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

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CHAPTER 12

SENTINEL NODE BIOPSY FOR PROSTATE CANCER: A HYBRID APPROACH

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ABSTRACT

To provide surgeons with optimal guidance during interventions, it is crucial that the molecular imaging data generated at the diagnostic departments finds its way to the operating room. Sentinel node (SN) biopsy provides a textbook example in which molecular imaging data acquired in the department of nuclear medicine guides the surgical management of patients. For prostate cancer, in which SNs are generally located deep in the pelvis, procedures are preferably performed via a (robot-assisted) laparoscopic approach. Unfortunately, in the laparoscopic setting the senses of the surgeon are reduced. This topical review discusses technologic innovations that can help improve surgical guidance during SN biopsy procedures.

INTRODUCTION

Metastasis in pelvic lymph nodes is considered an important prognostic factor in prostate cancer. Prostate-specific antigen levels, pathologic stage, and Gleason score are predictors for lymph nodes involvement; the higher these factors are, the greater is the chance of nodal involvement. Postoperative (histo-)pathologic examination of tissue samples obtained during (extended) pelvic lymphadenectomy is considered the gold standard in assessing metastatic spread. With an increasing lymph nodes dissection template, the prognosis of both N0 and N1 groups increases ("Will Rogers" phenomenon). Unfortunately, (extended) pelvic lymphadenectomy also increases the chance of postoperative complications such as lymphoceles, injuries to the obturator nerve or the ureter, and lymphedema of the lower extremity. Such complications can lead to a decrease in the patient's quality of life.

Sentinel node (SN) biopsy focuses on the identification, subsequent minimally invasive excision, and pathologic and histopathologic evaluation of the lymph nodes that drain directly from the primary tumor. Assuming the orderly spread of tumor cells through the lymphatic system, SN biopsy can be used for lymph nodes staging. After staging, therapeutic follow-up can be decided on.

The potential of SN biopsy for detecting lymph nodes metastasis has been validated in several studies. The Augsburg group validated the SN biopsy procedure in more than 2,000 patients with prostate cancer and reported a high sensitivity and an overall false-negative rate of 5.9% [1]. Moreover, SN biopsy allows the identification of SNs outside the pelvic lymphadenectomy field [2-4]. Recently, Joniau et al. showed that 44% of SNs were located outside the extended pelvic lymphadenectomy field; in 6% of patients, a positive lymph nodes was located exclusively in the presacral or para-aortic region [2].

Ideally, a surgeon is able to identify and excise the preoperatively identified SNs in a minimally invasive manner, with a high sensitivity and specificity. This topical review discusses technologic improvements that may help improve the different aspects involved in (robot-assisted) laparoscopic SN biopsy for prostate cancer; SN biopsy for the prostate is often performed in combination with laparoscopic radical prostatectomy. Potential improvements can be found in (hybrid) tracers that are radioactive and fluorescent, the injection procedure, preoperative SN identification and planning of the surgical procedure, translation of the preoperatively acquired imaging data to the operating room (e.g. via navigation), and intraoperative imaging for SN identification. A schematic overview of these points is given in Figure 1. Similar technologies are also expected to help improve guidance for other SN indications and in the future may even help enable tumor-specific resections.

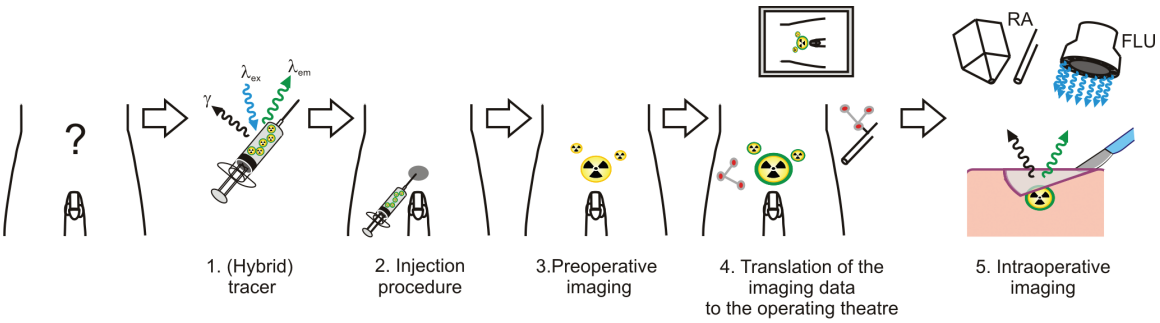

Figure 1. Schematic overview of the integrated hybrid sentinel node biopsy procedure. On presentation of the patient, a hybrid SN tracer (1) is injected into the prostate (2). Preoperative imaging is performed to identify the SNs (3). Preoperatively acquired images can be directly translated to operating room - for example, via augmented-reality-based navigation (4) - to provide both radio- and fluorescence-based surgical guidance toward SNs (5). SN = sentinel node; FLU = fluorescence imaging; λem = emission wavelength of the fluorophore; λex = excitation wavelength of the fluorophore; γ = gamma signal coming from the radioisotope; RA = radioactivity-based detection (i.e., gamma imaging or -tracing).

(HYBRID) TRACERS

Despite the success of radioguided surgery, to provide optical guidance blue dyes are often injected before the start of the operation. However, for prostate cancer, in which SNs are generally localized deep within the tissue, blue dye is of little value. An alternative optical detection technology can be found in near-infrared fluorescence imaging, which allows for real-time optical detection of lesions less than 10 mm deep [5]. The requirement of preoperative SN mapping data for surgical planning, however, dictates that fluorescence guidance has to be used in combination with the more common radioguided procedures.

Conventional SN mapping is performed using 20-600 nm radiocolloids. Because of their size, these exogenous compounds are recognized by the immune system, leading to accumulation in the SN [6]. We found that premixing of the clinically approved near-infrared dye indocyanine green (ICG) and an albumin-based radiocolloid (^{99m}Tc-nanocolloid) yields the non-covalent ICG-^{99m}Tc-nanocolloid complex. This complex has migratory properties similar to the parental ^{99m}Tc-nanocolloid [7]. Other hybrid nanoparticles also have the potential to guide SN biopsy [8]. A recent preclinical example of a hybrid SN tracer can be found in ^{99m}Tc-Tilmanocept labeled with the near-infrared dye Cy7 [9]. Alternatively, Cerenkov imaging of positron-emitting radionuclides has been proposed as a hybrid imaging technology; Thorek et al. demonstrated that lymph nodes could be detected after a subdermal injection of ^{18}F-FDG in the tail of a mouse [10].

Ideally, for more accurate lymph nodes staging, direct identification of nodal metastases would be preferred. Research is now focusing on the introduction of hybrid tracers that specifically target tumor tissue [11,12]: for example, by targeting prostate specific

biomarkers such as prostate specific membrane antigen or the gastrin-releasing peptide receptor. In this light, a hybrid prostate-specific membrane anti gentracer, labeled with indium-111 and the near-infrared dye CW800, was shown to facilitate radioactivity- and fluorescence-based detection of prostate specific membrane antigen-overexpressing tumors in mice [13].

INJECTION PROCEDURE

Before SN biopsy, transrectal ultrasound guidance is used to direct the tracer deposition toward the peripheral zone of the prostate (Figure 2A). Nevertheless, a recent study showed that in only 53% of patients was the tracer actually deposited in this area [14]. Interestingly, the same study also suggested that the location of tracer deposition influences the lymphatic drainage pattern. The main question is whether, in order to identify the true tumor-draining SNs, the tracer should be injected randomly in the peripheral zone of the prostate. It might be better to aim for peri- or intratumoral tracer deposition as is common in, for example, breast cancer and melanoma.

Multiparametric magnetic resonance (MR) imaging (T2-weighted, contrast-enhanced, and diffusion weighted) was shown to be promising in the identification of localized prostate cancer [15]. Integrating such MR imaging information with real-time acquired contrast-enhanced transrectal ultrasound may allow MR imaging-based navigation of injection needles toward the intraprostatic tumor foci.

PREOPERATIVE SENTINEL NODE IDENTIFICATION AND PLANNING OF THE SURGICAL PROCEDURE

After tracer injection, obtaining sequential anterior (Figure 2B) and posterior lymphoscintigraphic images is recommended in order to differentiate early draining SNs from higher-echelon nodes [16]. Via the introduction of single photon emission computed tomography imaging combined with computed tomography (SPECT/CT) imaging, the three-dimensional (3D) distribution of the radiocolloid can be directly placed in the anatomic context provided by the CT component (Figure 2C, D). Moreover, with SPECT/CT imaging, SNs not seen on lymphoscintigraphic images, such as those in the presacral region, can be identified [17]. As such, preoperative identification of the lymphatic drainage patterns allows surgeons to decide beforehand on the optimal and least invasive surgical approach.

Position emission tomography (PET)/CT, PET/MR imaging, or multiparametric MR imaging may, in the future, also be of value in planning surgical procedures. For example, lymph nodes mapping can be performed using radiocolloids suitable for PET imaging, via the direct identification of lymph nodes metastasis using targeted PET tracers or using ultrasmall superparamagnetic iron oxide particles or targeted dendrimers suitable for MR imaging.

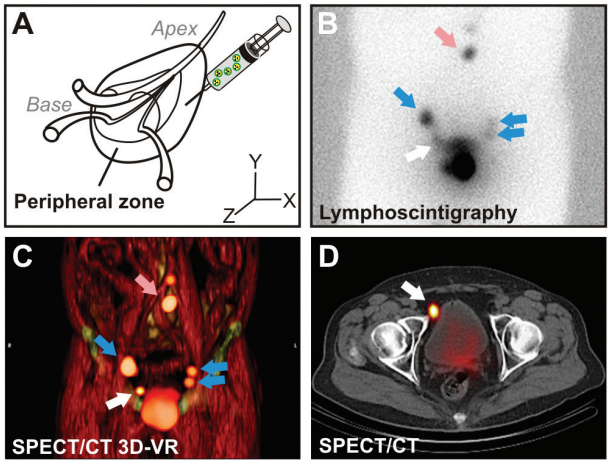

Figure 2. Preoperative Sentinel node mapping. After tracer injection in the peripheral zone of prostate (A), planar lymphoscintigraphic images are acquired to identify the SNs (B). SPECT/CT imaging allows identification of the anatomic location of the SNs and, in some cases, identification of SNs outside extended pelvic lymphadenectomy field; here, a paravesical SN (white arrow) not clearly detectable on the lymphoscintigraphic image was identified after SPECT/CT imaging (C-D). In this patient, five SNs were detected, with two being located outside extended pelvic lymphadenectomy field (white and pink arrows). SN = sentinel node; SPECT/CT = single photon emission computed tomography combined with computed tomography; 3D-VR = three-dimensional volume rendering.

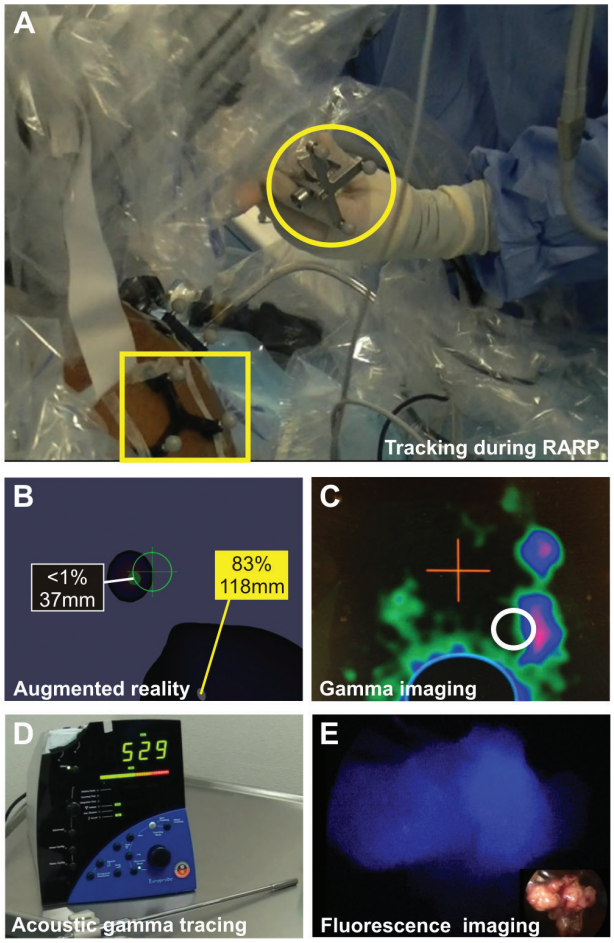

Figure 3. Intraoperative sentinel node identification. Via patient and tool tracking (yellow square and circle, respectively) (A), preoperatively acquired images can be translated into the operating room via 3D virtual reality navigation (B). A portable gamma camera allows visualization of the radioactive hot spots in 2D whereby a iodine-125 seed placed on the tip of the laparoscopic gamma probe (white circle) can be used for navigation (C). Hybrid tracers allow SNs to be acoustically traced using a gamma probe (D) and optically detected via fluorescence imaging (E). SN = sentinel node; 3D = three-dimentional; 2D = two-dimentional; RARP = robot-assisted radical prostatectomy.

TRANSLATION OF THE PREOPERATIVELY ACQUIRED IMAGING DATA TO THE OPERATION ROOM

Ideally, preoperatively acquired two-dimensional (2D) and 3D imaging data can be directly translated into the operating room to help navigate the surgeon to the areas of interest. Improvement is especially desired in localization of SNs near vital structures. Most straightforward is 2D navigation provided by a portable gamma camera [18]. By placing a iodine-125 seed on a laparoscopic gamma probe and performing dual-isotope gamma imaging, it is possible to surgically navigate a laparoscopic gamma probe toward the SNs (Figure 3C) [18].

The freehandSPECT technology, which is based on real-time tracking of both the patient and a gamma probe, enables the generation of intraoperative 3D SPECT data that can be viewed in augmented- or virtual-reality (i.e. mixed-reality) as an improvement over 2D imaging [19]. Alternatively, virtual-reality images can be generated using segmentation of SPECT scans (Figure 3B), CT scans [20] or using transrectal ultrasound images [21]. For robot-assisted procedures, one can load virtual-reality images and/or the preoperatively acquired 3D images into the TilePro function of the da Vinci robot (Intuitive Surgical Inc.). By attaching a 3D motion controller, it even becomes possible to manually manipulate these images [22].

For mixed-reality-based navigation in soft tissue, organ deformation and movement of organs or the cameras can be a serious problem. Hence, one must compensate for such movements by placing internal [20] or external [23] navigation aids (Figure 3A). A disadvantage of that approach is that it is difficult to correct for motion and organ deformation.

The fluorescence signature of a hybrid tracer, in combination with the tracking of a fluorescence laparoscope, can potentially be used to compensate for navigation errors of less than 10 mm [23].

INTRAOPERATIVE SENTINEL NODE IDENTIFICATION

Intraoperative SN identification is traditionally facilitated via acoustic gamma tracing (Figure 3D). With the introduction of robot-assisted laparoscopic procedures, not only are the senses of the surgeon reduced but also new challenges are faced for intraoperative gamma tracing. For example, the reduction in the movement of the gamma probe reduces the spatial accuracy of this technology even further. This is particularly problematic in areas near the injection site, where the high background signal hinders SN identification. With regard to a two dimensional protocol, the natural decay of the radioactive signal over time can reduce the detection sensitivity, which is already relatively low for the prostate.

Hybrid tracers such as ICG-^{99m}Tc-nanocolloid can be used to extend the conventional radioguided surgical procedure with the benefits that near-infrared fluorescence imaging

has to offer [24]. With this tracer, gamma tracing can be used to obtain a rough localization of the SN while the increased spatial resolution provided by the fluorescent signature enables accurate delineation of the SN (Figure 3E). An excellent example of the spatial information that fluorescence imaging provides during laparoscopic surgery was demonstrated by Jeschke et al., who showed lymphatic tracts draining from the prostate to the SN, as well as the SN itself [25].

PATIENT BENEFIT

We envision that symbiosis between the above-mentioned surgical guidance technologies may, in the future, provide patient benefit. Diagnostic images may help surgeons to select the least invasive surgical approach. Such planning should result in minimization of the exploration time. A one-to-one correlation between pre and intraoperatively generated images helps validate complete excision of lesions. Finally, more accurate surgical identification of diseased and anatomic structures may result in further reduction of complications associated with nodal dissection.

CONCLUSION

Optimal use of interventional molecular imaging techniques is expected to lead to new surgical treatment paradigms for indications such as the SN biopsy procedure for prostate cancer. One of the major challenges in the wide implementation of such technologies is their clinical translation. The first proof-of-concept studies, however, can provide a clinical basis for further improvements in this research field.

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