

ORIGINAL ARTICLE

Comparison of mediastinal lymph node status and relapse pattern in clinical stage IIIA non-small cell lung cancer patients treated with neoadjuvant chemotherapy versus upfront surgery: A single center experience

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Keywords

N2; non-small cell lung carcinoma; neoadjuvant chemotherapy; prognosis; stage IIIA.

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Abstract

Background: In spite of the progress made in neoadjuvant therapy for operable non small-cell lung cancer (NSCLC), many issues remain unsolved, especially in locally advanced stage IIIA.

Methods: Retrospective data of 163 patients diagnosed with stage IIIA NSCLC after surgery was analyzed. The patients were divided into two groups: a preoperative chemotherapy group including 59 patients who received platinum-etoposide doublet treatment before surgery, and an upfront surgery group including 104 patients for whom surgical resection was the first treatment step. Adjuvant chemotherapy or/and radiotherapy was administered to 139 patients (85.3%), while 24 patients (14.7%) were followed-up only.

Results: The rate of N2 disease was significantly higher in the upfront surgery group ($P < 0.001$). The one-year relapse rate was 49.5% in the preoperative chemotherapy group compared to 65.4% in the upfront surgery group. There was a significant difference in relapse rate in relation to adjuvant chemotherapy treatment ($P = 0.007$). The probability of relapse was equal whether radiotherapy was applied or not ($P = 0.142$). There was no statistically significant difference in two-year mortality ($P = 0.577$). The median survival duration after two years of follow-up was 19.6 months in the preoperative chemotherapy group versus 18.8 months in the upfront surgery group ($P = 0.608 > 0.05$).

Conclusion: There was significant difference in preoperative chemotherapy group regarding relapse rate and treatment outcomes related to the lymph node status comparing to the upfront surgery group. Neoadjuvant/adjuvant chemotherapy is a part of treatment for patients with stage IIIA NSCLC, but further investigation is required to determine optimal treatment.

Introduction

Stage IIIA non-small cell lung cancer (NSCLC) is heterogeneous. Tumor extension is restricted to the affected lung (T3N1), but also includes metastatic disease to the ipsilateral mediastinal lymph nodes (stage IIIA N2). This results in a heterogeneous group of patients with tumors ranging from

minimal N2 (found incidentally during or after surgery) to multistation bulky N2 disease.¹ Historical series from experienced centers document dismal survival (7–16% at five years) for patients with clinically obvious N2 NSCLC treated with primary surgery.^{2–5} The five-year survival ranges from 5% to 8% in patients with bulky N2 disease to nearly 35% in patients with single station, microscopic N2 disease.⁶

Neoadjuvant (preoperative) therapy for operable NSCLC has been the subject of a large number of studies, but in spite of the progress evidenced by well designed and well conducted phase III randomized trials and meta-analyses, many issues remain unsolved, especially in locally advanced IIIA stage. In operable stage III NSCLC, there is still considerable debate regarding the best treatment strategy, which can include surgery followed by chemotherapy with or without radiotherapy; neoadjuvant chemotherapy followed by surgery with or without postoperative radiotherapy; neoadjuvant chemoradiation followed by surgery; comprehensive chemoradiation without surgery, preceded by neoadjuvant chemotherapy or not; and several other strategies.^{7,8}

Although surgery offers the best chance of survival to patients with distinct limited N2 disease (“low-burden” N2), not all patients with N2 disease are appropriate candidates for surgical resection. For those with resectable disease, the administration of neoadjuvant chemotherapy has the potential to reduce tumor volume, address micrometastatic disease early and improve outcome. A small group of patients in whom “unforeseen N2 involvement” is detected at thoracotomy (despite adequate preoperative staging), might benefit from resection.⁹ Good prognostic variables (factors) include lobectomy, downstaging, and complete resection, but these conditions are difficult to predict preoperatively.

A retrospective study was performed to estimate pathoanatomical substrate in stage IIIA NSCLC patients who initially received surgery and those operated upon after preoperative, induction, or neoadjuvant chemotherapy and to compare the relapse rate (RR) within a year after surgery, the median survival duration over a two year follow-up period, and two year mortality rates between two groups.

Methods

The study was conducted using data of patients diagnosed with stage IIIA NSCLC after surgery at the Belgrade University Hospital of Thoracic Surgery from 1 January 1999 until 31 December 2005. The study sample comprised 163 patients in stage cIIIA before surgery and stage pIIIA after surgery. Preoperative tumor node metastasis categorization and clinical staging was performed based on computed tomography scans of the thorax and upper abdomen, bronchoscopy with biopsies, and ultrasound examination. Preoperative mediastinoscopy was not performed because of the lack of technical availability at that time. Patients were divided into two groups: a preoperative chemotherapy group including 59 patients who received platinum-etoposide (PE) doublet neoadjuvant chemotherapy, and an upfront surgery group including 104 patients for whom surgical resection was the primary treatment choice. No significant difference regarding preoperative disease characteristics was noted between the groups.

Adjuvant treatment – chemotherapy or/and radiotherapy – was applied in 139 patients (85.3%), while 24 patients (14.7%) were followed-up only. The mean age was 56.76 years (range 38–79), the average age of the patients in the preoperative chemotherapy group was 55–56 years, and in the upfront surgery group 57–58 years. In regard to tumor size, 49.2% of patients in the preoperative chemotherapy group and 52.9% of patients in the upfront surgery group had tumors with a diameter over 30mm.

The study included all patients who had undergone a complete resection (R0) for whom data was available, including the pre-treatment tumor, patient characteristics and comorbidities; a detailed post-surgical pathohistological report; and precise data about neoadjuvant/adjuvant therapy and follow up for two years.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Results were expressed as means (standard deviation) and percentages. An independent sample *t*-test was used to compare continuous variables, while categorical data was compared using χ^2 tests. Survival analysis was observed using the Kaplan–Meier method and comparisons between groups were performed using the log-rank test. *P* values < 0.05 were considered statistically significant.

Results

Our study comprised 163 stage IIIA NSCLC patients, with a mean age of 56.76 years (range 38–79). The preoperative chemotherapy group included 59 patients, while the upfront surgery group included 104. In the preoperative chemotherapy group, 78% of patients were male compared with 84.6% in the upfront surgery group. There was no significant difference regarding gender (*P* = 0.591) or patient age between the groups.

To define disease stage, the 7th Tumor Node Metastasis classification was applied. Approximately half of the patients in each group had T2: 49.2% (29 patients) in the neoadjuvant chemotherapy and 52.9% (55 patients) in the upfront surgery group. There was no statistically significant difference between the groups regarding the characteristics of the T descriptor, or tumor localization (*P* = 0.374) (Table 1).

Pneumonectomy and lobectomy were performed in 42 (71.25) and 17 patients (28.8%) in the preoperative chemotherapy group and 65 (62.5%) and 36 patients (34.6%) in the upfront surgery group, respectively.

Similar rates of postoperative complications were observed in both groups (35.8% in the preoperative group vs. 32.0 in the upfront surgery group), but the details were

Table 1 Baseline (demographic and clinical) patient characteristics

Variables	Induction		P
	chemotherapy and surgical resection (n = 59)	Surgical resection (n = 104)	
Age (year)	55.6 ± 6.7	57.4 ± 8.8	0.175
Gender			
Male	46 (78.0)	88 (84.6)	0.286
Female	13 (22.0)	16 (15.4)	
Pathology			
Squamocellular carcinoma	34 (57.6)	56 (53.8)	0.759
Adenocarcinoma	23 (39.0)	42 (40.4)	
Adenosquamous carcinoma	2 (3.4)	6 (5.8)	
Surgery			
Pneumonectomy	42 (71.2)	65 (62.5)	0.314
Lobectomy	17 (28.8)	36 (34.6)	
Bilobectomy	0 (0.0)	3 (2.9)	
Gradus			
G1: Well differentiated	17 (28.8)	25 (24.0)	0.360
G2: Moderately differentiated	27 (45.8)	49 (47.1)	
G3: Poorly differentiated	15 (25.4)	25 (24.0)	
G4: Undifferentiated	0 (0.0)	5 (4.8)	
Tumor (T) status			
T1	7 (11.9)	5 (4.8)	0.606
T2	29 (49.2)	55 (52.9)	
T3	19 (32.2)	44 (42.3)	
T4	4 (6.8)	0 (0.0)	
Localization			
Upper right lobe	28 (47.5)	36 (34.6)	0.126
Middle right lobe	1 (1.7)	0 (0.0)	
Lower right lobe	7 (11.9)	23 (22.1)	
Upper left lobe	14 (23.7)	34 (32.7)	
Lower left lobe	9 (15.3)	11 (10.6)	
Vascular invasion			
Yes	49 (83.1)	85 (81.7)	0.832
No	10 (16.9)	19 (18.3)	
Pleural status†			
p1	30 (50.8)	37 (35.6)	0.162
p2	22 (37.3)	50 (48.1)	
p3	7 (11.9)	17 (16.3)	

Significant $P < 0.05$, mean ± standard deviation, number(%). †p1, pleural invasion beyond the elastic layer; p2, pleural invasion to the pleural surface, p3, pleural invasion into any component of the parietal pleura.

only available for the preoperative group. Prolonged postoperative recovery as a result of cardiovascular complications (heart failure and/of heart rhythm disturbance) was observed in 16.7%, postoperative empyema and/or bronchopleural fistula in 16.7%, and dehiscence in 2.4%. The postpneumonectomy mortality rate was 6.7%.

Adjuvant treatment – chemotherapy or/and radiotherapy – was applied in 139 patients (85.3%), while 24 patients (14.7%) were followed-up only. Chemotherapy was administered in an adjuvant setting in 18 patients (30.5%) in the preoperative chemotherapy group and 23 (22.1%) in the upfront surgery

Table 2 Treatment outcome - localization and status of mediastinal lymph nodes, tumor size

Variables	Induction		P
	chemotherapy and surgical resection (n = 59)	Surgical resection (n = 104)	
Postoperative treatment			
Chemotherapy	18 (30.5)	23 (22.1)	0.805
Radiotherapy	23 (39.0)	53 (51.0)	
Chemo/radiotherapy	6 (10.2)	16 (15.4)	
Symptomatic therapy	7 (11.9)	11 (10.6)	
Systematic controls	5 (8.5)	1 (1.0)	
Lymph node status			
N0 (without metastasis)	9 (15.3)	0 (0.0)	<0.001†
N1	29 (49.2)	22 (21.2)	
N2	21 (35.6)	82 (78.8)	
Number of positive lymph nodes			
≤3	47 (79.7)	81 (77.9)	0.791
>3	12 (20.3)	23 (22.1)	
Tumor diameter (cm)	CT – preoperative scan method	PH – postoperative pathohistological finding	P
≤30	9 (15.3)	14 (23.7)	0.003†
30–50	9 (15.3)	11 (18.6)	
>50	41 (69.5)	34 (57.6)	

†Significant $P < 0.05$, number (%).

group, and radiotherapy in 23 (39.0%) and 53 patients (51.0%), respectively (Table 2).

Nine patients (15.3%) in the neoadjuvant chemotherapy group were registered with N0 status; however, there were no records for the upfront surgery group. Twenty-nine patients (49.2%) in the neoadjuvant chemotherapy group had N1 status and 22 (21%) in the upfront surgery group ($P < 0.01$). The rate of N2 disease was significantly higher in patients who were not treated with neoadjuvant chemotherapy ($P < 0.001$). Ipsilateral mediastinal lymph node metastases were recorded in 21 patients (35.6%) in the neoadjuvant chemotherapy group and 82 (78.8%) in the upfront surgery group.

We also analyzed status and the number of positive lymph nodes and found significant differences between the neoadjuvant chemotherapy ($P < 0.001$) and upfront surgery groups ($P = 0.005$).

The involvement of ≤ 3 lymph nodes was significantly more frequent in the neoadjuvant (E) N1 subgroup (59.6%) and significantly less frequent in the N2 subgroup compared to the upfront surgery group (27.2% and 72.8%; $P < 0.001$, respectively). In the N2 subgroup, > 3 lymph nodes were more often involved in both groups, regardless

Table 3 Localization and status of mediastinal lymph nodes and tumor size

Variables	Induction chemotherapy and surgical resection (n = 59)	Surgical resection (n = 104)	P
Lymph node status			
N0 (without metastasis)	9 (15.3)	0 (0.0)	< 0.001*
N1	29 (49.2)	22 (21.2)	
N2	21 (35.6)	82 (78.8)	
Number of positive lymph nodes			
≤ 3	47 (79.7)	81 (77.9)	0.791
> 3	12 (20.3)	23 (22.1)	
Tumor diameter (cm)	CT – preoperative scan method	Postoperative pathohistological finding	P
≤ 30	9 (15.3)	14 (23.7)	0.003*
30–50	9 (15.3)	11 (18.6)	
> 50	41 (69.5)	34 (57.6)	

*Significant at P < 0.05, number (%). CT, computed tomography.

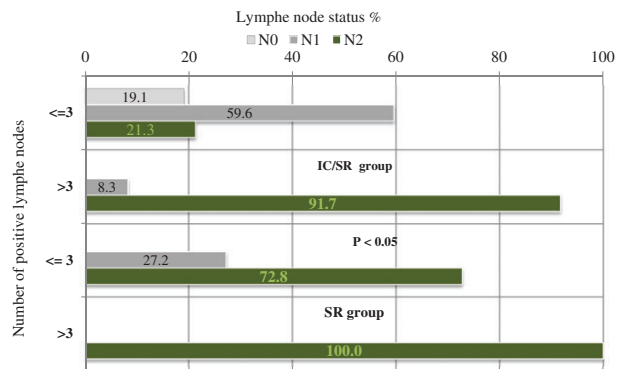


Figure 1 Status and number of positive lymph nodes (induction chemotherapy/surgical resection [IC/SR] vs. SR alone).

of whether the patient was treated with neoadjuvant therapy (91.7–100%) (Table 3). It should be stressed that nearly 20% (19.1%) of the preoperative chemotherapy group patients with ≤ 3 positive lymph nodes had no lymph node metastasis at all (Fig 1).

Finally, we analyzed the treatment outcomes after one year in both groups. In the preoperative chemotherapy group the RR was 49.2% (29 patients), significantly lower than in the upfront surgery group at 65.4% (68 patients; P = 0.002) (Fig 2).

We compared treatment outcomes related to lymph node status and found the difference between the groups was significant (P = 0.001). In the preoperative chemotherapy group there was a significantly lower RR for N0 and N1 mediastinal lymph node status (33.3% and 34.5%,

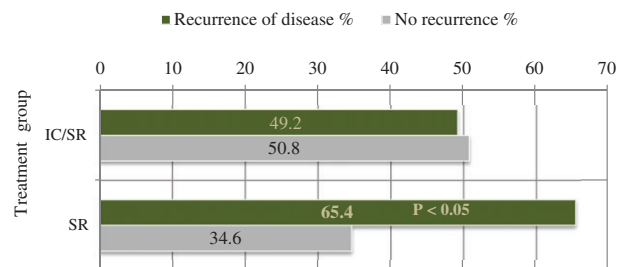


Figure 2 Treatment outcome (after one year) (induction chemotherapy/surgical resection [IC/SR] vs. SR alone).

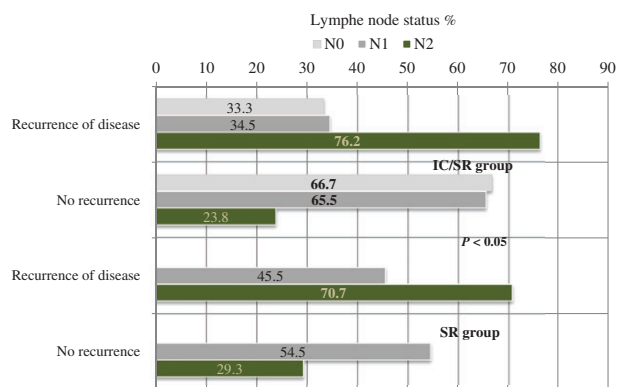


Figure 3 Treatment outcome according to lymph node status (induction chemotherapy/surgical resection [IC/SR] vs. SR alone).

respectively; P = 0.03), while in the upfront surgery group there were no N0 cases, but in N1 disease the RR was significantly higher at 45.5% (P < 0.05). In cases of N2 disease, the RR was high in both groups, (76.2% in the preoperative chemotherapy group and 70.7% in the upfront surgery group; P < 0.001), significantly higher than rates observed for lower N status (P < 0.001) (Fig 3).

There was significant difference in RRs in relation to the treatment applied after surgery (P = 0.007), as well as a significantly higher probability that no relapse would occur when adjuvant chemotherapy was applied (77.8% in the preoperative chemotherapy group vs. 22.2% in the upfront surgery group; P = 0.02). The probability of relapse was equal whether radiotherapy was applied or not (P = 0.142 > 0.05).

Over a follow-up period of two years, 19 patients (32.2%) from the preoperative chemotherapy group died, and 38 patients (36.5%) from the upfront surgery group died. Statistically, this did not represent a significant difference (P = 0.577 > 0.05) in the two-year mortality rate.

The median survival duration over the two-year follow-up period was 19.6 months (95% confidence interval 17.5–21.8) in the preoperative chemotherapy group, and 18.8 months (95% confidence interval 17.2–20.5) in the upfront surgery group.

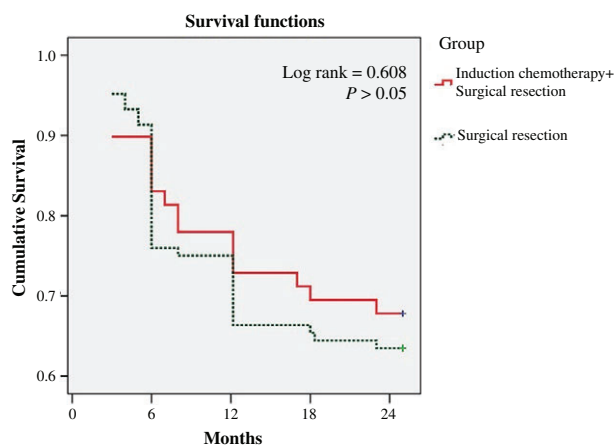


Figure 4 Kaplan–Meier survival curves comparing different treatments (induction chemotherapy/surgical resection [SR] vs. SR alone).

Kaplan–Meier survival curves comparing the patients by different treatment approaches (preoperative chemotherapy/surgical resection vs. upfront surgical resection) revealed no significant difference in survival between the groups (log rank = 0.608 > 0.05) (Fig 4).

Discussion

Treatment of stage III NSCLC remains difficult and controversial, mainly because of the large heterogeneity of this stage in terms of tumor volume and bulk, and lymphogenic spread.⁸ Thus, different subgroups of stage III NSCLC patients may require different strategies and personalized treatments.⁸

Patients with confirmed stage IIIA NSCLC represent a very heterogeneous group that includes those with limited microscopic ipsilateral mediastinal lymph node involvement discovered after surgical resection as well as those who have radiologically evident bulky subcarinal lymph node involvement at presentation. Different therapeutic options for stage IIIA disease include neoadjuvant therapy followed by surgery, primary surgery followed by adjuvant chemotherapy with or without sequential adjuvant radiation therapy, or definitive chemoradiation without surgery. When surgery is not considered an option, a combination of chemotherapy and radiotherapy can be delivered with curative intent^{10,11} and the concomitant administration of cisplatin-based chemotherapy and radiation represent the standard of care.¹²

There is inadequate randomized trial data to inform the optimal treatment strategy for patients with stage IIIA NSCLC, particularly in patients with non-bulky node disease. Randomized trials that have evaluated the role of adding surgery in various combined modality treatments have failed to show a survival advantage when comparing

the results of radiotherapy following induction chemotherapy or chemoradiotherapy.^{10,11} These trials, however, did not take into account the heterogeneity of stage IIIA disease. Many large volume centers offer surgery to patients with mediastinal involvement limited to one ipsilateral station and a lymph node smaller than 3 cm (non-bulky). In a survey of National Comprehensive Cancer Network institutions, 90% of responders would offer surgery to these patients.¹³

In our study, we compared treatment outcomes in preoperative chemotherapy and upfront surgery groups related to the lymph node status and found a significant difference between the groups ($P = 0.001$). In the preoperative chemotherapy group, there was significantly lower RR at mediastinal lymph node status N0 and N1 (33.3% and 34.5%, respectively; $P = 0.03$), which might be explained as an effect of neoadjuvant chemotherapy. In the upfront surgery group, the RR was significantly higher in patients with N1 disease (45.5% vs. 34.5% in the preoperative chemotherapy group; $P < 0.05$), which may be the result of a pathologic response to neoadjuvant chemotherapy. It should be stressed that nine patients (15.3%) in the preoperative chemotherapy group had no lymph node metastasis. In cases of N2 disease, the RR was high in both groups (76.2% in the preoperative chemotherapy group and 70.7% in the upfront surgery group; $P < 0.001$), indicating that patients did not respond to preoperative chemotherapy.

The two-year survival rate after preoperative chemotherapy treatment for patients with stage IIIA NSCLC in our study was not significantly longer than for patients at the same stage of disease not treated with preoperative chemotherapy.

For stage III NSCLC, overall survival (OS) after surgery alone is generally poor at 5–10% at five years, mainly because of the high incidence of local and distant failures. Randomized trials and meta-analyses have shown a modest improvement in survival with neoadjuvant chemotherapy, but local and distant failure rates remain high.¹⁴ Neoadjuvant or adjuvant chemotherapy is a part of a multimodality treatment approach for stage IB–IIIB, because of the high risk of distant metastases after surgery alone.^{15–19}

The results of two small, randomized trials, published in early 1994, have important implications for the treatment of patients with stage IIIA. These trials confirmed the superiority of induction chemotherapy followed by surgery over surgery alone for patients with stage IIIA disease.^{20,21} Subsequent randomized trials and two meta-analyses have compared neoadjuvant chemotherapy followed by surgery versus surgery alone in patients with stage IIIA NSCLC, and demonstrated a significant benefit in favor of neoadjuvant chemotherapy. The data of both systematic reviews show a 6–7% absolute benefit in five-year survival in cIIIA

patients, improving their outcome from 15–35% to 21–42%.^{22,23}

Two large randomized clinical trials have been conducted to evaluate the role of surgical resection after induction chemotherapy in patients with clinically proven stage IIIA-N2. In the EORTC (08941) trial, 582 patients with cytologically or histologically proven unresectable stage IIIA-N2, were enrolled.¹⁰ Patients received three cycles of platinum-based chemotherapy. The 332 patients who responded (complete, partial or minor response on chest computed tomography) were then randomly allocated to receive surgery or radiotherapy (at least 60 Gy to the primary tumor and 40–46 Gy to the mediastinum). Postoperative radiotherapy was later administered to 62 (40%) patients in the surgical arm. The complete resection rate was 50%, with 5% pathologic complete responses (CRs). There was no significant difference in median survival (17.5 months in the radiotherapy arm vs. 16.4 in the surgery arm), five-year OS (14% vs. 15.7%, respectively) or progression-free survival (PFS). The authors concluded that surgery did not improve OS or PFS compared to radiotherapy in stage IIIA initially unresectable N2 patients who responded to induction chemotherapy.

The North American Intergroup Trial enrolled 492 patients with histologically proven stage IIIA-N2 that were technically resectable.¹¹ Patients were randomized to either concurrent chemoradiotherapy (two cycles cisplatin/etoposide and 45Gy radiotherapy) followed by surgery, or the same chemoradiotherapy with consolidation radiotherapy with a tolerated dose up to 61 Gy. Both arms received consolidation chemotherapy with two cycles of cisplatin/etoposide. The OS rate was not significantly improved with the addition of surgery, although the PFS rate was significantly better and local RRs were lower in patients who underwent trimodality treatment. PFS was significantly better in the surgery group but OS did not differ, mainly because of postoperative mortality. Mediastinal downstaging occurred in 48% of patients with trimodality treatment, but only 15% had a pathological CR. Multivariate analysis revealed that three factors were associated with improved outcome: lobectomy, pathological downstaging, and completeness of resection.^{9,11,24–33}

Hence, both trials showed equivalence in OS between surgery and thoracic radiotherapy and better local control with surgery than radiotherapy. Exploratory subgroup analyses of both trials showed an improved outcome in patients who are downstaged and/or in whom a complete resection could be obtained with lobectomy.

Despite the negative results of these studies, it is clear that a subset of patients benefits from surgery; however, in part because of the heterogeneity of the disease, the identification of such patients is extremely challenging.³⁴ The

recommendation shared among other cancer centers is to offer surgery to patients with stage IIIA disease when only one mediastinal lymph node station is involved and if the node is < 3 cm. A survey of National Comprehensive Cancer Network institution members showed that 90% of responders consider surgery a part of therapy in this clinical scenario.¹³

A recent meta-analysis on neoadjuvant chemotherapy for NSCLC included 15 controlled randomized trials based on the individual data of 2385 patients.¹⁵ The primary outcome was OS. The results showed a 13% reduction in the relative risk of death, with an absolute survival improvement of 5% at five years, from 40% to 45%. In this meta-analysis, stage did not seem to be crucial for the effect of chemotherapy: local recurrence occurred in 24%, distant recurrence in 31%, and both local and distant recurrence in 9%. Altogether, 33% of first events included a local failure.¹⁵ In a previous meta-analysis of 13 randomized clinical trials (not based on individual patient data), the positive effect of chemotherapy was also noted. After specific analysis of eight studies of patients with stage III NSCLC, the increase in OS after chemotherapy was statistically significant.¹⁶ In three randomized trials comparing neoadjuvant chemotherapy followed by surgery to surgery alone in stage III NSCLC patients, the complete pathological response in the neoadjuvant chemotherapy arm was between 6% and 10.5%.^{17–19} In a phase II trial of the Swiss cooperative group, in which patients received neoadjuvant docetaxel plus cisplatin for stage IIIA NSCLC, there was a good correlation between pathological response and resectability. In addition, resectability and mediastinal clearance were strongly prognostic for survival, whereas patients with no mediastinal clearing and/or an incomplete resection did poorly.³⁵ At five-year follow-up, 60% of patients experienced a local relapse.³⁶

In our study there was significant difference in RRs in relation to treatment applied after surgery ($P = 0.007$), as well a significantly higher probability that no relapse would occur when adjuvant chemotherapy was applied (77.8% in the preoperative chemotherapy group vs. 22.2% in the upfront surgery group; $P = 0.02$). The probability of relapse was equal whether radiotherapy was applied or not ($P = 0.142 > 0.05$). This is consistent with results in the available literature on adjuvant chemotherapy.

Since 2004, three large trials have shown the benefit of adjuvant cisplatin-based chemotherapy.^{37–39} Although JBR10³⁹ only included patients with stages IB and II, both the International Adjuvant Lung Cancer Trial (IALT)³⁷ and the Adjuvant Navelbine International Trialist Association (ANITA) trial³⁸ included patients with resected stage IIIA. In IALT, 25% of the patients had N2 node disease and when compared to patients with N0 or N1 disease, this group

derived the highest benefit from adjuvant chemotherapy. Similarly, patients with N2 node disease represented 29% of those treated in the ANITA trial. Consistent with the IALT results, the survival benefit hazard ratio (HR) with adjuvant chemotherapy was better for patients with stage III (HR 0.69, 0.53–0.90) in comparison to patients with stages IB (HR 1.1, 0.76–1.57) and II (HR 0.71, 0.49–1.03). The Lung Adjuvant Cisplatin Evaluation meta-analysis of 4584 patients documented that adjuvant chemotherapy increases five-year survival from 39% to 49% for stage II and from 26% to 39% for stage III,⁴⁰ providing evidence in favor of the European Society for Medical Oncology recommendation of the use of adjuvant chemotherapy in stage II–III radically resected NSCLC patients.¹

Our finding that the probability of relapse is equal whether radiotherapy is applied or not ($P = 0.142 > 0.05$) might be at least partly the result of a high rate of pneumonectomies with postoperative complications, the old radiotherapy techniques applied, and subsequent comorbidities.

The role of radiotherapy in the management of patients with IIIA and particularly N2 involvement is controversial. Once patients are considered candidates for surgical resection, radiotherapy can be used either before surgery in combination with chemotherapy (induction therapy), or in the postoperative setting after surgery with adjuvant chemotherapy. Although adequate randomized data are lacking in the induction setting, trials comparing the use of chemotherapy alone to the use of chemoradiotherapy indicate that the addition of radiotherapy may be associated with an increase in CR in the mediastinum, although this is not associated with an increase in OS.^{11,41,42} Moreover, indirect evidence indicates that this may be achieved at the expense of increased postoperative morbidity.

Numerous retrospective studies and phase II trials have been conducted on the potential added value of radiotherapy in the neoadjuvant setting. The addition of radiotherapy to chemotherapy has been associated with a high rate of complete resection, a satisfying rate of complete pathologic response, and high mediastinal clearance in cases of N2 disease. Until recently, only small randomized trials have compared neoadjuvant chemoradiation to neoadjuvant chemotherapy, but were not sufficiently conclusive.^{42–45} The recently published Swiss cooperative group phase III randomized trial is the only one to include a sufficient number of patients. It demonstrated the superiority of neoadjuvant chemoradiation over neoadjuvant chemotherapy regarding overall response rate, complete resection rate and local control, while no increased hematologic toxicity or postoperative death occurred.⁴⁵ However there was no difference in OS between the two arms. Still, under certain conditions, in which the risk of local failure is very high after surgery, studies on neoadjuvant chemoradiation

might be performed using novel radiotherapy techniques and schemes, and novel systemic treatments associated with radiotherapy.

The role of adjuvant radiotherapy in patients with completely resected stage IIIA is also unclear. Recent non-randomized data point to a possible benefit; however, these results may have been influenced by selection bias.^{46–48} The results of the Lung ART trial (EORTC 22055C) investigating the role of adjuvant conformal radiotherapy are pending.⁴⁸

The limitations of this study are as follows. Being a retrospective study, it suffers from the obvious risks of bias associated, namely patient selection, surgeon bias, etc. It should be noted that one of the study's weaknesses is the lack of reliable clinical staging procedures because PET, EBUS, and EUS were not available in Serbia and mediastinoscopy was not often performed. Finally, this was a large volume lung cancer surgery center experience, but as a single center experience, the results are not generalizable.

In conclusion, the management of patients with stage IIIA NSCLC is controversial because of the heterogeneity of the disease. The best management can only be achieved by a multidisciplinary team, which includes a thoracic surgeon dedicated to lung cancer. Chemotherapy in a neoadjuvant/adjuvant setting is part of the treatment approach for patients with stage IIIA disease who are able to receive cisplatin-based chemotherapy. In spite of the progress in neoadjuvant therapy evidenced by phase III randomized trials and meta-analyses, many issues remain unsolved. Concern over the role of radiotherapy associated with neoadjuvant chemotherapy before surgery or in an adjuvant setting requires further investigation using novel radiotherapy techniques, schemes, and novel systemic treatments.

Disclosure

No authors report any conflict of interest.

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