Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

SCIENZE CARDIO NEFRO TORACICHE

Ciclo 34

Settore Concorsuale: 06/D1 - MALATTIE DELL'APPARATO CARDIOVASCOLARE E MALATTIE DELL'APPARATO RESPIRATORIO

Settore Scientifico Disciplinare: MED/21 CHIRURGIA TORACICA

SURGERY AFTER BIOLOGICAL THERAPY IN LOCALLY ADVANCED NSCLC WITH MOLECULAR DRIVER: FEASIBILITY AND EFFECTIVENESS OF A NEW MULTIDISCIPLINARY APPROACH.

Presentata da: Lara Girelli

Coordinatore Dottorato

Gaetano Domenico Gargiulo

Supervisore

Niccolò Daddi

Co -Supervisore

Lorenzo Spaggiari

Esame finale anno 2022

ABSTRACT

Introduction: Surgical outcomes after biological therapy have not been investigated yet and no information about timing, postoperative complications and survival have been recorded.

Methods: This is a prospective study which compares a group of stage IIIA and IIIB NSCLC patients treated with biological therapy with patients undergoing standard induction chemotherapy.

Data reported are preliminary results on the safety and effectiveness of surgery after target therapy.

Results: We compared 22 patients treated with standard chemotherapy (Group 1) and 6 patients who received target therapy (Group 2). No differences were observed with an important bias due to the limited number of cases.

The median time of resection was 159.8 ± 62.8 for group 1 and 201 ± 57.8 for group 2 (p=0.194).

Complete resection was obtained in all Group 1-cases. Post-operative complication rate was 22% vs 16% (p=1).

Pathologists reported necrosis >50% in 13% in group 1, Fibrosis >50% was presents respectively in 27% and 33% of patients (p=1). Residual vital tumor was >50% in 77% of patients undergone CT and in 66% of patients undergone TT (p=0.622).

A total of 6 (31%) patients in the CT-group developed recurrence, 3 in the TT- group (64.2%), p was 0.634.

No difference was observed both in terms of OS (P=0.29, Figure 3) and in term of DFS (P=0.106, Figure 4).

Discussion:

There is no consensus in the use of target therapy for advanced tumor in association with surgery.

EGFR-tyrosine kinase inhibitors showed higher and more rapid response and our study wants to demonstrate that surgery after target therapy gives full access to the advantage of definitive local treatment.

In our series, despite fibrosis, radical surgery has been achieved in all patients operated. The intraoperative blood loss, operation time, postoperative hospital stay and postoperative complication rate seems to be similar.

Abbreviations

- NSCLC - Non-Small Cell Lung Cancer
- PET - Positron Emission Tomography
- TBNA - Transbronchial Needle Aspiration
- EBUS - Endobronchial Ultrasound
- ROSE - Rapid On-Site Evaluation
- PS - Performance Status
- ICU-Intensive Care Unit
- CT - Chemotherapy
- TT- Target Therapy
- RT - Radiotherapy
- OS-Overall Survival
- DFS-Disease Free Survival

INTRODUCTION

Every year, 1.5 million of new cases of lung cancer are diagnosed and about 85% of the worldwide incidence are NSCLC. (1)

Surgery with a curative intent is considered the best treatment option, but only the 20-25% of the tumours are suitable for potentially radical resection. (2)

In recent years, the potential role of pre-operative chemotherapy has been largely investigated and accepted to reduce tumour size, increase operability and eradicate micro metastasis. (3-9)

Many randomised controlled trials have also suggested a role in improving overall survival, but this aspect has been discuss in recent meta-analysis. (10)

Nowadays, neoadjuvant platin-based chemotherapy is recommended in case of locally advanced NSCLC. (11)

The optimal management of local advanced pulmonary tumours requires a multidisciplinary approach, which provide the adequate therapeutics options considering the extension of the disease at the diagnosis, the patient's general conditions and co-morbidities, surgical operability and potential toxic effects of an induction systemic treatment.

Local advanced tumours are considered NSCLC including Pancoast's tumours, chest wall infiltrating neoplasia and tumours with invasion of the main bronchus, the carina o the pulmonary artery, which normally requires pulmonary extended resections and complex reconstructions of the chest-wall, airways, and vessels. (12-13)

However, locally advanced tumours also include a very heterogeneous group of patients with NSCLC at stage IIIA or IIIB for mediastinal lymph node involvement.

All these cases should be discussed in a multidisciplinary board in order to establish the benefit of a neo-adjuvant treatment, which normally includes a platinum-based chemotherapy and, in particular cases, also radiotherapy with the aim to reduce the tumour to further complete resection (R0) and mediastinal down staging, improving the long-term survival. On this topic, different studies tried to evaluated differences in

terms of survival between definitive chemo-radiotherapy and surgery after chemotherapy or chemo-radiotherapy induction treatment. (14)

In the last ten years, numerous molecular alterations have been identified in NSCLC patients as a therapeutic target conditioning the cancer's biology. In particular, in adenocarcinoma setting, different mutations were identified activating gene K-RAS end EGFR (15), re-arranged genes ALK and ROS-1 (16, 17) and many others.

The latest AIOM guidelines confirmed that all patients with non-squamous histology or mixed and also young non-smokers patients with squamous histology should be tested for ALK and EGFR. (11,18)

Systemic treatment with the employment of biological target drugs based on EGFR mutations or ALK re-arrangement and PDL-1 expression in correlation with clinical characteristics of patients were used in NSCLC in advanced stages, such as IIIB no susceptible of loco-regional treatment and stage IV, and not recommended in disease stage III. However, a great interest both for clinicians and surgeons is growing and clinical controlled trials are opening in referral oncological centres. (11)

In fact, great results observed in reducing tumour size can change surgical planning in terms of indications and on extension of resection but most of all the response can be so surprising to change the first evaluation of a non-operable disease in surgically resected tumours.

In these perspectives, surgery can become an option also for patients that have been initially excluded from surgery at the time of diagnosis.

Surgical outcomes after biological therapy have not been investigated yet and none information about timing, surgical technical aspects, postoperative complications and survival have been recorded. Besides, also the changes in pattern on pathological examinations and their correlation with surgical observations are still undefined.

The aim of this prospective study was to assess the safety and effectiveness of surgical approach in patients with locally advanced NSCLC after biological therapy in terms of oncological and surgical outcome

STATE OF THE ART IN LOCALLY ADVANCES NSCLC-stage III

The classification of stage III non-small cell lung cancer (NSCLC) requires cyto-histological typing of the disease and complete staging. Lung cancer presentation in these patients is heterogeneous both for the extension of the disease (T), the involvement of large vessels and invasion of mediastinal structures (T3-4), both for the lymph node involvement (N1- 3).

Therefore, stage III lung cancer includes different diseases, with different prognoses and different treatment modalities.

For this reason, accuracy in the initial staging is essential for the therapeutic choice.

Staging should include total body computed tomography (CT) with contrast medium, positron emission tomography (PET) FDG, and EBUS / TBNA bronchoscopy or mediastinoscopy to precisely define the spread of thoracic disease.

The therapeutic program can include surgery, chemotherapy, radiotherapy or immunotherapy, also integrated in a multimodal approach. The judgment of the feasibility of a radical surgical resection is the first step of this decisional process.

MEDIASTINAL STAGING

Most patients with NSCLC at clinical stage IIIA have mediastinal (N2) lymph node involvement on chest CT and PET-18FDG. The mediastinal lymph node sites potentially affected by neoplastic localization from NSCLC are the upper paratracheal (R2 and L2), lower paratracheal (R4 and L4), pretracheal (station 3), subcarinal (station 7), para-aortic (station 6) lymph node stations, the aortopulmonary window (station 5), para-esophageal (station 8) and the inferior pulmonary ligament (station 9) (19). Mediastinoscopy is a minimally invasive surgical procedure that is performed under general anesthesia and consists in a small skin cervical incision, the exposition of the tracheal plane. It allows to reach the upper and lower paratracheal, subcarenal and pretracheal lymph node stations and collect histologic samples.

The morbidity and mortality rates of this procedure are low (2% and 0.08%, respectively) [83]. The mediastinoscopy, although it has a high sensitivity, is now replaced, where feasible, by endobronchial ultrasound with nodes needle aspiration via the transbronchial route in real time (EBUS-TBNA). This

procedure has now become the first-choice in diagnostic standard. In fact, it maintains a high diagnostic accuracy in the staging of the mediastinal (N2, N3) and hilar lymph nodes, with less invasiveness and risk of complications compared to mediastinoscopy. It also allows to obtain adequate tissue to perform both a disease typing and the necessary molecular analyzes (20-23). Mediastinoscopy should be used in those cases where a strong clinical suspicion of pathological lymphadenopathy has not been confirmed by EBUS-TBNA.
In conclusion, tissue confirmation of N2, N3 lymphadenopathy should be performed with EBUS-TBNA where feasible, with mediastinoscopy in sites not accessible to EBUS or when there is a strong suspicion of EBUS-TBNA false negative. EBUS-TBNA can be performed in a room specially set up in the presence of a pathologist who immediately confirms the adequacy of the sampling (ROSE technique: Rapid onsite cytology evaluation).
Studies suggest that patients with early stage IIIA and mediastinal downstaging after neoadjuvant treatment obtain a survival benefit from surgical treatment (24-26). However, morbidity and mortality may be higher after resection following neoadjuvant treatment.
Therefore, mediastinal re-staging after induction therapy would be necessary to correctly select patients who can really benefit from surgical treatment but in clinical practice due to its difficulty of execution and comorbidities it is generally not performed.

MULTIMODAL TREATMENT IN OPERABLE DISEASE: ADJUVANT AND NEOADJUVANT CHEMOTHERAPY

The first-line therapy in patients with stage IIIA N0-1 is surgical.
Several prospective phase III studies have investigated the role of adjuvant chemotherapy [56] and the 5% advantage over 5 years has been demonstrated by the addition of a platinum-based chemotherapy to surgery, in order to reduce the presence of micro metastases and therefore the possibility of relapses.
In stage IIIA NSCLC therapies and prognosis largely depend on lymph node involvement. Within the same stage IIIAN2 some patients are considered potentially operable, while those with extensive involvement of the mediastinal lymph nodes (multistational and / or bulky N2) are not eligible for surgery. The purpose of any neoadjuvant chemotherapy becomes the down-staging of the disease. Chemotherapy as a first

therapeutic approach determines an early systemic treatment of the disease and allows immediate assessment of responsiveness to drugs (27).

In 2006 was published a review of the literature with a meta-analysis of randomized clinical trials on the efficacy of preoperative chemotherapy in NSCLC. Survival data were analyzed in 12 studies, for a total of 988 patients. Data analysis shows a significant increase in survival after neoadjuvant chemotherapy ($p = 0.02$). The HR value was 0.82 (95% CI 0.69-0.97) corresponding in an 18% relative reduction in the risk of death. The study revealed an absolute improvement of 6% in 5 years, and OS increased from 14% to 20%. Currently, the use of neoadjuvant chemotherapy in stage IIIA N2 is widely used in clinical practice, with the aim of improving the prognosis of these patients. The standard of neoadjuvant chemotherapy is represented by two platinum-based regimens: cisplatin-gemcitabine, cisplatin-docetaxel and carboplatin-paclitaxel with mean response rates between 70.2% and 63% (28-30). The hypothesis of using three-drug combinations was first posed in advanced NSCLC disease to improve outcomes. In 2004, a meta-analysis evaluated mono-chemotherapy regimens compared with two-drug combinations and the latter with therapeutic triplets in advanced NSCLC (31).

The results confirmed the advantage of two drugs over one while the triplets showed a clear advantage in terms of response to the doublets, without any impact on survival but with an important toxicity. The purpose of a significant pre-operative down staging induced to investigate the potential of the use of the triplets in neoadjiuvant regimens. De Marinis enrolled 49 patients at stage IIIA N2 treated with the triplet based on cisplatin, gemcitabine and paclitaxel (32). The response rate was 73.5% with 16% pathological complete response with 33% of grade 3-4 hematological toxicity. These results were confirmed by Cappuzzo (33) who published in 2003 the data of a multicenter study on patients at stage IIIA N2-IIIB treated with the same triplet. He observed a response rate of 71%. In 2007 Garrido (34) enrolled 124 patients at stage IIIA N2-IIIB using a 3-drug regimen with cisplatin gemcitabine-docetaxel with a response rate of 56% versus a grade 3-4 toxicity of 65.5%. The data available indicate that the use of triplets is possible in patients selected at stage IIIA N2 with an advantage in terms of local responses.

Currently, the use of two platinum-based drugs in neoadjuvant therapy remains the standard option.

The comparison between neoadjuvant and adjuvant treatments has been investigated in literature.

Lim et al. (35), in 2009 published a meta-analysis of 32 randomized trials comparing adjuvant chemotherapy with neoadjuvant for all operable stages.

Regarding survival (OS), the hazard ratio was 0.80 (95% CI 0.74-0.87; p = 0.001) in the group of postoperative chemotherapy and 0.81 (95% CI 0.68-0.97; p = 0.024) in the preoperative chemotherapy group.

For disease-free survival (DFS) the HR was 0.76 (95% CI 0.67-0.86; p for disease-free survival (DFS), the HR was 0.76 (95% CI 0.67-0.86; p <0.001) for adjuvant chemotherapy and 0.79 (95% confidence interval 0.63-1.00; p = 0.050) for neoadjuvant chemotherapy (35). The authors conclude finding no difference in OS and DFS between patients undergoing neoadjuvant or adjuvant chemotherapy.

Another meta-analysis published in 2014 (36), collected individual data from 15 studies randomized for a total of 2385 patients at stage I-IIIA. OS was statistically better in the group of patients treated with neoadjuvant chemotherapy with an HR of 0.87 which corresponds to a 5% improvement in 5-year survival. Similar results were observed for adjuvant chemotherapy (36).

Currently neoadjuvant chemotherapy in stage IIIA N0-1 is not yet part of clinical practice, but is only used in clinical trials, while is mostly the option for N2 patients.

NON-CHEMOTHERAPY NEOADJUVANT SYSTEMIC TREATMENTS

To date, chemotherapy is the only recognized standard treatment in the neoadjuvant setting of non-small cell lung cancers. However, increasing evidence suggests the possibility of customizing neoadjuvant treatment with new therapeutic strategies, with the aim of increasing the rate of mediastinal downstaging.

Preliminary data are available in patients with driver mutations. In a phase II study, neoadjuvant therapy with erlotinib was evaluated in sixty patients with EGFR mutated NSCLC: at the pathological evaluation of surgery, a tumor necrosis rate greater than 50% was observed in 23% of cases; In the 5% of these cases, the tumor necrosis rate was greater than 95% (37). A good safety profile, high compliance, and good response rate were achieved in an additional phase II study with gefitinib in patients with stage I NSCLC (38). As for rearranged ALK disease, preliminary data on the use of neoadjuvant crizotinib in 11 patients showed a good response rate (39).

Great attention is paid to the potential use of immunotherapy in the neoadjuvant setting. A pilot study with nivolumab (anti-PD1) demonstrated a 45% major pathological response rate (MPR) in patients with operable NSCLC (40). Similar results were obtained with atezolizumab, with a good tolerability profile (41)and were confirmed in the NEOSTAR phase II study involving nivolumab alone or in combination with ipilimumab (anticytotoxic T-lymphocyte antigen 4, CTLA- 4) (42).

Neoadjuvant chemoimmunotherapy was evaluated in a phase II study with atezolizumab in combination with platinum-based chemotherapy: the rate of MPR was 50% (43), comparable to the result of the phase II NADIM study with the combination of nivolumab and chemotherapy (44).

The Checkmate 816 study is the first phase III study which compare the efficacy of the combination of nivolumab and platinum salt doublet chemotherapy versus chemotherapy alone as a neoadjuvant treatment in patients with resectable stage IB-IIIA NSCLC wild type for EGFR and ALK mutations (45).

The primary endpoint of the study, the pathological complete response (PCR), was achieved, with 24% in the experimental arm versus 2.2% in the standard arm. MPR was 36.9% vs 8.9% respectively (45)

RADIOTHERAPY

To increase local control and survival and the chances of complete surgical resection, CT-RT combinations were investigated.

The SWOG study 8805 (46) employed the combination of etoposide and cisplatin with concurrent RT (45 Gy) followed by surgery.

The results were encouraging in terms of survival with the demonstration that the pathological response of the mediastinal lymph nodes after neoadjuvant therapy was an important prognostic factor.

Study INT 0139 (23) enrolled approximately 400 patients with stage T1-3N2 NSCLC potentially operable on concomitant CT-RT (cisplatin / etoposide and 45 Gy). Patient who were not in progression were randomized to surgery with subsequent 2 cycles of CT or to curative RT (up to 61 Gy) also followed by CT.

The two arms did not differ in overall survival, although DFS favored the surgical arm, 12.8 months versus 10.5 months, respectively.

Treatment-related deaths were more frequent after surgery, with worse median survival in patients undergoing pneumonectomy.

An important feature of the trimodal treatment was the decreased local relapses compared to the bimodal (23). Almost all other induction CT-RT studies reported interesting survivals (30% at 5 years), but frequently burdened by an increase in the toxicity of neoadjuvant treatment (especially esophageal compared to CT alone) and possible surgical complications. [118]

In 2015, were presented results of a study that randomized 219 patients at stage IIIA N2 to receive three cicles of cisplatin and docetaxel followed by surgery versus radiotherapy (44 Gy in 22 fractions) and then surgery. The primary endpoint disease-free survival was similar at 11.8 and 12.8 months, respectively (47).

Concerning the volumes of neoadjuvant radiotherapy, is usual clinical practice to irradiate where there is evidence of disease on CT, PET, mediastinoscopy or bronchoscopy (48). The recommended doses are not higher than 45-50 Gy with dose limits to critical organs similar to those of radical RT (49).

In conclusion, radiotherapy in the neoadjuvant setting has not a well-defined role.

In most of the studies it is shown that the administration of a total radiation dose greater than 45 Gy constitutes a high-risk factor for postoperative complications. (50-53)

The use of Post operative radiotherapy (PORT) in patients with mediastinal lymph node (pN2) involvement has remained a debated topic for many years.

Recently, some data seemed to be in favor of the use of PORT after neoadjuvant chemotherapy (54) . To definitively answer the question, the results of the phase III study LungART were finally presented at ESMO 2020.

501 radically operated patients were randomized to receive PORT or not (252 PORT, 249 no PORT) (55).

The disease-free survival (DFS -) interval was 47.1% in the PORT arm versus 43.8% in the control arm (HR 0.85, 95% CI 0.67-1.07, p = 0.16).

No difference was also observed in the three-year overall survival (66.5% in the PORT arm vs 68.5% in the control arm) (55).

In patients radically operated with pN2 (or ypN2) postoperative radiotherapy is not recommended.

STUDY DESIGN

This is a prospective study which compares a group of patients with locally advanced stage IIIA and IIIB NSCLC treated with biological therapy before surgery with patients undergoing standard induction chemotherapy. It has been conducted in Thoracic Surgery Division,at Istituto Europeo di Oncologia , Milan.

INCLUSION CRITERIA

- Patients with diagnosis of NSCLC stage IIIA/B for mediastinal ipsilateral lymph node involvement (N2) or local advanced disease include Pancoast's tumors, and tumors with invasion of the chest wall, main bronchus, the carina o the pulmonary artery (T3 or T4).
- Patients underwent platinum-based induction chemotherapy (at least 2-3 cycles) and molecular therapy in patients with EGFR mutation (exon 19-20) –
- All patients have been staged by total body CT scan and PET-FDG, Mediastinal histological staging by EBUS-TBNA.
- No distant metastasis clinically evident.
- Age between 18 and 80 years old.

EXCLUSION CRITERIA

- Patients with progression after induction therapy (bulky N2 or infiltration of surrounding mediastinal structures, N3 disease or distant metastasis) of after biological therapy.
- Surgery as "salvage- treatment".
- Patients unfit for surgery.
- Previous thoracic surgery on the same side.

CLINICAL EVALUATION AND PROCEDURES

Pre-operative evaluation

Preoperative evaluation included staging exams such as chest CT scan and PET scan. Standard functional evaluation included ECG, cardiorespiratory evaluation, anesthesia evaluation. When

required by the physician additional tests has been introduced as stress test, heart ultrasound, and pulmonary scintigraphy.

Surgery

All patients underwent anatomical lung resection and radical lymphadenectomy. Systematic lymph node dissection according to the classification of the American Thoracic Society was performed in all patients removing all lymphatic tissue from stations 2R, 4R, 7 and 10R for right-sided tumors and from stations 5, 6, 7 and 10L for left-sided tumors.

Open surgery was preferred in order to have a homogeneous and reproducible surgical approach.

Post-Intervention and follow-up period

Patients were admitted to an intensive care unit following surgery only if required by the anesthesiologist based on ASA score.

Post-operative period was regularly in thoracic surgery unit and all events were recorded.

Histological staging was discussed in a multidisciplinary board and adjuvant treatment eventually were programmed. After discharge, patients were followed with a physical exam, chest X-ray and blood tests at 1 month after surgery and with a physical exam plus CT scan of the chest and upper abdomen every 4 months for 3 years, then every 6 months until the fifth year, and annually after 5 years.

OBJECTIVES

Data recorded included intra and postoperative complications (30 and 90-day), intra and postoperative mortality (30 and 90-day), duration of surgery and postoperative stay.

Overall survival and Disease-free survival and Local and distant recurrences patterns were obtained from follow-up.

Histological pattern (necrosis, neoplastic cells vitality, fibrosis, inflammatory infiltration down-staging) was described by pathologist report.

PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS

The primary end point of the study included the evaluation of in-hospital morbidity (minor and major complication) and mortality, and peri and post-operative outcomes, including operating time, amount of bleeding, duration of thoracic drainage, and the days of hospitalization

The secondary endpoints were overall survival at 12, 24 and 36 months and the disease-free interval of patients with local and distant recurrence.

The secondary endpoints were also the correlation between pathological characteristics and the down-staging with surgical and oncological outcomes.

STATISTICAL METHODS

The evaluation of primary end points (in-hospital morbidity and mortality, and peri and post-operative outcomes, including operating time, amount of bleeding, duration of thoracic drainage, and the days of hospitalization) were reported using descriptive statistics.

Continuous variables are reported as mean and standard deviation; categorical variables are reported as frequency and proportion.

The statistical analysis has been performed by X^2 test for categorical variables and Student's t test and Mann–Whitney test for continuous variables, utilizing SPSS (IBM SPSS Statistics, Version 21.0. Armonk, NY: IBM Corp. Released 2012). The difference was considered as significant for p values B0.05.

Survival analysis using Kaplan-Meier curve and log-rank tests evaluated the secondary endpoints (overall and disease free survival .

ETHICAL CONSIDERATIONS

This study is conducted in agreement with the Declaration of Helsinki. The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http.//www.ifpma.org/pdfifpma/e6.pdf).

A sequential identification number was automatically attributed to each patient enrolled in the trial. This number identify the patient and must be included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters), and year of birth were reported on the case report forms.

All patients were informed of the aims of the study, the procedures and possible hazards to which they were exposed, and the study procedures. They were informed as to the strict confidentiality of their patient data, but that authorized individuals other than their treating physician may review their medical records for trial purposes. The patient's informed consent statement is given at the end of the protocol. It emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. Documented informed consent was obtained for all patients included in the study before they were enrolled. The informed consent procedure was conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

LIMITS OF THE STUDY

The purpose of the study was the prospective observation and the comparison of surgical outcomes between patients with locally advanced NSCLC treated with standard induction therapy and target therapy.

The main limit of the study is represented by the limited number of patients enrolled.

For this reason, we can consider data reported as preliminary results on the prospective evaluation on the safety and effectiveness of surgery after target therapy used in induction regimen.

Another limit of the study could be represented by the short follow-up due to the relative recent beginning of the enrolment started in 2018.

RESULTS

Since November 2018, 28 patients were enrolled in the study registered as IEO940 and operated in our unit for locally advanced NSCLC with radical intent. All patients were pre-operatively treated with systemic therapy to reduce the size of tumor and mediastinal nodes involvement. Only 6 of these patients received biological target therapy based on molecular drivers identified at the diagnosis. Neoadjuvant treatments were performed both in our institution and in other centers. Patients were included in the study at the preoperative evaluations and with strict adherence to the inclusion criteria.

Demographic-clinical characteristics

Clinical-demographic characteristics of the 28 patients enrolled are shown in Table 1. The median age was 64 years (range 43-80 years), and a total of 15 females (53%). Eight (29%) patients were former smoker, six (21%) non-smoker, and 14 (50%) smokers in the past. Twelve patients (42%) had a previous history of cancer. Based on clinical staging with CT scan and PET, 24 patients (85%) underwent EBUS-TBNA mediastinal staging in case of suspected mediastinal lymph node involvement. Only one patient underwent mediastinoscopy. Three patients (10%) did not perform histological staging of the mediastinum. The final clinical stage was IIIA in 20 (71%) patients, IIIB in 8 (29%) cases. The histology was mostly adenocarcinoma (n=24; 86%), whereas four (14%) patients had squamous cellular carcinoma.

All patients underwent surgery after induction therapy: 22 (79%) underwent to chemotherapy treatment. Cisplatin based chemotherapy was administered in 16 patients (57%), in association with Gemcitabine in 15 cases (53%) and Pemetrexed in 1 case. Carboplatin based chemotherapy was used in 6 patents in association with Gemcitabine.

Biological drugs were administered in 6 patients (21%) considering molecular drivers. Four (9.5%) patients underwent to target therapy with Afatinib, one patient received Gefitinib and one patient received Erlotinib associated with bevacizumab. Molecular drivers, Epidermal Grow Factor Receptor gene mutations in all cases, were identified in cytologic specimen in three cases and in histologic specimen in other three cases.

All patients were re-staged before the surgical procedure to confirm the feasibility of surgical resection and all patients had a partial response.

At the pulmonary pre-operative tests, median percentage forced expiratory volume in the 1st second (FEV1%) was 97.6% (71-131%), the diffusing capacity (DLCO/VA) was 82.9 % (39-138%). The ASA score was 2 in the 68 % of patients, and 3 in the remaining 32 %.

Table 1. Patient's clinical characteristics

	N = 28 (100%)
Age, years (range)	64 (43-80)
Male **Female**	13 (47%) 15 (53%)
Smoking status	
Yes Ex	8 (29%) 14 (50%)
No	6 (21%)
Former smoker	
Histology	
Adenocarcinoma	24 (86%)
Squamous cell carcinoma	4 (14%)
Clinical stage (after mediastinal staging)	
cIIIA	20 (71%)
cIIIB	8(29%)
Induction treatment	
Chemotherapy	22 (79%)
Target therapy	2 (21%)
Reponses to induction therapy	
Partial response	28 (100%)
Cardiopulmonary test	
FEV 1 % (range)	97.6 % (71-131%)
DLCO/VA (range)	82.9% (39-138%)
ASA score	
2	19 (68%)

3	9 (32%)

Surgical Results

All patients underwent lateral muscle-sparing thoracotomy: 24 (85%) for lobectomy, one for typical segmentectomy, two (7%) for pneumonectomy. One patient underwent explorative thoracotomy for intraoperative evidence of pleural and pericardial metastasis. Most of the patients underwent right upper lobectomy (42%). The median size of the tumor was 36.8 mm (range 10-85 mm).

The median time of surgery was 168.6 minutes (range 40-266 minutes). Median amount of bleeding was 61 ml (range 0-400 ml).

Twenty-seven patients (96%) had a complete resection (R0).

The surgical results were listed in Table 2. The median number of hilar lymph node (N1) was 4.5 (range 0-21) whilst the median number of mediastinal lymph node (N2) was 12 (range 4-26).

Besides, the median number of total lymph node station was 6 (range 4-9).

Minor post-operative complications occurred in 6 patients (21%) and included chylothorax (1 patient), anemia, prolonged air leak, dysphonia and atrial fibrillation. Major complications did not occur.

The median time of chest tube was 5 days (range 5-25). The median length of hospital stay was 6 days (range 4-26), and only 2 patients went to ICU after surgery.

Adjuvant treatment was indicated in 8 patients (29%): mediastinal radiotherapy was indicated in 3 patients (10%) for N2 persistent disease whereas 3 patient underwent post-operative chemotherapy (10%). Two patients continued their target therapy (7%).

Table 2: Surgical and post-operative information

Surgical Results	**N = 28 (100%)**
Lobectomy	24 (85%)
Right upper lobe	12 (42%)
Right lower lobe	5(18%)

Left upper lobe	5(18%)
Left lower lobe	2 (7%)
Segmentectomy	1 (3%)
Pneumonectomy	2 (7%)
Explorative Thoracotomy	1 (3%)
Size mm (range)	36.8 (10-85)
Duration of surgery min (range)	168.6 (40-266)
Bleeding ml	61 ml (0-400)
ICU stay, days (range)	0 (0-1)
Post-operative stay, days (range)	6 (4-26)
Complete surgery	
R0	27 (96%)
R2	1 (4%)
Pathological stage	
yIA2	1 (3.5%)
yIB	2 (7%)
yIIB	5 (18%)
yIIIA	13 (46%)
yIIIB	4 (14%)
Post-operative complication	
None	22 (78%)
Minor	6 (21%)
Drainage removal, median days (range)	5 (3- 25)
Adjuvant treatment	
No	20 (71%)
Yes	8 (29%)
Mediastinal radiotherapy	3 (10%)
Chemotherapy	3 (10%)
Target therapy	2 (7%)

Survival and Disease- Free Survival at the follow up

The median Overall Survival (OS) was 30 ± 2 months [IC 25.9-34.1].
The median Disease-Free Survival (DFS) was 21.6 ± 2.8 months [IC 15.9-26-.9].
Recurrences were detected in 9 patients (32%): 5 (18%) had loco-regional relapses and 4 (14%) had distant metastases (i.e. brain or liver, lung metastasis). All these patients are alive with disease and are under treatment with radiotherapy and immunotherapy in case of N2 relapses, and chemo-radiotherapy for the distant metastasis. Patients with molecular drivers are continuing their target therapies.
At the last follow-up, 15 (53%) patients were alive without any evidence of the disease, 10 (36%) were alive with disease under treatment, one patient died for recurrence and 2 patients died for other causes (respiratory failure 30 days after surgery).

Comparison between Chemotherapy and Target therapy

We performed a comparison between 22 patients who received standard chemotherapy (Group 1) and 6 patients who received target therapy (Group 2).
The main clinical characteristics of patients and surgical results in the two matched groups are shown in Table 3.
No significative differences were observed at the analysis, but we consider an important bias due to the limited number of cases included.
The median age was 58.3 years ± 21.5 for Group 1 and 66.3 years ± 4.7 for Group 2 (p=0.764).
Female were 10 in group 1 and 5 in group 2 (p=0.173). Smokers were 86% versus 50% (p=0.09).
Forty percent of patients undergone CT had a previous cancer, which is registered in 50% of the group TT group (p=1).
Histology was Adenocarcinoma in 18 (81%) of cases in Group 1 and in all cases of Group 2 (p=0.54).
The median time of resection was 159.8 ± 62.8 for group 1 and 201 ± 57.8 for group 2 (p=0.194).
Type of resection was lobectomy (90.9%), Pneumonectomy (4.55%), Segmentectomy (4.55%) in CT-Group.
Type of resection was lobectomy in 66% of cases, pneumonectomy in 16% and a single case of explorative thoracotomy in TT-Group (p=156).
Complete resection was obtained in all cases of Group 1. Group 2 presents incomplete resection (R2) in the patient undergone to explorative thoracotomy for intraoperative evidence of pleural and pericardial metastasis.
Bleeding was more than 200 ml in 13% of cases in group 1 and in 33% of group 2 (p= 0.285).
The median duration of Intensive Care Unit recovery and of hospital stay was comparable (p=0.892 and p= 0.566 respectively).
Post-operative complication rate was 22% vs 16% (p=1). Post operative mortality at 30 days was 9% in group 1 where two patients died after discharge for respiratory failure.

Pathologists reported necrosis >50% in 13% of cases of group 1, whist all cases treated with biological drugs reported necrosis <50% (p=1). Fibrosis >50% was presents respectively in 27% and 33% of patients (p=1). Residual vital tumor was >50% in 77% of patients undergone CT and in 66% of patients undergone TT (p=0.622).

A total of 6 (31%) patients in the CT-group developed recurrence of the disease.

In the TT- group, 3 patients had recurrence (64.2%), p was 0.634.

No difference was observed between the groups both in terms of OS (P=0.29, Figure 3) and in term of DFS (P=0.106, Figure 4).

Table 4. Clinical features and Surgical outcomes analysed for two groups. *Mann-Whitney test ** X^2 test

	Group 1 standard therapy (22 patients)	Group 2 Target therapy (6 patients)	p
Age	58,3 ± 21.5	66.3 ± 4.7	0.764*
Sex (F/M)	10/12	5/1	0.173**
Smoking	19/22 (86%)	3/6 (50%)	0.09**
Previous cancer	9/22 (40%)	3/6 (50%)	1**
Adenocarcinoma	18/22 (81%)	6/6 (100%)	0.54**
ASA (2/3)	14/8	5/1	0.630**
Type of Resection			
Lobectomy	20/22 (90.9%)	4/6 (66)	0.156**
Pneumonectomy	1/22 (4.55%)	1/6 (16%)	
Segmentectomy	1/22 (4.55%)	0/6 (0%)	
Exp. thoracotomy	0/22 (0%)	1/6 (16%)	
Bleeding (> 200cc)	3/22 (13%)	2/6 (33%)	0.285**
Incomplete resection	0/22	1/6 (16%)	0.214**
Operative time (min)	159.8 ± 62.8	201 ± 57.8	0.194*
Hospitalization (d)	6.9 ± 4.6	6.1 ± 1.7	0.892*
Chest drain (d)	5.9 ± 4.5	5.6 ± 1.8	0.566*
Necrosis (>50%)	3/22 (13.6%)	0/6 (%)	1**
Fibrosis (>50%)	6/22 (27%)	2/6 (33%)	1**
Residual tumor (>50%)	17/22 (77%)	4/6 (66%)	0.622**
Necessity of ICU	2/22 (9%)	0/6 (0%)	1**
Complications	5/22 (22%)	1/6 (16%)	1**
30-days mortality	2/22 (9%)	0/6 (0%)	0.821**
Recurrence	/22 (31%)	3/6 (50%)	0.634**

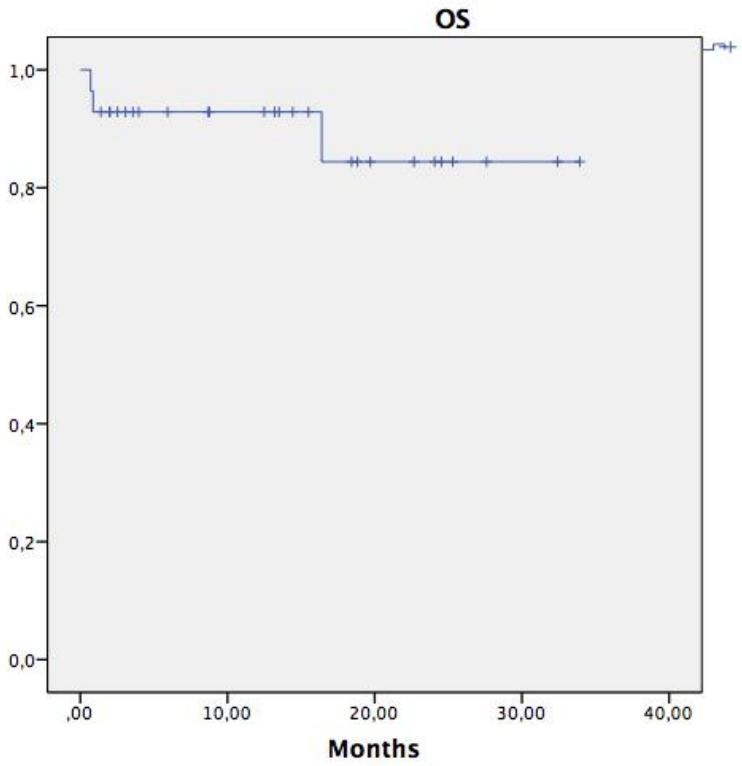

Figure 1. Overall Survival for all patients

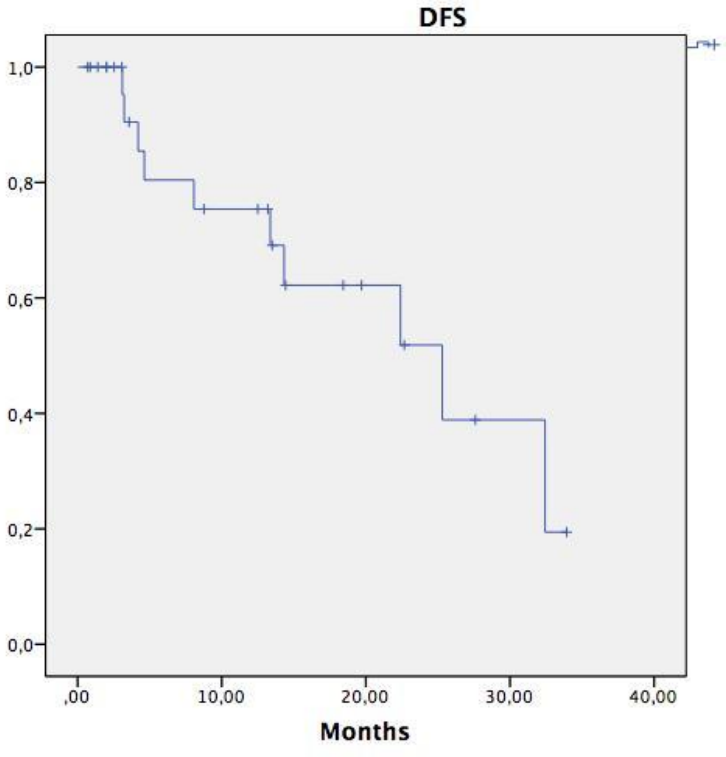

Figure 2. Disease Free Survival for all patient

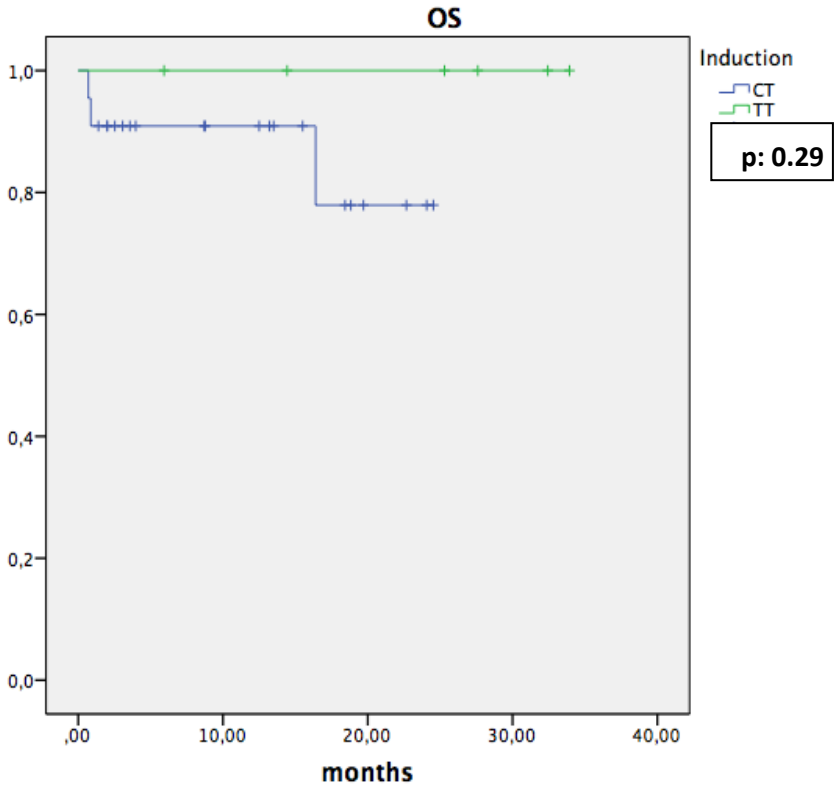

Figure 3. Overall Survival for two groups (chemotherapy versus target therapy)

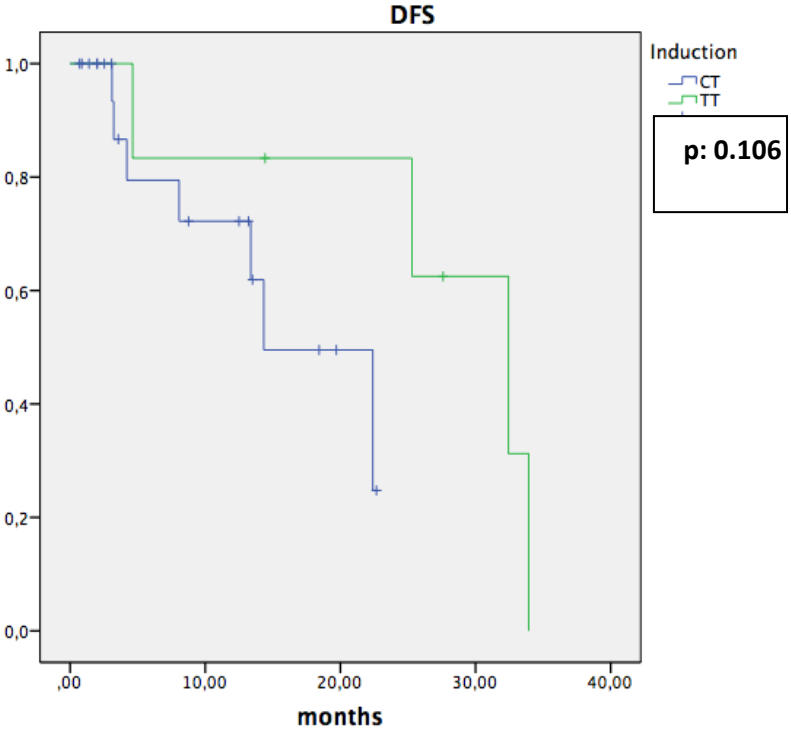

Figure 4. Disease Free Survival for two groups (chemotherapy versus target therapy)

DISCUSSION

In recent years major therapeutic successes in treatment of NSCLC have been achieved by pharmacological innovations with the introduction of target therapy and immunotherapy in advanced stages. Efforts are now being made to replicate the success obtained using these innovations in the setting of neoadjuvant treatments.
In this prospective study our purpose was to analyze the feasibility and efficiency of surgery in patients with locally advanced NSCLC after targeted therapy. With this purpose we performed a case control study to compare results with the standard chemotherapy therapy, commonly used in clinical practice.
To best of our knowledge, no prospective study has already been reported in literature. We can consider our data enough only as for preliminary results, mainly because of the limited number of enrolled patients and for the short follow-up. Currently there is no consensus in clinical practice in the use of target therapy for advanced tumor in association with surgery.
In our analysis we focused on patients with locally advanced NSCLC including only stage IIIA and IIIB, for which commonly surgery follows a cytoreductive therapy.
Few case series were reported in literature.
Song et all. (56) recently reported a case series of 9 patients diagnosed with stage IIIA and IVb, undergone salvage surgery for residual tumor. Negative surgical margins were achieved in all cases. Postoperative complication rate was 11.1% (1/9). All patients were alive at time of the analysis and two of them presented disease recurrence. After a median follow up of 17 months (range 5-44 months), the median event free survival and postoperative survival was 14 months and 17 months respectively.
Hishida et all. (57) evaluated salvage surgery after response to gefitinib in 9 patients with stage III-IV. Complete resection was achieved in all cases, with median hospitalization of 9 days. No deaths were registered. Median OS was 32 months, median recurrence free survival was 6 months. The most interesting suggestion of Authors is that radiological response does not necessary correlate with cell death. Infact 7 of 9 patients had further advanced pathologic stage than preoperative clinical stage. It seems to suggest that the systemic attitude of the disease persist despite the radiological downstaging.
None deaths were registered in our TT-Group and median OS was 22.4 months but looking these results we have to considered that we excluded stage IV and that the follow up is relatively short.
The assumption of retrospective studies cited is that surgery can be a “salvage treatments” for patients with residual tumors o localized recurrence after target therapies in cancers unresectable at the diagnosis.
It has been observed that EGFR-tyrosine kinase inhibitors have both higher and more rapid responses, better toxicity profiles than standard chemotherapy for cancers harboring EGFR mutation (58).
Pursuing the idea of multidisciplinary and individualized therapy, our study wants demonstrate that surgery after effective target therapy gives full access to the advantage of definitive local treatment of an advance and unresectable disease. The great limitation is that target therapy in neoadjuvant setting is currently feasible only in clinical trial and this compromises the enrollment.
With the same purpose of studies on target therapies, also the role of immunotherapy in pre-operative regimen is under investigation. Few series were reported in literature. Bott et al. (59) concluded that pulmonary

resection was feasible without undue morbidity. Chaft et al.(60) suggested that pulmonary resection was feasible but observed that mediastinal and hilar fibrosis developed because of the response to treatment can represent a challenge for surgeon. Yang et al. (61) demonstrated that resection was safe and feasible with perioperative outcomes like those in a cohort of patients who received neoadjuvant therapy.

Surgical risks and postoperative outcomes are the main concern of surgery after inductive treatment. Infact surgery can be more difficult for the presence of fibrosis. The performance status of the patient can also be compromised due to the side effects of preoperative treatments.

In our series, despite fibrosis, radical surgery has been achieved in all patients operated. The intraoperative blood loss, operation time, postoperative hospital stay and postoperative complication rate seems to be similar in two groups. Furthermore, reliable and definitive data on pathological response and on downstaging from the specimen exam are necessary.

CONCLUSIONS:

In our experience surgery after target therapy is feasible and safe and perioperative outcomes are similar to surgery after chemotherapy. More experience and more data are essential to confirm the role of these innovative treatment in induction regimens. Prospective studies like the project here presented are required.

BIBLIOGRAPHY

1. Global cancer statistics.Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. A Cancer J Clin. 2011 Mar-Apr;61(2):69-90.
2. Preoperative evaluation of patients undergoing lung resection surgery. Datta D, Lahiri B. Chest. 2003 Jun; 123(6):2096-103.
3. Survival improvement in resectable non-small cell lung cancer with (neo) adjuvant chemotherapy: results of a meta-analysis of the literature. Berghmans T1, Paesmans M, Meert AP, Mascaux C, Lothaire P, Lafitte JJ, Scuiler JP, Lung Cancer. 2005 Jul;49(1):13-23
4. Role of preoperative chemotherapy for non-small-cell lung cancer: a meta-analysis. Nakamura H1, Kawasaki N, Taguchi M, Kabasawa K. Lung Cancer. 2006 Dec;54(3):325-9
5. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Burdett S1, Stewart LA, Rydzewska L. J Thorac Oncol. 2006 Sep;1(7):611-21
6. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. Song WA1, Zhou NK, Wang W, Chu XY, Liang CY, Tian XD, Guo JT, Liu X, Liu Y, Dai WM
7. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. Rosell R1, Gómez-Codina J, Camps C, Maestre J, Padille J, Cantó A, Mate JL, Li S, Roig J, Olazábal A, et al. N Engl J Med. 1994 Jan 20;330(3):153-8.
8. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Gilligan D1, Nicolson M, Smith I, Groen H, Dalesio O, Goldstraw P, Hatton M, Hopwood P, Manegold C, Schramel F, Smit H, van Meerbeeck J, Nankivell M, Parmar M,Pugh C, Stephens R. Lancet. 2007 Jun 9;369(9577):1929-37
9. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer.Scagliotti GV1, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Maiorino L, Hetzel M, Leschinger M, Visseren-Grul C, Torri V. J Clin Oncol. 2012 Jan 10;30(2):172-8.
10. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014 May 3;383(9928):1561-71
11. Linee guida neoplasia del polmone. Edizione 2017. AIOM
12. Salvage Surgery After Definitive Chemoradiotherapy for Non-small Cell Lung Cancer.Casiraghi M1, Maisonneuve P2, Piperno G3, Bellini R4, Brambilla D4, Petrella F4, Marinis F5, Spaggiari L. Semin Thorac Cardiovasc Surg. 2017 Summer;29(2):233-241.
13. Surgical management of advanced non-small cell lung cancer. Varela G1, Thomas PA1. J Thorac Dis. 2014 May; 6 Suppl 2:S217-23
14. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence. Pöttgen C1, Eberhardt W2, Stamatis G3, Stuschke M1. Oncotarget. 2017 Jun 20;8(25):41670-41678
15. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Paez JG1, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ,

Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson MScience. 2004 Jun 4;304(5676):1497-500

16. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. Kwak EL1, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Jänne PA, Costa DB, Varella-Garcia M, Kim WH, Lynch TJ, Fidias P, Stubbs H, Engelman JA, Sequist LV, Tan W, Gandhi L, Mino-Kenudson M, Wei GC, Shreeve SM, Ratain MJ, Settleman J, Christensen JG, Haber DA, Wilner K, Salgia R, Shapiro GI, Clark JW, Iafrate AJ N Engl J Med. 2010 Oct 28;363(18):1693-703
17. Crizotinib in ROS1-rearranged non-small-cell lung cancer.Shaw AT1, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG, Wilner KD, Clark JW, Iafrate AJ. N Engl J Med. 2014 Nov 20;371(21):1963-71
18. Comprehensive Genomic Profiling Facilitates Implementation of the National Comprehensive Cancer Network Guidelines for Lung Cancer Biomarker Testing and Identifies Patients Who May Benefit From Enrollment in Mechanism-Driven Clinical Trials. Suh JH1, Johnson A2, Albacker L2, Wang K3, Chmielecki J2, Frampton G2, Gay L2, Elvin JA2, Vergilio JA2, Ali S2, Miller VA2, Stephens PJ2, Ross JS2. Oncologist. 2016 Jun;21(6):684-91
19. Mountain, C.F. and C.M. Dresler, Regional lymph node classification for lung cancer staging. Chest, 1997. 111(6): p. 1718-23.
20. Smit, E.F., et al., Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. Journal of Clinical Oncology, 2020. 38(15_suppl): p. 9504-9504.
21. Nakagawa, K., et al., OA04.05 Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer: Interim Results of DESTINY-Lung01. Journal of Thoracic Oncology, 2021. 16(3, Supplement): p. S109-S110.
22. Liu, S.V., et al., LBA61 First analysis of RAIN-701: Study of tarloxotinib in patients with non-small cell lung cancer (NSCLC) EGFR Exon 20 insertion, HER2-activating mutations & other solid tumours with NRG1/ERBB gene fusions. Annals of Oncology, 2020. 31: p. S1189.
23. Socinski, M.A., et al., LBA60 ZENITH20, a multinational, multi-cohort phase II study of poziotinib in NSCLC patients with EGFR or HER2 exon 20 insertion mutations. Annals of Oncology, 2020. 31: p. S1188.
24. Moore, A.R., et al., RAS-targeted therapies: is the undruggable drugged? Nature Reviews Drug Discovery, 2020. 19(8): p. 533-552.
25. Hong, D.S., et al., KRAS(G12C) Inhibition with Sotorasib in Advanced Solid Tumors. N Engl J Med, 2020. 383(13): p. 1207-1217.
26. Addeo, A., et al., Immunotherapy in Non-small cell lung cancer harbouring driver mutations. Cancer Treatment Reviews, 2021: p. 102179.
27. Reck, M., et al., Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med, 2016. 375(19):p. 1823-1833.

28. Reck, M., et al., Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%. Journal of Clinical Oncology. 0(0): p. JCO.21.00174.

29. Brahmer, J.R., et al., Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol, 2017. 18(12): p. 1600-1609.

30. Herbst, R.S., et al., Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. New England Journal of Medicine,2020. 383(14): p. 1328-1339.

31. Sezer, A., et al., Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet, 2021. 397(10274): p. 592-604.

32. Gandhi, L., et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med, 2018. 378(22): p. 2078-2092.

33. Gadgeel, S., et al., Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol, 2020. 38(14): p. 1505-1517.

34. Paz-Ares, L., et al., Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med, 2018.

35. Paz-Ares, L., et al., A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. J Thorac Oncol, 2020. 15(10): p. 1657-1669.

36. West, H., et al., Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol, 2019. 20(7): p. 924-937.

37. Yang, Y., et al., Efficacy and Safety of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 Study (Oncology pRogram by InnovENT anti-PD-1-11). J Thorac Oncol, 2020. 15(10): p. 1636-1646.

38. Zhou, C., et al., LBA56 ORIENT-12: Sintilimab plus gemcitabine and platinum (GP) as first-line (1L) treatment for locally advanced or metastatic squamous non-small-cell lung cancer (sqNSCLC). Annals of Oncology, 2020. 31: p. S1186.

39. Hellmann, M.D., et al., Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med, 2019. 381(21): p. 2020-2031.

40. Paz-Ares, L., et al., First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lungcancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol, 2021. 22(2): p. 198-211.

41. Passaro, A., I. Attili, and F. de Marinis, CheckMate 9LA: broadening treatment options for patients with non-small-cell lung cancer. Lancet Oncol, 2021. 22(2): p. 157-159.

42. Rizvi, N.A., et al., Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non–Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA Oncology, 2020.
43. Leighl, N.B., et al., CCTG BR.34: A randomized trial of durvalumab and tremelimumab +/- platinum-based chemotherapy in patients with metastatic (Stage IV) squamous or nonsquamous non-small cell lung cancer (NSCLC). Journal of Clinical Oncology, 2020. 38(15_suppl): p. 9502-9502.

44. Middleton, G., et al., Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial. Lancet Respir Med, 2020.

45. Passaro, A., et al., Clinical features affecting survival in metastatic NSCLC treated with immunotherapy: a critical review of published data.Cancer Treatment Reviews, 2020: p. 102085.

46. Passaro, A., et al., 104P Fast progression in high PD-L1 NSCLC treated with pembrolizumab in first-line: A prognostic scoring system basedon clinical features. Journal ofThoracic Oncology, 2021. 16(4, Supplement): p. S754-S755

47. Schiller, J.H., et al., Comparison of Four Cemotherapy Regimens for Advanced Non−Small-Cell Lung Cancer. New England Journal of Medicine, 2002. 346(2): p. 92-98.

48. Kelly, K., et al., Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol, 2001. 19(13): p. 3210-8.

49. Scagliotti, G.V., et al., Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol, 2002. 20(21): p. 4285-91.

50. Le Chevalier, T., et al., Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. Lung Cancer, 2005. 47(1): p. 69-80.

51. Douillard, J.Y., et al., Comparison of docetaxel- and vinca alkaloid-based chemotherapy in the first-line treatment of advanced non-small cell lung cancer: a meta-analysis of seven randomized clinical trials. J Thorac Oncol, 2007. 2(10): p. 939-46.

52. Grossi, F., et al., Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: meta-analytical approach. Oncologist, 2009. 14(5): p. 497-510.

53. Klastersky, J., et al., A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small-cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. J Clin Oncol, 1990. 8(9): p. 1556-62.

54. Rosell, R., et al., Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. Ann Oncol, 2002. 13(10): p. 1539-49.
55. Salvage surgery for advanced non-small cell lung cancer after targeted therapy: A case series.Song W, Di S, Liu J, Fan B, Zhao J, Zhou S, Chen S, Dong H, Yue C, Gong T.Thorac Cancer. 2020 Apr;11(4):1061-1067. doi: 10.1111/1759-7714.13366. Epub 2020 Feb 28

56. Salvage surgery for advanced non-small cell lung cancer after response to gefitinib. Hishida T, Nagai K, Mitsudomi T, Yokoi K, Kondo H, Horinouchi H, Akiyama H, Nagayasu T, Tsuboi M; Japan Clinical Oncology Group.J Thorac Cardiovasc Surg. 2010 Nov;140(5):e69-71. doi: 10.1016/j.jtcvs.2010.06.035. Epub 2010 Aug 2.

57. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M.N Engl J Med. 2009 Sep 3;361(10):947-57. doi: 10.1056/NEJMoa0810699. Epub 2009 Aug 19.

58. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer.Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, Downey RJ, Brahmer JR, Battafarano R, Bush E, Chaft J, Forde PM, Jones DR, Broderick SR.J Thorac Cardiovasc Surg. 2019 Jul;158(1):269-276. doi: 10.1016/j.jtcvs.2018.11.124. Epub 2018 Dec 13.

59. Initial Experience With Lung Cancer Resection After Treatment With T-Cell Checkpoint Inhibitors. Jamie E Chaft 1, Matthew D Hellmann 1, Moises J Velez 2, William D Travis 2, Valerie W Rusch 3. Ann Thorac Surg 2017 Sep;104(3):e217-e218.

60. Surgical Outcomes After Neoadjuvant Chemotherapy and Ipilimumab for Non-Small Cell Lung Cancer. Chi-Fu Jeffrey Yang 1, Frances McSherry 1, Nicholas R Mayne 1, Xiaofei Wang 1, Mark F Berry 2, Betty Tong 1, David H Harpole Jr 1, Thomas A D'Amico 1, Jared D Christensen 1, Neal E Ready 1, Jacob A Klapper 3