Oral Oncology 45 (2009) 492–495

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

^{99m}Tc(V)-dimercaptosuccinic acid scintigraphy in detecting neck metastases in oral squamous cell carcinoma with clinically negative necks

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ARTICLE INFO

Article history:
Received 13 March 2008
Received in revised form 20 June 2008
Accepted 24 June 2008
Available online 11 October 2008

Keywords:
Radioautography
Dimercaptosuccinic acid
Technetium squamous cell carcinoma
Lymph node

SUMMARY

This study compares the accuracy of ^{99m}Tc(V)-dimercaptosuccinic acid (^{99m}Tc(V)-DMSA) Single Photon Emission Computer Tomography (SPECT) by intravenous or local injection in the detection of occult cervical lymph node metastases in clinically N0 squamous cell carcinoma of the oral cavity. Fifty-eight previously untreated patients without clinically detectable cervical metastases were included in the study and were divided into two groups. Twenty-eight patients were in the intravenous injection group and 30 patients were in the local injection (around primary tumors) group. Both groups received ^{99m}Tc(V)-DMSA, and ^{99m}Tc(V)-DMSA SPECT was performed on all patients. All isolated lymph nodes in neck dissection specimens were stained using H & E. The sensitivity, specificity, and accuracy for intravenous injection of ^{99m}Tc(V)-DMSA was 62.5%, 95.0%, and 85.7%, respective, and 84.6%, 82.4%, and 83.3%, respectively, for local injection. SPECT scan of ^{99m}Tc(V)-DMSA injected around the tumor is a simple and efficient approach to detecting metastatic lymph nodes in clinically N0 patients with oral cancer.

Introduction

Neck dissection is generally performed when patients with oral carcinoma present with clinically positive necks. In the case of occult cervical lymph node metastases, however, treatment of the neck is controversial because of the difficulty in diagnosis by palpation and various imaging procedures, such as CT, MRI, or ultrasonography.[1] Although pathological biopsy of sentinel lymph nodes can solve this clinical problem, it is complicated by the possibility of misdiagnosis and emission, as well as by radioactive contamination and prolonged operation times.[2–6]

Dimercaptosuccinic acid (DMSA), similar to PO_4^{3-} in structure and property, is involved in the metabolism of phosphoric acid and phospholipids, high levels of which characterize strong cancer cell to proliferation.[7,8] ^{99m}Tc(V)-DMSA was routinely intravenously injected into patients and accumulated at the primary foci and metastatic lymph nodes in the neck. Watkinson showed that metastatic lymph nodes in the neck were too small to be detected by ^{99m}Tc(V)-DMSA SPECT, and the sensitivity and accuracy was less than that of CT.[9] According to the injection method of sentinel lymph node biopsy (SLNB), we injected ^{99m}Tc(V)-DMSA around the primary tumor and assumed that ^{99m}Tc(V)-DMSA might drain to the lymph nodes via lymphatic vessels, remain in the suspected lymph nodes, and be imaged by SPECT; this method is different from the currently used sentinel biopsy mechanism. The purpose of this study was to compare two methods of applying DMSA, namely intravenous and local injection, with regards to feasibility and accuracy in detecting neck lymph metastases.

Patients and methods

Patients

A total of 58 patients with oral squamous cell carcinoma were enrolled from June 2002 to January 2006. All patients were diagnosed as having negative necks by physical and radiological examination. The intravenous injection group had 28 patients (males = 18, females = 10). Ages ranged from 28 to 77 years, with a mean age of 57.1 years. The local injection group had 30 patients (male = 19, females = 11). Ages ranged from 24 to 76 years, with a mean age of 56.4 years. Primary sites and TNM stages are shown in Table 1.

Labeling and imaging

555 MBq (15 mCi) of ^{99m}Tc(V)-DMSA were injected in the intravenous group, while the local injection group received 37 MBq (1 mCi) of ^{99m}Tc(V)-DMSA at four different sites into the perimeter of the tumor and the contra-lateral sites. SPECT scan was performed with the use of a Vertex dual-head gamma camera (AOAC Laboratories, Milpitas, CA) 4 h after injection of ^{99m}Tc(V)-DMSA in the intravenous group and 2 h after injection of ^{99m}Tc(V)-DMSA in the local group. Radiochemical purity was higher than 95%.

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doi:10.1016/j.oraloncology.2008.06.008

Table 1
Tumor primary location and TNM stage

		Intravenous group	Local group
Primary site	Tongue	11	13
	Gingival	7	7
	Oral floor	6	4
	Mandible	1	1
	Maxillary sinus	1	0
	Buccal mucosa	1	2
	Oropharynx	1	3
	Total	28	30
TNM stage	T1N0M0	5	1
	T2N0M0	12	17
	T3N0M0	5	6
	T4N0M0	6	6
	Total	28	30

Acquisition was based on 360° noncircular rotation with 6° step angles, 60 s per frame, a 128 × 128 matrix, and a zoom factor of 1.33 (pixel size, 5 mm). Images were reconstructed with a Butterworth filter (order 5, cutoff 0.35, 1-pixel images) obtained in the sagittal, coronal, and transverse planes.

Image analysis

SPECT images of the head and neck were examined by two experienced nuclear medicine physicians and by the study authors. Coronal SPECT images of the two groups were analyzed quantitatively by drawing regions of interest (ROI) over the area of increased uptake corresponding to the suspect metastatic lymph node and the contra-lateral normal area, or the adjacent normal region (for bilateral metastases). Radioactive intussusception ROI values were recorded. Abnormal accumulation of nuclide in the neck was regarded as lymph node positive, and these results were compared with the pathological examination.

A ^{99m}Tc(V)-DMSA SPECT scan was performed on all patients before operation. Neck dissection at levels I–III and I–V was carried out in all patients. Five patients with a midline tumor underwent bilateral neck dissection, resulting in dissection of 63 neck sites (Table 2). All isolated lymph nodes in neck specimens were examined by hematoxylin–eosin staining. Suspected enlarged nodes (more than 1 cm in diameter) were analyzed in serial section with 500 μm intervals to identify possible metastases. 1627 nodes were revealed pathologically, of which 51 were malignant (Table 3).

Statistical method

The radioactive intussusception value of the ROI was analyzed statistically using paired two-tailed *t*-tests (SPSS for WINDOWS software, version 10.0).

Table 2
Number of neck dissections

	Intravenous group	Local group
Levels I–III	16	18
Levels I–V	15	14
Total	31	32

Table 3
Number of lymph nodes

	Lymph nodes	Metastatic lymph nodes
Intravenous group	822	27
Local group	805	24
Total	1627	51

Results

Intravenous injection group

Of the eight cases with pathologically diagnosed neck lymph node metastases in the intravenous injection group, five cases were positively screened by SPECT. Statistical analysis indicated that there was a significant difference in radioactivity between the normal and isotope-hot areas (paired *t*-test, $t = 8.182$, $p = 0.00004$). In 20 cases with pathologically negative lymph nodes, 19 cases were found to be negative by ^{99m}Tc(V)-DMSA SPECT. The sensitivity, specificity, and accuracy for intravenous administration of ^{99m}Tc(V)-DMSA were 62.5% (5/8), 95.0% (19/20), and 85.7% (24/28), respectively.

Local administration group

In the local administration group, 11 of 13 cases with pathologically diagnosed lymph node metastases were positively detected by SPECT, whereas 14 of 17 cases without pathologically diagnosed lymph node metastases cases were negatively diagnosed by SPECT. Statistical analysis showed a significant difference in radioactivity between the normal and isotope-hot areas (paired *t*-test, t = 18.71, $p = 0.0000$). The sensitivity, specificity, and accuracy for intravenous administration of ^{99m}Tc(V)-DMSA were 84.6% (11/13), 82.4% (14/17), and 83.3% (25/30), respectively.

Intravenous administration of ^{99m}Tc(V)-DMSA could detect the smallest 1 cm-in-diameter lymph nodes, while local administration reached the minimum 0.5 cm nodes. The suspected lymph nodes (more than 1 cm in diameter) of one false positive case in the intravenous administration group and three false positive cases in the local administration group were pathologically negative by serial section with 500-μm intervals and HE staining, which microscopically exhibited lymph reactive proliferation.

Discussion

A negative neck has several different meanings. The neck may negative to physical examination (palpation), to radiological evaluation, or to pathological interpretation. A clinically negative neck (cN0) means no clinical or radiological signs of neck metastases. Staging by palpation has been demonstrated to be inaccurate, while various imaging procedures have limits. Van den Brekel's comparative study showed that the accuracy of CT, MRI, and ultrasound-guided fine needle aspiration cytology was 66%, 75%, and 86%, respectively.[1]

It was reported that the risk of cervical nodal metastases in N0 patients with oral cancer was between 12% and 50%, with a medium value of 33%.[10–13] Remarkably, it is inappropriate for more than 50% patients with no lymph node metastases to receive neck dissection. Controversy continues regarding cN0 neck management. Some surgeons treat cN0 patients with a "wait-and-see" policy.[14]

Some studies stated that patients with T1-2 N0 tumors received definitive chemoradiation as an alternative to surgery, and achieved cure rates as high as 80%. Conversely, in the case of positive lymph nodes, surgery followed by radiotherapy or chemoradiation would be the treatment of choice.[15] However, the majority of T1 and T2 tumors of the oral cavity are treated with initial surgical resection because of radiation complications such as xerostomia, dysphagia, caries, and osteoradionecrosis.[16,17]

Since Cabanas described the penile cancer sentinel lymph node (SLN) concept, it has been applied to and proven in the management of breast cancer and melanoma.[18,19] Identifying and analyzing the SLN may aid in the selection of patients who will benefit

from further surgical treatment of the neck. The SLN biopsy is a good and novel approach to clarifying cervical lymph node metastases. At the Second International Conference on Sentinel Node Biopsy, 366 (97%) of 379 patients with cN0 disease were reportedly identified for SLN, among which 103 (29%) cases were positive for lymph node metastases. The sensitivity was between 80% and 100%, with a medium value of 90.3%.[4]

Neck SLN biopsy sheds light on determination of the operation mode and in some sense improves clinical treatment for patients with cN0 carcinoma; however, some problems still exist. First, the head and neck region has approximately 300 lymph nodes, which challenges SLN localization. Therefore, dissection of selected lymph nodes will not necessarily reflect all head and neck lymph nodes.[2] Second, using isotope labeling to detect and dissect the SLN is difficult because the primary tumor site of head and neck carcinomas is close to the initial lymph nodes, which are easily metastasized.[2] Third, radioactive contamination should be emphasized, despite the short half life time of ^{99m}Tc and weak penetration of the γ-rays released from ^{99m}Tc. Fourth, this approach can not directly detect lymph node metastases, and pathological diagnosis would prolong operation times.[4,20] For these reasons, neck SLN biopsy can not be easily or widely used in clinics.

^{99m}Tc(V)-DMSA is widely used in detecting lung cancer, liver cancer, breast cancer, and osteosarcoma because of its high affiliation to tumor cells. In the present study, ^{99m}Tc(V)-DMSA was locally injected quadruply around oral carcinoma and SPECT was performed 2 h later. Radioactive ^{99m}Tc(V)-DMSA accumulation indicated risk of lymph node metastases. Local isotope administration might compensate for the weakness of SLN biopsy, as above. Sensitivity was 84.6% higher than that of intravenous administration (62.5%), and consistent with the SLNB.[2–6] Blue dye or a radiotracer, such as sulfur colloid, used in SLNB remained in lymph nodes nonspecifically, while ^{99m}Tc(V)-DMSA remained in metastatic lymph nodes only selectively. Local injection of ^{99m}Tc(V)-DMSA can be used in clinical practice to determine lymph node metastases.

The minimum lymph node diameter detected using intravenous administration was 1 cm. The maximum lymph node diameters were 1.2 cm, 1.1 cm, and 0.5 cm, respectively, for three false negative cases. In contrast, the minimum lymph node diameter detected using local administration was 0.5 cm, and the longest lymph nodes diameters were less than 0.5 cm for two false negative cases. Radioactive reagents enter lymph nodes via blood. It was easy to determine large lymph nodes with metastases, but difficult to determine small, positive nodes. We speculated that radioactive substances enter lymph nodes through lymphoducts at amounts large enough to be detected by SPECT; this was the case even for small nodes using local administration.

Our method largely met the challenge of confirming local lymph node metastases of oral carcinoma, but mapping metastases distribution was difficult due to the low resolution of nuclide images. It has been documented that oral squamous carcinoma generally metastasizes to levels I, II and III, but rarely to levels IV and V, which is the theoretic basis for supraomohyoid neck dissection.[2,13] Therefore, it is more important and significant to identify metastatic lymph nodes than to localize them.

Although the SPECT resolution is lower than those of CTs and MRIs, it could be employed to discriminate between the upper, middle, and lower regions of the neck. Figure 1 indicates left oropharyngeal carcinoma with bilateral lymph node metastases in the submandibular region, and Figure 2 shows that a patient with left tongue carcinoma was accompanied with lymph node metastases in upper region of the neck.

Hamakawa[21] thought that the minimum axial length of lymphatic metastases was 1.36 ± 0.85 mm and consecutive sections within 1 mm intervals can omit less than 1 mm metastases. However, appropriate intervals for semiserial sectioning within 500 μm intervals can equal complete serial sections. In both venous and local administration groups, the enlarged lymph nodes (more than 1 cm in diameter) of four false positive cases were analyzed in serial sectioning at 500 μm intervals; no metastatic cancer cells were found, but lymph reactive proliferation was apparent. Until now, it is believed that DMSA, similar to PO_4^{3-} in structure and property, was involved in the metabolism of phosphoric acid and phospholipids, high levels of which characterize strong cancer cell proliferation. Further investigation is required to determine whether strong metabolism of fatty acids occur in lymph nodes with reactive proliferation.

Figure 1 Left oropharyngeal carcinoma, bilateral cervical lymph node metastases in submandibular region.

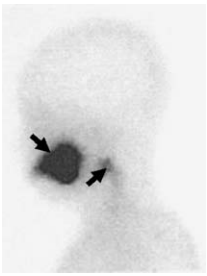

Figure 2 Left tongue carcinoma, ipsilateral upper neck lymph node metastases.

This study was limited by a relatively small number of patients; therefore, these results should be confirmed by further intensive investigation.

Conflict of Interest Statement

None declared.

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