

Outcomes of patients undergoing lung resection for drug-resistant TB and the prognostic significance of pre-operative positron emission tomography/computed tomography (PET/CT) in predicting treatment failure



Gregory L. Calligaro,^{a,h} Nevadna Singh,^{a,h} Timothy C. Pennel,^{b,h} Rachele Steyn,^c Anita Brink,^c Aliasgar Esmail,^a Lynelle Mottay,^a Suzette Oelofse,^a Barbara L. Mastrapa,^d Wisdom Basera,^{e,f} Kathryn Manning,^e Chima Ofoegbu,^b Anthony Linegar,^b and Keertan Dheda^{a,g,*}



^aCentre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute and South African MRC/UCT Centre for the Study of Antimicrobial Resistance, University of Cape Town, Cape Town, South Africa

^bChris Barnard Division of Cardiothoracic Surgery, Department of Surgery, University of Cape Town, Cape Town, South Africa

^cDivision of Nuclear Medicine, Department of Radiology, University of Cape Town, Cape Town, South Africa

^dDistrict Clinical Specialist Team, Namakwa District, Springbok, South Africa

^eDepartment of Medicine, University of Cape Town, Cape Town, South Africa

^fBurden of Disease Research Unit, South African Medical Research Council, South Africa

^gFaculty of Infectious and Tropical Diseases, Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Summary

Background Surgery remains an adjunctive treatment for drug-resistant tuberculosis (DR-TB) treatment failure despite the use of bedaquiline. However, there are few data about the role of surgery when combined with newer drugs. There are no outcome data from TB endemic countries, and the prognostic significance of pre-operative PET-CT remains unknown.

Methods We performed a prospective observational study of 57 DR-TB patients referred for surgery at Groote Schuur Hospital between 2010 and 2016. PET-CT was performed if there was nodal disease or disease outside the area of planned resection but did not influence treatment decisions. 24-month treatment success post-surgery (cure or treatment completion), including all-cause mortality, was determined.

Findings 35/57 (61.4%) patients (median age 40 years; 26% HIV-infected) underwent surgery and 22/57 (38.6%) did not (11 patients were deemed unsuitable due to bilateral cavitary disease and 11 patients declined surgery). Treatment failure was significantly lower in those who underwent surgery compared to those eligible but declined surgery [15/35 (43%) versus 11/11 (100%); relative risk 0.57 (0.42–0.76); $p < 0.01$]. In patients treated with surgery, a post-operative regimen containing bedaquiline was associated with a lower odds of treatment failure [OR (95%CI) 0.06 (0.00–0.48); $p = 0.007$]. Pre-operative PET-CT ($n = 25$) did not predict treatment outcome.

Interpretation Resectional surgery for DR-TB combined with chemotherapy was associated with significantly better outcomes than chemotherapy alone. A post-operative bedaquiline-containing regimen was associated with improved outcome; however, this finding may have been confounded by higher use of bedaquiline and less loss to follow-up in the surgical group. However, PET-CT had no prognostic value. These data inform clinical practice in TB-endemic settings.

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Keywords: Drug-resistant tuberculosis; TB surgery; PET/CT

*Corresponding author. Centre for Lung Infection and Immunity, H46.41 Old Main Building, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa.

E-mail address: keertan.dheda@uct.ac.za (K. Dheda).

^hThese authors contributed equally.

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Research in context

Evidence before this study

Surgery remains an adjunctive treatment for drug-resistant tuberculosis (DR-TB) treatment failure despite the use of bedaquiline. However, there are few data about the role of surgery when combined with newer drugs. There are no outcome data from TB endemic countries, and the prognostic significance of pre-operative PET-CT remains unknown. We searched PubMed and Google Scholar for articles published in all languages up to 1st September 2020 using the search terms “drug resistant tuberculosis”, “resectional surgery”, “XDR-TB”, “PET/CT” and “outcomes”. We identified almost 50 observational studies and a systematic review (which included patient-level data from over 5000 participants) showing encouraging outcomes in patients who undergo lung resection for DR-TB.¹⁴ However, only one was from a HIV-endemic or resource-poor (African) setting, none had high rates of XDR-TB in their patient population, and none included PET/CT as a pre-operative investigation.

Added value of this study

This study adds to the limited data on surgical outcomes for DR-TB in high HIV burden settings and sub-Saharan Africa and is, to our knowledge, the first to examine the role of PET-CT in surgery for DR-TB. We showed that resectional surgery in a cohort of patients with predominantly XDR-TB in combination with available chemotherapy resulted in a cure in ~50% of patients. This was in contrast to only ~20% cure in patients managed with medical chemotherapy alone (and ~0% cure in the patients that turned down surgery if eligible). The main risk factor for poor outcome was the degree of drug resistance. Secondly, we showed that an effective post-operative regimen is essential and thus post-operative bedaquiline was an independent predictor of a post-surgical favourable outcome. Thirdly, treatment outcomes were not modified by the presence of PET-positive disease, regardless of activity in the contralateral lung or its radiological type. This finding suggests that factors other than the burden of FDG-avid disease in the non-resected lung are associated with treatment outcome.

Introduction

Multi drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) are global public health priorities, with limited pharmacological options for cure.^{1,2} The overall treatment outcomes of pre-XDR and XDR-TB in particular are far from satisfactory.^{3–6} A retrospective study from our setting (in the era before linezolid, bedaquiline and delamanid) showed that only 19% of patients culture-converted on the pharmacotherapy available at the time.⁷ Even with newer drugs like bedaquiline, a third of patients have unfavourable outcomes.⁸ Thus, in the absence of effective drug regimens, and in appropriate patients, surgery has been employed as a form of adjunctive treatment.^{9,10} The rationale behind surgery for TB is to dramatically reduce the overall organism burden in the lung (while simultaneously removing the sites of high concentrations of drug-resistant bacilli) by excising thick-walled cavitary lesions and areas of destroyed lung, which may harbour up to 10^7 – 10^9 *M.tb* organisms.¹¹ This ‘debulking’ hopes to enhance the sterilizing properties of post-surgical chemotherapy and to increase the likelihood of treatment success.^{12,13}

Observational studies and a systematic review (which included patient-level data from over 5000 participants) have shown encouraging outcomes in patients who undergo lung resection for DR-TB.¹⁴ The treatment benefit seems to be more pronounced in patients with a higher resistance profile, supporting the widely held view that surgery as a therapeutic option becomes even more attractive as effective chemotherapeutic options

dwindle. However, the role of selection bias in the favourable outcomes seen post-surgery requires clarification. Indeed, there are hardly any data comparing surgical outcomes against chemotherapy alone and there is a lack of data from under-resourced TB-endemic settings, where more than 95% of the DR-TB burden lies. A single report from KwaZulu Natal in South Africa on surgery for DR-TB (of which only 26% had XDR-TB) reported a culture conversion rate of 87.5% at 2 months but did not look at long term outcomes.¹⁵ Moreover, there are no post-surgical outcome data in patients treated with newer drugs like bedaquiline or in HIV-infected persons, and little is known about factors that may influence patient selection and treatment outcomes.

Active tuberculosis infection (including asymptomatic and extrapulmonary disease) may be detected with 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), which may provide additional information about parenchymal and nodal metabolic activity¹⁶ and in those with previous TB may distinguish active tuberculous lesions from previous lesions of healed TB. However, the role of areas of FDG-avid nodular disease or consolidation (which contain exponentially less organisms than thick-walled cavitary lesions and are better penetrated by antituberculous drugs¹⁷) on treatment outcomes in DR-TB is unknown.

We hypothesised that patients undergoing lung resection would have improved outcomes as compared to the cohort of patients who were not managed with

surgery. We also hypothesised that PET activity distant from the site of resection, either cavitary or non-cavitary parenchymal change in the contralateral lung or adjacent lung lobe or in the mediastinum, measured preoperatively before surgery, would influence treatment outcomes.

Methods

Study design

We conducted a single-centre prospective study of patients evaluated for lung resection with DR-TB in Cape Town, South Africa. The study is reported in accordance with the STROBE statement for observational trials.¹⁸

Ethics

The study was approved by the local ethics committee (UCT Research Ethics Committee reference #038/2008), and informed consent was waived in acknowledgement that investigations were performed as part of routine clinical workup for resectional surgery.

Study population

Groote Schuur Hospital (GSH) is a large government-funded teaching hospital affiliated to the University of Cape Town, South Africa, serving a population of approximately 3 million, largely underprivileged people in Cape Town and the surrounding informal settlements. Patients with DR-TB in the National Treatment Programme network of clinics and hospitals who were referred for resectional surgery at GSH between July 2010 and December 2016 were enrolled in a registry. Most patients who were considered for surgical intervention were failing medical therapy, remaining persistently sputum culture positive despite appropriate therapy. Potential surgical candidates were offered resectional surgery or continued medical therapy based on conventional physiological and radiological assessments of operability and resectability, as determined by a multidisciplinary team (pulmonologists, thoracic surgeons, infectious disease clinicians, nuclear medicine physicians and radiologists). Selection criteria for resectional surgery were not protocolised but factors considered were the severity and/or bilaterality of radiological disease, co-existing comorbidities, adherence to the current treatment regimen, presence of active drugs in a salvage postoperative regimen and cardiopulmonary reserve. Patients who were not surgical candidates were deemed as screen failures. The interventional decision was in no way related to this study. Patients who were surgical candidates (but refused the intervention) constituted a control group.

Study procedures

Socio-demographic and clinical data on our patients was extracted from the XDR Registry. The degree of drug

resistance was determined by the National Health Laboratory Services (NHLS) using the BACTEC MGIT 960 system¹⁹ and line probe assays (MTBDRplus, Hain Lifesciences, Nehren, Germany). A subset of patients had extended drug sensitivity determined preoperatively by whole genome sequencing (WGS) as part of a related pharmacokinetics study conducted at the same centre.¹⁷ In the control group, sputum was collected at the time of presentation for surgical intervention and then at 6-month intervals for a period of 2 years. Sputum samples were collected and cultured from surgical patients either on the day of or the day prior to resectional surgery and then at the same time intervals as the control group. Pre-assessment drug regimens were documented as part of the work-up for all patients presented for surgery and for enrolment into the XDR-TB registry. Where drug sensitivity was known, the number of effective drugs in each regimen was ascertained. Surgery was performed within six weeks of the most recent imaging to ensure radiological progression had not occurred.

Preoperative PET/CT

A subset of patients included in the registry, after a time-point when this service became accessible, underwent PET/CT as part of the pre-operative workup prior to their surgical resection. The presence of FDG-avid disease in the contralateral lung (in the case of proposed pneumonectomy) or remaining ipsilateral lung lobe or lobes (in the case of proposed lobectomy), or if there was contralateral intrathoracic lymphadenopathy, did not influence the decision to operate. 18-FDG was used as the nuclear tracer. Patients were imaged using the GEMINI TF Big Bore PHILIPS whole-body scanner (Philips Healthcare, Eindhoven, Netherlands), and were prepared and imaged in accordance with the FDG PET/CT EANM guidelines for tumour imaging: version 2.0.²⁰ Images were viewed with Hermes Hybrid Viewer PDR v.2.2C.21 and interpreted by two independent nuclear medicine physicians and a radiologist.

In the absence of a standardised method of quantifying tuberculous disease burden in PET/CT, various measures of 18-FDG-avidity (visual score, highest SUV, mean SUV, and volumetric determinations) were measured.²¹ Regions of interest (ROIs) were defined as areas of increased 18-FDG uptake within the remaining lung parenchyma. These regions were drawn semi-automatically on transaxial slices, with a standard uptake value (SUV) threshold of 2.5 being used for automatic edge detection. Standard uptake values were calculated using the following formula: $SUV_w = A \times W/D \times 1000 \text{ g/c}$ (where SUV_w = normalization to body weight, A = activity concentration in Becquerel/cubic centimetres (Bq/cm^3), W = patient weight in kg and D = injected dose in Bq decay corrected to the time of injection. The following parameters were recorded in

regions of interest (ROIs) in the residual lung tissue after resectional surgery: SUV max, SUV mean, residual metabolic disease volume (MDV) and residual total disease glycolysis (TDG). Presence or absence of cavities, nodules or consolidation in remaining lung parenchyma was also documented. A visual score ranging from 0 to 4 of the residual metabolically active disease was also performed, as follows: 0 = no visible uptake; 1 = uptake lower than mediastinal blood pool activity; 2 = uptake comparable to mediastinal blood pool activity; 3 = uptake greater than mediastinal blood pool activity, and; 4 = uptake significantly greater (3 times higher) than mediastinal blood pool activity.

Follow up

Study patients were followed for two years from the date of surgical resection, or for two years from the date of presentation at the surgical meeting for the cohort that did not undergo surgery. During the 2-year follow-up, sputum culture status as well as mortality was evaluated at 6-monthly intervals. Many patients followed up and submitted sputum samples at their local clinics after discharge from GSH, and their data was collected by a field nurse who visited these clinics as part of this study. Patients from other provinces were tracked with the assistance of doctors at TB clinics at these centres. Post-operative treatment regimens were also documented if different from the pre-operative regimen.

Outcomes

The primary measure was the outcome of patients with DR-TB at 24 months after undergoing surgical resection or continued medical management, using the WHO treatment outcome definitions from 2013.^{22,23} Treatment outcome was considered a 'success' if it resulted in treatment completion or cure, and a 'failure' if treatment failed (persistent sputum culture positivity), the patient died, or the patient defaulted. Loss to follow up was recorded. Secondary measures included clinical predictors of treatment failure, sputum conversion, and quantitative PET/CT measures associated with unsuccessful outcomes.

Statistical analyses

Continuous variables were presented as means with standard deviation (for normally distributed data) and medians with interquartile range (for non-normally distributed data), and categorical data as frequencies and percentages. Assumption of normality was determined by the Shapiro–Wilk test; normally and non-normally distributed data was compared between groups using students t-test or Wilcoxon rank sum test, respectively. Categorical data was analysed using the Chi-squared test or Fishers exact test depending on their distributions. We analysed associations between

outcome (composite treatment failure) and clinically important variables using univariate and multivariate logistic regression. Different measures of disease burden using 18-FDG uptake were also explored in univariate and multivariate analysis. Statistical analyses were performed using GraphPad Prism (V-5-0, GraphPad Software, USA) and Stata (V.12.1, Stata Corp, College Station, Texas, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first and last authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study population

Between July 2010 and December 2016, 57 patients with DR-TB were presented for surgical resection at our institution. Of these, 35 (61%) patients underwent resectional surgery, whilst the remaining 22 (39%) did not; half these patients were deemed to be unsuitable for surgical intervention because of radiological extent, comorbidities, and/or cardiopulmonary reserve (not surgical candidates), and the other half did not consent to surgery (control group) (Fig. 1). The characteristics of the control group are shown in the supplementary appendix (Table S1). In the surgical group, the number of patients with XDR-TB, pre-XDR-TB and MDR-TB was 27 (77%), 5 (14%) and 3 (9%), respectively (Table 1). The vast majority of patients had treatment failure and were culture-positive at the time of surgical evaluation; 29 (83%) in the surgical arm and 10 (91%) in the control arm. In the surgical group, 9 patients (26%) were HIV positive, with a median (IQR) CD4 count of 407 (274–435); all were on antiretroviral therapy. The surgical procedure was a pneumonectomy in 20 (57%) of cases, and a lobectomy in 15 (43%) (one patient underwent a completion pneumonectomy after initial lobectomy). Only about a quarter of patients who underwent surgery had exposure to bedaquiline and linezolid (23% and 29%, respectively); these patients were all recruited in the latter part of the study period, as these drugs became more available within the National Treatment Programme in South Africa. In the control group, a comparable 6 patients (27%) were HIV positive with a median CD4 (IQR) of 351 (187–1173), all on treatment. No patient who declined surgery received either linezolid or bedaquiline.

Treatment outcomes

At 24 months after surgery, 15/35 (43%) of patients were considered programmatically cured; 5/15 (14%) had failed treatment, and 3/15 (9%) had defaulted or were lost

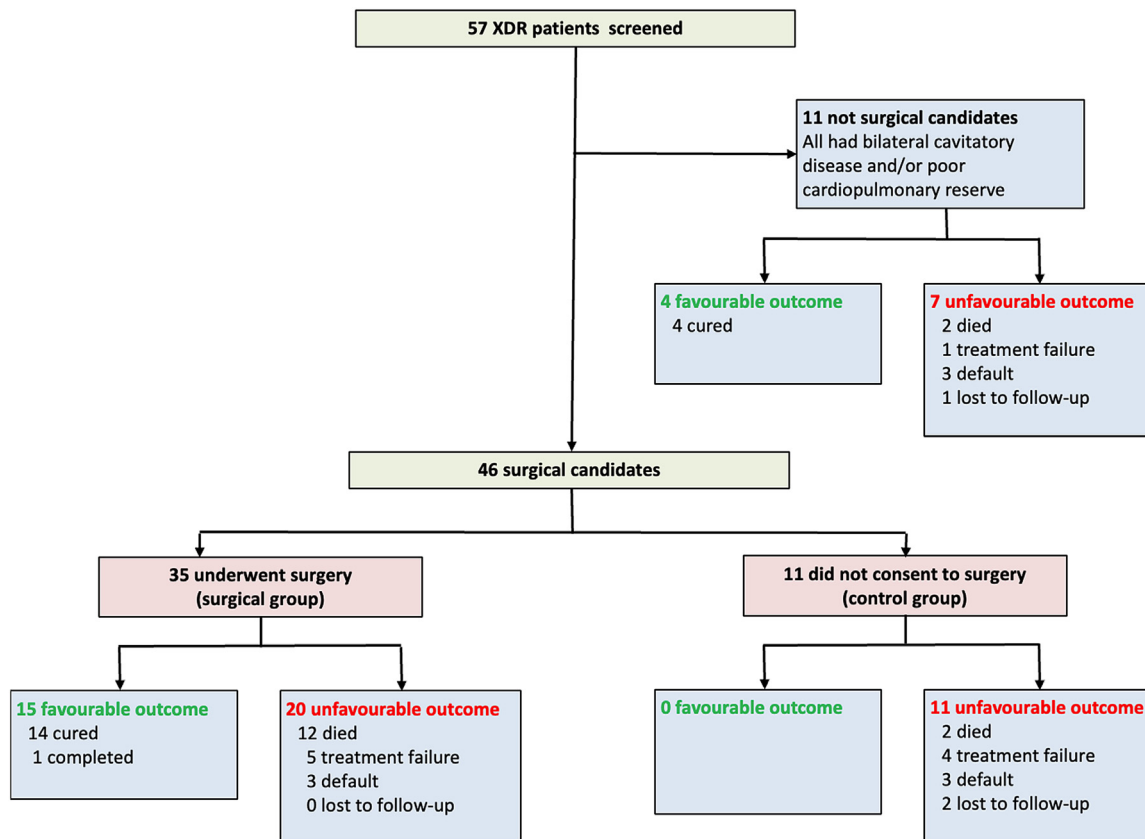


Fig. 1: CONSORT diagram.

to follow-up. All-cause mortality at 24 months was 12/35 (34%). There were 2/35 (5%) early post-operative deaths (within 30 days) and 6/35 (16%) died by six months. The group who received surgery had better overall outcomes

at 2 years compared to the group that did not receive surgery (odds ratio for treatment failure 0.57, 95% CI 0.42–0.76, $p = 0.008$) (Table S1, supplementary appendix). Univariate predictors of treatment failure in patients

Characteristic	Total n = 35	Failure (n = 20)	Success (n = 15)	p-value
Age, median (IQR)	40 (28–47)	42 (28–29)	35 (28–41)	0.171
Male, n (%)	17 (49%)	7 (35)	10 (67)	0.064
HIV positive, n (%)	9 (26%)	8 (40)	1 (7)	0.048
CD4, median (IQR)	407 (274–435)	418 (274–579)	142	0.120
Preoperative drug resistance profiles				
XDR, n (%)	27 (77%)	19 (95)	8 (53)	0.011
Pre-XDR, n (%)	5 (14%)	1 (5)	4 (27)	0.141
MDR-TB, n (%)	3 (9%)	0 (0)	3 (20)	0.097
Current smokers, n (%)	15 (43%)	10 (50)	4 (27)	0.148
Previous episode of DR-TB, n (%)	20 (57%)	11 (55)	9 (60)	0.767
Sputum culture positivity at time of surgery, n (%)	29 (83%)	18 (90)	11 (73)	0.367
BDQ exposure pre- or post-surgery, n (%)	8 (23%)	0 (0)	8 (53)	<0.001
LZD exposure pre- or post-surgery, n (%)	10 (29%)	3 (15)	7 (47)	0.062
Procedure				
Pneumonectomy, n (%)	20 (57%)	13 (65)	9 (60)	0.762

Abbreviations: IQR, interquartile range; HIV, Human Immunodeficiency Virus; XDR, extensively drug-resistant; DR-TB, drug-resistant tuberculosis; BDQ, bedaquiline; LZD, linezolid.

Table 1: Baseline characteristics of patients undergoing lung resection for DR-TB.

Variable	n	Crude OR (95% CI)	P-value	Adjusted OR (95% CI) ^a	P-value
Age (per year increase)	35	1.03 (0.97–1.10)	0.299		
Male sex (vs. female)	35	0.27 (0.07–1.11)	0.069		
HIV status (vs. negative)	9	9.33 (1.02–85.70)	0.048	3.63 (0.39–300.00)	0.280
Current/former smoking status (vs. non-smoking)	14	2.75 (0.65–11.62)	0.169		
XDR status (vs. MDR and pre-XDR)	27	16.63 (1.78–158.09)	0.014	4.89 (0.73–207.03)	0.137
DR-TB treatment (vs. no previous treatment)	20	0.81 (0.21–3.17)	0.767		
Pneumonectomy (vs. lobectomy)	22	1.24 (0.31–4.93)	0.762		
Positive pre-operative sputum culture (vs. negative)	29	3.27 (0.51–20.93)	0.210		
Post-operative bedaquiline (vs. no bedaquiline)	8	0.02 (0.00–0.42) ^b	<0.001	0.06 (0.00–0.50)	0.007
Post-operative linezolid (vs. no linezolid)	10	0.20 (0.04–0.99)	0.049	1.52 (0.09–91.74)	1.00
Post-operative regimen with at least 3 effective drugs	4	0.72 (0.09–5.81)	0.760		

Abbreviations: OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; XDR-TB, extensively drug-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis. ^aAdjusted for HIV status, XDR status, post-operative bedaquiline and post-operative linezolid use. ^bNo treatment failures in patients treated with bedaquiline; Haldane-Anscombe correction applied.²⁴

Table 2: Predictors of treatment failure in patients who underwent surgery (n = 35).

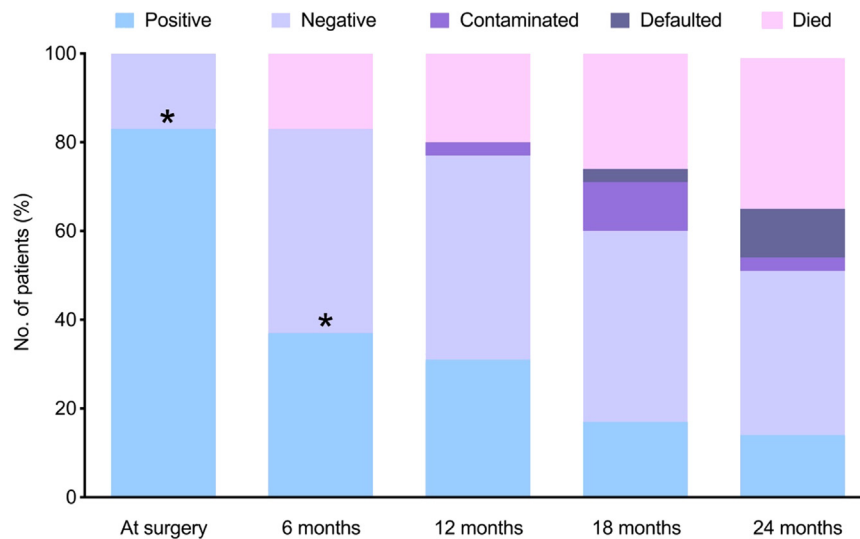


Fig. 2: Treatment outcome status during 24-month follow-up period for patients undergoing surgery (n = 35)]. *P < 0.001 for comparison between culture positives at 0 and 6 months.

undergoing surgery were HIV positivity, degree of drug resistance (XDR-TB vs. pre-XDR-TB and MDR-TB), and post-operative bedaquiline and linezolid use; only bedaquiline use was significant on multivariable analysis (Table 2). Survival analysis by pre-operative culture status also did not differ significantly (Fig. S1, supplementary appendix). Sputum culture conversion, if it occurred and was durable, was most likely to occur early: 12/35 (35%) culture-converted by six months (Fig. 2). In a multivariable analysis in patients undergoing surgery, only XDR status (adjusted OR 0.17, 95% CI 0.03–0.87, p = 0.03), and the use of post-operative bedaquiline (adjusted OR 28.5, 95% CI 2.40–339.0, p < 0.01) were associated with sputum conversion.

Outcomes in the control group showed that at 2 years from the date of presentation at the surgical candidacy meeting no patient achieved treatment success. Of the 11 treatment failures, the breakdown was 2/11 (18%) deaths, 4/11 (36%) medical treatment failures and 5 (45%) either defaulted or lost to follow up. All of the six control patients that defaulted or were lost to follow up were culture positive at the time of their last recorded sputum samples (100%). Amongst patients who were not candidates for surgery, 4/11 patients (36%) achieved treatment success with medical therapy alone; 3 (75%) of these patients received linezolid, whilst only 1 (25%) received linezolid and bedaquiline.

Radiological measure	Total (n = 25)	Failure (n = 12)	Success (n = 13)	p-value
Ipsilateral disease (in non-resected lobes)^a				
Any, n (%)	4 (16)	2 (16)	2 (15)	0.93*
Nodularity, n (%)	4 (16)	2 (16)	2 (15)	0.93*
Cavitation, n (%)	1 (4)	1 (8)	0 (0)	0.29*
Consolidation, n (%)	1 (4)	1 (8)	0 (0)	0.29*
Contralateral disease				
Any, n (%)	21 (84)	10 (83)	11 (85)	0.93*
Nodularity, n (%)	21 (85)	10 (83)	11 (85)	0.93*
Cavitation, n (%)	5 (20)	3 (25)	2 (15)	0.55*
Consolidation, n (%)	0 (0)	0 (0)	0 (0)	N/D
Extrapulmonary disease				
Visceral nodules, n (%)	3 (12)	1 (8)	2 (15)	0.55*
Bone, n (%)	1 (4)	0 (0)	1 (8)	0.33*
Lymphadenopathy, n (%)	8 (32)	5 (42)	3 (23)	0.32*
PET/CT measures of activity				
Visual, median (IQR)	2 (0-3)	1 (0-3)	2 (0-3)	0.61 [#]
SUV max, median (IQR)	2 (0-4)	1.7 (0-4.8)	2 (0-3.1)	0.96 [#]
SUV peak, median (IQR)	0 (0-2.5)	0 (0-2.8)	0 (0)	0.58 [#]
Metabolic Disease Volume, median (IQR)	2.9 (0-16)	2.8 (0-71.6)	2.9 (0-6.5)	0.62 [#]
Total disease glycolysis, median (IQR)	4.5 (0-34)	3.2 (0-144.4)	5.6 (0-10.3)	0.74 [#]

p-values determined by: *Z-test; [#]Mann-Whitney U test. Abbreviations: PET/CT, positron emission tomography/computed tomography; SUV, standardised uptake values.
^aApplicable in 13 patients who underwent lobectomy only.

Table 3: Characteristics of pre-operative 18-fluorodeoxyglucose-avid lesions as detected by positron emission tomography/computed tomography (PET/CT) by treatment outcome (n = 25).

Variable	Crude OR (95% CI)	P-value
PET/CT measures of activity		
Visual	0.83 (0.47-1.47)	0.520
SUV max	1.09 (0.85-1.40)	0.478
SUV peak	1.14 (0.83-1.56)	0.409
Metabolic Disease Volume	1.03 (0.98-1.08)	0.238
Total disease glycolysis	1.01 (0.99-1.03)	0.222

Abbreviations: PET/CT, positron emission tomography/computed tomography; SUV, standardised uptake values; MDV, metabolic disease volume; TDG, total disease glycolysis.

Table 4: Regression analysis for treatment failure based on the characteristics of pre-operative 18-fluorodeoxyglucose-avid lesions as detected by positron emission tomography/computed tomography.

Univariate predictors of poor outcome (composite treatment failure) in all 35 patients eligible for surgery (i.e. combining surgical and control groups) were control arm status, degree of drug resistance and HIV infection. In the multivariable model, only nonsurgical arm status was significant (and as there were no successful outcomes in this group, no adjusted odds ratio could be calculated).

Pre-operative PET/CT

PET/CT was performed and analysed in 25/35 (71%) patients in the surgical arm; in the remaining 10 (29%),

the absence of intrathoracic lymphadenopathy or any radiological disease outside of the planned anatomical resection on plain CT was deemed sufficient evidence by the MDT to proceed without PET. The commonest FDG-avid radiological abnormality seen was contralateral nodularity (85%), followed by intrathoracic lymphadenopathy (32%) (Table 3). There was no difference in either the burden of FDG-avid radiological disease (cavities, nodules, consolidation or extrapulmonary disease), visual scores, or quantitative estimates of FDG-avidity [either absolute (SUV max and peak, or volumetric (MDV and TDG)] between patients with treatment failure or success (Table 4). In a regression analysis, there was no PET/CT value associated with shorter time to treatment failure (Table 4). Receiver operating characteristic curve analysis showed that sensitivity and specificity for treatment failure of all PET/CT measures of non-resected disease burden for treatment outcome was poor (Fig. 3).

Discussion

This study, which adds to the limited data on surgical outcomes for DR-TB in high HIV burden settings and sub-Saharan Africa and, to our knowledge, the first to examine the role of PET-CT in surgery for DR-TB, has three main findings. First, it demonstrates that resectional surgery for DR-TB in combination with available chemotherapy resulted in a cure in ~50% of patients.

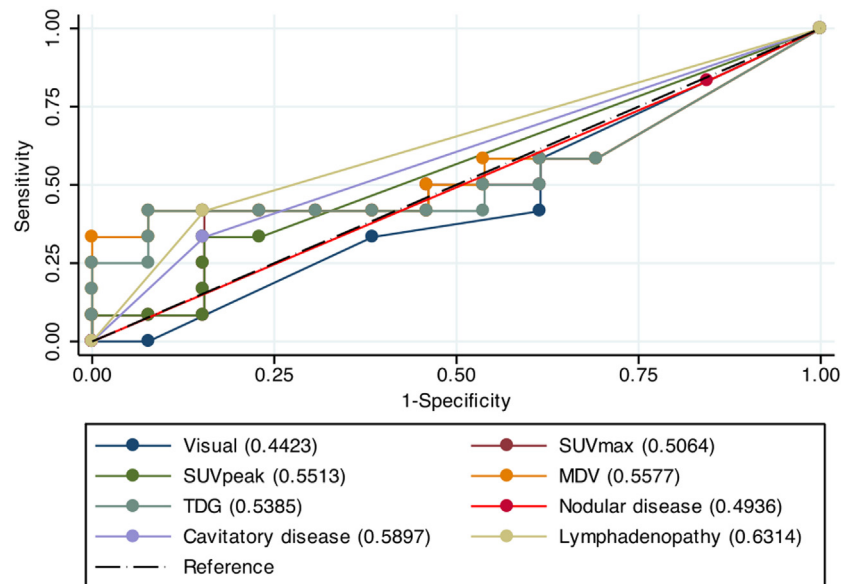


Fig. 3: Receiver operating characteristic (ROC) curves for PET/CT readouts using the binary predictor of treatment failure. Abbreviations: PET/CT, positron emission tomography/computed tomography; SUV, standardised uptake values; MDV, metabolic disease volume; TDG, total disease glycolysis. Area under the ROC curve (AUC) shown in parentheses in the legend.

This was in contrast to only ~20% cure in patients who were not surgical candidates (and ~0% cure in the patients in the control group that turned down surgery). The main risk factor for poor outcome was the lack of BDQ usage in the postoperative regimen. Secondly, an effective post-operative regimen is essential and thus post-operative bedaquiline was an independent predictor of a post-surgical favourable outcome. Thirdly, treatment outcomes were not modified by the presence of PET-positive disease, regardless of activity in the contralateral lung or its radiological type. This finding suggests that factors other than the burden of FDG-avid disease in the non-resected lung are associated with treatment outcome.

The post-surgical outcomes reported in this study are considerably worse than in previous reports for DR-TB from other settings and eras.^{14,25–30} However, bedaquiline and linezolid were not widely available at the time, and the degree of drug resistance, prevalence of pre-operative culture positivity, and degree of HIV positivity at the time of surgery were much higher in our study. Nevertheless, our outcomes are better than those of historical cohorts of XDR patients treated with conventional chemotherapy alone,³¹ but worse than those of recent cohorts treated with bedaquiline and linezolid, with or without surgery.^{8,15,32} This could be explained by the above-mentioned microbiological and patient-specific factors including disease extent, HIV status, and likely later presentation in our setting with poor access to cardiothoracic services. Nevertheless, the dismal outcomes without surgery in patients without

newer chemotherapeutic options underscores the need to support and develop thoracic services in resource-poor settings and TB endemic countries, where they are hardly ever available.^{33–36} It is also important to appreciate that there are no randomised controlled trials comparing surgery with medical therapy versus medical therapy alone, and meta-analyses of observational studies have considerably underrepresented TB endemic countries.^{14,37–39}

Our findings imply that treatment outcomes are highly dependent on the efficacy of post-surgical effective medical chemotherapy, which has increased with the introduction of linezolid and bedaquiline to the DR-TB regimen. Indeed, all patients treated with a bedaquiline-containing regimen and surgery in our cohort had a successful outcome; this is in keeping with a recent report.³² Culture conversion tended to occur mainly in the first 6-months with diminishing conversion returns thereafter. Although intuitive that both surgery and an effective rescue regimen are needed, this finding is worth emphasising because it creates an imperative for more widespread roll out of newer drugs and extended drug susceptibility testing in TB endemic settings and underscores the need for a multidisciplinary approach when treating these patients.

To our knowledge, there are no data about the use of PET/CT as a potential aid in surgical decision-making in DR-TB or as a predictor of treatment outcome. Indeed, none of the previous studies of adjunctive surgery for drug-resistant tuberculosis have included PET/CT as a pre-operative investigation. In the absence of a

standardised method, we measured both FDG-avid intensity and volumetric estimations, neither of which were associated with worse outcome. Even the presence of contralateral cavitary disease, which is associated with poor drug penetration and higher mycobacterial burden, was not a risk factor for treatment failure. The overall implication is that remaining FDG-avidity, in the context of surgery planned to resect the major radiological burden of disease, does not influence treatment outcome in the setting of appropriate chemotherapy. This may be because the associated mycobacterial population is more accessible to drug-related killing during post-surgical therapy, or that the PET activity is related to host-specific inflammation and not mycobacterial burden, or a combination of these factors. Indeed, macaque studies have shown that TB-associated lesions detectable on imaging or histologically are often sterile and migratory over short periods of time.⁴⁰

Several limitations of this study deserve emphasis. Adjunctive surgery is likely to be offered to patients with better physiological status, more localised disease, and fewer co-morbidities, and we tried to remove these confounders by only comparing patients who received surgery versus those who were surgical candidates but refused surgery. However, statistically valid comparisons of outcomes between the surgical and control groups were not possible due to the small patient numbers. Secondly, as this was not part of the clinical treatment protocol, data on extended drug sensitivity was only collected on a subset of patients, so the influence of exact number of confirmed effective drugs in the post-operative regimen could not be properly interrogated. Thirdly, these data are from a single centre, and combined with the small numbers, the influence of FDG-avid disease on outcome may have been falsely underestimated (type II error). Nevertheless, the analyses of PET/CT data as predictors of outcome were all resoundingly non-significant. Lastly, as the study straddled the era in which bedaquiline and linezolid – the two most important additions to the DR-TB treatment regimen in recent times – were introduced as standard-of-care in South Africa, these therapies were infrequently prescribed either before or after surgery, or to patients who refused surgery. “Therapeutically destitute” cases were routinely discussed at specially convened review meetings and patients assessed as “programmatically incurable” often chose to have their treatment stopped and were referred to community stay and palliative care facilities to prevent ongoing community transmission. This may explain the lack of use of these agents in the control group and confounds the effect of surgery on outcome.

In summary, resectional surgery for DR-TB in combination with chemotherapy resulted in cure in just under half of the patients, whilst medical therapy alone resulted in cure in only about a fifth of patients. Despite surgery, an effective medical post-operative medical

regimen was essential. Our data do not support the use of PET-CT to preselect patients or prognosticate about their outcome. These data inform clinical practice and underscore the need to support antibiotic stewardship strategies in TB-endemic settings. Prospective and adequately powered studies are needed to understand when to surgically intervene on difficult-to-treat TB cases in the era where bedaquiline and linezolid are available.

Contributors

GC, NS and KD were involved in the conception and design. GC, NS, TP, RS, AB, AE, LM, SO, BM, CO and AL were involved in study implementation and data collection. GC, WB and KM did the analysis. GC, NS, TP, and KD interpreted the data and provided important intellectual input. GC, NS and KD wrote the first draft. All authors read and commented on the manuscript.

Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Declaration of interests

There are no conflicts of interest to declare for any authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2022.101728>.

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