Setting-up a training programme for intraoperative molecular imaging and sentinel node mapping: how to teach? How to learn?

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REVIEW ARTICLE

Setting-up a training programme for intraoperative molecular imaging and sentinel node mapping: how to teach? How to learn?

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Abstract

Background The current expansion of image-guided surgery is closely related to the role played by radio-guided surgery in supporting the sentinel node (SN) procedure during more than three decades. The so-called triple approach (lymphoscintigraphy, gamma probe detection and blue dye) was not only essential in the seminal validation of the SN procedure but also a first collective learning effort based on skill transfer and outcome-related evaluation which laid the fundaments to delineate the field of intraoperative molecular imaging (IMI) based on a similar multimodality approach and multidisciplinary practice.
Methods These elements are also becoming valid in the current incorporation of SPECT/CT and PET/CT to existing and new protocols of IMI procedures and SN mapping concerning other clinical applications. On the other hand, there is a growing tendency to combine novel modern technologies in an allied role with gamma guidance in the operating room following the development of hybrid tracers and multimodal detection approaches. Against this background, learning initiatives are required for professionals working in this area.
Results This objective has led to a group of European practitioners with large experience in SN mapping and IMI applications to give shape to a programme made up out of specific learning modules aimed to be used as a conductive thread in peripherical or centralised training instances concerning the topic.
Conclusion The presented work, written as a tutorial review, is placed in an available prior-art context and is primarily aimed at medical and paramedical practitioners as well as at hardware and software developers.

Keywords Image-guided surgery · Sentinel node mapping · Intraoperative molecular imaging · Learning programme · Multimodality approach · Multidisciplinary practice

Introduction

The field of intraoperative molecular imaging (IMI) currently concerns multiple clinical applications and involves numerous modalities. Regarding nuclear medicine, the IMI development is narrowly related to the role played by radio-guided surgery in the validation and expansion of the sentinel node (SN) procedure in the past three decades. During this process, nuclear medicine has been part of a multimodal approach and a multidisciplinary practice. For instance, the seminal publications concerning SN biopsy in the last decade of the past century accentuated the need of a practice based on the triple approach (lymphoscintigraphy, gamma probe detection and blue dye) and sustained by specific medical disciplines (nuclear medicine, surgery, pathology). To homogenise SN practice, protocols for application in melanoma and breast cancer were elaborated and a learning period including thirty

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procedures for the involving clinical specialties was recommended and followed in most centres practising SN biopsy [1]. Skill-based aspects were stimulated through knowledge transfer initiatives (basic and advanced courses, supervised clinical stages, hands on workshops etc.) and outcome-based evaluation was recommended not only on the basis of SN identification rates to assess methodologic effectiveness, but also by assessment of false negative rates or eventually recurrence rates to measure reliability of the respective clinical series [2]. The evaluation of this successful validation process was performed in 2016 by a historical meta-analysis; it showed high SN identification rates together with low false negative rates for 154 studies including more than forty-four thousand patients in the period 1992–2012 [3]. Subsequently, the field of clinical applications of the SN procedure was extended to other malignancies such as penile cancer and vulvar cancer, and in this century oral cavity cancer, gynaecological malignancies (cervix, endometrial, ovary), urological cancers (prostate, bladder), gastrointestinal malignancies (stomach, colorectal) and others following similar models of quality assessment. The complexity of the procedure for many of these applications required the participation of new medical disciplines and a more sophisticated approach integrating modern imaging modalities able to combine functional and morphological aspects in the SN localisation. Here, the role of SPECT/CT has been essential becoming mandatory for clinical malignancies with complex lymphatic drainage. At the same time, due to higher requirements in the operating room, there was a growing tendence to incorporate novel modern technologies (more complex portable devices for gamma detection, fluorescence, navigation systems etc.) to complement gamma guidance in standard and robot-assisted surgical procedures. This process of expansion and evolution of the SN approach has been illustrated by the universal evaluation of the procedure which showed a significant increase in the number of publications on the National Library of Medicine website related to SN applications from 17 in 1992 to 15,618 in 2019 [4].

Based on the increasing clinical application of the SN procedure, various international scientific associations like the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Asociación Latinoamericana de Sociedades de Biología y Medicina Nuclear (ALASBIMN) and national societies prepared guidelines and recommendations to implement training and homogenise practice not only for the SN procedure but also for the ever growing field of IMI applications in different malignancies [5–9].

Moreover, in other organisations like the International Atomic Energy Agency (IAEA) efforts were made for knowledge transfer encompassing all radio-guided procedures in a wide concept known as GOSTT (Guided Intra-Operative Scintigraphic Tumour Targeting), which included not only SN applications but also other radio-tagged applications beyond the SN procedure [10, 11]. This was a first major integrative attempt concerning learning of image radio-guided procedures for countries outside Europe and many of the aspects integrated in GOSTT at that time are valid today to set-up a training programme in SN mapping and IMI applications.

Due to the current expansion of IMI applications as well as the rapid emergence of novel technologies, both learning and quality related aspects are required for future professionals working in this area. This objective has led to a group of European practitioners with large experience in SN mapping and IMI procedures to give shaping to a programme made up of specific modules aimed to be used as a conductive thread in peripherical and centralised training instances concerning the topic. The presented work is placed in an available prior-art context and is primarily aimed for medical and paramedical practitioners as well as developers.

This overview will be divided in eleven modules varying from clinical indications to how to set-up a training programme for SN mapping and IMI applications (Fig. 1). For every module, two knowledge levels will be distinguished:

a. Procedural knowledge which is defined as the "know how to do it" and is related to all applications in which SN and IMI technology play an important role. To evaluate this aspect for all novel IMI applications, it is possible to take the SN learning model based on both skill-related aspects and outcome-based evaluation as discussed previously in this introduction. Of course, skilled people cannot dominate all disciplines, but they can be trained in all of them (if available) in order to know, not only how to use, but also, how to indicate them in every clinical case. On the other hand, this is a pluridisciplinary effort.
b. Content knowledge which refers to the scientific basis involved in the SN and IMI applications (theories, principles etc.).

Because of didactic reasons, SN and IMI work will be repeatedly related in this review to the route of tracer administration to depict a target or index lesion. This may be based on local or systemic injections following three principal approaches: local radiocolloid administration as applied for SN biopsy, intralesional injection of a radiocolloid without migration or implantation of a radioactive seed in use for malignant lesion resection, and systemic administration of a tumour-seeking tracer for radio-tagged tumour resection. Since today, the majority of clinical IMI applications are related to local tracer administration, in this overview, emphasis is given to regional dissemination and consequently to N staging in the TNM classification. However, M staging is discussed in the light of the increasing role

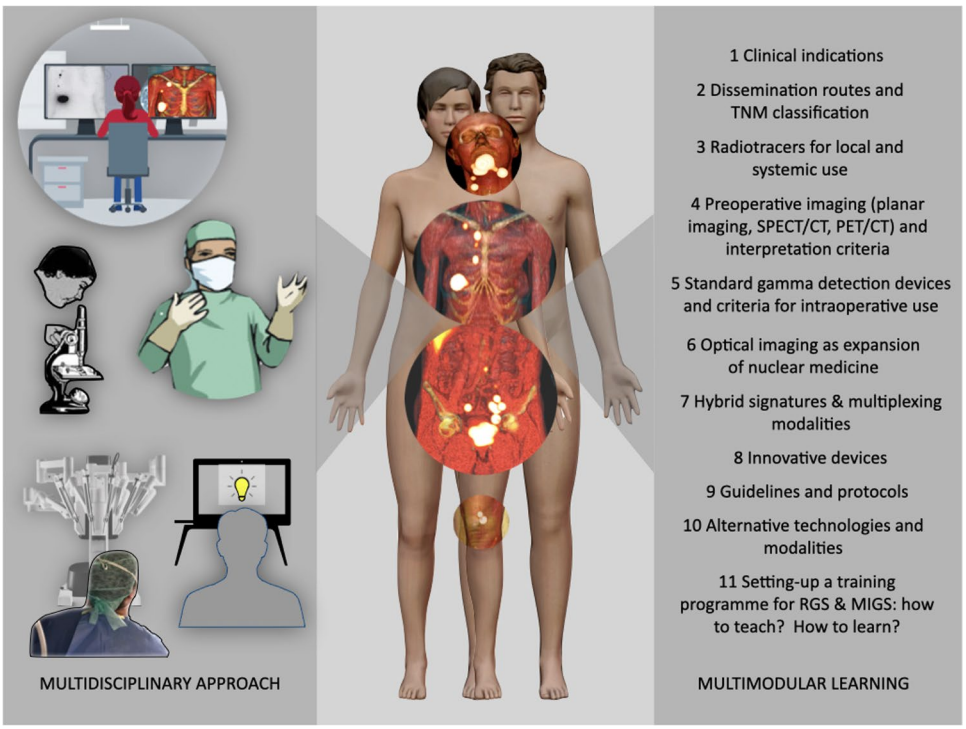

Fig. 1 Multidisciplinary approach on the left and proposed multimodular learning on the right. Both aspects are considered as key elements of how to set-up a training programme in molecular imaging-guided surgery

played by the use of systemic tracers for detection of distant metastases and the potential role of IMI for image-guided resection in the future. Finally, it is important to emphasise that the learning programme for SN and IMI proposed in this review is based on a multidisciplinary approach and a multimodular model (Fig. 1). For every discussed module, recommended key publications are indicated. The first ten modules refer to basic background information topics to be incorporated in teaching programmes whereas the last module addresses the possible organisational aspects to be delineated in their implementation.

Clinical indications

For this topic, and in the framework of the objectives of this review, we have consulted the most recent guidelines elaborated by international oncological and nuclear medicine societies as well as publications generated by field experts. Indications for IMI are directly related to the clinical problems to be solved. For SN applications, indications are oriented to detect metastases in early stages of cancer. For malignant lesion resection, for instance, in the context of oligometastatic cancer, clinical indication refers to advanced disease stages with as objective salvage surgery or radiotherapy intervention.

Regarding to SN biopsy, most clinical indications have been discussed and agreed on by several oncologic and nuclear medicine scientific associations or in consensus expert meetings. In the following paragraphs, clinical indications for the malignancies with SN biopsy playing a prominent role are summarised.

1. *Melanoma*: Initially indicated for lesions with intermediate thickness (T2 or T3; Breslow thickness of > 1–4 mm) in the most recent practice guideline update of the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) SN biopsy may also be considered for thin melanomas that are T1b (0.8–1-mm Breslow thickness or < 0.8 mm with ulceration). The procedure may be recommended for thick melanomas (T4; Breslow thickness of > 4 mm), after discussion with the patient of the potential benefits and risk of harms [12]. The guidelines elaborated by the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC) match the American recommendations with the additional precision that SN biopsy is generally recommended in patients with tumour thickness ≥ 1 mm or ≥ 0.8 mm with additional histological risk factors (ulceration, ≥ 1 mitosis/mm^2, microsatellites etc.) [13].
2. *Breast cancer*: SN biopsy is indicated in early-stage (cT1 or cT2 tumours) without cytological or histological evidence of axillary lymph node metastases. Furthermore, the ASCO advices to offer SN biopsy to patients who have operable breast cancer under the following strength of recommendation [14]: multicentric tumours (recom-

mendation: moderate), ductal carcinoma in situ (DCIS) when mastectomy will be performed (recommendation: weak), prior breast and/or axillary surgery (recommendation: strong), and preoperative neoadjuvant systemic therapy (recommendation: moderate). These categories were still considered as subject of discussion in the earlier published practice guidelines of the EANM and SNMMI [7]. Furthermore, SN biopsy is recommended for elderly and obese patients as well as for male breast cancer patients.

3. *Oral cavity cancer (OCC)*: SN biopsy is generally recommended for T1 or T2 squamous cell carcinoma. Recent surgical consensus guidelines recommend that the principal selection criteria for SN biopsy are that the tumour can be reliably resected with adequate margins and the defect repaired locally without requiring access to the neck. This may allow the patient to avoid adjuvant therapy to the primary site [15]. Eligibility for SN biopsy consists of patients with biopsy-proven OCC with clinically and radiologically established cN0-neck.
4. *Gynaecological cancer*: The common indications for SN biopsy are for early cervical cancer those carcinomas with > 5-mm depth of stromal invasion and ≤ 2 cm in greatest dimension (T1b1), carcinoma > 2 cm and ≤ 4 cm in greatest dimension (T1b2) and those with involvement limited to the upper two-thirds of the vagina without parametrial invasion and ≤ 4 cm in greatest dimension (T2a1) [16]. In endometrial cancer, SN biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease. It can be omitted in cases without myometrial invasion. On the other hand, surgical lymph node staging should be performed in patients with high–intermediate-risk/high-risk disease. SN biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II [17]. The SLN procedure is recommended in patients with unifocal squamous cell vulvar cancers of < 4 cm, > T1a, without suspicious inguinofemoral nodes [18].
5. *Urogenital cancer*: In penile cancer, patients with high-risk (≥ pT1b) tumours with cN0 groins are eligible for SN biopsy according to the EAU (European Association of Urology)-ASCO guidelines [19]. In prostate cancer, SN biopsy could be performed in intermediate- and high-risk patients if the estimated risk of lymph node metastases exceeds 5% with EAU guidelines or 2% with NCCN (National Comprehensive Cancer Network) guideline nomograms and PSMA PET/CT or any other conventional imaging modality without evidence of metastases.

Different from SN biopsy which is indicated in early cancer without evidence for regional metastases, in advanced cancer, IMI procedures have traditionally been indicated for resection of isolated malignant lesions in patients with suspected biochemical recurrence. This resection may be performed not only using intralesional radioactive tracer administration or seed implantation but also by systemic administration of tumour-seeking radiopharmaceuticals. Currently, in the context of oligometastatic disease, localisation diagnosis in patients with biochemical recurrence is predominantly based on imaging with an emerging important role for PET/CT following systemic tracer injection [20]. The most recent example is the use of PSMA ligands to guide metastases-directed interventional therapy in oligometastatic recurrent prostate cancer taking absolute PSA values and localisation of PSMA PET/CT-positive lesions as eligibility criteria [21]. However, although there is agreement to consider oligometastatic disease as an intermediary state between localised disease and widespread metastases, some discordance is rising about the number of metastases with indication for IMI guided resection. Also important is the characterisation of the disease recognising the categories de novo and repeat for oligometastases [20].

Dissemination routes and TNM classification

Knowledge about this issue is essential to understand the possibilities of SN mapping and IMI guidance and in this context, the model presented by Nathanson et al. [22] is recommended as a basic text to learn the mechanisms of metastasis through the lympho-vascular system. Although originally related to breast cancer, this model may be useful to understand the routes by which tumour cells gain access to blood and lymphatic capillaries. Recent evidence appears to indicate that tumour cells could enter the systemic circulation through the SN, which contradicts in a certain sense the current paradigm that access is only gained through blood vessels into and around the tumour. In this respect, the routes of lymphatic drainage from the site of primary tumours and the further dissemination in relation to the current TNM classification acquire relevance as study material and lymphoscintigraphy appear as mandatory in the majority of indications [23–25]. In the following paragraphs, we summarise the routes for the malignancies for which current clinical applications of SN mapping and IMI procedures play an important role:

1. *Melanoma*: Depending on the skin localisation of the primary lesion, the habitual drainage routes may concern the lymph node stations of the groins, axillae and neck. Less common routes are the epitrochlear/epicondyleal for melanomas of hands/forearms and the popliteal for those of foot/leg. For melanomas of the trunk besides groin or axilla, drainage to lymph nodes of the triangular intermuscular space on the back, bicipital sulcus and subcutaneously in the flank or adjacent to the

areola may occur. For head melanomas, frequent routes are the periauricular, parotid, submandibular and cervical. For a more detailed overview of the lymphatic routes of melanomas, the computer model of skin drainage configurated by Reynolds et al. [26] on the basis of lymphoscintigraphies in more than five thousand patients is recommended. With respect to the current TNM staging [24], N1/N2/N3 refers not only to regional dissemination on the basis of the number of involved lymph nodes in the draining basin but also to the presence of microsatellitosis, satellitosis or metastasis in transit indicated with "c" in addition to "a" (microscopic nodal metastasis, clinically occult), "b" (macroscopic nodal metastases, clinically detected). Concerning distant metastases, involvement of the central nervous system (CNS) is indicated as M1d in addition to M1a (skin, soft tissue including muscle and/or non-regional lymph nodes), M1b (lung) and M1c (non-CNS visceral).

2. *Breast cancer*: The principal lymphatic route concerns the axillary basin. Other lymph node groups for regional drainage are the internal mammary chain, intramammary, interpectoral, periclavicular and paramammary. In the axilla, caudal from the axillary vein, the three Berg's lymph node levels defined in relation to the pectoralis minor muscle. Level I includes the nodal external mammary, lateral axillary vein, subscapular and axillary vein groups. Lymph nodes of level II receive drainage directly from the breast but also from afferent vessels of level I lymph nodes. Most medial axillary nodes corresponding to level III may drain from other axillary groups but also from the subclavicular group and the subclavian trunk. Level III can also direct drainage from the breast through retromammary lymphatic vessels. Nodes located between the pectoral muscles are also known as Rotter's nodes. With respect to the internal mammary chain, the nodes of the first to fifth intercostal spaces drain the posterocentral and posteromedial parts of the breast. To deepen the lymphatic routes of the breast, the work of Clough et al. [27] is recommended. Concerning clinical regional staging, according to the eighth TNM edition, the ipsilateral supraclavicular nodal metastases are no longer considered stage IV disease in the American Joint Commission on Cancer (AJCC) Staging System, because of the direct drainage of the upper inner portion of the breast to the supraclavicular nodes. Involvement of these lymph nodes results in classification of these patients as AJCC nodal stage N3. IMC metastases result in classification as N1, N2 or N3 [28].
3. *Oral cavity cancer*: Based on the classification according to Robbins et al. [29], the lymph nodes in the neck have been subdivided into specific anatomic subsites and grouped into seven levels in each side of the neck. Level I includes the submental and submandibular lymph nodes. Level II contains the upper jugular lymph nodes that extend from the inferior border of the hyoid bone to the base of the skull. Level III includes the middle jugular nodes, and level IV the lower jugular nodes. The posterior border of regions II, III and IV is the posterior border of the sternocleidomastoid muscle, which is the anterior border of level V. Level VI contains the pretracheal and paratracheal nodes, the precricoid Delphian node and the perithyroidal nodes including the ones along the recurrent laryngeal nerves. Finally, level VII includes the superior mediastinal lymph nodes above the level of the innominate artery. Levels VI and VII have recently been subdivided in sublevels VIa (anterior jugular nodes), VIb (prelaryngeal, pretracheal and paratracheal nodes), VIIa (retropharyngeal nodes) and VIIb (retro-styloid nodes) in order to facilitate the daily practice of radiation oncology [30]. This latter approach also recognises the levels VIII (parotid group), IX (buccofacial group) and X (posterior skull group) that is subdivided in Xa (retroauricular and subauricular nodes) and Xb (occipital nodes). Some important reference anatomical points to localise SNs in relation to lymph node basins are muscles (e.g. sternocleidomastoid, digastric, omohyoid); vessels (e.g. jugular vein); organs (e.g. parotid gland) and other structures (hyoid bone, cricoid cartilage).
4. *Gynaecological cancer*: In vulvar cancer, lymphatic drainage is mainly bilateral and directed to the inguinal nodes whereas the lymphatic spread in cervical cancer may be bilateral because of the midline position of the uterine cervix; dissemination principally occurs to pelvic stations (parametrial, intern iliac, external iliac and presacral). For endometrial cancer, the pelvic pathway is the most common route principally for tumours located in the middle and lower parts of the uterus whereas for cancer in the upper corpus and fundus, the routes to junctional lymph nodes as well as common iliac and para-aortic nodes are also important. For ovarian cancer, the pattern of spread may be multidirectional with possible peritoneal, lymphatic and hematogenous dissemination. With respect to lymphatics, para-aortic and the lateral pelvic pathways are the principal routes. A compilation of the lymphatic spread in gynaecologic malignancies is given by Paño et al. [31]. In cervical and endometrial cancer, nodal involvement is designed as stage IIIC in the revised FIGO staging system with IIIC1 for pelvis lymph nodes and IIIC2 for para-aortic involvement [32].
5. *Urogenital cancer*: In penile cancer, lymphatic drainage is almost always bilateral with the inguinal lymph nodes as the first station. In prostate cancer, most common pathways include the extern iliac and obturator nodes as well as the internal iliac nodes. Less frequent

are the direct pathways to the common iliac lymph nodes as well as mesorectal and presacral regions [33]. All lymph nodes between the level of the iliac bifurcation and the level where the inferior epigastric artery arises from the external iliac artery are considered as regional lymph nodes and their involvement is indicated as N1. Nodal metastases above or below this pelvic area are considered distant metastases and indicated as M1a. M1b (skeleton) and M1c (lung, liver) indicate organ metastases [24].

Detection and resection of distant metastases become relevant for IMI-guided resection in patients with indication of biochemical recurrence. In general, recurrent cancer may be local (in the same place as the original cancer or very close to it), regional (in lymph nodes or tissues near the primary tumour) or distant (in lymph nodes outside the regional area or in organs or tissues far from the original cancer).

Local and systemic radiotracers for image-guided surgery

Due to the irruption of the SN procedure three decennia ago, nuclear medicine was abruptly confronted with the search for adequate radiocolloids in order to depict lymphatic drainage and SN identification immediately after their administration around the primary tumour [34]. In most countries, existing registered radiocolloids were preferred explaining in a certain manner both the geographical variability and the differences in particle size of the radiocolloids validated in the SN procedure and currently in use in the various continents. These aspects, as well as the new challenges in preparing albumin nanoparticle-based radiopharmaceuticals, are extensively discussed by Ballinger in a recent publication, which can be used as basic material for this study module in the aspects related to SN tracers [35]. The first generation of radiocolloids is until today the one most used for surgical SN biopsy. In Europe, there are various albumin nanoparticle-based radiopharmaceuticals varying from Nanocoll (Sorin/GE Healthcare) with $\geq 95\%$ of particles < 80 nm in diameter to SentiScint (Medi-Radiopharma) with $> 80\%$ of 100–600-nm particles. With approximately the same particle range as Nanocoll are Nanotop (Rotop), Nanoscan (Medi-Radiopharma) and Nanoalbumin (Medi-Radiopharma) also available.

In the last years, albumin nanoparticle-based radiotracers have been modified to facilitate their use in specific SN procedures. For instance, the fluorophore indocyanine green (ICG) has successively been added to Nanocoll [36], Nanotop [37] and more recently Nanoscan [38] to prepare hybrid tracers for use in SN biopsy of various malignancies and robot-assisted laparoscopic surgery. Probably ^{99m}Tc-tilmanocept is the first agent of a next SN tracer generation. This tracer appears to selectively bind to mannose receptors expressed on the surface of lymph node macrophages and dendritic cells reducing its migration to higher echelon nodes, despite a 7-nm diameter particle size. ^{99m}Tc-tilmanocept was commercially introduced this century and recently its current use in SN surgery, increasing in last years, has extensively been reviewed [39].

With respect to intravenously administered systemic tracers with subsequent accumulation in target lesions, in addition to the classical examples of [^{99m}Tc]Tc-sestamibi for SPECT/CT-guided resection of parathyroid adenomas and ^{99m}Tc-biphosphonates for image-guided resection of bone lesions, new approaches have become possible with different tracers for PET/CT such as [^{18}F]FDG, PSMA ligands and more recently FAPI ligands. The strength of these tracers rests on the possibility to perform diagnostic imaging when cancer recurrence is biochemically suspected and at the same time is eventually helpful to plan subsequent radio-tagged resection when malignant lesions are detected. To implement this latter option, the original radionuclide of the PET tracer can in some cases be replaced by technetium-99 m to enable SPECT/CT radio-guided resection. However, in the case of PSMA, this option is not able to detect all lesions depicted by PET/CT. In this context, efforts are being made to incorporate fluorophores to PET tracers in order to facilitate intraoperative bimodal detection. The potential of these approaches has been discussed in various recent publications which can be used as starting point to upgrade the topic [40–42].

Preoperative imaging and interpretation criteria

For this module, the emphasis will be on the contribution of nuclear medicine imaging (planar, SPECT/CT, PET/CT) which has become the standard for precision surgery in many applications. The underlying principles of nuclear medicine imaging as well as the design and capabilities can be found in a leading article on this issue [43]. A more recent review discussed not only basic aspects of SPECT and PET but also the advances in hybrid imaging including SPECT/CT, PET/CT and PET/MRI [44].

Concerning SN aspects, the combination of lymphoscintigraphy and SPECT/CT is the most frequently used for SN identification in the diverse clinical applications. Criteria to identify SNs on lymphoscintigraphy are based on the visualisation of lymph ducts, the time of appearance, the lymph node basin and the intensity of nodal uptake. Due to the integration of a fast high-end CT component to modern LVOF dual-head gamma cameras, SPECT/CT can be acquired in the same session as planar lymphoscintigraphy. SPECT/

CT-fused images based on multiplanar reconstruction (MPR) are able to visualise SNs in an anatomical environment indicating their location in relation to muscles, blood vessels and lymph node groups. The use of cross-reference lines allows the navigation between axial, coronal and sagittal planes. This facilitates the correlation with the CT component to assess which lymph nodes correspond with the radioactive SNs depicted on fused SPECT/CT images. The use of volume rendering may complement three-dimensional display by assigning different colours to anatomical structures such as vessels, muscle, bone and skin in order to obtain improved anatomical reference points. Essential for the subsequent search of SNs in the operating room is the nuclear medicine imaging report which needs to include the described SN location as accurately as possible; the discussion of the images with surgeons previous to the operation as well as the surgical and pathological feedback concerning operative findings is strongly recommended [45]. The impact of SPECT/CT has been evaluated in an international study supported by the IAEA which resulted in a surgical adjustment varying from 17% for breast cancer to 37% for melanoma and 64% for pelvic malignancies [46]. Due to the incorporation of the three-dimensional tomographic information to preoperative imaging protocols, the surgical paradigm evolved from "see and open" to "see, open and recognise", based on the anatomical landmarks provided by SPECT/CT to be identified by surgeons during the resection procedure (Fig. 2).

Regarding PET/CT, the preoperative approach is similar to that of planar images and SPECT/CT. MPR helps to identify target lesions and the correlation of fusion images with CT for anatomical feedback. However, it is necessary to consider some possible sources of false-positive and false-negative findings. In the case of the systemic tracer [^{18}F]FDG, the pattern of physiologic uptake needs to be evaluated in relation to the possible lesions to be resected. A practical approach is well-described by Kobayashi et al. for biopsy guided by FDG imaging [47] and is also recommended for PET/CT with PSMA ligands [48] and FAPI ligands [49].

Gamma detection devices and criteria for intraoperative use

Although the concept of radioguidance for surgery originated approximately seven decennia ago, it was only with the introduction of the SN procedure that its use gained in popularity and the acquisition of gamma probes became essential in most medical centres [50]. Basic considerations and criteria for use of intraoperative gamma detection devices can be found in the work of Heller and Zanzonico which emphasises some essential parameters such as sensitivity (or efficiency), energy resolution, contrast and spatial resolution [51]. In a recent overview, these parameters are discussed in relation to new devices for radioguidance classifying detection probes in four categories: low- to mid-energy ($\leq$400 keV) also called "gamma probes", high-energy (>400 keV) known as "high-energy gamma probes", beta + particle detection (positively charged electrons or

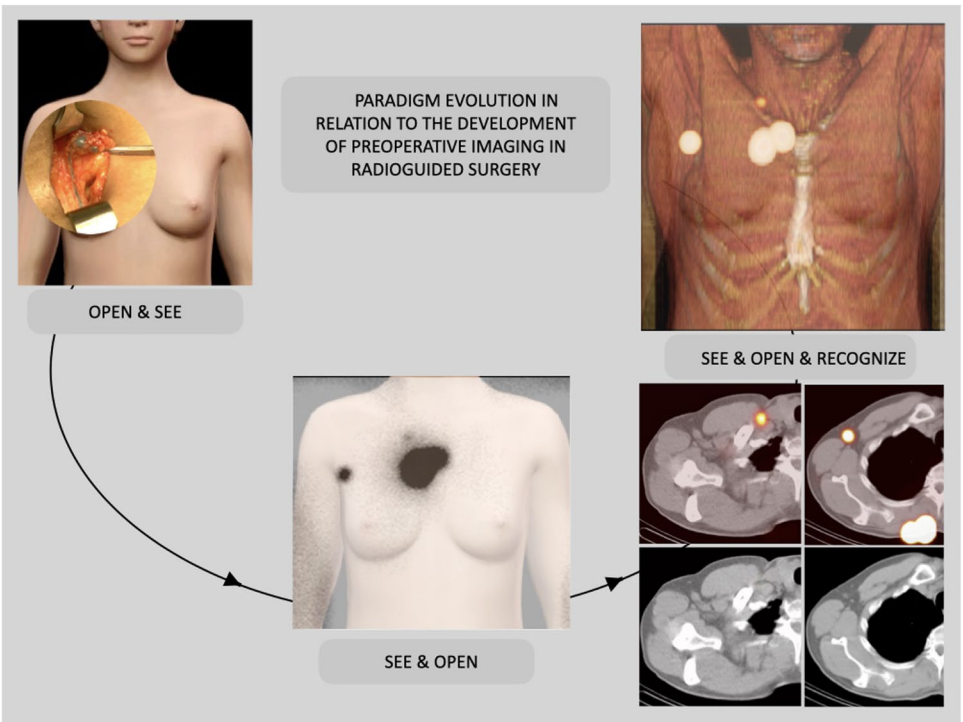

Fig. 2 Conceptual evolution of the role of preoperative sentinel node mapping for intraoperative molecular image guidance of surgery in a patient with a melanoma on the back. In addition to the two-dimensional information of planar images which transformed the initial paradigm from "open & see" (on the left) to "see & open" (middle), the incorporation of SPECT/CT three-dimensional information as illustrated on the right (top: volume rendering, below: cross sectional reconstruction) enables "see & open & recognise" by providing anatomical landmarks to localise sentinel nodes in right axillary and supraclavicular regions

positrons) called "beta + probes" and beta − particle detection (negatively charged electrons or negatrons) also called "beta − probes" [52]. Currently, most procedures are based on technetium-99 m (and to a lesser extent iodine-125 and indium-111) and this explains the popularity of gamma probes as standard of care for RGS; the other detection probes are principally used for investigational objectives. In spite of the efficiency of gamma probes, their main limitation is the inability to determine where the radiation is coming from. This limits the detection of small lesions, principally those located in the vicinity of the radiotracer injection.

The limitations of gamma probes have led to the development of portable gamma cameras (PGC) which are able to reduce the localisation time of targeted tissues by allowing two-dimensional mapping in a larger field of view. PGC can make images from different directions increasing the diagnostic accuracy of overlapping lesions or when the lesion is near the injection site. However, PGC are more voluminous than gamma probes reducing their manoeuvrability in the operating room. In analogy with gamma probes, PGC are designed for low- to mid-energy gamma ray detection and are popular in Spain and Latin American countries due to their high-resolution SN imaging. To study the development and future outlook of intraoperative PGC, we recommend a recent review of Farnworth and Bugby [53]. Also, the aspects related to radioprotection are included in this module.

Optical imaging as expansion of nuclear medicine

The concept of optical imaging as an expansion of nuclear medicine was introduced in 2013 in a tutorial review by Chin et al. in relation to hybrid imaging agents which can use both radionuclear and optical properties rather than using two separate chemical entities to achieve this extension [54]. Two types of specific luminescence imaging can illustrate this concept. On the one hand, hybrid agents generated following the addition of a fluorescent dye as ICG to a radioactive tracer. On the other hand, hybrid imaging agents resting on Cerenkov luminescence imaging (CLI) of beta-emitters. In this approach, both CLI and fluorescence detection were considered as allied technologies of radioguidance. Ten years later, the hybrid tracer based on the combination of a radioisotope and a fluorophore has demonstrated its value in different image-guided surgery applications using near-infrared (NIR) devices. By contrast, Cerenkov-based hybrid agents, despite their initial investigational success [55], have been less successful in clinical practice probably due to their much lower luminescence intensity which makes it necessary to develop specific imaging devices in contrast to fluorescence which can be used with existing equipment already applied for separate imaging in operating rooms.

The field of hybrid equipment for IMI procedures is currently in progress with increasing applications as reviewed by Bugby et al. [56]. They describe various categories with gamma-bright field imaging (e.g. freehand SPECT, PGC with optical support) and gamma-NIR fluorescence imaging as the most important. This development has led to a concept of multiplexing modalities which will be enunciated in the next module.

Hybrid signatures and multiplexing modalities

This study module is closely related to the previous one and refers to the integration of allied guidance technologies during the same procedure. This multiplexing of the complementary information of different signatures into a single procedure has received the denominations of hybrid, bimodal or multimodal in clinical practice and has significantly contributed to an expansion of IMI modalities. As emphasised by van Leeuwen et al. [42], integration of two signatures in a single bimodal/hybrid tracer ensures colocalisation of both signatures and promotes an advanced form of symbiosis (the best of both worlds) that empowers surgeons to improve intraoperative target delineation. The proof of concept has been exemplified by the integration of the radiotracer ^{99m}Tc-nanocolloid and the fluorescent dye ICG to obtain a hybrid tracer which has been used in different SN clinical applications with special value for head/neck and pelvic malignancies as evaluated by KleinJan et al. [57]. They concluded that: (a) bimodal identification is highly sensitive and concerns the same SN, as corroborated in their study (> 98% radioactive and > 95% fluorescent); (b) in contrast to the unimodal use of fluorescence, the identification of the SN by the hybrid radiotracer did not influence operative logistics in relation to the intervals between injection and detection (prolonged diagnostic window); (c) the hybrid radiotracer allowed excision of the SN without performing a previous resection of the primary tumour as is the usual practice when using only radiocolloids and the SN is located in the vicinity of the primary lesion; and (d) the margins of primary tumour resection can be determined without impediments in contrast to what usually occurs when using only blue dye. Another important aspect concerns the nodal uptake mechanism. For this, it is important to solve the gap in sensitivity between radiotracers, which due to their high specific activity can be used for imaging at a picomolar dose, and fluorescent agents, which are frequently used in the micromolecular range. Although the clinical application of hybrid tracers for SN surgery appears to support the use of lower quantities of fluorescent dye, it is necessary to optimise the proportions of radiotracer and fluorophore in the design of hybrid tracers for systemic use in the context of IMI. This is a crucial

aspect because of fluorescence guidance may become less accurate in tissues with relatively low accumulative rates leading to an underestimation of the number of targets when fluorescence is not supported by nuclear medicine [56]. With respect to IMI-related detection equipment in the operating room, hybrid tracer surgery for resection of metastases may be logistically performed with the same devices used for hybrid SN surgery. Novel devices for this objective will be discussed in the following module.

Innovative devices

The essential of the learning programme discussed in this tutorial review for IMI is based on the cumulative knowledge and experience of the last 30 years of SN surgery which has strongly been characterised by technological advances enabling its evolution to a wider IMI concept (Fig. 3). This has been one of the fields where nuclear medicine has continuously contributed with important tools and devices, many of them falling into the category of disruptive innovations [58]. A classic example has been the incorporation of preoperative gamma camera imaging and intraoperative gamma counting to the SN procedure in the early nineties of the past century. This technological contribution gave the SN concept the necessary impulse to be validated replacing extended lymph node dissection by selective SN biopsy as standard of care in melanoma, breast cancer and other malignancies. Although technological advances of nuclear medicine may be unprecedented transforming protocols and operating modes to conform the new technologies, with respect to precision surgery, most innovations have been oriented to provide tools to optimise existing approaches making them widely available through successive incremental developments. An example concerns the development of specific tools for robot-assisted surgery which has disruptively replaced standard surgical procedures. For robot-assisted laparoscopy in the context of SN biopsy and regional lymph node dissection, an adjustment of nuclear medicine contribution has been necessary with the incorporation of hybrid tracers and flexible laparoscopic gamma probes (Drop-In devices) replacing both unimodal tracers and rigid laparoscopic gamma probes. Drop-In devices, currently commercially available, enable a superior detection rate and manoeuvrability than the traditional laparoscopic gamma probes when used in robot-assisted procedures and have optimised SN detection in territories of pelvic lymphatic drainage even in combination with fluorescence. A further incremental development inspired on the Drop-In concept is the recently designed Click-On probe which allows integration of the device in the same pincers of the robot. Due to a better dexterity, the Click-On device appears to provide a 40% reduction in movements compared with the Drop-In probe. The advances of robotic IMI-related surgery and the engineering steps towards a full integration of radioguidance with allied technologies in a hybrid concept have been recently reviewed by van Oosterom et al. [59]. In another review, Wendler et al. [60] didactically explain other

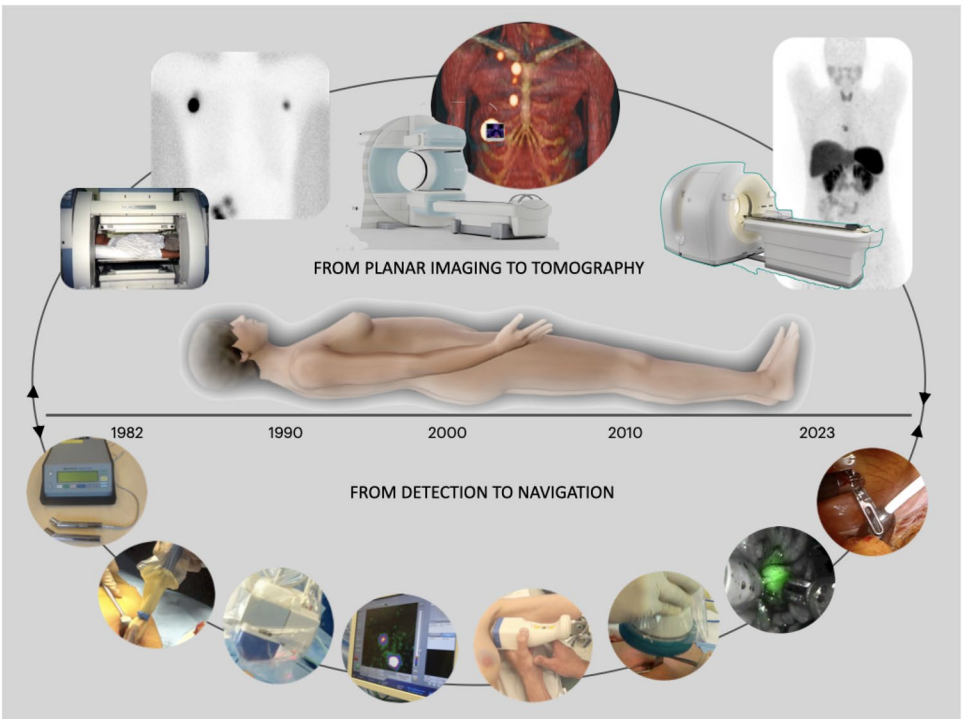

Fig. 3 Technological evolution in the last decades concerning image-guided surgery using radioguidance and allied technologies. Gamma camera-related planar scintigraphy (left) evolves to SPECT/CT (middle) and PET/CT (right) for preoperative mapping (top half). In addition, for intraoperative target identification (bottom half), technological evolution is illustrated from left to right by the successive incorporation of gamma probes, portable gamma cameras, free-hand SPECT 3D navigation, fluorescence imaging and flexible laparoscopic gamma probes

innovative aspects like artificial intelligence and navigation as well as virtual and augmented reality strategies in addition to freehand emission tomography and intraoperative scintigraphy.

Also, in the field of preoperative molecular imaging, new devices have been introduced in recent years. These technological advances have recently been discussed in the above-mentioned review of van der Meulen et al. [44]. With respect to SPECT/CT, a new generation of cameras with a ring-configuration detector using the semiconductor CZT (Cadmium-Zinc-Telluride) offers improved sensitivity and resolution together with the possibility to replace the current acquisition and display of planar lymphoscintigraphy in a new concept of lymphotomography as standard of imaging for both dynamic and static images. Concerning PET/CT, the recently introduced long axial scanner will reinforce the role of molecular imaging in the detection of metastases for IMI guidance with tumour-seeking PET tracers [57].

The module innovative device is a dynamic one and needs to be continuously upgraded for every teaching programme. A literature review of Bugby et al. [56] concerning hybrid intraoperative imaging techniques evaluated 60 papers directly related to hybrid IMI out a total of 2367 yielded using online reference databases. These findings not only confirm the growing applications of hybrid imaging for surgery but also illustrate the technological challenges for teaching and future practice for all specialised disciplines involved in IMI procedures.

Guidelines, protocols and textbooks

As mentioned in the introduction of this review, various international scientific associations and national societies prepared guidelines and recommendations to implement training and homogenise practice of both the SN procedure in different malignancies and other IMI applications. Specific guidelines elaborated by the EANM, mostly in collaboration with the SNMMI, can be found for melanoma [5, 6], breast cancer [7], oral cavity cancer [8] and gynaecological malignancies [9]. In general, EANM guidelines, summarising all clinical and technological recommendations for validated applications, constitute a valid future study material for professionals in the field of IMI. Also, specific guidelines elaborated by oncological societies give extensive information about clinical indications and practice of SN biopsy [11–14]. Additionally, in the course of the years, various textbooks concerning SN mapping and IMI procedures have been published of which the most recent are recommended [61, 62].

Furthermore, in the past decade, the IAEA started a programme for knowledge transfer encompassing all surgical applications based on preoperative scintigraphy and intraoperative radioguidance in the wide concept known as GOSTT which included not only SN applications but also other IMI applications beyond the SN procedure. This major integrative attempt concerned knowledge transference for countries outside of Europe in the context of a training programme in surgery related to radioguidance. IAEA workshops were based on the designation of a medical centre in a country as a course venue and during 1 to 2 weeks, practitioners from countries of the area were involved in surgical operations, seminars, hands on practices etc. with specific technological tools under supervision of teachers recognised by the IAEA as experts. A textbook elaborated by the same IAEA containing excellent study material was used as textbook for participants. This multidisciplinary teaching initiative still can be used as common thread of the topic and may constitute one of the fundaments for the expansion of IMI possibilities [10].

Until now, guidelines, protocols and textbooks have been principally oriented to the SN procedure which may be considered as a model for IMI following local tracer injection. In the near future, attention must be given to the generation of specific guidelines for IMI based on systemic tracers. In this, the model validated for PSMA image-guided surgery may contribute to a separate teaching module [63]. Similar to multidisciplinary consensus initiatives reached in the past for novel SN applications (e.g. prostate cancer) by means of the Delphi methodology [64] also for PSMA, a discussion procedure incorporating the involved disciplines is necessary; a first step in this has recently been effectuated for both IMI procedure [65] and cancer-related image [66]. The PSMA model may also constitute a good basis for work with other systemic PET tracers.

Alternative technologies and modalities

Concerning the SN procedure in recent years, various alternative methods have been introduced for intraoperative detection. The majority of these modalities have been found to be comparable but not superior to radioguidance for SN detection in the operating room which is the standard of care today. However, most of these validations have been focussed on SN biopsy in breast cancer. Furthermore, they are limited in providing imaging for preoperative mapping with a similar effectiveness as SPECT/CT in combination with lymphoscintigraphy. This may be explained by a reduced sensitivity for imaging outside the body (e.g. fluorescence as monomodality) or by logistical reasons (e.g. MRI with superparamagnetic iron oxide nanoparticles). By contrast, the improved accessibility of SPECT/CT in most departments of nuclear and molecular imaging together with well-standardised protocols facilitates preoperative imaging for the SN procedure in virtually all applications including

those for complex procedures like robot-assisted surgery. The same conclusion can be drawn for the accessibility of PET/CT for preoperative imaging in oligometastatic disease. An extensive review on the role of radioguidance for surgery in comparison to new alternative methods principally for SN biopsy in breast cancer recently summarised technical and practical aspects as well as advantages and limitations [67].

Setting-up a training programme for preoperative mapping and IMI: how to teach? How to learn?

This last module, addressing organisational aspects, concerns the initial question of this proposal: how to set-up a training programme in preoperative mapping and IMI? In this tutorial review, we previously have proposed ten modules concerning basic background information to be used as a conductive thread to configurate specific programmes in the future. Probably during the implementation of these programmes, other modules will be added or fused according to the teaching praxis. In approximately three decades after the introduction of SN biopsy, several teaching initiatives in this issue have been implemented principally based on knowledge transference of the preoperative and intraoperative aspects of the SN procedure (Fig. 4). In this respect, training efforts concerning current and future IMI procedures can take the lessons from the previous period to delineate specific teaching programmes.

For example, some important organisational aspects to take into account in the design of teaching prospects for IMI might be:

- Incorporation of basic IMI knowledge to nuclear medicine bundles in medical, paramedical and technological training studies. Due to the scarce space given to nuclear medicine in current teaching curricula in most European countries, the preparation of a compact document on IMI procedures by national nuclear medicine societies may be helpful to implement this aspect.
- Incorporation of advanced interventional IMI aspects in training programmes for clinical and technological specialisms. Since significant inter-centre heterogeneity exists concerning the application and technical implementation of SN procedures on a national and international level, it is of outmost importance that basic and

Fig. 4 Examples of image-guided surgery teaching initiatives with audio-visual course on CD (top left), symposium with hands-on sessions (bottom left), learning course by webinar (bottom right) and textbooks (top right and middle)

Fig. 5 Hands-on simulating practice for target detection in open surgery (above) using a standard gamma probe (on the left), a portable gamma camera in combination with a gamma probe (middle) and a freehand SPECT probe (on the right). For laparoscopic surgery (bottom), a portable gamma camera in combination with a rigid laparoscopic gamma probe for standard laparoscopy (on the left) and a flexible Drop-In probe in combination with fluorescence imaging (circles) for robot-assisted surgery (on the right) are tested

advanced IMI teaching becomes incorporated in specialty programmes of those disciplines involved in SN biopsy. This accounts for nuclear medicine physicians as well as for surgeons, urologists, gynaecologists and ear-nose-throat specialists. Implementation of interdisciplinary teaching modules as part of their training programmes, both theoretical and practical, will help to homogenise daily practices and maintain high-quality state-of-the-art IMI procedures among centres.

– Promotion of fellowships and internships in recognised reference IMI-related centres. A necessary process of certification based on external review (e.g. EANM, IAEA) after visitation to give accreditation to centres with intensive IMI practice will help to give structure to this activity. The experience in past decades of centres such as the NKI/AVL (Netherlands Cancer Institute/Antoni van Leeuwenhoek) of Amsterdam and the University Hospital Clinic of Barcelona illustrates the potential of this approach. In these centres, dozens of trainees received both theoretical and practical expertise on SN mapping and IMI procedures.
– Master-class courses and hands-on practice for experts in accredited reference centres and/or specialised instances. In these courses, both standard of care SN/IMI procedures and novel technological approaches can be treated. An illustrative model can be found in the experience of the NKI/AVL of Amsterdam where in 1998 and 1999, more than two hundred surgeons, nuclear physicians and pathologists from different countries were trained in specific aspects of the SN procedure. Similar master-class courses were organised by the IAEA in the last two decades in Latin America, Africa and Asia. This model has also been followed in different countries under auspice of some national scientific societies. An illustrative example is constituted by the biannual workshops organised at the University Hospital Clinic of Barcelona concerning all IMI aspects on the basis of seminaries and hands on sessions (Fig. 5).
– Specific skills to be acquired in recognised specialised centres for technological assisted surgery. Examples of the potential teaching of advanced technological assisted aspects can be found in centres like the ORSI Academy of Melle, Belgium (https://www.orsi-online.com) and the Amsterdam Skill Centre (ASC Academy) in the Netherlands (https://asc.amsterdam).
– Elaboration of specific guides for use of new techniques and technologies concerning surgical innovation and good practice robotic-assisted surgery as effectuated by the Royal College of Surgeons of England [68, 69]. Also, e-learning initiatives may be useful. An example can be found in the IAEA site (https://www.iaea.org/resources/e-learning-course/advances-in-radioguided-surgery). Also, consensus meetings with participation of the disciplines involved in IMI procedures are necessary not only to clarify clinical indications but also to homogenise current and future technological standards. Methodological processes as Delphi may play an important supportive role in this matter.

For all above-mentioned teaching prospects, it is necessary to emphasise that SN mapping and IMI procedures are based on teamwork, where development and teaching follow a multidisciplinary approach with integration of different disciplines and the necessary collaboration between medical and technical developers in a context of continuous knowledge transfer.

Conclusions

The field of IMI applications is growing and currently concerns not only SN biopsy for different malignancies but also other image-guided procedures related to local and systemic tracer administration. This process has been characterised by the gradual incorporation of imaging technologies for preoperative mapping like SPECT/CT and PET/CT as well as for intraoperative use. In this context, teaching initiatives for clinical specialties and technical developers appear to be necessary. Therefore, the presented work has intended to give shape to a programme made up out of specific basic knowledge learning modules as well as organisational aspects aimed to be helpful as an eventual conductive thread in training instances concerning the topic.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma. A multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. Ann Surg. 1999;230:453–65.
2. Nieweg OE. False-negative sentinel node biopsy. Ann Surg Oncol. 2009;16:2089–91.
3. Niebling MG, Pleijhuis RG, Bastiaannet E, et al. A systematic review and meta-analyses of sentinel lymph node identification in breast cancer and melanoma, a plea for tracer imaging. Eur J Surg. 2016;42:466–73.
4. Moncayo VM, Grady EE, Alazraki NP, Aarsvold JN. Sentinel-lymph-node multicenter trials. Semin Nucl Med. 2020;50:56–74.
5. Alazraki N, Glass EC, Castronovo F, et al. Procedure guideline for lymphoscintigraphy and the use of intraoperative gamma probe for sentinel lymph node localization in melanoma of intermediate thickness 1.0. J Nucl Med. 2002;43:1414–8.
6. Bluemel C, Herrmann K, Giammarile F, et al. EANM practice guidelines for lymphoscintigraphy and sentinel lymph node biopsy in melanoma. Eur J Nucl Med Mol Imaging. 2015;42:1750–66.
7. Giammarile F, Alazraki N, Aarsvold JN, et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging. 2013;40:1932–47.
8. Giammarile F, Schilling C, Gnanasegaran G, et al. The EANM practical guidelines for sentinel lymph node localization in oral cavity squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2019;46:623–37.
9. Giammarile F, Bozkurt MF, Cibula D, et al. The EANM clinical and technical guidelines for lymphoscintigraphy and sentinel node localization in gynaecological cancers. Eur J Nucl Med Mol Imaging. 2014;41:1463–77.
10. International Atomic Energy Agency (IAEA), ed. Guided intraoperative scintigraphic tumour targeting (GOSTT): implementing advanced hybrid molecular imaging and non-imaging probes for advanced cancer management. Vienna: IAEA; 2014. https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1648web-19833477.pdf
11. Valdés Olmos RA, Vidal-Sicart S, Giammarile F, et al. The GOSTT concept and hybrid mixed/virtual/augmented reality environment radioguided surgery. Q J Nucl Med Mol Imaging. 2014;58:207–15.
12. Wong SL, Faries MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology clinical practice guideline update. J Clin Oncol. 2018;36:399–413.
13. Garbe C, Amaral T, Peris K, et al. European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – update. Eur J Cancer. 2020;126:159–77.
14. Lyman GH, Somerfield MR, Bosserman LD, et al. Sentinel lymph node biopsy for patients with early-stage breast: American Society of Clinical Oncology clinical practice guide update. J Clin Oncol. 2017;35:561–4.
15. Schilling C, Stoeckli SJ, Vigili MG, et al. Surgical consensus guidelines on sentinel node biopsy (SNB) in patients with oral cancer. Head Neck. 2019;41:2655–64.
16. Cibula D, Raspollini MR, Planchamp F, et al. ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer – Update 2023*. Int J Gyn Cancer. 2023;33:649–66.
17. Concin N, Matias Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gyn Cancer. 2021;31:12–39.
18. Oonk MHM, Planchamp F, Baldwin P, et al. European Society of Gynaecological Oncology guidelines for the management of patients with vulvar cancer - update 2023. Int J Gyn Cancer. Published Online: 27 June 2023. https://doi.org/10.1136/ijgc-2023-004486.
19. Brouwer OR, Albersen M, Parnham A, et al. European Association of Urology-American Society of Clinical Oncology collaborative guideline on penile cancer:2023 update. Eur Urol. 2023;83:548–60.
20. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21:e18–28.
21. Alberto M, Yim A, Papa N, et al. Role of PSMA PET-guided metastases-directed therapy in oligometastatic recurrent prostate cancer. Front Oncol. 2022;12: 929444.
22. Nathanson SD, Krag D, Kuerer HM, et al. Breast cancer metastasis through the lympho-vascular system. Clin Exp Metastasis. 2018;35:443–54.
23. Ji H, Hu C, Yang X, et al. Lymph node metastasis in cancer progression: molecular mechanisms, clinical significance and therapeutic interventions. Signal Transduct Target Ther. 2023;8:367.
24 Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 8th ed. Wiley Blackwell: Hoboken; 2017.

25. Donohoe KJ, Carroll BJ, Chung DKV, et al. Summary: appropriate use criteria for lymphoscintigraphy in sentinel node mapping and lymphedema/lipedema. J Nucl Med. 2023;64:525–8.
26. Reynolds HM, Walker CG, Dunbar PR, et al. Functional anatomy of the lymphatics draining the skin: a detailed statistical analysis. J Anat. 2010;216:344–55.
27. Clough KB, Nasr R, Nos C, et al. New anatomical classification of the axilla with implications for sentinel node biopsy. Br J Surg. 2010;97:1659–65.
28 Giuliano AE, Conolly JL, Edge SB, et al. Breast cancer - major changes in the American Joint Committee on Cancer eight edition cancer staging manual. CA Cancer J Clin. 2017;67:290–303.
29 Robbins KT, Shaha AR, Medina JE, et al. Committee for neck dissection classification, American Head and Neck Society. Consensus statement on the classification and terminology of neck dissection. Arch Otolaryngol Head Neck Surg. 2008;134:536–8.
30 Grégoire V, Ang K, Budach W, 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;110:172–81.
31. Paño B, Sebastià C, Ripoll E, et al. Pathways of lymphatic spread in gynecologic malignancies. Radiographics. 2015;35:916–45.
32. WHO classification of tumours. Female genital organ tumours, international agency for research on cancer. IARC, 5th edn. Lyon, 2020.
33. Paño B, Sebastià C, Buñesch L, et al. Pathways of lymphatic spread in male urogenital pelvic malignancies. Radiographics. 2011;31:135–60.
34. Valdés Olmos RA, Hoefnagel CA, Nieweg OE, et al. Lymphoscintigraphy in oncology: a rediscovered challenge. Eur J Nucl Med. 1999;26:S2–10.
35. Ballinger JR. Challenges in preparation of albumin nanoparticle-based radiopharmaceuticals. Molecules. 2022;27:8596.
36. KleinJan GH, Bunschoten A, van den Berg NS, et al. Fluorescence guided surgery and tracer-dose, fact or fiction? Eur J Nucl Med Mol Imaging. 2016;43:1857–67.
37. Manca G, Garau LM, Mazzarri S, et al. Novel experience in hybrid tracers: clinical evaluation of feasibility and efficacy using ICG-99mTc Nanotop for sentinel node procedure in breast cancer patients. Clin Nucl Med. 2021;46:e181–7.
38 Vreeburg MTA, Azargoshasb S, van Willigen D, et al. Comparison of two hybrid sentinel node tracers: indocyanine green (ICG)-99mTc-nanocolloid vs. ICG-99mTc-nanoscan from a nuclear medicine and surgical perspective. Eur J Nucl Med Mol Imaging. 2023;50:2282–91.
39. Rovera G, de Koster EJ, Rufini V et al. 99mTc-Tilmanocept perfomance for sentinel node mapping in breast cancer, melanoma, and head and neck cancer: a systematic review and meta-analysis from a European expert panel. Eur J Nucl Med Mol Imaging. 2023;50:3375–89
40. Azari F, Zhang K, Kennedy GT, et al. Precision surgery guided by intraoperative molecular imaging. J Nucl Med. 2022;63:1620–7.
41. Boekestijn I, van Oosterom MN, Dell'Oglio P, et al. The current status and future prospects for molecular imaging-guided precision surgery. Cancer Imaging. 2022;22:48.
42. van Leeuwen FWB, Schottelius M, Brouwer OR, et al. Trending: radioactive and fluorescent bimodal/hybrid tracers as multiplexing solutions for surgical guidance. J Nucl Med. 2020;61:13–9.
43. Zanzonico P. Principles of nuclear medicine imaging: planar, SPECT, PET, multi-modality, and autoradiography systems. Rad Research. 2012;177:349–64.
44 van der Meulen NP, Strobel K, Viana Miranda Luna T. New radionuclides and technological advances in SPECT and PET scanners. Cancers. 2021;13:6183.
45. Valdés Olmos RA, Vidal-Sicart S. SPECT/CT image generation and criteria for sentinel lymph node mapping. In: Mariani G, Vidal-Sicart S, Valdés Olmos RA, editors. Atlas of lymphoscintigraphy and sentinel node mapping. Italy: Springer; 2020. p. 171–83.
46. Jimenez-Heffernan A, Ellman A, Sado H, 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;56:1338–44.
47. Kobayashi K, Bhargava P, Raja S, et al. Image-guided biopsy: what the interventional radiologist needs to know about PET/CT. Radiographics. 2012;32:1483–501.
48. Barbosa FG, Queiroz MA, Nunes RE, et al. Revisiting prostate cancer recurrence with PSMA PET: atlas of typical and atypical patterns of spread. Radiographics. 2019;39:186–212.
49. Chandekar KR, Prashanth A, Vinjamuri S, Kumar R. FAPI PET/CT imaging-an updated review. Diagnostics (Basel). 2023;13:2018.
50. Povoski SP. The history of radioguided surgery: early historical milestones and the development of later innovative clinical applications. In: Herrmann K, Nieweg OE, Povoski SP (eds) Radioguided surgery. Springer International, Switzerland, 2016, pp 3–12
51. Heller S, Zanzonico P. Nuclear probes and intraoperative gamma cameras. Sem Nucl Med. 2011;41:166–81.
52. Vidal-Sicart S, Valdés Olmos RA. New devices in radioguided surgery. Clin Transl imaging. 2023. https://doi.org/10.1007/s40336-023-00566-4
53. Farnworth AL, Bugby SL. Intraoperative gamma cameras: a review of development on the last decade and future outlook. J Imaging. 2023;109:102.
54. Chin PTK, Welling MM, Meskers SCJ, et al. Optical imaging as expansion of nuclear medicine: Cerenkov-based luminescence vs fluorescence-based luminescence. Eur J Nucl Med Mol Imaging. 2013;40:1283–91.
55. Klein JS, Mitchell GS, Cherry SR. Quantitative assessment of Cerenkov luminescence for radioguided brain tumor resection surgery. Phys Med Biol. 2017;62(10):4183–201.
56. Bugby SL, Lees JE, Perkins AC. Hybrid intraoperative imaging techniques in radioguided surgery: present clinical applications and future outlook. Clin Transl Imaging. 2017;5:323–41.
57. KleinJan GH, van Werkhoven E, van den Berg NS, et al. The best of both worlds: a hybrid approach for optimal pre- and intraoperative identification of sentinel lymph nodes. Eur J Nucl Med Mol Imaging. 2018;45:1915–25.
58. Valdés Olmos RA, Rietbergen DDD, Vidal-Sicart S. About disruptive innovations in radioguided precision surgery. Clin Trans Imaging. 2023. https://doi.org/10.1007/s40336-023-00553-9
59. van Oosterom MN, Azargoshasb S, Slof LJ, et al. Robotic radioguided surgery: toward full integration of radio- and hybrid-detection modalities. Clin Trans Imaging. 2023. https://doi.org/10.1007/s40336-023-00560-w.
60 Wendler T, van Leeuwen FWB, Navab N, et al. How molecular imaging will enable robotic precision surgery. The role of artificial intelligence, augmented reality, and navigation. Eur J Nucl Med Mol Imaging. 2021;48:4201–24.
61. Mariani G, Vidal-Sicart S, Valdés Olmos RA, editors. Atlas of lymphoscintigraphy and sentinel node mapping, a pictorial case-based approach. Italy: Springer; 2020.
62. Hermann K, Nieweg OE, Povoski SP, Eds. Radioguided surgery: current applications and innovative directions in clinical practice, 1st, editors. New York. Springer: NY; 2016.
63. Berrens AC, Knipper S, Marra G, et al. State of the art in prostate-specific membrane antigen-targeted surgery – a systematic review. Eur Urol Open Sci. 2023;54:43–55.
64. Van der Poel HG, Wit EM, Acar C, et al. Sentinel node biopsy for prostate cancer: report from a consensus panel meeting. BJU Int. 2017;120:204–11.
65. DellÓglio P, Mazzone E, Buckle T, et al. Precision surgery: the role of intra-operative real-time image guidance – outcomes from

a multidisciplinary European consensus conference. Am J Nucl Med Mol Imaging. 2022;12:74–80.
66 Fendler WP, Eiber M, Beheshti M, et al. PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. Eur J Nucl Med Mol Imaging. 2023;50:1466–86.
67. Cuccurullo V, Ropa M, Catalfamos B, Cascini GL. Role of nuclear sentinel lymph node mapping compared to new alternative imaging methods. J Pers Med. 2023;13:1219.
68. Robotic-assisted surgery: a pathway for the future. A guide to good practice. Royal College of Surgeons of England. https://www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/robotic-assisted-surgery/. Accessed July 2023
69. Surgical innovation, new techniques and technologies. A guide to good practice. Royal College of Surgeons of England, February 2019. https://www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/robotic-assisted-surgery/