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The additional diagnostic value of virtual bronchoscopy navigation in patients with pulmonary nodules – The NAVIGATOR study

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ABSTRACT

Background: The number of solitary pulmonary nodules to be evaluated is expected to increase and therefore we need to improve diagnostic and therapeutic tools to approach these nodules. To prevent patients from futile invasive procedures and receiving treatment without histological confirmation of cancer, we evaluated the value of virtual bronchoscopy navigation to obtain a diagnosis of the solitary pulmonary nodule in a real-world clinical setting.

Methods: In the NAVIGATOR single center, prospective, observational cohort study patients underwent a virtual bronchoscopy navigation procedure with or without guide sheet tunnelling to assess a solitary pulmonary nodule. Nodules were considered not accessible if a diagnosis could not be obtained by either by CT-guided transthoracic biopsy or conventional bronchoscopy.

Results: Between February 2021 and January 2022 35 patients underwent the virtual bronchoscopy navigation procedure. The overall diagnostic yield was 77% and was dependent on size of the nodule and chosen path, with highest yield in lesions with an airway path. Adverse events were few and manageable.

Conclusion: Virtual bronchoscopy navigation with or without sheet tunnelling is a new technique with a good diagnostic yield, also in patients in whom previously performed procedures failed to establish a diagnosis and/or alternative procedures are considered not feasible based on expected yield and/or safety. Preventing futile or more invasive procedures like surgery or transthoracic punctures with a higher complication rate is beneficial for patients, and allowed treatment adaptation in two-third of the analyzed patient population.

1. Introduction

The number of solitary pulmonary nodules (SPNs) to be evaluated is expected to increase due to the introduction of lung cancer screening programs and the increasing amount of cardiac CT scans. Simultaneously it is necessary to improve diagnostic and therapeutic tools to approach the SPNs [1].

CT guided transthoracic procedures are the current gold standard for obtaining diagnostic biopsies of SPNs in the periphery of the lung [2]. Despite its accuracy in lesions of >20 mm, this technique is associated with a significant risk of complications [3,4]. Pneumothorax is reported in up to 26 % of cases, with need for chest tube insertion and hospitalization in up to 5.6 % of cases, and bleeding is reported in up to 18 % of cases [3–5]. The diagnostic yield of a CT guided transthoracic biopsy in selected peripheral lesions is around 75 % [6]. Alternative for a CT guided biopsy is Video- or Robotic-Assisted Thoracic Surgery with or without hookwire localization for wedge resection of SPNs located within 30 mm of the pleural surface [7]. Although a high diagnostic yield is reported, disadvantages are the invasiveness of the procedure and risk of conversion to a thoracotomy. Furthermore, this technique is not suited in case of a more centrally located SPN, as lobectomy is usually required.

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Historically, lesions in the periphery of the lung are considered not accessible by conventional bronchoscopy [8]. To advance the range and diagnostic yield, and to improve safety of bronchoscopic procedures, several approaches have been developed using techniques like ultrathin bronchoscopy and radial endobronchial ultrasound (rEBUS) to confirm access to the SPN [9]. Guidance to the SPN was achieved with electromagnetic navigation bronchoscopy (EBN) and for verification of the correct position rEBUS, C-arm fluoroscopy or cone beam CT scanning were added [10–13]. Dependent on localization and size of the lesion, generally ENB reported a diagnostic yield of above 70 % and low complication rate with 2 % pneumothorax [10–13]. Additionally, in a substantial number of patients, clinicians still decide to irradiate a nodule or resect a lung lobe without histologic confirmation of an SPN in advance [14].

One of the newer techniques for obtaining diagnostic biopsies of SPNs uses virtual bronchoscopy navigation (VBN) to calculate the access to an SPN via a trans parenchymal route [15]. Here, the overall sensitivity to obtain a histopathologic diagnosis has been found to be around 77 % (72–82 %). The complication rate was low, with pneumothorax in 2 % of the cases and bleeding in 0.8 %, without additional safety issues in severe emphysema patients [11,16–19]. With this technique, in contrast to the CT guided transthoracic approach, also very small lesions (up to 7 mm diameter), and lesions that cannot be reached via the transthoracic route – located in the inner two thirds of the lung - can be approached. However, detailed clinical data, like the relation of the diagnostic yield to the specific location of the pulmonary nodule, and data about the accessibility of nodules in a real-world clinical population are needed [1,20]. Because of the increasing number of nodules to be assessed, and to prevent patients from receiving treatment without histological confirmation of cancer [21], the aim of this study was to evaluate the performance of VBN to obtain a diagnosis of SPNs in a real-world clinical setting.

2. Methods

We performed a single center, prospective, observational cohort study of patients undergoing the novel standard of care VBN procedure to assess an SPN – "The NAVIGATOR" – study. The protocol was approved by the Medical Ethical Committee of the University Medical Center Groningen (UMCG) and registered centrally (UMCG METC 202100352, ClinicalTrials.gov identifier NCT05383105).

Patients with a suspicious pulmonary nodule were recruited in the Multidisciplinary Board of Thoracic Oncology of the UMCG and in the regional multidisciplinary boards. In these meetings potential procedures to obtain a sample of the SPN and technical aspects of these procedures were discussed. Patients were available for the VBN procedure when alternative procedures were considered not feasible based on expected yield, safety, and/or if previously performed procedures failed to establish a diagnosis. All patients provided informed consent for the procedure.

Additional inclusion criteria were: age $>$ 18, pulmonary nodule(s) suspicious for malignancy or metastases of a known primary tumor, a distinct nodule with a diameter of $>$ 6 mm in its largest dimension, nodule located in the parenchymal tissue $>$ 5 mm from the parietal pleura and considered accessible by VBN.

Exclusion criteria were any contraindication to undergo bronchoscopy, inability to stop anticoagulants or antiplatelet medication around time of the procedure, pregnant or breastfeeding women, moderate to severe pulmonary fibrosis, severe emphysema with bullae $>$ 5 cm in the vicinity of the target nodule or tunnel.

Before the procedure a dedicated high-resolution CT scan was performed from eligible subjects and assessed using the Archimedes VBN System (Broncus Medical, Inc., San Jose, California, USA) [22,23]. This image-guided navigation system comprises a workstation and software that reconstructs CT data into a 3D model, including the airways, blood vessels, ribs and lungs and provides features to mark the pulmonary nodule. The system calculates an airway path and suitable points of entry (POE) locations with a straight line, vessel-free access to the pulmonary nodule (the tunnel path), as well as bronchoscopy paths for guiding the bronchoscopist to the POE locations [18,19,22,23].

During the procedure nodules were assessed with VBN in combination with fluoroscopy guidance and biopsies (preferred) or samples for cytology were obtained. Evaluation of a pneumothorax was performed with fluoroscopy at the end of the procedure. Specimen were evaluated by a dedicated pulmonary pathologist according to standard of care. The diagnostic yield was calculated according to the 'intermediate' definition by Vachani, et al, considering malignant and true benign outcomes as diagnostic and allowing for follow up on nodules [24]. After the procedure, results were discussed in the Multidisciplinary Board of Thoracic Oncology for each patient resulting in a definitive treatment proposal.

Patients characteristics including previously performed procedures and outcomes, as well as treatment plan without the VBN procedure, characteristics of the SPN, details of the procedure including but not limited to procedure time, radiation dose and duration of radiation, adverse events of special interest (respiratory failure, pneumothorax, subcutaneous emphysema, hemorrhage according to Common Terminology Criteria for Adverse Events (CTCAE v5) [25,26]), and treatment plan after the VBN procedure were recorded.

Given the nature of the study, descriptive statistics were applied using SPSSv23.

3. Results

Between February 2021 and January 2022, 35 patients underwent the VBN procedure in our center. Patient and SPN characteristics are listed in Table 1. Main indications to request a biopsy were SPNs without a history of a solid malignancy (43 %), and SPNs in patients with a history of a solid malignancy other than lung cancer (37 %). In the minority of cases, a repeat biopsy was requested for mutation analysis in relapsing or progressive lung cancer harboring an oncogenic mutation. The majority of SPNs were solid lesions, mainly located in the upper lobes (66 %). About one third of the population underwent at least one diagnostic procedure before the VBN procedure.

In Table 2 the procedural characteristics are given. The route with an airway path, tunnel path, or a combination, was chosen based on the navigational planning and at the discretion of the bronchoscopist. In half of the cases an airway path was chosen (51 %). Fig. 1 depicts a procedure with a tunnel path.

Adverse events of special interest were few and manageable (Table 2). Grade 3 hemorrhage according to CTCAE criteria, needing additional bronchoscopic hemostasis, occurred in two patients (6 %). One of these patients also needed noradrenalin due to hypotension with signs of secondary cardiac ischemia during the procedure. This patient was diagnosed with a primitive neuroectodermal tumor. In the second patient no diagnosis was obtained. Both patients recovered without any sequelae. In our case series no pneumothorax occurred, in one case however, three days after the VBN procedure a self-limiting subcutaneous emphysema of the neck region without other signs of a pneumothorax was diagnosed.

The overall diagnostic yield leading to a classifying diagnosis of the VBN procedure was 77 % (27/35 cases, Table 2). The diagnostic yield was dependent on SPN size and chosen path, with highest yield in lesions with an airway path on CT imaging 89 % (15/18 lesions), and 78 % in SPNs with a diameter $>$ 20 mm (18/23 lesions). The median diameter of SPN with diagnosis was 25 mm (range 10–57).

The diagnostic yield per lobe is reflected in Fig. 2. In 22 cases we established a malignancy, and in 5 cases a benign diagnosis. In all cases of malignancy, the obtained tissue was sufficient for additional molecular testing to aid treatment decisions.

Two benign SPNs were based on an infection, one on a *Streptococcus pneumoniae* infection, and another on a *Streptococcus mitis* infection. One

Table 1
Patient and nodule characteristics NAVIGATOR.

Total number of patients	N = 35
Age, median (range; in years)	68 (45 – 80)
Sex, number (%)	
• Male	18 (51)
• Female	17 (49)
Indication for the procedure, number (%)	
• SPN without history of solid malignancy	15 (43)
• SPN in patients with history of solid malignancy other than lung cancer	13 (37)
• Nodule, relapse/progression of prior lung cancer considered	7 (20)
Biopsy procedure before VBN procedure, number (%, multiple procedures per patient possible)	
• None	
• Procedure before VBN	22 (63)
o Diagnostic bronchoscopy	13 (37)
o EBUS FNA	9
o EUS FNA	2
o CT guided transthoracic biopsy	1
o Thoracoscopy	3
	1
Morphology SPN, number (%)	
• Solid	33 (94)
o Spiculated	15
o Lobulated	15
o Cavitated	3
• Subsolid	1 (3)
• Ground glass opacity	1 (3)
Localisation SPN, number (%)	
Right upper lobe	13 (37)
Middle lobe	2 (6)
Right lower lobe	8 (23)
Left upper lobe	10 (28)
Left lower lobe	2 (6)
SPN longest diameter, median (range; in mm)	24 (10 – 57)
SPN, grouped per diameter, number (%)	
• Diameter ≤ 20 mm	12 (34)
• Diameter > 20 mm	23 (66)
Bronchus sign visible, number (%)	22 (63)

SPN, solitary pulmonary nodule; VBN, virtual bronchoscopy navigation; EBUS, endobronchial ultrasound; FNA, fine needle aspiration; EUS, endoscopic ultrasound.

Table 2
Procedural characteristics NAVIGATOR.

Procedure (bronchoscopy) time, median (range; in minutes)	43 (25–89)
Fluoroscopy time, median (range; in minutes)	2.5 (0.3–7.8)
Radiation dose during procedure, median (range; in mSv)	16.6 (0.7–85.5)
Chosen path to SPN, number (%)	
• Airway path	18 (51)
• Tunnel path	13 (37)
• Both	4 (11)
Adverse events of special interest, number (% of procedures)	
• Hemorrhage	9 (26)
o Grade 1	5
o Grade 2	2
o Grade 3	2
• Pneumothorax	-
• Late subcutaneous emphysema*	1 (3)
• Respiratory failure	-
Diagnostic yield of VBN procedure (%)	
• Overall	77
• Per SPN diameter	
o Diameter ≤ 20 mm	37
o Diameter > 20 mm	78
• Per chosen path	
o Airway path	89
o Tunnel path	62
o Both	75
Size of SPN grouped by VBN result, median (range; in mm)	
Diagnosis obtained	25 (10–57)
Diagnosis not obtained	18 (10–30)

SPN, solitary pulmonary nodule; VBN, virtual bronchoscopy navigation.
*no intervention necessary.

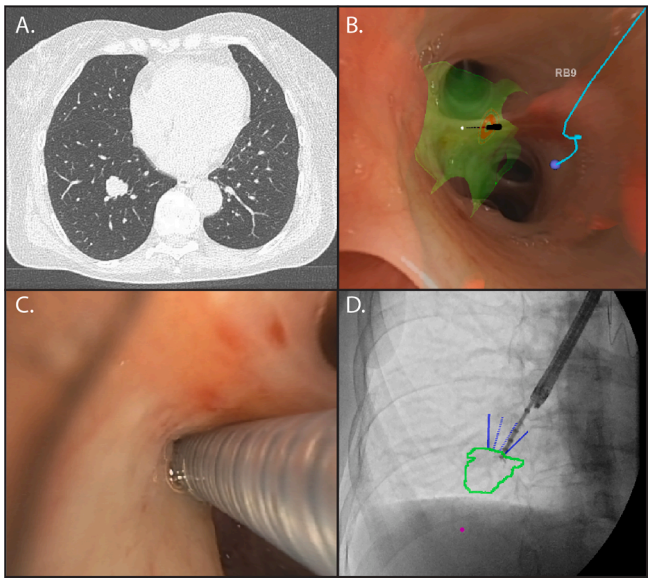

Fig. 1. Procedure with a tunnel path.

pulmonary nodule was formed by reactive changes of the lung tissue after chemotherapy, and was fully resolved in time. One lymphocytic SPN was considered malignant by the treating physician and the patient underwent stereotactic radiotherapy without a confirmative diagnosis of a malignancy. An SPN with eosinophilic inflammation was also considered malignant, and the patient went for thoracic surgery. In the resection specimen a typical carcinoid was found.

In all patients we proposed an a-priori advice for presumed treatment in case of no histological confirmation of the nodule (Table 3). After the VBN procedure, this treatment plan was adapted in 24 patients (69 %).

4. Discussion

We investigated the value of the new VBN in our first series of 35 cases with a pulmonary nodule. In our study we only selected SPNs that were not otherwise accessible or for which other diagnostic procedures were considered less successful or less safe. With a diagnostic yield of 77 %, our findings are in line with previous data [22,27 –30]. The performance of our first cohort of VBN procedures was comparable to other studies, taking into account the differences in technique. Due to small patient numbers we need to extend our cohort to make data more robust. An important advantage of a successful VBN procedure is that patients obtain a definite tissue based diagnosis and therefore can be offered appropriate treatment, avoiding more invasive procedures or futile treatment. Without this VBN procedure almost all patients would not have had a definite diagnosis. In our set, the treatment plan of two third of the patients was adjusted based on the definitive diagnosis after the VBN procedure.

In this observational cohort study we confirmed that VBN can be performed with manageable adverse events. No pneumothorax or respiratory failures were observed. There was, however, one patient with subcutaneous emphysema 3 days after the procedure. Fluoroscopy after the procedure and a PET-CT scan one day after did not show any signs of a pneumothorax. In a multicenter study of 1388 patients in 37 centers, the VBN-related grade 2 or higher bronchopulmonary hemorrhage and grade 4 or higher respiratory failure rates were 1.5 % and 0.7 %, respectively [29]. In a single-center study assessing 114 nodules, pneumothorax occurred in 1.9 % and mild bleeding in 1.0 % [30]. In our study grade 2 and 3 bronchopulmonary hemorrhage rate was 11.5 %,

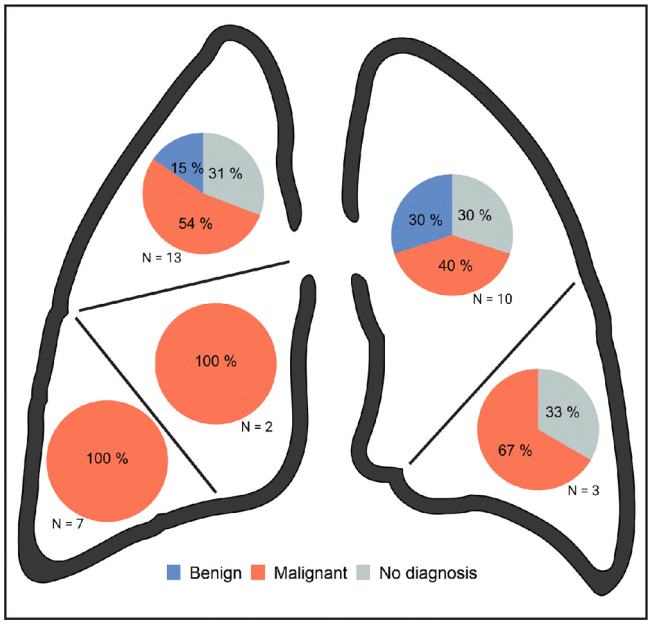

Fig. 2. Distribution of diagnostic yield per lobe. N = number of procedures per lobe.

with relevant (grade 3) hemorrhage occurring in two patients (5.7 %), which resolved without sequelae.

The diagnostic yield of bronchoscopic procedures is partly dependent on the presence of a bronchus sign [30–32]. A positive bronchus sign refers to the presence of a bronchus leading directly to a peripheral lung lesion, as observed on CT. A previous study using VBN reported an overall diagnostic yield of 67 % (34/51), increasing to 79 % (30/38) when only patients with a bronchus sign on CT were considered [31]. In cases without a bronchus sign, the reported yield was only 31 %. In our cohort, the diagnostic yield was also highest when considering only cases in which the SPN could be approached by an airway path (89 %). However, in contrast to earlier data, the diagnostic yield of procedures approaching lesions without a bronchus sign by following a *trans*-parenchymal route, was greatly improved (62 %) [19,22]. In our study we created 17 tunnel paths between the central airways and the lesions. Thorough preparation, including a dedicated pre-procedural CT scan and constructing airway- and tunnel paths, was crucial to obtain a diagnosis. Procedural issues possibly hampering the accurate planning of the virtual pathways to the nodule were resolution of the lesion on the pre-procedural CT scan, physical blockades like mucus impaction in smaller airways [33], mismatches occurring due to inadequate positioning of the patient on the table in comparison to the CT scan, as well as the difference between patient triggered deep inhalation during the scan and intraprocedural breath hold under anesthesia [34,35]. Especially in the lower lobes, the accordance of the appointed region of the nodule compared to the planning can be low. This discrepancy due to 'movement' of the pulmonary nodule during anesthesia is reported to be up to 2.5 cm when the nodule is located in the lower lobes [36]. Better imaging techniques such as cone-beam CT with body-shape sensing are available to overcome problems of respiration and CT-to-body divergence, and can increase diagnostic accuracy [13,37–39]. Additional confirmation of the position of the nodule can also be achieved with rEBUS which may contribute to an even higher diagnostic yield [40,41]. Additional localization confirmation is attributable for lesions in the right upper lobe, lesions not visible on fluoroscopy and lesions in the peripheral third of the lung [42–44]. Finally, improved localization of the nodule is also necessary to be able to safely apply local ablative therapies with minimal damage of healthy lung tissue in the future.

Next to the bronchus sign, size of the nodule is an important parameter in determining the diagnostic success of a procedure. In a large *meta*-analysis, a CT-guided biopsy was superior to VBN plus rEBUS for the evaluation of lesions smaller than 2 cm and located in the outer third of the lung [6]. For larger peripherally located lesions the endobronchial approach may be preferred, as it has a high diagnostic yield (80 %) and a low risk of procedure-related complications [6].

The location of the lesions in our cohort were not equally distributed over all lobes, with more lesions present in the upper lobes. This upper lobe predominance reflects the findings of screen-detected lung cancers in the NELSON trial, where 65 % of nodules were located in the upper lobes [20]. Furthermore, it indicates the difficulty to obtain a diagnosis via conventional bronchoscopy or CT-guided transthoracic biopsy in the apical segments of the upper lobes. Also procedures with VBN in the upper lobes are challenging due to angulation of the scope and related difficulties with advancing the forceps, brush or needle into the working channel. In our experience, use of ultrathin bronchoscopes can be disappointing due to little amount of tissue that can be obtained with the small biopsy tools. Endoscopic tools with greater flexibility, but large enough to obtain a sufficient amount of tissue, are still needed.

The additional value of the new VBN technique to be able to further personalize treatment of our patients, can only be achieved by an extra investment of time and human resources. Pre-procedural CT scan and route planning, is followed by a procedure with median time of 50 min during which next to the anesthesiologist, a radiology technologist, the bronchoscopist, a 'co-pilot' for the navigation and endoscopy staff is needed [45].

5. Conclusions

In view of the expected lung cancer screening program leading to increasing numbers of especially small pulmonary nodules, better tools to reach SPNs are needed to help select the right treatment for the right patient. VBN with the possibility to also use a *trans*-parenchymal route is a new technique with a good diagnostic yield, also in patients in whom previously performed procedures failed to establish a diagnosis and/or alternative procedures are considered not feasible based on expected yield and/or safety. Preventing futile or more invasive procedures like surgery or transthoracic punctures with a higher complication rate is beneficial for patients. Using the new VBN technique, we reached a diagnostic yield of 77 %, and allowed treatment adaptation in two-third of the analyzed patient population.

CRediT authorship contribution statement

Birgitta I. Hiddinga: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Dirk-Jan Slebos:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **T. David Koster:** Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Lucie B.M. Hijmering-Kappelle:** Investigation, Writing – review & editing. **T. Jeroen N. Hiltermann:** Investigation, Writing – review & editing. **Hanneke Kievit:** Investigation, Writing – review & editing. **Anthonie J. van der Wekken:** Investigation, Writing – review & editing. **Gonda de Jonge:** Investigation, Writing – review & editing. **Rozemarijn Vliegenthart:** Investigation, Writing – review & editing. **Caroline Van De Wauwer:** Writing – review & editing. **Wim Timens:** Investigation, Writing – review & editing. **Frederike Bensch:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 3
Per case data NAVIGATOR.

	Segment	Indication	Path	SPN largest diameter (mm)	Diagnostic procedures performed before VBN	Empiric treatment advise without VBN	Consequence of VBN (yes/no)	Definitive pathology diagnosis after VBN	Definitive treatment advise after VBN
1	RB3	SPNdd	AP	26	BS	Empiric RT in lung cancer dose (high dose)	yes	MALT-lymphoma	RT low dose, curative for lesion lymphoma
2	LB3	SPNpr NSCLC stage IVB, progression on EGFR-TKI	TP	41	BS	No certain options	yes	NSCLC, Adenocarcinoma EGFR-mutation exon 19 del, no resistance mechanisms.	Chemo-immunotherapy
3	LB6	SPNdd	TP	36	EBUS	TTP	yes	NSCLC, adenocarcinoma, EGFR mutation exon 19 del, PD-L1 = 80 %. cT2aN3M0.No metastasis thyroid, no AML	Chemoradiotherapy
4	RB2	SPNpr NSCLC stage IVB, EGFR mutation exon 19 del. Progression on EGFR-TKI	TP	24	Thoracoscopy	TTP	no	Atypical cells	Chemo-immunotherapy because of NSCLC (by additional TTP: not sufficient tissue to reveal resistance mechanisms)
5	RB8	SPN	AP	57	None	EBUS or lobectomy	yes	NSCLC adenocarcinoma, no drivermutations. cT3N0M0	Lobectomy RLL + neoadjuvant chemo-immunotherapy in study ypT1aN0PL1
6	RB1	SPNdd	AP	35	BS	Empiric SBRT	yes	NSCLC adenocarcinoma, cT2aN0M0, EGFR mutation exon 19 del, PD-L1 = 70 %	High dose radiotherapy
7	RB9	SPN	TP	19	None	Empiric SBRT	yes	NSCLC adenocarcinoma, cT1bN0M0, no driver mutations, PDL1 = 0 %,	Lobectomy RLL; adenocarcinoma, pT1bN0PL0R0
8	RB1	SPNdd	AP + TP	26	None	Empiric SBRT	no	No diagnosis, nodule not reached.	Empiric SBRT in suspected lung malignancy cT1cN0M0 with partial response.
9	RB4	SPNpr NSCLC stage IVB with EGFR mutation exon 19 del. Progression on first generation EGFR-TKI	TP	20	None	None	yes	NSCLC adenocarcinoma, EGFR exon 19 del, EGFR T790M, no other resistance mechanisms.	Targeted treatment for EGFR T790M.
10	LB9	SPNdd	AP	22	None	High risk TTP	yes	Metastasis oropharynx carcinoma	Systemic therapy
11	LB1	SPNpr Suspected progression on chemoimmunotherapy in NSCLC IVB with EGFR exon 19 deletion	AP	22	None	High risk TTP	no	Reactive changes (was resolving nodule in follow up)	Empiric switch to afatinib due to progression in other lesions. Not histology proven.
12	LB1	SPNdd	AP	16	None	High risk TTP	yes	Focal pneumonia, Culture: infection with S. pneumoniae	Antibiotic therapy, resolved nodule.
13	RB9	SPNdd	AP + TP	25	None	High risk TTP	no	Metastasis of SCC, can either be lung or larynx.	BSC due to fast deterioration
14	RB5	SPNpr	TP	14	None	High risk TTP	yes	Dysplasia: atypical p40 + cells, suspected primary SCC of the lung.	Radical RT
15	RB3	SPN	AP	27	None	High risk TTP	yes	Lung SCC	Radical RT in study with immunotherapy
16	RB8	SPN	TP	35	TTP	Unclear	yes	Melanoma	Systemic therapy
17	LB6	SPN	TP	11	None	High risk TTP	no	Lung tissue, considered non-representative	Follow up: indolent (1 year follow up)
18	RB3	SPNdd	AP	11	None		no		

(*continued on next page*)

Table 3 (*continued*)

	Segment	Indication	Path	SPN largest diameter (mm)	Diagnostic procedures performed before VBN	Empiric treatment advise without VBN	Consequence of VBN (yes/no)	Definitive pathology diagnosis after VBN	Definitive treatment advise after VBN
						High risk TTP		Bronchial epithelial tissue, cartilage and connective tissue.	Follow up: Considered metastasis of thyroid carcinoma.
19	LB1	SPN	AP	22	None	Resection of a brain metastasis	yes	NSCLC, adenocarcinoma, KRAS-mutation G13C, PD-L1 = 0 % cT1cN0M1c	SBRT on brain metastases and lesion LUL + chemoimmunotherapy
20	LB 1	SPN	AP	25	EUS + TTP	Diagnostic resection	yes	NSCLC adenocarcinoma, cT1cN0M1b, EGFR mutation exon 21 insertion, PDL1 = 60 %.	Targeted therapy in study
21	LB1	GGO	TP	25	BS	Diagnostic resection	yes	Lung tissue with epithelial tissue, oedema and chronic infiltration	Follow up
22	LB3	SPNpr	TP	19	None	Diagnostic resection or empiric SABR	no	Lung tissue, connective tissue and anthracosis.	Empiric SABR
23	RB3	SPN	TP	11	None	Follow up	yes	NSCLC, Adenocarcinoma, cT1bN0M0 with ALK-EML4 fusion, PD-L1 = 5 %	Lobectomy RUL pT2N1PL0R0 + adjuvant chemotherapy
24	RB1	SPN	AP	20	BS	Empiric SBRT	yes	NSCLC Adenocarcinoma, cT1bN0M0, KRAS G12C mutation, PD-L1 = 0 %.	SBRT
25	RB3	SPNdd	AP	30	None	Follow up	no	Lung tissue with fibrosis and macrophages.	Suspicion of NSCLC. Follow up
26	RB6	SPN	TP	40	BS + EBUS	Resection	yes	NSCLC adenocarcinoma cT2aN2M0, no mutations, PD-L1 = 0 %	Chemoradiotherapy
27	RB2	GGO with solid component	AP	40	BS + TTP	Diagnostic resection	yes	NSCLC adenocarcinoma cT2aN0M0, EGFR mutation exon 19 del, PDL1 = 0 %	SBRT
28	LB1	SPNdd	TP	10	BS	Follow up	no	Reactive changes with fibrosis and bronchial mucosa	Follow up: indolent
29	LB3	SPNpr	AP	10	None	SBRT	yes	Focal pneumonia, Culture: infection with S. mitis	Follow up, resolving nodule
30	RB9	SPN	AP	48	None	BS	yes	NSCLC adenocarcinoma cT2bN0M1c, KRAS mutation G12C, PD-L1 = 0 %	SBRT brain metastases + BSC (due to deterioration with COVID19 infection)
31	RB7	SPNdd	AP + TP	24	None	BS	yes	Lung SCC cT1cN0M0	High dose RT
32	RB2	SPNdd	AP	34	None	High risk TTP	yes	Primitive neuroectodermal tumor	High dose RT
33	RB2	SPN	AP	13	None	Resection	no	Eosinophilic pneumonia	Sublobar resection: typical carcinoid pT1bN0
34	LB1	SPNdd	AP	47	BS	Follow up	yes	Large cell neuroendocrine carcinoma cT3N2M0	Concomitant chemoradiotherapy
35	RB2	SPN	TP	17	None	Follow up	no	Non-malignant lymphoid lesion	SBRT (considered malignant)

the work reported in this paper.

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