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NARRATIVE REVIEW

THE PREDICTIVE ACCURACY OF SYSTEMATIC *VERSUS* SELECTIVE ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION FOR ASSESSING MEDIASTINAL STAGING IN NON-SMALL CELL LUNG CANCER

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ABSTRACT: Lung cancer maintains a dismal prognosis despite diagnostic and therapeutic advancements, with 5-year survival hovering around 16%. The majority of cases are diagnosed at an advanced, incurable stage, contributing significantly to the poor prognosis. This study investigates whether the endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) approach can facilitate early detection of lymph node metastases in non-small cell lung cancer (NSCLC), thereby improving patient selection for surgical intervention. Data from the Reggio Emilia Cancer Registry, Northern Italy, covering NSCLC incidents from 2017 to 2019, were utilized. Patients were categorized based on diagnostic approach (systematic or selective) and information on stage and treatment was collected. Outcomes, including recurrence and mortality, were assessed. Among the 68 patients included (47 systematic, 21 selective), no significant differences in sex or age were observed. However, discrepancies were found in stage distribution. The systematic group exhibited fewer stage I (25.5% *vs.* 47.6%), but more stage II (36.2% *vs.* 14.3%), while no differences were accounted for stage III (34% *vs.* 33.3%) and stage IV (4.3% *vs*. 4.8%). Surgical intervention (74.5% *vs.* 100%), neoadjuvant chemotherapy (4.3% *vs.* 14.3%), and adjuvant radiotherapy (17% *vs.* 28.6%) were less frequent in the systematic group, while adjuvant chemotherapy (42.5% *vs.* 33.3%) and neoadjuvant radiotherapy (4.3 compared to 0%) were more common. The systematic group showed fewer recurrences (25.5% *vs.* 52.4%; P-value <0.05), though mortality (59.6% *vs*. 57.1%) and the disease-free survival (DFS) (40.9% *vs* 41.2%) rates showed no significant difference. However, a higher percentage of deaths without recurrence (34.1% *vs.* 17.6 %) was observed in the systematic group. Despite the study's limited sample size, findings suggest a greater sensitivity of the systematic approach in detecting lymph node metastasis and identifying surgical candidates. While the EBUS-TBNA approach appears to influence recurrence rates, its impact on mortality remains inconclusive.

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Impact statement: Lung cancer continues to be a disease with a poor prognosis as more than 50% of tumors are diagnosed at an advanced stage. New diagnostic procedures such as EBUS-TBNA (endobronchial ultrasound-guided transbronchial needle aspiration) could facilitate the early diagnosis of lymph node metastases, thus improving the selection of patients who are candidates for surgery. This population-based study appears to be able to confirm the usefulness of this approach.

Key words: *lung cancer; EBUS-TBNA; stage; treatment; recurrence; mortality.*

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INTRODUCTION

Non-small cell lung cancer (NSCLC), despite significant efforts in diagnosis and treatment, continues to pose a substantial challenge, with a 5-year survival rate of approximately 16% (1). However, survival rates vary significantly depending on the stage at diagnosis. Thus, accurate staging of the disease is crucial, particularly in determining the burden of nodal involvement, as it greatly influences therapeutic decisions, especially regarding surgical resection (2). Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as the technique of choice for invasive mediastinal staging (3). Current guidelines recommend systematic mediastinal staging with EBUS-TBNA before surgical intervention for resectable NSCLC (4). This systematic approach has proven to be more accurate than imaging-guided sampling methods, such as computed tomography (CT) or positron emission tomography (PET/CT), in identifying pathologic lymph nodes (5). However, the prognostic implications of this systematic approach remain less explored.

The objective of this study is to present data on recurrence and mortality among NSCLC patients undergoing preoperative EBUS-TBNA for staging purposes, comparing a systematic approach to imaging-guided selection at a tertiary oncology center.

METHODS

Utilizing data from the population-based Cancer Registry of Reggio Emilia Northern Italy (approved by the provincial Ethics Committee of Reggio Emilia, Protocol no. 2014/0019740 of 04/08/2014), we identified 47 patients undergoing systematic EBUS-TBNA between 2017 and 2019 (systematic group) and 21 patients undergoing selective approach between years 2015 and 2017 (selective group).

In the systematic group are included patients in which a systematic staging has been performed, thus identifying all the recognizable mediastinal nodal stations reachable with EBUS and sampling all the stations where the nodes had a smaller diameter of 5 mm or more. These procedures were performed either under deep or moderate sedation. The systematic approach has been applied in all surgical candidates with a peripheral lesion of 3 cm or more, a central lesion and where there is a suspicion of mediastinal nodal involvement (2). In the selective group are included surgical candidate patients who underwent a nodal sampling driven by the imaging, that is where PET or CT scan showed suspicious nodes due to the FDG uptake, the dimensions or the contrast-enhancement features. These procedures were performed usually under moderate sedation.

Recurrences at 12- and 24-months post-diagnosis, disease-free survival (DFS), and mortality in the absence of recurrence were calculated. Fisher's exact and t-tests as appropriate, were performed to evaluate differences between groups. The four outcomes were defined as follows: disease-free for the duration of the observation period, a recurrence occurred within 12 months, a recurrence between 12 and 24 months, or death (without recurrence) occurred within the designated time frame. Analyses were performed using STATA® 16.1 software and a P-value <0.05 was considered significant.

RESULTS

The demographic characteristics of the patients are summarized in **Table 1**. While there were no significant differences in sex or age between the two groups (average age 70 *vs.* 71.2), there were differences in clinical stage distribution. Less stage I (25.5% *vs*. 47.6%) and greater stage II (36.2% *vs*. 14.3%) were seen in the systematic group, but the prevalence of stage III (34% *vs*. 33.3%) and stage IV (4.3% *vs*. 4.8%) was comparable. Even yet, there was no significant difference in the overall comparison. It is worth mentioning that all 3 patients with stage IV disease had resectable metastases.

Regarding treatments, the systematic group, compared to the selective group, underwent significantly fewer surgeries (74.5% *vs*. 100%, P < 0.01) albeit only operated patients were selected in the latter group. There were non-significantly fewer instances of neoadjuvant chemotherapy (4.3% *vs*.14.3%), and adjuvant radiotherapy (17% *vs*. 28.6%) in the systematic group. Conversely, the systematic group received more adjuvant chemotherapy (42.5% *vs*. 33.3%) and neoadjuvant radiotherapy (84.3 *vs*. 0%) although the difference was not significant.

The mean age at diagnosis was 70 years in the systematic group and 71.2 years in the selective group. Concerning outcomes (**Table 2**), the systematic group exhibited significantly fewer recurrences

Table 1. *Reggio Emilia Cancer Registry. Years 2017-2019. Clinical features and therapies adopted in patients divided into systematic and selective approaches.*

	SYSTEMATIC		SELECTIVE		P-VALUE	TOTAL
	n	%	n	%		
Sex						
Female	18	38.3	7	33.3	0.7	25
Male	29	61.7	14	66.7		43
Clinical Stage						
I	12	25.5	10	47.6	0.21	22
II	17	36.2	3	14.3		20
III	16	34	7	33.3		23
IV	2	4.3	1	4.8		3
Surgery						
No	12	25.5	0	0	<0.01	12
Yes	35	74.5	21	100		56
Neoadjuvant chemotherapy						
No	45	95.7	18	85.7	0.1	63
Yes	2	4.3	3	14.3		5
Adjuvant chemotherapy						
No	27	57.5	14	66.7	0.5	41
Yes	20	42.5	7	33.3		27
Neoadjuvant radiotherapy						
No	45	95.7	21	100	0.3	66
Yes	2	4.3	0	0		2
Adjuvant radiotherapy						
No	39	83	15	71.4	0.3	54
Yes	8	17	6	28.6		14
Age at diagnosis	mean	SD *	mean	SD *	0.61	
	70	9.6	71.2	6.8		
Total	47	69.1	21	30.9		68

** SD: Standard Deviation.*

compared to the selective group (25.5% *vs*. 52.4%; P-value <0.05). However, there were no significant differences in mortality (59.6% *vs*. 57.1%) or DFS rates (40.9% *vs*. 41.2%). Specifically, the systematic group experienced fewer recurrences at 12 months (9.1% *vs*. 17.6%) and between 12-24 months (15.9% *vs*. 23.5%), but a higher proportion of deaths occurred without recurrence (34.1% *vs*. 17.6%).

Table 2. *Reggio Emilia Cancer Registry. Years 2017-2019. Outcomes in patients divided into systematic and selective approaches.*

	SYSTEMATIC		SELECTIVE		P-VALUE
	n	%	n	%	
Recurrence					
No	35	74.5	10	47.6	<0.05
Yes	12	25.5	11	52.4	
Death					
No	19	40.4	9	42.9	0.85
Yes	28	59.6	12	57.1	
Patient's disease status					
Disease-Free	18	40.9	7	41.2	0.48
Recurrence 12 months	4	9.1	3	17.6	
Recurrence 12-24 months	7	15.9	4	23.5	
Died without recurrence	15	34.1	3	17.6	

The 15 patients in the systematic group who died without recurrence were, on average, older (72 *vs*. 68 years), had more advanced stage disease (stage III-IV 53% *vs*. 0%), and exhibited greater comorbidity burden (Charlson Index 5 -7 47% *vs*. 33%) compared to the selective group.

DISCUSSION

The study aimed to demonstrate whether an EBUS-TBNA technique approach could provide better insight into the lymph node status of patients with NSCLC.

While the data originate from a single center, they suggest a favorable trend in this direction. Specifically, the EBUS-TBNA approach appears capable of identifying the involvement of a greater number of lymph node stations, reflected in fewer patients classified as stage I and more as stage II compared to the selective approach. The EBUS approach allowed 36% of patients to be classified as stage II (*vs*. 14% of the selective group) and instead the opposite occurs with the selective approach where approximately half of the patients were diagnosed in stage I. This discrepancy likely contributes to the observed reduction in both surgical interventions and recurrences at 12 and 24 months after diagnosis in the systematic group, underscoring the potential of the systematic EBUS-TBNA as the preferred technique for invasive lung cancer staging. Indeed, EBUS-TBNA exhibits high sensitivity and specificity, rivaling even surgical techniques (6) and potentially influencing prognosis (7).

The accuracy of EBUS-TBNA in detecting specific N2 lymph node stations is of growing importance given their prognostic relevance (8, 9). Moreover, the value of N2 stations lymph nodes will be a matter of discussion in the upcoming ninth edition of lung cancer staging (10).

Finally, our study did not uncover a significant effect of the selective approach on mortality. Nonetheless, patients in the systematic group who died without recurrence tended to exhibit more advanced disease and comorbidities.

CONCLUSIONS

In conclusion, our study, despite its limitation in sample size and single-center focus, suggests that a systematic EBUS-TBNA approach for mediastinal staging in NSCLC patients may enhance the accurate identification of true positives lymph node status at an early stage. This could enable the multidisciplinary team to tailor treatment strategies more effectively, whether surgical or not. Validation of the study could be guaranteed by expanding the study population by including more years of incidence or by including other centers.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings

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Conflict of interests

The Authors have declared no conflict of interests.

Availability of data and materials

The data presented in this study are available on request from the Corresponding Author. The data are not publicly available due to ethical and privacy issues; requests for data must be approved by the Ethics Committee after the presentation of a study protocol.

Authors' contributions

Conceptualization, investigation, writing-original draft, visualization, supervision, LM; Conceptualization, investigation, writing-original draft, visualization, MF; formal analysis, FM; visualization, supervision, RP; visualization, supervision, EC; visualization, supervision, PR; data collection, writing-review and editing, visualization, supervision, IB; data collection, AP; visualization, supervision, MSS; visualization, supervision, MT; visualization, supervision, AM; visualization, supervision, SR; visualization, supervision, CP; visualization, supervision, FMo; conceptualization, writing-original draft, investigation, and management, NCF. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Institutional review board statement

This population-based cohort study uses data from the Reggio Emilia Cancer Registry, approved

by the Provincial Ethics Committee of Reggio Emilia (ref. no. 2014/0019740 of August 4, 2014). The Ethics Committee authorized, even in the absence of consent, the processing of personal data, including those suitable for revealing the state of health of patients who are deceased or untraceable for the execution of the study.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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