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Operative complications and early mortality after induction therapy for lung cancer☆

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Abstract

Objective: Induction therapy for advanced lung cancer allows improvement of completeness of resection and survival. However, predictive risk factors for postoperative complications and early mortality remain controversial. We report our 14-year experience with this combined approach. **Methods:** One hundred and thirty-nine patients (100 males and 39 females) underwent induction therapy and surgery for stage IIIA and B lung cancer. The mean age was 58.4 ± 7.7 years. We retrospectively collected demographic data, preoperative functional parameters, type of operation, associated disorders, staging, induction regimen (chemotherapy alone or associated with radiotherapy). Univariate and multivariate analyses were performed to identify predictors of postoperative complications and early mortality. **Results:** One hundred and nine patients received chemotherapy (mainly based on cisplatin and gemcitabine) and 30 received chemoradiotherapy (median dose 50 Gy). Complications developed in 49 patients (35%). The most frequent was persistent air leakage (23—30% of the lobectomies), followed by cardiac complications, respiratory failure, and infections. Five patients (3.5%) died in the postoperative period and four of them had received pneumonectomy (mortality for pneumonectomy: 12.5%). The statistical analysis demonstrated that only pneumonectomy was associated with an increased mortality risk with no differences between intra- and extrapericardial dissection or right and left pneumonectomy. **Conclusions:** Induction therapy seems to be associated with an increased incidence of air leakage; the risk of other complications is acceptable. Pneumonectomy is associated with an increased risk of mortality and should be performed in selected patients.

Keywords: Lung cancer; Induction; Neoadjuvant therapy; Morbidity; Mortality

1. Introduction

Lung cancer is a leading cause of death worldwide. Similar to many other solid cancers, surgical treatment offers the best chance for cure for patients with lesions at early stages. However, only a few patients with non-small-cell lung cancer (NSCLC) in stage III A and B show a primary indication for surgery alone [1—3]; at this stage a combination of local and systemic therapy has progressively gained acceptance, and induction strategies have been tested in extended Phase II trials and randomized trials [4,5]. Induction (neoadjuvant) chemo- and radiotherapy, alone or in association, have been proposed to downstage the tumors and improve completeness of resection and survival. Although there is a general acceptance that this approach contributes to ameliorate outcome at this advanced stage, the influence of induction therapy on postoperative outcomes remains controversial [6,7]. Some studies reported an increased incidence of postoperative complications and mortality [7—9], while others observed an early outcome comparable with that of patients receiving surgery alone [6].

We retrospectively reviewed our group of patients undergoing preoperative chemotherapy or chemoradiation to identify potential predictive factors for postoperative morbidity and mortality.

2. Patients and methods

We retrospectively reviewed our experience since 1992 with patients receiving preoperative chemotherapy or chemoradiation before thoracotomy for stage IIIA and B NSCLC. Patients with N2 disease were staged by mediastinoscopy; T4 invasion was assessed clinically (CT, RMN). Patients with N3 disease were not included as this is considered a contraindication for surgery. Most of T4 patients had extended invasion of the mediastinum. Remediastinoscopy after induction was not routinely performed. Patients

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undergoing exploratory thoracotomy (#2) were not included in the present study. Six patients were lost to long-term follow-up, but their data were available for the evaluation of postoperative morbidity and mortality.

Preoperative data collection included age, sex, stage of the tumor, forced expiratory volume in one second (FEV_1), and arterial oxygen pressure tension (PaO_2). Details of the surgical procedure were also collected: type of operation (lobectomy, bilobectomy, wedge resection or pneumonectomy; side of the operation, association to reconstruction of the bronchus and/or pulmonary artery). Length of thoracic drainage and hospital stay, as well as postoperative complications occurring within 30 days after surgery, and death, were noted.

We analyzed age (threshold 60 years), stage (IIIA vs IIIB), gender (male vs female), FEV_1 (threshold 70% predicted), and type of induction (chemo vs chemo plus radiotherapy), presence of associated disorders, type of operation (lobectomy vs pneumonectomy, right vs left pneumonectomy, bronchovascular reconstructions).

Univariate analysis of factors associated with postoperative morbidity and mortality was performed fitting the unconditional logistic regression models of Breslow and Day [10]. The reviewed predictive factors for complications and mortality were age, stage, FEV_1, PaO_2, as well as variables related to the surgical procedure. A multivariate analysis was performed fitting a Cox proportional hazard model [11]. Statistical tests (two-tailed) were considered significant at the 0.05 level.

3. Results

We reviewed the charts of 139 patients (100 males and 39 females; mean age 58.4 ± 7.7 years). The mean preoperative FEV_1 was 2.2 l/s (range 1.3—3.1), the mean PaO_2 was 84 ± 6 mmHg, and the mean hemoglobin level before surgery was 11.3 g/dl. The median ECOG score was 0. Histologic tumor analysis detected 63 (45.3%) epidermoid carcinomas, 48 (34.6%) adenocarcinomas, 9 (6.5%) large cell neuroendocrine carcinomas, 7 indifferentiated carcinomas (5%), 6 large cell carcinomas (4.3%), and 6 mixed adenosquamous tumors (4.3%). Seventy-four (53.3%) patients were staged IIIA and 65 (45.7%) were staged IIIB.

All patients received preoperative chemotherapy: cisplatine—gemcitabine in 96 patients (69%), cisplatin—paclitaxal in 9 (6%), carboplatine—vinorelbine in 6 (4%), and other cisplatinum-based regimen in the rest of the patients. One hundred and nine patients (78.4%) received chemotherapy alone and 30 (21.6%) received chemoradiotherapy (40—50 Gy). The heterogeneity of the induction regimen is related to the fact that many patients (especially T4 tumors) were referred to our center after being evaluated by others. All patients were taken to thoracotomy 3—5 weeks after the end of induction treatment.

Associated disorders were chronic obstructive pulmonary disease (COPD) ($FEV_1 < 70\%$) in 34 patients (23.5%), diabetes in 54 (38.9%), systemic hypertension in 42 (30.2%), and cardiac disorders in 9 (6.5%).

We performed 34 pneumonectomies (24.4%): 18 right and 14 left, 8 intrapericardial, 2 associated to carinal resection; 7 bilobectomies (5%) were performed, 1 (0.7%) wedge resection, and 99 lobectomies (71.2%): 2 were associated to resection and reconstruction of the superior vena cava, 24 to a bronchial sleeve resection (22%), 15 to a reconstruction of the pulmonary artery (14%), and 7 to a combined bronchovascular reconstruction (6.5%). Postoperative thoracic drainage lasted 8 ± 6 days; hospitalization lasted an average of 15 ± 12 days.

Fifty-three patients showed complications (38%); the most frequent was a prolonged air leakage (30% of the lobectomy patients); cardiac arrhythmia and myocardial failure were present in nine cases (6.5%), pneumonia in three (2.2%), bronchopleural fistula in one patient receiving pneumonect-

Table 1
Univariate analysis for morbidity

Variables		No. pts. (%)	No. compl. (%)	*p*-value
FEV_1	>70%	105 (75.5)	33 (31.4)	0.2
	<70%	34 (24.5)	16 (47)	
Age	>60 y	66 (47.5)	22 (33.3)	0.8
	<60 y	73 (52.5)	27 (37)	
Gender	Male	100 (72)	35 (35)	0.9
	Female	39 (28)	14 (36)	
Stage	IIIA	74 (53.3)	30 (40.5)	0.1
	IIIB	65 (46.7)	19 (29.2)	
Induction	CHT alone	109 (78.4)	38 (35)	0.7
	CHT + RT	30 (21.6)	11 (37)	
Comorbidities	Yes	73 (52.5)	24 (33)	0.5
	Not	66 (47.5)	15 (23)	
Surgery	Pneumo	32 (23)	9 (28)	0.5
	Lobe	106 (77)	40 (37)	
Surgery	Right PN	18 (56.2)	5 (28)	0.9
	Left PN	14 (43.8)	4 (29)	
Bronchovascular	Yes	39 (28)	12 (31)	0.1
	Not	100 (72)	37 (37)	

Table 2
Univariate analysis for mortality

Variables		No. pts (%)	Death (%)	*p*-value
FEV_1	>70%	105 (75.5)	3 (2.8)	0.4
	<70%	34 (24.5)	2 (5.8)	
Age	>60 y	66 (47.5)	2 (3)	0.7
	<60 y	73 (52.5)	3 (4.1)	
Gender	Male	100 (72)	4 (4)	0.6
	Female	39 (28)	1 (2.5)	
Stage	IIIA	74 (53.3)	3 (4)	0.5
	IIIB	65 (46.7)	2 (3)	
Induction	CHT alone	109 (78.4)	3 (3)	0.3
	CHT + RT	30 (21.6)	2 (6)	
Comorbidities	Yes	73 (52.5)	3 (4.1)	0.7
	Not	66 (47.5)	2 (3)	
Surgery	Pneumo	32 (23)	4 (12.5)	0.002
	Lobe	106 (77)	1 (0.9)	
Surgery	Right PN	18 (56.2)	3 (16.6)	0.7
	Left PN	14 (43.8)	1 (7.2)	
Bronchovascular	Yes	39 (28)	1 (2.5)	0.6
	Not	100 (72)	4 (4)	

Table 3
Multivariate analysis for morbidity

Variable	SE	*p*-value	OR	−95%CL	+95%CL
Age	0.458	0.98	1.012	0.406	2.519
FEV_1	0.552	0.14	2.247	0.749	6.736
Comorbidities	0.446	0.81	1.113	0.459	2.705
Gender	0.589	0.42	0.621	0.192	2.003
Sleeve	0.59	0.35	0.578	0.178	1.871
Pneumonectomy	0.604	0.43	1.612	0.486	5.347
Stage	0.473	0.25	0.581	0.227	1.490
Induction regimen	0.547	0.83	1.126	0.379	3.347

Cut-off for age: 60 years; cut–off for FEV_1: 70%.

Table 4
Multivariate analysis for mortality

Variable	SE	*p*-value	OR	−95%CL	+95%CL
Age	1.435	0.322	4.139	0.238	71.72
FEV_1	1.417	0.486	0.373	0.022	6.23
Comorbidities	1.454	0.309	4.382	0.243	78.86
Gender	1.752	0.684	2.038	0.062	66.35
Sleeve	1.856	0.326	6.193	0.155	24.75
Pneumonectomy	1.448	0.05	16.76	0.942	298.1
Stage	1.448	0.106	10.34	0.562	183.8
Induction regimen	1.626	0.434	0.28	0.011	7.108

Cut-off for age: 60 years; cut–off for FEV_1: 70%.

omy (0.7%), emphyema in two (1.4%), and respiratory failure in three (2.1%); three patients (2.2%) required multiple fiberoptic bronchoscopies for retention of secretions.

Overall, five patients died after surgery (3.5%): three after right pneumonectomy (two septic shock, one myocardial failure), one after left pneumonectomy (myocardial failure), one after right upper lobectomy (respiratory failure). Univariate (Tables 1 and 2) and multivariate (Tables 3 and 4) analyses showed that no variable had an impact on morbidity; only pneumonectomy showed an impact ($p = 0.05$) on mortality with no differences between right and left pneumonectomy.

4. Discussion

The heterogeneity of stage III patients has led to controversies regarding their management. This subset of patients includes some T3 patients with chest wall invasion and positive lymph nodes, patients with mediastinal fat involvement, patients with N2 and N3 disease, or with extended invasion of the mediastinal structures. They are reported as stage IIIA and B. Some clinical presentations are clearly not suitable for surgery (N3, T4 with extended invasion of vital or unresectable structures); some other cases could and should be resected. It is now accepted that stage IIIA (N2) lesions and some stage IIIB tumors may benefit form induction chemotherapy or chemoradiotherapy.

Even if this approach is now well accepted, controversies still exist about the surgical risk related to the administration of neoadjuvant therapy. The incidence of postoperative morbidity and mortality has been retrospectively analyzed in several studies [4–6,8,9,12–14] (Table 5); Depierre et al. [8] and a few other authors [7,9] showed increased post-operative complications after induction chemotherapy, while

Table 5
Postoperative morbidity and mortality in studies including patients receiving induction therapy for non small cell lung cancer

Author	Year	Nr. Pts.	Stage	Morbidity (%)	Mortality (%)
Pass et al. [14] (*)	1992	13	IIIA	23	0
Rosell et al. [5] (*)	1994	60	IIIA	(***)	7
Roth et al. [4] (*)	1994	28	IIIA	10	0
Depierre et al. [8] (*)	2001	167	IB, II, IIIA	14	6.7
Perrot et al. [6]	2005	114	I, II, III	29	1.8
Daly et al. [20] (**)	2006	30	II, III	17	13.3
Brunelli et al. [21]	2006	70	I, II, III	36	2.9
Martin et al. [9]	2001	470	I, II, III, IV	38	2.4
Doddoli et al. [17] (**)	2005	100	III, IV	(***)	12
Venuta (PS)	2006	139	III	37	3.5

(*): Randomized studies; in the table only the arm receiving induction has been included. (**): Only pneumonectomis are included in these studies. (***): Precise value not available in the manuscript. PS: present study. Nr. Pts: number of patients.

others did not observe such an increase [6]. Mortality ranges from 0 to 20% [9,15–21] while the rate of postoperative complications is around 30%. The causes of death reported more frequently were respiratory distress, pneumonia, bronchopleural fistulas, and emphyema. The analysis of the literature shows that both postoperative morbidity and mortality are higher after pneumonectomy [6,9,13], with an increased risk of respiratory complications [7] over the age of 70. Our study confirmed these data: also in our group of patients pneumonectomy was a predictive factor for increased risk of death; in our experience, there was no difference between right and left pneumonectomy and intra- and extrapericardial pneumonectomy.

It has been postulated that the increased rate of respiratory complications in patients undergoing induction chemotherapy may be related to the temporary decrease in the diffusion capacity of the alveolo–capillary membrane (between 15 and 40%) [22]. This would amplify the damage induced by one lung ventilation and fluid and pressure overload. The concurrent administration of chemo and radiotherapy did not add any additional risk. Mortality after pneumonectomy in our experience was 12.5%; it was lower when compared with the series from Martin et al. [9], but in line with other reports [6]. From a review of the literature the most frequent causes of death after pneumonectomy were respiratory distress, broncho–pleural fistula and infections, and our experience confirmed this information. However, larger series of patients undergoing pneumonectomy should be considered to assess the potential role of the intrapericardial dissection or the association with resection and reconstruction of the superior vena cava and carina.

Age, FEV_1, and the presence of associated disorders did not show an impact on morbidity and mortality; this certainly reflects the improvement in surgical technique, anesthesia, and postoperative management. However, in the lobectomy patients the incidence of prolonged air leaks is certainly higher when compared with the standard population [23]; this complication was not related to any of the variables considered for statistical evaluation, even if we would have expected an higher incidence in patients with COPD.

In conclusion, after induction chemoradiotherapy for NSCLC the incidence of postoperative complications is certainly acceptable, although an increased incidence of

prolonged air leaks can be expected after lobectomy. Pneumonectomy is associated with an increased risk of mortality; this observation strongly suggests the importance of postinduction restaging avoiding pneumonectomy in nonresponders; it should also encourage more attention to alternative options as bronchovascular reconstructions whenever feasible (to avoid pneumonectomy), and also radiotherapy.

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Appendix A. Conference discussion

Dr F. Leo (*Milan, Italy*): Do you have any information about the type of chemotherapy used in these patients?

Dr Venuta: Yes. All the patients had a cisplatin-based regimen, and most of them had an association between cisplatin and gemcitabine.

Dr B. Yildizeli (*Istanbul, Turkey*): I noticed that 22% of patients have undergone sleeve lobectomy. This is a little bit of a high number. You should be congratulated because I think you tried to preserve the lung. Do you think that the cause of the increased incidence of air leakage is because you have performed many sleeve lobectomies?

Dr Venuta: No, we believe that there is no correlation between the increased incidence of air leaks and the percentage of sleeve lobectomies performed.

Editorial comment

Dr Venuta and colleagues have provided a well written and important report on their fourteen year experience of pulmonary resection in patients with non-small cell lung cancer who have received neo-adjuvant chemo or chemo-radiotherapy [1]. The main import from this retrospective study is that lobectomy can be performed safely after neoadjuvant chemo-radiotherapy in experienced hands. Several previous articles have also supported this finding. The importance of muscle flaps or pedicled flaps to protect the bronchus, although not mentioned in this article cannot be underestimated. Thus, the only controversy presented is the risk of pneumonectomy after induction chemotherapy or concomitant chemo-radiotherapy.

The most striking finding from Dr Venuta's study is that four of the five operative deaths occurred in patients who underwent pneumonectomy. First, this means that only one of the 106 patients who underwent lobectomy experienced an operative mortality. This fantastic result lauds the outstanding technical expertise of Dr Venuta and his surgical colleagues, since lobectomy after preoperative therapy is