Current application of sentinel lymph node lymphoscintigraphy to detect various cancer metastases

Abstract

In this review article, the application of sentinel lymph node (SLN) lymphoscintigraphy not only in breast cancer and melanoma but also in cancers of the genital organs and the lungs is described. After a brief historical background, including Virchow's and Cabanas' views, a description of the basic technique and the sensitivity and specificity of this technique in identifying SLN in breast cancer and melanoma are presented. In cervical and vulvar cancer and also in lung cancer, special techniques are applied before and during surgery and evaluated after surgical operation. The advantages and disadvantages of using SLN lymphoscintigraphy are described. Finally, our experience from using SLN lymposcintigraphy, especially in cervical cancer, is presented. The technique for SLN mapping may save the patient from extended surgical procedures, indicate the pathways of lymph drainage and identify skip metastases. Nevertheless, the sensitivity of this technique should further improve in order to provide information concerning the extent of surgical treatment required.

Hell J Nucl Med 2006; 9(1): 5-9

Historical aspects and introduction

"Sentinel node" (SLN) is the first regional lymph node to receive the metastatic tumor cells [1,2]. Virchow (1962) postulated the theory that lymph nodes are the first barriers in the defense of our body against metastases [1]. The hypothesis of the sequential spread of tumors, first to lymph nodes, and later by haematogenic metastases, was based on Virchow's studies [3]. As a result, regional lymphadenectomy is performed in many solid tumors as part of the initial surgical treatment and later for staging of the disease. Lymphatic spread of tumor cells occurs early. When first examined by the physician, about 30% of the patients have clinically detectable metastases and another 30% micrometastases, depending on the kind of the primary tumor [2,4]. Nevertheless, according to Cady's hypothesis (1984), lymphatic and haematogenic metastases are thought to develop simultaneously [5].

The first radiological technique to have been applied in the detection of lymph node metastases was lymphangiography, performed by the injection of contrast media into small distal lymphatic vessels [6]. Besides its lack of sensitivity and specificity, lymphangiography is not free from side effects [7]. This technique has almost completely been replaced by non-invasive and more sensitive techniques like ultrasound (US), computerized axial tomography (CT) and magnetic resonance imaging (MRI) [8-10]. The size of the lymph nodes, although not highly reliable [11,12], remains a major criterion of malignancy [2,3,9,13].

Cabanas (1977), was the first to define the term "sentinel lymph node" (SLN) and to test its application for the treatment of penile cancer [14]. He injected into the dorsal lymphatics of the penis in patients with penile carcinoma radiographic contrast media, followed by radiographic imaging of the pelvis. The first visualized inguinal lymph node was considered as the SLN. The skin over the SLN was marked and biopsy followed [14]. The principle of the sentinel node biopsy was reintroduced by Morton et al. (1992) in melanoma patients [15]. Alex et al. (1993) injected ^{99m}Tc-sulphur colloid (^{99m}Tc-SC) next to the tumor and used a portable gamma probe in search for the radioactive SLN [16]. In another study by Krag et al. (1995) of 121 patients, the SLN could be identified in 98% of the cases studied [17]. When using a portable gamma probe during operation, the SLN may be located and then excised by an incision site of 2-3 cm. Following a negative SLN biopsy, recurrence as mentioned in the above work, occurred in only one patient (negative predictive value: 99%) [17].

The techniques of identifying the SLN

Many techniques of lymphoscintigraphy for the detection of the SLN are now available. One of them is described below: The day before the operation or on the same day, a dose about 60

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Keywords: Sentinel node – Lymphoscintigraphy – Blue dye technique – ^{99m}Tc-nanocolloid

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Received:
7 November 2005
Accepted revised:
10 January 2006

MBq of ^{99m}Tc-nanocolloid (^{99m}Tc-NC) or another radiopharmaceutical such as ^{99m}Tc-antimony (^{99m}Tc-Sb) or ^{99m}Tc-SC, is injected around or inside the primary tumor [18]. According to Krynyckyi et al. (2002), increasing the specific activity of ^{99m}Tc-NC or ^{99m}Tc-SC preparations of the same dose, increases the counts measured over the SLN [19]. After the tracer injection, static lymphoscintigraphy is performed. On the day of surgery about 1 ml of blue dye is injected around the primary tumor to facilitate SLN detection [18]. The SLN and the afferent lymphatic vessels will be stained blue. The SLN can be exactly located either by using a portable gamma-probe before or during surgery or visually by the dye technique. Then, the SLN is easily removed through a small skin incision. It appears that both radioactive and blue dye techniques are complementary for locating the SLN [18]. The strategies of identification of the SLN depend largely on the results of lymphoscinigraphy [20].

Applications of the technique in breast cancer and melanoma

In this article we will mention briefly some of the interesting points of the application of the SLN techniques.

In breast cancer, a slow lymphatic drainage pattern exists, which may hamper image interpretation. The first appearing lymph node and the visualization of an afferent lymphatic vessel are the major criteria to identify the SLN. Scintigraphy may be considered conclusive in approximately 75% of the cases. In the remaining 25% of the cases, two or more lymph nodes appear simultaneously without lymph vessel delineation. In these cases, additional lymphatic mapping with the blue dye is recommended in order to identify the SLN. According to Chicken and Keshtgar (2004) in breast cancer, SLN biopsy enables highly accurate lymphatic staging with minimal morbidity, and it is likely that this procedure will soon be part of the routine management of breast carcinoma [21]. After radiotherapy or surgery, upper limb oedema may appear. Lymphosctintigraphy can provide information for physiotherapy and / or reconstructive surgery [22].

In melanoma, the variability of SLN drainage in areas such as the trunk, the head and the neck makes lymphoscintigraphy very useful [20]. Intraoperative gamma probe detection may also be performed.

In melanoma patients with lower extremity oedema after groin dissection, lymphoscintigraphy is also useful to document altered drainage patterns not only after surgery but also after radiotherapy. In these cases lymphoscintigraphy can provide information for physiotherapy and / or reconstructive surgery of the patients [22]. The probability of melanoma metastases to lymph nodes, depends on the stage of the regional melanoma. In patients with regional lymph node melanoma metastases, the five years survival rate is about 30% whereas after complete lymphadenectomy, the mean survival rate increases to 50% [22].

In cervical and vulvar cancer

Techniques employed to identify the SLN in cervical and vulvar cancer are the isosulfan blue dye [23], the radiocolloid tracer [24], or a combination of both [25]. Malur et al. (2001) in 50 women with cervical cancer in stages I, II or IV as classified according to the International Federation of Gynecology and Obstetrics (FIGO), injected intraoperatively into the cervix 50 MBq of ^{99m}Tc-albumin resin (^{99m}Tc Albu-Res) at 3, 6, 9 and 12:00 h sites and afterwards injected a blue dye [26]. The SLN was confirmed in 78% of the cases. Sensitivity and negative predictive value for SLN lymphoscintigraphy alone were 83.3% and 97.1% respectively. After both injections, the sensitivity, and negative predictive values were 100%. The SLN was located mainly in the paracaval region in 67% of the cases. Also at the bifurcation of the common iliac artery and at the origin of the uterine artery in about 26% of the cases [26]. Lavenback et al. (2002) conducted lymphatic mapping and SLN identification in 39 women with cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy [27], preoperatively with SLN lymphoscintigraphy and intraoperatively with a portable gamma probe and a blue dye injection [27]. Preoperative lymphoscintigraphy revealed at least one SLN in 33 patients, including 21 patients with bilateral SLN. Intraoperatively all 39 patients had at least one SLN identified. Eighty percent of the SLN were identified in three pelvic locations: the illiac, the obturator, and the parametrial. Out of the 132 nodes identified as SLN, 65 (49%) were both blue and radioactive, 35 (27%) were blue only, and 32 (24%) were radioactive only. Eight patients had metastatic disease and in five of these patients, SLN were the only positive lymph nodes. The sensitivity of the SLN was 87.5% and the negative predictive value, 97%. The authors concluded that preoperative SLN lymphoscintigraphy and intraoperative lymphatic mapping are highly successful at identifying SLN in patients undergoing radical hysterectomy [27]. Smaller studies with similar results were conducted by others [28-32].

Sentinel lymph node procedures have also been applied in squamous cell cancer of the vulva. Keith et al. (2000) described 10 women with this cancer [33]. These women underwent intraoperative SLN lymphoscintigraphy after the intradermal injection of ^{99m}Tc-SC at the site of the primary tumor. Isosulfan blue dye was also injected at the tumor site in the groin. In all patients SLN were identified and removed. Only one node was found positive by the blue dye technique. Two of the three nodes that were found negative for micrometastases by the conventional histologic techniques, after serial sectioning and immunohistochemical staining were found positive.

Advantages and disadvantages

SLN lymphoscintigraphy has both advantages and drawbacks. A main advantage is that SLN dissection removes only the node most likely to harbor metastatic disease. The whole dissection is simple and its complications are minimal. There is no numbness reported, no edema in the associated extremity, no wound breakdown and no reported long-term sequelae of this procedure [33]. Of course, by removing a single node it is suggested to submit the node to a thorough histopathology and immunohistochemistry examination [33]. Combined use

of a radioactive isotope and blue dye injection allows for a more precise examination of the most critical nodes [34, 35]. The combination of intraoperative laparoscopic SLN mapping and laparoscopic radical surgery, in the context of minimally invasive surgery for the management of patients with early cervical cancer, has recently been suggested [36].

The main reasons for a false-negative SLN are technical errors and false negative pathology findings. Technical failure is minimized by using both the radiocolloid and the blue dye techniques simultaneously. Tsopelas C. (2005) has recently presented a new technique for SLN lymphoscintigraphy by using Evans blue labelled with ^{99m}Tc, thus combining two techniques in one [37]. As already mentioned, false negative pathology findings can be overcome by serial sections examined immunohistochemically [33,38].

A sampling error in testing SLN pathology may underestimate metastatic disease in the regional lymphatics [33,39,40]. Serial sections of the SLN tested by immunohistochemical staining should be used in order to identify subclinical micrometastases [33,41]. According to Angioli et al. (2005), a high percentage of patients is found with bilateral and/or more than one SLN, therefore, improvement of the actual technique and better pathology analysis are important before SLN biopsy becomes a routine procedure in cervical cancer patients [42]. Of course the status of regional lymph nodes is a powerful predictor of survival in patients with early cancer of the vulva, the cervix or the uterus, since radical resection of primary cancer and an extensive lymphadenectomy remain the standard of treatment for these cancers [43].

In lung cancer

Lung cancer is the number one cause of cancer-related mortality in the United States in both men and women [44]. Surgical resection of localized tumors remains the main treatment having a curative potential. However, even after "complete resection", up to 40% of the patients will relapse and die of their disease [45].

Clinical and computed tomography (CT) staging of intrathoracic lymph nodes, underestimates lymph node involvement in approximately 25% of the cases [46,47]. A significant proportion of patients with normal mediastinal lymph nodes on CT scan may harbor lymph node metastases. Thoracic nodal dissection including mediastinal nodes has been called the most accurate method of staging patients and defining prognosis, although recurrent laryngeal nerve injury, chylothorax, bronchial devascularization and excess blood loss have been reported [46].

Little et al. (1999) used the SLN technique in 36 patients with non-small cell lung cancer (NSCLC) undergoing lung resection [48]. Peritumoral tissue was infiltrated with isosulfan blue dye. SLN was identified in 17 of these patients (47%). In 9 of these 17 patients neither the SLN nor any other proximal lymph node contained metastatic NSCLC, so nodal staging was N0 (false positive). The SLN in the remaining eight of the 17 patients were true positive for tumor. The SLN were found in the intraparenchymal, the interlobal, the paratracheal or the subcarinal area. All mediastinal nodes were negative. In 19 of the 36 patients no sentinel node was found [48].

Liptaj et al. (2000) intraoperatively injected 74 MBq ^{99m}Tc-SC in 52 patients before resection of the NSCLC [49]. The primary tumor and the regional lymph nodes were surveyed in the thorax and also after the resection, with the use of a portable gamma counter. Findings were correlated with histologic examination. The mean time from injection of the tracer to identification of the SLN was 63 min. In 37 patients (82%) SLN was identified out of which in 35 patients (94%) the SLN were true positive [49]. No metastases were found in other intrathoracic lymph nodes. Forty-five patients had the NSCLC completely resected. Similar results were reported by others [50].

Sugi et al. (2003) compared three tracers for detecting SLN in patients with clinically N0 lung cancer [51]. Forty eight patients with clinically N0 NSCLC were enrolled in this study. Indocyanine green or isosulfan blue were injected around the tumor intraoperatively, or ^{99m}Tc tin colloid (^{99m}Tc-TC) was injected under CT guidance preoperatively. SLN were detected in 6.3% of the patients by indocyanine green, in 50% by isosulfan blue and in 64.3% by ^{99m}Tc-TC.

Advantages and disadvantages

Intraoperative SLN identification in cases of NSCLC can assist the surgeon in performing a complete nodal dissection and give real-time feedback to the adequacy of resection [49]. It can also allow pathologists to focus on certain lymph nodes [49]. In brief, SLN identification contributes to the diagnosis and prognosis of NSCLC.

On the other hand, the role of SLN lymphoscintigraphy in limiting mediastinal node dissection is doubtful [49]. Performing the SLN identification procedure in lung cancer patients requires a radiology-guided needle access that places the patient at significant risk of complications such as pneumothorax, bleeding, and the potential of pleural seeding by the tumor [52].

In patients diagnosed as having NSCLC it is important to choose the proper treatment and predict prognosis [53]. It seems that both isosulfan blue and ^{99m}Tc-TC are suitable for the intraoperative SLN mapping in these patients. Based on the recommendations of the American Joint Committee for cancer, a tumor, nodule, metastases (TNM) staging is used for NSCLC. Clinical staging (c TNM) is determined by using non-invasive techniques such as clinical assessment and radiologic testing. Pathology staging (p TNM) is determined using invasive techniques such as bronchoscopy, mediastinoscopy and video-assisted thoracoscopic surgery, or thoracotomy. Recently, new staging modalities such as positron emission tomography (PET) and intraoperative SLN mapping have been used with promising results [53]. These methods may improve the precision of pathologic staging and limit the need for mediastinal node dissection in selected patients [49].

Our experience with SLN lymphoscintigraphy, especially in cervical cancer

In the Nuclear Medicine Unit of the Endocrinology Department of Jagiellonian University in Krakow, Poland, the SLN

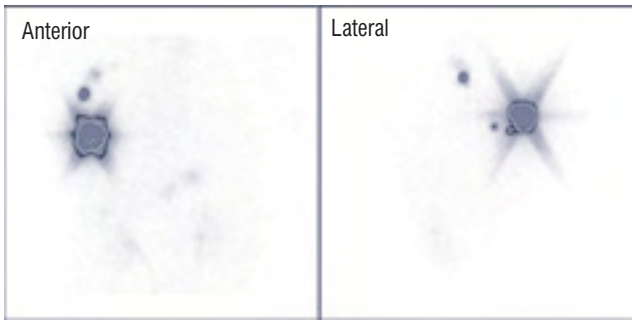

Figure 1a. Sentinel nodes in breast cancer

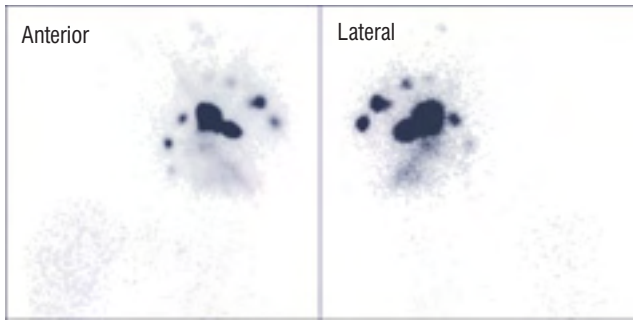

Figure 1b. Sentinel nodes in breast cancer. The sentinel nodes in the mediastinum and the axilla were detected

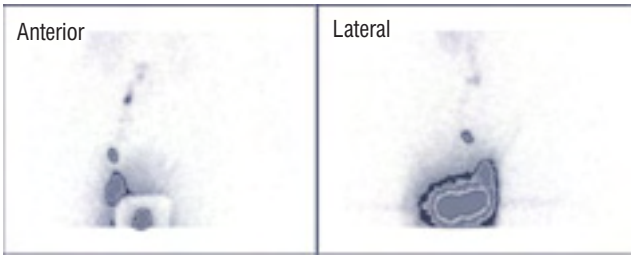

Figure 2. Sentinel nodes in cervical cancer

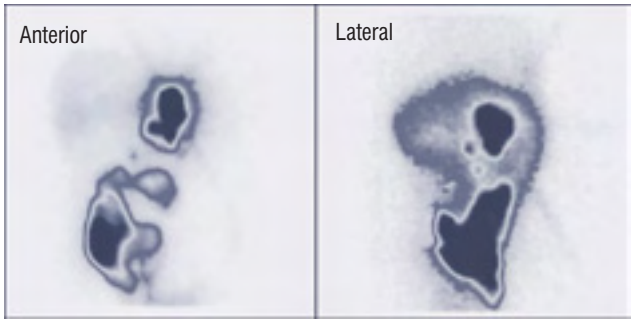

Figure 4. Sentinel nodes in colon cancer

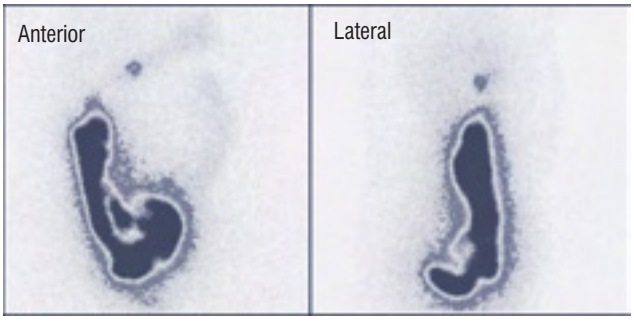

Figure 3. Sentinel nodes in gastric cancer

technique is used to detect SLN in breast cancer (Fig.1a, b), cervical cancer (Fig. 2), thyroid cancer, gastric (Fig. 3) and colorectal cancers (Fig. 4). We have examined 37 patients with cervical cancer stage I-IIa according to FIGO classification. The day before surgery 100 MBq of ^{99m}Tc-NC (0.5-1.0 ml in volume) were applied in each quadrant of the cervix or around the tumor. Static scintiscans were performed 2 h post injection using dual-head large field of view Siemens gamma-camera (E.CAM, USA) equipped with high resolution collimators. SLN were identified intraoperatively using a portable gamma detector (Navigator GPS-Tyco, USA) and intraoperative lymphatic mapping with methylene blue. After resection of SLN a standard radical hysterectomy with pelvic and low para-aortic lymph node resection was performed. Tumor characteristics were compared with SLN characteristics histopathologically and immunohistochemically. Intraoperative detection of SLN was successful in 36/37 cases (97.30 %). The mean number of SLN detected in every patient was 3.43 (range 0-7). The total number of SLN found was 119. In 28 patients (75.68%) the SLN were blue and radioactive, in 2 cases (5.41%) only blue and in 6 cases (16.22) only radioactive. Out of the 119 SLN detected, 92 (77.31%) were found in the region of the bifurcation of the hypogastric artery. Scintigraphy showed focal uptake in 35 of the 37 patients. In these patients at least one SLN was detected. In 13 cases SLN were shown to be next to the cervix (in 6 patients unilaterally and in 7 cases bilaterally). The remaining cases had hot spots indicating SLN above and laterally or bilaterally to the cervix on the pelvic walls. Histologically positive SLN were found in 5 women. One patient had a false negative SLN with lymph node metastases [54].

In all our studies of various neoplasms, better results in diagnosing the SLN were achieved when the radionuclidic technique was combined with the dye technique. It is the opinion of the authors that this combined technique induces better diagnostic and prognostic results and suggests the proper surgical treatment.

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