Title: Neoadjuvant treatment followed by surgery versus definitive chemoradiation in stage IIIA-N2 non-small-cell lung cancer: A multi-institutional study by the oncologic group for the study of lung cancer (Spanish Radiation Oncology Society)

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Neoadjuvant Treatment Followed by Surgery versus Definitive Chemoradiation in Stage IIIA-N2 Non-Small-Cell Lung Cancer: a Multi-institutional Study by the Oncologic Group for the Study of Lung Cancer (Spanish Radiation Oncology Society).

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HIGHLIGHTS

- Neoadjuvant treatment plus surgery yields better OS than chemoradiotherapy
- Neoadjuvant treatment plus surgery yields better PFS than chemoradiotherapy
- Surgery-related mortality in our sample was low and comparable to chemoradiotherapy

Abstract

Objectives: The role of surgery in stage IIIA-N2 non-small cell lung cancer (NSCLC) is an actively debated in oncology. To evaluate the value of surgery in this patient population, we conducted a multi-institutional retrospective study comparing neoadjuvant chemoradiotherapy or chemotherapy plus surgery (CRTS) to definitive chemoradiotherapy (dCRT).

Material and methods: A total of 247 patients with potentially resectable stage T1-T3N2M0 NSCLC treated with either CRTS or dCRT between January 2005 and December 2014 at 15 hospitals in Spain were identified. A centralized review was performed to ensure resectability. A propensity score matched analysis was carried out to balance patient and tumor characteristics (n = 78 per group).

Results: Of the 247 patients, 118 were treated with CRTS and 129 with dCRT. In the CRTS group, 62 patients (52.5%) received neoadjuvant CRT and 56 (47.4%) neoadjuvant chemotherapy. Surgery consisted of either lobectomy (97 patients; 82.2%) or pneumonectomy (21 patients; 17.8%). In the matched samples, median overall survival (OS; 56 vs 29 months, log-rank p=0.002) and progression-free survival (PFS; 46 vs 15 months, log-rank p<0.001) were significantly higher in the CRTS group. This survival advantage for CRTS was maintained in the subset comparison between the lobectomy subgroup versus dCRT (OS: 57 vs 29 months, p<0.001; PFS: 46 vs 15 months, p<0.001), but not in the comparison between the pneumonectomy subgroup and dCRT.

Conclusion: The findings reported here indicate that neoadjuvant chemotherapy or chemoradiotherapy followed by surgery (preferably lobectomy) yields better OS and PFS than definitive chemoradiotherapy in patients with resectable stage IIIA-N2 NSCLC.

Keywords: NSCLC; stage IIIA; neoadjuvant treatment; chemoradiation; surgery.

1. Introduction

Patients with stage IIIA non-small cell lung cancer (NSCLC) comprise a highly heterogeneous group due to a wide range of differences in the size and localization of the primary tumor and the extent of mediastinal lymph node involvement. The presence of N2 disease implies a worse prognosis and higher rates of loco-regional and distant relapses; in these cases, the entire therapeutic strategy must be reconsidered [1,2].

The management of patients with potentially resectable stage IIIA-N2 NSCLC is controversial and the optimal therapeutic strategy remains unclear. Although definitive chemoradiotherapy (dCRT) is a standard treatment option in these patients [3], the role of surgery following chemotherapy (CHT) or neoadjuvant CRT is intensely debated in thoracic oncology [4] because no definitive conclusions can be drawn from the current evidence base [5].

Although findings from several uncontrolled phase II studies seem to indicate that surgery is superior to other treatments [6-8], randomized phase III trials have been unable to demonstrate a clear advantage in overall survival (OS) for neoadjuvant treatment (CHT or CRT) plus surgery (CRTS) compared to dCRT [9-11]. Nonetheless, the Intergroup 0139 trial [10] demonstrated an increase in 5-year progression-free survival (PFS) in patients treated with CRTS vs dCRT alone, although there was no OS advantage, probably due to the high post-operative mortality rate in the pneumonectomy

patients. Importantly, a post hoc subset analysis showed that OS was better in patients who underwent lobectomy compared to dCRT. Recent findings from several retrospective single-center studies [12-14], a population-based study [15] and a meta-analysis [16] indicate that OS is better in patients treated with neoadjuvant CRT or CHT plus surgery versus dCRT.

Given the difficulty of completing clinical trials in this patient population, we performed a retrospective multicenter study to clarify the role of surgery in potentially-resectable stage IIIA-N2 NSCLC. The primary objective was to compare OS in two patient cohorts diagnosed and treated with either CRTS or dCRT for stage IIIA-N2 NSCLC during the 2005-2014 time period. Secondary outcome measures included PFS, locoregional and distant relapse rates, and treatment-related toxicity and mortality

2. Materials and methods

2.1. Study design

This was a multicenter, retrospective study involving patients from 15 hospitals in Spain. The study was supported by the Radiation Oncology Clinical Research Group (GICOR) and the GOECP-SEOR (Oncologic Group for the Study of Lung Cancer-Spanish Society of Radiation Oncology). The study sample included patients diagnosed and treated for clinically or pathologically-proven stage IIIA-N2 (T1-3 N2 M0) NSCLC between the years 2005-2014 (inclusive). Inclusion criteria were: potentially-resectable stage IIIA-N2 (T1-3 N2 M0) NSCLC treated with either radical intent CRTS or dCRT, (see Supplemental Data Figure 1). Given that both CRTS and dCRT are considered adequate options in the management of these patients, the specific treatment decision depended on two main factors: 1) the management protocol in place at the treating center, and 2) definitive radiochemotherapy was preferred when the mediastinum

remained histologically positive after induction therapy. In addition, patients with comorbidities use to be treated with definitive radiochemotherapy. Nevertheles, it is important to highlight that the vast majority of all patients included had a good ECOG score (0-1).

Patients with radiological evidence of disease progression after induction treatment, patients treated with radiotherapy or surgery alone, and those who underwent sequential CRT, or concomitant CRT with unresectable NSCLC were excluded.

A centralized review was performed by two thoracic surgeons using a double-blind system (both were unaware of treatment outcomes and of the other reviewer's assessment) to determine resectability in the patients who did not undergo surgery. We only included those cases in which the two surgeons were in agreement regarding tumour resectability. Borderline cases or cases in which the surgeons differed in their assessment of tumour resectability were excluded from the final analysis.

Exclusion criteria were: stage T4 disease with mediastinal invasion; bulky nodal disease with loss of the tissue plane separating the mediastinal nodes from the trachea; invasion of the large vessels or heart; and presence of nodules in the contralateral lung. Staging was performed according to the 7th edition of the TNM Classification of Malignant Tumors.

2.2. Treatment

Staging was based on pre-treatment systemic imaging (computed tomography [CT],18-F fluorodeoxyglucose positron emission tomography-computed tomography [PET/CT], and/or bone scan) and brain imaging (magnetic resonance imaging [MRI] or

CT if MRI unavailable/ contraindicated). Baseline mediastinal disease was assessed by PET/CT or CT and confirmed histologically when feasible by mediastinoscopy, endobronchial ultrasound (EBUS), or endoscopic ultrasound (EUS).

Neoadjuvant treatment consisted of three cycles of alone CHT (generally platinum-doublet) or concomitant CRT. Radiotherapy doses ranged from 45-66 Gy (1.8-2 Gy/fraction) to the tumor volume (defined by CT or PET/CT). The radiotherapy modality was three-dimensional conformal radiotherapy. No respiratory motion control techniques (e.g., fluoroscopy, four-dimensional CT simulation scans) were used.

Response to neoadjuvant treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) using CT or PET-CT. Depending on the treating hospital's protocol, histological reassessment of the mediastinal nodes was performed using EUS, EBUS, or mediastinoscopy. The time elapsed between completion of neoadjuvant treatment and surgery was measured in days. Surgical treatment consisted of lobectomy or pneumonectomy with homolateral and mediastinal hilar lymphadenectomy. Complete pathological response (pCR) was defined as the absence of viable tumor in the surgically resected specimen. Postoperative radiotherapy and postoperative CHT were performed according to the protocol in place at each hospital.

Patients treated with dCRT underwent various chemotherapy regimens (platinum-based doublets) depending on the protocol at the treating hospital, delivered weekly or every 21 days concurrently with radiotherapy (60-70 Gy). Patients in the dCRT group received the same neoadjuvant treatment as described above. Patients treated with neoadjuvant CRT or CHT who presented a radiological response to the disease and who did not undergo surgery due to the presence of persistent positive mediastinal nodes were included in the dCRT group,

2.3. Follow-up

Acute and late toxicity were evaluated according to the Common Toxicity Criteria for Adverse Events (v. 4.0). Follow up was performed weekly during treatment. Post-treatment follow up was performed every 3-6 months for the first 2 years, every 6-12 months for the next three years, and annually thereafter. The date of recurrence was defined as the day an abnormal imaging test was detected during follow-up. Locoregional relapse was defined as a recurrence to the ipsilateral lung and/or nodal regions (hilum, mediastinum, or supraclavicular fossa). Distant relapse was defined as a recurrence in other locations (AJCC staging criteria, 7th edition).

2.4. Statistical analysis

The patients' baseline characteristics were compared using the Chi square test or the Fisher exact test for categorical variables. The Student's t test or the Mann-Whitney U-test was used, as appropriate, to compare quantitative variables based on the data distribution (parametric or non-parametric).

OS was calculated from the date of pathological diagnosis until the date of death or last follow-up. PFS was measured from the date of the pathological diagnosis until first recurrence, death from any cause, or final follow-up. OS and PFS were estimated using the Kaplan-Meier method. The log-rank test was used to compare survival curves between the surgery and non-surgery groups.

To minimize possible biases due to treatment selection related to patient and/or tumor characteristics, a rigorous propensity score adjustment was performed. Any variable that

could not be balanced (i.e., age; gender; ECOG score; smoking history; clinical T stage; number and size of involved nodal stations; histology; baseline histologic confirmation of the mediastinal nodes) were adjusted to create two comparable patient groups: the CRTS group and the dCRT group (Table 1). Patients in the CRTS group were further subdivided into the two subgroups according to the type of surgery performed (lobectomy or pneumonectomy). Thus, three different groups were defined: 1) dCRT, 2) CRTS-lobectomy, and 3) CRTS-pneumonectomy.

Finally, we analyzed the effect of these covariates (including the different treatment arms) on OS and PFS using the Cox proportional hazards model. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the SPSS statistical software, version 22.0 (SPSS Statistics for Windows, IBM Corporation, Armonk, NY).

3. Results

Initially, 294 patients diagnosed with stage IIIA-N2 NSCLC (T1-3 N2 M0) were identified. After the centralized review to determine resectability, a total of 247 patients with potentially-resectable stage IIIA-N2 disease were included in the final analysis: of these, 129 (52.2%) were treated with dCRT and 118 (47.8%)with CRTS, (see Supplemental Data Figure 1).

3.1. Patient characteristics

Patient characteristics are shown in Table 1. Histological evaluation of the mediastinal nodes was performed to confirm the diagnosis in 89 patients (68.9%) in the dCRT group and 69 patients (58.4%) in the CRTS group ($p = 0.08$). The median age in the CRTS group (62 y; range, 41-78) was slightly (but non-significantly, $p = 0.085$) lower than in the dCRT group (65 y; 37-82). There were 24 women in the CRTS group (20.3%) and

16 (12.4%) in the dCRT group (p=0.091). Most patients in both groups had an ECOG score of 0-1. Involvement of a single mediastinal lymph node station at diagnosis was more frequent in the CRTS group (72 pts [61%] vs. 55 pts [42.6%], p=0.004). Only a limited number of cases (22 patients) with mediastinal bulky disease (> 3 cm) were considered to have potentially resectable disease in the evaluation performed by the two thoracic surgeons who reviewed the cases. Of these 22 patients, 14 were treated with dCRT and 8 CRTS (in all cases according to the criteria in place at the treating center). The 8 surgical patients with bulky mediastinal disease (> 3 cm) met all of the resectability criteria for the present study. The propensity score-matched cohorts included 78 patients in each group (i.e., the CRTS and the dCRT groups) (Table 1). The subset analysis (CRTS-lobectomy and CRTS-pneumectomy versus dCRT) revealed that the pneumonectomy subgroup contained a significantly higher percentage of patients with stage cT3 disease compared to the CRT group (66.7% vs. 32.6%, p = 0.003). However, this variable could not be adjusted due to the limited number of pneumonectomies (n = 19) in the matched sample.

3.2. Treatment characteristics

All patients in the dCRT group received CHT plus concomitant radiotherapy (Table 2). In most cases (92.2%), CHT consisted of a platinum-based doublet. Similarly, the radiotherapy dose range was 60-66 Gy in most (92.2%) cases, delivered at 2 Gy/session (80.6% of cases). Table 3 shows the treatments administered in the CRTS group: 62 patients (52.5%) underwent neoadjuvant CRT while the remaining patients received CHT alone. The radiotherapy dose was > 50 Gy in 43 patients (69.4%). In the CRTS group 82.2% of patients underwent lobectomy and 17.8% pneumonectomy. Thirty-two patients (27.2%) achieved a pCR in the primary tumor and mediastinal lymph nodes

(pT0pN0); of these, 26 (81.2%) had received induction CRT and 6 (18.8%) chemotherapy alone (p <0.001). Postoperative radiotherapy was given to 57.6% of patients receiving pCHT. Adjuvant CHT was given to 26.3% of patients.

3.3. Overall Survival

Median follow-up was 25 months (range, 2-134 months) in the dCRT arm and 42.5 months (5-128 months) in the CRTS arm. Specifically, the median follow up in surviving patients was high in both treatment cohorts (40 months in the dCRT group and 51 months in the CRTS group). Respectively, 53 (66.7%) and 38 (48.7%) deaths were recorded in the dCRT and CRTS groups by the final follow-up.

OS was higher in the surgical cohort (Figure 1). These findings were confirmed in the matched sample analysis (Figure 1): in the CRTS group, median survival was 56 months (95% confidence interval [CI]: 51.14-60.86), with a 3-year OS rate of 67.7% (95% CI: 56.9 -78.4); these outcomes were significantly higher (HR=0.51, 95% CI: 0.33-0.78, p = 0.002) than the corresponding figures in the dCRT group: median survival, 29 months (95% CI: 23.65-34.35) and 3-year OS, 39.2% (95% CI: 27.6-50.9).

After adjusting the propensity scores, we evaluated outcomes according to type of surgery. Median survival time and 3-year OS rates in the pneumonectomy subgroup were 35 months [95% CI: 20.04-49.96] and 48.9% [95 % CI: 24.50-73.30]). These outcomes were comparable (HR = 0.71; 95% CI: 0.36 0.36-1.41; p=0.515) to the corresponding results in the dCRT group: 29 months [95% CI: 23.65-34.35] and 39.2% [95% CI: 27.60-50.9] (Figure 2). By contrast, both median survival and 3-year OS were significantly higher in the lobectomy subgroup versus dCRT (HR =0.46, [95% CI: 0.28-0.73], p=0.001) (Figure 2) as follows: median survival was, respectively, 57 months [95% CI: 51.62-60.38] vs 29 months [95% CI: 23.65-34.35], with 3-year OS rates of 73.4% [95% CI: 61.80-85.0] vs 39.2% [95% CI: 27.6 – 50.9].

In the matched samples, the only factors independently associated with improved OS (Cox regression analysis) were CRTS (vs dCRT; p = 0.002) and neoadjuvant treatment plus lobectomy (vs dCRT; p = 0.001) (see Supplemental Data Tables 1 and 2).

3.4. Progression-free survival

PFS was significantly greater (HR=0.46; 95% CI 0.30-0.71; p<0.001) in the surgical arm vs. the dCRT arm, both in the overall cohort (Figure 1) and in the adjusted samples (Figure 1). Median PFS in the CRTS group was 46 months [95% CI:30.54-61.46] vs 15 months [95% CI:11.75-18-25] in the dCRT group, while 3-year PFS rates were, respectively, 53.7% [95% CI: 42-65.4] vs. 27% [95% CI: 16.4-37.6].

In the matched samples, median PFS in the pneumonectomy subgroup was similar to PFS in the dCRT group (Figure 2), as follows: 26 months (95% CI: 14.48-37.25) vs 15 months (95% CI: 11.75-18.25), with 3-year PFS rates, respectively, of 42.9% (95% CI: 19.4-66.4) and 27% (95% CI: 16.4-37.6) [HR= 0.58, 95% CI, 0.30 – 1.15; p=0.124]. By contrast, the lobectomy subgroup presented a significantly higher PFS (HR =0.36, [95% CI: 0.22 – 0.58], p<0.001) than dCRT (Figure 2): median PFS, 46 months (95% CI: 29.82-62.17) vs 15 months (95% CI: 11.75-18.25), with 3-year PFS rates, respectively, of 57.1% (95% CI: 43.7-70.5) vs. 27% (16.4-37.6), p<0.05.

On the adjusted Cox regression analysis, the factors independently associated with improved PFS included CRTS (vs dCRT; p<0.001) and lobectomy (vs dCRT; p<0.001) (see Supplemental Data Tables 1 and 2).

3.5. Recurrence Patterns

In the overall cohort, 93 dCRT patients (72.7%) and 55 CRTS patients (46.6%) developed recurrent disease. Median time to first recurrence was significantly greater in the CRTS group (32 months, interquartile range [IQR], 36.5) than in the dCRT group (13 months; IQR,18). Moreover, patients in the CRTS group experience fewer locoregional recurrences vs. the dCRT group (29 patients [24.6%] vs 57 [44.5%)]; p = 0.001) and fewer distant recurrences (39 patients [33.1%] vs 63 [49.2%], p < 0.001). In the matched samples, the pneumonectomy subgroup and the dCRT had similar rates of locoregional and distant recurrences: 52.6% vs. 75.3% (a non-significant difference, p=0.051). By contrast, the lobectomy group presented a significantly lower rate of locoregional and distant recurrence versus the dCRT group (47.5% vs. 75.3%, p = 0.001).

3.6. Treatment-related toxicity and mortality

Table 4 summarizes toxicity data for the overall sample. Hematologic toxicities (anemia, neutropenia, thrombocytopenia) were the most common ≥ grade 3 toxicity, affecting 22 patients (17.6%) in the dCRT group and 2 (1.9%) in the CRTS group (p<0.001). On the adjusted analysis, these findings were maintained (p <0.001), without significant differences between the groups in other toxicities. On the matched sample analysis, two patients (5.3%) in the CRTS group (one each in the lobectomy and pneumonectomy subgroups) died within 90 days of surgery due to acute respiratory distress syndrome. Two patients (3.8%) in the dCRT group died from treatment-related causes: haemorrhage (n = 1) and unknown reason (n = 1).

4. Discussion

The findings of this retrospective, multicenter study show that neoadjuvant treatment plus surgery yields better OS and PFS than definitive CRT in patients with potentially resectable stage IIIA-N2 NSCLC. This survival benefit was maintained on the propensity score-matched analysis. Both treatments had acceptable toxicity rates and low treatment-related mortality, findings that are consistent with other published reports [12-16]. By type of surgery (i.e., lobectomy vs. pneumonectomy), the survival benefit for CRTS vs. dCRT was maintained for lobectomy but not for pneumonectomy (in which survival outcomes were comparable to dCRT).

The optimal management of patients with stage IIIA-N2 NSCLC, and in particular the role of surgery, is among the most intensely debated topics in thoracic oncology [4,5,17], mainly because no definitive conclusions in this regard can be drawn from the limited scientific evidence [5,17]. Very few randomized controlled trials (RCT) have been conducted and those that are available present important limitations [9-11]. The largest RCT performed to date was the EORTC 08941 study [9], with 582 stage IIIA-N2 patients. Because that study was performed before the emergence of combined PET/CT imaging, staging was based on chest CT scans and abdominal ultrasound. Patients received three cycles of platinum-based CHT and those who showed a radiological response were randomized to surgery (n=167) or radiotherapy (n=165). At a median follow-up of 73 months, there were no statistically significant differences in median survival (17.5 vs 16.4 months) nor in 5-year OS (14% vs 15.7%). A subgroup analysis revealed that the type of surgery (lobectomy vs pneumonectomy, p=0.03) was a significant predictor of OS, a finding that is consistent with our results. However, that study had two important limitations; 1) the inclusion of patients with initially unresectable tumours, and 2) sequential rather than concomitant (the current standard) CRT.

The Intergroup 0139 trial [10] evaluated 396 patients, all of whom received induction CRT (two cycles of cisplatin and etoposide plus 45 Gy of radiotherapy). After induction therapy, patients without evidence of radiological progression were randomized to surgery (n=202) or to continued uninterrupted radiotherapy up to 61 Gy (n=194). As in our study, all patients in the sample were considered to have resectable disease at diagnosis; in addition, only a single mediastinal node station was involved in most (76%) cases (versus only 53.8% in the two groups in our study [adjusted data]). No differences in OS were observed between the dCRT and CRTS groups (23.6 vs. 22.2 months). However, consistent with our findings, the surgical group had a significantly better median PFS: 12.8 vs. 10.5 months (p=0.017). Due to the unusually high postoperative mortality rate (26%) in the pneumonectomy patients, the percentage of treatment-related deaths in the surgery arm was notably higher than in the dCRT group (8% vs 2%). A subsequent post hoc analysis found a survival benefit in the lobectomy subgroup (33.6 months vs 21.7 months, p = 0.002), similar to our findings.

In the ESPATUE trial [11], 246 patients diagnosed with potentially-resectable stage III NSCLC were randomized to induction CRT followed by surgery or continued radical dose (65-71 Gy) CRT. In that sample, 32% of patients were stage T4N1 and 37% stage IIIB (T4N2 or N3). After induction chemotherapy, 161 (65.4%) of the 246 patients had resectable disease and were randomized to either surgery or dCRT. There were no significant differences in 5-year OS between the groups: 44% vs. 40% for CRTS and dCRT, respectively (p=0.34). Unfortunately, the limitations of that trial (i.e., the highly heterogeneous patient sample and premature termination due to slow recruitment) do not allow for any definitive conclusions with regard to the optimal management of stage IIIA-N2 patients.

Apart from our multi-institutional retrospective study, at least four large retrospective studies [12-15] and one meta-analysis [16] have reported a survival benefit in patients who undergo surgery. In this context, the median OS in our patient sample (61 months in the whole sample, 56 months in the matched samples) is among the highest among the published studies that have evaluated surgical patients. However, our results may be partially attributable to stage migration related to the use of PET/CT or brain MRI, or possibly because mediastinal disease was not confirmed histologically in all patients. Nonetheless, survival in our sample was slightly better than the outcomes reported by Darling et al. [12] in a study involving 215 patients with potentially-resectable, pathologically-confirmed stage IIIA-N2 NSCLC. In that study, the median OS was 4.2 years (50.4 months) in the surgical arm (n=111) vs. 1.7 years (20.4 months) in the dCRT arm (n=104). Another recent study [14] reported similar outcomes (OS = 59.9 months) in 88 patients with stage IIIA/IIIB NSCLC staged with PET/CT and brain MRI and treated with high dose (≥60 Gy) neoadjuvant CRT followed by surgery. Even considering the design limitations in those studies, it would be difficult to achieve comparable survival outcomes using current dCRT treatment schemes given that the best reported survival figures are only around 38 months [18] (29 months in our study).

We included patients treated with neoadjuvant CRT (52.5%) as well as patients who received neoadjuvant CHT alone (47.5%). To evaluate the efficacy of these two induction treatment options, many studies have evaluated pCR in the primary tumor and mediastinal lymph nodes as a surrogate endpoint for local and systemic control [11]. Induction CRT seems to achieve higher pCR rates than CHT alone, as evidenced by our findings, in which more than 80% (n=26) of the 32 patients (27.1%) with a pCR had received CRT (the remaining 6 patients [18.8%] received CHT alone [p <0.001]). Although several studies have shown that downstaging is a favourable prognostic factor

for OS, [19-20] none of the studies performed to date to compare CRT to CHT alone have managed to find any significant differences in OS or PFS [2,21,22]. Therefore, the higher response rate achieved with neoadjuvant CRT (despite the lack of survival differences in patients with borderline resectable tumors at diagnosis) would seem to support the use of noadjuvant CRT versus neoadjuvant CHT alone. Moreover, if surgery is not performed (for any reason), the patient would still benefit from the improved treatment efficacy of concomitant (neoadjuvant CRT) vs sequential CRT.

Importantly, only approximately 40% of patients in our sample underwent invasive mediastinal restaging after neoadjuvant treatment. Although published reports suggest that survival rates appear to be better in patients with pCR or mediastinal nodal clearance after neoadjuvant therapy [19,20] we found that OS rates were very good even among the 25% of patients who still had persistent mediastinal disease after neoadjuvant treatment. Similar results have been reported in other studies [12,23].

Surgery-related mortality in our sample was low and comparable to the rates observed in the dCRT group, even though a substantial portion of patients (17.8%) underwent pneumonectomy and nearly 40% received high dose (> 50 Gy) induction radiotherapy. The low postoperative mortality rate (most deaths occurred in the pneumonectomy subgroup) may have contributed to the final differences in survival between CRTS and dCRT, as suggested by the findings in the Intergroup 0139 study [10]. Notably, lung cancer was the main cause of death in both the pneumonectomy subgroup and in the dCRT group. The percentage of patients diagnosed with stage cT3 disease was significantly greater in the pneumonectomy subgroup versus the dCRT group (66.7% vs 32.6%, $p = 0.003$). Although we were able to adjust for other variables, it was not possible to adjust for this particular variable due to the limited number of pneumonectomies (n=19), thus we cannot determine whether between-group differences

in stage T3 disease influenced the lack of survival benefit for pneumonectomy compared to dCRT. However, these findings are consistent with those reported by Aggarwal et al., [13] who compared 103 patients treated with dCRT to 41 patients treated with pneumonectomy, finding no significant differences in OS between the two groups (median 28 vs 22 months, p=0.534), even with a low postoperative mortality rate.

An important limitation of the present study is the non-randomized, retrospective design, with the attendant risk of bias. However, to minimize possible bias, we reviewed all cases to ensure resectability; in addition, we performed a rigorous propensity score-matched analysis to normalize the sociodemographic, clinical, and tumor characteristics of patients treated with and without surgery. Although the ECOG status of both treatment cohorts was 0-1, patients in the dCRT group might have presented greater comorbidity than those in the CRTS arm. The main strength of this study is that it is among the largest multicenter studies performed to date to evaluate the role of surgery in potentially resectable stage IIIA-N2 NSCLC; moreover, to our knowledge, it is the first multicentric study in the modern era of conformal 3DRT plus concomitant chemotherapy to show a clear benefit for surgery. Given the difficulties of completing RCTs in this clinical context, observational studies such as ours can provide—as noted in a recently published study [24]— highly valuable scientific evidence that may to inform decision-making in routine clinical practice.

5. Conclusion

The findings of this study suggest that surgery should be considered in patients with potentially resectable stage IIIA-N2 NSCLC who are in good general condition. Considering the high mortality rate for pneumonectomy performed outside of

specialized centres together with the lack of a clear survival benefit for this procedure in patients with NSCLC, definitive CRT may be preferable in these patients. This finding underscores the need for appropriate multidisciplinary assessment in order to properly select candidates for multimodal management. A randomized controlled trial comparing neoadjuvant treatment plus lobectomy to definitive chemoradiotherapy is needed to confirm the findings presented here.

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Conflicts of interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

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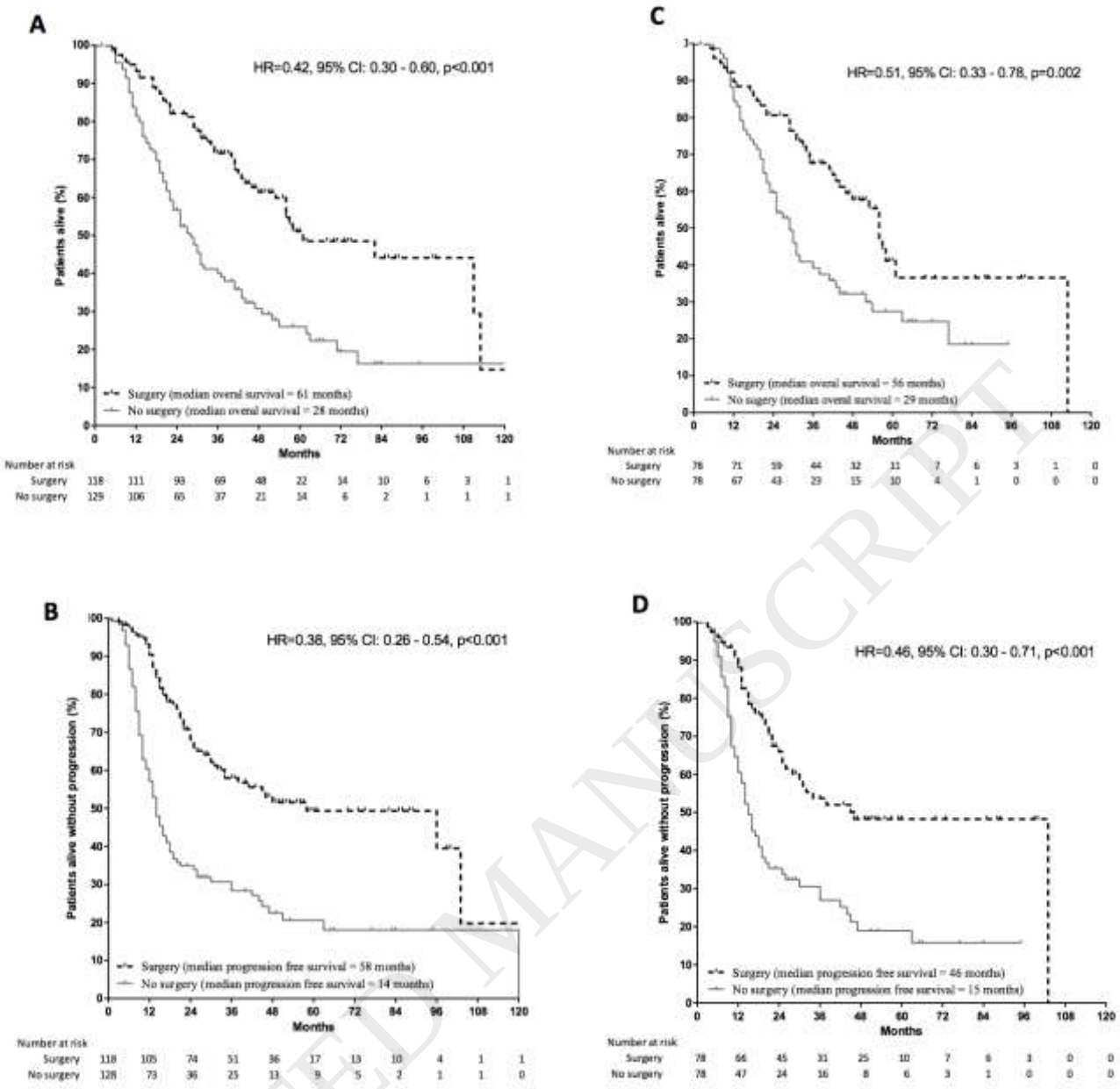

Figure 1. Overall survival (A) and progression free survival (B) for all patients.

Matched samples: overall survival (C) and progression free survival (D).

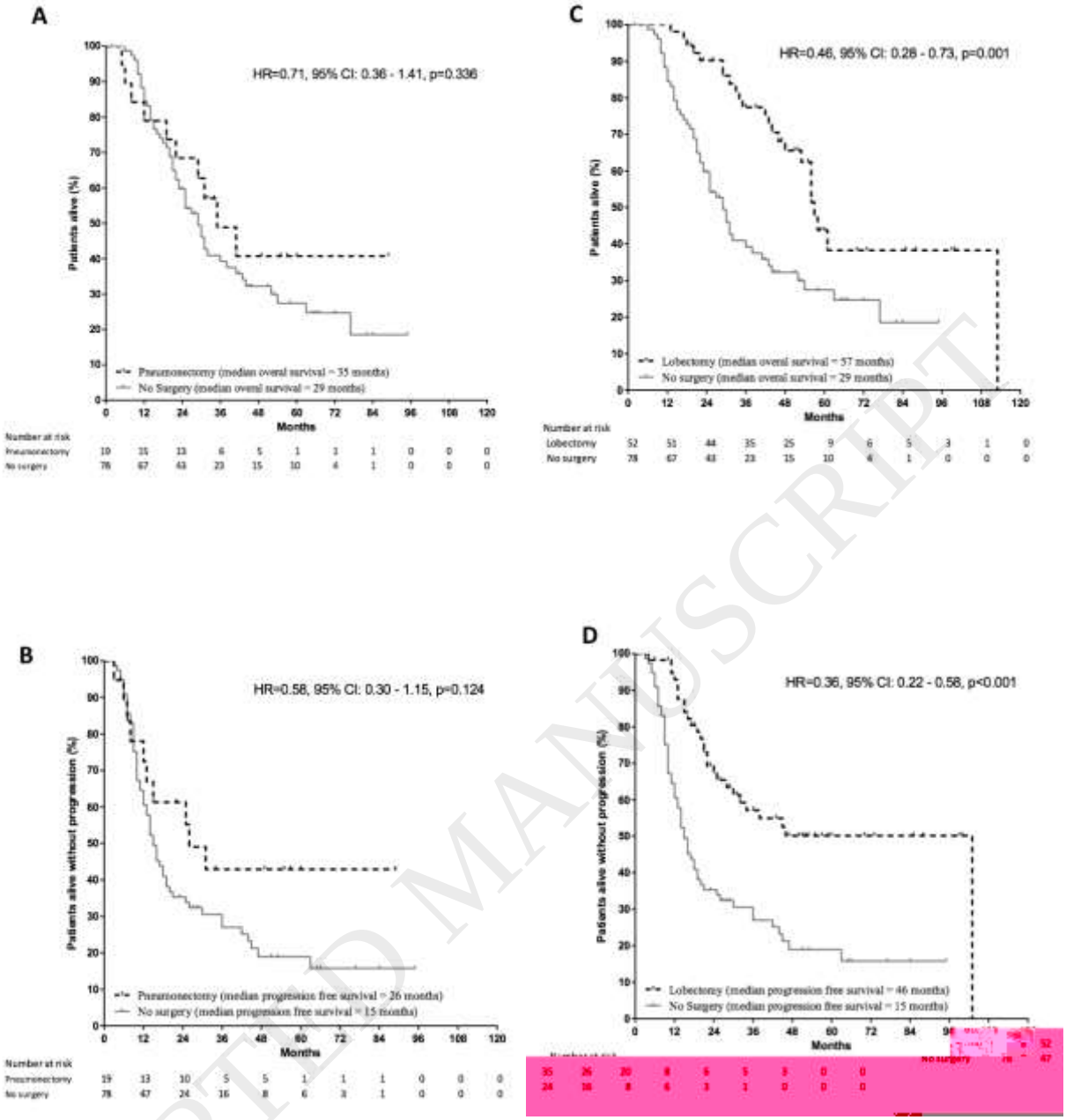

Figure 2. Matched samples: overall survival (A) and progression free survival (B) for patients undergoing pneumonectomy vs definitive CRT; and overall survival (C) and progression free survival (D) for patients undergoing lobectomy vs definitive CRT.

Table 1. Baseline characteristics of the study population before and after propensity score matching.

	Before Matching				After Matching		
Variable	**TOTAL N=247 (%)**	**Definitive CRT N=129 (%)**	**Surgery N=118 (%)**	**p-value**	**Definitive CRT N=78 (%)**	**Surgery N=78 (%)**	**p-value**
Age				0.085			1.000
>60 y, n (%)	156 (63.2)	88 (68.2)	68 (57.6)		50 (64.1)	50 (64.1)	
≤60 y, n (%)	91 (36.8)	41 (31.8)	50 (42.4)		28 (35.9)	28 (35.9)	
Median (range)	63 (37-82)	65 (37-82)	62 (41-78)		64 (37-82)	63 (41-78)	
Sex				0.091			1.000
Male, n (%)	207 (83.8)	113 (87.6)	94 (79.7)		72 (92.3)	72 (92.3)	
Female, n (%)	40 (16.2)	16 (12.4)	24 (20.3)		6 (7.7)	6 (7.7)	
ECOG				1.000			0.095
1-0	244 (98.8)	127 (98.4)	117 (99.2)		45 (57.7)	55 (70.5)	
2	3 (1.2)	2 (1.6)	1 (0.8)		33 (42.3)	23 (29.5)	
Smoking status				0.334			–
Never, n(%)	14 (5.7)	10 (7.8)	4 (3.4)		4 (5.1)	2 (32.6)	
Former, n(%)	112 (45.3)	57 (44.2)	55 (46.6)		33 (42.3)	35 (44.9)	
Current, n (%)	121 (49.0)	62 (48.1)	59 (50.0)		41 (52.6)	41 (52.6)	
T stage				0.085			0.153
T1, n (%)	54 (22.0)	24 (18.6)	30 (25.6)		12 (15.4)	13 (16.9)	
T2, n (%)	104 (42.3)	63 (48.8)	41 (35.0)		41 (52.6)	29 (37.7)	
T3, n (%)	88 (35.8)	42 (32.6)	46 (39.3)		25 (32.1)	35 (45.5)	
Number of positive nodal stations				0.004			1.000
1, n (%)	127 (51.4)	55 (42.6)	72 (61.0)		42 (53.8)	42 (53.8)	
>1, n (%)	120 (48.6)	74 (57.4)	46 (39.0)		36 (46.2)	36 (46.2)	
Mediastinal bulk				0.262			1.000
<3 cm, n (%)	225 (91.1)	115 (89.1)	110 (93.2)		75 (96.2)	75 (96.2)	
≥3 cm, n (%)	22 (8.9)	14 (57.4)	8 (6.8)		3 (3.8)	3 (3.8)	
Histology				0.897			1.000
Adenocarcinoma and others, n (%)	135 (57.0)	69 (56.6)	66 (57.4)		38 (48.7)	38 (48.7)	
Squamous, n (%)	192 (43.0)	53 (43.4)	49 (42.6)		40 (51.3)	40 (51.3)	

CRT, chemoradiation; ECOG, eastern cooperative oncology group.

Table 2. Characteristics of definitive CRT treatment.

Variable	Definitive CRT N=129
Induction CHT	
Yes, n (%)	69 (53.9)
No, n (%)	60 (46.5)
CHT Scheme	
Platinum-based, n (%)	119 (92.2)
Other, n (%)	10 (7.7)
RT Dose	
<60 Gy, n (%)	5 (3.8)
60-66 Gy, n (%)	119 (92.2)
>66 Gy, n (%)	5 (3.8)
Fractionation size	
1.8 Gy/f, n (%)	25 (19.3)
2 Gy/f, n (%)	104 (80.6)
RT planner	
Eclipse	46 (35.6)
PCRT	25 (19.3)
XIO	34 (26.3)
Others	24 (18.6)
Interruptions of RT	
No interruption/<1 week, n (%)	108 (83.7)
Interruption >1 week, n (%)	21 (16.2)
Adjuvant CHT	
No, n (%)	124 (96.8)
Yes, n (%)	4 (3.1)
Histopathological mediastinum confirmation	
No, n (%)	40 (31.01)
Yes, n (%)	89 (68.9)

CHT, chemotherapy; CRT, chemoradiation; RT, radiotherapy.

Table 3. Characteristics of surgical treatment.

Variable	Surgery N=118
Histopathological mediastinum confirmation before neoadjuvant treatment	
No, n (%)	49 (41.5)
Yes, n (%)	69 (58.4)
Neoadjuvant treatment	
CHT, n (%)	52 (44.1)
CRT, n (%)	66 (55.9)
CHT Scheme	
Platinum-based, n (%)	110 (93.2)
Other, n (%)	8 (6.7)
RT Dose	
45-50 Gy, n (%)	19 (28.8)
>50 Gy, n (%)	47 (71.2)
Radiological evaluation before surgery	
CT	63 (53.3)
PET-CT	55 (46,6)
Histopathological evaluation before surgery	
Yes, n (%)	48 (40.7)
No, n (%)	70 (59.3)
Histopathological mediastinal status before surgery	
Negative, n (%)	42 (87.5)
Positive, n (%)	6 (12.5)
Time between end of neoadjuvant treatment and surgery (days)	67.7
Type of surgery	
Lobectomy, n (%)	97 (82.2)
Pneumonectomy, n (%)	21 (17.8)
Pathologic stage pT	
pT0, n(%)	34 (28.8)
pT1, n(%)	49 (41.5)
pT2, n (%)	22 (18.6)
pT3, n (%)	13 (11.0)
Pathologic stage pN	
pN0, n(%)	81 (68.6)
pN1, n (%)	7 (5.9)
pN2, n (%)	30 (25.4)
Pathologic complete responses (pCR); (pT0pN0)	32 (27.1)
Surgical margins	
Positive	4 (3.4)
Negative	113 (96.5)
Postoperative RT	
No, n (%)	87 (73.7)
Yes, n (%)	31 (26.3)
Postoperative CHT	
No, n (%)	87 (73.7)
Yes, n (%)	31 (26.3)

CHT, chemotherapy; CRT, chemoradiation; RT, radiotherapy; CT, computed tomography ;

PET-CT, positron emission tomography - computed tomography.

Table 4. Overall toxicities for all patients

Variable	TOTAL N=247 (%)	Definitive CRT N=129	Surgery N=118	p-value
Haematological toxicity (Anemia, Neutropenia, Thrombopenia)				<0.001
<3, n (%)	209 (89.7)	103 (82.4)	106 (98.1)	
≥3, n (%)	24 (10.3)	22 (17.6)	2 (1.9)	
Gastrointestinal toxicity (Mucositis, Esophagitis)				0.755
<3, n (%)	227 (95.8)	121 (95.3)	106 (96.4)	
≥3, n (%)	10 (4.2)	6 (4.7)	4 (3.6)	
Gastrointestinal toxicity (Nausea, Vomiting)				–
<3, n (%)	237 (100)	127 (100)	110 (100)	
≥3, n (%)	0	0	0	
Thoracic toxicity (Chest pain)				–
<3, n (%)	237 (100)	127 (100)	110 (100)	
≥3, n (%)	0	0	0	
Thoracic toxicity (Pneumonitis)				0.126
<3, n (%)	233 (98.3)	123(96.9)	110 (100)	
≥3, n (%)	4 (1.7)	4 (3.1)	0	

CRT, chemoradiation. HR, hazard ratio; CI, confidence interval.

Statistically significant value, $p<0.05$ are in bold.