Surgery in the Current Era

David Griffith, MD
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• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Surgery for Pulmonary and Pleural Tuberculosis

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Indications for Lung Resection with Pulmonary TB

**Classic Indications**
- Recurrent infections
- Recurrent hemoptysis
- Massive hemoptysis
- Drug Resistant TB
- Broncho-pleural fistula
- Empyema/fibrothorax
- Persistent culture positivity with irreversible pulmonary destruction

**MDR- XDR-TB**
- Persistently positive sputum cultures despite appropriate therapy
- Relapse
- High risk for relapse
- Debunking disease with limited antibiotic choices (high drug resistance with low likelihood of cure)
- Localized disease
Surgical Approaches for PTB

- Pneumonectomy, lobectomy, segmentectomy
- VATS: limited and localized disease, no peribronchial reactive lymph node enlargement, without severe pleural adhesions
- Muscle sparing thoracotomy
- Limit extent of lung resection
- Extra-pleural dissection when possible
- Bronchial stump reinforcement (pericardial fat pad, chest wall muscle)

Adverse Events and Complications of Lung Surgery for TB

- Bleeding
- PAIN
- Inadequate lung expansion with post-operative space
- Broncho-pleural fistula with persistent air leak
- Surgical stump dehiscence
- Post-operative infection (pulmonary, pleural)
- Prolonged chest tube drainage
- Nosocomial TB transmission
- ARDS/Death
Variables to Consider for PTB Surgery
Patients and Studies

- Type and extent of PTB disease
- Cardiopulmonary status of the patient
- Nutritional status of the patient
- MTB drug susceptibility
- Number of effective medications available
- Duration of therapy before surgery
- Sputum AFB smear/culture status
- Patient co-morbidities
- Expertise of surgeons
- Available facilities
- There are no consensus guidelines for which TB patients should be selected for surgery
Favorable Outcomes for MDR- and XDR-TB Patients Undergoing Surgery

• MDR- XDR-TB patients who underwent thoracic surgery at the NTBC Tbilisi, Georgia 2008-2011 (single arm)
• Indications for surgery:
  – presence of MDR- XDR-TB,
  – localized pulmonary disease,
  – fit to undergo surgery,
  – either medial treatment failure or
  – extensive disease likely to fail RX
• Second line TB RX administered per WHO recommendations

Favorable Outcomes for MDR- and XDR-TB Patients Undergoing Surgery

• 72 evaluable patients (50 MDR-, 22 XDR- PTB) who underwent adjunctive surgery
• Mean duration of RX before surgery and followup after surgery: 1 year
• Pneumonectomy 11%, lobectomy 54%, segmentectomy 35%
• 59 (82%) favorable outcomes including 90% MDR- and 67% XDR PTB
• No post-operative mortality, “low” rates of complications
Surgical Interventions for PTB in Mumbai, India: Surgical Outcomes and Programmatic Challenges
Shirodkar et al, Pub Health Action, 2016; 6: 193

• Surgical interventions for PTB 2010-2014 in 2 Mumbai hospitals (single arm)
• 85 patients, most procedures performed on an emergency basis, eligibility established late in the course of treatment
• 5 (6%) died, 17 (20%) surgical complications (wound infection most common)
• Repeat operation required in 12 (14%)
• Culture results, DST patterns and final treatment outcomes not systematically collected

Adjunctive Surgery Improves Treatment Outcomes Among Patients with MDR- and XDR-TB

• Prospective, observational cohort (comparison) study
• 179/380 (47%) MDR- XDR-TB patients had a poor outcome
• 59 (16%) died, 37 (10%) failed, 83 (22%) defaulted
• Newly diagnosed significantly more likely to have favorable outcome than retreated (OR 4.26)
• Independent risk factors for a poor treatment outcome: previous treatment, bilateral disease, BMI ≤ 18.5, and XDR-TB
• Patients who had sputum culture conversion by 4 months and/or had surgical resection were significantly less likely to have poor outcome.
Outcomes of surgical interventions in the treatment of drug-resistant pulmonary tuberculosis: a systematic review and meta-analysis

Michael Marrone

Existing Evidence

- *Retrospective* observational cohorts
  - few *prospective* studies
- Single-arm surgical case series and case reports
- No RCT’s looking at surgical interventions
- Cochrane Reviews examining surgery for spinal TB and TB pericarditis,
  - *but not pulmonary disease*
Study Objectives

- Critically evaluate and summarize existing literature on the effectiveness of surgical interventions in the treatment of drug-resistant TB
- Secondary outcomes of interest: all-cause mortality and adverse effects
- Identify sources of heterogeneity among included studies
- Identify potential confounders influencing surgical outcomes

Selection Process

3681 potentially relevant studies identified

- 3113 studies excluded after review of title and abstract
- 410 studies excluded after 2nd review of title and abstract

182 studies reporting treatment outcomes for MDR and/or XDR TB

- 138 studies excluded after full-text review

21 comparison studies
23 single-arm studies
Characteristics of Included Studies

- **41** retrospective studies
- **3** prospective studies
- **21** comparison studies with surgical and non-surgical group
- **23** single-arm studies with surgical patients only
- **21** countries
- **7** languages: English, Russian, Korean, Japanese, Bulgarian, Lithuanian, Spanish

Comparison Study Results

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Odds ratio</th>
<th>(95% CI)</th>
<th>Overall OR (95% CI)</th>
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<td><strong>Overall OR (95% CI)</strong></td>
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\( P = 36\% \)
### XDR TB Outcomes

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\( I^2 = 29\% \)

### Single-arm Study Results

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\( I^2 = 67\% \)

\( I^2 = 74\% \)
Surgical Interventions for drug-resistant TB: a systematic review and meta-analysis
Marrone et al, IJTLD, 2013; 17: 6

• Comparison studies revealed a significant association between surgery and successful treatment compared to non-surgical interventions (OR 2.24)

• Subgroup analysis from comparison studies showed that favorable surgical outcomes were associated with increased drug resistance

• Single arm studies demonstrated that 92% and 87% of surgical patients achieved, respectively, short and long term success

TB Surgery Meta-analyses
2011-2016


The Effect of Surgery on the Outcome of Treatment for MDR-TB: A systemic review and meta-analysis
Harris et al, 2016, BMC Infect Dis; 16: 262

• Databases and grey literature sources searched using terms incorporating “surgery” and “MDR-TB”.
• 1024 unique citations: 15 retained, 4 included after bibliography/citation search and 1 unpublished study included; **20 total including 6 meta-analyses/systematic reviews and 14 primary research articles.**
• Unsuccessful outcome: death, lost to followup, treatment failure, relapse

The Effect of Surgery on the Outcome of Treatment for MDR-TB: A systemic review and meta-analysis
Harris et al, 2016, BMC Infect Dis; 16: 262

• Only 4 observational studies and one meta-analysis reported the numbers of study participants receiving each type of surgical procedure
• None of the observational studies reported outcomes of interest stratified by surgical type
• Only 3 of the 14 primary research articles focused specifically on the outcomes of surgery as compared to medical treatment alone
The Effect of Surgery on the Outcome of Treatment for MDR-TB: A systemic review and meta-analysis
Harris et al, 2016, BMC Infect Dis; 16: 262

• 14 primary research articles
• Cured or completed therapy: 81.9% and 59.7% respectively
• Summary OR comparing surgery versus non-surgery 2.62, 95% CI 1.94-3.54
• Similar results when restricted to an outcome of cure (5 studies)
• Summary OR for death following surgery, c/w medical treatment 0.82 (95% CI 0.41-1.63)

The Effect of Surgery on the Outcome of Treatment for MDR-TB: A systemic review and meta-analysis
Harris et al, 2016, BMC Infect Dis; 16: 262

• “Substantially increased likelihood of a successful treatment outcome (cure or treatment completion) in MDR-TB patients undergoing adjunctive surgery (OR 2.62)”
• “Overall, the quality of evidence across each outcome measure with available data was assessed as “very low”.”
Prior Meta-analyses of surgery for MDR-TB

• Confounding by indication: a form of bias that occurs when patients most likely to benefit are selected for therapy
• There was no distinction between different forms of resection surgery
• Antibiotic regimens were not standardized across studies
• Timing of surgery in relation to culture conversion could not be accounted for

Individual Patient Data Meta-Analysis (IPD-MA)

• Authors from selected studies contacted and asked to provide patient information:
• Gender, age, initial smear status, chest radiographic results, HIV status, medical treatment regimen and past 1st and 2nd line drug treatment
• DST results, timing of culture conversion
• Extent and timing of surgery
• Treatment outcome: cure, completion, failure, relapse, death, and default
Surgery as an Adjunctive Treatment for MDR-TB: An Individual Patient Data Meta-Analysis (Fox et al, CID, 2016)

• Individual patient data obtained from 26 cohort studies, identified from 3 systematic reviews of MDR-TB treatment

• Primary analysis compared treatment success (cure and completion) to a combined outcome of failure, relapse and death.

• The effects of all forms of resection surgery, pneumonectomy, and partial lung resection were evaluated.

Surgery as an Adjunctive Treatment for MDR-TB: An Individual Patient Data Meta-Analysis (Fox et al, CID, 2016)

• Patients:
  – 67 individual cohort studies,
  – 36 studies excluded ( 
    • Surgical status not available, EP TB, HIV +, insufficient data
  
• Pulmonary resection surgery performed on 478 patients
  – Pneumonectomy 117
  – Partial lung resection 220
  – Lung resection NS 132
Surgery as an Adjunctive Treatment for MDR-TB: An Individual Patient Data Meta-Analysis
(Fox et al, CID, 2016)

• Timing of surgery in relation to culture conversion:
  – Surgery before culture conversion 102
  – Surgery after culture conversion 145

• Treatment outcomes:
  – Treatment success 333
  – Treatment failure 49
  – Death 40
  – Lost to followup 56

Surgery as an Adjunctive Treatment for MDR-TB: An Individual Patient Data Meta-Analysis
(Fox et al, CID, 2016)

• Partial lung resection surgery was associated with improved treatment success (aOR, 3.0) and lower rates of failure or death than patients who had either pneumonectomy or no surgery

• Pneumonectomy was not associated with improved treatment success (aOR, 1.1)
  – 8.5% mortality vs 2.2% for partial lung resection

• Treatment success was more likely when surgery was performed after culture conversion than before conversion (95.2% vs 91.2%: aOR, 2.16)

• The odds of success for XDR-TB patients who underwent surgery were significantly lower compared with other patients (aOR, 0.40)
WHO Treatment Guidelines for Drug Resistant Tuberculosis, 2016 Update

• The rates of death in the IPD for surgical outcomes did not differ significantly between patients who underwent surgery and those who received medical treatment only.
• There were not enough data on adverse events, surgical complications or long term outcomes - some of which may be fatal - to allow meaningful analysis
• Despite the unknown magnitude of perioperative complications, WHO assumed that overall there is a net benefit from surgery.

Maximizing the potential benefit of surgery for TB patients:

(Drug Resistant TB, A Survival Guide for Clinicians, 3rd ED)

• The patient must be an acceptable surgical risk with adequate pulmonary function reserves to tolerate resectional surgery
• Surgery should be performed by an experienced surgeon and only after several months of chemotherapy
• Whenever possible, the surgery should be performed after smear conversion has occurred, and ideally after culture conversion
• After surgery, the patient must complete a full course of TB therapy. If cultures are negative after surgery, the date of surgery is the date of culture conversion
The elephant in the room

20 year old patient from Myanmar living in the Heartland Region diagnosed with drug susceptible TB by mediastinal lymph node aspiration Spring 2015

Patient non-communicative, had guardian who spoke little English

Placed on standard TB therapy to be administered by the guardian

6 months into treatment, dramatic increase in size of intrathoracic lymph nodes

Guardian had not been giving the patient her TB medications as directed

The elephant in the room (MONEY)

No enthusiasm for restarting RIPE
Local Public Health authority asked for surgical biopsy of intrathoracic lymph node to obtain new specimens for culture...no takers

Contacted Heartland / UTHSCT for possible transfer...no can do without funding

Intense huddling of all concerned parties: patient granted emergency Medicaid coverage, UTHSCT agreed to accept low Medicaid reimbursement

Patient had VATS in Tyler, LN biopsy yielded drug susceptible TB, unremarkable surgical course

Patient returned home to complete therapy
Variables to Consider for PTB Surgery Patients and Studies

- Type and extent of PTB disease
- Cardiopulmonary status of the patient
- Nutritional status of the patient
- MTB drug susceptibility
- Number of effective medications available
- Duration of therapy before surgery
- Sputum AFB smear/culture status
- Patient co-morbidities
- Expertise of surgeons
- Available facilities

Remaining Questions

- Surgery + Chemotherapy vs. Chemotherapy Alone
- Timing of surgery
- Invasive vs. Conservative surgical procedures
- More beneficial in specific subgroup of TB patients?
Should we routinely surgically remove cavities and/or destroyed lung?

A Systematic Review of the Prevalence and Pattern of Imaging Defined Post-TB Lung Disease
Meghji et al, PLoS One, 2016; epub

- Literature review to define the prevalence and pattern of lung pathology at end of medical treatment for pleuro-pulmonary TB disease: **37 studies**
- The principal features were:
  - Cavitation 8.3-83.7%
  - Bronchiectasis 4.3-11.2%
  - Fibrosis 25-70.4%
- The prevalence of cavitation was generally lower (7.4-34.6%) and bronchiectasis higher (35-86%) on CT vs CXR imaging
- Only ONE study looked at cavitation 6 months after therapy: 68.8% vs 83.7% at end of treatment
End of Therapy (EOT) Cavity: A Risk Factor for Relapse

Independent of culture results

Additional Drug Resistance in MTB Isolates From Resected Cavities Among Patient with MDR- or XDR-PTB
Kempker et al, CID, 2012; 54: e51

- 23 patients with MDR-XDR-TB who had both pre-operative sputum and resected cavitary tissue cultures positive for MTB
- 18/23 with positive culture from resected cavity and DST for FLD’s and SLD’s on specimens from both sources
- 7/18 (37%) cultures from tissue with additional drug resistance compared with sputum
- 6/7 additional drug resistance to a FQ or injectable
TB Pleural Effusion

- The mean duration for complete resorption of the pleural fluid is about 6 weeks, but it can be as long as 12 weeks (Tani et al, Acta Tuberc Scand, 1964)
- The incidence of pleural thickening at 6 to 12 months after beginning treatment is approximately 50%, not related to pleural fluid findings. (Barbas et al, 1991, Chest)
Early Effective Drainage in the treatment of loculated tuberculosis pleurisy

• 64 consecutive patients with TB pleural effusion with pigtail catheter inserted
  – Free flowing fluid with saline irrigation
  – Loculated effusion with streptokinase infusion
  – Loculated effusion with saline infusion

• Free flowing and streptokinase patients with improved FVC (80, 80 vs 78 % pred) and lower occurrence of residual pleural thickening (3.6, 4.7 vs 19.2 mm) C/W loculated and saline infusion

Diseases of the Pleura Vol IV
Richard Light

• “Although the pleura may be thickened when the patient’s disorder is first diagnosed, the thickening decreases with treatment so decortication should not be considered until the patient has undergone treatment for at least 6 months. After this period of observation, decortication is rarely necessary.”