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Adjunctive surgery versus medical treatment among patients with cavitary multidrug-resistant tuberculosis

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Key question

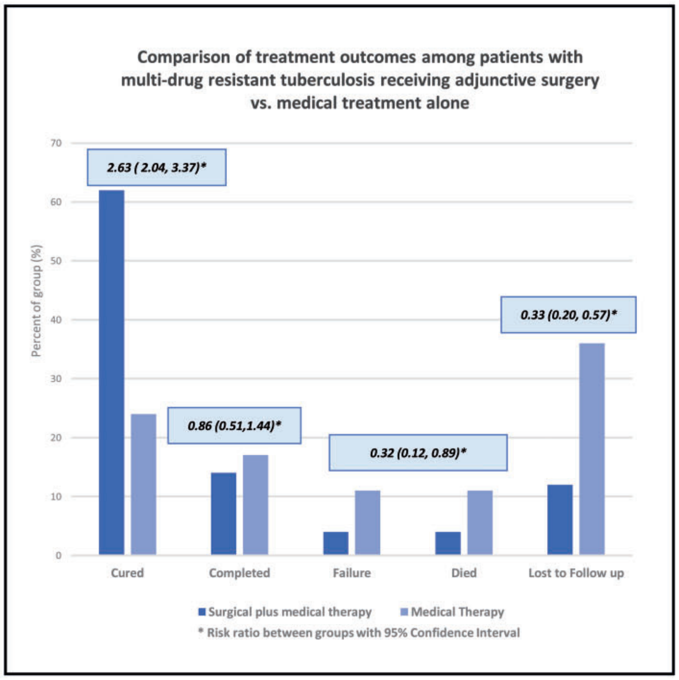
Does adjunctive surgery improve outcomes compared to medical therapy alone in patients with cavitary drug-resistant tuberculosis?

Key finding(s)

Adjunctive surgical therapy was associated with considerably increased rates of cure compared to medical therapy alone.

Take-home message

Patients with cavitary multi/extensively drug-resistant tuberculosis may benefit from adjunctive surgical therapy.



Abstract

OBJECTIVES: Surgical resection is recommended as adjunctive treatment for multidrug-resistant (MDR) tuberculosis (TB) in certain scenarios; however, data are limited. We sought to evaluate the impact of surgery by comparing TB outcomes among patients with cavitary disease who received medical versus combined medical and surgical treatment.

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METHODS: A cohort of all patients with cavitary MDR or extensively drug-resistant (XDR) TB treated in Tbilisi, Georgia, between 2008 and 2012. Patients meeting indications for surgery underwent adjunctive resection in addition to medical treatment. We compared TB outcomes (proportions achieving cure/complete) among patients who received adjunctive surgery to those who received medical treatment alone using an adjusted robust Poisson regression.

RESULTS: Among 408 patients, 299 received medical treatment alone and 109 combined medical and surgical treatment. Patients in the non-surgical group were older and had higher rates of tobacco and alcohol use and bilateral disease compared to the surgical group. Patients in the surgical group had higher rates of XDR disease (28% vs 15%). Favourable outcomes were higher among the surgical versus non-surgical group cohort (76% vs 41%). After adjusting for multiple factors, the association between adjunctive resection and favourable outcome remained (adjusted risk ratio 1.6, 95% confidence interval 1.3–2.0); the relationship was also observed in secondary models that excluded patients with bilateral disease (contraindication for surgery) and patients receiving <6 months of treatment. Major postoperative complications occurred among 8 patients (7%) with no postoperative mortality.

CONCLUSIONS: Adjunctive surgery is safe and may improve the effectiveness of treatment among select patients with cavitary MDR- and XDR-TB.

Keywords: Pulmonary tuberculosis • Drug resistance • Surgical resection • Cavitary

ABBREVIATIONS

CI	Confidence interval
DST	Drug susceptibility testing
LTFU	Loss to follow-up
MDR	Multidrug resistant
NCTLD	National Center for Tuberculosis and Lung Disease
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensively drug resistant

INTRODUCTION

The emergence and persistence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) is a major obstacle to achieving TB elimination goals [1]. According to the most recent World Health Organization (WHO) Global TB Report, the worldwide prevalence of MDR-TB remained high with an estimated 465 000 cases in 2019 and the overall treatment success rate low at 57%. Alarmingly ∼20% of *Mycobacterium tuberculosis* isolates tested had further resistance to fluoroquinolones, a key second-line drug, leading too hard to treat pre-XDR and XDR-TB [1]. The recent introduction of new and repurposed drugs including bedaquiline and linezolid has provided much needed new treatment options and led to improved outcomes among patients with MDR and XDR-TB [2]. However, favourable outcome rates are lower than for drug-susceptible TB, and reports of drug resistance to new drugs have emerged [3–5]. Thus, alternative treatment options including adjunctive surgical resection may be needed in cases of severe disease and those unresponsive to treatment.

Adjunctive surgical therapy was one of the earliest treatment modalities used for pulmonary TB but the advent of effective chemotherapy led to a decline in its use [6]. Recently, there has been an increase in reports on the use of adjunctive surgery that parallels the rise in MDR and XDR-TB. Three recent separate meta-analyses (including an individual patient data meta-analysis) each suggested adjunctive surgery is associated with favourable outcomes among patients with MDR-TB; however, the data quality was deemed to be low and potentially biased by unknown patient selection factors [7–9]. Utilizing the results of the individual patient data meta-analysis, the most recent WHO drug-resistant TB treatment guidelines give a provisional recommendation with a very low certainty of evidence to use elective partial lung resection in certain cases of MDR-TB [7, 10]. Improved data are needed to further define the role of adjunctive surgery in treatment of patients with MDR and XDR-TB.

Similar to other countries of the former Soviet Union, Georgia has been and remains a country with a high burden of MDR- and XDR-TB. Despite the early implementation of universal access to diagnosis and treatment of drug-resistant TB in 2009, initial outcomes among patients with MDR and XDR-TB remained poor and surgical resection was utilized when needed for patients meeting designated criteria [11]. In a prior study, we demonstrated a high rate of favourable outcomes among patients with MDR- and XDR-TB in Georgia; however, the study was limited by lack of a non-surgical comparison group [12]. To better understand the impact of adjunctive surgery, we carried out a study comparing the outcomes among patients with cavitary MDR- or XDR-TB disease who did or did not receive surgical resection. We hypothesized that patients undergoing adjunctive surgical resection would have improved clinical outcomes. The goal of our work is to provide data to help inform the use of adjunctive surgical resection in difficult to treat TB disease.

PATIENTS AND METHODS

This study was approved by the institutional review boards of the National Center for Tuberculosis and Lung Disease (NCTLD) (IORG0006411) on 21 February 2014 and Emory University (IRB00073233) on 25 March 2014. Informed consent for all of the patients was waived by both institutional review boards due to the retrospective nature of this study.

We conducted a cohort study from 2008 to 2012. First, we conducted a retrospective medical chart review of patients receiving treatment for pulmonary MDR and XDR-TB at the NCTLD in Tbilisi, Georgia, from October 2008 through February 2012. Patients with cavitary disease identified on baseline chest radiography per radiology report were included. All patients were treated according to the WHO Directly Observed Treatment plus protocol [13]. Criteria for surgical intervention among patients with MDR or XDR-TB included (i) failure of medical therapy (persistent sputum culture positive for *M. tuberculosis*), (ii) a high likelihood of treatment failure or disease relapse, (iii) complications from the disease, (iv) localized cavitary lesion and (v) sufficient pulmonary function to tolerate surgery. A high likelihood for failure and relapse was determined based on drug susceptibility testing (DST) results with resistance to ≥4 second-line drugs considered as an indication of a low likelihood of response to available treatment, the presence of clinically significant parenchymal lung damage (either cavitary or destroyed lungs) and clinician assessment. Patients with localized bilateral cavitary disease were considered for surgery on a case by case basis. Contraindications for surgery included a forced expiratory volume in 1 s <1000 ml, severe malnutrition (body mass index ≤50% of the normal range) or patients at high risk for perioperative cardiovascular complications (New York Heart Association Class III–IV). The decision to recommend adjunctive surgery was made by the M/XDR-TB Committee at the NCTLD. The committee consists of TB clinicians and surgeons and meets twice weekly to review and make management recommendations regarding all patients with MDR- and XDR-TB. The medical treatment regimen was guided by DST results and was designed to include ≥4 active drugs including a fluoroquinolone and either kanamycin or capreomycin. Bedaquiline, delamanid and linezolid were not implemented into routine care during the study period.

Sputum cultures were performed monthly until 3 consecutive negative cultures and then every 2–3 months until treatment completion. Sputum cultures positive for *M. tuberculosis* had first- and second-line DST performed as previously described [14].

Surgery

All patients undergoing adjunctive surgery were admitted preoperatively to undergo counselling and an extensive preoperative evaluation including chest imaging, fibre-optic bronchoscopy (to identify possible endobronchial lesions), electrocardiography, and spirometry to assess preoperative lung function. Surgical procedures were performed in accordance with WHO guidance [15]. All patients received general anaesthesia, intubation with a double lumen endotracheal tube and had a temporary chest tube placed for 24–48 h in cases where the postoperative period was uneventful. Resections were performed through a posterolateral thoracotomy and the resection type was determined according to the extent of the lesion. For all patients, the bronchial stump was closed with titanium staples and the mechanical suture was strengthened with a propylene suture. No pre-emptive technique was performed to buttress the bronchial stump. Patients received aggressive postoperative physiotherapy. Postoperative follow-up was conducted through outpatient visits to the NCTLD surgery clinic. After surgery, patients were recommended to remain on anti-TB treatment for ≥12 months.

Treatment outcomes

Final treatment outcomes were classified according to WHO criteria [13]. A favourable outcome was defined as cure or completion of treatment; a poor outcome was defined as treatment failure, death during treatment or loss to follow-up (LTFU). Operative mortality was defined as any death occurring ≤30 days after surgery, or anytime during the same postoperative hospitalization [16].

A Robust Poisson regression model was used to estimate adjusted risk ratios and 95% confidence intervals for the association between treatment group (surgical versus non-surgical group) and favourable TB outcome [17–19]. Three additional regression models were performed excluding patients with <6 months of treatment (surgery typically performed after this time), with LTFU, and with bilateral disease (generally a contraindication for surgery). For regression models, a purposeful selection of covariates was chosen based on observed bivariate associations (with surgery and outcomes separately) and based on previous literature.

Medical chart abstraction was performed to collect demographic and treatment data and managed using a REDCap database, which is a secure, web-based application designed to support data capture for research studies [17]. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Loss to follow-up

Through March 2019, we prospectively collected information on patients with an outcome of LTFU by (i) querying the NCTLD database to determine re-entry into care, (ii) searching the Ministry of Justice database to evaluate for death (queried in February 2019), (iii) contacting the patient via phone and (iv) communication with the patients' physician to obtain follow-up information. All patients who could be contacted and had not re-entered into care were asked to come in for evaluation including a chest X-ray and sputum sample for smear and culture.

RESULTS

A total of 408 patients with cavitary MDR-TB were identified including 299 patients who received medical treatment alone (non-surgical group) and 109 who received medical and adjunctive surgery (surgical group). The mean age of the cohort was 36.8 years, 79% of patients were male, and most had a history of prior TB treatment (78%). Patients in the surgical group were younger (mean age 30.7 vs 39.0 years) and had higher rates of XDR disease as compared to patients in the non-surgical group (28% vs 15%). Conversely, patients in the non-surgical group had higher rates of tobacco and alcohol use, hepatitis C virus antibody positivity, and prior history of TB and bilateral disease on chest radiography (Table 1).

Among the 109 patients in the surgical group, the most common indications for surgery were a high likelihood of treatment failure or disease relapse (69%) and medical treatment failure (26%) (Table 2). The median duration of medical treatment prior to surgery was 462 days (IQR 320–666) and 36% of patients had a positive preoperative sputum culture for *M. tuberculosis*. The most common types of surgical resection were lobectomy (47%) and segmentectomy (36%). There were 9 postoperative complications, of which 2 minor complications had occurred in the same patient; no postoperative deaths occurred and the 90 days postoperative mortality was 0%. Five patients required subsequent surgical intervention for treatment of complications, including 2 for fistula repair, 2 for bleeding, and 1 for empyema. Among the 102 patients who had their resected tissue cultured, 29 (28%) had a positive culture for *M. tuberculosis*.

Treatment outcomes were available for 402 (99%) patients. There was a higher rate of favourable outcomes (cured plus completed) in the surgical (76%) versus non-surgical group (41%) (Table 3) [unadjusted risk ratio 1.9, 95% confidence interval (CI) 1.6–2.2]. Final sputum culture conversion was achieved in 92% of

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Table 1: Baseline characteristics of patients treated for cavitary multidrug-resistant tuberculosis by treatment group

Characteristic	Total, *n* = 408 (%)	Surgery, *n* = 109 (%)	Non-surgery, *n* = 299 (%)	Prevalence difference (95% confidence)
Median age (IQR)	36.8 (27.5–45.5)	28.4 (22.5–36.5)	37.2 (30.4–40.0)	NA
Male	324 (79)	69 (63)	255 (85)	-22% (-32, -12)
Tobacco use	214 (53)	43 (40)	171 (57)	-18% (-29, -7)
Alcohol use	132 (33)	13 (12)	119 (40)	-28% (-36, -20)
Illicit drug use	29 (7)	11 (10)	18 (6)	4% (-2, 10)
Comorbidities				
Diabetes	24 (6)	8 (7)	16 (5)	2% (-4, 8)
CV disease	13 (3)	4 (4)	9 (3)	1% (-3, 5)
Hepatitis C Ab positive	76 (19)	7 (6)	69 (23)	-17% (-23, -10)
HIV	9 (2)	1 (1)	8 (3)	-2% (-4, 1)
Case definition				
New	88 (22)	47 (43)	41 (14)	29% (19, 39)
Prior 1st-line treatment	230 (56)	48 (44)	182 (61)	-17% (-28, -6)
Prior 2nd-line treatment	90 (22)	14 (13)	76 (25)	-13% (-21, -5)
Radiology				
Multilobar disease	272 (67)	44 (41)	228 (76)	-36% (-46, -26)
Bilateral disease	225 (55)	27 (25)	198 (66)	-42% (-51, -32)
Bilateral cavity	116 (28)	12 (11)	104 (35)	-24% (-32, -16)
Drug susceptibility testing				
XDR-TB	76 (19)	30 (28)	46 (15)	12% (3, 21)
Ofloxacin R (*n* = 403)	109 (27)	43 (40)	66 (22)	17% (7, 28)
Capreomycin R (*n* = 400)	95 (24)	32 (30)	63 (21)	8% (-1, 18)
Kanamycin R (*n* = 401)	146 (36)	46 (43)	100 (34)	9% (-2, 20)
Initial drug treatment				
Pyrazinamide (*n* = 350)	257 (73)	53 (50)	204 (84)	-20% (-30, -9)
Prothionamide (*n* = 393)	362 (92)	91 (84)	271 (95)	-7% (-15, 1)
Kanamycin (*n* = 295)	140 (48)	29 (27)	111 (59)	-11% (-21, -1)
Capreomycin (*n* = 342)	248 (73)	67 (64)	181 (76)	1% (-10, 12)
Levofloxacin (*n* = 386)	333 (86)	74 (68)	259 (94)	-19% (-28, -9)
Moxifloxacin (*n* = 251)	70 (28)	34 (33)	36 (24)	19% (10, 29)
Cycloserine (*n* = 398)	390 (98)	108 (99)	282 (98)	5% (2, 8)
PAS (*n* = 401)	384 (96)	99 (91)	285 (98)	-5% (-10, 1)
Clofazimine (*n* = 251)	71 (28)	38 (36)	33 (23)	24% (14, 34)

Ab: antibody; CV: cardiovascular; HIV: Human immunodeficiency virus; IQR: interquartile range; MDR-TB: multidrug-resistant tuberculosis; XDR: extensively drug resistant.

the surgical patients and 53% of the non-surgical patients. Cavitary disease was present on chest imaging at the end of treatment in more patients in the non-surgical (69%) versus surgical group (4%). In an adjusted Robust Poisson regression, adjunctive surgery was associated with a favourable outcome (adjusted risk ratio 1.6, 95% CI 1.3–2.0). All 3 additional models found adjunctive surgery to be associated with a favourable outcome (Table 4).

Loss to follow-up

The National Death Registry was checked for all patients LTFU, and 16 (13%) patients were confirmed to have died after LTFU, including 1 (8%) in the surgical group and 15 (14%) in the non-surgical group (Table 5). A follow-up sputum sample was obtained in 64 patients and 1 (8%) patient in the surgical group and 41 (38%) in the non-surgical group had *M. tuberculosis* identified by culture. More patients in the non-surgical group re-entered (46%) TB care than in the surgical group (15%).

DISCUSSION

In a large cohort of patients with cavitary MDR and XDR-TB, we found a high rate of favourable outcomes (76%) among patients undergoing adjunctive surgery and notably better outcomes when compared to patients receiving medical treatment alone. The high rate of favourable outcomes among patients receiving adjunctive surgery is especially notable given the study period was prior to the introduction of new and repurposed anti-TB drugs and the high rates of high-level drug resistance (pre-XDR and XDR) and prior TB disease in the cohort. We also found that receiving adjunctive surgery was associated with higher rates of favourable outcome after controlling for potential confounders and in various additional regression models limited to patients meeting the main eligibility criteria for surgery. Among patients LTFU, those having received adjunctive surgery were also less likely to re-enter care or have a follow-up sputum culture positive for *M. tuberculosis*. Our findings highlight that certain patients with cavitary M/XDR-TB disease benefit from adjunctive surgery and provide an impetus to consider studies designed to specifically address the role on adjunctive surgery in patients with cavitary disease.

The primary rationale for adjunctive surgery is to remove a reservoir of *M. tuberculosis* bacilli within a section of destroyed or necrotic lung tissue (cavity). The centre of cavitary lesions is generally avascular and filled with necrotic material termed caseum, which is characterized by a high burden of bacilli [20]. Emerging data have found that *M. tuberculosis* bacilli in caseum undergo metabolic shifting to a slow growth state marked by drug

Table 2: Surgical characteristics of patients undergoing adjunctive lung resection (*N* = 109)

Variable	Result, n (%)
Surgical indication	
Medical treatment failure	28 (26)
High drug resistance	75 (69)
Massive haemoptysis	2 (2)
Others	4 (4)
Pre-surgery sputum smear positive	21 (19)
Pre-surgery sputum culture positive (*n* = 107)	38 (36)
Surgery performed	
Pneumonectomy	11 (10)
Lobectomy	51 (47)
Segmentectomy	39 (36)
Others	8 (7)
Time to surgery, days (IQR)[a]	462 (320–666)
Duration of hospitalization for surgery, days (IQR)[b]	26 (17–36)
Postoperative complications	9 (8)
Major complications	
Fistula	5 (5)
Empyema	1 (1)
Haemorrhage	2 (2)
Minor complications[c]	
Wound infection	1 (1)
Pneumothorax	1 (1)
Subsequent surgery performed	
Fistula repair	2 (2)
Thoracotomy	2 (2)
Others	1 (1)
Lung tissue smear positive (*n* = 105)	33 (31)
Lung tissue culture positive (*n* = 102)	29 (28)

[a]Median time to surgery from date of diagnosis.
[b]Median duration of hospital stay.
[c]One patient experienced both of the minor complications.
IQR: interquartile range.

Table 3: Comparison of treatment outcomes in the surgical and non-surgical groups

Overall treatment outcomes[a]	Total (%)	Surgery, *n* = 109 (%)	Non-surgery, *n* = 299 (%)
Cured	139 (34)	68 (62)	71 (24)
Completed	67 (16)	16 (14)	51 (17)
Failure	38 (9)	4 (4)	34 (11)
Died	38 (9)	4 (4)	34 (11)
Loss to follow-up (default)	120 (29)	13 (12)	107 (36)
Non-evaluable[b]	6 (2)	4 (4)	2 (1)
Favourable versus poor[c] (*n* = 402)	206 (51)	84 (77)	122 (41)
Favourable versus poor[d] (*n* = 291)	206 (73)	84 (77)	122 (41)
Final sputum culture conversion	258 (63)	100 (92)	158 (53)
Cavity present at end of treatment[e]	208 (51)	4 (4)	204 (69)

[a]Outcomes defined by WHO Criteria [13].
[b]Patients left Georgia to seek treatment and final outcomes were not available.
[c]Excluding patients who are non-evaluable.
[d]Excluding patients who are non-evaluable and loss to follow-up.
[e]Based on end of treatment chest X-ray.

tolerance. Most drugs do not diffuse well into caseum and for those that do, the increased minimal inhibitory concentration found in caseum makes it challenging to sterilize necrotic granuloma lesions [21, 22]. Thus, surgical resection removes a reservoir of hard to reach, eradicate *M. tuberculosis* bacilli, and allows anti-TB chemotherapy to more easily eliminate any remaining bacilli. Many clinical studies have also shown that the presence of cavitary lesions among patients with pulmonary TB has been associated with worse clinical outcomes including longer time to culture conversion, acquired drug resistance, disease relapse, and post treatment obstructive lung disease [8, 23–26].

Our study provides important comparative data on outcomes among patients with cavitary MDR and XDR-TB and is one of the largest individual cohorts of adjunctive surgery patients to date. We found a remarkably high favourable outcome rate among patients undergoing surgery (76%) especially taking into account high rates of XDR disease, prior treatment and treatment with less effective traditional second-line agents. In comparing outcomes to patients with cavitary M/XDR-TB who received medical treatment alone, we were attempting to identify a 'counterfactual' group who by having cavitary disease met the essential criteria for being eligible for surgical treatment. However, we realize this still represents an imperfect comparison group and may not account for potential unmeasured confounders and selection bias. To provide further strength to our findings, we utilized a Robust Poisson regression model to carry out additional models which included patients with a minimum of 6 months treatment, without LTFU, and with unilateral cavitary disease (bilateral cavitary disease is generally a contraindication to surgery). In all regression models, we found surgery was associated with a favourable outcome in both unadjusted and adjusted analyses. Our results are similar to and support findings of published meta-analyses. A meta-analysis by Marrone *et al.* [27] evaluated 24 comparative studies (5284 patients, 706 undergoing surgery) and found surgical intervention was associated with treatment success among patients with drug-resistant TB (odds ratio, 2.24, 95% CI 1.68–2.97). Furthermore, an individual patient data meta-analysis (6431 patients, 478 undergoing surgery) by Fox and colleagues found partial lung resection (adjusted OR, 3.0, 95% CI 1.5–5.9) was associated with treatment success but pneumonectomy was not (aOR 1.1, 95% CI 0.6–2.3) [7]. Notably, the majority of surgical patients in our cohort had partial lung resection performed. Our data along with reports from the literature support a role for surgical resection among patients with cavitary drug-resistant TB and call for prospective controlled studies to be performed.

To our knowledge, our study was the first to compare long-term outcomes after LTFU among patients receiving adjunctive surgery versus medical therapy alone. Alarmingly, the death rate and persistent sputum culture positive rate were high among non-surgical patients after LTFU, while only person died in the surgical group. The poor outcome rate in the non-surgical group is likely an underestimate also given follow-up data were available for just over half the group. This result suggests that adjunctive surgery may lessen the need for prolonged treatment and have some protective effect versus relapse. Importantly, our results also demonstrate the safety of adjunctive surgery as our postoperative complication rate (8%) was low with the majority being minor complications.

This study had several limitations. Given we utilized a retrospective cohort design, we were only able to collect information commonly available for all patients and selection bias for patients selected for surgery may have existed [28]. Our cohort design also did not account for competing risks. We were unable to

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Table 4: Risk ratio for achieving a favourable outcome among patients with cavitary multidrug-resistant tuberculosis

	Cure or complete, *N*/total (%)	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
Model 1: all patients, *N* = 408			
Surgery	84/109 (77)	1.9 (1.6–2.2)	1.6 (1.3–2.0)
No surgery	122/299 (41)	REF	REF
Model 2: patients >6 months treatment, *N* = 368			
Surgery	84/109 (77)	1.6 (1.4–1.9)	1.5 (1.2–1.8)
No surgery	122/259 (47)	REF	REF
Model 3: patients without loss to follow-up, *N* = 288			
Surgery	84/96 (88)	1.4 (1.2–1.6)	1.2 (1.1–1.4)
No surgery	122/192 (64)	REF	REF
Model 4: patients with unilateral cavitary disease and receiving >6 months of treatment, *N* = 267			
Surgery	76/97 (78)	1.5 (1.3–1.8)	1.4 (1.2–1.8)
No surgery	87/170 (51)	REF	REF

Quasi-likelihood modified Akaike information QIC/QICu ratios: model 1: 0.998; model 2: 0.998; model 3: 0.999; model 4: 0.998.

[a]Robust Poisson model adjusted for age, sex, prior tuberculosis treatment, smoking status, alcohol use, bilateral cavity, XDR-TB and hepatitis C.

CI: confidence interval; RR: risk ratio; REF: referent group; TB: tuberculosis; XDR: extensively drug resistant.

Table 5: Follow-up information for patients with an outcome of loss to follow-up

Characteristic	Total *n* = 120, *n* (%)	Surgical (*n* = 13), *n* (%)	Non-surgical (*n* = 107), *n* (%)
Median days to follow-up (IQR)	1680 (1279–1977)	1890 (1547–1980)	1538 (1260–1989)
Died	16 (13)	1 (8)	15 (14)
Follow-up sputum sample	64 (53)	13 (100)	52 (49)
Positive sputum smear	43 (36)	1 (8)	42 (39)
Positive culture	42 (35)	1 (8)	41 (38)
Re-entered care	51 (43)	2 (15)	49 (46)

IQR: interquartile range.

collect information on which patients in the non-surgical group were referred for surgical evaluation and did not have access to chest radiology images which would have allowed for a more detailed characterization of lung lesions. In addition, the Georgian National Tuberculosis program guidelines did not recommend performing tissue cultures until late 2011, and thus, we were not able to obtain tissue cultures from the patients who had surgery performed prior to this time. We also were unable to obtain data on treatment adherence and adverse events which can impact clinical outcomes. To help control for confounders including factors that may have impacted selection for surgery, we utilized a Robust Poisson regression model and several additional models limited to patients who met the eligibility criteria for surgery. All models found a notable association with adjunctive surgery. Our study was also conducted before the roll out of newly implemented drugs including bedaquiline and linezolid which have led to improved outcomes among patients MDR and XDR-TB [2]. Preliminary data suggest linezolid penetrates well into caseum while bedaquiline does not [29, 30]. Studies evaluating adjunctive surgery within the context of newer, more effective drugs are needed.

CONCLUSION

Our study is one of few comparative studies evaluating the impact of adjunctive surgery among patients with cavitary MDR and XDR-TB and utilizing robust analysis methods we found higher rates of improved outcomes among patients undergoing surgery. These results along with published meta-analyses indicate surgery can improve outcomes for certain patients and highlight the need for a controlled study of surgical resection to better understand which patients would benefit the most from adjunctive surgery.

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Author contributions

Sergo A. Vashakidze: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Writing—original draft; Writing—review & editing. **Shota G. Gogishvili:** Data curation; Investigation. **Ketino G. Nikolaishvili:** Investigation; Supervision. **Zaza R. Avaliani:** Project administration; Resources. **Abivarma Chandrakumaran:** Formal analysis; Software; Validation; Writing—original draft; Writing—review & editing. **Giorgi Sh. Gogishvili:** Formal analysis; Validation. **Mathew Magee:** Data curation; Formal analysis; Visualization; Writing—original draft; Writing—review & editing. **Henry M. Blumberg:** Funding acquisition;

Supervision; Validation. **Russell R. Kempker:** Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing—original draft; Writing—review & editing.

Reviewer information

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