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Is the initial feasibility of lobectomy for stage I non-small cell lung cancer in severe heterogeneous emphysema justified by long-term survival?

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Abstract:

Background: We have previously confirmed the feasibility of anatomical lobectomy in patients with bronchial carcinoma in an area of severe heterogeneous emphysema whose respiratory reserve is outside operability guidelines. We now reviewed our cumulative experience to determine whether this approach is justified by long-term survival.

Methods: We reviewed a single-surgeon's 8-year experience of 118 consecutive patients [74 male and 44 female, median age 70 (range 45 to 84) years] who underwent upper lobectomy for pathological stage I non-small-cell lung cancer (NSCLC). The pre-operative characteristics, perioperative course and survival of the 27 cases with severe heterogeneous emphysema of apical distribution and a predicted postoperative FEV_1 ($PpoFEV_1$) of less than 40% (lobarLVRS group) were compared to the remaining 91 cases with a $PpoFEV_1$ greater than 40% (control group).

Results: Postoperative mortality were 1 of 27 after lobarLVRS and 2 of 91 in the control (p=ns). 5-year survival after lobar LVRS was 35% and in the control group without concomitant severe emphysema was 65% (p=0.001), although rates of tumour recurrence were similar.

Discussion: Long-term survival after lobar LVRS for stage I lung cancer is limited by physiological rather than oncological factors. However, outcomes are still better than reported for any other modality of treatment in this group of high risk patients. We feel justified in continuing to offer lobectomy in these selected cases

Introduction:

When possible, anatomical lobectomy is the procedure of choice in Stage I NSCLC [1]. However, reports and available guidelines for operability in the management of these patients state that patients with a predicted postoperative FEV1 (ppoFEV1) of less than 40% of predicted are at risk of complications if surgical resection is undertaken [2,3]. As a result, other alternatives have been suggested for these patients: palliative care, radiation therapy, sublobar resections [4-7]. Increasing experience with surgical treatment of severe emphysema led to some authors to apply the principles of lung volume reduction surgery (LVRS) to the management of lung cancer in emphysematous patients [8-10]. We have previously described the short-term feasibility of performing a lobectomy in patients with resectable NSCLC located within an area of severe emphysema who would lay outside published guidelines of fitness for surgery [11]. Based on the finding that actual postoperative lung function was significantly better than predicted, we coined the phrase "lobar lung volume reduction for cancer". We have continued to employ this approach as part of our commitment to improve resection rates [12], and also to provide the best surgical option to patients who may have been previously deemed unfit for a lobectomy. However we were conscious of the argument that although feasible this strategy must be justified by long term outcome to gain wider acceptance. We therefore followed the long-term outcomes between patients with heterogeneous emphysema of apical distribution and impaired respiratory reserve (ppoFEV_1 of less than 40%) and those without severe emphysema who underwent upper lobectomy and systematic nodal dissection for Stage I NSCLC.

Methods:

Over an 8-year period (April 1997 to March 2005) 118 patients underwent upper lobectomy with systematic lymph node dissection for Stage I NSCLC under a single surgeon's care. 27 of them (23%) had severe heterogeneous emphysema of apical distribution with a predicted postoperative FEV_1 (ppoFEV_1) of less than 40% (LobarLVRS group). Their perioperative course, tumour recurrence and survival were compared to the remaining 91 (77%) patients (control group).

Preoperative Characteristics

The median age of the 74 males and 44 females was 69 (range 45 to 84) years. 28 patients (24%) were older than 75 years. The median FEV_1 was 70 (range 17 to 118) % of predicted, with a median ppoFEV1 of 54% (14% to 99%). The median preoperative DLCO in the Lobar LVRS group was 47 (range 32 to 97) % of predicted. The preoperative characteristics and operative details of the two groups were compared (Table 1).

Selection criteria

Resectability was defined in this study by a staging CT scan with a negative cervical mediastinoscopy if lymph nodes were greater than 1 cm in their short axis on CT scan. We now perform integrated PET/CT scan but it was not available during the period of the study. Predicted postoperative FEV_1 (ppoFEV_1) was calculated according to a segment counting equation, system that we have used since our original report [11]. Fitness for surgery for lobectomy was defined by ppoFEV_1 > 40%. In cases of ppoFEV_1 < 40% we performed a lung perfusion scan with regional distribution to confirm that the cancer was located within an area of emphysema (Figure 1) [13]. Based on the results of the perfusion scan we defined a Q score as the fraction of perfusion of the affected lung region. A Q score of less than 10 (less than 10% of total) would define a lung region hypoperfused due to emphysema. However, we do not employ the Q score to calculate ppoFEV_1 as it is a non-anatomical

method and the three zones do not correspond with the anatomical lobes. The selection criteria for these patients followed our standard selection for lung volume reduction surgery [14]. Thus patients with a ppoFEV1<40% and homogeneous emphysema on perfusion scintigraphy were excluded and received non-surgical treatment because of their high risk of perioperative death [15].
All patients are followed-up in the surgical outpatient clinic and survival was confirmed via a national registry.

Statistical analysis
The data is presented as median (range) and number (percentage) unless stated. Univariate analysis was performed using the χ^2 test for qualitative and Wilcoxon rank test for quantitative data. Postoperative survival was plotted according to the Kaplan-Meier method and any difference in survival between the groups was evaluated with the Log-Rank test. Statistical significance was defined by p values <0.05 throughout the study.

Results:
There were 65 right upper and 53 left upper lobectomies with no differences in distribution between the two groups (Table 1). Histology revealed adenocarcinoma in 6 (22%) and 36 cases (40%), squamous cell carcinoma in 17 (63%) and 42 (46%) and large cell carcinoma/undifferentiated in 4 (15%) and 13 (14%) of the LobarLVRS group and control group respectively. Four patients (15%) in the LobarLVRS and 21 (23%) in the control group had a pathological stage Ia while 23 and 70 had stage Ib respectively.

Postoperative Course
There were 3 postoperative deaths (2.5%). In the LobarLVRS group a 76 year-old male (ppoFEV_1 of 20%) died of MRSA pneumonia 26 days after a right upper lobectomy. In the control group two patients (with ppoFEV_1 of 52% and 41%) died of myocardial infarction within 48 hours of surgery. The median length of chest drainage and hospital stay were 5 (1 to 36) days and 7.5 (3 to 63) days respectively. There were no differences between the two groups (Table 2).

Survival
At the end of the study 26 patients (76.5%) were alive. With a median follow-up of 57 (1 to 95) months, the overall 5-year survival was 58.3 (± 5) %. There were no significant differences in survival (Figure 2), disease-free survival, or loco-regional recurrences between the two groups (Table 3).

Discussion:
In recent years we have achieved a better understanding of the consecuences of surgery for end-stage emphysema and the management of its complications. This has led to authors aiming to extend the indications of surgery for non-small-cell lung cancer (NSCLC) to patients previously deemed unfit for surgery due to concomitant severe emphysema [8-10].
To date, the limited data available includes mostly patients undergoing sublobar resections in areas of emphysema [7] and feasibility studies of lobectomy for NSCLC on an emphysematous lung [11,16,17]. The rationale of performing sublobar resections for early stage NSCLC is based in the principle that surgery only achieves control of local disease and

that can be achieved with limited removal of lung parenchyma therefore minimizing morbidity/mortality [7]. We have previously reported a case-match comparative study between anatomical segmentectomy and lobectomy for early NSCLC in compromised patients obtaining similarly good outcomes in both groups [5]. The difference with the current report is that the majority of patients in that study suffered from cancer located in the lower lobes. However, reasonable doubts still remain about the oncological value of sublobar or non-anatomical resections for NSCLC [1].

Our own report of "lobarLVRS" [11] did concur with other authors in that lobectomy for carcinoma in patients with heterogeneous emphysema with severely impaired respiratory reserve is feasible with acceptable mortality and with preservation/improvement of the respiratory function after surgery [8,16,17]. However, there is very little data regarding the long-term outcomes of these patients to determine whether this aggressive approach is justified with survival. In the report by Cerfolio et al. reported a 54% %-year survival in patients with Stage I disease which compares favourably with our series. In addition, in an extensive series of 106 patients (73 undergoing lobectomy) Magdeleinat et al. reported a hospital mortality of 8.5% with a 5-year survival of 33% (44% in stage I, compared to 35% in our series) [18]. We note with interest that in their report, spirometry values were better and the patients were younger than in our series. Birim et al reported a 36% 5-year survival after surgery for early carcinoma in high-risk group (according to a Charlton comorbidity index) [19].

We did not find significant differences in terms of cancer recurrence between the groups. Our findings concur with Sekine and colleagues who reported an increase in non-cancer related death in patients undergoing pulmonary resection for cancer with concomitant COPD [20].

It is also important to take into consideration the natural history of patients with severe emphysema in the absence of lung cancer. Although the data is limited in terms of follow-up, some of the recent reports of patients undergoing LVRS for heterogeneous emphysema did include long-term survival. The National Emphysema Treatment Trial Research Group reported a 60% 5-year survival in both surgical and medical groups of the NETT trial [21]. Other reports are similar with survival rates between 56% and 71% at 4 or 5 years after LVRS [22-27]. A recent follow-on report of the NETT trial estimates survival around 60% 5 years after LVRS [28]. The implication for our series is that the expected survival for the patients in our lobarLVRS group is less than in the control group because of the COPD, so one could not expect similar survival between the groups after surgery.

Another important point to consider when deciding in the therapeutic approach in this group of patients is to evaluate non-surgical treatment options. There is very little evidence reporting the use of radical radiotherapy in medically inoperable patients with lung cancer [29]. The subgroup analysis of the CHART trial reported 5 year survivals of 12-18% depending of the method of delivery of radical radiotherapy [30]. Results of survival of non-randomized studies vary between 0-42% at 5 years [29].

We acknowledge the pitfalls of our study. It is the result of a retrospective study and in no way randomized. Data and follow-up was complete in all cases, but information of patients who did not undergo surgery was not available. Also the use of other preoperative tests such as transfer factor measurement and nuclear perfusion scans were not obtained in all patients of the control group, so there are not included in our report. Our follow-up protocol does not include routine CT scans to exclude recurrences unless it is indicated by clinical examination, symptoms or new abnormalities on chest radiograph.

In summary, we have followed on our feasibility report with a long term follow-up of a cohort of patients undergoing upper lobectomy for stage I lung cancer in an emphysematous lobe who would be suitable for LVRS but not for lobectomy according to guidelines. The long term results are affected by death without evidence of cancer recurrence. However, the survival is better than other reported modalities of treatment. This aggressive approach is therefore justified in this group of high-risk patients. A prospective randomized controlled trial between surgery and radical radiotherapy is needed and may confirm or not our conclusions.

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Table 1. Preoperative characteristics between the two groups. Expressed as median (range) or number (%).

	LobarLVRS N=27	**Lobectomy N=91**	***P***
Male:Female	20:7	54:37	NS
Age (years)	69 (51-79)	70 (45-84)	NS
Over 75 years	7 (26%)	21 (23%)	NS
FEV_1 (%predicted)	45 (19- 54) %	77 (53- 118) %	0.001
$PpoFEV_1$ %	34 (14-39) %	61 (41-99) %	0.001
Right:Left	13:14	52:39	NS
Preop. DLCO	47 (32-97) %	na	
Q score	7.5 (1.5-13)	na	
Body mass index	23 (18-30)	24 (18-33)	NS

Table 2. Perioperative results. Expressed either as median (25%-75% interquantile range) or number (%).

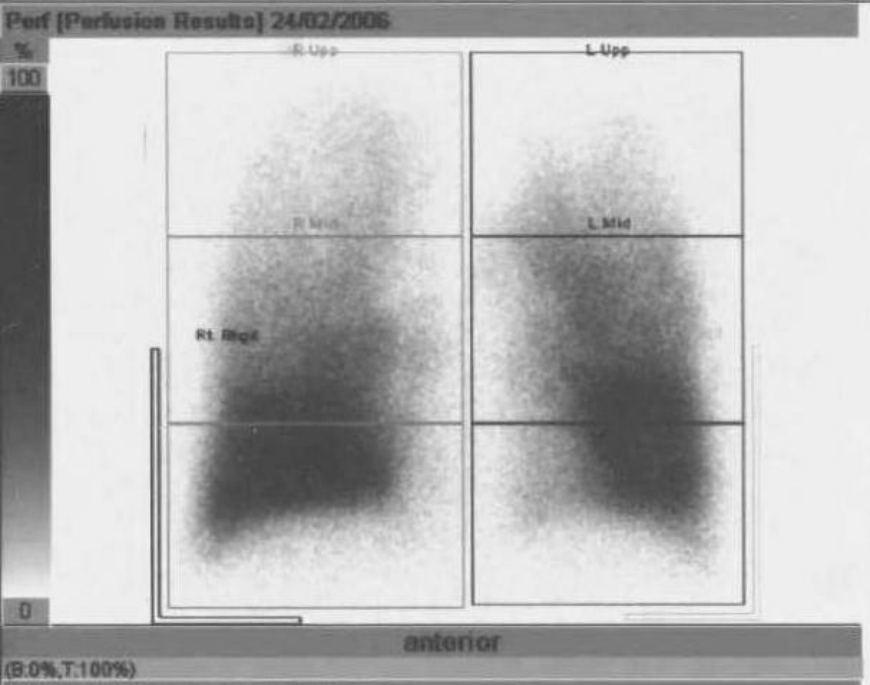
	LobarLVRS N=27	**Lobectomy N=91**	***p***
Hospital mortality	1 (3.7%)	2 (2.2%)	NS
Hospital stay	8 (5.5-13) days	7 (6-11) days	NS
Duration drainage	5 (3.5-10) days	5 (4-7) days	NS
Stage Ia:Ib	4:23	21:70	NS

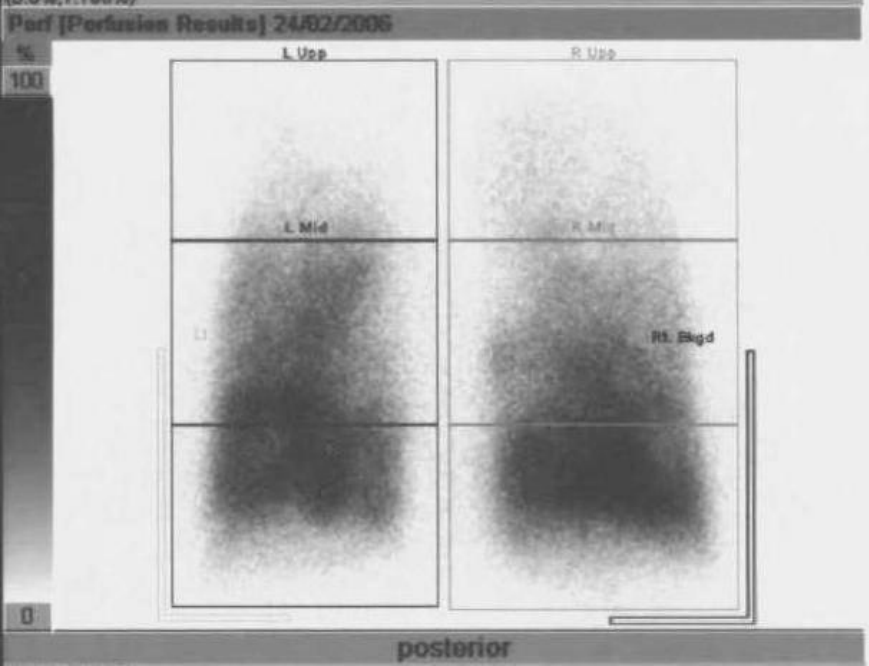
Table 3. Long term results. Expressed as median (25%-75% interquantile range) or number (%). *According to Kaplan-Meier (in % ± Standard Error)

	LobarLVRS N=27	**Lobectomy N=91**	***p***
Follow-up	57 (29-72) months	57 (36-75) months	NS
Total recurrence	6 (22%)	16 (18%)	NS
Loco-regional recurrence	3 (11%)	10 (11%)	NS
Actuarial 3-year survival*	48% ± 11	75% ± 4	0.001
Actuarial 5-year survival*	35% ± 11	65% ± 5	0.001

Figure 1. Perfusion scan revealing bilateral apical perfusion defects consistent with emphysematous regions. The Q score is the fraction of perfusion of the apical zone divided by the total lung perfusion.

Figure 2. Survival according to the Kaplan-Meier method of LobarLVRS group vs Lobectomy group (Log-rank). P=0.001





Perfusion
posterior

POSTERIOR

(% Ratios)	Left	Right
Upper	2.47	2.64
Middle	22.69	20.18
Lower	21.92	30.09
Total	47.09	52.91

ANTERIOR

(% Ratios)	Left	Right
Upper	4.04	4.03
Middle	24.53	23.56
Lower	17.14	26.70
Total	45.71	54.29

Geometric Mean

GEOMETRIC MEAN

(% Ratios)	Left	Right
Upper	3.11	3.28
Middle	23.85	22.14
Lower	19.22	28.39
Total	46.19	53.81