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

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This thesis is submitted in a publication-ready format with a literature review and completed manuscript.

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DECLARATON

I, **Nevadna Singh**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or will be submitted for another degree in this or any other university.

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ABSTRACT

Background:

Even with newer and repurposed anti-TB drugs almost a third of patients with XDR-TB have unfavourable outcomes. In patients with localised disease and adequate pulmonary reserve, surgery is an important adjunctive treatment. However, there are no outcome data from TB endemic countries, and the prognostic significance of pre-operative PET-CT findings remains unknown.

Objectives:

To report outcomes for resectional surgery in our setting, and to study whether PET activity outside of the resection influences treatment outcomes.

Methods:

A retrospective study of all XDR-TB patients undergoing surgery at Groote Schuur Hospital (GSH) between July 2010 and December 2016 was performed. PET-CT was performed in a subgroup. Patients were followed up to determine treatment outcomes at 24-months post-surgery. Treatment success and failure, including all-cause mortality, was determined.

Results:

In total, 35 patients underwent surgery. The mean age was 36, 49% were male and 26% were HIV-infected. Pneumonectomy was the most common procedure (57%). Three patients (9%) were lost to follow up by 24 months. Total all-cause mortality was 34%. Treatment success was achieved in 15/35 (43%). In patients who underwent pre-operative PET-CT, there were no overall radiological features or PET parameters that were found to be prognostic for treatment failure.

Conclusion:

Resectional surgery for DR-TB in combination with chemotherapy resulted in cure in less than half of patients. 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.

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CONTRIBUTIONS

- **Dr Gregory L Calligaro (primary supervisor)**: Concept for thesis, planning, data synthesis, interpretation of results and manuscript preparation.
- **Professor Keertan Dheda (co-supervisor)**: Planning and oversight of final manuscript preparation.
- **Dr Rachelle Steyn**: Analysis and interpretation of PET/CT data.
- **Dr Anita Brink**: Analysis and interpretation of PET/CT data.
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- **Dr Barbara L Mastrappa**: Follow-up of patient outcomes in Northern Cape
- **Ms Kathryn Manning**: Statistical support and data analysis
- **Mr Wisdom Basera**: Statistical support and data analysis

LITERATURE REVIEW

INTRODUCTION

Background of drug resistant Tuberculosis

Pre-XDR and XDR-TB are public health emergencies in South Africa with limited pharmacological options for cure. The overall treatment outcomes of pre-XDR and XDR-TB in South Africa are far from satisfactory (1). A retrospective review (in the era before new and repurposed drugs) showed that only 19% of patients culture-convert on currently available therapy (2). In the absence of readily accessible and effective drug regimens, and in appropriate patients, surgery with resection of involved lung tissue is employed as a form of adjunctive treatment. Even with the development and approval of the novel anti-tuberculous agents bedaquiline and delaminid, which have shown good success, the overall cure rates for drug- resistant TB still remain well below those of drug-sensitive disease (3-6). Furthermore, accessibility to these drugs still remains challenging in parts of South Africa.

These dismal cure rates, ranging from 11-19% with medical therapy alone for XDR-TB are comparable to those for drug-sensitive TB in the earlier half of the 20th century when effective anti-tuberculous drugs were not yet available (2, 7). During this time, surgical resections were commonplace and formed an important part of therapy. Over the past century, surgical techniques have developed and improved dramatically and the old techniques of collapsotherapy and thoracoplasty have been largely replaced by anatomical resections in the form of lobectomies or pneumonectomies.

Rationale for resectional surgery

The rationale behind surgery for TB is to dramatically reduce the overall organism burden in the lung by excising thick-walled cavitatory lesions and areas of destroyed lung. This involves

the removal of sites with highest concentrations of drug resistant bacilli, as we know that cavities may harbour up to 10^7 to 10^9 *M.tb* organisms, which is exponentially higher than in areas of non-cavitatory parenchymal disease (8). These cavitatory areas have been shown to act as reservoirs where mycobacterial replication can proceed with significant protection from the effects of anti-tuberculous drugs (9). This “debulking” hopes to enhance the sterilizing properties of post-surgical chemotherapy and increase the likelihood of treatment success (10, 11). In appropriate patients with localized disease and adequate pulmonary reserve, surgery is an important adjunctive part of management.

Indications for surgical resection

The two most commonly accepted indications for surgical intervention in drug-resistant TB are:

- Patients who have failed medical therapy and remain persistently sputum culture positive
- Patients who are sputum culture negative, but have established localised cavitatory disease that may serve as an ongoing nidus for infection.

The vast majority of patients undergoing surgery fell into the first category of failed medical therapy, defined as failure to induce a sustained sputum-negative culture conversion (12-14). This was consistent throughout the literature, with only few patients having been operated on with persistent cavitatory, sputum-negative disease. The role for surgery in patients who remain sputum culture-negative with localised cavitatory disease is slightly less well defined. The rationale for resection in sputum culture-negative patients is the belief that antibiotic therapy penetration into thick-walled cavities is poor and that there remains a high burden of viable bacilli within these cavities, putting patients at high risk of relapse and treatment failure (8, 15).

The general consensus between many international reviews and studies seems to be that adjunctive surgical management, in appropriately selected patients, is superior to medical therapy alone in cases of all forms of drug-resistant tuberculosis. This will be explored in further detail by this review of current literature.

Definition and utility of PET/CT

Positron emission tomography-computer tomography (PET/CT) is a nuclear medicine technique, which combines both the PET and CT modalities into a single test to produce images in which the two results are superimposed.

PET imaging uses radiotracers, which are molecules labelled with small amounts of radioactive material, that can be detected by PET scan. The most commonly used tracer is F- 18 fluorodeoxyglucose (FDG) which is taken up more by tissues with higher metabolic activity. CT scanners use radiation to produce detailed anatomical images of the region of interest. PET/CT therefore produces a combination of both the functionality, as measured by FDG uptake, and anatomy of a given area. This technique has been used widely in the field of oncology to determine the extent of disease, as well as the response to treatment, as many cancers have higher metabolic demands than their surrounding tissue.

The utility of PET/CT in detection and evaluation of response to treatment in tuberculosis has not been as wide spread as in oncology. Current literature seems to suggest that PET/CT is a sensitive tool to both detect TB and differentiate between active TB and previous infection especially in cases with cavitatory disease (16). It has also been shown that PET/CT is superior to CT or MRI alone in detecting active tuberculous disease (17). Given that areas with active TB have a higher metabolic activity than surrounding tissues, a few studies have proposed use of PET/CT as a modality to detect early responses to anti-tuberculous treatment, but no definitive guidelines have been drawn as yet (18). Little is known about the

role of PET/CT as a prognostic tool to predict treatment outcomes in patients with pulmonary TB.

LITERATURE REVIEW OBJECTIVES

Firstly, this literature review shall present the current state of evidence of what is known about outcomes of resectional surgery for drug resistant TB in other centres, with an emphasis on pre-XDR and XDR-TB. Alongside detailing the outcomes of resectional surgery, we will also explore the rationale and timing for surgery in these patients. The duration of post-operative medical treatment will also be described where possible. We also seek to describe whether there are any known patient or treatment characteristics that predict treatment outcomes in settings similar to our own.

Secondly, we shall review whether PET-CT has been used for prognostic purposes in patients undergoing resectional surgery for drug-resistant TB. If such data does exist, we will describe the role of PET-CT as a modality to predict treatment outcomes.

LITERATURE SEARCH STRATEGY

The electronic database, PubMed, was used to search for relevant literature. Literature was reviewed up until January 2019. Only English and full text articles were included. All study types were included, although all the studies reviewed were retrospective cohort analyses. Literature was also searched for manually by screening the references of studies identified in the electronic search. The following search terms were used for the primary objective:

- Resectional surgery

- Drug-resistant tuberculosis
- XDR-TB
- Africa

The following search terms were used for the secondary objective:

- PET-CT
- Prognostic value
- Drug resistant tuberculosis
- XDR-TB

SUMMARY OF FINDINGS

Primary aim(s)

Outcomes for resectional surgery for multidrug-resistant tuberculosis

Two frequently cited and accepted bodies of work define outcomes for TB therapy and are used in many of the studies included in this review. Outcomes were reported in the studies according to standardised definitions by Laserson or the World Health Organisation, which are comparable (14, 19, 20). Successful treatment outcomes include cure and treatment completion, whilst unsuccessful treatment outcome refer to death, defaulting and treatment failure. These categories are further detailed below.

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of *cured* and *treatment completed.*

Marrone *et. al.* published the first large international systematic review and meta-analysis of patient outcomes after resectional lung surgery for all types of drug-resistant tuberculosis in 2013, including a total of 47 studies (21). Due to the nature of this illness and the usual indications for surgery, there are no randomised controlled studies in this field, and all evidence is drawn from observational studies. Collated findings from 24 comparative studies showed that those who received medical therapy and adjunctive resectional surgery had better overall outcomes than those who had medical therapy alone (OR 2.24, 95% CI 1.68-2.97). A total of 706 patients who underwent surgical resection for drug-resistant TB were described by Marrone *et. al.* in these 24 papers, but as is the case in many studies, patients with all forms of drug-resistant TB were combined in the meta-analyses, and it is often difficult to isolate the results in pre- and XDR-TB patients alone. The vast majority (21/24) of comparative studies reported outcomes in MDR-TB patients. In the remaining (3/24) comparative studies focussing on XDR-TB patients, the outcome benefits for surgical resection seemed even more pronounced, but we are cautious that fewer

absolute numbers may lead to over-powering of results in these smaller groups. In the 23 single-arm studies included in the Marrone *et. al.* meta-analysis, they found overwhelming positive outcomes following surgery. They found that 92% (95% CI 88.1-95) and 87% (95% CI 83-91) of patients had successful short and long term treatment outcomes respectively. They defined short-term as 30 days post-operatively, and long term outcomes were measured at 12 months. This long term follow-up was extremely heterogeneous between studies, with a mean of 40 months, but starting from as little as 12 months. Notably only 2 of the 23 studies describe XDR-TB patients alone, with the other 23 studies describing either MDR-TB or a combination of all forms of drug-resistance. In addition to improved overall outcomes in the surgical groups, there was also a favourable association between surgical resection and all-cause mortality in all forms of drug-resistant TB.

Very little could be deduced about specific characteristics regarding patient demographics, treatment regimens, surgical techniques used and duration of follow up, as studies were markedly varied and heterogenous in the Marrone *et. al.* review. Interestingly, HIV status was not described in relation to patient outcomes in this large meta-analysis. It was noted that in all the studies included, the main indication for surgical intervention was failure of medical therapy, with only a small minority being performed for other indications.

In the more recent systematic review by Harris *et. al.* in 2016, results were largely comparable to the Marrone paper (22). Again, all studies were observational and included a combination of MDR- and XDR patients. In the 14 primary review articles, they reported successful outcomes in 81.9% of the surgical group, as compared to 59.7% in the non-surgical groups with an odds ratio of 2.62 (95% CI 1.94-3.54) (23). They did note that loss to follow-up was greater in the medical group, which may have negatively biased their findings. This recent review also comments on the introduction of new agents into the armamentarium against drug-resistant TB, specifically bedaquiline and delamanid, acknowledging the

positive impact they have made on the medical management of this disease (4, 6). Although the positive impact of these new drugs is highlighted, it is also reiterated that the cure rate for drug-resistant TB still remain far below those for drug-sensitive TB, and that the role for surgery is not negated. The role of these newer agents in surgical patients was not reviewed in these large meta-analyses.

Although there are discrepancies in the degrees of resistance profile ranging from MDR- to XDR-TB, these systematic reviews certainly seem to give strength to the widely held opinion that surgical resection improves outcomes for patients with drug resistant TB.

Notably, a very recent South African paper published in May 2020 has shown drastically improved outcomes for MDR-TB treatment failure and XDR-TB patients using medical therapy alone, as compared to many historical cohorts (24). The Nix-TB trial included 109 patients with DR-TB (65% XDR-TB, 35% MDR-TB). They used a novel treatment regimen comprising bedaquiline, linezolid and pretomanid for 26 or 39 weeks, depending on treatment response. This treatment duration is far shorter than the minimum standard duration of treatment for DR-TB being used in most other studies, which is greater than 12 months. At 6 months after the end of the treatment period, 90% of patients had a positive outcome, which is far in excess of anything shown in previous DR-TB studies. In fact, this treatment success rate is one of the first in the literature that rivals that of drug-sensitive TB. It is prudent to note that this trial is ongoing and durable results proving treatment success at 24 months are yet to be shown. This study was based at 3 small centres in South Africa and is not the current national standard of care for DR-TB, making it difficult to accurately gauge the true national treatment success rates for DR-TB in this era of new and developing regimens. If these positive outcomes can be shown to be sustained and these drugs become widely available, the face of DR-TB may dramatically change for the better. The possibility of

achieving such high treatments success rates for DR-TB in the order of 90% will challenge the utility for surgical resection in such cases. The question remains, whether like almost all other classes of anti-tuberculous drugs, resistance will develop to these newer agents over time as they become more widely available and surgery may again feature as an important tool in the armamentarium against DR-TB, despite these promising results.

There was only one study by Borisov *et. al.* that evaluated the outcomes of patients with drug- resistant TB treated specifically with bedaquiline-containing regimens who underwent adjuvant surgical resection (25). This was a retrospective review and included 55 surgical patients from 9 countries. In this cohort, the majority of cases (90%) had pre-XDR or XDR-TB, with only a small minority having MDR-TB. Only 5 cases were new TB cases with 52/55 having had previous drug-resistant TB. The indications for surgery were in keeping with the accepted criteria as described by Iseman *et. al*, with 50% of this cohort having persistent sputum culture- positivity (12). The median number of drugs prescribed was 5 and 6 pre- and post-operatively. Bedaquiline was initiated in most patients (33/55, 60%) as part of the post-operative regimen. In the remaining cases, the bedaquiline course was initiated prior to surgery and completed post-surgically. Treatment success was achieved in 69% of patients (65% cured and 4% completed). There was a 20% treatment failure rate, but no reported mortalities. There was no significant difference in outcomes between the pre-operative and post-operative bedaquiline groups. Only 5% of patients included were HIV positive, but results were not stratified by HIV status. The duration of the follow-up period in this study was not clear and was heterogenous amongst the centres. This study deduced that the combination of surgery and bedaquiline was likely responsible for an additional 40% bacterial conversion from baseline. They also state that although the overall treatment success (69%) was lower than in the previous meta-analyses (80-90%), there was a far greater proportion of patients with pre- XDR and XDR-TB than in these large reviews with

predominantly MDR patients (21, 22, 25). Limiting factors in this review are the small patient numbers and the lack of clarity regarding follow-up period, but the overall impression is that in specifically selected patients, the combination of bedaquiline therapy and surgery may produce positive outcomes in the majority of patients.

Smaller single review studies including sub-analyses of pre-XDR and XDR-TB were also informative, but again absolute numbers of patients were relatively small, and firm conclusions are difficult to extrapolate.

One such observational study from Seoul evaluated outcomes of 26 XDR- and 46 MDR-TB patients and showed overwhelmingly positive results for patients following surgical resection (23). The majority of patients underwent surgery for medical failure (71%), and had received medical therapy for a minimum of 3 months. The other 24% of patients were operated on after being deemed to have ‘high risk of relapse’ due to persistent localised cavitatory disease. Unfortunately, many of the results reported in this study combined patients with MDR- and XDR-TB. Successful outcomes, however, were reported separately for the MDR- and XDR- TB groups and was found to be 85% in the XDR-TB group. This was not significantly different from the MDR-TB group.

Another study from KwaZulu-Natal showed promising results with adjunctive surgical therapy and is included in this review as it is contextually relevant to South Africa (26). The group aimed to look into surgical resection as part of the management of XDR-TB as medical therapy alone was proven to be insufficient, with 73% mortality at 5 years (7). A total of 10 XDR-TB patients were reviewed for surgical intervention, but 6 were excluded due to bilateral extensive cavitatory disease, as is widely practiced. This left only 4 patients to undergo adjunctive surgical resection. All 4 patients had failure of medical treatment as the indication for surgery. The successful outcome rate in this small cohort was 100%, with all 4

patients being cured. They also reported no peri-operative morbidity. Given the very small number of patients in this report, it is difficult to regard their positive findings as anything beyond anecdotal for this particular XDR-TB cohort.

Two particular studies showed results markedly deviating from those reviewed above; with much poorer overall outcomes in their surgical cohorts (27, 28). A European study based in Latvia retrospectively reported surgical outcomes in 17 patients from 2000-2003 (27). Although XDR was only defined in 2006, these patients were found to meet criteria for XDR-TB based on drug-sensitivity testing (DST). The main indication for surgery remained in line with other reports, with failed medical therapy being the indication in 15/17 patients, and only one patient having surgery for presumed high risk of relapse due to cavitatory disease and one for emergency resection for pulmonary haemorrhage. At the time of surgical intervention, 94% of patients were sputum culture positive. Although 5 patients were reported to have bilateral cavitatory disease based on chest radiographs, they were still eligible for surgery, which is not common practice in other centres. The Latvian group found that only 47% of patients were cured, while the rest had unsuccessful outcomes, with 47% having treatment failure and 6% death. Despite their much lower treatment success rates than in other studies, the success rate of 47% still exceeded the background cure rates for medical therapy alone for XDR-TB across other parts of Europe during the same time**.**

The second study showing poor outcomes was conducted in Beijing, China and followed patients with DR-TB from 1992-2012 (28). They were able to report findings on 21 patients in total after following them up for 3 years. Only a third of these patients had XDR-TB, with the reminder having MDR-TB. The exact indications for surgical intervention were not well detailed in this study and the breakdown was unclear. Overall, only 38% of patients had favourable outcomes after 3 years. The small XDR group showed far worse outcomes than the MDR group, with only 14% successful outcomes as compared to 50% in the MDR group.

In the subset of patients who had negative outcomes, the surgical complication rate was also high, with 46% of patients experiencing septic or fistulizing post-post-operative complications. The overall mortality rate in this Beijing cohort was 24%, which was much higher than in other groups, and not in keeping with the large meta-analyses conducted by Marrone *et. al.* and Harris *et. al*. It is unclear why the success rate was much lower in this paper than in many other international centres, but the lack of clarity surrounding patient selection and inclusion criteria for surgery does raise the concern of whether this may have played an important role.

Optimal timing of surgical intervention

The optimal timing for surgical intervention still remains unclear after reviewing the recent literature. Two opposing theories exist and are raised in the large meta-analyses by Marrone *et. al.* and Harris *et. al.* again in 2016**.** Once school of thought is that early surgical intervention within 4 months potentially optimises the chances of cure. The rationale behind this is that patients will have less morbidity with non-advanced tuberculous disease and would be in better physiological condition for surgery if they were not left on failing medical regimens for a protracted time. It was also postulated that the prolongation of failing medical therapy may lead to higher degrees of drug-resistance. The other school of thought is that longer exposure to anti-tuberculous therapy allows for time to optimise nutritional status and other medical co- morbidities prior to surgery and may produce better outcomes. There is no direct evidence to support or refute either of these strategies and the timing of surgery tends to be in line with institutional practices at various centres. It also seemed that the timing of surgical intervention after medical therapy varied vastly between centres, and also often within centres themselves, ranging from 2.3 months to more than 12 (23, 26, 27).

In the bedaquiline-regimen study, the median (IQR) time to surgical intervention was 8 (5-13)

months on a regimen with an average of 5 presumed effective drugs (25). No patients were on delaminid and bedaquiline concurrently. Notably in this study, only half the patients were sputum culture-positive at the time of surgical intervention, which was lower than in the other studies included in this review (21). The overall success rate in this study was 69%. It is unclear how sputum status at the time of surgery may have affected overall treatment outcomes in this particular study. It is considered that pre-operative used of bedaquiline may have reduced the need for surgery in some patients, but their data could not support this theory.

In the Seoul cohort, the median time to surgery was approximately 5.2 months on effective medical therapy (23). Effective therapy was considered 3 drugs with proven sensitivity, or in cases without proven sensitivity, drugs in line with accepted XDR-TB regimens. This timing for surgery was adopted to attempt to remain in line with the WHO recommendation to consider surgery after failed medical therapy after 3-4 months (27). In this group, 85% of XDR-TB patients has successful surgical outcomes.

In the Latvian study, the median duration of pre-operative medical therapy was 12 months, which was significantly longer than in other studies (28). They did have much lower success rates with only 47% cure as compared to 85%, but the exact reason for this difference is unclear, and could not directly be attributed to the longer pre-operative medical therapy and delayed approach to surgical resection. In the exceptionally small cohort of patients from KwaZulu-Natal, the pre-operative medical therapy ranged from 2.3-10.8 months with 100% successful outcomes reported, which again does not shed light the optimal timing for surgical intervention as these patients has both very early and very late intervention.

The optimal timing for surgery remains to be determined, given the conflicting findings from many studies and lack of clarity in the 2 large meta-analyses.

Post-operative chemotherapy duration

As with the timing of surgery, the duration of post-operative chemotherapy is also unclear from the literature. Marrone *et. al.* comment that a minimum of 12 months of post-operative chemotherapy is required to increase the likelihood of cure, but many studies included in the meta-analyses did not specify the duration the of post-operative chemotherapy and this was not formally analysed (21). They, along with Harris *et. al.* recommend 12-24 months of post-operative chemotherapy as a standard approach, but could not elaborate further (21, 22).

In the Kwa-Zulu Natal group, post-operative chemotherapy was continued for 14.5-15.8 months in their small subset of 5 patients, all of whom has successful outcomes. In the Latvian study, the mean duration of post-operative chemotherapy was 14.5 months, but their overall success rate in the surgical group was only 47%.

The median (IQR) duration of post-operative anti-tuberculous therapy in the bedaquline-regimen study was shorter than any of the previously described studies and was only 10 (7-14) months (25). The majority of patients (60%) in this study were treated with bedaquiline as part of their post-operative management. The individual effect of this particular drug on treatment outcomes was not quantified in the study, but it was noted that this effect should probably be defined further.

It is clear that there are many determinants to successful outcomes and that the duration of post-operative chemotherapy is not the only factor at play. Having said this, many of the studies tended to continue treatment for a period of 12-24 months and classified patients as cured once they remained sputum culture-negative for 12 consecutive months on treatment. The duration of treatment after this point tended to be more highly variable.

Factors influencing treatment outcomes

The durations of both pre- and post-post-operative medical therapy and their potential influence on treatment outcomes have been described above.

In the large meta-analyses, little could be deduced about other specific factors that influenced outcomes either positively or negatively, as studies were extremely heterogenous, and details recorded in studies were not standardised. We felt that HIV may be a relevant factor, but this was not described extensively in the literature. Marrone *et. al.* did not explicitly report the HIV prevalence, nor was this analysed as a potential mediator of outcomes. All patients in the Latvian surgical cohort were tested for HIV, but none were found to be HIV-infected**.** Again in the small surgical cohort in Kwa-Zulu Natal, only 1 of the 5 patients was HIV-infected and was reported to have a suppressed viral load on antiretroviral therapy (ART), making it difficult to draw any conclusions as to the role HIV might play in determining patient outcomes. In this particular study, inclusion criteria stipulated that HIV-infected patients must be on established ART and meet criteria for viral suppression. Two different South African studies followed XRD- TB patients treated only with medical therapy and found culture conversion rates from 11-19% (2, 7). Both these studies included patients with HIV and neither showed any significant difference in treatment outcomes. Both ART-naive and ART-established patients were included in these studies. The Nix-TB trial, looking at outcomes for DR-TB patients with medical management alone, found no significant differences between HIV infected (51%) and HIV non-infected patients (24). All HIV positive patients in this trial were managed with concomitant TB and ART therapy. With limited available robust data, it remains unclear as to whether HIV co-infection, clinical staging or treatment with ART in XDR-TB plays a significant modulatory role in either medical or surgically managed patients.

The number of drugs used is also widely thought to influence outcomes. It is important to

differentiate between the absolute number of anti-tuberculous drugs used and the number of effective anti-tuberculous drugs with proven sensitivity. The effect of the number of total and effective number of drugs was difficult to determine, as this varied both between and within studies. In the Marrone *et. al.* meta-analysis, the mean number of drugs in a regimen was 5.3 and 4.4 in the comparative and single-arm groups respectively In both groups, p-values showed that no significant difference could be determined in outcomes when comparing patients on regimens of 5 or more drugs to those on less than 5 drugs. These drug regimens were not all stratified according to known number of effective drugs, as extended sensitivities were not available in many reviews, and no conclusion can be drawn as to whether a minimum number of effective drugs may play a positive role. The current WHO guidelines suggest a minimum of 5 effective agents based on drug-susceptibility testing (DST) in regimens for drug- resistant TB (19, 29). A major barrier in determining resistance profiling and DST is the lack of laboratory resources and other infrastructure in developing and third world countries (1). Another issue is the long delay required for full DST to be conducted, as this requires prolonged incubation and culture time**.** This seemed to be evident in studies published from Latvia, South Africa and South Korea, where none of the studies were able to accurately report on the number of effective drugs as determined by DST. The NIX study used a unique trial regimen of 3 effective anti-tuberculous drugs (linezolid, bedaquiline, and pretomanid) and was one of the few studies where drug levels and minimum inhibitory concentrations were determined in a large proportion of patients (52%) to ensure treatment efficacy (24). The mean numbers of drugs used varied between 3-7 drugs in the above-included studies with no correlations between the number of drugs and outcomes being determined.

According to the recommendation by WHO, all patients undergoing surgical resection must be deemed to have sufficient cardiopulmonary reserve post-surgery. This was stipulated in

most studies included and was determined by a multi-disciplinary group. This selection bias of only including patients deemed to have better physiological reserve to withstand surgery has been highlighted in a number of papers. It is acknowledged that this bias may sway benefit in the favour of surgery as these patients may have less extensive disease and therefore a higher likelihood of treatment success.

Secondary Aim

Role of PET/CT as predictor of outcomes

In all the studies included above to report treatment outcomes, none included PET/CT as a routine pre-operative investigation, nor did they comment on its role as a potential modulator for outcomes. Thus far, to the best of our knowledge, there is no robust data on the use of PET/CT as a tool to predict treatment outcomes in either drug-sensitive or drug-resistant TB. This is regardless of whether patients are treated medically only or with adjunctive surgery.

One South African paper in 2017 did evaluate the role of radiology alone in predicting treatment outcomes in patients who underwent adjunctive lung resection for drug-resistant TB in a high HIV-burden area (18). They proposed that although pulmonary nodules have a lower burden of disease and bacilli than cavities, they may represent active infection and perhaps should be resected to reduce overall bacillary load. It was acknowledged that this was not always possible due to anatomical distribution and/or residual pulmonary reserve. They described the association between peri-operative pulmonary nodules, as seen on plain chest radiograph and CT, and sputum culture conversion in 47 HIV-positive and negative patients. Chest radiography (performed a week prior to surgery) and high-resolution CT (performed 2 months prior to surgery) showed that a total of 60% of patients had nodular disease pre- operatively. Both modalities showed that the majority of patients had nodules in the upper lobes (50% and 61% respectively). The distribution of lesions was similar in both

modalities of imaging, and in HIV-positive (57%) and negative groups. Most patients who underwent surgery were sputum culture-negative at the time of surgery (66%) which was not associated in any way with the presence of pulmonary nodules. Post-operative chest radiography and sputum culture were performed at 6 weeks after resection. Nodules were either new or residual from the non-resected tissue. No follow up CT imaging was performed. Sputum cultures were performed up until 6 months. In keeping with WHO guidelines, successful outcome was defined as persistently negative culture following resection (17). This local study showed no associations between composite sputum culture outcomes at 6 months and the presence of nodules, either pre-operatively (p=0.73) or post-operatively (p=0.52). There was also no difference shown in the HIV infected and non-infected groups. Although no association was found in this small study, the investigators did comment that the use of 18-FDG PET/CT may be a useful tool to evaluate the activity of such nodules to better characterise disease activity.

In another paper from our setting, it is also stated that PET/CT may be included in the work up of the potential surgical candidates to confirm contralateral metabolically active disease in the form of nodal or parenchymal disease (1). They also postulate that this may be useful to determine disease activity in patients with radiological changes secondary to prior TB infection. This theory is supported by current literature, which suggests that PET/CT is a sensitive tool to detect TB and differentiate between active and previous tuberculous infection, especially in cases with cavitatory disease (16). It has also been shown that PET/CT is superior to CT or MRI alone in detecting active tuberculous disease (17). There is no information to guide whether the burden of disease at the start of treatment, as detected by PET/CT, predicts outcomes in anyway. Furthermore, there is no data to guide whether the burden of disease, in the form of cavities, nodes, parenchyma infiltrates or other radio-tracer measurements at the start of treatment, should or can be used to select whether patients

should undergo surgical management or not. The role of PET/CT remains unclear in guiding clinical practice in this field.

Gaps and direction for our study

We aim to describe the outcomes of our surgical XDR-cohort and compare our results to those reported in various other centres, taking note to try and account for variances that may be observed. We acknowledge that our study will take place in a developing country context and our results may be more aligned with those from similar contextual backgrounds. We also aim to describe any patient or treatment characteristics that may significantly affect outcomes. We would like to describe the role of HIV co-infection in our cohort, given the high burden of this disease in South Africa and determine whether this plays a bigger role than in other reports where prevalence is lower.

The value of PET/CT as a non-invasive clinical investigation to assist with patient selection for surgery will also be explored in our study. We aim to determine whether any specific radiological or metabolic activity measurements may be useful markers to guide clinical practice, given that this question remains unanswered in current literature.

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PUBLICATION-READY MANUSCRIPT

TITLE PAGE:

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

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INTRODUCTION

Multi drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are public health emergencies in South Africa, with limited pharmacological options for cure. The overall treatment outcomes of pre-XDR and XDR-TB in particular are far from satisfactory(1). A retrospective study from our setting (in the era before linezolid, bedaquiline and delaminid) showed that only 19% of patients culture-converted on the pharmacotherapy available at the time(2). In the absence of effective drug regimens, and in appropriate patients, surgery with resection of involved lung tissue has been employed in selected patients as a form of adjunctive treatment in DR-TB. 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 cavitatory lesions and areas of destroyed lung, which may harbour up to 10^7 to 10^9 *M.tb* organisms(3). This “debulking” hopes to enhance the sterilizing properties of post-surgical chemotherapy and to increase the likelihood of treatment success(4, 5).

Many comparison studies and a systematic review (which included patient-level data from over 5000 participants) have shown improved outcomes in patients who undergo lung resection for DR-TB(6). 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, there are no data from under-resourced, high HIV-burden settings like South

Africa. Little is known about factors that may influence patient selection and that may be associated with treatment outcomes.

Active tuberculosis infection (including asymptomatic and extrapulmonary disease) may be detected with 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT)(7). PET/CT is a non-invasive imaging method that may give additional information about tuberculous disease status, including parenchymal as well as nodal metabolic activity. As patients with drug-resistant tuberculosis usually have been treated for TB in the past, PET/CT may distinguish active tuberculous lesions from the fibrotic consequences of previous episodes of healed TB.

In our centre, current practice is to usually exclude patients where lung resection would still leave a FDG-avid cavity or cavities in the contralateral lung (in the case of pneumonectomy) or remaining ipsilateral lung lobe or lobes (in the case of lobectomy). The rationale for this is that cavities have exponentially more actively replicating bacilli than other parenchymal lesions and are penetrated poorly by antituberculous drugs, substantially reducing the chance of a postoperative cure with antituberculous therapy. The role of areas of FDG-avid nodular disease or consolidation (which contain exponentially less organisms) on treatment outcomes is unknown.

We hypothesised that patients undergoing lung resection would have improved outcomes compared to historical cohorts in whom surgery was not offered. We also hypothesised that PET activity distant from the site of resection, either cavitatory or non-cavitatory 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 and oversight

We conducted a single-centre, retrospective study of patients undergoing lung resection in patients with DR-TB in Cape Town, South Africa. The study was approved by the local ethics committee. The study is reported in accordance with the STROBE statement for observational trials(8).

Study population

All DR-TB patients undergoing resectional surgery at Groote Schuur Hospital (GSH) between July 2010 and December 2016 were enrolled in a registry. 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 were offered resectional surgery based on conventional physiological and radiological assessments of operability and resectability, as determined by a multidisciplinary team (pulmonologists, thoracic surgeons, nuclear medicine physicians and radiologists).

Study procedures

Socio-demographic and clinical data on our patients was extracted from the XDR-registry using the UCT Research Ethics Committee reference #038/2008. The degree of drug resistance was determined by the National Health Laboratory Services (NHLS) using the BACTEC MGIT 960 system(9) and line probe assays (MTBDR*plus*, Hain Lifesciences, Nehren, Germany). A subset of patients had extended drug sensitivity determined pre-operatively by whole genome sequencing (WGS) as part of a related pharmacokinetics study conducted at the same centre(10). Sputum samples were collected and cultured from these patients either on the day of or the day prior to resectional surgery. Pre-operative drug regimens were documented as part of the work-up for surgery and for enrolment into the XDR- TB registry. Where drug sensitivity was known, the number of effective drugs in each regimen

was tallied.

Preoperative PET/CT

A subset of patients included in the registry underwent PET/CT as part of the pre-operative workup prior to their surgical resection. PET/CT was performed to aid surgical decision-making in cases where there was radiological 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. 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(11). 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(12). 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 × W/D × 1000 g/c (where SUV w = normalization to body weight, A = activity concentration in Becquerel/cubic centimeters (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 post-operatively. During this time, 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.

Outcomes

The primary measure was the outcome of patients undergoing lung resection for DR-TB at 24 months after surgery, using the WHO treatment outcome definitions(13). Treatment outcome was considered a “success” if it resulted in completion or cure, and a “failure” if treatment failed (persistent sputum culture positivity), the patient died, or the patient defaulted or was lost to follow up. 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. 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).

RESULTS

Study population

Between July 2010 and December 2016, 35 patients with DR-TB underwent lung resection at our institution (table 1). The number of patients with XDR-TB, pre-XDR-TB and MDR-TB was 27 (77%), 5 (14%) and 3 (9%), respectively. Twenty patients (57%) had previously been treated for DR-TB, and 29 (83%) were culture-positive at the time of surgery. Nine 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 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.

Treatment outcomes

At 24 months after surgery, 15 (43%) of patients were considered programmatically cured, 5 (14%) had failed treatment, and 3 (9%) had defaulted or were lost to follow-up. All-cause mortality at 24 months was 10/37 (27%). There were 2 (5%) early post-operative deaths (within 30 days) and 6 (16%) died by six months. Univariate peri-operative predictors of treatment failure were HIV positivity, degree of drug resistance (XDR-TB vs. pre-XDR-TB and MDR-TB), and post-operative bedaquiline and linezolid use; only degree of drug resistance and bedaquiline use were significant on multivariable analysis (table 2). Sputum culture conversion, if it occurred and was durable. was most likely to occur early: 12/35 (35%) culture- converted by six months (figure 1). Sputum culture conversion at 6 months was a significant post-operative measure associated with successful outcome; however, this became non- significant if corrected for degree of resistance. In a multivariable analysis, 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.

Pre-operative PET/CT

PET/CT was performed in 25 (71%) patients; 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%). 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 3). In multivariable Cox proportional 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 (figure 2).

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 two main findings. First, it demonstrates that resectional surgery for XDR-TB in combination with available chemotherapy at the time resulted in a cure in ~ 50% of patients. The main risk factor for poor outcome was the degree of drug resistance. Second, treatment outcomes were not modified by the presence of PET-positive disease, regardless of its radiological type. This finding supports the rationale that adjunctive surgery for TB is primarily a debulking procedure and suggests that factors other than the burden of FDG-avid disease in the non-resected lung are associated with treatment outcome. Thirdly, it shows – as with patients treated with chemotherapy alone – that sputum conversion is most likely in the first six months, and that this is a predictor of durable outcome.

The outcomes reported in this study are considerably worse than those in previous reports of surgery for DR-TB from other settings and eras (6, 14-19) during which bedaquiline and linezolid were not widely available; however, our cohort differs in that the degree of drug resistance and the prevalence of culture positivity at the time of surgery was much higher than in those studies. Our outcomes are better than those of historical cohorts of XDR patients treated with chemotherapy alone (20), but worse than those of recent cohorts treated with bedaquiline, linezolid and other newer agents, with or without surgery (21-23, 24). The implication is that treatment outcomes are highly dependent on the efficacy of pre- and post-surgical chemotherapy, which has increased with the introduction of linezolid and bedaquiline to the DR-TB regimen. It is notable, however, that 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 (22). The role for resectional surgery may evolve as success rates with newer bedaquiline- and linezolid-containing treatment regimens increase and become more widely available and accessible.

To our knowledge, none of the previous studies of adjunctive surgery for drug-resistant tuberculosis have included PET/CT as a pre-operative investigation, nor are there any data of its use as a potential aid in surgical decision-making or as a predictor of treatment outcome. 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 cavitatory disease, with its 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.

Several limitations of this study deserve emphasis. First, as there was no non-operative group, the impact of adjunctive surgery on TB outcomes cannot be directly compared. Adjunctive surgery is likely to be offered to patients with better physiological status, more localised disease and fewer comorbidities, so there is inherent bias in such a comparison; randomised trials on this question are also unlikely to ever be performed. The opposite may also be true: in the era of more effective chemotherapy, surgery may be reserved for patients who are already failing complex treatment regimens, and thus have higher resistance patterns (and worse outcomes). 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, this is data from a single centre, and our numbers were

small, so 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, 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, diluting the potential effect of surgery alone on treatment outcomes.

In summary, resectional surgery for DR-TB in combination with chemotherapy resulted in cure in less than half of the patients. 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.

Conflict of interest

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

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LIST OF ABBREVIATIONS

AUC	Area under curve
BDQ	Bedaquiline
CI	Confidence interval
CT	Computer tomography
DR	Drug resistant
DST	Drug sensitivity testing
FDG	FLuorodeoxyglucose
HIV	Human immunodeficiency virus
MDR	Multi-drug resistant
MDV	Metabolic disease volume
MRI	Magnetic resonance imaging
PET	Positron emission tomography
ROC	Receiver operator curve
ROI	Region of interest
SUV	Standard uptake volume
TB	Tuberculosis
TDG	Total disease glycolysis
WHO	World Health Organization
XDR	Extremely drug resistant

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ANNEXE:

TABLES AND FIGURES

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

Characteristic	**n=35**
Age, median (IQR)	40 (28-47)
Male, n (%)	17 (49%)
HIV positive, n (%) CD4, median (IQR)	9 (26%) 407 (274-435)
Preoperative drug resistance profiles XDR, n (%) Pre-XDR, n (%) MDR-TB, n (%)	 27 (77%) 5 (14%) 3 (9%)
Current smokers, n (%)	15 (43%)
Previous episode of DR-TB, n (%)	20 (57%)
Sputum culture positivity at time of surgery, n (%)	29 (83%)
Capreomycin resistant, n (%)	6 (17%)
BDQ exposure pre- or post-surgery, n (%)	8 (23%)
LZD exposure pre- or post-surgery, n (%)	10 (29%)
Procedure Pneumonectomy, n (%) Lobectomy, n (%)77%	 20 (57%) 15 (43%)

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

Table 2. Predictors of treatment failure in all patients (n=35)

Variable	n	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)†	P-value
Peri-operative measures					
Age (per year increase)	35	1.03 0.97-1.10)	0.30		
Male sex (vs. female)	35	0.27 (0.07-1.11)	0.07		
HIV positive status (vs. negative)	9	9.33 (1.02-85.70)	0.05		
Current/former smoking status (vs. non-smoking)	14	2.75 (0.65-11.62)	0.17		
XDR status (vs. MDR and pre-XDR)	27	16.63 (1.78-158.09)	0.01	14.25 (1.16-174.80)	0.04
DR-TB treatment (vs. no previous treatment)	20	0.81 (0.21-3.17)	0.77		
Pneumonectomy (vs. lobectomy)	22	1.24 (0.31-4.93)	0.76		
Positive pre-operative sputum culture (vs. negative)	29	3.27 (0.51-20.93)	0.21		
Post-operative bedaqualine (vs. no bedaqualine)	8	**	**	**	**
Post-operative linezolid (vs. no linezolid)	10	0.20 (0.04-0.99)	0.05		
Drugs in regimen with confirmed sensitivity (per one drug increase)	35	0.86 (0.50-1.47)	0.56		
Post-operative measures					
Sputum culture conversion at 6 months	35	0.10 (0.02-0.51)	<0.01	0.17 (0.02-1.38)	0.10
Sputum culture conversion at 12 months	45	1.33 (0.41-4.29)	0.48		

Abbreviations: OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; XDR-TB = extensively drug-resistant tuberculosis; MDR-TB = multidrug-resistant tuberculosis.

† Adjusted for HIV status, XDR .

** Unable to calculate OR as there were no treatment failures in this category.

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

Radiological measure	Total (n=25)	Failure (n=12)	Success (n=13)	p-value
Ipsilateral disease (non-resected lobes)				
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				
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*
Intrathoracic 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.

p-values determined by: *Z-test; #Mann-Whitney U test
Abbreviations: PET/CT - positron emission tomography/computed tomography; SUV – standardised uptake values

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

Variable	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)†	P-value
PET/CT measures of activity				
Visual	1.01 (0.77-1.32)	0.97		
SUV max	1.10 (0.95-1.27)	0.21		
SUV peak	1.12 (0.96-1.31)	0.16		
Metabolic Disease Volume	1.01 (1.00-1.02)	0.06		
Total disease glycolysis	1.00 (1.00-1.01)	0.02	1.00 (1.00-1.01)	0.025
Abbreviations: HR = Hazard ratio; CI = confidence interval; SUV = Standard Uptake Units † Adjusted for HIV status				

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

Figure 1. Sputum culture status during study period

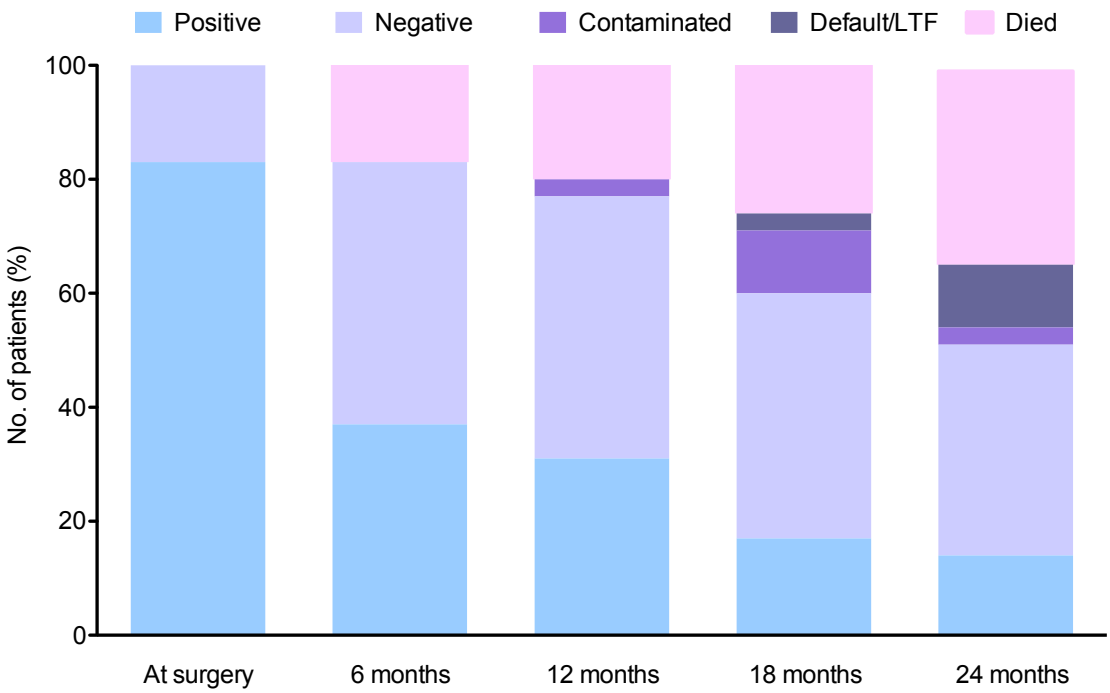
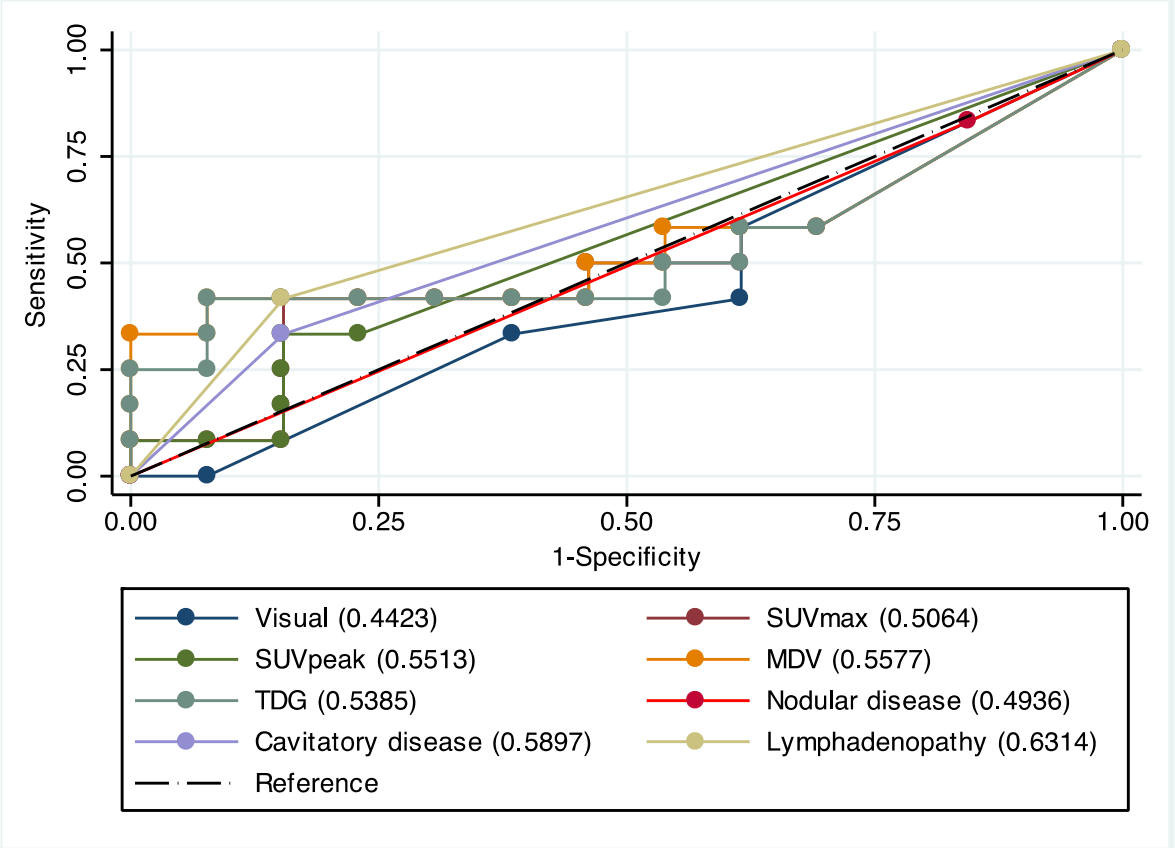


Figure 2. Receiver operating characteristic (ROC) curves for PET/CT readouts



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

Receiver operating characteristic curves for each PET/CT readout using the binary predictor of treatment failure with the area under the ROC curve (AUC) in parentheses in the figure legend.

ETHICS APPROVAL

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03 July 2017

HREC REF: 463/2017

Dr G Calligaro
Dept of Pulmonology
UCT Lung Institute

Dear Dr Calligaro

PROJECT TITLE: OUTCOMES OF PATIENTS UNDERGOING RESECTIONAL SURGERY FOR EXTENSIVELY DRUG-RESISTANT (XDR) PULMONARY TUBERCULOSIS, AND THE PROGNOSTIC SIGNIFICANCE OF PRE-OPERATIVE 18-FLUORODEOXYGLUCOSE (FDG)-AVID NON-CAVITATORY PARENCHYMAL LESIONS DETECTED BY POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (PET/CT) IN PREDICTING TREATMENT FAILURE-(MMeD-candidate-Dr N Singh)-sub-study linked to 038/2008

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th July 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student will be involved in this study: Dr N Singh

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.