

Neo-adjuvant chemotherapy in early stage non-small cell lung cancer

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ABSTRACT

Lung cancer treatment has evolved during the last decade from the non-specific cytotoxic drugs to targeted therapy. New diagnostic equipment such as the endobronchial ultrasound bronchoscopy and positron emission tomography has enhanced early lung cancer diagnosis. However; we still need additional novel biomarkers to assist the already used diagnostic techniques. Surgery is still the best treatment for early lung cancer treatment. Several surgical techniques are being used based on the tumour location and cardiothoracic centre's experience. There are however marginal situations where neo-adjuvant chemotherapy provides a "pre-step" for the patient. In the current work we will provide current data for the patients needing neo-adjuvant chemotherapy before proceeding to curative surgery.

KEY WORDS

Lung cancer; neo-adjuvant; early stage

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Neo-adjuvant or preoperative chemotherapy is still considered an experimental modality of treatment mainly because it has been evaluated in only a small number of randomized trials, exploring the safety and activity of different platinum regimens. Theoretically the neo-adjuvant approach has a number of advantages: it can reduce the tumour volume and facilitate the control of micro-metastatic diffusion or prevent it; The neo-adjuvant treatment allows a careful evaluation of chemotherapy response giving critical information on tumour biology in adequate tumour samples: the compliance of chemotherapy in untreated patients is certainly better than after surgery and its dose intensity higher. On the other hand, its toxicities and a delay to surgery could be disadvantages, although up to now these issues seem to be scarcely relevant.

A meta-analysis (1) based upon seven trials involving 988 patients suggested that neo-adjuvant chemotherapy improved survival with a HR of 0.82 (95% CI: 0.69-0.97), equivalent to

an absolute benefit of 6% at 5 years. They furthermore found an incremental benefit by stage: stage IA: +4%, stage IB: 6%; stage II-III: +7%, but did not observe any interaction between the kind of platinum-containing regimen or the kind of adjuvant treatment (chemo- or radiotherapy). The exploratory nature of these subgroup analyses warrants an IPD approach, which is ongoing. When the mature results of the European Intergroup trial added to the previous meta-analysis a shift of the hazard ratio observed to 0.87, with loss of the significance of the improvement in outcome.

The range of results observed with neo-adjuvant chemotherapy is illustrated by several contemporary phase III trials:

In a French trial, 355 patients with non-small-cell lung cancer (NSCLC) (stage IB, II, or IIIA, including 35% with N2 disease) were randomly assigned to surgery with or without two cycles of preoperative cisplatin-based chemotherapy (2). Responding patients were eligible for postoperative chemotherapy, as well. Neo-adjuvant chemotherapy was associated with a trend toward a longer median disease-free survival (P=0.15). At a median follow-up of 14 years, the 10-year recurrence-free survival rate was significantly increased with chemotherapy plus surgery compared to surgery alone (HR 0.78, 95% CI: 0.62-0.98) (3). There was a trend toward increased overall survival with neo-adjuvant chemotherapy compared to surgery alone (P=0.12), and the difference was statistically significant when multivariate analysis incorporated age, T stage, and N stage (HR 0.69, 95%

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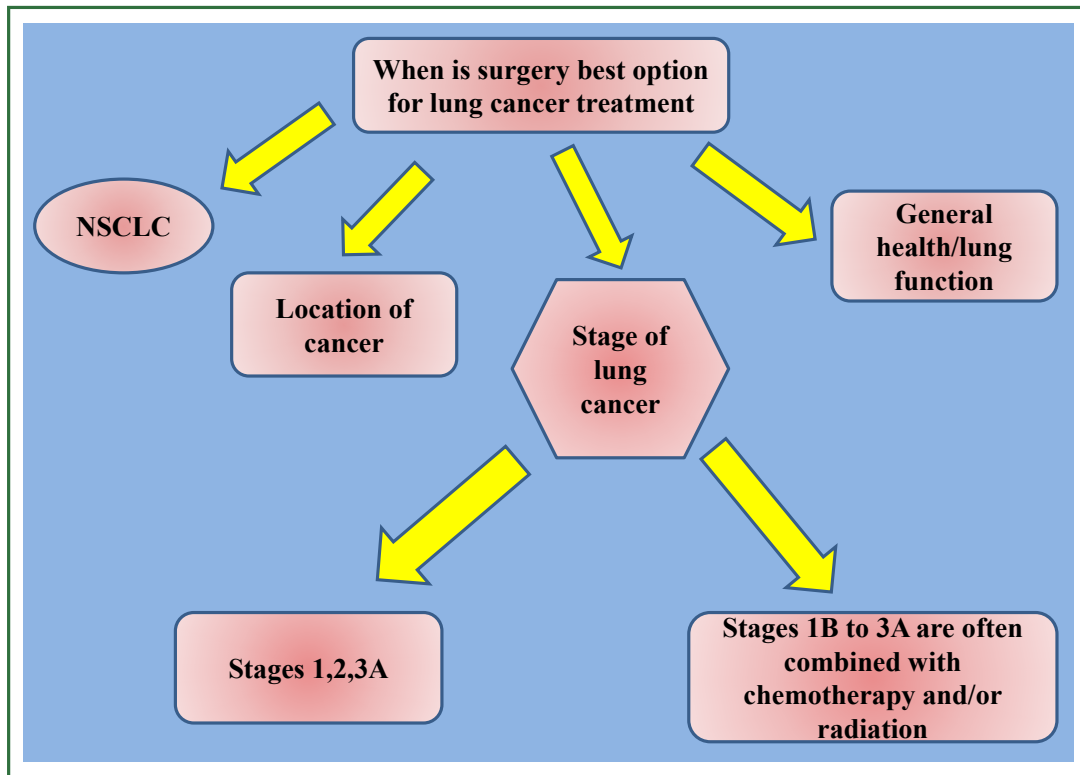


Figure 1. Schematic presentation of surgical treatment in non-small cell lung cancer.

CI: 0.64-0.90).

In the multicentre European LU22 trial, 519 patients with resectable NSCLC were randomly assigned to three cycles of platinum-based chemotherapy followed by surgery or to immediate surgery (4). At randomization, 93% of patients had clinical stage I or II disease. The chemotherapy regimen varied at different sites; the two most widely used combinations were vinorelbine plus cisplatin and gemcitabine plus cisplatin. Overall 75% of patients completed all three cycles of chemotherapy, and the objective response rate to chemotherapy was 47%. Despite the observed antitumor activity from chemotherapy, there was no improvement in PFS with neo-adjuvant treatment (HR for recurrence 0.96, 95% CI: 0.77-1.21). Similarly, there was no improvement in overall survival with preoperative chemotherapy (five-year survival 44% versus 45%, HR for death 1.02, 95% CI: 0.80-1.31). Results were not reported as a function of stage. The negative results in this trial may be attributed to the very high percentage of patients enrolled with stage I disease. This trial also underscores the difficulties in accurately staging patients preoperatively, as 59% of patients on the control arm (surgery alone) had either pathological upstaging or down-staging at the time of surgery.

In Southwest Oncology Group trial SWOG 9900, 354 patients with resectable stage IB-III A NSCLC were randomly assigned to three cycles of chemotherapy with paclitaxel plus carboplatin followed by surgery or immediate surgery (5). PFS was

prolonged with neo-adjuvant chemotherapy compared to immediate surgery (HR 0.80, 95% CI: 0.619-1.04). Overall survival was also non-significantly longer with neo-adjuvant chemotherapy (median 62 versus 41 months, HR 0.79, 95% CI: 0.60-1.06). The trial was terminated prematurely when positive results were obtained in large trials using adjuvant chemotherapy.

Neo-adjuvant and adjuvant chemotherapy were compared to surgery alone in the three-armed NATCH trial (6). In this trial, 624 patients with IA, IB, II, or III (T3N1) NSCLC were randomly assigned to surgery alone, neo-adjuvant chemotherapy followed by surgery, or surgery followed by adjuvant chemotherapy. Chemotherapy consisted of three cycles of paclitaxel plus carboplatin. Compliance with chemotherapy was significantly higher with neo-adjuvant rather than adjuvant chemotherapy (90% versus 61% receiving three cycles of chemotherapy). Despite this, there were no significant differences in the five-year disease-free survival rates (34%, 38%, and 37% for surgery alone, neo-adjuvant chemotherapy, or adjuvant chemotherapy, respectively) or five-year overall survival rates (44%, 47%, and 46%, respectively) possibly due to the predominance of stage I patients.

A smaller European trial randomly assigned 141 patients to chemotherapy with gemcitabine plus cisplatin followed by surgery or to surgery alone (7). There was a trend toward improved overall three-year survival with the combined modality approach ($P=0.053$). In a subset analysis, the benefits appeared to

be limited to patients with stage IIB/IIIA disease (three-year overall survival 70% versus 47%). The trial was terminated prematurely when positive results were obtained in large trials using adjuvant chemotherapy.

A common feature of these trials is that they have all been confronted with accrual problems, leading in some studies to their early closure, when the results of randomized trials showing a benefit of adjuvant chemotherapy were published.

Besides their low power and accrual, these trials have two further weaknesses in common: the survival in their control arms treated with immediate surgery is better than initially estimated, confounding the under-powering caused by the early closure of these trials; stage I (clinical or pathological) accounted for >50% of the enrolment and hence of the better than expected survival. As the accumulated evidence in the adjuvant setting has not found a statistically significant survival benefit for adjuvant chemotherapy in stage I disease, the implication of this finding in the neo-adjuvant setting might imply that a possible benefit for higher stages has been diluted by the majority of stage I cases (8).

Decisions on giving neo-adjuvant chemotherapy depend upon accurate clinical staging, while the decision to give adjuvant therapy is based upon the more accurate pathologic staging. Although 98% of patients in the NATCH trial had clinical stage I or II disease at protocol entry, 28% of those who underwent immediate surgery (with or without adjuvant chemotherapy) were reclassified as pathologic stage III based upon surgical findings.

The results of these trials and the meta-analysis do not support the use of a neo-adjuvant approach in stage I, II rather than immediate surgery with postoperative adjuvant chemotherapy for patients with resectable NSCLC (9) (Figure 1).

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