CLINICAL FORUM

Morbidity and mortality in the surgery arm of EORTC 08941 trial

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ABSTRACT: Controversial results of surgical treatment after induction chemotherapy, especially in relation to the extent of resection, have previously been reported. Mortality and morbidity were studied in the surgical arm of the European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial.

EORTC 08941 is a multicentre, prospective, randomised, phase-III trial of surgical resection *versus* radiotherapy in patients with proven stage IIIA-N2 nonsmall cell lung cancer after an objective response to platinum-based induction chemotherapy. Operative results in the 167 patients randomised in the surgical arm are presented within this study. Among these patients, one switched to the radiotherapy arm and 17 patients did not get any protocol treatment or information is not yet available.

Radical resection with negative surgical margins was obtained in 74 patients (49.7%). In 61 patients (40.9%), a pathological down-staging to N0 or N1 was present. Operative 30-day mortality was 4.0%. Post-operative complications were mainly pneumonia, respiratory insufficiency, arrhythmias, air leak, cardiac decompensation, empyema and bronchopleural fistula. In total, 12 (8.1%) patients underwent re-operation due to positive margins, haemothorax, empyema and bronchopleural fistula.

In conclusion, surgical resection after induction chemotherapy in the multicentre European Organisation for Research and Treatment of Cancer trial has yielded acceptable rates of morbidity and mortality.

KEYWORDS: Chemotherapy, lung cancer, morbidity, mortality, neoadjuvant therapy, surgery

Stage IIIA nonsmall cell lung cancer (NSCLC) with involvement of ipsilateral mediastinal or subcarinal nodes (N2) represents a heterogeneous group of patients, ranging from minimal intranodal involvement to extracapsular bulky disease [1]. To date, management of pathologically proven stage IIIA-N2 disease is controversial and the precise role of surgery to obtain local control has not yet been established. Many phase-II, and two smaller phase-III, studies have demonstrated favourable results with induction chemotherapy followed by surgical resection [2]. However, the role of surgical resection *versus* radiotherapy for optimal local control has not been addressed in these studies. For this reason, large, multi-centre phase-III trials were initiated in the USA and Europe to provide a more definitive answer [2, 3]. In the European Organisation for Research and Treatment of Cancer (EORTC)

08941 trial, patients with proven stage IIIA-N2 disease were randomised to either surgery or radiotherapy after a response to induction chemotherapy.

Variable results of surgical treatment after induction chemotherapy or chemoradiotherapy have been reported, and high mortality rates after right pneumonectomy are of special concern [4, 5]. In the present study, the surgical results of the operated patients in EORTC 08941 trial, with special emphasis on mortality, are reported in relation to the extent of resection.

PATIENTS AND METHODS
The general treatment scheme of the EORTC 08941 trial is depicted in figure 1 and eligibility criteria at registration are given in table 1. In the study, patients with proven stage IIIA-N2 NSCLC underwent cisplatin-based induction
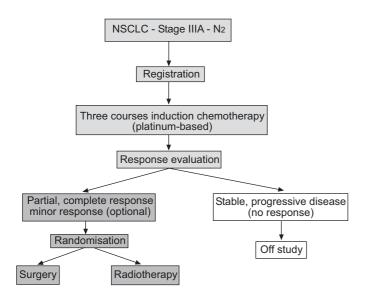
FIGURE 1. General treatment scheme of European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial. NSCLC: nonsmall cell lung cancer.

TABLE 1	Eligibility criteria of European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial

Proven clinical stage IIIA-nonsmall cell lung cancer

Cytological or histological proof of N_2 disease

Uni- or bi-dimensional measurable tumour

Irresectable N_2 disease

No symptomatic central nervous system involvement

No prior chemotherapy or radiotherapy

No other malignancies

Informed consent

chemotherapy. In case of a response on computed tomography scan of the chest, patients were randomised between surgery and radiotherapy. Patients with progressive disease were included in the study, but not considered for randomisation (off study).

The final aim of surgical treatment in the present trial was complete resection, *i.e.* radical removal of the primary tumour, hilar and mediastinal lymph nodes. A distinction was made between the following: R_0 resection, *i.e.* complete resection, no macroscopic tumour left behind, negative surgical margins and highest mediastinal node negative on pathological examination; R_1, microscopic residual disease; and R_2 resection with macroscopic residual tumour. Post-operative additional radiotherapy was only administered in case of incomplete resection (R_1 or R_2). Staging was carried out according to the most recent tumour, node, metastasis (TNM) classification [6]. Mortality, acute post-surgical events and morbidity data were prospectively collected for each individual patient. The study was performed in centres with a specific interest in thoracic surgery. For this reason, a general outline of complications was provided, but management was left to the local policy of the institution.

Registration of the EORTC 08941 trial closed in December 2002. In total, 333 patients were randomised, 166 to the radiotherapy arm and 167 to the surgical resection group. The latter patients are described in the present study.

At registration, the median age of the patients randomised to surgery was 60 yrs (range 29–78), of which 119 were males and 48 females.

Proof of N_2 disease was obtained by cervical mediastinoscopy in 127 patients, anterior mediastinoscopy in 14, video-assisted thoracic surgery in four, thoracotomy in eight and *via* needle biopsy in 14 patients.

All patients except one had three cycles of platinum-based induction chemotherapy. The regimens used most often were cisplatin–gemcitabine, carboplatin–paclitaxel, cisplatin–etoposide and cisplatin–vindesine. Combination chemotherapy with mitomycin, which may be associated with a higher incidence of respiratory complications, was only used in seven patients [7].

The histological types at randomisation were: squamous cell carcinoma in 65 patients (38.9%); adenocarcinoma in 57 (34.1%); large cell carcinoma in 41 (24.6%); and mixed cell or other malignant type in four patients (2.4%).

Treatment received in the surgical arm was: surgery in 127 patients (76.0%); surgery followed by adjuvant radiotherapy in 22 (13.2%); one patient (0.6%) switched to the radiotherapy arm; nine patients (5.4%) had no treatment according to protocol; and information on treatment actually received was not available for eight patients (4.8%). The group of 149 patients who had surgery (n=127) or surgery followed by radiotherapy (n=22) was considered for further analysis.

Regarding the type of surgery, pneumonectomy was performed in 69 patients (46.3%), lobectomy or bilobectomy in 58 (38.9%), exploratory thoracotomy in 21 (14.1%) and another intervention in one patient (0.7%) who underwent remediastinoscopy, which was a protocol violation. As remediastinoscopy remained positive, this patient had no surgical resection.

There were 35 (50.7%) pneumonectomies on the right side, 33 (47.8%) on the left side and, for one patient (1.4%), the side of pneumonectomy was unknown.

The impact of several baseline factors on the risk of post-surgical morbidity and mortality was investigated using univariate and multivariate (with backward selection) logistic regression models. These analyses need to be considered as exploratory.

RESULTS

A radical R_0 resection was performed in 74 patients (49.7%), R_1 in 53 (35.5%), R_2 in 21 patients (14.1%). In addition, one patient (0.7%) had no thoracotomy, but underwent remediastinoscopy as previously mentioned.

Clinical (c), tumour (T) and nodal (N) staging before induction chemotherapy *versus* pathological (p), T and N staging after surgery is depicted in table 2. The latter is more specifically called ypT and ypN as all these patients had induction chemotherapy. Down-staging to N_0 or N_1 disease was obtained in 40.9% of patients.

TABLE 2 Clinical, tumour and nodal (cTN) staging before induction chemotherapy *versus* pathological, tumour and nodal (ypTN) staging after surgery and induction chemotherapy

	T category[#]					N category[#]	
	cT before induction chemotherapy					cN before induction chemotherapy	
	cT_1	cT_2	cT_3	Total		cN_2	Total
ypT_0	3	7	1	11 (7.4)	ypN_0	37	37 (24.8)
ypT_1	8	24	4	36 (24.2)	ypN_1	24	24 (16.1)
ypT_2	4	48	9	61 (40.9)	ypN_2	84	84 (56.4)
ypT_3	0	14	4	18 (12.1)	ypN_3	1	1 (0.7)
ypT_4	2	8	2	12 (8.1)			
ypT_x	1	6	2	9 (6.0)	ypN_x	2	2 (1.3)
Missing	0	1	1	2 (1.3)	Missing	1	1 (0.7)

Data are presented as n (%). [#]: n=149.

Operative 30-day mortality was 4.0% (six patients). Of these patients, five had a pneumonectomy (three on the left and two on the right side), and one a right-sided exploratory thoracotomy. Therefore, 30-day mortality after exploratory thoracotomy occurred in one out of 21 patients (4.8%), after lobectomy 0% and after pneumonectomy five out of 69 patients (7.2%). Thirty-day mortality after right pneumonectomy was 5.7% and after left pneumonectomy 9.1%. One patient died on post-operative day (POD) 4 due to adult respiratory distress syndrome (ARDS), one on POD 5 due to pulmonary hypertension and cardiac decompensation, one on POD 7 because of post-operative bleeding, two on POD 11 due to cardiac decompensation and respiratory insufficiency, and one on POD 26 presumably due to cardiac arrhythmias, although the exact cause of death could not be determined.

Ninety-day mortality was 8.7% (13 patients), seven patients died between 31 and 90 days post-operatively. Three of these patients had a pneumonectomy, two had a lobectomy, one a bilobectomy and one an exploratory thoracotomy. The causes of death were progressive disease in two patients, infections in two, toxic death in one and other causes in two patients.

In total, 12 patients (8.1%) underwent re-operation due to haemothorax (four patients), bronchopleural fistula (five patients), empyema (one patient) and positive margins (two patients).

Regarding the re-operations for haemothorax, in two cases a specific cause could be determined, no precise reason was found in one patient, and the fourth patient had no haemothorax, but a thrombopathy was discovered. Four out of the five bronchopleural fistulas were treated by a Clagett procedure (open window thoracostomy) and one by direct closure of the fistula.

Specific morbidity data was available for 136 patients. These were subdivided into pulmonary, cardiac, pleural space and other complications. The different categories are listed in table 3. Pulmonary complications were most frequent, especially pneumonia and respiratory insufficiency. The observed bronchopleural fistulas all occurred after pneumonectomy. The incidence of this complication after pneumonectomy was 8.7%. Other respiratory complications include mainly cough and dyspnoea due to sputum retention, bronchitis and exacerbation of chronic obstructive pulmonary disease.

Other events in the complications group included urinary tract infection, thrombopathy and uncontrolled diabetes.

TABLE 3 Pulmonary, cardiac, pleural space and other complications of the 136 patients

Pulmonary	38 (27.9)[#]
Atelectasis	4
Pneumonia	9
Respiratory insufficiency	9
Prolonged ventilation	4
ARDS	4
Other	25
Cardiac	19 (14.0)[¶]
Arrhythmias	13
Myocardial ischemia	1
Cardiac decompensation	5
Pleural space	25 (18.4)[+]
Air leak	12
Empyema	11
Bronchopleural fistula	6
Haemothorax	3
Space problems	2
Other	19 (14.0)[§]
Thromboembolic disease	2
Wound haematoma	6
Wound infection	5
Other	7

Data are presented as n or n (%). ARDS: adult respiratory distress syndrome. [#]: total events=55; [¶]: total events=19; [+]: total events=34; [§]: total events=20.

Investigating the impact of age, sex, histological subtype, cT stage, side of surgery, type of surgery and presence of radical resection on the risk of morbidity or 30-day operative mortality, univariate and multivariate analyses showed that only the type of surgery was significantly associated with occurrence of such an event. Although patients with bilobectomy did not appear to have a significantly different risk of morbidity or mortality (p=0.9341) than patients with pneumonectomy, patients with exploratory thoracotomy and other surgery did have a significantly lower risk of such an event (p=0.0048) than patients with a pneumonectomy.

DISCUSSION

In 1994, the EORTC initiated a prospective multicentre trial in which patients with proven N2 disease were initially treated by induction chemotherapy, and subsequently, randomised between surgery and radiotherapy in case of response [2]. The study closed for accrual in December 2002. The primary endpoint was survival. At the time of reporting these results (November 2004), the final results were not yet available, as the number of events allowing statistical analysis had not been reached.

In the present study, the surgical results in the patients randomised to the surgery arm were focused upon. Surgical resection after induction chemotherapy, and especially after chemoradiotherapy, is technically more demanding due to a variable degree of fibrosis that is often encountered after neoadjuvant therapy [8]. This fibrosis renders surgical dissection more tedious, as it is often pronounced at the sites of initial involvement of the different lymph node stations. Therefore, the hilar and mediastinal regions are frequently involved. Frozen section analysis of these lymph nodes can be useful in determining the extent of resection but can be unreliable, especially when only micrometastases persist. When extensive adhesions are present, freeing of the pulmonary artery in the hilum or its branches in the major fissure can be quite difficult, even for an experienced thoracic surgeon, necessitating intrapericardial, retrograde or posterior dissection.

For this reason, it is not surprising that controversial results have been reported on surgical morbidity and mortality after induction chemotherapy or chemoradiotherapy. In the surgery arm of the prospective international multicentre EORTC 08941 trial, mortality was 4.0% and 8.7% for operative 30- and 90-day, respectively. Morbidity consisted mainly of respiratory (27.9%) and pleural space problems (18.4%).

Older reports already emphasise the higher risk encountered with pneumonectomy in this setting. In a smaller series of 13 patients, FOWLER et al. [4] reported an overall operative mortality of 23%, which increased to 43% after pneumonectomy. An accompanying editorial cautioned for this excessively high risk [9].

In a large series from the Memorial Sloan-Kettering Cancer Center (New York, USA), 470 patients undergoing lobectomy or pneumonectomy after induction chemotherapy or chemoradiotherapy were retrospectively reviewed [5]. Overall mortality was 3.8%, 2.4% after lobectomy and 11.3% after pneumonectomy. Right pneumonectomy in this series carried a mortality rate of 23.9%, the specific cause of which could not be determined. Overall morbidity was 38.1%, rising to 58.7%

after right pneumonectomy. Cardiac complications occurred in 12.3% of the patients and respiratory complications in 25.7%; consisting mainly of pneumonia, respiratory insufficiency, empyema and bronchopleural fistula. Multivariate analysis demonstrated right pneumonectomy, blood loss >500 mL and forced expiratory volume in one second <80% to be independent risk factors for morbidity; whereas the type of induction therapy had no specific effect [10]. In the EORTC 08941 trial a higher mortality after right pneumonectomy was not observed.

In a series from Houston, USA [11], 76 patients undergoing surgical resection after induction chemotherapy were compared with a series of 259 patients undergoing only surgical resection. Although this was not a randomised study, data on post-operative morbidity and mortality were prospectively collected. Mortality in the surgery-only group was 5.0% and the combined induction chemotherapy surgery group only 1.3%. However, the number of pneumonectomies was low in this series, being only 10.5%. Major pulmonary complications, including pneumonia, re-intubation, tracheotomy and ARDS, occurred in 13.2% of patients having surgical resection after induction chemotherapy, but there were no cases of empyema or bronchopleural fistula. The conclusion of the current study was that induction chemotherapy does not significantly affect overall morbidity and mortality of surgical resection. However, it should be emphasised that most patients had a lobectomy or bilobectomy.

Another large series of 350 patients who had surgical resection after induction chemoradiotherapy was reported by STAMATIS et al. [12]. In this retrospective study, 35% of patients underwent a pneumonectomy and 45% a lobectomy. Hospital mortality was 4.9%, 7.2% after pneumonectomy, and 3.8% after lobectomy or bilobectomy. Early or late complications occurred in 44% of patients, which were mainly cardiac arrhythmias (13%, 27% after pneumonectomy), prolonged air leakage (16%), pneumonia (5.1%), atelectasis (4.3%), and septic complications including bronchopleural fistula (4.1%) and empyema without bronchopleural fistula (1.7%). Risk factors for pneumonia were high age and a low Karnofsky index, and, for cardiac arrhythmias, abnormal echocardiographic findings prior to surgery. Absence of bronchial stump coverage was another risk factor for peri-operative morbidity. Rethoracotomy for post-operative bleeding was necessary in nine patients (2.6%), five after lobectomy and four after pneumonectomy, with a specific cause being found in four patients.

Initial results of the North American Intergroup Trial 0139 investigating the relative role of surgery versus radiotherapy for stage IIIA-N2 NSCLC were recently reported [3]. In contrast to the EORTC study, patients were upfront randomised between a full course of chemoradiotherapy and induction chemoradiotherapy followed by surgical resection. In total, 429 patients were randomised, with 392 being evaluable. In the induction therapy surgery arm, 201 patients participated, with 14 dying from treatment (6.9%), four post-operatively and 10 during or after consolidation. The most frequent cause of death was ARDS. There was no difference in 3-yr overall survival between both arms, but progression-free survival was significantly better in the induction therapy surgery group [3].

In a very recent study from the University of Pittsburgh, 115 patients who underwent a pneumonectomy from 1990 to 2002 were reported [13]. In total, 50 patients had a right-sided and 65 a left-sided pneumonectomy. Fifty-two patients (45%) had neoadjuvant therapy, of which 25 had a right and 27 a left pneumonectomy. Median length of stay was 5 days. Right and left pneumonectomies were compared. Thirty-day mortality was 6% on the right side and 3% on the left side. Supraventricular arrhythmias were more frequent on the left side, and bronchopleural fistulas more frequent on the right side. Median survival time was not different, being 18.5 months for right-sided and 19.1 months for left-sided interventions. Neoadjuvant therapy increased the risk of postoperative arrhythmias, but not the incidence of bronchopleural fistulas [13].

In conclusion, surgical resection after induction chemotherapy for proven stage IIIA-N2 nonsmall cell ling cancer was found to be feasible in the EORTC 08941 trial, a prospective randomised international multicentre study. In total, six patients died during the first post-operative month, giving a 30-day mortality of 4.0%. Five of the patients who died had a pneumonectomy, three on the left and two on the right side. Morbidity was not very different compared with other large reported series, warranting further studies on combined modality treatment, including surgery for early-stage or locally advanced nonsmall cell lung cancer.

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