Introduction

After the introduction of efficient drug therapy in the 1950-1960s, the surgical treatment of tuberculosis (Tb) has been partly abandoned in many parts of the world. The priority of Russia in the field of Tb surgery was pointed out. An overview of literature on the surgical treatment and bronchoscopy in Tb is provided here. Despite the lack of reliable clinical trial data on efficacy and safety of adjunctive surgical therapy, some countries of the former Soviet Union continue to perform numerous lung resections. Tuberculoma has been one of the most frequent indications for lung surgery in Tb patients, which is generally at variance with the international practice. Besides, the use of bronchoscopy in Tb is briefly overviewed. In conclusion, some papers containing questionable recommendations have remained without due commentaries, so that a persistence of suboptimal practices or reversion to them is not excluded.

Materials and Methods

This article is a commentary based on the mini-review predominantly of Russian-language professional literature that is insufficiently known and partly unavailable outside the former Soviet Union (SU). Where necessary, comparisons with the foreign literature are made. The search of international literature was performed using PubMed. Russian-language professional publications were searched in the Internet and the electronic database eLibrary.Ru. Apart from the analysis of literature, this commentary is based on the observations by the author, who entered the I.M. Sechenov Medical University (named Institute at that time) in 1973, later practiced at the same and other academic and clinical institutions in Moscow.

Results

From 1973 through 1987, 285,000 patients with pulmonary Tb were operated on in the former Soviet Union (SU), in 1987 – 26,000, while 85% of the operations were lung resections [6]. In the period 1986-1988, 17,000-18,000 operations for pulmonary Tb were performed in Russia yearly only in specialized tuberculosis hospitals [3]. In 2003, 10,479 surgeries were performed in Russia for respiratory Tb, which was deemed “extremely insufficient” [7]. In 2006, 12,286 operations were carried out for pulmonary Tb including 9300 (75.7%) lobectomies and other resections as well as 399 (3.2%) pneumonectomies [4]. According to another report, the forms of Tb most frequently treated by resections and pneumonectomies were cavitary Tb (52.2%) and tuberculoma (43.9%) [8]. The above-named surgeries were performed and recommended also for patients with inactive post-tuberculosis fibrosis including cases with sparse symptoms [9]. At the same time, surgeries were performed in the active phase of Tb. In some provinces (Kemerovo, Chelyabinsk, Mordovia), 25-40% of patients with destructive Tb were operated on [10]. At the time of initial Tb diagnosis, an operation was deemed reasonable in 15-20% of patients [3]. According to another paper by the same authors, indications for surgery were found in 20-30% of patients at the initial diagnosis and/or among cases of active Tb [11]. In Yekaterinburg and the surrounding province (2006-2008), indications for surgery were determined in 1784 from 4402 (40.5%) patients with pulmonary Tb while 1079 (24.5%) were operated on. Among reasons of the comparatively “low” surgery rate were the patients’ non-compliance and unavailability [12]. In the international literature, corresponding figures are generally lower e.g. <5% of pulmonary Tb patients were supposed to require surgery [13]. The same percentage is given in the reviews [14,15]. The topic of Tb surgery may become more relevant due to the multidrug resistance. According to a current estimate from Russia, the need for surgery has increased from 5% to 15% over the last twenty years [16]. However, the recent systematic review and metaanalysis concluded that, compared with chemotherapy alone, the survival benefit of pulmonary resection combined with chemotherapy is not significant, although the quality of data was deemed “relatively poor” [17]. According to another metaanalysis, partial lung resection, but not pneumonectomy, was associated with improved treatment success in multidrug-resistant Tb. It was not excluded, however, that “healthier” patients were preferentially chosen for surgery, leading to a bias. The confounding by indication, as patients most likely to benefit are selected for the treatment, has been a limitation in many countries.
Indications

Irreversible Tb progression despite adequate anti-Tb chemotherapy;

References apart from [2]
[18,21-24]

Profuse hemorrhage;

Tuberculoma as an indication for pulmonary resection

asymptomatic patients with an unchanging solid focus do not require
treatment. Tuberculoma as an indication for pulmonary resection
do not generally justify thoracic surgery and that

There has been an opinion since the 1950s that potential instability
which is generally at variance with the international practice [18,30].

routinely operated on also without preceding anti-Tb therapy [27-29],
an absolute indication for surgery [26]. Tuberculomas >1 cm were

Associates [25,26]. The same experts designated fibrocavitary Tb as

mass index up to 40-50% of the normal range; active bronchial Tb;

extension, preservation of the cardiopulmonary function and the

general state of heath [19,21,23]. The following contraindications for
elective surgery of pulmonary Tb (including multidrug-resistant Tb)
are listed in the WHO publication [2]: Extensive cavitary lesions of
both lungs; forced expiratory volume in 1 sec <1.5 L for lobectomy
and < 2.0 L for pneumonectomy; pulmonary-heart failure III-IV
(functional classification of the New York Heart Association); body
mass index up to 40-50% of the normal range; active bronchial Tb;
severe co-morbidity [2]. Tuberculoma (>2 cm, also in children) has
been generally regarded as an indication for surgery by Giller and
associates [25,26]. The same experts designated fibrocavitary Tb as
an absolute indication for surgery [26]. Tuberculomas >1 cm were
routinely operated on also without preceding anti-Tb therapy [27-29],
which is generally at variance with the international practice [18,30].
There has been an opinion since the 1950s that potential instability
of tuberculoma does not generally justify thoracic surgery and that
asymptomatic patients with an unchanging solid focus do not require
treatment. Tuberculoma as an indication for pulmonary resection
was seen differently from other forms of Tb where surgical risks could
in some cases be justified by a poorer prognosis [31]. Nonetheless,
tuberculoma was the most frequent indication for lung surgery in
Tb patients at the Moscow I.M. Sechenov Medical Academy (44.2%)
[4], while at other institutions this percentage reached 50-80% [30].
In particular, tuberculoma has been the most frequent indication for
surgery among adolescent Tb patients [25]. Children were routinely
operated for tuberculomas, non-specific inflammatory, fibrotic
lesions and bronchiectasis [32]; more references are in the preceding
review [33]. Bilateral resections were performed in various Tb forms
including solitary tuberculomas on both sides [34-36]. A study from
the above-mentioned Institute for Phthisiopulmonology reported 771
lung surgeries, including 168 pneumonectomies, 181 lobectomies and
bilobectomies, 180 smaller resections, performed in 700 Tb patients
with drug resistance, up to 4 operations per patient. Postoperative
complications were observed in 100 cases (12.9%), fatal cases - 12
(1.5%) [37]. Another example from the same institution: among 60
operated Tb patients (16 pneumonectomies, 24 lobectomies and
smaller resections) the complication rate was 37%, mortality – 5%;
18.3% were discharged from the hospital with persisting complications
[38].

Resections were performed for tuberculoma, infiltrative and
cavitary Tb without preceding medical treatment or within one
month after the diagnosis i.e. when the drug therapy could have
been efficient [28,39]. In diabetics, it was recommended to operate
tuberculoma after 2-5 months of medical therapy [40]. The authors
operated asymptomatic patients and recorded the 15.73% rate of
postoperative complications [41]. Apparently, complication rates
have been sometimes underestimated due to limited follow-ups.
Lung operations for Tb were performed and recommended also for
aged patients with comorbidities [42-44]. Sokolov found indications
for surgery in 210 from 289 (72.6%) aged Tb patients (50-73 years
old) and operated on 180 (62.2%) of them, 144 operations being lung
resections. Among the latter 144 patients, 93 (66.4%) had cavitary
disease and 43 (30.8%) – tuberculoma. Reactivation of Tb early
after surgery was noted in 8.6% of cases, fistula - 27.2 %, atelectasis
or incomplete lung re-expansion - 20%, pneumonia - 5.7%, pleural

Studies [1]. Despite the lack of reliable clinical trial data on efficacy
and safety of adjunctive surgical treatment, some countries of the
former SU continued to perform a high number of lung resections
[18]. A summary of indications from the World Health Organization
(WHO) publication compiled under participation of Russian experts
Drs. Dmitriy Giller (cited below), Boris Kazenniy and Denis Krasnov
is presented here Tables 1,2 [2].

Apparently, the WHO document was influenced by the Russian
experts, which is recognizable especially from Table 2 [2]. There
is an opinion that indications for surgery in Tb are rarely absolute
[14]. As for contraindications, they largely depend on the process
extension, preservation of the cardiopulmonary function and the
general state of heath [19,21,23]. The following contraindications for
elective surgery of pulmonary Tb (including multidrug-resistant Tb)
are listed in the WHO publication [2]: Extensive cavitary lesions of
both lungs; forced expiratory volume in 1 sec <1.5 L for lobectomy
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A/H1N1 influenza diagnosing endobronchial TB [70,71]. Bs does not usually improve in all Tb patients [69]. There is an opinion that in children Bs is young (19.5 ± 0.1 years old) as well as in other patients diagnosed with some military doctors performed many Bs e.g. 1478 procedures in 977 older than 65 years, at the Tb hospital No. 3 in Moscow (705-1225 22,469 Bs were performed in 5195 patients, including 1766 (34%) Bs as a second step of screening for Tb in children [60]. Therapeutic a screening tool for Tb in patients with general malaise, both with were recommended by the Ministry of Health [58]. Bs was used as (cavitary) Tb, repeated therapeutic Bs (1-2 weekly during 2-4 months) diagnostic methods for focal non-destructive Tb [57]. In destructive indication for Bs in children [56]. Bs was designated as one of the main M. tuberculosis was suspected (references are in the preceding article [53]); it was been applied in all forms of Tb in children and adults also when Tb infection occurred after fiberoptic instruments were used [81-83]. Reportedly, Mycobacteria were the greatest obstacle to the epidemiological considerations i.e. potential indication, and lobectomy – the most frequent modality in elderly Tb patients, whereas epidemiological considerations i.e. potential contagiousness was listed among arguments in favor of the surgical treatment [43]. Statements of this kind can be found also in recent papers e.g.: “Surgery in patients with tuberculomas is recommended to reduce their infectiousness” [16]. In the author’s opinion, it is unethical to subject a patient to a thoracic surgery just because he or she is potentially contagious. In any case, the patient must be comprehensively informed about potential benefits and risks so that he or she could make an independent decision according to the principle of informed consent.

Bilateral resections were performed in various Tb forms including solitary tuberculomas on both sides or tuberculosis and cancer [34-36,45-47]. Indications for a second lung surgery were found in 20-37% of previously operated Tb patients [48]. Postoperative relapses of Tb were regarded as indications for repeated surgeries up to “concluding pneumonectomy” and resections of the remaining lung after pneumonectomy [35,46]. For example, repeated resections on both sides with a subsequent pneumonectomy were performed in one patient along with 52 bronchoscopies [49]. Lung resection or pneumonectomy was deemed permissible even in cases of severe respiratory insufficiency [45,46,50,51]. Bilateral resections or pneumonectomy plus contralateral “economic” (sparing) resection were regarded to be indicated for patients with a Tb lesion on one side and non-specific inflammatory and/or fibrotic lesion on the other side [52].

Several words should be said about bronchoscopy (Bs) that has been applied in all forms of Tb in children and adults also when Tb was suspected (references are in the preceding article [53]); it was recommended for young patients with “hyperergic” (high degree of hypersensitivity) tuberculin tests or within the diagnostic algorithm for suspected Tb in smear-negative cases [54,55]. After a detection of M. tuberculosis, an urgent hospitalization and examination including Bs is currently recommended [55]. Primary Tb was regarded as an indication for Bs in children [56]. Bs was designated as one of the main diagnostic methods for focal non-destructive Tb [57]. In destructive (cavity) Tb, repeated therapeutic Bs (1-2 weekly during 2-4 months) were recommended by the Ministry of Health [58]. Bs was used as a screening tool for Tb in patients with general malaise, both with positive and negative tuberculin tests [59]. Some researchers used Bs as a second step of screening for Tb in children [60]. Therapeutic Bs and bronchoscopic monitoring has been applied in pulmonary Tb also with non-specific bronchial lesions [61-63]. For example, 22,469 Bs were performed in 5195 patients, including 1766 (34%) older than 65 years, at the Tb hospital No. 3 in Moscow (705-1225 beds at different times) from 1994 through 2013 [64]. In particular, some military doctors performed many Bs e.g. 1478 procedures in 977 young (19.5 ± 0.1 years old) as well as in other patients diagnosed with community-acquired pneumonia [65-68].

Outside the former SU, Bs has not been routinely performed in all Tb patients [69]. There is an opinion that in children Bs is usually unnecessary, although the procedure may be useful in diagnosing endobronchial Tb [70,71]. Bs does not usually improve the microbiological diagnosis being not more sensitive for the culture than properly obtained gastric aspirates [70,72-75]. Endoscopic biopsy is a reliable sampling method for endobronchial Tb as well as for hilar and mediastinal lymph nodes. Bs is generally regarded to be indicated for patients with persistent cough, haemoptysis and signs of bronchiostenosis such as wheezing and stridor [69]. Bs is performed before surgery in Tb patients to rule out endobronchial disease at the proposed site of the bronchial stump [14]. As endobronchial Tb may mimic neoplasms, Bs plays an important role to rule out cancer. In this connection, Bs is complementary to computed tomography (CT), which evaluates the bronchial involvement and luminal patency. In particular, the multiple detector CT with post-processing tools such as virtual bronchoscopy is an efficient diagnostic method for central airway lesions [76]. Reportedly, CT depicted the cause of bleeding more frequently than Bs (77% vs. 8%, p < 0.001), whereas the two methods were comparable for identifying the site of bleeding [77]. Some data suggested that CT can replace Bs e.g. as the first-line procedure for the screening patients with massive hemoptysis. Replacing Bs with induced sputum testing removes the risks from bronchoscopy including that of nosocomial infection [78]. Of note, endoscopy is among the risk factors of nosocomial infections e.g. viral hepatitis [79], especially in conditions of suboptimal procedural quality assurance. Not surprisingly, the incidence of viral hepatitis (predominantly B) was reported to be 5 times higher in Tb patients than in the general population of Russia [80]. Outbreaks of infections including Tb occurred after fiberoptic instruments were used [81-83]. Reportedly, Mycobacteria were the greatest obstacle to the infection control in Bs units [83]. It has been suggested that Bs may spread infection within the lung, from one patient to another, and - by triggering coughing - cause airborne infection of other people [84]. The use of Bs with questionable indications has been reviewed previously [53].

The surfactant (Sf) therapy of pulmonary diseases (Tb, acute respiratory distress syndrome, pneumonia etc.), excluding neonatal respiratory distress syndrome (RDS) with primary surfactant deficiency, and bronchoscopy as the delivery method have been discussed previously [85-88]. Sf-BL from bovine lungs has been developed and permitted for clinical use in Russia. The manufacturing method is described in the patent [89] (partly translated in [85,86]), where it is noted that Sf-BL contains -2% of protein. Endobronchial instillations of xenogeneic proteins may cause immune reactions and transmission of infection [90]. In older patients, a more pronounced immune response can be expected than in premature infants with RDS. Endobronchial instillations of porcine Sf were accompanied by an augmentation of eosinophilic inflammation in patients with bronchial asthma [91]. Rosenberg et al. used St-BL in asthma, bronchitis, pneumonia, chronic obstructive pulmonary diseases and Tb (more references are in the review and patent [89,92]), as well as in COVID-19 [93], where immune and inflammatory reactions might contribute to the “cytokine storm” and collagen synthesis. Bs was used as the delivery method of Sf [92,94-101] with a biopsy of lung tissue in [95]; other studies used inhalations. Apart from inhalations, Bs was used within the framework of Sf research in Tb patients [101,102]. Sf-BL was recommended by a Letter of the Health Ministry for the treatment of viral (A/H1N1 influenza) pneumonia [103]. This Letter refers to the manufacturer’s instruction No. 003383/01-230710, where
it is stated that the optimal method of the Sf delivery is Bs with an instillation into individual segmental bronchi [104]. No comparable recommendations have been found in the literature. Until recently, Oleg Rosenberg had been director of the manufacturing firm Biosurf (https://biosurf.ru/). No conflicts of interest have been declared in his publications. Rosenberg applied misquoting in his papers on Sf, specified in detail previously [87,88]. Some studies from Russia have reported that inhalations of Sf improve effectiveness of the anti-Tb therapy, significantly accelerating healing, dissolution of specific infiltrations and closing of caverns, while M. tuberculosis disappeared from sputum at an early date [89,102,105-107]. No similar reports have been found in the international literature. Finally, intravenous injections of stem cells to Tb patients should be mentioned together with the warning against unjustified use of Bs for such purposes as it has previously been done concerning intracoronary injections of cells obtained from the abortion material [108-112].

The treatment of patients suffering both of Tb and alcoholism needs a special comment. According to official instructions, indications for surgery were broader in alcoholics than in other Tb patients [113]. In case of alcoholism, the surgical treatment was recommended earlier i.e. after a shorter period of medical therapy [29]. Among other things, vocal cord injuries were observed after repeated Bs sometimes performed in conditions of suboptimal procedural quality assurance. It was noticed that vigorous apomorphine-induced vomiting as emetic or aversive therapy of alcoholism provoked hemoptysis [114]. The following treatments were applied to alcoholics: prolonged intravenous infusions, sorbent hemoperfusion, endobronchial and endolymphatic drug delivery, pyrotherapy with sulfazine (oil solution of sulphur for intramuscular injections), endoscopic and surgical biopsies, sometimes without clear indications also for research [115-118]. Infusions for the purpose of detoxification were generally recommended for patients with alcohol dependence and alcoholism including moderately severe withdrawal syndrome [119-122]. The prescribed duration of detoxifying treatment was 10-12 days [119]. This included intravenous drip infusions of solutions: sodium and calcium chloride, sodium thiosulfate, magnesium sulfate, glucose, dextran etc. (7-10 infusions daily, alternating with intramuscular injections). The latter is at variance with the international literature. Alcohol and its metabolites are eliminated spontaneously while rehydration can be normally achieved per os. Intravenous glucose and magnesium are generally not recommended for patients with alcohol withdrawal syndrome [123,124]. Excessive infusions of magnesium-containing solutions are associated with adverse effects also in treated alcoholics [125]. Moreover, the detoxifying treatment of alcoholics included intramuscular injections of 10-15 ml of 25% magnesium sulfate solution together with 10 ml 40% glucose, 10 ml of 10% calcium chloride and 10 ml 30% sodium thiosulfate solutions, subcutaneous infusions of up to one liter of isotonic saline etc. [119,126,127]. In conditions of suboptimal procedural quality assurance, repeated infusions, endovascular and endoscopic manipulations can lead to the transmission of viral hepatitis, which was known to occur to treated alcoholic patients.

Discussion

The outpatient treatment of Tb patients, usual in other countries, was supposed to be hardly applicable in Russia [128]. According to the governmental Ordinance No. 378 of 16 June 2006, patients with infectious Tb are not allowed to live in one apartment with other people. As per the Federal Law No. 77 “Prevention of the spread of Tb in Russia” of 18 June 2001 (amended 2013), “Patients with contagious forms of Tb, repeatedly violating the sanitary and anti-epidemic regime, as well as those deliberately evading examinations for Tb or [emphasis added] the treatment of Tb, are hospitalized into phthisiological institutions for obligatory examination and treatment by court decisions.” It is stipulated by the same Law that the principle of informed consent is not applicable in this connection (Articles 7,9,10). A survey conducted across Russian phthisiological institutions found >6000 relevant trials in the period 2004-2008 whereas 3163 patients were hospitalized after court decisions [129]. For example, in the study from Kemerovo province, 463 trials were reported resulting in 421 decisions of compulsory hospitalization of Tb patients [130]. There are administrative and legal mechanisms e.g. hospitalization of Tb patients with the help of police and criminal proseuction in case of non-compliance. Among others, the latter pertains to non-contagious Tb patients released from prison [131].

The compulsory treatment was endorsed by regulations [115]; more details and references are in the review [118]. Reportedly, in 1994 about 60% patients of one of the “phtisio-narcological” institutions for compulsory treatment escaped while a half of them were returned by the police (militia) [132]. The duration of compulsory treatment in such institutions was around one year or longer [115]. In 1974, chronic alcoholism was officially declared to be a ground for the compulsory treatment; the regulation was hardened in 1985, making the compulsory hospitalization and treatment of chronic alcoholics independent of anti-social behavior. This practice has been designated in 1990 as contradictory to the human rights [133]. The system of compulsory treatment for Tb was partly dismantled during the 1990s; but some experts recommended its restoration and further development [129,130].

Conclusion

The surgical treatment of Tb is indicated for life-threatening conditions such as massive hemoptysis from cavitory disease or bronchiectasis. Adjuvant surgical therapy may be recommended for selected patients especially with multidrug resistant Tb; however, indications are rarely absolute [1,14,134]. The role of surgery remains controversial. Clinical recommendations are not the goal of this commentary. The message is that patients should not undergo surgeries and other invasive procedures to comply with instructions and doctrines fed by motives like personnel training, especially of military surgeons, endoscopists, etc., without sufficient evidence-based indications [33]. The approach should be individual based on the consensus expressed in the recent international literature. The principle of informed consent must be observed - patients comprehensively informed on potential benefits and risks to be able to make an independent decision.

The principle of informed consent has not been uniformly adhered to in the former SU, which was facilitated by the widespread paternalistic attitude to patients. Informed consent started only recently to be mentioned in papers reporting research using invasive methods e.g. bronchoscopic study of childhood asthma, where the consent of parents was regarded to be sufficient [135]. Note that the
principle of informed consent or assent is applicable also to adolescents and children [136,137]. Even today, patients are sometimes requested to sign in advance a form certifying their blanket consent to unnamed diagnostic and therapeutic procedures. The factors contributing to the persistence of suboptimal practices included the authoritative management style, disregard for the rules of scientific polemics, insufficient use of the foreign literature and absence of many internationally used handbooks even in central medical libraries [138,139]. Thanks to the Internet, the foreign literature is used increasingly, while the practice is adjusted to international standards. However, some papers containing questionable recommendations have remained without due commentaries, so that persistence of suboptimal practices or reversion to them is not excluded. Other invasive procedures applied with questionable indications have been reviewed previously [33,53,140,141].

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