ORIGINAL ARTICLE

What Is the Accuracy of Clinical Staging for Stage III-Single-station N2 NSCLC? A Multi-Centre UK Study

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ABSTRACT

Introduction: Single-station N2 (ssN2) versus multi-station N2 has been used as a selection criterion for treatment recommendations between surgical versus non-surgical multimodality treatment in stage III-N2 NSCLC. We hypothesized that clinical staging would be susceptible to upstaging on pathologic staging and, therefore, challenge this practice.

Methods: A retrospective study of prospectively collected routine clinical data for patients with stage III-N2 NSCLC that had completed computed tomography (CT), positron emission tomography (PET), and staging endobronchial ultrasound (EBUS) and had been confirmed clinical stage III-ssN2 at multidisciplinary team discussion and went on to complete surgical resection as the first treatment to provide pathologic staging. The study was completed in two cohorts (A) across a single cancer alliance in England (Greater Manchester) January 1, 2015 to December 31, 2018 and (B) across five United Kingdom centers to validate the findings in part A January 1, 2016 to December 31, 2020.

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Results: A total of 115 patients met the inclusion criteria across cohort A (56 patients) and cohort B (59 patients) across 15 United Kingdom hospitals. The proportion of cases in which clinical stage III-ssN2 was upstaged to pathologic stage III-multi-station N2 was 34% (19 of 56) in cohort A, 32% in cohort B (19 of 59), and 33% across the combined study cohort (38 of 115). Most patients had a single radiologically abnormal lymph node on CT and PET (88%, 105 of 115). In the majority, the reasons for missed N2 disease on staging EBUS were due to inaccessible (stations 5, 6, 8, 9) N2 nodes at EBUS (34%, 13 of 38) and accessible lymph nodes not sampled during staging EBUS as not meeting sampling threshold (40%, 15 of 38) rather than false-negative sampling during EBUS (26%, 10 of 38).

Conclusions: During multidisciplinary team discussions, clinicians must be aware that one-third of patients with stage III-ssN2 on the basis of CT, PET, and staging EBUS do not truly have ssN2 and this questions the use of this criterion to define treatment recommendations.

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Introduction

The optimal management of stage III-N2 NSCLC is a long-standing topic of great debate.[1,2] International guidelines provide conflicting recommendations and often include multiple treatment options without preference.[3–6] This debate has become increasingly complex with a paradigm shift in the multimodality treatment of stage III NSCLC in the past five years, driven by practice-changing randomized controlled trials. These randomized controlled trials have revealed improved progression-free survival and overall survival (OS) from maintenance immunotherapy (IO) versus placebo after concurrent chemoradiotherapy in unresectable stage III NSCLC,[7] adjuvant third-generation tyrosine kinase inhibitor therapy versus placebo in EGFR mutation-positive NSCLC after surgical resection and adjuvant chemotherapy,[8] adjuvant chemotherapy and IO versus adjuvant chemotherapy alone after surgical resection of NSCLC[9,10] and neoadjuvant chemotherapy and IO versus neoadjuvant chemotherapy alone before surgical resection in resectable NSCLC.[11] Therefore, the standards of care in both resectable and unresectable stage III-N2 NSCLC are changing dramatically but the lack of a standardized definition of "resectable" continues to drive the debate over patient selection for different treatment modalities. In the United Kingdom (UK), and beyond, the division between single-station N2 (ssN2) and multi-station N2 (msN2) disease has been used to inform treatment decisions between surgical and non-surgical multimodality treatment.[6,12] Part of the reasoning behind this is an analysis of an international thoracic surgery database which revealed that patients who undergo surgical resection of NSCLC and have pathologic staging of ssN2 have a similar five-year OS to those with multi-station N1 disease at approximately 35%.[13] The same database revealed that five-year OS was worse for those with pathologic staging of msN2 disease at 20%.[13] This led some to conclude that ssN2 is an important surgical selection criterion for patients with N2 disease, given its similar long-term outcomes to resected N1 disease. An opposing view is that while the differentiation between ssN2 and msN2 is prognostic, it is not predictive of response to specific treatment modalities and given there was no comparator of non-surgical treatment within this international database it is not possible to say whether surgical multi-modality treatment would have provided better or worse outcomes in either ssN2 or msN2 compared with nonsurgical multimodality treatment.

When considering this topic of debate, we hypothesized that clinical staging of ssN2 would be susceptible to discordance with pathologic staging (upstaging to msN2) in a considerable proportion of cases, as has been revealed in another study of clinical versus pathologic staging in lung cancer in which 34% of cases of clinical stage I to IIIA upstaged by pathologic staging.[14] The current TNM eighth edition international lung cancer staging system does not incorporate ssN2 versus msN2[15] and therefore has not been studied for discordance between clinical and pathologic staging. If our hypotheses were true, the clinical staging of ssN2 could not be relied on to define "resectability" or inform multidisciplinary team (MDT) treatment recommendations.

Materials and Methods

The primary objective of this study was to report the accuracy of clinical staging in patients with stage III-ssN2 NSCLC. The inclusion criteria were patients with clinical stage III-ssN2 NSCLC after staging computed tomography (CT) of the thorax, positron emission tomography-CT (PET-CT), and staging endobronchial ultrasound (EBUS) that also went on to have surgical resection as their first treatment and therefore had pathologic staging to provide the accepted standard comparator for the clinical stage. All patients must have been discussed at a lung cancer MDT with a final MDT-agreed clinical staging of stageIII-ssN2 and completed all three staging investigations of PET, CT, and staging

EBUS. Staging EBUS was defined as a systematic examination of all accessible lymph nodes starting at N3 stations, followed by N2 stations, followed by N1 stations. Any lymph node station that is abnormal on the basis of either pre-procedure CT or PET or on sonographic assessment during EBUS using established criteria[16] was sampled. Surgical resection included intra-operative lymph node sampling in line with the International Association for the Study of Lung Cancer minimum standards: a minimum of six lymph node stations sampled (three hilar and three mediastinal stations) and station 7 (subcarinal station) in all.[17]

The study was completed in two cohorts: (A) a retrospective study of consecutive patients meeting the inclusion criteria across Greater Manchester (GM) Cancer Alliance, in the North-West of England, and (B) a second retrospective study across multiple UK centers, outside of GM, to validate the findings reported in cohort A. GM contains 10 acute National Health Service Hospitals with five EBUS centers all of whom submit annual data on every EBUS procedure for performance monitoring.[18] For cohort A, we retrospectively analyzed the GM EBUS database and identified all patients categorized as ssN2 disease on staging EBUS from January 1, 2015 to December 31, 2018. These patients were further reviewed for the results of staging CT and PET-CT, and subsequent MDT discussion. Those patients that remained clinical stage ssN2 without distant metastases on all three staging investigations were checked against the GM thoracic surgery database to identify those that also underwent surgical resection and this completed cohort A. All ssN2 cases were classified as "true" (where pathologic staging confirmed ssN2) or "false" (where pathologic staging upstaged to msN2). From this, we were able to calculate the accuracy of clinical staging for ssN2 as the primary outcome of the study. The reasons for "false" clinical ssN2 staging were recorded and categorized as radiologically occult N2 metastases that were not accessible by means of EBUS (stations 5, 6, 8, 9) and therefore not sampled and missed during staging EBUS, false-negative sampling during staging EBUS (lymph node sampled during EBUS—regardless of whether adequate or inadequate sampling—and no malignancy reported, subsequent found to have nodal metastases at surgical staging) or lack of sampling of accessible lymph nodes (the additional nodal metastases found at surgical staging were not sampled during staging EBUS). Additional clinical factors were also recorded including the primary tumor size (mm), laterality of the primary tumor, lobar location of the primary tumor, standardized uptake value (SUV) of the primary tumor on PET-CT, and histologic subtype. Nonparametric Wilcoxon ranked sum tests, Fisher's exact test, and chi-square tests were used to analyze for any clinical variables associated with a statistically significant increase in upstaging from clinical ssN2 to msN2. The p values less than 0.05 were considered significant.

Cohort B of the study mirrored cohort A exactly in the inclusion criteria, data collection, and analysis. Twelve centers across the UK were invited to participate in the study and five centers submitted data on consecutive patients that met the inclusion criteria (Glasgow, Leeds, Royal Papworth Hospital, Birmingham, Leicester). The study period for cohort B was January 1, 2016 to December 31, 2020. In response to feedback during the presentation of cohort A of the study at the 2021 British Thoracic Oncology Group conference, we, in addition, collected the type of nodal metastases that were missed by clinical staging; micrometastatic (defined as small clusters of malignant cells within lymph node tissue measuring <2 mm),[19] macro-metastatic (metastatic lymph node metastases >2 mm in diameter) and extracapsular spread (malignant cells breaching the outer capsule of the lymph node) and the time between staging EBUS and surgery to evaluate if there is a difference between "true" and "false" clinical ssN2 according to time from EBUS to surgery. Results are presented here for cohort A, cohort B, and the combined study cohort. All data were recorded prospectively in all centers, although the design of the study is retrospective. Ethical approval was not required, confirmed at the local review board, given the observational design. Centers submitted anonymized data with no patient-identifiable data through password-protected communications.

Results

In cohort A, a total of 2447 consecutive staging EBUS procedures were reviewed from the GM EBUS database. Of these, 15% (380 of 2447) were confirmed to be stage III-ssN2 on staging CT, PET-CT, and staging EBUS and of these, 15% (56 of 380) had undergone surgical resection as the first treatment and could be included in cohort A. The other 85% (324 of 380) of patients had undergone non-surgical multimodality treatment (chemoradiotherapy) due to being classified as unresectable (bulky, invasive ssN2 disease) or were deemed medically inoperable due to comorbidities and frailty requiring de-escalation of treatment to curative intent radiotherapy alone, palliative systemic therapy or best supportive care.

In cohort A, the mean age was 68 years ($\pm$7) and 52% (29 of 56) were male. In terms of radiological findings, 84% (47 of 56) of patients had evidence of a single radiologically abnormal N2 lymph node station on either CT, PET or both (Table 1). The remaining 16% (9 of 56) had a radiologically normal mediastinum and the N2 was only identified by staging EBUS. The mean primary tumor size was 33mm ($\pm$4.6 mm) and the mean SUVmax

Table 1. Study Outcomes Across Cohort A, Cohort B, and Combined Study Cohort

Outcomes		Cohort A (GM)	Cohort B (UK)	Combined Study Cohort
Upstaging clinical ssN2 to pathologic msN2		19/56 (34)	19/59 (32)	38/115 (33)
Clinical staging (radiology—CT and PET)	Normal mediastinum	9/56 (16)	2/59 (3)	11/115 (10)
	Single radiologically abnormal LN	47/56 (84)	54/59 (92)	101/115 (88)
	Multiple radiologically abnormal LNs	0/56 (0)	3/59 (5)	3/115 (2)
Reason for upstaging (missed N2 nodes by staging EBUS)	Inaccessible LN during EBUS[5,6,8,9]	9/19 (47)	4/19 (21)	13/38 (34)
	False-negative EBUS sampling	6/19 (32)	4/19 (21)	10/38 (26)
	Accessible LN but not sampled during EBUS	4/19 (21)	11/19 (58)	15/38 (40)
The radiological appearance of missed N2 nodes	Radiologically normal	19/19 (100)	18/19 (95)	37/38 (97)
	Radiologically abnormal	0/19 (0)	1/19 (5)	1/38 (3)

Note: All values are given in n/N (%).
CT, computed tomography; EBUS, endobronchial ultrasound; GM, Greater Manchester; LN, lymph node; msN2, multistation N2; PET, positron emission tomography; ssN2, single-station N2; UK, United Kingdom.

was 11.6 (±1.4). Most primary tumors were right-sided (79%, 44 of 56) with 52% (29 of 56) classified as adenocarcinomas (ADCs) or NSCLC-not-otherwise-specified (NOS) and 48% (27 of 56) were squamous cell carcinomas (SqCCs) (Table 2). For the primary outcome, 34% (19 of 56) of patients with clinical stage III-ssN2 were upstaged to pathologic stage III-msN2. Clinical staging, therefore, had a diagnostic accuracy of 66% (37 of 56) for ssN2. Of the 19 cases in which upstaging occurred, 47% (9 of 19) were due to radiologically occult N2 positive lymph nodes in stations that were not accessible with EBUS, 32% (6 of 19) were due to false-negative sampling of a lymph node during EBUS and 21% (4 of 19) were due a lymph node not being sampled during staging EBUS. In all 19 cases, the lymph nodes that were positive for metastases at pathologic staging but not detected in clinical staging were radiologically occult with no abnormal findings on CT, PET-CT, and sonographic assessment (Table 1).

For cohort B, 12 UK centers identified 59 patients who met the inclusion criteria. The mean age was 66 years (±9) and 51% (30 of 59) were female. In total, 92% (54 of 59) of patients had evidence of a single radiologically abnormal N2 lymph node station on CT and/or PET-CT, 3% (2 of 59) had a radiologically normal mediastinum and the N2 was only identified by staging EBUS and 5% (3 of 59) had multiple radiologically abnormal lymph nodes on CT and/or PET-CT but were downgraded to ssN2 on staging EBUS and the final clinical staging, agreed at MDT, was stage III-ssN2. The mean primary tumor size was 41mm (±22 mm) and the mean SUV was 11.1 (±4.9). Right-sided primary tumors made up 59% (35 of 59) of the cases with 68% (40 of 59) sub-typed as ADC or NSCLC-NOS and 32% (19 of 59) as SqCC (Table 2). For the primary outcome, 32% (19 of 59) of patients with clinical stage III-ssN2 were upstaged to pathologic stage III-msN2. Clinical staging, therefore, had a diagnostic accuracy of 68% (40 of 59) for ssN2. Of the 19 cases in which upstaging occurred, 21% (4 of 19) were due to radiologically occult N2 positive lymph nodes in stations that were not accessible with EBUS, 21% (4 of 19) were due to false-negative sampling of a lymph node during EBUS and 58% (11of 19) were due a lymph node not being sampled during staging EBUS. In 95% (18 of 19) of cases, the lymph nodes that were positive for metastases at pathologic staging but not detected in clinical staging were radiologically occult with no abnormal findings on CT, PET-CT, and sonographic assessment. However, in 5% (1 of 19) of cases, the lymph node was radiologically abnormal but negative at staging EBUS and defined as a low probability of false-negative sampling at MDT. The lymph nodes responsible for upstaging that were not detected by clinical staging contained micrometastasis in 11% (2 of 19), macrometastasis in 53% (10 of 19), and extracapsular spread in 32% (6 of 19) with one case without this data (Table 1). The median length of time from staging EBUS to surgery was 33 days (interquartile range [IQR]: 24–42) with no statistically significant difference between "true" cases and "false" cases (true 32 days, IQR: 24–42 versus false 35 days, IQR: 27–40, $p = 0.6$).

Table 2. Clinical Variables Stratified According to "True" Or "False" Clinical Stage III-ssN2

Clinical variable		Cohort A (GM) (n = 56)			Cohort B (UK) (n = 59)			Combined study cohort (N = 115)		
		True: ssN2 (n = 37)	False: msN2 (n = 19)	*p*-Value	True: ssN2 (n = 40)	False: msN2 (n = 19)	*p*-Value	True: ssN2 (n = 77)	False: msN2 (n = 38)	*p*-Value
Tumor size (mm)	Median (IQR)	29 (22–36)	32 (20–44)	0.33	35 (23–46)	36 (30–60)	0.39	32 (26–43)	34 (24–52)	0.44
Tumor SUVmax	Median (IQR)	10 (8.1–14)	12 (9.3–14.7)	0.25	9.9 (8–13.4)	13.3 (8.4–15.1)	0.29	9.9 (8–13.6)	12.8 (8.8–14.9)	0.21
Tumor location (side)	Right n (%)	32 (87)	12 (63)		24 (60)	11 (58)	0.88	56 (73)	23 (61)	
	Left n (%)	5 (13)	7 (37)	0.08	16 (40)	8 (42)		21 (27)	15 (39)	0.18
Tumor location (lobe)	RUL	19 (51)	5 (26)		6 (15)	8 (42)		25 (33)	13 (34)	
	RML/RLL	13 (35)	7 (37)		18 (45)	3 (16)		31 (40)	10 (26)	
	LUL	1 (3)	4 (21)		12 (30)	6 (32)	0.12	13 (17)	10 (26)	
	LLL	4 (11)	2 (11)		4 (10)	2 (11)		8 (10)	4 (11)	
	LMB	0 (0)	1 (5)	0.08	0 (0)	0 (0)		0 (0)	1 (3)	0.47
Tumor sub-type	Adenocarcinoma/ NOS	23 (62)	6 (32)		28 (70)	12 (63)		51 (66%)	18 (47)	
	Squamous cell carcinoma	14 (38)	13 (68)	0.05	12 (30)	7 (37)	0.60	26 (34)	20 (53)	0.052

GM, Greater Manchester; IQR, interquartile range; LLL, left lower lobe; LMB, left main bronchus; LUL, left upper lobe; msN2, multi-station N2; NOS, not otherwise specified; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; ssN2, single-station N2; SUVmax, maximum standardized uptake value.

For the entire combined cohort, compromising patients from 15 UK hospitals, 33% (38 of 115) of patients were upstaged from clinical stage III-ssN2 to pathologic stage III-msN2. The diagnostic accuracy for clinical stage ssN2 in the entire study cohort was 67% (77 of 115). Across the study cohort, there was no statistically significant difference in upstaging related to primary tumor size on CT, primary tumor maximum SUV on PET-CT, laterality of the primary tumor, or lobar location of the primary tumor. There was an increase in upstaging in SqCC versus ADC/NSCLC-NOS that was bordering statistical significance (44%, 20 of 46, of SqCC cases upstaged versus 26%, 18 of 69, of ADC/NSCLC-NOS cases, $p = 0.052$) (Table 2).

Discussion

In this study of 115 patients from 15 hospitals across the UK, a clinical staging of stage III-ssN2 on the basis of staging CT, PET-CT, staging EBUS, and MDT discussion was accurate in 67% of cases when compared with pathologic staging, while the remaining 33% were proven to have stage III-msN2. This does not seem to be due to poor quality of staging given that upstaging frequently occurs in lymph node stations inaccessible from EBUS and in radiologically normal lymph nodes. This is a recognized limitation of radiologically and minimally invasive staging modalities available in the diagnostic pathway. The proportion of cases that were upstaged is virtually identical to a study of 698 patients with clinical stage I-IIIA NSCLC which found an upstaging rate of 34%.[14] This did not examine clinical staging in stage III-ssN2 as ssN2 versus msN2 does not form part of lung cancer staging, though it has been proposed for future editions given its prognostic significance.[20]

The treatment landscape in stage III NSCLC is undergoing a seismic change that requires clear and standardized definitions of "resectable" disease to guide treatment decisions and ensure equity of access to optimal treatment & outcomes. This work demonstrates that clinical staging of stage III-ssN2 is inaccurate in a significant proportion of patients which, therefore, questions using it as a criterion for defining resectability, as it will often not reflect the true underlying nodal staging. Furthermore, the published evidence base does not support excluding patients from surgery on the basis of msN2 alone (assuming the lymph nodes themselves are technically resectable, non-bulky, and well-defined). Although published in 2007, the European Organisation for Research and Treatment of Cancer (EORTC) 08941 study remains the only randomized controlled trial to directly compare surgical multi-modality treatment versus non-surgical multimodality treatment in stage III-N2 with msN2 disease as an inclusion criterion (N2 disease exceeding the right paratracheal station for right-sided tumors and the prevascular stations for left-sided tumors in nonsquamous histologic subtypes). The trial found no difference in OS.[21] A meta-analysis of the EORTC trial and the RTOG 89-01,[22] a similar trial design that recruited 73 patients against a target of 224, also found no difference in OS (hazard ratio = 1.01, 95% confidence interval: 0.82–1.23, $p = 0.954$).[23] Rather than the data from the study presented here sparking a debate about whether we should more aggressively search for msN2 (e.g., more widespread use of EBUS-endoscopic ultrasound, more mediastinoscopy after EBUS with ssN2) we believe it adds further evidence that any definition of "resectable " stage III-N2 should not be on the basis of ssN2 versus msN2 and should focus on the technical logistics of resection and the likelihood of achieving complete resection. A standardized definition of "resectable stage III-N2" has been proposed previously and supported within a national UK survey of practice.[1,12] Furthermore, a consensus definition on a standardized definition of resectable stage III NSCLC by the EORTC is eagerly awaited.

A strength of this study is the number of contributing centers, a necessity to achieve the numbers presented as patients with stage III-N2 represent a small proportion of patients diagnosed with NSCLC.[24] This is further refined by the criteria of ssN2 and to have completed surgical resection as the first treatment restricting the number of eligible cases. However, the inclusion criteria allowed confidence in the findings through the use of the pathologic stage as the gold standard comparator. The findings were tested across a regional system and then validated across a national footprint with remarkably similar findings, adding further weight to the confidence of conclusions. The limited sample size does, however, make the identification of clinical variables associated with upstaging very challenging.

The manuscript presents several limitations worth addressing. Notably, within the group A cohort, data regarding the number and proportion of micrometastasis, macrometastasis, and extracapsular invasion were not captured. However, this information was obtained in the Group B cohort after feedback and review of group A results. The analysis did not include data on the size and location of both accessible and inaccessible nodes in either cohort, owing to the logistical challenges associated with collecting such data across multiple sites within a limited time frame.

In conclusion, there is a critical need for a standardized definition of "resectable" stage III NSCLC, driven by rapidly changing paradigms in multi-modality treatment, but our data adds further evidence against

using ssN2 versus msN2 as a criterion within this definition.

CRediT Authorship Contribution Statement

Christopher Craig: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Supervision.

Janet Johnston: Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization.

Patrick Goodley: Data curation, Formal analysis.

Paul Bishop: Investigation, Writing - review & editing.

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Natalie Smith: Investigation, Writing - review & editing.

Anna Bibby: Investigation, Writing - review & editing.

Matthew Evison: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision.

Disclosure

The authors declare no conflict of interest.

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