Review Article

Neoadjuvant chemoradiotherapy followed by surgery for stage IIIa and IIIb non-small-cell lung cancer (NSCLC): is it still justified?

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Abstract: For stage III non-small-cell lung cancer (NSCLC), overall survival after surgery alone is quite poor, in the range of 5% to 10% at five years, mainly due to the high incidence of local and distant failures. Randomized trials and meta-analyses have shown a modest improvement in survival with neo-adjuvant chemotherapy, however the local and distant failure rates remain high. Numerous retrospective studies and phase II trials have been published on the potential added value of radiotherapy in the neoadjuvant setting and are reviewed here. These studies have shown that the addition of radiotherapy to chemotherapy is followed by a high rate of complete resection, an encouraging rate of complete pathologic response, a high mediastinal clearance in case of N2 disease, all of which represent potential surrogates for survival. Until recently, only small randomized trials have compared neoadjuvant chemoradiation to neoadjuvant chemotherapy, and were not contributory. The recently published Swiss cooperative group (SAKK) phase III randomized trial is the only one to have accrued a sufficient number of patients for interpretation. It showed a superiority of neoadjuvant chemoradiation over neoadjuvant chemotherapy regarding overall response rate, complete resection rate and local control, with no increased haematologic toxicity or post-operative deaths. However there was no difference in the event-free survival (the primary endpoint) nor in overall survival between the two arms. Following the results of this trial, opposite opinions have been expressed regarding the possible causes of failures of this trial, and on the future role or not of radiotherapy associated with neoadjuvant chemotherapy before surgery. It is suggested that under certain conditions, in which the risk of local failures is quite high after surgery, studies on the role of neoadjuvant chemoradiation should be pursued, using novel radiotherapy techniques and schemes, and novel systemic treatments associated with radiotherapy.

Keywords: Neoadjuvant; radiotherapy; chemotherapy; surgery; non-small-cell lung cancer (NSCLC)

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Introduction

Neo-adjuvant or preoperative therapy for operable non-small-cell lung cancer (NSCLC) has been the subject of a large number of studies in the literature, and in spite of progress demonstrated by well conceived and well conducted phase III randomized trials and meta-analyses, many issues remain unsolved as of today, especially in locally advanced (LA) stages. In operable stage III NSCLC, there is still a considerable debate regarding the best strategy, which can include surgery followed by chemotherapy with or without radiotherapy, neo-adjuvant chemotherapy followed by surgery with or without post-operative radiotherapy, neo-adjuvant chemoradiation followed by surgery, comprehensive chemoradiation without surgery, proceeded or not by neo-adjuvant chemotherapy, and several other strategies (1,2). Neo-adjuvant treatments are aimed at improving the overall outcome of LA NSCLC by decreasing the rate of local failures and distant metastases observed after surgery alone.

After a brief reminder on the role of neo-adjuvant chemotherapy in NSCLC, this article will focus in more details on the potential added value of radiotherapy in the neoadjuvant setting.

Neoadjuvant chemotherapy in LA NSCLC

In non-metastatic NSCLC surgery still represents the mainstay of curative treatments from stage IA to IIIA and even for part of stage IIIB. However, especially in LA NSCLC, overall survival after surgery alone remains poor, in the range of 5–10% at 5 years (3). The domain of neo-adjuvant or adjuvant chemotherapy spans from stage IB to part of stage IIIB (4-8), due to the subsequent high risk of distant metastases after surgery alone.

The recent meta-analysis on neo-adjuvant chemotherapy for NSCLC has collected individual participant data from 2,385 patients included in 15 controlled randomized trials (4). Patients were centrally analyzed, and the primary outcome was overall survival. The results showed a 13% reduction in the relative risk of death, with an absolute survival improvement of 5% at 5 years, from 40% to 45% (4). In

this meta-analysis, stage did not seem to alter the effect of chemotherapy. Looking at the first events, local recurrence occured in 24%, distant recurrence in 31% and both local and distant recurrence in 9%. Altogether 33% of first events included a local failure (4). In a previous meta-analysis, which was not based on individual patient's data, the positive effect of chemotherapy was also observed, and looking specifically at 8 studies on stage III, the improvement in overall survival with chemotherapy remained statistically significant (5). However neo-adjuvant chemotherapy alone in stage III may not be sufficient, since even with this approach, the pathological complete response (pCR) rate was low, and the local-regional recurrence rate was high. For example, in three randomized trials comparing neo-adjuvant chemotherapy followed by surgery to surgery alone in stage III NSCLC, the complete pCR in the induction arm was only between 6% and 10.5% (6-8). As pCR is an indicator of response and a possible surrogate for survival (see below), it seems logical to improve pCR by an additional local treatment to surgery such as radiation therapy. In a phase II trial of the Swiss cooperative group (SAKK), in which patients received neo-adjuvant docetaxel and 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 (9). A subsequent analysis of this phase II revealed that at 5-year follow-up, as many as 60% of patients suffered from a local relapse (10). For these different reasons, it appears that the addition of radiotherapy to chemotherapy in neo-adjuvant strategies deserves to be strongly considered.

Neoadjuvant radiochemotherapy in LA NSCLC: retrospective studies, database and phase II trials

Retrospective studies

A large number of retrospective studies on neo-adjuvant radiochemotherapy for stage III NSCLC have been published. The overall results of a selection of eight of these are briefly discussed here (11-18). They represent altogether a total of about 1,100 patients with operable stage IIIA and IIIB (11-18). In the majority, chemotherapy consisted of cisplatin doublets, with a few carboplatin doublets, and the radiotherapy schedules were mainly conventional fractionation schemes with a few hyperfractionated schemes, with doses between 43 and 60 Gy. The pCR, when reported, varied between 16% and 27 % (11,13-15,18), except in one study where it was as high as 40% (17). The median survival was between 21 and 36 months, and the 5-year overall survival between 31% and 40% (11-18). In several reports, a pCR was associated with an increased survival (11,12,17,18), and a mediastinal downstaging and/or pathological clearing was also heralding a superior outcome (12-14,16,17). Evidently, results from these retrospective studies are to be interpreted with caution due to patients' selection and other bias. However some striking results, like the rates of pCR and the relationship between pCR, downstaging and survival are encouraging and may be hypothesis-forming for prospective randomized trials.

Results of the American National Cancer Database (NCDB)

A cohort of 11,242 patients included in the NCDB, treated from 1998 to 2004 for stage IIIA (N2) NSCLC were analyzed according to the 5 following treatment categories: neoadjuvant chemoradiation followed by a lobectomy, neo-adjuvant chemoradiation followed by pneumonectomy, lobectomy followed by adjuvant treatment, pneumonectomy followed by adjuvant treatment, or concomitant chemoradiation without surgery (19). Adjuvant treatments consisted of either chemotherapy alone, radiotherapy alone, or chemoradiation following surgery. Five-year overall survival was 33.5%, 20.7%, 20.3%, 13.3%, and 10.9%, respectively for the five treatment categories (19). On multivariate analysis, the hazard ratio (HR) in favor of the neo-adjuvant chemoradiation treatment was 0.51 (CI: 0.45–0.58) (19). Of note however, no neo-adjuvant chemotherapy alone category was described in this report. A more recent study from the NCDB analyzed 1,076 patients with stage IIIA (N2) NSCLC, treated between 2003 to 2005, either with neo-adjuvant chemoradiation followed by surgery or neoadjuvant chemotherapy followed by surgery (20). Outcomes included overall survival, residual nodal disease, any adverse pathologic features, and 30-day postoperative mortality. The 5-year overall survival for the entire cohort was 39%, namely 39.2% for the neo-adjuvant chemoradiation category *vs*. 38.6% for the neo-adjuvant chemotherapy (P= NS). On multivariate analysis, neo-adjuvant chemoradiation was associated with an improved pathological outcome (20).

Phase II trials

Results of 7 selected prospective one-arm phase II studies are presented on *Table 1* (21-27). In 5 of these trials, there was a

Table 1 Overall results of 7 phase II, one-arm trials of neoadjuvant chemoradiotherapy for non-small-cell lung cancer

Study (reference)	Stage IIIA/IIIB (%)	Patient's number	CXT	RT (Gy)	Resection rate (%)	Operative mortality (%)	pCR (%)	Median survival (months)	3-y survival (%)	5-y survival (%)
Albain *et al*. (21)	60/40	126	[1]	Conc 45	80–85	7	21	13–17	24–27	NR
Ichinose *et al*. (22)	0/100	27	[2]	Conc 40	93	4	19	NR	56	NR
Edelman *et al*. (23)	70/30	47	[3]	Conc HF 69.6	62	0	28	29.6	64	NR
D'Angellilo *et al*. (24)	58/42	50	[4]	Conc 50.4	82	8	26	21.8	40.2	NR
Stupp *et al*. (25)	0/100	46	[5]	Sequ AF 44	76	6	13	29	47	40
Friedel *et al*. (26)	25/75	120	[6]	Conc AF 45	75	5	NR	19	NR	21.7
Eberhardt *et al*. (27)	39/61	64	[7]	Conc AF 45	89		44			26 (10 year)

CXT, types of chemotherapy: (I) cisplatin plus etoposide; (II) cisplatine plus tegafur; (III) carboplatin plus vinorelbine; (IV) cisplatin and gemcitabine; (V) cisplatin plus docetaxel; (VI) carboplatin and docetaxel; (VII) cisplatin and paclitaxel; and (VIII) cisplatin and etoposide. RT, radiotherapy schedules; Conc, concomitant chemoradiotherapy; Sequ, sequential chemoradiotherapy; HF, hyperfractionated radiotherapy; AF, accelerated fractionation radiotherapy; pCR, complete pathologic response; NR, not reported.

mixture of stage IIIA and IIIB, whereas 2 have included stage IIIB only (22,25). In all studies, chemotherapy consisted of cisplatin doublets or carboplatin doublets. All trials but one (25) included a concomitant chemoradiotherapy regimen, and radiotherapy schedules delivered doses between 40 and 50.4 Gy, except for one in which a hyperfractionated scheme of 69.6 Gy was administered (23). Surgical results showed a resectability rate between 62% and 93%, with a post-operative mortality between 0% and 8%. pCR, looking at the surgical specimen of the primary tumor, was reported to be between 13% and 44%. Median survival was between 13 and 29.6 months, and 3-year survival between 24% and 64%. When overall survivals of stage IIIA and IIIB were compared, there was no difference (21,26). This most likely reflected a favorable selection of operable stage IIIB patients, but at the same time it indicated that at least a subset of stage IIIB patients could benefit from neoadjuvant chemoradiation (21,22,25,26). Finally, when reported, there was a strong correlation between complete resection (R0) and survival (25,26), mediastinal clearing and survival (21,24,25), and pCR and survival (24,25).

Surrogates for survival

From a number of retrospective studies and prospective phase II studies mentioned above, it appears thus than pCR, mediastinal downstaging or clearing, and R0 resection were associated with an improved survival. It should be reminded that after neoadjuvant chemotherapy alone, pCR was between 6% and 10% only in stage III, whereas it was between 16% and up to 40% in retrospective neo-adjuvant chemoradiation studies, and between 13% and 44% in phase II prospective neoadjuvant chemoradiation trials. Radiotherapy has not only the potential to improve pCR of the primary tumor, but to increase mediastinal clearing in case of N2 disease and to ameliorate the R0 resection rate. Yet its impact on survival would have to be demonstrated by phase III randomized trials only.

Neoadjuvant radiochemotherapy in LA NSCLC: prospective randomized trials

Neo-adjuvant chemoradiation followed by surgery versus neo-adjuvant chemotherapy followed by surgery and post-operative radiotherapy: the German phase III randomized German Lung Cancer Cooperative Group (GLCCG) trial (28)

The GLCCG in a large phase III trial has randomized 558 patients with stage IIIA and IIIB NSCLC into two treatment groups (28). The intervention group received three cycles of cisplatin and etoposide, followed by twice daily radiation to 45 Gy and concurrent carboplatin and vindesine, followed by surgical resection. The control group received three cycles of cisplatin and etoposide, followed by surgery, followed by postoperative radiotherapy to 54–68 Gy. Primary endpoint was progression-free survival and secondary endpoints were overall survival and resectability. Results showed no significant difference in progression-free survival (37% *vs.* 33%) and no difference in overall survival

(39% *vs*. 31%) between the two groups (28). However the group with preoperative chemoradiation showed a better pathological response, defined here as >90% tumor clearing, with 60% *vs*. 20% (P=0.0001), and a better mediastinal downstaging, with 46% *vs*. 29% (P=0.002), with no difference in the occurence of treatment-related deaths (6.4% *vs*. 5.7%) (28).

Thus, this important trial could clearly demonstrate a greater local efficacy of chemoradiation compared to chemotherapy alone, but there was no impact on progression-free survival and overall survival. It may be that in the control group (neo-adjuvant chemotherapy alone), the systematic use post-operative radiotherapy may have «blurred» the impact of neo-adjuvant radiotherapy of the other arm. In any case, and unfortunately, this trial did not answer the question whether the addition of radiotherapy to chemotherapy in the neo-adjuvant setting improves or not the overall outcome.

Neo-adjuvant chemoradiation followed by surgery versus neo-adjuvant chemotherapy: phase II randomized (29) and incomplete phase III randomized trials (30)

A French phase II randomized study on 47 patients with stage IIIA N2 NSCLC aimed at comparing standard induction chemotherapy (arm A: cisplatin and gemcitabine), with 2 different induction chemoradiation regimens (arm B: cisplatin and vinorelbine) and radiotherapy dose: 46 Gy, arm C: carboplatin and paclitaxel and radiotherapy dose 46 Gy (29). Response rate was higher in the 2 chemoradiation arms compared to the chemotherapy only arm (87% *vs*. 57%, P=0.049). Feasibility rate was the same in the 3 arms, the overall survival for the entire cohort was 43% at 3 years, with no difference between the 3 arms (29). Neither the study design nor the small number of patients could allow to evaluate a possible difference in overall survival.

A Japanese phase III randomized trial for stage IIIA N2 NSCLC was sought to ascertain whether induction concurrent chemoradiation followed by surgery could improve survival compared to induction chemotherapy followed by surgery (30). Patients received either carboplatin and docetaxel plus concurrent radiation therapy to 40 Gy followed by surgery, or induction chemotherapy alone followed by surgery (30). The study had to be stopped because of slow accrual, but 60 patients could finally be randomized. Treatments were well tolerated and there was no toxic deaths. Combined chemoradiation conferred a better local control, however there was no differences in progression-free survival or overall survival when radiotherapy was added to chemotherapy (30).

Thus these two small randomized trials showed clearly a greater measurable therapeutic effect of neoadjuvant chemoradiation compared to adjuvant chemotherapy alone, but were unable to demonstrate any impact on progression-free survival or overall survival, and this was, possibly in part, due to the small numbers of patients.

Neo-adjuvant chemoradiation followed by surgery versus neo-adjuvant chemotherapy: the Swiss phase III randomized SAKK trial (31)

The Swiss cooperative group, the SAKK, in a phase III randomized trial has enrolled 232 patients with stage IIIA N2 NSCLC into two treatment groups (31). At this time, it is the only fully completed phase III randomized trial with this design. The radiochemotherapy group (117 patients) received three cycles of neoadjuvant cisplatin and docetaxel, followed by radiotherapy with 44 Gy in 22 fractions over 3 weeks. The control group (115 patients) received the same chemotherapy alone, and all patients were scheduled to undergo surgery. Primary endpoint was event-free survival. Overall tumor response rate was 61% after chemoradiation, *vs*. 44% after chemotherapy alone (P=0.012). Overall, chemotherapy-related effects were moderate and similar in the two groups, and radiotherapy-related toxic effects were also moderate with 9 grade 3 events (31). Eighty five percent in the chemoradiotherapy group and 82% in the chemotherapy group underwent surgery. A R0 resection was performed in 91% and 81%, respectively (P=0.06). In the 30 days after surgery, 3 patients in the chemotherapy group died, compared with none in the chemoradiotherapy group. Nodal downstaging (to N1 or N0) was observed in 64% and 53%, respectively, and the pCR in 16% and 12%, respectively in the chemoradiation group and chemotherapy only group (P= NS). The first event was death in 13% patients in the chemoradiation group *vs*. 8% in the chemotherapy group, and was local progression in 15% and 28%, respectively. The median event-free survival was 12.8 months in the chemoradiotherapy group and 11.6 months in the chemotherapy group (P=0.67). Median overall survival was 37.1 months in the chemoradiotherapy group, and 26.2 months in the chemotherapy group, but survivals at 2, 3 and 4 years were identical in the 2 treatment arms (31).

Thus, this study showed that patients who received chemoradiotherapy before surgery had an objective

response, a pCR, a R0 resection rate and a mediastinal downstaging more frequently and less local progression than patients in the chemotherapy alone group. In spite of all of these, the addition of radiotherapy did neither improve event-free survival (the primary endpoint) nor overall survival (31). The reasons for this may have been due to several factors. Firstly radiotherapy was given sequentially to chemotherapy, and not concomitantly, whereas concomitant chemoradiation was shown in the NSCLC Collaborative Group meta-analysis to be superior to sequential schedules in LA disease (32). Secondly the radiotherapy dose (44 Gy), although given in a slightly accelerated schedule (equivalent to 48–50 Gy in conventional daily fractions of 2 Gy), may have been insufficient. These two factors may explain a pCR of 16%, which is inferior to the pCR rates observed in retrospective data and in phase II trials using concomitant schedules and/or higher RT doses (see *Table 1*). Other factors, including the high distant failure rates in both arms (37% and 33% rates of first relapse), the patients' selection and the relatively small number of patients may have contributed. On the other hand, the addition of radiotherapy was well tolerated and did neither increase hematological toxicity nor post-operative mortality, which were altogether low in this trial.

Discussion

Although results from retrospective data and from phase II trials have suggested that the addition of neo-adjuvant radiotherapy to chemotherapy could improve the outcome of operable stage III NSCLC, none of the small randomized trials, including the recent SAKK trial could demonstrate any advantage in event-free, progression-free or overall survival (29-31). Does it mean that radiotherapy should be banned from the adjuvant setting in the future? At the present time, different opinions prevail:

(I) Pless *et al*. in the conclusion of their SAKK trial, have argued that in stage III NSCLC, three modalities are not superior to two modalities, and that one local treatment may be enough (31). The main reasons were that on one hand, neoadjuvant chemotherapy alone gave similar results as neoadjuvant chemoradiation in the three published randomized trials (29-31), and that on the other hand three other large randomized trials have shown that after neoadjuvant chemotherapy, either high-dose radiotherapy alone or surgery alone were equivalent in terms of overall survival (33-35);

(II) Eberhardt and Stuschke in an editorial commenting the results of the SAKK trial, consider that for most patients, the combination of chemotherapy and concurrent radiotherapy represents an acceptable standard (2). One of their arguments is based on their own data on intensive neoadjuvant concurrent chemoradiotherapy in which they found fairly high rates of pCR, between 30% and 40% (27,35), which were substantially higher than the 16% pCR of the SAKK study (31). They also stress that stage III disease is heterogeneous in terms of tumor volume and bulk, lymphogenic spread and co-morbidity (2). Thus, different subgroups of stage III may deserve different strategies, and personalized treatments based on co-morbidities might be a better solution (2).

Indeed, as almost all studies have shown better results with chemoradiation concerning response rate, pathological response, mediastinal clearing and local control of the disease, all of which being potential surrogates for survival, it seems justified to pursue the study of the role of concomitant chemoradiotherapy in the neoadjuvant setting, however only under certain conditions.

(I) Better selection of patients: one should first identify subgroups of operable stage III NSCLC who probably do not need additional RT, for example stage IIIA with minimal N2 disease, and exclude this group from radiochemotherapy trials. New trials should then be dedicated to subgroups with a higher risk of local failure, such as stage III-N2 bulky disease, stage IIIB, and superior sulcus tumors. In the latter situation in particular, neoadjuvant chemoradiation gave excellent results in phase 2 studies (36,37);

(II) Better radiotherapy: new trials should include innovative, high-technology radiotherapy capable of delivering safely high doses of radiation, concomitantly (and not sequentially) to chemotherapy. Techniques using intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) (17), and/or adaptive radiotherapy would be essential, and schedules like accelerated fractionation (26,27), concomitant boost (35), dose-escalation or hypofractionated schemes should be worth studying;

(III) Better systemic treatments in combination with radiotherapy: it should be remembered that current "standard" cisplatin doublets have their limitations. The pCR and local control with currently available

chemotherapy alone is low, and the rate of distant failures is still high (vide supra), indicating a limited efficacy even on microscopic disease.

In conclusion, neoadjuvant chemoradiotherapy for stage III NSCLC is safe and efficient, with higher overall clinical response, higher pCR rates and a higher mediastinal clearing compared to neoadjuvant chemotherapy alone. Contrary to previous fears, radiotherapy does not add a higher toxicity nor does it increase post-operative mortality compared to chemotherapy alone. Numerous phase II trials have shown encouraging survival rates, up to 30–40% at 5 years. On the other hand, the yet available randomized studies have failed to demonstrate any advantage of adding radiotherapy in the neoadjuvant setting regarding progression-free survival or overall survival. Admittedly the number of patients enrolled was modest. Still the controversy is not being solved and further trials taking into account a better patients' selection, innovative radiotherapy and more efficient systemic treatments need to be undertaken.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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