Advancing surgical guidance: from (hybrid) molecule to man and beyond

Berg, N.S. van den

Author: Berg, Nynke van den
Title: Advancing surgical guidance : from (hybrid) molecule to man and beyond
Issue Date: 2016-11-10

CHAPTER 10

A PILOT STUDY OF SPECT/CT-BASED MIXED-REALITY NAVIGATION TOWARDS THE SENTINEL NODE IN PATIENTS WITH MELANOMA OR MERKEL CELL CARCINOMA

Adapted from: van den Berg NS, Brouwer OR, Mathéron HM, Nieweg OE, Valdés Olmos RA, van Leeuwen FWB. Nucl Med Comm. 2016;37:812-7.

ABSTRACT

OBJECTIVE To explore the feasibility of an intraoperative navigation technology based on preoperatively acquired single photon emission computed tomography combined with computed tomography (SPECT/CT) images during sentinel node (SN) biopsy in patients with melanoma or Merkel cell carcinoma.

MATERIALS AND METHODS Patients with a melanoma (n=4) or Merkel cell carcinoma (n=1) of a lower extremity scheduled for wide re-excision of the primary lesion site and SN biopsy were studied. Following a ^{99m}Tc-nanocolloid injection and lymphoscintigraphy, SPECT/CT images were acquired with a reference target (ReTp) fixed on the leg or the iliac spine. Intraoperatively, a sterile ReTp was placed at the same site to enable SPECT/CT-based mixed-reality navigation of a gamma ray detection probe also containing a reference target (ReTgp). The accuracy of the navigation procedure was determined in the coronal plane (x, y-axis) by measuring the discrepancy between standard gamma probe-based SN localization and mixed-reality-based navigation to the SN. To determine the depth accuracy (z-axis), the depth estimation provided by the navigation system was compared to the skin surface-to-node distance measured in the CT component of the SPECT/CT images.

RESULTS In four of five patients, it was possible to navigate towards the preoperatively defined SN. The average navigational error was 8.0 mm in the sagittal direction and 8.5 mm in the coronal direction. Intraoperative sterile ReTp positioning and tissue movement during surgery exerted a distinct influence on the accuracy of navigation.

CONCLUSION Intraoperative navigation during melanoma or Merkel cell carcinoma surgery is feasible and can provide the surgeon with an interactive three dimensional roadmap towards the SN or SNs in the groin. However, further technical optimization of the modality is required before this technology can become routine practice.

INTRODUCTION

In patients with intermediate-thickness melanoma, sentinel node (SN) biopsy has become a routine procedure that provides staging and prognostic information, reduces the risk of nodal recurrence and results in improved melanoma-specific survival when combined with completion node dissection in patients who are node positive [1]. The procedure typically entails the injection of a radiocolloid around the melanoma site, followed by two-dimensional lymphoscintigraphy to outline the lymphatic drainage pattern [2]. Nowadays, single photon emission computed tomography (SPECT) is combined with computed tomography (CT) imaging providing three-dimensional (3D) images. As a result, SNs are depicted within their anatomical context, facilitating the planning of the surgical procedure [3].

Intraoperatively, most surgeons use a gamma-ray detection probe (hereafter referred to as a gamma probe) to find the hot node that is depicted on the preoperative images. Yet a gamma probe only provides an acoustic signal and no visual information or read-out for the distance to the SN. Moreover, the commonly used blue dye can only be seen when the SN is already exposed. It would thus be beneficial if the spatial anatomical information provided by preoperative SPECT/CT imaging can also be used in the operation theatre. Recently, navigation in a mixed-reality environment using preoperatively acquired SPECT/CT images has shown potential during SN biopsy procedures for urological malignancies [4,5]. The current pilot study explores the feasibility of this technology in four patients with melanoma and one patient with a Merkel cell carcinoma.

MATERIALS AND METHODS

PATIENTS

Five patients (mean age 47.4 years, range 29-65) were enrolled in the current study. Four of these five patients presented with a melanoma (average Breslow thickness 3 mm, range 1.7-5.3) of a lower extremity (Table 1). The other patient presented with a Merkel cell carcinoma of a lower extremity (Table 1), which, in our institution, is also indicated for SN biopsy [6]. All patients were scheduled for wide re-excision of the primary lesion site and SN biopsy.

All procedures performed in our study were in accordance with the ethical standards of our institution and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients who participated in the current study.

Table 1. Patient characteristics, pre- and intraoperative findings, and pathology outcome

Patient	*Age*	*Primary*	*Injected dose (MBq)*	*# SNs identified on SPECT/CT*	*Patient target location*	*Error in coronal plane (X,Y-position; mm)*	*Error in sagittal plane (Z-position; mm)*	*# Excised SNs*	*# Blue SNs*	*# Tumor-positive nodes*
1	50	Melanoma, thigh L	73.5	1	ASIS, R	10	-4	1	1	0
2	54	Melanoma, thigh R	67.8	1	ASIS, L	10	-10	2	2	0
3	29	Melanoma, thigh R	139.4	1	Thigh, R	not determined	>45 mm	1	0	0
4	65	Melanoma, lower leg R	79.7	3	Thigh, R	9	-2	3	2	0
5	39	Merkel cell carcinoma, lower leg R	70.4	2	ASIS, L	5	-16	3	3	0
Average	47.4		86.2			8.5±2.1	-8.0±5.5			
Total				8				10		

L = left; R = right; ASIS = anterior superior iliac spine.

PREOPERATIVE PROCEDURE

^{99m}Tc-nanocolloid was administered intradermally in four deposits surrounding the primary lesion site (0.4 mL; average 86.2 MBq, range 68-139). Dynamic lymphoscintigraphy was performed immediately after tracer injection and was followed by static imaging at 15 min and 2 h after injection using a dual-head gamma camera (Symbia-T; Siemens, Erlangen, Germany) (Figure 1A). Following late imaging, a reference target (ReTp) was placed on the contralateral anterior superior iliac spine in three patients and on the ipsilateral thigh in two patients. The location of the ReTp was marked on the skin with indelible ink. Thereafter, SPECT images were acquired with a 128 x 128 matrix and 60 frames at 25 s per view. This was combined with a low-dose CT (40 mAs, 5 mm slices). Attenuation-corrected SPECT and CT images were fused using Osirix medical imaging software (Pixmeo, Geneva, Switzerland). Orthogonal multiplanar reconstructions and three dimensional volume-rendered images (Figure 1B) were generated from the fused images. Afterwards, the nuclear medicine physician determined the number and location of SNs and marked these on the skin with indelible ink. An SN was defined as a lymph node on a direct lymphatic drainage pathway from the primary lesion [7].

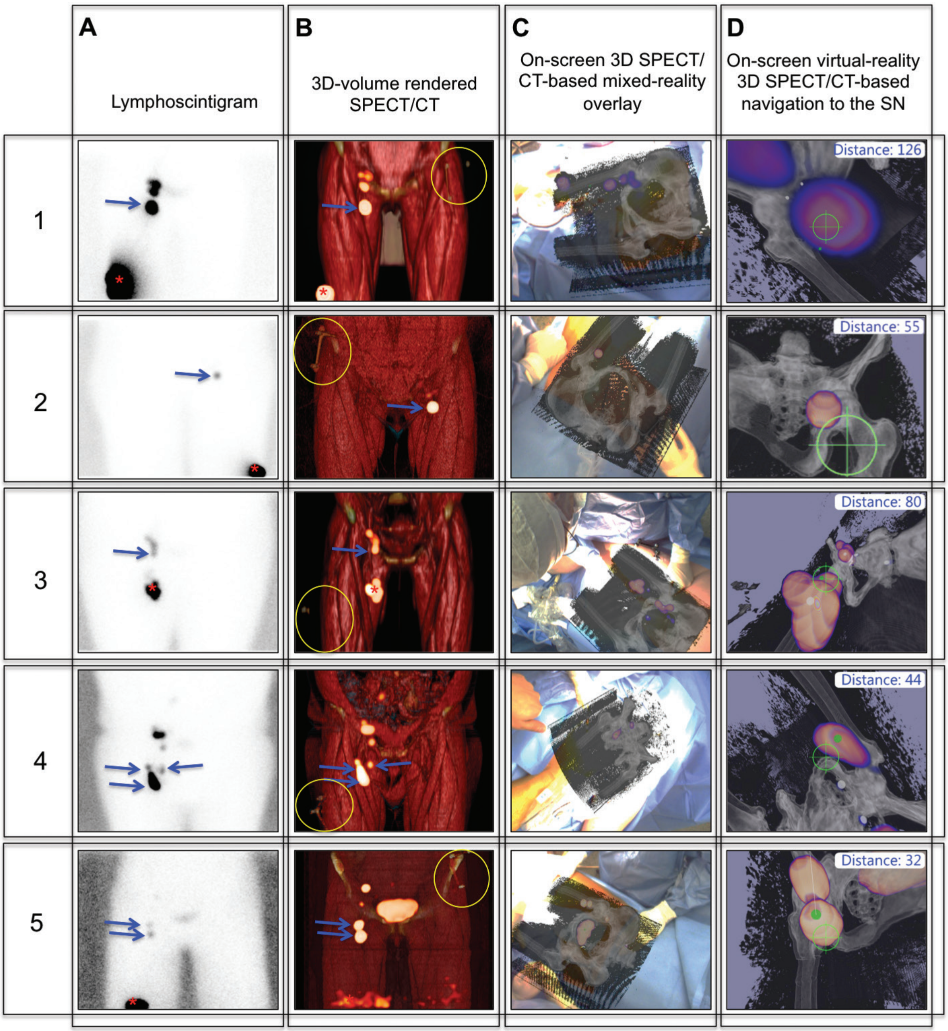

Figure 1. Imaging datasets of the five included patients. A) Anterior lymphoscintigram taken 2 h after a radiocolloid injection showing the sentinel node in the groin (arrow) and the injected site (asterisk); B) 3D volume-rendered SPECT/CT image showing the sentinel node in the groin (arrow) and the patient reference tracer (circle); C) The mixed-reality overlay of the preoperatively acquired SPECT/CT and the video feed of the patient is presented onscreen; D) On-screen 3D virtual-reality based navigation to the sentinel node in the groin. 3D = three-dimensional; SPECT/CT = single photon emission computed tomography/computed tomography.

NAVIGATION SYSTEM: IMAGE REGISTRATION IN THE OPERATION THEATRE

The tracked attenuation-corrected SPECT images and the low-dose CT images were loaded into the navigation system (declipseSPECT; SurgicEye, Munich, Germany) and the location of the reference target on the patient (ReTp) was automatically segmented from the low-dose CT.

After sterile prepping and draping, a sterile ReTp was again placed on the patient at the preoperatively marked position and fixed with Steri-Strips (3M Health Care, St. Paul, Minnesota, USA). A video camera at the top of the navigation system provided an on-screen image-feed of the surgical field. This real-time video signal was then combined with the SPECT/CT information and matched to the location and orientation of the patient ReTp, which resulted in a (on-screen) mixed-reality representation (Figure 1C). Subsequently, a second sterile reference target (ReTgp) was placed on the gamma probe (Crystal Photonics, Des Plaines, Illinois, USA). After calibration, this allowed for navigation of the tip of the gamma probe in the on-screen in 3D, SPECT/CT-based, virtual-reality view (Figure 1D).

NAVIGATION PROTOCOL IN THE OPERATION THEATRE

To determine the accuracy of the intraoperative navigation in the coronal plane, the gamma probe was navigated in the on-screen 3D SPECT/CT-based virtual-reality view to the location of the SN over the intact skin without the acoustic signal. This location was then marked on the skin with indelible ink. Subsequently, the SN was localized through the intact skin in the conventional manner using the acoustic signal of the gamma probe (Neoprobe; Johnson & Johnson Medical, Amersfoort, the Netherlands). The point with the highest gamma ray count rate was also marked on the skin. The accuracy error of the SPECT/CT-based virtual-reality view in the coronal plane (x and y position) was then determined by measuring the distance between the two marks using a caliper.

During the navigation process, the system provided an estimate of the distance between the center of the SN and the tip of the gamma probe, which enabled determination of the depth of the node (z position; sagittal plane) for surgical exploration. This estimate was compared with the depth measured on the corresponding low-dose CT image that served as the gold standard.

SENTINEL NODE EXCISION AND (HISTO-)PATHOLOGICAL EVALUATION

After completing the experimental preincision navigation procedure, the SN biopsy procedure was performed as described previously [8]. Serial sectioning, haematoxylin-eosin and immunohistochemistry staining of the SNs were performed as described previously [9].

RESULTS

Preoperative lymphoscintigraphy and SPECT/CT imaging revealed a total of eight inguinal SNs (Figure 1A, B). The intraoperative feasibility of the navigation approach was assessed for one SN in each of the five patients (Table 1).

Intraoperative placement of the sterile ReTp was easy and did not affect the surgical workflow. Superimposition of the SPECT/CT images onto the patient image provided a visual confirmation of the ReTp repositioning accuracy. The anterior superior iliac spine was found to be the most suitable location for ReTp placement as it provided a rigid orientation point in comparison with the soft tissue of the thigh. Although the latter location ensured constant visibility of the tracker, in one patient, it yielded a 45 mm error, which could be attributed to intraoperative abduction and rotation of the leg compared with the patient position during SPECT/CT acquisition (Figure 1, patient 3). Such an obvious movement artifact led us to exclude this patient from further analysis, a point that is addressed further in the discussion section.

In the remaining four patients, the navigation approach could be executed successfully. The locating error of 3D virtual-reality SPECT/CT-based navigation, compared with conventional gamma probe localization, in the coronal plane was found to be 8.5 mm on average (SD 2.1 mm, range 5.0-10.0; Table 1). The average sagittal (in-depth; z-position) error was found to be 8.0 mm (SD 5.4 mm, range 2.0-16.0; Table 1). Compared with the low-dose CT measurement, navigation underestimated the depth in all four patients.

After completion of the navigation protocol, a total of ten SNs were excised. Histopathological evaluation indicated one SN to be tumor-positive.

DISCUSSION

The current pilot study shows the feasibility of on-screen navigation in a mixed-reality environment using preoperatively acquired SPECT/CT images. Preoperative SPECT/CT imaging has been shown to make intraoperative SN biopsy procedure in melanoma patients easier [10,11], with significantly more SNs detected [12] as well as patient benefit [13]. In this context, intraoperative technologies that exploit the 3D SPECT/CT information may increase its value even further. The additional information provided by 3D SPECT/CT-based navigation helped not only to reproduce the anatomical environment as preoperatively displayed by SPECT/CT, but also has the potential to facilitate intraoperative SN localization. This can be especially useful in localizing SNs that contain little radioactivity, SNs deeper inside the body, near the primary lesion or in areas with an intricate anatomy.

It is generally assumed that in soft tissues, registration and motion artefacts limit the value of navigation technologies [14]. The current proof-of-concept study shows that on-screen 3D virtual-reality SPECT/CT-based navigation is feasible with reasonable accuracy. On average, navigation errors were found to be around 8 mm in both the x,y-direction (coronal) and the z-direction (sagittal). This study also shows the importance of correct placement of the patient ReTp as the error was larger when the ReTp was placed on the thigh (non-rigid anatomy) compared with the anterior superior iliac spine (rigid anatomy). This indicates that the ReTp should be placed on a rigid reference point rather than in a non-rigid area that is prone to change during the operation compared with preoperative image acquisition. This was underlined in one patient, where the ReTp was placed on the thigh (error >45 mm; Table 1). The deviation in the z-direction may be explained by the pressure that surgeons intuitively place on the gamma probe to increase the count rate. Although the navigation errors that we encountered did not limit the identification of the relatively large lymph nodes in the groin, this could prove a limitation in the head-and-neck area. The SNs in the latter area are considerably smaller, often in close proximity to non-SNs, and are surrounded by important structures that the surgeon should preserve [15].

Our current study clearly indicates that SPECT/CT-based navigation is feasible in this patient group, but at the same time suggests that this type of navigation is susceptible to movement-induced errors. Intraoperatively obtained freehandSPECT datasets could help omit errors as result of patient positioning differences in the preoperative or intraoperative setting. This alternative approach has shown clinical potential in a number of SN related studies [16-18]. Nevertheless, compared with the use of preoperative SPECT/CT data sets, the generation of freehandSPECT data sets is more time consuming, lacks the anatomical detail provided by the (low-dose) CT image and may have a lower image quality. One could, however, envision that in the future, intraoperative freehandSPECT could be used to correct for motion-induced artefacts in the SPECT/CT-based navigation set-up.

Intraoperative guidance modalities that help correct for the navigation-induced error can be especially beneficial. Here, the conventionally used gamma probe already provides a means to validate the navigation accuracy because of its real-time acoustic feedback, but the spatial resolution and in-depth view of the technology is limited. Other disadvantages of the gamma probe are that it does not provide images and the tracing process can be time consuming. Alternative to gamma ray-based guidance, blue dye or even fluorescence guidance may be used to confirm the accuracy of the navigation procedure as they provide the surgeon with real-time visual feedback in terms of the location of the lymphatic ducts and/or SNs [4,19]. Incorporation of fluorescence imaging into the navigation approach can be a particularly interesting technique for further refinement of the navigation procedure.

CONCLUSION

Surgical navigation in preoperatively acquired SPECT/CT images in patients with melanoma or Merkel cell carcinoma of a lower extremity is feasible. For wider implementation, the accuracy of the procedure needs to be optimized.

REFERENCES

1. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014; 370:599-609.
2. van den Berg NS, Buckle T, Kleinjan GI, Klop WM, Horenblas S, van der Poel HG, et al. Hybrid tracers for sentinel node biopsy. Q J Nucl Med Mol Imaging. 2014; 58:193-206.
3. van der Ploeg IM, Valdés Olmos RA, Nieweg OE, Rutgers EJ, Kroon BB, Hoefnagel CA. The additional value of SPECT/CT in lymphatic mapping in breast cancer and melanoma. J Nucl Med. 2007; 48:1756-1760.
4. Brouwer OR, Buckle T, Bunschoten A, Kuil J, Vahrmeijer AL, Wendler T, et al. Image navigation as a means to expand the boundaries of fluorescence guided surgery. Phys Med Biol. 2012; 57:3123-3136.
5. Brouwer OR, van den Berg NS, Mathéron HM, Wendler T, van der Poel HG, Horenblas S, et al. Feasibility of intraoperative navigation to the sentinel node in the groin using preoperatively acquired single photon emission computerized tomography data: transferring functional imaging to the operating room. J Urol. 2014; 192:1810-1816.
6. Ortin-Perez J, van Rijk MC, Valdes-Olmos RA, Vidal-Sicart S, Nieweg OE, Vilalta A, et al. Lymphatic mapping and sentinel node biopsy in Merkel's cell carcinoma. Eur J Surg Oncol. 2007; 33:119-122.
7. Nieweg OE, Tanis PJ, Kroon BB. The definition of a sentinel node. Ann Surg Oncol. 2001; 8:538-541.
8. Nieweg OE, Jansen L, Kroon BB. Technique of lymphatic mapping and sentinel node biopsy for melanoma. Eur J Surg Oncol. 1998; 24:520-524.
9. van den Berg NS, Brouwer OR, Schaafsma BE, Mathéron HM, Klop WM, Balm AJ, et al. Multimodal surgical guidance during sentinel node biopsy for melanoma: combined gamma tracing and fluorescence imaging of the sentinel node through use of the hybrid tracer indocyanine green-(99m)Tc-nanocolloid. Radiology. 2015; 275:521-529.
10. van der Ploeg IM, Valdés Olmos RA, Kroon BB, Wouters MW, van den Brekel MW, Vogel WV, et al. The yield of SPECT/CT for anatomical lymphatic mapping in patients with melanoma. Ann Surg Oncol. 2009;16:1537-1542.
11. Veenstra HJ, Vermeeren L, Olmos RA, Nieweg OE. The additional value of lymphatic mapping with routine SPECT/CT in unselected patients with clinically localized melanoma. Ann Surg Oncol. 2012;19:1018-1023.
12. Jimenez-Heffernan A, Ellmann A, Sado H, Huić D, Bal C, Parameswaran R, et al. Results of a prospective multicenter international atomic energy agency sentinel node trial on the value of SPECT/CT over planar imaging in various malignancies. J Nucl Med. 2015; 56:1338-1344.
13. Stoffels I, Boy C, Pöppel T, Kuhn J, Klötgen K, Dissemond J, et al. Association between sentinel lymph node excision with or without preoperative SPECT/CT and metastatic node detection and disease-free survival in melanoma. JAMA. 2012; 308:1007-1014.

14. Baumhauer M, Feuerstein M, Meinzer HP, Rassweiler J. Navigation in endoscopic soft tissue surgery: perspectives and limitations. J Endourol. 2008; 22:751-766.
15. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014;110:172-181.
16. Bluemel C, Herrmann K, Kübler A, Buck AK, Geissinger E, Wild V, et al. Intraoperative 3-D imaging improves sentinel lymph node biopsy in oral cancer. Eur J Nucl Med Mol Imaging. 2014; 41:2257-2264.
17. Engelen T, Winkel BM, Rietbergen DD, KleinJan GH, Vidal-Sicart S, Olmos RA, et al. The next evolution in radioguided surgery: breast cancer related sentinel node localization using a freehandSPECT-mobile gamma camera combination. Am J Nucl Med Mol Imaging. 2015; 5:233-245.
18. Heuveling DA, Karagozoglu KH, van Schie A, van Weert S, van Lingen A, de Bree R. Sentinel node biopsy using 3D lymphatic mapping by freehand SPECT in early stage oral cancer: a new technique. Clin Otolaryngol. 2012;37:89-90.
19. Kapteijn BA, Nieweg OE, Liem I, Mooi WJ, Balm AJ, Muller SH, et al. Localizing the sentinel node in cutaneous melanoma: gamma probe detection versus blue dye. Ann Surg Oncol. 1997;4:156-160.