Sentinel node imaging and radioguided surgery in the era of SPECT/CT and PET/CT: toward new interventional nuclear medicine strategies

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Sentinel Node Imaging and Radioguided Surgery in the Era of SPECT/CT and PET/CT

Toward New Interventional Nuclear Medicine Strategies

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Abstract: We review recent technological advances and new clinical indications for sentinel node (SN) and radioguided surgery in order to delineate future tendencies of interventional nuclear medicine in this field. A literature research was performed in PubMed to select relevant articles to be used as key references for analysis of the current approaches and tendencies in SN and radioguided surgery, as well as the evolving contribution of nuclear medicine intervention techniques to the various clinical applications. For classic indications such as melanoma and breast cancer, the incorporation of the SN approach based on the combined use of existing and new preoperative and intraoperative technologies in high-risk patient categories is becoming an emerging area of clinical indication. For SN biopsy staging in other malignancies with more complex lymphatic drainage, the incorporation of sophisticated tools is most helpful. The consecutive use of PET/CT and the SN procedure is increasing as a potential combined approach for the management of specific areas such as the axilla and the pelvis in patients at high risk of regional dissemination. Also, for the management of locoregional metastasis and oligometastatic disease, interventional nuclear medicine techniques are becoming valuable alternatives. The extended experience with SN biopsy is leading to technological advances facilitating the incorporation of this procedure to stage other malignancies with complex lymphatic drainage. New nuclear medicine–based approaches, incorporating SPECT/CT and PET/CT to guide resection of SNs and occult metastases, have recently been gaining ground.

Key Words: new tracers and technologies, interventional nuclear medicine, radioguided surgery, sentinel node

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After almost 3 decades since the introduction of sentinel node (SN) biopsy for melanoma and breast cancer, there is an increasing use of this procedure in the staging of other malignancies. New technological tools for both preoperative imaging mapping and intraoperative detection have enabled the application of the procedure even in deeply located cancers in situations of complex lymphatic drainage such as oral cavity, urological, and gynecological malignancies.[1] Extended experience with SN procedure currently constitutes one of the fundaments for the expanse of radioguided surgery to other fields in which systemic tracer administration or intralesional radioactive deposition is necessary to detect and remove malignant lesions. In the same area, various allied technologies such as fluorescence and ultrasound have reinforced in the last years the use of radioguided surgery in a hybrid direction. Most recent advances are based on growing interactions among these different tools now available for nuclear medicine and cancer surgery. This includes hybrid imaging (SPECT/CT, PET/CT), hybrid tracers, and virtual navigation systems, as well as robot-assisted surgery.

Against this background, the dynamic concept of GOSTT ("guided intraoperative scintigraphic tumor targeting")[2,3] was incorporated a few years ago to englobe all developments in this area of nuclear medicine intervention, which include both preoperative image mapping and intraoperative detection. A common aspect for all nuclear medicine intervention techniques is the administration of a radiotracer to depict a target or index lesion, and in this context, 4 approaches have been delineated. For the first approach, SN procedures today follow the classic approach for SN biopsy based on the local administration of a radiocolloid at the tumor site, enabling the subsequent localization of draining SNs by means of lymphoscintigraphy and SPECT/CT. To accomplish this, objective radiocolloids with different particle sizes are available.[4] A second approach targets the resection of primary tumors or metastases with the use of direct intralesional administration of a radiotracer with relatively large particle size facilitating retention at the injection site and subsequently the resection of the lesion following a procedure known as ROLL ("radioguided occult lesion localization").[5] In recent years, radioactive ^{125}I seeds have been introduced as an alternative for intralesional tracer injection principally in patients receiving neoadjuvant treatment. This approach is known as RSL ("radioguided seed localization").[6] The third approach regarding breast cancer and other malignancies uses a combination of SN biopsy with simultaneous lesion excision where a radiocolloid with appropriate particle size enabling both lymphatic migration and injection site retention is used in an approach known as SNOLL ("SN and occult lesion localization") and has been applied for breast cancer and other malignancies.[7] Finally, the fourth approach uses the systemic administration of radiotracers with preferential accumulation in target lesions facilitating tumor visualization by SPECT/CT or PET/CT and subsequent resection by radioguided surgery. Examples include the use of ^{99m}Tc-sestamibi for SPECT/CT-guided resection of parathyroid adenomas, PET/CT to guide resection of different ^{18}F-FDG–avid tumor lesions, and more recently PET/CT

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in combination with SPECT/CT to localize metastases expressing prostate-specific membrane antigen (PSMA) in prostate cancer.[8] Figure 1 shows a schematic overview of clinical applications where nuclear medicine intervention is required.

Preoperative Mapping Using SPECT/CT and PET/CT as Roadmap for Image-Guided Surgery

Either by local or systemic radiotracer administration, the key for radioguided intervention is the generation of preoperative imaging to localize SNs and target lesions accumulating tracers. This preoperative mapping has constituted an important component of the SN procedure as a helpful roadmap for surgeons and nuclear physicians. The first and most classic example of preoperative mapping has been lymphoscintigraphy following radiocolloid injections, and a time sequential approach generated suitable images to depict lymphatic drainage and the lymph node basins at risk of metastatic dissemination from a primary tumor. Lymphoscintigraphy transformed the paradigm of radioguided surgery personalizing SN biopsy for every individual patient by identifying SNs in both expected and unusual locations, as well as enabling their marking on skin in order to subsequently guide the surgical approach.[9] Recently, SPECT/CT was added to SN mapping as a new component in the protocol of preoperative mapping. In addition to the functional SPECT information, this tool contributed with the morphologic elements of CT. Incorporating anatomical landmarks, the resulting SPECT/CT fused images provide detailed information about the SN location in relation to blood vessels, muscles, and other structures essential for optimal surgery.[10] The combination of lymphoscintigraphy and SPECT/CT facilitates the extension of SN procedures to other malignancies with complex lymphatic drainage such as oral cavity cancer,[11] prostate cancer,[12] and cervical cancer.[13]

In general, the contribution of SPECT/CT to both SN visualization and surgical approach in proportion to the complexity of lymphatic drainage as demonstrated in a large multicenter study.[14]

In search of improved resolution for preoperative mapping in comparison with SPECT/CT, procedures using PET tracers have been proposed. An interesting example is the use of interstitial injections of ^{18}F-FDG into the uterine cervix followed immediately by dynamic PET along with delayed 1-hour PET/CT in cervical and endometrial malignancies.[15] The rationale for the locally administered FDG is an attempt to identify metastasis in FDG-avid lymph nodes, and in this series, 3 true-positive and 2 false-positive cases out of 23 patients were found.[15] A most basic approach to apply PET has been based on the conversion of chemical entities traditionally used for lymphatic mapping, and in this context, lymphoscintigraphy with locally administered ^{68}Ga-NOTA-Evans blue was used for SN mapping in combination with systemically administered ^{68}Ga-NOTA-RM26 for detection of lymph node metastases in breast cancer patients. In this study, the SUVmax of ^{68}Ga-NOTA-RM26 was significantly higher in metastatic SNs than in nonmetastatic SNs.[16] A different approach has been based on ^{89}Zr-nanocolloid preoperatively injected under guidance of endoscopy to map drainage to SNs in early-stage colon cancer using PET/CT. In this study, the intraoperative exploration at the sites indicated by PET/CT along with indocyanine green (ICG) was not able to find 6 SNs located close to the primary tumor.[17] A similar preoperative approach with a high-energy gamma probe for intraoperative localization was used in a feasibility study in oral cavity carcinoma after injections of ^{89}Zr-nanocolloid around the primary lesion. The intraoperative probe missed 3 of 13 SNs.[18]

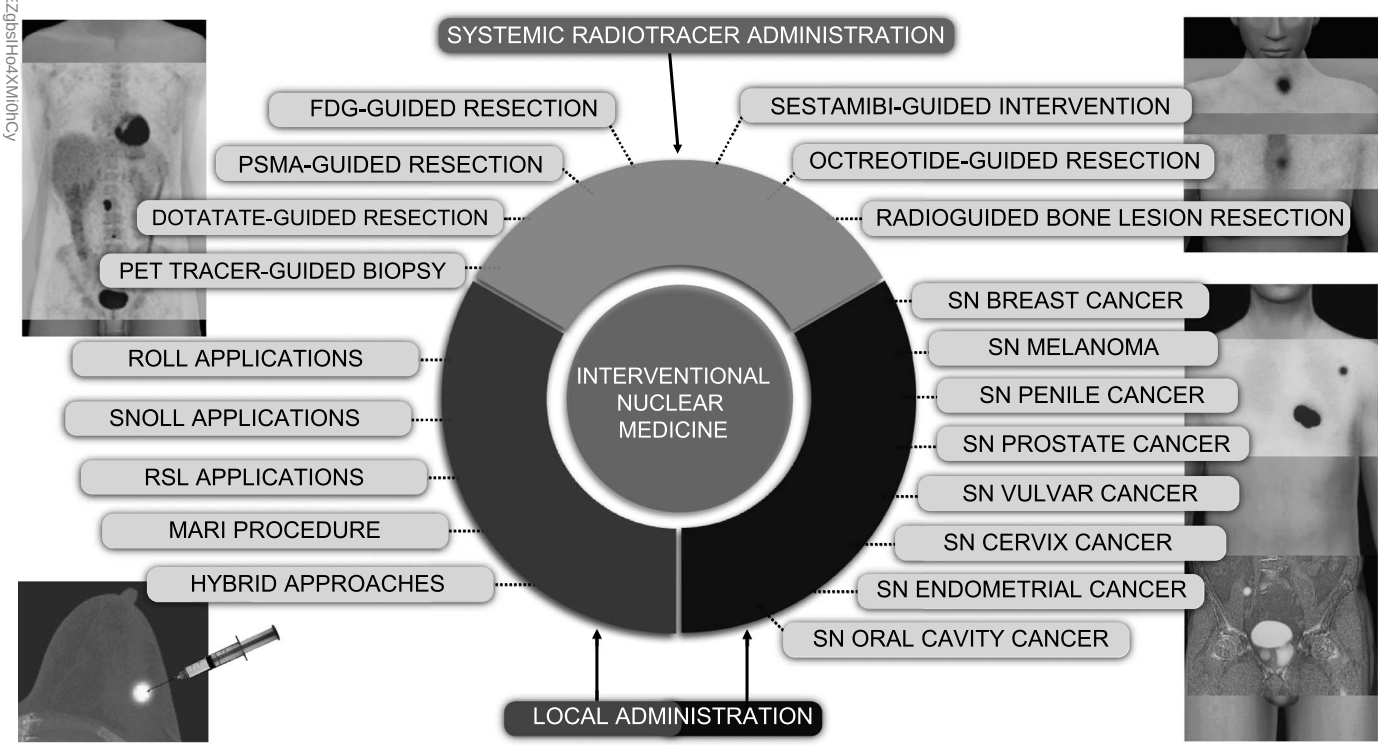

FIGURE 1. Schematic overview illustrating current interventional nuclear medicine possibilities. Most frequent SN applications are related to black in the diagram, whereas applications for radioguided lesion resection after local administration are part of the dark gray group. The upper section is related to light gray and includes various examples of nuclear medicine interventions after systemic radiotracer administration.

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Developing New Radiotracers and Hybrid Intervention Approaches to Improve Sentinel Node Identification

Recently, more specific GOSTT tracers have been developed. The radioactive component of SN biopsy has relied on first-generation radiotracers. These radiocolloids were already in use prior to the SN era for lymphoscintigraphy in the differential diagnosis of peripheral edema and intracavitary lymph effusion or for oncological purposes such as irradiation of the internal mammary chain in breast cancer.[9] When SN biopsy was introduced, the procedure rapidly incorporated preoperative lymphoscintigraphy and intraoperative gamma probe detection using a single radiotracer administration. However, because of its prompt migration from the injection site and the necessity to identify lymph nodes directly draining from the primary tumor as SNs, lymphoscintigraphy had to incorporate a dynamic study to cover the drainage as soon as possible after injection. This early study was sequentially followed by early and delayed planar static images to facilitate the differentiation between SNs and non-SN lymph nodes, which are both seen as radioactive nodes on imaging due to the passage of tracer particles from the first- to the second-tier nodes. Based on this approach, the biodistribution of a wide variety of radiocolloids used for SN identification in different countries and continents has been established,[4] leading in general to the prevailing paradigm that not all depicted radioactive nodes are necessarily SNs. A new paradigm associating all radioactive nodes with SNs was hypothetically considered feasible for radiotracers with high uptake retention at first echelon lymph nodes and negligible overflow to secondary lymph nodes. This goal is difficult to achieve with the first generation of radiocolloid tracers and probably constitutes the principal challenge for a next generation of SN radiotracers and approaches.

A new-generation radiotracer is ^{99m}Tc-tilmanocept, which is available in the United States and Europe. With an average molecular size of 7 nm, ^{99m}Tc-tilmanocept can be considered as a small particle (same size as human serum albumin) radiotracer for SN detection. However, because of the improved CD206 receptor affinity of its mannose component in surface macrophages, this tracer may combine increased SN uptake with accelerated migration from the injection site.[19] In recent literature, the use of ^{99m}Tc-tilmanocept has been found to be effective for SN localization in melanoma,[20] breast cancer,[21] and oral cavity malignancies.[22] Despite the high effectivity of the tracer for lymphatic drainage and SN mapping, less attention has been given to the evaluation of aspects such as clearance from the injection site and the relationships between uptake in SNs and non-SN lymph nodes. In a series including 29 patients with melanoma or breast cancer, non-SN ^{99m}Tc-tilmanocept uptake was perceived only in 16 of a total of 35 draining lymph node basins with an SN/non-SN ratio averaging 6.6 at the 2-hour images. The ratio between injection site radioactivity and SN uptake decreased with an average of 68% at 2 hours in comparison with ratios at 15 minutes, which is associated with a rapid migration of the tracer from injection site accompanied by increasing SN uptake.[23] The rapid migration of ^{99m}Tc-tilmanocept from the injection site could facilitate the detection of SN in the vicinity of the primary lesion. This may be helpful in malignancies located in areas of dense lymphatic network such as the head and neck. However, series based on a head-to-head comparison in the same patient illustrating the superiority of ^{99m}Tc-tilmanocept over conventional radiocolloids have not been reported.[19]

A different rationale aiming to solve similar limitations in the operating room has been based on the development of fluorescent radiocolloids combining radioactivity and fluorescence signature in 1 agent.[24] This approach requires both a hybrid tracer and specific equipment for near-infrared (NIR) fluorescence detection in addition to that used for gamma guidance. The combination of gamma guidance (high tissue penetration and limited spatial resolution) and NIR imaging (limited tissue penetration and high resolution) is complementary.[25] Most clinical investigations have used the self-assembling of ICG and ^{99m}Tc-nanocolloid to form the hybrid tracer ICG-^{99m}Tc-nanocolloid for SN mapping in a wide gamma of applications in different malignancies varying from head and neck and melanoma to urological and gynecological cancers.[25] With a similar biodistribution for lymphatic mapping as ^{99m}Tc-nanocolloid,[26] ICG-^{99m}Tc-nanocolloid preserves preoperative imaging for the intraoperative procedure including reliable SN identification, not influenced by surgical logistics such as timing between dye administration and surgery or the necessity to perform primary lesion resection prior to SN biopsy. The resection margins of the primary lesion are not visually hindered as they might be with the use of blue dye.[27]

In general, the use of ^{99m}Tc-tilmanocept as well as ICG-^{99m}Tc-nanocolloid could be advantageous in areas such as head and neck with lymph nodes located in the proximity of primary tumors.[28,29] With a similar objective, ^{99m}Tc-tilmanocept for preoperative SPECT/CT mapping has been combined with ICG-nanocolloid (without ^{99m}Tc) for intraoperative SN detection in oral cavity cancer.[30] Figure 2 illustrates the approaches based on the separate use of ^{99m}Tc-tilmanocept and ICG-^{99m}Tc-nanocolloid.

Technological Developments Facilitating Radioguided Work Under Sophisticated Conditions Such as Robot-Assisted Procedures

Sentinel node biopsy localizing operating room equipment for melanoma and breast cancer was established 30 years ago. The original approach was based on guidance by means of a gamma probe providing acoustic signals for SN detection and blue dye, which gave surgeons a visual aid to individualize lymphatic channels and lymph nodes. Currently, the procedure has gradually evolved to a unimodal approach resting almost exclusively on gamma-probe detection. Not only some disadvantages of blue dye (surgical field blurring, skin coloring, possibility of anaphylactic reactions) but also its negligible additional contribution (<1%) to identify nonradioactive SNs have led to the substantial reduction of this modality.[31] In some hospitals, the intraoperative work with a gamma probe has been complementarily supported by the use of sensitive portable gamma cameras, which better demonstrate SNs, increasing surgical confidence.[32]

In many centers, the use of a portable gamma camera has also been a valuable tool for SN resection by means of standard laparoscopy in patients with pelvic malignancies.[33,34] However, with the introduction of robot-assisted laparoscopy for SN biopsy, the portable gamma camera fell into disuse for this particular role. In addition, rigid laparoscopic gamma probes are increasingly being complemented or replaced, by NIR fluorescence detection.[25,35] Illustratively, gamma probes and NIR equipment have both recently been incorporated by consensus to the SN practice in prostate cancer.[36]

In the field of specific instrumentation for nuclear medicine intervention, the introduction of a tethered DROP-IN small probe may stimulate the use of radioguidance for laparoscopy. This original innovation solves many of the limitations of rigid laparoscopic gamma probes and is able to freely scan every direction in the abdominal cavity without requiring a separate trocar. The probe, particularly developed for robot-assisted laparoscopy, is connected to a wire resulting in its freely maneuvering by the surgeon using the forceps of the robot. The rotational freedom of the DROP-IN probe enables tracing of SNs even in dorsal locations.[37] Besides SN resection, the DROP-IN probe has been successfully used to localize and remove lymph node metastases expressing PSMA in robot-assisted salvage

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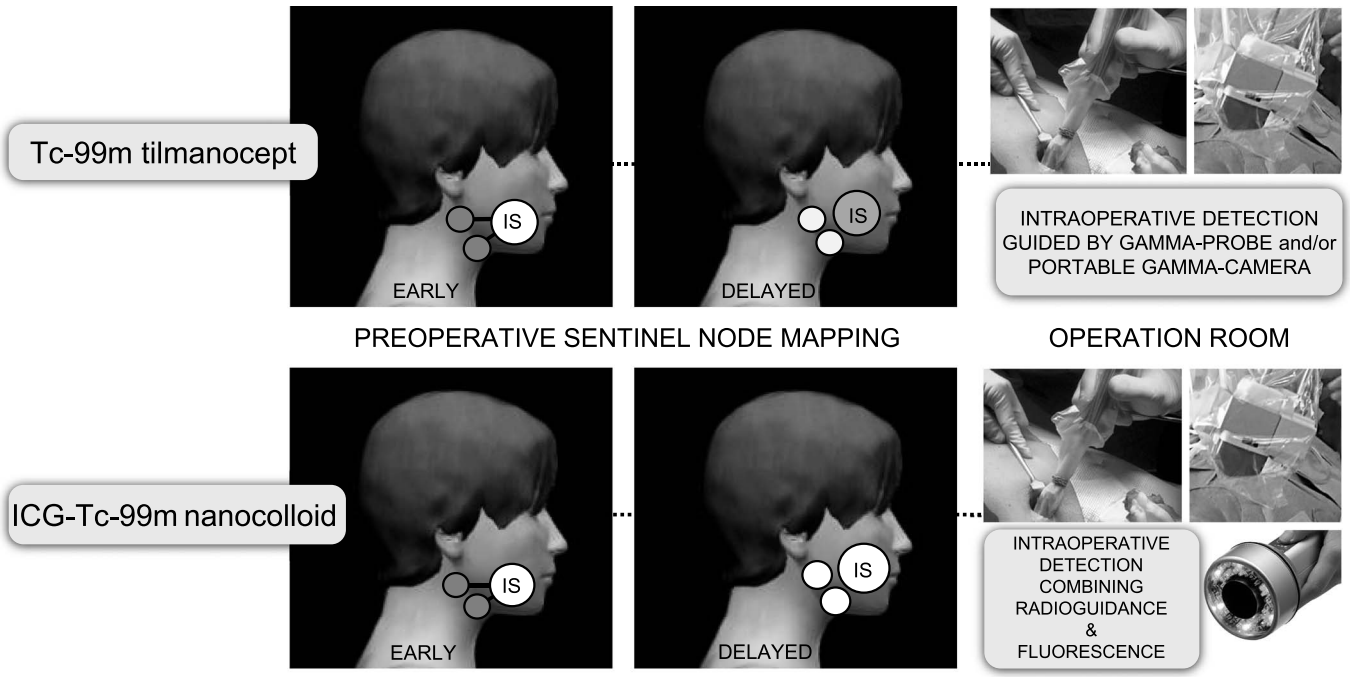

FIGURE 2. Schema illustrating strategies with new-generation tracers for SN detection in the vicinity of the injection site (IS). On preoperative SN imaging, ^{99m}Tc-tilmanocept increasing uptake in 2 SNs is accompanied by fast tracer migration from IS (upper row) that facilitates its radioguided identification at the operating room. For the hybrid tracer ICG-^{99m}Tc-nanocolloid (lower row), migration from IS is slower, but the high resolution of fluorescence signals is added to radioguidance for accurate intraoperative SN identification.

surgery for recurrent prostate cancer.[38] In recent years, the DROP-IN gamma probe[39] has become commercially available (Fig. 3).

Future Challenges for Interventional Nuclear Medicine

The consecutive use of PET/CT and SN location and biopsy is increasing as a potential combined approach in the specific management of patients at high risk of metastatic dissemination.

For instance, in patients with resectable early-stage breast cancer, neoadjuvant systemic treatment (NST) has become a standard of care, and the pattern of response is currently used to tailor systemic and locoregional treatment. This implies management based on escalating treatment in nonresponders and de-escalating treatment in responders.[40] With respect to the axilla, de-escalating surgery may help both patients without axillary lymph node involvement and patients with low-burden node-positive lymph node disease.[41] The incorporation of the latter category is relatively new for interventional nuclear medicine and has become available

FIGURE 3. Available DROP-IN probes for robot-assisted radioguided surgery. On the left, the first introduced model (Eurorad, Eckbolsheim, France) in use during an intraoperative procedure. The other 2 models are displayed together with an AA battery to illustrate their dimensions and correspond to, respectively, Lightpoint Medical (Chesham, United Kingdom) and Crystal Photonics (Berlin, Germany).

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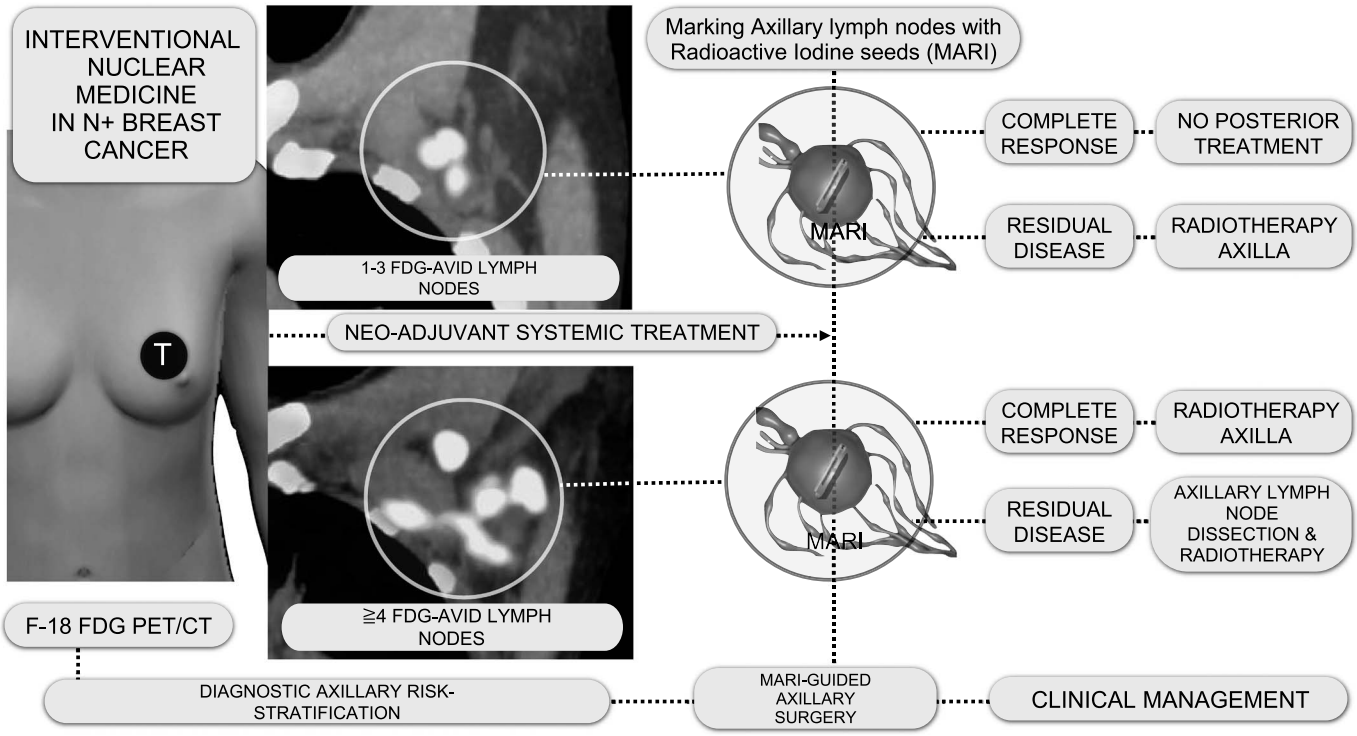

FIGURE 4. Schematic summary of algorithm[42,43] proposed to manage the axilla using ^{18}F-FDG PET/CT previous to NST to stage and stratify the axilla, and the MARI procedure for post-NST staging in breast cancer patients with initial axillary lymph node involvement (N+).

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following the evaluation with ^{18}F-FDG PET/CT, SN biopsy and more recently with the so-called MARI (**m**arking **a**xillary lymph nodes with **r**adioactive **i**odine seeds) procedure.[42] Because of the high positive predictive value of ^{18}F-FDG PET/CT and the acceptable false-negative rate of the MARI procedure, a specifically designed algorithm to manage axillary treatment resulted in a reduction of 82% in axillary lymph node dissection. In this approach, ^{18}F-FDG PET/CT is used pre-NST to stage and stratify the axilla, and the MARI procedure for post-NST staging (Fig. 4).[43] The additional incorporation of SN biopsy to MARI appears to further reduce the false-negative rates when the approach is combined.[44]

A similar example of combined approach concerns the use of PSMA PET/CT and the SN procedure to stage the pelvis in high-risk prostate cancer in an attempt to find an alternative to extended pelvic lymph node dissection. Although most evaluations have used both nuclear medicine modalities separately, recently their combined application led to 100% sensitivity in the identification of N1 patients with a correct pelvic regional staging in 94%. In this evaluation concerning clinically N0 intermediate or high-risk prostate cancer, PSMA PET/CT was first used in all patients, and the SN procedure only in patients with negative PSMA.[45]

Another challenge concerns the use of nuclear medicine intervention in oligometastatic disease for which the diagnosis frequently is based solely on imaging findings.[46] One of the most recent examples of this approach concerns the use of radioguidance to remove PSMA-expressing lymph nodes in salvage surgery for prostate cancer recurrence. Using ^{68}Ga-PSMA PET/CT for diagnosis followed by ^{99m}Tc-PSMA for SPECT/CT and subsequent radioguided resection, all visualized lesions on preoperative scanning could be removed.[47]

Recently, the combined use of lymphatic mapping procedures for identifying micrometastases and PSMA PET/CT to yield the most reliable identification of macrometastases has been discussed emphasizing the essential aspect of preoperative imaging to guide the urologist to the area of interest at the operating room (Fig. 5).[48]

Other examples of recent nuclear medicine innovation for intervention are stereotactic breast biopsy guided by lesion uptake of ^{99m}Tc-sestamibi systemically administered,[49] ^{68}Ga-PSMA Cerenkov luminescence to assess prostate surgical margins in prostate cancer patients undergoing radical prostatectomy,[50] ^{68}Ga-DOTATATE for preoperative PET/CT imaging followed by intraoperative gamma probe–guided resection of neuroendocrine tumors,[51] and the use of RSL to guide resection of suspicious nonpalpable lymph nodes in the groin, axilla, and head and neck.[52]

CONCLUSIONS

The large experience with SN biopsy has been the basis for the development of technological tools facilitating the incorporation of this procedure to stage other malignancies with complex lymphatic drainage. This reinforces the role of nuclear medicine for image-guided surgery contributing to the increasing use of SPECT/CT and PET/CT for preoperative mapping to guide resection of SNs and occult metastases. The consecutive use of PET/CT and radioguided procedures has gained ground as a potential combined

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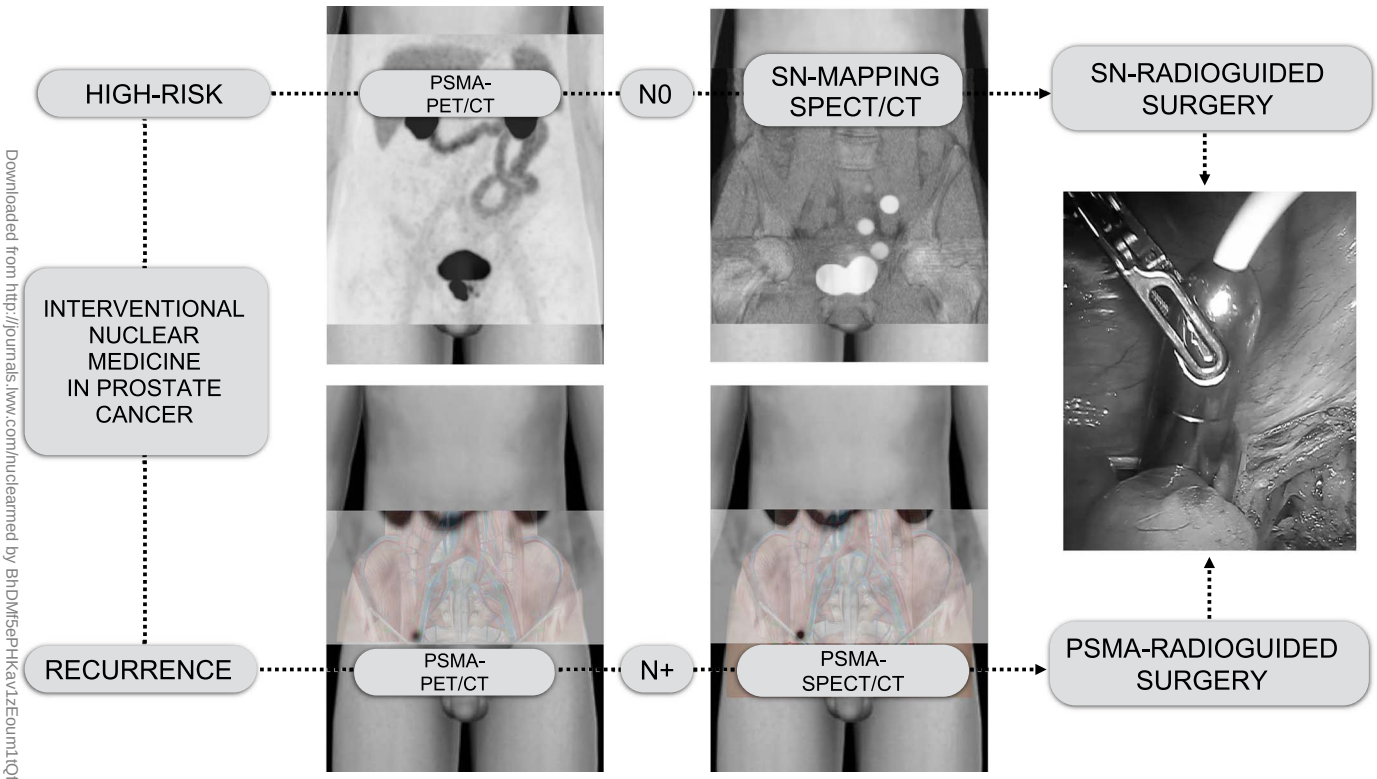

FIGURE 5. Schematic illustration of algorithm proposed for radioguided surgery in prostate cancer.[48] The upper row concerns high-risk patients at initial diagnosis, and the lower row, patients with biochemical recurrences. For both categories, PET/CT is initially used to detect PSMA-expressing lymph node metastases. This is followed by SN biopsy in the case of a negative PET/CT in the upper row and by PSMA-SPECT/CT in the case of a positive PET/CT in the lower row. For both situations, intraoperative equipment for radioguided resection is required.

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approach in the specific management of patients at high risk of metastatic dissemination in areas such as the axilla and the pelvis.

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