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ORIGINAL ARTICLE

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

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ABSTRACT

Background

Stage IIIA/B-N2 is a very heterogeneous group of patients and accounts for one third of NSCLC at diagnosis. The best treatment strategy is established at a Multidisciplinary Tumor Board (MTB): surgical resection with neoadjuvant or adjuvant therapy versus definitive chemoradiation with immune checkpoint inhibitors consolidation. Despite the crucial role of MTBs in this complex setting, limited data is available regarding its performances and the reproducibility of the decision-making.

Methods

Using a large cohort of IIIA/B-N2 NSCLC patients, we described patient's characteristics and treatment strategies established at the initial MTB: with a "surgical strategy" group, for potentially resectable disease, and a "medical strategy" group for non-resectable patients. A third group consisted of patients who were not eligible for surgery after neoadjuvant treatment and switched from the surgical to the medical strategy. We randomly selected 30 cases (10 in each of the 3 groups) for a blinded re-discussion at a fictive MTB and analyzed the reproducibility and factors associated with treatment decision.

Results

Ninety-seven IIIA/B-N2 NSCLC patients were enrolled between June 2017 and December 2019. The initial MTB opted for a medical or a surgical strategy in 44% and 56% of patients respectively. We identified histology, tumor size and localization, extent of lymph node involvement and the presence of bulky mediastinal nodes as key decision-making factors. Thirteen patients were not eligible for surgical resection after neoadjuvant therapy and switched for a medical strategy. Overall concordance between the initial decision and the re-discussion was 70%. The kappa correlation coefficient was 0.43. Concordance was higher for patients with limited mediastinal node invasion. Survival did not appear to be impacted by conflicting decisions.

Conclusions

Reproducibility of treatment decision-making for stage IIIA/B-N2 NSCLC patients at a MTB is moderate but does not impact survival.

KEY WORDS

Non-small cell lung cancer

Radiotherapy

Surgery

Immunotherapy

Multidisciplinary Tumor Board

HIGHLIGHTS

-Treatment strategy for stage III NSCLC is either surgical or medical and is established at a Multidisciplinary Tumor Board.

-In a cohort of 97 patients, histology, tumor size and localization, lymph node involvement and presence of bulky mediastinal nodes were key decision-making factors.

-Concordance between the initial MTB decision and the blinded MTB rediscussion was 70%, with a kappa correlation coefficient of 0.43.

ABBREVIATIONS

18-FDG-PET: 18-Fluorodeoxyglucose Positron Emission Tomography

ADK: Adenocarcinoma

AI: Artificial intelligence

cN2: clinical N2 [on physical examination and imaging]

CT: Computed Tomography

DFS: Disease Free Survival

EBUS: EndoBronchial UltraSound

IASLC: International Association for the Study of Lung Cancer

ICI: Immune Checkpoint inhibitors

MTB: Multidisciplinary Tumor Board

NSCLC: Non-Small Cell Lung Cancer

OS: Overall Survival

pN2: pathological N2 [on pathology specimen]

SCC: Squamous Cell Carcinoma

TNM: Tumor, Nodes, Metastases

WFO: Watson For Oncology

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide [1]. Treatment strategies are based on TNM staging, histology, and molecular characteristics [2, 3]. About one third of NSCLC patients are diagnosed with locally-advanced disease. In stage IIIA/B-N2 disease (ipsilateral mediastinal and/or subcarinal lymph node involvement), [2], multimodal treatment is the standard-of-care, consisting of either surgical resection followed or preceded by chemotherapy, or of concurrent or sequential chemo-radiotherapy followed by immune checkpoint inhibitors (ICI) [3]. Assessment of resectability of the tumor is crucial to drive the decision-making between the “surgical” or the “medical” strategy, but limited data is available to actually define specific criteria [4, 5, 6]. The size and location of the primary tumor, the number and size of invaded lymph node stations, metabolic features, and response to induction therapy may be considered as key elements to choose treatment modalities [7-10]. Given the heterogeneity of clinical/imaging presentations of stage IIIA/B-N2 disease, the majority of available literature, including clinical trials comparing surgical or chemo-radiotherapy based strategies [10-13], only refer to resectable vs. unresectable tumors. This complexifies the analysis of outcomes given the potential biases in the initial assessment of the disease. Ultimately, in the setting of resectable disease, only a few randomized trials compared multimodal strategies with or without surgery of the tumor [9, 10], failing to demonstrate the benefit of resection in terms of survival, which may be related to patient selection issues. Interpreting recent results of perioperative or consolidation treatment with ICI [11-13] or targeted agents [14] is therefore challenging.

The outcomes of stage IIIA/B-N2 NSCLC patients remain poor, with 5-year survival rates ranging from 23% to 40% [2, 9], and a high risk of disease recurrence after first-intent treatment, ranging from 40% to 80% [9-14]. This further highlights the need for a better stratification of patients to define personalized treatment strategies. In this matter, it is recommended to discuss each patient case at a Multidisciplinary Tumor Board (MTB) before initiating the treatment [15]. A MTB is a dedicated meeting in which different specialties – medical and radiation oncologists, surgeons, radiologists and nuclear medicine physicians, pulmonologists, pathologists - review patient cases and consensually define the management based on best available evidence. Despite the widespread use of MTBs in oncology, limited data is available regarding the best way to organize these meetings, about their concordance of

treatment strategies with published guidelines, about their outcomes, or their reproducibility in terms of decision [15-18].

Here we took advantage of a large cohort of consecutive patients with stage IIIA/B-N2 NSCLC to describe treatment strategies and outcomes, assess the reproducibility of the MTB conclusions, and understand the factors associated with the decision-making.

MATERIALS AND METHODS

Study design

We retrospectively collected baseline characteristics, histology, stage, treatment strategies, and outcomes of consecutive patients with stage IIIA/B-N2 NSCLC. Patients were treated at the Thorax Institute Curie-Montsouris, a leading center for the treatment of thoracic cancers in France with a dedicated team of four thoracic surgeons, five pulmonologists, five thoracic oncologists, two radiation oncologists and two pathologists, together with radiologists and nuclear medicine physicians. In France, it is mandatory to discuss the management of all newly diagnosed patients at a MTB, with a full review of the medical records and imaging. A standardized report is established and inserted in the patient's electronic medical file. Our MTB followed the ESMO clinical practice guidelines for the management of non-metastatic that were available during of the study period [19].

We randomly selected cases for a blinded new discussion at a second MTB, separating two main populations, “surgical” (surgery can be considered) or “medical” (surgery has no role in the patient’s treatment). The primary endpoint is the concordance between the decisions about treatment strategies taken at the initial and blinded fictive MTB.

The Institutional Data Review Committee of Institute Curie approved the study. All patients gave consent for the retrieval of healthcare information from their electronic medical record.

Patient population

Patients were identified through institutional databases. Of a total of 1786 consecutive, newly diagnosed patients with NSCLC referred to our center between June 2017 and December 2019, 97 had stage IIIA/B-N2 on initial staging [2]. We used the 8th edition of the TNM classification [2]. Minimal initial work-up included Computed-Tomography (CT)-scan, 18-Fluoro-Deoxy-Glucose Positron Emission Tomography (18-FDG-PET), and EndoBronchial UltraSound (EBUS) that was systematically performed if indicated [20]. Beyond the clinical stage,

inclusion criteria were the following: age \geq 18 years, histological confirmation of NSCLC, discussion of initial treatment at the Thorax Institute Curie-Montsouris's MTB, available data and follow-up. Patients initially classified cN0/1 who had been reclassified as pN2 after pathological examination of a surgical specimen were not included. N2a was defined as a single mediastinal station invasion without hilar station invasion. Single mediastinal station invasion with hilar station invasion was referred as N2b and N2c if multiple mediastinal stations were invaded. This classification was made on invasive staging when indicated and on imaging when invasive staging was not recommended.

Patient groups

Patients were classified based on the decision made at the initial MTB, into two groups: a “surgical strategy” group, for patients considered to harbor resectable disease, either upfront or after neoadjuvant therapy; and a “medical strategy” group, for patients for whom consensual decision was that of non-resectability. Patients' operability was taken into account [21]. A third group of patients consisted of those initially considered resectable, who were switched to medical treatment after neoadjuvant therapy because of non-resectability. In this group, rediscussion after neoadjuvant therapy was taken by the same MTB members than for the initial MTB.

Blinded MTB review

We randomly selected 10 patients from each of the above groups for a blinded new discussion at a fictive MTB. The participating physicians at the two MTBs were the same, with at least three thoracic surgeons, three pulmonologists, three thoracic oncologists, one radiation oncologist, one radiologist, and one nuclear medicine physician. All participants, including the presenting physician who was independent from the group, were blinded to the original treatment decision. To ensure that all relevant information was available, we used a standardized case presentation form (Supplementary Table 1), that included gender, age, performance status, weight loss, smoking status, symptoms, comorbidities, cardiology and pulmonary function tests, histological type, PD-L1 expression, staging reports including CT-scan, 18-FDG-PET, invasive staging and brain imaging. Relevant imaging tests were reviewed after anonymization.

Statistical analyses

The primary endpoint is the concordance between the decisions about treatment strategies taken at the initial and at the blinded fictive MTBs. All patients were included in the statistical calculations. Categorical variables were compared using the Chi-square test or Fisher test when appropriate. The differences were considered as statistically significant at the 0.05 level (bilateral test). All analyses were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. Overall survival (OS) was defined as the time interval from diagnosis to death. Disease Free Survival was defined as the time interval from diagnosis to recurrence of tumor or death. Survival data were censored at the date of last follow-up. Survival curves were estimated by the Kaplan–Meier method, and compared using the Log-Rank test. The Cohen kappa coefficient was used to evaluate reproducibility.

RESULTS

Patients' characteristics

During the study period, 97 consecutive patients were diagnosed with stage IIIA/B-N2 NSCLC. Clinical and tumor's characteristics are summarized in **Table 1**. Briefly, median age was 65 years [range: 32-86], 51 (53%) patients were men, 58 (60%) had adenocarcinomas, 20 (34%) of which had oncogenic driver alteration – six EGFR mutations, three ALK fusion, ten KRAS mutations, one HER2 mutation. Performance status was 0-1 in 92 (95%) patients. The population was representative of cN2 heterogeneity, with an equal distribution of patients across all T and N2 stage groups.

Treatment strategies

Treatment strategies after the initial MTB are shown on **Figure 1**; treatment strategies were in accordance with published guidelines. Decision of a medical strategy was made for 43 (44%) patients, consisting of chemo-radiotherapy in 36 (37%) patients. Twenty-eight (29%) patients received consolidation with ICI.

Decision of a surgical strategy was made for 54 (56%) patients, with upfront surgery for 15 (15%) patients followed by adjuvant treatment in 12 (12%) patients, and neoadjuvant treatment delivered to 39 (40%) patients. Ultimately, after neoadjuvant treatment, 25 (26%) patients underwent surgery, followed by adjuvant radiotherapy in 13 (13%) patients. Thirteen (13%) patients were finally deemed not eligible for surgical resection of the tumor, and received a

medical treatment, consisting of chemoradiotherapy; seven patients (7%) received consolidation with ICI.

Clinical and tumor's characteristics according to the treatment received are summarized in **Table 1**. Patients' baseline characteristics were not different among those three groups, with the exception of histology ($p=0.03$) and size of mediastinal nodes ($p=0.04$). In the surgical arm we observed less bulky mediastinal involvement and adenocarcinomas were more represented than squamous cell carcinomas. Patients who finally received a medical treatment strategy, displayed more often squamous cell carcinomas ($p=0.01$), T3-T4 tumors ($p=0.01$), right inferior lobe or middle lobe located tumors ($p=0.01$), a higher number of mediastinal stations invaded ($p=0.04$) and had more often bulky mediastinal nodes $>20\text{mm}$ ($p=0.01$).

Ultimately, 40 (41%) patients underwent surgical resection of the tumor, consisting of 35 (87%) lobectomies, four (10%) bi-lobectomies, and one left side pneumonectomy. Lymph node dissection led to the analysis of an average of 15.5 nodes [range: 3-45]. Post-operative staging was pN0 for seven (18%), pN1 for three (7%) and pN2 for 30 (77%) with more than one mediastinal nodal station invaded in 14 patients.

After induction treatment, upstaging was never noted, and 44% of the 25 operated patients had mediastinal downstaging. One toxic death was observed during neoadjuvant treatment. Per or postoperative mortality was not observed. Postoperative complications were observed in 19 (49%) patients; mostly consisting of infection (seven patients), recurrent nerve palsy (five patients), prolonged air leakage (four patients) or/and hemorrhage (one patient). The median hospital stay was six days [range: 2-18].

A total of 49 patients received chemo-radiotherapy as a locoregional treatment with a total radiation dose ranging between 60 to 66 Gy in 2 Gy daily fractions. Chemotherapy was delivered sequentially in 8 patients and concurrently to radiotherapy in 41 patients. The main acute side effects were esophagitis (25 patients), radiation induced pneumonitis (7 patients) and fatigue (4 patients). Supplementary Table 2 displays the adverse events of chemotherapy and radiotherapy according to the CTCAE v4.0.

Blinded MTB review

Among the 97 patients, 30 were randomly determined by drawing lots to be rediscussed at the second MTB, including 10 of the 41 patients with an initial decision of surgical strategy, 10 of the 43 patients with an initial decision of medical strategy, and 10 of the 13 patients who switched from surgical to medical strategy after induction treatment. **Supplementary Table 3** displays the characteristics of the 30 selected patients. The median time between the initial

MTB and the blinded new discussion at the second MTB was 25 months. On average, each patient case was discussed for 4.40min [1.30-9.50].

Overall concordance between the initial decision and the one taken at the blinded MTB was (21/30) 70%. Details of decisions are shown in **Table 2**. The kappa correlation coefficient was 0.43. Discrepancy was observed in 8/20 (40%) patients initially directed to surgical strategy, with a decision of medical treatment at the blinded MTB; interestingly, six of those patients belonged to the group of patients who ultimately switched to the medical treatment. Among patients who were initially oriented for medical treatment, the discrepancy rate was as low as 10%. Clinical and tumor characteristics according to concordance are shown in **Table 3**. Concordance was 100% in patients who presented with only one mediastinal station invaded without any N1/hilar node invasion and was 39% if nodal invasion affected hilar and mediastinal station or more than one mediastinal station ($p=0.03$). The nodal invasion extent was the only identified factor of discrepancy.

Outcomes

With a median follow up of 49 months, median OS in the whole cohort was 43.6 months (IC95% 16.2-70.9); OS and DFS were not statistically different between treatment strategy's arms. OS and DFS were not statistically different in case of conflicting MTB decisions (**Figure 3**).

DISCUSSION

Patients with stage IIIA/B-N2 NSCLC are a heterogeneous subgroup with respect to prognosis and treatment strategies. Although MTBs are mandatory in the management of cancer patients in France and are time consuming, their reproducibility has never been assessed. In our cohort of patients, MTB decided on a medical strategy in 44% (43/97) and on a surgical strategy in 56% (54/97) of patients; among the so-called surgical strategy patients, 40 patients were ultimately resected, and 13 were finally not deemed resectable after neoadjuvant therapy and switched to a medical strategy. Smaller T stage, limited mediastinal invasion, and non-bulky disease were, as expected, characteristics directing decision towards a surgical strategy. The key finding of our study is that, after a blinded re-discussion at the MTB, concordance of the decision regarding surgical vs. medical strategy was 70%, with a kappa coefficient of 0.43. The discrepancy increased with hilar and mediastinal nodal spread. Despite a limited follow-up, survival was not affected by conflicting MTB decisions.

As randomized studies conducted in stage III NSCLC are considering the definition of resectability as a prerequisite before patient enrollment, the question of the reproducibility or the factors ultimately taken into account by MTBs to decide treatment has never been formally addressed. Previous studies focusing on MTB performances questioned the accuracy of staging, care coordination, clinical outcomes, accordance to published guidelines, implementation of the decision taken at the meeting, but never reproducibility [15-18]. In our study, we found a reproducibility of 70%, with a moderate Cohen kappa coefficient. One study evaluated the reproducibility between an artificial intelligence (AI) program called WFO (Watson for Oncology) and MTBs in lung cancer [22]. Concordance between MDTs and WFO occurred in 92.4% [$\text{kappa}=0.881$, $P<0.001$] in the entire NSCLC population and was lower in stage III NSCLCs [concordance 80.8%, $\text{kappa}=0.622$]. In this matter, our study has an original design, with a team of expert physicians in the treatment of thoracic cancers who dedicated time to simulate MTB meetings in the exact same setting as routine MTBs. We minimized evaluation biases with a standardized and complete presentation form. One strength of our study is the representativeness of the population from one of the largest centers for NSCLC treatment in Europe.

In our study, we identified key characteristics orienting MTB decision-making towards a surgical strategy, some of which were expected because they are commonly used to define resectability: smaller T stage, limited mediastinal invasion, and non-bulky diseases. We also identified a higher proportion of adenocarcinomas in the surgical strategy arm. There are two hypotheses to explain this: it may be due to chance regarding the small number of patients, or the clinical presentation of adenocarcinomas that may drive the strategy towards surgery and the presentation of squamous cell carcinoma (SCC) towards a medical strategy. SCCs occur in heavier smokers; the tobacco related comorbidities can limit operability. SCCs tend to be larger, more centrally located and to present with higher lymph node involvement at diagnosis [23]. For patients presenting with a single mediastinal nodal station invaded without N1 invasion, MTB was reproducible in 100% of cases. As already published, patients with unique, non-bulky disease, single stations mediastinal node involvement are good candidates for surgery and decision making is therefore easier [4-6].

Still, we did not clearly identify risk factors for switching to a medical strategy after neoadjuvant treatment. Three of the 13 patients in this group were not downstaged by

chemotherapy, and were not considered resectable at imaging re-assessment, two patients had high PDL1 expression, a known prognostic factor of response to ICI maintenance, which might have oriented toward this treatment strategy [11]. For the eight other patients, they were probably not good candidates for surgery upfront; some patients even had bulky mediastinal disease in this group. In some doubtful cases, the initial MTB may choose to start with induction chemotherapy and after two cycles decide between surgery or radiotherapy, without any loss of opportunity for concurrent chemoradiotherapy. Most experts agree that operating on persisting N2 after induction therapy is harmful and surgery is usually reserved for patients experiencing a mediastinal downstaging (pN1 and pN0) [24]. Dichotomizing at the initial MTB between a surgical and non-surgical strategy is hence precocious, as mediastinal downstaging is known to occur in 20-40% of patients receiving induction therapy [24-28]. Repeated multidisciplinary discussions and monitoring of patients allow to quickly switch decisions, in particular in the absence of downstaging, and are a key for multidisciplinary care coordination. Ultimately, preoperative invasive restaging is infrequently performed, and may actually be recommended in specific groups of patients.

Interestingly, another finding in our study was the moderate reproducibility of MTB decision, with a discrepancy rate even higher when the initial MTB decided on surgery, especially if neoadjuvant treatment was delivered. This first highlights the continuous debate about the indication for surgery in stage III NSCLC [9,10]. Recent trials investigating ICI as neoadjuvant strategies found a resection rate of 83% with the ICI + chemotherapy combination, vs 75% with chemotherapy alone [13]. Furthermore, there is a need to better understand the actual role of induction treatment for stage III resectable NSCLC, primarily to reduce the risk of disease recurrence, and not to render a non-resectable tumor resectable.

This study has several limitations. First, it is a retrospective observational study conducted at a single cancer center. A next step would be to validate our results with other centers. Secondly, the decisions were not made simultaneously but the inclusion period was chosen so no major change in guidelines were published. The PACIFIC trial was published and non-resectable patients were treated accordingly. The last limitation is the small number of rediscussed patients. Organizing fictive MTBs is time consuming; a dozen physicians must give off some of their precious medical time, preparation of the standardized presentation forms and anonymization of imaging tests take time. Indeed, increasing the number of cases presented would increase the statistical power but is hard to achieve.

Finally in our study, with the limitation regarding the small numbers of patients, a reassuring message is that survival was not impacted by a discrepant MTB decision. This finding may have been expected given the limited differences for stage III NSCLC patients in terms of long-term survival outcomes for the surgical strategies, possibly combined with neo- and adjuvant treatments, and the medical strategies based on chemoradiotherapy [9,10,11]. This has to be put in line with the fact that many studies demonstrated that MTB's discussion improves survival in the treatment of lung cancer [16,29,30]. Our work does not call into question the usefulness of MTBs in clinical practice. Ultimately, treatment strategies are evolving quickly in NSCLC; ICI in the neoadjuvant or adjuvant setting might soon redefine treatment strategies in stage III NSCLC [12,13].

CONCLUSION

In our study, reproducibility of decision-making at a multidisciplinary tumor board for the management of stage III NSCLC was moderate. We strongly encourage such continuous assessment to be included as an indicator of quality of a MTB. This further highlights the need for an optimized stratification of patients in clinical trials assessing the management of those patients, and a special attention to MTB discussions in a routine practice setting.

TABLES AND FIGURES

Table 1: Clinico-biological characteristics of 97 patients with stage IIIA/B-N2 NSCLC according to received treatment

1- χ^2 or fischer test when appropriate comparing the 3 groups

2- χ^2 or fischer test when appropriate comparing patients treated with surgical vs medical strategy

a-large cell or undifferentiated removed from analysis, data on 87

b-information available for 96 patients

c- information available for 73 patients

NA= not applicable, SCC= squamous cell carcinoma, ADK= adenocarcinoma, N2a= single mediastinal station invasion without hilar station invasion N2b= single mediastinal station invasion with hilar station invasion, N2c= multiple mediastinal stations invasion

Table 2. Treatment decision made at the initial and blinded fictive MTB for 30 randomly selected stage IIIA/B-N2 patients

MTB: Multidisciplinary Tumor Board

Switch: tumor initially considered resectable but ultimately no more eligible for surgery after neoadjuvant treatment, and switched to medical treatment

green: concordant decision

red: discrepant decision

Table 3. Clinico-biological characteristics of 30 patients according to the treatment decision reproducibility

a. information available for 87 patients

b. information available for 89 patients

c. information available for 96 patients

d. χ^2 test or Fisher when appropriate

MTB= Multidisciplinary Tumor Board, SCC= Squamous Cell Carcinoma, ADK= adenocarcinoma, N2a= single mediastinal station invasion without hilar station invasion

N2b= single mediastinal station invasion with hilar station invasion, N2c= multiple mediastinal stations invasion

Figure 1. Flow chart representing treatment strategies for 97 stage IIIA/B-N2 patients

CT: chemotherapy

RT: radiotherapy

NSCLC: non-small-cell lung cancer

1: immune checkpoint inhibitor n=1, CT+RT 45 Gy n=1, afatinib n=1

2: exclusive RT n=2, exclusive CT n=1, immune checkpoint inhibitor n=1,
immune checkpoint inhibitor + RT n=1, progression n=1, treatment refusal n=1

3: One toxic death during neoadjuvant regimen

Figure 2. Overall Survival and Disease-Free Survival depending on reproducibility of Multidisciplinary Tumor Board decision making and received treatment in stage IIIA/B-N2 patients

MTB= Multidisciplinary Tumor Board

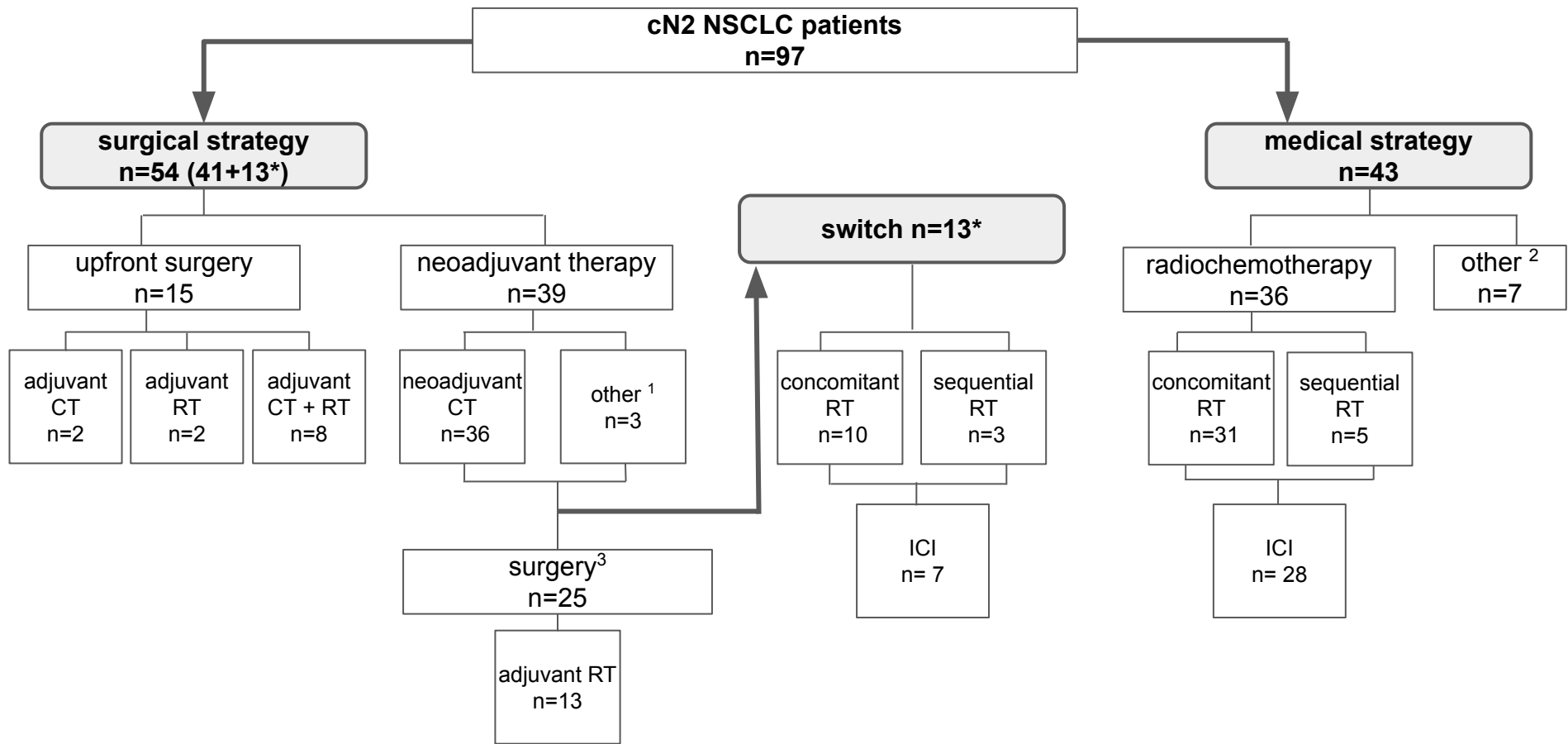
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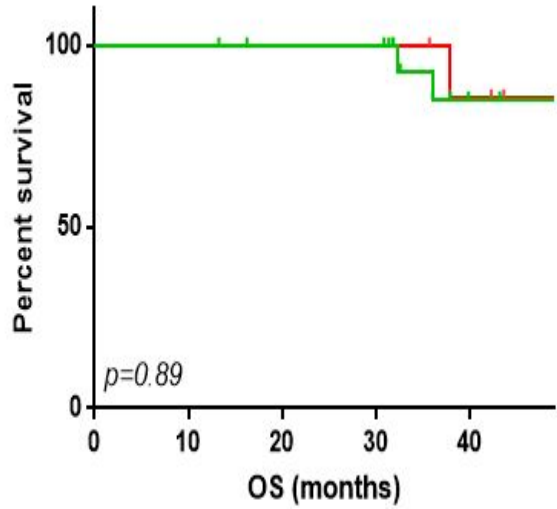
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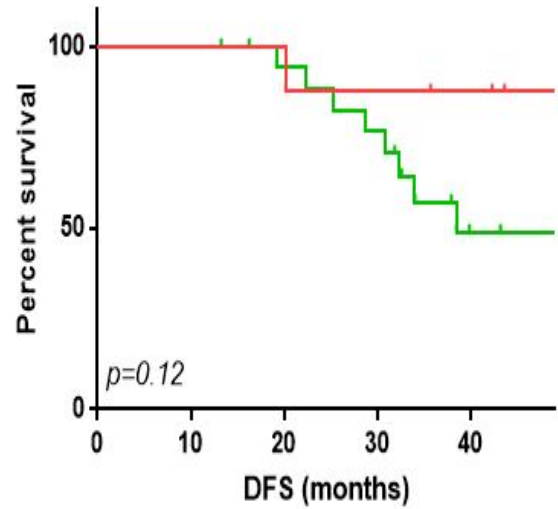
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Overall Survival depending on MTB decision reproductibility

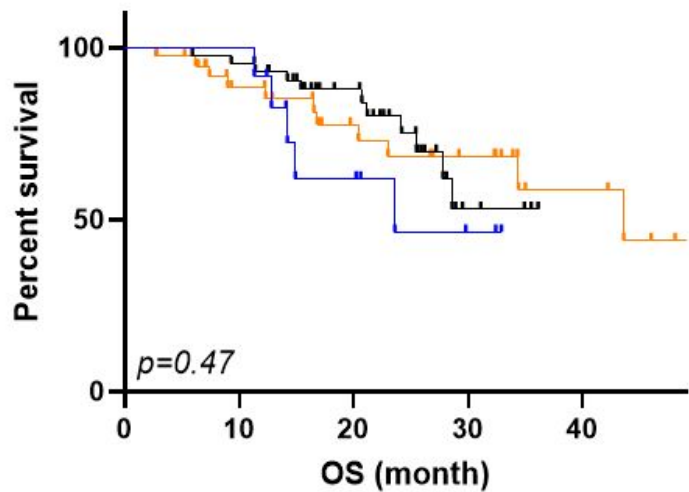


Disease Free Survival depending on MTB decision reproductibility

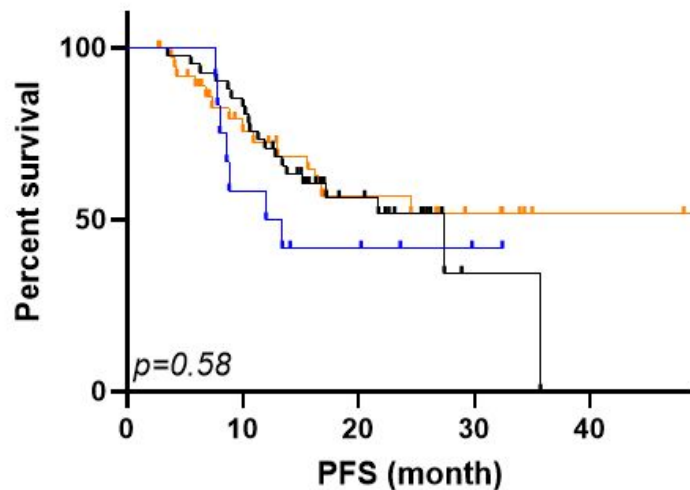


— patients with a concordant decision
— patients with a discordant decision

Overall survival depending on treatment arm



Progression free survival depending to treatment arm



- + switch
- + medical
- + surgical

		Number of patients (%)				
	<i>Total</i>	<i>Surgical strategy</i>	<i>Medical strategy</i>	<i>Switch from surgical to medical strategy</i>	<i>p¹</i>	<i>p²</i>
Total	97	41	43	13		
Gender						
female	46(47)	20(49)	18(42)	8(62)	0.45	0.82
male	51(53)	21(51)	25(58)	5(38)		
Age						
≤65 years	49(51)	17(41)	23(53)	9(69)	0.19	0.15
>65 years	48(49)	24(59)	20(47)	4(31)		
Histology^a						
ADK	58(67)	31(82)	22(56)	5(50)	0.03	0.01
SCC	29(33)	7(18)	17(44)	5(50)		
Smoking						
nonsmoker	12(12)	4(10)	7(16)	1(8)	0.57	0.55
former or active	85(88)	37(90)	36(84)	12(92)		
PS						
0	57(59)	25(61)	25(58)	7(54)	0.9	0.70
1-2	40(41)	16(39)	18(42)	6(46)		
T^b						
T1	20(21)	12(29)	6(14)	2(15)	0.06	0.01
T2	22(23)	14(34)	6(14)	2(15)		
T3	29(30)	8(20)	15(36)	6(46)		
T4	25(26)	7(17)	15(36)	3(23)		
Side^b						
right	54(56)	21(51)	25(60)	8(62)	0.69	0.39
left	42(44)	20(49)	17(40)	5(38)		
Tumor localization						
upper right lobe	42(41)	18(44)	18(43)	6(46)	NA	0.01
upper left lobe	32(33)	16(39)	12(29)	4(31)		
inferior left lobe	9(9)	4(10)	4(9)	1(8)		
inferior right lobe	9(9)	2(5)	5(12)	2(15)		
right middle lobe	4(3)	1(2)	3(7)	0		
N						
N2a	32 (33)	19(46)	10(23)	3(23)	0.17	0.04
N2b	31 (32)	9(22)	16(37)	5(38)		
N2c	34(35)	12(29)	17(40)	5(38)		
largest N2^b						
<20mm	60 (63)	31(78)	22(51)	7(54)	0.04	0.01
bulky ≥20mm	36 (37)	9(22)	21(49)	6(46)		
PDL1 status						
<1%	15 (20)	8(27)	4(11)	3(43)	0.09	0.38
≥1%	58 (80)	22(73)	32(89)	4(57)		

	BLINDED MTB STRATEGY			
INITIAL MTB STRATEGY		Surgical	Medical	Total
	Surgical	12	8	20
	Medical	1	9	10
	total	13	17	30

		Number of patients (%)		p ^d
		MTB decision concordant	MTB decision discrepant	
Total	30	21	9	
Gender				
Female	17	11	6	0.69
Male	13	10	3	
Age				
≤65 years	14	10	4	0.99
>65 years	16	11	5	
Histology^a				
ADK	20	13	7	0.41
SCC	9	8	1	
large cell	1	1	1	
Weight^b				
< 70 kg	14	9	5	0.69
≥ 70 kg	16	12	4	
Smoking				
no	2	2	0	0.99
yes	28	19	9	
PS				
0	19	11	8	0.10
1-2	11	10	1	
T^a				
T1	6	4	2	0.26
T2	7	7	0	
T3	10	6	4	
T4	7	4	3	
Side^c				
right	17	11	6	0.70
left	13	10	3	
Tumor localization				
Right upper lobe	14	10	4	0.58
Left upper lobe	10	8	2	
Left inferior lobe	3	2	1	
Right inferior lobe	3	1	2	
N				
N2a	7	7	0	0.03
N2b	10	8	2	
N2c	13	6	7	
Largest node size				
<20mm	16	11	5	0.99
bulky ≥20mm	14	10	4	
Number of invaded station				
1	6	6	0	0.08
2	12	9	3	
3	8	5	3	
4	4	1	3	