

Chapter **3**

Evaluation of a treatment strategy for optimising preoperative chemoradiotherapy in stage III non-small-cell lung cancer

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Abstract

Objective: Concurrent chemoradiotherapy is standard of care in stage III non-small-cell lung cancer, although surgery may be beneficial in selected patients in whom induction therapy has achieved 'down-staging' of mediastinal nodal disease. Previous studies incorporated treatment 'splits' for re-evaluation, and such gaps lead to poorer survival in patients undergoing chemoradiotherapy. We describe the outcome of a treatment strategy to limit the duration of treatment splits.

Methods: A prospective database (2003-2007) of stage III non-small-cell lung cancer patients treated with concurrent chemoradiotherapy outwith clinical trials at our centre was reviewed. Preoperative chemoradiotherapy consisted of one induction course of cisplatin-gemcitabine, followed by two courses of cisplatin-etoposide with once-daily thoracic radiotherapy using four-dimensional involved-field treatment planning. After a dose of 46-50 Gy, potentially resectable patients without disease progression underwent immediate planned mediastinal re-staging and patients with persistent N2 disease or who were unfit for surgery continued to full-dose radiotherapy. Effort was made to shorten the treatment split by substituting mediastinoscopy for endoscopic procedures (transbronchial and -oesophageal).

Results: A total of 34 patients had potentially resectable disease at the start of treatment. Toxicity of chemoradiotherapy was predominantly leucocytopenia grade III/IV in 38% of courses and grade III oesophagitis in five patients (15%), but was manageable and reversible. After re-staging, 24 patients (71%) proceeded to surgery. A radical resection was achieved in 23 patients; nine had a complete pathological response. Re-staging was accurate with only one false-negative mediastinoscopy. One patient died 10 days after surgery. Median time from end of induction treatment to re-staging or surgery was 12 (range: 0-51 days) and 35 days (range: 18-63 days), respectively. Median survival for resected patients was not reached. Six patients had persisting N2 disease, of which two continued radiotherapy after a split of 3 and 4 days.

Conclusions: Image-guided, involved-field preoperative chemoradiotherapy can be performed with acceptable toxicity, and the present strategy achieves the goal of limiting splits in treatment delivery that may adversely affect survival in patients who do not undergo downstaging with induction therapy.

Introduction

Surgery after chemo(radio)therapy in unresectable stage III non-small-cell lung cancer (NSCLC) patients is still controversial [1]. The American College of Chest Physicians (ACCP) guidelines recommend chemoradiotherapy (CRT) as the standard treatment for most stage III NSCLC patients [2,3], although subgroups may benefit from additional surgery [4]. Two recent large phase III trials have investigated the role of local therapy in stage IIIA (pN2) NSCLC. The EORTC 08941 study compared resection with radiotherapy after a response to induction chemotherapy [5], and the North American Intergroup 0139 trial compared surgery after CRT with CRT alone [6]. Both studies showed no significant survival benefit for patients in the surgery arm (median: 16.4 and 23.2 months, respectively) versus CRT (median: 17.5 and 23.6 months, respectively). However, patients with a complete resection and mediastinal clearance (N0) after surgery did have statistically significant better outcomes. In both the phase III studies, a major drawback of the design was that the treatment 'splits' introduced for re-evaluation led to a delayed completion of CRT in patients. Non-down-staged patients constituted the majority of patients, and splits in delivery of full-dose standard CRT can lead to inferior survival [7]. In addition these randomised studies were performed using elective nodal irradiation and predominantly two-dimensional radiotherapy techniques, both of which can lead to suboptimal target coverage [8] and increased toxicity [9]. Recent advances in radiotherapy planning and delivery have the potential to reduce the risks of toxicity, including postoperative lung toxicity [10]. Strategies to optimise the role of surgery in stage III NSCLC require good patient selection, image-guided radiotherapy and appropriately timed mediastinal re-staging is important in identifying patients who may benefit from surgery. We report our experience with such a strategy.

Patients and methods

Patient selection and staging

A prospective database including all patients treated with concurrent CRT at our centre was reviewed. The first patient started CRT in October 2003, and the cut-off date chosen for this analysis was 1 May 2007 (n = 67). All cases were initially discussed at multidisciplinary meetings. The multidisciplinary team comprised lung physicians, thoracic surgeons, medical

oncologists, radiation oncologists and (nuclear) radiologists. Prior to treatment initiation, potential resectability was evaluated in all the patients. Patients with stage III NSCLC and the Eastern Cooperative Oncology Group Performance Status (PS) 0-2 were eligible for CRT if they had adequate haematological, renal and hepatic functions, and sufficient pulmonary function according to the Dutch practice guidelines (<http://www.cbo.nl/product/richtlijnen/folder20021023121843/longc-ri-2004.pdf>). Patients previously treated for NSCLC were given definite CRT, and patients in whom a pneumonectomy was likely were excluded. Staging methods included physical examination, chest X-ray, computer tomography (CT) of thorax and upper abdomen and whole-body fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Endoscopic transoesophageal ultrasound (US) with fine-needle aspiration (EUS-FNA), endoscopic transbronchial FNA (TBNA) and transthoracic US-guided FNA or biopsy were initially used to obtain pathological proof of NSCLC (and N2/N3 disease), before using mediastinoscopy or even thoracotomy.

Chemoradiotherapy treatment

Chemotherapy

After pre-treatment evaluation by both a lung physician and a radiation oncologist, treatment was initiated, consisting of one course of cisplatin 80 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8. Subsequently, cisplatin 80 mg/m² (days 21 and 42) and etoposide 100 mg/m² (days 21-23 and 42-44) were administered. All chemotherapy agents were administered as an intravenous infusion. Anti-emetics used on a regular basis included aprepitant, ondansetron HCL and dexamethasone.

Radiotherapy

Thoracic radiotherapy was started concurrently with cisplatin and etoposide on day 22, 5 days per week for 5 weeks. All patients underwent a CT-thorax for planning purposes; planning was based on conventional 3D-CT until 2003, after which a 4D-CT scan was introduced, during which spatial and temporal information on organ mobility are generated by scanning while synchronously recording respiration waveforms [11]. The gross tumour volume (GTV) was identified using pre-treatment investigations, and involved-field radiotherapy (IF-RT) was exclusively used. IF-RT describes the treatment for primary tumour and regional lymph nodes with metastatic disease. This contrasts with elective nodal

irradiation, which is an approach of routinely including all regional nodes in the radiation field. IF-RT is currently recommended as this approach reduces the incidence of radiation oesophagitis and lung toxicity [9,12]. Treatment plans were generated using Eclipse (Varian Med. Systems, Palo Alto, CA, USA) and generally consisted of two to six fields using 6- and/or 15-MV photons. All the initial treatment plans aimed at achieving the ICRU objectives [13] by having the 95% isodose volume (at a minimum) conform as accurately as possible to the planned tumour volume (PTV), while respecting dose constraints to organs at risk. Specifically, the percentage volume of lung tissue outside the PTV planned to receive 20 Gy was limited to 42% ($V_{20} \leq 42\%$), and the maximum spinal cord dose was limited to 50 Gy. Maximum effort was made to spare the contralateral lung. Radiotherapy was delivered on a Varian 2300 C/D linear accelerator to doses varying between 46 and 60 Gy in daily fractions of 2.0 Gy. Respiration-gated radiotherapy was performed for all patients in whom tumour motion exceeded 7.5 mm [11]. Gating is of greatest benefit for mobile tumours as limiting irradiation to pre-selected phases of the respiratory cycle can minimise the volume of irradiated pulmonary tissue [14].

Toxicity

Toxicity was measured according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system v3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf). Of special interest for non-haematologic toxicity were oesophagitis \geq grade III and radiation pneumonitis \geq grade II. In case of insufficient bone marrow recovery and/or any toxicity grade III other than nausea/vomiting, alopecia or oesophagitis, the next chemotherapy course was delayed until the toxicity was resolved, or was no longer clinically significant. During this period, radiotherapy was not interrupted. In case of more than 2 weeks' delay, further induction chemotherapy stopped but radiotherapy continued. If serum creatinine clearance fell below 60 ml/min (using the Cockcroft-Gault formula) during treatment or had been marginal at the start of the treatment, cisplatin was substituted by carboplatin.

Response measurement, re-staging and surgery

During CRT, the best radiological response was measured according to the response evaluation criteria in solid tumours (RECIST) [15]. Potentially resectable patients without progression of disease, technically resectable primary tumour (no pneumonectomy) and good performance status were re-staged immediately after 46-50 Gy with mediastinal

re-staging procedures, consisting of EBUS, EUS-FNA and mediastinoscopy. Repeat mediastinoscopies were avoided by substituting for EUS-FNA or TBNA, and the latter two procedures were also used when suspicion for persisting N2 disease was high. In our hands, TBNA has been shown to be a reliable technique [16], which, together with EUS-FNA, permits a rapid diagnosis and shortens a potential gap in the delivery of CRT. If no N2/N3 disease was found, patients underwent a resection of the primary tumour with mediastinal lymph node dissection. Where surgery was not an option, definitive radiotherapy delivery continued to a dose of up to 60 Gy when permitted by normal-tissue dose constraints.

Statistical analysis

The time to re-staging or surgery was defined as time from the last day of radiotherapy to the date of (first) re-staging procedure or thoracotomy, respectively. If an additional course of chemotherapy followed after completing radiotherapy, then the last day of preoperative treatment was day 1 of this fourth chemotherapy course. Survival was calculated from day 1 of the first course of chemotherapy (start treatment) until death or 1 February 2009 (date of last follow-up). Progression-free survival is defined as the period from the start of treatment to the date of disease progression, relapse or death. The Kaplan-Meier method was used to estimate the survival curve [17].

Results

Patient characteristics

Thirty-four patients were initially treated with the preoperative CRT scheme (potentially resectable); all but one had pathologically proven NSCLC. Mediastinal lymph node involvement was present in 21 and pathologically proven in 14 (67%) patients. A cohort of 33 unresectable patients underwent definite CRT in the same period, including 14 with previously treated NSCLC, technically unresectable disease in nine patients and 10 patients who were medically unfit to undergo surgery. The clinical characteristics of all 67 patients are summarised in **Table 1**.

Table 1. Patient characteristics

Characteristic	Potentially resectable	Contemporary cohort of unresectable patients
Sex		
Male	19	22
Female	15	11
Age (year)		
Median	56 (range 39-76)	65 (range 42-79)
ECOG performance status		
0	10	10
1	23	21
2	1	2
Smoking status		
Smoker	19	16
Former smoker	13	16
Non-smoker	2	1
Histology		
Squamous	10	16
Adeno	13	6
Large cell	10	11
None	1	
Clinical stage		
IIIA	11	10
IIIB	23	9
Recurrent NSCLC		14
N2/N3-disease		
Total	21	26
Biopsy-proven	14 (67%)	18 (69%)
Resectability		
Potentially resectable	34	
Unresectable		23
Medically inoperable		10
Clinical response		
Partial response	29	20
Stable disease	4	7
Progressive disease	1	4
Not evaluable		2

Chemoradiotherapy

Thirty-one potentially resectable patients received at least three courses of chemotherapy (91%). Haematologic toxicity was evaluable for all 107 courses. Grade III/IV toxicities were reported in 44 courses (41%): grade III/IV anaemia in two courses (2%), grade III/IV thrombocytopenia in nine (8%) and grade III/IV leucocytopenia in 41 (38%). Only one patient had to be hospitalised for neutropenic fever. Red blood cell transfusions were given to five symptomatic patients. All 34 patients completed the planned radiotherapy scheme, including 11 who underwent respiration-gated treatment. Radiotherapy planning parameters are shown in **Table 2**. Five (15%) patients suffered from an acute oesophagitis grade III, requiring tube feeding. No life-threatening oesophagitis or clinically significant radiation pneumonitis was observed. Twenty-nine patients had an objective response after concurrent CRT, and four had stable disease.

Table 2. Radiotherapy parameters for potentially resectable patients

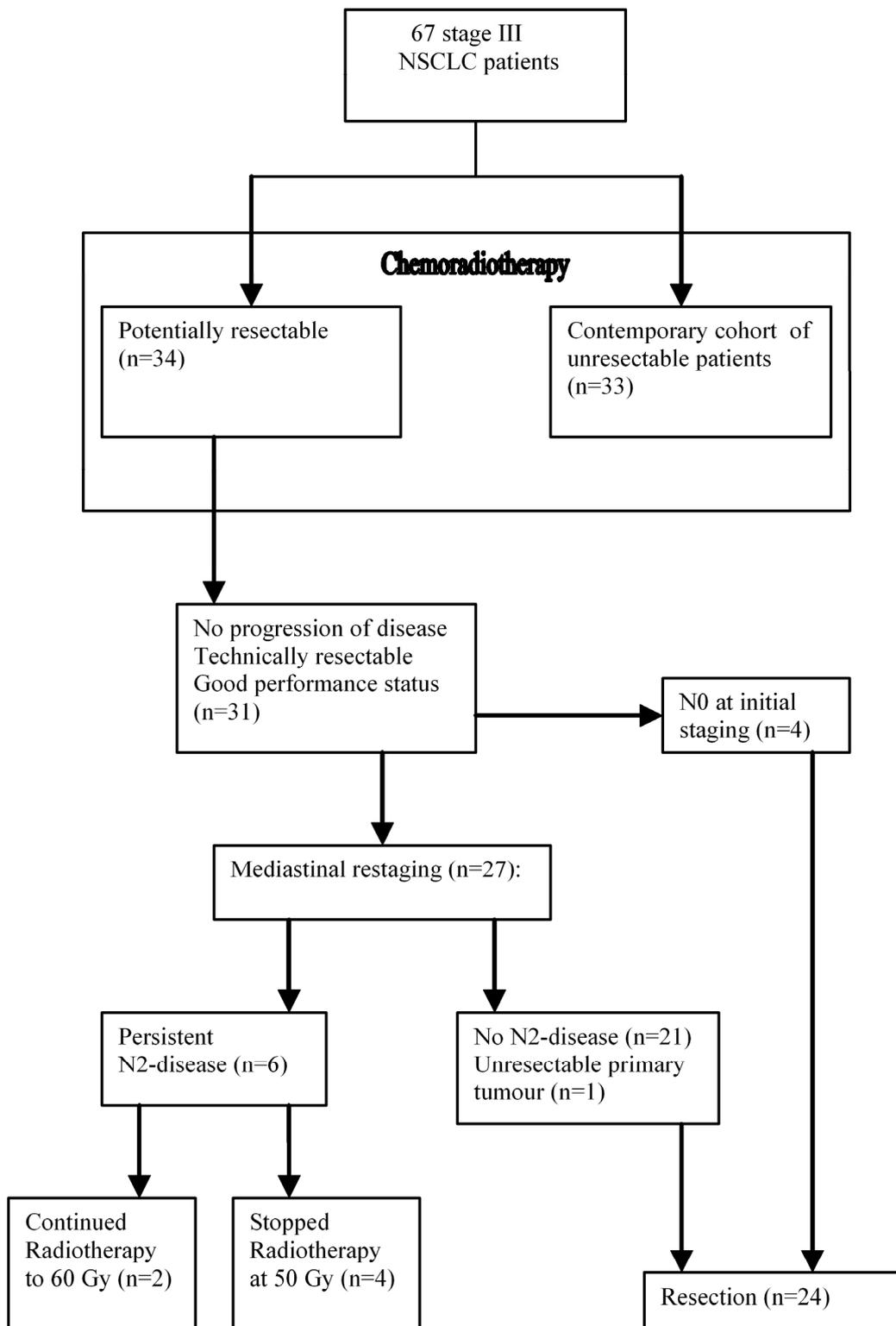
Characteristic	Result	Range	%
Delivery (patients)			
Finished treatment plan	34		100
Respiration-gated	11		32
Median dose			
Overall	50	(46-60)	
Dose to re-staging	50	(36-60)	
Radiotherapy planning parameters (median)			
Mean lung dose (Gy)	10.5	(1.2-19.6)	
Maximum dose to spinal cord (Gy)	48.2	(2-53.8)	
V ₂₀ (%)*	18.7	(1.8-34.8)	
V ₅ (%)*	36.2	(2.7-80.5)	
V ₅ contralateral lung (%)*	27.9	(0-87.7)	

* Percentage volume of lung tissue outside the planned tumour volume (PTV) receiving 20 Gy and 5 Gy, respectively.

Re-staging

After preoperative CRT, two patients were not re-staged because of progressive or unresectable disease, and one patient with a deterioration of PS declined re-staging after FDG-PET scan. Of the remaining 31 patients, 19 had N2/N3 disease at initial staging. Four patients proceeded immediately to surgery on the basis of a partial primary tumour response while no mediastinal lymph node involvement (N0) was present at initial staging. Finally, 27 patients underwent mediastinal re-staging procedure(s) after a median dose of 50 Gy (range: 36-60 Gy), with a median time to (first) procedure of 21 days (range: 0-51 days). Excluding three patients who underwent a fourth course of PE after finishing radiotherapy, median time to (first) re-staging procedure is 12 days (range: 0-51 days). Increased time to re-staging was observed for patients with acute oesophagitis grade III. The results of re-staging are summarised in **Table 3**. Of the 24 re-staging mediastinoscopies performed, three were re-mediastinoscopies, one parasternal, and four mediastinoscopies followed by EUS-(FNA) (three) or US-guided supraclavicular FNA (one). Re-staging resulted in 21 patients without evidence of N2/N3 disease, of whom 13 had N2/N3 disease at initial staging (eight pathologically proven). However, one of them still had a technically unresectable primary tumour. N2 disease was persistent for six patients, and two of them continued radiotherapy to 60 Gy after a split of 3 and 4 days between the cessation of preoperative treatment to recommencing radiotherapy. The other four patients had already received a dose of 50 Gy, and no further radiotherapy was delivered after re-staging as the spinal cord dose limit of 50 Gy would have otherwise been exceeded (**Figure 1**).

Figure 1. Treatment flow chart



Surgery

Finally, 24 patients (71%) were resectable, with a median time to surgery of 35 days (range: 18-63 days). The results are summarised in **Table 3**. The resections performed include lobectomy (n = 19), bilobectomy (n = 3), pneumonectomy (n = 1) and wedge resection (n = 1). One patient died 10 days after lobectomy due to respiratory insufficiency; the 90-day mortality rate was 8%. A radical resection was achieved in 23 patients, and microscopic residual disease was present in one. Pathological complete remission was observed in nine patients, 11 had mediastinal down-staging and persistent microscopic N2 disease was seen in one patient, who had a false-negative re-staging mediastinoscopy. Overall, 21 patients were staged pN0 after surgery.

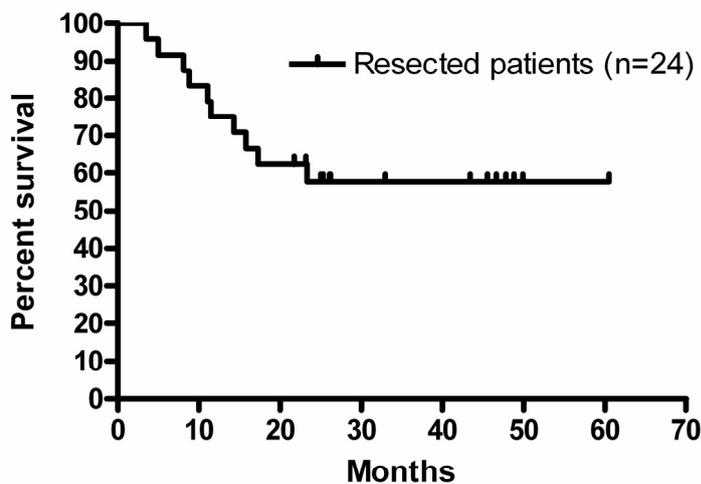
Table 3. Restaging procedures and surgery

Characteristic	No. of patients
Potentially resectable after CRT	31
Re-staging procedure(s)	27 (19 N2/N3 at initial staging)
N0 at initial staging	4
Re-staging procedure	
Mediastinoscopy	24 (including 3 repeat mediastinoscopies)
EUS-FNA	3
TBNA	3
Supraclavicular FNA	1
Results from re-staging	
No N2 disease	21
Persistent N2 disease	6
Unresectable primary tumour	1
Surgical procedure	
Lobectomy	19
Bilobectomy	3
Pneumonectomy	1
Wedge resection	1
Completeness of resection	
R0	23
R1	1
Pathological response	
Complete remission	9
T1-4 N0 M0	12
Tx N1 M0	2
T1 N2 M0	1

Survival

Survival analysis has been carried out at reference date 1 February 2009, after a median follow-up of 24.1 months. Median survival was not yet reached for resected patients (**Figure 2**), but progression-free survival was 21 months with distant failure in six patients, mainly brain metastases.

Figure 2. Survival curve



Discussion

In stage III NSCLC, the results of phase III trials suggest that surgery should not be carried out after induction therapy in patients who have persisting mediastinal nodal disease. The use of concurrent chemoradiotherapy increases the incidence of mediastinal down-staging, but concerns about the operative and postoperative toxicity has led to the use of radiation doses of around 46 Gy [6]. Consequently, re-staging has to be performed prior to the delivery of full-dose radiotherapy (generally 60-66 Gy), which requires fast and accurate mediastinal re-staging during treatment in order to permit ineligible patients to continue with full-dose CRT. The main findings of our analysis were the low toxicity observed when applying trimodality therapy using image-guided radiotherapy. In contrast to the previous studies where elective nodal irradiation was mandatory [5,6], our approach mandated the use of IF-RT, which allowed for smaller radiation fields [9,12], and care was taken to restrict radiation to the contralateral lung.

In addition, this strategy resulted in a mediastinal down-staging (from N2/N3 disease to N0/N1) in 63% of cases. The approach required a median time to re-staging of 12 days and was incorrect in only one patient.

Shortening the overall treatment times using this strategy can be challenging, as several departments are involved in such multimodality treatments. For example, response after induction treatment was only evaluated using CT scans in the EORTC 08941 trial, but the median time from the end of chemotherapy to surgery was 49 days [5]. As the preoperative doses of radiation were limited to 50 Gy or less, the finding that only 37.5% of resected patients had a pathological complete response was not surprising and comparable to that reported by others [6,18]. Other investigators had pursued an approach of using higher doses (60-70 Gy), followed by surgery in biopsy-proven, non-bulky stage IIIA-N2 NSCLC [19]. However, although uninterrupted CRT to full doses of 60 Gy or higher can avoid treatment gaps, a radical resection was only achieved in 28% of these carefully selected patients, with a pathological complete response in 30% of the latter. It should, however, be noted that these authors evaluated carboplatin combinations concurrent with chemotherapy, even though carboplatin as a single agent has not been shown in the previous trials to improve local control over that achieved using only radiotherapy [20,21]. The pattern of distant relapses, especially brain metastases, following CRT is also a topic of studies evaluating prophylactic cranial irradiation in this setting [22,23].

In conclusion, image-guided, involved-field preoperative CRT can be performed with acceptable toxicity and the present strategy achieves the goal of limiting splits in treatment delivery that may adversely affect survival in patients who do not undergo down-staging with induction therapy. Despite the fact that median survival was not reached in patients who proceeded to surgical resection, our study does not support a role for routine surgery in stage III NSCLC. However, the approach is a feasible design that minimises the adverse impact of delays in the delivery of full dose CRT in the majority of patients who will not achieve mediastinal down-staging. Only a new phase III trial that randomises down-staged patients to either surgery or full dose CRT will establish conclusively the role of trimodality treatment in stage III NSCLC.

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