An innovative multimodality approach for sentinel node mapping and biopsy in head and neck malignancies

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RÉSUMEN

Objetivo: Se ha evaluado innovaciones recientes como la SPECT/TAC, dispositivos portátiles de imagen intraoperatorios y un trazador híbrido en el contexto de un abordaje multimodalidad para el mapeo y biopsia del ganglio centinela (GC) en tumores de cabeza y cuello. Material y métodos: Se evaluaron 25 pacientes consecutivos con tumores de cabeza y cuello (16 melanomas y 9 carcinomas de células escamosas). Se inyectaron peritumoralmente con el trazador híbrido ICG-99mTc-nanocolloide. Los GC se identificaron inicialmente mediante imágenes plana y a las 2 horas postinyección del trazador se realizó una SPECT/TAC. Intraoperatoriamente se utilizó una gammacámara portátil en combinación con una cámara infrarroja de fluorescencia y una sonda detectora de rayos gamma para localizar los GC. Resultados: En todos los casos las imágenes plana, la SPECT/TAC, y en un caso con la gammacámara portátil, se lograron identificar un total de 67 GC (55 con las imágenes plana, 11 adicionales con la SPECT/TAC y uno con la gammacámara portátil), Además de los 67 previamente definidos, se identificaron y extrajeron 22 GC adicionales intraoperatoriamente de los cuales 12 se encontraban cerca del punto de inyección en zonas como las regiones periauricular y submandibular. Los 10 restantes se encontraron mediante control radiográfico del lecho ganglionar postextracción. Conclusión: En nuestra serie se encontraron un 26% de GC adicionales. Este abordaje multimodalidad parece ser útil en tumores en los que el drenaje linfático es muy próximo al sitio de inyección como en la región periauricular y en cavidad oral.

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Técnica multimodalidad innovadora en el abordaje de la biopsia selectiva del ganglio centinela en tumores de cabeza y cuello

ABSTRACT

Purpose: Recent innovations such as preoperative SPECT/CT, intraoperative imaging using portable devices and a hybrid tracer were evaluated in a multimodality approach for sentinel node (SN) mapping and biopsy in head and neck malignancies. Material and methods: The evaluation included 25 consecutive patients with head and neck malignancies (16 melanomas and 9 oral cavity squamous cell carcinomas). Patients were peritumorally injected with the hybrid tracer ICG-99mTc-nanocolloid. SNs were initially identified with lymphoscintigraphy followed by single photon emission computed tomography (SPECT/CT) 2 hours after tracer administration. During surgery a portable gamma camera in combination with a near-infrared fluorescence camera was used in addition to a handheld gamma ray detection probe to locate the SNs. Results: In all patients the use of conventional lymphoscintigraphy, SPECT/CT and the additional help of the portable gamma camera in one case were able to depict a total of 67 SNs (55 of them visualized on planar images, 11 additional on SPECT/CT and 1 additional with the portable gamma camera). A total of 67 of the preoperatively defined SNs together with 22 additional SNs were removed intraoperatively; 12 out of the 22 additional SNs found during operation were located in the vicinity of the injection site in anatomical areas such as the periauricular or submental regions. The other 10 additional SNs were found by radioguided post-resection control of the excision SN site.

Keywords:
Multimodality approach
Sentinel node
Head and Neck
SPECT/TAC
Melanoma
Squamous cell Carcinoma

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Conclusion: In the present series 26% additional SNs were found using the multimodal approach, that incorporates SPECT/CT and intraoperative imaging to the conventional procedure. This approach appears to be useful in malignancies located close to the area of lymphatic drainage such as the periauricular area and the oral cavity.

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Introduction

Sentinel node biopsy (SNB) in the head and neck area is usually more challenging than in other areas, because of its complex anatomy, the presence of numerous vital structures and the variable drainage patterns in this region.

Previous studies suggest that malignant head and neck tumours such as melanoma and squamous cell carcinoma (SCC) of the oral cavity can obtain important benefit of the SNB. Even in the era of emerging tumour-imaging modalities, such as positron emission tomography (PET), SNB is considered the most reliable method for identifying micro-metastatic disease in regional lymph nodes. Preliminary information suggests that there is a survival benefit if a node dissection is done at an early stage and has proven to provide relevant prognostic information and is widely performed to accurately stage melanoma patients. In SCC of the oral cavity, the use of SNB may avoid an unnecessary elective neck dissection in 70-80% of the cases. Positive sentinel nodes (SNs) have shown to be a negative prognostic factor in oral cancer and several authors have published good results regarding staging accuracy of the SNB in this group of patients.

The contribution of nuclear medicine to the SN procedure has been based on lymphoscintigraphy for preoperative lymphatic mapping and the use of a handheld gamma ray probe for intraoperative SN detection. However, the head and neck is an area of complex anatomy, so SNs in this region can be difficult to localize with conventional planar lymphoscintigraphy because it is not possible to visualize the three-dimensional structures of the head, doesn’t help us with the description of unexpected drainage patterns, and is not unusual to find SNs very close to the injection site that can be missed on this images. A few years ago SPECT/CT was introduced to anatomically localize SNs. Also it is well known that with the help of SPECT/CT more SNs can be identified compared to conventional scintigraphy.

Intraoperative SN detection with the handheld gamma ray probe can be complicated as well. More than 95% of the administered radioactivity stays behind at the injection site and may cause nearby SNs to be missed, no overview can be provided, so certainty about removal of all radioactive nodes cannot be confirmed. In the last years with the availability of portable gamma cameras, an overview of all radioactive hotspots in the surgical field is possible. Its position can be easily adjusted and approximated to a millimetric distance from the injection site to check if there are SNs close to this area. Differentiation between SNs and second echelon nodes is facilitated because of the camera’s capability of radioactivity quantification and also pre-surgical scintigraphic images can be compared with later ones during the intervention.

A third innovation in the SN procedure has been the introduction of the hybrid tracer ICG (99mTc-nanocolloid); in this tracer ICG adopts the lymphatic migration properties of the radiocolloid, resulting in a significantly longer retention time in the SNs as compared to ICG alone. Also ICG is not visible by the naked eye and as such does not interfere with the visual identification of tumour borders. With this hybrid tracer being both radioactive and fluorescent, preoperative surgical planning can be combined with intraoperative radio and fluorescence guidance towards the SNs. The fluorescent properties of the hybrid tracer extend the radioguided procedure by providing real-time optical localization using a handheld near-infrared (NIR) fluorescence camera.

The main purpose of the present study was to evaluate a protocol of SN detection including these recent innovations in a multimodality approach for SN mapping and biopsy in patients with head and neck malignancies.

Patients and methods

Patients

The evaluation included 25 consecutive patients. Sixteen patients with melanoma of the head and neck with a Breslow-thickness of at least 1 mm or Clark level IV (Table 1) and nine patients with oral cavity squamous cell carcinoma (SCC) with T1/2 tumours (Table 2). For both melanoma and oral cavity cancer lymphatic mapping is a routine procedure at our institute and informed consent was obtained in all patients. Ultrasound of the neck and parotid region was routinely carried out and was combined with fine needle aspiration cytology in case of a suspicious node.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>58 (41–77)</td>
</tr>
<tr>
<td>Genre, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Melanoma site, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Scalp</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Ear</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Breslow thickness, mm</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean</td>
<td>2.7</td>
</tr>
<tr>
<td>Range</td>
<td>1.0–6.0</td>
</tr>
</tbody>
</table>

The evaluation included 25 consecutive patients. Sixteen patients with melanoma of the head and neck with a Breslow-thickness of at least 1 mm or Clark level IV (Table 1) and nine patients with oral cavity squamous cell carcinoma (SCC) with T1/2 tumours (Table 2). For both melanoma and oral cavity cancer lymphatic mapping is a routine procedure at our institute and informed consent was obtained in all patients. Ultrasound of the neck and parotid region was routinely carried out and was combined with fine needle aspiration cytology in case of a suspicious node.

Preoperative imaging

After the preparation of 99mTc-Nanocolloid (GE Healthcare, Eindhoven, The Netherlands), hybrid ICG-99mTc-nanocolloid was used forming a dose of 0.25 mg of ICG (ICG-Pulsion, Pulsion Medical Systems, Munich, Germany) as previously described.

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>60 (52–71)</td>
</tr>
<tr>
<td>Genre, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Tumor site, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Tongue R</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Tongue L</td>
<td>2 (22)</td>
</tr>
<tr>
<td>FOM midline</td>
<td>3 (33)</td>
</tr>
<tr>
<td>FOM R</td>
<td>1 (12)</td>
</tr>
<tr>
<td>TMN, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>6 (67)</td>
</tr>
<tr>
<td>T2</td>
<td>3 (33)</td>
</tr>
</tbody>
</table>

FOM Floor of the mouth, R right, L left.
A median of 85 MBq (range 66-158 MBq) ICG-99mTc- nanocolloid was injected in three or four deposits around the primary tumour (total volume 0.4 ml). We think it is important to mention that the use of this hybrid tracer adds a cost of approximately 20 euros more per patient.

For lymphatic duct(s) visualization and its subsequent SN(s), anterior and lateral dynamic images were obtained during the first 10 min after the injection using a dual-head gamma camera (Symbia T, Siemens, Erlangen, Germany). Static planar images were acquired 15 min and 2 h post-injection. The latter was immediately followed by SPECT/CT (Symbia T, Siemens, Erlangen, Germany). SPECT and CT images were obtained on the basis of 2-mm slices. After tissue attenuation correction for the SPECT, fused SPECT/CT images were generated. SPECT (Table 3), CT and fused SPECT/CT were simultaneously evaluated using orthogonal multiplanar reconstruction. In addition, three-dimensional display using volume rendering was performed in order to improve anatomical neck level recognition.

SNs were defined as the lymph nodes on a direct lymphatic drainage pathway from the primary tumour17. All lymph nodes draining from the site of the primary tumour through an afferent lymphatic vessel or a single radioactive lymph node in a lymph node basin were considered as SNs18. Also lymph nodes appearing between the injection site and the first draining node, or nodes with increasing uptake appearing in other lymph node stations were considered as highly probable SNs. Skin marking of the SN(s) node was performed prior to surgery as a reference for aiming the portable gamma camera laser and gamma ray detection probe for incision planning.

Surgical procedure

SNB started 3–24 hours after ICG-99mTc-nanocolloid administration. In the operating room, a portable gamma camera (Sentinella equipped with Sentinella suite software version 7.5; Oncovision, Valencia, Spain) was used to acquire a pre-incision overview image and to determine the location for the incision(s)19. Initial SN exploration was guided by a handheld gamma ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany). Fluorescence imaging with a dedicated handheld NIR fluorescence camera (PhotoDynamic Eye, Hamamatsu Photonics, Hamamatsu, Japan) was used to optically detect the SNs. After excision of the SN(s), the portable gamma camera was used to control for remaining radioactive hot spots in the SN excision area as was previously described by Vermeeren et al.19. Second echelon nodes (defined by preoperative lymphoscintigraphy and SPECT/CT) were not removed. Additional resected nodes were evaluated concerning amount of radioactivity in correlation to nearby SNs, their location in relation to the primary tumour and other SNs. Macroscopic aspects valued by the surgeon such as size and consistency were also considered.

Analysis

All the tools used in the multimodality approach mentioned above, were analyzed separately and as a group to assess their contribution to the SN mapping in head and neck malignancies. Primary outcome characteristics were preoperative detection of the SN(s) and its anatomical localization by SPECT/CT. It was evaluated whether SPECT/CT detected more SNs than conventional scintigraphic imaging and if better localization information was provided. During the surgical procedure information was gathered evaluating the contribution of innovative intraoperative imaging tools to the routine radioguided procedure with the handheld gamma ray detection probe.

Histological examination

SNs were fixed in formalin, bisected, embedded in paraffin, cut at a minimum of six levels in 50- to 150 µm intervals and evaluated for the presence of metastases with hematoxylin–eosin and immunohistochemical CAM 5.2 staining.

Results

Preoperative findings

In all 25 patients a total of 55 SNs were visualized with conventional lymphoscintigraphy, whereas SPECT/CT showed a total of 66 SLNs (20% more than planar images). SPECT/CT depicted additional SNs in 32% of all patients. It is important to mention that in 1 patient neither the planar images nor the SPECT/CT were capable to depict SNs, due to the possibility that the SN was found near the site of injection, the portable gammacamera was used to make a close image of the area and was able to spot 1 additional SN (Figure 1). With this contribution a total of 67 SNs were preoperatively defined.

Intraoperative findings

A total of 89 SNs were identified and removed (see Table 4 for details). In total, 22 additional SNs were removed compared to the preoperatively defined. Two preoperatively defined SNs were not

Table 3
Preoperative findings with SPECT/CT.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of patient</th>
<th>Lymphoscintigraphy No. SNs</th>
<th>SPECT/CT No. SNs</th>
<th>SPECT/CT No. additional SNs</th>
<th>Additional SNs found NIS</th>
<th>Additional SNs in Level II</th>
<th>No. Basins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>16</td>
<td>33</td>
<td>41</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Oral SCC</td>
<td>9</td>
<td>22</td>
<td>25</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>55</td>
<td>66</td>
<td>11</td>
<td>8</td>
<td>3</td>
<td>55</td>
</tr>
</tbody>
</table>

NIS Near injection site.

Table 4
Intraoperative findings characteristics.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of patients</th>
<th>Total Removed SNs</th>
<th>No. SNs found with GRDP (%)</th>
<th>No. SNs fluorescent invivo (%)</th>
<th>No. SNs found with PGC</th>
<th>Total SNs found with combined MMA of total POD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>16</td>
<td>59</td>
<td>51 (86%)</td>
<td>56 (95%)</td>
<td>59 (100%)</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>Oral SCC</td>
<td>9</td>
<td>30</td>
<td>28 (93%)</td>
<td>30 (100%)</td>
<td>28 (93%)</td>
<td>23 (94%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>89</td>
<td>79 (89%)</td>
<td>86 (97%)</td>
<td>87 (98%)</td>
<td>66 (98%)</td>
</tr>
</tbody>
</table>

GRDP Gamma ray detection Probe, PGC Portable gamma camera, MMA multimodality approach, POD preoperatively defined.
found in two different patients (both oral cavity SCC patients) due to their proximity to injection site.

Table 5 shows a description of the role that additional intraoperative imaging devices play in the location of additional SNs. In patient number 11 (Table 5) surgery was perfomed 5 hours after injection and 5 additional very active SNs were easily found in level II with all three devices. In patient number 13 there was an important contribution of fluorescence in finding an additional SN that was located on the right lateral side of the hyoidus muscle close to the injection site, this node would have been missed without fluorescence. 12 out of the 24 additional SNs found during surgery were located in the vicinity of the injection site in anatomical areas such as the periauricular or submental regions.

Pathologic examination revealed nodal metastases in 6 patients (26%). Four of these patients belonged to the group of 13 patients were additional SNs were found, patients 2, 6, 8 and 9.

Discussion

Accurate staging with SNB can be achieved only if all nodes on a direct drainage pathway from the tumour are identified and harvested. If SNs are left behind, this constitutes one of the potential causes for false-negative results. With the implementation of the multimodal approach in this study 26% additional SNs were found and removed in the head and neck area. Such additional nodes may potentially be the only node to harbour metastases. Once

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Tumour location and type</th>
<th>Additional SNs and localization</th>
<th>SNs localized with probe</th>
<th>SNs localized with portable gamma camera</th>
<th>Fluorescent invivo SNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>Retro auricular right (1)</td>
<td>1 NIS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>Retro auricular right (1)</td>
<td>3 NIS</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Above right eyebrow (1)</td>
<td>1 Lev II</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>Above right eyebrow (1)</td>
<td>3 NIS</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>Left cheek (1)</td>
<td>1 Lev II</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>Right cheek (1)</td>
<td>1 NIS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>Left temporal (1)</td>
<td>1 NIS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>Left ear (1)</td>
<td>4 Lev II</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>Crown (1)</td>
<td>1 Lev II</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>Crown (1)</td>
<td>1 NIS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>Tongue left (2)</td>
<td>5 LevII</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>FOM right (2)</td>
<td>1 NIS</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>55</td>
<td>FOM midline (2)</td>
<td>1 NIS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

NIS Near injection site, FOM Floor of the mouth, (1) Melanoma, (2) Squamous cell carcinoma.
Figure 2. Fluorescence guided SN biopsy. Images (A,B) show a SN visualized with the fluorescence camera in the neck and demonstrates how the signal is blocked by a blood vessel (arrow), this exemplifies how fluorescence imaging is useful, but because of the limited penetration depth, the radioactive component remains indispensable. Images (C,D) show a non blue SN in a patient with head/neck melanoma which is clearly visible using fluorescence imaging.

Figure 3. 67 year-old woman with squamous cell carcinoma right lateral side of the tongue. Conventional planar images after 2h(A), show two hot spots in the right cervical area that were considered as sentinel nodes. The 3-dimensional reconstruction of the SPECT/CT (B) gives important information of the precise localization of the sentinel nodes (levels II and III). In this case the portable gamma camera (D,E) was used successfully for a precise skin marking of the two sentinel nodes.
again, a single injection of ICG-99mTc-nanocolloid enabled preoperative SN mapping and intraoperative radio- and fluorescence guided identification of the SNs draining from primary head and neck malignancies as described in previous reports\textsuperscript{15,16}. Regarding the preoperative procedure, the obtained results are also in line with recent studies\textsuperscript{14,21,22} also showing that SPECT/CT improved the localization of SNs in this region\textsuperscript{15,16}. The addition of SPECT/CT to the conventional lymphoscintigraphy procedure allowed to determine in what specific area the SN was located, its relation to nearby structures and its depth\textsuperscript{15,16}. Moreover, analysis of both the SPECT/CT fused images and the CT slices can play an important role in determining whether the radioactive hotspot found on fused SPECT/CT corresponds with a single SN or a cluster of SNs. Specifically in the head and neck area where lymph nodes are quite small (3–4 mm) and its not uncommon to find SN clusters or SNs close to the injection site. In this study 9 out of the 11 additional SNs that were depicted by SPECT/CT and subsequently found by the portable gamma camera were located in the surroundings of periarterial and submental regions close to injection sites; a similar pattern was also seen in 50% of the additional SNs found during surgery as we described earlier (Table 5).

Furthermore, it is of considerable importance to identify the relation of SNs to several vital vascular and neural structures in order to be able to safely remove these nodes\textsuperscript{14}. This is valuable information that the CT field gives us and will define surgical approach in a good number of patients. Also three-dimensional reconstructed images seem to be of aid because they give an overall perspective of the location of all the SN.

Intraoperatively, combined radio- and fluorescence guidance is capable of playing an important role in the head and neck areas. The fluorescent signature of the hybrid tracer image is not hampered by the background signal coming from the injection site or nearby SNs and therefore this can be used to accurately discriminate the SNs (Figure 2). The limited penetration depth (15 mm at most) of fluorescence imaging compared to modalities based on radioactivity may even be useful, since it can help the surgeon to estimate the depth at which an SN can be localized in order to decide if further exploration is needed\textsuperscript{16}.

With portable gamma cameras it was possible to more accurately study the injection site and as such detect potential radioactive node clusters. Also views of the injection area from different angles can be used to optimally imaging the SN located close to the injection area. Also in some cases it’s very useful for a more precise skin marking of the SNs (Figure 3). Still, with the camera pointing at the most optimal angle, background radioactivity can still be a problem, but with fairly recent improvements in the gamma camera software it has become possible to block the activity coming from the injection site and/or other nodes with a masking application. Also the portable gamma camera is equipped with software that allows to measure radioactivity at different regions of interest (ROIs) which can be an important tool to evaluate remaining activity in relation to the initial uptake after SN resection. In contrast, the handheld gamma ray detection probe has its limitations when it comes to this scenery because of background signal coming from the injection site or nearby radioactive nodes that in most of the times is very difficult to avoid.

The identification rate of SNs with the conventional approach in the head and neck is around 85%, which is less than the almost 100% described for other locations\textsuperscript{17}. The overall lower incidence of successful SN identification in the neck may reflect the complex lymphatic anatomy, the generally small size of lymph nodes and the location of SNs in the vicinity of the primary lesions which may be masked by the injection site activity. In our study the SN identification rate was 98% which is a very encouraging result.

### Conclusion

In the present series a 26% additional SNs were found using a multimodal approach, which incorporated SPECT/CT and intraoperative radio- and fluorescence imaging to the conventional procedure of lymphoscintigraphy and gamma probe. This approach might be useful in malignancies located close to the area of lymphatic drainage such as the periauricular area and the oral cavity.

### References