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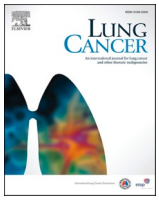

Research Paper

A prospective analysis of the management practices for patients with Stage-III-N2Non-Small-Cell lung cancer (OBSERVE IIIA–B GFPC 04-2020Study)

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A B S T R A C T

Background: Management of stage-III-N2 non-small-cell lung cancer (NSCLC) based on a multimodal strategy (surgery or radiotherapycombined with systemic drugs) remains controversial. Patients are treated with a curative intent, and available data suggestprolonged survival after complete resection. However, no consensual

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definition of "tumor resectability" exists. This study aimed to analyze the concordanceamong French tumor board meeting (TBM)-emittedtherapeutic decisions forstage-III-N2 NSCLC.

Methods: Six patients with stage-III-N2 NSCLC discussed at Saint-Etienne University Hospital'sthoracic TBMs were selected, anonymouslyreported, and submitted to the participating TBMs. The primary goal of this multicenter, prospective, observational study was to assess the consistency of TBMpanel decisions for each case. The secondary endpointwas identifying the demographic or technical factors that potentiallyaffected decision-making.

Results: Twenty-seven TBMs from university hospitals, a cancer center, general hospitals, and a private hospitalparticipated in this study. None of their decisions for the six cases were unanimous.The decisions were homogenous for three cases (78%, 85%, and 88% TBMs opted for medical treatment, respectively),andmore ambivalent for the other three (medical versus surgical strategies were favored by 44%/56%, 46%/54%, and 58%/42% TBMs, respectively). Interestingly, decisions regarding chemoradiationand perioperative chemotherapyinthe medical and surgical strategies, respectively, were also discordant. Hospital type, specialist participation in TBMs, and activity volumes were not significantly associated with therapeutic decisions.

Conclusion: The results of this study highlight substantial disparities amongFrench TBMs regarding therapeutic management of stage-III-N2 NSCLC. The decisions were not associated with local conditions.

1. Introduction

Up to 35 % of newly diagnosed non-small-cell lung cancers (NSCLCs) are already stage III, which represents locally advanced disease [1]. According to the 8th edition of the Tumor Node Metastasis (TNM) classification of NSCLCs [2], clinical or pathological N2 status indicates ipsilateral mediastinal or subcarinal lymphnode invasion. N2 NSCLCs can belong to subgroupsIIIA or IIIB, depending on tumor size, adjacent organ invasion, and local extent [1].

Despite significant risks of loco-regional recurrence and metastatic relapse due to micrometastases, patients with stage-III-N2 NSCLC are eligible for radical treatment, with curative intent [3,4]. However, heterogeneous prognoseshave beenreported for stage-III-N2 NSCLC, with 5-year overall survival (OS) ranging between 5 and 35 % [4–6]. Survival discrepancies seem to closely reflect tumor dissemination and lymph-node features [6–8]. In particular, N2 NSCLCcovers diverse lymph-node–invasion patterns: single or multiple station(s), limited size or bulky (usually described as short-axis $>$ 2 cm)lymphnodes, intranodal or extracapsular involvement, or the lymphnodesmay even harbor unexpected microscopic spread (undetectable on imaging) [7,9,10].

At present, the management of stage-IIIA–B-N2 NSCLCremains highly controversial, but international data and current guidelines advocate multimodal treatments thatprolongprogression-free survival (PFS), OS, and quality of life [11–13]. Multimodal approaches combine local treatment (surgery or radiotherapy) with a wide variety of systemic agents [12]. Therapeutic strategies for all patients with stage-III-N2 NSCLCare discussed in thoracic tumor board meetings (TBMs) [14]. In France, to improve the TBM quality, a specific quorum must be reached, requiring the attendance of at least one onco-pulmonologist (or one medical oncologist), one radiation oncologist, and one thoracic surgeon [15,16].

The possibility of surgical resection with mediastinal lymphadenectomy must be considered as often as possible during decision-making [6,17]. Indeed, data suggest prolonged survival ofpatients with stage-III-N2disease who have undergone microscopically complete resection (R0), defined as negative surgical margins and no gross residual tumor [18–21]. Selecting patients likely to achieve successful R0is challenging because there is no consensual definitionfor"tumor resectability [13,22,23]". Among resected NSCLCs, 15–20 % turn out to be microscopically incomplete and 25–35 % are associated with incomplete lymphadenectomy [19]. Case-by-case analysis of "tumor resectability"relies substantially on the thoracic surgeon's expertise [11,14,24] and accurate mediastinal staging [9,25,26]. However, sensitivity, specificity, and positive- and negative-predictive values for imaging staging, based on computed tomography (CT) and positron-emission tomography (PET) scans,vary widely [10,27,28]. For central tumors, those exceeding 3 cm, or with image-based N1 invasion, minimally invasive sampling by endobronchial ultrasonography-guided *trans*-bronchial needle aspiration (EBUS-TBNA) is usually recommended and is sometimes supplemented by mediastinoscopy [29–32].

In light ofthe equivocal recommendations and lack of a consensualdefinition for "resectability", focusing on real-life clinical practices concerning stage-III-N2 NSCLCis gaining increasing interest. A French monocenter study that blindly rediscussed stage-III-N2 NSCLCs within the same TBM revealed poor reproducibility of therapeutic decisions between the two meetings [33]. Likewise, the results of a two-round Delphi-based study involving 30 French experts highlighted disagreements about management of patients of stage-IIIA–BNSCLC [14]. Kommalapati et al. even mentioned significant OS differences according to the type of hospital [34].

In this context, the primary goal of the multicenter, prospective OBSERVE IIIA–B N2 study was to examine the consistency of therapeutic decisions (medical versus surgical options) among French TBMsconcerning patients with stageIIIA–B-N2 NSCLC. The secondary endpoints aimed to identify the technical and medical demographic factors that might influence therapeutic management.

2. Methods

TBMs held by members of the academic GroupeFrançais de Pneumo-Cancérologie (GFPC)were invited to participate in this multicenter, prospective, exploratory study. At the participating TBMs,six distinctstage-III-N2 NSCLC cases were discussed during one of their usual meetings, under real life conditions. The inclusion criterion was making a therapeutic decision for at least one case. They were also requested to provide information about their hospital, including themedical demographics, activity volumes, and access to technical equipment and infrastructure. All participating TBMs consented to their therapeutic decisions being used and analyzed in the framework of this study.

The clinical information of six distinct cases with stage-III-N2 NSCLC that were discussed during the Saint-Etienne University Hospital (SE-UH) thoracic TBMs between 2017 and 2022 was anonymously reported. Hence, the SE-UH thoracic TBM was excluded from the analysis. For each clinical case, the following medical data were provided: age, sex, medical history, comorbidities, clinical status according tothe World Health Organization performance status (WHO-PS), cancer characteristics including bronchoscopy results, thoracic CT and PET-CT findings, histological and cytological sample investigations (CT-guided percutaneous transthoracic needle biopsy, EBUS staging, or mediastinoscopy), histological examination observations, immunochemical (including PDL1 status) and molecular features, as well as pulmonary and cardiac function tests. CT and PET-CT scans were anonymously duplicated on CDsand transmitted to the participating TBMs. The six anonymous patients,summarized in **Supplementary Table S1** were numerically submitted to TBMs in October 2022 usingPowerPoint slides.

For every case, TBM participants were requested to report on a dedicated 2-part form with multiple choice responsesthe clinical TNMstaging attributed to each patient at diagnosis and their therapeutic orientation, that isthe medical or surgical strategy, andto state whether a concurrent or sequential regimen would be preferred for medical management and whether upfront surgery or neoadjuvant chemotherapy

would be administered for surgical management. They also had to indicate their decisionsconcerning adjuvant osimertinibfor epidermal growth factor receptor (*EGFR*)-mutant carriers and R0 tumors, and durvalumabconsolidation after chemo-radiotherapy. Part 1 of the questionnaire provided space forthe panel to relatetheir decision-making process.

Furthermore, TBMpanel features were collected, mainly data pertaining to its organization, contents of discussions, pulmonological and oncological expertise, surgical expertise, radiation expertise, pathological expertise, and access to research.

The primary outcome was the concordance among the TBM-emitted decisions for each of the six cases, especially regarding the medical or surgical strategies. Agreement was based on the percentages of the medical or surgical strategies decided for each case. The consistency of therapeutic sequence within each treatment modality was also described and analyzed; that is, we focused on concurrent or sequential schemes withinthemedical strategy, and induction chemotherapy or upfront surgery within the surgical approach. We also comparedthedecisions of theexternal TBMsto the options initially validated at SE-UHunder real-life conditions.

The secondary endpoint was identifying which TBM characteristics, among medical demographics and technical factors, couldtiltthe decision-making towards a surgical or medical approach. Some TBMpanel characteristics were selected as explanatory variables to identifypotential associations with the therapeutic orientation. Items reflectingTBMsession organization were analyzed (type of hospital, specialists participating in the TBMs, and number of patient records discussed at each session). Items about pulmonological, surgical, and radiation expertise (annual stage III NSCLC incidence rates and activity volumes) were also evaluated.

Qualitative variables are expressed asnumbers (%),and quantitative variables as means ± standard deviation (SD) or medians [25th–75th interquartile range].

Univariate analyses explored the potential impact of the TBMpanel characteristics (organization of TBMs based on the type of hospital, specialists participating in the TBMs, number of patients discussed at each session, and expertise level based on annual activity volumes) on therapeutic decisions. As six cases were discussed in the panels, every TBM participated several times, and the therapeutic decisions could not be considered independent outcomes. Indeed, it was hypothesized that each TBM would adopt the same decision-making process for the six cases, even though the cases were very different. Therefore, logistic

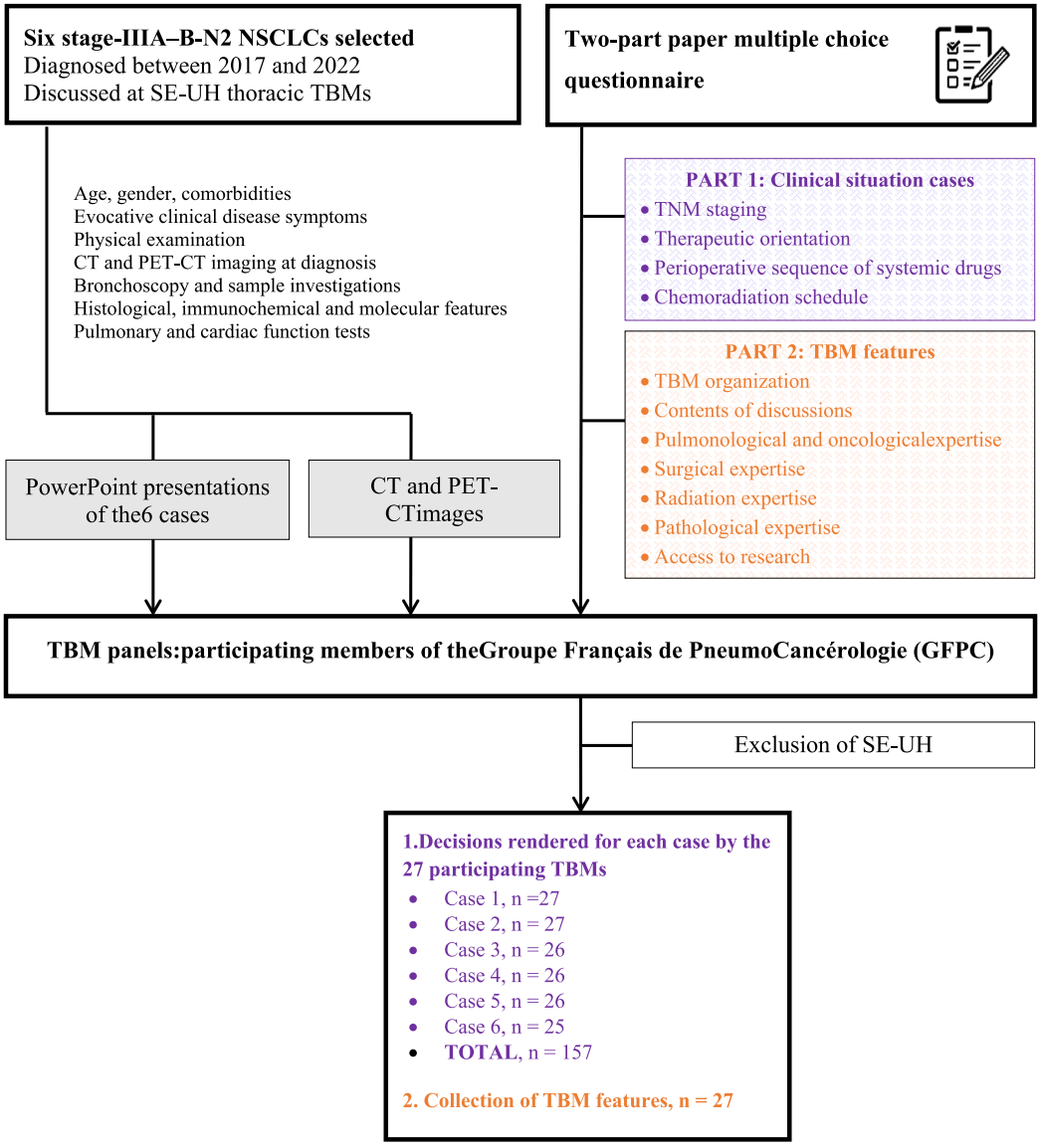

Fig. 1. Flow-chart of the tumor board meetings (TBMs) participating in the OBSERVE IIIA–B study. SE-UH, Saint-Etienne university hospital; CT, computed tomography; PET, positron-emission tomography; TNM, Tumor Necrosis Metastasis.

regression with random effects was used to analyze the relationship between TBM features and therapeutic decisions. A 5 % statistical significance threshold was applied for the univariate analyses.

This study was approved by the local SE-HU Ethics Committee (IRBN1362022/CHUSTE) and conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

3. Results

Members of 27 French TBMs participated in the study between November 2022 and March 2023, and rendered 157 of the 162 expected decisions(Fig. 1**)**. At the end of the participatingTBMs' deliberations, there were seven "inconclusive responses" between medical and surgical options, including five missing responses(Figs. 2 and 3**A**).

Most participatingcenters (56 %) were general hospitals, including one private and one military facility,whereas the remaining centers were university hospitals (44 %), including one cancer center. Additionally, 26 % of the TBMs were held in a hybrid face-to-face and videoconference format. At all centers, at least one onco-pulmonologist and at least one radiation oncologist attended the thoracic TBMs. However, two hospitals declared having no thoracic surgeon at the TBMs, and four facilities had no imaging specialists (Table 1). Amedian of approximately 30 patients' records werediscussed per session.Members of all but three TBMs relied onnationalguidelines for decision-making (Table 1).

The average number of incident NSCLC cases exceeded 300 per year and per center (Table 2). All centershad access to PET scans, minimally invasive EBUS staging, and mediastinoscopy, if needed, whether directly on-site or by referral to another center. At the time of analysis, immunotherapy or immunochemotherapy were not accessible in France in theneoadjuvant setting. Durvalumab was accessible for locally advanced disease after concomitant or sequential chemoradiotherapy, including for patients with PDL1 <%,as part of an early access program, while osimertinib was accessible.

Lung resections were predominantly lobectomies, and thoracic surgical procedures performed in half of the hospitalswerevideo-assisted thoracoscopic surgeries (Table 3). All participating centers had easy access to linear accelerators delivering 3D-conformal radiotherapy, including high-precision techniques suchasintensity-modulated radiation therapy, volumetric-modulated arc therapy, and stereotactic bodyradiation therapy.

For cases 1, 2, and 3, the medical strategy was validated by 78 %, 85 %, and 88 % of the TBMdecisions, respectively (Figs. 2 & 3**A, Supplementary Table S1**), reflecting fairly good concordance. In contrast, decisions were more ambivalentand concordance was more limited for cases 4, 5, and 6, with 56 %, 54 %, and 42 % of the TBM decisionsoptingfor a surgical strategy, and 44 %, 46 %, and 58 % of them validating a medical strategy, respectively (Fig. 3**A, Supplementary Table S1**). Notably, for all cases(Fig. 3**A**), the predominant TBM-decidedstrategy at all centers agreed with the real treatment originally validated for the patients at SE-UH.

Chemoradiation schemes withinthe medical strategy and perioperative chemotherapy sequences within thesurgical strategy were thesources of divergencein the six cases (**Supplementary Table S1**). For case 1, 100 % of the medical strategies comprised concurrent chemoradiation, and 83 % of the surgical strategies began with neoadjuvant chemotherapy (Fig. 3**B**). For cases 2 and 3, 74 % and 70 % of the TBM panels, respectively, validated a medical strategy that opted for a sequential regimen (Fig. 3**B**). For cases 4 and 5, 64 % and 57 % of thechosen surgical strategies consisted of neoadjuvant chemotherapy followed by surgical resection, respectively (Fig. 3**B**). For case 4, medical strategies werealmost equally divided between concurrent (55 %) and sequential (45 %) chemoradiation schedules, whereasfor case 5, all medical strategies adhered to a concurrent regimen (Fig. 3**B**). For case 6, among the medical strategies, 86 % of the TBM panels preferred a concurrent scheme. Among the surgical strategies, 70 % favored a sequence that included neoadjuvant chemotherapy (Fig. 3**B**).

For cases 1, 2, 4, and 6, among the medical strategies, most TBM-panel decisions approved the use of consolidation durvalumabforpatients with non-progressive disease after chemoradiotherapy. However, only 8 % and 17 % of the medical strategies decided for cases 3 and 5, whose tumors harbored an *EGFR* exon-20 insertion and*EGFR* exon-19 deletion, respectively, included consolidation durvalumab. Among the surgical strategies for case 5, 93 % of TBM deliberations also validated adjuvant osimertinib, independentof the perioperative chemotherapy sequence.

Univariate analyses exploring the potential associations between TBM characteristics and therapeutic decisions were performed in three different configurationsestablished according to the therapeutic concordance level obtained for each case (Fig. 3**A**).

Analysis configuration 1 pooled cases 1–3, for whomthe TBMpanel decisions predominantly validated the medical strategies. Analysis configuration 2combined cases 4–6, for whichthe therapeutic decisions were more equally distributed between the two main strategies **(**Fig. 3**,** Table 4). No significant association was found between the TBM organization, expertise, and therapeutic choice for the two configurations. Analysis configuration 3, which tested the same explanatory variables for cases 4–6 individually,also revealed no significant association between TBM features and therapeutic decisions.

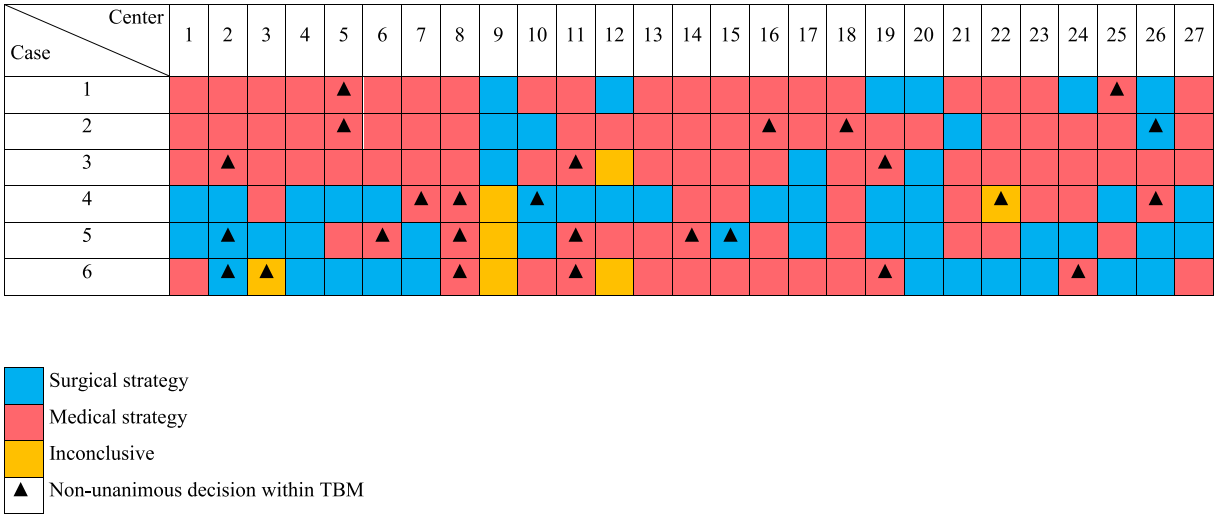

Fig. 2. Details of the tumor board meeting (TBM)-rendered therapeutic decisions by care center for each of the six cases.

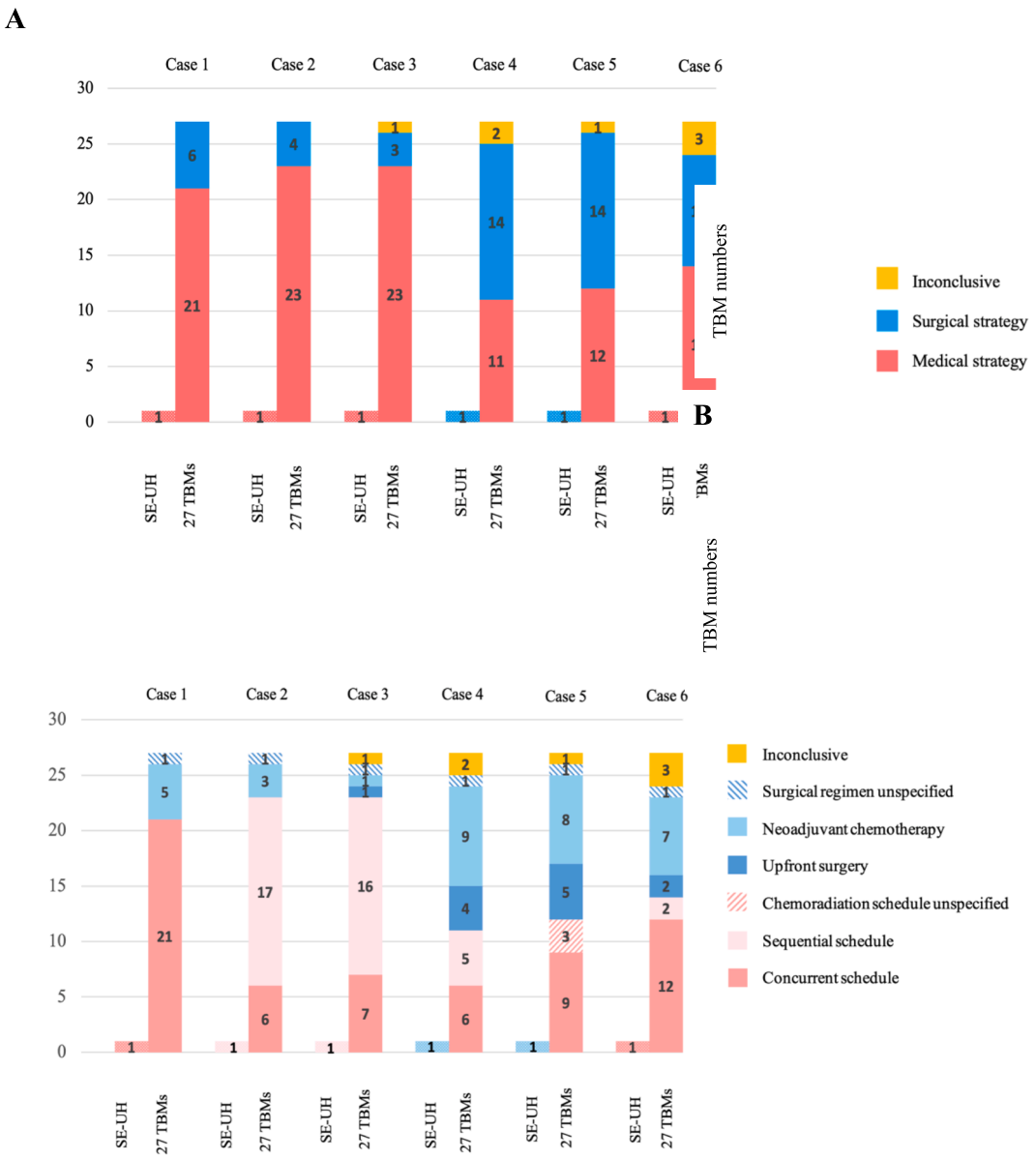

Fig. 3. Therapeutic decisions of the tumor board meeting (TBM) panelsfor each of the six cases. (***A***) Medical versus surgical strategies for each clinical situation. (***B***) Details of the therapeutic regimens by treatment modality. SE-UH: Saint-Etienne University Hospital.

4. Discussion

Since the end of the last century, TBMs have been recognized worldwide as a means to optimize survival outcomes of patients with lung cancer [35,36]. In France, although submission of newly diagnosed NSCLCs toTBM decision-making is compulsory, data regardingthe reproducibilityand consistency of therapeutic strategies are scarce [33]. The key result of OBSERVE IIIA–B study is that heterogeneous therapeutic decisions were issued for all six submitted cases in the TBMs, with none receivinga uniform strategy. Many TBM reports specified that some of their decisions were not unanimous amongthe session participants. These different outcomesbetween and within the TBMsreflect the complexity of decision-making for stage-III-N2 NSCLC, regardless of thebaseline clinical presentation, locoregional extent, and mediastinal invasion. The few studies dealing with the reproducibility of therapeutic management of stageIII disease were based on different designs with distinct biases [14,33,34,37]. Nevertheless, all of them converged towards a lack of agreement in decision-making. This recurring observation mightreflect the assumption in guidelinesthat "resectability" assessment is a prerequisite, defined upstream of the decision trees [32,33]. The main strength of the OBSERVE IIIA–B study lies in its prospective, multicenter design, unlike Mainguené's study that retrospectively explored reproducibility of therapeutic strategies in a single center [33].

In addition, the OBSERVE IIIA–B study reliably depicts French clinical practices and real-life decision-making, as it was based on TBM discussions, unlikeScherpereel et al.'sstudy,in which the opinions of individual expert panelists were collected [14]. Hospitals with significant thoracic oncology activity, that is, a median of 20 % stageIII NSCLCs diagnosedannually, in line with the worldwide epidemiological data, participated in OBSERVE IIIA–B.[1]Among these, 44 % were regional or national referral centers, and therapeutic decisions were not significantly different from those of local general hospitals. The participation of general hospitals in the study, including one private facility, provided a good representation of the medical practices in France. TBM features reflected state-of-the-art practices, with good levels of expertise across centersin thoracic oncology, surgery,and radiotherapy.

The best therapeutic agreement was observed for cases 2 and 3,

Table 1
Organization of the 27 Participating Tumor Board Meetings (TBMs).

Type of hospital, n (%)	
University	12 (44)
General	15 (56)
TBM frequency, n (%)	
Weekly	23 (85)
Twice-weekly	2 (7)
Twice-monthly	2 (7)
Physicianparticipation at each session	
Mean (SD)	11 (4)
Median (Q1–Q3)	10 (8–13)
Range	6–20
Participating specialist(s), n (%)	
Onco-pulmonologist	
1	1 (4)
>1	26 (96)
Radiation oncologist	
1	16 (59)
>1	11 (41)
Thoracic surgeon	
0	2 (7)
1	6 (22)
>1	19 (70)
Imaging	
Radiologist **and** Nuclear medicine physician	11 (41)
Radiologist **or** Nuclear medicine physician	12 (44)
No imaging specialist	4 (15)
Pathologist	
0	15 (56)
1	12 (44)
Type of meeting, n (%)	
On-site only	20 (74)
Hybrid	7 (26)
Number of patients' records discussed at each session	
Mean (SD)	31 (13)
Median (Q1–Q3)	29 (25–39)
Range	6–70

SD: standard deviation; Q1–Q3: 25th–75th interquartile range.

Table 2
Onco-pulmonological expertise of the 27Participating Tumor Board Meetings (TBMs).

	Value
Incident lung-cancer cases /year	
Mean (SD)	307 (168)
Median (Q1–Q3)	265 (178–388)
Newly diagnosed stage-III NSCLCs/year (%)	
Mean (SD)	21 (12)
Median (Q1–Q3)	20 (16–21)
Newly diagnosed stage-III-N2 NSCLCs/year (%)	
Mean (SD)	14 (8)
Median (Q1–Q3)	15 (10–15)
EBUS device accessibility, n (%)	
≥1 EBUS	26 (96)
0 EBUS	1 (4)
Number of EBUS stagings/year	
Mean (SD)	94 (69)
Median (Q1–Q3)	85 (63–103)
New patients givendurvalumab consolidation /year and /center, n	
Mean (SD)	23 (17)
Median (Q1–Q3)	16 (10–25)
New patients given adjuvant osimertinib /year and /center, n	
Mean (SD)	4 (5)
Median (Q1–Q3)	3 (1–5)

SD: standard deviation; Q1–Q3: interquartile range (25th–75th); NSCLCs: non-small cell lung cancers; EBUS: endobronchial ultrasonography.

which had bulky and multisite lymphnode involvement on CT- and PET/CT-based staging at diagnosis. Theseimaging findings discouraged most TBM participants from choosing surgical resection. Indeed, combined bulky and multi-station disease suggests a high-risk of incomplete resection, and usually leads toapplication of a medical strategy, even in

Table 3
Surgical and Radiation expertises of the 27 Participating Tumor Board Meetings (TBMs).

Surgical expertise	
Thoracic surgery department, in the same hospital, n (%)	
Yes	19 (70)
Surgical staff /center, n (%)	
≤2	15 (56)
>2	12 (44)
VATS, n (%)	
No VATS	2 (7)
<50 %	3 (11)
>50 %	13 (48)
Unknown	9 (33)
Segmental resections[a]	
Mean (SD)	47 (52)
Median (Q1–Q3)	30 (10–60)
Lobectomies[a]	
Mean (SD)	139 (99)
Median (Q1–Q3)	120 (50–200)
Pneumonectomies[a]	
Mean (SD)	13 (15)
Median (Q1–Q3)	6.5 (3–20)
Mediastinoscopies	
Mean (SD)	32.8 (27)
Median (Q1–Q3)	22 (15–50)
Radiation	
Radiation Department, n (%)	24 (89)
Access to IMRT, n (%)	27 (100)
Access to VMAT, n. (%)	18 (67)
Access to SBRT, n (%)	25 (93)
Thoracic radiations /year, n	
Mean (SD)	79 (59)
Median (Q1–Q3)	60 (40–95)

VATS: video-assisted thoracoscopic surgery; SD: standard deviation; Q1–Q3: 25th–75thinterquartile range; IMRT: intensity modulation radiotherapy; VMAT: volumetric modulated arctherapy; SBRT: stereotactic body radiotherapy.
[a] Lung resection types independent oftumor stage.

the absence of pathological staging (case 3), in accordance with the reported practices [14,21,38]. In contrast, for cases 1 and 6, with bulky and mono-station involvement, decisions were more divergent; moreover, therapeutic choices wereparticularly heterogeneousfor cases 4 and 5 with non-bulky and multi-station invasion on imaging, aspreviously emphasized [5,25]. Pathological staging resultswere available for cases 5 and 6 (mediastinoscopyand EBUS, respectively);but histological examination of pathological samples did not contribute to more homogenous therapeutic decisions compared to those for cases with only imaging staging. This observation underscores that some uncertainty remains about the reliability of pathological staging methods [14]. Nevertheless, except for peripheral tumors, those smaller than 3 cm, and those with no mediastinal invasion on imaging (cN0), pathological staging should be systematicallyplanned to avoid inadequateevidence for exclusion of surgery or conversely, incomplete resection [29–32]. Pathological staging also remains relevant forunresectable tumors to guide the mediastinal radiation dose and field [39,40].

Notably, variationsin medical strategies were observed amongthe centers in terms of chemoradiation scheduling. International guidelines recommend concurrent chemoradiotherapy, as it was shown to confer higher 5-year OS rates than a sequential regimen [41,42]. However, forolder patients with poor Eastern Cooperative Oncology Group or WHO PS, or relevant comorbidities, sequential chemoradiation remains an alternative [43]. The choice of sequential treatment must be discussed in TBMs and depends on the physicians' expertise, which guides their attribution ofdifferent weights to the abovementioned patient characteristics. Herein, TBM participants harmoniously chose a concurrent medical strategy scheme forcases 1, 5, and 6, who were under 75 years of age and had no remarkable medical history. When one or more unfavorable parameters werepresent, the chemoradiationsequence choice was subject to divergence (cases 2, 3, and 4).

Table 4
Associations between Tumor Board Meeting (TBM)characteristics and therapeutic strategies: configuration 1: analysis of pooled cases 1–3, configuration 2: analysis of pooled case 4–6, and configuration 3: individual analyses of cases 4–6.

TBM characteristic	Configuration 1 Cases 1–3 OR [95 % CI]	*p*	Configuration 2 Cases 4–6 OR [95 % CI]	*p*	Configuration 3 Case 4 OR [95 % CI]	*p*	Case 5 OR [95 % CI]	*p*	Case 6 OR [95 % CI]	*p*
Type of care structure	3.61 (0.48–27.1)	0.10	2.02 (0.78–5.2)	0.15	5.83 (0.98–34.6)	0.05	0.83 (0.17–4.1)	0.82	2 (0.35–11.4)	0.43
Thoracic surgeon at TBMs	No convergence	–	No convergence		No convergence		No convergence		No convergence	
Imaging physician at TBMs	3.29 (0.36–30.1)	0.29	1.68 (0.58–4.85)	0.34	1.8 (0.26–12.3)	0.54	1.2 (0.21–6.88)	0.84	2.44 (0.41–14.8)	0.33
Mean patient files /session, n	1.1 (0.97–1.14)	0.21	1.01 (0.97–1.06)	0.49	1.1 (0.99–1.22)	0.08	1 (0.94–1.07)	0.93	0.97 (0.9–1.04)	0.42
Annual incident cases, n	1 (0.99–1.01)	0.97	1 (0.99–1)	0.36	1.01 (0.99–1.01)	0.07	1 (0.99–1.01)	0.73	0.99 (0.99–1)	0.46
Stage III at diagnosis, %	–	–	1.06 (0.99–1.14)	0.11	1.02 (0.92–1.14)	0.71	1.06 (0.94–1.19)	0.30	1.19 (0.94–1.52)	0.06
Mean EBUS stagings /year and /center, n	0.99 (0.97–1.01)	0.40	1 (0.98–1.01)	0.64	0.99 (0.97–1.01)	0.38	1.01 (0.99–1.03)	0.27	0.98 (0.96–1.01)	0.22
Mean mediastinoscopies /year and /center, n	1.01 (0.97–1.05)	0.58	1 (0.97–1.02)	0.87	0.98 (0.94–1.03)	0.50	1.01 (0.96–1.05)	0.74	1 (0.95–1.05)	0.98
Lobectomies/year and /center, n	No convergence	–	1 (0.99–1.01)	0.48	1 (0.99–1.01)	0.99	1 (0.99–1.01)	0.83	1.01 (0.99–1.02)	0.22
Pneumonectomies /year and /center, n	No convergence	–	1 (0.99–1.01)	0.48	0.96 (0.89–1.04)	0.30	1 (0.93–1.08)	0.94	1 (0.93–1.08)	0.97
Thoracic radiations /year and /center, n	1 (0.99–1.02)	0.77	1 (0.99–1.01)	0.70	1 (0.98–1.02)	0.88	1.01 (0.99–1.03)	0.29	0.99 (0.98–1.01)	0.56

EBUS: endobronchial ultrasonography.

Regardless of whether the concurrent or sequential scheme is validated, consolidation durvalumab is now being used extensively forpatients with non-progressive disease after chemo-radiation, independentof their programmed cell death protein-1 ligand (PD-L1) status [44–46]. However, with regard to cases 3 and 5 who harboredEGFR mutations, a sticking point fordurvalumab lies in its relevance against tumors with actionable or non-actionable oncogene addiction [14]. The PACIFIC trial included patients irrespective of the *EGFR* mutation status, and recent post-hoc exploratory analyses indicated unclear OS benefit of durvalumabfor this subgroup [44,47,48]. Durvalumab may carry an unfavorable benefit/risk ratio for this subgroup, especially considering the cumulative toxicities when switching to tyrosine kinase inhibitors (TKIs)in cases that relapse on durvalumab [44,47]. Theanticipatedresultsof the phase III LAURA trial may soon lead to the approval of osimertinib as post-chemoradiationmaintenance for patients with common sensitizing *EGFR* mutations [49].

Similarly, TBMpanel-approved surgical strategies consisted of diverse perioperative sequences. To date, no randomized trial has compared neoadjuvant and adjuvant strategies, and the results of *meta*-analyses based on indirect comparisons have provided no evidence favoring one over the others in terms of PFS or OS [50–52]. The adopted sequence is left to the discretion of TBM participants and thoracic surgeons. In OBSERVE IIIA–B, the TBM surgical strategy decisions favored neoadjuvant chemotherapy rather than adjuvant chemotherapy. This preference for preoperative chemotherapy was probably driven by its good observance rate, acceptable safety profile, and ability to treat micrometastatic disease early [50,53]. Neoadjuvant chemotherapy can also result in downstaging and is sometimes deemed to improve resectability [50,53]. Notably, when confronted with borderline resectability, TBMmembers resorted to choosinginduction chemotherapy followed by new imaging assessment. This strategic decisionleavessurgery an option in case of a partial or complete response. However, in the absence of downstaging, radiation will have to be delayed, and chemoradiation will be more sequential than concurrent, potentially limiting locoregional control outcomes [3,41]. In addition, the choice of induction strategy raises questions about mediastinal restaging. Mediastinal clearance seems to be a good prognostic factor, but there is no evidence suggestingthat patients with nodal downstaging or tumormass reduction will benefit from surgeryor that patients with stable disease or persistent N2 will not [19,54].

Currently, decision trees for immune checkpoint inhibitors (ICIs)are being revised forresectable locally advanced NSCLC. They seem to havesignificant advantages, specifically in the neoadjuvant context [55]. Neoadjuvant nivolumab recently received European and French approval, in combination with chemotherapy, based onCheckMate 816 findings [56]. In this trial, nivolumabprovided significant benefits in terms of major pathologic response and pathological complete response, which are the new surrogate endpoints for survival in the assessment of preoperative ICIs. Other promising phase II and III trials are evaluating neoadjuvantprogrammed cell death protein-1 (PD-1)/PD-L1 blockade in combination with chemotherapy as well as neoadjuvant double checkpoint inhibition [57–59]. A large panel of neoantigens expressed by macroscopic lesions has been reported to promote antitumor immunity and immunotherapy efficacy in the preoperative setting [55].

Targeted therapies are also revolutionizing the therapeutic management of stageIII NSCLC. Some TBM reports acknowledged that the presence of the *EGFR* exon-19 deletion in case 5 directed their decision towards a surgical strategy. Indeed, since the ADAURA results were published [60–62], three years of adjuvant osimertinibhas been recommended after optional adjuvant chemotherapy for completely resected *EGFR*-mutant tumors. In light of the NEOADAURAtrial on the preoperative implementation of osimertinib, questions about neoadjuvant and adjuvant osimertinibtimingmay soon emerge [61,63]. Nonetheless, the prolonged benefits ofadjuvant TKI seem relevant, as recentlyhighlightedfor osimertinib, which achieved higher 5-year OS rates [64]. Similarly, for locally advanced anaplastic lymphoma kinase-translocation (*ALK*)-rearranged NSCLC, many trials are testing the potential benefits of perioperative anti-ALK TKIs [65].

Another key factor contributing to decision-making is the type of surgical procedure that must be considered to achieve R0. In OBSERVE IIIA–B, many TBMreports indicated that members would havepreferentially opted for surgical resectionforcases 1, 4, and 6 if the intervention was lobectomy rather than pneumonectomy. Indeed, right pneumonectomies are known to increase postoperative morbidity and mortality [14,66,67]. Several TBM panels validatedupfront surgical resection for case 4 because of the necrotic aspect of the mass, usually described as a harmful prognostic factor that increases radiation resistance and side effects [68,69].

The OBSERVE IIIA–B study has several limitations. The main limitationwas the selection biasintroduced during the screening of patient records to establish the distinct six-case set sent to the 27 participating TBMs. In an attempt to avoid this predictable pitfall, the cases were selected from among resected and non-resected stage-III-N2 NSCLCs, with the intent of covering most clinical N2 presentations (mono-station, multi-station, limited, or bulky involvement). Tumor size, distance fromthe hilum, invasion of adjacent organs, histological pattern, molecular alterations, and patient characteristics were considered to obtain a sample that was as diverse as possible to approximate real-life situations to the greatest extent.

Another limitation of this study is that only partial quorum was attained insome TBMs. Specifically, two TBM reports declared the absence of a thoracic surgeon, even though surgeons play a key role in the assessment of tumor resectability [24]. Moreover, surgeons and radiation oncologistsshould ideally participatein these multidisciplinary debates. The results ofa Swiss study demonstrated specialty biases in decision-making, as radiation oncologists more systematically tended towards chemo-radiation, while surgeons tended to opt for surgery [9]. Notably, 15 % of TBMs took place without any imaging specialist, which might have hampered the accuracy of baseline staging. The identification of frailty in olderpatients was potentially limited because no oncogeriatrician attended the sessions; this situation might have influenced decisions concerning cases 2 and 3.

Third, our study failed to identify any technical or demographic criteria that might affect therapeutic decisions. Indeed, approving a surgical or medical approach might not have been influenced by the hospital characteristics, especially because all the enrolled hospitals were modern, specialized, and well-equipped. Nevertheless, the negative results of this study must be interpreted with caution, and no formal definitive conclusion should be drawn from the statistical analysesas they were based on only six cases submitted to the TBMs. Although a higher statistical power would have been reached if many more cases were selected for review by the participating TBMs, such an approach would have been time-consuming, and thus, more difficult to achieve.

Fourth, although the selected cases were close to reality, the study did not address the potential impact of therapeutic divergenceonthe survival outcomes. To the best of our knowledge, only a few studies, mostly retrospective, have addressed the impact on patients [34,70]. Finally, certain factors, such as the distance separating the patient from a radiotherapy center or access to clinical trials,were not studied in this analysis.

5. Conclusion

This multicenterprospective study conducted among French TBMs highlighted substantial differences in the therapeutic choices for the management of stage-III-N2 NSCLCacross care facilities. Indications for surgery remain unclear, and future studies will have to address the therapeutic challenges of managing the heterogeneousdisease subgroups in this stage. Considering the continuous therapeutic repositioning of ICIs and targeted therapies for locally advanced stages, strategies are expected to change markedly for both resectable and non-resectable tumors. In this shifting therapeutic landscape, it can beargued that—more than ever—TBMs are essential tools for providing each patient with personalized multimodal treatment.

CRediT authorship contribution statement

Mathilde Jacob: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Pierre Fournel:** . **Claire Tissot:** . **Jacques Cadranel:** Writing – review & editing, Formal analysis. **Olivier Bylicki:** Writing – review & editing, Validation, Resources, Investigation, Funding acquisition. **Isabelle Monnet:** Writing – review & editing, Investigation, Data curation. **Grégoire Justeau:** Writing – review & editing, Validation, Investigation. **Charles Ricordel:** Writing – review & editing, Validation, Investigation. **Pascal Thomas:** Writing – review & editing, Validation, Investigation. **Lionel Falchero:** Writing – review & editing, Validation, Investigation. **Chrystel Locher:** Writing – review & editing, Validation, Investigation. **Marie Wislez:** Writing – review & editing, Validation, Investigation. **Alain Vergnenegre:** Writing – review & editing, Funding acquisition. **Samir Abdiche:** Writing – review & editing, Validation, Investigation. **Floran Guisier:** Writing – review & editing, Validation, Investigation. **Acya Bizieux:** Writing – review & editing, Validation, Investigation. **Regine Lamy:** Writing – review & editing, Validation, Investigation. **Geraldine François:** Writing – review & editing, Validation, Investigation. **Gonzagues De Chabot:** Writing – review & editing, Validation, Investigation. **Thomas Pierret:** Writing – review & editing, Validation, Investigation. **Marie Sabatini:** Writing – review & editing, Validation, Investigation. **Marion Abeillera:** . **Sabine Vieillot:** Writing – review & editing, Validation, Investigation. **Stephanie Martinez:** Writing – review & editing, Validation, Investigation. **Hugues Morel:** Writing – review & editing, Validation, Investigation. **Hélène Doubre:** Writing – review & editing, Validation, Investigation. **Anne Madroszyk:** Writing – review & editing, Validation, Investigation. **Margaux Geier:** Writing – review & editing, Validation, Investigation. **Jean LucLabourey:** Writing – review & editing, Validation, Investigation. **Christos Chouaïd:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Laurent Greillier:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.107868.

References

[1] A. Casal-Mouriño, A. Ruano-Ravina, M. Lorenzo-González, et al., Epidemiology of Stage III Lung Cancer: frequency, Diagnostic Characteristics, and Survival, Transl Lung Cancer Res. 10 (2021) 506–518.
[2] W. Lim, C.A. Ridge, A.G. Nicholson, S. Mirsadraee, The 8th Lung Cancer TNM Classification and clinical Staging System: Review of the Changes andClinical Implications, Quant Imaging Med Surg. 8 (2018) 709–718.
[3] P.E. Postmus, K.M. Kerr, M. Oudkerk, et al., Early and locally Advanced Non-Small-Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, AnnOncol. (2017;28:iv1–iv21.).
[4] J.P. Van Meerbeeck, C. De Pooter, J. Raskin, A. Janssens, P.E. Van Schil, Local treatment of Stage IIIA-N2 Non-Small Cell Lung Cancer: surgery and/or radiotherapy, CurrOpinOncol. 32 (2020) 54–62.
[5] P.M. Putora, P. Leskow, F. McDonald, T. Batchelor, M. Evison, International Guidelines on Stage III N2 Non-Small Cell Lung Cancer: surgery or radiotherapy? ERJ Open Res. 6 (2020) 00159–02019.
[6] P.L. Su, G.C. Chang, S.H. Hsiao, et al., An Observational Study on Treatment Outcomes in Patients with Stage III NSCLC in Taiwan: the KINDLE study, JTO ClinResRep. 3 (2022) 100292.
[7] D.V. Flury, F. Minervini, G.J. Kocher, Heterogeneity of Stage IIIA Non-Small Cell Lung Cancer—different tumours, different nodal status, different treatment, different prognosis: a narrative review, Curr Chall Thorac Surg. 4 (2022) 13.
[8] C. Yoo, S. Yoon, D.H. Lee, et al., Prognostic Significance of the Number of Metastatic pN2 Lymph Nodes in Stage IIIA-N2 Non–Small-Cell Lung Cancer after Curative Resection, ClinLung Cancer. 16 (2015) e203–e212.
[9] M. Glatzer, P. Leskow, F. Caparrotti, et al., Stage III N2 Non-Small Cell Lung Cancer Treatment: Decision-Making Among Surgeons And Radiation Oncologists, Transl Lung Cancer Res. 10 (2021) 1960–1968.
[10] Z. Aoun-Bacha, N. Bitar, W. Abi Saleh, et al., Diagnosis and Management of Patients with Stage III Non–Small-Cell Lung Cancer: A Joint Statement by the Lebanese Society of Medical Oncology and the Lebanese Pulmonary Society (Review), Oncol Lett. 25 (2023) 113.
[11] T. Allaeys, L. Berzenji, P. Lauwers, et al., Multimodality Treatment Including Surgeryrelated to the Type of N2 Involvement In Locally Advanced Non-Small Cell Lung Cancer, Cancers 14 (2022) 1656.

[12] F. Petrella, S. Rizzo, I. Attili, et al., Stage III Non-Small-Cell Lung Cancer: an Overview of Treatment Options, CurrOncol. 30 (2023) 3160–3175.
[13] P.E. Van Schil, Stage IIIA-N2 Non Non–Small-Cell Lung Cancer: from 'surprise' involvement to surgical nightmare, Eur J Cardiothorac Surg. 49 (2016) 1613–1614.
[14] A. Scherpereel, E. Martin, L. Brouchet, et al., Reaching Multidisciplinary Consensus On The Management Of Non-Bulky/Non-Infiltrative Stage IIIA N2 Non-Small Cell Lung Cancer, Lung Cancer 177 (2023) 21–28.
[15] C.C. Pan, P.T. Kung, Y.H. Wang, et al., Effects Of Multidisciplinary Team Care On The Survival Of Patients With Different Stages Of Non-Small Cell Lung Cancer: A National Cohort Study, PLoS One 10 (2015) e0126547.
[16] Y. Lievens, European Cancer Organisation Essential Requirements for Quality Cancer Care (ERQCC): Lung cancer, Lung Cancer (2020).
[17] T. Bilfinger, R. Keresztes, D. Albano, B. Nemesure, Five-Year Survival among Stage IIIA Lung Cancer Patients Receiving Two Different Treatment Modalities, Med Sci Monit. 22 (2016) 2589–2594.
[18] D. Yusuf, R.N. Walton, M. Hurry, et al., Population-Based Treatment Patterns and Outcomes for Stage III Non-Small Cell Lung Cancer Patients, A Real-World Evidence Study.*AmJClinOncol*. 43 (2020) 615–620.
[19] H. Decaluwé, P. De Leyn, J. Vansteenkiste, et al., Surgical Multimodality Treatment For Baseline Resectable Stage IIIA-N2 Non-Small Cell Lung Cancer. Degree Of Mediastinal Lymph Node Involvement And Impact On Survival, EurJCardiothoracSurg. 36 (2009) 433–439.
[20] M.J.A. Rasing, M. Peters, M.J. Aarts, et al., Adjuvant Treatment Following Irradical Resection of Stage I-IIINon-Small Cell Lung Cancer: A Population-Based Study, CurrProblCancer. 46 (2022) 100784.
[21] M.J.A. Rasing, M. Peters, A.C. Moreno, et al., Predicting Incomplete Resection In Non-Small Cell Lung Cancer Preoperatively: A Validated Nomogram, AnnThoracSurg. 111 (2021) 1052–1058.
[22] P.E. Van Schil, K. Yogeswaran, J.M. Hendriks, P. Lauwers, C. Faivre-Finn, Advances in the use of Surgery And Multimodality Treatment for N2 Non-Small Cell Lung Cancer, Exp RevAnticancer Ther. 17 (2017) 555–561.
[23] B. Jeremic, F. Casas, P. Dubinsky, et al., Combined Modality Therapy in Stage IIIA Non-Small Cell Lung Cancer: Clarity or Confusion Despite The Highest Level of Evidence? JRadiatRes. 58 (2017) 267–272.
[24] P.E. Van Schil, Berzenji L, Yogeswaran SK, Hendriks JM, Lauwers P. Surgical management of Stage IIIA Non-Small Cell Lung Cancer, Front Oncol, 2017.
[25] D. Brascia, G. De Iaco, M. Schiavone, et al., Resectable IIIA-N2 Non-Small-Cell Lung Cancer (NSCLC): in search for the proper treatment, Cancers 12 (2020) 2050.
[26] D.LX. QingWY, B.W. Liang, et al., Identification of resectable N2 in NSCLC: a single center experience and review of the SEER database. *Front*, Oncol. (2021).
[27] J. Lin, F. Fernandez, Indications for invasive mediastinal staging for Non-Small Cell Lung Cancer, JThoracCardiovascSurg. 156 (2018) 2319–2324.
[28] J.A. Gullón, M.A. Villanueva, A.A. Sánchez-Antuña, et al., Predictors of mediastinal staging and usefulness of PET in patients with stage IIIA (N2) or IIIB (N3) Lung Cancer, Clin Respir J. 15 (2021) 42–47.
[29] P. De Leyn, C. Dooms, J. Kuzdzal, D. Lardinois, B. Passlick, R. Rami-Porta, et al., Revised ESTS Guidelines for Preoperative Mediastinal Lymph Node Staging for Non-Small-Cell Lung Cancer, EurJCardiothoracSurg. 45 (2014) 787–798.
[30] D.S. Ettinger, D.E. Wood, C. Aggarwal, et al., NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. *Jnatlcomprcancnetw*. 17 (2019) 1464–1472.
[31] G.A. Silvestri, A.V. Gonzalez, M.A. Jantz, et al., Methods for staging Non-Small Cell Lung Cancer, Chest 143 (2013) e211S–e250.
[32] W.E.E. Eberhardt, D. De Ruysscher, W. Weder, et al., 2nd ESMO Consensus Conference in Lung Cancer: Locally Advanced Stage III Non-Small-Cell Lung Cancer, AnnOncol 26 (2015) 1573–1588.
[33] J. Mainguené, Surgical or Medical Strategy for Locally-Advanced, Stage IIIA/B-N2 Non-Small Cell Lung Cancer: reproducibility of decision-making at a Multidisciplinary Tumor Board, Lung Cancer (2022 Jan).
[34] A. Kommalapati, S.H. Tella, A.K. Appiah, L. Smith, A.K. Ganti, Association between treatment facility volume, therapy types, and Overall Survival in patients with Stage IIIA Non-Small Cell Lung Cancer, JNatlComprCancNetw. 17 (2019) 229–236.
[35] T.V. Bilfinger, D. Albano, M. Perwaiz, R. Keresztes, B. Nemesure, Survival Outcomes among lung Cancer Patients treated using a Multidisciplinary Team Approach, ClinLung Cancer. 19 (2018) 346–351.
[36] M.L. Specchia, E.M. Frisicale, E. Carini, et al., The impact of Tumor Board on cancer care: evidence from an umbrella review, BMC Health Serv Res. 20 (2020) 73.
[37] M.S. Kim, H.Y. Park, B.G. Kho, et al., Artificial Intelligence and Lung Cancer Treatment Decision: agreement with recommendation of Multidisciplinary Tumor Board, Transl Lung Cancer Res. 9 (2020) 507–514.
[38] R. Kremer, Y. Peysakhovich, L.F. Dan, et al., FDG PET/CT for assessing the resectability of NSCLC patients with N2 disease after neoadjuvant therapy, Ann Nucl Med. 30 (2016) 114–121.
[39] D.P. Steinfort, S. Siva, K. Rangamuwa, et al., Systematic Endoscopic Staging of mediastinum to determine impact on radiotherapy for Locally Advanced Lung Cancer (SEISMIC): protocol for a Prospective Single Arm Multicentre Interventional Study, BMC Pulm Med. 22 (2022) 364.
[40] D.P. Steinfort, S. Siva, T.L. Leong, et al., Systematic Endobronchial Ultrasound-guided mediastinal staging versus Positron Emission Tomography for comprehensive mediastinal staging in NSCLC before radical radiotherapy of Non-Small Cell Lung Cancer: a pilot study, Medicine 95 (2016) e2488.
[41] W.J. Curran, R. Paulus, C.J. Langer, et al., Sequential vs Concurrent Chemoradiation for Stage III Non-Small Cell Lung Cancer: randomized phase III trial RTOG 9410, Jnatl Cancer Inst. 103 (2011) 1452–1460.
[42] A. Aupérin, C. Le Péchoux, E. Rolland, et al., Meta-Analysis of Concomitant versus Sequential Radiochemotherapy in Locally AdvancedNon–Small-Cell Lung Cancer, J Clin Oncol. 28 (2010) 2181–2190.
[43] M.E. Daly, N. Singh, N. Ismaila, et al., Management of Stage III Non–Small-Cell Lung Cancer: ASCO guideline, J Clin Oncol. 40 (2022) 1356–1384.
[44] C. Faivre-Finn, D. Vicente, T. Kurata, et al., Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an update from the PACIFIC trial, JThoracOncol. 16 (2021) 860–867.
[45] S.J. Antonia, A. Villegas, D. Daniel, et al., Overall Survival with Durvalumab after Chemoradiotherapy In Stage III NSCLC, NEnglJMed. 379 (2018) 2342–2350.
[46] M.C. Garassino, J. Mazieres, M. Reck, et al., Durvalumab after sequential chemoradiotherapy in stage III, unresectable NSCLC: the phase 2 PACIFIC-6 trial, JThoracOncol. 17 (2022) 1415–1427.
[47] J.V. Aredo, J.A. Hellyer, J.W. Neal, H.A. Wakelee, Consolidation Durvalumab should not be administered to patients with Stage III *EGFR*-mutant NSCLC, JThoracOncol. 16 (2021) 1994–1998.
[48] S.J. Antonia, A. Villegas, D. Daniel, et al., Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer, NEnglJMed. 377 (2017) 1919–1929.
[49] S. Lu, I. Casarini, T. Kato, et al., Osimertinib maintenance after definitive chemoradiation in patients with unresectable *EGFR*mutation Positive Stage III Non–Small-Cell Lung Cancer: LAURA trial in progress, ClinLung Cancer. 22 (2021) 371–375.
[50] R. Palmero, N. Vilariño, A. Navarro-Martín, E. Nadal, Induction treatment in patients with Stage III Non-Small Cell Lung Cancer, Transl Lung Cancer Res. 10 (2021) 539–554.
[51] NSCLC Meta-analysis Collaborative Group, Preoperative chemotherapy for Non-Small-Cell Lung Cancer: a Systematic Review and Meta-Analysis of individual participant data, Lancet 383 (2014) 1561–1571.
[52] E. Lim, G. Harris, A. Patel, I. Adachi, L. Edmonds, F. Song, Preoperative versus Postoperative Chemotherapy in patients with resectable Non-Small Cell Lung Cancer: systematic review and Indirect Comparison Meta-Analysis of Randomized Trials, JThoracOncol. 4 (11) (2009) 1380–1388.
[53] J.E. Chaft, Y. Shyr, B. Sepesi, P.M. Forde, Preoperative and Postoperative systemic therapy for operable Non–Small-Cell Lung Cancer, J Clin Oncol. 40 (2022) 546–555.
[54] W. Andrews, Persistent N2 after induction is not a contraindication to surgery for Lung Cancer, AnnThoracSurg. (2022).
[55] M. Provencio, Treatment sequencing in Resectable Lung Cancer: the good and the bad of Adjuvant versus Neoadjuvant Therapy, *Am SocClinOncoL*. (2022).
[56] M. Provencio, Neoadjuvant Nivolumab (NIVO) + Platinum-Doublet Chemotherapy (Chemo) Versus Chemo For Resectable (IB–IIIA) Non-Small Cell Lung Cancer (NSCLC): association of Pathological Regression with Event-Free Survival (EFS) in CheckMate 816, J Clin Oncol. (2022).
[57] S.I. Rothschild, A. Zippelius, E.I. Eboulet, et al., SAKK 16/14: Durvalumab in addition to Neoadjuvant Chemotherapy in patients with Stage IIIA (N2) Non-Small Cell Lung Cancer—A Multicentre Single-Arm Phase II Trial, J Clin Oncol. 39 (2021) 2872–2880.
[58] C.A. Shu, J.F. Gainor, M.M. Awad, et al., Neoadjuvant Atezolizumab And Chemotherapy in patients with resectable Non-Small-Cell Lung Cancer: an Open-Label, Multicentre, Single-Arm, Phase 2 Trial, Lancet Oncol. 21 (2020) 786–795.
[59] T. Cascone, W.N. William, A. Weissferdt, et al., Neoadjuvant Nivolumab Or Nivolumab Plus Ipilimumab In Operable Non-Small Cell Lung Cancer: the Phase 2 Randomized NEOSTAR trial, Nat Med. 27 (2021) 504–514.
[60] Y.L. Wu, R.S. Herbst, H. Mann, Y. Rukazenkov, M. Marotti, M. Tsuboi, ADAURA: Phase III, Double-Blind, Randomized Study Of Osimertinib Versus Placebo in *EGFR*mutation-positive Early-Stage NSCLC after Complete Surgical Resection, ClinLung Cancer. 19 (2018) e533–e536.
[61] M. Tsuboi, W. Weder, C. Escriu, et al., Neoadjuvant Osimertinib with/without chemotherapy versus Chemotherapy alone for *EGFR*-mutated Resectable Non-Small-Cell Lung Cancer: NeoADAURA, Future Oncol. 17 (2021) 4045–4055.
[62] Y.L. Wu, T. John, C. Grohe, et al., Postoperative Chemotherapy use and outcomes from ADAURA: Osimertinib as Adjuvant therapy for Resected *EGFR*-mutated NSCLC, JThoracOncol. 17 (2022) 423–433.
[63] C. Lv, W. Fang, N. Wu, et al., Osimertinib as Neoadjuvant Therapy in patients with *EGFR*-mutant Resectable Stage II-IIIB Lung Adenocarcinoma (NEOS): A Multicenter, Single-Arm, Open-Label Phase 2B Trial, Lung Cancer 178 (2023) 151–156.
[64] M. Tsuboi, Overall Survival with Osimertinib in Resected *EGFR*-mutated NSCLC, N Engl J Med. (2023).
[65] M. De Scordilli, A. Michelotti, E. Bertoli, E. De Carlo, A. Del Conte, A. Bearz, Targeted Therapy and Immunotherapy in Early-Stage Non-Small Cell Lung Cancer: current evidence and ongoing trials, Int J Mol Sci. 23 (2022) 7222.
[66] Z. Shen, Y. Lu, Y. Sui, S. Feng, J. Feng, J. Zhou, Therapeutic strategies for resectable Stage-IIIA N2 Non-Small Cell Lung Cancer Patients: A Network Meta-Analysis, Clin Med Insights Oncol. 16 (2022).
[67] P.E. Van Schil, M. De Waele, J.M. Hendriks, P.R. Lauwers, Surgical Treatment of Stage III Non-Small Cell Lung Cancer, EurJCancer. 45 (2009) 106–112.
[68] S.W. Moon, J.J. Kim, S.C. Jeong, Y.H. Kim, J.W. Han, Clinical Significance of Tumor Necrosis and Viability In Non-Small Cell Lung Cancer, J Thorac Dis. 14 (2022) 892–904.
[69] S.Y. Park, H.S. Lee, H.J. Jang, G.K. Lee, K.Y. Chung, J.I. Zo, Tumor Necrosis as a Prognostic Factor for Stage IA Non-Small Cell Lung Cancer, AnnThoracSurg. 91 (2011) 1668–1673.
[70] Y. Zhao, W. Wang, H. Liang, et al., The Optimal Treatment for Stage IIIA-N2 Non-Small Cell Lung Cancer: A Network Meta-Analysis, AnnThoracSurg. 107 (6) (2019) 1866–1875.