2419-1

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A novel classification scheme for advanced laryngeal cancer midline involvement: implications for the contralateral neck

Arne Böttcher[1] · Heidi Olze[2] · Nadine Thieme[3] · Carmen Stromberger[4] · Steffen Sander[5] · Adrian Münscher[1] · Johannes Bier[1] · Steffen Knopke[2]

Received: 2 March 2017 / Accepted: 6 April 2017 / Published online: 10 April 2017

Abstract
Purpose There are insufficient data concerning risk factors for contralateral regional metastases in laryngeal cancer. The aim of this study was to investigate the frequency and risk factors for contralateral lymph node metastases and their dependence on midline involvement of the primary tumor in patients with advanced laryngeal squamous cell carcinoma.
Methods 58 consecutive patients (8 females, 50 males; mean age 64.2 ± 9.8 years; AJCC stage III disease in 43.1%, IVA disease in 54.4%) undergoing primary total laryngectomy with bilateral neck dissection between 2002 and 2016 have been retrospectively investigated at one of the largest university medical centers in Europe. Preoperative staging computed tomography (CT) scans were analyzed for midline involvement of the primary laryngeal cancer. As a result, a classification scheme has been established (type A: clear, type B: involved, type C: exceeded, and type D: bilateral/origin side indeterminable).
Results Contralateral lymph node metastases (pN2c necks) were found in six cases (10.3%), from which four were diagnosed with type D (23.5% of type D cases), and one each with type B and type C midline involvement. In cases with no midline involvement (type A), a risk ratio reduction of 100% was seen. CT-based midline typing resulted in fourfold increased sensitivity for predicting contralateral metastases compared to conventional staging. Positive nodal status (pN+) significantly reduced overall and disease-free survival (HR 2.706, $p < 0.05$).

✉ Arne Böttcher
ar.boettcher@uke.de

Heidi Olze
heidi.olze@charite.de

Nadine Thieme
nadine.thieme@charite.de

Carmen Stromberger
carmen.stromberger@charite.de

Steffen Sander
steffen.sander@charite.de

Adrian Münscher
amuenscher@uke.de

Johannes Bier
jbier@uke.de

Steffen Knopke
steffen.knopke@charite.de

[1] Department of Otorhinolaryngology, Head and Neck Surgery and Oncology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany

[2] Department of Otorhinolaryngology, Head and Neck Surgery, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

[3] Department of Radiology, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

[4] Department of Radiation Oncology and Radiotherapy, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

[5] Clinical Cancer Registry, Charité Comprehensive Cancer Center, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany

Conclusions As a consequence, for type A category, a contralateral neck dissection might be avoidable accompanied by a reduction in surgical complications and operating time.

Keywords Laryngectomy · Laryngeal cancer · HNSCC · Regional metastases · Neck dissection · Midline involvement

Introduction

There is still an ongoing debate about technique, extent, and nomenclature of neck dissections in the treatment of head and neck squamous cell carcinomas (HNSCC) (Coskun et al. 2015). Furthermore, 110 years after Crile first presented his series of cervical lymphadenectomies, the controversy concerning the therapeutic benefit from neck dissections is still continuing (Silver et al. 2007). At present, there are no clear and well-defined guidelines concerning bilateral neck dissection during total laryngectomy (TL) for advanced laryngeal squamous cell carcinoma (ALSCC). The National Comprehensive Cancer Network Guidelines recommend "total laryngectomy with thyroidectomy as indicated, ipsilateral or bilateral neck dissection" for T3N+ and T4a glottic carcinomas (National Comprehensive Cancer Network 2014). A lack of literature references and subsequent agreed guidelines, especially for contralateral nodal involvement in ALSCC (Hamoir et al. 2014), has led to an essentially subjective approach by surgeons in the management of the neck in TL procedures.

The aim of this study was to investigate the frequency of contralateral regional lymph node metastases and its dependence on midline involvement of the primary tumor in patients with ALSCC undergoing primary TL with concurrent bilateral neck dissection.

Materials and methods

Ethical considerations, study population, and database

This article does not contain any experimental study with human participants performed by any of the authors. For this type of work formal consent is not required due to its retrospective nature.

Written informed consent was obtained from all individuals before surgical intervention. No identifying information is included in this article.

Following institutional review board approval (Appl. No.: EA2/021/15), data were reviewed from all patients with histologically confirmed laryngeal SCC (glottic, supraglottic, subglottic or transglottic) who underwent TL with concurrent elective or therapeutic neck dissection for curative intent at the Charité-Universitätsmedizin Berlin between 2002 and 2016. Using specially trained coordinators, data were obtained from an Oracle database management system using GTDS (Gießener Tumordokumentationssystem; http://www.med.uni-giessen.de/akkk/gtds/), which thoroughly documents the number of harvested lymph nodes from neck dissection samples using the original pathology reports. A bilateral selective neck dissection (primarily of levels II–IV/V) was performed in all cases. Preoperative clinical staging of the primary tumor and neck was determined using computed tomography (CT) in 58 subjects. Data were verified by authors A.B. and S.K. Exclusion criteria included salvage TL, TL following induction chemotherapy, TL due to hypopharyngeal SCC, functional TL, TL for non-SCC tumors, and the absence of radiological imaging.

Histopathologic examination

Neck dissection specimens were submitted either en bloc or divided into nodal levels, fixed in 4% phosphate-buffered formalin, and palpated for lymph nodes and other solid areas including salivary glands. Suspicious areas and nodes were dissected, counted, embedded in paraffin, sectioned, and stained with hematoxylin–eosin. Microscopic evaluation was performed by a pathology resident or specialist and reviewed by a senior consultant from the Institute of Pathology at our university medical center.

Radiologic examination

For assessment of tumor midline involvement, the preoperative radiological imaging was reevaluated by a senior consultant from the Department of Diagnostic Radiology (N.T.). Midline involvement was classified as "type A: clear", "type B: involved", "type C: exceeded" or "type D: bilateral growth/origin side indeterminable" (Fig. 1; Table 2).

The neck and chest CT scan staging protocol was performed with the patient placed in the head first, supine position. A normal amount of 120 ml contrast medium was administered using the split bolus technique (80 ml contrast medium with a flow rate of 3 ml/s followed by 63 ml saline flush at 0.7 ml/s, 40 ml contrast medium at 3 ml/s and 40 ml saline flush at 3 ml/s). In order to acquire a high soft tissue contrast combined with excellent vessel delineation, the neck CT scan was performed with arms next to the body followed by a chest CT scan with elevated arms using the following parameters: voltage 120 kV; maximum amperage 300 mA, with automatic setting; scan field of view (SFOV) and display field of view (DFOV)—neck: 25 cm; and SFOV—chest: 50 cm, DVOV—chest: 35–50 cm adapted to

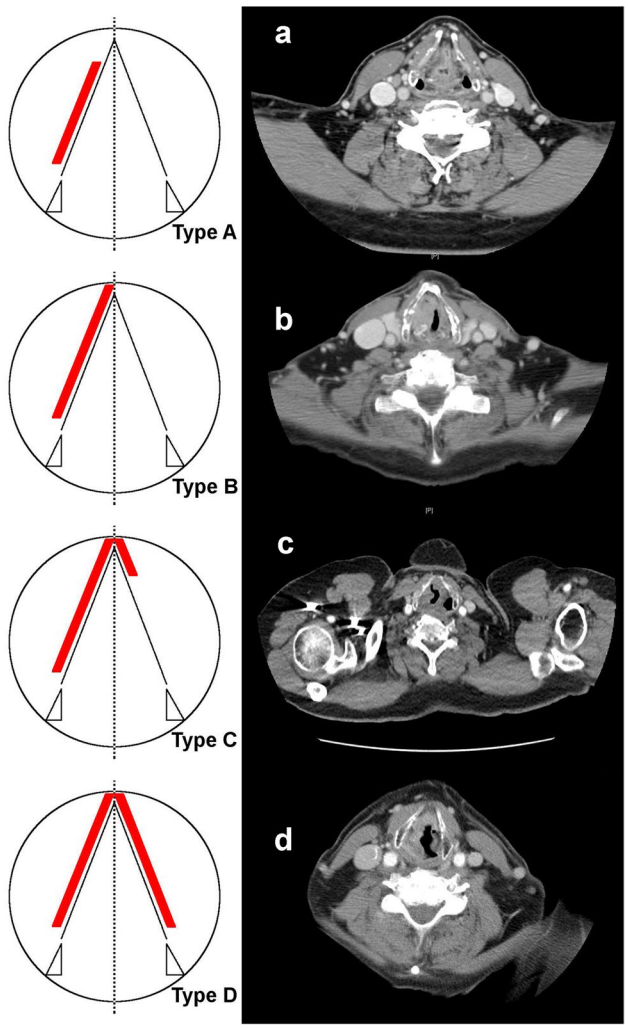

Fig. 1 Proposed classification scheme for midline relation of laryngeal cancer with corresponding CT scans. Type A: clear (**a**), type B: involved (**b**), type C: exceeded (**c**), type D: bilateral growth/origin side indeterminable (**d**)

the patient's constitution; pitch factor 1.375; slice thickness 0.625 with reformatting in 5 mm slices; additionally, multiplanar reformatting was regularly performed with 1 mm slice thickness.

Staging was completed with ultrasound of the abdomen.

Statistical analysis

Statistical analysis was performed using SPSS software (v22; IBM SPSS Statistics, Chicago, IL, USA). Statistical significance was set at a level of $\alpha = 0.05$ ($p < 0.05$).

For correlation analysis, Spearman's rank correlation coefficient (Spearman's rho, r_s) was calculated. Laryngeal midline involvement dependency on regional metastatic spread was tested using the Wilcoxon signed-rank test for related samples. For the null hypothesis (H_0) in two-sided testing, a bilateral cervical lymph node involvement was assumed in cases of midline infiltration on CT scan. The alternative hypothesis (H_1) was a preference for ipsilateral neck levels.

Survival was calculated from the date of surgery (or date of completion of postoperative adjuvant therapy) to the date of death or last known follow-up (OS) or to the date of first disease recurrence or death from any cause (DFS). Differences in survival were analyzed using univariate regression analysis (generalized Wilcoxon with Gehan–Breslow weighting for short-term follow-up and Mantel–Cox log-rank for long-term follow-up) using the Chi-square (χ^2) statistic. Survival curves were generated using the Kaplan–Meier method.

Results

Fifty-eight patients were identified (8 female, 50 male), having a mean age of 64.2 ± 9.8 years, with AJCC stage III disease in 43.1% and IVA disease in 53.4% of cases. All patients underwent bilateral selective neck dissection (primarily of levels II–IV/V). A pN2c neck was found in six cases (10.3%) (Table 1).

When correlating the pathological contralateral regional lymph node involvement (pN2c) to other investigated clinical parameters, a significant association was detected between ipsilateral and contralateral lymph nodes on pathology ($r_s = 0.537$; $p < 0.01$) as well as to laryngeal midline involvement (type A–D) ($r_s = -0.225$; $p = 0.045$). Other parameters such as age, gender, subsite, and ipsilateral nodal yield showed no significant correlation ($p > 0.05$).

There was a balanced distribution of nodal states for tumor types (χ^2, 4.652, $p = 0.589$). In type A cases ($n = 6$, 10.3% of all TL cases), a significant preference for the ipsilateral neck on pathology becomes evident (ipsilateral $n = 6$, 100.0%; contralateral $n = 0$, 0.0%). Both type B ($n = 16$, 27.6% of all TL cases) and type C ($n = 19$, 32.8% of all TL cases) cases each showed one case of contralateral lymph node involvement on pathology (type B: ipsilateral n = 15, 93.8%; contralateral $n = 1$, 6.3%; type C: ipsilateral = 18, 94.7%; contralateral $n = 1$, 5.3%). In bilateral laryngeal tumor growth (type D, $n = 17$, 29.3% of all TL cases), two cases (2/17, 11.8%) revealed an ipsilateral and four cases (4/17, 6.9%) a contralateral regional metastatic spread (pN2c), while 11 cases (11/17, 64.7%) turned out to have no regional metastases (pN0) at all (Table 2).

Regarding to the null hypothesis (H_0), a significant difference between ipsilateral and contralateral lymph node involvement depending on tumor midline relation becomes evident for type C ($p = 0.026$) and type D ($p = 0.020$)

Table 1 Patient characteristics ($n = 58$)

Age	*n* (%)
<65	32 (55.2)
≥65	26 (44.8)
Sex	
Female	8 (13.8)
Male	50 (86.2)
pT[a]	
1	0 (0)
2	2 (3.4)
3	31 (53.4)
4a	25 (43.1)
4b	0 (0)
Subsite	
Supraglottis	7 (12.1)
Glottis	9 (15.5)
Subglottis	2 (3.4)
Transglottic	40 (69.0)
cN[a]	
0	41 (70.7)
1	5 (8.6)
2a	0 (0)
2b	8 (13.8)
2c	4 (6.9)
3	0 (0)
pN[a]	
0	39 (67.2)
1	7 (12.1)
2a	1 (1.7)
2b	5 (8.6)
2c	6 (10.3)
3	0 (0)
AJCC-stage[a]	
I	0 (0)
II	2 (3.4)
III	25 (43.1)
IVA	31 (53.4)
IVB	0 (0)
Adjuvant treatment	
None	28 (48.3)
RT	17 (29.3)
RCT	12 (20.7)
Unknown	1 (1.7)

RT radiotherapy, *RCT* radiochemotherapy

[a] According to AJCC Cancer Staging Manual, 7th ed., American Joint Committee on Cancer, 2010

cases. Both type A and B showed no significant differences ($p > 0.05$).

The odds ratios (OR) for contralateral regional lymph node involvement are in type A cases, OR = 0.0 (Fisher exact probability test, $p = 0.501$), in type B, OR = 0.051 ($p = 0.466$), in type C, OR = 0.378 ($p = 0.350$), and in type D, OR = 6.0 ($p = 0.055$). The relative risk reduction in missing midline involvement is 100%.

Thus, a preoperative laryngeal CT staging type D has a sensitivity rate of 66.6% and a specificity of 75.0% in predicting contralateral lymph node involvement in advanced laryngeal SCC.

When comparing cN stage with pN stage, 37 patients (63.8%) remained at their initial staging. Twelve cases (20.7%) experienced regional upstaging, whereas another nine cases (15.5%) had to be down-staged after histopathological examination. In 5 of 6 detected pN2c necks initial clinical staging showed no signs of contralateral metastases. The sensitivity rate for preoperative evaluation of contralateral regional metastases (cN2c necks) via CT scan was 16.6% and the specificity rate was 94.2% (Table 3).

In pN2c/type D cases, the mean maximum distance from laryngeal midline at the suspected contralateral side (originating from the suspected primary side in indeterminable cases defined as yielding the higher count of pathological regional lymph nodes in pN2c necks) was 21.3 mm (range 16–26 mm). Compared to pN2c/type D cases, the mean contralateral laryngeal midline excess in type C cases was significantly lower (13.6 ± 6.7 mm, range 6–27 mm, $p < 0.05$).

Survival analysis

After dividing the total cohort into four groups based on midline involvement (type A–D), no significant association in pairwise comparison to OS was detected neither in weighting for long-term nor for short-term (χ^2, ≤ 1.413, $p \geq 0.234$). Similar results were obtained regarding to DFS (χ^2, ≤ 1.429, $p \geq 0.232$) (Fig. 2a, b).

No significant associations towards OS (χ^2, ≤ 3.067, $p \geq 0.080$) and DFS (χ^2, ≤ 3.400, $p \geq 0.065$) were seen when dividing regional lymph node stages into three groups (pN0, pN1-2b, and pN2c) in pairwise comparison neither in weighting for long-term nor for short-term (Fig. 2c, d). A significant benefit was seen for pN0 necks when compared pairwise to pN+ necks for OS (χ^2, 4.387, log-rank $p = 0.036$) and DFS (χ^2, 4.476, log-rank $p = 0.034$) (Fig. 2e, f). The 5-year-OS rate decreases significantly from 67.1% in pN0 cases to 0.0% in pN+ cases [hazard ratio (HR) 2.706, $p = 0.044$]. The estimated median OS for pN0 necks was 94 vs. 34 months for pN+ necks.

Pattern of contralateral metastatic spread

As far as involved levels have been documented, preferences for level II and III in contralateral regional metastases were seen (Table 4).

Table 2 Laryngeal midline relation and regional lymph node involvement

	Whole cohort ($n = 58$) n (%)	pN0 n (%, acc. to type)	pN1-2b n (%, acc. to type)	pN2c n (%, acc. to type)	significance, p (Wilcoxon signed-rank test, referring to H_0)
Type A (clear)	6 (10.3)	4 (66.7)	2 (33.3)	0 (0.0)	0.180
Type B (involved)	16 (27.6)	12 (75.0)	3 (18.8)	1 (6.3)	0.083
Type C (exceeded)	19 (32.8)	12 (63.2)	6 (31.6)	1 (5.3)	0.026
Type D (bilateral growth/ origin side indeterminable)	17 (29.3)	11 (64.7)	2 (11.8)	4 (23.5)	0.020

Table 3 Accuracy of CT-based regional lymph node staging (cN stage)

cN stage	pN stage				
	0	1	2a	2b	2c
0					
n	33	4	0	1	3
% in cN	80.5	9.8	0.0	2.4	7.3
% in pN	84.6	57.1	0.0	20.0	50.0
1					
n	1	1	1	1	1
% in cN	20.0	20.0	20.0	20.0	20.0
% in pN	2.6	14.3	100.0	20.0	16.7
2b					
n	4	1	0	2	1
% in cN	50.0	12.5	0.0	25.0	12.5
% in pN	10.3	14.3	0.0	40.0	16.7
2c					
n	1	1	0	1	1
% in cN	25.0	25.5	0.0	25.0	25.0
% in pN	2.6	14.3	0.0	20.0	16.7

Two-sided Fisher's exact test for correlation between cN and pN staging $p < 0.01$

Subsite analysis

Subgroup testing revealed no significant subsite preference for contralateral metastatic lymph node involvement (Wilcoxon signed-rank test: glottis, supraglottis, subglottis $p < 0.05$, transglottic tumors $p < 0.01$).

Discussion

The basis for knowledge in patterns of regional metastatic spread in HNSCC is grounded on studies by Lindberg (1972), Byers (1985), and (Shah 1990). Reported data on contralateral regional expansion for laryngeal SCC are rare. Marks et al. (1992) described contralateral lymph node metastasis in 4% of the reviewed transglottic carcinomas and in 7–26% of supraglottic carcinomas.

Supraglottic carcinomas are associated with significantly higher rates of contralateral lymph node metastases compared to other subsites (Marks et al. 1992; Ozturkcan et al. 2009; Weber et al. 1994). Furthermore, a risk of contralateral metastasis unrelated to primary tumor size (Marks et al. 1992), a higher risk for contralateral metastasis in subjects with ipsilateral lymph node invasion with or without extracapsular spread (Ozturkcan et al. 2009), and a higher risk for occult metastases for supraglottic cancer in cN0 necks (Kowalski et al. 1995) have all been described. Thus there was no difference between the rates of contralateral neck lymph node metastases and midline involvement/crossing in lateral supraglottic cancer (Yilmaz et al. 2015). Therefore, bilateral neck dissection is recommended in supraglottic cancer as regional recurrence rates decreased from 20 to 9% with bilateral neck dissection and the 2-year survival rate increased from 72 to 76% (Weber et al. 1994).

The reported incidence of contralateral lymph node invasion of 27% in carcinoma with subglottic extension is also high (Plaat et al. 2005). The risk for contralateral metastasis of 4% is related to transglottic tumors with fixed true vocal folds (T3–T4) (Marks et al. 1992). Occult nodal disease has an incidence of 19% in advanced glottic carcinoma (T3–T4) (Yang et al. 1998). Risk factors such as perineural invasion of the tumor may be associated with contralateral regional neck recurrence (Lanzer et al. 2014).

There is no clear midline distinction and no separation between subglottis, glottis and supraglottis as a result of collateral lymph capillaries. Mann stated that only the free edge of the true vocal fold (up to 5 mm) constitutes a kind of border in the lymph capillaries between the supraglottis and subglottis (Mann 1979). This could not be confirmed by the work of Werner et al. (2003) who found that true vocal fold lymphatic drainage appears to be towards the arytenoids and thus, similar to the supraglottic area into levels II and III. They also stated that both mucosal and submucosal lymphatic vessels were seen to cross the midline.

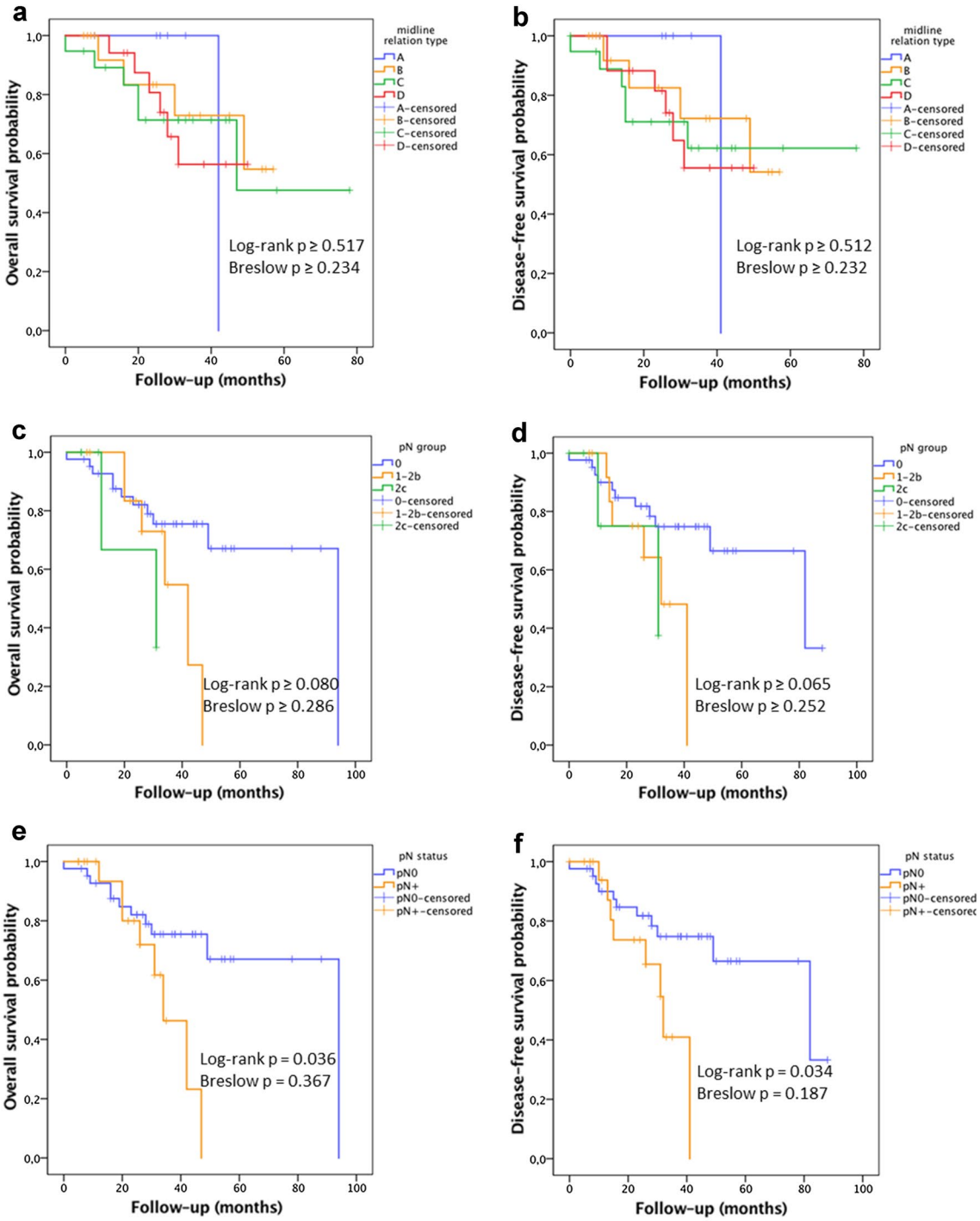

Fig. 2 Kaplan–Meier curves. **a** Overall survival and **b** disease-free survival according to tumor midline relation types. **c** Overall survival and **d** disease-free survival according to pN groups. **d** Overall survival and **e** disease-free survival according to pN status (negative, pN0 vs. positive pN+)

Comprehensive knowledge of anatomic compartments, cervical lymphatic drainage, and survival outcomes has led to more functional and less mutilating approaches in lymphadenectomy, which is supported by decreased perioperative complications (Coskun et al. 2015). Postoperative complications in neck dissections include hematoma (9.5%), seroma (5.0%), and bleeding (4.8%) (Möckelmann et al. 2015) as well as wound infections (<5%) and chylous fistulas (2%) (Balm et al. 2005). Because surgical radicality has a major impact on morbidity and may

Table 4 Patterns of contralateral neck level involvement

Level	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Level involvement per case (%)	Involved lymph nodes per case (%)
I	–	–	–	–	–	–	0.0	0.0
II	–	2		1	–	1	50.0	66.7
III	1	–	1[a]	1[b]	1[c]	–	66.7	66.7
IV	–	–	–	–	–	–	0.0	0.0
V	–	1	–	–	–	–	16.6	16.6

[a] Neck specimen named "level I–V" containing one positive lymph node

[b] Neck specimen named "level III–V" containing one positive lymph node

[c] Neck specimen named "level II–IV" containing one positive lymph node

lead to prolonged hospitalization and reduced quality of life (Gourin et al. 2015), there is a need for reevaluation of bilateral neck treatment indications not only in TL procedures, but also in radio-oncological cases. Interestingly, in the United States during the period from 1990 to 1992, 34.8% of all TL (767/2204) were performed without any neck dissection, most likely due to cN0-status (Shah et al. 1997). Another study was able to show that disease-specific survival after TL was independent from neck treatment modality in stage IV ALSCC (Spector et al. 2004). Recent results demonstrated neck dissection nodal yield to have no significant impact on survival in patients undergoing TL for ALSCC (Böttcher et al. 2016).

This study has shown no increased contralateral lymph node involvement for supraglottic or subglottic carcinomas compared to glottic ones, even though there should have been increased involvement according to the literature (Marks et al. 1992; Ozturkcan et al. 2009; Kowalski et al. 1995; Yilmaz et al. 2015), but the difference was not statistically significant most likely due to limited sample size.

Our study supports the approach of omitting the contralateral neck in type A cases of ALSCC. A precondition for avoiding elective contralateral neck dissection is an appropriate preoperative staging. The routinely used CT scan of the neck is of rather limited eligibility as magnetic resonance imaging (MRI) provides increased sensitivity and specificity in detecting pathological lymph nodes (Plaat et al. 2005; Yang et al. 1998; de Bondt et al. 2009; Peters et al. 2012). The advantages of a CT scan are the comparably short duration of examination and quick scheduling, whereas an MRI scan takes about 45 min, which makes it difficult to tolerate, especially for multimorbid patients or for those with a tracheostomy cannula. As an alternative diagnostic tool, 18 F-FDG PET/CT has shown a sensitivity of 79.6% and specificity of 95.8% in preoperative detection of contralateral positive lymph nodes in HNSCC (Joo et al. 2014).

Limitations of this study are its retrospective design and the limited sample size of 58 cases. Additionally, an inconsistent surgical approach to neck dissection and consequent high variance of nodal yield represent a bias for N stage determination.

Conclusion

Preoperative radiological evaluation of midline involvement in ALSCC using the proposed classification scheme is a promising approach as it leads to increased sensitivity in predicting pathological contralateral lymph nodes. For type A category and cN0-2b neck staging, a contralateral neck dissection might be avoidable accompanied by a reduction in surgical complications and operating time. A positive nodal (pN+) status remains a significant negative prognosticator for OS and DFS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Funding This work has not received any funding.

Ethical approval This article does not contain any experimental study with human participants performed by any of the authors. For this type of work formal consent is not required due to its retrospective nature. Written informed consent was obtained from all individuals before surgical intervention. No identifying information is included in this article. Institutional review board approval (Appl. No.: EA2/021/15) was given.

References

Balm AJ, Lohuis PJ, Copper MP (2005) Surgical technique–unwrapping the neck node levels around a sternocleidomastoid muscle bar: a systematic way of performing (modified) radical neck dissection. Eur J Surg Oncol 31(10):1216–1221 **(Epub 2005 Sep 19)**

Böttcher A, Dommerich S, Sander S, Olze H, Stromberger C, Coordes A, Jowett N, Knopke S (2016) Nodal yield of neck dissections and influence on outcome in laryngectomized patients. Eur Arch Otorhinolaryngol 273(10):3321–3329. doi:10.1007/s00405-016-3928-2

Byers RM (1985) Modified neck dissection. A study of 967 cases from 1970 to 1980. Am J Surg 150(4):414–421

Coskun HH, Medina JE, Robbins KT et al (2015) Current philosophy in the surgical management of neck metastases for head and neck squamous cell carcinoma. Head Neck 37(6):915–926. doi:10.1002/hed.23689 **(Epub 2014 Jun 30)**

de Bondt RB, Nelemans PJ, Bakers F et al (2009) Morphological MRI criteria improve the detection of lymph node metastases in head and neck squamous cell carcinoma: multivariate logistic regression analysis of MRI features of cervical lymph nodes. Eur Radiol 19(3):626–633. doi:10.1007/s00330-008-1187-3 **(Epub 2008 Oct 7)**

Gourin CG, Starmer HM, Herbert RJ et al (2015) Quality of care and short- and long-term outcomes of laryngeal cancer care in the elderly. Laryngoscope 125(10):2323–2329. doi:10.1002/lary.25378

Hamoir M, Schmitz S, Gregoire V (2014) The role of neck dissection in squamous cell carcinoma of the head and neck. Curr Treat Options Oncol 15(4):611–624. doi:10.1007/s11864-014-0311-7 **(Review)**

Joo YH, Yoo IR, Cho KJ, Park JO, Nam IC, Kim CS, Kim SY, Kim MS (2014) The value of preoperative 18F-FDG PET/CT for the assessing contralateral neck in head and neck cancer patients with unilateral node metastasis (N1-3). Clin Otolaryngol 39(6):338–344. doi:10.1111/coa.12295

Kowalski LP, Franco EL, de Andrade Sobrinho J (1995) Factors influencing regional lymph node metastasis from laryngeal carcinoma. Ann Otol Rhinol Laryngol 104(6):442–447

Lanzer M, Gander T, Kruse A, Luebbers HT, Reinisch S (2014) Influence of histopathologic factors on pattern of metastasis in squamous cell carcinoma of the head and neck. Laryngoscope 124(5):E160–E166. doi:10.1002/lary.24458 **(Epub 2013 Nov 19)**

Lindberg R (1972) Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1446–1449

Mann W (1979) The lymphatic system of the larynx. A lymphangioscopic and ultrastructural study (author's transl). Arch Otorhinolaryngol 225(3):165–180

Marks JE, Devineni VR, Harvey J, Sessions DG (1992) The risk of contralateral lymphatic metastases for cancers of the larynx and pharynx. Am J Otolaryngol 13(1):34–39

Möckelmann N, Busch CJ, Münscher A, Knecht R, Lörincz BB (2015) Timing of neck dissection in patients undergoing transoral robotic surgery for head and neck cancer. Eur J Surg Oncol 41(6):773–778. doi:10.1016/j.ejso.2015.02.002 **(Epub 2015 Feb 17)**

National Comprehensive Cancer Network (2014) NCCN clinical practice guidelines in oncology (NCCN Guidelines)—Head and Neck Cancers, Version 2.2014

Ozturkcan S, Katilmis H, Ozdemir I, Tuna B, Guvenc IA, Dundar R (2009) Occult contralateral nodal metastases in supraglottic laryngeal cancer crossing the midline. Eur Arch Otorhinolaryngol 266(1):117–120. doi:10.1007/s00405-008-0721-x **(Epub 2008 Jun 10)**

Peters TT, Castelijns JA, Ljumanovic R, Witte BI, Leemans CR, de Bree R (2012) Diagnostic value of CT and MRI in the detection of paratracheal lymph node metastasis. Oral Oncol 48(5):450–455. doi:10.1016/j.oraloncology.2011.12.003 **(Epub 2012 Jan 4)**

Plaat RE, de Bree R, Kuik DJ et al (2005) Prognostic importance of paratracheal lymph node metastases. Laryngoscope 115(5):894–898

Shah JP (1990) Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg 160(4):405–409

Shah JP, Karnell LH, Hoffman HT et al (1997) Patterns of care for cancer of the larynx in the United States. Arch Otolaryngol Head Neck Surg 123(5):475–483

Silver CE, Rinaldo A, Ferlito A (2007) Crile's neck dissection. Laryngoscope 117:1974–1977

Spector GJ, Sessions DG, Lenox J, Newland D, Simpson J, Haughey BH (2004) Management of stage IV glottic carcinoma: therapeutic outcomes. Laryngoscope 114:1438–1446

Weber PC, Johnson JT, Myers EN (1994) The impact of bilateral neck dissection on pattern of recurrence and survival in supraglottic carcinoma. Arch Otolaryngol Head Neck Surg 120(7):703–706

Werner JA, Dunne AA, Myers JN (2003) Functional anatomy of the lymphatic drainage system of the upper aerodigestive tract and its role in metastasis of squamous cell carcinoma. Head Neck 25(4):322–332

Yang CY, Andersen PE, Everts EC, Cohen JI (1998) Nodal disease in purely glottic carcinoma: is elective neck treatment worthwhile? Laryngoscope 108:1006–1008

Yilmaz T, Suslu N, Atay G, Gunaydin RO, Bajin MD, Ozer S (2015) The effect of midline crossing of lateral supraglottic cancer on contralateral cervical lymph node metastasis. Acta Otolaryngol 135(5):484–488. doi:10.3109/00016489.2014.986759 **(Epub 2015 Feb 12)**