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ORIGINAL ARTICLES

Radio-guided thoracoscopic surgery (RGTS) of small pulmonary nodules

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Abstract

Background The demand for adequate tissue sampling to determine individual tumor behavior is increasing the number of lung nodule resections, even when the diagnosis is already recognized. Video-assisted thoracic surgery (VATS) is the procedure of choice for diagnosis and treatment of small pulmonary nodules. Difficulties in localizing smaller and deeper nodules have been approached with different techniques. Herein we report our 13-years' experience with radio-guided thoracoscopic resection.

Methods Patients with pulmonary nodules smaller than 1 cm and/or deeper than 1 cm, below the visceral pleura, underwent computed tomography (CT)-guided injection of a solution, composed of 0.2 ml ^{99}Tc-labeled human serum albumin microspheres and 0.1 ml nonionic contrast, into the nodule. During the VATS procedure, an 11-mm-diameter collimated probe connected to a gamma ray detector was introduced to scan the lung surface. The area of major radioactivity, which matched with the area of the nodule, was resected.

Results From 1997 to 2009, 573 patients underwent thoracoscopic resection of small pulmonary nodules, 211 with the radio-guided technique. There were 159 men and 52 women, with an average age of 60.6 years (range = 12–83). The mean duration of the surgical procedure was 41 min (range = 20–100). The procedure was successful in 208/211 cases. Three patients (0.5%) required conversion to a minithoracotomy. The mean length of pleural drainage and hospital stay was 2.3 and 3.7 days, respectively. Histological examination showed 98 benign lesions and 113 malignant lesions (61 metastases and 52 primary lung cancers).

Conclusion This study confirms that radio-guided localization of small pulmonary nodules is a feasible, safe, and quick procedure, with a high rate of success. The spread of the sentinel lymph node technique has increased the availability of technology required for RGTS.

Keywords Pulmonary nodule · Technetium-99m aggregated albumin · Thoracoscopy · VATS · NSCLC · Pulmonary metastasis

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In recent years, widespread utilization of computed tomography and the diffusion of screening programs in smokers has allowed identification of a larger number of small pulmonary lesions. Early diagnosis of small indeterminate nodules is important because in cases of lung cancer, the prognosis is correlated with their size [1, 2]. However, transbronchial or transthoracic needle biopsy and positron emission tomography (PET) scans do not always allow definite exclusion of the malignant nature of these lesions [3–5]. Therefore, surgical exeresis of the nodule becomes necessary.

Video-assisted thoracic surgery (VATS) resection is the preferred surgical procedure for diagnosis and, in selected cases, treatment of pulmonary nodules [6]. Nevertheless, VATS can be difficult in the event of small or nonperipheral pulmonary lesions due to the impossibility of localizing them by endoscopic instruments. Many techniques have been developed to identify such nodules that are invisible or impalpable during thoracoscopy, and to thus avoid conversion to open thoracotomy. Among the preoperative techniques, those most used are percutaneous hook-wire placement, staining with methylene blue, and endothoracic pulmonary sonography (ETUS) [7–9]. These methods are generally effective but burdened with significant rates of failure and complications. To increase the efficacy of thoracoscopic resection of smaller pulmonary nodules, in our department we developed the radio-guided technique that was already described in a previous preliminary report [10]. Recently, the spread of techniques, like that of the sentinel lymph node, has increased the availability of the required technology, making radio-guided thoracoscopic surgery (RGTS) more accessible. Moreover, the development of proteomic knowledge and the possibility of determining individual tumor behavior have increased the demand for adequate tissue sampling, even when the diagnosis is already known.

In this study we describe results, lessons learned, and future predictable development and application of RGTS based on our 13 years' experience and on data reported in the literature.

Materials and methods

We retrospectively reviewed all patients with indeterminate lung nodules who underwent radio-guided localization for thoracoscopic resection. The primary end point of the study was to evaluate the efficacy of the procedure and to compare it with the others reported in the literature. Secondary objectives were to confirm the safety and, above all, analyze the merits and pitfalls of the technique.

Selection criteria

Patients selected to undergo radioactive marking of the lesion before VATS resection, according to the technique previously described and summarily reported below, were those with nodules less than 10 mm and/or more than 10 mm from the visceral pleura (Fig. 1A). Patients with a nodule with maximum diameter greater than 3 cm and more than 3 cm from the pleural surface were excluded.

Devices

A solution composed of 0.2 ml of ^{99}Tc-labeled human serum albumin microspheres (5–10 MBq) and 0.1 ml of nonionic contrast was used for marking the target nodule by CT guidance. Technetium-99m (^{99}Tc), a radionuclide with principal gamma photon emission energy of 140 keV, was used because of its half-life of about 6 h and, as a consequence, a low patient-absorbed radiation dose. Moreover, it is a low-cost and easily available radionuclide.

In the operating room, under thoracoscopic vision, a hand-held, 11-mm-diameter collimated gamma probe connected to a gamma ray detector unit (ScintiProbe MR 100, Pol.Hi.Tech., Carsoli, Italy) was used to detect ^{99}Tc radioactivity. The detector unit converted gamma ray emissions into audiovisual signals, proportional to the detected radioactivity. The biggest audiovisual signal matched with the area of the previously injected nodule.

Technique

The ^{99}Tc-labeled human serum albumin microsphere solution was injected using a 22G needle under CT guidance into the lesion or into the area just in contact with it. A postprocedure CT scan confirmed the presence of the radiotracer within the nodule, thanks to the nonionic contrast material within the solution (Fig. 1B). Afterward, the patient was brought into the operating room for thoracoscopic resection of the lesion. All thoracoscopic resections were performed under general anesthesia with selective intubation through a double-lumen tube to obtain ipsilateral lung collapse. The patient was placed in a lateral decubitus position and a pneumothorax was induced. In all patients, a 7-mm trocar for the videothoracoscopy was inserted into the sixth or seventh intercostal space along the midaxillary line. After a preliminary exploration of the pleural space, a second 11.5-mm trocar was placed according to the needs of strategic visibility and manipulation of the target lesion. Through this second incision the thoracoscopic gamma probe, connected to the gamma ray detector, was introduced. The surface of the lung was scanned, starting far from the area of the lesion, in order to calculate the radioactive ground and to reset the system. Then the probe was maneuvered close to the area of the lesion, searching for the major point of radioactivity. A third incision was then made for the endostapler device, which allows a wedge resection of the radioactive area to be made. During resection, before firing the endostapler, the probe was used to guide the resection itself by verifying the absence of radioactivity just over and, above all, beyond the stapler line. Once the wedge resection was performed, the nodule was extracted from the pleural cavity into an endoscopic bag through the largest port hole to avoid tumor seeding to the chest wall. The presence of the nodule in the surgical specimen was immediately verified and was then sent for pathological examination. In cases where there was suspicion of primary lung cancer and the patient had an

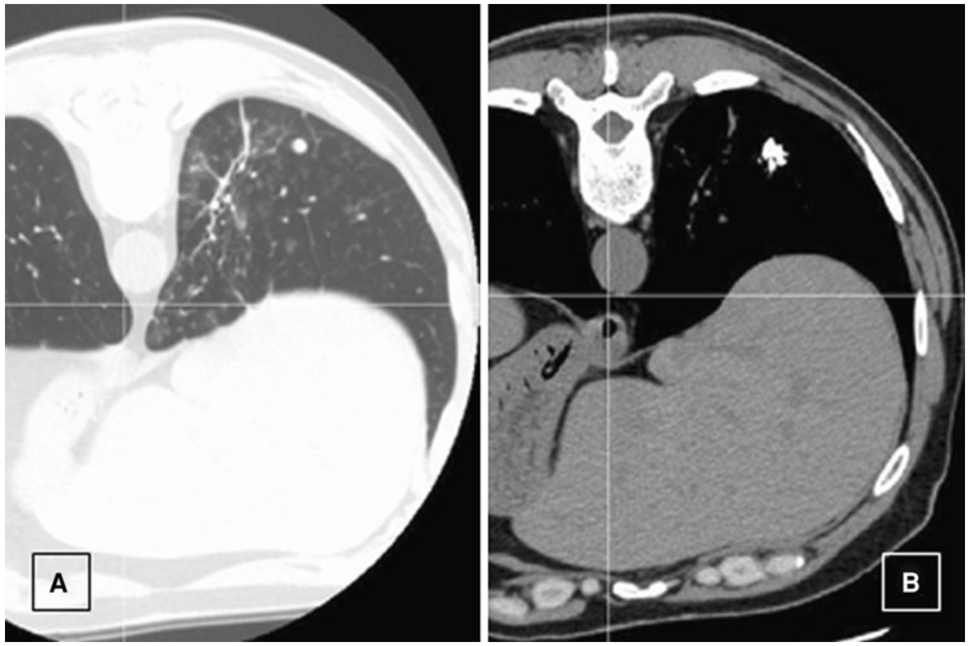

Fig. 1 **A** CT scan of a typical lesion that requires preoperative marking. **B** After CT-guided injection, the correct placement of the radiotracer within the nodule is confirmed by contrast material enhancement

adequate pulmonary reserve, an intraoperative frozen section examination was performed to complete the resection with a lobectomy and lymphoadenectomy when non small cell lung cancer (NSCLC) was diagnosed.

Results

From January 1997 to December 2009, we utilized the RGTS technique in 211 of 573 patients (36.8%) with small pulmonary lesions who underwent surgical resection. There were 159 men and 52 women, with a mean age of 60.6 years (range = 12–83). Forty-two percent ($n = 89$) of these patients had anamnesis for malignancies. The mean lesion size was 8.3 mm (range = 0.3–28), and the mean distance from the visceral pleura was 13 mm (range = 6–30) (Table 1).

No significant complications occurred in relation to CT-guided marking of the lesion, except for 22 patients (10.4%) who developed a small pneumothorax (Fig. 2A) and none of the latter required chest tube placement. All patients underwent VATS resection within 4 h of the radiological procedure. The length of the surgical procedure was, on average, 41 min (range = 20–100). The mean length of pleural drainage was 2.3 days (range = 1–5), and hospital discharge was possible, on average, after 3.7 days (range = 1–8). No mortality or perioperative complications were reported. A summary of operative and postsurgical results is given in Table 2.

The procedure was successful in correctly localizing and resecting the nodule in 99% of the cases (208/211 patients). In three patients, certain localization of the nodule was not possible and conversion to a small thoracotomy was necessary. In these cases, the gamma probe was unable to detect a restricted area of major radioactivity. In two patients with severe bullous emphysema there was an area with a high level of radiotracer uptake that was too extensive, which did not allow us to securely establish the site for surgical resection. After resection, the nodules were found inside the radioactive area in both cases. A second look at the CT scans taken after the labeling procedures revealed that some contrast media expanded into the bullae around the lesions. In another case, a pneumothorax occurred during the labeling procedure and some radiotracer expanded into the pleural space. Therefore, during thoracoscopy the ground radioactivity was too high to

Table 1 Clinical and radiological characteristics

No. patients	211
Male/female	159/52
Mean age (range)	60.6 years (12–83)
Anamnesis for malignancies	89 (42%)
Mean nodule size (range)	8.3 mm (0.3–28)
Mean pleura distance (range)	13 mm (6–30)

Table 2 Operative and postoperative results

CT-guided marking complications (rate)	22 (10.4%)
Mean time from marking to resection (range)	113 min (85–230)
Mean surgical time (range)	41 min (20–100)
Conversion to minithoracotomy (rate)	3 (1%)
Mean hospital stay (range)	3.7 days (1–8)
Mean resection margin (range)	13 mm (11–21)

Fig. 2 **A** Small pneumothorax occurred in 10% of patients. **B** In most cases, postinjection CT scan confirmed the presence of radiotracer within the target lesion

allow localization of the target. Post-CT-guided injection pneumothorax occurred in this patient, and it was probably responsible for such an unsuccessful case. In this case it was argued that part of the radiotracer was wasted in the pleural space, thereby increasing ground radioactivity, which interfered with the correct location of the nodule. Therefore, when the problem presented itself again in two other cases, it was successfully resolved by repeatedly washing the pleural space with a saline solution during thoracoscopy, thus reducing the pleural space ground radioactivity; this was sufficient for correctly localizing the site for primary injection within the nodule.

Histological examination of the lesions revealed that a safe margin from the nodule and the stapler line was at least 1 cm. The pathological diagnosis was 98 benign lesions (46.4%) and 113 malignant lesions (53.6%), which included 61 metastases and 52 primary lung tumors (Table 3).

In all those patients with NSCLC and an appropriate cardiopulmonary reserve, a lobectomy with ileomediastinal lymphoadenectomy was performed by open thoracotomy in 19 cases, VATS in 7 cases, and robotic surgery using the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) in 15 cases.

Table 3 Pathological findings

Primary lung tumors	52
Adenocarcinoma	32
Squamous cell carcinoma	11
Carcinoid	5
Large cell carcinoma	3
Leiomyosarcoma	1
Metastasis	61
Colorectal carcinoma	27
Renal carcinoma	8
Prostatic adenocarcinoma	6
Sarcomas	5
Urethral carcinoma	3
Others	12
Benign lesions	98
Hamartoma	31
Sarcoidosis	15
Antracotic pulmonary node	13
Tuberculosis	11
Inflammatory pseudotumor	9
Others	19

Discussion

In patients with malignant lesions, diagnosis and treatment in the early stages are fundamental to improve survival. Today, VATS is the preferred surgical procedure for the diagnostic resection of indeterminate lung nodules. Unfortunately, during thoracoscopy, surgeons have difficulty in detecting smaller or nonperipheral nodules that are invisible and not palpable with endoscopic instruments. Thus, they are frequently forced to conversion to thoracotomy [11]. To reduce the rate of conversion to open surgery, several techniques have been developed to help the surgeon localize small nodules during thoracoscopic resection. Those most widely used are percutaneous hookwire placement, staining with methylene blue, and endothoracic ultrasonography (ETUS). All these techniques have been shown to be useful, although none is without faults or disadvantages. Many of these weaknesses seem to be solved or reduced by RGTS [12–14]. As in the case of RGTS, the percutaneous placement of hooks or staining with vital dye of the nodule is performed under CT guidance. This part of the procedure is associated with some complications, the most common being pneumothorax (PNX). The rate of PNX is 20–32% in patients who undergo the hook-wire (or spira-wire) technique and 25–33% in those who undergo staining with methylene blue [15–18]. In our experience [10], as well as in that of Grogan et al. [12], the rate of PNX is significantly smaller, ranging from 5 to 10%. In the case of methylene blue injection, it is described that diffusion of dye on the visceral pleural surface or the heavy anthracotic pigmentation of the lung (very frequent in smokers) is responsible for a significant number of failures in localizing the lesion, thus leading to a high rate of conversion to an open procedure. Also, the hook-wire technique is associated with a high incidence of dislodgement of the hook, generally during transportation to the operating room or during lung deflation for thoracoscopy, inducing PNX, or during the maneuvers for pulmonary surgical resection, thereby rendering the procedure unsuccessful. Moreover, and probably due to this same dislodgement, the hook-wire technique may lead to pulmonary hemorrhage, which is reported in about 12–35% of cases, and pleuritic pain, seen in 5–6% of patients [17, 18]. These problems have never been observed with RGTS.

The main advantage of the intraoperative thoracoscopic ultrasonography (ETUS) technique for the localization of pulmonary nodules is that it does not require preoperative procedures. Unfortunately, this technique has an intrinsic limitation due to the absence of propagation of ultrasound in the presence of air. Therefore, in patients with emphysematous lung, in case of an incomplete pulmonary collapse due to an unsuccessful selective intubation and in case of the presence of small and deep lesions, which is the object of this article, the rate of successful localization is seen to reduce significantly [19–21]. Moreover, its success is strongly operator-dependent. In a previous paper we recommended such a technique only for lesions greater than 1 cm and where an experienced thoracic sonographer is available [19].

RGTS seems to overcome many of the limitations of the previously mentioned techniques, has a higher success rate, and has fewer procedure-related complications. The marking of a nodule with a radiotracer is possible in any portion of the lung and does not interfere with the histological examination. Furthermore, the technique can increase the accuracy of the resection by verifying in real time the absence of radioactivity just above and below the stapler line, thus assuring an adequate oncological margin.

Some pitfalls have been experienced but have been adjusted for. The first pitfall, occurring twice in our experience, is the possibility of an outsized diffusion of the radiotracer inside the lung parenchyma, in case of bullous emphysema adjacent to the nodule. This can lead to a wider area of radioactivity, which reduces the precision of the resection. In the case described in our experience, we preferred to convert to a small thoracotomy, with the nodule nonetheless found inside the radioactive area. On the basis of this experience, we can say that bullous emphysema around the target lesion may be considered the only true contraindication for this technique. A second and very common pitfall, described by us and by Grogan et al. [12], is the spillage of the radiotracer into the pleural space. This generally happens if the radiotracer is injected near the pleural surface of a major fissure, or, more frequently if a pneumothorax develops during injection. This increases the ground radioactivity, thus enabling the correct localization of the lesion, even if, as happened in our experience, part of the radiotracer was correctly injected within the nodule. In fact, we inject a solution that also contains a small amount of nonionic contrast material; thus, at the end of the procedure, we always verify by CT scan the presence of the solution within the lesion, and, if necessary, perform a second injection (Fig. 2B). In contrast, Grogan et al. [12] modified our technique by injecting a solution without contrast material. This is probably why they experienced 4/81 conversions to thoracotomy compared to our 1/211. Successively, they overcame this pitfall by adopting routine post-CT-placement nuclear medicine scintigrams to confirm parenchymal placement of the radiotracer. Then, as we also did, during thoracoscopy they adopted repeated pleural washing with saline solution to reduce pleural ground radioactivity.

A third limit of RGTS could be the relatively short half-life of the radionuclide, which may lead to some difficulties in scheduling the injection procedure and the operation. As for the other described techniques, the preoperative marking of the lesion must be followed by surgical resection, either immediately or within a few hours. Thus, in case the planned operation must be postponed, the radiotracer could have dissolved the day after its introduction and no longer be detectable. Taking this into account, Grogan et al. [12] used a modified solution with macroaggregated albumin (MAA), instead of ours with microaggregate albumin, and they also increased the volume of injection from 0.2 to 0.4 ml of Tc-99m MAA. In this way, they were assured of a radiotracer that was stable in the lung for up to 18 h without an increased hazard of radioactivity to the patient and the hospital personnel, making the surgical timing of resection more flexible with respect to the preoperative radiological marking. Finally, one previous criticism of the procedure, i.e., its being an expensive method due to the required technology, has been overcome in recent years thanks to the spread of the sentinel lymph node technique, which utilizes the same devices and is therefore now available in most referral centers.

In the future, the development of radiolabeled monoclonal antibodies against lung tumor cells, a technology now available for colorectal cancer, might expand the potential of RGTS [22, 23]. Thoracoscopic surgical resection could be feasible without preoperative CT-guided procedures. Moreover, by radioimmunoguided thoracoscopic surgery (RIGTS), it could be possible to identify tumor-free margins to ensure radical exeresis and to establish the involvement of lymphatic stations.

Over the last few years, the introduction of new technologies and proteomic knowledge has been rapidly changing the management algorithm of pulmonary nodules. The possibility of determining individual tumor behavior by verifying the gene array of the tumor tissue relies more and more on obtaining adequate tissue sampling. Therefore, thoracic surgeons will be faced with an increased request for lung nodule resections, even when the diagnosis is already recognized, and RGTS could be a supportive and indispensable technological tool.

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