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ORIGINAL ARTICLE

Lymphoscintigraphy and radio-guided neck dissection in oral cavity squamous cell carcinoma

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Summary

Purpose: *The development of erratic distribution of cervical metastases from oral cavity squamous cell carcinoma (OSCC) bypassing the typical metastatic pattern can possibly challenge the role of the classic neck dissection. The purpose of this study was to assess the role of lymphoscintigraphy (LS) and radio-guided neck dissection as a simple and widely accessible method with a favorable cost/benefit ratio, able to improve the OSCC staging and possibly to tailor the surgical approach to cervical lymph node dissection.*

Methods: *From June 2015 to December 2018, 16 patients (5 women, 11 men, median age 59.5±12.5 years) with cN0 (10) and cN+ (6) OSCC were enrolled. The day before surgery all patients underwent LS with acquisition of planar and SPECT (Single Photon Emission Computed Tomography)/CT images, after a peritumoral injection of ^{99m}Tc-Nanocoll® (median 74±1.2 MBq). Patients underwent tumor excision and a radioguided neck dissection, using a portable gamma camera. The sentinel lymph nodes (SLNs) were isolated and separately analyzed in 200-micron sections and pancytokeratin immunohistochemistry assessment, looking for micrometastases. reverse transcription polymerase chain reaction (qRT-PCR).*

Results: *A homolateral lymphatic spread on LS was observed in all cases, whereas in 5 cases (31.3%) lymphatic drainage was contralateral to the OSCC site. In one cN0 patient, a skip micrometastasis has been identified in a SLN.*

Conclusion: *The results of the present study may suggest a role of LS and radioguided neck dissection in detecting the real lymphatic spread of OSCC, in order to improve the oncological assessment and to tailor the neck dissection.*

Key words: *radio-guided neck dissection, tumour, oral cavity, metastasis, lymphoscintigraphy*

Introduction

Oral cavity squamous cell carcinoma (OSCC) represents about 90% of all head and neck malignant tumours and the sixth most common cancer worldwide [1]. Regional node metastases at presentation are reported to be evident in about 30% of cases [2] and to have a significant influence on the overall prognosis [3,4], since the involvement of cervical nodes has been associated to a survival rate reduced by 50% [5,6]. Nevertheless, the risk of nodal involvement may vary according to the site of the primary tumour: cancers of the hard palate or the alveolar ridge rarely determine a neck involvement, while primaries of the anterior tongue are often associated to occult lymph node metastases in about 50-60% [2,7]. Moreover, skip metastases have been described to be not so infrequent in OSCC: the presence of skip metastasis to level III (with no metastases in levels I and II) has been identified in 10% of patients affected by oral and oropharyngeal squamous cell carcinomas [8];

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other authors assessed the presence of skip metastasis to level III or IV in 6% of patients with N0 and N1 OSCC [9]. Contralateral metastases to the primary lesion have been reported to vary between 0.9% and 36%, to determine about 5 years reduction of the survival rate and to be related especially to poorly differentiated tumours and to primaries with mouth floor invasion and midline crossing [10,11]. Small metastases in cervical lymph nodes (micrometastases) can be present at diagnosis and are difficult to detect even by the most modern diagnostic technologies [5]; the reported prevalence of occult nodes metastases in patients affected by OSCC without clinical suspect of nodal involvement is reported to be greater than 30% [5,12].

The purpose of this study was to use lymphoscintigraphy (LS) and an intraoperative gamma detection probe, as adjuvant tools in oncological neck dissection, in order to guide and identify the cervical nodes involved. LS can identify possible uncommon lymphatic drainage pathways, different from those node levels classically included in the selective neck dissection, and the intraoperative gamma probe scan may help the surgeon to perform a personalized therapeutic approach. This technique has already been reported for thyroid papillary carcinoma [13].

Methods

This was a prospective - observational study. A total of 17 patients with OSCC suitable for surgery were enrolled at our University from the 1st June 2015 to the 31st December 2018.

Written informed consent was collected from each patient included in the study prior to LS and surgery, according to Italian laws and in compliance to the Helsinki Declaration (2008). The study was approved by the Ethics Committee of our University Hospital (ref. no. 151099).

Inclusion criteria were: (1) patients with diagnosis of OSCC; (2) patients suitable for surgery. Exclusion criteria were: (1) history of previous head and neck tumors; (2) previous neck surgery or irradiation; (3) patients not suitable for surgery; (4) pregnant/lactating women. The main parameters collected were: sex, age, smoking and alcohol habits, oral cavity subsite, clinical TNM staging, 7th edition [14] until December 2017, 8th edition [15] since January 2018, lymphatic drainage type at LS, sentinel lymph node (SLN) and other possible SLN sites at LS, date and type of surgical procedures, SLN site(s) intraoperatively detected by gamma probe, radioactivity level of SLN(s), OSCC HPV and p16 status, pathologic TNM staging, micrometastases in SLN(s), adjuvant treatment (systemic therapy/radiotherapy), local, nodal or distant tumor relapse, follow-up period. In this paper the term "sentinel" lymph node(s) was used in order to indicate the most radioactive lymph node(s) (the node(s) with the highest absolute radioactivity or "hottest" lymph node(s)) detected by LS and by gamma probe during the surgical procedure.

The day before surgery all patients underwent LS with acquisition of planar and SPECT (Single Photon Emission Computed Tomography)/CT images (Siemens Symbia Intevo Excel), approximately 3 h after a peritumoral administration of ^{99m}Tc-albumin nanocolloid (Nanocoll®, GE Healthcare S.r.l. Milano, Italy) (median 74±1.2 MBq) with 4 superficial injections at cardinal points, where possible, or at least 2 superficial perilesional injections, with a low radiation risk, according to the most recent guidelines [16]. Images were acquired by a static planar image acquisition, obtained for a present time interval (variable from 3 to 10 min) during which a certain amount of gamma photons is collected. The tomographic acquisition was obtained collecting 48 images from detector 1 and 48 images from detector 2; each image (frame) lasted 7 s. CT was performed with a low voltage, to correct the attenuation and to have anatomical references, in particular for the localization of lymphatic compartments of the neck (Figure 1).

All patients underwent tumor excision and radioguided elective (for cN0 patients) or therapeutic (for cN+ patients) neck dissection, using intraoperatively a

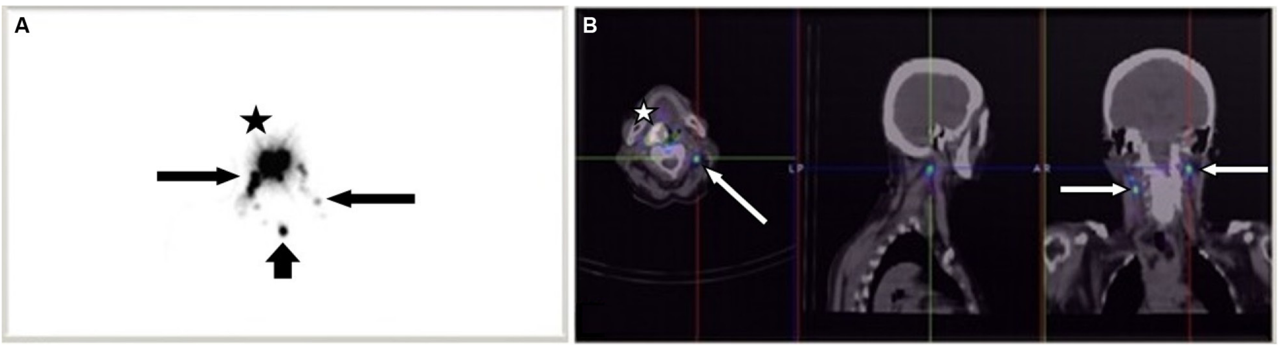

Figure 1. SPECT/CT acquisition features. **A:** Anterior planar image of tracer injection site around the tumour (asterisk), showing cervical lymphatic drainage ipsilateral and contralateral to the lesion (long and thin arrows) and central lymphatic drainage (short and thick arrow) in a 68-year-old female patient with tongue cancer. **B:** SPECT/CT showing axial, sagittal and coronal sections; the asterisk shows the site of tracer injection; the arrows show the cervical lymphatic drainage ipsilateral and contralateral to the lesion.

portable gamma camera (MR-100, Pol.hi-technologies, Carsoli, Italy) in order to scan all cervical node levels and to identify the location of SLN(s) [16]. After performing the neck dissection, the SLNs were isolated and resected. The *ex vivo* radioactivity of the SLNs was measured and the absence of radioactivity in the neck was confirmed. Every single SLN was separately analyzed by the pathologist in 10% neutral buffered formalin, according to the SLN biopsy technique (200-micron sections and pancytokeratin immunohistochemistry), searching for micrometastases. All other nodes from the neck dissection specimens were histologically analyzed with the traditional procedure (one slide in a half-sectioned node and stained with hematoxylin and eosin).

Table 1. Clinicopathological features of the studied population

Characteristics	*Patients, n (%)*
Sex	
Male	11 (68.8)
Female	5 (31.2)
Age, years (Mean±SD)	59.5±12.5
Tobacco	
Yes	9 (56.3)
No	4 (25)
Former	3 (18.7)
Alcohol	
Yes	4 (25)
No	11 (68.8)
Former	1 (6.2)
Tumour site	
Lower alveolar ridge	1 (6.2)
Upper alveolar ridge	2 (12.5)
Floor of the mouth	2 (12.5)
Anterior two-thirds of the tongue	
Lateral border	8 (50)
Undersurface	3 (18.8)
Clinical T classification	
T1	7 (43.8)
T2	4 (25)
T3	0 (0)
T4a	5 (31.2)
T4b	0 (0)
Clinical lymph node involvement	
N0	10 (62.5)
N1	2 (12.5)
N2	
N2a	0 (0)
N2b	3 (18.8)
N2c	1 (6.2)
N3	
N3a	0 (0)
N3b	0 (0)
N4	0 (0)
HPV and p16 status	
HPV negative and p16 negative	14 (87.6)
HPV negative and p16 positive	1 (6.2)
HPV positive and p16 negative	0 (0)
HPV positive and p16 positive	1 (6.2)

Statistics

Statistical analysis of the data was performed through descriptive tests using the SPSS statistical software (SPSS for Windows Inc, Chicago, IL, USA).

Results

A total of 17 patients were enrolled in the study and underwent LS, but 1 patient has been excluded as the radiocolloid dropped out during the injections. Sixteen patients with OSCC underwent tumor excision and radio-guided neck dissection (RGND) at our University hospital from the 1st June 2015 to the 31st December 2018. The main features of the studied population are presented in Table 1. All tumors were well lateralized, except one patient (case 10) with a cT2 of the anterior floor of the mouth. Eleven patients had a cT1-2 OSCC, while 5 had cT4a OSCC. Ten patients were clinically classified as cN0 and 6 as cN+. A homolateral lymphatic spread on LS was observed in all cases, but 5 cases (31.3%) showed also a contralateral lymphatic drainage, contralateral to the OSCC site (Table 2). Eleven patients underwent homolateral neck dissection, while 5 patients bilateral neck dissection. Metastases were not histologically documented in any SLN harvested contra-laterally. In 1 (6.25%) cN0 patient (case 8), a micrometastasis has been identified in a SLN, allowing a nodal staging to pN1(mi) (Figure 2). No other node metastases were found in the neck dissection specimens in all patients with histologically negative SLNs, except in 2 patients (case 3 and 16), that presented a locally advanced oral tumor (both cT4a). All nodal metastases were found only in SLNs except for 2 patients. Case 16 was classified as Mx because of a pulmonary suspected lesion, which has been controlled up to now with a radiological follow-up and has appeared to be stable in dimensions.

9/16 patients received adjuvant treatment (radiotherapy or chemoradiotherapy).

At the follow-up (mean 16.38±10.82 months), only one patient (case 5) had a loco-regional recurrence 6 months after the end of the adjuvant treatment.

Table 2. Oncologic classification and sentinel lymph node (SLN) site and status

No.	*Sex*	*Age*	*Tumor site*	*cTNM*	*SLN in atypical site at LS*	*SLN intraoperatively harvested*	*SLN histological status*	*pTNM*
1	M	78	Left lateral border of the tongue	cT1 N0 M0	1 right level IV	1 right level IV	Negative	pT1 N0 cM0
2	F	66	Left upper alveolar ridge	cT1 N0 M	1 right level IIA	1 left level IIB and 1 left level IIA	Both negative	pT1 N0 cM0
3	M	64	Left undersurface of the tongue and floor of the mouth	cT4a N2b M0	None	1 left level IIA	Negative	pT4a N1 cM0
4	M	65	Left anterior floor of the mouth	cT1 N0 M0	None	1 left level IB	Negative	pT1 N0 cM0
5	F	49	Right lateral border of the tongue	cT1 N0 M0	None	1 right level IIA and 1 right level III	Metastasis in right SLN level IIA; negative the right SLN level III	pT1 N2b cM0
6	M	31	Right undersurface of the tongue	cT2 N0 M0	None	1 right level IIA	Negative	pT1 N0 M0
7	M	75	Left lateral border of the tongue	cT2 N0 M0	None	1 left level IIA and 1 left level III	Metastasis in left SLN level IIA; negative the left SLN level III	pT4a N2b M0
8	F	53	Right anterior undersurface of the tongue	cT1 N0 M0	1 left level IV and 1 left level II	1 right level III and 1 right level IV	Negative the right SLN level III; micrometastasis in right SLN level IV	pT4a N1(mi) M0
9	M	67	Right mid-posterior lateral border of the tongue	cT4a N2b M0	None	1 right level III	Negative	pT3 N0 M0
10	M	44	Anterior floor of the mouth	cT2 N2c M0	None	1 right level III	Negative	pT2 N0 M0
11	M	72	Left upper alveolar ridge	cT4a N1 M0	None	1 left IB level and 1 left III level	Both negative	pT4a N0 M0
12	F	58	Right posterior lateral border of the tongue	cT1 N0 M0	None	2 right level IIA, 1 right level III	Both negative the right SLNs level IIA; metastasis in right SLN level III	pT2 N1 M0
13	F	71	Left lower alveolar ridge	cT4a N0 M0	None	1 left level III	Negative	pT4a N0 M0
14	M	43	Left lateral border of the tongue	cT2 N1 M0	1 right level IB	1 left level IIA and 1 right level IB	Both negative	pT2 N0 M0
15	M	57	Left lateral border of the tongue	cT1 N0 M0	None	1 left level III	Negative	pT1 N0 M0
16	M	59	Right posterior lateral border of the tongue	cT4a N2c Mx	1 left level IIA	1 right level IB	Negative	pT4a N2b Mx

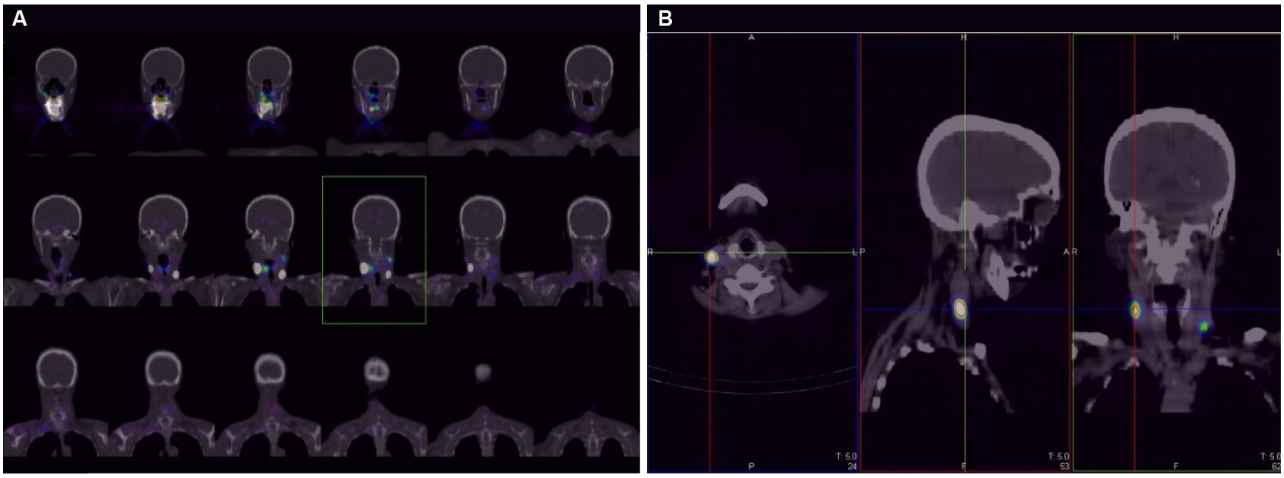

Figure 2. A: Coronal SPECT/CT images of 53-year-old female patient (case 8 of the present sample) with OSCC of the right anterior undersurface of the tongue showing an ipsilateral (level III) and 2 contralateral (level IV and level II) SLNs. **B:** Axial, sagittal and coranal SPECT/CT sections focusing on the right SLN (level III).

Discussion

Despite the improvement of the multimodal therapy in the last decades, surgery still represents the primary treatment strategy [1] and especially neck treatment plays a central role in the overall management of OSCC. Traditionally, a therapeutic radical or modified radical neck dissection represent the treatment of choice in case of clinically detectable node metastases (cN+) [17,18]. More recently, several authors assessed the appropriateness of a selective neck dissection in certain patients with early neck disease (cN1-2), since it could reduce morbidity with the same regional control and survival rates [19-22].

The selective neck dissection aims to remove only the lymph node levels draining the site of the primaries. In 1990, Shah proposed the pattern of nodal metastases for each primary head and neck squamous cell carcinoma, establishing the first draining cluster of lymph nodes and defining the lymph node levels boundaries of the neck [23]. For oral cavity, the first draining nodal cluster was identified in levels I-III [23]. An elective/selective neck dissection performed according to the site and to the infiltration of the primary tumor, represents a standardized procedure recommended in a clinically negative neck (cN0) with an occult metastasis risk exceeding 20% [1,24-26]. A superselective neck dissection, characterized by the removal of only two contiguous node levels has been proposed as an elective treatment for selected cN0 cases [27].

The optimal surgical treatment for N0 and for some N+ OSCC is still an open issue [1,2,28-32]. Since errors in the pathological staging of the nodal status could occur with the classic selective neck dissection procedure, both for the possible involvement of lymph nodes in atypical levels (such as in level IV, reported in about 1.5-5% of the patients), and for the standard histopathological processing technique (not sensible to detect micrometastases [33]), the use of LS with an intraoperatively gamma probe could represent a reliable procedure, especially in cN0 patients, in order to tailor the neck dissection improving nodal staging. We have also detected a skip micrometastasis in the SLN in the homolateral level IV in a cN0 patient (case 8) with squamous cell carcinoma of the tongue (right anterior ventral surface); only levels I to III would have been included in a classical selective neck dissection. LS and the RGND allowed a complete patient staging, also including the pathological nodal status pN1(mi).

The RGND could be proposed in cN0 and also in cN+ patients, since LS, SPECT/CT images and the intraoperative use of the gamma probe may add detailed information also in these cases. We noticed a contralateral lymphatic drainage at LS in about 31% of the sample. The use of this technique could allow to detect skip metastases, therefore achieving a drastic improvement of patient prognosis, considering the high mortality after neck recurrences [34,35].

Major drawbacks of this technique are: (i) a possible “shadow effect” of the radioactive signal interference originating from a close injection site which may interfere with the SLN location, such as for mouth floor tumors, where the distance between the primary site and the SLN in the submandibular level is slight [36,37]; (ii) clinically positive necks [16], due to the distortion of the normal lymphatic architecture, and due to the presence of metastatic nodes may lead to a high risk to identify false SLNs. In the procedure proposed in this paper, we used LS also in cN+ patients, since it could help highlight atypical drainage and atypical SLN(s), possibly involved by micrometastases. Another possible limitation is represented by (iii) advanced primary tumours (T3-4), since performing peritumoral injections around a larger tumour may be more difficult and be associated to higher failure rate in SLN identification [38]. Finally, another drawback of this study is also (iv) the limited number of patients involved.

Conclusion

Since there are still neither universally accepted guidelines about the optimal neck treatment of cN0 OSCC nor about the contralateral neck dissection in cN+ OSCC, LS and RGND could be considered as simple and widely accessible adjuvant methods to the neck dissection with a favorable cost/benefit ratio, able to improve OSCC staging and to implement a tailored surgical approach to cervical lymph node dissection and a more accurate cancer staging.

In the present sample, LS and RGND could identify (i) a non-negligible percentage of atypical lymphatic drainage in patients affected by OSCC (31.3%), and (ii) also a micrometastasis, therefore allowing to improve patients staging.

In our opinion, implementing this procedure may determine a reduction of "skip" metastases occurrence in cN0 patients and contralateral late metastasis in cN+ patients. RGND could represent a cost/effective procedure in the identification of skip metastases and micrometastases, without significant increase of morbidity, hospital stay or health costs. Also, considering the very low dose of radiation of the radiocolloid, there are no risks for patients' health.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of our University Hospital, ref. no. 151099) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interests

The authors declare no conflict of interests.

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