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Pneumonectomy with and without induction chemo-radiotherapy for non-small cell lung cancer: short and long-term results from a single centre

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Abstract. – BACKGROUND AND OBJECTIVES: Pneumonectomy for non small cell lung cancer (NSCLC) after induction radio-chemotherapy (IT) has been associated with high peri-operative risk and its safety and efficacy is still debated. The aim of this retrospective study was to compare short and long-term results of pneumonectomy in patients treated with and without IT (radiotherapy plus chemotherapy) for NSCLC.

MATERIALS AND METHODS: From 1995 to 2008, 85 consecutive patients underwent pneumonectomy: 49 received pre-operative radiotherapy and chemotherapy (IT group), and 36 patients did not (non-IT group). Peri-operative and long-term outcomes were compared.

RESULTS: Major complications rate was 14.3% for IT group and 16.7% for non-IT group (p = n.s.). Mortality rate was 2% in IT group and 5.5% in non-IT group (p = n.s.). Post-operative hospital stay was significantly longer in the IT group (p < 0.0001) as the need for blood transfusion (p = 0.002). Indeed, the mortality rate was similar in the left- and right-sided operations. 5 years survival was 45.3% for IT group and 38.4% for non-IT group (p = n.s.) and 5 year disease free survival rates were 42.3% vs. 37.8% for the two groups, respectively (p = n.s.). Among the clinical, surgical and pathological features no differences on long term outcomes were found with regards to IT.

DISCUSSION: Pneumonectomy is a feasible and safe procedure even after pre-operative IT. Our results showed a prolonged hospitalization and the need for blood transfusion in the IT group.

Key Words:
Non small cell lung cancer, Pneumonectomy, Radio-chemotherapy, Long term survival, Morbidity, Mortality.

Introduction

On average, 75% of newly diagnosed non small cell lung cancer (NSCLC) cases present with a locally advanced (IIIa/IIIb) or metastatic disease: this is directly associated with a poor prognosis. The chance of cure offered by single therapeutic options (chemotherapy, radiotherapy, surgery) are very limited. This represented the rationale for the many tries of improvement realized in recent years, which had the aim to offer to the patients the most beneficial therapy possible in an attempt to downstage their mediastinal nodes status before surgery. Recent data show that survival in locally advanced NSCLC is improved by the addition radiotherapy plus chemotherapy induction therapy (IT) to surgery[1,2]. However, the risks of intra- and post-operative complications after the implementation of this therapeutic approach are still being debated, especially in patients undergoing pneumonectomy[3-5] where earlier series have reported increased morbidity and mortality[6,7]. Martin et al[6] reported an operative mortality of 23.9% after right-sided pneumonectomies. More recent series have questioned these high morbidity and mortality figures, reporting a post-operative mortality rate ranging from 0% to 4%[8-10]. Initially criticized because of the presumed higher prevalence of post-operative morbidity and mortality, IT protocols based on the concurrent administration of chemotherapy and radiotherapy are now more frequently applied.

In our Institution, a combination of pre-operative chemotherapy and radiotherapy has been

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used for two decades to treat patients with locally advanced (IIIa-IIIb) NSCLC[11]. After the promising results of this first attempt, we continued to implement and refine our approach until now.

The aim of this study was to estimate a measure of the risk of the post-operative mortality and specific morbidity following pneumonectomy in patients treated with bi-modal IT and in those treated by surgery alone, and to compare their long-term outcomes.

Materials and Methods

We retrospectively reviewed the clinical records of all patients who underwent pneumonectomy for NSCLC in a 13 year period. Institutional Review Board approval has been preliminarily obtained for the research purpose use of the data stemming out from standard clinical practice, since no additional interventions were planned (observational study). Generic eligibility criteria for oncologic treatment, including age under 70 years, adequate blood chemistry, hepatic and renal function, no pulmonary or cardiovascular contraindications and life expectancy longer than 6 months were applied.

Oncological criteria for IT were NSCLC in clinical stage IIb, IIIa, IIIb (not N3+) and IV (only patients with single brain metastases radically excised and N2+ disease).

Based on the information available from the clinical records, demographic and clinical features were collected and taken into consideration in the statistical analysis. Follow-up informations were obtained from our data-base, or by direct telephonic interview with the patient or with a next of kin in the case of the patient's death.

Pre-treatment evaluation included patient history, physical examination, standard chest X-ray, complete blood chemistry, computed tomography (CT) of the chest, brain and upper abdomen, whole-body radionuclide scan, fiberoptic bronchoscopy.

In addition to the staging procedure, lung function tests were performed to assess the general status of each patient. The diagnosis of NSCLC was obtained by pathological and/or cytological examination of the material obtained via endo-bronchial biopsy or CT guided fine needle aspiration. The mediastinal involvement was always pathologically confirmed. Pneumonectomy was controindicated if the predicted postoperative forced expiratory volume in one second (FEV_1) was 30% or less.

Induction Therapy

Radiotherapy was administered with an angled field technique modulated on the volume and location of the disease so as to include in the isodose of 100% (±5%) area all the target volume, with a maximum dose to the spine of 36 Gy. The target volume was the primary tumor and the metastatic lymph node area plus the surrounding 1.5 cm margin. The median total referred dose was 50.4 Gy with classical or hyper fractionation. In every case, the treatment was supported by CT results. The treatment was CT planned with lung parenchyma correctional factors, and a linear photon accelerator was used in all cases.

There was no uniform chemotherapy protocol during the study period. Different chemotherapy regimens were used: carboplatin, during days 1-4 of the first and last week of treatment (1991-2002); cisplatin plus 5-Floruracil, during days 1-4 of the first and last week of treatment (1998-2002); cisplatin on days 1 and 8, gemcitabine on days 1 and 8, and paclitaxel on days 1 and 8, every 21 days cycle (since 2002).

A complete clinical and radiological re-evaluation was performed 4 weeks after the end of treatment. Restaging occurred with CT scan, redo mediastinoscopy was performed in selected cases. Complete response was defined as the disappearance of all neoplastic tissue. Partial remission was defined as a reduction of more than 50% of the sum of products of the two greatest perpendicular diameters of the neoplastic lesion. Stable disease was defined as a less than 25% response. Patients with progressive neoplastic disease were excluded from the treatment.

Surgery

Surgery was performed, on average, six weeks after the beginning of the IT (two weeks after the clinical restaging) in the IT group. Pneumonectomy was decided only if less extensive resections were not adequate in planning a radical approach to the removal of the diseases and consisted of intrapleural pneumonectomy plus hilar and mediastinal systematic lymph node dissection. The resection was considered complete if proximal resection margins were free of tumor on frozen section examination and if the highest mediastinal resected node was free of tumor. Patients who underwent "enlarged" pneumonectomy (extrapleural pneumonectomies, concurrent chest

wall resections, superior vena cava resections, sleeve pneumonectomies) were excluded. A pedicled flap of intercostal muscle was applied on the bronchial stump on the right side in case of suspicion of weakness of the bronchial stump itself and in the IT group.

With respect to the surgical and pathological features, we collected details on the extent of resection, the pathological staging, the completeness of resection, the hospital stay, the post-operative morbidity and mortality rates.

Statistical Analysis

Heterogeneity between the IT group and the Non-IT group with respect to all demographics and clinical features was tested by means of univariate statistics. A linear regression analysis on the length of hospitalization was performed and factors predicting a prolonged stay were identified. The frequency of major complications was analyzed by means of the Pearson's Chi-Square and the Fisher's Exact tests. The long-term survival and disease free survival were investigated with the Kaplan-Meier survival function methodology and the survival curves compared with the Log-Rank test. The Cox multiple regression analysis was subsequently applied and the risk factors for both the mortality and the relapse of the tumor were identified. A p-value of 0.05 was set as the critical limit for significance. All analyses were performed in STATA Release 10.

Results

From january 1995 to december 2008, 85 consecutive patients underwent pneumonectomy: 49 received IT and 36 did not. Demographics, pre and peri-operative sample characteristics for the two pre-surgery treatment groups are shown in Table I. Clinical, pathological and histotype features are summarized in Table II.

Table I. Demographics, pre-operative and peri-operative features in patients undergone pneumonectomy with and without induction therapy.

	IT group (n = 49)	Non-IT group (n = 36)	*p*-value
Age			
Mean ± SD	62.4 ± 10.1	58.4 ± .10.6	0.08T
Gender			
Male	41 (83.7%)	32 (88.9 %)	0.54F
Female	8 (16.3%)	4 (11.1 %)	
Co-morbidity	27 (55.1%)	13 (36.1%)	0.08P
Heart disease	16 (32.7%)	5 (13.9%)	0.07F
Hypertension	20 (40.8%)	6 (16.7%)	0.02F
Diabetes mellitus	8 (16.3%)	2 (5.6%)	0.18F
COPD	20 (40.8%)	9 (25.0%)	0.13P
Symptoms	27 (55.1%)	10 (27.8%)	0.012P
FEV_1 (liters)	2.50 ± 0.76	2.35 ± 0.40	0.28T
Side			
Right	22 (44.9%)	9 (25.0%)	0.06P
Left	27 (55.1%)	27 (75.0%)	
Pericardium	1 (2.0%)	3 (8.3%)	0.31F
Hospital stay (days)	16.35 ± 7.98	9.5 ± 4.33	< 0.0001T
Blood transfusion (n non-IT = 34)	19 (38.8%)	3 (8.3%)	0.002F
Mortality	1 (2.0%)	2 (5.6%)	0.57F
Major Complications	7 (14.3%)	6 (16.7%)	0.76P
Fistula/empyema	1 (2.0%)	2 (5.6%)	0.57F
Pneumonia	1 (2.0%)	0 (0%)	1.00F
Myocardial infarction	1 (2.0%)	0 (0%)	1.00F
Pulmonary embolism (n non-IT = 35)	1 (2.0%)	2 (5.7%)	0.57F
Bleeding	3 (6.1%)	1 (2.8%)	0.63F
Minor complication	13 (26.5%)	6 (16.7%)	0.28P
Arrhythmia	6 (12.2%)	3 (8.3%)	0.73F
Wound infection	1 (2.0%)	0 (0%)	1.00F

Note: T = T-test; F = Fisher's exact test; P = Pearson's χ^2 test.

Table II. Clinical and pathological staging, and histotype features in patients undergone pneumonectomy with and without induction therapy.

	IT group (n = 49)	Non-IT group (n = 36)	*p*-value
cT			
T1	0 (0%)	1 (2.8%)	< 0.0001P, F
T2	7 (14.3%)	27 (75.0%)	
T3	14 (28.6%)	7 (19.4%)	
T4	28 (57.1%)	1 (2.8%)	
cN			
N0	8 (16.3%)	15 (41.7%)	< 0.0001P, F
N1	1 (2.1%)	11 (30.5%)	
N2	40 (81.6%)	10 (27.8%)	
N3	0 (0%)	0 (0%)	
cM			
M1	2 (4.1%)	0 (0%)	0.051F
Clinical stage			
Ib	0 (0%)	11 (30.6%)	< 0.0001P, F
IIa	0 (0%)	2 (5.5%)	
IIb	1 (2.0%)	11 (30.6%)	
IIIa	19 (38.8%)	11 (30.6%)	
IIIb	27 (55.1%)	1 (2.7%)	
IV	2 (4.1%)	0 (0%)	
Histotype			
Adenocarcinoma	23 (46.9%)	16 (44.4%)	0.95F
Squamous	23 (46.9%)	17 (47.3%)	
Large cells	3(6.2%)	3 (8.3%)	
pT			
T0	9 (18.4%)	0 (0%)	< 0.0001F
T1	11 (22.4%)	3 (8.3%)	
T2	8 (16.3%)	23 (63.9%)	
T3	12 (24.5%)	7 (19.5%)	
T4	9 (18.4%)	3 (8.3%)	
pN			
N0	29 (59.2%)	13 (36.1%)	0.11P
N1	10 (20.4%)	11 (30.6%)	
N2	10 (20.4%)	12 (33.3%)	
pM			
M1	5 (10.2%)	0 (0%)	0.07F
Pathological stage			
0	9 (18.4%)	0 (0%)	< 0.0001F
Ia	7 (14.3%)	1 (2.8%)	
Ib	4 (8.2%)	9 (25.0%)	
IIa	1 (2.0%)	1 (2.8%)	
IIb	8 (16.3%)	9 (25.0%)	
IIIa	9 (18.4%)	13 (36.1%)	
IIIb	6 (12.2%)	3 (8.3%)	
IV	5 (10.2%)	0 (0%)	

Note: T = T-test; F = Fisher's exact test; P = Pearson's χ^2 test.

A standard pneumonectomy was performed in 78 cases (91.8%) and an intra-pericardial pneumonectomy was needed in 7 cases (8.2%). In the IT group, 27 (55.1%) patients underwent left pneumonectomy and 22 (44.9%) right pneumonectomy, in the non-IT group 9 (25%) patients underwent right-sided resections and 27 (75%) left-sided resections. The bronchial stump coverage with intercostal pedicled flap was performed in 16 (32.7%) patients in the IT group on the right side, while this procedure was never adopted in the non-IT group.

Overall thirty-day mortality was 3.5% (3/85), where 1 case of myocardial infarction occurred in the IT group and 2 cases of pulmonary embolism occurred in non-IT group.

Major complications occurred in 7 subjects (14.3%) in the IT group and in 6 (16.7%) in the non-IT group ($p = 0.76$). Three patients (3.5%) experienced a late broncho-pleural fistula (1 case in the IT group on the right side and 2 cases in the non-IT group, both on the left side). Two cases of lobar pneumonia required 48 hours of mechanical ventilation and prolonged antibiotic therapy (over 7 days) and 3 cases of segmental pulmonary embolism. The remaining non-respiratory complications were 2 cases of myocardial infarction. Post-operative bleeding was observed in 3 patients in the IT group and 1 in the non-IT group. Nineteen (38.8%) patients in the IT group and 3 (8.8%) in the non-IT group received intra- or post-operative red blood cell transfusion ($p = 0.002$). Among the minor complications we observed supra-ventricular arrhythmias (medically treated), wound infection, fever and disorientation without any difference between the two groups.

Indeed, the mortality and morbidity rates were similar in both sides of pneumonectomy. In particular, in the whole population the deaths were 2/1 for right/left interventions, where 1/0 occurred in the IT group and 1/1 in the non-IT group. The observed morbidity rates for right/left pneumonectomy were 5/8 ($p = 0.87$) in the whole population, and 3/4 ($p = 0.91$) and 2/4 ($p = 0.61$) for the IT and non-IT groups.

The post-operative hospital stay was noticeably longer in the IT group (16.4±8 vs 9.5±4.3). A linear regression on the log-normal transformation of the days of hospitalization suggested that the time of hospitalization was dependent on whether or not pre-operative IT was administered ($p < 0.0001$) and on whether there was a need for red blood cell transfusion during the hospital stay ($p = 0.046$). No evidence for an effect modification of these two factors was found ($p = 0.46$). The model estimation was performed without the inclusion of the interaction term and the results are reported in Table III.

The histological distribution and the pathological stage of the whole study group are shown in Table IV. Five patients in the sole IT group had M1 disease as a result of either solitary brain metastasis (2 patients) or ipsilateral tumor of identical histological type in a separate lobe (3 patients).

Long-term Outcomes

The mean follow-up duration was 36.3±38.1 months.

From the Kaplan-Meier overall long-term survival function (Table IV) it emerged that the 1, 3 and 5 year survival rates were 72%, 48.7% 42.3%. In the whole population, evidence for different survival functions was found for patients who experienced a recurrence vs. those who did not ($p < 0.0001$), and with regards to the pathological staging of the T ($p = 0.028$). With regards to the recurrence, the estimated 5 year survival rates were 14.9% vs. 76.7%.

No evidence of different survival functions for the IT and the non-IT groups of patients was found ($p = 0.63$). The estimated 5 year survival rates were 45.3% and 38.4%, respectively.

Even if the survival rates were slightly higher in patients undergone left pneumonectomy, no significant evidence of different survival functions for the patients who had a left resection and those who had a right resection was found ($p = 0.09$). The survival functions for the patients on and off induction therapy and who had left or right resection were also compared, but no evidence to reject the hypothesis of no difference between the curves was found ($p = 0.34$). Plots of the survival functions are reported in Figure 1.

The Cox multiple regression analysis confirmed the recurrence as a risk factor for earlier death. In particular, it was estimated that patients with a recurrence died at about 5.5 times (95% CI: 2.38-12.82) the rate of patients who did not experience a relapse of the tumor.

Table III. Estimated number of days of hospitalization for patients undergone pneumonectomy with and without induction therapy, and who did, or did not, require a red cells blood transfusion (mean (95% CI)).

	IT group (n = 49)	Non-IT group (n = 36)
No red cells blood transfusion	11.57 (9.43; 14.20)	18.10 (15.59; 21.02)
Red cells blood transfusion	8.68 (7.70; 9.78)	13.57 (12.02; 15.23)

Mean (95% CI).

Table IV. Kaplan-Meier Survival Rates Estimates (95% CI) and Comparison of Survival Curves.

	Follow-Up			Comparison of curves
	1 year	3 years	5 years	Log-rank *p*-value
Long-term survival				
Overall	0.7201 (0.6032 – 0.8079)	0.4871 (0.3603 – 0.6024)	0.4231 (0.2961 – 0.5444)	0.77
Non-IT group	0.6977 (0.4984 – 0.8302)	0.4756 (0.2838 – 0.6450)	0.3844 (0.2020 – 0.5646)	
IT group	0.7348 (0.5798 – 0.8401)	0.4937 (0.3236 – 0.6431)	0.4526 (0.2813 – 0.6092)	
No recurrence	0.8180 (0.5832 – 0.9279)	0.7669 (0.5252 – 0.8964)	0.7669 (0.5252 – 0.8964)	< 0.0001
Recurrence	0.5996(0.4369 – 0.7290)	0.2557 (0.1268 – 0.4063)	0.1491 (0.0517 – 0.2945)	
Left resection	0.7641 (0.6139 – 0.8621)	0.5505 (0.3850 – 0.6885)	0.4520 (0.2869 – 0.6035)	0.09
Right resection	0.6466 (0.4424 – 0.7920)	0.3821 (0.1947 – 0.5679)	0.3821 (0.1947 – 0.5679)	
pT0	1.0000 (. – .)	0.7143 (0.2582 – 0.9198)	0.7143 (0.2582 – 0.9198)	0.15
pT1	0.6923 (0.3734 – 0.8718)	0.3846 (0.1405 – 0.6280)	0.3846 (0.1405 – 0.6280)	
pT2	0.8486 (0.6449 – 0.9404)	0.5778 (0.3517 – 0.7499)	0.5253 (0.3017 – 0.7076)	
pT3	0.3529 (0.1322 – 0.5850)	0.3529 (0.1322 – 0.5850)	0.1765 (0.0145 – 0.4915)	
pT4	0.7407 (0.3907 – 0.9086)	0.4938 (0.1650 – 0.7586)	0.2469 (0.0151 – 0.6271)	
pStage 0/Ia	0.8667 (0.5639 – 0.9649)	0.5778 (0.2899 – 0.7843)	0.5778 (0.2899 – 0.7843)	0.60
pStage Ib	0.9167 (0.5390 – 0.9878)	0.6429 (0.2982 – 0.8510)	0.5357 (0.2104 – 0.7788)	
pStage IIa/IIb	0.4392 (0.1993 – 0.6573)	0.2635 (0.0722 – 0.5084)	0.2635 (0.0722 – 0.5084)	
pStage IIIa	0.6810 (0.4195 – 0.8437)	0.5417 (0.2793 – 0.7448)	0.4063 (0.1342 – 0.6677)	
pStage IIIb/IV	0.7792 (0.4590 – 0.9232)	0.4383 (0.1294 – 0.7170)	0.2192 (0.0138 – 0.5841)	
Left resection – non-IT group	0.7251 (0.4864 – 0.8664)	0.5184 (0.2865 – 0.7080)	0.3950 (0.1803 – 0.6043)	0.34
Left resection – IT group	0.7970 (0.5782 – 0.9103)	0.5782 (0.3370 – 0.7588)	0.5059 (0.2633 – 0.7061)	
Right resection – non-IT group	0.6250 (0.2293 – 0.8607)	0.3750 (0.0870 – 0.6744)	0.3750 (0.0870 – 0.6744)	
Right resection – IT group	0.6555 (0.4094 – 0.8189)	0.3831 (0.1572 – 0.6080)	0.3831 (0.1572 – 0.6080)	

Table continued

Table IV *(Continued)*. Kaplan-Meier Survival Rates Estimates (95% CI) and Comparison of Survival Curves.

	Follow-Up			Comparison of curves
	1 year	3 years	5 years	Log-rank *p*-value
Long-term disease free survival				
Overall	0.7424 (0.6257 – 0.8276)	0.4838 (0.3578 – 0.5987)	0.4027 (0.2782 – 0.5238)	
Non-IT group	0.7282 (0.5279 – 0.8543)	0.4673 (0.2756 – 0.6381)	0.3304 (0.1585 – 0.5139)	0.72
IT group	0.7515 (0.5955 – 0.8543)	0.4970 (0.3298 – 0.6436)	0.4231 (0.2571 – 0.5799)	
Left resection	0.7408 (0.5882 – 0.8440)	0.5229 (0.3645 – 0.6593)	0.4055 (0.2523 – 0.5534)	0.38
Right resection	0.7436 (0.5348 – 0.8691)	0.4056 (0.2043 – 0.5988)	0.4056 (0.2043 – 0.5988)	
pT0	1.0000 (. – .)	0.7143 (0.2582 – 0.9198)	0.7143 (0.2582 – 0.9198)	0.03
pT1	0.8333 (0.4817 – 0.9555)	0.6250 (0.2762 – 0.8423)	0.6250 (0.2762 – 0.8423)	
pT2	0.8486 (0.6449 – 0.9404)	0.4903 (0.2867 – 0.6659)	0.4011 (0.2107 – 0.5853)	
pT3	0.2787 (0.0877 – 0.5115)	0.2787 (0.0877 – 0.5115)	0.1394 (0.0115 – 0.4191)	
pT4	0.8333 (0.4817 – 0.9555)	0.3704 (0.0638 – 0.6987)	0.1852 (0.0094 – 0.5436)	
pStage 0/Ia	0.9333 (0.6126 – 0.9903)	0.7000 (0.3825 – 0.8760)	0.7000 (0.3825 – 0.8760)	0.11
pStage Ib	0.9167 (0.5390 – 0.9878)	0.6429 (0.2982 – 0.8510)	0.5357 (0.2104 – 0.7788)	
pStage IIa/IIb	0.4054 (0.1682 – 0.6330)	0.2027 (0.0497 – 0.4281)	0.2027 (0.0497 – 0.4281)	
pStage IIIa	0.6753 (0.4119 – 0.8405)	0.4297 (0.1981 – 0.6436)	0.3223 (0.1031 – 0.5688)	
pStage IIIb/IV	0.8571 (0.5394 – 0.9622)	0.5143 (0.1796 – 0.7729)	0.1714 (0.0093 – 0.5143)	
Left resection – non-IT group	0.7228 (0.4830 – 0.8652)	0.4771 (0.2558 – 0.6692)	0.3635 (0.1629 – 0.5687)	0.76
Left resection – IT group	0.7551 (0.5332 – 0.8820)	0.5710 (0.3469 – 0.7434)	0.4497 (0.2294 – 0.6480)	
Right resection – Non-IT group	0.7292 (0.2764 – 0.9254)	0.4375 (0.1014 – 0.7419)	0.4375 (0.1014 – 0.7419)	
Right resection – IT group	0.7451 (0.4905 – 0.8856)	0.3871 (0.1532 – 0.6186)	0.3871 (0.1532 – 0.6186)	

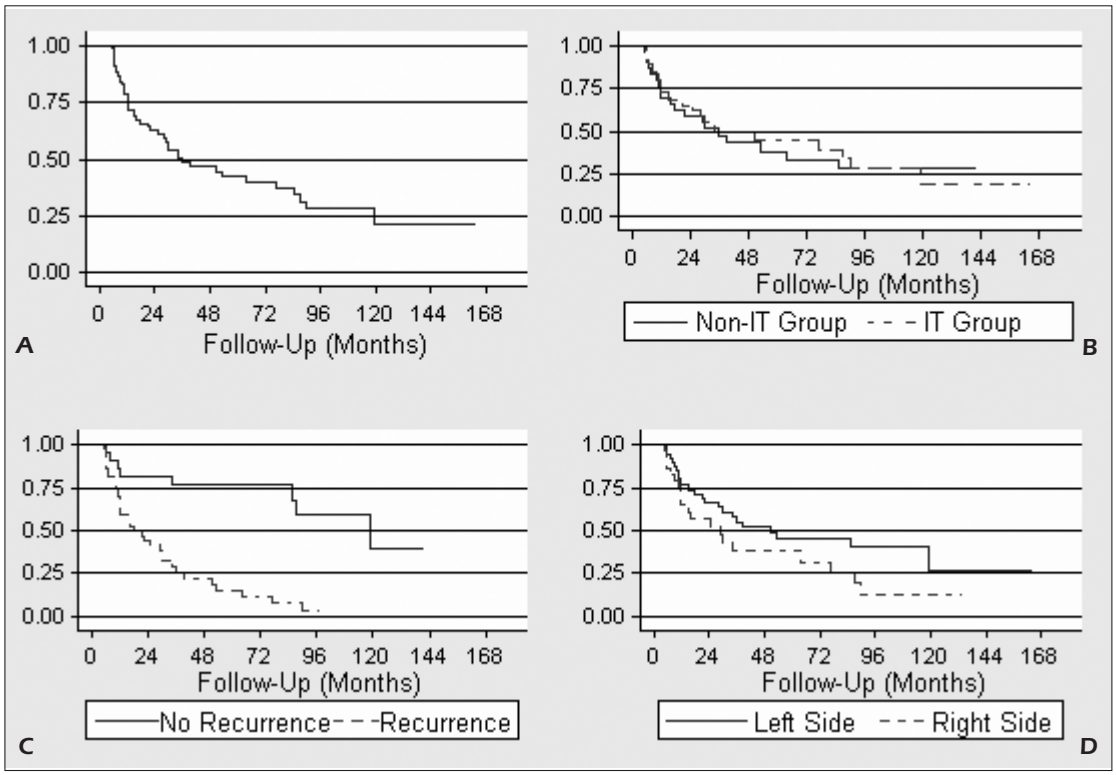

Figure 1. Overall Survival Function ***(A)*** and survival functions for the induction therapy – IT ***(B)***, recurrence ***(C)*** and side of pneumonectomy ***(D)***.

From the Kaplan-Meier disease free survival functions, the following 1, 3 and 5 year overall disease free survival rates were estimated: 74.2%, 48.4% and 40.3%, respectively. No evidence of different disease free survival responses was found for the two pre-resection treatment groups ($p = 0.72$). With regards to the two induction therapy groups the estimated 5 year rates were 42.3% for the IT group and 37.8% for the non-IT group.

Evidence of different curves was found for pathological stage ($p = 0.02$), T staging ($p = 0.03$) and even more N staging.

Finally, no evidence of different disease free survival functions for the patients who had a left resection and those who had a right resection was found ($p = 0.38$). The disease free survival functions for the patients on and off induction therapy and who had left or right resection were also compared, but no evidence to reject the hypothesis of no difference between the curves was found ($p = 0.76$). Plots of the disease free survival functions are reported in Figure 2.

The Cox multiple regression analysis could not confirm with strong evidence the role of the pathological tumor size and the pathological staging as risk factors for the event of a recurrence. Selected output from the survival analysis is reported in Table IV.

Discussion

Today, one of the goals of modern surgery is to obtain the best oncological results removing any functioning healthy tissue to the minimum extent while still maintaining the criteria for completeness. The rationale beyond this attitude lays in the need to avoid "larger" resections, often correlated with worse morbidity and mortality rates. This evidence is particularly and specifically true for pulmonary resections where morbidity and mortality are positively related to the extent of parenchymal resection and where the damage of the lung function after surgery can have a negative impact on the long term survival and quality of life. However, the pneumonectomy is a relatively safe operation with a 30-day mortality rate of 6-12% and remains the unique

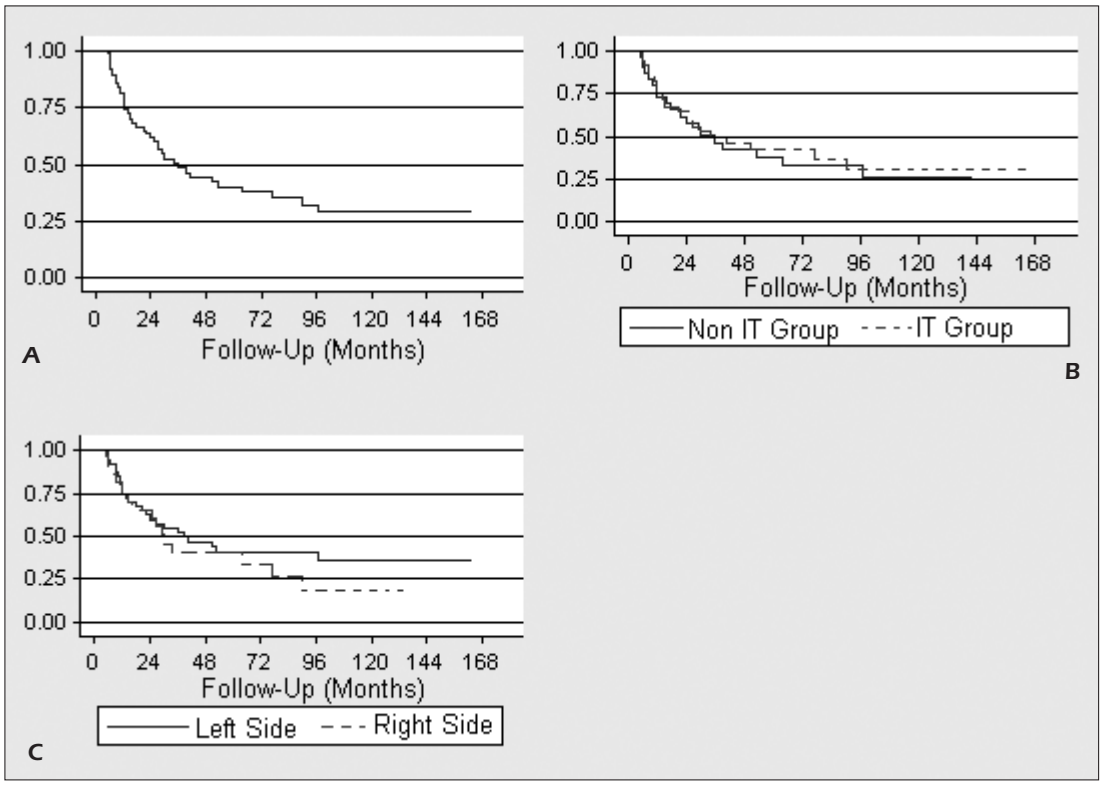

Figure 2. Overall Disease Free Survival Function ***(A)*** and disease free survival functions for the induction therapy – IT ***(B)*** and side of pneumonectomy ***(C)***.

chance of cure in patients where pulmonary lobectomy or parenchymal sparing procedures are unviable[12].

Surgery, except in NSCLC stage I-II diseases, often follows the IT chemo or radio-therapy. Pre-operative IT has increased the number of patients who, initially judged to be inoperable, re-enter the criteria for the indication of a radical procedure. In fact, there is a general consensus that a multimodality treatment offers a clear survival benefit for these patients[1,2,8,11].

On the other hand, the administration of any IT protocol is, to a various extent, correlated with an increased rate of intra and post-operative complications and overall long term survival. The risks of intra and post-operative complications after IT have been largely debated in literature, especially in patients undergoing pneumonectomy, with emphasis on side effects peculiarly induced by radiotherapy[4,13,14]. Indeed, several Authors[6,7] have shown that pneumonectomy is more risky after IT and concluded that a pneumonectomy, particularly if right sided, should follow IT only in selected cases. This finding has raised skepticism towards pneumonectomy as a surgical option for patients with regionally advanced non small-cell lung cancer, initially treated by a combination of chemo and radiation therapy.

The recent implementation of protocols administering chemotherapy followed by chemo-radiation has raised an issue on pneumonectomy[10,15,16]. The initial postulate affirming the absence of justification for pneumonectomies following IT for unacceptable peri-operative risk[6,7] is being revised in the light of enhanced and optimized IT treatments (i.e. the uniform adoption of linear accelerators instead of Co60 apparatuses, ameliorated treatment plans aided by computer-simulated verifications and better peri-operative management as more extensively discussed below[17]).

Very recently on this line of reasoning, Gaissert et al[10] reported an hospital mortality of 4.3% following pneumonectomy after IT and 6.6% after pneumonectomy alone; Stamatis et al[4] reported similar figures: post IT pneumenctomy 30-day mortality of 7.2%; and Gudbjartsson et al[9] described only one patient dead in patients group undergone surgery and no-one in patients undergone pneumonectomy after IT. Therefore, limited

published series have reported pulmonary resection after higher dose radiotherapy treatments (>59 Gy) and concurrent chemotherapy, with acceptable post-operative morbidity and mortality rates[8,18,19].

Our findings are in line with those of the recent literature: we report a post-pneumonectomy overall mortality rate of 3.5% , with a 30-day mortality rate of 2% in the IT group, and 5.5% in the non-IT group. Our investigation neither showed any particular association between post-operative mortality and preoperative features, and, most importantly, no association with the side of pneumonectomy. The ability to safely perform a pneumonectomy after radiotherapy in our and other series may be attributed to several factors. First the development of sophisticated 3D-radiation treatment planning systems over the last decade has provided the opportunity to maximize radiation doses to the intended targets minimizing exposure to surrounding normal tissue. Second, we could also hypothesize that removal of all irradiated lung by pneumonectomy after induction radio-chemotherapy may reduce the appearance of complications due to actinic damages to the lung.

In our single-institution study we report a major complication rate of 14.3% in IT group vs. 16.7% in non-IT group with non statistically significant differences between the two groups. We report only 1 case (2%) of broncho-pleural fistula in the IT group after right pneumonectomy and 2 cases in the non-IT group (5.5%) both operated on the left side, and no differences in bronchopleural fistula, empyema, pneumonia and pulmonary embolism were found. Similar results derive from the Gudbjartsson et al[9] and Stamatis et al[4] series.

Controversy exists about the need for, and the benefit deriving from, the coverage of the bronchial stump by different techniques[20], including the use of pleural, pericardial, mediastinal fat pad grafts and pedicled intercostal muscle flaps, with various degrees of success[20,21]. Based on this situation, we prefer to cover the bronchial stump after IT and on the right side with intercostal muscle pedicled flaps. This approach is shared by several other thoracic surgery centers[21,22].

The post-operative hospital stay was significantly higher in the IT group. However, the difference among the major and minor complication rates in the two IT groups was not significant. The frequency of the need for transfusion was significantly higher in the IT. We could speculate that the patients in the IT group need more often blood transfusions due to the clinically significant lower baseline hemoglobin levels and for the relatively higher appearance of bleeding (6.2%). This situation may, in turn, justify the significantly higher prolonged hospital stay, even though no evidence for an association between complications and prolonged hospital stay emerged from our study.

The long term survival is directly correlated with the staging and the indications for the IT are strictly linked to a particular clinical stage. For this reason, many Authors did not report the comparison of IT vs. non-IT groups on the long term survival (LTS) outcome focusing their discussion on the peri-operative mortality and complications rate. However, taking into account the differences between clinical and pathological stages of the two groups, we could observe a good, and non-statistically different, long term survival rates in both groups. This could be justified by the relatively high number of "responders" as evidenced at the pathological staging in the IT group: we reported a complete pathological rate of 18.4% (9/49) with an overall pathological downstaging rate of 77.5%. Good levels of survival rates following IT have been recently reported by the recent experiences of Daly et al[23], who described a 5-yr survival of 33% in 30 patients who underwent pneumonectomy after high-dose IT, and of Gudbjartson et al[9], who reported figures of 46% in IT and 34% in the non-IT group. Althought several Authors have experiences good long-term survivals in patients underwent pneumonectomy after IT, only few papers have been planned to find all the prognostic factors that may have a potential impact on the LTS in these patients. Kim et al[24] in their retrospective analysis of 129 pneumonectomies after IT showed different outcome according with pathological N-status changes after IT, with a worst prognosis for patients with persistent N2-disease after IT. In this setting, the rationale to perform a pneumonectomy after IT seems to be closely related also with oncological considerations. Indeed long-term outcome is poor if a persistent of N2-disease is found at pathological evaluation as clearly reported in our recent paper regards of LTS in patients with persistent N2-disease after IT[25]. Thus even if pneumonectomy after IT in N2-patients could be technically feasible with reasonable morbidity/mortality

rates, it should be limited only in very selected cases and, in principle, not recommend. Finally, no differences were observed stratifying for gender, age, smoking habits, respiratory functional parameters, and different co-morbidities. Despite the fact that post-operative mortality and morbidity rates did not increase after right-side operations as reported by Stamatis et al[4] ans Daly et al[23], patients undergoing right pneumonectomy in our study had a slightly worse long term outcome than those operated on the left side (5-yr survival of 38.2% vs. 45.2%, p = 0.09. The datum for patients who underwent IT is not confirmed by Kim et al[24]. We can hypothesize that the potential causes for such an imbalanced laterality risk was perhaps not related to a different relapse rate between right and left side. Instead, we believe it could be the consequence of a tendency towards a greater risk to develop respiratory or cardiac complications in the right resections, independently from IT administration.

The main limitation of our study is its retrospective nature. Indeed, the size of the IT group in our investigation is relatively small and this may lead to an imprecise estimation of the effects of the IT on mortality. Another point of weakness is the very long period (13 years) covered by the study, where IT protocols have changed. This has certainly introduced heterogeneity due to the peculiarities (response rates, side effects, etc.) of each one of the adopted chemotherapy regimens, radiotherapy administration and their combinations.

Conclusions

Our findings indicated that pneumonectomy is a feasible and safe procedure even after IT. We can summarize that neither operative mortality nor morbidity seem to be directly associated with IT, even if the length of hospital stay and the need for blood transfusion in the IT group were significantly higher. Regarding the long term results (survival), we report acceptable long term and disease free survival rates even in right resections.

On the basis of our results, pneumonectomy shall be indicated when lesser resection cannot allow a radical resection in the context of a multidisciplinary approach, also including IT.

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