

# Neoadjuvant chemotherapy in stage IIIa non-small cell lung cancer

Robert Milroy, Fergus Macbeth\*

Department of Respiratory Medicine, Stobhill Hospital NHS Trust, Glasgow, UK;

\*Beatson Oncology Centre, Western Infirmary, Glasgow, UK

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## Introductory articles

### A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small cell lung cancer

Rafael Rosell, José Gómez-Codina, Carlos Camps, José Maestre, José Padille, Antonio Cantó, José Luis Mate, Shanrong Li, Jorge Roig, Angel Olazábal, Mercedes Canela, Aurelio Ariza, Zdeněk Skácel, José Morera-Prat, Albert Abad

**Background.** The efficacy of surgery for patients with non-small cell lung cancer is limited, although recent studies suggest that preoperative chemotherapy may improve survival. We conducted a randomized trial to examine the possible benefit of preoperative chemotherapy and surgery for the treatment of patients with non-small cell lung cancer. **Methods.** We studied 60 patients (59 men and 1 woman) with stage IIIA non-small cell lung cancer. The patients were randomly assigned to receive either surgery alone or three courses of chemotherapy (6 mg of mitomycin per square meter of body-surface area, 3 g of ifosfamide per square meter, and 50 mg of cisplatin per square meter) given intravenously at three-week intervals and followed by surgery. All patients received mediastinal radiation after surgery. The resected tumors were evaluated by means of K-ras oncogene analysis and flow cytometry. **Results.** The median period of survival was 26 months in the patients treated with chemotherapy plus surgery, as compared with 8 months in the patients treated with surgery alone ( $P<0.001$ ); the median period of disease-free survival was 20 months in the former group, as compared with 5 months in the latter ( $P<0.001$ ). The rate of recurrence was 56 percent in the group treated with chemotherapy plus surgery and 74 percent in the group treated with surgery alone. The prevalence of mutated K-ras oncogenes was 15 percent among the patients receiving preoperative chemotherapy and 42 percent among those treated with surgery alone ( $P=0.05$ ). Most of the patients treated with chemotherapy plus surgery had tumors that consisted of diploid cells, whereas the patients treated with surgery alone had tumors with aneuploid cells. **Conclusions.** Preoperative chemotherapy increases the median survival in patients with non-small cell lung cancer. (N Engl J Med 1994;330:153-8)

### A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell lung cancer

Jack A Roth, Frank Fossella, Ritsuko Komaki, M Bernadette Ryan, J B Putnam Jr, Jin Soo Lee, Hari Dhingra, Louis De Caro, Marvin Chasen, Malcolm McGavran, E Neely Atkinson, Waun Ki Hong

**Background.** Patients with resectable stage IIIA non-small cell lung cancer have a low survival rate following standard surgical treatment. Nonrandomized trials in which induction chemotherapy or a combination of chemotherapy and radiation prior to surgery were used to treat patients with regionally advanced primary cancers have suggested that survival is improved when compared with treatment by surgery alone. **Purpose.** We performed a prospective, randomized study of patients with previously untreated, potentially resectable clinical stage IIIA non-small cell lung cancer to compare the results of

**perioperative chemotherapy and surgery with those of surgery alone.** **Methods.** This trial was designed to test the null hypothesis that the proportion of patients surviving 3 years is 12% for either treatment group against the alternate hypothesis that the 3-year survival rate would be 12% in the surgery alone group and 32% in the perioperative chemotherapy group. The estimated required sample size was 65 patients in each group. The trial was terminated at an early time according to the method of O'Brien and Fleming following a single unplanned interim analysis. The decision to terminate the trial was based on ethical considerations, the magnitude of the treatment effect, and the high degree of statistical significance attained. In total, 60 patients were randomly assigned between 1987 and 1993 to receive either six cycles of perioperative chemotherapy (cyclophosphamide, etoposide, and cisplatin) and surgery (28 patients) or surgery alone (32 patients). For patients in the former group, tumor measurements were made before each course of chemotherapy and the clinical tumor response was evaluated after three cycles of chemotherapy; they then underwent surgical resection. Patients who had documented tumor regression after preoperative chemotherapy received three additional cycles of chemotherapy after surgery. **Results.** After three cycles of preoperative chemotherapy, the rate of clinical major response was 35%. Patients treated with perioperative chemotherapy and surgery had an estimated median survival of 64 months compared with 11 months for patients who had surgery alone ( $P<0.008$  by logrank test;  $P<0.018$  by Wilcoxon test). The estimated 2- and 3-year survival rates were 60% and 56% for the perioperative chemotherapy patients and 25% and 15% for those who had surgery alone, respectively. **Conclusions.** In this trial, the treatment strategy using perioperative chemotherapy and surgery was more effective than surgery alone. **Implications.** This clinical trial strengthens the validity of using perioperative chemotherapy in the management of patients with resectable stage IIIA non-small cell lung cancer. Further investigation of the perioperative chemotherapy strategy in earlier stage lung cancer is warranted. (J Natl Cancer Inst 1994;86:673-80)

Few of us need reminding that lung cancer is a leading cause of death and the commonest cancer in the western world. Provisional mortality figures for 1993 from the Office of Population Censuses and Surveys show that nearly 38 000 people died of lung cancer in the UK.<sup>1</sup> Any new development that might lead to an improvement in these figures may affect a large number of patients and should be carefully considered. One such development is the use of chemotherapy before surgery in patients with locally advanced (stage IIIA) non-small cell lung cancer. In particular the two randomised trials in patients with stage IIIA disease which are summarised in the introductory articles, have recently reported highly significant improvements in overall survival in patients treated with chemotherapy.<sup>2,3</sup>

About 40% of patients with non-small cell lung cancer will have locally advanced (stage III) disease confined to the chest.<sup>4</sup> Stage III lung cancer is defined in terms of the TNM staging system described by the American Joint Committee on Cancer (table 1).<sup>5</sup> In the UK

these patients have traditionally been regarded as having inoperable disease. However, there is now evidence to suggest that surgery offers a real chance of long term survival in a small but significant percentage of selected patients with stage IIIA disease. Eight years ago Martini and Flehinger<sup>6</sup> suggested that, for the majority of patients presenting with N2 disease, surgical treatment should be considered seriously. More recently, Mountain reported 28% five year survival for patients with stage III non-small cell lung cancer treated surgically.<sup>7</sup> In this series of stage IIIA patients, those with N2 disease had a significantly poorer five year survival (21%) than those with T3, N0, or N1 disease (39%). However, overall in this group of patients, surgery appeared to offer a chance of long term survival, although even in patients completely resected five year survival was still only about 30%.

These disappointing results for the surgical treatment of stage IIIA non-small cell lung cancer has led to considerable effort to investigate the role of chemotherapy either before surgery (so called neoadjuvant chemotherapy) or after surgery (adjuvant chemotherapy). The hope is that, by using such approaches, it may be possible to eliminate micrometastatic disease and so prolong overall survival.

In this review we will look particularly at the evidence supporting the view that chemotherapy may be helpful in this situation, and then specifically consider the two recently published randomised studies of neoadjuvant chemotherapy in stage IIIA non-small cell lung cancer.

**Table 1 American Joint Committee on cancer staging criteria for lung cancer**

Stage I	T1,2	N0	M0
Stage II	T1,2 and	N1	M0
Stage IIIA	T3 and/or	N2	M0
Stage IIIB	T4 and/or	N3	M0
Stage IV	Any T	Any N	M1

T=primary tumour, N=regional lymph node, M=distant metastases.

T3=tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, or parietal pericardium; tumour in the main bronchus <2 cm distal to the carina but without involvement of the carina. N2=metastases in ipsilateral mediastinal and/or subcarinal lymph nodes.

#### Adjuvant chemotherapy

Many trials have assessed the value of chemotherapy given after surgery, with or without radiotherapy to the

thorax.<sup>8-20</sup> These have given conflicting results, but the earlier studies which used regimens that did not include the drug cisplatin appeared to have a small adverse effect on survival.<sup>8,10</sup> However, more recent studies have included cisplatin-containing regimens and some of these suggest a survival benefit.<sup>19,20</sup> However, the studies include heterogeneous groups of patients, with some studies including patients with very early disease, and this makes interpretation of results difficult. Nonetheless, a recent meta-analysis which reviewed all adjuvant chemotherapy studies in non-small cell lung cancer has been published in abstract and suggests absolute five year survival benefits from cisplatin-based chemotherapy of 5% for surgery alone, and 2% for surgery and radiotherapy.<sup>21</sup>

### Neoadjuvant chemotherapy

A number of non-randomised studies have investigated the role of chemotherapy, sometimes combined with radiotherapy, given preoperatively to patients with stage III non-small cell lung cancer – so called neoadjuvant chemotherapy.<sup>22-36</sup>

Overall, significant responses were seen in more than 50% of patients and a response usually indicated an improved chance of successful resection. Resection rates ranged from 0% to 88%, with an overall resection rate of more than 50%. The use of preoperative radiotherapy in addition to chemotherapy sometimes made surgery technically more difficult because of post-irradiation fibrosis.<sup>25,35</sup>

The theoretical concern with neoadjuvant chemotherapy is that some patients might progress before surgery. However, the incidence of tumour progression during treatment appears to be quite low; for instance, in one study only seven of 85 patients actually progressed during chemotherapy.<sup>26</sup> If patients do progress it seems likely that they would have fared badly even if they had been operated on immediately because of the subsequent appearance of metastatic disease. It therefore seems unlikely that delaying surgery by giving neoadjuvant chemotherapy will adversely affect those patients who are potentially curable.

Some of the studies have suggested that neoadjuvant chemotherapy may improve resectability<sup>22,28,31</sup> and that a response to the neoadjuvant chemotherapy may allow a less aggressive surgical approach.<sup>29</sup> However, response to neoadjuvant therapy and increased resectability are only minor issues. The most important question is whether neoadjuvant therapy can improve survival. So far this question has not been satisfactorily answered because there have been no randomised trials which have specifically addressed it. The studies quoted so far have not been randomised and it is difficult to compare one with another because, like many of the adjuvant studies, they include heterogeneous patient populations. For example, one study included patients with stage I to stage III disease,<sup>29</sup> while others have included only patients with stage IIIa and IIIb disease.<sup>22</sup> One study has even included patients with stage IV disease.<sup>31</sup> Long term survival in some of the studies was better than the 30% five year survival reported by Mountain for stage IIIa patients treated with surgery alone.<sup>37</sup> For instance, Martini *et al* recorded a 34% five year survival in 41 patients with stage IIIa N2 disease, compared with 9%

in historical control subjects who underwent surgery alone.<sup>28</sup>

It also appears from these non-randomised studies that long term survival is most likely in patients who had a complete response to neoadjuvant chemotherapy compared with those who had either microscopic or macroscopic residual tumour at the time of surgery.<sup>26</sup>

Until recently the question of whether neoadjuvant chemotherapy has an impact on survival in patients with stage IIIa disease remained unresolved. It is for this reason that the papers by Rosell *et al*<sup>2</sup> and Roth *et al*<sup>3</sup> are so important. Both studies are randomised, prospective trials comparing a policy of perioperative chemotherapy and surgery with surgery alone in patients with resectable stage IIIa non-small cell lung cancer. Both studies were closed early because of significant survival benefit in the chemotherapy arm.

### Randomised neoadjuvant studies

#### STUDY BY ROSELL AND COLLEAGUES<sup>2</sup>

In this trial from Barcelona 60 patients with histologically confirmed stage IIIa non-small cell lung cancer, who were considered on preoperative staging investigations to be potentially resectable, were randomised to receive either preoperative chemotherapy or immediate surgery. The two groups were well matched in terms of histology and TNM stage, but were not well matched in terms of K-ras oncogene expression (table 2). Patients with T3N0 and T3N1 disease were also included. Although the surgery alone group had slightly larger tumours, the differences were not statistically significant.

If the preoperative computed tomographic (CT) scan did not show mediastinal lymphadenopathy, the patient was considered to have no mediastinal involvement. N2 disease was confirmed histologically by mediastinoscopy or mediastinotomy in 44 of the 60 patients; the remainder had T3 disease with unfavourable prognostic factors such as soft tissue infiltration, rib involvement, or pericardial invasion.

Patients in the neoadjuvant arm were treated with three courses of chemotherapy consisting of mitomycin (6 mg/m<sup>2</sup>), ifosfamide (3 mg/m<sup>2</sup>), and cisplatin

Table 2 Patient baseline and tumour characteristics compiled from study by Rosell *et al*<sup>2</sup>

Characteristic	Chemotherapy + surgery (n=30)	Surgery (n=30)
Mean (range) age (years)	60 (39-78)	63 (43-72)
Sex (male/female)	29/1	30/0
Mean Karnofsky score	80	80
Histology		
squamous	19	23
adeno	8	6
large cell	3	1
TNM stage		
T1N2	2	1
T2N2	15	14
T3N0	4	9
T3N1	1	2
T3N2	8	4
Mean (range) tumour size (cm)	5 (2-10)	6 (4-15)
Tumour size		
<3 cm	1	0
3-5 cm	14	9
>5 cm	15	21

(50 mg/m<sup>2</sup>) as described by Cullen *et al.*<sup>38,39</sup> All patients received mediastinal radiotherapy following surgery (50 Gy) and were followed up three monthly. The overall response rate in the patients receiving chemotherapy was 60%, with 7% (two patients) achieving a complete response. Only one patient actually had progressive disease during chemotherapy and did not undergo surgery, and two patients refused surgery following chemotherapy. Of the 27 patients operated on in the chemotherapy group, 23 had a complete resection, and in the surgery alone group 27 of the 30 patients had a complete resection. There was no significant difference between the two groups with respect to the surgical procedures that were used or in postoperative complications. There were, however, strikingly significant differences in disease-free and overall survival between the two groups, in both cases favouring the patients who had received preoperative chemotherapy.

The median overall survival in the patients receiving surgery plus radiotherapy alone was eight months compared with 26 months in the group receiving chemotherapy in addition ( $p<0.001$ ). The differences in survival between the groups were significant irrespective of the patient's age or tumour histology, location, size, or the number of N2 nodes involved.

Figure 1 shows the survival curves for the two patient groups. What is most striking about this is not the very good survival of the patients treated with chemotherapy before surgery, but the poor survival of the patients who underwent immediate surgery. In this group the median survival was only seven months and there were no patients alive beyond 18 months. Previous studies involving a large number of patients who had surgery for N2 disease achieved a median survival beyond 12 months<sup>40</sup> and a five year survival exceeding 15%.<sup>41-43</sup> Others report a median survival of 12 months following surgical resection for patients with clinically obvious N2 disease, with a 10–20% three year survival.<sup>44-46</sup> Survival in the combined modality arm in this trial is therefore comparable to what one might have anticipated from a radical surgical approach alone. This throws some doubt on the authors' conclusion that neoadjuvant chemotherapy has *improved* survival in their study.

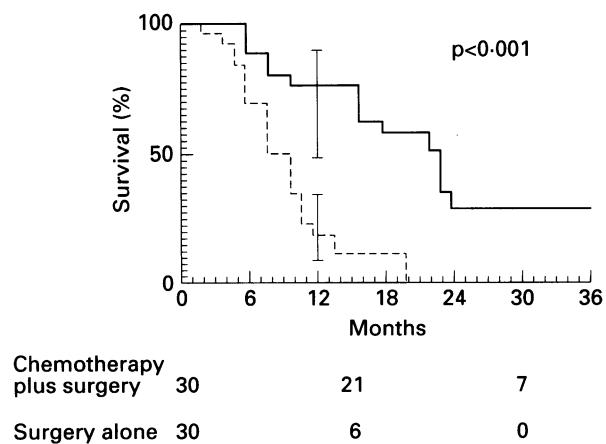


Figure 1 Survival in 60 patients with stage IIIa non-small cell lung cancer: comparison of surgery alone with surgery and chemotherapy. Reproduced from Rosell *et al.*<sup>2</sup> with permission of The New England Journal of Medicine. Copyright (1994), Massachusetts Medical Society.

Most series that have reported the effect of radical radiotherapy in patients with stage III disease show a two year survival of 15–20%.<sup>47</sup> Moreover, a recent study of palliative radiotherapy in good performance status patients with non-small cell lung cancer carried out by the MRC has shown a 13% two year survival with high dose palliative radiotherapy.<sup>48</sup>

In addition, Rosell and coworkers examined tumour specimens obtained at surgery for the presence of the K-ras oncogene by a technique described by Slebos *et al.*<sup>49</sup> The presence of K-ras oncogene point mutation has previously been shown to be a significantly adverse prognostic factor in lung cancer.<sup>50-52</sup> Such mutations were found in 15% of the patients treated with chemotherapy and in 42% of the control group of patients, and this may account for the very poor survival in the latter group of patients.

As it took 3–4 days to obtain the K-ras oncogene results,<sup>49</sup> it was not possible to stratify patients according to the presence or absence of K-ras oncogene point mutations before randomisation. However, technology continues to progress and, indeed, a new and more sensitive assay for K-ras oncogene has recently been described,<sup>53</sup> which could mean that this approach may be possible in the future.

In addition, tumour samples from surgery were analysed by flow cytometry to assess the proportion of diploid and aneuploid cells.<sup>46</sup> Five of 17 tumour specimens from the chemotherapy plus surgery group (29%) were aneuploid, compared with 14 (70%) of the 20 tumour specimens from the surgery alone group. Radiation therapy has been reported to reduce the aneuploid population in patients with cervical carcinoma,<sup>54</sup> so it is possible that the chemotherapy in the neoadjuvant group altered the DNA ploidy of the tumour.

#### STUDY BY ROTH AND COLLEAGUES<sup>3</sup>

Sixty patients were entered into this study, all of whom were thought to have resectable stage IIIa disease. Those with clinically obvious N2 disease on CT scanning underwent mediastinoscopy, but those patients with unequivocal plain radiographic evidence of T3 or N2 tumour involvement did not require mediastinoscopy. T3N0 patients were classified separately because they are known to have a better prognosis than other patients with stage IIIa disease.

Twenty eight patients were randomised to receive preoperative chemotherapy and 32 underwent surgery alone. The groups were well balanced for age, sex, histology, performance status, clinical stage, and post-operative stage. Only six patients had T3N0 tumours following thoracotomy. The preoperative chemotherapy regimen consisted of cyclophosphamide (500 mg/m<sup>2</sup>), etoposide (100 mg/m<sup>2</sup> for three days), and cisplatin (100 mg/m<sup>2</sup>) repeated every four weeks. Patients had three courses of chemotherapy before surgery and, if they showed any response to chemotherapy, were given a further three cycles afterwards. The objective response rate to chemotherapy was 35%, including one complete response. In addition, 31% of patients showed some tumour shrinkage. Only 15% progressed while receiving chemotherapy.

At surgery all patients underwent formal mediastinal lymph node dissection. The resectability rates did not

## LEARNING POINTS

- \* The role of neoadjuvant and adjuvant chemotherapy in non-small cell lung cancer still remains undetermined.
- \* Clinicians are encouraged to participate in existing or planned large clinical trials, rather than routinely using perioperative chemotherapy for all cases of non-small cell lung cancer.

differ significantly between the two treatment groups, with 61% of patients in the neoadjuvant chemotherapy group and 66% of patients in the surgery alone group having resectable disease. However, only 39% of patients in the chemotherapy group and 31% in the surgery alone group achieved a complete resection. Patients who were incompletely resected or had unresectable disease were considered protocol failures and could receive radiation therapy (60–66 Gy) off protocol at the discretion of the treating physician. Fifteen patients in the chemotherapy group and 19 patients in the control group were treated with radiotherapy.

A significant difference in overall survival between the two treatment groups was seen and is highlighted in figure 2. The estimated median survival in the chemotherapy group was 64 months compared with 11 months for surgery alone ( $p<0.01$ ). In addition, the estimated rates of survival in the chemotherapy group were significantly higher at one, two, and three years than in the surgery alone group (70% versus 45% at one year, 60% versus 25% at two years, and 36% versus 15% at three years).

This study therefore appears to show a significant survival benefit from the addition of neoadjuvant chemotherapy. In fact, as with the study by Rosell *et al*, it was closed early because such significant survival differences were found. The survival rate for the surgery alone group is what one might have anticipated from previous studies, and the difference between the two arms of the survival curves relates to the extremely good survival of the patients treated with neoadjuvant chemotherapy.

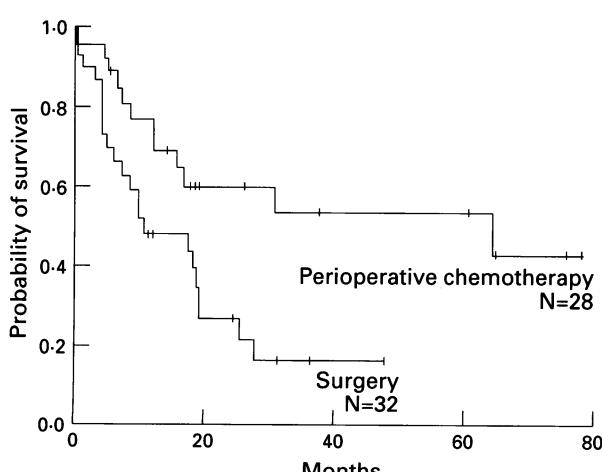


Figure 2 Survival in 60 patients with stage IIIa non-small cell lung cancer: comparison of surgery alone with surgery and chemotherapy. Reproduced from Roth *et al*<sup>3</sup> with permission.

## Concluding comments

Both studies showed a highly significant survival benefit from the addition of perioperative chemotherapy to surgery (with or without radiotherapy) in patients with stage IIIa non-small cell lung cancer. However, some caution still needs to be exercised before we adopt this policy as standard for this group of patients, as was suggested at the World Lung Cancer Conference in Colorado last summer. Both studies are relatively small and, in fact, only a total of 120 patients have been randomised. The survival of the surgery alone patients in the study by Rosell *et al* was surprisingly poor, and the survival for the combined modality group reported by Roth *et al* extraordinarily good.

Stage IIIa includes two very distinct groups of patients (T3N0 and T1–3N2) who have different survival outcomes. "Potentially resectable" stage IIIa disease is not an easy group to define and is, in our experience, quite unusual. This heterogeneity makes it difficult to interpret the results of such small studies.

The role of neoadjuvant and adjuvant chemotherapy in non-small cell lung cancer still remains, in our view, undetermined, but there are some encouraging pointers. The question of whether perioperative chemotherapy will have a significant influence on the survival of lung cancer patients remains a very important one. This not only applies to stage IIIa disease but also to stage I and stage II disease treated surgically. A small improvement in the five year survival of successfully resected patients may result in a large number of patients living longer.

Very large clinical trials with permissive entry criteria and simple end points are currently being planned or are already open for recruitment. We would urge practising clinicians to participate in these trials as enthusiastically as possible. It would not be appropriate for British doctors managing lung cancer to launch wholeheartedly and uncritically into perioperative chemotherapy, but neither must we be left behind when the rest of the world moves on.

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