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ORIGINAL ARTICLE

Role of a portable gamma-camera with optical view for margins assessment of pulmonary nodules resected by radioguided surgery

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Abstract

Purpose Radioguided occult lesion localization (ROLL) of pulmonary nodules is an alternative to hook-wire. Both required of a histological margin assessment. The activity emerging from the radiotracer allows to obtain an intraoperative scintigraphic image of the surgical specimen by a portable gamma-camera (PGC) fitted with an optical view, which provides information about the localization of the nodule in relation to the margins. The aim of this study was to evaluate the intraoperative use of a PGC for margin assessment of pulmonary nodules.

Methods ROLL technique was used in 38 nodules (36 pulmonary, 1 chest wall, and 1 pleural nodules). A PGC intraoperative image of the surgical specimen was obtained in 32. Scintigraphic results were compared to the histological assessment. Other factors, such as nodule size, distance from the pleural surface, or distance covered by the needle, were considered as possible factors for non-centered lesions.

Results PGC images showed that the lesion was in contact with the margins in 8/32 cases and centered in 24. In all cases in which the lesion was considered as centered by the PGC, the margins were free of involvement (NPV 100%), although the PPV is low.

Conclusions The use of a PGC for margin assessment after pulmonary nodule resection is feasible and provides a high NPV in our series. In addition, the short intraoperative time required for its use makes the PGC a useful tool for providing supplementary information to histopathologic results. Further studies from different surgical teams are required for an external validation.

Keywords Radioguided surgery · Portable gamma-camera · Pulmonary nodules · Margin assessment

Introduction

The use of high-resolution imaging techniques during the surveillance of malignant diseases, such as colorectal cancer or renal tumors, has increased the detection of previously unknown small pulmonary nodules. An increase in the size of a nodule observed during surveillance requires

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a histological diagnosis. Non-invasive imaging techniques such as computerized tomography (CT) or positron emission tomography (PET)/CT can be used to characterize these lesions, although they do not always preclude biopsy, guided by CT or surgery [1, 2]. Video-assisted thoracic surgery (VATS) is the approach of choice over thoracotomy for performing surgical biopsy, due to its lower morbidity [3, 4] and reduction in the length of hospital stay.

Some pulmonary nodules are difficult to access because of their location or size, requiring the need for radiological guidance [5]. Different guides have been used for preoperative localization of pulmonary nodules [6], including intraoperative ultrasonography [7] or dyes such as indocyanine green [8], but the hook-wire is the most commonly used [9, 10]. Radioguided occult lesion localization (ROLL) was first used in the localization of pulmonary nodules in 2000 [11]. Since then, ROLL has become a well-known technique for use in difficult-to-locate lesions, being most commonly applied in breast cancer [12, 13]. It consists of intralesional injection of a radiotracer by means of radiological guidance (CT or ultrasonography) and surgical resection of the lesion with the help of a gamma-probe. The gamma-probe locates the highest area of activity and the region at which the activity starts fading, thereby defining the surgical resection margins. It can be used with VATS and has demonstrated a resection success rate of 99%, with low morbidity [14–16], even in subsolid nodules [17].

Following nodule resection, hand-held scanning of the surgical area with the gamma probe allows confirmation that the activity is only located within the lung specimen and there is no residual activity requiring further excision. Nevertheless, the surgical specimen must be analyzed to ensure not only correct resection of the lesion but also to check if the margins are wide enough to be considered as safe and free of involvement. Histological analysis is needed regardless of the hook-wire, dye, or radiotracer guidance method used. Nevertheless, the gamma emission involved in the ROLL technique allows monitoring inside the operating room by means of a portable gamma-camera (PGC). PGCs have been used for radioguided surgery of parathyroid adenomas [18], breast cancer resection [19, 20], and sentinel lymph node biopsy [21, 22]. It has been also evaluated in margin assessment of breast lesions removed with the ROLL technique [23], showing a correlation of 60% with the histological study results, with the posterior margin in contact with the chest wall being the most commonly involved.

The aim of this study was to evaluate the intraoperative use of a PGC for the assessment of margins after the use of ROLL of pulmonary nodules.

Material and methods

Patients

Twenty-nine patients (mean ± standard deviation [SD] age 64 ± 12.4 years; range 27–79) were referred to our Nuclear Medicine Department for radioguided surgery of a pulmonary nodule and were prospectively included in the study as shown in the flowchart (Fig. 1). Patients were consecutively recruited by consensus on the thoracic tumor board when presenting a nodule difficult-to-locate by palpation during surgery due to its size or deepness. Inclusion criteria were as follows: (a) non-palpable solid pulmonary nodules with a size ≥ 5 mm; (b) subsolid pulmonary nodules with a solid component ≥ 5 mm; and (c) other nodules on the chest wall difficult-to-locate by palpation. Exclusion criteria were (a) non-solid pulmonary nodules or subsolid pulmonary nodules with solid component < 5 mm; (b) pregnancy, and (c) breast-feeding period. Patients in which ROLL resection was performed but PGC was not available during surgery were not included.

The patients (16 men, 13 women) presented 36 pulmonary nodules and 1 nodule of the chest wall and 1 pleural nodule. A PGC was used to assess the margins in 32 cases: 31 pulmonary nodules and 1 pleural lesion. In the remaining 6 cases, the PGC was not available. All lesions were non-palpable either due to their small size or deep location. The mean size of the pulmonary nodules was 10.1 ± 4.9 mm, ranging from 3 to 22 mm. Table 1 shows the characteristics of the nodules. Informed consent was obtained from all the participants included in the study. The study was approved by the local Ethics Committee of our hospital (HCB/2016/0417).

Imaging and injection

Radiotracer injection was performed the day before or the same day of the surgery (2–18 h prior to surgery) guided by real-time CT fluoroscopy (Sensation® 16, Siemens®, Erlangen, Germany) using 4.6 mm collimation. Albumin macroaggregates (LyoMAA®, Mallinckrodt Radiopharmaceuticals, Madrid, Spain) labelled with ^{99m}Tc ([^{99m}Tc]Tc-MAA) was injected at a volume of 0.2 ml with an activity of 37–111 MBq, depending on the time remaining for surgery. Additionally, 0.05 ml of iodinated contrast (Ultravist®, Bayer Hispania, Barcelona, Spain) was injected with the radiotracer, except in 4 cases, where it was not available. After administration of local anesthesia, a 22-gauge spinal needle was used to perform the radiotracer injection procedure. The tip of the needle was placed inside the nodule and not in its vicinity (Fig. 2).

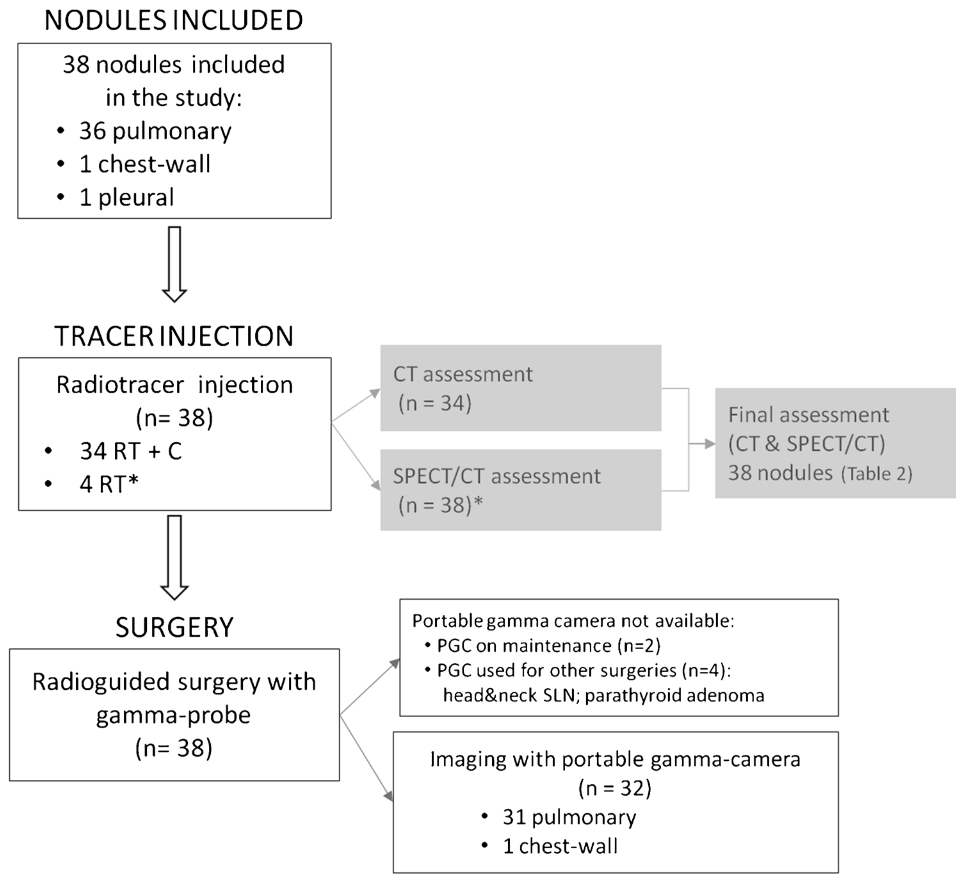

Fig. 1 Flowchart of the patients and nodules included in the study

The distance traveled by the needle on the path towards the nodule, which would indicate the length of a hook-wire path through the lung, was registered as well as the distance to the nearest pleural surface, which was not necessarily the same as that of the needle path.

Once injected, a chest CT was performed in the Radiology department with a dual purpose: to detect complications such as pneumothorax or hemorrhage and to assess the correct placement of the tracer inside the nodule, and that is the reason for the use of iodinated contrast. Mild hemorrhage was considered when an area of ground glass was located in the path of the needle, and severe hemorrhage was considered when ground glass or consolidation areas were seen distal to the needle path.

Afterwards, a single photon emission computed tomography (SPECT)/CT of the thoracic region was performed in the Nuclear Medicine department to confirm correct placement of the radiotracer inside the lesion and to dismiss spillage along the needle pathway or on the pleural surface.

Two groups were considered depending on the location of the radiotracer inside the nodule: centered and non-centered according to each technique (centered by CT or by SPECT/CT), establishing a final classification (centered or non-centered) according to the two procedures (CT and SPECT/CT). The radiotracer was considered as being centered when perfectly located in the middle of the nodule and was considered as non-centered when located in the center and the periphery of the nodule. Lesions were considered to be well-centered when CT and SPECT/CT were both congruent or when the radiotracer was centered in SPECT/CT in lesions in which iodinated contrast was not injected. Deep lesions were considered as those requiring a needle path of 20 mm or more to avoid a bias secondary to nodules bigger in size placed at 10 mm or less. Then, we compared the number of cases with the radiotracer centered inside the nodule depending on the length of the needle path (<20 or ≥ 20 mm).

We analyzed the influence of the distance from the nodule to the pleura, the path of the needle to the nodule, and the size of the nodule with respect to the location of the radiotracer because these are variables that may affect a correct intraoperative resection.

Preoperative equipment

For preoperative imaging, chest CT was performed in the same CT equipment. Afterwards, a dual-head gamma-camera (Infinia Hawkeye 4, General Electrics, Milwaukee, USA) fitted with a low-energy, high-resolution collimator was used to perform SPECT/CT. After SPECT/CT fused-image reconstruction, 3D volume-rendering images

Table 1 Characteristics of the nodules

	Frequency (n/%)
Histology	
Metastatic nodules	24 (63%)
Intestinal	*16*
Breast	*1*
Melanoma	*5*
Sarcoma	*2*
Primary lung neoplasm	8 (21%)
Adenocarcinoma	*3*
Carcinoid	*3*
SCC	*2*
Benign lesions	6 (16%)
Nodule location	
RUL	8 (21%)
ML	1 (2.6%)
RLL	8 (21%)
LUL	10 (26.3%)
LLL	9 (23.7%)
NA	2 (5.3%)
Type of nodule	
Solid	32 (84.2%)
Subsolid	2 (5.3%)
Non-solid	2 (5.3%)
Wall/pleural	2 (5.3%)

SCC squamous cell carcinoma; *RUL* right upper lobe; *ML* mid-lobe; *RLL* right lower lobe; *LUL* left upper lobe; *LLL* left lower lobe; *NA* not applicable

Fig. 2 CT scan performed during the injection of the radiotracer. A 6-mm nodule located in the left upper lobe. A 22-gauge needle was inserted inside the nodule without complications

were generated using a Dicom viewer (OsiriX, Pixmeo SARL, Geneva, Switzerland) to obtain a volumetric presentation to improve localization of the activity in the pulmonary nodule (Fig. 3).

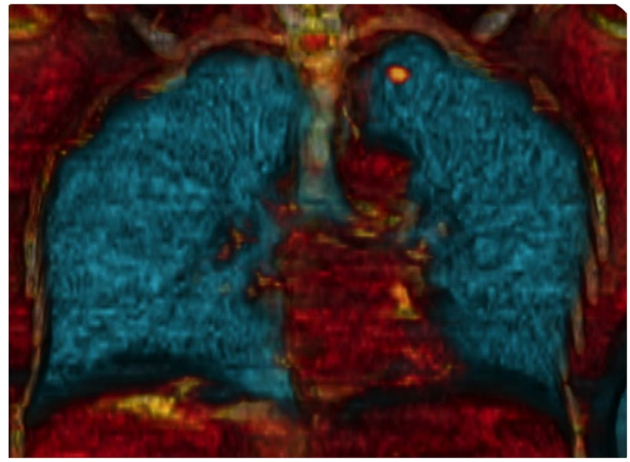

Fig. 3 Coronal slice of 3D volume-rendering image of fused SPECT/CT obtained preoperatively to verify the presence of the radiotracer inside the pulmonary nodule in the left upper lobe (yellow spot)

Surgery and intraoperative equipment

For intraoperative navigation, two different gamma probes were used depending on the depth of the nodule. For superficial nodules, a 14-mm diameter hand-held gamma detection probe was used while for deep nodules, a 10-mm diameter laparoscopic gamma detection probe (Navigator; USSC, Norwalk, CT, USA) was needed.

Nodule excision was performed with the aid of the hand-held gamma probe. Once the lesion was removed, the nuclear medicine physician performed a surgical bed scan with the gamma probe to check for residual activity and the need to widen margins.

A PGC (Sentinella S102, Oncovision, Valencia, Spain) was also used for margin assessment after the lesion had been removed. A detailed technical description of this equipment has been published previously [20]. This camera is provided with a 40×40 mm field of view, continuous scintillating crystal (CsI)(Na) and a position-sensitive photomultiplier tube (Hamamatsu H8500) and was fitted with a pinhole collimator with a 4 mm opening. The optical image is incorporated beside the camera and angled to ensure correct anatomical fusion of both the scintigraphic and optical images. Using this pin-hole collimator, the whole surgical field can be fully scanned in a single view.

A pair of images (anterior and lateral view) of the tumoral specimen was intraoperatively obtained by means of the PGC to confirm the presence or absence of activity (Fig. 4). The mean pinhole–object distance was approximately 5–10 cm. In wedge resections of pulmonary lesions, two of

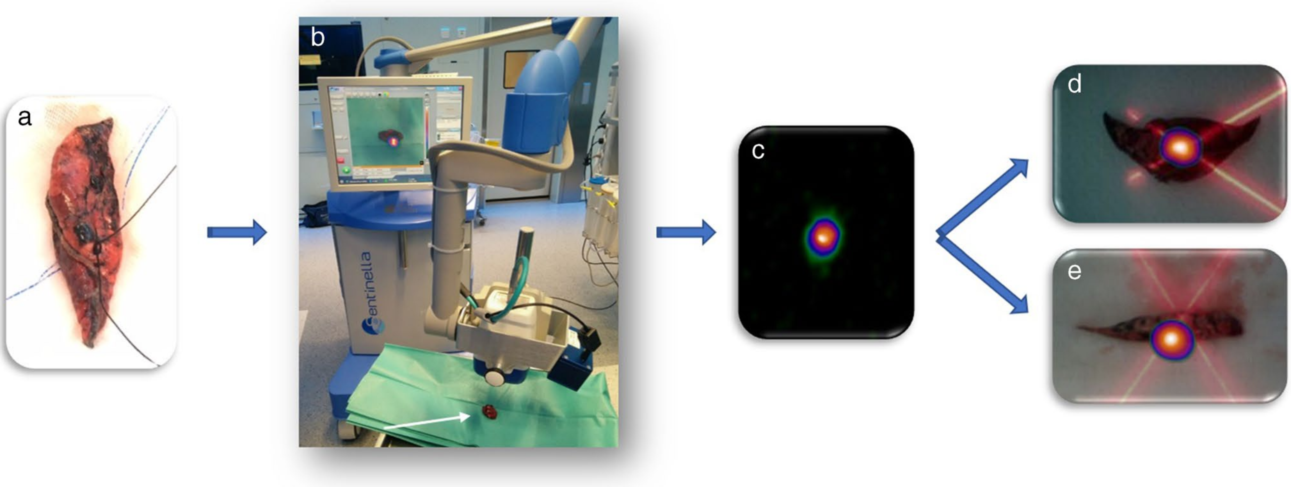

Fig. 4 Portable gamma camera (PGC) inside the theatre, which images the pulmonary specimen after the surgical resection. The image was acquired beside the operating table, before sending the specimen to the pathologist. **a** Surgical specimen after resection; **b** PGC imaging the surgical specimen (white arrow). The image appears on the screen; **c** scintigraphic image obtained by means of the PGC; **d** and **e** fused images (scintigraphic and optical view) which show the activity (coloured spot) inside the lesion and centred, without any contact with margins (**d**) or the active lesion in close contact with the margins with stitches (**e**), so the nodule is considered to be in contact with margins

the three sides are defined by pleural surfaces and only one in contact with healthy tissue; therefore the most important assessment is on that side in order to verify that the deep margin is free of involvement. Activity near the stitches margin in the surgical specimen implied the need for a wider excision. The activity on this margin assessed by PGC was considered as "contact with margins." When the lesion was in contact with the pleural surface, there was no need for widened margins, being classified as "free margins."

While the scintigraphic image was being acquired, the optical mode was switched on, obtaining a fused image (scintigraphic over optical data) inside the operating room (Fig. 5). These images were correlated with the final pathological report. The whole acquisition time for the tumoral specimen with the optical reference was a maximum of 1 min.

Pathology

An intraoperative pathological examination was performed to verify lesion inclusion with free margins. A lesion to non-pleural margin distance of the specimen greater than 1 mm was considered as a non-involved margin.

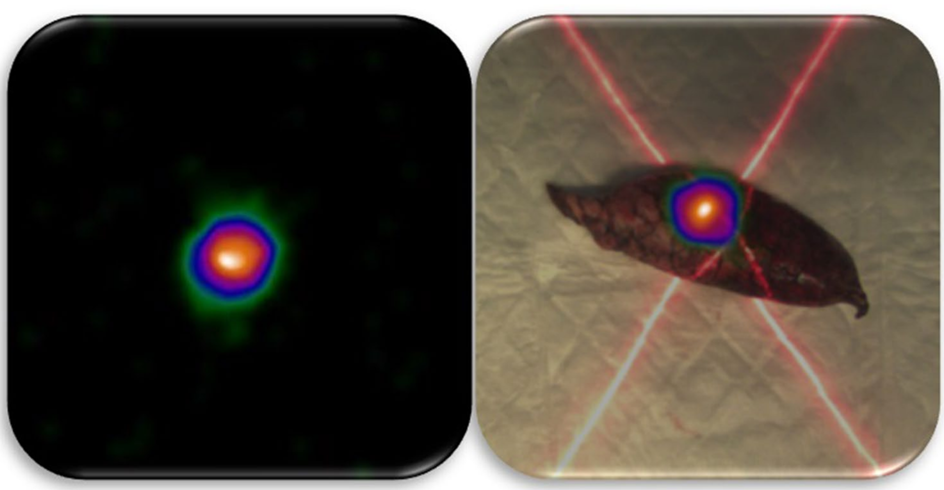

Fig. 5 Intraoperative image obtained with the portable gamma camera to assess the margins. Left image shows the activity detected by the PGC as a focal uptake which confirms the presence of the activity (nodule) in the specimen. Right image results from the fusion with the optical view. It shows the activity centred inside the surgical specimen

Statistical analysis

Patient characteristics (categorical data) are presented as absolute values and percentage frequencies. Quantitative variables are described as mean and standard deviation. A paired *t* test (with Fisher correction when needed) was used to evaluate the significance of differences between the two groups (centered and non-centered). Differences were considered significant when the p value was less than 0.05. A commercial statistical package (StatCrunch; Pearson Education 2019) was used for the statistical analyses.

Results

Injection

In pulmonary nodules, the distance from the nodule to the pleural surface was 8.25 mm (SD 8.86), ranging from 0 to 43 mm. On the other hand, the length of the needle path was 26.91 mm (SD 19.51), ranging from 0 to 97 mm.

There were no severe complications. Mild hemorrhage was observed in 42% of cases (16/38), and pneumothorax was present in 21% of cases (8/38). Only two patients needed aspiration of the pneumothorax, which was performed in the CT room with the help of a syringe. No pleural catheter was needed in either case. One case presented a significant pneumothorax, but the other case was a patient with 5 marked nodules in both lungs that presented with bilateral pneumothorax. In the latter case, we performed aspiration of the mild pneumothorax of the hemithorax which, according to surgical decision, would be intervened later during the procedure.

Table 2 Localization of the different markers inside the nodule

		SPECT/CT		
		Centered	Non-centered	
CT	Centered	17	5	22 (57.9%)
	Non-centered	4	8	12 (31.6%)
	No contrast injected	3	1	4 (10.5%)
		24 (60.6%)	14 (39.4%)	

Chest CT and SPECT/CT images assessment

In the global sample, based on the information of both techniques and the assessment of the radiologist and the nuclear medicine physician, the radiotracer was centered inside the lesion in 19 lesions. The radiotracer was inside the remaining 19 lesions, but a proportion of the tracer was in contact with the nodule but not deviated from it. There was no radiotracer spillage along the pleural surface or inside the lung parenchyma. There was no need for radiological guidance (hook-wire or ultrasonography) in any case.

On CT images, iodinated contrast was centered in the middle of the lung nodule in 22/34 lesions (64.7%) and was displaced in only 12 lesions (35.3%). Based on SPECT/CT images, the radiotracer was centered in 24/38 lesions (63.2%) and displaced in 14 (36.8%). Results from both techniques and the final assessment are shown in Table 2. Both techniques were congruent in 25/34 lesions (73.5%). In 17 nodules both the radiotracer and iodinated contrast were well-centered, and in 8 both were slightly displaced from the center of the lesion. The congruence of the results of both techniques was analyzed using the Fisher's exact test which showed good concordance (p 0.025).

We analyzed the influence of the distance from the nodule to the pleura, the path of the needle to the nodule, and the size of the nodule with respect to the location of the radiotracer inside the pulmonary nodules (excluding chest wall and pleural nodule) and found no significant differences between both groups (Table 3). However, the proportion of cases with centered radiotracer was higher when the path of

Table 3 Tracer location (centered or non-centered) related to pulmonary nodule characteristics**

	Pulmonary nodules (n 36)		*p* value
	Centered *(n,%)* (18, 50%)	Non-centered *(n,%)* (18, 50%)	
Distance between nodule and pleura (mm) *mean (SD)*	9.3 (4.1)	10.4 (5.4)	0.49
Distance < 10 mm *(n,(%))* Distance ≥ 10 mm *(n,(%))*	13 (52%) 5 (45.5%)	12 (48%) 6 (54.6%)	0.72
Length of the needle path (mm) *mean (SD)*	7.2 (6.3)	9.3 (10.9)	0.47
Distance < 20 mm *(n,(%))* Distance ≥ 20 mm *(n,(%))*	13 (65%) 5 (31.25%)	7 (35%) 11 (68.75%)	*0.04**
Nodule size (mm), *mean (SD)*	22 (23.0)	25 (15.5)	0.65
Nodule size < 10 mm *(n,(%))* Nodule size ≥ 10 mm *(n,(%))*	10 (47.6%) 8 (53.3%)	11 (52.4%) 7 (46.7%)	0.73

the needle was less than 20 mm in length (65% vs. 31.3%; p 0.04).

Surgery

All lesions were correctly located by means of the gamma-probe (detection rate of 100%), and all but one lesion were successfully removed (intraoperative success rate of 97%). In one case, VATS needed to be converted to thoracotomy due to the deep localization of the nodule. The mean and median length of the procedure were 19 min (SD 18) and 12 min (range 3–85), respectively, including the lesion that was not possible to resect, which required 85 min. In one case VATS was converted into thoracotomy due to a laceration of the lung during surgery. We did not observe any differences by gender in the volume of the specimen or the number of centered cases.

The PGC images revealed that the lesion was centered in 24 cases and in close contact with margins in 8 specimens (Figs. 4d and e). The results are described in Table 4, with excellent negative predictive value (100%) but low positive predictive value (1/8: 12.5%).

Pathology

The pathological exam identified 6 benign lesions, 8 primary lung tumors (2 squamous cell carcinoma, 3 carcinoid tumors, and 3 adenocarcinoma), and 24 metastatic nodules (16 digestive cancers, 5 melanomas, 2 sarcomas, and 4 others).

The volume of the specimen was 19.8 cc (SD 18.35). The volume of the surgical specimen was smaller in cases in which the SPECT/CT showed that the radiotracer was centered (17.7 cm^3 (SD 12.7) in centered cases vs. 23.30 cm^3 (SD 18.8) in non-centered cases), although without significant differences ($p = 0.38$).

Table 4 Portable gamma-camera findings

Portable gamma camera	Pathology		
	Margins involvement	Free margins	
Contact with margins	1	7	8
Lesion centered (no contact with margins)	0	24 (NPV 100%)	24

NPV negative predictive value

Margin assessment

When margin involvement was shown by the PGC, the lesion was in contact with the margins in only 1 case, indicating the need for wider excision. In this case, the radiotracer was not centered inside the nodule, and a wider resection was deemed necessary, but histological involvement was diagnosed, being a true positive case. In all cases in which PGC showed the lesion to be centered, the margins were free of involvement, with a negative predictive value (NPV) of 100% (Table 4).

Discussion

Surgical biopsy of pulmonary nodules by VATS approach needs the intraoperative confirmation of successful resection and safe margins. In our series, we have used a PGC inside the OR after resection by ROLL approach for margins assessment with a NPV of 100%.

Radioguided surgery or ROLL, which was initially designed for breast cancer, was applied two decades ago to respond to this clinical situation with excellent results in the detection rate of pulmonary nodules, reaching 99% of cases. In a retrospective analysis of the last 20 years, including 395 patients, Manca et al. [16] reported an adequate resection of the pulmonary nodules in 99% of cases, with only 1% of conversion to thoracotomy. The ROLL technique, applied with either a radiotracer or with iodine seeds, depends on correct placement of the radioactive tracer. It is crucial to achieve not only correct identification and resection of the nodule but also to ensure safe margins. Once the nodule has been removed, a pathological study is needed to confirm a successful resection, which can take 20 min on average.

In the past, a homemade pointer with a ^{99m}Tc activity of 11 MBq was used to outline the surgical specimen [23] after nodule resection. For the present study, we used a PGC fitted with an optical view to assess margin involvement, providing a high NPV (100%).

More than 10 years ago, a PGC was used to assess margins resection for breast lesions [23], thanks to the short time period required to obtain an intraoperative image. It should be noted that the main difference with breast tissue is the inability to reach the nodule by palpation during the entire procedure with the VATS approach. Therefore, it is crucial to ensure that the target nodule is within the portion of lung tissue to be removed. In a previous study by our group [23], we included 42 women with breast cancer with the aim of replacing, once validated, the intraoperative histopathologic study. Nevertheless, there was only 60% of concordance between intraoperative scintigraphic and histopathologic results and a NPV of 83%. In radioguided surgery, the greatest development has come from instrumentation, mainly with improvement of spatial resolution and optical fusion. The addition of an optical camera to the PGC provides complete visualization and integration of functional imaging into the actual specimen. There was a high NPV (100%) in our series, which contrasts with 83% in the breast cancer series, and it can be partially explained by the technological improvements.

The results obtained by assessing the centering of the marker in the CT or SPECT/CT study suggest that one of the two post-procedure techniques could be omitted. We consider that post-marking CT only contributes to the diagnosis of potential marking complications (pneumothorax, hemothorax, or pulmonary hemorrhage). These complications can also be assessed by SPECT/CT; therefore, in asymptomatic individuals, SPECT/CT could be performed directly after intralesional injection of the radiotracer. In our series, the only factor that correlated with the centering of the tracer inside the nodules was the length of the needle. The absence of significant differences between both groups, centered and non-centered tracer inside the nodule, with respect to the size of the nodule and the distance between the nodule and the pleura suggest that our marking and resection technique is satisfactory for any type of nodule, regardless of its size, or depth to the pleural surface. So, this technique could be reproducible in centers where there are no skilled interventional radiologists in the puncture of very small nodules. The path of the needle is also one of the main problems when using hook-wire techniques because the intrapulmonary path of the wire should also be removed [10]. In our study, the path determines the centering of the tracer; therefore, it is recommended to inject the tracer using the shortest length, which is feasible with ROLL technique but not always when using a hook-wire.

The resection volume was smaller, although without significant differences, in the cases in which SPECT/CT showed that the radiotracer was centered. However, we consider that a larger sample would be necessary to be able to demonstrate that smaller resections are achieved when the radiotracer is properly centered inside the pulmonary nodule.

PGC has been intraoperatively used for real-time resection of parathyroid tumors after [^{99m}Tc]Tc-MIBI injection [18] with outstanding results. Evangelista et al. [19] used the gamma-camera to guide the resection margins in 18 breast cancer patients. Unfortunately, there is no specific radiotracer for pulmonary nodules. Furthermore, some surgical biopsies are indicated for the characterization of pulmonary nodules, and thus, a radiotracer with high affinity for malignancy would not be useful for benign nodules. However, the strength of the ROLL technique is the possibility of being able to resect the nodules and assess the margins within the same procedure.

Other tracers have been used for ROLL in pulmonary lesions, such as 125-Iodine (^{125}I) seeds [24]. Gobardhan et al. reported 100% of success with complications similar to those of hook-wire localization. In 18% of cases, the seed was dislocated after placement, which is greater than the number of cases observed in our series. It can be explained by the needle gauge needed, requiring a one-shot placement to avoid severe complications such as pneumothorax or bleeding. Another reason for seed displacement is that this is an operator-dependent technique, which requires dedicated physicians. Nevertheless, PGCs can detect different isotopes, including ^{125}I, and thus, once the lesion has been resected, margin assessment can be performed regardless of the radiotracer or isotope used.

Kondo et al. [25] described the capacity of intraoperative ultrasonography in detecting non-solid pulmonary nodules. They also evaluated the resection margins obtaining a high correlation with histological examination ($r^2 = 0.954$, $p < 0.001$). In case of segmentectomy, not for wedge-resection, a re-ventilation is needed to define the border of the lung segment which makes it difficult to value with ultrasound. The development of hand-held gamma cameras combined with an ultrasound probe performs a good overlapping between both with an error less than 1 mm [25], but its use in pulmonary resections would be limited due to the air trapped inside the specimen [26]. Lung collapse is not required when using a PGC, and therefore, margins can be assessed in any type of surgical resection.

Other devices combining more than one image technique have been developed [27]. Cerenkov radiation produced by some isotopes as ^{18}F, ^{64}Cu, or ^{124}I can be detected with higher sensitivity than gamma or beta radiation in tumor detection at a depth of less than 2 mm. The main strength relies on the direct emission of Cerenkov radiation from the target lesion because the tracer is systemically injected, and it is uptaked by the lesion. So, margins could be better assessed. The main disadvantage is the interference of ambient light in the detection of Cerenkov radiation [27]. Freehand SPECT has been used for perioperative margins assessment of breast lesions marked with ^{125}I seeds. The device identifies the seed inside the specimen, and it calculates the distance from the seed/lesion to the narrowest margin, with high congruence with CT. The difference with handheld gamma cameras is the ease of moving the gamma probe from Freehand SPECT in three dimensions [28].

To date, to our knowledge, there are no reports about lung nodule excision with the aid and guidance of an intraoperative PGC. During resection, the main tool to guide surgery is a hand-held gamma probe, although the use of only a PGC should not be ruled out. The main pitfall is the great distance between the nodule and the PGC inherent to the

VATS approach, which hampers the direct assessment during resection. However, it would be an excellent tool in case of open surgery.

The procedure with PGC lasts a maximum of 5 min (a few minutes for positioning the specimen and 1 min to acquire the scintigraphic image; optical view and image capture are immediate).

The main drawback of this study is the low positive predictive value. We think that it was due to the wide scatter activity from the nodule that could be solved by adjusting the threshold for each specimen. However, manual thresholding is a subjective method, and it is not recommended if there is no experience with this kind of images. With this new setting, more surgical specimens would, therefore, have been classified as free margins, as the activity would have appeared on the screen at a substantial distance from the margins. Once the scatter activity is solved, it could be an added value for intraoperative pathologic assessment in some clinical situations (benign nodules, metastatic lesions, among others) and to facilitate surgical planning. Moreover, the main goal of pulmonary nodule resection is to ensure free margins without an intraoperative histological analysis. The intraoperative study requires freezing the specimen which leads to possible damage, hindering further histologic examinations. An image technique with a high NPV allows the surgeon to complete the procedure without waiting for the histological results. On the other hand, the pathologist can carry out the deferred histologic analysis under the best conditions. In our series, there is only one case with involved margins, which can overestimate the NPV, and becomes another drawback of the study, besides the small number of nodules assessed. Other studies with larger number of cases are required to confirm our findings. Another limitation is the fact that the PGC does not measure the distance between the margin and the nodule itself, but the distance between the margin and the radiotracer placed inside the margin. Therefore, the preoperative SPECT/CT image is essential to ensure that the radiotracer is correctly placed inside the lesion in order to avoid an unnecessary resection of healthy tissue or to avoid a wrong margin assessment.

In conclusion, the use of a PGC for the assessment of margins after pulmonary nodule resection is feasible and provides a high NPV in our series. In addition, the short intraoperative time required for its use makes the PGC a useful tool for providing supplementary information to histopathologic results. Further studies from different surgical teams are required for an external validation of the technique.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital Clinic de Barcelona (approval registration number HCB/2016/0417).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article. S. Vidal-Sicart had served on advisory boards for Oncovision®, Spain.

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