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A quarter of a century experience with sleeve lobectomy for non-small cell lung cancer☆

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Abstract

Objective: Sleeve lobectomy represents an effective and widely accepted surgical therapy for non-small cell lung carcinoma (NSCLC). We sought to review our experience in terms of mortality, early and late morbidity, and long-term survival evaluating the technical progresses overtime. **Material and methods:** From 1980 to 2005, 199 patients underwent sleeve lobectomy. Pathology revealed 167 (83.9%) squamous carcinomas, 23 (11.6%) adenocarcinomas, 7 (3.5%) large cell and 2 (1%) adenosquamous carcinomas. In 39 (19.6%) patients a vascular procedure was associated. Nineteen (9.5%) patients had preoperative radiotherapy, 14 (7%) preoperative chemotherapy and 10 (5%) chemoradiotherapy. **Results:** Overall postoperative mortality was 4.5% ($n = 9$) and morbidity was 17.9% ($n = 34$). Preoperative radiotherapy was identified as a significant risk factor for perioperative mortality (OR: 5.34, 95% CI: 1.16—24.47; $p = 0.03$) and early anastomotic complications (OR: 3.73, 95% CI: 1.01—13.68; $p = 0.04$). Overall 5-year survival rate was 39.7% and stage-by-stage analysis did not reach a significant survival difference. With growing skills the number of procedures, associated angioplasty and difficult sleeves (such as sleeve bilobectomy) increased. Also in term of mortality, in the last 10 years we had 0.8% of mortality rate. **Conclusions:** Sleeve lobectomy is a safe and effective therapy for selected patients with NSCLC. Vascular procedures and the use of induction chemotherapy did not increase mortality and morbidity; otherwise, the use of preoperative radiotherapy is not recommended. Overtime trend showed a significant lower mortality in the last period. This emphasises the importance of a learning curve and encourages the performance of this procedure in experienced centres.

Keywords: Sleeve lobectomy; Lung cancer; Survival; Morbidity; Mortality

1. Background

The principle of bronchial sleeve resection was first introduced in 1947 by Sir Clement Prince Thomas [1], and the first sleeve lobectomy for bronchogenic carcinoma was reported by Allison in 1954 [2]. At first many surgeons were reluctant to apply this procedure due to reports of high operative mortality and morbidity rates. However, with better understanding of bronchial healing, improvement in suture material and technical skills, the procedure gradually gained wide acceptance among thoracic surgeons [3].

Nowadays, in centres with large experience in broncho-plastic surgery, sleeve lobectomy has become a well accepted procedure for centrally located carcinoma invading the origin of a lobar bronchus and/or the distal main bronchus not only for patients with compromised pulmonary function but also for patients who can tolerate pneumonectomy [4—6].

A concern still exists on the possibility of increased risk of local recurrence; also, there are different opinions about the application of the procedure in patients with lymph node involvement [7].

Our experience covers a period of 25 years, in which a total of 296 sleeve resections (199 for NSCLC) were done.

The purpose of this retrospective study was to assess short and long-term results of sleeve lobectomy for NSCLC, analyzing factors influencing outcome and long-term survival and describing technical progresses over time.

2. Materials and methods

Between 1980 and 2005, 4027 patients underwent curative resection for NSCLC at the Division of Thoracic Surgery, University of Padua. Out of these, 199 (4.9%) patients underwent sleeve lobectomy and represent the

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Table 1
Patient characteristics

		Number (%)
Age	Median 65 years	Range (45—79 years)
Gender	M/F	182/17 (91.5/8.5)
Neo-adjuvant treatment	Y/N	43/156 (21.6/78.4)
Side	Right/left	136/63 (68.3/31.7)
pT-status	Tx	2 (1)
	T2	120 (60.3)
	T3	67 (33.7)
	T4	10 (5)
pNodal status	N0	84 (42.2)
	N1	81 (40.7)
	N2	34 (17.1)
pTNM stage	x	2 (1)
	I	51 (25.6)
	II	81 (40.7)
	III	65 (32.7)
Histology	Squamous	167 (83.9)
	Adenocarcinoma	23 (11.6)
	Adenosquamous	2 (1)
	Large cell carcinoma	7 (3.5)
Vascular procedures	Y/N	39/160 (19.6/80.4)
Positive bronchial margin	Y/N	16/183 (8/92)

subject of the study. Patients with benign or other malignant pathology were not considered in this study.

The study was approved by the institutional review board. Data were obtained from the hospital database, referring physicians, patients or their families.

Table 1 summarises demographic, surgical and pathological data.

Preoperative staging included a chest X-ray and chest and upper abdomen computed tomography (CT). Additional investigations for detecting distant metastases included head CT, a bone scan and, starting from January 2000, positron emission tomography (PET). Every patient underwent bronchoscopy to carefully assess the extent of airway involvement and to plan the surgical operation.

Induction therapy was planned in patients who were diagnosed to have N2 disease by mediastinoscopy on the basis of CT and PET scans features. Also at the beginning of our experience patients with a tumor in proximity to the pulmonary artery received radiotherapy.

All patients operated on before 1997 were restaged according to the revised international TNM staging for lung cancer [8].

The technique of sleeve lobectomy has been described in many works [9,10]. Our technique in brief: after careful dissection and resection of the target lobe, bronchial anastomosis is usually performed with 3-0 polyglactin (Vicryl, Ethicon, Inc., Somerville, NJ), using interrupted sutures technique. In some cases of difficult sleeves (e.g. left lower sleeve lobectomy, right lower sleeve bilobectomy) we adopted a multiple running suture technique by using three continuous sutures of 4-0 polydioxanone suture (PDS, Ethicon, Inc., Somerville, NJ). In most patients ($n = 155$; 77.9%) we covered the anastomosis with a viable tissue flap (pericardial $n = 120$, pleural $n = 19$ or intercostal muscle $n = 16$) with the primary aim being to separate the bronchial anastomosis from the vascular structures and to create a blood support to the suture line.

At the end of the procedure, the anastomosis was checked with bronchoscopy and any blood clots or secretions were carefully cleaned up. Starting from 1995 a low dose of systemic and inhaled steroid therapy as described by Rendina et al. [11] was prescribed for the postoperative period in order to reduce the oedema of bronchial mucosa.

Anastomosis was checked by bronchoscopy before discharge and, during follow-up at the end of the first, third and sixth postoperative months, then every year or when clinically indicated afterwards.

Operative mortality included all deaths observed within 30 days of the operation or during the same hospitalisation. Locoregional recurrence was defined as recurrence of the original histological type in the ipsilateral hemithorax.

2.1. Statistical analysis

The relationships between short-time events (perioperative mortality and bronchial morbidity) and predictive factors have been evaluated by means of chi-square test. Unadjusted OR (95% CI) were estimated by means of logistic regression models. The same approach was applied to identify the predictors of long-term events (local and distant recurrences). In these analyses, histology, stage and nodal status were dichotomised as follow: squamous versus non-squamous, stage I/II versus III, and N0 versus N1/2, respectively.

Survival was measured from the date of surgery to death or the last follow-up (March 2006) and was calculated according to the Kaplan—Meier method. Survival curves were compared statistically using the log rank test. Cox proportional hazard multivariate regression model was used to evaluate the independent role of different prognostic factors on survival.

In the analyses, significance level was set at 0.05.

3. Results

A total of 43 (21.6%) patients received induction therapy. Fourteen (7%) patients received neoadjuvant chemotherapy, 10 (5%) chemo-radiotherapy and, in the early period of the study 19 (9.5%) patients received low-dose (30 Gy) radiotherapy.

We performed 136 (67.8%) sleeve resections on the right side and 63 (32.2%) on the left. In 14 (7%) patients a concomitant sleeve resection of the pulmonary artery was done; in 25 (12.6%) patients a partial resection of the pulmonary artery was performed and the defect was reconstructed with direct suture in 22 patients and with a fresh autologous pericardial patch in 3 patients. Complete resection was achieved in 183 (92%) patients; in 16 (8%) patients there were microscopically positive margins on definitive examination, despite negative frozen sections at the time of surgery in all cases.

pTNM stages were as follow: 51 (25.9%) stage IB, 3 (1.5%) stage IIA, 78 (39.1%) stage IIB, 55 (27.9%) stage IIIA and 10 (5.1%) stage IIIB.

No intraoperative death occurred, nine patients (4.5%) died within 30 days of surgery. The causes of death were

Table 2
Postoperative complications

Type of complication	Number of patients	Mortality (*n*)
Early		
Bronchovascular fistula	4	4
Bronchopleural fistula	1	
Bronchial stenosis	9	
Pulmonary embolism	4	3
Respiratory failure	1	
Atrial fibrillation	11	
Myocardial infarction	1	1
Empyema	1	
Haemothorax	1	
Chylothorax	3	
Prolonged air leak	8	
Laryngeal nerve paralysis	1	
Acute renal failure	1	1
Late		
Bronchial		
Moderate bronchial stenosis	9	
Severe bronchial stenosis	12	
Bronchopleural fistula	1	
Pneumonia	4	
Cardiac complications	4	
Empyema	1	

bronchovascular fistula in four patients, pulmonary embolism in three, myocardial infarction in one and acute renal failure in one.

Thirty-four (17.9%) patients experienced one or more perioperative complication (Table 2). Ten (5.3%) patients developed early anastomotic complications: nine had a bronchial stenosis, managed by endoscopic dilatation and stent insertion ($n = 4$), by completion pneumonectomy ($n = 2$) or by laser therapy ($n = 1$). In two patients with mild asymptomatic stenosis, no treatment was required and a strict endoscopic follow-up was planned.

One patient developed a bronchopleural fistula that was successfully managed conservatively.

Statistical analysis (Table 3) revealed that induction radiotherapy was the only independent risk factor for perioperative mortality (OR: 5.34, 95% CI: 1.16–24.47; $p = 0.03$) and early bronchial complications (OR: 3.73, 95% CI: 1.01–13.68; $p = 0.04$).

Late complications (at least after three months) occurred in 31 (16.3%) patients with 22 (11.6%) anastomosis-related complications: in one patient a bronchopleural fistula was successfully treated with local application of silver nitrate and drainage; however, later on, this patient developed a bronchial stenosis that required a stent insertion.

In 12 patients with severe bronchial stenosis an endobronchial procedure was necessary: stent insertion ($n = 8$), dilatation ($n = 3$) and laser therapy ($n = 1$).

Sixty-six (35.3%) patients received adjuvant therapy (radiotherapy $n = 30$, chemo-radiotherapy $n = 24$, chemotherapy $n = 10$, and brachytherapy $n = 3$).

At last follow-up, excluding the 9 perioperative deaths, 107 (56.3%) patients were dead, 74 (38.9%) were alive and 9 (4.8%) patients were lost during follow up.

Causes of death were distant metastasis (60.7%; $n = 65$), no cancer-related causes (28%; $n = 30$) and loco-regional recurrence (11.3%; $n = 12$).

Overall 5- and 10-year survival rates were 39.7% and 28.7%, respectively (Fig. 1).

According to pTNM stage, 5- and 10-year survival rates were 48% and 35% for stage I, 40% and 25% for stage II, 33% and 28% for stage III. No significant difference in survival was present between stages with a trend toward significance when we compared stages I/II with stage III ($p = 0.06$).

Survival by pN-status was 45%, 39% and 29% for N0, N1 and N2, respectively ($p = 0.30$). On univariate analysis squamous cell histology was a significant predictor of better survival (5-year survival of squamous vs non-squamous cell carcinoma 43% and 35%, respectively; $p = 0.04$).

Multivariate analysis did not find any independent significant predictors of survival, however there was a trend toward significance for histology ($p = 0.08$) and stage ($p = 0.07$).

Loco-regional recurrence occurred in 21 (11.6%) patients, and according to nodal status it was 10.3% for N0, 11.2% for N1 and 12.2% for N2 ($p = 0.61$).

Recurrence was pulmonary in 13 (6.8%) patients and mediastinal in 8 (4.2%). A positive bronchial margin was

Table 3
Univariate analysis of factors affecting mortality, morbidity, local and distant recurrence

Factors	Perioperative mortality, *p*-value	Early bronchial complications, *p*-value	Loco-regional recurrence, *p*-value	Distant recurrence, *p*-value
Gender	ns	ns	ns	ns
Age	ns	ns	ns	ns
Neo-adjuvant treatment				
Induction RT	0.04	0.03	ns	ns
Induction CT	ns	ns	ns	ns
Induction CT-RT	ns	ns	ns	ns
Side	ns	ns	ns	0.04
Use of vital flap	ns	ns	ns	ns
pN status	ns	ns	ns	ns
pTNM stage	ns	ns	ns	ns
Histology	ns	ns	ns	ns
Adjuvant RT	Not evaluable	Not evaluable	ns	ns
Adjuvant CT	Not evaluable	Not evaluable	0.001	ns
Vascular procedures	ns	ns	ns	ns
Invaded bronchial margin	ns	ns	0.01	ns

ns = not significant.

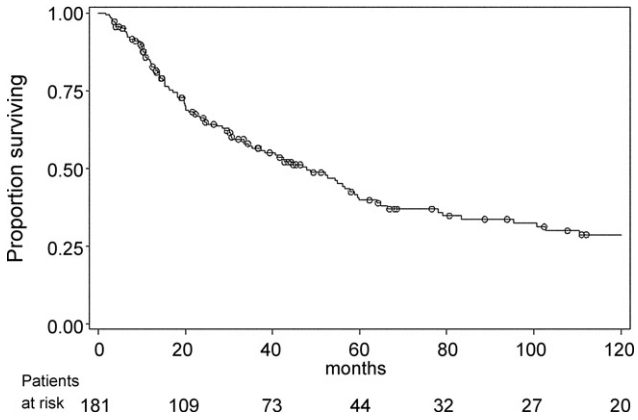

Fig. 1. Overall survival.

predictor of local recurrence (OR 5.03, 95% CI: 1.52—16.67; $p = 0.01$).

Distant recurrence was diagnosed in 71 (39.2%) cases. The recurrence rate was 30%, 38.7% and 39.4% in N0, N1 and N2 patients, respectively ($p = 0.23$).

Four patients developed a metachronous secondary lung cancer: all of them underwent curative resection with contralateral lobectomy in two, segmentectomy in one and atypical resection in one.

4. Discussion

Nowadays, sleeve lobectomy is widely accepted as a standard procedure in patients affected by NSCLC, regardless of their pulmonary reserve [12]. The reason for this is the reported results of long-term survival rates are comparable with those after pneumonectomy. In addition sleeve lobectomy has the advantage of preserving functional lung tissue with subsequent increased pulmonary reserve, better quality of life and the possibility for a subsequent resection in case of development of a second primary lung cancer. Furthermore, the parenchyma-sparing procedures can be performed safely after neoadjuvant chemotherapy in comparison to pneumonectomy [13].

In our study, we reported an overall postoperative mortality of 4.5%, similar to other recent works [6—14]; however, if we consider the last 10 years of our experience, the results have become more favourable and mortality reached a value of 0.8%, which is similar to the results published by Deslauriers et al. (1.3%) [5] and Massard et al. (1.6%) [15].

This is a good indicator of the importance of the learning curve in such a technically demanding operation. Interestingly, the total number of sleeve lobectomy performed in the last 10 years is 1.3 times the number in the first 15 years; moreover the number of angioplastic procedures and sleeve bilobectomy has doubled in the last 10 years.

Bronchovascular fistula was responsible for 44.4% of perioperative mortality, all were early in our experience. However, with improved technical skills, the avoidance of preoperative radiotherapy, which was the risk factor, and routine use of viable flap, we did not face this complication anymore.

Overall postoperative morbidity was 17.9%, in line with the last major published series [6—16]. In particular, our rate of early anastomotic complication (5.3%) is comparable with the study of Tronc et al. [16], Icard et al. [17] and Yildizeli et al. [6].

Interestingly, we found that angioplastic procedure was not a risk factor for postoperative morbidity; this supports the previously reported results by Rendina et al. [18] and Cerfolio et al. [19].

Early anastomotic complications range from granulation with mild to severe stenosis, to dehiscence with subsequent bronchopleural or bronchovascular fistula. The most important aspect in order to prevent bronchial complications is to avoid performing the anastomosis under tension and devascularisation of the bronchus at the time of surgery.

In case of airway stenosis, we believe in the fundamental role of strict and regular endoscopic control that allows early diagnosis and a subsequent correct management.

Moreover, this protocol of follow-up could help us to achieve a low rate of completion pneumonectomy.

Bronchoscopy may also give early evidence of anastomotic dehiscence, favouring the most appropriate treatment, surgical or conservative, before progression toward life-threatening complications such as pleural empyema or bronchovascular fistula.

The main debate regarding long-term results of sleeve procedures is the incidence of loco-regional recurrence, which in literature ranges between 13% [20] and 24% [17].

Most authors point to the attention on nodal involvement as the most important parameter for recurrences [4—21].

Tronc et al. [16] reported an overall local recurrence rate of 22% with significant variations from 14% to 42% based on nodal status.

In our experience loco-regional recurrence was found in 21 (11.6%) patients without significant difference on the basis of nodal status. Regarding distant metastasis on the other hand, there was a trend to an increased rate in patients with N2 involvement, even if not statistically significant. Regarding N1 disease we observed no significant difference in survival in comparison with N0, therefore we do not consider N1 disease a contraindication for sleeve lobectomy. However, our policy is to proceed to pneumonectomy in cases of positive N1 in the fissure near the artery of the remaining lobe.

On the basis of pathologic stage, our 5-year survival rate in stage I is lower than that reported by other authors [5,6] and also compared with our survival rate after standard lobectomy, which is around 60%. We could not find an explanation for this. Regarding stage III (N2), a possible explanation for our high survival rate could be found in the high number (26/34, 76.5%) of single station mediastinal nodal involvement. In particular, 16 patients submitted to right upper sleeve lobectomy had metastasis only in 4R nodal station.

In conclusion, sleeve lobectomy represents a safe and effective surgical procedure in terms of perioperative and long-term oncological results, although it is a technically demanding procedure with specific related complications.

Overtime trend showed a significant lower mortality in the last period. This emphasises the importance of learning curve and encourages the performance of this procedure in experienced centres.

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Appendix A. Conference discussion

Dr A. Oliaro (*Torino, Italy*): You reported the use of absorbable suture only in two groups, and also in the 1980s. In this period we use not absorbable suture but Ethibond. Which type of suture did you use in the 1980s?

Dr Rea: I believe that just in few cases at beginning of our experience we were not able to use the absorbable suture. In about 95% of patients we used absorbable sutures starting with Dexon suture; now we use for all patients Vicryl, and PDS for the running suture.

Dr P. De Leyn (*Leuven, Belgium*): So the difference in the two groups was the experience of the surgeon but also the coverage of the bronchial stump and the anastomosis. In the first periods you had more complications, bronchial, bronchovascular, and about half of the patients got a wrap around the sutures. Was there a relation between rate of complications and wrapping of the sutures.

Dr Rea: No, we analysed this group. All patients that received in the first time sleeve resection and died due to bronchovascular fistula received even pedicle flap. Radiotherapy was the only independent factor for this complication.

Dr P. van Schil (*Antwerp, Belgium*): I have two questions. I noticed that quite a lot of patients had preoperative radiotherapy, even more than preoperative chemotherapy. What were the indications for preoperative radiotherapy?

And secondly, did you look at the survival in accordance to the nodal stage of the patients?

Dr Rea: Regarding the use of the type of neoadjuvant therapy, at the beginning of our experience we used just radiotherapy. And induction chemotherapy was used in the second part. We're using adjuvant chemotherapy. The use of radiotherapy at the beginning of our experience was routine when patients had lymph node enlargement found at CT scan. The induction chemotherapy in the last period was used when we found lymph nodes enlargement at CT scan, in these patients we perform mediastinoscopy, i.e. we perform mediastinoscopy selectively in patients with enlarged lymph nodes.

Dr van Schil: And survival according to the nodal status?

Dr Rea: Yes, the survival according to the nodal stage. We differ from other series, like the series of Professor Dartevelle, that had no survival in N2 disease. In our group we have 20% 5-year survival in N2 disease. But the majority of these patients (out of 34, 26 patients) had lung cancer on the right upper lobe with single station metastasis in 4R station.

Dr M. Saute (*Petach-Tikva, Israel*): Do you still think that it is important to wrap the anastomosis? Because we have our series of 220 lung transplantations from the last 6 years and we didn't wrap the anastomosis at all. And also, our sleeve resections, we don't do any wrapping procedure. And we see in the literature there are several papers that the wrapping can cause a stenosis of the anastomosis.

Dr Rea: First of all, lung transplantation and sleeve lobectomy are completely different; as we have no tension in lung transplantation.

Regarding the wrapping of the anastomosis, I believe that it is important to separate the bronchus from the artery. You have not to wrap all the circumference of the anastomosis, but just part of the anterior, the cartilaginous part, to separate the artery from the bronchus.