ORIGINAL ARTICLE

OUTCOMES OF SURGICALLY TREATED N2-POSITIVE NON-SMALL CELL LUNG CANCER

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Abstract

Introduction: *The role of surgery in the treatment of stage IIB/IIIA lung cancer is still a matter of debate. To assess the outcomes of N2-positive patients, we performed a retrospective 10-year study including all patients with histologically proven N2 disease submitted to lung resection surgery by the same surgical team in three different hospitals.*

Materials and Methods: *Demographic, clinical, surgical and survival data were collected from patients' clinical registries. Patients were divided into groups according to evidence of neoadjuvant chemotherapy and number of positive N2 stations. Outcomes regarding survival time within and between groups were calculated and compared.*

Results: *Sixty-four patients were included in our study, with a mean age of 62,2 years. Surgery was performed by uniportal VATS in 43.8% of cases. A mean of 3 nodal stations were sampled and 35 patients (54.7%) had one single positive N2 station. Post-operative complications occurred in 27% of patients but no post-operative mortality was recorded. Twenty-seven patients (42.2%) were submitted to neoadjuvant chemotherapy. Survival time within this group was of 67,7±10,5 months, which was not statistically different from those who performed upfront surgery (survival time 48±5,2 months). Patients with single N2 positive stations had a longer survival time than those with multiple N2 positive stations ($p<0.05$). Within the group of patients with single N2 disease (n=35), no difference in survival time was found regarding neoadjuvant therapy.*

Conclusions: *Surgery is effective in selected patients with N2 disease, in particular those with single-N2 positive stations. Neoadjuvant chemotherapy may not grant survival benefit. Adequate pre-operative staging is essential.*

Keywords: *Surgery, NSCLC, Staging, Lung Cancer*

INTRODUCTION

Treatment strategies in lung cancer are clearly defined in both early and advanced stages. Conversely, stage IIIA non-small cell lung cancer is an heterogenous entity, depending on T and N definition.[1, 2] Choosing between upfront surgery followed by adjuvant chemotherapy (CT), with or without radiotherapy (RT), neoadjuvant CT/RT followed by surgery or solely CT/RT, as well as the timings for each (concomitant vs. sequential), is a difficult and case-specific multi-disciplinary decision.[1-3] Regardless, it is widely accepted that stage IIIA N2 patients should receive systemic treatment for distant disease control (CT) combined with local therapy for focal disease control (either RT or surgery).[4] The overall 5-year survival rate for these patients is reported to range from 19.2% to 40% in the literature. [3]

Considering the evolution in both surgery (with minimally invasive techniques and optimized post-operative care), radiotherapy and even in chemotherapic agents, the best treatment for potentially resectable N2 disease becomes an even greyer zone.[5]

The aim of this study is to evaluate the outcome of histologically proven N2 patients submitted to surgery for local disease control, comparing outcomes between patients submitted to neoadjuvant treatment with those solely submitted to post-operative chemotherapy, as well as the survival difference between patient with single-station and multi-station N2. Lastly, the impact of the extension of the surgical procedure on outcomes will also be analyzed.

METHODS

DATA

We conducted a retrospective study, analyzing the outcomes of all patients with histologically proven N2 disease submitted to surgery at three northern portuguese surgical centers (CHVNGE, CSB, CUF) between January 2011 and December 2020. Patients' records were analyzed up until the time of data collection in January 2021, preserving patient confidentiality and with the approval of the ethics committee.

All patients were operated on by the same surgical team.

To characterize our population, we collected data on patient's age, sex, habits (smoking and alcohol use) and comorbidities (hypertension, chronic pulmonary obstructive disease, stroke history and ischemic heart disease). We characterized lung function through pulmonary function tests, collecting data on preoperative fractional FEV1 (forced expiratory volume in one second) and DLCO (diffusing capacity for carbon monoxide).

Regarding pre-operative staging, we recorded the number of patients submitted to PET scan and/or invasive mediastinal staging with either EBUS or mediastinoscopy, as well as the number and location of positive lymph nodes. Staging was performed according to the 8th edition of the TNM staging system.

Surgical information concerning the performed resection, surgical approach (VATS vs thoracotomy) and side were collected. Both early and late post-operative complications (such as respiratory insufficiency, prolonged air leak, cardiac arrhythmia, surgical site infection, empyema or bronchopleural fistula) were registered to evaluate patient's post-operative morbidity.

All surgical specimens were sent for histological analysis. Data on the completeness of resection, histological classification of the disease, pathological T and N status were collected.

The use of neoadjuvant therapy and consequent restaging was also evaluated.

All data were collected through patients' medical records and information conceded by the patients' pulmonologist.

OUTCOMES

Post-operative N2-positive surgically treated patients' prognosis was evaluated through analysis of their disease-free and overall survival as well as 90-day mortality.

After populational analysis, we divided patients into groups to compare their postoperative prognosis according to different variables.

Patients were also divided in groups regarding the number of positive N2 stations (single vs multiple) and their prognosis compared accordingly.

Differences in outcomes between patients submitted to neoadjuvant therapy and those solely submitted to adjuvancy (mainly platinum based chemotherapy in both groups) were analyzed.

At last, the impact of pneumonectomy on outcome in N2 positive patients (either single or multiple) was also evaluated.

STATISTICS

Statistical analysis was performed using SPSS Statistics software.

RESULTS

POPULATION AND DEMOGRAPHICS

A total of 64 patients from three different northern Portuguese surgical centers were included in our study. Two thirds of the patients were male (64.1%) and a third (35.9%) female with a mean age was of 63,5 years (median=63,5[31-84]). The majority of our patients had a history of tobacco abuse (64.1%) while only 9 patients (14.1%) had a history of alcohol abuse. The high incidence of tobacco smokers also accounted for a high obstructive pulmonary disease burden in our population,

Figure 1

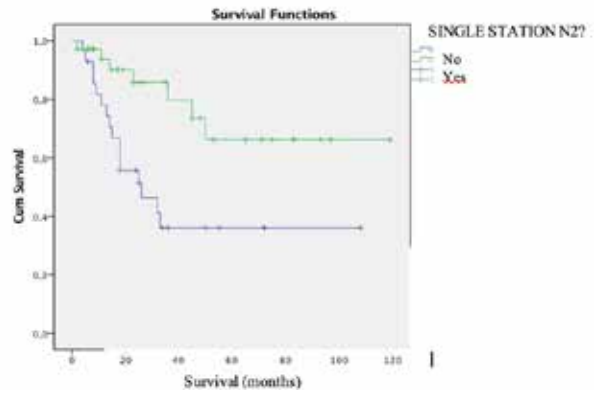

Figure 1 *Survival curves according to number of positive N2-lymph node stations*

Figure 2

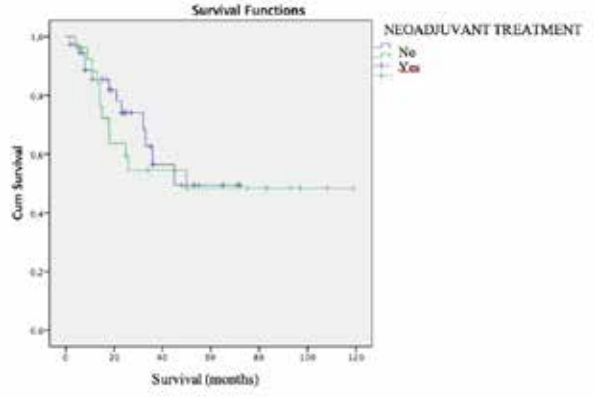

Figure 2 *Survival curves for patients depending on performance of neoadjuvant treatment*

with 39,1% of patients suffering from COPD. Eight patients suffered from cardiovascular disease. The mean %FEV1 was of 91±18,4% [40-135%] and %DLCO/VA was of 85,8±18,7% [42-122%].

SURGICAL DATA

All patients had a diagnosis of lung cancer and were operated by the same surgical team. Twenty-eight procedures (43.8%) were performed through video-assisted thoracic surgery (VATS), implemented in 2014, while the remaining were performed through antero-lateral thoracotomy. In three cases, intra-operative conversion of VATS to standard thoracotomy was performed due to intraoperative complications, namely hemorrhage. Only 2 patients (3.1%) received a non-anatomical lung resection given their poor performance on pre-operative lung function tests. Nine procedures (14,1%) were pneumonectomies. There was a similar distribution of right and left-sided procedures, with a higher frequency of upper-lobe surgery. There were no re-operations. During surgery, the median number of mediastinal lymph nodes stations sampled were 3 (mean= 3,2±1,1 [0-5]).

Post-operative complications occurred in 17 patients (27%), contributing to patients' morbidity, hereby defined by the occurrence of one or more either early or late post-operative complications, given its impact on patients' quality of life. The most frequent post-operative complication was prolonged air leak (n=10). Mean length of stay was of 7.35 ± 6,3 days (median = 5,5 [2-40]). A summary of all performed procedures and post-operative complications is depicted in table 1.

All resections were R0 on histological specimen analysis.

DIAGNOSIS AND STAGING

All patients included in our study had a confirmed histological diagnosis of N2-positive lung cancer on histology. The most frequent histological subgroups were adenocarcinoma (64.1%, n=41) and squamous cell carcinoma (21.9%, n=14). Histological subgroup distribution is depicted in Table 2.

Pre-operative staging was performed using radionucleotide PET scan and, in specific cases, invasive mediastinal staging through either EBUS (Endobronchial Ultrasound) – 13 patients - or videomediastinoscopy - 8 patients. Thirty-eight patients (59,4%) showed pre-operative lymph node positivity on PET-scan. Of these, 12 were submitted to EBUS and 7 to videomediastinoscopy. In the remaining, hypermetabolism was either considered due to inflammatory disease or concerned solely N1 stations and upfront surgery was decided and performed. Two patients had pre-operative N2 disease defined by EBUS in one case and by mediastinoscopy in another without evidence of hypermetabolism on PET scan.

In total, 32 patients were staged pre-operatively as IIIA disease, 31 of which with cN2 and one with T3cN1. Within this group, 24 patients were submitted to neoadjuvant treatment, 22 to CT and 2 to concomitant CT/RT. A total of 3 patients previously staged as cN0 were submitted to neoadjuvant CT for local disease control and size reduction. Restaging was performed solely by CT analysis; PET scan was repeated in 4 cases. Preoperative clinical and postoperative pathological staging of all patients, highlighting all unforeseen N2, is presented in Table 3.

After histological analysis and restaging after surgery, 52 patients were histologically proven N2 on the surgical specimen, while 12 cN2 had been pathologically downstaged either to pN0 (9 patients) or pN1 (3 patients) after neoadjuvant treatment. Given so, half of all patients (50%) who were submitted to neoadjuvancy evidenced pathological downstaging. Thirty-five(54,7%) of patients were single-station N2, while the remaining proved to have multi-station N2 disease.

OUTCOMES

The mean overall survival time was 69,19 +-7,27 months and mean disease-free survival was of 55,4 +-6,2 months. Disease recurrence occurred in 34 of our patients during follow-up time (53,1%). The most frequent location of metastases occurred at the cerebral level, followed by recurrence within the lung (whether same lung, local recurrence, or contralateral recurrence). Mean disease-free survival (DFS) time was of 23,56 ± 20.97 months while 1-year survival rate was of 94,7% and 2-year survival of 71,43%.

There was no 30-day mortality, although 90-day mortality was of 3,1% (2 patients died within the first two post-operative months).

Single-N2 positive patients showed a longer survival time compared to their multi-station counterparts (89,3±9,5 months within the single-station N2 group and 49±9 months within the multi-station group, $p<0.01$). Comparison of survival functions is depicted in Figure 1.

Patients submitted to neoadjuvant therapy displayed a mean survival time of 67,7 months, while those who were solely conceded post-operative adjuvant therapy had mean survival time of 47,3 months. Survival functions within these groups are pictured in Figure 2. Despite the 20 months difference in survival time, statistical significance was not achieved ($p>0.005$).

Within the group of single station N2, corroborating the tendency, although patients who had been submitted to neoadjuvant therapy showed a slightly prolonged survival (single N2: 93±12,9 months vs multi-N2: 56±6,2 months), this difference was not statistically significant.

Our mean follow-up time ranged from 2 to 119 months (u=33.41±28.05).

Patients submitted to pneumonectomy showed an overall survival of 55,2 ± 11,98 months, while those who performed a lobectomy or any other parenchymal sparing surgery had an overall survival of 67,46 ± 7,92 months.

DISCUSSION

Ten to twenty percent of all NSCLC patients present with stage IIIA disease at the time of diagnosis. 5IIIA NSCLC represents a considerably heterogenous group, depending mainly on T and N subgroups, which reflects on its variable prognosis and clinical management. [2, 3]

Many studies divide patients with N2 disease into further subgroups. In the most recent staging system by the American Joint Committee, categories N2a1 (single

N2 nodal station, without N1 involvement), N2a2 (single N2 nodal station with N1 involvement), and N2b (multiple N2 nodal stations) were introduced.6 Sanchez-Lorente et all furtherly divide N2 disease according to pre-operative suspicion grade into "unsuspected N2", harboring the best prognosis among the three and representing 10% of patients at time of surgical resection, "ignored N2" and "underappreciated N2".[7, 8]

Stage IIIA-N2 NSCLC has potential features of a systemic disease, with micrometastases being the main causes for disease recurrence, thus a multimodal approach including systemic treatment for local and systemic control is preferred.[9] Treatment itself is highly variable, with a multitude of combinations and timings between radiotherapy, chemotherapy and surgery.

In resectable cN2 NSCLC, bimodality treatment with chemotherapy and radiotherapy has not been shown to be superior to either chemotherapy or radiotherapy plus surgery.[4, 10] As so, surgery remains an important part of treatment whenever an R0 resection is possible, especially giving the improvements in lung cancer treatment in the modern era (lung sparing techniques, minimally invasive surgeries and optimized post-operative care).[5] Beyond local disease control, surgery confers a matchless advantage, allowing for advanced molecular studies on the surgical specimen to identify targetable mutations and to confirm pathologically the stage of the disease (namely true N stage). When comparing with PORT for local disease control, it outweighs the detrimental cardiopulmonary effects of PORT on N2 disease and leaves space for additional either adjuvant or neoadjuvant radiotherapy as an additional weapon to surgery.[11]

The 5-year survival rate of patients with N2 disease has been reported to range from 19.2% to 40%. 3Given the short follow up time in our study, 5-year survivals were not calculated. According to Zhao et al's meta-analysis, overall survival times for IIIA-N2 lung cancer patients may range from 16,4 to 83,5 months, regardless of treatment strategy. In our population of surgically resected N2 patients, overall survival time was of 69,19 ± 7,27 months, falling within the reported range.[9]

Clinical practice and investigation have shown us that there is more to N2 disease than what is currently determined in NSCLC guidelines. Single-station N2 has consistently proven to have a far more favorable outcome than multi-station N2 disease.[12-14] Our study clearly corroborates this finding, with patients with single-station N2 showing overall survival time an overall survival near double than those with multi-station N2. This brings awareness to the relevance of an adequate pre-operative staging. Adequate pre-operative staging may reveal a multi-station N2 disease than may not benefit from surgical treatment for local disease control, directly influencing outcomes and prognosis. Those who, despite adequate staging, are post-operatively found to be pN2, still have better prognosis that those with pre-operative cN2.[1]

The second goal of our study was to investigate whether neoadjuvant treatment improved outcomes in surgically treated N2 patients. The use of neoadjuvant therapy relies on its role in tumor downstaging, facilitating surgery, and elimination of microresidual disease, which could confer survival benefit.[9] Overall survival reports range from 16 to 59 months after neoadjuvant treatment. [5] In our series, survival after neoadjuvant therapy was of 67,7 months, which exceeded these reports. Survival time in these patients exceeded in 20 months that of patients who had not been submitted to pre-operative therapy. Although this difference could not be statistically proven, in a patients' point of view, over a year longer in life expectancy can be relevant. Most patients in our study were submitted solely to neoadjuvant chemotherapy. Comparison between radiotherapy and chemotherapy was beyond the scope of this study, although we believe pre-operative radiotherapy may forfeit surgical procedures and outcomes. One important aspect we must keep in mind while proposing a patient with neoadjuvant therapy is that it might decrease patients' adherence to post-operative (adjuvant) therapies, embargoing optimal treatment, which could ultimately adversely affect patient survival.

Treatment strategies should always be discussed in a multidisciplinary fashion. Surgeons play a relevant role in the discussion, particularly while evaluating if the patient is a candidate either for lobectomy or if a pneumonectomy is needed for complete tumor resection. Pneumonectomies have the greatest morbidity and mortality in lung resection surgery. Performing a pneumonectomy in a multi-station N2 patient might have a negative impact on survival. In our study, patients submitted to pneumonectomy had a slightly shorter overall survival than those submitted to lobectomy, but this difference was not statistically significant. Behera et al has also found that pneumonectomy in the setting of N2 disease is associated with a higher mortality compared with lobectomy, and a tendency to avoid pneumonectomy in these patients is also evident in the Society of Thoracic Surgeons' databases.[2, 16]

Our study, although small and retrospective, constitutes a plea for adequate staging in order to pursue surgery in carefully selected N2 patients, with particular regard to the difference between N2a1 and N2a2 patients. We also plea for the use of upfront surgery given the absence of evidence of clear benefit of neoadjuvant treatment and the timing limitations it imposes, although it might be used, whenever it does not compromise further treatment and has a predicted benefit for surgery itself.

Despite the short sample size and its retrospective nature, it shows promising outcomes and survival times in all groups of N2 surgically treated patients in comparison with other studies. Comparing outcomes with those who were treated non-surgically is needed in future studies, especially in an era when the relevance and efficacy of targeted therapies and immunotherapy is rising.

Table 1 **Surgical proceduresa nd post-operative complications**

Procedure		n	%
Lobectomy		46	71,9%
	Superior	29	45,3%
	Middle	4	6,3%
	Inferior	13	20,3%
Bilobectomy		6	9,4%
	Superior	3	4,7%
	Inferior	3	4,7%
Pneumonectomy		9	14,1%
	Left	8	12,5%
	Right	1	1,6%
Segmentectomy	Left superior	1	1,6%
Wedge resection		2	3,1%

Post-operative complications		
Atrial fibrillation	1	1,6%
Atelectasis	1	1,6%
Hemorrhage	2	3,2%
Prolonged air leak	10	15,9%
Empyema	2	3,2%
Bronchopulmonary fistula	1	1,6%
Overall Morbidity	17	27%

Table 2 **Histological distribution of lung cancer patients**

Histology	n	%
Adenocarcinoma	41	64,1%
Squamous cell carcinoma	14	21,9%
Bronchiolo-alveolar	1	1,6%
Large cell carcinoma	1	1,6%
Sarcomatoid carcinoma	2	3,1%
Small cell carcinoma	1	1,6%
Carcinoid	3	4,7%
Adenosquamous	1	1,6%

Table 3 **Pre and post-operative staging**

Pre-operative Staging			Post-operative Staging		
IIIa	T3	N2	IIb	T3	N0
IIa	T2b	N0	IIIa	T2b	N2
IIIa	T1b	N2	Ib	T2a	N0
IIIa	T2b	N2	IIIb	T4	N2
IIIa	T2b	N2	IIIa	T1b	N2
Ib	T2a	N0	IIIa	T2a	N2
IIIa	T2b	N2	IIIa	T3	N2
IIIa	T2a	N2	Ia	T1b	N0
IIIa	T2b	N2	IIa	T2a	N1
IIIa	T2b	N2	Ib	T2a	N0
IIIa	T1a	N2	IIIa	T1a	N2
IIIa	T1a	N2	IIIa	T0	N2
IIIa	T4	N0	IIIa	T1b	N2
IIIa	T2a	N2	IIIa	T2a	N2
IIIa	T3	N2	IIIa	T3	N1
IIIa	T4	N2	IIa	T2b	N0
IIIa	T3	N2	IIIa	T2b	N2
IIIa	T3	N2	IIIa	T3	N2
IIIa	T2b	N2	Ib	T2a	N0
IIIa	T2a	N2	Ib	T2a	N2
Ib	T1b	N0	IIIa	T1b	N2
IIIa	T3	N2	IIIa	T2a	N2
IIIa	T2a	N2	Ib	T2a	N0
IIb	T3	N0	IIIa	T2b	N2
IIIa	T3	N2	IIIa	T3	N2
Ib	T2a	N0	IIIa	T1b	N2
IIIa	T2a	N2	IIIa	T2a	N2
Ib	T2a	N0	IIIa	T1b	N2
Ib	T2a	N0	IIIa	T2a	N2
IIIa	T1b	N2	IIIa	T1b	N2
Ib	T2a	N0	IIIa	T2a	N2
Ib	T2a	N0	IIIa	T2a	N2

Pre-operative Staging			Post-operative Staging		
IIIa	T2b	N2	IIIa	T2b	N2
IIIa	T2b	N2	Ib	T2a	N0
Ib	T2a	N0	IIIa	T2a	N2
Ib	T2a	N0	IIIa	T2a	N2
Ia	T1a	N0	IIIa	T1a	N2
IIb	T3	N0	IIIa	T3	N2
Ia	T1b	N0	IIIa	T1b	N2
Ia	T1a	N0	IIIa	T3	N2
IIa	T2b	N0	IIIa	T2a	N2
IIIa	T2a	N2	IIIa	T1b	N2
IIIa	T2a	N2	IIIa	T2a	N2
IIb	T3	N0	IIIa	T3	N2
IIIa	T2b	N0	IIIa	T2b	N2
IIIa	T1c	N2	IIIa	T2a	N2
Ib	T2a	N0	IIIa	T2a	N2
IIa	T2a	N0	IIIa	T2a	N2
IIIa	T2a	N2	IIIa	T2a	N2
Ib	T2a	N0	Ib	T2a	N2
IIa	T2a	N1	IIIa	T2a	N2
IIIa	T2b	N2	IIIa	T2b	N2
Ib	T2a	N0	IIIa	T2a	N2
Ib	T1b	N0	IIIa	T1a	N2
IIa	T2a	N0	IIIa	T2a	N2
IIIa	T3	N2	Ia	T1c	N0
Ib	T2a	N0	IIIa	T2b	N2
Ib	T1b	N0	Ia	T1b	N2
Ib	T1b	N0	IIIa	T2a	N2
Ib	T1c	N0	IIIa	T2a	N2
IIIa	T3	N2	IIIb	T3	N1
IIb	T3	N0	IIIa	T3	N2
IIIa	T2a	N2	IIIa	T2a	N2
IIb	T3	N0	IIIb	T3	N2

CONCLUSION

Our study corroborates existing evidence that upfront surgery in single-station N2 positive patients is both safe and the best path for patient treatment, given that pre-operative staging is adequate and reliable, and conditions for an R0 resection are guaranteed.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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