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BRONCHOPLEURAL FISTULA COMPLICATING PNEUMONECTOMY: RESULTS OF EARLY REDO-SUTURE WITH MYOPLASTY

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SUMMARY

Treatment of bronchopleural fistula complicating pneumonectomy classically requires multiple staged operations and a prolonged period of treatment. This study presents the results of an attempt at immediate primary repair with myoplasty. From 1995 to 2003, 377 patients underwent pneumonectomy for primary lung cancer. Bronchopleural fistula developed in 15 (3.9 %). Three patients did not undergo ideal repair because of moribund status for 2 and concomitant esophageal leak in 1. Twelve patients underwent rethoracotomy for repair ; 2 of them had patent empyema. Protection of the bronchial suture was made with the serratus anterior muscle in 5, latissimus dorsi in 3, and diaphragm in 4. Ideal repair was successful in 10 of the 12 patients, who were discharged at a mean delay of 18.5 days. There was no late recurrence of fistula. Two repairs failed in patients with patent empyema, who required subsequent thoracoplasty. Immediate repair with protective muscular flap is a viable option to treat bronchopleural fistula at the very early stage before patent empyema has declared.

РЕЗЮМЕ

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**ПНЕВМОНЭКТОМИЯ, ОСЛОЖНЕННАЯ
БРОНХИАЛЬНЫМ СВИЩОМ: РЕЗУЛЬТАТЫ
СРОЧНОЙ ПОВТОРНОЙ ОПЕРАЦИИ С
ПОВТОРНЫМ ШВОМ И МИОПЛАСТИКОЙ**

Традиционное лечение бронхоплеврального свища после пневмонэктомии требует нескольких повторных операций и продолжительного периода лечения. Это исследование представляет результаты использования неотложного повторного шва с миопластикой для безотлагательного первичного заживления. В период с 1995 по 2003 проведено 377 пневмонэктомий, причиной которых явился первичный рак легких. Бронхиальный свищ развился у 15 (3.9 %) больных. Состояние 3-х пациентов не позволило проведение повторной операции, так как 2 из них умирали от сепсиса, и у 1 – обнаружен сепсис с пищеводным свищом. Повторная торакотомия была проведена у 12 пациентов; у 2-х из них диагностирована от эмпиемы. Повторный шов провели посредством миопластики зубчатой передней мышцей у 5 больных, широчайшей мышцей спины у 3 человек, и диафрагмой у 4. Полное заживление прошло у 10 пациентов и они были выписаны через 18,5 дней. Рецидива свища не было. У 2 больных с эмпиемой зарегистрирована несостоятельность повторного шва, поэтому им проведена торакопластика. Таким образом, повторный шов с миопластикой является оптимальным лечением у пациентов после пневмонэктомии, осложненной бронхиальным свищем до появления эмпиемы.

Pneumonectomy is certainly the most deleterious routine operation. Classic studies report an operative mortality of 5 to 8% [1, 2, 3]. More recent data suggest a higher mortality rate, in excess of 10%; this could be the result of elder patients included in contemporary series, and of the increased proportion of patients undergoing neoadjuvant chemotherapy [1, 4, 5]. The mortality originates not only from cardiovascular complications, but also from procedure-specific complications: post-pneumonectomy pulmonary edema, empyema, and bronchopleural fistula.

Prevalence of bronchopleural fistula varies from 1 to 8% and occurs with increased frequency on the right side [1]. Thirty to 80% of bronchopleural fistulas lead eventually to the patient's death.

Classic treatments of bronchopleural fistulas are prolonged and expensive, and in addition mutilating. They combine open window thoracostomy, muscle flap transfers and thoracoplasty [6].

In order to shorten duration of treatment and to lessen mutilation, we have adopted since 1995 a policy of early reoperation with excision of necrotic bronchial tissue, secondary bronchial suture, and protection with a muscle flap. The present study reviews results of this innovative strategy.

Patients and Methods

Patients. From 1995 to 2003, we have performed 377 pneumonectomies (186 right-sided, 191 left-sided) for primary bronchial cancer, of whom 117 underwent induction chemotherapy. As a principle, we used muscle sparing anterolateral or posterolateral thoracotomy according to the surgeons preference. Most bronchial sutures were performed with staplers, only 16 % were handsewn with absorbable monofilament sutures. Right-sided sutures were covered with a pericardial fat flap. A balanced drainage was used for 48 hours.

Post-operative monitoring. The goal of post-operative monitoring was to detect bronchopleural fistula at an early stage, before formation of empyema.

Temperature and heart rate were carefully reported by nursing staff; bronchial secretions were routinely collected and inspected at rounds. Repeated physical examination checked for basal rhonchi suggestive of pleural fluid aspiration. Chest films were repeated each 48 hours to watch the pleural fluid level and the contralateral lung. Blood cell count and determination of CRP level was repeated every 48 hours. Bronchoscopy was liberally used on any clinical suspicion of fistula, drop of fluid level or contralateral infiltrate at X-ray, and in case of persistent high white blood cell count or high CRP level.

Surgical strategy. Once the diagnosis of fistula had been established, the patient underwent reoperation on an emergency basis. Double lumen intubation was used routinely. The previous thoracotomy was reopened, and the pleural space was carefully cleaned of fluid and clots; several samples for microbiology were harvested. The bronchial stump was then exposed, and necrotic bronchial tissues were excised. A transverse closure suturing cartilage to cartilage and membranosa to membranosa

was performed with interrupted 2-0 or 3-0 absorbable monofilament sutures. This suture was carefully covered with a well vascularized muscle flap: latissimus dorsi, serratus anterior or diaphragm. Latissimus or serratus were inserted into the chest through a separate incision in the second intercostals space. A double drainage system was inserted, and pleural lavages with polypovidone diluted in normal saline were initiated until receipt of microbiologic assessment.

Criteria. All patient files were reviewed for demographic data, circumstances of pneumonectomy and post-operative course, early result of repair and long term survival updated for September 1st, 2005.

Results

Prevalence of bronchial fistula. Fifteen patients of the present series (3,9 %) developed a bronchial fistula; 11 occurred on the right side and 4 on the left. Hence, prevalence was 5,9% following right pneumonectomy, and 2% following left pneumonectomy. Only 2 patients of those having undergone induction chemotherapy developed a bronchial fistula (1,7 %).

All 15 patients were males, with a mean age of 58.2 years (range, 45-72 years). Tissue diagnosis was squamous cell carcinoma in 11, adenocarcinoma in 2, large cell carcinoma in 1 and neuroendocrine carcinoma in 1. Pathologic staging was stage I in 2 patients, stage II in 5, and stage IIIA in 8. Four patients with stage IIIA disease had residual disease at the bronchial resection margin.

Diagnosis and treatment. Diagnosis of bronchial fistula was made during the initial hospital stay in all patients but 1; mean delay after operation was 8 days (range, 1-120 days). In 5 patients, initial presentation heralded a poor prognosis: 2 were with post-pneumonectomy pulmonary edema, and 3 had obvious empyema with severe sepsis. The remaining 10 patients had few symptoms; bronchoscopy was performed because of sudden drop of fluid level in 6, persistent cough in 3, and sudden fever in 1.

Active treatment was initiated in less than 12 hours in all patients.

In 3 patients, the ideal strategy was not applicable. Two patients underwent drainage and palliative care: one of them presented with intractable septic choc, and the second had severe post-pneumonectomy pulmonary edema. A third patient was found to have concomitantly an esophago-pleural fistula which required bipolar exclusion.

Twelve patients underwent the «ideal» treatment. Protection of the bronchial suture was made with the serratus anterior muscle in 5, latissimus dorsi in 3, and diaphragm in 4.

Immediate results. Three patients died during the first 30 days; 2 were with post-pneumonectomy pulmonary edema, and 1 with intractable septic shock.

Two early repairs failed with relapse of the fistula at 6 and 34 days respectively. Both patients were with patient empyema at the time of reoperation; they eventually closed their fistula after extended thoracoplasty.

The remaining 10 patients had a satisfactory recovery, with however a mean hospital stay of 18,5 days following reoperation (range, 12-40 days).

Medium term results. Mean follow-up of surviving patients was 20.5 months (range, 6-84).

None of the 10 successful repairs developed recurrent fistula at the medium term. None of the patients developed local recurrence, including those with R1 resection.

At the conclusion of the study, 6 patients were alive without evidence of disease. Four patients died with metastatic progression, and 2 died from unrelated causes.

Discussion

The present series demonstrates efficacy of secondary bronchial repair as straight forward management for bronchopleural fistula complicating pneumonectomy. It further underscores the importance of early diagnosis, the key for successful repair being absence of empyema.

Hence, the importance of close monitoring of patients is obvious. Thoracic surgeons should have a special scrutiny for patients at risk for bronchial fistula. A first factor is prolonged artificial ventilation, especially if the tidal volume is in excess of 10 ml/kg, if positive end expiratory pressure is used, and if inspired fraction of oxygen is close to 100% [2, 4]. A second important factor is the side of pneumonectomy. Most published work stresses an increased risk on the right side, the prevalence of fistula being 3 fold on the right side compared to the left. In the present series, prevalence was 5.9% on the right side, and only 2% on the left side [1, 2, 3, 7, 8, 9]. The explanations are the anatomic particularities of the right bronchus: the calibre is much larger, the blood supply is compromised because of the recurrent course of the right bronchial artery, and finally the bronchial stump is not covered by the mediastinum as it is on the left. Radical lymph node dissection has also been subjected to criticism, though there is no scientific prove of its deleterious effect. On the other hand, the type of suture, i.e. mechanical or hand-sewn, seems of no importance [2]. It is true that the most difficult sutures are usually hand-sewn; on the other hand, comparison of manual and stapled sutures performed in standard situations do not differ. In case of a bronchus at risk, it has been shown that the type of stump protection is of importance: pleural or intercostals flaps offer less protection than large peripheral muscles such as serratus or latissimus dorsi, or even diaphragm [7].

One of the major contemporary discussions in thoracic surgical oncology is the potential deleterious effect of neoadjuvant chemotherapy. Some recent publications underlined that induction chemotherapy jeopardizes outcome after pneumonectomy [5, 10]. In such patients, an increased rate of bronchial fistulae and an increased incidence of ARDS has been reported, which translates itself in an increased mortality rate. In one recent series, mortality following right-sided pneumonectomy performed after induction chemotherapy was close to 25% [5]. Other series challenge this pessimistic view and obviate excellent results even after chemo-radiation therapy [11]. In the present series, incidence of bronchial fistula was

only 1,7% in patients having undergone preoperative chemotherapy; however, we should stress that none of our patients had received concomitant radiation therapy. The second important factor is that most of our patients were included in prospective randomized trials, and hence were low-risk patients carefully selected in accordance with the criteria set by the protocol. It is unfair to compare this series with others including salvage pneumonectomy after failure of chemotherapy and/or radiation therapy [10].

Many different treatment options have been described, and often local traditions and inherited dogmas rule the choice of treatment.

The most simple type of treatment is tube thoracostomy, which aims to clean the pleural space and to drain excessive air. As simple drainage is insufficient for adequate detersion of the pleural surface, careful lavage and use of smooth suction are used. On the long term, small fistulae may close spontaneously. While this strategy is neither mutilating nor aggressive, it carries the disadvantage of taking a long time, and with variable success rates [12].

Thoracoscopic debridement is of certain interest in the event of empyema without fistula, and could be a useful adjunct to fasten pleural detersion in patients with patent fistula [13]. In the same concept, Schreiner and his colleagues from the Zurich group propose repeated thoracotomies at 2 day intervals with repeated debridement and packing with povidone-soaked sponges [14].

In case of major pleural infection however, the gold standard remains open window thoracostomy [6]. Cleaning is repeated at each dressing, and small fistulae may close at medium term. Detersion might be fastened with use of the vacuum-assisted closing device [15]. A potential complication during changing of dressings is erosional bleeding from hilar vessels [12]. Open window thoracostomy is a rather mutilating procedure; further, closure of thoracostomy is not always possible. Filling with muscle flaps as recommended by Pairolero and Arnold [8] may be compromised in malnourished patients, and hence the final solution may consist of a large thoracoplasty to suppress the residual cavity.

Once pleural infection is controlled, there are 2 possible situations. In the first, more favourable, the bronchial stump eventually heals spontaneously. In the second, less favourable situation, the persistent fistula needs additional care. The classic option is to attempt a repair with myoplasty or omentoplasty, or to obliterate the space with a thoracoplasty. Thoracoplasty is well tolerated because of a rigidified mediastinum, but needs removal of the thickened parietal pleural peel in order to allow for an adequate collapse of parietal muscles. Authors from Russia have popularized the transsternal approach, which has subsequently been described by North American and Western European teams [16, 17]. The ideal patient for transternal approach is the patient with a long bronchial stump. Trans-sternal and transpericardial approach of the bronchial bifurcation allows for safe reamputation of the bronchial stump flush with the main carina. Exposure can be improved by extension of the neck, and by intrapericardial transection of the right pulmonary artery if right pneumonectomy has been per-

formed. Azorin and colleagues have described a minimally invasive variant: the long bronchial stump is dissected by videomediastinoscopy and transected with an endoscopic stapling device [18]. Porhanov and colleagues [19] have reported excellent results in patients with short or absent bronchial stump; in the latter category, a excision of a tracheo-bronchial wedge with lateral suture is required. Though the results are excellent, the intraoperative conditions may be challenging because of dense cicatricial adhesions.

All previous strategies are time consuming, require repeated operations, and hence cause increased expenditures. In addition, patients with lung cancer have a dismal prognosis and most of them will survive for a limited time only.

Therefore, a prolonged period of treatment interferes with quality of life and with possible projects of a patient going to dye at short term.

So called «patient-friendly» management aims to get optimal results by minimally invasive techniques, in order to pool together low cost, low duration of treatment, and minimal mutilation of the patient. During the most recent years, some endoscopic techniques have been described to obliterate bronchial fistulae. Endoscopic application of glue has been successfully used to close small bronchial leaks [20]. Some other reports describe successful covering of larger leaks with self-expandable covered stents [21, 22]. However, most of these successful cases have been published on the basis of isolated case reports, so that it remains impossible to assess the real success rate of such treatments on a larger scale. Further, covering a bronchial defect does not resolve the problem of an associated empyema.

In fine, the strategy we describe offers several advantages. There is no further mutilation as it utilizes the existing thoracotomy. Revision of the pleural space allows for extensive cleaning of clots and fibrinous deposits, and to perform large samplings for microbiologic assessment. At the bronchial level, a precise excision of all necrotized tissues is performed under direct vision and the new suture is performed within healthy tissues. Protection of the suture with a latissimus or serratus muscle flap, or with a diaphragmatic flap, is a well tolerated procedure. A double drainage inserted at the end of the procedure allows for irrigation-lavage with antiseptics, especially when pleural infection has been documented. Our small series demonstrates that a straightforward recovery taking a reasonable amount of time, and preventing further mutilation beyond pneumonectomy, is possible in patients with early-diagnosed bronchial fistula. We stress that absence of patent pleural infection is a mandatory pre-requisite for successful secondary repair, and insist on the importance of a very close clinical, radiological and biological monitoring of the pneumonectomy patient.

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PROGNOSTIC ROLE OF TUMOR MARKERS IN OPERABLE NON-SMALL CELL LUNG CANCER

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РЕЗЮМЕ

SUMMARY

The aim of the present study was to evaluate whether tumor markers Cyfra 21 and NSE may contribute to staging and evaluation of prognosis in patients with operable lung cancer. 432 operated patients (mean age 61±9) were involved in the study. There were 278 (bi)lobectomies, 120 pneumonectomies, 12 segmental resections and 22 explorative thoracotomies. Pathologic staging was stage I in 195, stage II in 86, and stage IIIA in 151. The relationship between the level of tumor markers and the postoperative pathologic staging was studied. Survival estimates (Kaplan Meier) were made with reference to the preoperative level of Cyfra-21, crossed with TNM stage and type of resection. Relative risk was estimated with the Cox proportional hazard model. Cyfra-21 was increased in 32% of patients, 69% of whom had squamous cell carcinoma (SCC). NSE was elevated in 57, 40% of whom had adenocarcinoma. Despite a low sensitivity, there was a correlation to tumor size and N-stage: sensitivity for both markers was highest in stages T3/T4, or N2. Elevated Cyfra-21 levels heralded a poor prognosis in patients with stage I or III disease, and following (bi)lobectomy, (mean survival 101 and 46 months respectively, $p<0.005$). Relative risk for death in presence of elevated Cyfra 21 level was 1.4. Low sensitivity makes that Cyfra-21 and NSE are inappropriate tools for staging of operable lung cancer. An elevated Cyfra-21 level indicates a poor prognosis.

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ПРОГНОСТИЧЕСКАЯ РОЛЬ ОНКОМАРКЕРОВ
ПРИ ОПЕРАБЕЛЬНОМ
НЕМЕЛКОКЛЕТОЧНОМ РАКЕ ЛЕГКИХ

Цель настоящего исследования – оценить возможность опухолевых маркеров Cyfra-21 и NSE определять патологическую стадию и давать прогноз пациентам с операбельным раком легких. Было обследовано 432 прооперированных больных (средний возраст 61±9). Выявлено 278 случаев (би)лобэктомии, 120 пневмоэктоми, 12 сегментальных резекций и 22 таракомий. Патологическая стадия: стадия I была у 195, стадия II – у 86 и IIIA – у 151 больного. Изучалась взаимосвязь между уровнем опухолевых маркеров и послеоперационных патологических стадий. Оценка выживаемости (Kaplan Meier) была сделана с ссылкой на дооперационный уровень Cyfra-21, пересекаясь со стадией TNM и типом резекции. Относительный риск оценивался моделью Сох пропорционального вредного фактора. Cyfra-21 был увеличен у 32% больных, 68% из которых имели плоскоклеточный рак (SCC). NSE повышен у 57%, 40% из которых имели аденокарциному. Несмотря на низкую чувствительность, отмечена взаимосвязь размера опухоли и N-стадии: чувствительность обоих маркеров была самой высокой на стадии T3/T4 или N2. Повышенные Cyfra-21 уровни предвещали неблагоприятный прогноз для больных на I и III стадии болезни с последующей (би)лобэктомией, (средняя выживаемость 101 и 46 месяцев соответственно, $p<0,005$). Относительный риск смерти при наличии повышенного уровня Cyfra-21 составил 1,4. Низкая чувствительность показывает, что Cyfra-21 и NSE не под-