Candidates for surgery in the combined modality therapy of stage III non-small cell lung cancer

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Introduction

The role for surgery in combined modality treatment for stage III non-small cell lung cancer (NSCLC) is controversial. Until recently, mature results from phase III trials were not available, so treatment decisions were informed by many phase II trials plus the early results of Intergroup trial 0139 [1]. In addition, outcomes across phase II trials were often difficult to interpret because of variable sub-stage mix and inconsistent use of pathological documentation of T4, N2 or N3 disease. Determination of which patients with stage IIIA(N2) or selected IIIB disease qualified for trials on the basis of presence of ' potentially resectable' disease was difficult to standardise. The studies also varied regarding accrual of clearly unresectable tumours versus those that might be technically resectable prior to induction therapy (or a mix). This review will consider whether 2005 updates of phase II and III [2–7] studies provide new evidence to guide practice decisions on the application of a surgical resection in stage III disease. The reader is also referred to a more comprehensive recent review on this subject [8]. Superior sulcus tumours, for which most agree that trimodality therapy is standard of care, will not be addressed in this discussion.

This report considers patients with stage III NSCLC for whom the standard treatment recommendation is chemoradiotherapy. It will not consider those with ' minimal' N2 disease or earlier stage tumours for whom upfront surgical resection is an acceptable approach. Patients with low volume or microscopic mediastinal nodal involvement have a 5-year survival of 25–40% when treated with surgical resection alone, whereas the same treatment in patients with macroscopic N2 metastases results in less than 10% 5-year survival [9–11]. Similarly, survival within the stage IIIB category (T4 and/or N3) is heterogeneous, dependent upon the substage and tumour volume, so selected IIIB subsets will also be discussed. For all these scenarios with high tumour and/or mediastinal or supraclavicular disease volume, initial surgical resection even if technically feasible initially would not offer a survival advantage. However, it is possible that surgical resection might improve on the potential for longer survival and cure when it is employed following chemotherapy or chemoradiotherapy. Which patients might be appropriate for this approach will be discussed based on available literature.

Induction chemotherapy followed by resection

The use of chemotherapy alone followed by surgical resection has been studied in a large number of phase II trials with encouraging results, but the majority of these studies involved patients with minimal N2 disease, for whom initial surgical resection would also have been an option [2,8]. That is, patients with ' higher volume' stage III disease were rarely selected for an approach that did not employ chemoradiation. Several of these phase II studies in lower volume disease either allowed or mandated postoperative radiotherapy. Thus, there are no phase III trials in advanced stage III NSCLC using chemotherapy followed by surgery versus chemotherapy alone, since the latter is not standard treatment.

Furthermore, several phase II trials in which either higher volume clinical N2 disease or pN2 disease was treated with induction chemotherapy alone followed by surgery demonstrated sub-optimal resection rates [2, 12–15]; and, in the study of DePierre and colleagues, the subset of patients with clinically evident N2 disease (not confirmed pathologically) treated with pre-operative chemotherapy followed by surgery did not have survival superior to those who had a surgical resection alone [16]. An exception may be the trial of Betticher and colleagues for the Swiss Group for Clinical Cancer Research (SAKK) [2,12]. Ninety potentially operable patients with stage IIIApN2 disease received 3 cycles of cisplatin 40 mg/m^2 on

day 1–2 plus docetaxel 85 mg/m^2 on day 1, followed by surgical resection. Postoperative radiotherapy to 60 Gy was administered for positive resection margins or involvement of the uppermost mediastinal lymph node. Seventy-five patients (83%) underwent resection. The overall response rate was 66%, with 19% pathological complete responses. The median survival was 27.6 months and the 3-year survival was 33%. Mediastinal nodal clearance and complete surgical resection were strong independent predictors of increased survival in a multivariate analysis.

The European Organisation for Research and Treatment of Cancer (EORTC) (trial 8941) completed the only phase III trial reported to date for patients with higher volume, stage III(pN2) disease for whom the control arm of chemotherapy followed by radiotherapy was considered standard [5,7]. The experimental arm tested induction chemotherapy followed by surgery. The tumours were considered unresectable by the local surgeon, although it is not clear whether this designation was always due to anatomical reasons, or perhaps simply due to the presence of N2 nodes. After three cycles of carboplatin- or cisplatin-based chemotherapy were given (specific regimen was choice of physician), those patients with no response or progression were taken off study. Patients with an objective response were randomised to surgical resection or to radiotherapy with 60 Gy (2 Gy/fraction/d). However, radiotherapy was also given postoperatively (PORT) for incomplete (non-R0) resections.

The study had a unique design in that randomisation did not occur upfront at registration. Therefore, the role of surgery was not being tested on an intent-to-treat basis against radiotherapy for all eligible patients. Instead, only those with a response were continued on to the test of surgery versus radiation. Furthermore, due to the use of PORT for R1/R2 resections in the surgical arm, this is not a completely pure test of the surgery versus radiotherapy question. The results are summarised in Table 1 [5,7]. Forty percent of patients in the surgical arm received PORT. There was no difference in progression-free or overall survival. The complete resection rate was 50%, with 5% pathological complete remissions. In a subset analysis on the surgical arm, 5-year survival was longer if nodal downstaging to N0 (29%) versus not (7%) and if a lobectomy was done (27%) versus pneumonectomy (12%) [7].

From the EORTC study plus the phase II data reviewed above, it is clear that induction chemotherapy alone followed by surgery for unresectable or high volume stage III disease should not be recommended as standard of care. By extrapolation from the bimodality trials without surgery, since concurrent chemoradiation is superior to short course induction chemotherapy followed by radiotherapy [8,17], treatment according to either arm of the EORTC phase III study perhaps now may be considered sub-optimal.

Table 1
EORTC phase III trial 8947 in stage IIIpN2 non-small cell lung cancer[a]

Variable	CT×3 → RT	CT×3 → Surgery (±PORT)
Number randomised (of 579 registered)	165	167
Median follow-up (months)	73.1	67.2
Postoperative radiotherapy	NA	40%
Complete resection	NA	50%
Median PFS (months)	11.3	9.0
Median survival (months)[b]	17.5	16.4
2-year survival	40.7%	34.7%
5-year survival	14.0%	15.7%
lobectomy	–	27%
pneumonectomy	–	12%
downstage to N0	–	29%
PORT: no versus yes	–	19%, 13%

[a] van Meerbeeck and colleagues [5,7].
CT, chemotherapy; RT, radiotherapy; PFS, progression-free survival; PORT, postoperative radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer.
[b] Hazard ratio 1.06 (0.84, 1.35).

Induction chemoradiotherapy followed by surgery

Generally, phase II trials of trimodality therapy for stage III disease were conducted in patients with higher volume local disease for whom chemoradiotherapy was standard of care, preferably given concurrently [8,17]. This approach was feasible and provided encouraging survival outcomes. In fact, long-term survival is possible for some of these patients [3,18], including the IIIB subset of T4N0/1 [8,17]. However, given the strict selection criteria employed in the phase II studies of trimodality therapy, the precise contribution of the surgical modality cannot be clearly ascertained (except perhaps for T4N0/1 disease) apart from a phase III trial.

The North American Intergroup 0139 trial is the first phase III study reported to date that prospectively addressed this question [1]. Eligible patients had T1–3pN2 disease that was potentially resectable, had appropriate lung function, and were medically fit. All patients received concurrent chemoradiation to 45 Gy

with cisplatin 50 mg/m^2 d 1, 8, 29, 35 and etoposide 50 mg/m^2 d 1–5, 29–33. If there was no progression at re-evaluation following induction, one arm underwent surgical resection with mediastinal nodal sampling and the other arm completed (uninterrupted) radiotherapy to 61 Gy. Both groups received consolidation chemotherapy with two cycles of cisplatin and etoposide.

Intergroup 0139 closed to accrual with 429 patients in 2001. The first interim analysis was presented at the 2003 ASCO meeting [1]. Two updates were provided recently, one of overall survival [4] with a median follow-up of 81 months, and the other of surgical issues [6]. Outcomes are summarised in Table 2 for the 396 eligible patients. For the group assigned to surgical resection, thoracotomy was performed in 81%, and in 71% the resection was complete. Pathological complete response occurred in 18% and mediastinal nodal clearance was noted in 46%. The rate of grade 3 or 4 oesophagitis was significantly higher in the chemoradiation-alone arm (23% versus 10%). The treatment-related mortality was higher in the surgery arm, with 16 deaths (7.9%), versus 4 deaths (2.1%) in the chemoradiation group. Most postoperative deaths were due to adult respiratory distress syndrome (ARDS). Fourteen (26%) patients with pneumonectomy died, after 29% right simple, 50% right complex and 16% left complex pneumonectomies. Eleven of these were due to ARDS or respiratory cause. Many of the pneumonectomies were done in patients with minimal or no residual tumour [6].

Table 2
North American Intergroup phase III trial 0139 (R9309)[a] in stage IIIpN2 non-small cell lung cancer

Variable	CT×2+RT → RT → CT×2	CT+RT → S → CT×2
Number eligible randomised	194	202
Median follow-up (months)	81	81
Complete resection	NA	71%
Completed consolidation CT	75%	56%
RT according to protocol	79%	96%
Pathology		
pCR (T0N0)	–	15%
pN0	–	46%
pN1–3	–	54%
Median PFS (months)	10.5	12.8
Median OS (months)		
Matched pneumonectomy	–	29, 19 (CT/RT better)
Matched lobectomy	–	22, 34 (S better)
5-year PFS	11%	22%
5-year OS	20%	27%

[a] Albain and colleagues [4]; Rusch and colleagues [6].
CT, chemotherapy; RT, radiotherapy; S, surgery; pCR, pathological complete response; PFS, progression-free survival; OS, overall survival.

Progression-free survival was significantly prolonged in the surgery arm (12.8 versus 10.5 months, $P = 0.017$), but overall survival did not differ (23.6 versus 22.2 months) [4]. Eight percent more patients in the chemoradiation-surgery arm died without disease progression, but 10% more patients on this arm achieved long-term survival ($P = 0.008$). The overall survival curves crossed in year 2 of follow-up and began to separate, such that the 5-year overall survival was 7% better for the surgery arm (27% versus 20%), odds ratio 0.63 ($P = 0.10$). N0 status predicted the best median and 5-year survivals of 34 months and 41% in the surgery arm, compared with 8 months and 8% in the group who did not undergo resection in the surgery arm and 26 months and 24% for those with residual nodal disease ($P = 0.0001$).

An exploratory analysis was conducted that matched patients in the surgical arm who had a lobectomy or a pneumonectomy to those with similar characteristics on the non-surgical arm [4]. Survival was much better for the trimodality arm if lobectomy (medians 34 versus 22 months and 5-year 36% versus 18%, $P = 0.002$) but reversed if pneumonectomy (trimodality with pneumonectomy worse than CT/radiotherapy arm, medians 19 versus 29 months).

Perspectives on selection of candidates for surgical resection

Based on all these data, can a surgical resection be recommended for any patient with stage III disease (apart from the special group with T4N0/1 or Pancoast presentations)? Table 3 provides a comparison of several major aspects of the two phase III trials. Induction chemotherapy followed by surgery (and variable PORT) yielded disappointing results in a group of patients with advanced local disease, so concurrent chemoradiotherapy without surgery would seem to be the standard choice for this group. However, based on the Intergroup trial results, if a lobectomy can be performed, concurrent chemoradiotherapy followed by surgical resection using the regimen tested in this study is also a valid and possibly preferable option. This is with the caveat that the patient must meet the strict selection criteria of the trial and be treated by a multidisciplinary team experienced in this approach. The application of surgery in stage III disease should not be done outside

Table 3
Comparison of the two phase III trials for stage IIIpN2 NSCLC: EORTC 8941 and INT0139 (R9309)[a]

Trial characteristic	EORTC	Intergroup
Patient population	T1–3 pN2	T1–3 pN2
Surgical pre-study assessment	Pre-registration ' unresectable'	Pre-registration ' potentially resectable'
Randomisation	Only after response to induction	Upfront; all CR, PR and SD resected
Chemotherapy		
Full dose	Yes	Yes
Number of cycles	3	4
Cisplatin to all	No	Yes
Pneumonectomy	47%	26%
Complete resection	50%	71%
Surgical arm mortality	4%	8%
pCR	5%	15%
Downstaged to N0	NA	46%
PFS benefit	No	Yes
OS benefit	No	No
Subset analyses	Lobectomy longer 5-year survival than pneumonectomy	OS significantly better if lobectomy versus matched cohort CT/RT

[a] CR, complete response; PR, partial response; SD, stable disease; pCR, pathological complete response; PFS, progression-free survival; OS, overall survival; CT, chemotherapy; RT, radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer.

the context of the eligibility criteria for these trials. That is, the patients had excellent performance status, lacked major co-morbidities and had good pulmonary function. Surgical resection after chemoradiation if a pneumonectomy is needed is a questionable approach. If considered, it should be done only with great caution and informed consent and only in a very fit patient by a highly experienced surgical team.

The two trials used very different criteria for entry and resection. The EORTC surgeons referred patients with ' irresectable' (unresectable) disease, whereas the Intergroup surgeons enrolled ' potentially resectable' tumours; and in both of these trials, the control arm was either concurrent or sequential chemoradiotherapy alone. Thus, the entry criteria regarding the degree of advanced stage III disease may in fact not have been that much different. However, the EORTC trial tested the role for surgery only in patients who achieved a radiographic response to chemotherapy, and thus excluded a large number of registered patients from the randomisation; whereas, the Intergroup trial randomised patients upfront and mandated resection of radiographically stable disease (many of whom had significant pathological downstaging). Therefore, the achievement of a clinical response should not be used as sole criteria for selecting patients for surgery.

A common interpretation of the results of both trials is that downstaging to N0 yielded the best long-term survival, and only those patients should be selected to undergo surgical resection. Since the survival in the Intergroup trial was also quite good in those with residual nodal disease, a benefit to the surgical resection in this group cannot be ruled out. Results in the surgical arm of the EORTC trial are confounded by the use of PORT, which in previous reports may adversely impact survival.

Conclusion

In conclusion, these two large phase III trials provide some direction to the practising clinician who is regularly faced with treatment decisions for the patient with advanced, high-volume stage III NSCLC. Concurrent chemoradiotherapy should be considered standard in this subset, with one exception: if a lobectomy can be performed, this appears to be a reasonable option following concurrent chemoradiotherapy. Extrapolation of this recommendation to chemoradiotherapy regimens not tested in these trials should not be done, since many of these regimens do not employ full-dose chemotherapy with radiotherapy, or only prescribe two cycles of chemotherapy. Overall, the role of surgery should be reserved for selected patients and following the guidelines of the phase III trials.

Conflict of interest statement

None declared.

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