Original Article

Diagnostic accuracy of MRI and PET/CT for neck staging prior to salvage total laryngectomy

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Abstract

Aim: Lymph node (LN) metastases are associated with poor outcomes in patients with recurrent larynx squamous cell carcinoma (LSCC). Neck dissection (ND) is therefore commonly performed along with salvage total laryngectomy (STL). Here, we assess the rate of occult LN metastases and the diagnostic value of MRI and PET/CT for detecting them in recurrent LSCC.

Methods: This retrospective study included patients with recurrent LSCC after primary (chemo)radiotherapy [(C)RT] who were re-staged by MRI and/or PET/CT and treated with STL and ND between 2004 and 2019. The histopathology of ND samples was used as the reference standard.

Results: Forty-one patients were included. The prevalence of occult metastases in MRI-negative and PET/CT-negative neck nodes was between 3.2% and 6.1%. Negative predictive values of neck node re-staging were 93.9% for MRI, 96.8% for PET/CT, and 96.2% for MRI and PET/CT combined.

Conclusion: Both MRI and PET/CT afforded good negative predictive values for nodal staging in patients with recurrent LSCC after (C)RT prior to STL. In selected patients, these radiological modalities, particularly PET/CT, could help to avoid unnecessary surgery to the neck and its associated morbidity.

Keywords: Laryngeal squamous cell carcinoma, recurrence, salvage total laryngectomy, re-staging, neck dissection, MRI, PET/CT, occult nodal metastasis

INTRODUCTION

Laryngeal squamous cell carcinomas (LSCC) account for approximately 25% of all head and neck cancers[1]. Management approaches for LSCC depend on several factors, including tumor stage and the patient's comorbidities. Since the early 1990s, organ-preserving strategies encompassing primary radiotherapy with or without concomitant chemotherapy [(C)RT] have been alternatives to primary surgery for advanced-stage LSCC[2-4].

Recurrences after (C)RT occur in approximately one-third of advanced cases and are most often local. In such scenarios, salvage total laryngectomy (STL) is usually the only curative option available[5].

Staging and management of the previously irradiated neck in recurrent LSCC remains challenging because of the tissue changes induced by (C)RT, including edema and fibrosis[6-8]. In the absence of clinically detectable neck lymph node (LN) metastases, it remains unclear whether the risk of occult neck metastases warrants elective neck dissection (ND) and its associated morbidity. On one hand, missed metastases can potentially lead to decreased disease control, especially considering that most patients do not qualify for adjuvant therapy following STL (i.e. re-irradiation), whereas on the other hand, ND after (C)RT carries significant morbidity, including wound healing disorders, injury to cranial nerves (marginal mandibular branch of the facial nerve, hypoglossal nerve, and spinal accessory nerve) and chyle leak[9,10]. Moreover, ND increases the risk of pharyngocutaneous fistula when performed along with STL[9,11].

In this context, a number of studies have addressed the question of whether or not ND is needed at the time of STL in patients with rcN0 necks. Reported rates of occult nodal metastases in recurrent LSCC range from 0% up to 28%[12,13]. The conclusions of these studies are discordant, with some authors favoring ND[14,15], whereas others advocate a watchful surveillance of the neck instead[12,16,17].

To date, only a limited number of studies have focused on the diagnostic value of currently used radiological modalities for re-staging of the neck, namely magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT). Both modalities are key elements in the decision-making process in patients with recurrent head and neck squamous cell carcinoma. A recent study by Rosko *et al.* showed that PET/CT for neck re-staging in recurrent LSCC had a low sensitivity of 16.7% but high specificity of 97.1%, and rather low positive predictive value (PPV) of 66.7% and negative predictive value (NPV) of 76.7%[18]. The role of MRI in this disease setting has not yet been comprehensively explored.

The aim of the current study was to assess the rate of occult neck node metastases in PET/CT-negative and MRI-negative neck node disease in a cohort of patients with recurrent LSCC who underwent STL and ND, and to examine the diagnostic value of MRI and PET/CT for neck node re-staging with histopathological evaluation used as the reference standard.

METHODS

Ethical issues

Approval for this study was obtained from our ethics committee (Cantonal Ethics Committee of Bern). All patients included in this study were treated at Bern University Hospital (Inselspital), Bern, Switzerland. The patients' data were stored anonymously in a database only accessible to the principal investigators of this study (Galli J, Giger R, Nisa L).

Patients and inclusion criteria

This retrospective study included patients with histopathologically confirmed recurrent LSCC treated between January 2004 and January 2019. The inclusion criteria were: (1) STL performed with curative intent after failed (C)RT for LSCC; (2) ND performed along with STL; (3) preoperative staging by MRI and/or PET/CT; (4) clinical remission for at least 6 months after the end of primary treatment; and (5) follow-up of at least 12 months in event-free patients.
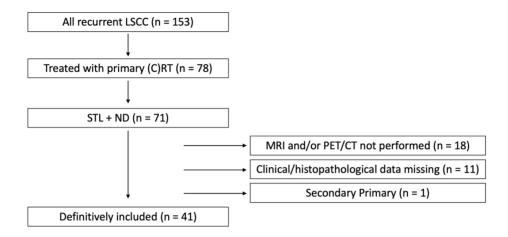
Extraction of data and evaluation of imaging

The following variables were retrieved and double-checked in a non-blinded manner by two authors (Galli J, Nisa L): age, initial TNM staging, initial treatment, recurrence TNM staging, details of salvage surgery performed, results of histopathologic neck node analysis from the salvage surgery, postoperative adverse events within 30 days scored according to the Clavien-Dindo classification and long-term sequelae, and status at the time of follow-up[19]. The 7th edition of the UICC classification was used for tumor staging[20].

MRI and PET/CT sequences were acquired as previously described[21,22]. Briefly, contrast-enhanced MRI included coronal inversion recovery, axial T1-weighted, axial T2-weighted, and diffusion-weighted sequences. For PET/CT, a non-contrast-enhanced CT scan from the skull base to midthigh was performed with the arms elevated, 60 minutes after tracer injection (FDG). This was followed by a dedicated head and neck acquisition. Then, a contrast-enhanced CT scan was performed. The criteria for classifying LNs as suspect for metastatic disease on each imaging modality were as follows:

● MRI: LNs with a diameter equal or greater than 10 mm, long/short ratio < 2, presence of necrotic areas, evidence of extranodal extension, rough borders, ill-defined margins, infiltration of adjacent structures, and diffusion restriction.

● PET/CT: LNs with a diameter equal to or greater than 10 mm, long/short ratio < 2, perinodal stranding, rough borders, ill-defined margins, perinodal fat stranding, and high maximum standardized uptake value (SUVmax). For calculation of SUVmax, circular regions of interest (ROIs) were drawn around LN metastasis with focally increased uptake on axial slices, and these ROIs were then automatically grown to a three-dimensional volume of interest according to a 40% isocontour. The SUVmax of the LN metastasis was calculated according to the formula: standardized uptake value (SUV) = tissue concentration (Bq/g)/(injected dose [Bq]/body weight [g]). The cut-off value for suspicious LN was two times the blood pool value.

For the purpose of this study, when suspicious LNs were described on either one or both of the imaging modalities (MRI and PET/CT), the neck was scored as positive for metastatic involvement. Only when both modalities were negative were neck LNs considered as being radiologically rcN0. Analysis was performed on a per-patient basis.

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│   All recurrent LSCC (n = 153) │
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│  Treated with primary (C)RT (n = 78) │
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│       STL + ND (n = 71)        │
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              │        ──────▶  ┌─────────────────────────────────────────┐
              │                 │  MRI and/or PET/CT not performed (n = 18) │
              │                 └─────────────────────────────────────────┘
              │        ──────▶  ┌─────────────────────────────────────────┐
              │                 │ Clinical/histopathological data missing (n = 11) │
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              │                 │        Secondary Primary (n = 1)          │
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│   Definitively included (n = 41) │
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Figure 1. Flowchart with considered, excluded, and included patients. (C)RT: Radiotherapy with or without concomitant chemotherapy; ND: neck dissection; STL: salvage total laryngectomy.

Data analysis

Summary statistics and diagnostic values were calculated using SPSS statistics software version 25 (IBM, New York, USA). Survival curves were plotted according to the Kaplan-Meier method and were compared using the log-rank test performed with GraphPad Prism (GraphPad Software Inc., San Diego, USA). All *P*-values were two-sided and statistical significance was set at $P < 0.05$.

RESULTS

Characteristics of the patients with recurrent LSCC

Of 153 patients with recurrent LSCC who were managed at our institution during the study period, 71 underwent STL along with ND following local or loco-regional failure after (C)RT. Out of these patients, 18 were excluded because of unavailable MRI and/or PET/CT, 1 because of a secondary primary tumor after 21 years, and 11 because of incomplete clinical/histopathological data, bringing the final number of included patients to 41 [Figure 1].

The median age at the time of STL was 67.5 years (range: 49.7-85.1 years). The median time to relapse after (C)RT was 24.4 months (range: 6.2 months to 6.7 years). All but one patient were male. Table 1 summarizes the baseline characteristics of the patients included in this study. Sixty-one percent of the patients initially had glottic carcinomas, and 70.7% had early-stage local disease (UICC Stage I-II). Only 12.2% of the patients had regional LN metastases at initial diagnosis.

While all primary tumors were irradiated with a median dose of 72 Gy (range: 60-72 Gy), 24 (58.6%) patients received unilateral or bilateral neck irradiation. Sixteen patients (39.0%) had no primary neck RT, with 2 of these 16 patients (11.1%) having nodal metastasis at the time of STL, both staged as rpN2c. In the 24 patients (58.6%) with primary neck RT, two (8.3%) had LN metastasis, with one of these being staged as pN1 and the other as pN2c.

In contrast to the initial tumors, most patients (69%) with disease failure had advanced recurrent stage cancers (UICC Stage III-IV). Bilateral and unilateral NDs were performed along with STL in 82.9% and 17.1% of these patients, respectively [Table 2]. ND was carried out from at least level II-IV in all cases. Four patients underwent modified radical ND including level I and V, and six underwent modified radical ND with additional dissection of level VI.

Table 1. Patient demographics and initial tumor characteristics (*n* = 41)

Feature		Number of patients (%)
Gender	Male	40 (97.6)
	Female	1 (2.4)
Initial tumor subsite	Supraglottic	9 (22.0)
	Glottic	25 (61.0)
	Subglottic	2 (4.9)
	Transglottic	5 (12.2)
Initial clinical T classification	T1-2	30 (73.2)
	T3-4	11 (26.8)
Initial clinical N classification	N0	36 (87.8)
	N1	2 (4.9)
	N2	3 (7.3)
Initial UICC staging	I-II	29 (70.7)
	III-IV	12 (29.3)
Initial treatment	(C)RT	39 (95.1)
	Primary surgery + (C)RT	1 (2.4)
	ND + (C)RT	1 (2.4)
Initial (C)RT	Primary tumor RT	41 (100.0)
	Bilateral neck RT	22 (53.7)
	Only ipsilateral neck RT	2 (4.9)
	No neck RT	16 (39)
	N/A**	1 (2.4)

(C)RT: Radiotherapy +/- concomitant chemotherapy; N/A: data not available; ND: neck dissection; UICC: union for international cancer control. **Only with respect to neck irradiation.

Table 2. Characteristics of recurrent laryngeal squamous cell carcinomas (*n* = 41)

Feature		Number of patients (%)
Recurrence pT classification	T1-2	8 (22.9)
	T3-4	27 (77.1)
	N/A*	6 (14.3)
Recurrence pN classification	N0	37 (90.2)
	N1	1 (2.4)
	N2	3 (7.3)
UICC stage recurrence	I-II	7 (19.4)
	III-IV	29 (80.6)
	N/A*	5 (11.2)
Type of salvage surgery	STL + ND unilateral	7 (17.1)
	STL + ND bilateral	34 (82.9)

ND: Elective neck dissection; N/A: data not available; STL: salvage total laryngectomy; UICC: union for international cancer control. *The percentage of missing data was calculated using the total number of patients (*n* = 41), while the other percentages were calculated for the number of patients for whom data were available.

Patterns of occult neck node metastases and diagnostic value of MRI and PET/CT in patients with recurrent LSCC undergoing STL

For re-staging purposes, 35 (85.4%) patients underwent MRI, 35 (85.4%) underwent PET/CT, and 29 (70.7 %) underwent both imaging modalities. The concordance between these two modalities with respect to rcN-staging was moderate (Cohen's kappa = 0.47).

Among the 41 patients undergoing ND at the time of STL, 4 (9.7%) had histopathological evidence of neck node metastases (i.e., pN+). In the MRI group, two pN+ cases were not properly identified and only one out of two metastases shown on MRI was confirmed on histopathological analysis [Figure 2A].

PET/CT correctly staged one pN+ case and missed one metastasis in another case [Figure 2B]. The rates of occult metastases in the MRI-negative and PET/CT-negative neck node disease were 6.1% (2/33) for MRI and 3.2% (1/31) for PET/CT. Twenty-nine patients underwent both MRI and PET/CT, and 26 of these were staged as cN0. Occult LN metastasis was found in 3.8% of these patients (1/26). In three patients, nodal disease was suspected on imaging, but was not confirmed on histopathological work-up [Figure 2C]. Figures 3 and 4 show radiological examples of false positive and false negative LN on PET/CT and MRI. In the false positive PET/CT case [Figure 3A], no concrete histopathology was diagnosed within the LN. Histopathology revealed sinus histiocytosis in the corresponding LN of the false positive MRI case [Figure 4A].

The disease prevalence rates in the groups were 8.6% (3/35) for MRI, 5.7% (2/35) for PET/CT, and 3.4% (1/29) for both modalities combined.

The diagnostic values of each modality in this specific disease setting are displayed in Table 3. Briefly, for neck node re-staging, MRI and PET/CT had good specificities (96.9% and 91.0%, respectively) and NPV (93.9% and 96.8%, respectively), but low sensitivity and PPV. Using both modalities together resulted in a high NPV of 96.2%.

Of the four patients with neck node metastases, information about the neck levels was available only for two: in one patient a single metastasis occurred in the ipsilateral level IIA, while in the second patient metastases occurred in the ipsilateral level IIA and contralateral level III. At initial tumor diagnosis, only one of these patients had clinically and radiologically positive neck nodes.

Among the five patients with initial nodal disease, only one was classified as pN+ at the time of salvage surgery; this was an occult metastasis (i.e., rcN0).
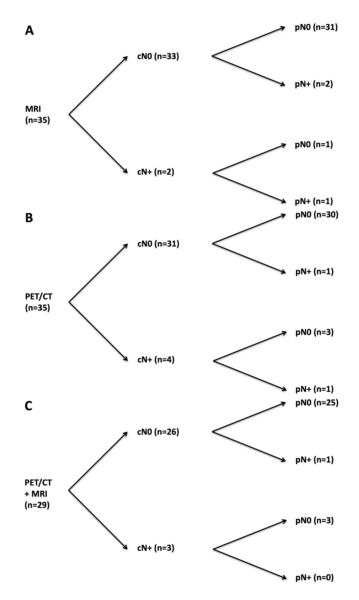
When the distributions of the two occult metastases were examined in relation to the initial and recurrent tumor stages, one patient initially staged as UICC I-II was found to have an occult metastasis. At recurrence, this patient had an rcT2 rcN0 tumor (MRI and PET/CT: cN0). The second occult metastasis occurred in a patient who had only undergone MRI imaging (MRI: cN0). The patient was initially staged as UICC III-IV, then as rcT4 rcN0 at recurrence. We did not encounter a situation with a true positive neck side and a false positive contralateral neck side in our cohort.

Oncological outcomes and adverse events
The median follow-up time after STL was 3.1 years (range: 0.6 months to 11.1 years). At the last follow-up, 60.9% of all patients were alive without recurrent disease, and 4.9% were with disease [Figure 5]. Nineteen percent of patients had died because of tumor progression, and the remaining deceased patients had died of non-cancer related causes. With respect to disease control, 10 patients (23.8%) presented with disease recurrence within a median time of 25.9 months (range: 9 months to 8.1 years). Among these, eight patients had regional recurrences within a median time of 9.5 months following STL + ND (range: 0.5-1.5 years). Eight patients had parastomal recurrences and two had lung metastasis. None of the recurrences occurred in neck lymph nodes.

Table 3. Diagnostic values for LN metastases of MRI and PET/CT in recurrent laryngeal squamous cell carcinomas

Feature	MRI	PET/CT	PET/CT + MRI
True positive	1	1	0
True negative	31	30	25
False positive	1	3	3
False negative	2	1	1
Sensitivity	33.3%	50.0%	0.0%
Specificity	96.9%	91.0%	89.3%
Positive predictive value	50.0%	25.0%	0.0%
Negative predictive value	93.9%	96.8%	96.2%

Figure 2. (A) Flowchart displaying the clinical and pathological neck staging for MRI alone. (B) flowchart displaying the clinical and pathological neck staging for PET/CT alone. (C) flowchart displaying the clinical and pathological neck staging for PET/CT + MRI.
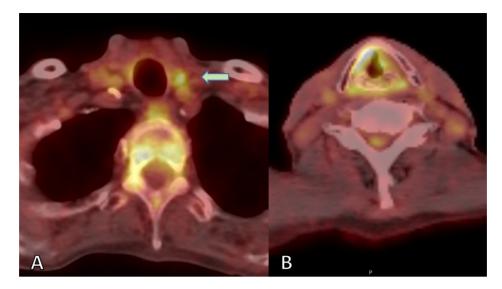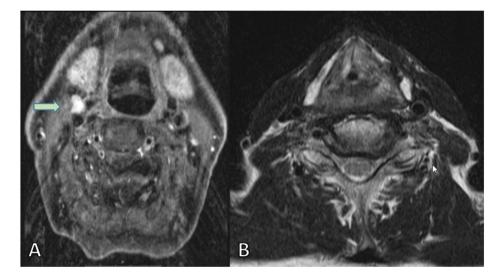
Figure 3. (A) False positive PET/CT with FDG-positive paratracheal LN suspicious for nodal metastasis. Histopathology did not reveal any concrete LN alterations. (B) false negative PET/CT with histopathologically proven occult metastases in neck level II on the right side.

Figure 4. (A) False positive MRI with suspicious LN metastasis in level II. Histopathology revealed sinus histiocytosis. (B) false negative MRI with histopathologically proven occult metastasis in neck level II on the right side.

Early adverse events within 30 days after surgery were scored by the Clavien-Dindo Classification[19]. Eighteen patients (51.4%) showed no or grade I adverse events, 6 patients (17.1%) had grade II adverse events including postoperative anemia with the need for blood transfusion or wound dehiscence treated conservatively. Ten patients (28.6%) demonstrated grade III adverse events requiring surgical intervention under general anesthesia, including bleeding or fistulae. One patient (2.9%) died within 30 days due to severe wound dehiscence and superinfection (grade V). In six patients, no data on adverse events were available, and these patients were not included in the percentage calculations. At the last follow-up, persistent dysphagia was the only long-term sequelae noted in 15 patients (36.6%). Two of these 15 patients developed tracheo-esophageal fistulas for which surgical repair was indicated.
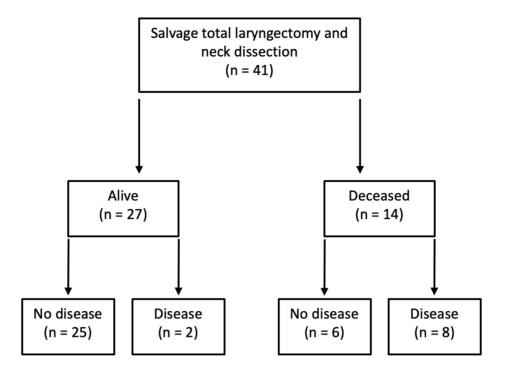
Figure 5. Flowchart with status of all 41 patients at last follow-up after salvage total laryngectomy and neck dissection.

DISCUSSION

In this study, we assessed the diagnostic value of MRI and PET/CT in the re-staging of the neck of patients with recurrent LSCC undergoing STL after failed (C)RT. The main findings were: (1) the prevalence of occult metastases in this disease setting is low (6.1% in patients staged with MRI, 3.2% in patients staged with PET/CT, and 3.8% in patients staged with MRI + PET/CT); (2) both MRI and PET/CT have a good NPV (93.9% and 96.8%, respectively) but their combination is not superior (96.2%), with both modalities having poor sensitivity and PPV [Table 3]; (3) loco-regional disease control after STL and ND at last follow-up was 60.9%.

The indications for ND and its prognostic impact in patients with recurrent LSCC are not fully clear. In the context of recurrences after (C)RT, patients with obvious nodal disease require elective ND at the time of STL. However, those with rcN0 necks pose more of a challenge, as both under-treatment and unnecessary surgery may have potentially negative effects in terms of prognosis and adverse events. It has to be kept in mind that tissue changes to the neck following (C)RT, particularly fibrosis, often lead to increased morbidity during and after ND[23]. For primary head and neck squamous cell carcinoma (HNSCC), a risk threshold of 20% for occult metastasis is generally accepted as an indication for ND or RT on the neck[24]. Whether this 20% threshold can be applied to recurrent cancer is disputed, with some authors claiming that a more stringent threshold of 15% is more appropriate in this setting[25,26]. Given that curative options in the case of treatment failure after STL are scarce, it could be argued that a more aggressive attitude is indeed meaningful, especially in the case of supraglottic recurrences and initially advanced neck nodal disease[25].

It should be noted that systematic reviews and meta-analyses by Gross *et al.*, Lin C *et al.*, and Lin D *et al.* did not demonstrate a significant pooled 5-year disease-free and overall survival advantage for ND *vs.* observation of the neck after STL in rcN0 individuals[27-29], although there was a trend for improved survival with ND in supraglottic and locally advanced recurrent LSCC[28,29].

While therapeutic indications largely rely on pre-therapeutic staging, radiological staging of the neck after (C)RT is challenging because irradiation induces several morphological changes that render imaging interpretation more difficult. Microscopically, (C)RT induces the presence of atypical fibroblasts, swollen endothelial cells, and telangiectasia of thin-walled vessels. These changes manifest macroscopically and radiologically with the presence of tissue edema, fibrosis, and recurrent or chronic tissue inflammation, leading to possible erroneous interpretation of LN pathology[30-32]. In a study by our group, Sheppard *et al.* demonstrated a significant reduction of LN yield in NDs of previously irradiated patients[33].

Detection of neck recurrence after irradiation is radiologically challenging. There is no definite agreement on the imaging interpretation of pathological LNs in post-irradiated necks. Comparison of studies is therefore difficult, as most studies do not provide precise descriptions of the radiological criteria used for diagnosing LN metastases. Our criteria for MRI are in line with the methods described by Mundada *et al.* for detection of recurrence after treatment (66% with CRT) in the neck[22]. These authors showed an NPV > 90% and LN metastasis prevalence of 14.9%. The prevalence of LN metastasis in our cohort was also low at 9.7%. Mundada *et al.* found that the NPV of MRI with diffusion-weighted imaging was very high, independent of the disease prevalence[22]. The high NPV in our cohort may be explained by the low prevalence of the disease itself, as well as the accuracy of the imaging modality. As such, our findings and those of previous studies need to be interpreted cautiously.

For PET/CT, the criteria for defining a suspicious LN used by our nuclear physicians are SUVmax and morphological findings. Rosko *et al.* only reported an FDG uptake above background as a criterion for LN metastasis[18]. Therefore, a comparison with our PET/CT scoring criteria is not feasible. Rosko *et al.* showed an NPV of 76.7%, which is lower than our own NPV of 96.9% attained with the consideration of several radiological criteria. Gilbert *et al.* reported an NPV of 63% with PET/CT-staged neck, but did not report the radiological criteria used[34]. In all the above-mentioned studies, histopathological confirmation of the radiological diagnosis was considered the reference standard.

The reported rates of occult LN metastasis in recurrent HNSCC show considerable variation. In a recent meta-analysis, Finegersh *et al.* found an overall rate of occult nodal metastases of 15.4% in primary irradiated recurrent HNSCC, and a rate of 27.2% in recurrent supraglottic/transglottic LSCC[35]. This meta-analysis indicates that patients with hypopharyngeal, supraglottic, or transglottic primaries, locally advanced disease at the time of recurrence, and with pretreatment LN metastases are at high risk of presenting with occult neck node disease[35]. A review of the literature by Sanabria *et al.* found a substantially lower rate of occult metastases (ranging from 17.6%-19% in patients undergoing STL for recurrent LSCC) than in the above-mentioned recurrent supraglottic/transglottic LSCC[25]. A recent systematic review and meta-analysis by Lin *et al.* demonstrated occult nodal disease in 13.7% of radio-recurrent LSCC, without any statistically significant difference between supraglottic and glottic cancers (17.8% *vs.* 12%, $P = 0.18$)[27]. A similar rate of 11% occult neck node metastasis was shown in a systematic review and meta-analysis of elective ND during STL by Gross *et al.*[28].

The difference between the rates reported in the literature and our low prevalence of occult neck node metastases may be explained by the different imaging modalities used for re-staging. CT-scan was the predominant modality in the above-mentioned systematic reviews and meta-analyses, whereas only patients with MRI and/or PET/CT re-staging were included in our study. Given the superior performance of these two modalities, a lower rate of occult metastases is expected. Consequently, the prominent role of PET/CT in patients with curative options is widely recognized[36]. Nevertheless, a previous study by Rosko *et al.* showed that PET/CT had an inadequate sensitivity (16.7%) and NPV (76.7%) in neck node re-staging in a

cohort of patients with recurrent LSCC undergoing STL after (C)RT[18]. To our knowledge, a consensus regarding radiological scoring criteria for suspicious LN has not been published. Our results for PET/CT show an excellent NPV of 96.9%. The role of MRI in the re-staging of the neck in patients with recurrent LSCC seems largely underexplored in previous studies. Similar to PET/CT, our results showed MRI to have a very good NPV (94.1%). The rationale for both modalities is that PET/CT is a staging method for the neck as well as for distant metastases. Nevertheless, it provides limited additional information over other imaging techniques with regard to the primary tumor. MRI complements PET/CT for morphological characterization, and thus staging of the primary, and can equally help with neck staging given that the main downside of PET/CT in the irradiated neck is the high rate of false positives. We therefore recommend performing both imaging modalities before committing to a salvage procedure. In the future, the diagnostic yield of novel combined imaging modalities such as PET/MRI should be investigated in this field.

While ultrasound and fine needle aspiration (FNA) cytology have been routinely and consistently used for assessing lymph node status at our institution over the last decade, they are mostly used in the context of follow-up, not to confirm radiographically suspicious LNs in the neck. In the literature, assessment of nodal status with ultrasound of recurrent laryngeal cancer previously treated with (C)RT has not been evaluated by any study in the past 10 years. However, it is possible to confirm radiographically suspicious LN metastases with FNA. In the study of Fleischman *et al.*, specificity of up to 100% was found for FNA performed to confirm persistent head and neck SCC after CRT in neck LNs[37]. However, FNA harbors a non-negligible false negative rate of up to 33%[38], and LN metastases will be missed if ND is omitted.

Salvage total laryngectomy has a high adverse event rate compared with primary total laryngectomy, with this being reported to be up to 67.5% in a review by Hasan *et al.*[39]. Likewise, our cohort had a high early adverse event rate (grades I-V, Clavien-Dindo score) of 51.4%. Hasan *et al.* showed that concomitant ND is a risk factor for complications in STL[39]. Therefore, in radiologically staged cN0 necks, ND should be discussed in multidisciplinary team meetings and may be omitted to avoid postoperative complications.

There are several limitations to our present study, including the modest cohort size and the retrospective study design. Moreover, the low disease prevalence influences the application of Bayes' theorem and limits the results of our study. Furthermore, routine histopathological assessment of neck specimens, as performed in our patients, may overlook up to 15% of micrometastases, and the real number of occult metastases may be higher[40].

It should be noted that existing cohorts tend to be small, given the need to select a homogeneous population. Furthermore, although our findings suggest that occult neck nodal metastatic disease is uncommon in patients undergoing STL with negative nodal stage on MRI and/or PET/CT, they do not exclude the possibility that there may be a subset of patients at increased risk of harboring metastases. The small number of pN+ cases in our series precluded meaningful evaluation of such risk factors. By contrast, the widespread use of MRI and/or PET/CT likely facilitated a high degree of accuracy and consistency in preoperative staging of recurrence in the neck.

CONCLUSION

We found rates of occult neck node metastasis of 3.2%, 6.1%, and 3.8% in recurrent LSCC re-staged with PET/CT, MRI, and MRI + PET/CT together. High negative predictive values were found for both modalities. In cases in which preoperative MRI or PET/CT suggests nodal metastases, ND is clearly indicated. In contrast, in patients with a negative nodal stage on MRI and/or PET/CT, omitting the ND

might be an option that could be discussed with the patient. In such cases, the balance between a watchful surveillance *vs.* an ND with its potential adverse events and long-term sequelae should be individually weighed.

DECLARATIONS

Authors' contributions

Conception and design: Nisa L, Giger R

Data acquisition and analysis: Galli J, Nisa L

Manuscript drafting: Galli J, Giger R, Nisa L

All authors revised the final version, approved the submitted version and have agreed both to be personally accountable for the author's own contributions and do ensure that questions related to the accuracy or integrity of any part of the work, even ones in which each author was not personally involved, are appropriately investigated, resolved, and the resolution is documented in the literature.

Availability of data and materials

Anonymized version of the data is available upon reasonable request.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Our institutional and regional ethics committee (Cantonal Ethics Committee of Bern) granted approval to perform the present study. Patients' data were stored anonymously in a database only accessible to the principal investigators of this study.

Consent for publication

In line with the Declaration of Helsinki and the Swiss Ordinance on Human Research, all patients provided written consent for research and publication.

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