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**COMPLETION PLEUROPNEUMONECTOMY IN COMPLEX TREATMENT OF PATIENTS WITH MDR/
XDR LUNG TUBERCULOSIS**

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Introduction

Completion pleuropneumonectomy (CPPE) is a surgical intervention which includes final removal of residual part of the previously resected lung and parietal pleura due to the progression of the MDR/XDR tuberculous process despite medicament treatment. Among the phthisiosurgical patients recurrent operations are technically complicated in cause of adhesions in the pleural cavity and disorders in the topography of structural elements of the root of the lung which are characterized by a high level of lethal cases. Cicatricial changes around the main bronchus and lung vessels as well as by root reactive lymphadenopathy complicate the separation of pulmonary vessels and bronchus [7]. Such operations in the majority of cases are followed with significant blood loss and cortical damages as result of pneumolysis [8]. If CPPE is performed several months or years later after previous surgical intervention as a result of progressing disease, recurrence or a new case of disease, such surgery is called "conventional". Very rare, some hours, days or even weeks later after the first operation it is necessary to perform CPPE in consequence of early postoperative complications and it is defined as "rescue" [12]. In the literature, this type of intervention is often described in relation of patients with lung cancer and fungal infection. Reports of systematization of the experience of performing CPPE with MDR/XDR tuberculosis are very few in the literature. In the article we present the experience of performing CPPE in patients with MDR/XDR lung tuberculosis who were treated in our clinic.

Materials and methods

Clinical records of 21 patients whom CPPE with MDR/XDR lung tuberculosis was performed in 2004–2014 were analyzed retrospectively. This amount was 0,79 % out of all patients with MDR/XDR lung tuberculosis who were operated within this period. All of them were operated at the thoracic surgery and invasive diagnostic methods department of State institution "National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky NAMS of Ukraine". Primary surgery in the vast majority were performed outside of our clinic. Only two patients (9,5 %) were operated primarily in our clinic. Conservative treatment was applied in the TB department of the institute. 20 patients (95,2 %) were performed "conventional" CPPE and one patient (4,8 %) — "rescue" CPPE. Age varied from 17 to 42 years (average 28,7 years). From the moment of the beginning of disease to the CPPE the patients were treated on average 54,7 months (from 14 to 108 months) and the average interval between the primary operation and "conventional" CPPE was 27,6 months (from 7 to 71 months). The only patient after "rescue" CPPE had the interval of 2 days. In the research group males were 10 (47,6%), females

— 11 (52,4%). CPPE more often performed on the right — 12 (57,1%) cases, left-sided — 9 (42,9%) circumstances. Tuberculosis of tracheobronchial tree was diagnosed in 6 (28,6 %) patients before the operation. In 12 (57,1%) cases in the preoperative period patients had mycobacterial excretion. Bilateral tuberculosis was diagnosed in 11 (52,4%) patients. The rate of comorbidity among operated patients was 7 (33,3%) cases: 2 (9,5%) patients had gastric ulcer, the same number of patients had toxic medicament hepatitis and hypotensive type of vegetative-vascular dysfunction, one patient (4,8%) had hepatitis C.

All of the patients had distinct signs of respiratory distress syndrome — level I — 3 (14,3%) patients, level II — 16 (76,2%) cases, level III — 2 (9,5%) patients.

Table 1 shows the clinical characteristics of the investigated patients.

The most frequent primary operative intervention were bilateral upper lobectomy — 9 (42,9%) cases and upper segmentectomies and S6 — 7 (33,3%) cases. Very important feature is a fact that in 16 (76,2%) cases have been performed atypical lung resection without separate handling of root elements of the resected part. In 2 (9,5%) cases after primary surgery there were residual pleural cavity with bronchial fistula. Before CPPE in patients were diagnosed the following forms of lung tuberculosis — 15 (71,4%) cases of fibrocavernous, 5 (23,8%) — cirrhotic, and one (4,8%) case of caseous pneumonia.

All patients in preoperative and postoperative periods were consulted by the phthisiatrician of the institute to optimize the dosage regimen of TB drugs. The course of preoperative chemotherapy lasted from 3 weeks to 10 months with the use of drugs I-II series, and broad-spectrum antibiotics, active against *Mycobacterium tuberculosis*. Clinical, laboratory and instrumental examination included general blood and urinalysis, blood chemistry, blood gases, testing for the AIDs virus, hepatitis C and B, spirometry, electro- and echocardiography, spiral computer tomography of the chest and videobronchoscopy. All patients underwent preoperative preparation aimed at achieving a possible stabilization of tuberculous process, compensation of physiological functions and systems.

Conditions of performing CPPE were following:

- absence of inflammatory changes of the mucous membrane of the main bronchus within the distance of two rings from the zone of planned intersection;
- absence of destructive changes in the opposite lung with of more than subsegment, confirmed by a chest tomography;
- sufficient functional reserves of the respiratory system (VC — more than 50% preoperatively);
- absence of somatic pathology in the decompensation phase;
- patient's adherence to the treatment.

General statistic methods were used to evaluate the surgical treatment. Survival was carried out by using Kaplan-Meyer's method. Some variables are presented as mean \pm standard deviation. Statistical processing was performed using the SPSS 17.0 software package.

Table 1

Clinical characteristics of the researched patients

| Patient | Age | Sex | Side of surgery | Primary surgery | Interval between operations, months | Form of tuberculosis |
|---------|-----|-----|-----------------|-----------------|-------------------------------------|----------------------|
| 1 | 30 | F | Left | S1S2S3 (A) | 71 | C |
| 2 | 25 | F | Right | UL(A) | 15 | F |
| 3 | 29 | M | Left | S1S2S6 (A) | 15 | C |
| 4 | 23 | F | Left | S1S2S3 (A) | 27 | CP |
| 5 | 29 | M | Right | S1S2S6 (A) | 36 | F |
| 6 | 31 | M | Left | UL(A) | 14 | F |
| 7 | 26 | F | Right | UL(A) | 18 | C |
| 8 | 42 | M | Left | S1S2S3 (A) | 14 | C |
| 9 | 27 | M | Left | UL | 38 | F |
| 10 | 34 | F | Left | S1S2S3 (A) | 25 | F |
| 11 | 17 | F | Right | UL | 18 | F |
| 12 | 25 | M | Left | LL | 17 | F |
| 13 | 36 | M | Right | LB(A) | 24 | F |
| 14 | 25 | F | Right | S2S6 (A) | 25 | F |
| 15 | 31 | M | Right | UL(A) | 26 | F |
| 16 | 30 | M | Right | UL+T | 48 | F |
| 17 | 23 | F | Right | UL (A) | 7 | C |
| 18 | 31 | F | Right | UL (A) | 60 | F |
| 19 | 29 | F | Right | UL | 2 days | F |
| 20 | 40 | M | Left | UL (A) | 30 | F |
| 21 | 19 | F | Right | LL (A) | 24 | F |

Remarks to the Table1: UL — upper lobectomy, LL — lower lobectomy, LB — lower bilobectomy, UL+T — upper bilobectomy with intrapleural thoracoplasty, S1-S6 — segmental resection, C — cirrhotic, F — fibrocavernous, CP — caseous pneumonia. In a primary surgery (A) indicates atypical resection.

Results and discussion

All CPPE's were performed according to the rules of the thoracic surgery but there were some technical features:

- surgical access was performed lying on a healthy side with by posterolateral thoracotomy with removing of fragment of V rib that allows to increase area of the operative field and safer manipulate in the pleural cavity;
- central vein catheterization was obligate in all cases;
- additional strengthening of bronchial stump by one of the methods worked out in our clinic was performed for all patients. In our opinion, important moment is a gentle

manipulation on the main bronchus on the perimeter with maximum preservation of the surrounding tissue, this preserving the blood supply and innervation of the bronchial stump. More often we decreased the diameter of the bronchial stump by Litkin in clinical modification. With two stitches on the distal part of the main bronchus we did invagination of membranous part into the bronchial lumen. It gave the possibility to reach the equal thickness of a stump, distribute intrabronchial pressure evenly and compare the cartilaginous part of the bronchus one to one, which contributed better supply of bronchial stump. After that the main bronchus was stitched parallel to the bronchial rings with suturing device. Bronchus was intersected distal from the mechanic suture, stump was lubricated with 5% iodine to prevent infection in the pleural cavity. Then bronchial stump was sutured with additional knots by Sweet with absorbable suture. Further stump was powdered with antibiotic and covered with thrombin-collagen plate. After that we did a pleurisation of bronchus stump or fortification of it with flap of pericardial fat on vascular pedicle [1,2,3];

- intraoperative we performed sanitation of the pleural cavity with antiseptic solutions (decamethoxin, chlorhexidine and others). Considering that almost all patients had a lesion of cortical layer of the lung on a stage of pneumolysis, such measure was strictly required;

- operation ended with draining of pleural cavity in the bottom place (for the control of hemostasis in the early postoperative period) and in suprascapular part by microdrainage (for infusing into the pleural cavity solutions with antibiotics and evacuating of air out of it). Microdrainage we left in the pleural cavity for approximately 10-14 days, and later we made pleural puncture to control the consistency of the [3];

- bronchoscopy was performed to all patients during intubation and removing of endotracheal tube.

Postoperatively patients had medicament treatment according to the conventional principles of proven medicine. It should be admitted, great attention was given to the prevention of thromboembolic and hemorrhagic complications. For the prevention of the thrombosis in our clinic, we widely use low molecular weight heparins. To prevent bleeding into the pleural cavity and intraoperative disseminated intravascular coagulation (DIC) in the early postoperative period, we used proteolytic enzyme inhibitors (aprotinin) and fresh frozen plasma. It is worth noting that we support the tactic of using both low molecular weight heparins and proteolytic enzyme inhibitors, as their mechanisms of action are related to the different clotting factors, and therefore the effectiveness of their parallel application is obvious [7].

Bronchoscopy in the postoperative period used in order to aspirate the pathological content from the bronchial tree to prevent the onset of specific process in the remaining lung tissue.

Using all above measures allows to achieve the following results in the treatment of patients with MDR/XDR lung tuberculosis, whom CPPE was performed. Average intraoperative blood loss was $(388,8 \pm 286,2)$ ml and ranged from 150 ml to 1500 ml. Average duration of surgery — $(270 \pm$

52,6) minutes (from 160 to 360 min). Average hospital stay was (48,3 ± 34,6) days (from 14 to 181 days).

Detailed results of treatment are presented in Table 2.

Table 2

The results of CPPE among the patients with MDR/XDR lung tuberculosis

| Patient | Duration of operation, min | Blood loss, ml | Duration of hospital treatment, days | Late postoperative complications | Survival |
|---------|----------------------------|----------------|--------------------------------------|----------------------------------|----------|
| 1 | 270 | 230 | 36 | | 29 A |
| 2 | 360 | 350 | 42 | BPF | 17 D |
| 3 | 240 | 350 | 35 | | 29 A |
| 4 | 210 | 280 | 55 | | 30 A |
| 5 | 180 | 300 | 55 | E | 63 A |
| 6 | 270 | 370 | 71 | BPF | 24 D |
| 7 | 240 | 380 | 30 | | 126 A |
| 8 | 220 | 200 | 42 | | 85 A |
| 9 | 285 | 250 | 28 | | 75 A |
| 10 | 260 | 400 | 35 | | 119 A |
| 11 | 330 | 250 | 41 | | 117 A |
| 12 | 270 | 250 | 35 | | 118 A |
| 13 | 330 | 350 | 32 | | 50 A |
| 14 | 300 | 350 | 27 | | 103 A |
| 15 | 290 | 650 | 29 | | 42 A |
| 16 | 330 | 1500 | 32 | Exac. | 37 D |
| 17 | 250 | 200 | 79 | | 20 A |
| 18 | 235 | 315 | 181 | | 8 A |
| 19 | 160 | 150 | 41 | | 6 A |
| 20 | 320 | 690 | 74 | | 5 A |
| 21 | 320 | 350 | 14 | | 118 A |

Remarks to the Table 2: BPF — broncho-pleural fistula, E — empyema of pleural cavity without broncho-pleural fistula, Exac. — exacerbation in the only lung. In the column "Survival" number is displaying the duration of the postoperative period in months and outcome (A — alive, D — dead).

Intraoperative complications were diagnosed in 2(9,5%) patients. Injuring of internal thoracic artery during pneumolysis was revealed in one (4,8 %) patient, bleeding was stopped by clipping the artery. In one more case (4,8 %) three branches of the intercostal arteries in their place of origin from the aorta were damaged. Complication emerged because the bottom of residual pleural cavity was aortic wall with intercostal arteries. The complication was eliminated by ligation and clipping of the vessels.

Early postoperative complications were found in 6 (28,6%) patients. Bleeding occurred in the early postoperative period in 3 (14,3%) patients: in one case hemorrhage managed conservatively and had been stopped, in the second — rethoracotomy with completion hemostasis (source

of bleeding was not identified) have been performed. In one patient bleeding was as an element of DIC and it was eliminated therapeutically. In case of rethoracotomy, patient was operated on fibro-cavernous tuberculosis of the left operated lung (previously she had left-sided atypical upper lobectomy), complicated with the recurrent lung hemorrhage. Intrapleural hemorrhage in postoperative period occurred on day 4 and coincided with the onset of menses. In all cases the results of operation were positive. In one (4,8%) case there was diagnosed pulmonary embolism of small and middle branches of pulmonary artery which required prescribing anticoagulant therapy (low-molecular weight heparins in maximum dose) lasting 7 days with a gradual transition to a preventative dose of indirect anticoagulants. The overall result of the operation is positive. In one (4,8%) patient 5 days after left-sided completion pleuropulmoectomy chylothorax was diagnosed. Completely balanced parenteral nutrition and huge doses of proteolytic enzyme inhibitors was prescribed for 10 days to this patient. Suspension of lymph discharge into the pleural cavity observed after 4 days of treatment and clarification of exudate was observed on the day 20 after surgery. The overall result of the operation is positive. One (4,8%) patient 16 days after surgery on the right had signs of infection of postoperative pleural cavity. We took the decision to apply videothoroscopic sanitation of postpulmoectomy space. This complication was successfully eliminated.

Half of the patients for the second-fourth day after surgery had short-time (5–10 days) reversible relapse of specific process in residual lung which was eliminated by intensive medical therapy and bronchoscopic sanitations. Thus, at the time of hospital discharge effectiveness of completion pleuropulmoectomy was 100,0%.

Late postoperative complications were diagnosed in 4 (19,0%) patients — bronchial fistula with further development of empyema occurred in 2(9,5%) patients (4 and 6 months later accordingly). One (4,8%) case of empyema of the residual pleural cavity without bronchial fistula 1,5 years after CPPE (overall long-term results of surgery were negative).

In 1 (4,8%) patient since 19 months after surgery there was an exacerbation of tuberculosis in a single lung, which can be explained by the early refuse from anti-TB drugs. This complication pathogenically is not associated with surgery. The patient died 2 years after surgery.

Overall effectiveness of CPPE for patients with MDR/XDR lung tuberculosis within long-term period was 85,0% and ten-year survival was 81,2% (Figure 1).

It is necessary to note that in patients with lung tuberculosis CPPE was always performed at the background of one or the other comorbidity — all patients had signs of respiratory distress, degenerative changes in the myocardium, etc. [10]. More often than other patients, specific and non-specific inflammatory changes in mucosa of tracheo-bronchial tree have been diagnosed preoperative, sometimes with considerable deformation and atrophy. This state needs a long preparation using inhalation therapy and videobronchoscopy [8,10]. Retreat from these measures significantly increases the risk of broncho-pleural fistula and empyema of postpulmoectomy pleural cavity.

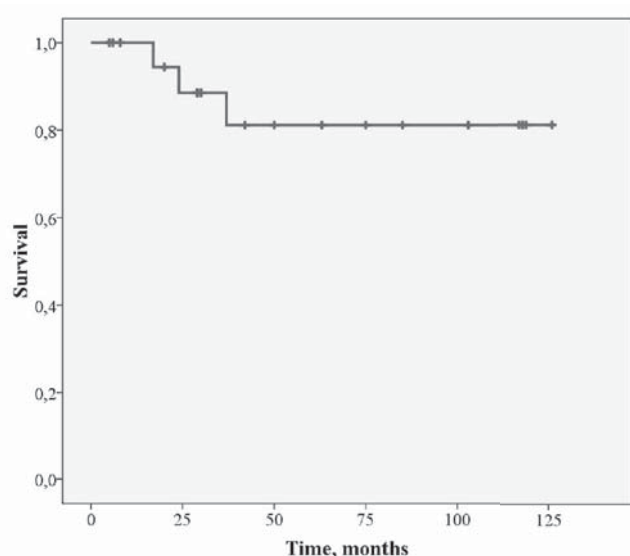


Figure 1. Visual presentation of 10-years survival (Kaplan-Meier's curve)

The method of primary surgery in some way can influence the complexity of CPPE [13]. These factors are:

- performing atypical resections which causes rough deformation and significant fibrosis in the lung root;
- unreliable hemostasis during lung resection leads to the formation of severe adhesion of the pleural cavity, which greatly complicates pneumolysis during CPPE.
- unreliable aerostasis after lung resection is cause of prolonged drainage of the pleural cavity, which also affects the development of adhesions;
- using of non-absorbable material for rib attaching causes the onset of polyspases and significant atrophy of the ribs which complicates reliable germetisation of thoracothomic incision while performing CPPE (thin and osteoporotic ribs are eliminated during thoracotomy);
- presence of empyema of residual pleural cavity with bronchial or pleuro-thoracic fistula or ethmoidal lung can greatly complicate pneumolysis and increase the risk of infection;
- presence of elements of previous corrective thoracoplasty in combination with resection of the lung.

Features which characterize the postoperative period in patients after CPPE for MDR/XDR lung tuberculosis are:

- high risk of intrapleural hemorrhage which is associated with frequent extrapleural pneumolysis and negative pressure in the pleural cavity;
- significant risk of exacerbation of a specific process in a single lung;
- definite risk of DIC and pulmonary embolism;
- necessity of prescribing a prolonged intensive TB and nonspecific antibiotic therapy, which has a toxic effect on the organs and systems of the body and requires a medical support in the early postoperative period;
- necessity of local (intrapleural) antibacterial therapy because of high possibility of infection in pleural cavity after injury of lung parenchyma at the phase of pneumolysis. This measure is connected with the fact that this cohort of patients, despite their young age, exhausted long course of the disease, burdened with toxic chemotherapy drugs intake, and therefore has a significantly reduced immune response and

very high risk of septic complications in the pleural cavity.

After analyzing the data of investigated patients, we have identified surgical risk factors that affect the progression of tuberculous process after the primary surgery:

- performing atypical resection (un mass) without separation of elements of the root of the resected lung. In consequence of this, there is a possibility of incomplete resection of the affected lung parenchyma with tuberculous process and significantly increased risk of broncho-pleural fistula with formation of residual pleural cavity;
- absence of the artificial pneumoperitoneum in the postoperative period leads to the hyperextension of the remain part of the lung;
- early cancelation or inadequate TB chemotherapy after primary surgery.

Concluding the mentioned above, CPPE in patients with MDR/XDR lung tuberculosis is very traumatic, technically complicated and pathogenically difficult surgery, which requires highly professional approach in the pre-, postoperative periods, and during operation. It is extremely important a continuity of care after surgery — adequate TB chemotherapy under the supervision of phthisiatrician.

In the literature, different data marked effectiveness, complications and postoperative mortality in the performance of CPPE. In the English-language sources often published experience in performing this surgery in cancer patients and in patients with fungal infection of the lung parenchyma. Reports on the treatment of patients by this method is very few. Kiral H. [8] in his research reports about 27 CPPE for 14 years. Only 5 (18,5%) of them had lung tuberculosis, 22 (81,5%) patients had oncologic, fungal and other lung diseases. Among the early postoperative complications, failure of bronchial stump was observed in 22,2 % cases. Level of hospital postoperative mortality was 7,4 %. Kiral H. notes that the risk of complications is significantly higher in patients with tuberculosis and technique of intervention is important for its prevention [8].

According to the US surgeons, 26 CPPE for lung tuberculosis had been performed for 9 years while the level of postoperative mortality was 23,1%. Causes of death are the following: 2 (7,7 %) patients died of progressive respiratory failure and respiratory distress syndrome, another 2 (7,7%) patients had sepsis, broncho-pleural fistula with progressing empyema caused death in one (3,8%) patient and another one (3,8%) had pulmonary embolism [10].

German colleagues from the clinic of Freiburg investigated 86 CPPE for 17 years. The main contingent were cancer patients. It is reported that a 30-day postoperative mortality was 20,2 %. In 41,0 % of patients who died in the postoperative period, there was the failure of the main bronchus stump [9].

According to Radionov B.V. and co-authors, deaths occurred in 4 (25,0 %) out of 16 cases in patients with lung tuberculosis whom CPPE had been performed. 5 (31,3%) patients had insufficiency of bronchial stump [4].

Shuji H. and co-authors reported about the rate of intraoperative blood loss (2423 ± 2888) ml during CPPE for malignant tumors or lung tuberculosis (from 110 to 12500 ml) [11]. Peng Z. and others [5] noted the average blood loss during this surgery of 1854 ml (from 200 to 9100 ml).

Many studies have reported a greater risk of postoperative complications in patients who underwent right-sided CPPE [5, 7, 11]. Five-year mortality after CPPE for various reasons, according to the different authors ranged from 24,5 % to 42,5 % [6, 7, 12].

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ЗАКЛЮЧНА ПЛЕВРОПУЛЬМОНЕКТОМІЯ В КОМПЛЕКСНОМУ ЛІКУВАННІ ХВОРИХ НА МУЛЬТИРЕЗИСТЕНТНИЙ ТУБЕРКУЛЬОЗ ЛЕГЕНЬ

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Резюме

У статті представлені результати виконання заключної плевропульмонектомії у 21 хворого з мультирезистентним туберкульозом легень в період з 2004 по 2014 роки. У 76,2 % випадків досліджуваним пацієнтам при першому оперативному втручанні були виконані атипів (апаратні) резекції легень без роздільної обробки елементів кореня резектованого відділу легені. Заключна плевропульмонектомія проводилася з приводу наступних клінічних форм туберкульозу: фіброзно-кавернозний — 15 (71,4 %) випадків, циротичний — 5 (23,8 %) спостережень і казеозна пневмонія — 1 (4,8 %) хворий. Рівень інтраопераційних ускладнень склав 9,5 %. Ранні післяопераційні ускладнення були виявлені у 6 (28,6 %) осіб, пізні — у 4 (19,0 %) хворих. Загальна ефективність лікування на момент виписки зі стаціонару склала 100,0 %. Загальна ефективність виконання ЗППЕ у пацієнтів з МРТБ легень у віддаленому періоді склала 85,0 %, а десятирічна виживаність — 81,2 %.