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Does Gelfoam slurry embolization post-pulmonary biopsy reduce risk of pneumothorax? A prospective randomized control study

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Abstract

Background: CT-guided percutaneous transthoracic biopsy has become a widely accepted safe method in establishing the etiology of lung masses. Pneumothorax is the most commonly faced complication requiring further therapeutic intervention for treatment with chest tube drainage adding to the time of hospital stay.

Aim of work: We aim to evaluate the effect of Gelfoam mixture biopsy tract embolization as a minimal added cost in reducing the overall rate of complications, the need of chest tube placement, and hospital stay.

Patient and methods: A total of 138 transthoracic CT-guided lung biopsies were randomized to 70 track embolized patients and 68 control. The study protocol was approved from the National Cancer Institute ethical committee review board. Data were collected from the local PACS system and analyzed, reviewed and performed by one of three interventional radiologists. Patient records were analyzed for primary health risks, pre-procedural CT was analyzed for lesion-related risk factors, and intra-procedural CTs were analyzed for procedure-related risk factors. Outcome measures include incidence of pneumothorax, pneumothoraxes requiring chest tube insertion and hospital admission rates.

Results: Marked pneumothorax requiring chest tube insertion and hospital admission were significantly reduced in the embolized group as 7.1% compared to 19% in the non-embolized group with significant *p* value of 0.037. Hospital admissions reduced from 19% down to 4.3% in embolized cases with a significant *p* value of 0.007. On univariate regression analysis, embolization reduced chest tube placement odds by 68% (OR = 0.32, 95% CI 0.109–0.97, $p = 0.044$). The only significant procedural-related factor was needle pleural angle > 70° where it increased the risk of pneumothorax by 2.85 times and chest tube placement by 3.10 times. Gelfoam embolization significantly reduces the odds of post-procedural hospital admission by 81% (OR = 0.189, 95% CI 0.051–0.699, $p = 0.012$). In multivariate regression analysis, Gelfoam was significantly protective against chest tube insertion and prolonged hospital stay, by reducing the odds 74.3% (OR = 0.257, 95% CI 0.082–0.808, $p = 0.020$) and 86% (OR = 0.133, 95% CI 0.027–0.662, $p = 0.014$), respectively. Needle pleural angle more than 70° increased odds of chest tube insertion by 252%. Lesions that were in very low position related to the diaphragm and just behind ribs were less prone to chest tube insertion by 83% (OR = 0.164, 95% CI 0.035–0.779, $p = 0.02$), while those showing mediastinal invasion and central lung lesions had increased odds by 6.812 times (95% CI 1.452–31.958, $p = 0.015$) for longer hospital stays.

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Conclusions: Gelfoam embolization post-CT-guided lung biopsy has proven to statistically reduce large pneumothoraces requiring chest tube insertion, longer hospital stay, and reduced unnecessary expenses.

Keywords: Lung biopsy, Gelfoam, Pneumothorax, Hospital admission, Chest tube insertion

Background

CT-guided percutaneous transthoracic biopsy has become a widely accepted safe method in establishing the etiology of lung masses/nodules and/or assisting in treatment, with limited morbidity and extremely rare mortality [1]. The recent advances in the specific chemotherapy and novel targeted therapy and the increasing need for specific diagnosis of tumor histopathological subtypes and molecular markers have led to increasing need for more amount of tissue [2]. The frequency of pneumothorax after CT-guided lung biopsy is variable in the literature, with reported rates ranging from 8 to 64%. Furthermore, between 1.6 and 17% of these pneumothoraces require further therapeutic intervention for treatment. Treatment of pneumothorax with chest tube drainage adds radiological costs (equipment pre- and post-procedure imaging, professional fees, etc.), pharmaceutical cost (fluids, anesthetic agents, etc.), nursing care, and hospitalization charges [1].

Risk factors for pneumothorax after lung biopsy have been identified. These are related to the patient, lesion characteristics, and/or interventional techniques: (1) Patient-related risk factors include underlying lung conditions, in particular emphysema. The rate of pneumothorax increases with the severity of disease and is more likely to require chest tube placement [3]. (2) Lesion characteristics: Smaller, deeper, and central lesions are risky, as they require longer needle paths to target lesions. In contrast, larger lesions closer to the pleural and chest wall have a smaller risk of pneumothorax [3]. (3) Technical factors include the increased number of pleural punctures, multiple attempts repositioning the needle, transgression of fissures, biopsies in the middle or lower lobe, and wider insertion angle of the needle at the level of the pleura [3].

Iatrogenic air embolism, tumor seeding of the pleura and chest wall, chylous leak and diaphragmatic injuries are far rare complications of needle biopsy of the lungs [3].

Variable materials and maneuvers are being developed aiming to reduce the risk of complications to cut down the hospital expenses [4].

Autologous blood patch is most widely known, but this has yielded varying results. Injection of saline into the tract and the use of hydrogel and collagen plugs have also been evaluated for their protective effect; however, these are unreliable [4].

Gelfoam sponge is an inexpensive, currently available material that can readily be prepared in the form of an injectable slurry to seal the biopsy tract and prevent further progression of pneumothorax or pulmonary hemorrhage [4].

Aim of the study

To evaluate the use of Gelfoam slurry post-biopsy tract embolization, as a minimal added cost, to reduce the rate of complications, the need of chest tube placement, and hospital stay.

Methods

This is a single-institute, prospective randomized controlled study; 70 track embolized patients after CT-guided lung biopsy and 68 control were included. The patients were recruited between March 2018 and August 2019. The study protocol was approved from the cancer institute ethical committee review board (IRB 0004025). All procedures were reviewed and performed by one of three interventional radiologists with 5, 7, and 17 years of attending experience with the aid of one attending radiology resident.

Patient medical records and procedural follow-up imaging were reviewed by two radiology residents and one attending interventional radiologist for iatrogenic pneumothorax, hemothorax, symptomatic dyspnea, their rate of progression and further need for chest tube insertion and extended hospital stays. The study was ended upon completion of the patient sample size.

Inclusion criteria:

- Both genders.
- Aged above 18 years.
- New or enlarging solitary nodule or mass which was inaccessible by bronchoscopy.
- Equivocal pulmonary nodules.
- Cases of suspected more than one primary malignancy.
- Persistent focal infiltrates, either single or multiple.

Exclusion criteria include:

- Patients refusing the interventional procedure.
- Noncompliant, uncooperative and unconscious cases.

- Central lesions and endo-bronchial lesions better biopsied trans-bronchial.
- Patients with non-correctable coagulation defect or low platelet count.
- Patients contraindicated for CT examination (e.g., during pregnancy).
- Patients having a single lung, post-pneumonectomy or severe bullous emphysema.
- Patients having massive contralateral or ipsilateral pleural effusion are assigned for image-guided pleural tapping to improve the overall respiratory reserve prior to lung biopsy.

The procedure was performed on one of two multislice CT machines, one of which was Asteion™ Super 4 Toshiba and the other was GE 16 Slice Optima™, positioning into the safest needle access with the shortest possible needle tract and the best perpendicular access to minimize injurious risk to mediastinal structures. Whole non-contrast CT chest was done and compared to the old films provided to account for any time interval regression/resolution. In this case, the biopsy is postponed and another follow-up CT was assigned for the patient after adequate antibiotic therapy.

In stationary or progressive cases, the proper cut is chosen, the skin is sterilized with Betadine®10% povidone iodine solution, and the area is properly draped.

Deep central sedation was avoided to ensure patient cooperation and to note for any deterioration of the consciousness or breath. Local anesthesia 5–10 cc of 2% lidocaine was usually enough to numb the area according to the depth of the subcutaneous tissues. 17 or 18 coaxial needle *(HS hospital services S.p.A, Aprilia, Italy)*, with appropriate length depending on the depth of lesion, was utilized. Patients were asked to hold their breath neutral during imaging and during coaxial pass to ensure the needle still lies within the target cut. Last-minute adjustments for the coaxial needle position checked with limited CT images. The central guiding trocar was removed, and the sample was obtained using an 18-gauge spring-loaded semiautomated biopsy device *(MedPlus, BN-G2, China)*. Gelfoam mixture was prepared before starting the biopsy; doubled quantities were prepared for biopsy tracks ≥ 5 cm. A standard of the 3 cores was obtained per 1 coaxial pass preserved in a small jar filled with formaldehyde solution. Each time, the semiautomated tru-cut needle was removed and the coaxial hub was closed by a saline syringe to provide a watertight seal.

The Gelfoam slurry was prepared prior to the biopsy as follows:

A single 3×3 cm Cutanplast® sterile reabsorbable gelatin sponge sheet was compressed to eliminate as much of the air as possible and then cut into thin strips that were back-loaded into a 10-mL syringe. 4 mL of sterile saline and 2 mL of Ultravist® 300 mg contrast were drawn up in a second 10-mL syringe that was connected by a three-way stopcock. The mixture was agitated to produce a smooth consistency. The 2 cm of slurry is then gently injected as the coaxial needle is withdrawn 1 cm outwards, thus depositing the material as evenly as possible along the parenchymal tract up to the pleural surface. Although the amount of added contrast was minimal (2 ml in tracts less than 5 cm and up to 4 ml in longer biopsy tracts), the added benefits include the following:

Ultravist contrast material improves visualization of Gelfoam in lung parenchyma.

It helps to well differentiate the Gelfoam slurry from parenchymal hemorrhages (where they may be isodense on CT). On follow-up, it helped to localize any unexpected trans-bronchial migration of Gelfoam. Although statistically rare, we aimed to use contrast as well to localize possible distant vascular embolization.

At the end of the biopsy:

Another whole non-contrast CT chest was done to account for any complications, primary hemorrhage and pneumothorax.

The patients were then transferred to a hospital bed to minimize exertion and were maintained in the same bed during recovery with the site of the biopsy being most dependent. Non-contrast chest CTs were obtained during a 4-h period of observation, usually on patient arrival to the recovery area 1 h and 2–3 h afterward to see if delayed pneumothorax had developed or an existing pneumothorax has progressed.

Radiographs were reviewed by one of the operators before discharge. A longer period of hospital observation was considered if there was an evolving pneumothorax or the patient lived 1 h driving distance away from the hospital. The indications for chest tube placement were dyspnea and hypoxemia with rapidly progressing pneumothorax having enough space for chest tube placement between the first and second ribs.

Upon discharge, patients were provided with a detailed medical report to present any ER unit outside our institute if they lived 1 h driving distance away from the hospital. Patients were firmly instructed to avoid as much as possible straining, coughing, exertion, and smoking at least 24 h after the biopsy.

Data analysis

All CT images and post-procedure chest radiographs were reviewed to identify study outcome measures. Data parameters collected included patient age, gender, relevant medical history, mass versus nodule, mean distance of nodule/mass from pleura, and procedure traversing lung fissure, the angle of the coaxial needle in relation

to the pleural surface and average time per procedure. Outcomes were recorded for both groups, including procedure-related pneumothorax, need for chest tube placement, and further hospitalization if required.

Statistical methods

Data were analyzed using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 21 for Microsoft Windows. Numerical data were tested for the normal assumption using Kolmogorov–Smirnov test. Normally distributed variables were described as mean ± standard deviation (± SD), median and range; categorical variables were described as frequencies (number of cases) and percentages. All numerical data were normally distributed or approximately normal with large sample size; a comparison between cases and control groups was made using Student's t test for independent samples. For comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Univariate followed by multivariate binary logistic regression was performed for statistically significant variables on the univariate analysis to identify independent preoperative, procedure, and postoperative factors affecting the occurrence of complications following needle biopsy. p values less than 0.05 were considered statistically significant; all tests were two-tailed.

Results

One hundred and thirty-eight patients were randomly allocated into 70 patients with Gelfoam slurry tract embolization (embolized group) and 68 patients with no tract embolization (control group).

The control and the Gelfoam-embolized groups were comparable. The patients in the Gelfoam-embolized group were statistically significant older than the control group ($p = 0.013$) as given in Table 1.

Reviewing Tables 1 and 2, it is noted that randomization fulfilled homogenous representation of patient characteristics, lesion-related and patient-related risk factors with generally insignificant p values of ≥ 0.05. The only occasions where p values were significant were lesion location (central or peripheral) and pericardial invasion. More patients were assigned with central lesions 46 (65.7%) to the cases group with a p value of (0.007). More patients had pericardial invasion in the control group 23 (33.8%) vs. 7 (10%) in the embolized group ($p = 0.001$).

From our study, the rate of occurrence of pneumothoraces was not reduced by Gelfoam significantly

Table 1 Patient characteristics

	Control		Embolized		*p* value
	N = 68	%	N = 70	%	
Age					
Mean ± (SD)	55.2 (± 12.8)		60.3 (± 8.3)		0.013
Median (range)	56.5 (22–80)		61 (41–83)		
Sex					
Male	50	73.5	55	78.6	0.488
Female	18	26.5	15	21.4	
Tobacco					
No	35	51.5	31	44.3	0.398
Yes	33	48.5	39	55.7	
Occupational exposure					
No	64	94.1	61	87.1	0.16
Yes	4	5.9	9	12.9	
Emphysema and ILD					
No	41	60.3	38	54.3	0.476
Yes	27	39.7	32	45.7	
Asthma					
No	57	83.8	53	75.7	0.236
Yes	11	16.2	17	24.3	
Pre-procedural rim pneumothorax					
No	66	97.1	68	97.1	0.977
Yes	2	2.9	2	2.9	

Table 2 Procedure-related risk factors:

	Control		Embolized		*p* value
	N = 68	%	N = 70	%	
Difficult positioning					
No	53	77.9	61	87.1	0.154
Yes	15	22.1	9	12.9	
Trans-fissure needle passage					
No	58	85.3	51	72.9	0.073
Yes	10	14.7	19	27.1	
Biopsy track length (cm)					
Mean ± (SD)	4.4 (1.6)		5.2 (2.3)		0.264
Median (range)	4 (2–8.4)		4.8 (1.4–14.7)		
Needle pleural angle (°)					
Mean ± (SD)	62.2 (21)		66.9 (15.4)		0.101
Median(range)	65 (15–95)		65.5 (35–90)		

Table 3 Complication rates and sequel in both embolization group and controls

	Control		Embolized		*p* value
	N	%	N	%	
Pneumothorax					
No	44	64.7	49	70.0	0.507
Yes	24	35.3	21	30.0	
Chest tube					
No	55	80.9	65	92.9	0.037
Yes	13	19.1	5	7.1	
Hospital admission					
No	55	80.9	67	95.7	0.007
Yes	13	19.1	3	4.3	

($p = 0.507$). However, the rate of their progression to marked pneumothorax requiring chest tube insertion and hospital admission has been significantly reduced in the embolized group compared to the control group. The patient undergoing post-procedural Gelfoam embolization required chest tube insertion 7.1% compared to 19% in the non-embolized group with a significant p value of 0.037. Hospital admissions were greatly reduced from 19% in controls to 4.3% in embolized cases with a significant p value of 0.007 as illustrated in Table 3.

Gelfoam embolization was associated with some specific complications in a minority of cases. Hilar lesions, cavitating lesions, and those invading a main bronchi were shown to associate with endobronchial leak of Gelfoam material detected as a minimal smear of Gelfoam slurry in the dependent bronchi close to the biopsy site. This was encountered in a total of 8 cases, i.e., 11.4%. This was generally a self-limiting condition associated by mild cough and discomfort and frothy sputum expectoration, resolving spontaneously during the follow-up period. Only 2 (2.9%) cases reported minor contrast allergy (itching and skin rash only) to the non-iodinated contrast mixed with Gelfoam and were controlled immediately after intramuscular anti-histaminic injection.

Univariate analysis was performed for pneumothorax, chest tube placement, and hospital admission (Table 4).

Univariate regression analysis for evaluated risk factors pneumothorax: showed that the only procedural-related factor showing significant p value of 0.005 was the needle pleural angle > 70° where it increased the risk of pneumothorax by 185% (OR = 2.85 95% CI 1.372–5.957, $p = 0.005$). The rest of the evaluated risk factors showed no statistical significance.

Univariate regression analysis for chest tube placement: patients undergoing tract embolization with Gelfoam slurry had a decreased chest tube placement rate compared to non-embolized patients with reduced odds by 68% (OR = 0.32, 95% CI 0.109–0.97, $p = 0.044$). As with pneumothorax, still the needle pleural angle more than 70° showed an increased rate of chest tube insertion by 3.106 times (95% CI 1.091–8.844 and $p = 0.034$).

Univariate regression analysis for hospital stay: showed that Gelfoam embolization significantly reduces the odds of post-procedural hospital admission by 81% (OR = 0.189, 95% CI 0.051–0.699, $p = 0.012$). Central lung lesions were more prone to complications and hospital admission up to 4.194 times than cases with peripheral lung lesions (95%CI 1.138–15.458, $p = 0.031$). Small rims of pre-procedural pneumothorax increased the odds of hospital admission 8.571 times (95% CI 1.118–65.698, $p = 0.039$). Difficult patient positioning associated with dyspnea, pleural or pericardial effusion was accompanied with increased odds of admission also (OR = 3.467, 95%CI 1.121–10.721, $p = 0.031$). It was noted that patients suffering mediastinal pericardial invasion faced higher rates of complications by 354% (OR = 4.545, 95% CI 1.539–13.428, $p = 0.006$). Compared with pneumothorax, chest tube insertion univariate regression analysis, needle pleural angle ≥ 70° increased the likelihood of hospital admission by 1.85 times, yet no statistical significance was noted $p = 0.251$.

Multivariate regression models were generated for the variables that only showed statistical significance on the univariate level.

In multivariate regression analysis, the variables that had an influence on chest tube insertion were as follows: (1) Gelfoam track embolization showed a significant protective effect reducing the odds by 74.3% (OR = 0.257,

Table 4 Univariate regression analysis of risk factors for pneumothorax rates, chest tube placement, and hospital admission

	Pneumothorax		Chest tube insertion		Hospital admission	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Group	0.786 (0.38–1.6)	0.508	0.325 (0.10–0.97)	0.044	0.189 (0.05–0.7)	0.012
Age (years)	1.008 (0.97–1.04)	0.618	0.998 (0.95–1.04)	0.938	0.999 (0.95–1.05)	0.966
Sex (male/female)	1.483 (0.65–3.34)	0.342	0.897 (0.27–2.93)	0.857	1.069 (0.32–3.57)	0.914
Tobacco (no/yes)	0.939 (0.46–1.91)	0.862	0.905 (0.33–2.43)	0.843	1.613 (0.52–4.71)	0.382
Lesion size (mass/nodule)	0.789 (0.31–1.96)	0.61	0.76 (0.20–2.83)	0.683	0.527 (0.11–2.47)	0.417
Lesion location (peripheral/central)	1.406 (0.68–2.89)	0.355	1.81 (0.63–5.13)	0.265	4.194 (1.13–15.46)	0.031
Pre-procedural PTX (no/yes)	2.116 (0.28–15.5)	0.461	2.294 (0.22–23.33)	0.483	8.571 (1.12–65.70)	0.039
Difficult portioning (no/yes)	1.612 (0.65–3.98)	0.3	1.429 (0.42–4.79)	0.564	3.467 (1.12–10.27)	0.031
Encase bronchus (no/yes)	0.792 (0.37–1.67)	0.54	0.833 (0.29–2.37)	0.733	1.837 (0.64–5.24)	0.255
Encase vessel (no/yes)	1.214 (0.57–2.54)	0.608	1.226 (0.44–3.4)	0.695	2.05 (0.71–5.86)	0.18
Cavitating (no/yes)	1.536 (0.45–5.14)	0.486	1.375 (0.27–6.85)	0.698	2.897 (0.69–12.07)	0.144
Para-cardiac invasion (no/yes)	1.515 (0.656–3.5)	0.331	2.684 (0.93–7.67)	0.066	4.545 (1.54–13.43)	0.006
Para-aortic (no/yes)	0.807 (0.33–1.93)	0.63	1.391 (0.45–4.25)	0.564	1.173 (0.35–3.93)	0.796
Trans-fissure (no/yes)	1.113 (0.46–2.64)	0.809	1.538 (0.5–4.73)	0.453	2.583 (0.85–7.83)	0.094
Lesion position rib or diaphragm	0.512 (0.23–1.13)	0.1	0.208 (0.04–0.95)	0.043	0.244 (0.053–1.13)	0.07
ILD emphysema (no/yes)	0.642 (0.30–1.33)	0.236	1.082 (0.39–2.93)	0.876	1.392 (0.49–3.95)	0.534
Asthma (no/yes)	0.974 (0.40–2.6)	0.953	1.622 (0.52–5.00)	0.4	1.957 (0.62–6.18)	0.253
Number of coaxial passes > 1	2.656 (0.94–7.43)	0.063	2.352 (0.67–8.22)	0.18	1.78 (0.45–7.03)	0.41
Coaxial path (cm)	0.921 (0.76–1.11)	0.403	1.039 (0.81–1.31)	0.752	1.051 (0.82–1.34)	0.688
Needle pleural angle > 70	2.859 (1.37–5.95)	0.005	3.106 (1.09–8.34)	0.034	1.851 (0.65–5.29	0.251
Patient position (VS supine)						
Prone	0.83 (0.40–1.71)	0.615	0.758 (0.27–2.10)	0.595	0.451 (0.14–1.43)	0.176
Lateral	0.253 (0.02–2.19)	0.213	0.825 (0.09–7.53)	0.865	1.926 (0.334–11.08)	0.463
Location (vs. LLL)						
LUL	1.518 (0.554.16)	0.417	1.741 (0.41–7.39)	0.452	3.562 (0.72–17.56)	0.119

Table 5 Multivariate regression analysis for risk factors influencing the chest tube insertion

	OR	95% CI		*p* value
		Lower	Upper	
Angle > 70	3.526	1.175	10.58	0.025
Group	0.257	0.082	0.808	0.020
Lesion position rib or diaphragm	0.164	0.035	0.779	0.023

Table 6 Multivariate analysis of the risk factors related to hospital admission

	OR	95% CI		*p* value
		Lower	Upper	
Group	0.133	0.027	0.662	0.014
Lesion location (peripheral/central)	6.812	1.452	31.958	0.015
Difficult position	3.927	0.978	15.765	0.054
Pneumothorax (pre) (no/yes)	19.618	1.884	204.3	0.013
Para-cardiac invasion (no/yes)	1.992	0.495	8.019	0.332

95% CI 0.082–0.808, $p = 0.020$). (2) Needle pleural angle more than 70° increased the odds of chest tube insertion by 252%. (3) Lesions that were in very low position related to the diaphragm and just behind ribs were less prone to chest tube insertion by 83% (OR = 0.164, 95% CI 0.035–0.779, $p = 0.02$) (Table 5).

In multivariate regression analysis including all the risk factors influencing the likelihood of hospital admission, Gelfoam embolization showing a significant protective effect of 86% (OR = 0.133, 95% CI 0.027–0.662, $p = 0.014$). On the other hand, tumors surrounded by pre-procedural rim of pneumothorax showed 19.6 times more odds of hospital admission and central lung lesions had increased odds by 6.812 times (95% CI 1.452–31.958, $p = 0.015$). Difficult positioning and poor respiratory control due to dyspnea, with or without pericardial or pleural effusion, raised odds by 3.9 times (95% CI 1.884–204.3, $p = 0.013$) (Table 6).

Pericardial mediastinal invasion increased the risk for hospital admission (OR = 1.992), but the *p* value remained insignificant (0.332) for that factor.

As noted, from the above univariate and multivariate regression analyses, the only procedure-related risk factor in common between pneumothorax and chest tube insertion was pleural needle angle more than 70°. Additionally, Gelfoam embolization seemed protective against all complications where it succeeded to show its statistical significance on both univariate and multivariate regression levels.

Finally, it is to be noted that none of all the biopsied cases in both groups, as cases or controls, required further surgical intervention and no mortalities were recorded.

Discussion

With an estimated 2.1 million cases and 1.8 million deaths per year, lung cancer remains one of the leading causes of cancer mortality worldwide due to inadequate tobacco control polices. The geographic patterns of lung cancer mortality copy those of incidence due to the relatively poor prognosis of the disease after diagnosis [5]. Nearly a third of cancer patients are dying with evidence of pulmonary metastases; those patients satisfying the criteria for surgical resection represent a much smaller subgroup. Pulmonary metastases in adults are usually from breast, GI tract, kidney, testes, head, and neck tumors or from a variety of bone and soft tissue sarcomas [6].

The need for immunohistochemistry and genetic studies is crucial to help personalize treatment strategies for advanced lung cancer patients. The new classification for small biopsies and cytology as proposed by the 2011 IASLC/ATS/ ERS Classification was a different approach in classification of lung cancers compared to the prior classification of resected lung cancers [7].

The most commonly recorded complication post-biopsy was pneumothorax, needing chest tube insertion [8]. In spite of being relatively safe procedure with low rates of morbidity and mortality, great interest has been propagating since 1970s in reducing post-procedural complications and thus hospital expenditure and stay [4].

A meta-analysis published by Huo et al. [8] pooling results from 21 articles on 8133 patients showed pneumothorax to be the most frequent complication of CT-guided lung biopsy cases. The pooled rates of pneumothorax were between 12 and 45%, and the chest tube placement was 5.6% according to some studies and as high as 17% in others.

Our study is a prospective randomized control study where 138 patients underwent CT-guided percutaneous thoracic tru-cut biopsies. Seventy cases underwent biopsy track embolization by Gelfoam slurry, and 68 cases were non-embolized.

Gelfoam is a porcine gelatin material prepared either in a Gelfoam injectable slurry [9], or prepared from gelatin powder into a thick injectable paste [1]. Being a viscous material more than air, it absorbs fluid from the surrounding tissue to seal the biopsy tract [1].

Similar materials for lung sealants (autologous blood patch, saline, gelatin, hydrogel plugs, or fibrin glue) have been proposed, but none of them gained popular use nor have been added to the international guidelines [8].

The best comparable studies regarding the utilization of Gelfoam material in track embolization after biopsy and statistical models of analysis were done by Tran et al. [4], Baadh et al. [1], and Renier et al. [9]. Although retrospective, they all were case–control studies where non-embolized control cases were compared to Gelfoam-embolized lung biopsy cases. Tran et al. [4] and Renier et al. [9] used Gelfoam in slurry form, while Baadh et al. [1] used gelatin powder. The rates of pneumothorax and chest tube insertion were then recorded and correlated with the pre-procedural and procedure-related risk factors in univariate and multivariate analytical models.

Our study was able to fulfill the homogenous risk factor representation with no statistical significance regarding most of the risk factors studied. However, more cases with central lung lesions were allocated to the embolized group in contrary to control cases with significant *p* value of 0.007. The patients in the embolized group were significantly older than those in the control group. In addition, more patients with pericardial invasion were noted in the control cases than in the embolized cases.

In our study, a total of 50 out of 138 patients (i.e., 36%) developed at least one complication during or after the biopsy. A total of 90 complications were recorded. The majority (45%) were pneumothoraces, 20% required chest tube, 12.2% had hemothorax, and only a total of 17.8% required hospital admission. These findings were in total keeping with the Society of Interventional Radiology (SIR) quality improvement guidelines; the suggested threshold rates for image-guided percutaneous needle biopsy in adults are 45% for all pneumothorax, 20% for all thoracostomy tube placement for pneumothorax [10].

In general, our study showed same proportions of patients suffered pneumothorax complications in both embolized and control cases, where 30% had pneumothoraces of the embolized group compared to 35% of the controls, yet this reduction was insignificant $p = 0.507$.

Tran et al. [4] showed in their study till no significant reduction in pneumothorax rates; however, most of them were small pneumothoraces in both cases and controls requiring no intervention $p = 0.06$.

On the contrary, Renier et al. [9] study successfully showed a reduction in the rates of pneumothorax occurrence with only 10% of the embolized group compared to 25.8% in control with a significant p value of 0.0001.

This statistical difference noted in the pneumothorax occurrence by Renier et al. [9] was owing to their exclusion criteria. In their study, they excluded all patients with pneumothorax occurring during the biopsy process and accounted only for post-procedural pneumothoraces. In our study and Tran et al. [4], we did not exclude these patients. It was worthy to mention that we found that some of the pneumothoraces occurring during the biopsy either did not progress to need chest tube insertion or even regressed on 4-h follow-up scans.

Our study was yet able to show a significant reduction in rates of chest tube insertion for pneumothorax occurrence 7.1% (i.e., 5 cases) of the embolized group compared to 19.7% (13 cases) of the controls ($p=0.037$).

This finding correlated well with both Tran et al. [4] and Renier et al. [9].

Tran et al. [4] 10.7% of the non-embolized cases required a chest tube, whereas only 6.9% of the patients embolized needed a chest tube ($p=0.01$). Renier et al. [9] showed also a reduction from 12.2% of the controls down to 3.5% in the embolized cases ($p=0.0005$). Baadh et al. [1] showed statistically significant reduction ($p=0.007$) in the total rate of procedure-related pneumothorax in track embolization patients (8.8%) when compared to controls (21%). There was a substantial reduction in the incidence of post-procedure chest tube placement in track embolization patients (4%) compared to controls (8.1%); however, conversely to our study they it did not reach statistical significance ($p=0.195$) in their study.

In attempt to compare our results with the available literature, we correlated with a study dehydrated hydrogel done by Grage et al. [11] using prospective randomized control design. They applied it via Bio-seal biopsy seal lung plug deploying system®. Dehydrated hydrogel was close to Gelfoam being a solid material absorbing fluid from the lung interstitium after deployment and thus occluding the pleural puncture by a viscous plug.

Grage et al. [11] showed similar results regarding pneumothorax rates, with pneumothoraces occurring the rates of 29% compared to 31% in the controls. Their study showed a reduction in chest tube insertions from 10 to 2% only with $p=0.032$.

Additionally, our study noted a significant reduction in post-procedural hospital admission. 19% of the controls were admitted compared to 4.3% of the embolized group with $p=0.007$. These results correlated well with those of Grage et al. [11] study, where they showed reduction in the mean hospital stay from 0.44 nights to 0.07 nights.

An older study on Bio-seal biopsy seal lung plug deploying system® *by* Zaetta et al. [12] showed that hospitalization post-biopsy track embolization was reduced to 9.4% vs. 13.6% in the control group. Compared to this study our results remain still more significant regarding this aspect.

In our study, we did not witness any features of distant embolization or air embolization from Gelfoam slurry. Gelfoam remains more viscous than air and mixing with CT contrast agent would have enabled us to visualize such a potential hazard.

Baadh et al. [1] agreed that no features of distant (including neurological or peripheral vascular deficits), relative to the hemostat gelatin paste embolization during patient follow-up and clinical assessment.

In our study, a minority cases (8 patients) showed endobronchial leak in relation to cavitary lesions; however, this caused only self-limiting cough and required no management. Owing to the use of small amount of contrast in the slurry mixture, only 2 patients were recognized with minor contrast allergy.

Tran et al. [4] and Renier et al. [9] did not show these complications in their studies because they did not add contrast to the mixture. In spite of that, we still think contrast addition is beneficial in terms of visualization of the slurry throughout the follow-up period.

Univariate analysis was performed for pneumothorax occurrence, chest tube placement, and hospital admission. Multivariable models were developed for variables that were statistically significant at the univariate level or that differed significantly between study groups.

Univariate analysis showed that needle angle more than 70° increased the odds of pneumothoraces and the need for chest tube placement significantly by 2.859 and 3.106, respectively.

Lesion position has been accused of increasing odds of complications. We detected a significant correlation between hospital admission and central lesions and those invading the pericardium where they increased the odds of admission by 4.194 ($p=0.031$) and 4.545 ($p=0.006$) times, respectively. A number of cases with significant emphysematous lung changes had a minimal rim of pneumothorax prior to biopsy as in Fig. 1. These cases were associated with an increased risk of hospital admission by 8.571 times ($p=0.039$). We were faced with some instances where the patients failed to follow respiratory instructions due to large tumor sizes, orthopnea, effusion, or even some cases of parkinsonism-induced truncal tremors. They accordingly required needle manipulation and repositioning. We found that this increased the odds of hospitalization by 3.467 times ($p=0.031$).

The patient group seemed as the common protective factor throughout the univariate analysis of chest tube

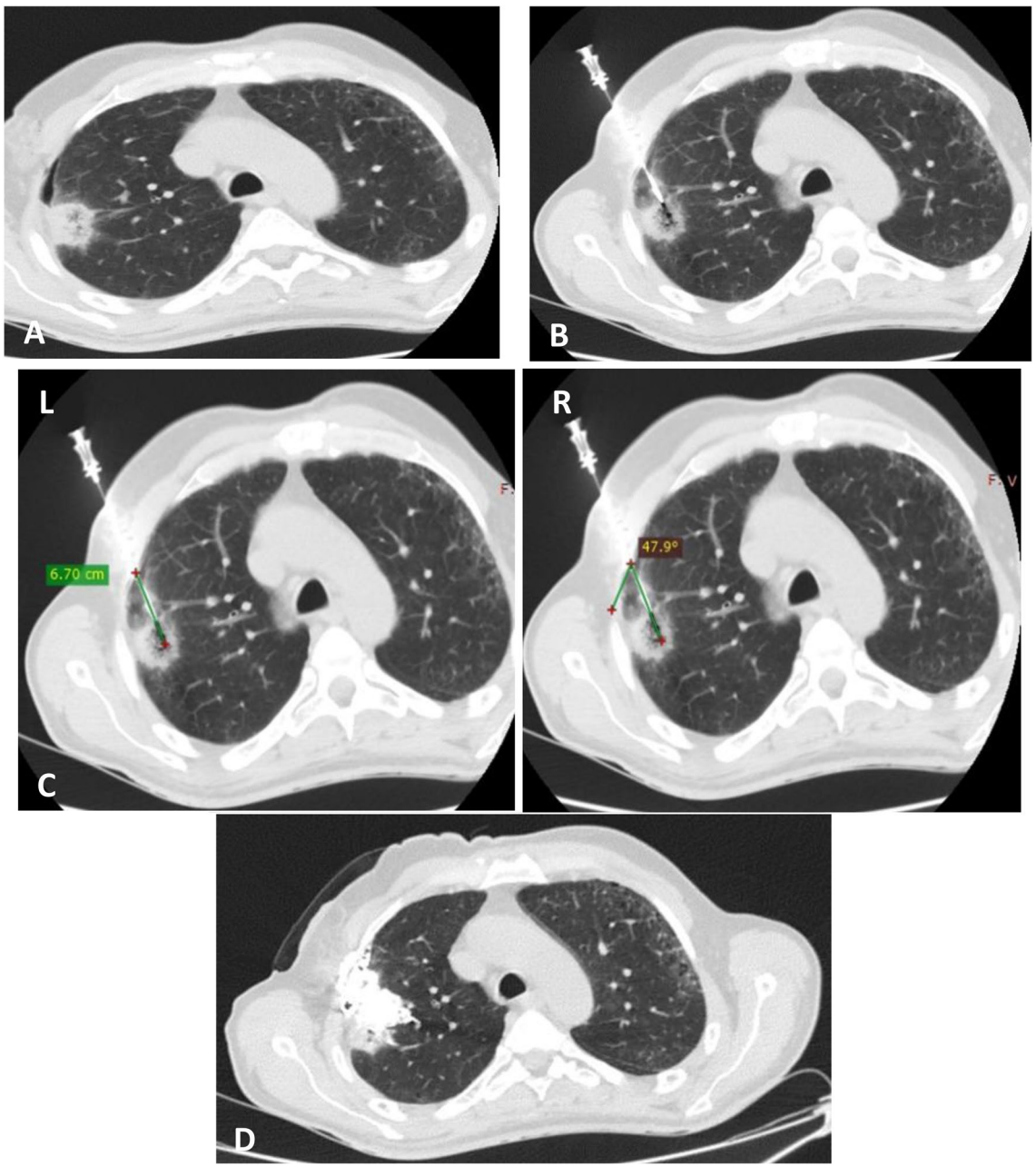

Fig. 1 **A** Right upper lobe ground glass nodule with pre-procedural rim of pneumothorax prior to intervention, the lesion was invading the adjacent pleural surface. **B** Single coaxial pleural pass 4.5 cm till the edge of the lesion. **C** Left: 18-G tru-cut needle was inserted with 2-cm throw. Right: needle pleural angle was 48. **D** Gelfoam injection sealed the coaxial pathway and the pre-procedural pneumothorax

placement and hospital admission. It reduced chest tube placement by 68% ($p=0.044$) and hospitalization by 81% ($p=0.012$).

Multivariate regression models were carried out on chest tube insertion and hospital admission. Needle angle still significantly increased chest tube insertion rate by 3.526 times ($p=0.025$). While in lesion location being more central or invading the pericardium increased hospitalization by 6.812 and 1.992, respectively.

Lesions close to the rib and peripheral position were significantly protective against chest tube insertion by 83% with a p value of 0.015.

Other risk factors were clinically significant, but as a result of their sparse incidence in the examined patient

samples we could not statistically signify for their importance. For example, patients with cavitary lung lesions were more prone to hospitalization by 2.897 ($p=0.144$). Multiple pleural punctures increased the risk of pneumothorax and chest tube insertions with an OR of 2.656 and 2.352; however, p values remained insignificant. Further future larger patient samples may help magnify the impact of such factor and assess their relevance (Fig. 2).

On the other hand, similar analysis by Tran et al. [4] showed increased odds of the same adverse events with track length more than 24 mm increased chest tube

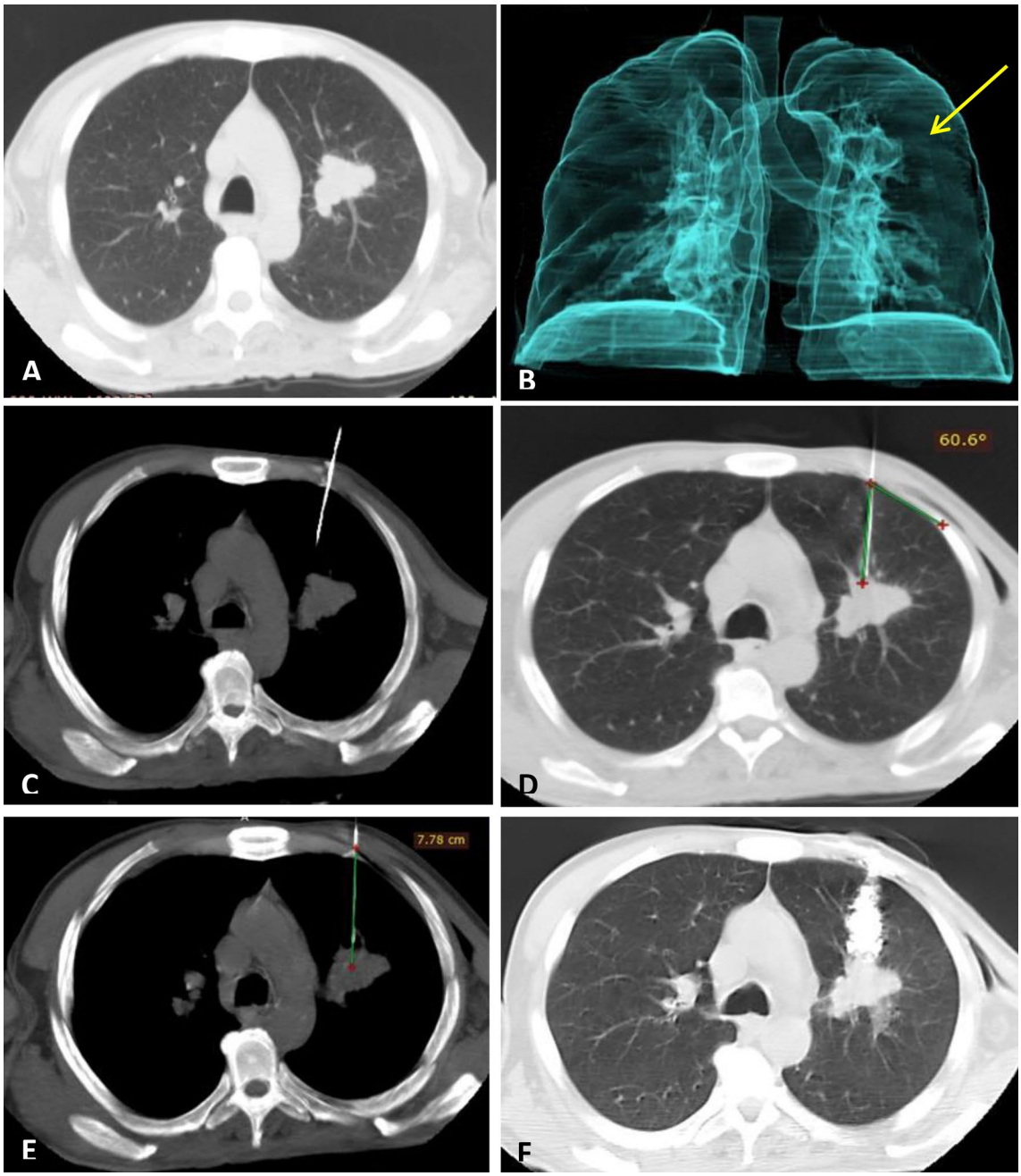

Fig. 2 **A** Axial CT images showing left upper lobe mass. **B** 3D VR of airways showing encased apicoposterior bronchus (arrow). **C** Coaxial pass out of trajectory. **D** Coaxial pass in trajectory, needle pleural angle 65o. Note developing surgical emphysema. **E** Coaxial pass in trajectory, biopsy track length 7.7 cm. **F** Gelfoam embolization of biopsy track with no complications

insertion chances by 262% ($p = 0.003$). Deep lesions biopsies are often more challenging due to anatomic obstacles and may require multiple adjustments of the needle during advancement or necessitate additional pleural passes [4].

According to logistic regression analysis by Renier et al. [9], they agreed that Gelfoam embolization was a protective parameter against pneumothorax and chest tube insertion in both univariate and multivariate models. In univariate analysis, it reduced the rate of pneumothorax by 68% in their study and chest tube by 74%. In multivariate model, it decreased the rate of pneumothorax by 69% and chest tube by 75% [9].

Although our study did not assess for added cost calculation, Gelfoam is still relatively a minimal added cost and relatively safe maneuver compared to the added cost of chest tube placement and overnight hospital stay. It can be used to finish up a properly planned lung biopsy considering all features of patient positioning to avoid anatomical obstacles. Additionally, we believe it remains more reliable and needs minimal training regarding preparation and deployment after completion of the biopsy. With proper preparation of the material, the odds of pneumothorax requiring chest tube insertion and hospital admission have been shown clinically and statistically to reduce. It was even noted in some patients developing pneumothorax during the biopsy, to regress over the follow-up period; however, we had no attempts of quantification of pneumothorax as its assessment remains still more subjective.

In Baadh et al. [1] study, they showed a marked reduction in cost owing to reduced rates of chest tube placement, resulting in higher costs per patient due to subsequent imaging, procedures, and hospitalization. The average cost per patient utilizing the track embolization technique was $262.40 compared to $352.07 for the non-track embolization group, which was statistically significant ($p = 0.044$).

Compared to Gelfoam utilizing studies, our study is a prospective randomized control study, assessing the frequency of the same range of complications including pneumothorax, chest tube insertion, hospitalization, and Gelfoam-related hazards. The mode of preparation of Gelfoam slurry was different from Tran et al. [4] and Renier et al. [9]. By adding 4 cc of CT contrast, we improved its visualization in the lung parenchyma over the follow-up period and improved the visualization of any leakage and potential embolization. We injected the slurry throughout the tract not only at the pleural puncture site aiming to seal the pleural puncture site and subcutaneous tissues to avoid external air from being sucked to the potential pleural space.

Our study still showed some drawbacks. In spite of randomization, still some risk factors were more represented in the controls than in the cases group; like the lesion position being more central in the embolized groups, this did not impact the rates of complications reduction. We also did not attempt quantification of time spent during the biopsy to see if Gelfoam was more time-consuming in preparation and injection. In further research, we wish to quantify further details about hospital expenditures in relation to complications and other commercially available sealants in our market, to see how far can Gelfoam stand the comparison and prove helpful financially and clinically.

It is worth noting that our sample size fulfilled our primary research question and gave satisfying results regarding a reduction in post-biopsy adverse events. However, we are still interested in evaluating the risk factors by attempting logistic regression models with a larger sample size.

Conclusions

Although initial analysis showed that there was no statistical significant reduction in pneumothorax rates, embolized cases required significantly less chest tube insertion, reducing their hospital admissions and patient compromise. Logistic regression analysis showed that Gelfoam had a protective effect against chest tube insertion and hospital admission.

Additionally, side findings of logistic regression analysis noted that more perpendicular needle pleural angles were associated with increased risk of pneumothorax and chest tube insertion. The patients with mediastinal invasion, central lesions, difficult positioning, and perilesional pre-procedural minimal pneumothoraces were all culprit factors for significant increased odds of hospitalization in both univariate and multivariate levels of analysis.

Finally, we recommend Gelfoam for routine utilization with highly beneficial features in central lung lesions and in patients with emphysematous lung disease through a 17-G coaxial needle system with 18-G tru-cut needle for tissue sampling.

Abbreviations

PACS: Picture Archiving and Communicating System; Pre-procedural rim PTX: Pre-procedural rim pneumothorax; IASLC/ATS/ ERS: International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification.

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Author contributions

NS, RT, and IM selected the patients and reviewed their images and did the interventional procedure. AA as the head of the thoracic surgical team

provided us with cases and supervised management of their complications. NS and DM collected, tabulated, and analyzed the data. NS and HE interpreted the patient data and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
National Cancer Institute, Cairo University Institutional Review Board approval was taken before conducting this prospective study; March 2018—IRB number: IRB00004025. Approval number: 201617084.3. Written consent was obtained from patients or their authorized representatives.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old when consent for publication was requested, written informed consent for the publication of these data was given by their parent or legal guardian.

Competing interests
The authors declare that they have no competing interests.

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