Original Article

Recurrence and disease-free survival outcomes after computed tomography-guided needle biopsy in stage IA non-small cell lung cancer patients in China: a propensity score matching analysis

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Background: Whether preoperative biopsy before radical resection can lead to recurrence and impact patient survival in non-small cell lung cancer (NSCLC) remains controversial. In this study, we carried out a retrospective analysis to determine whether preoperative biopsy can cause disease recurrence and influence disease-free survival (DFS) in patients with stage IA NSCLC.

Methods: Patients diagnosed with stage IA NSCLC (solid nodule) between January 2010 and December 2014 were identified from the databases of 7 Chinese medical centers and divided into two groups: a preoperative computed tomography (CT)-guided needle biopsy (CTNB) plus radical resection group, and a non-CTNB group. The propensity score matching (PSM) method was adopted to balance the observed covariates, and Kaplan-Meier estimates were used for survival analysis. Cox regression was used in a single-factor analysis to identify the factors affecting DFS in stage IA NSCLC.

Results: After initial screening, 730 patients were enrolled in this study, with 186 and 544 patients in the CTNB group and the non-CTNB group, respectively. After PSM, 186 patients were eventually included in each group. No significant differences in basic clinical features were identified between the two groups (P>0.05). The rates of recurrence were 17.2% and 14.0% in the CTNB and non-CTNB groups (χ^2=0.735, P=0.391), respectively. No notable differences in DFS (χ^2=1.895, P=0.173) or overall survival (OS, χ^2=1.785, P=0.182) were observed. Lung adenocarcinoma [hazard ratio (HR), 0.167, P=0.001] and lesion size (>2 cm) (HR, 2.712, P=0.000) were identified as risk factors for DFS in stage IA NSCLC.

Conclusions: CTNB does not increase the incidence of recurrence in stage IA NSCLC or affect patient survival; therefore, it is not a risk factor for DFS. Lung adenocarcinoma and lesion size are risk factors for DFS.

Keywords: Computed tomography-guided needle biopsy (CTNB); stage IA non-small cell lung cancer (stage IA NSCLC); disease-free survival (DFS)

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Introduction

Low-dose spiral computed tomography (CT) screening for the high-risk lung cancer population can reduce lung cancer mortality by 20% (1). Through the application of low-dose spiral CT, more solid pulmonary nodules can be discovered. In China, surgery is the preferred treatment for lung nodules in patients highly suspected with lung cancer (2). In a study of direct surgical resection of 8–20-mm pulmonary nodules, 35% of nodules were found to be benign postoperatively (3); thus, patients with benign pulmonary nodules may benefit from preoperative biopsy. CT-guided percutaneous biopsy is one of the easiest and fastest methods for the preoperative diagnosis of nodular lung cancer; it has high diagnostic accuracy (4), can provide a decision-making basis for appropriate clinical procedures, and can also relieve the psychological pressure on patients. However, biopsy has also been reported to lead to disease recurrence and may affect patients' long-term survival (5,6). In cases of cancerous lung nodules, whether the percutaneous biopsy process increases the likelihood of recurrence and affects long-term survival remains controversial.

To address this uncertainty, we designed a retrospective cohort study which enrolled patients from multiple centers in China to evaluate whether preoperative biopsy increases the recurrence rate of early-stage non-small cell lung cancer (NSCLC) and affects patient survival. Additionally, we preliminarily investigated the factors influencing recurrence in patients with stage IA NSCLC (solid nodule).

Methods

Study population

We collected the clinical information of patients who underwent radical resection and were postoperatively diagnosed with stage IA NSCLC between January 2010 and December 2014 from the databases of 7 medical centers. All data were processed according to the 8th edition of the Union for International Cancer Control's tumor, node, metastasis (TNM) staging system (7). The following patient information was obtained: sex, age, smoking history, lesion size (≤2 *vs.* 2–3 cm), preoperative biopsy (yes *vs.* no), lesion location (left lung *vs.* right lung), pathological subtype (adenocarcinoma *vs.* squamous cell lung cancer and other types of NSCLC), and postoperative adjuvant chemotherapy within 6 months (platinum-based chemotherapy regimens). The CT-guided needle biopsy (CTNB) group mainly included patients with atypical imaging features or patients who refused direct surgical resection.

The exclusion criteria were as follows: (I) a postoperative diagnosis of small cell lung cancer; (II) concurrent cancer; (III) a ground-glass nodule; (IV) non-tumor–related death; (V) a surgical approach using wedge resection; (VI) radiofrequency ablation or radiotherapy; (VII) loss to follow-up; and (VIII) an unclear time or location of recurrence. Finally, 730 patients were included in the study (*Figure 1*).

Evaluation of recurrence and survival

The patients' CT scan information was reviewed; postoperatively, scans had been conducted at intervals of 6–12 months for a 5-year period. Metastatic lesions were diagnosed based on the occurrence of new lesions, as well as an increased size and number of lesions during the CT follow-up. The first instance of disease recurrence was defined as the endpoint of disease-free survival (DFS). If CT follow-up data could not be obtained, the time at which metastasis was first discovered (based on the patient's complaint) was considered to be the endpoint of DFS.

Observation indicators

The incidence of recurrence, DFS, and overall survival (OS) were observed among the patients. DFS was defined as the time from surgery to the first confirmed recurrence event or death due to disease progression. OS was defined as the time from surgery to the last follow-up or tumor-related death. The survival time was measured from the date of surgery to October 30, 2018 (the deadline for the final visit).

Statistical analysis

All data were described as the means ± standard deviation for continuous variables and as numbers (percentages)

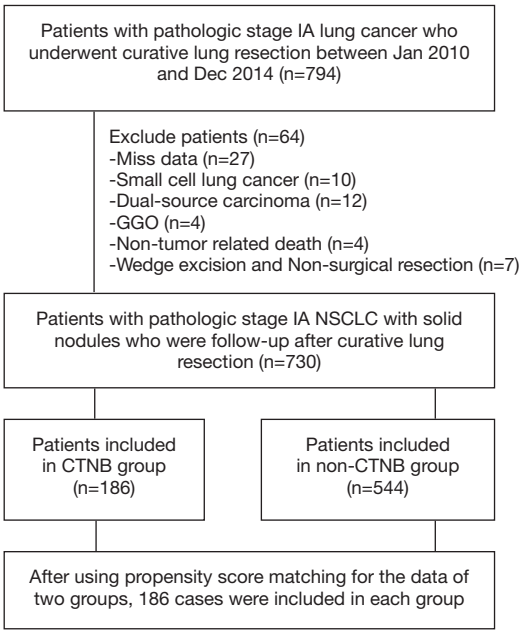

Figure 1 Flowchart showing the patient selection criteria. GGO, ground-glass opacity; NSCLC, non-small cell lung cancer; CTNB, computed tomography-guided needle biopsy.

for categorical variables. Data were compared using the *t*-test for continuous variables, and Pearson's χ^2 test or Fisher's exact test for categorical variables. To ensure balance between the groups, propensity score matching (PSM) was carried out to match the patients in both groups (caliper value of 0.05). The matched variables included sex, age, smoking history, lesion size (≤2 *vs.* 2–3 cm), lesion location (left lung *vs.* right lung), and pathological type (adenocarcinoma *vs.* non-adenocarcinoma). The Kaplan-Meier method with the log-rank test was used to estimate the difference in time-to-event outcomes between the CTNB and non-CTNB groups using two-sided P values. Cox regression was used in a single-factor analysis to identify the factors affecting DFS in stage IA NSCLC patients. In all analyses, a two-sided P value <0.05 was considered to be an indication of a statistically significant difference. Statistical analyses were performed using SPSS version 25.0 software (SPSS, Chicago, Ill, USA).

Results

Clinical and pathological characteristics

Of the 730 patients initially screened, 186 (25.5%) underwent CTNB as a diagnostic procedure before radical resection and 544 (74.5%) underwent radical resection without biopsy. After radical surgery, all patients were diagnosed with stage IA NSCLC. The baseline characteristics of the patients are summarized in *Table 1*. The study population comprised 392 males, with an average age of 59.51±8.85 years, and 338 females, with an average age of 58.23±8.79 years. The mean lesion size was approximately 2.05±0.65 cm (0.4–3 cm). Right lung lesions and left lung lesions accounted for 59.2% (432/730) and 40.8% (298/730) of all tumors, respectively. After radical resection of the lung tumors, pathological diagnosis was performed; 80.7% (589/730) of the patients were diagnosed with adenocarcinoma, 18.4% (134/730) were diagnosed with squamous cell carcinoma, and 0.01% (7/730) were diagnosed with other types of NSCLC, including 68 cases of pT1aN0M0 (≤1 cm), 349 cases of pT1bN0M0 (1–2 cm), and 313 cases of pT1cN0M0 (2–3 cm). In the CTNB group, the biopsy pathology of 1 patient was a false-negative result, and the biopsy pathological types in 4 patients were inconsistent with the postoperative outcomes. The coincidence rate of pathological diagnosis between the 2 diagnostic methods was 97.3% (181/186). Metastatic sites primarily included the lung, bone, and craniocerebral regions (*Table 2*).

PSM

Before PSM, significant differences in the proportion of patients aged >60 years and the number of smokers were identified between the CTNB and non-CTNB groups (P<0.05). Also, a significant difference in the proportion of patients with a lesion size ≤2 cm was found between the groups (P<0.05). A total of 372 patients were selected using PSM, and the differences in the baseline data between the two groups after PSM were not statistically significant (P>0.05, *Table 1*).

Recurrence rates and mortality

Before PSM, the rate of recurrence in the CTNB and non-CTNB groups was 18.8% (35/186) and 8.6% (47/544), respectively. Therefore, the incidence of recurrence in the CTNB group was significantly higher than that in the non-CTNB group (χ^2=11.014, P=0.000). After PSM, the rate of recurrence in the CTNB and non-CTNB groups was 17.2% and 14.0% (χ^2=0.735, P=0.391), respectively (*Table 2*).

Before PSM, the mortality rate in the CTNB and non-CTNB groups was 11.8% (22/186) and 4.2% (23/544), respectively. Therefore, the mortality rate in the CTNB

Table 1 Clinical characteristics of the patients

Clinical factors	Overall cohort (n=730)			Propensity score-matched cohort (n=372)		
	CTNB (n=186)	Non-CTNB (n=544)	P	CTNB (n=186)	Non-CTNB (n=186)	P
Sex			0.483			0.834
Male	104	288		104	106	
Female	82	256		82	80	
Age (years)			0.004			0.600
≤60	109	252		109	104	
>60	77	292		77	82	
Smoker			0.008			0.834
Yes	79	173		79	77	
No	107	371		107	109	
Size (cm)			0.014			0.917
≤2 cm	92	325		92	93	
2–3 cm	94	219		94	93	
Location (lung)			0.853			0.753
Left	77	221		77	80	
Right	109	323		109	106	
Pathology[#]			0.289			0.042
Ad	155	434		155	139	
Non-Ad	31	110		31	47	
Chemotherapy[#]			<0.001			<0.001
Yes	80	82		80	34	
No	106	462		106	152	

[#], it is not a variable of propensity score matching. Ad, adenocarcinoma; non-Ad, non-adenocarcinoma; CTNB, computed tomography-guided needle biopsy.

group was significantly higher than that in the non-CTNB group (χ^2=13.841, P=0.000). After PSM, the mortality rate in the CTNB and non-CTNB groups was 11.8% (22/186) and 8.6% (16/186), respectively (χ^2=1.055, P=0.305).

Survival analysis

The DFS (χ^2=13.131, P=0.000) and OS (OS, χ^2=15.657, P=0.000) in the CTNB group before PSM were both markedly shorter than those in the non-CTNB group. After PSM, the median survival time was 62 months (interquartile range, 45, 66.7). The OS rates at 1, 3, and 5 years were 99.7%, 95.4%, and 89.8%, respectively. There was no significant difference in DFS (χ^2=1.895, P=0.173) or OS (OS, χ^2=1.785, P=0.182) between the CTNB and non-CTNB groups after matching (*Figures 2,3*).

Univariate and multivariate analyses of recurrence

Before PSM, the univariate analysis of time to recurrence revealed significant differences in pathological type (P=0.034), tumor size (P=0.000), and preoperative biopsy (P=0.000) between the groups (*Table 3*). Statistical analysis showed that when all factors were included in the multivariate analysis, preoperative biopsy [hazard ratio (HR), 1.854, P=0.007], lung adenocarcinoma (HR, 0.340, P=0.003), and tumor size (HR, 2.425, P=0.000) were risk factors for DFS.

After PSM, the univariate analysis of DFS showed statistically significant differences in tumor size (P=0.002) and pathological type (P=0.003) between the groups. The multivariate analysis of DFS after PSM showed that lung adenocarcinoma (HR, 0.167, P=0.001) and tumor size (HR, 2.712, P=0.000) were risk factors for DFS (*Table 3*).

Table 2 Recurrence in patients with resected stage IA NSCLC

Variables	Overall cohort (n=730)			Propensity score-matched cohort (n=372)		
	CTNB (n=186)	Non-CTNB (n=544)	P	CTNB (n=186)	Non-CTNB (n=186)	P
Recurrence, n (%)	35 (18.8)	47 (8.6)	0.000	32 (17.2)	26 (14.0)	0.391
Brain	6 (3.2)	3 (0.6)		6 (3.2)	2 (1.1)	
Lung	14 (7.5)	10 (1.8)		11 (5.9)	6 (3.2)	
Bone	3 (1.6)	10 (1.8)		3 (1.6)	5 (2.7)	
Lymph node	2 (1.1)	10 (1.8)		2 (1.1)	6 (3.2)	
Pleural	1 (0.5)	2 (0.4)		1 (0.5)	0 (0.0)	
Adrenal gland	1 (0.5)	0 (0.0)		1 (0.5)	0 (0.0)	
Eyeball	1 (0.5)	0 (0.0)		1 (0.5)	0 (0.0)	
Liver	0 (0.0)	1 (0.2)		0 (0.0)	1 (0.5)	
Combined recurrence[#]	7 (3.8)	11 (2.0)		7 (3.8)	6 (3.2)	

[#], multisystem transfer. NSCLC, non-small cell lung cancer; CTNB, computed tomography-guided needle biopsy.

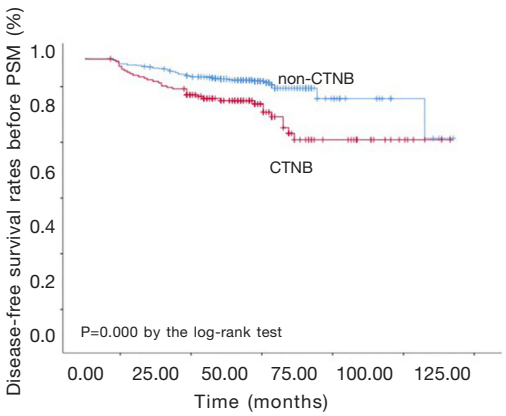

Figure 2 Comparison of disease-free survival (DFS) between the computed tomography-guided needle biopsy (CTNB) and non-CTNB groups. Kaplan-Meier analysis of the time to total recurrence between the CTNB and non-CTNB groups.

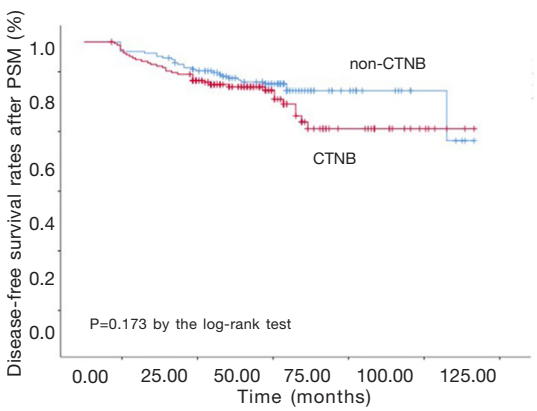

Figure 3 Comparison of disease-free survival (DFS) between the computed tomography-guided needle biopsy (CTNB) and non-CTNB groups. Kaplan-Meier analysis of the time to total recurrence after propensity score matching between the CTNB and non-CTNB groups.

Discussion

Compared with transbronchial lung biopsy, percutaneous biopsy has higher accuracy for diagnosing lung nodules (8). The diagnostic accuracy of biopsy for sub-centimeter lung nodules can reach 88–95% (9). Our study showed that the diagnostic accuracy of pathological biopsy for benign and malignant nodules reached 99.5% (185/186). Moreover, comparing the results of our team's previous study (4) with those of the study by Tanner *et al.* (3), no significant differences in the two methods (biopsy *vs.* surgery) exist in the observation rates for benign and malignant pulmonary nodules (χ^2=0.568, P=0.451). Hemorrhage and pneumothorax are the common complications of solid nodule percutaneous biopsy (10). With the development of percutaneous biopsy instruments and advances in surgical techniques, the incidence of both common and rare surgical complications can be effectively controlled.

Puncture biopsy needle track implantation is a clinical issue that cannot be ignored. Studies have reported the rate

Table 3 Univariate and multivariable analysis of predictors of DFS

Clinical factors	Univariate analysis of DFS before PSM			Multivariable analysis of DFS before PSM			Univariate analysis of DFS after PSM			Multivariable analysis of DFS after PSM		
	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI
Sex												
Female* *vs.* male	0.358	1.230	0.791–1.915	0.545	1.202	0.663–2.180	0.633	0.885	0.536–1.462	0.518	1.254	0.631–2.492
Age (years)												
≤60* *vs.* >60	0.416	0.835	0.541–1.289	0.260	0.774	0.496–1.208	0.625	0.881	0.531–1.463	0.268	0.745	0.433–1.253
Smoker												
No* *vs.* yes	0.060	1.522	0.982–2.358	0.112	1.605	0.898–2.874	0.867	0.958	0.577–1.588	0.731	1.127	0.570–2.230
Size (cm)												
≤2* *vs.* 2–3	0.000	2.327	1.483–3.649	0.000	2.425	1.538–3.825	0.002	2.322	1.353–3.986	0.000	2.712	1.573–4.675
Location (lung)												
Left* *vs.* right	0.328	0.804	0.520–1.244	0.335	0.803	0.515–1.253	0.135	0.683	0.415–1.126	0.112	0.661	0.397–1.101
Pathology												
Ad* *vs.* non-Ad	0.034	0.486	0.250–0.948	0.003	0.340	0.169–0.685	0.003	0.218	0.079–0.603	0.001	0.167	0.058–0.474
Biopsy												
No* *vs.* yes	0.000	2.208	1.422–3.430	0.007	1.854	1.188–2.894	0.176	1.417	0.855–2.346	0.354	1.271	0.765–2.109

*, baseline reference. HR, hazard ratio; DFS, disease-free survival; PSM, propensity score matching; Ad, adenocarcinoma; non-Ad, non-adenocarcinoma.

of needle track implantation with osteosarcoma biopsy to be as high as 20% (11,12). Some reports have also described needle track implantation with lung cancer biopsy, and this difference in the incidence of needle metastasis may be attributable to different tumor types. Needle-track metastasis may be caused by the presence of tumor cells in the needle track after biopsy or biopsy resulting in increased messenger RNA levels of tumor biomarkers. However, tumor cells are eliminated by the autoimmune system. Clinically significant lesions due to needle track implantation are present in a small number of cases, and the incidence of clinical needle track implantation is approximately 0.016–0.018% (13-18). In this study, no needle-track metastasis was found in the CTNB group. After PSM, the rate of pulmonary recurrence and metastasis in the CTNB group was similar to that in the non-CTNB group, although the rate in the CTNB group was slightly higher. However, we did not document the specific sites of pulmonary metastases, and the lack of in-depth analysis was a shortcoming of this study.

With the continuous improvement of treatment methods, especially targeted and immunotherapeutic applications, patients with recurrence can achieve better OS. Therefore, we primarily used DFS as the study endpoint. The CTNB group in this study had significantly increased recurrence rates before PSM, and the DFS was also significantly shortened. To standardize the baseline data of the two groups, the PSM method was used. After PSM, no significant differences were noted between the recurrence rates of the two groups, or in DFS or OS. Therefore, we believe that preoperative biopsy does not promote recurrence or affect the DFS or OS of patients, which reinforces the results of previous retrospective research (19-22). However, other retrospective studies have reported that percutaneous biopsy may promote recurrence and metastasis of early-stage lung cancer and is extremely likely to affect the long-term survival of patients (5,23). At the same time, our study showed that adjuvant chemotherapy in the biopsy group did not have a DFS benefit for patients (χ^2=0.001, P=0.970) and that adjuvant chemotherapy is not recommendable for patients after percutaneous biopsy. However, further prospective studies are needed to confirm these findings.

Recurrence following radical resection of early-stage

NSCLC remains poorly understood and is multifactorial in nature. Multivariate analysis before PSM demonstrated that preoperative biopsy, lung adenocarcinoma, and tumor size were factors affecting the DFS of patients. The influencing factors of DFS in stage IA NSCLC were also analyzed after PSM. After matching the two datasets, we found that tumor size and lung adenocarcinoma were the influencing factors of DFS. Significant differences in DFS were observed between patients with tumor sizes ≤2 cm and those with tumor sizes of 2–3 cm (log-rank/χ^2=9.960, P=0.002), which is consistent with the results of Zhang *et al.* (24). In the current multivariate analysis, tumor size (>2 cm) was again confirmed to be an important predictor of recurrence following resection of stage IA NSCLC. Studies have shown that non-squamous cell carcinoma is a risk factor for the prognosis of NSCLC (25). The present study categorized the pathological types into adenocarcinoma and non-adenocarcinoma, with the latter comprising squamous cell carcinoma and NSCLC with other pathological types. Lung adenocarcinoma type was also found to be a risk factor for the prognosis of NSCLC, with the DFS of patients with adenocarcinoma being statistically significantly shorter than that of non-adenocarcinoma patients (log-rank/χ^2=10.428, P=0.001).

Limitations

This study has some limitations that should be noted. Firstly, this study did not provide accurate and complete data for analyses of whether or not the lesions were subpleural nodules, the degree of pathological differentiation, the extent of infiltration, or the specific specifications of the percutaneous biopsy needles, which is the primary drawback of this study. Secondly, the design of retrospective studies has inherent flaws, which make further validation by prospective studies necessary. Thirdly, in the CTNB and non-CTNB groups, bias existed in the patient selection; although, we did attempt to reduce this bias through PSM analysis. Fourthly, this study utilized the overall recurrence rate, and metastatic sites were not included in the analyses. Finally, although we used DFS as the primary endpoint, the small number of DFS outcomes reduces the reliability of the multivariate analysis results.

However, this research also provides valuable information. In our Chinese study population, we found that the use of preoperative biopsy in patients with stage IA NSCLC undergoing radical resection of lung cancer did not increase the incidence of recurrence and did not affect patient survival. Moreover, this study is the first multicenter retrospective cohort study on preoperative biopsy for early lung cancer in China and provides guidance for future clinical practice.

Conclusions

CTNB performed in patients with stage IA NSCLC (solid nodules) does not increase the incidence of recurrence or affect patient survival, and is not a risk factor for DFS. Therefore, this procedure can be safely used to diagnose stage IA NSCLC. Lung adenocarcinoma and lesion size are risk factors for the DFS of patients with stage IA NSCLC (solid nodules). However, prospective randomized trials are needed in the future to confirm our findings.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-931). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of the First Affiliated Hospital of the Army Medical University (IRB No. KY201905). Informed consent for the use of medical data was waived as the patient information was anonymized and de-identified prior to analysis.

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