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Does postpneumonectomy empyema improve long-term survival for patients with lung cancer?

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Postpneumonectomy empyema (PPE) is life-threatening morbidity that affects up to 10% of patients and carries a 9–13% mortality risk. Treatment can take a long time, and the prognosis is uncertain. Forty years ago, improved survival was reported among patients with lung cancer and pleural empyema compared to those with lung cancer and no empyema. Here we investigated this potential association among patients with PPE. The present study included 38 patients who underwent pneumonectomy between 1995–2007 (7 females, 31 males, median age of 62 years) and then developed PPE, which was treated with the accelerated treatment (AT) method. Thirty-five of these patients had been diagnosed with lung cancer (including one case of carcinoid with infiltration), of whom 31 were matched with 31 lung cancer patients who underwent uncomplicated pneumonectomy at the same center between 1997-2009. The two groups did not significantly differ regarding sex, age, histology, TNM, FEV1, major co-morbidities, or received neoadjuvant or adjuvant therapy. Thirty-five (92.1%) patients from the initial group were treated successfully and the 5- and 10-year survival rates were 69% and 51%, respectively. Comparison between the matched groups revealed longer survival rates in the empyema group (5-year, 70%; 10-year, 49%) compared to the group without empyema (5-year, 38%; 10-year, 18%). Compared to the group without empyema, the empyema group showed significantly longer survival for all-cause mortality (p=0.004) and a lower incidence of cancer-unrelated mortality (p=0.02). The two groups did not significantly differ with regard to cancer-related mortality (p=0.09). In conclusion, accelerated treatment is a safe and effective method for the treatment of pleural empyema after pneumonectomy. The presently achieved results indicate improvement in survival of lung cancer patients with PPE in comparison to lung cancer patients after uncomplicated pneumonectomy.

Key words: empyema; lung cancer; accelerated treatment

Postpneumonectomy empyema (PPE) is a life-threatening complication that affects up to 10% of patients and carries a 9–13% mortality risk [1–3]. In the majority of cases, PPE treatment is focused on controlling the acute phase of empyema with drainage or repeated punctures of the pleural cavity, supporting the transition to the chronic phase of empyema [4]. Stabilization of the patient's metabolic, functional, and oncologic status allows the performance of a final treatment based on open-window thoracostomy, myoplasty, omentoplasty, thoracomyoplasty, accelerated treatment (AT) and videothoracoscopic (Vats) technique, vacuum-assisted closure (VAC) – therapy, or a combination of these methods [1, 2, 5–15]. Forty years ago, a survival benefit was described among patients with lung cancer who suffered from pleural empyema compared to lung cancer patients without empyema [16]. In 2013, we described current report of this phenomenon in the group of patients after pneumonectomy due to lung cancer complicated by PPE syndrome [10]. The 5- and 10-year survival rates were 69% and 51%, respectively (Figure 1) [10]. Here we further investigated this potential association among patients with PPE.

Patients and methods

Study design. The initial group comprised 38 patients with pneumonectomy who developed PPE between 1995–2010 (Table 1) [10]. Within this group, 36 patients had been diagnosed with malignant disease, and only two patients were pneumonectomized due to benign disease. Thirty-five patients had non-small cell lung cancer (NSCLC), of whom nine patients underwent neoadjuvant chemotherapy, 10 underwent adjuvant radiotherapy, and one patient received adjuvant chemotherapy. Sixteen cases (42.1%) developed bronchopleural fistulas (BPF) that healed earlier endoscopi-

cally or by myoplasty during the final treatment [10, 17, 18]. In 15 of the 16 cases with BPF (93.75%), the acute phase of empyema started during the first four postoperative weeks. Only one case with BFP (6.25%) involved late fistula development more than four weeks following pneumonectomy. The acute phase of empyema was controlled by a drainage system, repeated punctures, or a combination of both methods. Cases that developed BPF were treated only with a drainage system. Final operative treatment was conducted according to the accelerated treatment method, involving the repeated performance of open pleural debridement and lavage, which was previously described [1, 9, 10]. Using follow-up data,

Table 1. Characteristics of the entire PPE-group [10]. NSCLC classification – (UICC-6th edition).

PPE/BPF incidence rate for 928 pneumonectomies performed in 1995-2010 years (%)	4.2/1.8
No. of patients of the presented group	38
Female/male	7/31
Age-median	62
Side right/left	19/19
BPF right/left	8/8
Preoperative closure of BPF	13
Myoplasty closure of BPF	3
Occurrence of BPF after pneumonectomy (days)	5-1460
Duration of PPE treatment before AT (months) range/median	1-47/7
NSCLC-squamous cell carcinoma	24
NSCLC-adenocarcinoma (including solid version)	8
NSCLC-mixed carcinoma	2
Carcinoid with infiltration (included to the NSCLC group)	1
Malignant mesothelioma (pleuropericardiopneumonectomy)	1
Lung abscess	2
T1bN0M0 (TNM classification of malignant mesothelioma)	1
T2 (NSCLC)	8
T3 (NSCLC)	25
T4 (NSCLC)	2
N0 (NSCLC)	20
N1 (NSCLC)	6
N2 (NSCLC)	9
IB (NSCLC)	3
IIB (NSCLC)	17
IIIA (NSCLC)	13
IIIB (NSCLC)	2
Success rate after first treatment (number/%)	29/76.3
Recurrence rate of PPE (number/%)	6/15.7
Complete treatment with additional thoracomyoplasty/fenestration (recurrence)%	6/15.7
Overall success rate (including second attempt) (number/%)	35/92.1
30-d mortality (number/%)	1/2.63
Interrupted treatment (drain carrier), NSCLC-1, mesothelioma-1	2
Deceased NSCLC patients - number/(%) (revised data)	13/35 (37.1)
Post-hospitalization cancer-unrelated deaths	9
Post-hospitalization cancer-related deaths	3
Follow up time for NSCLC patients (months) range/median	8-148/67
Median follow up time for N0-patients (months)	72
Median follow up time for N1-patients (months)	65
Median follow up time for N2-patients (months)	58
5-year survival for NSCLC patients including carcinoid case - revised data (20/35) %	57.1
5-year survival N0-group (13/20) (follow-up analysis) %	65
5-year survival N1-group (3/6) (follow-up analysis) %	50
5-year survival N2-group (4/9) (follow-up analysis) %	44

Abbreviations: NSCLC-Non-small cell lung cancer; UICC-Union for International Cancer Control; PPE-Postpneumonectomy empyema; BPF-Bronchopleural fistula

we assessed the effectiveness of PPE treatment and the long-term survival of lung cancer cases. 33 NSCLC- patients who completed the treatment were qualified to be included in the statistical analysis [10]. In the present evaluation, 31 of these patients were paired with the control group using the propensity score matching rule (using nearest neighbor, 1:1 and radius of 10 years matching rules), in order to minimize the variance due to variability in clinical characteristics of the examined subjects. The control group comprised 31 NSCLC patients who underwent uncomplicated pneumonectomy in the Szczecin center between 1997–2009 from the group of 66 patients who met the eligibility criteria from the pneumonectomy patients in total (928). Two patients from the study group (mixed carcinoma) with follow-up of 148 and 9 months were excluded from comparison due to the unavailability of similar cases in the control group. Similarly, patients with large cell carcinoma from the control group were excluded due to the lack of cases for comparison in the study group. The study and control groups did not significantly differ regarding sex, side of the operation, histopathology (although G class data were incomplete), 6th TNM staging edition, age, FEV1 (Forced expiratory in one second), additional treatment rate, and major co-morbidities (Table 2).

Table 2. Characteristics of the study and control groups.

Variable	Study group	Control group
Number of patients	31	31
Males/female	25/6	25/6
Age-range/median (at pneumonectomy) (Wilcoxon test Z=0.13, p=0.89)	42–74/60	42–77/62
Period of pneumonectomy	1995–2007	1997–2009
Right/left side	14/17	14/17
Squamous cell carcinoma	21	21
Adenocarcinoma (all class according solid version)	9	9
Carcinoid with infiltration	1	1
T2	6	6
T3	23	23
T4	2	2
N0	19	19
N1	3	3
N2	9	9
Stage-IB	2	2
Stage-IIB	16	16
Stage-IIIA	11	11
Stage-IIIB	2	2
Tumor G class (defined/undefined)	20/11	25/6
G1	5	5
G2	13	19
G3	2	1
Diabetes n/% (McNemar test χ^2=0.12, df=1, p=0.72)	6/19.3	4/12.9
Atherosclerosis of arteries n/% (McNemar test χ^2=0.25, df=1, p=0.62)	3/9.6	1/3.2
Coronary artery disease n/% (McNemar test χ^2=0.125, df=1, p=0.62)	1/3.2	3/9.6
Preoperative FEV1% range/median (Wilcoxon test Z=0.43, p=0.67)	53.6–125/82.5	57–119/84.3
Coexisting morbidities (diabetes, coronary artery disease or atherosclerosis other arteries) and radio- or chemotherapy	5/16.1	4/12.9
Neoadjuvant chemotherapy n/% (McNemar test χ^2=2.5, df=1, p=0.11)	8/25.8	2/6.4
Adjuvant chemotherapy n/%	1/3.2	2/6.4
Adjuvant radiotherapy n/% (McNemar test χ^2=0, df=1, p=1.0)	10/32	11/35.4
Neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy frequency n (%)	19 (61.3)	15 (48.4)
Follow-up after pneumonectomy range	8–138	3–144.4
Follow-up median (months) (Wilcoxon test Z=2.02, p=0.04)	86	31.2
Cancer-related deaths n/% (follow-up analysis)	3/9.6	7/22.6
Cancer-unrelated deaths n/% (follow-up analysis)	9/29	16/51.6
5-year survival n/% (follow-up analysis)	17/54.8	7/22.6
7-year survival n/% (follow-up analysis)	15/48.4	5/16.1
10-year survival n/% (follow-up analysis)	5/16.1	4/12.9

Notes: McNemar χ^2-test was used for comparison of qualitative variables and Wilcoxon signed-rank quantitative was used for comparison of quantitative variables between paired study group subjects and controls

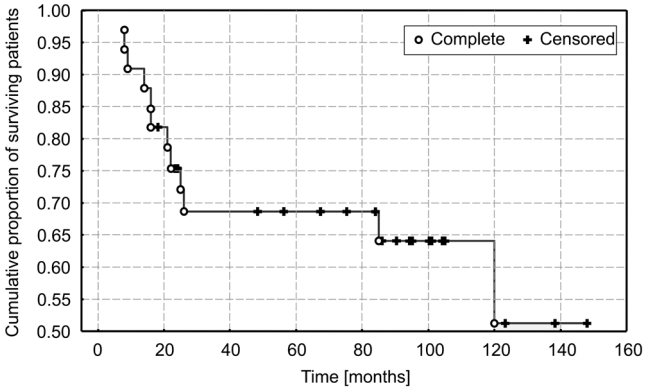

Figure 1. Kaplan-Meier survival curves for all-cause mortality among 33 NSCLC patients with postpneumonectomy empyema (5-year survival 69%; 10-year survival 51%) [10].

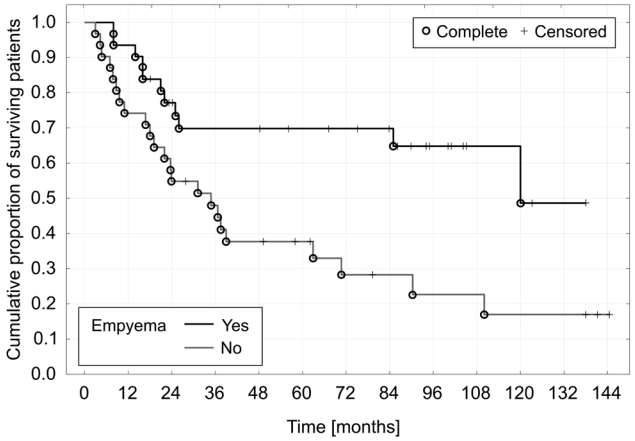

Figure 2. Kaplan-Meier survival curves for all-cause mortality compared between 31 NSCLC patients with postpneumonectomy empyema (5-year survival 70%, 10-year survival 49%) and 31 controls without postpneumonectomy empyema (5-year survival 38%, 10-year survival 18%) (log-rank test p=0.004).

All patients gave informed consent to treatment and participation in the therapeutic program. The local Ethical Committee approved the AT method as one of the standard ways of PPE treatment. The approval of the Ethical Committee for patients with the uncomplicated postpneumonectomy course was not required because of the retrospective character of the study based exclusively on hospital records of typical procedures.

Statistical analysis. Statistical analysis was performed using Wilcoxon and McNemar tests to compare quantitative and qualitative parameters, respectively, between paired patients and controls. Kaplan-Meyer curves were compared with log-rank test, and uni- and multivariate Cox proportional hazard model was used to find predictors of the analyzed end-points: all-cause death, cancer-unrelated death, and cancer-related death. The proportional hazards assumption for Cox model was verified by visual assessment of scaled Schoenfeld residuals for all independent variables. No deviation from the assumption has been observed.

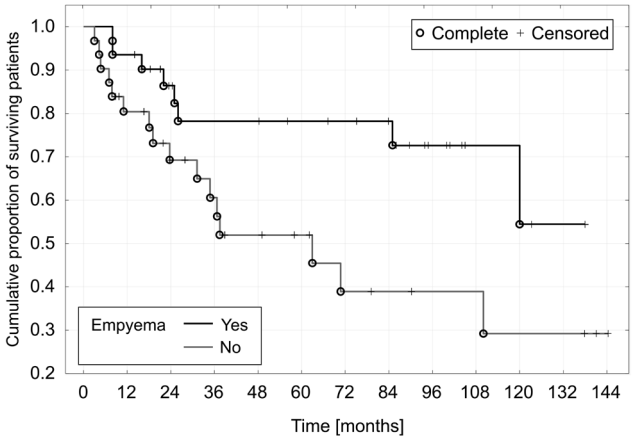

Figure 3. Kaplan-Meier survival curves for cancer-unrelated mortality compared between 31 NSCLC patients with postpneumonectomy empyema and 31 controls without postpneumonectomy empyema (log-rank test p=0.02).

Results

Table 1 presents the results of PPE treatment and revised follow-up of the 38-patients PPE-group [10]. The analysis of the results of the entire PPE-group was continued during the assessment of selected 31-patients' groups. Comparison between the two matched groups showed improved long-term results in the study group with 5- and 10-year survival rates of 70% and 49% in the PPE-group and of 38% and 18% in the group without PPE, respectively (Figure 2). The study group showed significantly longer median follow-up times (p=0.04, Table 2), and longer survival for all-cause mortality and cancer-unrelated mortality (Figures 2, 3). The between-groups difference in cancer-related mortality did not achieve statistical significance (Figure 4). These observations were confirmed by Cox proportional hazards model. The univar-

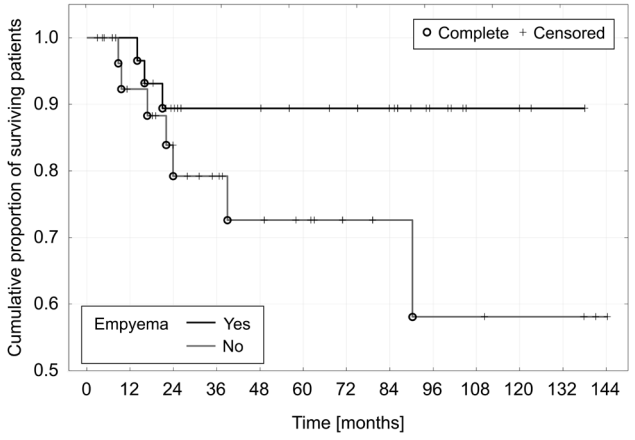

Figure 4. Kaplan-Meier survival curves for cancer-related mortality compared between 31 NSCLC patients with postpneumonectomy empyema and 31 controls without postpneumonectomy empyema (log-rank test p=0.09).

iate Cox proportional hazards model revealed an HR of 0.37 (95% CI=0.18–0.76, p=0.006) for all-cause deaths and an HR of 0.38 (95% CI=0.16–0.9, p=0.02) for cancer-unrelated deaths when patients with postpneumonectomy empyema were compared to controls without postpneumonectomy empyema. A multivariate Cox proportional hazard model considering presence of postpneumonectomy empyema, age, sex, T-stage, and N-stage as independent variables showed an HR of 0.29 (95% CI=0.13–0.63, p=0.001) for all-cause deaths and an HR of 0.27 (95% CI=0.11–0.68, p=0.005) for cancer-unrelated deaths in relation to postpneumonectomy empyema. For cancer-related deaths univariate Cox proportional hazard model showed an HR of 0.33 (95% CI=0.08–1.27, p=0.11) and a multivariate Cox proportional hazard model considering presence of postpneumonectomy empyema, age, sex, T-stage, and N-stage showed an HR of 0.32 (95% CI=0.08–1.3, p=0.11) in relation to postpneumonectomy empyema.

Discussion

PPE treatment changes toward the most effective procedures [1, 2, 4, 5–15, 17]. First described 20 years ago, accelerated treatment is currently one of the leading PPE treatment methods [1, 9, 10]. AT is a current version of the modified Clagett procedure that involves open repeated peritoneal lavage for peritonitis [1, 9, 10, 19]. AT is based on the concept of sterilizing the pleural cavity without an open-chest window, thoracoplasty, or thoracomyoplasty and with definitive closure of the thoracic approach. The effectiveness of AT is comparable to that of other methods. To be eligible for AT, the patient must agree to undergo repeated interventions and there must exist the possibility of a tight closure of the thoracic approach. The AT method is mainly useful in patients with the pleural infection without BPF or with preoperatively healed BPF. AT can also be used in patients with active BPF if there is the possibility to close the BPF during the AT procedure. The AT approach is also useful for patients with a large empyema chamber. The concept of AT improved the potential to treat a large, non-collapsed, and infected cavity. Prior to the introduction of AT, the elimination of such cavities was the most commonly encountered surgical problem often resulting in severe chest deformity [1, 9, 10]. The AT method enables preservation of the pleural cavity, chest symmetry, and chest shape with a low level of severe complications. In the 38-patients PPE-group, there was one postoperative death due to pulmonary embolism [1, 9, 10]. The long-term survival rates reported in our PPE-study group were better than those previously reported for lung cancer cases [20]. The follow-up results of our present study group were better than the results in the control group; however, it should be noted that data regarding G classification were incomplete. Positive follow-up results of the entire 38-patients PPE-group were achieved despite cancer recurrences and cancer-related deaths. Cancer recurrence or second neoplasm occurred in 8 of the 35 NSCLC cases (22.8%). Three patients died and five patients were treated successfully [10]. In the 38-patients PPE-group majority of assessed features were not statistically significant predictors of survival [10]. There was a statistical difference in survival rates between T2 and T4 class patients (log-rank test p=0.04). T4 stage was an independent death risk factor in multivariate Cox hazard model (HR=3.83, 95% CI=1.08–13.58, p=0.03). Cancer-related death risk was significantly correlated with NSCLC recurrence (log-rank test p=0.01) and requirement of more than three lavages (log-rank test p=0.01). Among 6 patients who required four lavages (five with malignancy and one with lung abscess), two patients died due to recurrent NSCLC [10]. The evaluation of the existing and current research raises the issue of the mechanism of this phenomenon. The mechanism of the survival advantage seen in the PPE-group is probably based on nonspecific immunotherapy [21–25]. The main difference between the two assessed groups in the present study was the long-term immunization before completion of treatment in the study group (median: 7 months). Further investigation is warranted regarding the conditions in the present study group including radical surgery (pneumonectomy) followed by a development of postpneumonectomy pleural cavity empyema. Other consecutive conditions of potential importance include the common location of cancer and empyema with relatively safe long-term (months or years) immunization by empyema. The main limitation in this evaluation was an incomplete G type of tumor data. In the future, G-class, PET/CT (positron emission tomography/computed tomography), genes mutation, and the use of tyrosine kinase inhibitors will probably become additional criteria for this type of comparison. In conclusion, the accelerated treatment is a safe and effective method for the treatment of pleural empyema after pneumonectomy. The presently achieved results indicate improvement in survival of lung cancer patients with postpneumonectomy empyema in comparison to lung cancer patients after uncomplicated pneumonectomy.

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