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Outcomes and prognostic factors of non-small-cell lung cancer with lymph node involvement treated with induction treatment and surgical resection[†]

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Abstract

OBJECTIVES: Induction therapy (IT) has gained popularity in recent years, becoming a standard of treatment in resectable lymph node-positive NSCLC. IT aims to downstage the disease (shrinkage of tumour and clearance of lymph node-metastases), clear distant micrometastases and prolong survival. Potential disadvantages are increased morbidity and/or mortality after surgery and risk of progression of disease that could have been initially resected. The purpose of this study was to evaluate the outcomes and prognostic factors in a series of patients with lymph node-positive NSCLC receiving IT followed by surgery.

METHODS: A total of 86 patients (75.6% males, median age 63 years) affected by NSCLC in clinical stage IIIA ($n = 80$) or IIIB ($n = 6$), with pathologically proven lymph node involvement, underwent platinum-based IT followed by surgery between 2000 and 2009.

RESULTS: Eighty (93%) patients received a median of 3 cycles of chemotherapy, and 6 (7%) underwent induction chemoradiotherapy. Response to IT was complete in 3.5%, partial in 59.3% and stable disease in 37.2% of patients. Postoperative morbidity and mortality were 25.6 and 2.3%, respectively. At pathological evaluation, 38.4% of patients had a downstaging of disease with a complete lymph node clearance in 31.4%. Median overall survival was 23 months (5-year survival 33%). Univariate analysis found clinical stage ($P = 0.02$), histology ($P = 0.01$), response to IT ($P = 0.02$) and type of intervention ($P = 0.047$) to have predictive roles in survival. A better but not significant survival was also found for pN0 vs pN+ ($P = 0.22$), downstaged tumours ($P = 0.08$) and left side ($P = 0.06$). On multivariate analysis, clinical response to neoadjuvant therapy ($P = 0.01$) and age ($P = 0.03$) were the only independent predictors of survival.

CONCLUSIONS: The use of IT for lymph node-positive NSCLC seems justified by low morbidity and/or mortality and good survival rates. Patients with response to IT showed greater benefit in the long term.

Keywords: Neoadjuvant therapy • Mediastinal nodal involvement • N2 non-small-cell lung cancer • Induction chemotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide, accounting for approximately 1.2 million deaths each year [1]. At the time of diagnosis, 30% of patients are found to have locally advanced disease, for which the treatment is still controversial and may depend on the type of lymph node involvement. In fact, patients with confirmed Stage IIIA NSCLC represent a heterogeneous group: according to Ruckdeschel [2], ipsilateral mediastinal involvement may be roughly divided into 3 groups: patients with minimal or microscopic N2 involvement, found incidentally during or after surgery; patients with N2 disease diagnosed preoperatively, with imaging or surgical procedures; and patients with multistation bulky-N2 involvement. Although these patients are determined to have the same disease stage, they are different in terms of prognosis and therapeutic approach: in fact, although there is consensus to treat patients with bulky-N2 in the same group as locally advanced IIIB disease and to treat with primary surgical resection patients with incidental or minimal N2 involvement [3], there is no agreement yet on the best approach to patients with ipsilateral mediastinal lymph node metastasis diagnosed preoperatively, although considered technically potentially resectable. Reports indicate that at least 80% of patients treated with localized measures alone have micrometastatic disease and, therefore, will relapse [4, 5]. Throughout the past 20 years, several different strategies have been reported to treat patients with Stage III lung cancer resulting from N2 disease [6]: the different therapeutic options include neoadjuvant chemotherapy or chemoradiotherapy followed by surgery, primary surgery followed by

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adjuvant chemotherapy with or without sequential adjuvant radiation therapy and definitive chemoradiation without surgery [7–9]. The administration of neoadjuvant chemotherapy before definitive local therapy may offer several potential advantages: (i) delivery of chemotherapy through an intact vasculature; (ii) early eradication of micrometastases; (iii) downstaging of disease (with shrinkage of the primitive tumour and clearance of mediastinal lymph node metastases), which could increase surgical resection rate in patients initially judged inoperable or only marginally suitable for surgery; (iv) *in vivo* assessment of chemoresponsiveness, which may guide appropriate postoperative therapy and has prognostic implications; (v) prevention of tumour seeding at the time of surgery; (vi) increase in patient acceptance, compliance and tolerance to treatment [10, 11]; and (vii) prolongation of overall survival. Potential disadvantages of neoadjuvant chemotherapy are related to an increased risk of perioperative morbidity and/or mortality and the exclusion from potentially curative locoregional treatments, in case of an ineffective induction regimen with progression of local disease, in patients whose tumour could have been initially resected [12]. However, despite limitations, several phase II and III trials of neoadjuvant therapy have consistently demonstrated clinical feasibility, safety and improved survival [7, 9, 13–19]. Although these studies are limited by their size, heterogeneity of disease stage in the study population and perhaps inadequate pretreatment staging, the results nonetheless offer optimism and suggest a distinct role for neoadjuvant chemotherapy. In particular, downstaging of mediastinal lymph nodes and complete surgical resection are reliable predictors of long-term survival in most of these studies [13, 14]. The purpose of the current study was to assess the outcomes and prognostic factors in a series of chemotherapy-naïve patients with lymph node-positive Stage III NSCLC, who received induction treatment (IT) followed by surgery.

MATERIALS AND METHODS

Patients with locally advanced (Stage III) NSCLC with mediastinal nodal involvement, treated between January 2000 and December 2009 with neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection, were identified and reviewed in this study.

Selection criteria and preoperative assessment

The inclusion criteria were male or female patients with histologically diagnosed NSCLC who had never received any treatment for lung cancer before neoadjuvant therapy and who were fit for chemotherapy or chemoradiotherapy and the proposed surgery. The patients must have at least 1 measurable disease or evaluable lesion at baseline. All the patients were restaged according to the TNM classification of the American Joint Committee on Cancer, 7th edition, by using bronchoscopy, total-body scan and/or positron emission tomography (PET). The mediastinal lymph node involvement was confirmed pathologically by trans-bronchial needle aspiration biopsy (TBNA) or endobronchial ultrasonography-guided TBNA, video-assisted thoracoscopy or mediastinoscopy. Clinical data collection included patients' birthdate, sex, tumour histology, clinical stage, clinical response to induction treatment, number of administered cycles, types of drug used, adverse events, post-treatment stage, adjuvant treatments, tumour relapse, progression or death. Clinical response was defined by using the Response Evaluation Criteria in Solid Tumors [20]. A resection was considered complete (R0) when there was no residual tumour detected at the bronchial or vascular margins and no residual disease in the mediastinal area. Mediastinal downstaging was defined as no gross and microscopic disease in the resected mediastinal nodes. Complete pathological response was defined as no viable tumour cells in the resected tumour or lymph nodes. The treatment toxicity was described by using the Common Terminology Criteria for Adverse Events of the National Cancer Institute. The number of cycles of chemotherapy regimen was determined based on clinicians' discretion according to clinical and radiological response. The patients were restaged by total-body CT scan and/or PET after neoadjuvant therapy, and tumour resection was performed for those who had no evidence of progressive or metastatic disease and for those who had no contraindications to surgery. Stable disease (SD) was not considered a contraindication for surgery and, therefore, a pathological restaging of nodal status was not considered necessary.

Surgery and postoperative treatment

Every patient who underwent surgery received an anatomical lung resection and systematic mediastinal lymph node dissection in an attempt to eradicate the whole tumour. Postoperative treatment was administered as follows: adjuvant chemotherapy was usually given for patients with residual lymph node metastasis, and adjuvant radiotherapy was given for patients with a positive resection margin or extranodal extension of residual metastatic mediastinal lymph nodes. Patients with no residual disease, nodal downstaging or considered unfit for adjuvant therapy did not receive any postoperative treatment.

Follow-up

The patients were followed up every 2 weeks during chemotherapy treatment. After surgical resection, the patients were followed up every 3 months for the first 2 years and then every 6 months until tumour recurrences, death or last follow-up.

Statistical analysis

In the statistical description, dichotomous variables were expressed as absolute numbers and percentages and quantitative variables were summarized as median values with first and third quartiles.

The association between qualitative variables was verified by means of the χ^2 test, or Fisher's test, as opportune. Statistical significance of difference between median values was tested by means of the Mann–Whitney *U*-test for unpaired samples. The Kaplan–Meier method was used to model survival during follow-up to estimate the median survival time and the 95% confidence interval (CI) and to compare survival curves with the log-rank test. Simple Cox proportional hazard regression was used to calculate unadjusted hazard ratios (HRs) for clinical (age, C-stage, histology, type of surgery side), postinduction (clinical response, downstaging and N0/N+ status) and postintervention adjuvant (radiotherapy chemotherapy) features. A forward stepwise Cox regression model, with entry and stay of variables showing a significance level of at least 0.1, was applied to obtain adjusted HRs. All

statistical analyses were performed with Statistica, setting the significance level at 0.05.

RESULTS

Patient characteristics

The baseline characteristics of the 86 patients are detailed in Table 1. Males were predominant ($n = 65$; 75.6%), the median age being 63 years. Squamous cell carcinoma ($n = 44$; 51.2%) was the most common histological type. All patients had a pretreatment histological diagnosis of mediastinal nodal involvement (N2), and most were in clinical stage IIIA ($n = 80$; 93%).

Neoadjuvant therapy

Among the 86 patients, 80 (93%) received chemotherapy and 6 (7%) chemoradiotherapy. The median number of cycles of chemotherapy administered was 3 (range 2–4): 6 (7%) patients received 2 cycles, 48 (55.8%) received 3 cycles and 32 (37.2%) received 4 cycles. Most patients were treated with a combination of 2 drugs ($n = 76$; 88.4%), cisplatin plus gemcitabine being administered in most cases ($n = 40$; 52.6%), followed by carboplatin plus gemcitabine ($n = 29$; 38.2%) and cisplatin plus paclitaxel ($n = 7$; 9.2%). In 10 (11.6%) patients, a combination of 3 drugs (carboplatin plus gemcitabine plus paclitaxel) was administered. Preoperative concurrent radiotherapy was delivered in 6 (7%) patients with a total dose of 45 Gy. The toxicity of neoadjuvant therapy encountered mainly mild or moderate (Grade 1–2) adverse events (haematological toxicities: leukocytopenia in 29.4%, anaemia in 25.8%, thrombocytopaenia in 7%; non-haematological toxicities: gastroenteric including mainly nausea, vomiting or diarrhoea in 37.6%, fatigue in 25.8%, alopecia in 14.1% and other in 8%). Ten (11.6%) patients had grade 3/4 toxicities, which included 3 leukocytopenia, 2 thrombocytopenia, 1 anaemia, 1 esophagitis, 1 vomiting, 1 diarrhoea and 1 deep venous thrombosis complicated with pulmonary embolism. No mortality resulted from drug-related toxicities in this study.

Table 1: General characteristics of study population

Characteristics	Number (%)
Overall number	86 (100)
Gender	
Male	65 (75.6)
Female	21 (24.4)
Median age (range)	63 years (41–78)
Histology	
Squamous cell carcinoma	44 (51.2)
Adenocarcinoma	40 (46.5)
Large-cell carcinoma	2 (2.3)
C stage	
IIIA	80 (93)
IIIB	6 (7)
C–T status	
T1	18 (20.9)
T2	29 (33.7)
T3	33 (38.4)
T4	6 (7)

Clinical response was evaluated by CT scan and showed 3 (3.5%) complete response (CR), 51 (59.3%) partial responses and 32 (37.2%) SD. The overall clinical response rate to neoadjuvant therapy was 62.8%.

Surgery

Fifty-one (59.3%) of 86 patients received lobectomies, 12 (14%) bilobectomies and 23 (26.7%) pneumonectomies. Systematic lymph node dissection was performed in every patient. In 11 cases, a sleeve resection was performed, in 5 a bronchoplasty and in 13 a vascular procedure (sleeve or partial resection on pulmonary artery or superior vena cava) was carried out. In 7 patients, a chest wall resection was associated with lobectomy. Eighty-three (96.5%) patients received a complete resection and 3 (3.5%) had an incomplete resection. Two (2.3%) patients died within 30 days of surgery: one because of pulmonary embolism after lobectomy and chest wall resection and another because of acute respiratory distress syndrome after pneumonectomy. Postoperative complications were seen in 22 (25.6%) cases (10 atrial fibrillation, 4 persistent air leaks, 2 anaemia, 1 empyema, 1 pneumonia and 4 other) with no difference between patients who underwent pneumonectomy and who underwent lobectomy and/or bilobectomy.

Pathological response

Complete pathological response was observed in 3 (3.5%) patients: all were alive and free of disease at the last follow-up. Residual N2 disease was present in 44 (51.2%) patients, whereas 42 (48.8%) had mediastinal downstaging to N0 ($n = 27$; 31.4%) or N1 ($n = 15$; 17.4%) disease. Finally, 33 (38.4%) patients had a downstaging of the original disease and the pathological stage was: no residual disease in 3 cases, Stage IA in 9, IB in 6, IIA in 7, IIB in 6, IIIA in 51 and IIIB in 4 cases. There was no significant association detected between clinical and pathological response or mediastinal downstaging and sex, age, histology, cycle number, types of chemotherapy regimen or clinical response to chemotherapy.

Postoperative treatment

Among the 84 patients who underwent tumour resection and survived the postoperative period, 36 (42.9%) did not receive any adjuvant chemotherapy or radiotherapy. Twenty-one (25%) patients received adjuvant radiotherapy, 18 (21.4%) underwent adjuvant chemoradiotherapy and 9 (10.7%) received adjuvant chemotherapy.

Survival

After a median follow-up of 55 months (range 20–127 months), 57 (66.3%) patients died (48 from recurrent disease and 9 from other causes) and 29 (33.7%) were alive (25 with no evidence of disease and 4 with recurrence). The median overall survival was 23 months, with a 5-year survival rate of 33% (Fig. 1). On univariate analysis, the patients with squamous cell carcinoma had a significant better prognosis than adenocarcinoma patients (5-year survival rates: 48 vs 21%, $P = 0.01$). Other significant predictors of better survival were: partial and/or complete clinical response after IT vs SD (5-year survival rates: 43 vs 13.5%, $P = 0.02$), clinical stage with Stage

IIIA having a better survival than Stage IIIB (5-year survival rates: 36 vs 0%, $P = 0.02$) and type of intervention with pneumonectomy having a poorer prognosis compared with lobectomy and bilobectomy (5-years survival: 40, 38 and 15% for lobectomy, bilobectomy and pneumonectomy, respectively; $P = 0.047$. Lobectomy vs pneumonectomy: $P = 0.02$, bilobectomy vs pneumonectomy: $P = 0.12$, lobectomy vs bilobectomy: P = NS) (Fig. 2). Although not statistically significant, downstaging of the tumour ($P = 0.08$), clearance of mediastinal nodes after neoadjuvant therapy ($P = 0.22$) and left side ($P = 0.06$) were associated with a trend towards improved survival (Fig. 3). On multivariate analysis, clinical response to neoadjuvant therapy ($P = 0.01$) and age ($P = 0.03$) were the only independent predictors of survival (Table 2).

DISCUSSION

Lung cancer represents one of the main causes of death from cancer worldwide [1], often because only a few patients are found to have an early-stage tumour that is suitable for surgical resection. In approximately 30% of cases, a locally advanced (Stage III) NSCLC is evidenced, but the optimal treatment of these patients has not yet been well defined and depends on a variety of factors [21]. The prognosis for patients with Stage III NSCLC treated with a single therapeutic option such as chemotherapy, radiotherapy or surgery, is generally poor. In particular, the reported 5-year survival rate for patients with clinical or pathological N2 who undergo surgical resection alone is unsatisfactory, ranging from 9 to 16%, and most patients die of local and systemic relapses after primary resection [4, 5]. For these reasons, the management of N2 node-positive lung cancer remains controversial; in fact, although most surgeons believe that there is an important role for surgery in the treatment of this disease, there is a lack of consensus as to the extent of resection, the role of downstaging and the optimal chemotherapy and radiation regimens to adopt.

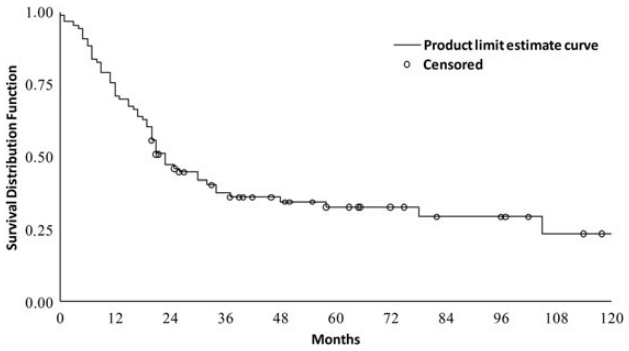

Figure 1: Overall survival.

History and role of induction therapy

The earliest uses of neoadjuvant chemotherapy date from the end of the 1980s, when it was restricted to cases of locally advanced NSCLC (IIIA-N2–IIIB stages) and introduced in an effort to improve the poor survival rates seen historically in this cohort. A series of prospective randomized trials and retrospective reviews revealed better survival rates for patients who received neoadjuvant chemotherapy compared with surgery alone [9, 13–20]. On the basis of these data, in September 2001, the European Society for Medical Oncology (ESMO) task force established treatment guidelines that recognized neoadjuvant chemotherapy as the new standard treatment for resectable stage III NSCLC [22]. A recent meta-analysis of 13 randomized control trials, including 3224 patients, confirmed the appropriateness of these guidelines, demonstrating a survival benefit with a HR of 0.84 (95% CI 0.77–0.92; $P < 0.0001$) in patients treated with neoadjuvant chemotherapy

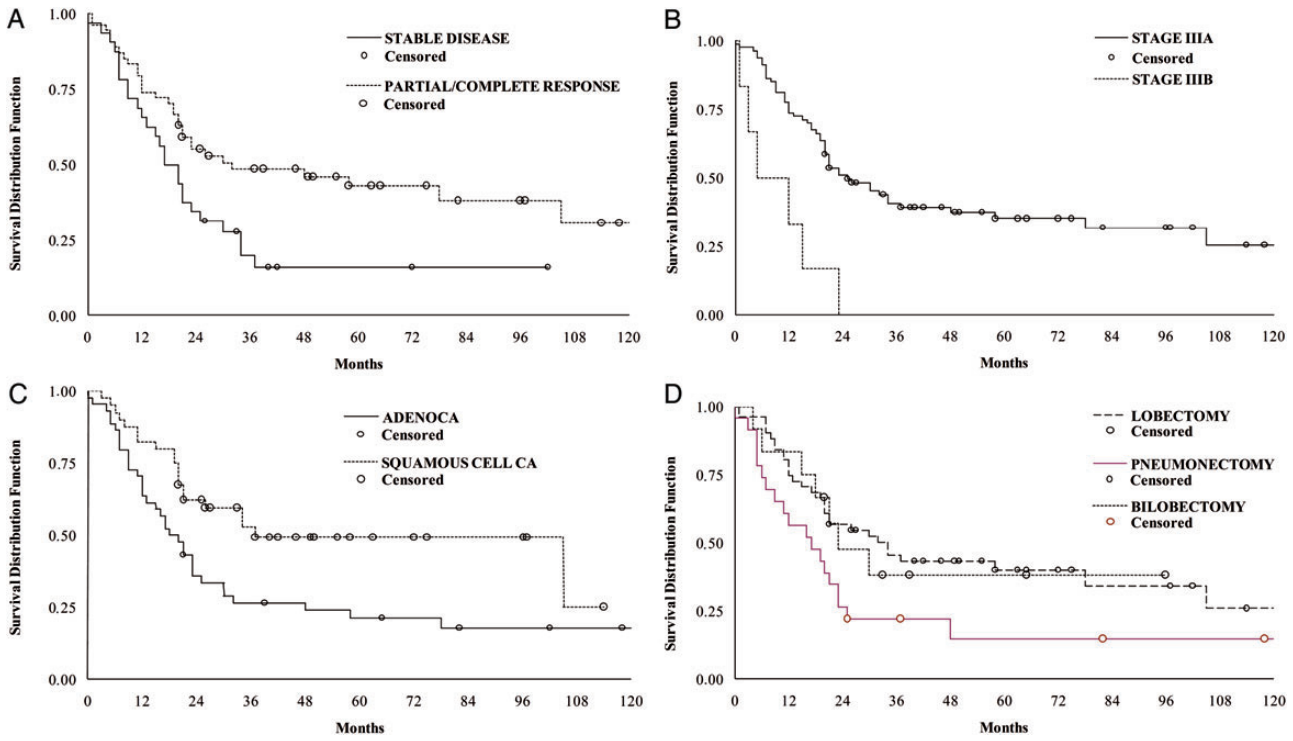

Figure 2: Survival curves based on: (**A**) clinical response to neoadjuvant therapy, (**B**) clinical stage, (**C**) histology and (**D**) type of intervention.

compared with surgery alone [23]. In terms of survival, our experience was in line with or slightly better compared with most published studies, with a median overall survival of 23 months and a 5-year survival rate of 33%.

Prognostic factors

Several factors were previously shown to improve disease-free survival and overall survival in patients treated with induction chemotherapy, including clinical and pathological response to chemotherapy, complete tumour resection and mediastinal downstaging [13–24]. As a consequence, during the mid-1990s, phase II trials with Stage IIIA-N2/IIIB NSCLC were carried out utilizing a chemoradiation regimen, with the aim of enhancing downstaging and, thus, increasing the percentage of complete surgical resection [13, 15, 16]. Despite the higher percentage of downstaging obtained in these studies, with a complete surgical resection rate approaching 93% and pathological CR between 15 and 24%, there was a slight increase in perioperative morbidity and/or mortality without any significant increase in survival compared with the previous studies of neoadjuvant chemotherapy. In a recently published phase III study, Intergroup 0139, 396 patients with Stage IIIA-N2 disease were randomized either to neoadjuvant chemoradiation plus surgical resection and consolidative chemotherapy or to concurrent chemoradiotherapy alone. The median overall survival rate in the neoadjuvant group vs chemoradiation alone group did not differ significantly (5-year survival 27 vs 20%, odds ratio 0.63; 95% CI 0.36–1.10). However, a subgroup analysis revealed a statistically significant 5-year survival advantage for patients who received neoadjuvant chemoradiotherapy plus lobectomy compared with those who underwent chemoradiation alone (36 and 18%, respectively; $P = 0.002$), finding a negative prognostic role for pneumonectomy [7]. In our experience, no differences were found between patients treated with neoadjuvant chemo- or chemoradiotherapy, in terms of overall survival and complications, although the number of patients receiving a combination of chemotherapy and radiotherapy was limited. Regarding the type of surgery, we did not find increased morbidity and mortality rates for those patients receiving pneumonectomy, probably because of a preoperative selection of this group of patients that were in good general and functional status, thus potentially avoiding an increased risk of postoperative morbidity and mortality, in the absence of a clear clinical advantage. In fact, similar to the Intergroup 0139 trial, also in our series patients submitted to pneumonectomy had poor long-term survival (15% at 5 years), therefore underlining the need to evaluate carefully the

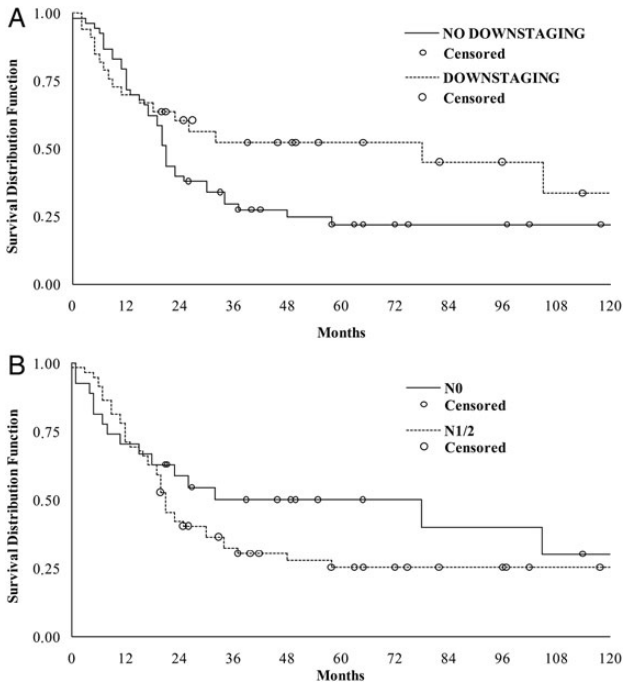

Figure 3: Survival curves based on: (**A**) downstaging of disease and (**B**) pathological nodal status.

Table 2: Unadjusted and adjusted hazard ratios (HR) of death for clinical, postinduction and post-surgery conditions obtained by means of Cox regression models

Conditions	Unadjusted HR (95% CI)	*P*	Adjusted* HR (95% CI)	*P*
Clinical				
Age	1.05 (1.01–1.09)	0.008	1.05 (1.01–1.09)	0.03
C stage	4.17 (1.75–9.93)	0.001	2.22 (0.85–5.83)	0.10
Histology	0.50 (0.29–0.86)	0.01	0.58 (0.33–1.02)	0.06
Type of surgical resection	0.51 (0.22–1.27)	0.16	–	
Side	0.59 (0.33–1.07)	0.08		–
Postinduction				
Clinical response	0.51 (0.30–0.88)	0.01	0.49 (0.28–0.87)	0.01
Downstaging	0.61 (0.34–1.09)	0.09	–	
N+ vs N0	1.43 (0.79–2.61)	0.24		
Post-surgery				
Radiotherapy	1.25 (0.74–2.11)	0.40		
Chemotherapy	1.13 (0.65–1.95)	0.66		

A forward stepwise Cox regression model obtained adjusted HR. Age, C stage, histology, clinical response to IT, surgical type, side and downstaging were independent variables in the model.
A significance level of 0.10 for entry and stay in the model was applied.
CI: confidence interval.

benefit of an aggressive multimodality strategy in such patients. Also in our experience, the response to IT was the most important prognostic factor and, strictly correlated with this finding, the downstaging of the tumour and the clearance of nodal metastases also had a positive impact on long-term survival, although not reaching a statistical value. Thus, the correct re-evaluation, particularly regarding the nodal status, of patients after neoadjuvant therapy becomes of paramount importance. In our experience, all patients received a pathological confirmation of lymph node involvement before starting induction treatment, mainly by surgical approach (mediastinoscopy or thoracoscopy) and, therefore, the re-evaluation was not surgical but through radiological exams (chest CT scan and/or PET-CT scan). The enhancement of noninvasive bronchoscopic methods for lymph node examination could help in the future for better assessment of the pathological response after neoadjuvant therapy by combining noninvasive techniques in the pretreatment period and invasive surgical biopsies in the post-treatment period, thus avoiding a redo-mediastinoscopy. Similar to Liao *et al*. [25], in our study histology was also a prognostic factor on univariate analysis, and patients with squamous cells carcinoma had a significantly better 5-year survival rate compared with adenocarcinoma patients (48 vs 21%, $P = 0.01$). However, unlike this study, we did not find any difference in treatment response to neoadjuvant therapy or downstaging between the two main histological types.

Limitations of the study

Our study has several limitations, including: the retrospective fashion, the absence of a control group, the non-homogeneous nature of the neoadjuvant scheme with different combinations of 2 or 3 drugs reflecting the evolution of chemotherapy over the past few years and the evaluation being limited only to the surgical group with the exclusion of patients who progressed after IT.

CONCLUSION

The results of our experience support the administration of IT in patients with Stage III-N2 NSCLC considered surgically resectable. The adverse effects related to neoadjuvant regimen are of low grade and manageable, with good patient compliance. The high rate of complete surgical resection and the low mortality rate suggest that the preoperative treatment can be considered effective and safe. Patients with response to induction treatment and squamous cell carcinoma seem to benefit better from this multimodality approach. Further investigation of combined modality treatments is warranted to find more effective drugs to improve survival, particularly in the adenocarcinoma subset of Stage III-N2 NSCLC.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr A. Chapelier *(Suresnes, France)*: This report from Dr Marulli and colleagues concerns N2 non-small-cell lung cancer treated with induction chemotherapy and surgical resection with a 2.3% mortality rate in a 10-year period. The lymph node involvement was confirmed pathologically in all patients, and you advocate, like many, that proven N2 disease and lung cancer are not an indication for primary surgery. Your results show that 6 out of 10 patients had a clinical response to chemotherapy and 30% had mediastinal downstaging to N0.

You were able to do a lobectomy or bilobectomy in the vast majority of your patients, and among them you performed 11 sleeve resections. Would you discuss a little further your decision-making with regard to the airway involvement? In other words, do you operate to resect the bronchus on the basis of the original findings, or do you make your decision only on the basis of current findings and perioperative frozen section?

Dr Marulli: Absolutely our decision is based on the pre-treatment evaluation. Also, after a good response to chemotherapy, there is scar, there is very strong tissue, and that is not vascularized. So if you have to plan a sleeve resection, you have to be sure to have healthy tissue, so usually the plan is made before surgery. I have to say that the reason for sleeve resection was because a high number of these patients also had N1 disease.

Dr Chapelier: I have a couple of quick technical questions. After sleeve resection, do you wrap the anastomosis and how?

Dr Marulli: Yes. We wrap the anastomosis usually with a pericardial flap, normally not the full circumference but just to separate the anastomosis from the artery, and that is generally sufficient.

Dr Chapelier: And the last question, in your manuscript you mentioned a partial resection of the superior vena cava in some cases. How did you manage them?

Dr Marulli: In one case we did a prosthetic replacement with clamping only, without cardiopulmonary bypass, and in two cases used a tangential suture, so it was not necessary for any technical skill because it was a tangential clamp along the superior vena cava and a running suture. One case was a complete replacement and two cases were a tangential suture with a patch.

Dr M. Dusmet *(London, UK)*: I have a comment and a question. The comment is relative to the whole session. When you look at those papers that you cited as the historical basis, in those days the mortality for surgery after induction therapy was in the 5% to 6% range. It is now 2.3%. That is relevant to the first paper that was presented today.

The question is, could you give us a little bit more information about the pneumonectomies? In the presentation itself, we didn't get the basis for the 'avoid pneumonectomy' statement at the end, and I think we would all be curious to know on what basis you said that, and do you have a different feeling about a right pneumonectomy and a left pneumonectomy?

Dr Marulli: My response is the same for the comment and for the question. Regarding the comment as to today's mortality, to be honest, we had three other deaths in the first five months. So if we analysed it, probably the real mortality related to the procedure is higher. All three of these deaths were patients who received a right pneumonectomy. When we followed the patients, among 57 deaths, nine patients died for non-oncological reasons. Among them, eight were pneumonectomy patients, of whom six were right pneumonectomies. So I have to say that now, if you have a patient with adenocarcinoma, multi-station, older than 60 years, no response to chemotherapy, we absolutely don't think to do a right pneumonectomy. Usually a left pneumonectomy is probably better tolerated. Sometimes we have pressure from young patients, from oncologists. You are confident with your technique. You are confident to resect the disease completely. On the left side, you can do that. On the right side, we are very cautious.

Dr Dusmet: Please include your late mortality data in the manuscript. It is nice and refreshing to see some honest reporting.

Dr G. Rocco *(Naples, Italy)*: I would like to echo Alain Chapelier's comments about the interesting value of your contribution. I need a clarification. First of all, does it make any difference in your practice to operate straight away in single nodal station disease versus multiple nodal station? I noticed that more than 30% were stable disease after chemo or chemoradiation. You operated on these patients anyway. Did you perform any restaging procedures on them?

Dr Marulli: For the second question, most of the pre-staging of these patients was with mediastinoscopy or VATS. All of these patients were re-evaluated with radiological tools. We did TBNA in a few patients. So all these patients were evaluated by radiological criteria.

Regarding the difference between single-station and multi-station, I have no reply for that. I have to say, first of all, that not all of the stations were sampled during mediastinoscopy or VATS. So I have no reply about the multi-station or single-station. If we have a diagnosis of single-station disease, usually we do induction chemotherapy. Most of all, in the early experience, the single-station metastases were found incidentally during the surgical procedure.

Dr M. Zielinski *(Zakopane, Poland)*: Maybe my question will not be easy to answer. You found that persistent N2 had an adverse prognostic effect, but some patients had 5-year survival. Are you able to subanalyse this group of patients to ascertain the sub-factors that caused these patients to survive 5 years with persistent N2?

Dr Marulli: I did not analyse that. This is a good suggestion. I think that probably there is a difference between the single-station and multiple-station, but I was unable to analyse that because you have only the pathological post-treatment response, and sometimes it is not enough.

Dr Zielinski: It would be very interesting.

Dr Marulli: What we showed (but it was not statistically significant) was that some of these patients who were squamous cell carcinoma patients had a slightly better response than adenocarcinoma patients. However, there is not a correlation for that.