

The multimodal management of locally advanced N2 non-small cell lung cancer: is there a role for surgical resection? A single institution's experience

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Abstract

Background The management of operable locally advanced N2 non-small cell lung cancer (NSCLC) is a controversial topic. Concurrent chemoradiation (CT-RT) is considered the standard of care for inoperable or unresectable patients, but the role of trimodality treatment remains controversial. We present our institution's experience with the management of stage III (N2) NSCLC patients, analyzing whether the addition of surgery improves survival when compared with definitive CT-RT alone.

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Methods From 1996 to 2006, 72 N2 NSCLC patients were treated. Thirty-four patients received cisplatin-based induction chemotherapy, followed by paclitaxel-cisplatin CT-RT, and 38 patients underwent surgery preceded by induction and/or followed by adjuvant therapy. Survival curves were estimated by Kaplan–Meier analysis, and the differences were assessed with the log-rank test.

Results Most of the patients (87 %) were men. The median age was 59 years. A statistically significant association between T3–T4c and definitive CT-RT as well as between T1–T2c and surgery was noted ($p < 0.0001$). After a median follow-up period of 35 months, the median overall survival (OS) was 42 months for the surgery group versus 41 months for the CT-RT patients ($p = 0.590$). The median progression-free survival (PFS) was 14 months after surgery and 25 months after CT-RT ($p = 0.933$). Responders to radical CT-RT had a better OS than non-responders (43 vs. 17 months, respectively, $p = 0.011$). No significant differences were found in the OS or PFS between the pN0 [14 (37.8 %) patients] and non-pN0 patients at thoracotomy. Three treatment-related deaths (7.8 %) were observed in the surgical cohort and none in the CT-RT group.

Conclusions The addition of surgery did not render a median OS or PFS benefit when compared with CT-RT alone in our series of stage III-N2 NSCLC patients, in accordance with previously published data. However, responses to CT-RT had a greater impact in terms of OS and PFS. Although the patients selected for management including surgery showed a favorable T clinical staging in comparison to patients exclusively treated with definitive CT-RT, similar survival outcomes were found.

Keywords Non-small cell lung cancer · N2 · Lung surgery · Chemoradiation · Locally advanced lung cancer · Multimodal treatment

Introduction

Lung cancer currently represents the largest cause of death from cancer among men and women in the USA and Europe. An estimated 1.3 million new cases of lung cancer occur yearly worldwide, resulting in 183,000 annual fatalities in Europe [1] and 160,000 in the USA [2]. The early stages of non-small cell lung cancer (NSCLC) can be effectively treated with surgical resection, achieving a 5-year survival of 70 % for stage I patients and 50 % for stage II patients. However, about 15 % of patients diagnosed with NSCLC present with stage IIIA-N2 disease [3]. Although a complete surgical resection for IIIA-N2 disease is sometimes technically feasible, the 5-year survival rate for patients undergoing such procedures exclusively does not exceed 10 % in most studies [4]. Preoperative chemotherapy raises the 5-year survival rate to 17–36 % [5]. For patients with unresectable or inoperable stage IIIA disease, a combination of platinum-based chemotherapy and radiotherapy yielded a 5-year survival rate of 20–30 % in different studies [6–8]. Thus, this combination therapy has been considered the standard treatment for this group of patients.

Recently, the results of two randomized controlled trials have been published [9, 10] comparing concurrent induction therapy followed by surgical resection with standard concurrent chemotherapy and definitive radiotherapy without resection. Despite the fact that no significant overall survival (OS) differences were observed between these treatment arms, the European series concluded that radiotherapy should be considered the standard treatment for these patients, while the American study emphasized surgical resection as an important part of the treatment for selected patients.

Based on these data, we aimed to determine, through our own experience, whether adding surgical resection to stage III-N2 NSCLC treatment improved the long-term survival outcomes when compared with chemotherapy plus radiotherapy (CT-RT) alone.

Patients and methods

Patient selection

All consecutive patients with clinical or pathological stage T1–T4 N2 M0 NSCLC treated and followed at the Clínica Universidad de Navarra (CUN) between 1996 and 2006 were included. All cases were histologically proven at the time of diagnosis.

Clinical staging using the TNM classification was performed as follows: (a) the evaluation of M1 disease included results from chest and abdominal computed

tomography (CT), brain CT or MRI and 18F-FDG PET-CT; (b) the evaluation of T and N disease was performed by both chest CT and PET-CT.

Patients with bulky N2 disease, two or more lymph node stations involved or inoperable or unresectable tumors were treated with cisplatin-based induction chemotherapy, followed by concurrent chemotherapy and hyperfractionated 3D radiotherapy. The remainder of the patients underwent surgery in addition to neoadjuvant and/or adjuvant therapy. Because N2 disease did not preclude surgery and most cases had PET-CT-positive N2 nodes (>1 cm or high uptake values), mediastinoscopy was seldom performed.

In all potential candidates for surgical resection, N3 disease was histologically ruled out if there was a contralateral mediastinal lymph node larger than 1 cm or if these nodes were metabolically active as determined by PET.

The study protocol was approved by the institutional medical ethics committee.

Treatment arms and response assessment

In one group, stage IIIA/IIIB (N2) NSCLC patients selected for CT-RT alone were radically treated with induction platinum-based chemotherapy, followed by concurrent chemotherapy and hyperfractionated 3D-CRT [1.2 Gy b.i.d.; median dose: 66.5 Gy (range: 64–74)]. Paclitaxel (50 mg/m²) and cisplatin (30 mg/m²) were administered intravenously over a 60-min period on days 1, 8, 15, 22, 29 and 36 after confirmation of adequate blood cells counts. In the other group, patients selected for management including surgical resection underwent surgery (lobectomy or pneumonectomy), followed by or preceded by adjuvant therapy. All surgical patients underwent a systematic lymph node dissection. When neoadjuvant therapy was used, surgical resection was performed 2–6 weeks after completion.

The responses to induction chemotherapy were assessed by chest and abdominal CT after two cycles according to the revised RECIST criteria [11]. A complete response (CR) was defined as the disappearance of all target lesions at 4 weeks after treatment. A partial response (PR) was defined as at least a 30 % decrease in the sum of the diameters of target lesions, with the baseline sum diameters used as reference. Progressive disease (PD) was defined as at least a 20 % increase in the sum of the diameters of target lesions, with the smallest sum on the study (including the baseline sum) used as the reference point. In addition to the relative increase of 20 %, the sum must also demonstrate either an absolute increase of at least 5 mm or the appearance of one or more new lesions to be considered PD. Stable disease (SD) was defined as having neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest diameter sum during the study used as the reference.

Hospital mortality included 30-day mortality and surgical or treatment-related deaths. Cancer recurrence was divided into two categories according to the site of initial relapse: locoregional recurrence was defined as any site within the ipsilateral hemithorax; all other sites of recurrence were considered to be distant metastases.

Definitions and statistical analysis

An analysis was performed for both progression-free survival (PFS) and OS. The PFS was calculated from the beginning of treatment until tumor progression occurred. The OS was calculated from the first day of treatment until death, loss of follow-up or time of evaluation, as previously published [12]. The time to definitive treatment was calculated from the date of histopathologic diagnosis until the date of the beginning of CT-RT or the date of pulmonary resection.

Kaplan–Meier survival curves were generated to evaluate the PFS and OS of both groups. A log-rank test was performed to find statistical differences in the Kaplan–Meier survival analyses. A p value of <0.05 was considered to be statistically significant. The response and toxicity were analyzed using descriptive statistics. SPSS (V15.0; SPSS Inc., Chicago, IL) software was used for statistical analysis.

Results

Patient characteristics

A total of 72 stage IIIA/IIIB (N2) NSCLC consecutively treated patients were evaluated. Of those patients, 34 were radically treated with cisplatin-based concurrent chemotherapy and hyperfractionated 3D-CRT [1.2 Gy b.i.d.; median dose: 66.5 Gy (range: 60–72)]. The remaining 38 patients underwent multidisciplinary management including surgery (lobectomy or pneumonectomy), followed by adjuvant therapy or preceded by induction therapy.

The patients' characteristics (Table 1) were well balanced between the two treatment arms, with no statistically significant differences in age, gender or histologic type. Overall, 63 patients (87.5 %) were men and 9 (12.5 %) were women. Nineteen patients had adenocarcinomas, 43 patients had squamous cell carcinomas and 10 patients had other histologic subtypes (including 4 patients with large-cell carcinomas).

Although no specific selection criteria of patients were used for deciding the therapeutic management in this study, a significant difference was noted between the initial cT stages (T1 and T2) versus the advanced cT stages (T3 and T4), with more advanced cT stages in the CT-RT group ($p < 0.0001$).

Table 1 Patient characteristics

Characteristics	Surgery	Non-surgery	p value
Number of patients	38	34	–
Median age (years)	58	59	0.603
Gender, n (%)			
Male	34 (90 %)	29 (85 %)	0.595
Female	4 (10 %)	5 (15 %)	
Histologic type			
Adenocarcinoma	12 (32 %)	7 (20 %)	0.371
Squamous cell	21 (55 %)	22 (65 %)	
Other	5 (13 %)	5 (15 %)	
Initial cT, n (%)			
cT1	13 (34 %)	2 (5 %)	$<0.0001^*$
cT2	13 (34 %)	5 (15 %)	
cT3	10 (26 %)	6 (18 %)	
cT4	2 (5 %)	21 (62 %)	
Median follow-up (months)	35	36	0.914

* This p value corresponds to the differences observed between cT1–cT2 versus cT3–cT4

All 34 patients treated in the definitive CT-RT arm had clinically N2-positive disease, whereas 6 patients who were clinically considered to have N1 disease and undergoing surgery presented an incidental N2 pathologic stage.

The median follow-up period was 35 months (QI: 17–56), with 35 months in the surgery group (QI: 20–57) and 36 months (QI: 14–50) in the CT-RT group.

Efficacy analysis

As summarized in Table 2, no significant differences were observed between both groups in the OS rate at 5 years (point estimate 33 % in the surgery group and 23 % in the definitive CT-RT group). Accordingly, the difference noted in the median OS between the two groups was not statistically significant (42 months in the surgical group and 41 months in the non-surgical group, $p = 0.590$) (Fig. 1a). The overall median PFS was 19 months: 14 months for patients undergoing pulmonary resection and 25 months for the CT-RT group ($p = 0.933$) (Fig. 1b).

Multimodality group including surgery

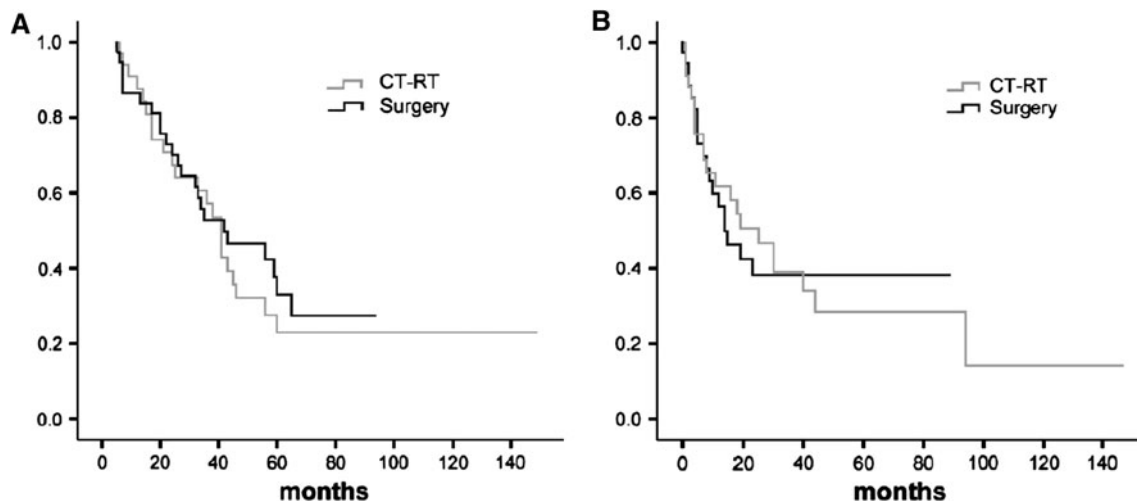
Surgical procedures included 33 lobectomies (L) and 5 pneumonectomies (P). The multimodal management of these patients included neoadjuvant therapy in 25 (81 %) patients, as described in Table 3. Induction chemotherapy consisted of two cycles of cisplatin-based chemotherapy.

The induction treatment achieved PR in 15 patients (60 %) and SD in 10 patients (40 %). Patients with PD were excluded from surgery and were not included in this

Table 2 Primary end-points used in this study

	Surgery	Non-surgery	<i>p</i> value
PFS (months)	14	25	0.933
OS (months)	42	41	0.590
Induction treatment in surgery group	Responders	Non-responders	<i>p</i> value
PFS (months)	15	14	0.811
OS (months)	33	59	0.064
CT-RDT	Responders	Non-responders	<i>p</i> value
PFS (months)	30	4	0.027*
OS (months)	43	17	0.011*

* $p < 0.05$ was considered statistically significant

**Fig. 1** **a** Overall survival of surgery and chemo-radiotherapy (CT-RT) groups. **b** Progression-free survival of surgery and chemo-radiotherapy (CT-RT) groups**Table 3** Toxicity in patients undergoing surgical resection

	Grade 2	Grade 3	Grade 4	Grade 5
Pulmonary embolism	–	–	–	2
Hemoptysis	–	–	–	1
Esophagitis	5	2	–	–
Empyema	–	2	–	–
Hematologic	2	–	1	–
Pneumonitis	–	–	1	–
Other	1	1	–	–
Total	8	5	2	3

cohort. There were no statistically significant differences between the responders and non-responders to induction treatment in terms of median PFS (15 vs. 14 months, $p = 0.811$) or median OS (33 vs. 54 months, $p = 0.055$).

Overall, 29 of 38 patients (76.3 %) in the surgically treated cohort also received radiotherapy. Induction radiotherapy was administered to 17 patients of the cohort

(44.7 %) with a median dose of 60 Gy (QI: 48–60). Adjuvant radiotherapy was administered to 12 patients (31.5 %) with a median dose of 46 Gy (QI: 44.5–50). No significant differences in the median OS were observed between patients receiving neoadjuvant radiotherapy, adjuvant radiotherapy or no radiotherapy (33 vs. 60 vs. 59 months, $p = 0.731$). In contrast, a significantly higher percentage of pN0 disease ($p = 0.001$) was observed in patients after induction radiotherapy ($n = 13$, 76.5 %) than among those for whom radiotherapy was not part of the neoadjuvant treatment ($n = 3$, 14 %). However, the post-radiotherapy pN0 status did not reflect a statistically significant difference in the median OS between the pN0 (34 months) and pN2 (56 months) ($p = 0.589$), or in the median PFS (12 months for the pN0 patients vs. 19 months for the pN2 subjects, $p = 0.954$). Pathologic T0 was observed in ten patients (26.3 %) receiving induction treatment. Although no significant differences were observed in the OS between pT0 and non-pT0 patients (43 vs. 42 months, respectively, $p = 0.377$), a statistically

significant difference in the PFS (12 months vs. not reached, respectively, $p = 0.013$) in favor of the pT0 subjects was obtained. This statistical discordance between the OS and PFS is explained because there was only one progression in the pT0 subgroup, but we observed five deaths (four patients died of other causes without evidence of disease relapse).

No significant differences in the median OS (42 vs. 27 months, respectively, $p = 0.374$) or PFS (14 vs. 15 months, respectively, $p = 0.118$) were observed between the pneumonectomy and lobectomy patients. The median time from diagnosis to surgery was 3 months (QI: 1–5 months). There were no statistically significant differences in the median OS in terms of the time to surgery (≤ 3 vs. >3 months; 56 vs. 35 months, respectively, $p = 0.925$) or TTP (19 vs. 10 months, respectively, $p = 0.599$).

CT-RT group

Among the non-surgical patients whose disease responded to chemo-radiotherapy (70 % PR/9 % CR), median OS was significantly greater than in patients with stable or progressive disease after the completion of definitive CT-RT (43 vs. 17 months, $p = 0.011$) (Fig. 2a). PFS showed similar results: 30 versus 4 months, $p = 0.027$, benefiting patients who achieve response to CT-RT (Fig. 2b).

The median time to the start of definitive CT-RT was also 3 months (QI: 2–5 months). No significant differences in the median OS regarding time from diagnosis to treatment were found (36 months for <3 months from diagnosis to treatment vs. 43 months for 3 months vs. 41 months for >3 months, $p = 0.948$). Similar results were observed in the PFS (25 vs. 19 vs. not achieved, $p = 0.613$).

Differences in the pattern of relapse

Overall, no statistically significant differences were observed between groups in terms of progression after CT-RT (67.6 %) or surgery (50 %) ($p = 0.1556$). Local failure occurred in ten patients (29.5 %) in the CT-RT group versus five patients (13 %) in the surgical group ($p = 0.057$). The distant failure rate was similar between both treatment arms: 13 patients (38.2 %) in the CT-RT group and 14 patients (36.8 %) in the surgical group ($p = 0.381$).

Safety analysis

Adverse effects of grade 2 or greater were registered. Grade 3 or greater toxicity was present in ten (26 %) patients in the surgical group and seven (20 %) patients in the CT-RT cohort. Importantly, three (7.8 %) treatment-related deaths were observed in the surgical group (two pulmonary embolisms and one massive hemoptysis), while no treatment-related deaths were observed in the definitive CT-RT group. Grade 2 and 3 esophagitis was the most frequent adverse effect in the CT-RT group with 13 cases (38 %), although these cases were usually of grade 2 (10/13). Other relevant (grade ≥ 2) adverse events registered are summarized in Table 3 (multimodality group including surgery) and Table 4 (CT-RT group).

Discussion

The role of the addition of surgery to the treatment of operable locally advanced N2 NSCLC remains controversial [13, 14]. Although multiple studies have evaluated the role of surgical resection and/or thoracic irradiation for

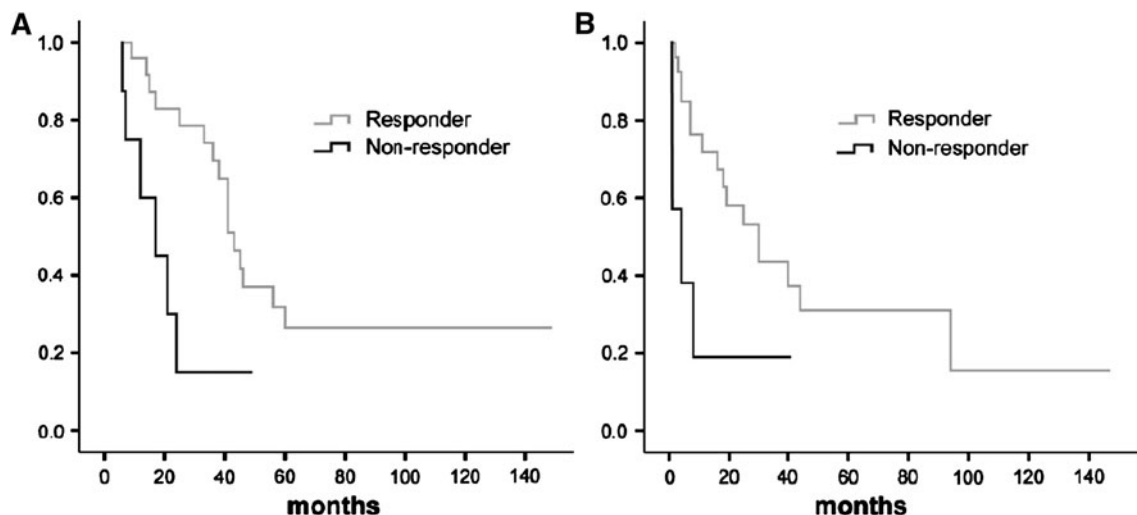


Fig. 2 **a** Overall survival of responders and non-responders in the chemo-radiotherapy (CT-RT) group. **b** Progression-free survival of responders and non-responders in the chemo-radiotherapy (CT-RT) group

Table 4 Toxicity in patients treated with definitive chemoradiation

	Grade 2	Grade 3
Esophagitis	10	3
Gastrointestinal	1	1
Hematologic	1	1
Asthenia	1	1
Skin	1	1
Total	14	7

stage IIIA (N2) NSCLC patients, few trials have focused on patients diagnosed with N2 NSCLC, regardless of the substage (IIIA or IIIB) [4, 13, 15, 16].

This retrospective study analyzes patients diagnosed with stage IIIA/IIIB (N2) NSCLC undergoing treatment with radical intent, comparing the outcomes for patients for whom surgical resection was part of the multimodality treatment with those in which no surgical treatment was included.

In accordance with previously published data, in our series, no statistically significant differences were observed among treatment arms in terms of the median OS (42 months for surgery vs. 41 months for CT-RT) or the PFS (14 vs. 25 months, respectively). However, in our study, a significant difference was observed between both therapeutic groups in terms of the initial cT stages, favoring the surgical group. Although no pre-designed specific selection criteria of patients was used for deciding the therapeutic management in this study, a significant difference was noted between the initial cT stages (T1 and T2) versus advanced cT stages (T3 and T4), with more advanced cT stages in the CT-RT group ($p < 0.0001$). This basal characteristic imbalance between the groups is probably due to a potential selection bias in actual clinical practice that directs patients with less bulky tumors to surgical resection, and cT3 and cT4 tumors to a CT-RT approach instead of radical surgery. Despite this potential bias, interestingly enough, no outcome differences were observed between both treatment modalities in our cohort, stressing the comparable efficacy of the CT-RT approach despite managing locally more advanced disease.

Two recent large multicenter randomized phase III trials have investigated the role of surgery in different populations of N2 NSCLC patients. Although these studies restricted the analysis to stage IIIA-N2 patients, both the EORTC 08941 study [10] and the IG 0139 trial [9] also failed to show an advantage in OS for either surgery or thoracic radiotherapy.

In the subgroup analysis of our study, we compared the median OS between patients responding to treatment and those who showed stable or progressive disease after

definitive CT-RT. In accordance with previous reports [17], patients in whom an objective response was confirmed after treatment showed a significantly longer OS with an increase in the median OS of 26 months in comparison to non-responders, as well as a dramatic significant advantage in the PFS in favor of responders (30 months for responders vs. 4 months for non-responders).

Two recent single-center studies have evaluated the role of induction chemotherapy followed by radical surgery in the N2 NSCLC setting [18, 19]. In a study by Stefani et al. [19] of 175 patients, nodal down-staging after induction chemotherapy was identified as an independent factor significantly affecting survival. Decaluwe et al. [18], however, evaluated 92 resectable IIIA-N2 NSCLC patients and reported down-staging of mediastinal lymph nodes in 43 % of the subjects. Although patients achieving nodal down-staging seemed to live longer, statistical significance was not reached in terms of a 5-year OS increase. In accordance with the latter study, in our subgroup analysis of patients undergoing surgery, there were no statistically significant differences between responders and non-responders to induction treatment in terms of the median PFS or OS.

In addition, among subjects receiving radiotherapy as part of the neoadjuvant treatment, a significantly higher percentage of pN0 disease was found (76.5 %), as expected. However, this downstaging effect did not translate into a significant PFS or OS benefit either. Nonetheless, a downstage confirmation in the pT status after induction therapy showed a slightly (although not significant) longer OS for patients achieving a pT0 (43 vs. 42 months, $p = 0.377$). However, a statistically significant benefit in terms of the PFS in favor of pT0 patients (12 months vs. not reached, $p = 0.013$) was found.

Another important issue in the management of locally advanced NSCLC is the local control rate, because local relapse frequently leads to retreatment, often causes new and quality of life-limiting symptoms and is ultimately also a cause of death in these patients. In our cohort, a trend toward a significant difference ($p = 0.057$) favoring the therapeutic management including surgery was noted when comparing the local failure rate. Only 13 % of patients in the surgery group showed local failure, whereas more than twice (30 %) the number of subjects receiving CR-RT without surgery progressed locally. This tendency reproduces the results of the EORTC 08941 trial [10], even though both NSCLC patient populations are different. A larger sample size could have possibly turned the trend observed in our analysis into statistical significance. Whether the aforementioned potential “tumor size selection bias” in both studies may account for the higher local relapse rates seen in patients undergoing an operation (less bulky tumors) compared to those not treated with radical

surgery (larger lesions) is unknown. In addition, no differences in distant failure rates were significant.

Potential differences in treatment-related toxicities between both therapeutic strategies were studied as well. The overall mortality rate for surgical patients in our institution was similar (7.8 %) to those previously published [20–22], with pulmonary embolism and severe hemoptysis as the causes of death in a similar proportion of our patients as compared to previous studies. Nonetheless, no treatment-related deaths were observed among CT-RT patients in our cohort as opposed to previous trials in which a median 2 % mortality rate was reported [9, 23]. The non-grade 5 toxicity rate observed for the CT-RT approach confirms other investigator observations [12, 24] when a hyperfractionated radiation modality is chosen. As expected, esophagitis was the most relevant grade 3 adverse event observed.

The present work represents a retrospective analysis of data and thus has some evident drawbacks and limitations. As previously mentioned, the small sample size and the heterogeneity of the treatments administered may be responsible for some of the observations. Nonetheless, this report comprises a valuable piece of evidence that can contribute to future systematic reviews and meta-analyses in which evidence-based medicine therapeutic guidelines are supported. Furthermore, this work, far from showing the results of a rigid inclusion/exclusion criteria study in a highly controlled setting, faithfully reflects the day-to-day clinical management of locally advanced N2 NSCLC patients in a tertiary referral hospital.

In conclusion, although no significant differences in survival have been demonstrated between radical CT-RT and surgery, including multimodality treatment in this study or in others, patients should be given a balanced view of both therapeutic options, taking into account the availability of local expertise and resources, patient's comorbidities and potential treatment complications.

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Conflict of interest The authors declare no competing interests.

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