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ORIGINAL ARTICLE

Surgery after chemotherapy for initially unresectable stage III non-small cell lung cancer

By the European Lung Cancer Working Party

ABSTRACT

BACKGROUND Stage III non-small cell lung cancer represents a heterogeneous group of diseases for which multimodal therapy is today recommended including surgery, radiotherapy and chemotherapy.

PATIENTS AND METHODS The purpose of the study was to retrospectively identify factors predictive of secondary complete resection, in a series of patients with initially unresectacle, non metastatic Non Small Cell Lung Cancer (NSCLC) who were treated with pre-operative chemotherapy. Patients were randomised between 3 courses of MIP (mitomycin C 6mg/m^2; ifosfamide 3g/m^2; cisplatin 50mg/m^2) or SuperMIP (mitomycin C 6mg/m^2; ifosfamide 4.5g/m^2; cisplatin 60mg/m^2, carboplatine 200mg/m^2). If, after 3 courses of chemotherapy, the tumour became resectable, surgery was performed followed by mediastinal irradiation.

RESULTS There were 351 ellgible patient: 176 in the MIP arm, 175 in the SuperMIP arm; 43% and 51% with stages II A and II B, respectively. After chemotherapy, surgery was performed in 54 (15%, 95% CI: 12%-20%) patients. Complete resection (R0) was obtained in 40 patients. Two independent predicting factors of complete resection were identified: N status (OR: 0.06 in disfavour of N3; 95% CI: 0.007-0.410; p=0.005) and objective response to chemotherapy (OR: 3.90 in favour of objective response; 95% CI: 1.90-7.98; p <0.001).

CONCLUSIONS In initially unresectable stage III NSCLC, the absence of N3 nodal involvement or a response to chemotherapy is associated with a higher chance to achieve a complete resection.

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KEY WORDS: *Non-small cell lung cancer, Stage III, Chemotherapy, Surgery*

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INTRODUCTION

Stage III non-small cell lung cancer (NSCLC) is a heterogeneous group of diseases for which multimodal therapy is today recommended, including surgery, radiotherapy and chemotherapy. Practically, various approaches are possible [1-3]: induction therapy followed by surgery in initially resectable tumours, chemotherapy combined with chest irradiation in case of unresectable disease, chemotherapy alone when disease extent is locoregionally too extensive precluding effective local treatment. In some situations, induction may render the tumour resectable. Surgery or radiotherapy as a single treatment modality should not be considered anymore as a first-choice option.

The main problem of the current staging classification of NSCLC is its operational

TABLE 1. Inclusion and exclusion study criteria

Inclusion criteria

- histologically proven NSCLC;
- initially unresectable non metastatic tumour without homolateral malignant pleural effusion;
- no prior history of malignancy except non melanoma skin cancer or in situ carcinoma of the cervix and "cured" malignant tumour (more than 5-year disease-free interval);
- no prior therapy with chemotherapy, surgery or irradiation;
- age ≤75 years;
- Karnofsky performance status (PS) ≥60;
- good renal (serum creatinine level ≤1.5 mg/dl), hepatic (serum bilirubin level ≤1.5 mg/dl) and haematological (WBC count ≥4,000/μl and platelet count ≥100,000/μl) functions;
- no recent (<3 months before the date of treatment) myocardial infarction and no active congestive heart failure or cardiac arrhythmia requiring medical treatment;
- no uncontrolled infectious disease or other serious medical or psychiatric illness precluding adherence to the study protocol
- Accessibility for follow-up and provision of informed consent

Exclusion criteria

- Patients requiring prompt irradiation (i.e. because of spine invasion by tumour)
- Functional or anatomical contra-indication to chest irradiation.

validity. Although the International Staging System (ISS) has a good prognostic value, it is not very helpful in making a therapeutic decision, particularly in stage III NSCLC. Indeed, the therapeutic decision is often guided by subjective parameters such as the local expertise. The consideration of a tumour as resectable or treatable with curative radiotherapy is often surgeon- or radiotherapist-dependent and it is thus a matter of some subjectivity due to a lack of objective criteria. This makes difficult the interpretation of the literature.

The European Lung Cancer working Party (ELCWP) has conducted, a couple of years ago, a randomised trial comparing two different dose-intensity induction chemotherapy regimens before chest irradiation in patients with initially non metastatic unresectable NSCLC [4]. The study failed to demonstrate survival improvement with a high dose induction chemotherapy despite a significantly increased objective response rate and the achievement of a higher dose-intensity. After induction chemotherapy and before chest irradiation, the disease was assessed for secondary surgery. Of 351 eligible patients included in the above trial, secondary surgery was performed in 54 [4]. In the present study, we retrospectively analyse factors predicting secondary complete resection in the above series of patients, initially considered as having unresectable tumour.

PATIENTS AND METHODS

Inclusion and exclusion criteria in the aforementioned ELCWP trial 01953 [4] are listed in table 1. Except for bulky involvement (defined as a disease considered by the local surgeon as too massive to permit surgical resection), mediastinoscopy with biopsy was recommended prior to chemotherapy to confirm mediastinal dissemination and unresectability.

Eligible patients were randomised to receive 3 courses of MIP (mitomycin C 6 mg/m^2; ifosfamide 3g/m^2; cisplatin 50 mg/m^2) or 3 courses of SuperMIP (mitomycin C 6 mg/m^2; ifosfamide 4.5 g/m^2; cisplatin 60 mg/m^2, carboplatine 200 mg/m^2). Stratification of patients was also performed according to the initial TNM stage, histological subtype, Karnofsky PS and treating centre. Courses were repeated every 3 to 4 weeks, according to haematological and renal function recovery. If delay between 2 courses was more than 5 weeks, patient went off treatment.

Evaluation of tumour response was performed on week 9 (later if chemotherapy had to be delayed). If the tumour was rendered resectable, surgery was performed followed by mediastinal irradiation. For responding but non resectable, stable or locally progressing tumours, chest irradiation was given (60 Gy over 6 weeks with 2 Gy daily fractions to the primary tumour and the known area of lymph node involvement). If the patient developed distant metastases, went off protocol.

Restaging, including all tests performed during the initial work-up [4] excepting mediastinoscopy, was repeated after the first three courses of chemotherapy and for responders and those with stable disease, again at the end of therapy. After treatment discontinuation, patients were examined with biological tests (as initially performed) and chest X-ray, every 2 months for the first 6 months and every 3 months thereafter. A complete work-up was recommended every 6 months.

Evaluation for response after completion of three courses of chemotherapy, as well as review of the initial TNM stage, was performed during regular meetings of the Group by at least three independent observers. Complete response (CR) was defined as disappearance of all parameters of disease. In cases of measurable disease, partial response (PR), was defined as a ≥50% greater decrease of the total tumour load (the tumour area calculated by the multiplication of the longest diameter by the greatest perpendicular diameter), without the appearance of new lesions or progression of any existing lesion. In assessable disease, PR was defined as an estimated decrease in tumour size of ≥50%. Progressive disease (PD) was defined as a >25% increase in one or more measurable or assessable lesions or the appearance of a new lesion. All other circumstances were classified as no change (NC). Patients with early death (ED) due to PD before evaluation or with toxic death due to chemotherapy or with early chemotherapy stopping for toxicity, were considered in response evaluation and

were characterised as treatment failures. WHO criteria were used to assess toxicity and histological subtypes.

In case of surgery, at least a lobectomy was required. An upper or lower radical dissection of the mediastinum was required in case of mediastinal node dissemination. Mediastinal nodes had to be looked for and picked up at 3 levels including paratracheal and subcarinal sites. Marginal tissue had to be collected at least at the level of the bronchial stump, the mediastinal lymph nodes and all structures in close contact with tumour infiltration. Other sites of possible intrathoracic metastases had to be thoroughly searched. For postoperative radiotherapy, the target volume had to include the areas of entire regional lymphatic drainage: ipsilateral hilum including the bronchial stump with a 2 cm margin of uninvolved pulmonary tissue (as seen on the radiographs), entire mediastinum from the suprasternal notch (including the mediastinoscopy scar) to not less than 5 cm below the carina and across the trachea to include 1 cm of contralateral lung. Inferior mediastinal nodes (down to the diaphragm) had to be irradiated in case of lower lobe tumours. The radiation dose was as follows: the dose to the isocenter in the central plane of the volume was 60 Gy with lung tissue correction factor (0.3 or CT-based) given as daily fraction of no more than 2 Gy; the isodose encompassing the target volume had to be not less than 56 Gy. Variation within the target volume should not exceed 10%.

According to pathological evaluation and pTNM staging, resected tumours were classified in 4 categories: I) complete response (R0) if no tumour was found in neither lung tissue, neither thoracic nodes; II) complete resection (R0) if all the margins and all distant nodes were free of tumour; III) incomplete resection if resection was performed with gross pathologic tissue left behind or if margins were still positive for tumour or if more distant nodes were still involved (R1= microscopical residual tumour and R2= macroscopical residual tumour); IV) unresectable if no tumour resection was performed at thoracotomy.

Overall survival and response duration were dated from the day of randomisation. Survival distributions were estimated by the Kaplan-Meier method. The log-rank test was used to compare survival distributions. P values (two-tailed) for testing the null hypothesis of the equality of proportions were calculated using a Fisher's exact test or a X^2 test. Univariate and multivariate analysis for prognostic factors were performed by adjusting the data with logistic regression models and choosing as dependent characteristic the surgery result, dichotomised as complete response/complete resection or incomplete resection/unresectable. Covariates with a p value <0.20 were retained to be tested in a multivariate model, using a backward stepwise method for the selection of variables to be retained in the final model. Coefficient estimates were obtained by the maximum likelihood method.

Among all eligible patients for the above mentioned EL-CWP 01953 protocol, only those with clinical stage III were included in the present analysis. Inoperable patients with stage I and II were eligible for the trial 01953 but not for the present analysis since the inoperable status could not be affected by induction treatment.

The present study was approved by the local ethical committee of the participating institutions.

TABLE 2. Main characteristics of the operated patients.

Characteristics		MIP	Super MIP
Number of patients		27	27
Age	Median (years)	58	54
Sex	Male	22	25
	Female	5	2
Histology	Squamous cell carcinoma	15	12
	Adenocarcinoma	7	10
	Other non-small cell	5	5
Initial Karnofsky PS	≥80	23	27
	≤70	4	0
Initial clinical stage	IIIA	19	21
	IIIB	8	6
Clinical response to induction chemotherapy	CR	1	0
	PR	18	18
	NC	7	5
	Stop for toxicity	1 *	4 **

PS: performance status; CR: complete response; PR: partial response; NC: no change; *: renal failure; **: renal failure in 3 and skin allergy in 1

RESULTS

Among 351 eligible patients randomised between January 1996 and April 2002, 340 had stage III; out of these 340, surgery was performed in 54 (15.4%, 95% confidence interval CI: 12% - 20%), 27 in the MIP arm and 27 in the SuperMIP. Characteristics of these patients according to the chemotherapy regimen, are shown in table 2 The two groups were not significantly different. The majority of patients had IIIA disease (74%) and were clinically documented as objective responders to chemotherapy (69%).

Lobectomy was performed in 30 cases, pneumectomy in 22 and exploration only in 2. Five postoperative deaths were documented (13%): 3 in the MIP arm and 2 in the SuperMIP (2 right pneumectomies, 2 left pneumectomies and 2 right upper lobectomies).

Clinical downstaging was achieved in 29 patients (54%): 16 in the MIP arm and 13 in the SuperMIP. T status was downstaged in 21 and N status in 18 cases.

Complete resection (R0) was obtained in 40 patients including 23 with clinical TN downstaging: 21 in the MIP arm and 19 in the SuperMIP; 29 in initial clinical stage IIIA and 11 in initial clinical stage IIIB (including one stage T2N3 with histologically proven supraclavicular adenopathy). Thus, the overall rate of complete resection was 11% (95% CI: 8%-15%). By excluding patients with stage I-II, it was 12% (95% CI: 9%-16%). There were 5 pathological complete responses (13%): 2 in the MIP arm and 3 in the SuperMIP one.

Survival of the 40 completely resected patients (median follow up: 43 months; range: 6-87) was 77% at one year, 54% at two years and 48% at three years with a median survival of 30 months. There was no difference according to chemotherapy regimen.

A prognostic factor analysis was performed to determine characteristics predicting complete resection. The following baseline characteristics were analysed: age, sex, histology, type of lesions, Karnofsky PS, initial T, N and stage and a single treatment variable: response to induction chemotherapy. Univariate analysis results are shown in table 3. Three factors were found to be statistically significant predictors for R0: N, stage and response to induction chemotherapy. Multivariate analysis with logistic regression identified two independent predicting factors: N status (OR: 0.06 in disfavour of N3; 95% CI: 0.007-0.410; p = 0.005) and objective response to induction chemotherapy (OR: 3.90 in favour of objective response; 95% CI: 1.90-7.98; p <0.001).

TABLE 3. Predictive factors of complete resection: univariate analysis (n = 340, excluding stages I-II patients)

Factor		N pts	N R0 (%)	p
age (years)	≤60	162	25 (15.4)	0.06
	>60	178	15 (8.4)	
Sex	Male	289	33 (11.4)	
	Female	51	7 (13.7)	0.64
Histology	Squamous cell	164	20 (12.2)	
	Adenocarcinoma	120	11 (9.2)	
	Other non-small cell	56	9 (16.1)	0.41
Initial Karnofsky PS	≥80	299	38 (12.4)	
	≤70	41	3 (7.3)	0.45
Type of lesion	Evaluable	127	12 (9.4)	
	Measurable	213	28 (13.1)	0.39
Weight loss	<5%	210	27 (12.9)	
	≥5%	100	8 (8)	0.25
T	1-2	140	22 (15.7)	
	3	82	8 (9.8)	
	4	117	10 (8.5)	0.12
N	0-1	54	10 (18.5)	
	2	196	29 (14.8)	
	3	90	1 (1.1)	0.001
Stage (ISS 86)	IIIA	162	29 (17.9)	
	IIIB	178	11 (6.2)	0.001
OR to induction chemotherapy	Yes	137	27 (19.7)	
	No	203	13 (6.4)	<0.001

RO: objective response; PS: performance status; ISS: international staging system

DISCUSSION

The important contribution of the present study is the information provided about the rate of secondary complete resections (12%) after induction chemotherapy in patients with NSCLC initially considered unresectable together with the identification of factors predicting successful outcome of surgery in this situation.

Our findings are based on a retrospective analysis of data obtained from a prospective randomised trial comparing two induction chemotherapy regimens prior to chest irradiation in patients with NSCLC [4]. Initially resectable cases were excluded by definition from the analysis. Among 340 eligible patients with stage III, surgery was performed in 16% and complete resection was obtained in 12% (40 among 54 operated patients). This observation demonstrates that secondary surgery with a R0 outcome can be applied in only a small minority of patients. Among other published randomised studies [5-26] including a sequential arm with chemotherapy followed by irradiation and performed in unresectable NSCLC, only three have reported the number of patients operated on after induction therapy: a French trial [9] reporting 5 patients from a total of 176 (2.8%), a Japanese study 5 patients from 320 (1.6%) [19] and a previous trial conducted by our Group [24] reporting 32 patients from a total of 462 (7%).

We acknowledge that our findings must be treated with caution due to some methodological problems: although the data were obtained from a prospectively randomised trial, the present analysis of the "surgical" results was retrospectively performed. The reason why it was not scheduled from the beginning was that on the basis of the available literature and of our previous study [24] we did not expect to have a 15% rate of successful secondary surgery with an overall 11% rate of complete resection. Because of the retrospective nature of the analysis:

1. it was practically impossible to establish the criteria on which the surgeon based his decision about the initial resectability of the tumour or its resectability after induction chemotherapy in each individual patient. Furthermore, PET scan was not available at that time.
2. some of the so called "no change" cases were in fact tumours with a minor response, not strictly stable disease and therefore the regression of the lesions, even if it did not reach the threshold requested by the WHO definition for PR characterisation, it could have been sufficient enough to convince the surgeon that full resection was possible. In addition, some recommend surgery in those situations because it is known that residual masses seen on chest CT scan may not contain viable tumour [27-29].

Resectability of a lung tumour depends on three main criteria: operability of the patient, disease extent (based on the tumour stage) and decision of the surgeon. The first criterion does not matter in the present analysis since an initial medical contra-indication for surgery would remain a cause of exclusion from surgery even after successful induction chemotherapy. On the contrary, disease extent can be modified by primary chemotherapy and clinical downstaging can be documented at the preoperative assessment, rendering the tumour resectable. In our series, TNM downstaging, allowing the surgeon to reconsider his/her decision, was observed in 54% of the patients.

A main problem interfering with surgeon's decision about resectability is the relative lack of objective criteria on which to base his/her decision. His/her own experience is important. Some surgeons perform extensive surgery for stage III NSCLC while others are more conservative. In our study, the decision on non-resectability was determined, before and after induction chemotherapy, by a multidisciplinary team including thoracic surgeon, chest physician, medical oncologist and radiation oncologist. Some criteria that we used are commonly accepted such as bulky mediastinal involvement already present on standard chest X-ray [30].

The high mortality rate (13%) observed is essentially due to the poor PS of the group of patients, initially considered unresectable and operated on after chemotherapy. Moreover, 4 of the 6 patients underwent pneumectomy.

Our analysis performed in initially unresectable NSCLC allowed us to identify two main factors predicting resectability after induction chemotherapy, pre-treatment clinical N status and response to chemotherapy. More specifically, initial N3 stage (although admittedly the confidence interval was large as there was only one N3 tumour completely resected in our series) or the absence of response to chemotherapy were associated with a low chance to achieve complete resection.

Our data do not support the mandatory role of surgery in stage III disease and this is in accordance with results reported by others [31,32]. Cure can be achieved with combined chemoradiotherapy only [31]. Recently, in a large randomised trial, no significant difference in survival was found, in pathological stage IIIA N2 NSCLC when surgery was added to chemoradiotherapy [32]. The impact of surgery on survival, in other stage III disease, remains to be demonstrated by controlled studies.

With the aforementioned methodological caution, our study shows that in initially unresectable stage III NSCLC, the absence of N3 lymphadenopathy or a response to chemotherapy is associated with a higher chance to achieve a complete resection after induction chemotherapy. Whether this approach is preferable than chemoradiotherapy alone remains to be demonstrated by prospective randomised trials.

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Participating institutions (investigators) of the European Lung Cancer Working Party to the present study were as fol-

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