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ORIGINAL ARTICLE

Questionnaire survey on patient awareness of invasive rebiopsy in advanced non-small cell lung cancer

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Abstract

Background: Treatment strategies for patients with non-small cell lung cancer (NSCLC) depend on various factors including physical condition, complications, tumor histology, and molecular profiling. Even if initial chemotherapy is efficacious, almost all patients develop treatment resistance. Invasive rebiopsy from sites of recurrence might provide insight into resistance mechanisms and aid in the selection of suitable sequential antitumor drugs. However, invasive rebiopsy might be challenging because of limited tissue availability and patient burden. Therefore, this study aimed to assess awareness of invasive rebiopsy among non-small cell lung cancer patients.

Methods: This prospective questionnaire survey was performed between June 2015 and March 2016 in patients with advanced non-small cell lung cancer. The survey was carried out at two time points: before starting first-line chemotherapy (cohort 1), and at the time of disease progression after initial chemotherapy, but before second-line chemotherapy (cohort 2).

Results: In this study, 50 and 30 patients were enrolled in cohorts 1 and 2, respectively. In cohort 1, 37 (74%) patients agreed to rebiopsy, if disease progression occurred, whereas 18 (60%) patients in cohort 2 agreed to invasive rebiopsy at disease progression. The primary reasons for rebiopsy rejection were poor physical condition and patient burden related to the initial biopsy. Seven patients answered the survey questions during the treatment course, and the acceptance rate was lower among patients who agreed to rebiopsy at disease progression than before treatment.

Conclusions: Invasive rebiopsy can lead to distress in some patients. To improve the consent rate for tissue rebiopsy, treatment strategies including rebiopsy should be discussed with patients during the early treatment phase.

Introduction

Although lung cancer remains the leading cause of death among all cancers,[1,2] progress in treatment has been remarkable in the past several decades because of molecular-targeted drugs, such as those used for epidermal growth factor receptor (*EGFR*)-positive and anaplastic lymphoma kinase (*ALK*)-positive tumors. Furthermore, immune-checkpoint inhibitors, including those targeting programmed cell death 1 and programmed death-ligand 1, have been developed for non-small cell lung cancer (NSCLC), with several chemotherapeutics already approved and in use. Therefore, sequential treatment strategies using chemotherapeutic agents among the several available classes should be considered in individual patients.

Almost all advanced or metastatic lung cancers progress after initial chemotherapy. In these cases, invasive rebiopsy should be considered for selecting appropriate sequential chemotherapy, given that tissue resampling can provide insight into the resistance mechanisms underlying chemotherapy, especially molecular-targeted drugs.[3,4] A recent study suggested that the most important factor for successful treatment of these patients was adequate tissue resampling to ensure the detection of novel mutations during disease progression.[5] For example, 50–60% of patients with mutations in *EGFR* conferring sensitivity to EGFR-tyrosine kinase inhibitors (TKIs), such as deletions in exon 19 and a point mutation substituting L858R in exon 21, treated with first-generation or second-generation EGFR-TKIs (gefitinib, erlotinib, and afatinib) were found to later acquire a second mutation in *EGFR* (T790M), which led to resistance;[6–9] a third-generation EGFR-TKI, osimertinib, has been developed to overcome this resistance.[3,10]

Appropriate treatment for NSCLC patients is determined with consideration of their physical condition, complications, histological type, pathological findings including immunostaining, and tumor mutation status. For diagnosis and molecular characterization of lung tumors,[11,12] adequate invasive tissue-sampling procedures, such as bronchoscopy, endobronchial ultrasound, computed tomography-guided biopsy, and even surgical biopsy, are necessary, all of which are associated with pain. In clinical practice, invasive rebiopsy is an essential approach for selection of the next chemotherapy, which, however, is limited by tissue availability[13–18] and patient burden related to the initial biopsy.

This study investigated patient awareness of invasive rebiopsy in advanced NSCLC, with the goal of determining factors that will improve the rate of this invasive procedure necessary for optimal treatment.

Methods

Study patients

This prospective study recruited patients with locally advanced or metastatic NSCLC under protocol approved by the Kitasato University Medical Ethics Organization (B15-31). Eligible patients were those with a pathological diagnosis of NSCLC and who had a planned first-line or second-line chemotherapy at Kitasato University Hospital in Kanagawa, Japan, between July 2015 and May 2016. We received written consent from each patient in this study. The third-generation EGFR-TKI, osimertinib, had not been approved in Japan at the time this study was carried out. After obtaining written consent, patient awareness was evaluated with a survey, and patient characteristics and clinical data were collected.

At diagnosis, invasive procedures including flexible bronchoscopy, computed tomography-guided percutaneous lung biopsy, open lung biopsy, cytopathological examination of pleural or pericardial fluid, transesophageal needle aspiration, or brain tumor resection were performed with or without conscious sedation, after appropriate informed consent was obtained (Table 1). After the diagnosis, a questionnaire was carried out using multiple selectable questionnaires (Table 2) at two time points: before starting first-line chemotherapy (cohort 1), and at disease

Table 1 Patient characteristics in this study

	Before first-line chemotherapy *n* = 50	Before second-line chemotherapy *n* = 30
Median age, years (range)		
≤70 years/>70 years	27/23	18/12
Sex		
Male/female	36/14	21/9
Smoking status		
Never/smoker	9/41	8/22
WHO performance status		
0/1/2/3	18/29/2/1	11/15/4/0
Procedure at diagnosis		
Bronchoscopy/others	42/8†	27/3‡
Clinical stage		
III/IV/postoperative recurrence	16/29/5	7/20/3
Histology		
Ad/Sq/NOS	33/7/10	21/7/2
Mutational status		
Wild-type/*EGFR*/*ALK*	36/13/1	19/10/1
Initial chemotherapy		
CRT/Chemo/targeted therapy	12/23/15	6/16/8

†Including three cytopathological examinations of pleural or pericardial fluid, two open lung biopsies, two transesophageal needle aspirations, and one computed tomography-guided percutaneous lung biopsy. ‡Including two brain tumor resections and one transesophageal needle aspiration. Ad, adenocarcinoma; Chemo, chemotherapy; CRT, chemoradiotherapy; NOS, not otherwise specified; Sq, squamous cell carcinoma.

Table 2 Survey on patient awareness of invasive rebiopsy for non-small cell lung cancer

If your lung disease progressed after initial chemotherapy, would you agree with invasive rebiopsy?

- 1. Accept, at doctor's recommendation
- 2. Accept, if therapeutic strategy changes based on the results
- 3. Accept, if there is no cost to undergo the test
- 4. Accept, for future medical progression
- 5. Reject, but accept if the test is non-invasive
- 6. Reject, because of poor physical condition
- 7. Reject, because of the difficulty of the test
- 8. Reject, because of other reasons
- 9. Cannot decide at this time

progression after initial chemotherapy and before second-line chemotherapy (cohort 2).

Statistical analysis

The impact of clinical factors on patients' decision on invasive rebiopsy was assessed using Pearson's κ^2 test. All analyses were performed using SPSS statistical software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

We enrolled two cohorts of patients depending on when we asked them about tissue rebiopsy: 50 patients who were asked before first-line chemotherapy about rebiopsy if their disease progressed after initial chemotherapy (cohort 1), and 30 patients who were asked at the time of disease progression after initial chemotherapy and when second-line chemotherapy was being planned (cohort 2; Fig 1). All patients were Japanese, including 36 men and 14 women in cohort 1, and 21 men and 9 women in cohort 2. Median ages were 69.5 years (range: 43–82 years) and 68.5 years (range: 48–81 years) in cohorts 1 and 2, respectively. Most of the patients in both cohorts (47/50 [94%] in cohort 1, and 26/30 [87%] in cohort 2) had an Eastern Cooperative Oncology Group performance status of 0 or 1. Most of the patients in both cohorts underwent flexible bronchoscopy for initial biopsy (42/50 [84%] and 27/30 [90%] in cohorts 1 and 2, respectively). In addition, 14 and 11 patients in cohorts 1 and 2, respectively, had driver mutations, including those in *EGFR* or *ALK* (Table 1).

Aggregate results of the survey

In cohort 1, 37 (74%) of the 50 patients eventually provided consent for rebiopsy, whereas 13 patients (26%) rejected rebiopsy (Fig 2a). In cohort 2, 18 (60%) of the 30 patients eventually provided consent for rebiopsy, whereas 10 patients (33%) rejected rebiopsy (Fig 2b). Reasons for the responses to the invasive rebiopsy option are shown in Figure 3. Briefly, 36 (97%) of the 37 patients in cohort 1 and 17 (100%) of the 17 patients in cohort 2 who accepted the rebiopsy (groups 1 and 2 in Fig 3a) followed their doctor's recommendation to select optimal treatment because of tissue sampling. Conversely, the reasons for refusal of invasive rebiopsy were according to painful experience of an initial biopsy (100% and 80% in cohorts 1 and 2, respectively) and apprehension because of poor physical condition (38% and 40% in cohorts 1 and 2, respectively; Fig 3b). Furthermore, five (38%) of the 13 patients in cohort 1, and four (40%) of the 10 patients in cohort 2 who rejected the rebiopsy stated that they would consider non-invasive examination if it were an option.

There were no associations between clinical factors and consent rate of invasive rebiopsy (Tables 3, S1). In this study, the number of biopsies performed before the survey were once (n = 71) or twice (n = 9) for confirmed diagnosis of lung cancer, and it was not associated with the patients' will to agree to tissue rebiopsy (P = 0.60). Although median durations from prior biopsy to the

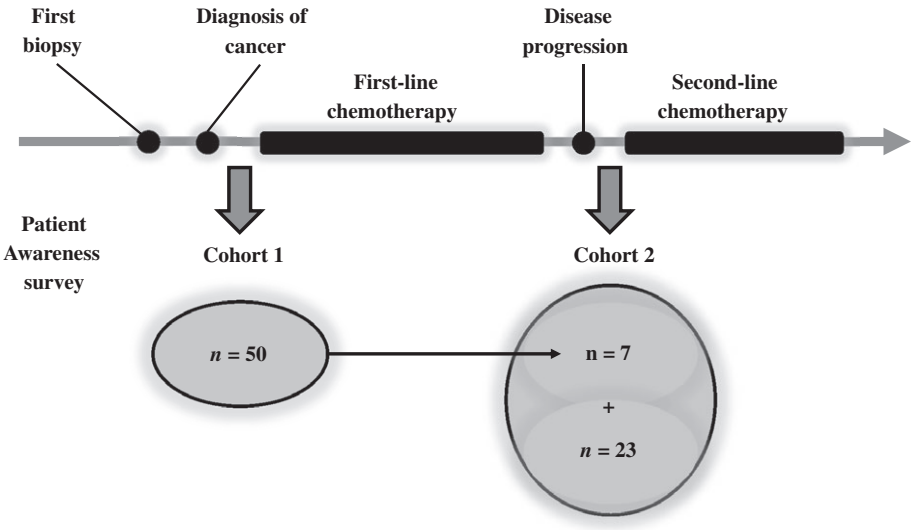

Figure 1 Clinical course and points of survey in this study. The patient awareness survey on invasive rebiopsy was performed before first-line chemotherapy (cohort 1, n = 50) or second-line chemotherapy (cohort 2, n = 30, including seven patients who answered the initial survey (cohort 1)).

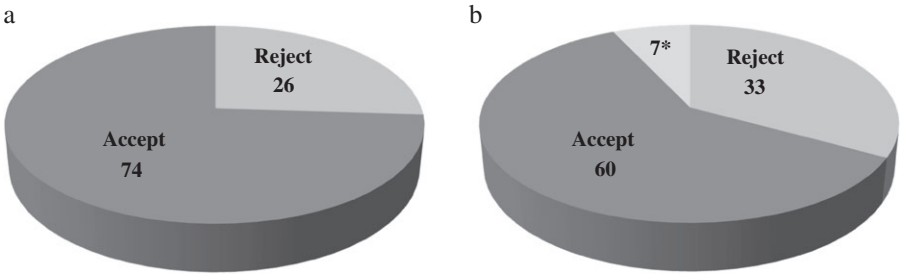

Figure 2 Rates of informed consent (%) for invasive rebiopsy in patients with advanced non-small cell lung cancer in cohorts (**a**) 1 (n = 50) and (**b**) 2 (n = 30). Accept: agree with invasive rebiopsy; reject: cannot agree with rebiopsy if the disease progresses after initial chemotherapy. *Ratio of the patients who could not reach a decision on invasive rebiopsy at the time.

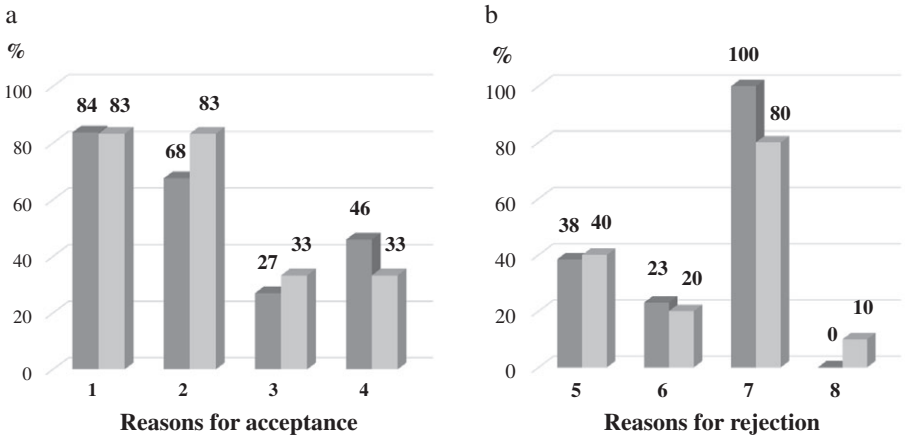

Figure 3 Reasons for the decision on invasive rebiopsy based on the study survey (see Table 2). (**a**) Reasons for accepting rebiopsy in cohorts 1 (n = 37) and 2 (n = 18). (**b**) Reasons for rejecting rebiopsy in cohorts 1 (n = 13) and 2 (n = 10). Scores on horizontal axes correspond to responses to the survey questions as follows: 1, accept, at doctor's recommendation; 2, accept, if therapeutic strategy changes according to the results; 3, accept, if there is no cost to undergo the test; 4, accept, for future medical progress; 5, reject, but accept if the test is non-invasive; 6, reject, because of poor physical condition; 7, reject, because of the difficulty of the test; 8, reject because of other reasons; and 9, cannot decide at this time. Black bar, cohort 1; gray bar, cohort 2.

survey were 42 days (range: 12–1434 days) in cohort 1, and 409 days (range: 12–2597 days) in cohort 2, there was no correlation between the periods and consent rate of rebiopsy (accepted group, median 70 days [range 12–2597 days]; rejected group, median 73 days [range 14–931 days]).

In cohort 2, on the relationship between the initial treatment effects and decision of rebiopsy, five (42%) of 12 patients who had partial response, 10 (83%) of 12 patients who had stable disease, and three (50%) of six patients who had disease progression agreed to invasive rebiopsy. During the study, seven (14%) of the 50 patients in cohort 1 had disease progression after initial chemotherapy and were included in cohort 2 as a survey respondent (Fig 1). Two (40%) of the five patients who accepted rebiopsy later changed their decision and refused invasive rebiopsy.

This study was carried out before approval of osimertinib, which requires rebiopsy to prove *EGFR* T790M mutation, and invasive rebiopsy was not performed before carrying out the questionnaire survey. After approval of osimertinib and PD-L1 immunostaining, 16 (32%) of 50 patients in cohort 1, and 10 (30%) of 30 patients in cohort 2 underwent invasive rebiopsy in the course of treatment. Among the 22 of 73 patients in cohort 1 and 2 who received invasive tissue-rebiopsy, which excluded pleural lavage cytology, 11 (45%) patients had rejected the questionnaire survey carried out in advance.

Discussion

With continuing advances in the treatment of advanced NSCLC, development of molecular-targeted drugs[19] and clinical indications of immune-checkpoint inhibitors[20–22] require treatment strategies on the basis of molecular profiling of tumors. Furthermore, elucidation of the resistance mechanisms can lead to new therapeutic strategies,[3,23,24] which are best illustrated by the discovery of the *EGFR*

Table 3 Associations between clinical factors and rate of informed consent for invasive rebiopsy in patients with non-small cell lung cancer in this study (n = 80)

Clinical factors	n	Agree	Reject	P (Pearson χ^2)
All	80	55	23 (29%)	—
Before first-line	50	37	13 (26%)	0.37
Before second-line	30	18	10 (33%)	
≤70 years	45	32	11 (24%)	0.40
>70 years	35	23	12 (34%)	
Male	57	40	16 (28%)	0.78
Female	23	15	7 (30%)	
ECOG PS 0	29	19	9 (31%)	0.70
ECOG PS 1–3	51	36	14 (27%)	
Never smokers	17	12	4 (24%)	0.66
Smokers	63	43	19 (30%)	
Bronchoscopy	69	47	21 (30%)	0.48
Others	11	8	2 (18%)	
Stage III	23	13	9 (39%)	0.17
Stage IV or Rec	57	42	14 (25%)	
Adenocarcinoma	54	38	14 (26%)	0.48
Others	26	17	9 (35%)	
Mutation-negative	55	37	16 (29%)	0.84
Mutation-positive	25	18	7 (28%)	
Chemoradiotherapy	18	10	6 (33%)	0.43
Chemotherapy†	62	45	17 (27%)	

†Chemotherapy included cytotoxic chemotherapy and targeted therapy. ECOG PS, Eastern Cooperative Oncology Group performance status; Rec, postoperative recurrence.

T790M mutation found after the implementation of first-generation and second-generation EGFR-TKIs, and approval of the third-generation EGFR-TKI, osimertinib.[10] Rebiopsy is a feasible approach with a reported technical success rate of approximately 80% in advanced NSCLC patients without severe complications.[15–17,25] Although reassessment of tumor at recurrence is also necessary in clinical practice, invasive rebiopsy is accompanied by pain. In this study, poor physical condition (option 6) and the difficulty of the test (option 7) were most of the reasons for refusal. Three of five patients who chose the option 6 were PS 2 or 3, and the remaining two had chosen the options 6 and 7 at the same time as reason for refusal. The option 7 indicated the difficulty of the invasive examination itself, especially bronchoscopy, which accounted for 86% in this study, was highly painful in patients. Strategies to improve the rate of agreement for rebiopsy should consider both the availability of lesions for rebiopsy and patient consent. We found that this painful procedure, which was accepted by approximately 60–70% of the patients as part of their own treatment strategy, was rejected by 30–40% of the patients; in addition, the rejection rate might increase with worsening disease. Our data suggested that explanation of rebiopsy as a potential therapeutic strategy to the patient during the early treatment phase might be important.

Although the standard genotyping approach includes invasive tissue biopsy, its clinical utility is limited by a lack of available tissue, potential complications, and patient discomfort.[26] Liquid biopsies, such as those evaluating circulating tumor DNA or RNA, circulating tumor cells, and exosomes, are potentially useful for the analysis of tumor cell genetics using blood samples in patients with malignancies, and these approaches have been increasingly translated from research to clinical practice.[27–30] For example, *EGFR* mutation testing using blood samples in advanced NSCLC patients is feasible and can be utilized in patient selection for targeted therapy in conditions where tissue testing cannot be achieved.[25,31–34] In the current study, approximately half of the patients expected the development of non-invasive approaches, although blood-based testing is considered to complement tissue biopsy.[35,36] Non-invasive liquid biopsy, which does not add burden on patients, should be validated as an alternative approach to evaluate tumor products comprehensively.

The current study has several limitations. First, this was a patient awareness survey from a single institution and the sample size was small; thus, the results cannot be regarded as definitive. However, there are no comprehensive reports on patient awareness of invasive rebiopsy, and the current data should be useful in the clinical setting. Second, patient background characteristics varied in the current study. In *EGFR*-mutant patients, the selection of therapeutic agents depends on the secondary mutation status in the resistant tumor; therefore, the significance of invasive rebiopsy is high. However, the current study was performed before osimertinib approval in Japan. Our data suggested that the rate of consent was not associated with patient background characteristics, which should aid clinicians in reassessment of recurrent tumors that might become increasingly necessary in patients with *EGFR* mutations and those with relapsed disease, because of the advances in molecular target therapy and immunotherapy. Finally, bronchoscopy is carried out with light sedation for local anesthesia at the study hospital, which might lead to experience of pain during the initial examination. Therefore, the impression of the initial examination might have contributed to the results of the survey.

Invasive rebiopsy at the time of recurrence has become increasingly important for treatment selection and therapeutic development in patients with advanced NSCLC. However, the findings of the current study were that the 20–30% of patients with advanced NSCLC experienced great pain; therefore, treatment strategies including rebiopsy as a potential approach for suitable tissue sampling should be discussed with patients during the early treatment phase. Furthermore, it is necessary to focus on the development and evaluation of non-invasive tests, such as liquid biopsy, that cause less pain and burden for

patients. We believe that the findings of the current study will aid clinicians by highlighting the need for less invasive methods to detect biomarkers and the importance of providing better information on rebiopsy probability to patients.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1. Associations of clinical factors and rate of informed consent for invasive rebiopsy in patients with advanced non-small cell lung cancer before first- and second-line chemotherapy
Table S1-1. Before first-line chemotherapy
Table S1-2. Before second-line-chemotherapy

