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Original article

Cryobiopsy and dye marking guided by electromagnetic navigation bronchoscopy before resection of pulmonary nodule

Olivier Taton[a,*], Youri Sokolow[b], Benjamin Bondue[a], Chloé Vandermeeren[b], Maarten Vander Kuylen[b], Pierre Alain Gevenois[c], Myriam Remmelink[d], Zita Mekinda Ngono[a], Thierry Berghmans[e], Dimitri Leduc[a]

[a] *Department of Pneumology, Hôpital Erasme, Université libre de Bruxelles (ULB), 808 Route de Lennik, Brussels 1070, Belgium*
[b] *Department of Thoracic Surgery, Hôpital Erasme, Université libre de Bruxelles (ULB), 808 Route de Lennik, Brussels 1070, Belgium*
[c] *Department of Radiology, Hôpital Erasme, Université libre de Bruxelles (ULB), 808 Route de Lennik, Brussels 1070, Belgium*
[d] *Department of Pathology, Hôpital Erasme, Université libre de Bruxelles (ULB), 808 Route de Lennik, Brussels 1070, Belgium*
[e] *Thoracic Oncology clinic, Institut Jules Bordet, Université libre de Bruxelles (ULB), 90 Rue Meylemeersch, Brussels 1070, Belgium*

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ABSTRACT

Background: Our aims were to explore the feasibility, safety, and efficacy of peroperative transbronchial lung cryobiopsy (TBLC) guided by electromagnetic navigation bronchoscopy (ENB) and ENB-guided methylene blue marking of presumably non-palpable pulmonary nodules, and to assess its impact on video-assisted thoracoscopic surgery (VATS) and postoperative lung function.
Methods: This approach was applied to 16 consecutive patients (Group A, mean age 64 years) who were compared retrospectively to a historical group of 49 patients (Group B, mean age 62 years) with similar nodules resected without guidance. The usefulness of dye marking was graded. The success rates of both ENB-guided TBLC and nodule localization through dye marking were computed. The type of resection, volume of resected parenchyma, duration of procedures, and postoperative lung function were compared between groups. Unpaired t-test, chi-square test, unpaired Wilcoxon test, and exact Fisher test were used when appropriate.
Results: Malignancy was pathologically proven in all patients. TBLC revealed malignancy in 9 patients in Group A. The success rate of ENB-guided dye marking was 94%. Lobectomy was less frequently performed in Group A than in Group B (p = 0.022). Forced expiratory volume in 1 s and total lung capacity were significantly less reduced in Group A than in Group B (p = 0.006 and p = 0.019, respectively). Combined procedure was longer than surgery alone (p<0.001), but its surgical part was shorter than VATS without guidance ($p < 0.001$).
Conclusion: Peroperative ENB-guided TBLC with methylene blue marking of non-palpable lung nodules is feasible. A sparing lung parenchyma procedure could be achieved thanks to the ENB-guided dye marking before VATS.

Introduction

The current strategy for the diagnosis and treatment of possibly malignant lung nodules is to perform diagnostic wedge resection or fine needle aspiration by video-assisted thoracoscopic surgery (VATS), wait for the results of the frozen section or cytologic analysis, and complete the resection, in case of malignancy, by segmentectomy or lobectomy with radical mediastinal lymphadenectomy [1]. However, this strategy is inapplicable to small sized, non-visible, or non-palpable nodules. As many as two thirds of nodules with a diameter ≤10 mm, with a distance from the pleura >5 mm, or with non-solid attenuation are not palpable during VATS [2]. In such cases, lobectomy has thus to be performed without preoperative histological diagnosis [3] with the risk of unnecessary resection of benign nodules or unnecessary extensive resection for limited cancers [4,5]. Therefore, it has been suggested that VATS resection should be guided if the nodule is preoperatively presumed as non-palpable [3].

Several methods have been proposed to localize small or non-solid nodules. Most of these methods are based on preoperative fluoroscopic-guided or CT-guided transthoracic approaches with dye

Abbreviations: ATS, American Thoracic Society; CT, computed tomography; DLCO, diffusing lung capacity for carbon monoxide; ENB, electromagnetic navigation bronchoscopy; FEV_1, forced expiratory volume in 1 s; ^{18}FDG-PET, ^{18}fluoro-desoxy-glucose positron emission tomography; FVC, forced vital capacity; Lung-RADS, Lung imaging reporting and data system; NA, not applicable; TBLC, transbronchial lung cryobiopsy; Tis, adenocarcinoma in situ; TLC, total lung capacity; SD, standard deviation; VATS, video-assisted thoracoscopic surgery; VO_2 max, maximum rate of oxygen consumption

* Corresponding author.
E-mail address: Olivier.Taton@erasme.ulb.ac.be (O. Taton).

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marking, coil, or hook-wire insertion. A recent meta-analysis reported that the success rates of pre-operative CT-guided localization and VATS resection ranged from 94 to 99% but were associated with complications such as pneumothorax (from 16 to 35%), hemorrhage (from 6 to 16%), and wire migration or dislodgement [6]. Since 2014, an endoscopic approach through electromagnetic navigation bronchoscopy (ENB) with transbronchial dye injection has been proposed [7–10]. Its success rate is similar to previously proposed techniques but its complication rate and the time delay before the surgical resection are lower, as the ENB-guided marking is performed in the operating room just before surgery [7–10]. Nevertheless, the evaluation of its impact on the efficacy of VATS resection is still limited as no study has compared such resection with and without ENB-guided localization of presumably non-palpable nodules. In addition, if the definitive pathological diagnosis could be obtained during the localization procedure, the diagnostic wedge resection could be avoided as well as unnecessary resection of benign nodules [11].

This pathological diagnosis could be obtained by transbronchial lung cryobiopsy (TBLC) guided by ENB, an already reported approach in the diagnosis of small peripheral nodules [12]. In this context, we propose a new approach combining both ENB-guided TBLC and methylene blue marking for obtaining the pathological diagnosis peroperatively and for guiding the VATS resection, respectively.

The aims of this study were to explore the feasibility, safety, and efficacy of this approach in presumably non-palpable pulmonary nodules, and to assess its impact on surgery in terms of type of resection, volume of resected parenchyma, pathological diagnosis, adverse events and postoperative lung function.

Materials and methods

Patients

Sixteen consecutive patients older than 18 years referred to our medico-surgical department for the management of an assumed non-palpable pulmonary nodule between September 2018 and September 2020 were included in our study group (Group A). They had ENB-guided TBLC and dye marking before VATS resection during a unique procedure. Patients with nodule location in the inner two thirds of the lung or in the middle lobe preventing safe VATS sublobar resection, who were not operable according to the ATS guidelines [13], or with evidence of loco-regional or distant metastasis assessed by ^{18}FDG-PET scan in case of suspected primitive pulmonary cancer and cerebral magnetic resonance imaging, were not considered. The nodules were suspected of malignancy according to the patient history (age, smoking history, or prior history of cancer), CT features, evolution (increase in size, solid component in previously non-solid nodule), or increased ^{18}FDG uptake at PET scan. Preoperative pathological diagnostic procedure was not performed as these patients were operable and highly suspected for resectable malignancy [13].

The nodules were assumed as non-palpable during VATS if they were solid with diameter ≤10 mm, non-solid of any size, or of any attenuation but located at a distance from the pleura >5 mm. These patients were compared to 49 patients selected from our center with the same criteria as those in Group A (i.e. solid nodule with diameter ≤10 mm, non-solid of any size, or of any attenuation but located at a distance from the pleura >5 mm, and for whom a sublobar resection was feasible) but who had VATS resection of a solid or a non-solid nodule without any guidance between January 2015 and September 2018. The patients' selection, the surgical team, and the multidisciplinary meeting discussion were very similar in both groups. The only difference was the guidance technique and the peroperative TBLC as performed in Group A.

The need for preoperative localization was assessed by the linear discriminant function (depth = 0.836 x size - 2.811) used to differentiate between non-palpable and palpable nodules [3]. The study protocol was approved by the institutional ethics committee under the reference P2016/393 for Group A and P2021/087 for Group B. A written informed consent was obtained from all patients in Group A and the patient informed consent was waived from those in Group B.

Collected data, definitions and procedures

Demographic information, lung function tests, nodule attenuation, nodule size, distance between the outer aspect of the nodule and the pleura, Lung-RADS assessment category [14], duration of preoperative work-up, type of VATS resection, volume of resected lung parenchyma evaluated during the definitive pathological analysis, TBLC and final pathological diagnosis, oncological stage, duration of procedures, adverse events, length of hospital stay, and post-operative follow-up at one year were collected. The type of VATS resection could be wedge resection, segmentectomy (one or two segments resected) or lobectomy (three to five segments resected, depending on which lobe resected, nodules from the middle lobe being excluded).

The success rate of TBLC was defined as the proportion of patients who did not need a diagnostic wedge resection. The success rate of endoscopic marking was defined as the proportion of patients in whom the pathologic examination confirmed that the nodule was within the marked lung parenchyma in the resected lung specimen.

Endoscopic procedure (applied only to patients in Group A) and surgical procedure (applied to patients in both groups) were detailed in supplementary materials.

After identification of the methylene blue marked nodule site, a wedge resection or a segmentectomy was performed, depending on nodule location. Wedge resection was planned for peripheral lung nodules with sufficient surgical margins whereas segmentectomy was planned for deep nodules for which wedge resection would not warrant sufficient margins. Pathological analysis on frozen sections from the resected specimen, orientated by the methylene blue marking, was performed in all patients and additional resection (segmentectomy or lobectomy) was performed immediately thereafter when this analysis revealed invasive cancer or malignant cells in the surgical margins. All patients also underwent radical mediastinal lymphadenectomy. The main steps of this surgical procedure are illustrated in Fig. 1. The surgery was performed by the same surgical team in both groups.

Recurrence was defined as any new growing lesion within the first year.

Perprocedural decision algorithm

The perprocedural decision algorithm is summarized in Fig. 2. Briefly, if the examination of the frozen sections on TBLC specimens revealed a benign nodule, the intervention was stopped. In case of malignancy, the nodule was marked with methylene blue for guiding its VATS resection. In case of non-specific diagnosis, the nodule was also marked, a wedge resection performed, and the lung specimen sent for pathology examination of frozen sections. If this examination revealed a benign nodule, the intervention was stopped. If this examination revealed a malignant nodule, the wedge resection was completed by segmentectomy or lobectomy in patients with lung function compatible with such resection [15], and if no other nodules might require future resection. Finally, VATS was ended by a radical mediastinal lymphadenectomy.

Endpoints

The primary endpoints were the success rates of TBLC and of nodule localization through ENB-guided dye marking. The secondary endpoints were comparisons of type of resection, volume of resected lung parenchyma, duration of procedures, adverse events,

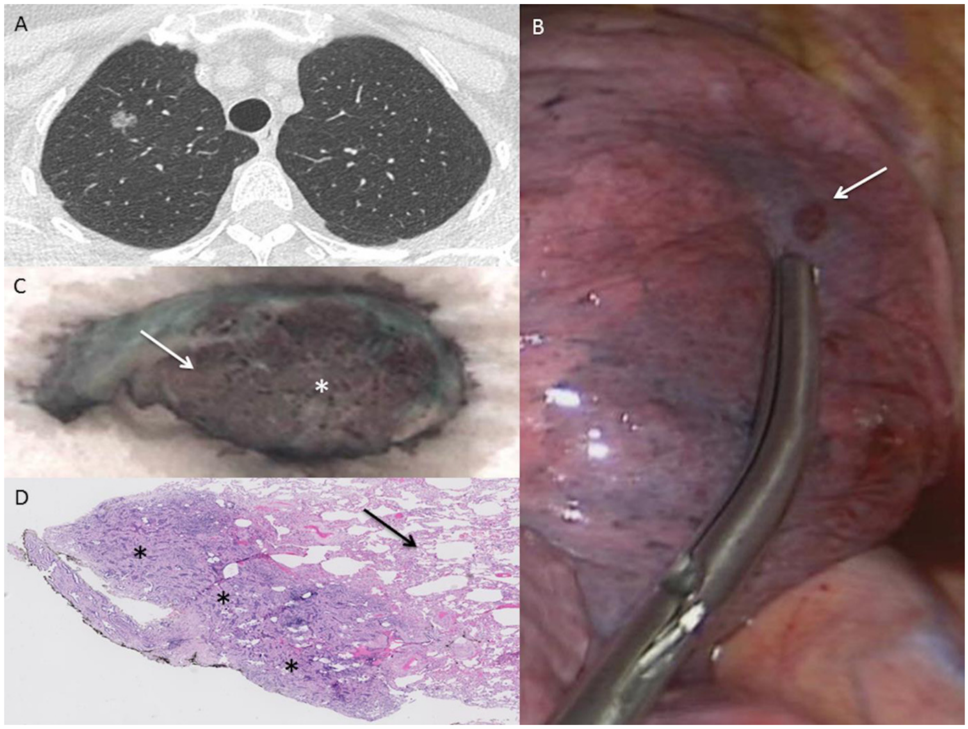

Fig. 1. A. CT scan of the patient showing a non-solid nodule of 12 mm in diameter within the right upper lobe. B. Methylene blue visualized at the pleural surface. The arrow shows the hematoma secondary to TBLC. C. Macroscopic view of the segmentectomy guided by the dye marking. The arrow shows the methylene blue within the lung parenchyma. The star shows the tumor. D. The pathological analysis of the segmentectomy revealed an adenocarcinoma (stars) with adjacent normal lung parenchyma (arrow).

postoperative lung function tests, and patient outcome between both groups. The usefulness of dye marking was graded retrospectively by the surgeon according to Sato et al. [16]: Grade A, the same level of operative precision was considered to be impossible without dye marking; Grade B, a similar level of precision was considered possible but dye marking improved confident performance of the operation; and Grade C, the same operation was considered possible without dye marking.

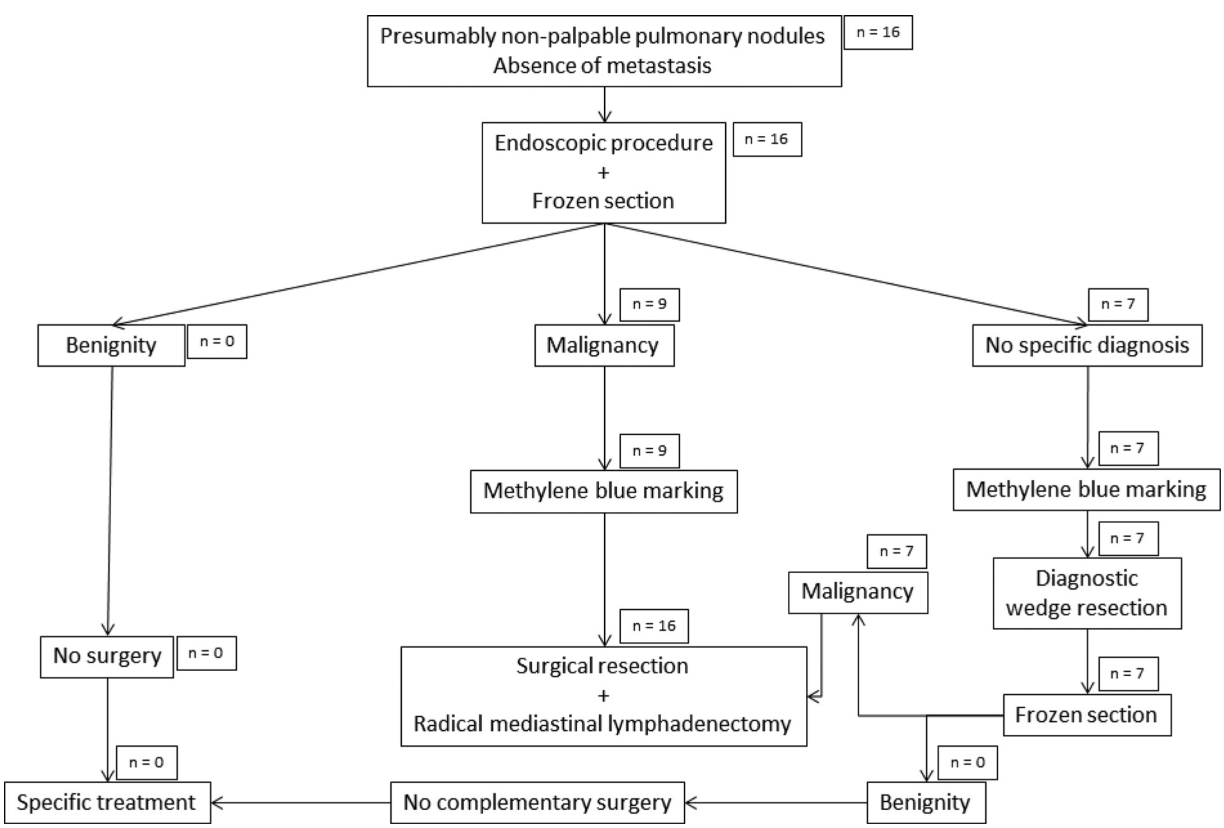

Fig. 2. Perprocedure decisional algorithm with the number of patients in each situation.

Statistical analysis

Continuous data were expressed using means, SD, medians, and ranges. Comparisons between continuous data were performed with unpaired t-test, chi-square test, or unpaired Wilcoxon test. Categorical data were expressed as percentages. Comparisons between percentages were performed with the exact Fisher test. Statistical significance for all tests was set at a p-value <.05. As the prospective part of the study was designed as a feasibility study, no power statistical analysis was performed. Statistical analysis was performed using SAS (SAS Institute, Cary, NC).

Results

In Group A, all patients but one underwent the full endoscopic procedure. In this particular patient, dye marking was performed but not TBLC. The failure rate of the endoscopic procedure was thus 6% (1/16). The pathology diagnosis of malignancy was obtained by TBLC before VATS in 56% (9/16) of the patients. The seven other patients had a diagnostic wedge resection with a second frozen section analysis on the resected lung specimen. The pathology examination of resected nodules showed that the nodules were within the marked parenchyma in all patients but one, corresponding to a success rate of ENB-guided dye marking of 94% (15/16). The usefulness of dye marking was graded by the surgeon as A in 12 patients (75%), B in 3 (19%) and C in 1 (6%).

Patients' and nodules characteristics are summarized and compared between both groups in Table 1. By applying the linear discriminant function taking into account nodules size and depth [3], 94 and 96 % of nodules in Group A and in Group B respectively (p = 0.901) were considered as non-palpable during VATS.

Results of endoscopic and VATS procedures are reported in Table 2. All nodules were resected by VATS with no conversion to thoracotomy. Lobectomy was significantly less frequently performed in Group A than in Group B (50% *vs*. 80%, p = 0.022), whereas more patients underwent segmentectomy alone in Group A (44 % *vs*. 14%, p = 0.013). The final pathology diagnoses and oncological stages are compared in Table 3. The results of the pathological analysis of the frozen sections and the final pathological diagnoses are summarized in Table 4. Malignancy was pathologically proven and the margins of the surgical specimens were free of malignant cells in all patients. The volume of the resected lung specimens and lung function tests are compared in Tables 2 and 5. The volume of the resected lung specimen was lower in Group A (284 ml *vs*. 539 ml, p = 0.032) with better preservation of lung function (forced expiratory volume in 1 s: -3% *vs*. -10%, p = 0.007 and total lung capacity: -5% *vs*. -11%, p = 0.023).

Discussion

This study shows that ENB-guided TBLC and methylene blue marking, respectively to obtain the peroperative pathologic diagnosis and to guide VATS resection of presumably non-palpable pulmonary nodules (1) is feasible, (2) provides the pathology diagnosis before VATS in 56% of the patients, and (3) by the ENB-guided methylene blue marking allows to guide the surgical resection. Moreover, our data suggest that the ENB-guided methylene blue marking could impact the type of lung resection with a lower proportion of lobectomy, a lower volume of resected lung, and a less impaired lung function.

With a success rate of the endoscopic procedure higher than 90% with negligible adverse events, ENB-guided TBLC associated with methylene blue marking is feasible. This rate is in accordance with those previously reported, ranging from 79 to 100% and averaging 95% [17]. Additionally, with only a few and no substantial adverse events, this technique appears safer than other localization techniques [18]. In addition to that, dye marking definitely guides the surgeon, at least in three fourths of patients. These results are in line with the 84% observed by Lachkar et al. in a study evaluating the added value of virtual bronchoscopy with dye marking [19]. In our study, the only patient in whom the surgeon considered that VATS resection would have been possible without dye marking corresponded to a failure of the nodule localization by ENB. With patients in whom the surgeon considered that a similar level of precision would have been possible but that dye marking improved his confidence, the nodules would have been localized as the adjacent pleural surface was irregular.

The pathology diagnosis of malignancy was obtained before VATS in 56% of the patients, thereby preventing the wedge resection otherwise necessary for this diagnosis. On one hand, this proportion is higher than that reported by W. Bolton *et al.* in two studies with a

Table 1
Patients and nodules characteristics.

	Group A n = 16	Group B n = 49	p
Patients			
Age (years)	64 ± 10	62 ± 9	0.355
Gender (% women)	75	63	0.389
FEV_1 (% predicted)	83 ± 18	82 ± 15	0.820
DLCO (% predicted)	67 ± 15	67 ± 16	0.870
VO_2 max (ml/kg/min)	15.9 ± 3.6	18.1 ± 4.4	0.262
Nodules			
Size in mm, mean ± SD	17.2 ± 6.3	17.5 ± 6.8	0.901
Distance from pleura in mm, median [range]	15.4 [1−28]	15.9 [1−48]	0.869
Attenuation			
Non-solid, frequency (%)	6 (38)	10 (20)	0.168
Part-solid, frequency (%)	9 (56)	18 (37)	0.169
Solid, frequency (%)	1 (6)	21 (43)	0.007
Presence of bronchus sign	4 (25)	/	/
Lung-RADS assessment category			
2, frequency (%)	5 (31)	8 (16)	0.195
3, frequency (%)	2 (12)	8 (16)	0.713
4a, frequency (%)	6 (38)	14 (29)	0.502
4b, frequency (%)	3 (19)	19 (39)	0.142
Duration of work-up before surgery in months, median [range]	13 [1−96]	14 [3−71]	0.202

Data are presented as mean ± SD or as median with ranges or as percentages. Abbreviations: FEV_1: forced expiratory volume in 1 second, DLCO: diffusing lung capacity for carbon monoxyde, VO_2 max: maximum rate of oxygen consumption.

Table 2
Endoscopic and surgical procedures.

	Group A n = 16	Group B n = 49	*p*
Results of TBLC diagnoses (*n* = 15)*			
Malignant, frequency (%)	9 (56)	/	/
Benign, frequency (%)	0	/	/
Aspecific inflammation, frequency (%)	4 (25)	/	/
Normal parenchyma, frequency (%)	2 (12)	/	/
Therapeutic VATS resection			
Lobectomy, frequency (%)	8 (50)	39 (80)	0.022
Segmentectomy, frequency (%)	7 (44)	7 (14)	0.013
Wedge resection, frequency (%)	1 (6)	3 (6)	>0.999
Lung resected volume in ml, median [range]	284 [43 - 995]	539 [42 - 2176]	0.032
Number of resected segments (n), mean ± SD	2.6 ± 1.2	3.4 ± 1.3	0.021
Duration of procedures			
Total in minutes, mean ± SD	235 ± 39	185 ± 51	<0.001
Endoscopic part in minutes, mean ± SD	98 ± 23	/	/
Surgical part in minutes, mean ± SD	137 ± 29	185 ± 51	<0.001
Evaluation of dye-marking			
Grade A, frequency (%)	12 (75)	/	/
Grade B, frequency (%)	3 (19)	/	/
Grade C, frequency (%)	1 (6)	/	/
Adverse events			
post TBLC bleeding			
Grade 0, frequency (%)	11 (69)	/	/
Grade 1, frequency (%)	5 (31)	/	/
Grade 2, frequency (%)	0	/	/
Grade 3, frequency (%)	0	/	/
post-surgery			
Total, frequency (%)	3 (19)	13 (26)	0.741
Air leak, frequency (%)	2 (12)	7 (14)	>0.999
Atrial fibrillation, frequency (%)	0	4 (8)	0.565
Pneumonia, frequency (%)	1 (6)	2 (4)	>0.999
Length of stay in days, mean ± SD	8.3 ± 4.6	8.9 ± 3.3	0.556

Data are presented as mean ± SD or as median with ranges or as percentages. * The nodule could not be reached by ENB and only methylene blue dye marking but no TBLC was performed in one patient in Group A. Abbreviations: TBLC: transbronchial lung cryobiopsy, SD: standard deviation, VATS: video-assisted thoracoscopic surgery.

perprocedural decisional algorithm similar to ours with a transbronchial needle aspiration yielding the peroperative pathology diagnosis in approximately one fourth of the patients [9,20]. On the other hand, this proportion is lower than the two thirds reported in two systematic reviews addressing the performance of ENB-guided forceps biopsy of peripheral lung nodules of any size [21,22]. This lower proportion could be assumedly related to our included patients who had small nodules with uncommon bronchus sign.

There are two manners to decrease the volume of lung parenchyma resection: to avoid systematic surgical resection in case of benignity; and to perform a lung-sparing surgical resection instead of lobectomy. As all investigated nodules were malignant, we were not able to evaluate the impact of ENB-guided TBLC on the pathology diagnosis of benign nodules. We could nevertheless assume that this approach could avoid futile lobectomy if the benignity would be proved before VATS as observed in previous series (ranging from 17 to 38%) [7–11,19,20].

Table 3
Final diagnosis at the end of follow-up and outcomes.

	Group A *n* = 16	Group B *n* = 49	*p*
Final pathologic diagnosis			
Lymphoma, frequency (%)	1 (6)	1 (2)	0.435
Adenocarcinoma, frequency (%)	15 (94)	46 (94)	>0.999
Metastasis, frequency (%)‡	0	2 (4)	>0.999
Oncologic stage	(n = 15)*	(n = 46)†	
Tis, frequency (%)	3 (20)	1 (2)	0.041
IA1, frequency (%)	7 (46)	21 (46)	>0.999
IA2, frequency (%)	4 (27)	11 (24)	0.728
IA3, frequency (%)	1 (7)	2 (4)	0.244
IIA, frequency (%)	0	5 (11)	0.323
IIB, frequency (%)	0	5 (11)	0.564
IIIA, frequency (%)	0	1 (2)	>0.999
Cancer recurrence within 1 year	0	0	NA

Data are presented as number of patients and percentages. ‡: Unique metastasis from colic adenocarcinoma. *: 15 patients had primary lung cancer in group A. †: 46 patients had primary lung cancer in group B. Abbreviations: Tis: adenocarcinoma in situ, NA: not applicable.

In order to determine the impact of ENB-guided methylene blue marking on the type of lung resection, resected lung volume, and lung function, we considered a historical group of patients who were similar in terms of age, gender, lung function, nodules size, distance between the nodule and the pleural surface, and Lung RADS classification, but who had VATS without any guidance. While there were more numerous solid nodules in this historical group, 96% (compared to 94% in Group A) of the nodules were assumed to be non-palpable during VATS, showing similar characteristics of the nodules between both groups.

In terms of type of lung resection and for similar oncologic stages (except a higher proportion of in situ carcinoma in Group A), the proportions of lobectomy and segmentectomy were respectively lower and higher in patients who had ENB-guided methylene blue marking than in the historical group. Even after exclusion of eleven patients in Group B (five with oncologic stage IIA, five with IIB and one with IIIA) to match both groups for TNM stage, the differences between them remained statistically significant regarding the frequency of segmentectomy and lung volume resected (data not shown). This low rate of lobectomy has also been observed by Marino et al. who reported proportions of 47% and 41%, respectively [8,20]. As compared to lobectomy, segmentectomy and wedge resection preserve the lung function and are associated with lower perioperative morbidity and mortality [23,24]. In terms of resected lung volume, it was significantly lower in patients who had ENB-guided methylene blue

Table 4
Pathological results in Group A.

Patient	FS TBLC	FS Diagnostic wedge resection	Final pathological diagnosis
1	Aspecific inflammation	Adenocarcinoma	Adenocarcinoma
2	Adenocarcinoma	/	Adenocarcinoma
3	Adenocarcinoma	/	Adenocarcinoma
4	Adenocarcinoma	/	Adenocarcinoma
5	Normal parenchyma	Adenocarcinoma	Adenocarcinoma
6	Adenocarcinoma	/	Adenocarcinoma
7	/	Lymphoma	Lymphoma
8	Normal parenchyma	Adenocarcinoma	Adenocarcinoma
9	Adenocarcinoma	/	Adenocarcinoma
10	Adenocarcinoma	/	Adenocarcinoma
11	Aspecific inflammation	Adenocarcinoma	Adenocarcinoma
12	Aspecific inflammation	Adenocarcinoma	Adenocarcinoma
13	Aspecific inflammation	Adenocarcinoma	Adenocarcinoma
14	Adenocarcinoma	/	Adenocarcinoma
15	Adenocarcinoma	/	Adenocarcinoma
16	Adenocarcinoma	/	Adenocarcinoma

Abbreviations: FS: frozen section, TBLC: transbronchial lung cryobiopsy.

marking than in the historical group. In terms of lung function, it was less impaired in patients who had ENB-guided methylene blue marking than in those in the historical group. As expected, ENB-guided TBLC and methylene blue marking lengthens the whole procedure but shortens its surgical part, assumedly facilitated by the endoscopic guidance. Interestingly, there was no difference between groups in terms of post-procedural complications or postoperative length of hospital stay.

Our study has limitations. First, our study group was not randomized and included a rather small number of patients who were evaluated in one single academic tertiary center. The small number of patients included in Group A could be explained by the high selection of patients. Indeed, we included only patients with small peripheral nodules assumed to be non-palpable and for whom a sublobar resection was feasible (i.e. central and middle lobe nodules were excluded). Results regarding safety and efficiency of our approach should be explored in large multicentric randomized trials. Indeed, even if there was a low proportion of adverse events in our study, the small number of patients cannot definitely exclude the occurrence of rare severe adverse events. Second, our study group did not include patients with benign nodules. This could be explained by the preoperative work-up and our multidisciplinary meeting decisions addressing part-solid and non-solid nodules with a selection bias in favor of malignant nodules as non-solid nodules are more likely malignant in 59 to 73% of patients as compared to 7 to 9% for solid nodules [25]. Again, this limitation would be overcome by large trials.

Table 5
Differences in pulmonary function tests before *vs.* after VATS.

	Group A $n = 16$	Group B $n = 49$	*p*
Days between VATS and lung function tests, median [range]	104 [26 -180]	101 [20 - 180]	0.790
FEV_1, l	-0.07 ± 0.1	-0.27 ± 0.27	0.006
FEV_1, % predicted	-2.6 ± 0,4	-9.7 ± 10	0.007
FVC, l	-0.1 ± 0.02	-0.22 ± 0.34	0.148
FVC, % predicted	-3,9 ± 0,4	-6.4 ± 10.9	0.377
TLC, l	-0.2 ± 0.07	-0.61 ± 0.63	0.019
TLC, % predicted	-5.1 ± 0,06	-10.9 ± 9.1	0.023

Data are presented as mean ± SD or as median with ranges or as percentages. Pulmonary function tests results are presented as differences between those before and those after VATS. Abbreviations: VATS: video-assisted thoracoscopic surgery, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, TLC: total lung capacity.

Conclusion

ENB achieves intraoperative localization of non-palpable pulmonary nodules before VATS. Peroperative pathologic diagnosis could be obtained through ENB-guided TBLC in approximately one half of patients avoiding the need for a diagnostic wedge resection. ENB-guided methylene blue marking could guide a sparing lung parenchyma surgical resection during VATS as suggested by the comparison with a group of patients having similar nodules characteristics resected without guidance.

Author contributions statement

OT, BB, DL, and YS designed the study. CV performed the analysis of the historical group. OT, BB, and DL performed the endoscopic part of the procedure. YS, CV, and MVK performed the surgical part of the procedure. PAG performed the chest CT scans mandatory for the ENB technique. MR performed the pathological analysis. ZMN and TB conducted the oncological multidisciplinary meeting that approved the combined approach for the diagnosis and treatment. All authors revised the manuscript and approved its final version. All authors agree to be accountable for its contributions of this work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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Declarations of Competing Interest

None.

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Supplementary materials

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