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Surgical Therapy for Patients with Drug-Resistant Tuberculosis: Report of 121 Cases Receiving Community-Based Treatment in Lima, Peru

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ABSTRACT

Introduction:
While the majority of patients with tuberculosis (TB) can be successfully treated using short-course medical chemotherapy, thoracic surgery is an important adjunctive strategy for many patients with drug-resistant disease. Although the need for physical, technical and financial resources present a potential challenge to implementing surgery as a component of MDR-TB treatment in resource-poor settings, we report here on a cohort of patients with drug-resistant tuberculosis in Lima, Peru who underwent surgery as part of their treatment for severe MDR-TB.

Methods:
A prospective case series of 121 patients undergoing pulmonary surgery for drug-resistant tuberculosis between May 1999 and January 2004 was performed. Surgery was performed by a team of thoracic surgeons under the Ministry of Health. Data was collected on patient demographics, clinical characteristics, surgical procedures, and surgical outcomes.

Results:
A total of 121 patients underwent thoracic surgery during this study. Most had failed multiple TB regimens and were resistant to a median of seven drugs. Median time of follow-up after surgery was 33 months. 79.3% of patients were culture-positive prior to surgery, and sustained

culture-negative status among survivors was achieved in 74.8% of patients. Among those with at least six months post-operative follow-up, 63% of patients are either cured or likely cured. Post-operative complications, observed in 22.6% of patients, were associated with pre-operative hemoptysis (p=0.03), vital capacity < 50% (p=0.004) and low forced expiratory volume in the first second (p=0.04).

Conclusions:

The cohort in this study represents one of the largest surgical experiences with MDR-TB and the first from a resource-poor setting with patients treated under program conditions. Although surgery is not often considered an option for patients in resource-poor settings, our experience supports the argument that adjunctive surgery should be considered an integral component of MDR-TB treatment programs, even in poor countries such as Peru.

Background

Mycobacterium tuberculosis infects more than one-third of the world's population and causes en estimated 2 to 3 million deaths annually.[1] In the 8th World Health Organization (WHO) annual report on global tuberculosis (TB) control, the WHO calculates that there were 8.8 million new cases of TB in 2002, of which 3.9 million were smear-positive. The global incidence of TB (per capita) was reportedly growing at approximately 1.1% per year, and the absolute number of cases at 2.4% per year.

A majority of patients with TB can be successfully treated using short-course medical chemotherapy, which consists of a four-drug regimen, including isoniazid, rifampin, pyrazinamide, and ethambutol.[2] A small proportion of patients with pulmonary TB, however, go on to require surgical therapy for their disease.[3] Indications for surgical therapy usually include: management of complications of TB—including hemoptysis, bronchiectasis, bronchial stenosis, bronchopleural fistula and aspergilloma; and management of drug-resistant forms of the disease.[4,5,6,7,8] A wide variety of procedures have been reported, including surgical resection and thoracoplasty.[9] Patients usually do well with surgery, with cure rates between 60% and 100% being achieved.[10,11]

Multidrug-resistant tuberculosis (MDR-TB)—a major indication for surgery—is defined as strains of *M. tuberculosis* with *in vitro* resistance to at least isoniazid and rifampin, the two most powerful existing antituberculous agents.[12] Because of this, treatment is prolonged and complicated —lasting 18 to 24 months—and often requires the use of at least five antibiotics, one of which is received as a daily injection.[13, 14] In many settings, rates of MDR-TB are increasing, and more international efforts have been mobilized to confront this emerging infectious disease.[15] Increasingly, a combined medical and surgical approach is being used to treat patients with MDR-TB.[16]

Several cohorts of patients with MDR-TB undergoing surgical therapy have been reported in the literature[17,18,19,20,21,22]. In general, the studies show excellent microbiologic outcomes with low complications rates, although it bears mentioning that most of the cohorts are small and all are from relatively wealthy nations in the world. To date, there has been no report on the use of surgical therapy for the management of MDR-TB under program conditions in resource-poor settings. This study will report on one cohort of patients with drug-resistant tuberculosis in Lima, Peru receiving treatment in conjunction with the Ministry of Health's DOTS-Plus treatment program.

Setting

Peru is one of the poorest countries in Latin America with limited resources for health care. The Gross National Product (GNP) of Perú in 2001 was 54,000 million US dollars, of which 2.8% (1512 million US dollars) was spent on health, on the lowest health expenditure figures in the region. Furthermore, Peru´s annual expenditure of 28,700 million US dollars (approximately 50% of the GNP) on external debts perpetuates a deplorable socioeconomics situation that contributes to the high prevalence of infectious diseases such as tuberculosis. The incidence of tuberculosis in Peru is among the highest in South America, with an incidence rate of 134 per

100,000 habitants in 2000[23]. The average annual cost of TB control in Peru is $94,446,000 per year, representing 14% of the total public health expenditure, and 4% of the total health expenditure[24].

In the densely populated periphery of metropolitan Lima, where half of all national cases are detected, the risk of infection with *M. tuberculosis* is estimated to be among the highest levels documented recently in any population[25],[26],[27]. Furthermore, the rate of MDR-TB continues to rise despite implementation of MDR-TB treatment strategies since 1996, with a national prevalence of 3% among newly diagnosed TB patients, and 12.3% among those previously treated for TB[28]

The Peruvian Ministry of Health operates a large and successful National TB Control Program (NTP) that has been working in partnership with non-governmental organizations since 1996 to provide treatment to patients with MDR-TB; beginning in May 1999, thoracic surgery was incorporated into the MDR-TB treatment program[29]. To date more than 2400 patients with MDR-TB have been treated using individualized regimens based on drug susceptibility testing, under directly observed therapy. Community-based service has been a key component of this program, including the use of community health workers to supervise treatment and carry out ambulatory-based management of complex adverse events and complications. Excellent outcomes have been achieved, with a cure rate of more than 80% in the first cohort[30]. Since May 1999 when surgery was integrated into this program, 121 patients have undergone thoracic surgery (approximately 5.6% of the total cohort).

Methods

A prospective case series of 121 patients undergoing pulmonary surgery for drug-resistant tuberculosis between May 1999 and January 2004 was performed. In this cohort, 119 patients had documented MDR-TB, two patients had presumed MDR (having failed previous treatments) but drug-susceptibility testing could not be obtained at the time of treatment initiation. All drug-susceptibility test were performed at the Massachusetts Sate Laboratory Institute and methods have been described elsewhere[31].

Pre-operative evaluation included standard radiography, computerized tomography, spirometry, arterial blood gas analysis, routine laboratory analyses and an enzyme-linked inmmunosorbant assay for HIV. As further evaluation, ventilation-perfusion lung scans were performed for patients with marginal spirometry. The medical and surgical staff clinically evaluated each patient individually with the following inclusion and exclusion criterias for an acceptable surgical candidate:

INCLUSIÓN CRITERIA		EXCLUSIÓN CRITERIA
All of the following	At least one of the following	None of the following

1.Unilateral or bilateral pulmonary lesions that are sufficiently localized to permit resection 2.Patients with sufficient pulmonary reserve to tolerate pulmonary resection, as determined by spirometry and assessment of residual parenchyma on pre-operative computerized tomography;	1. Poor treatment response, i.e. persistent or intermittent positive sputum culture despite at least four months of MDR-TB therapy including first- and second-line drugs based on individualized drug-susceptibility testing; 2. Infection with highly-resistant strains in a patient with localized disease amenable to resection; 3. Life-threatening hemoptysis. 4. Pulmonary aspergilloma	1.Patients with a vital capacity < 50% and FEV_1< 800cc 2.Cardiac insufficiency as per cardiologist evaluation 3.Severe malnutrition.

The risks and benefits of surgery, as well as the prognosis with and without a surgical intervention, were discussed with the patient; informed consent was obtained for all patients accepting surgery. Surgery was performed by a team of thoracic surgeons under the Ministry of Health; the majority of surgeries have taken place at a large public hospital in Eastern Lima. Patients were given general anesthesia combined with a thoracic epidural, and in a minority, general anesthesia alone. Patients were intubated with a double lumen endotracheal tube. Immediate post-operative pain was managed with an epidural catheter located at the T6 level, which remained in place for a maximum of 72 hours. Tuberculosis treatment was suspended at the time of surgery, with reinitiation 48 hours later for a period of at least one year after surgery. Routine post-operative follow-up was performed in outpatient clinic. All patients continued antituberculous therapy following surgery for at least 12 months.

Ethics Committee Approval

This study was approved by the human research committee at the Harvard Medical School, located in Boston Massachusetts, USA.

Analysis

Data were collected on patient demographics, clinical characteristics, surgical procedures, and surgical outcomes. All data was entered into Microsoft Excel (Microsoft Corporation, Seattle, WA) and analyzed using SAS Version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 121 patients underwent 138 procedures during the time of this study. Demographic and clinical characteristics of this cohort are summarized in Table 1. This was a population of chronically ill patients infected with highly drug-resistant strains of *M. tuberculosis*. Most had failed multiple previous TB regimens and were resistant to a median of 7.0 drugs. Most patients had cavitary disease (91.7%) and 43.8% had bilateral involvement. Approximately 30% of the

cohort had a low body mass index (defined as < 18.5 for women and < 20 for men). One patient underwent surgery prior to initiating MDR-TB treatment; for the remainder, surgery was performed after a median of 15 months after starting therapy. An average of 5.0 pulmonary segments were affected per patient; in the majority of cases more than one lobe was involved. Median time of follow-up at the time of analysis was 49 months (range 19 to 103 months). Median time of follow-up after surgery was 33 months (range 14 to 79 months).

Table 1: Baseline Characteristics of Surgical Patients with MDR-TB (N=121)

Characteristic	*Number (%)*	*Median [range]*
Median age in years		27 [16, 66]
Male	80 (66.1)	
Median number of prior treatments (115)		3 [0, 9]
Median number of months in current treatment prior to surgery (120)		15 [0.6, 41]
Median number of drugs to which resistance documented		7 [3, 11]
Resistance to: INH (119) RIF (119) EMB (119) PZA (118) SM (118) KM (115) CM (111) Fluoroquinolone (112) Ethionamide (114) CS (112) PAS (99)	 119 (100%) 119 (100%) 115 (96.6%) 94 (79.7%) 100 (84.8%) 60 (52.2%) 41 (36.9%) 31 (27.7%) 78 (68.4%) 1 (0.9%) 21 (21.2%)	
Massive hemoptysis (119)	35 (29.4)	
Bilateral disease*	53 (43.8)	
Type of lesion (pre-operative) Cavitary disease Bronchiestasis Bronchopleural fistula Pleural empyema Fibrosis and scarring	 111 (91.7) 27 (22.9) 4 (3.4) 5 (4.2) 101 (83.5)	
Bilateral cavitary disease	20 (17.4)	
Baseline low body mass index	38 (31.4)	
Pre-op low body mass index	43 (35.5)	
Vital capacity < 50%	22 (18.2)	
Forced expiratory volume in 1st second (FEV_1) (118) 800 - 1000 cc 1001 - 2000 cc > 2000 cc	 2 (1.7) 59 (50.0) 57 (48.3)	
Comorbid disease	23 (19.0)	

HIV	1 (0.8)	
Alcoholism and/or drug dependency	11 (9.1)	
Tobacco use	8 (6.7)	
Diabetes mellitus	6 (5.0)	
Chronic renal insufficiency	1 (0.8)	
Aspergilloma	6 (5.0)	
Positive culture status at time of surgery ‡	96 (79.3)	

* Bilateral disease was defined as involvement in both lungs, excluding small nodules or sub segmental scarring
‡ Positive culture includes any patient with persistent positive culture after at least four months of therapy

The surgical procedures performed are listed in Table 2 below. A majority of patients underwent lobectomy (63.7%) or pneumonectomy (21.8%). Among the 121 individuals in this cohort, subsequent surgery was required for 13 individuals. Among these, 11 underwent one further procedure, while one patient had two subsequent operations, and one had three further operations. Indications for re-operations included persistent pleural cavity (3), fistula (8) and hemorrhage (2). The median duration of hospitalization for surgery was seven days (range 4 to 114 days), as shown in Figure 1.

Table 2: Initial surgical procedures performed (N=121)

Procedure	*N*	*%*
Lobectomy	76	62.8
Pneumonectomy	27	22.3
Lobectomy and segmentectomy	11	9.1
Segmentectomy or wedge resection	3	2.5
Other	4	3.3

Prior to surgery, 20.7% of patients were culture-negative and 79.3% were culture-positive. The indication for surgery in culture-negative cases included high-grade drug resistance with a localized lesion, massive hemoptysis and pulmonary aspergilloma. Among the 115 patients for whom follow-up results were available, in the early post-operative period, 78.3% were culture-negative and at long-term post-operative follow-up, 74.8% remained culture-negative. Culture-conversion was achieved in the majority of individuals who were culture-positive prior to surgery: among the 91 individuals who were culture-positive pre-operatively and who had follow-up results, 72.5% were culture-negative immediately after surgery and 68.1% were culture-negative at the time of analysis. The rate of culture-conversion differed depending on whether the patient had unilateral or bilateral disease as well. Among individuals for whom follow-up data were avaiable, sustained culture-conversion was achieved in 85.7% of patients with unilateral disease versus 61.5% of patients with bilateral lesions. Furthermore, among patients who underwent lobectomy, the rate of sustained culture-conversion was high (82.4%), while those undergoing pneumonectomy was somewhat lower (60.9%).

The post-operative mortality (occurring within one month of surgery) in this cohort was 5.0%. Two patients died suddenly, one likely due to pulmonary embolism and one from respiratory insufficiency six days following resection. The majority of the patients who underwent surgery had substantial respiratory compromise and extensive pulmonary lesions prior to surgery. In the case of the patient who died from respiratory insufficiency, his vital capacity was 1180 mL, only

37% of predicted, and his FEV1 was only 980 mL (36% predicted). Another patient who died of respiratory insufficiency after a right pneumonectomy had an intact left lung. One patient who died had a history of gastrectomy and died of sepsis and multisystem organ failure. Finally, one patient presented with a pneumothorax on the contralateral side as well as subcutaneous emphysema. This patient required ventialatory support and had ventricular arrhythmias and ventricular fibrillation leading to cardiac arrest. Figure 2 shows the post-operative survival in this cohort.

Figure 2. Post-operative survival (N=121)

Figure 3 demonstrates current treatment status; overall, 63.0% of patients are either cured or likely cured (in treatment, culture-negative).

Figure 3. Current treatment status (N=121)

A total of 27 (22.6%) patients had a total of 43 post-operative complications; 9 experienced minor complications while 19 had major complications. Table 3 below lists post-operative morbid complications.

Table 3: Post-operative complications (N=27)

Complication	***N***
Major	
Bronchopleural fistula	8
Empyema	6
Pulmonary embolus	2
Hemorrhage	2
Wound dehiscence	2
Bronchopneumonia	2
Respiratory insufficiency	5
Minor	
Wound infection	6
Prolonged air leak	5
Recurrent nerve lesion	2
Pneumothorax	1

A univariate analysis shown in Table 4 revealed the following risk factors to be associated with post-operative complications: pre-operative hemoptysis (p=0.03), low vital capacity < 50% (p=0.004), low FEV_1 (p=0.04). On the other hand, patients with bilateral disease and low body mass index had higher rates of complications, but these were not statistically significant associations.

Table 4: Risk factors for post-operative complications

Variable	*Complication*	*No complication*	*p-value*
Male gender	19 (70.4)	61 (64.9)	0.59
Age (mean ± SD)	34.3 ± 12.5	29.8 ± 9.4	0.09
Comorbid condition	6 (22.2)	17 (18.1)	0.59
Pre-operative hemoptysis	16 (59.3)	34 (36.2)	0.03
FEV_1 < 1000	2 (8.0)	0 (0)	0.04
Vital capacity < 50%	10 (37.0)	12 (12.8)	0.004
Bilateral disease	14 (51.9)	39 (41.5)	0.34
Cavitary disease	18 (69.2)	72 (80.9)	0.20
Bilateral cavitary disease	6 (23.1)	14 (15.7)	0.39
Pre-op culture-positive status	21 (77.8)	75 (79.8)	0.79
Low baseline BMI	11 (40.7.)	27 (28.7)	0.24
Pre-operative low BMI	13 (48.2)	30 (31.9)	0.12
Procedure			
Lobectomy	14 (51.9)	62 (66.0)	0.18
Pneumonectomy	3 (11.1)	8 (8.5)	0.71
Lobectomy + segmentectomy	8 (29.6)	19 (20.2)	0.30
Segmentectomy or Wedge	2 (7.4)	1 (1.1)	0.12

DISCUSSION

A total of 121 patients underwent pulmonary resection. Comparisons with other surgical experiences among MDR-TB patients are summarized in Appendix I. Of note, this experience is similar to that of Pomerantz and colleagues who found adjuvant surgical therapy greatly improved outcomes among patients with MDR-TB. In addition, we note the following differences. Our cohort tended to be younger than other cohorts, where the majority of experiences have been among patients in their 3rd and 4th decade of life. High-grade drug resistance was observed in our cohort (resistance to a median of seven drugs), compared with the experience of Chang et al, Park et al, and Sung et al (who described resistance to an average of 3.9, 4.5, and 4.4 drugs, respectively). Only Pomerantz et al (2001) had a cohort with comparable drug-resistance, wherein the majority was resistant to at least six drugs.

In terms of the average number of months in MDR-TB treatment prior to surgery, our experience is comparable to that of Chang et al.; other cohorts received surgery earlier in the course of medical treatment for MDR-TB. Of note, the patients in this study had been in treatment for a significant time (median 15 months) prior to undergoing surgery[32]. In our experience, delays were due to programmatic constraints, in particular related to limited financial resources and difficulty accessing surgical suites. Prior studies have demonstrated that a shorter time interval to surgery is associated with better outcomes. Thus, the excellent results seen in this cohort are even more encouraging. Given the long waiting time to surgery, however, we recognize there may have been a bias toward patients who were able to survive their disease and receive surgery.

More needs to be done, however, to identify likely treatment failures sooner and move them to surgery in a more timely fashion, and our group is currently working towards this goal. Of note, our patients also had short inpatient stays which may have been more cost-effective and allowed for a larger programmatic role for surgical management of disease.

Indeed, we have observed that among MDR-TB patients failing individualized treatment, extended administration of failing regimens does not contribute to the cure of the patients and, on the contrary, permits the infection to disseminate beyond the initial sites of involvement. Such disease progression makes successful pulmonary resection even more challenging. Among the few patients who were operated upon in the early months of treatment, we have observed better outcomes. We therefore advocate early surgical interventions, even if the patient is culture-positive.

In our cohort, 43.8% of patients had bilateral disease, for whom resection of the dominant lesion was performed. Other series (Iseman et. al., Kir et. al., Sung et. al., and Park et. al.) describe cohorts with a predominance of cases with bilateral disease. The difference could be due to our exclusion among bilateral cases of those who had small nodules and scarring in the contralateral lung. Many other cohorts include in the definition of bilateral disease ay evidence of TB in the other lung. A majority of our patients had evidence of old TB in the contralateral lung and therefore we felt should not be included in the definition of bilateral disease.

More than half of the patients in our cohort had an FEV1 of less than 2000 cc and 18% displayed a limited vital capacity of less than 50%. These figures demonstrate the extensive degree of pulmonary compromise and high surgical risk. Park et. al. excluded patients with an FEV1 of less than 2000 cc, based on the experience in surgical oncology that defines high-risk surgery based on this threshold.[33,34] Unlike cases of lung cancer, however, the chronic nature of pulmonary TB permits a degree of physiologic adaptation; for this reason, we chose not to exclude patients with FEV1 values of less than 2000 cc, and have succeeded in demonstrating favorable outcomes nonetheless.

While lobectomy was the commonest procedure, 27 pneumonectomies were also performed. In other series, a higher proportion of patients undergoing pneumonectomy is observed (24.5-74.1%). It is notable that among the 20 patients with a vital capacity of under 1800 cc (minimum of 1160 cc) who underwent pneumonectomy, the post-operative mortality was 15%. The majority of authors do not consider patients within this range of vital capacity for pneumonectomy. Despite the high mortality, associated with this subgroup of patients, it is conversely notable that 85% of these patients were able to tolerate the procedure and achieve sustained culture-conversion.

We were careful to perform a meticulous dissection; indeed, 90% of our patients did not require a transfusion. In particular, we avoided excessive dissection of the peribronchial tissue in order to preserve perfusion and thus ensure adequate healing with minimal complications. Nonetheless, eight patients (6.5%) experienced bronchopleural fistulas, of which five occurred among patients who were culture-positive at the time of surgery. Among those who underwent the most common procedure, lobectomy, three patients (3.8%) had post-operative fistulas, while those undergoing other procedures, the rate of bronchopleural fistulas was higher. In other

experiences, Chiang reported post-operative fistulas in 3.7% of his cohort; Kir, a rate of 7.4%. Park did not report any bronchopleural fistulas, while Pomerantz' cohort experienced fistulas in 2.9%.

One explanation for the higher rate of bronchopleural fistulas in our cohort could be due to the severe fibrosis in many of our patients, in which the degree of pathologic involvement fails to respect segmental boundaries and therefore impedes an anatomic segmental resection. In such cases, hemostasis is more challenging, and the surgical closure of multiple minor bronchi is necessary. Additionally, it is important to take into consideration the poor nutritional status of these patients who generally come from the lower socioeconomic strata of our population. The great majority of these fistulas are not of the lobar bronchial stump, but rather from secondary bronchi, despite the fact that we did not utilize muscle or adjacent tissue flaps. The persistence of residual pleural space after upper and middle lobectomy procedures was minimized by liberating the triangular ligament, in order to favor the upward expansion of the remaining lung.

In our cohort, almost 80% of patients were culture-negative immediately post-operative; and 74.8% remained culture-negative at the time of follow-up, a median of 33 months after surgery. All patients continued medical therapy for their TB after surgery. Of note, the proportion of patients who were culture-positive prior to surgery in our cohort (79%) is greater than that observed in the other cohorts cited (3.7 – 69%). This difference is likely due to our limited resources and the prioritization of those patients who were deemed least likely to cure without surgery (i.e. those with positive culture status). It is noteworthy that among culture-positive patients, 68% achieved sustained culture-conversion with surgery, and even among patients with bilateral disease, 61.5% were able to maintain culture-conversion. Furthermore, among patients who underwent lobectomy, the rate of sustained culture-conversion was high (82.4%), while those undergoing pneumonectomy was somewhat lower (60.9%). This finding differs from that reported by Van Leuven et al, who observe that pneumonectomy achieves culture-conversion more frequently than lobectomy. In our experience, we observed that successful culture conversion depended not necessarily solely on the extent of pulmonary resection, but also to the successful removal of the most significant lesion. Our results support the approach of minimizing surgical resection to the removal of the most affected lesion(s), in particular among patients with low pulmonary reserve.

Among the risk factors associated with post-operative complications, low vital capacity and FEV1 are consistent with other experiences. Pre-operative hemoptysis was also associated with complications, although this was not statistically significant. Among those variables not associated with post-operative complications, pneumonectomy has been identified as a risk factor in other series.[35]

The post-opererative mortality in our series is similar to those observed among patients undergoing lobectomy and pneumonectomy for cancer.[33] There were no intra-operative deaths, although the mortality within 30 days of surgery was 5%.

Although surgery is not often considered an option for TB programs in poor settings, our experience supports the argument that adjunctive surgery should be considered an integral component of MDR-TB treatment programs, even in poor countries such as Peru.

The average cost of surgery in our program is $2,562. In comparison, the average cost of treating a patient for 18 months within this program is $5,908, while the average cost of treating a patient for 24 months is $7,878. Thus, if performed within the first six months of treatment, surgery could not only improve treatment outcomes but also shorten the duration of chemotherapy for little additional cost to the treatment program.

Conclusions

1.-The cohort reported in this study represents one of the largest surgical experiences with MDR-TB to date and the first from a resource-poor setting with patients being treated under program conditions.
2.- Excellent outcomes were achieved in the majority of patients with low rates of morbidity and mortality.
3.- Despite the fact that most patients had chronic disease and high-grade drug resistance, surgical therapy was an effective adjunctive strategy, resulting in favorable treatment outcomes in 73.7% of the cohort.4.- Based this experience, we conclude that adjunctive surgery should be considered an integral part of any MDR-TB treatment programs even in resource-poor settings, as long as adequate surgical expertise and facilities exist.
5.- Post-operative morbidity was comparable to other series, and was associated with low vital capacity, forced expiratory volume, and pre-operative hemoptysis.

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COMPETING INTERESTS

None of the authors have a competing interest(s).

Appendix 1: Review of MDR-TB surgical cohorts

	Iseman, et al. 1990 [36]	Kir et al, 1997 [37]	Sung, et al, 1999 [38]	Chiang, et al, 2001[39]	Park et al, 2002 [40]	Pomerantz, et al, 2001 [41]	Tahaoğlu et al, 2001 [42]	Van Leuven et al, 1997 [43]
Cohort size	29	27	27	27	49	172 (includes cohort described in Iseman, 1990)	36 (includes cohort described in Kir, et al)	62
Time period	1983-1989	1993-1996	1/1994-3/1998	12/1990-3/1999	1/1995-12/1999	8/1983 – 4/2000	3/1992 – 10/1999	1/1990 – 11/1995
Inclusion/exclusion criteria	**Inclusion**; High-grade drug resistance, disease sufficiently localized to resect preponderance of disease; sufficient drug	**Inclusion**: Same as Iseman, et al. **Exclusion**: HIV	**Inclusion:** Positive sputum despite MDR-TB therapy or significant parenchymal damage	**Inclusion**: Not noted	**Inclusion**: Failure to sputum convert or high risk of relapse due to remaining cavities **Exclusion:** HIV, FEV1 < 2.0, heart failure, renal insufficiency	**Inclusion**: same as Iseman, 1990	**Inclusion**: same as Iseman, 1990	**Inclusion**: Failure to convert, Previous relapse(s), high profile of drug resistance, or high or potential risk of relapse (as gauged by destroyed lung or lobe)

	activity to diminish mycobacterial burden and allow healing of bronchial stump							
Bilateral disease	93.1%	59.3%	70.4%	Not described	63.3%	Not noted	Not noted	Not noted
Pre-operative bacteriologic status	69.0% smear-positive prior to surgery	96.3% had negative smear and culture prior to surgery	40.7% smear-negative prior to surgery	22% with persistent culture-positive status prior to surgery	63.3% culture-positive pre-operatively	52.9% culture-positive at time of surgery	94% culture-negative pre-operatively	39% smear and/or culture positive at surgery
Length of pre-op treatment	5 (2-12) months (median)	5.8 (4-8) months	15 months (median)	10 months (mean) [2-23]	20 underwent surgery within 3 months of starting chemo and 4 within 6 months; 7 after 6 months	3 months in 20 patientsl 6 months in 4 patients; > 6 months in 7 patients	5.9 months mean [3-10]	Not noted
Bacteriologic outcome	Sustained conversion: 87.1% Culture-	100% with negative cultures 4 months post-	59.3% persistently culture-positive post-	88.9% with post-operative culture conversion; at 42 months follow-up: 1	90.3% of pre-op positive patients achieved smear-conversion; one	At 7.7 year follow-up: 2% remained sputum positive	89% with favorable outcome (with culture-	89% smear and/or culture negative immediately after surgery; 80% of

	positive after surgery: 6.9%	operative; 3.7% relapsed	op; at 29 month follow-up: 70.4% culture-negative in treatment	later relapsed	subsequent relapse		conversion)	those who converted with surgery remain disease-free at 36 months
Surgical outcomes	Intra-operative deaths: 0; Non-operative deaths within 30 days: 3.4 (6.8)% Complications: 6.9%	Operative deaths: 3.7% Complications: 14.8%	Operative deaths: 0 Complications: 25.9%	Operative deaths: 0 v. 3.7% Nonoperative deaths: 8% Complications: 11.1%	Intra-operativedeaths: 0 Complications: 16.3%	Operative deaths (within 30 days): 3.3%; Late mortality: 6.4% Complications: 11.6%	Operative deaths (within 30 days): 3.3%; late mortality: 6.4%; Complications: 11.6%	Operative deaths (30-day): 1.6%; Late mortality: 8.1%; Complications: 23%

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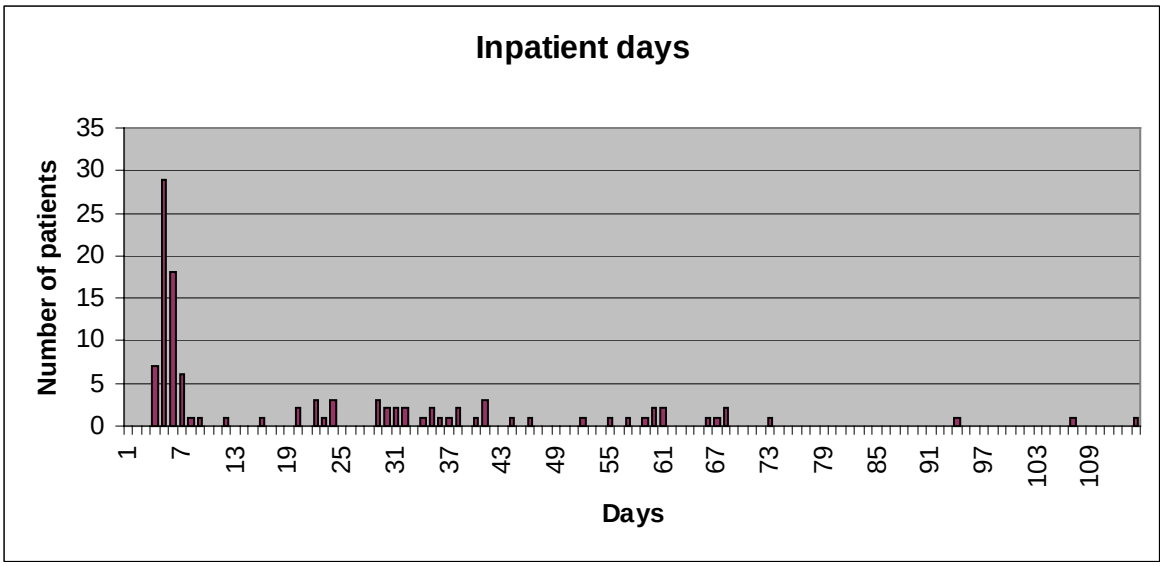


Figure 2. Post-operative survival (N=124)

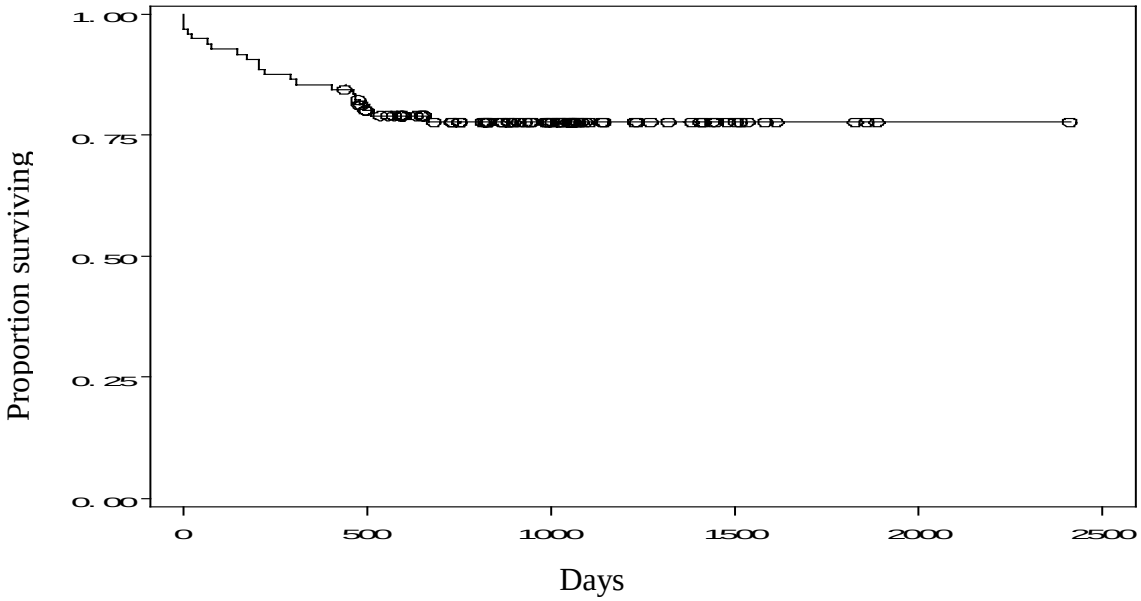
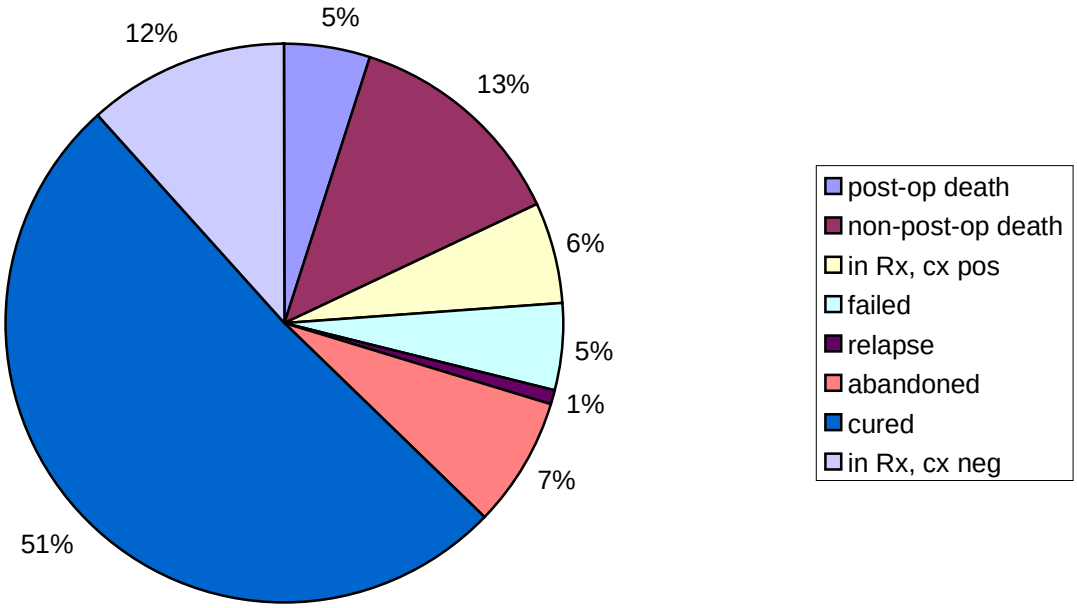


Figure 3. Current treatment status (N=121)



one year cessation rate in smokers with AL was 10.8% versus 8.4% in smokers with NLF (NS).''

Why are these findings being interpreted over-optimistically as evidence of the value of screening for mild COPD? The most likely reason is wishful thinking, since the evidence suggests the opposite conclusion to that supported in the editorial by Mannino. Perhaps it simply arises from the frustrating recognition that COPD is common in adults but is predominantly undiagnosed.

There is a serious consequence from promoting early detection of COPD if there is no evidence that it makes any difference. Putting resources into spirometry for the early detection of COPD draws resources from more effective work, the most compelling of which in this context is general smoking cessation. In the study by Bednarek *et al*,[1] 71 people needed to be screened for every additional 1 year smoking quit achieved. This is equivalent to a cost of about €650 per additional smoking quitter.

Smoking cessation is the most important intervention in the primary and secondary prevention of COPD. It is equally important in the primary and secondary prevention of cardiovascular disease and many cancers including lung cancer. Until there is some definite advantage to be gained from the early detection of COPD in improving cessation rates among smokers, there is no justification for promoting spirometric screening for mild COPD as a separate public health strategy. On current evidence, screening to detect mild COPD is not warranted and will waste resources that would be better employed to promote smoking cessation in general.

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Authors' reply

The World Health Organisation estimates that chronic obstructive pulmonary disease (COPD) affects 600 million people and that three million die every year from COPD. It is expected that, in 2020, COPD will be the third main cause of death worldwide.[1] Until now these estimates have proved valid. This worrying situation calls for action.

In the National Program of Early Detection and Prevention of COPD in Poland, >90 000 ''healthy'' smokers aged 40 years or more performed spirometric tests. It was found that 20.3% of them had signs of airflow limitation compatible with a diagnosis of COPD, and 72% of these already had moderate or severe airflow limitation. None had previously consulted their family physician about their respiratory problems and most of them needed immediate further evaluation and treatment.[2]

By combining spirometric testing with antismoking advice, sustained quitting of smoking was achieved in 16% of the COPD group and 11% of the ''healthy smoker'' group.[3] Similar results were obtained in the earlier pilot study based on a small group of subjects not included in the current study.[4] These results are better than those obtained by general antismoking advice.[5] The Lung Health Study confirmed that smoking cessation slows down the accelerated decline in forced expiratory volume in 1 s which occurs in patients with COPD with newly diagnosed disease. As many as 96.7% of subjects with moderate COPD who quit smoking still had moderate disease after 11 years of follow-up compared with 81.9% of those who continued to smoke. The initial success of quitting smoking in this group of patients turned out to be long lasting, with 93% still non-smokers after 11 years.[6]

Even if the cost of one additional person quitting smoking using our approach is €650, this is roughly half the cost of 1 year of treatment for one patient with COPD in the UK (US$1245).[7] It is also equivalent to the cost of one life-year saved by antismoking advice only, which ranges from €385 to €797.[8]

Although there is a lack of evidence of benefit related to the early diagnosis of mild COPD by spirometric testing,[9] this does not mean that such benefit does not exist. Fifty years ago systemic hypertension was frequently diagnosed when a patient had a stroke. Now early diagnosis and treatment of systemic hypertension are obligatory.

Early diagnosis of COPD defines a group of smokers at risk not only for the progression of COPD but also for lung cancer or ischaemic heart disease. Antismoking advice is an integral part of early diagnosis which will prevent many deaths from these diseases. For evidence of the benefits, we will have to wait.

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CORRECTION

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In table 1 of Somocurcio JG, Sotomayor A, Shin S, *et al* (Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. *Thorax* 2007;**62**:416–21) in the May issue the expansions of the abbreviations SM, CM, CS and PAS are streptomycin, capreomycin, cycloserine and para-aminosalicylic acid, respectively.