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The role of surgery in the treatment of pulmonary TB and multidrug- and extensively drug-resistant TB

ABSTRACT

The global spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *M. tuberculosis* have resulted in a resurgence of almost incurable and even fatal cases for which only a few therapeutic options are available. Surgery has been applied to improve treatment success rates in MDR-TB patients and a combined medical and surgical approach is increasingly being used to treat patients with M/XDR-TB. The effectiveness of surgery in the management of pulmonary TB (particularly MDR-TB) has not, however, been documented and evaluated, its role in the Tuberculosis Control Programme is not well-established and practices vary across the WHO European Region. The WHO Regional Office for Europe has decided, in collaboration with the Member States and other partners, to review existing practices and lessons learned and to document expert opinion based on the available evidence and consensus among the members of the European Task Force on the role of Surgery in MDR-TB. This consensus paper should not be considered as recommendations from WHO but as a document of expert opinion based on current evidence, which presents indications and contraindications for surgical treatment of pulmonary TB and M/XDR-TB, the conditions for and timing of surgery, types of operation, and preoperative and postoperative management.

Keywords

POSTOPERATIVE CARE
SURGERY
TUBERCULOSIS, EXTENSIVELY DRUG-RESISTANT
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List of abbreviations

CT	computed tomography
DST	drug-susceptibility testing
MDR-TB	multidrug-resistant TB
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
XDR-TB	extensively drug-resistant tuberculosis

Background

The Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis, endorsed at the 61st session of the WHO Regional Committee for Europe in Baku, Azerbaijan in September 2011, foresees, under activity 3.4.2, that “The Regional Office in collaboration with the Member States and other partners will develop a set of evidence-based criteria for surgery for M/XDR-TB patients...” (1).

The effectiveness of surgery in the management of pulmonary TB – and, in particular, of multidrug-resistant (MDR-)TB – has not yet been duly documented and evaluated, its role is not well-established and practices vary across the WHO European Region. It is, therefore, time for current practices and lessons learned to be reviewed and shared across the Region.

In 2011, the WHO Regional Office for Europe established a Task Force on the Role of Surgery in MDR-TB to review the current evidence base, to provide an expert opinion on the indications and contraindications for surgical treatment and the pre- and postoperative management of pulmonary TB and multidrug-/extensively drug-resistant (M/XDR-) TB patients, and to provide recommendations for further research on surgical treatment for pulmonary TB and M/XDR-TB. This consensus paper has been prepared by two reviewers at the WHO Regional Office for Europe, in conjunction with members of the Task Force and others, as part of this process.

The aims of the consensus paper

The aims of this paper are to:

- review the available studies on the role of surgery in the treatment of pulmonary TB and M/XDR-TB in adults;
- present an expert consensus on the indications and contraindications for surgical treatment based on the available evidence, as well as on the pre- and postoperative management of pulmonary TB and M/XDR-TB patients;
- define the limitations in the available studies and provide recommendations for further research on the surgical treatment of pulmonary TB and M/XDR-TB patients.

Literature search

A search of the literature for this paper was conducted over a one-year period from 2012–2013. New literature was reviewed on an ongoing basis during the preparation of the paper, and the results were updated accordingly. In consultation with the Task Force, two reviewers decided on what to include and exclude. The Task Force had virtual meetings and two face-to-face meetings to discuss the methodology, findings and overall quality of evidence.

Search methods

A comprehensive search of PubMed and Russian TB journals was carried out using a combined search strategy. For the PubMed search, medical subject headings were used in conjunction with text search terms following the strategy used by Marrone and colleagues (2). The time frame for publication of included studies was 1975 to 2013. Bibliographies of clinical practice guidelines

and published review articles were also manually searched for additional literature. Studies published in English or Russian were reviewed. Grey literature was also searched with corresponding parameters.

Inclusion criteria and quality of evidence

All studies found that presented the results of surgical treatment for pulmonary TB and M/XDR-TB patients and were considered to report quality methods and evidence were assessed. Since a systematic review published by Marrone and colleagues in 2013 (2) has rigorously evaluated the quality of many of the papers assessed in this consensus paper, no additional quality assessment was made of these papers. However, when papers (particularly from the Russian literature) were additionally evaluated, the quality of their methods and reporting was assessed against the STrengthening the Reporting of OBServational studies in Epidemiology guidelines for observational studies and by the opinion of the authors of this consensus paper. As there have been no recent randomized controlled trials on the efficacy of surgical treatment for the treatment of pulmonary TB and M/XDR-TB, all studies included in this review were observational. The specific types of surgery assessed are also discussed in detail.

Studies reviewed and analyses

Based on the Marrone study and using these search methods, 67 studies were initially identified. After taking into account the inclusion criteria and quality of the studies, 52 were retained in the final assessment.

Seven priority areas were identified by the Task Force as needing a consensus opinion:

- indications for surgical treatment
- conditions for and timing of surgery
- types of operation to treat TB
- contraindications for elective surgical treatment
- preoperative management
- patient-centred approach
- postoperative management.

Studies retained in the consensus paper were grouped according to these seven areas. The findings and conclusions of the studies were assessed for each category, and consensus opinions on each are presented in this paper.

Limitations

A limitation of the review was that articles and grey literature published in languages other than English or Russian were not searched or assessed.

Brief historical account

Surgical operations for the treatment of TB have a long history, predating the discovery of *M. tuberculosis*. For almost two centuries before the introduction of effective anti-TB medicines, surgery was one of the main treatment options for TB (3–7).

In 1726, the British surgeon E. Barry drained a purulent TB lung cavity (pneumotomy) (5). In 1882, Carlo Forlanini introduced collapsotherapy into the treatment of pulmonary TB, provoking artificial pneumothorax (8). However, it was only after the development of radiographic imaging methods and the introduction of the manometer that surgical procedures became safer and more reliable (4).

After the discovery of *M. tuberculosis* by Robert Koch in 1882, surgical intervention remained one of the most common therapeutic options for the treatment of TB patients, although this approach was not always successful. In 1890, Spengler successfully performed thoracoplasty (7) and in 1891, Theodore Tuffier performed a wedge lung resection in a TB patient (7). In the period 1910–1912, Hans Christian Jacobaeus developed thoracoscopy and an effective operation for closed cauterization of pleural adhesions (4). In 1938, Vincent Monaldi introduced thoracostomy (drainage) for the treatment of cavitory TB (5). In 1933, Heidenhain Lilienthal performed the first successful pneumonectomy for TB treatment, and the first lobectomy was reported by Samuel Freedlander in 1935 (4). In 1947, L.K. Bogoush performed the first pneumonectomy in the former Soviet Union for the treatment of a patient with progressive cavitory pulmonary TB (7).

With the introduction of modern anti-TB chemotherapy in 1952, surgery was largely abandoned (3) and, until the present day, chemotherapy has been the main treatment method for TB, including its drug-resistant forms. In the industrialized countries of Australia, Europe, Japan and North America, the number of operations fell considerably because the incidence and prevalence of TB declined and medicines were effective (4). Indications for surgery were further restricted in those areas, although only in the countries of the former Soviet Union has surgery remained a relatively widespread option for the treatment of TB (3–7). As Sir John Crofton emphasized, it should be possible to cure almost all TB patients without surgery (5). However, the global emergence and spread of MDR- and XDR-TB strains of *M. tuberculosis* has resulted in a resurgence of almost incurable and even fatal cases (9–10). M/XDR-TB currently represents a critical challenge for global TB control owing to the few therapeutic options available.

Indications for surgical intervention in the treatment of pulmonary TB

A recent systematic review (2) reported that pulmonary resection combined with anti-TB chemotherapy for MDR-TB has achieved treatment success rates in some settings of up to 88–92% of cases (3–4,11–26), as well as reduced odds of all-cause mortality. Despite these favourable results, the role of surgery remains rather controversial in the most recently published MDR-TB treatment guidelines (26–28). Its indication is limited to the management of complicated forms of TB (including massive haemoptysis, bronchiectasis, bronchial stenosis, bronchopleural fistula and aspergilloma) and, mostly, to cases in which medical treatment is failing (3,11,16,26,29–34).

Among studies assessing surgery for all forms of TB, several authors have postulated the following absolute indications for surgery in TB treatment:

- a high probability of failure of medical therapy in MDR-TB patients (due to persistent cavitory disease and lung or lobar destruction) and massive haemoptysis (11,33) or tension pneumothorax (4);
- persistent positivity of sputum-smear or sputum-culture despite adequate chemotherapy;

- a high risk of relapse (based on the drug-resistance profile and radiological findings);
- localized lesion (13,19,28,33);
- progression of TB despite adequate chemotherapy;
- repeated haemoptysis or secondary infection;
- localized disease amenable to resection (16);
- polyresistant and MDR-TB;
- absence of any radiological and/or bacteriological improvements during the initial three to four months of chemotherapy;
- allergic, toxic and mixed side-effects of drugs;
- chronic diseases of the gastrointestinal organs hindering effective chemotherapy (35).

Cases of extended disease were defined in patients in which the total cavity diameter was more than 15 cm or the bilateral parenchymal infiltration covered more than 75% of the total lung area (17). Resection is considered for patients with cavitary disease due to the difficulty of antibiotic penetration and the high number of organisms (10^7 – 10^9) contained within the cavity (11). Some authors emphasize that surgical treatment is most often used in cases of tuberculoma and fibrotic-cavitary TB (3,16–18,36–37,40), and one of the most important indications for surgery is irreversible morphological changes of the lungs and other respiratory organs due to the development of the fibrotic tissues during the progress of TB over the long term (4–5,18). In cases of tuberculoma of more than three centimetres, early pulmonary resection will prevent progression and shorten the period of treatment (4,7). In some cases, surgical treatment avoids errors in differential diagnosis of tuberculoma and lung cancer (4–5).

Among studies that specifically consider MDR-TB, while the majority of authors agree on the absolute indication for the surgical treatment of MDR-TB in cases of persistent cavitary disease with treatment failure, some authors consider that even in sputum-smear-negative MDR-TB patients a radiologically persistent fibrous cavitation or destroyed lung (suggesting no clinical improvement) represents an indication for surgery because of the high probability of relapse (13,17,36). Other investigators call to mind that the purpose of surgery is to remove a large, focal burden of bacilli localized in necrotic and non-viable lung tissue (13,38). The TB cavity is an ideal growth environment because its wall can restrict drug penetration, and it probably protects *M. tuberculosis* from the host's immune defences. Many patients who are preoperatively sputum-culture-negative have positive cultures from resected lung tissue (27–100%) (13,39). Furthermore, cavities might be sites for the development of drug resistance. In a study of resected TB lung tissue, bacillary growth was shown to be most active in macrophages located on the cavity surface, where the majority of new drug-resistance mutations occur. The investigators reported an absence of CD4 and CD8 T-cells at the luminal surface, which might explain active bacillary proliferation. Additionally, after removal of a major TB focus, the immune response to residual infection might be enhanced, similar to paradoxical reactions sometimes noted during TB treatment (13,39). The successful treatment of any infectious disease involves a delicate balance of host and pathogen processes. In the human lung, selection of drug-resistance mutations in *M. tuberculosis* occurs predominantly within lung cavities in which high bacterial loads, active mycobacterial replication and reduced exposure to the host's defence mechanisms can be detected (38). Incomplete resection of tuberculous lesions (in particular cavities, but also other irreversible lung lesions) is, therefore, one of the risk factors for disease relapse (4,26,38).

It should be emphasized, however, that most authors consider that cavitary M/XDR-TB with anti-TB chemotherapy failure is nowadays the main indication for surgical treatment, followed by an adequate course of postoperative anti-TB chemotherapy (2,3,5–6,11–16,18–24,26,29–32,34–38,40–52,54). Surgery is not, however, considered as a first-line option in the treatment of drug-susceptible TB (5).

Surgery is not often considered as an option for TB programmes in low-income settings, although experience in Peru supports the argument that adjunctive surgery should be considered as an integral component of MDR-TB treatment programmes, even in poor countries, as long as adequate surgical expertise and facilities are present (43). The average cost of surgery in the Peruvian programme in question was US\$ 2562. In comparison, the average cost of treating a patient for 18 months under this programme was US\$ 5908, and for 24 months it was US\$ 7878 (43). The authors concluded, therefore, that if performed within the first six months of treatment, surgery could not only improve treatment outcomes but also shorten the duration of chemotherapy required, with little additional cost to the treatment programme (43). The International Union against Tuberculosis and Lung Disease compared the estimated costs of treating one patient with MDR-TB (without surgery, but where medications and hospitalization play an important role) in four countries, with the following results: US\$ 4944 per patient in Peru, US\$ 5160 in the Philippines, US\$ 12 690 in the Russian Federation and US\$ 12 882 in Estonia (55).

Unfortunately, MDR-TB is more likely to occur in countries with a limited diagnostic capacity for culture and (rapid) drug-susceptibility testing (DST) for first-line drugs and, in particular, for second-line drugs. There is often a lack or limited supply of the expensive second-line drugs (3,11).

Thus, an approach combining chemotherapy and surgery is increasingly being used in many parts of the world to treat patients with M/XDR-TB. In one study, however, satisfactory evidence was not obtained in favour of surgery in MDR-TB cases (17). There was no significant difference between the survival rates of patients with surgery and those without: the cumulative survival rate in this study was 92.4% in patients who underwent surgery and 93.0% in patients who did not. In addition, resection surgery requires a team of specialists and facilities, as well as a centre of excellence in order to provide the required level of care throughout the process (before, during and after surgery). These teams and facilities are often not available in areas in which MDR-TB is prevalent, thus placing patients at potentially higher risk of severe complications. Adding resection surgery to a treatment regimen would also greatly complicate the logistics for a national TB programme and would make treatment significantly more expensive (17).

Finally, although most surgery for TB is elective, directly life-threatening conditions that may require emergency surgery are at times found with all forms of TB (4–5).

Based on the review of studies, as outlined above, it is the opinion of the experts contributing to this paper that the current indications for surgical treatment of pulmonary TB and M/XDR-TB are as follows.

(i) Emergency

Emergency indications (that is, without surgery death is imminent and unavoidable) include:

- profuse lung haemorrhage
- tension spontaneous pneumothorax.

(ii) Urgent

Urgent indications include:

- irreversible TB progression, despite adequate anti-TB chemotherapy
- recurrent haemoptysis that cannot be stopped by other treatment methods.

(iii) Elective

Although there is not enough evidence to define the characteristics of cavities and other irreversible changes in M/XDR-TB patients that can lead to a high probability of failure of TB chemotherapy and relapse, the majority of authors define the elective indications listed here:

- localized forms of cavitary TB with continuous *M. tuberculosis* excretion confirmed by bacteriological examination and DST after four to six months of supervised anti-TB chemotherapy;
- M/XDR-TB characterized by failure of anti-TB chemotherapy;
- complications and sequelae of the TB process (including M/XDR-TB), including:
 - spontaneous pneumothorax and pyopneumothorax
 - pleural empyema with or without bronchopleural fistula
 - aspergilloma
 - nodular-bronchial fistula
 - broncholith
 - pachypleuritis or pericarditis with respiratory and blood circulation insufficiency
 - post-TB stenosis of trachea and large bronchi
 - symptomatic and chronic post-TB bronchiectasis;
- other indications such as the elimination of complications of previous surgery.

Conditions for and timing of surgery

Proper patient selection and the timing of operations are crucial to avoid relapses and to provide a higher chance of cure. Good cooperation between treating physicians and thoracic surgeons, as well as patients' adherence to pre- and postoperative intervention chemotherapy, can increase the success rate of MDR-TB treatment (3,11,29).

For patients to be considered as candidates for surgery, three major criteria need to be met:

(i) the patient must have localized disease amenable to resection and with an adequate respiratory reserve; (ii) the patient must have extensive drug resistance, making the likelihood of treatment failure or relapse very high; and (iii) a sufficient quantity of second-line drugs must be available to ensure healing after surgery (3,11,29,38,42). In the case of bilateral lesions, resection should be performed on the side with the greater lesions (15,23,50).

Surgery should be seriously considered when:

- the disease is sufficiently localized to allow surgery;
- the remaining lung tissue around the resection margins is estimated to be free of TB;
- the patient's surgical risk level is acceptable, with sufficient pulmonary reserve to tolerate the resection.

In any case, irreversible pathomorphological changes in the affected lung(s) are a significant additional indication for surgery. In all cases, surgery is only indicated if it is possible to perform surgery (resection of the lung or other type of operation) without significant damage to the patient's lung function.

Types of operation

The following are the types of operation currently performed:

- lung resections of different size:
 - wedge resection
 - segmentectomy
 - lobectomy and bilobectomy
 - combined resection (lobectomy plus minor resection)
 - pneumonectomy or pleuropneumonectomy
 - lung resections with different correction methods of the haemithorax's volume;
- extrapleural thoracoplasty;
- extrapleural pneumolysis;
- thoracomyoplasty;
- pleurectomy and decortications of the lung;
- operations on the bronchi:
 - occlusion
 - resection
 - bronchoplasty
 - re-amputation of the stump;
- thoracocentesis and thoracostomy (drainage of the pleural space);
- artificial pneumothorax and pneumoperitoneum;
- operations on both lungs.

According to the literature analysed, the principal types of operation to treat TB today are lung resections of different sizes, using posterolateral thoracotomy under general anaesthesia with double-lumen endotracheal tube and artificial ventilation of the lung (11,16,18,30,36, 33). Mobilization of the lung (or the part of it to be resected) is approached in such a way as to avoid contamination of the pleural space. It should be mentioned, however, that anatomical resections are preferable.

It is also worth mentioning that in Kazakhstan, the Russian Federation and Ukraine, thoracoplasty is still widely used when lung resection is contraindicated (54,56). For instance, in the Novosibirsk Tuberculosis Research Institute, osteoplastic thoracoplasty (a variant of extrapleural thoracoplasty) has been used for the last 50 years for patients with complicated cavitory forms of TB for whom lung resection is contraindicated (56). This type of surgery allows the TB process to be stabilized so that lung resection can be performed later with a lower risk of postoperative complications. Thoracoplasty is also used in other countries to reduce the space in the chest cavity resulting from lung resection.

The operations for TB and M/XDR-TB patients listed above need to be managed in well-equipped and well-staffed clinics (that is, with experienced surgeons, anaesthesiologists and other specialists) with modern preoperative examinations, operating theatres and efficient postoperative care units, because of the associated high perioperative morbidity and mortality (5,11,26,33). Appropriate infection control measures should also be in place (57). In addition, it is of the utmost importance to remember that TB is an infectious disease and, therefore, the basic principles for TB control listed below should be followed (5,26):

- priority should be given to prevention (that is, full implementation of the Stop TB Strategy);
- a specialized unit should be used;
- reliable DST should be carried out for first- and second-line drugs, or a WHO-endorsed rapid molecular diagnostic test should be carried out;
- a reliable anti-TB drugs supply should be available;
- staff should be involved long-term and financial resources should be available.

The conditions listed above do not exist everywhere. A study from the Russian Federation published in 2012 revealed that surgery does not substantially cure TB, including new cases. The material and technical capacities of TB care facilities (such as equipment and staff skills) do not allow indications for surgery to be adequately determined. Furthermore, computed tomography (CT) scanning technology is only available in 15% of the institutions that have surgical units, and only 12% of operations on respiratory organs are carried out using such high technologies (53). The authors of the study concluded that substantial changes in the surgical treatment of TB are needed. Each federal district in the Russian Federation should set up two or three thoracic surgery departments and ensure that they have the necessary equipment and appropriately skilled staff.

Contraindications for elective surgical treatment of pulmonary TB and M/XDR-TB

In the majority of cases, contraindications for the surgical treatment of TB patients depend on how extensive the process is to be, assessment of the patients' cardiopulmonary function and their general state of health (3–5,19,33).

The following contraindications can be considered for lung resection:

- extensive cavitory lesion of the both lungs;
- impaired pulmonary function test; that is forced expiratory volume in one second less than 1.5 L in cases of lobectomy and less than 2.0 L where pneumonectomy is planned;

- pulmonary-heart failure III–IV (functional classification of the New York Heart Association);
- body mass index up to 40–50% of the normal range;
- severe co-morbidity (decompensation in diabetes, exacerbation of stomach and duodenum ulcers, hepatic or renal impairment);
- active bronchial TB.

It should be emphasized, however, that a multidisciplinary approach should be taken when a patient is being considered for surgery and the decision must be made together by physicians, surgeons, anaesthesiologists and other specialists.

Preoperative management

Present-day pulmonary resection combined with anti-TB chemotherapy for MDR-TB achieves high treatment success rates (up to 88–92% of the cases) (3,11). The mortality rate after lobectomy is about 2–3% and after pneumonectomy about 7–8% (5). It is clear that the success of surgery depends on good cooperation between chest physicians and thoracic surgeons, as well as surgical experience, ensuring that patients complete the required pre- and postoperative drug regimens and that preoperative and postoperative precautions are observed, and following up patients carefully.

Although surgery has been considered by some as a valid treatment method for patients with TB and M/XDR-TB, clinicians should carefully select the patients for surgery, taking into consideration possible poor prognostic factors, such as low body mass index, primary resistance to anti-TB drugs, resistance to fluoroquinolones and/or second line anti-TB injectables, and extensive and/or bilateral TB disease. The success of surgery depends very much on the comprehensive preoperative management of patients.

Patient-centred approach

Surgery is a very serious step for patients with TB, in particular for those with M/XDR-TB, given the history of their long and difficult-to-treat disease. For many of these patients, their disease will be too extensive and characterized by lung destruction and/or lung function that is too poor, making them unsuitable for surgery. In addition, each operation is rather dangerous and carries certain risks. It is, therefore, crucial to discuss individually with each patient and his/her family all details about the planned surgery and to perform all necessary preoperative examinations and treatments. The following steps are crucial.

- A comprehensive and open discussion should be carried out with patients and their relatives about the nature of their TB and the necessity of surgical intervention, as well as the risks and benefits of surgery, and the short- and long-term prognosis with and without surgical intervention. Possible complications in terms of anaesthesia and the operation must be discussed with all patients and their relatives. Consent for surgery must be obtained for all patients who are to undergo surgery.
- The following preoperative investigations need to be carried out: full blood analysis, biochemistry tests (liver and kidney, blood sugar, electrolytes and coagulation), HIV testing, sputum-smear microscopy, sputum-culture testing and DST, standard chest X-ray

and CT scan, and fibre-optic bronchoscopy (to rule out endobronchial TB, contralateral disease and malignancy).

- The patient's cardiorespiratory reserve must be carefully evaluated based on pulmonary function testing: body plethysmography (to evaluate vital capacity, forced expiratory volume in one second and diffusion of the lung(s)), electrocardiogram and echocardiogram (to rule out heart failure and pulmonary hypertension), perfusion lung scintigraphy (in patients with marginal spirometric results and diffusion of the lung(s)), arterial blood gas analysis and routine cardiological consultation.
- Nutritional assessment (body mass index) should be carried out to ensure the patient can tolerate and recover from surgery.
- Airways should be sanitized: respiratory exercises, postural drainage and routine aerosol inhalation should be carried out, or nebulized bronchodilators and antibiotics used.
- Smoking cessation must be encouraged.

Adequate anti-TB chemotherapy before and after surgery is essential in the management of TB (especially M/XDR-TB) patients. All TB cases referred for surgery (except in emergencies) should, therefore, have documented DST results (26).

The individual preoperative assessment of each patient is crucial and consists of the following criteria:

- which anti-TB chemotherapy regimen(s) a patient has previously received;
- whether the patient took all the drugs in each regimen prescribed and for how long;
- measurement of the bacteriological, clinical and radiological progress or deterioration during and since the administration of each regimen;
- evaluation of the current treatment strategy, including the indications for surgery.

Anti-TB chemotherapy before surgery should be at least four months (and between four and six months) in duration. Individual drug regimens (including at least five drugs for M/XDR-TB patients) should be administered in proper doses. In order to avoid serious and potentially fatal complications of TB surgery, it is recommended to perform the operation when the *M. tuberculosis* population is likely to be at its lowest level.

Postoperative management

The short- and long-term outcomes of surgery largely depend on the meticulous postoperative management of TB patients, beginning in the intensive care (high-dependency) unit immediately after the operation (11,15–16,18,30,33,36,38,41,43–44). This includes:

- using proper analgesia, including opioids;
- carrying out physiotherapy and respiratory exercises, including incentive spirometry;
- performing daily chest X-rays for the first three days;
- carrying out diagnostic and/or curative bronchoscopies if needed;
- removal of chest drains when their output has stopped;

- after the lung resections (in particular, after lobectomy and pneumonectomy), watching carefully for the early and late development of postoperative complications, such as air leaks, bronchopleural fistulas, residual pleural space and pleural empyema, and undertaking treatment procedures as necessary (including surgical interventions in the case of clear indications);
- transferring patients from the intensive care unit to the thoracic surgical ward once they are haemodynamically stable.

Postoperative management, including decisions relating to types of analgesia and timing of the removal of chest drains, does, of course, depend very much on the practices of the clinic concerned.

Anti-TB chemotherapy after surgery

Patients in all relevant studies recommenced their preoperative anti-TB chemotherapy regimen as soon as they resumed oral intake after surgery (4–6,11,15,18–24,32–38,41,43–52,58), with the possible adjustment of chemotherapy after analysis of the bacteriological results of the surgical material (resected lung tissue) (13,39). Postoperative chemotherapy is as indispensable as preoperative chemotherapy because after resection of the main lung lesion, scattered nodular lesions and tiny cavities may be left behind (42). It is, therefore, vital to ensure that all patients (in particular those with M/XDR-TB) remain on multidrug anti-TB regimens for a sufficiently long period to kill the bacilli present at the remaining lesions.

Based on the analysis of the literature cited above, the following durations of anti-TB chemotherapy are recommended, depending on whether patients are culture-positive or culture-negative at the time of surgery and the type of TB involved:

- culture-positive patients at the time of surgery:
 - with susceptible TB, four to six months after culture conversion
 - with MDR-TB, at least 18 months after culture conversion
 - with XDR-TB, at least 24 months after culture conversion;
- culture-negative patients at the time of surgery:
 - with susceptible TB, at least four months after surgery
 - with M/XDR-TB, six to eight months after surgery (depending on postoperative recovery).

It should be emphasized, however, that duration of postoperative chemotherapy also depends on the individual clinical condition of each patient (for example, whether the patient also has diabetes, the acute progression of the TB prior to surgery or the extent of the surgery carried out).

Conclusions

Since the studies evaluated in this paper were all observational studies and none were randomized controlled trials, it is not possible to make clear evidence-based recommendations regarding the role of surgery in the treatment of pulmonary TB and M/XDR-TB. Informed by careful review of the current literature, it is, however, the opinion of various experts involved in this review that:

- surgery is an option in the treatment of TB patients with drug-susceptible *M. tuberculosis* and M/XDR-TB in localized cavitory forms with continuous *M. tuberculosis* excretion, confirmed by bacteriological examination and DST, after four to six months of supervised anti-TB chemotherapy;
- pulmonary resection combined with appropriate pre- and postoperative anti-TB chemotherapy for M/XDR-TB enables treatment success rates to be achieved even in difficult clinical circumstances (in up to 88–92% of cases) (59);
- lung resection can and should be considered when the following criteria have been met:
 - adequate anti-TB treatment has failed to cure the patient;
 - the disease is sufficiently localized to allow anatomical lung resection;
 - the patient has sufficient pulmonary reserve and acceptable surgical risk with which to tolerate the resection;
- in cases in which contraindications exist for lung resection because of extensive lung lesions, collapsosurgical methods can be used (60);
- the success of surgery depends on: the strict following of infection control guidelines throughout all stages of the treatment (57); good cooperation between chest physicians, thoracic surgeons, anaesthesiologists and other staff; surgical experience; completion by patients of the required pre- and postoperative drug regimens; observing of pre- and postoperative precautions; and careful patient follow-up;
- the availability of specialized centres that are able to provide the required level of surgery and care – before and after surgery – is crucial.

The limitations of the current literature lead to the conclusion that additional research is necessary in order to make evidence-based recommendations and guidelines regarding the role of surgery in the treatment of pulmonary TB and M/XDR-TB (Table 1).

Table 1. Limitations in the available studies and recommendations for further research on surgical aspects of TB treatment

Limitations in the available studies	Recommendations for further research
The role of surgery is still not clearly defined and remains sometimes controversial.	Carry out a meta-analysis of all new publications on TB surgery, including those in Russian, after the publication of this document.
Not enough evidence exists on the indications for surgery in TB patients, including M/XDR-TB, with negative culture(s) after proper treatment in patients with tuberculoma and abacillary cavities.	To determine the evidence-based indications for surgery, compare the risk of relapse in TB patients (including those with M/XDR-TB) with tuberculoma and abacillary cavities treated by anti-TB chemotherapy alone and in combination with surgery.
The optimal duration of pre- and postoperative anti-TB chemotherapy and timing of surgery are not clearly defined.	Define the optimal duration of pre- and postoperative anti-TB chemotherapy.
The role of adjustment of anti-TB treatment based on bacteriological examination (including DST) of material recovered during surgery has not been evaluated.	Define the influence of an adjusted anti-TB treatment course (based on bacteriological examination, including DST, of the surgical material) on the outcomes of postoperative treatment.

Indications for surgery in TB and M/XDR-TB patients and selection criteria for different operations are not standardized and much depends on the pulmonologist and surgeon team, as well as on local experience and expertise.

None of the studies analysed compare the treatment outcomes of M/XDR-TB patients being prescribed drug treatment alone versus drug treatment plus resection surgery. In addition, none of the studies compare the characteristics of similar groups of patients undergoing surgery versus those not undergoing surgery.

Several authors have published results of cohort studies on cumulative long-term (two to five years) survival and relapse rate of patients with MDR-TB who underwent surgery (2, 11, 16–17, 30, 35, 37, 43, 48, 61–62). No recent randomized controlled trials have been documented on the short-term and, in particular, long-term efficacy of surgery for the treatment of TB.

No data are available on the outcomes of surgery in patients with TB/HIV co-infection.

No single terminology source (glossary) exists relating to TB surgery.

Define the evidence basis for the clarification of the indications for surgery in pulmonary TB and M/XDR-TB patients, as well as selection criteria for various operations.

Provide the relevant comparison of treatment outcomes for M/XDR-TB patients being prescribed drug treatment alone versus drug treatment plus resection surgery. The mandatory indicators for the successful treatment should be:

- culture conversion two, three or six months after decision (surgery vs no surgery);
- survival after one year;
- relapse within three years;
- dynamic of the disease(s) (analysed by radiology).

Elaborate protocols for prospective randomized control trials to determine the efficacy and safety of surgical treatment for TB and M/XDR-TB.

Develop a study protocol on the efficacy and safety of surgery in pulmonary TB patients with TB/HIV co-infection.

Develop a single terminology source (glossary) for TB surgery.

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