Radioguided Surgery: Novel Applications

50

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Abstract

A few years ago, the concept of Guided intraOperative Scintigraphic Tumor Targeting (GOSTT) was introduced to encompass the whole spectrum of basic and advanced nuclear medicine procedures required for providing a roadmap for radioguided surgery. This concept included the use of interventional nuclear medicine imaging to depict targets to be resected by radioguided surgery. With the incorporation of SPECT/CT and PET/CT, three-dimensional roadmaps to guide surgical procedures became possible. On the other side, new intraoperative portable imaging devices (gamma cameras and other tools) were added to conventional modalities such as gamma probes and blue dye. More recently, the development of hybrid tracers integrating radioactivity and fluorescence in one single signature has enabled the additional use of near-infrared cameras. All these advances have facilitated the extension of radioguided sentinel lymph node biopsy procedures from the classical applications in cutaneous melanoma and breast cancer to other fields such as oral cavity, gastrointestinal, urological, and gynecological malignancies. At present, three GOSTT working models can be defined in relation to radiotracer administration: intralesional without tracer migration for occult lesion localization, intralesional with tracer migration for occult lesion localization and sentinel lymph node biopsy, and systemic to enable excisional biopsy of primary lesions and recurrences as well as isolated regional and distant metastases. The latter is probably the field with the largest potential due to

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the continuous introduction of new PET and SPECT tracers. Novel modalities like luminescence detection and tracked image-guided navigation will further reinforce the role of GOSTT and radioguided intervention procedures.

Keywords

Guided intraoperative scintigraphic tumor targeting • GOSTT • Radioguided surgery • Novel applications • Sentinel lymph node biopsy • Lesion occult localization • Interventional SPECT/CT • Interventional PET/CT • Intraoperative portable imaging technologies

Glossary

[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
^{99m}Tc-MAA	^{99m}Tc-macroaggregated albumin
AJCC	American Joint Committee on Cancer
CT	X-ray computed tomography
GOSTT	Guided intraOperative Scintigraphic Tumor Targeting
ICG	Indocyanine green
M	Metastasis status according to the AJCC/UICC TNM staging system
MEN	Multiple endocrine neoplasm
MIBG	*meta*-Iodobenzylguanidine
MIP	Maximum intensity projection
MPR	Multiplanar reconstruction
N	Lymph node status according to the AJCC/UICC TNM staging system
NET	Neuroendocrine tumor
NIR	Near-infrared
PET	Positron emission tomography
PET/CT	Positron emission tomography/Computed tomography
PSMA	Prostate-specific membrane antigen
ROLL	Radioguided occult lesion localization
RSL	Radioguided ^{125}I seed localization
SLN	Sentinel lymph node
SNOLL	Combined sentinel lymph node biopsy and radioguided occult lesion localization
SPECT	Single-photon emission computed tomography
SPECT/CT	Single photon emission computed tomography/Computed tomography
T	Tumor status according to the AJCC/UICC TNM staging system
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)

Contents

Introduction

Radioguided surgery is one of the applications of nuclear medicine with more relevant growth in the last quarter-century. Radioguided surgery

constitutes a wide range of combined procedures involving close collaboration with other specialties like surgery, pathology, and radiology; correct application of such multidisciplinary procedures ensues obvious immediate and long-term benefits to the patient. In general, radioguided surgical procedures are less invasive than traditional surgical approaches, while they may also result in improved local-regional control of malignant disease [1].

In 2011 the term GOSTT (Guided intraOperative Scintigraphic Tumour Targeting) was introduced in order to encompass the whole spectrum of basic and advanced nuclear medicine procedures required for providing a roadmap for radioguided surgery [2]. The GOSTT concept was recently further updated incorporating the discussion of novel modalities such as hybrid tracers for simultaneous fluorescence and radioactive signal detection, sophisticated navigation approaches based on mixed-reality protocols, and the use of Cerenkov luminescence related to PET tracers [2]. An extensive overview of the GOSTT procedures is given in a book recently edited by the International Atomic Energy Agency (IAEA) [3].

Working GOSTT Models in Interventional Imaging and Radioguided Surgery

The GOSTT concept rests on both preoperative interventional imaging and intraoperative radioguided detection. To accomplish this approach, three working models based on the concentration of an administered radiopharmaceutical in a target or index lesion can be delineated (Fig. 1): (1) local administration of a radiocolloid at the site of a solid epithelial tumor that enables the depiction of the pattern of lymphatic drainage and the identification of the sentinel lymph nodes by means of lymphoscintigraphy; (2) direct intralesional administration of a radiopharmaceutical such as ^{99m}Tc-macroaggregated human albumin (^{99m}Tc-MAA) which is comprised of particles that, by virtue of their relatively large size, are lengthily retained at the site of interstitial injection enabling excisional biopsy; and (3) systemic administration of a radiopharmaceutical that preferentially accumulates in the target lesion, e.g., ^{99m}T-sestamibi for localization of parathyroid adenomas or [^{18}F]FDG for [^{18}F]FDG-avid tumor lesions.

The basic modality to illustrate and discuss the GOSTT concept is the sentinel lymph node (SLN) procedure. Historically, the term "sentinel lymph node" was introduced to describe a group of lymph nodes retrieved in patients with penile carcinoma under the assumption that they receive direct drainage from the site of the primary lesion [5]. In the last 25 years, radioguided surgical applications have rapidly expanded especially to perform sentinel lymph node (SLN) biopsy. In addition to ongoing applications in patients with breast cancer and cutaneous melanoma, radioguided SLN biopsy has been extended to a wide variety of other solid epithelial malignancies such as head and neck cancers, gynecological cancers (vulvar, cervical, and endometrial), gastrointestinal cancers (esophagus, stomach, colorectal, anus), urological malignancies (prostate cancer, bladder cancer, penile carcinoma, and others), non-small cell lung cancer, differentiated thyroid carcinoma, and others [1, 6–15].

A second field of GOSTT applications is constituted by the excisional biopsy techniques based on direct intralesional injection of ^{99m}Tc-MAA, which are expanding from the classical application of "radioguided occult lesion localization" (ROLL) for nonpalpable breast lesions to other tumors, such as solitary pulmonary nodules as well as others [16, 17]. In more recent years, the ROLL technique has been used in breast-conserving surgery combining lumpectomy and SLN biopsy [18, 19].

The model of systemic tracer administration is illustrated by radioguided parathyroid surgery with ^{99m}Tc-sestamibi, a radiotracer with preferential uptake and/or accumulation in tumor tissues. This approach has also been described using radiolabeled monoclonal antibodies against tumor-associated antigens. These procedures also include receptor-mediated uptake of radiolabeled agents by tumors such as neuroendocrine tumors or paragangliomas, accumulation of bone-seeking agents for radioguided excision of isolated bone metastasis, and radioiodine uptake in recurrences/metastases from differentiated thyroid carcinoma. The field of applications following systemic administration

has been extended to intraoperative radioguidance using [^{18}F]FDG or other positron-emitting radiopharmaceuticals using specific probes able to detect the high-energy gamma photons originated by the annihilation reaction or directly β^+ particles [20]. More recently, an intraoperative Cerenkov luminescence device for detection of [^{18}F]FDG-avid malignant lesions has been presented [21].

This chapter will focus on radioguided surgery in the context of the GOSTT concept, emphasizing the innovative methodological aspects for both novel clinical procedures and the more recent investigational applications.

General Background of SLN Biopsy

The rationale of SLN biopsy in solid epithelial tumors relates to the general concept that initial lymphatic spread of such tumors occurs to locoregional lymph nodes in an orderly way, generally from lower- to higher-echelon levels. Of course, this orderly progress does not exclude the potential of tumors to spread hematogenously, which is associated with most distant metastases. Probably in only few circumstances do distant metastases arise from progression of an initial lymphatic metastasis.

The modern SLN concept [22, 23] concerns not only the first lymph node encountered by lymphatic vessels draining the primary tumor but also all first-echelon lymph nodes upon which a lymph vessel originating in the tumor drains directly. This definition does not always correspond to the lymph node nearest to the tumor, as the route of the lymphatic vessels may be complex and unpredictable with different lymphatic pathways leading to different sentinel lymph nodes (Fig. 1); in practice each lymph node identified as SLN should therefore be investigated for the presence of metastasis. Lymphatic mapping following interstitial radiocolloid injection is essential to precisely visualize sequential lymphatic drainage of the radiopharmaceutical and to provide surgeons an intraoperative roadmap [24, 25].

The presence or absence of SLN metastasis usually has a significant impact on therapeutic strategy. In patients with early cancer, if the SLN does not contain metastasis, the surgical approach should aim at removing the primary tumor and avoiding unnecessary regional node dissection. The likelihood that non-SLNs contain metastasis is extremely low, thus making extensive node dissection unnecessary in case the SLN is free from metastasis. Patients whose SLN contains metastasis usually require dissection of regional lymph nodes [26].

The Evolution of Intraoperative Instrumentation for SLN Biopsy and Other GOSTT Applications

Gamma probes were incorporated into the procedure of SLN biopsy in the early years of the procedure [27]. These devices were able not only to count radioactivity in the surgical field intraoperatively but also to provide numerical readouts and audible signals proportional to the counting rate. The hand-held probe is connected to a counting unit either with a cable or with a wireless system. The detector is usually limited to a long narrow cylinder with a diameter varying from about 12 mm up to 16–18 mm. It may be slightly angled in order to allow for easier access in specific applications and easier manipulation within the surgical field.

Thanks to the auditory signals and digital readouts, gamma probes enabled the surgeon to localize and remove radioactive tissue like the SLN or tumor tissue. In fact, gamma-probe counting constituted the acoustic component of the SLN identification procedure in the operating room and for surgeons was the complement of the process of visual detection as implemented by the use of blue dyes. This acoustic/visual feature was introduced in the early 1990s as a step forward in comparison with the original approach, which was exclusively based on the injection of blue dyes to visualize lymphatic ducts and SLNs as originally described by Morton et al. [22].

The combination of gamma-probe counting and blue dyes represented the second step in the evolution of the procedure. On the other hand, this possibility to combine visual and acoustic signals during the surgical SLN procedure has become the cornerstone for new portable technologies, which now enable image generation in the operating room reinforcing the visual component in the guidance of

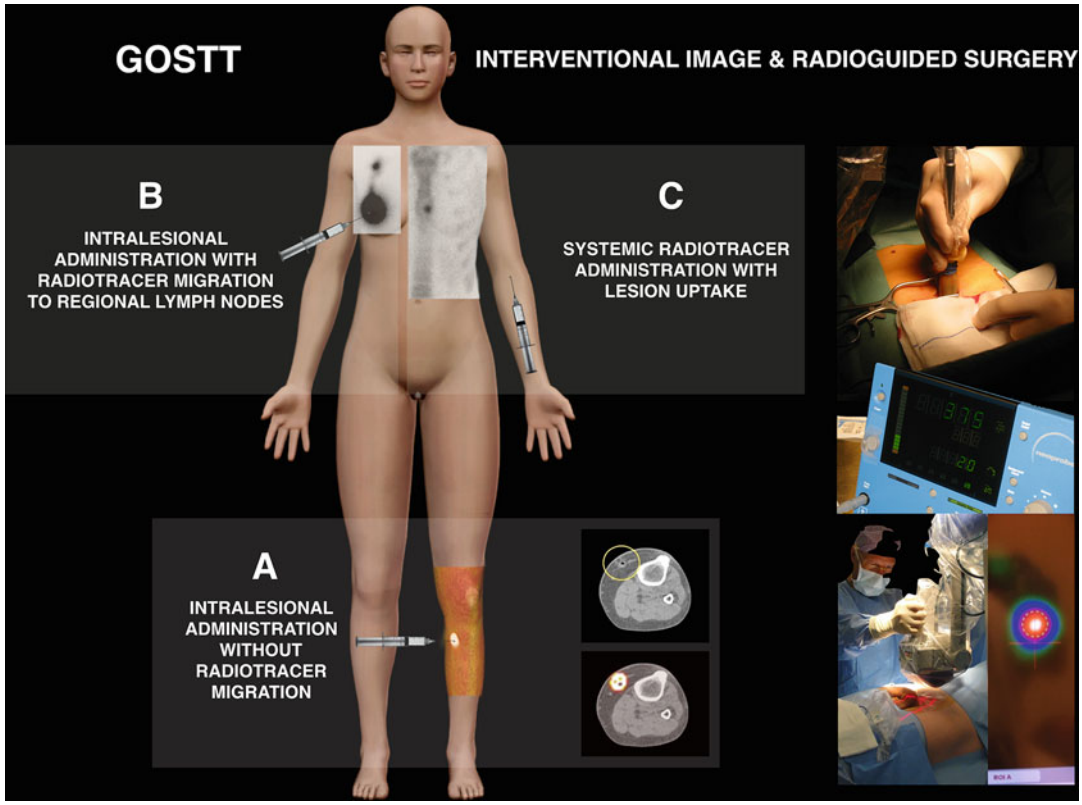

Fig. 1 Schematic working GOSTT (guided intraoperative scintigraphic tumor targeting) approaches including interventional imaging leading to radioguided surgery. (**a**) Intralesional administration of ^{99m}Tc-MAA in a melanoma metastasis of the *left* lower leg. (**b**) Intralesional administration of ^{99m}Tc-nanocolloid in a non-palpable tumor of the *right* breast with subsequent migration to axillary lymph nodes. (**c**) Systemic administration of ^{99m}Tc-diphosphonate with increased uptake in a solitary sternal metastasis

surgical excision [3]. These portable imaging technologies include devices like small gamma cameras for high-resolution planar imaging [28], gamma probe- or small camera-based devices for 3D intraoperative imaging [29], near-infrared (NIR) cameras used in combination with portable gamma devices when fluorescent detection is added to the SLN procedure [30], and cameras for Cerenkov luminescence imaging [21].

Preoperative Imaging: From Planar Images to Hybrid Computed Tomography

Lymphoscintigraphy constitutes the cornerstone of preoperative lymphatic mapping. Its incorporation to the SLN procedure helped to transform the paradigm in radioguided SLN surgery from the original "open and see" approach based on the use of vital dyes to visualize lymphatic ducts and SLNs to another "see and open" based on the gamma camera images acquired prior to the surgical procedure. This lymphatic mapping enabled not only to personalize imaging of lymphatic drainage for every individual patient but also made possible to mark with indelible ink the SLN site projection on the skin. This approach gained in popularity in Europe and was highly effective for SLN localization not only in the expected areas of drainage but also in unusual locations [24]. Lymphoscintigraphy was found to be 88–96% reproducible in melanoma [31, 32] and 100% in breast cancer as well as penile cancer [33, 34].

For SLN identification, early images, to depict first draining lymph nodes, and delayed images, to

differentiate second-echelon nodes, are required. The visualization of lymphatic ducts, the time of lymph node appearance, the lymph node basin, and the intensity of lymph node uptake are all important factors to take into account. Lymph nodes draining from the site of the primary lesion through their own lymphatic vessel, or a single radioactive lymph node in a basin, are considered as definitely SLN. Lymph nodes appearing between the injection site and a first draining node or nodes with increasing uptake appearing in other lymph node basin may be considered as SLN with a high probability. Higher-echelon lymph nodes in the trunk and extremities or lower-echelon nodes in the head and neck region may be included in the low-probability SLN category [35].

More than 10 years after planar lymphoscintigraphy, SPECT/CT imaging was introduced in the SLN procedure [36], thus enabling to incorporate an additional dimension to preoperative mapping. In fact, the functional information on draining lymph nodes provided by SPECT could be combined with the morphological information from CT by acquiring both modalities in one session. The resulting fused SPECT/CT images were able to depict SLNs in an anatomical landscape, thereby providing important reference landmarks to be recognized by surgeons in the operating theater. Lymphatic mapping complemented by SPECT/CT is currently applied both in malignancies with predominantly superficial drainage (e.g., breast cancer and melanoma) and in tumors draining to deep lymphatic basins or areas of complex anatomy such as the head and neck or the pelvis [37–46]. A specific requirement for SLN localization is that the CT component of SPECT/CT must be of sufficient high quality to provide optimal anatomical landmarks to be recognized by surgeons in the operating room. The CT component is also used to correct the SPECT signal for tissue attenuation and scattering; thanks to such corrections, SPECT/CT may be particularly useful in obese patients to detect SLNs not observed on planar images and additional SLNs in other basins. After these corrections, SPECT can be fused with CT. For fused images a gray scale is used to display the morphology in the background image (CT), whereas a color scale is used to display the SLN in the foreground image (SPECT). Most frequently, a radioactive hot spot corresponds to a single lymph node on CT, but in some cases it correlates with a cluster of lymph nodes [47].

Simultaneously with the evolution of the SLN procedure, a similar "see and open" approach is catapulting also other applications of radioguided surgery in which preoperative imaging plays an important role leading to surgical intervention. This interventional molecular imaging can be illustrated by the preoperative use of ^{99m}Tc-sestamibi scintigraphy for the localization of parathyroid adenomas, where preoperative imaging is used as a roadmap for radioguided surgery of these lesions [48]. Recently, the addition of SPECT/CT to planar imaging did significantly increase the accuracy in correctly identifying a parathyroid adenoma from 75% to 85% [49].

Radiopharmaceuticals for Interventional Molecular Imaging and Radioguided Surgery

As mentioned earlier, an important aspect in GOSTT possibilities is related to the choice of radiotracers for interventional imaging and radioguided surgery. For lymphoscintigraphy and radioguided SLN biopsy, the tracers most widely used are radiocolloids that, after their interstitial administration, migrate from the injection site allowing the visualization of the lymphatic vessels by lymphoscintigraphy and SPECT/CT [25]. These colloids are preferentially retained by the first lymph nodes encountered along the course of the draining lymphatic vessel(s), enabling their identification as SLN(s). Once within the lymph node, radiocolloids are phagocytized by macrophages lining the lymph node sinusoids. Such retention of radiocolloids in the SLN is a physiological process and does not indicate presence or absence of metastases in the lymph node. Radiocolloids can be constituted by an inorganic substance (^{198}Au-colloid, ^{99m}Tc-antimony sulfur, ^{99m}Tc-colloidal sulfur, ^{99m}Tc-stannous fluoride, ^{99m}Tc-rhenium sulfur) or can be derived from biological substances (nano- or micro-colloidal human serum albumin). Radiocolloid particle

size, varying from 5 to 1,000 nm, mainly determines the speed of lymphatic drainage from the interstitial injection site and the amount retained in the SLN. In particular, small-size radiocolloids (less than about 100 nm) migrate quite fast from the injection site through the lymphatic system. This factor underlines the need to sequentially perform dynamic images at short time intervals after interstitial injection as well as static early and delayed images in order to differentiate SLNs from secondary lymph nodes. Larger size radiocolloids are retained longer in the SLN, so that lymphoscintigraphy does not generally visualize more than one to two lymph nodes along a single lymphatic draining vessel. However, migration of larger particles from the interstitial administration site is very slow, so that a longer time, even 2 h or more, can be required to complete mapping. In Europe, ^{99m}Tc-albumin nanocolloid (which has a quite narrow range of particle size, with over 90% of the particles being smaller than 80 nm) is widely available and employed, while in the USA, ^{99m}Tc-sulfur colloid (with a wide range of particle size between about 20 and 400 nm) is the most employed; to overcome the problem of heterogeneous particle size distribution, in some nuclear medicine centers, ^{99m}Tc-sulfur colloid is filtered immediately after labeling and prior to administration, in order to remove particles with a diameter bigger than a certain size, usually 220 nm or other sizes [50, 51].

The radiopharmaceutical ^{99m}Tc-tilmanocept has recently been introduced for lymphatic mapping and SLN biopsy. This radiotracer accumulates in SLNs after binding the mannose-binding protein receptor expressed on the surface of phagocytes. ^{99m}Tc-tilmanocept contains 7 nm particles, which are rapidly cleared from the injection site through lymphatic vessels [52]. In contrast to larger particle radiocolloids, there is also significant diffusion into the blood capillaries. Although diffusion from the injection site via the blood route may limit the amount of lymphatic flow of the tracer, the reduction in signal intensity at the location of the primary lesion may facilitate identification of SLN located close to the injection site. ^{99m}Tc-tilmanocept has been used in oral cavity cancer [53], melanoma [54], and breast cancer [55].

More recently, the hybrid tracer indocyanine green-^{99m}Tc-nanocolloid (ICG-^{99m}Tc-nanocolloid) has been explored for clinical use. Concerning lymphatic drainage pattern and SLN location, this novel tracer showed a 100% reproducibility rate when compared with the parental ^{99m}Tc-nanocolloid in patients with different malignancies and lymphatic drainage basins [56]. Based on its radioactive signature, such hybrid tracer preserves the possibilities for perioperative imaging using conventional gamma cameras, SPECT/CT, and portable devices. At the same time, the added fluorescent signature leads to improved visual resolution and SLN detectability during surgery. A further validation of the clinical applicability of ICG-^{99m}Tc-nanocolloid has been reported for oral cavity cancer [57], vulvar cancer [58], penile cancer [59], prostate cancer [60], and more extensively in melanoma [61].

Intralesional tracer administration enabling excisional biopsy of primary tumors is a GOSTT application known as “radioguided occult lesion localization” (ROLL) , originally validated for breast lesions but with subsequent rapid extension to other malignancies. The first clinical validation of ROLL was based on a direct intralesional injection of ^{99m}Tc-MAA in nonpalpable breast lesions guided by ultrasonography or stereotactic mammography [16]. To accomplish concentricity in the distribution of the tracer into the tumor, the radiotracer must be injected as centrally as possible in the lesion. During excision, which can be performed on the same day or on the next day, the gamma probe is introduced through a small skin incision that can ensure an optimal cosmetic outcome without the topographic constraints required by the classical intralesional markers such as the carbon tracer of the hooked wire. Intraoperative gamma-probe counting enables the surgeon to easily localize the focal deposition of ^{99m}Tc-MAA, thereby facilitating the procedure. The surgical specimen is checked ex vivo with the gamma probe for further confirmation of radioactivity and can also be x-rayed to ensure complete removal of the area containing the lesion. The technique enabled a 99.5% lesion removal rate in the breast [62]. When used in combination with wire

localization in nonpalpable breast cancer, ROLL did significantly reduce reoperation from 21% to 2% [63]. In the last years, radioguided iodine-125 seed localization (RSL) has been introduced for excisional breast lesion [64]. Using similar gamma-probe devices, RSL appears to be comparable with ROLL concerning margin status and re-excision rates, but with significantly lower weight of the resected specimen in patients with nonpalpable ductal carcinoma in situ or invasive carcinoma [65]. In locally advanced breast cancer receiving neoadjuvant chemotherapy, RSL is also comparable with ROLL but with more practical advantages, due to the long halftime of iodine-125 which enables seed implantation before chemotherapy without additional tracer injection for excision of residual tumor [66]. The ROLL principle has been applied in other tumors such as papillary thyroid cancer [67], solitary pulmonary nodules [17], and lymph node metastases [68]. On the other hand, RSL has been helpful to localize axillary metastatic lymph nodes after neoadjuvant chemotherapy in breast cancer patients reaching a 97% identification rate [69].

More recently the ROLL technique has been used in breast-conserving surgery combining lumpectomy and SLN biopsy by means of a single intralesional tracer injection [18, 19]. This approach is known as SNOLL and is based on the use of a radiocolloid with the ability to migrate to the regional lymph nodes. Basic work based on ex vivo lymph node measurements effectuated in the 1990s when validating the SLN procedure demonstrated that when ^{99m}Tc-nanocolloid is administered into a breast tumor, only 2–3% migrate to the axillary SLNs, while the remaining predominant fraction remains at the injection site and can thus guide a ROLL procedure simultaneously with the SLN biopsy procedure [70].

Radioguided surgery related to the systemic administration of a tracer is probably the GOSTT working model with the greatest potential for the future. This potential is based on the detection by either SPECT/CT or PET/CT (depending on the radiopharmaceutical used) of target lesions with subsequent indication for resection for diagnostic or therapeutic purposes. The indication may be closely related to suspected cancer recurrence with elevation of tumor markers during follow-up. For example, PET/CT with [^{18}F]FDG in combination with a hand-held PET probe, suitable to detect 511 KeV gamma emissions, resulted in appropriate tissue sampling by excisional biopsy approach in patients with suspected lymphoma [71]. Also in patients with breast cancer, melanoma, and other malignancies, PET/CT led to the resection of [^{18}F]FDG-avid metastases using a high-energy gamma probe [72]. More recently, an intraoperative device for detection of [^{18}F]FDG-avid malignant lesions based on the detection of the Cerenkov luminescence, which is emitted by emitters of β-particles (both negatrons and positrons), has been used for optical lesion visualization [21].

Regarding radiopharmaceuticals for SPECT, besides the aforementioned ^{99m}Tc-sestamibi [48, 49], another example can be found in radioguided surgery of neuroendocrine tumors (NETs) using ^{111}In-DTPA-pentetreotide; this approach was found to be useful to guide cytoreduction in 29 out of 30 patients with abdominal NETs [73]. Also radiolabeled metaiodobenzylguanidine (MIBG) has been advocated to improve quality of resection in selected NET cases [74]. On the other hand, SPECT/CT led to improve lesion definition and localization with reduction of false-positive results in NET patients [75]. More recently, ^{68}Ga-labeled somatostatin analogues have been incorporated to radioguided surgery of NETs in a "see and open" approach on the basis of preoperative PET/CT and intraoperative gamma-probe guidance [76].

Interventional SPECT/CT and PET/CT for GOSTT

Both SPECT/CT and PET/CT may be considered as basic modalities for interventional hybrid imaging in GOSTT (Fig. 2). SPECT/CT has been incorporated in procedures for SLN localization with locally administered radiocolloids as well as for detection of metastasis with systemically administered tumor-seeking tracers. On the other hand, PET/CT using tracers as [^{18}F]FDG or ^{18}F-fluorocholine has been used to lead radioguided interventions in cases with isolated metastasis. In the SLN procedure, SPECT is primarily oriented to

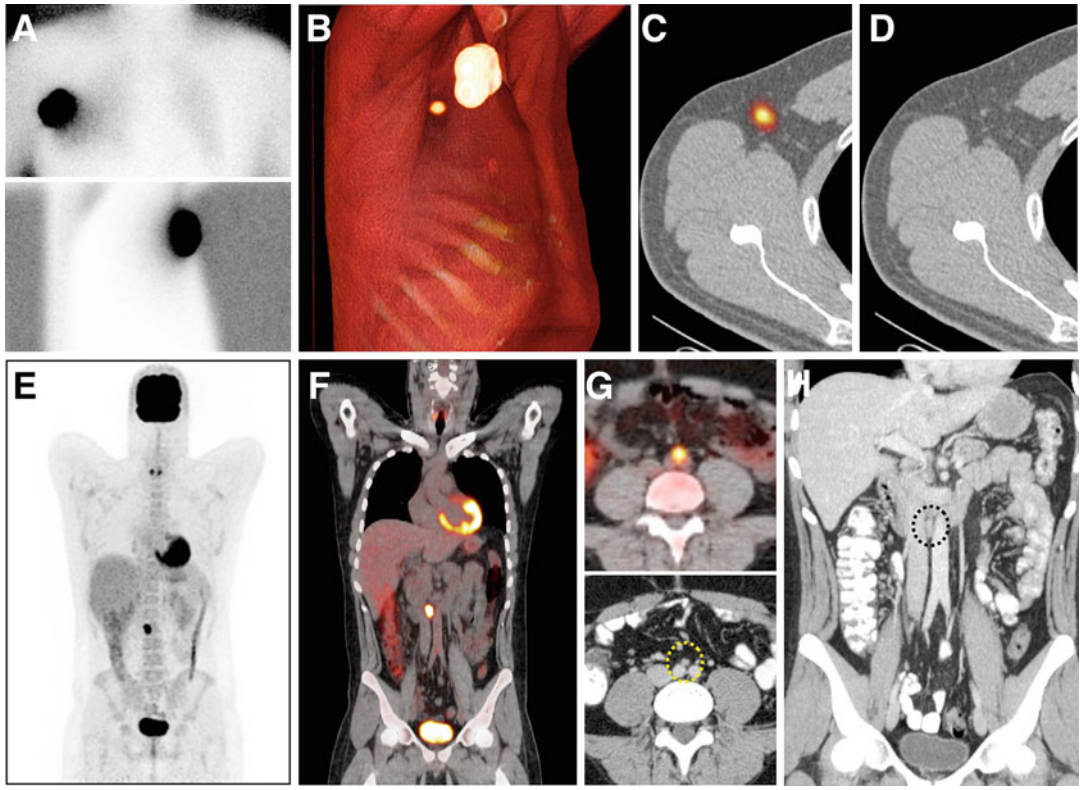

Fig. 2 Interventional molecular hybrid imaging leading to radioguided surgery. In *upper* row, planar images show no drainage to the axilla (**a**), whereas SPECT/CT (**b**–**d**) is able to depict an axillary sentinel lymph node near the injection site. In *lower* row, coronal PET (**e**) and PET/CT (**f**) showing an [^{18}F]FDG avid lymph node metastasis between aorta and cava inferior which is further localized on transversal PET/CT and CT (**g**) as well as on coronal CT (*circles*) (h)

the anatomical localization of SLNs, and protocols for imaging are, in principle, related to this goal. This also explains why SPECT/CT is usually acquired using a low-dose CT. Acquisition of a diagnostic high-dose CT, with or without intravenous contrast, is not really necessary because the SLN procedure aims at identifying subclinical metastases smaller than 2 mm in lymph nodes that are not enlarged or altered in their morphology. PET/CT is mostly acquired using a low-dose CT protocol similar as for SPECT/CT; however, high-dose CT with intravenous contrast is preferred in some cases to characterize PET-positive lesions, which are generally associated with metastases larger than 5 mm.

SPECT/CT is usually performed in addition to lymphoscintigraphy as a preoperative phase of the SLN procedure. SPECT/CT imaging with ^{99m}Tc radiocolloids is possible thanks to the prolonged lymph node retention after phagocytosis of such radiocolloids by the macrophages, which often results in an adequate detection window. This facilitates not only the acquisition of delayed planar images and SPECT/CT but also intraoperative gamma ray-guided SLN localization.

For detection of both SLNs (when patient is scheduled for SLN biopsy) and metastatic tumor tissue (when tumor-seeking radiotracers are used), a specific requirement for localization is that the CT component of SPECT/CT needs to be of sufficient quality to provide optimal anatomical information. The second generation of SPECT/CT gamma cameras includes an improved CT component; this enables the identification and evaluation of the lymph nodes corresponding with the radioactive nodes on fused SPECT/CT

images by acquiring a low-dose (e.g., 40 mAs) CT. In superficial areas such as the groin and the axilla, 5-mm slices may provide adequate anatomical details. For more complex anatomical areas (head/neck, pelvis, abdomen), 2-mm slices may be necessary. With this approach, SPECT/CT can accurately localize SLNs in relation to the vascular structures in deep anatomical areas.

The CT component is also used to correct the SPECT signal for tissue attenuation and scattering. After these corrections, SPECT can be fused with CT [77]. For fused images a grayscale is used to display the morphology in the background image (CT), whereas a color scale is used to display the SLN in the foreground image (SPECT).

For reading/reporting purposes, SPECT/CT or PET/CT images are mostly displayed in a similar manner as that of conventional tomography. Two-dimensional display of fused images to be correlated with CT and SPECT is facilitated by multiplanar reconstruction (MPR), and the use of cross-reference lines allows for the navigation between axial, coronal, and sagittal views. In the SLN procedure, this tool enables the correlation of radioactive SLNs seen on fused SPECT/CT with lymph nodes seen on CT. Most frequently, a radioactive SLN corresponds to a single lymph node on CT, but in some cases it correlates with a cluster of lymph nodes. This information may be useful for the intraoperative procedure and the post-excision control using portable gamma cameras or probes, as additional radioactive SLNs may be detected with the high-resolution portable gamma camera at the same location, then harvested for analysis.

The use of maximum intensity projection (MIP) to display fused SPECT/CT or PET/CT images may also help surgeons to anatomically recognize and localize SLNs or radiotracer-avid metastases. MIP is a specific type of rendering in which the brightest voxels are projected into a three-dimensional image. A limitation of MIP is that the presence of other high-attenuation voxels on CT may complicate recognition of the vasculature and other anatomical structures. Furthermore, MIP is actually a two-dimensional representation, which cannot accurately depict the actual relationships of the vessels and other structures [78]. Also localization of SLNs or of tracer-avid metastases in a three-dimensional context can be supported by the application of volume rendering. In this modality different colors are assigned to anatomical structures such as vessels, the muscle, bone, and skin. This results in easily recognizable anatomical reference points of the target lesions, for instance, in relation to the vasculature. By incorporating a color display, volume rendering improves visualization of complex anatomy and 3D relationships.

Retrieving SPECT/CT and PET/CT Findings in the Operating Room

The anatomical localization of SLNs or tracer-avid lesions does transform SPECT/CT and PET/CT in interventional imaging. Surgeons can use the anatomical landmarks so provided to retrieve these targets during operation. This evolution to a 3D roadmap after the incorporation of these hybrid molecular modalities has helped to further transform the GOSTT paradigm to one of "see, open, and recognize" (Fig. 3). This approach can potentially be reinforced by the synergy of SPECT/CT and PET/CT with the portable imaging technologies [3]. For instance, high-resolution portable gamma cameras are able to reproduce SPECT/CT findings in the intraoperative localization of SLNs or parathyroid adenomas in complex or difficult anatomical areas like the head and neck [25, 42, 79, 80]. These devices have been particularly helpful to depict SLNs at a distance of at least 3 mm from the injection site when equipped with a high-resolution pinhole collimator [81]. The new generation of portable gamma cameras has been upgraded with an optical module for fused optical/scintigraphic imaging resulting in improved anatomical localization [82, 83].

Another important possibility to utilize SPECT/CT and PET/CT findings during surgery is the intraoperative real-time generation of virtual elements. These elements can be added to the surgical environment in the context of an

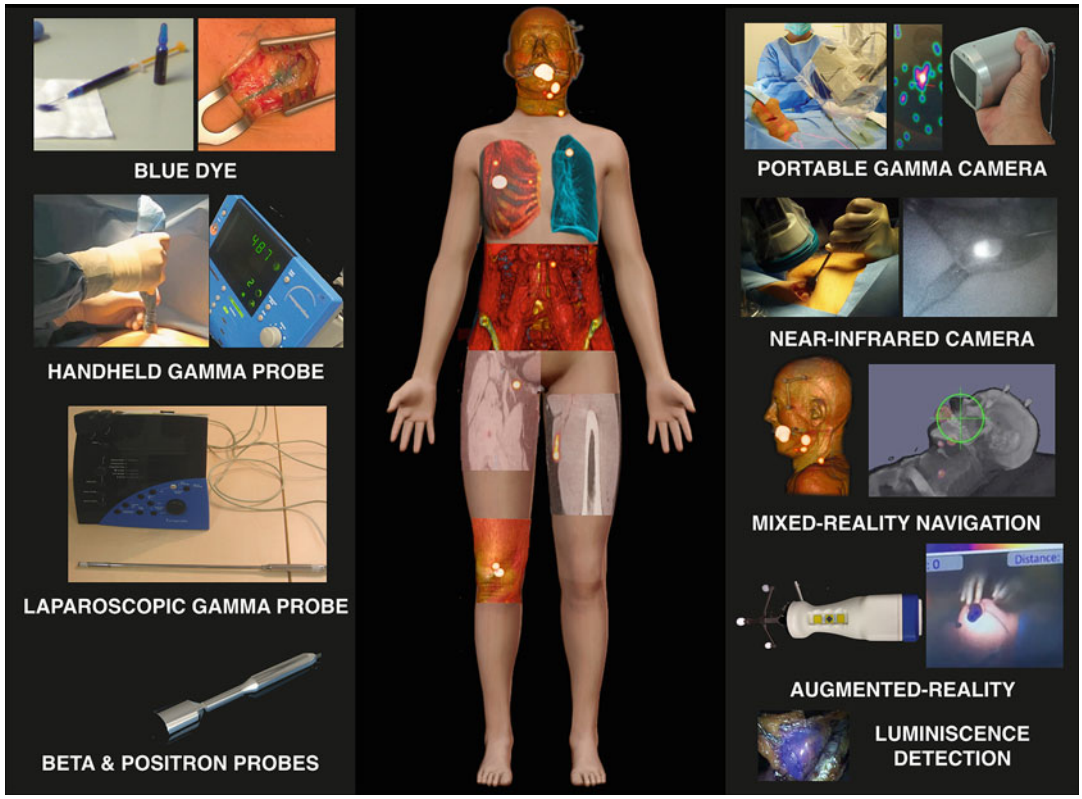

Fig. 3 Synergy of SPECT/CT and PET/CT with portable intraoperative technologies. Both sentinel lymph nodes (head/neck, axillary/intercostal, para-aortic, inguinal, popliteal) and [^{18}F]FDG avid metastases (*upper left* lung, *upper left* leg) can be preoperatively localized for further radioguided resection using conventional (*left* column) and novel (*right* column) intraoperative portable devices and modalities

augmented reality protocol. Augmented reality approaches can be considered as a part of mixed reality, but it is also an independent modality, which has been applied in radioguided surgery mainly after the introduction of the freehand SPECT technology based on a tracked gamma probe suitable for 3D image generation [84]. This device has been the basis for augmented reality experiences in SLN procedures in breast cancer [85], oral cancer [86], and melanoma [87], as well as for surgery of parathyroid adenomas [88]. The same freehand SPECT technology may be considered a helpful tool in transferring SPECT/CT, and potentially PET/CT, to the operating room using mixed reality protocols. The concept of mixed reality was introduced by Milgram and Kishino in 1994 and concerns the merging of *real* and *virtual* elements to produce new environments [89]. More related to the GOSTT approach, with the use of a tracked protocol, it has become possible today to transfer the virtual SPECT/CT images to the operating room, so that a merged environment can be created for adequate surgical navigation. This approach enabled to generate tracked 3D images of a phantom prepared with a reference target (ReT) and simulated SLNs containing ICG-^{99m}Tc-nanocolloid. After feeding the SPECT/CT images to the navigation system, optical tracking could be used to position the tip of the fluorescence endoscope relative to the preoperative 3D imaging data allowing accurate identification of the simulated

SLNs in the phantom. A similar approach was used to navigate toward the prostate and SLNs in a patient undergoing robot-assisted prostatectomy [90]. This navigation approach has been found to be feasible in areas of rigid anatomy like the retroperitoneal space and the groin [91]. However, more difficulties for SPECT/CT-based mixed reality surgery are to be expected for "non-rigid" anatomical areas. Recently, the use of freehand SPECT in combination with a mobile handheld gamma camera has been validated [92]. The freehand SPECT technology has also been used to generate intraoperative 3D navigation for single or multiple ^{125}I-seeds in RSL l [93] and ROLL [94] in breast-preserving cancer surgery.

Novel Clinical GOSTT Applications

The clinical SLN applications in breast cancer, cutaneous melanoma, and head and neck cancer are extensively discussed in other chapters of this book. This chapter mainly concerns novel clinical applications as well as the incorporation of new technologies for both preoperative imaging and intraoperative localization in existing GOSTT applications.

Head and Neck

Regional staging in the neck is performed according to the AJCC/UICC TNM staging system which differentiates seven lymph node levels in each side of the neck [95]. For GOSTT applications to localize SLNs on SPECT/CT and [^{18}F]FDG-avid metastases on PET/CT in the head and neck, the approximately 250–300 lymph nodes are divided into various nodal groups. This high lymph node density and the site of the primary lesion are the principal causes of the remarkable variations in lymphatic drainage and patterns of metastatic dissemination. For instance, scalp melanomas of the frontal zone can drain to different lymph nodes when compared with melanomas of the parietal or occipital areas. For facial and forehead melanomas, metastatic spread to different basins may occur. In the oral cavity, malignancies of the lingual apex may drain to other groups in comparison with well-lateralized lesions in the tongue or floor of the mouth. Identification of SLNs in the vicinity of periauricular melanomas may be critical. Also SLNs located near to floor-of-mouth tumors may be missed and can be accompanied by a decrease in detection rate from 97% to 80%, a decrease in sensitivity from 97% to 80%, and a reduction in the negative predictive value from 98% to 88%, respectively [96]. This has led to the conclusion that planar lymphoscintigraphy is not sensitive enough for predicting the SLN level in the neck [97]. In this scenario, SPECT/CT appears to be essential for the SLN procedure not only to accurately identify SLNs in an anatomical landscape but also to detect additional SLNs in the vicinity of the primary lesions or to personalize alternative drainage to different lymph node basins on an individual basis (Fig. 4).

In a recent study in which SPECT/CT imaging has been performed in a series of 58 patients with oral or oropharyngeal carcinoma, 11 additional SLNs were detected by SPECT/CT; one of these nodes contained metastases [98]. In another study concerning 34 patients, extra SLNs were found by SPECT/CT in 15 patients, and in seven the anatomical level of SLN location was reconsidered [99]. The superior anatomical information of SPECT/CT may lead to adjust surgical approach, as observed for 11 out of 38 patients (29%) with head and neck melanoma; in six patients of this group, SPECT/CT detected additional SLNs (16%) [46]. In another study SPECT/CT modified the surgical approach (more superficial incision or incision at other site) in 9 out of 34 (27%) patients with head and neck malignancies [100]. The surgical adjustment rate due to the additional information provided by SPECT/CT increases when SLNs are located in the periparotid areas; in 8 out of 14 patients (57%) with melanoma and drainage to the parotid region on planar lymphoscintigraphy, SPECT/CT was able to distinguish SLNs in level II of the neck from those located in or around the parotid [101]. In another evaluation in melanoma patients, SPECT/CT caused an increase of the detection rate from

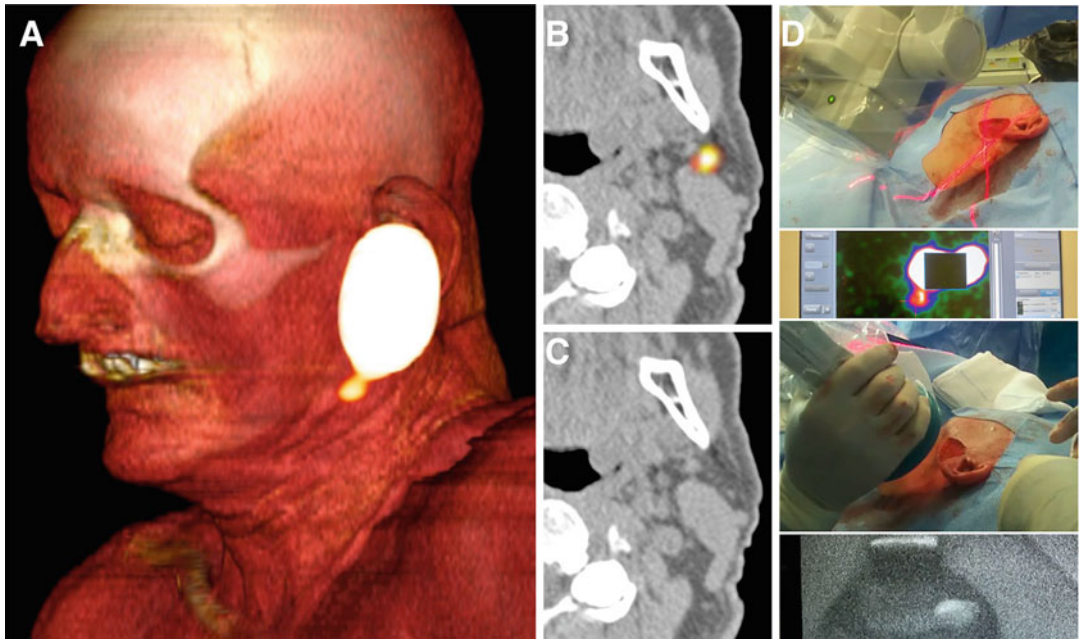

Fig. 4 SPECT/CT with volume rendering (**a**) showing drainage of ^{99m}Tc-nanocolloid to a sentinel lymph node close to the inferior border of the injection site in the left auricular area. This lymph node is further anatomically localized on SPECT/CT (**b**) and CT (**c**) to subsequently be intraoperatively recognized using a portable gamma camera and a fluorescence camera (**d**)

91% (planar scintigraphy) to 98% with a clinical impact of 63.6% [102]. The overall clinical value of the SPECT/CT anatomical information for lymph node mapping was also used to adjust super-selective prophylactic irradiation of the neck in a feasibility study including ten patients with squamous cell carcinoma of the head and neck [103]. Further GOSTT developments in the head and neck region include the hybrid tracer ICG-^{99m}Tc-nanocolloid that has been reported for oral cavity cancer [57], the use of high-resolution portable gamma cameras in addition to SPECT/CT [42], and freehand SPECT probes with 3D display [86]. The incorporation of SPECT/CT and a portable gamma camera in combination with a fluorescence camera to the SLN procedure has led to identify 26% additional SLNs [104].

Lymphoscintigraphy and SPECT/CT have also been validated for SLN identification in papillary thyroid cancer. In an initial study, SLNs were identified in 19 of 24 patients (79%); the identification rate increased to 96% during surgery using a handheld gamma probe. Multidirectional drainage to both central and laterocervical compartments was observed in 50% of the patients [105]. In another series concerning 23 clinically node-negative patients combined, visualization rate of lymphoscintigraphy and SPECT/CT was 91%. The two patients without drainage presented non-SLN positive for metastases. Most SLNs were located in levels VI (83%) and II (35%) of the neck, whereas in four patients, contralateral drainage was also noted [106].

The use of systemic administered radiotracers has been helpful to detect local regional recurrences of well-differentiated thyroid cancer; these cases were subsequently managed using radioguided surgical excision with ^{131}I-iodide in eight patients and [^{18}F]FDG in another five patients with a proven loss of iodine avidity [107]. In another study an optically tracked navigation system was used to navigate to suspected persistence or recurrence in seven patients with malignant skull base disease [108].

In the head and neck, radioguided minimally invasive surgery based on parathyroid ^{99m}Tc-sestamibi scintigraphy has been one of the classical GOSTT applications. The criteria for selection of patients for this radioguided procedure can be summarized as follows [4]:

1. Patients with primary hyperparathyroidism and rarely tertiary hyperparathyroidism
2. Scintigraphic visualization of a single site of tracer uptake
3. Good uptake of ^{99m}Tc-sestamibi by the hyperfunctioning parathyroid gland
4. Absence of concomitant solid thyroid nodules
5. Exclusion of the multiple endocrine neoplasm (MEN) syndromes

By adopting these criteria, minimally invasive radioguided surgery can be scheduled in 60–70% of the patients with primary hyperparathyroidism; in the remaining patients, it may be necessary to perform classical bilateral neck exploration. Based on preoperative ^{99m}Tc-sestamibi imaging and using a second administration of the tracer shortly before operation, even without intraoperative parathyroid hormone measurements, a 98% long-term success rate was reached in a series of 108 patients [48]. Further advances in this GOSTT application are based on the incorporation of SPECT/CT to the imaging protocol [49] and of portable imaging devices to the radioguided procedure [4]. A meta-analysis concerning 24 studies published between January 2003 and March 2014 including 1,276 patients showed a per-patient pooled sensitivity of 86% for SPECT/CT which was superior to the 74% value observed with standalone SPECT and 70% with planar scintigraphy. In this analysis the rate of ectopic parathyroid adenomas ranged between 4% and 20% with a clear added value of SPECT/CT for the localization of the ectopic sites [109]. Recently, ^{18}F-fluorocholine PET/CT has been found to perform better (92% sensitivity, 100% specificity) than ^{99m}Tc-Sestamibi SPECT/CT (49% sensitivity, 100% specificity) in localizing hyperfunctioning parathyroid tissue in 24 patients with primary hyperparathyroidism [110]. This superiority of imaging with ^{18}F-fluorocholine, mainly based on the detection of multiple lesions and hyperplasia, leads to consider this imaging modality as an indication of choice to localize parathyroid abnormal tissue in patients with negative ^{99m}Tc-sestamibi imaging (Fig. 5). This approach may lead to successfully image-guided surgery [111]. The intraoperative retrieval of ^{99m}Tc-sestamibi-avid parathyroid adenomas has been optimized using portable gamma cameras [80, 112]. An alternative to portable gamma cameras is the use of a freehand SPECT device with 3D image generation [113]. The freehand SPECT signal can be fused with real-time ultrasound when signals of both modalities are acquired in a tracked manner [114]. The potential of the tracked combination of these modalities for radioguided intervention in the head and neck area has also been illustrated by its use in targeted ultrasound-guided, fine-needle aspiration cytology of SLNs in head and neck cancer [115].

Urological Malignancies

In general, male and female urogenital malignancies located in the pelvis drain to lymphatic basins in the vicinity of the primary tumor and may follow a similar trajectory in the dissemination of regional metastases. There are different nodal groups receiving lymphatic drainage from the pelvic structures: the external iliac nodes whose medial subgroup includes the obturator nodes, the internal iliac lymph nodes, and the nodes in the trajectory of the common iliac vessels. Lymphatic spread of metastasis from malignancies of the prostate, bladder, cervix, and endometrium may frequently be found in these iliac basins. However, alternative lymphatic drainage to the para-aortic and aortocaval lymph nodes as well as to the proximity of the sacrum and anterior abdominal wall is also possible.

In penile cancer the SLN procedure was one of the first applications of SLN biopsy validated in patients with clinically negative lymph nodes, in order to select patients who can benefit from lymph node dissection. It is usually performed by intradermal peritumoral injection of the

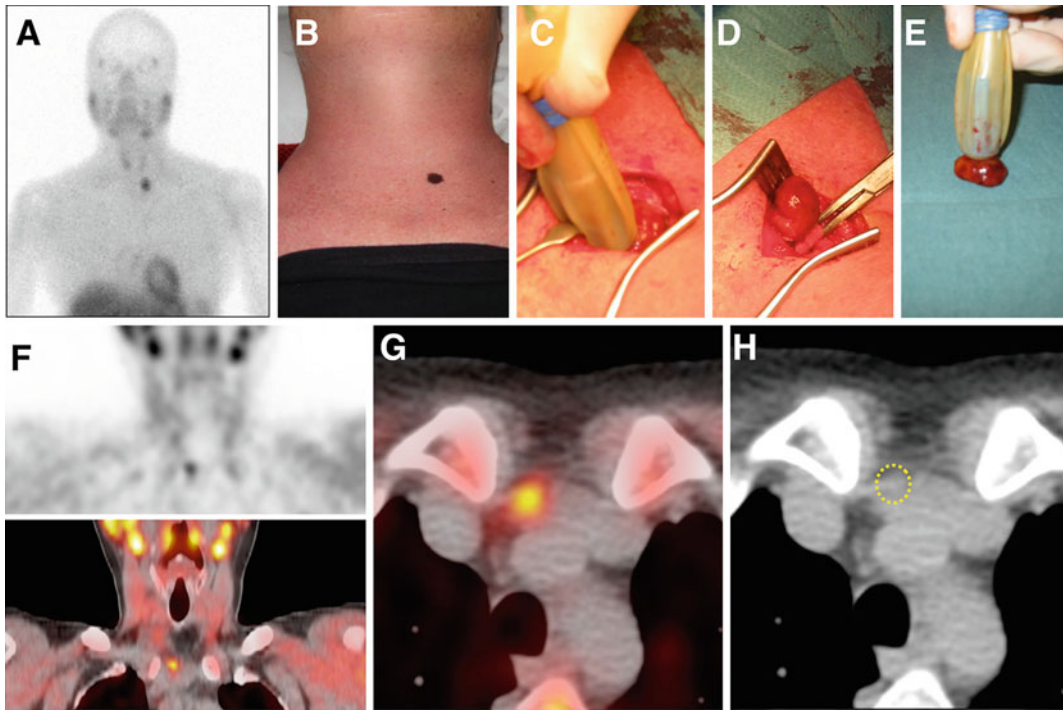

Fig. 5 Planar scintigraphy (**a**) showing increased ^{99m}Tc-sestamibi uptake near the *left lower* pole of the thyroid. Following skin marking (**b**), a parathyroid adenoma is intraoperatively localized and resected using a handheld probe (**c**–**e**). In another patient with primary hyperparathyroidism and negative ^{99m}Tc-sestamibi scintigraphy, PET/CT (F-H) using ^{18}F-fluorocholine is able to localize an ectopic parathyroid adenoma (*circle*) which is subsequently removed

radiocolloid, following the recommendation of injecting within 1 cm radius from the primary tumor, or from the surgical scar in case of prior excision of the primary tumor [116]. The SLN procedure has led to a SLN identification rate of 97% with an acceptable false negative rate of 7% [117] and to increase the 5-year survival to 91% in these patients [118]. SPECT/CT imaging has been used to optimize the procedure and to evaluate the pattern of lymphatic drainage from the malignancy by evaluating the possible implications for the extent of inguinal lymph node dissection. In a study including 50 patients, lymphatic drainage was visualized in 82 of 86 clinically node-negative groins (95%) scheduled for the SLN procedure. All SLNs were located in the inguinal zones medial superior (73%), lateral superior (8.7%), and central superior (18.3%) on SPECT/CT. No lymphatic drainage to the inferior zones of the groin was seen which suggests the possibility to exclude these zones from a subsequent inguinal lymph node dissection in the case of a tumor-positive SLN [119].

In prostate cancer, tracer administration is guided by transrectal ultrasound with usually two radiocolloid depots, one injection in each prostate lobe. Patients receive antibiotics prophylactically to prevent prostatitis. An alternative for transrectal injections is the transperineal tracer administration. Lymphoscintigraphy on the basis of 5-min planar images is performed 15 min and 2 h after injection. SPECT/CT is mostly performed subsequently to delayed planar images (Fig. 6). On early planar images, first draining lymph nodes are visualized in 88% of the cases. This visualization rate increases to more than 90% on delayed images [4]. SPECT/CT is particularly useful to anatomically localize SLNs in both the expected drainage basins of the pelvis and in alternative locations. A meta-analysis

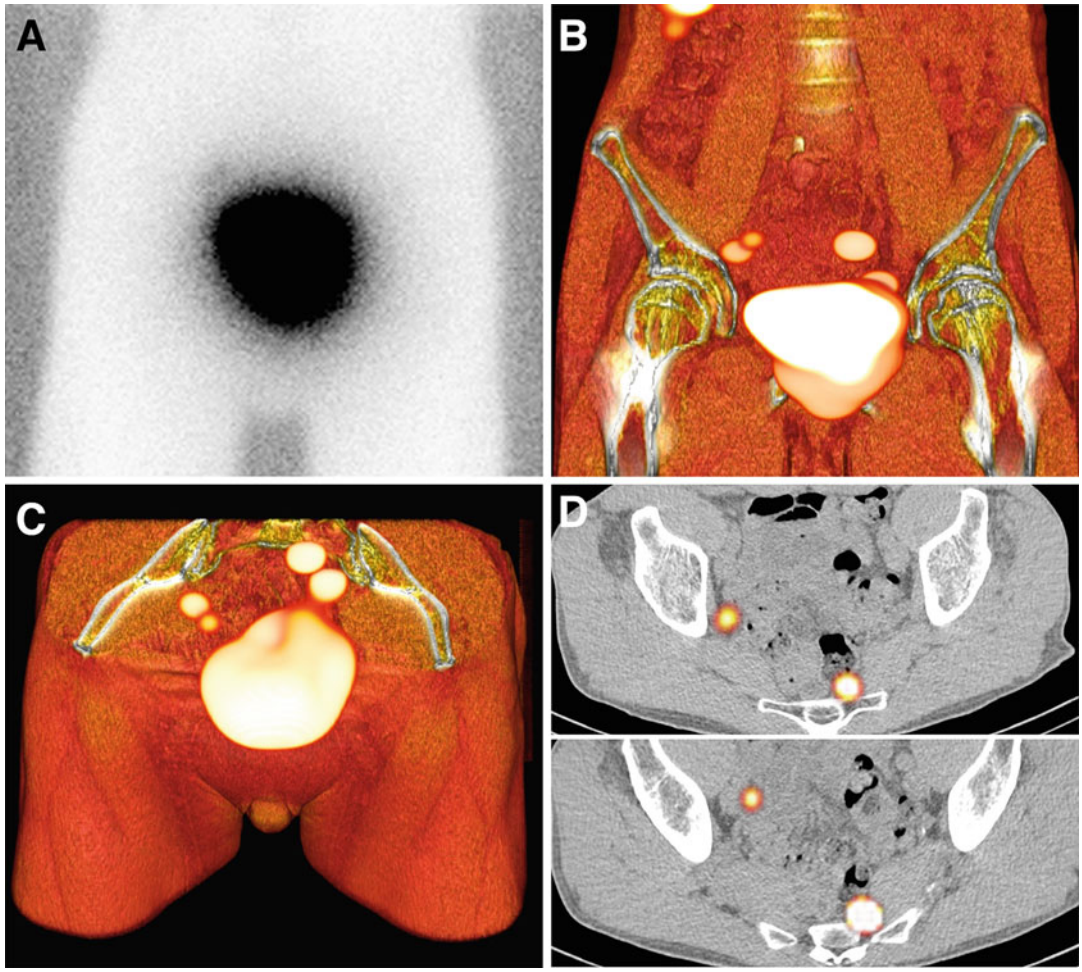

Fig. 6 Planar lymphoscintigraphy (**a**) showing some drainage to the right iliac area in a patient who has received four injections of ^{99m}Tc-nanocolloid into the prostate. By contrast on volume rendering (**b**), bilateral drainage is observed. Volume rendering with cranial tilt (**c**) and transaxial SPECT/CT (**d**) show sentinel lymph nodes in the right iliac region and in the left presacral area

evaluating the SLN procedure included mainly prostate cancer patients with intermediate risk (clinical stage > T2b/T3, PSA >10 ng/mL, or Gleason >6); the pooled detection rate scored 93.8% and pooled sensitivity 94% [120]. Sensitivity appears to decrease to 76% in high-risk patients [121]. In recent years the role of SPECT/CT has been evaluated in various studies. SPECT/CT did increase the SLN visualization rate from 91% for planar scintigraphy to 98%. SPECT/CT also depicted more SLNs than planar images (average 4.3 vs. 2.2 SLNs) in 46 patients; 44% of the SLNs containing metastases were visualized only by SPECT/CT [43]. In another study, SPECT/CT identified SLNs outside the area of extended pelvic lymph node dissection, often used to stage the pelvis, in 37 out of 121 prostate cancer patients (31%). These SLNs were found in different locations: presacral, Cloquet's node, inguinal, para-aortic, the abdominal wall, pararectal, behind the common iliac artery, and lateral to the external iliac artery [122]. In a study involving treated prostate cancer patients, SPECT/CT

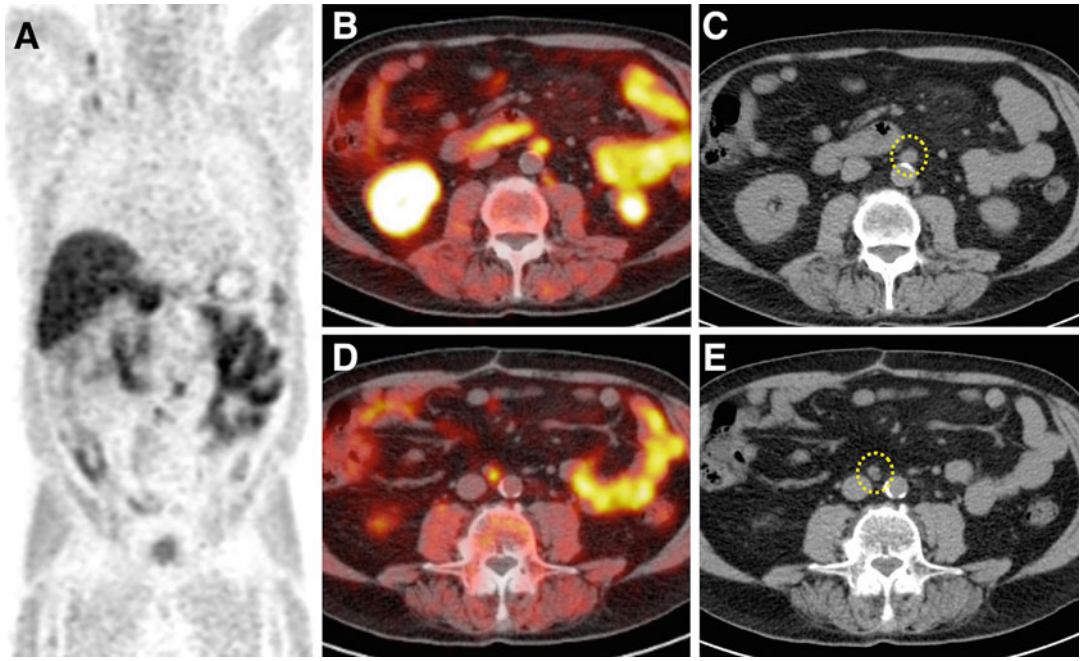

Fig. 7 Coronal PET displayed with maximum intensity projection (**a**) showing focal uptake of ^{18}F-fluorocholine in the *middle* areas of the abdomen in a prostate cancer patient with high risk of regional lymph node involvement. On fused PET/CT and CT, two radiotracer avid lymph nodes are depicted in the para-aortic area (**b**, **c**) and between the aorta and vena cava inferior (**d**, **e**). These findings led to image guided resection and histopathological confirmation of metastases

revealed a higher percentage of SLNs (80% vs. 34%) outside the pelvic para-iliac region in comparison to untreated patients [123]. In another series SPECT/CT findings led to a 25% impact of lymphatic drainage on conformal pelvic irradiation in 23 prostate cancer patients [124]. In a study designed to validate laparoscopic SLN versus hyperextended pelvic dissection for staging clinically localized prostate carcinoma, SPECT/CT identified SLNs in 191 of 203 patients (94%). Bilateral SLNs were found in 159 patients (83%) and unilateral in 32 (17%). The most frequent drainage site was the common iliac region (31%), followed by the internal iliac (20%), the obturator fossa (18%), the external iliac (15%), and the promontory/presacral area (6%) [125]. A similar presacral SLN rate (5.4%) was found in another study concerning 18 patients with prostate cancer of intermediate prognosis; in this series also para-aortic (5.4%), pararectal (5.4%), and paravesical (3.6%) SLNs were found outside the area of extended pelvic lymphadenectomy [126]. In the operating room, innovations in the SLN procedure for prostate cancer have been illustrated in recent years by the use of portable gamma camera to facilitate laparoscopic SLN biopsy [4] and the incorporation of robot-assisted SLN procedures with fluorescence/radioactivity guidance [60]. Finally, the gradual incorporation of high-risk patients for the SLN procedure has led to explore the possibility to detect macrometastases in these patients by using PET tracers before SLN biopsy (Fig. 7). This combined approach based on the use of SLN-SPECT/CT and ^{18}F-fluorocholine was found to be useful for target volume definition in high-risk prostate cancer aimed to receive radiotherapy [127]. Another PET tracer, ^{68}Ga-PSMA-ligand, has been found to be highly effective for lymph node staging in prostate cancer patients with intermediate- to high-risk prostate cancer; lymph node metastases were found in

41/130 patients (31.5%) with a patient-based accuracy of 88.5% for PET/CT increasing to 95.2% on the basis of template-based analyses [128]. The efficacy of ^{68}Ga-PSMA-ligand PET/CT has led to an innovative GOSTT approach for radioguided surgery in patients with lymph node metastases by coupling ^{111}In-PSMA-ligand with ^{68}Ga-PSMA-ligand in order to visualize PSMA-ligand-avid lymph nodes and primary tumor with SPECT/CT to enable radioguided resection [129].

In other urological malignancies, the SLN procedure has been validated only on an investigational basis in limited series of patients. In bladder cancer the imaging protocol, including lymphoscintigraphy and SPECT/CT, is similar to the one recommended for prostate cancer. Radiocolloid injection into the detrusor muscle and around the primary lesion is guided by cystoscopy [4]. Depending on the location of the primary tumor, lymphatic drainage may be unilateral or bilateral. The addition of SPECT/CT to planar lymphoscintigraphy did increase the detection rate from 33% to 83%. The negative predictive value of the SLN procedure has been found to be 92% on the basis of 156 patients reported in the literature [130]. In testicular cancer lymphatic drainage to lymph nodes along the abdominal aorta and vena cava is usually found after tracer administration with a single intratesticular injection; however, in some cases, SLNs are also found alongside the funicular vessels. SPECT/CT identified aortocaval or paracaval SLNs in five patients with right-sided testicular cancer and para-aortic SLNs in five patients with left-sided tumors; in three patients, SLNs along the funicular vessels were detected. All these SLNs were resected using a portable gamma camera [131]. Finally, in renal cell carcinoma, lymphatic drainage was seen in 14/20 patients (70%) and SPECT/CT detected 26 SLNs. The SLNs were most frequently located para-aortically, but also drainage to retrocaval, hilar, celiac trunk, and thoracic (internal mammary chain, mediastinal, and pleural) SLNs was seen [132]. The visualization of lymphatic drainage from renal cell carcinoma along the thoracic duct was further documented using SPECT/CT in 4 out 22 patients (18%) with SLN visualization [133].

Gynecological Malignancies

Gynecological GOSTT applications have been mainly limited to SLN biopsy in vulvar cancer, cervix cancer, and endometrial cancer. In vulvar cancer SLN biopsy is recommended for women with unifocal tumors <4 cm and clinically non-suspicious lymph nodes in the groin [134]. The incorporation of a radiocolloid tracer to the procedure improved the SLN detection rate to more than 95% from the 88% rate when only blue dyes were used [4]. Nevertheless, the most accepted approach is the combination of both agents with a SLN detection rate of 87% per groin, a false negative rate of 6.4%, and a recurrence rate of 2.8% according to a recent meta-analysis [134]. However, a long-term follow-up study showed a local recurrence rate at 5 years of 24.6% for patients with SLN negative and 33.2% for SLN positive [135]. The radiotracer is usually injected in three to four aliquots around the primary lesions; this is particularly important in lesions located close to mid-line, which frequently show contralateral drainage [136]. In spite of an extended validation of the SLN procedure in vulvar cancer, the role of SPECT/CT imaging in this malignancy has not been widely evaluated. In a series concerning 88 patients, SPECT/CT depicted drainage to groins not visualized on planar imaging and depicted more SLNs, but the difference was statistically not significant. However, SPECT/CT was of additional value to accurately indicate SLN location showing a 73% drainage rate to medial inguinal Daseler's zones, a 10% to the central zone around the saphenofemoral junction, and only 7% to the lateral zones. Different from drainage to the groin in penile cancer (Fig. 8), the SLN in vulvar cancer is found in 14% of the patients in the medial inferior zone; however, drainage to the lateral inferior region of the groin is only incidentally seen. Further drainage to higher-echelon lymph nodes was observed in the groin (15%) and in the pelvis (85%). SPECT/CT was found to be able to personalize lymphatic drainage and have potential use to limit extent of lymph node dissection in patients with positive SLNs [137]. Repeat SLN procedure appears to be also feasible in patients with recurrent

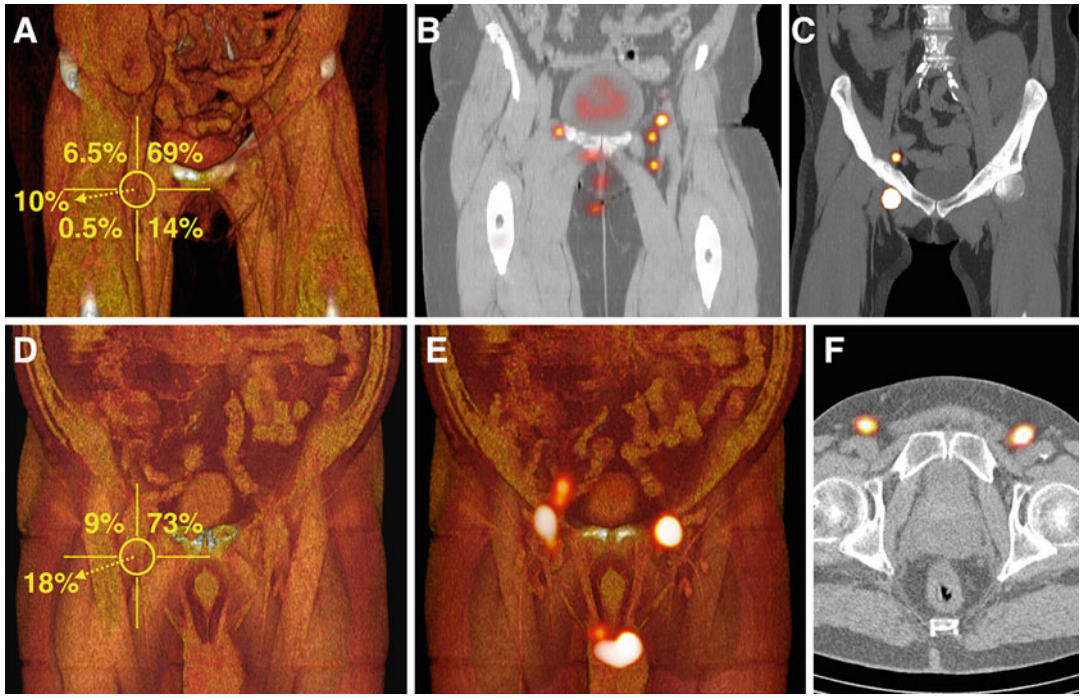

Fig. 8 Anatomical distribution (**a**) of inguinal sentinel lymph nodes according to Daseler's zones in vulvar cancer [137] showing most locations in the superior and central zones but also significant migration to the medial inferior quadrant as shown in two different patients (**b**, **c**). By contrast, in penile cancer (**d**), drainage to the inferior zones of the groin is not observed [119] as further illustrated by fused SPECT/CT images (**e**, **f**)

vulvar cancer, reaching a 78% detection rate [138]. The GOSTT concept of "see, open, and recognize" has been further explored in vulvar cancer on the basis of SPECT/CT and intraoperative SLN identification using combined NIR visualization and portable gamma devices following administration of the hybrid tracer ICG-^{99m}Tc-nanocolloid [58, 139].

Another important GOSTT application in gynecological surgical oncology concerns SLN biopsy in cervical cancer. A recent meta-analysis evaluating 67 studies resulted in a pooled detection rate of 89.2% and a pooled sensitivity of 90%; both SLN rates were related to mapping method (blue dye, radiotracer, or both) and history of preoperative neoadjuvant chemotherapy. Preoperative lymphatic mapping could also detect SLNs outside of routine lymphadenectomy areas, thus providing additional histological information important to optimize regional staging [140]. A prospective multicenter study evaluated the contribution of lymphoscintigraphy to the SLN procedure in 139 patients and concluded that, although the preoperative detection rate is lower than the intraoperative one (87.8% vs. 97.8%), the substantial proportions of SLNs in unusual drainage territories found by lymphoscintigraphy provide valuable guidance for the surgical exploration [141]. SLN visualization in preoperative lymphatic mapping can be optimized by the addition of SPECT/CT. This approach was evaluated in a meta-analysis including eight studies; the median overall detection rate was 98.6% for SPECT/CT and 85.3% for planar lymphoscintigraphy [142]. Indication for SLN biopsy in cervix cancer concerns patients with early stage (Ia2/Ib1, IIa1) and no clinical evidence of lymph node metastases. Radiocolloid administration is based on injecting peritumoral/periorificial aliquots into the four quadrants of the cervix or

pericicatricial in patients with prior conization. It is recommended to perform SPECT/CT after delayed planar imaging of lymphoscintigraphy and is crucial to assess deep lymphatic drainage and anatomical SLN localization in parametrial stations and in unusual locations [143].

In endometrial cancer a meta-analysis published in 2013 [144] resulted in a pooled SLN detection rate of 77.8% and a pooled sensitivity of 89%. The evaluation was based on 51 studies with enough information for detection rate evaluation and 35 studies providing false negative rates. The combination of blue dye and radiotracer resulted in higher detection rate and sensitivity. However, there are various approaches regarding the injection site: cervical, endometrial peritumoral, and myometrial/subserosal. Although the injection of the tracer into the four quadrants of the cervix is the easiest approach with also the highest detection rates, the other two routes appear to better reflect the drainage of endometrial cancer, with a higher incidence in drainage to the para-aortic lymph node basins [143]. SPECT/CT has been found to be helpful, and in 44 patients with high-risk endometrial cancer, SPECT/CT identified SLNs in 34 of them (77%) with a total of 110 depicted SLNs. The most frequent location was the external iliac chain (71%), but drainage to para-aortic SLNs was also common (44%). SPECT/CT was able to localize the only pelvic metastatic lymph node that was not depicted on planar images [145]. Also recently, in a study of 70 patients with endometrial cancer, SPECT/CT detected SLNs in 64 of them (91.4%). However, SPECT/CT could detect only 88.9% of the SLNs found during surgery; most of these undetected nodes on SPECT/CT had very low activity [146]. SPECT/CT SLN identification rate (94%) was significantly higher than that of planar lymphoscintigraphy (68%) in a series of 31 patients with endometrial cancer investigated after transcervical tracer injection into the isthmocervical myometrium [147].

Finally, radioguided SLN localization, without preoperative lymphatic mapping, was found to be feasible in a study including 21 patients who were at high risk of ovarian malignancy [148]; both radiocolloid and blue dye were intraoperatively injected into the proper ovarian ligament and suspensory ligament of the ovary. During open surgery the gamma probe identified SLN locations before retroperitoneal exploration; subsequently SLNs were detected in the para-aortic/paracaval regions only (67%), the pelvic region only (9%), and both the para-aortic/paracaval and the pelvic regions (24%).

Gastrointestinal Cancer

Since lymphatic drainage from the gastrointestinal tract is multidirectional and usually follows a random pattern, preoperative lymphatic mapping for SLN biopsy can be very helpful [7], considering that extensive dissection shows that metastases are found in lymph nodes nearest to the primary tumor site in, e.g., only about 60% of the gastric cancers or 40–50% of esophageal cancers. Also in lower rectal cancers, skip metastases and lateral lymph node metastases are found in a high number of the patients. However, these aggressive surgical procedures are burdened by high morbidity and even mortality.

In *esophageal cancer* the radiocolloid is administered endoscopically by injecting in the submucosal layer at the four quadrants closer to the primary lesion in the submuscosal layer, often the day before surgery. Lymphoscintigraphy is very useful to localize unexpected patterns of drainage to distant lymph nodes. In fact, in more than 80% of the cases, lymph drainage can be observed in a wide area extending from the cervical to the abdominal region. In a systematic review and meta-analysis including 23 studies of radioguided SLN mapping, the overall detection rate was 93% with a sensitivity of 87% [149].

In patients with *gastric cancer*, SLN biopsy aims at identifying clinically undetectable lymph node involvement and is generally reserved to T1 and T2 tumors (with diameter <4 cm), in which the type of resection can be modified toward function-preserving surgery whenever possible. The radiocolloid is injected endoscopically in the submucosal layers around the tumor. In a recent study involving patients with T1N0 or T2N0

operable gastric cancer [150], gamma probe in combination with blue dye identified SLNs in 372 out of 385 patients (96.6%).

Locoregional lymph node staging is an important prognostic factor for *colorectal malignancies*. In this regard, lymphatic mapping and SLN biopsy may be very important especially for identifying alternative mesenteric lymphatic drainage patterns and for detecting lymph node micrometastasis. Although at present the most popular technique is based on intraoperative subserosal injection of blue dye at the primary tumor, lymphoscintigraphy has proven definite advantages over the blue dye technique for SLNB [151]. However, evaluation of this approach in large-scale prospective investigations has not been performed. By contrast, in *anal cancer* radioguided SLN biopsy using preoperative imaging has had more acceptance; in a meta-analysis based on 16 studies including 323 patients, the best approach for SLN identification was found for the combined use of radiotracer and blue dye with a 90% detection rate [152].

GOSTT Applications in Other Malignancies

In lung cancer the GOSTT approach concerns both radioguided excision of solitary pulmonary nodules and radioguided SLN biopsy [4]. The radioguided excision has been extensively validated, and in 2012 Ambrogi et al. [153] reported radioguided video-assisted thoracoscopic surgery in 211 patients with pulmonary nodules smaller than 1 cm and/or deeper than 1 cm below the visceral pleura; the procedure was based on preoperative CT-guided administration of ^{99m}Tc-MAA into the nodule followed by lesion excision using video-assisted thoracic surgery with gamma ray probe guidance. The procedure was successful in 208 patients (98.6%) leading to histological confirmation of primary lung cancer in 113, metastases in 61, and benign lesions in 98. On the basis of a similar clinical indication and CT-guided radiotracer administration (^{99m}Tc-MAA) in or near the nodule, 112 patients underwent thoracoscopy or thoracotomy for lesion resection; in this series histology showed 14 benign lesions, 85 primary lung cancers, and 24 metastases [154]. Recently, ^{99m}Tc-sulfur colloid and a metallic clip were introduced into ground-glass opacities to enable resection; radiotracer administration was preceded by injection of cyanoacrylate that polymerizes immediately after injection into the lung parenchyma with the forming of a hard nodule enabling radiotracer retention, confirmed by SPECT/CT and easier identification during operation [155]. Concerning SLN biopsy and despite limited diffusion in surgical oncology, this GOSTT procedure has been evaluated for detection rate and sensitivity in 47 and 43 studies, respectively [156]; pooled detection was 80.6% and pooled sensitivity 87% with higher rates for the combination of radiotracer and dyes. In a pilot study, SPECT/CT has been found to be helpful in separate draining lymph nodes from the injection site of radiotracers [157].

In neuroendocrine tumors (NET) the GOSTT approach has been based on the systemic administration of radiotracers for radioguided detection and resection. In a systemic review [158], the use of the following radiotracers has been identified in various small series of radioguided surgery: ^{125}I-Tyr^3-octreotide, ^{111}In-DTPA-pentetreotide, ^{99m}Tc-somatostatin analogues, ^{123}I-metaiodobenzylguanidine, and ^{68}Ga-somatostatine analogues. Preoperative imaging has incorporated in recent years either SPECT/CT or PET/CT imaging, which has led to intervention and radioguided resection of small primary lesions, residual tumor, recurrences, and metastases (Fig. 9). The field of applications includes both pulmonary NET and gastroenteropancreatic NET.

Future GOSTT Scenarios

Current GOSTT advances open windows to new scenarios concerning clinical indications and modern technologies. In addition to the existing devices and modalities for radioguided surgery [159], some future possibilities and scenarios can be summarized as follows:

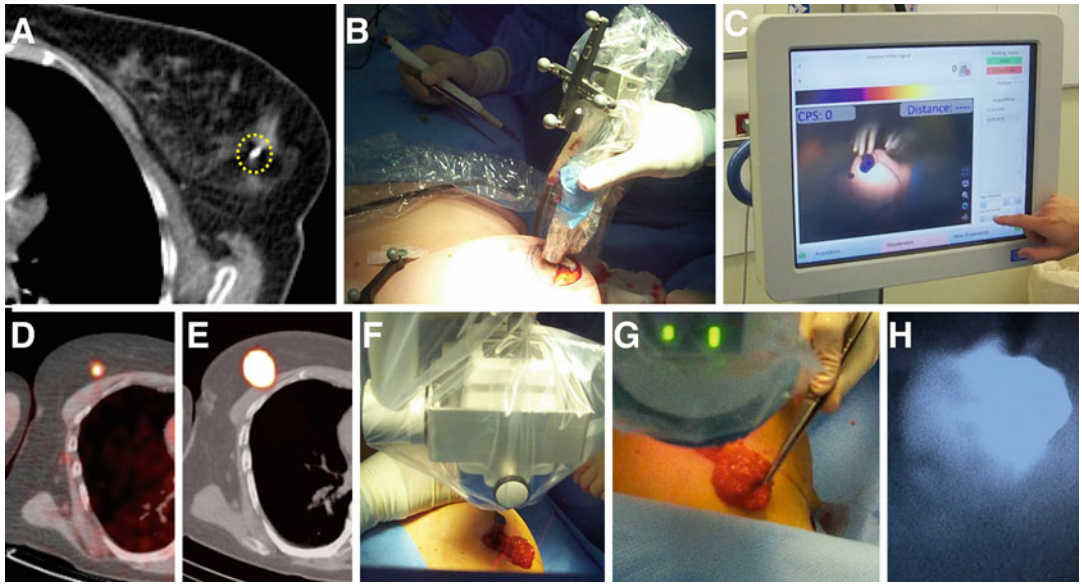

Fig. 9 Transaxial CT (**a**) showing an implanted ^{125}I-seed in the *left* breast of a patient scheduled for neoadjuvant chemotherapy. Following therapy, non-palpable residual tumor containing the radioactive seed is removed using tracked freehand SPECT (**b**, **c**). In another patient an [^{18}F]FDG-avid metastasis found on PET/CT (**d**) is subsequently removed after intralesional administration (**e**) of a hybrid tracer (ICG-^{99m}Tc-nanocolloid) using a portable gamma camera (**f**) and near-infrared camera (**g**) suitable for fluorescence detection (**h**)

1. Development of new systemic radiotracers for interventional imaging. The best example for this issue is illustrated by the recent introduction of ^{68}Ga-PSMA for prostate cancer and its interventional use in resection of lymph node metastases. The pairing of this PET tracer to ^{111}In-PSMA [129] not only enables preoperative SPECT/CT imaging but also radioguided surgery based on the more advantageous properties of ^{111}In. Similarly paired tracer use for interventional imaging and radioguided surgery can be found for iodine-based radiotracers and somatostatine analogues.
2. ROLL and SNOLL. The ROLL model can be extended to resection of recurrences, regional lymph node metastases [160], or isolated subclinical metastasis (Fig. 10). The SNOLL approach is of potential use in other malignancies like thyroid, lung, and stomach.
3. SLN-guided lymph node template resection. This model is currently discussed for prostate cancer with high-risk of regional lymph node involvement. The use of radiocolloids to guide SLN identification can help to optimize separate injection of fluorescent agents to guide lymph node resection in the basin of the SLN.
4. RSL following neoadjuvant chemotherapy. In analogy with the setting for locally advanced breast cancer and based on the practical advantages due to the long halftime of iodine-125, this approach enables seed implantation before chemotherapy and excision of residual tumor or lymph node metastasis after treatment in other local advanced malignancies scheduled for neoadjuvant therapy.
5. Mixed-reality navigation. Probably the use of new sensor technologies for tracking will help to transfer SPECT/CT, PET/CT, and PET/MRI with improved resolution to operation rooms in order to facilitate image-guided navigation to target regions.
6. Hybrid detection procedures. Portable imaging devices as gamma cameras probably will be integrated with other modalities as NIR cameras. On the other side, the integration of Cerenkov luminescence devices will extend the intraoperative applicability of PET tracers.

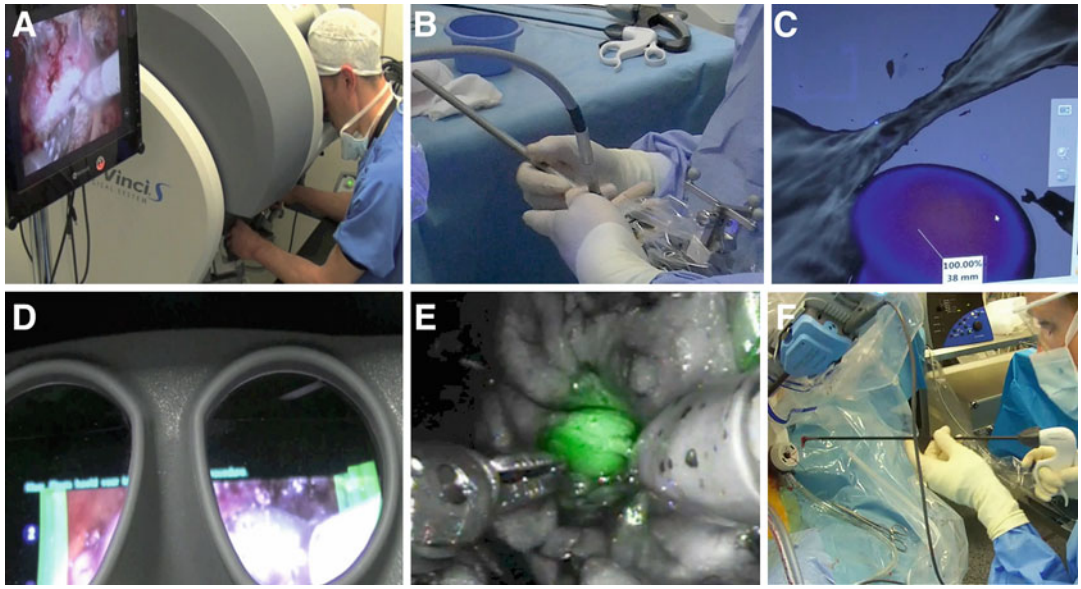

Fig. 10 Robot-assisted sentinel lymph node procedure following administration of ^{99m}Tc-nanocolloid into the prostate (**a**). A tracked laparoscopic freehand SPECT device (**b**) provides depth information for intraoperative navigation toward the sentinel lymph node, on the basis of a previous co-registered SPECT/CT (**c**). Subsequently, the integrated fluorescence signal display (**d**) enables sentinel lymph node resection (**e**, **f**)

7. Robot-assisted procedures with integrated radioguided navigation. In a similar approach as the one used for prostate cancer [60, 161], the fluorescence and probably the radioactive imaging will be integrated to robot-assisted procedures in other pelvic malignancies. Development of novel accessory devices like drop-in gamma probes [162] for insertion and residence inside the abdominal cavity using a robotic gripper will make identification of SLNs and tumor lesions during laparoscopic surgery more flexible by improving detector accessibility and geometry.

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