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Research article

The effect of intraparenchymal blood patching on the rate of pneumothorax in patients undergoing percutaneous CT-guided core biopsy of the lung

R.M. Perl[a,*], E. Risse[a], J. Hetzel[b,1], H. Bösmüller[c], C. Kloth[d], J. Fritz[e], M. Horger[a,1]

[a] Department of Diagnostic and Interventional Radiology, Eberhard Karls University, Tübingen, Germany
[b] Department of Internal Medicine II, Eberhard Karls University, Tübingen, Germany
[c] Institute of Pathology and Neuropathology and Comprehensive Cancer Center, Eberhard Karls University, Tübingen, Germany
[d] Department for Diagnostic and Interventional Radiology, University Hospital Ulm, Germany
[e] Johns Hopkins University School of Medicine, Russell H. Morgan Department of Radiology and Radiological Science, 601 N. Caroline Street, JHOC 3140A, Baltimore, MD, 21287, United States

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ABSTRACT

Purpose: To assess the effect of intraparenchymal blood patching (IBP) as well as tumor- and operator-related risk factors on the rate of pneumothoraxes after percutaneous CT-guided core needle biopsy of the lung.

Materials and methods: We performed a retrospective analysis of 868 CT-guided lung biopsies that were conducted at our institution between 2003 and 2018, of which 419 (48%) received an IBP. Outcome variable included the rates of pneumothorax and chest tube placement, as well as lesion size (< 3 cm versus ≥ 3 cm long axis diameter), lesion depth (≤ 2 cm, > 2-4 cm, > 4-5 cm and > 5 cm distance to the pleura), location within the lungs (upper lobe, lower lobe, middle lobe), needle caliber (13 G, 15 G, 17 G, 19 G), number of samples taken (1–3 versus ≥ 4 samples), and experience of the performing physician.

Results: The rate of pneumothorax was significantly ($p < 0.05$) lower in the group with IBP (10.7%) compared to the group without IBP (15.4%). The number of post-interventional chest tube placements was also lower in the IBP group (3.1% vs. 5.8%) but not statistically significant. The lesion size correlated negatively with the rate of pneumothoraxes, whereas in both groups (± IBP) lesions ≥ 3 cm showed a significantly lower rate of pneumothorax ($p < 0.05$). With increasing lesion depth, the pneumothorax rate increased with ($p < 0.01$) and without ($p < 0.001$) IBP. The rate of pneumothorax was significantly lower ($p < 0.05$) for 17 G needles with IBP, but not for other calibers. For biopsies in the lower lobe, the pneumothorax rate reduced significantly ($p < 0.001$) with IBP. In case of ≥ 4 tissue samples, the pneumothorax rate was significantly lower with IBP ($p < 0.01$). For experienced operators, the overall pneumothorax rate was significantly lower compared to less experienced operators ($p < 0001$).

Conclusions: IBP significantly reduces the rate of pneumothorax following CT-guided lung biopsies in particular for lesions located deeper in the lungs, when ≥ 4 samples are taken, when samples are taken by less-experienced operators, and when sampling from the lower lobes.

1. Introduction

Lung biopsy is an important alternative to open surgery for histologic and microbiologic characterization of pulmonary nodules that are not amenable for transbronchial biopsy [1,2]. Moreover, individualized oncological approaches aim to choose the most adequate treatment strategy for patients, for which repeated lung biopsies are more often required [3]. In light of these new trends in tumor treatment, the safety of repeated lung biopsy is becoming increasingly important for interventional radiologists. Pneumothorax is the most common complications following percutaneous CT-guided lung biopsy, which can cause considerable morbidity and discomfort and higher costs due to longer hospitalization, in particular if chest tube placement is needed [4].

Interestingly, the rate of pneumothorax after percutaneous CT-guided lung biopsy varies considerably ranging from below 10% up to more than 40%, with a mean of over 20% in most metaanalytic reports [5,6]. Known patient- and tumor-related risk factors for pneumothorax

* Corresponding author at: Department of Radiology, Eberhard Karls University, Tübingen, Hoppe-Seyler-Str. 3, Germany.
E-mail address: regine.perl@med.uni-tuebingen.de (R.M. Perl).
[1] both authors share equal contribution.

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include small size, unfavorable location, transfissural route, patient compliance, presence of emphysema and chronic obstructive lung disease and pulmonary hypertension [7]. The needle caliber, duration of transpulmonic needle placement, and the expertise of the physician performing the intervention are additional factors influencing the rate of complications [7].

In the more recent years, few reports indicated the potential role of intraparenchymal blood patching for reducing the incidence of post-interventional pneumothorax [8,9]. However, the effects of IBP on the rate of pneumothoraxes differ, as do the sites and utilized techniques of blood application [10–12]. Graffy et al. for example describes a reduction of the pneumothorax rate from 44% (non-IBP group) to 30% (IBP group), while the study by Herman et al showed no significant difference between the two groups [8,9,11].

Therefore, the purpose of our study was to assess the effect of intraparenchymal blood patching as well as tumor- and operator-related risk factors on the rate of pneumothoraxes after percutaneous CT-guided core needle biopsy of the lung.

2. Material and methods

2.1. Patient characteristics

Following approval from our local institutional review board and waiver for patient consent (545/2018BO2), we performed a retrospective evaluation of 868 consecutive patients (mean age, 63.9 years; range 16–95 years, 530 men and 338 women), who underwent percutaneous CT-guided core needle biopsy at our institution between 2003 and 2018. Of the 868 patients, 419 (48%) received an IBP.

2.2. Diagnostic chest CT protocol

All patients underwent a diagnostic chest CT prior to lung biopsy. The diagnostic chest CT studies were performed with 4/16/64/128/256-slice MDCT scanners (SOMATOM Plus 4 or 16, Definition AS + or SOMATOM Definition Flash, SOMATOM Definition Force, Siemens Healthineers, Forchheim, Germany). Intravenous contrast medium was administered only if the pulmonary masses were necrotic in order to be able to target vital tumor tissue, or if the lesion was located close to larger lung vessels. Scan parameters included 0.6–1 mm collimation with a reconstructed slice thickness of 3 mm using a 300–330 mm field of view and a 512 × 512 reconstruction matrix. The tube voltage ranged between 100–120 kV and the tube current between 100–200 mA s. Images were reconstructed with both a soft tissue (filter, B31f) and a sharp kernel (filter, B70 s).

2.3. Characteristics of pulmonary nodules

Multiplanar reconstructions were used to determine the size and location of the lesions. To measure the lesion size, the longest axial diameter was determined. Subsequently we dichotomized lesions into < 3 cm and ≥ 3 cm groups. The location of each pulmonary mass was assigned to a pulmonary lobe, whereas sampling from the mediastinum or pleura, where the needle was passed through the lungs, was classified as “others”. We measured the distance between the target lesion and the pleura and classified it accordingly into: ≤ 2 cm, > 2 - 4 cm, > 4- 5 cm and ≥ 5 cm. Finally, the number of tissue samples and the number of needle passes was documented for every patient and dichotomized into 1–3 versus ≥ 4.

2.4. Lung biopsy characteristics

Each patient was positioned individually on the CT table to allow best possible access to the lung lesion considering the most tissue sparing and shortest track to the targeted lesion, including avoidance of needle paths through fissures, lung bullae and larger vessels. Following CT imaging, proper preparation of the interventional site, sterile draping, local anaesthesia of all tissue layers was performed with 10–20 mL of lidocaine 1% in each patient. Patients received an oxygen mask with an O_2 flow of 3–5 L. All patients were instructed to breathe shallowly. A breath-hold technique was not used. Coaxial needle systems were used of various sizes, including 13 G, 15 G, 17 G and 19 G. The coaxial needle tip was placed behind the outer edge of the lesions (inside the lesion) in lesions > 2 cm in diameter whereas in smaller lesions the needle tip was placed shortly in front of the lesion (≤ 2 cm). The bore of the coaxial needle was covered during the time the biopsy needle was removed in order to avoid air aspiration.

The group of performing radiologists consisted of 6 diagnostic radiologists with comparable levels of experience on the field of chest interventions (< 30 lung biopsies each) and one experienced chest radiologist with over 10 years of lung biopsy experience (> 300 lung biopsies).

Based on the better results reported in the specialty literature in particular by Melone et al [12], all patients undergoing percutaneous lung biopsy by the experienced thoracic radiologist from 06/2013 were treated with IBP (410 of 868 cases). When IBP was performed by one of the other radiologist (9 cases) the decision of using IBP remained arbitrary and by now not traceable. IBP was performed at the end of the procedure by leaving the needle in place and injecting 5–10 mL autologous blood that was drawn from a peripheral vein of the patients. Autologous blood was instilled (without awaiting for clotting) in small portions along the biopsy path at 1 cm increments and 1 min intervals in-between while gently removing the needle from the patient’s lung. At the lung periphery, we removed the needle under continuous aspiration without performing additional intrapleural blood patching.

After the lung biopsy, patients were instructed to lay on the sampled side in bed for six hours and to avoid vigorous coughing. A chest radiograph was performed approximately two hours (1–3 hours) after the procedure, repeatedly thereafter in the case of pneumothorax. All cases with new pneumothorax after the biopsy and all cases that required a chest tube placement were document.

2.5. Statistics

All statistical calculations as well as all graphical illustrations were performed using Graph Pad Prism 5 (GraphPad Software Inc., San Diego, California, USA). The effect of IBP on the rate of complications was assessed with cross-tabulations. Normal distribution was assessed with the Kolmogorov–Smirnov method. Normally distributed data were evaluated for significant differences with the chi-square test. For small case numbers, Fischer's exact test was used. In order to prove the independence of the individual risk factors, we additionally conducted a one-way Anova with the Bonferroni multiple comparison test. A p-value of < 0.05 was defined statistically significant.

3. Results

Our cohort consisted of 868 patients undergoing CT-guided lung biopsy, in which IBP was performed in 419 (48.3%) patients, whereas IBP was not performed in 449 (51.7%) patients. The one-way Anova with Bonferroni multiple comparison test revealed no significant difference between the individual risk factors, therefore, the risk factors can be considered independently.

The rate of pneumothorax was significantly ($p < 0.05$) lower in the group receiving IBP (10.74%) compared to the non-IBP group (15.37%) (Fig. 1).

The rate of pneumothorax was significantly lower ($p < 0.05$) for lesions ≥ 3 cm than in lesions < 3 cm. This negative correlation was true in both the IBP and the non-IBP group (Fig. 2).

The evaluation of the different needle sizes with regard to their complication rates showed significant ($p < 0.05$) differences between the two patient groups (IBP vs. non-IBP) only for the 17 G needle which

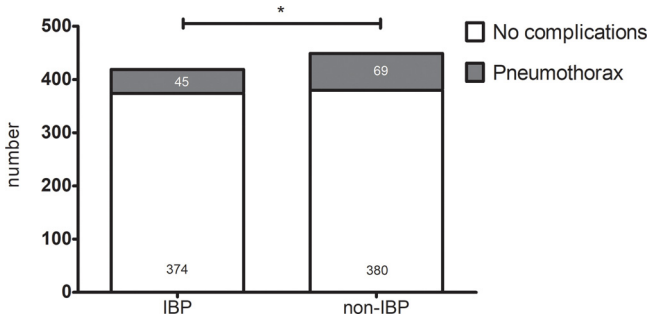

Fig. 1. Overall rate of pneumothorax in the group receiving IBP compared to the group without IBP.
The rate of pneumothorax proved significantly ($p < 0.05$) lower (10.74%) in the group receiving IBP compared to the non-IBP group (15.37%).

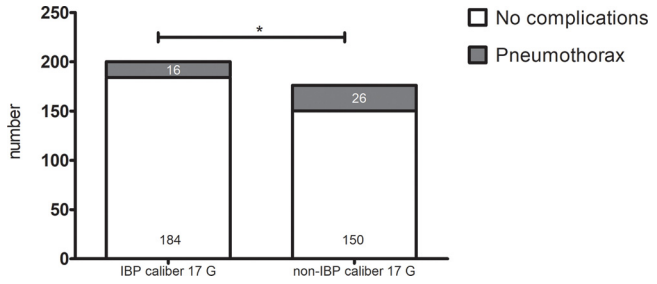

Fig. 3. Rate of pneumothorax according to needle calibers.
In the 17 G group, the pneumothorax rate was significantly ($p < 0.05$) lower in the IBP group. For all other needle calibers, there was no significant difference between the two groups.

was the needle that was most frequently used by the operators. For all other needle sizes (13 G, 15 G and 19 G), there was no significant difference (Table 3, Fig. 3).

In both groups with IBP and without IBP, the rate of pneumothorax increased significantly with the depth of the lesion (Table 1, Fig. 4): In the IBP group there was a significant difference in the pneumothorax rate between lesions < 2 cm and > 2-4 cm distance to pleura ($p < 0.01$) and between lesions < 2 and > 5 cm distance to pleura ($p < 0.001$). In the non-IBP group there was a significant difference between lesions at a depth of ≤ 2 cm and > 4–5 cm ($p < 0.01$) and between lesions at a depth of ≤ 2 cm and > 5 cm ($p < 0.01$). The comparison of the two groups (IBP and non-IBP) showed a significant difference for superficial lesions with a pleural distance of < 2 cm ($p < 0.05$) and for lesions deeper localized in the lung with a distance to the pleura of > 4–5 cm ($p < 0.05$, Table 1, Fig. 4).

In case of sampling from the lower lung lobes (LL), the rate of pneumothorax was significantly ($p < 0.001$) lower when IBP was administered. There was no difference in the rate of pneumothorax between the two groups when sampling from the upper lobes (UL) or when sampling from mediastinum (Fig. 5).

There was no significant difference in the pneumothorax rate between the IBP and the non-IBP group when a maximum of 3 samples were taken. However, when ≥ 4 samples were taken, the patients who underwent IBP had a significantly lower rate of pneumothorax compared to the non-IBP group (6 of 106 [5.4%] in the IBP-group vs. 22 of 114 [16.2%] in the non-IBP-group; $p < 0.01$). (Fig. 6).

The rate of pneumothorax for the experienced operator was almost identical in the IBP and non-IBP groups (10.7% for IBP vs. 10.5% without IBP). In less experienced operators, the pneumothorax rate in the non-IBP group was approximately twice as high than in the IBP group (24.8% in the non-IBP group vs. 11.1% in the IBP group), but the statistical evaluation showed no significant difference (Table 2). A comparison of the overall complication rates shows that experienced operators have a significantly lower rate of pneumothorax (10.6%) than less experienced operators (24.1%) ($p < 0.001$) (Fig. 7).

4. Discussion

Our results are in support of the use of intraparenchymal blood patching for percutaneous CT-guided lung biopsy with a significant difference in the frequency of pneumothorax between the group receiving IBP and the group of patients that underwent biopsy without IBP. All in all, the mean rate of post-interventional pneumothorax in our cohort was 13.1% with the need of chest tube placement in only 4.5%, which compares favorably to other studies that reported the use intraparenchymal blood patching [8–12]. In our study, as well as in the comparative studies, pneumothorax was diagnosed by chest x-ray 1–3 h after intervention. Interestingly, for the experienced operator, the rate of pneumothorax did not significantly differ when using IBP or not. However, for the less experienced operators performing CT-guided core lung biopsy, the rate of pneumothorax doubled in the group without IBP.

We also evaluated other factors for pneumothorax following percutaneous lung biopsy in order to identify potential co-existing or confounding factors that influence the comparison of patients receiving IBP or not. In both the IBP group and the non-IBP group, the rate of pneumothorax significantly decreased with increasing lesion size. This is partly because larger lesions are easier to hit, and thus a reposition of the introducer needle is less often necessary and also because with larger lesions, the needle can be placed directly in the lesion minimizing the risk of bronchopleural fistula formation. By comparison, for small lesions the coaxial needle must be placed outside the lesion in the normal lung tissue, which significantly increases the risk of pneumothorax. Expectedly so, the depth of the lesions inside the lung varied considerably. The deeper a lesion is located in the lungs, the longer the transpulmonic path of the needle, and consecutively the higher the likelihood that airways will be injured. Accordingly, the rate of pneumothorax in our cohort continuously increased with the distance between the chest wall and the targeted lesion. This was true for both groups receiving IBP or not.

Nonetheless, there was a significant difference between the two groups (IBP vs. non IBP) for lesions < 2 cm and > 4-5 cm distance to

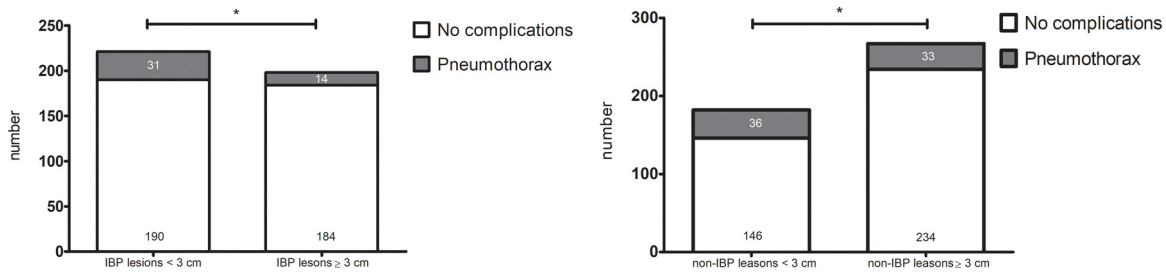

Fig. 2. Rate of pneumothorax according to lesion size.
In the IBP group (left graph) as well as in the non-IBP group (right graph) the lesion size correlated negatively with the rate of pneumothorax with lesions ≥ 3 cm showing a significantly lower rate of pneumothorax ($p < 0.05$) than lesions < 3 cm.

Table 1
Rate of pneumothorax according to lesion depth: Increasing lesion depth led to a significant raise in the rate of pneumothorax in the IBP group ($p < 0.001$) as well as in the non-IBP group ($p < 0.001$).

	lesion depth	no complications	pneumothorax	total	pneumothorax in %
IBP-group	≤ 2 cm	293	23	**316**	7.28
	> 2 – 4 cm	49	13	**62**	20.97
	> 4 – 5 cm	15	2	**17**	11.76
	> 5 cm	17	7	**24**	29.17
	IBP in total	**374**	**45**	**419**	**10.74**
non-IBP-group	≤ 2 cm	319	47	**366**	12.84
	> 2 – 4 cm	47	11	**58**	18.97
	> 4 – 5 cm	8	6	**14**	42.86
	> 5 cm	6	5	**11**	45.45
	non-IBP in total	**380**	**69**	**449**	**15.37**
	total	**754**	**114**	**868**	13.13

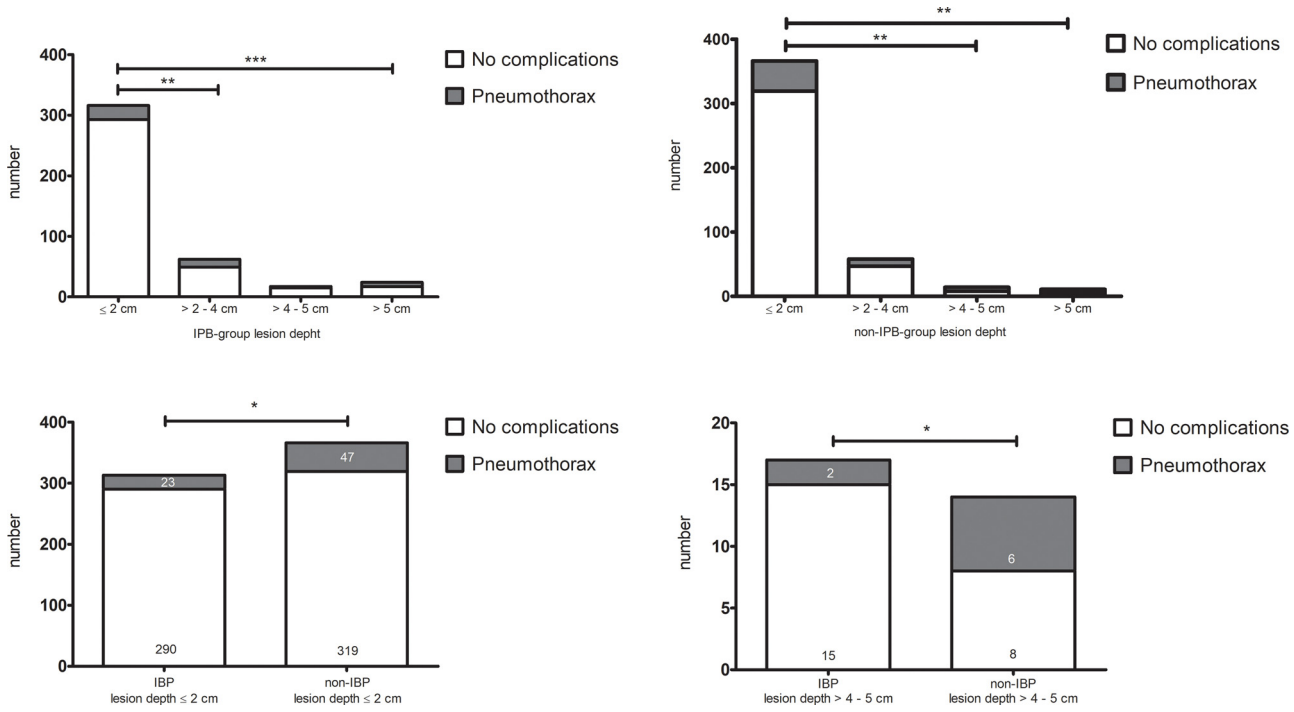

Fig. 4. Rate of pneumothorax according to lesion depth.
Upper row: Increasing lesion depth led to a significant raise in the rate of pneumothorax in the IBP group (≤ 2 cm vs. > 2–4 cm: $p < 0.01$ and ≤ 2 cm vs. > 5 cm: $p < 0.001$) as well as in the non-IBP group (≤ 2 cm vs. > 4–5 cm: $p < 0.01$ and ≤ 2 cm vs. > 5 cm: $p < 0.01$).
Bottom row: When comparing the two groups (IBP vs. non-IBP) there was a significant difference for lesions < 2 cm distance to the pleura ($p < 0.05$) and for more distant located lesions at a depth of > 4 – 5 cm ($p < 0.05$).

the pleura: In lesions < 2 cm distance to the pleura, the pneumothorax rate with IBP was 7.28% compared to 12.84% without IBP. In more distant located lesions (> 4–5 cm distance to the pleura) the difference was with 11.76% with IBP vs. 42.86% without IBP even clearer. Knowingly, biopsy of smaller lesions located close to the pleura are more challenging as the tip of the introducer needle lies close to the pleural space (negative pressure) during the procedure, thus, increasing the risk of pneumothorax while repeatedly extracting the biopsy needle. The alternative would be the choice of a longer transpulmonic needle insertion path parallel to the pleural lining, but this again is more risky in terms of pneumothorax rate because of crossing perpendicular to the physiological course of peripheral airways. Notably, there was no significant difference in the pneumothorax rate between biopsies with and without IBP in the group with a maximum of three tissue samples. However, with increasing number of tissue samples, the rate of pneumothorax tripled in the group without IBP (22/136; 16.2%) compared to the IBP-group (6/112; 5.4%). Also the lesion location inside the lung showed a clear benefit from using IBP in case of lesions located in the lower lobes. Knowingly the respiratory excursion of the lung increases from the upper lobe to the lower lobe so the lower lobes are prone to more lung and lesion shifting, requiring needle repositions more often and concomitantly, tissue injuries and pneumothoraxes are more frequent. Evaluation of complication rate according to needle size revealed a significant reduction in the rate of pneumothorax only in the subgroup of the most commonly used biopsy system at our institution (17 G): 8% when IBP was applied vs. 14.8% without IBP. Due to the low case numbers, there was no statistically significant difference in the complication rate with / without IBP for the 13 G and 15 G biopsy systems. In a similar retrospective analysis of the risk of pneumothorax related to percutaneous CT-guided lung biopsy, Kuban et al. reported significantly higher complication rates reaching 35% for 17 G introducer needles [13].

Taking all these variables together, it seems that the use of IBP has a considerable positive effect on the rate of post-biopsy pneumothoraxes reducing their absolute numbers and also the incidence of the more unfavorable cases requiring chest tube placement. Chest tube

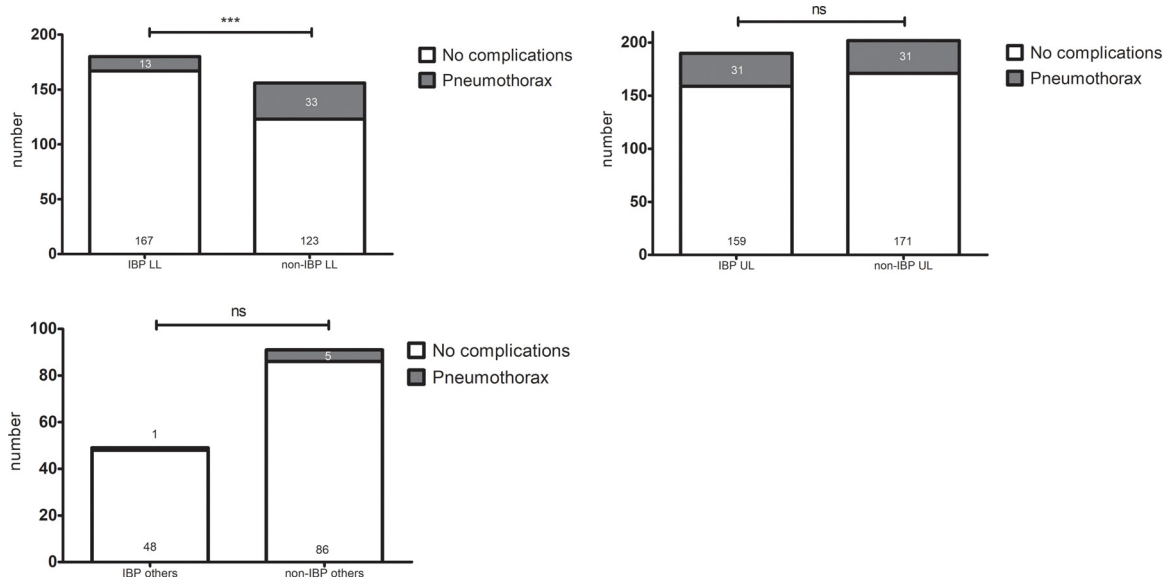

Fig. 5. Rate of pneumothorax when sampling from the lower lobe.
When sampling from the lower lung lobes, the rate of pneumothorax was significantly ($p < 0.001$) lower when IBP was performed. There was no difference when sampling from the upper lung lobes (UL) or when sampling from mediastinum or pleura (others).

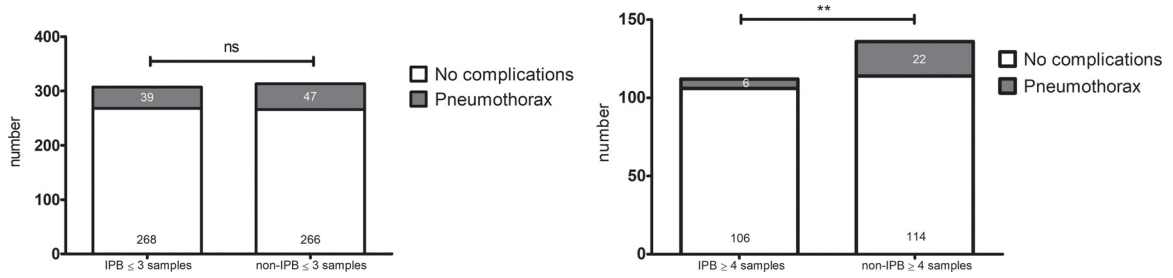

Fig. 6. Rate of pneumothorax according to the number of samples taken.
When more than 3 samples were taken the rate of pneumothorax was significantly lower ($p < 0.01$) in the IBP group compared to the non-IBP-group.

Table 2
Rate of pneumothorax according to the operator's experience: In experienced operators, the rate of pneumothorax was the same for IPN (10.7%) and non-IBP (10.5%) IBP. For less experienced operators the rate of pneumothorax differed from 11.1% for IBP to 24.8% for non-IBP.

	experience	no complications	pneumothorax	total	pneumothorax %	chest tube	chest tube %
IBP	> 300 punctures	366	44	410	10.73%	12	2.93%
	< 30 punctures	8	1	9	11.11%	1	11.11%
	IPB in total	**374**	**45**	**419**	**10.74%**	13	3.10%
non-IBP	> 300 punctures	265	31	296	10.47%	10	3.38%
	< 30 punctures	115	38	153	24.84%	16	10.46%
	non-IPB in total	**380**	**69**	**449**	**15.37%**	26	5.79%
	total	**754**	**114**	**868**	**13.13%**	**39**	**4.49%**

placement implies in-patient care and consecutively higher treatment costs. However, a more relevant effect on the rate of this complication seems to have the operator's experience. As this was a retrospective evaluation, we could not verify if less experienced operators had checked for and avoided all potential risk factors before planning the intervention and respected all known requirements for a safer lung puncture. Knowingly, needle redirection inside the lung and in particular the choice of a less favorable biopsy route can lead to needle repositioning or even to repeat pleural passes, thus increasing the risk for pneumothorax. Yeow et al. identified the operator's experience as a major risk factor for pneumothorax [7]. In a similar report, Graffy et al. found also that IBP was helpful for reducing the pneumothorax rate [8]. Interestingly, in their cohort, using a similar blood patch technique, the overall rate of pneumothorax was almost threefold higher compared to our series despite using mainly smaller caliber (19 G) of introducer needles. In the study by Lang et al. using also autologous blood clot seal to prevent pneumothorax, the rate of pneumothorax and treatment-requiring pneumothorax was also significantly higher compared to our results, but the authors documented a clear benefit from using IBP [9]. In particular, the frequency of pneumothorax significantly increased for lung lesions located deeper in the lung in their study which is in line with our results. These authors used a slightly different blood patch technique, allowing blood to clot first before it was injected in the lung along the biopsy route. In these latter two reports [8,9], the authors did not evaluate the potential relevance of the operator's experience. Bourgouin et al. using clotted blood obtained also superior results with IBP as without blood patching [10]. Nevertheless, there were also some controversial reports on this topic in the specialty literature. Hence, in an earlier study, Herman et al. found no benefit over the classical biopsy technique if using IBP [11]. In our study we adopted the IBP

Table 3
The rate of pneumothorax according to needle caliber. A significant reduction of the pneumothorax rate was only present in the subgroup of the most frequently used biopsy system (17 G) (14.8% without IBP vs. 8% with IBP; $p < 0.05$). The statistical analysis revealed no significant difference for the 19 G system, which was also widely used. Due to the low number of cases in the other biopsy systems (13 G, 19 G), no significant difference in the complication rate in biopsies with / without IBP could be detected.

	Caliber in G	no complications	pneumothorax	total	pneumothorax in %
IBP-group	13 G	2	1	3	33.33
	15 G	22	1	23	4.35
	17 G	184	16	200	8.00
	19 G	139	26	165	15.76
	unknown	27	1	28	3.57
	IBP in total	**374**	**45**	**419**	**10.74**
non-IBP-group	13 G	7	0	7	0.00
	15 G	27	1	28	3.57
	17 G	150	26	176	14.77
	19 G	153	32	185	17.30
	unknown	43	10	53	18.87
	non-IBP in total	**380**	**69**	**449**	**15.37**
	total	**754**	**114**	**868**	13.13

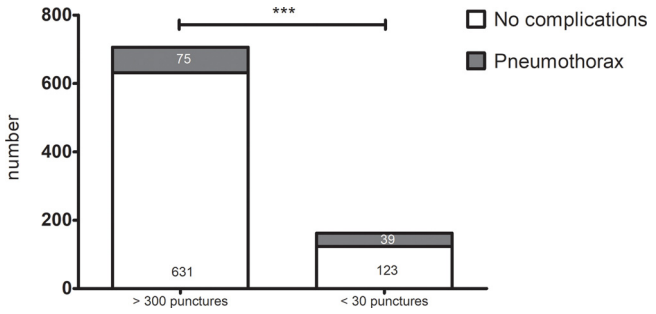

Fig. 7. Rate of pneumothorax according to operators experience.
Comparing the overall complication rates show that experienced users have a significantly lower rate of pneumothorax (10.6%) than less experienced users (24.1%) ($p < 0.001$),

technique described by Malone et al. but modified it by using fresh blood portionally distributed throughout the biopsy track over minutes in order to allow blood to clot intrapulmonary [12]. Their results resemble ours more closely, but the frequency of pneumothorax was higher in their study. A possible explanation therefore lays in the transfissural biopsy routes chosen in some of their patients, which we consequently avoided, but eventually also in the different technique of clot sealing. A transfissural needle path during biopsy is a known risk factor for prolonged chest tube requirement [5].

Previous reports evaluating biopsy tract sealing using other materials like fibrin glue or 0.9% NaCl solution showed also some benefit over the conventional biopsy technique [14,15].

We, in this work, did not address the issue of performing fine needle aspiration biopsy (FNAB), which is also practiced by many operators as the demands to our core lung biopsies are comparably higher in terms of getting enough samples for tumor characterization and increasingly for additional genome sequencing and therefore we do not practice the former technique, but in few critical cases with very high risk for complications. Being aware of the higher risk of pneumothorax with core biopsy technique, we always used a coaxial technique that avoids repeat lung passages and reduced the risk for pneumothorax [16].

Our study has some limitations. First, it is a retrospective analysis where not all data with respect to how the intervention was planned or carried out was available. Second, the rationale behind the choice of a particular needle caliber is not traceable with this retrospective study design. Moreover, the reasons for using IBP are not known when biopsies were performed by less experienced radiologists. Third, there was an imbalance between the number of performed biopsies between the less experienced operators and the operator with more experience. Fourth, other risk factors like patient's compliance were not available. Fifth, we did not evaluate the risk of parenchymal bleeding after percutaneous lung biopsy, which may have similar effects than intraparenchymal blood patching.

In conclusion, our results demonstrate that the use of IBP significantly reduces the rate of pneumothorax in CT-guided lung biopsies in particular when one or more of the following risk factors are present: a) When taking samples from small target lesions which are difficult to hit and thus the needle may need to be repositioned; b)when taking samples from very deep lesions, since a long way through the lungs is necessary and thus increases the risk of injuring larger airways resulting in a higher risk of pneumothorax; c) when sampling basal lesions, because of a higher pulmonic shifting in the lower lobes; d)when samples are taken by less experienced operators, because less expertise may be associated with higher complication rate.

Conflict of interest

Jan Fritz received institutional research funds and speaker's honorarium from Siemens Healthcare USA and is a scientific advisor of Siemens Healthcare USA and Alexion Pharamceuticals, Inc.

Marius Horger received institutional research funds and speaker's honorarium from Siemens Healthineers and is a scientific advisor of Siemens Healthcare Germany. The other authors have declared that no competing interests exist.

However, for this submitted work there was no involvement or financial interest with any organizations or entities.

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