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Incidence and management of complications after neoadjuvant chemotherapy followed by extrapleural pneumonectomy for malignant pleural mesothelioma☆

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Abstract

Objective: To investigate the incidence and management of postoperative complications after neoadjuvant chemotherapy followed by extrapleural pneumonectomy for malignant pleural mesothelioma. **Methods:** Patients with histologically proven mesothelioma of clinical stages T1—3, N0—2, M0 and considered to be completely resectable received neoadjuvant chemotherapy (cisplatin + gemcitabine or cisplatin + pemetrexed) followed by extrapleural pneumonectomy and postoperative radiotherapy. The incidence and management of postoperative complications in general and of bronchopleural fistula and postpneumonectomy-empyema in particular were analyzed. Univariate analysis was performed to identify prognostic factors [sex, age, side of operation, weight loss, smoking, chemotherapy, EORTC-score (European Organization for Research and Treatment of Cancer-classification) and duration of operation]. **Results:** Between 1st May 1999 and 15th August 2005, 63 patients underwent complete extrapleural pneumonectomy after neoadjuvant chemotherapy. Postoperative complications were observed in 39 cases (62%) and 2 patients died within 30 days (3.2%). Postpneumonectomy-empyema occurred in 15.8% of the patients ($n = 10$), six with a bronchopleural fistula on the right side. All empyemas were treated successfully. Five patients developed chylothorax (7.9%) and four patients had complications due to a patch failure: cardiac herniation ($n = 2$), restriction of cardiac output ($n = 1$) or gastric herniation ($n = 1$). Patients with higher EORTC-score presented significantly more postoperative complications ($p = 0.03$). A longer duration of surgery tended to be associated with a higher incidence of postoperative complications, especially of empyemas. **Conclusions:** Extrapleural pneumonectomy after neoadjuvant chemotherapy can be performed with mortality rates comparable to standard pneumonectomies. Complications are frequent but can be successfully managed; the EORTC-score seems to be a predictor for postoperative complications.

Keywords: Extrapleural pneumonectomy; Complications; Neoadjuvant chemotherapy; Malignant pleural mesothelioma; EORTC-score

1. Introduction

It is suggested that the number of men dying each year from malignant pleural mesothelioma (MPM) in Western Europe will almost double over the next 20 years from 5000 in 1998 to about 9000 deaths per year around 2018 [1]. Without treatment, the majority of patients die within 12 months [2].

There is no generally accepted therapy for MPM. Extrapleural pneumonectomy (EPP) is the most radical surgical procedure and might offer long-term survival, if used in a multimodality concept. In 1976, Butchart et al. [3] reported about 29 patients undergoing EPP for diffuse MPM with a very high perioperative mortality rate of 31%. In current series, mortality after EPP without previous chemo- or radiation therapy ranges from 4 to 15% [4—7]. However, morbidity stays high with postoperative complication rates around 60% [4,7].

With neoadjuvant chemotherapy, the incidence of postoperative complications as well as the mortality rate was expected to increase. However, our pilot study analyzing neoadjuvant chemotherapy with cisplatin + gemcitabine followed by EPP for MPM showed promising results [8] in terms of feasibility and tolerability as well as median survival, so that this concept was further investigated in our institution. In the underlying study, the postoperative course of a consecutive series of patients undergoing EPP after neoadjuvant chemotherapy is analyzed in detail.

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2. Patients and methods

2.1. Patients and indications

Patients were eligible for a neoadjuvant concept if they had a histologically confirmed diagnosis of MPM of any histology, clinical stages T1–3, N0–2, M0 and if they were considered to be completely resectable. Other inclusion criteria were adequate health status (serum creatinine < 150 mmol/l, predicted postoperative FEV1 > 1 l, adequate cardiac function), Eastern Cooperative Oncology Group (ECOG) performance status 0–2 [9], age older than 18 years, no prior pleurectomy or lung resection except for diagnostic purposes and written informed consent. Patients with contraindication for surgery, prior or coexisting malignancies (except adequately treated in situ carcinoma of the cervix or basal squamous cell carcinoma of the skin) or with other serious illnesses (cardiac disease preventing forced hydration or surgery, neurological or psychiatric disorders, uncontrolled infection, severe liver disease or uncontrolled diabetes) were excluded.

Patients were treated with neoadjuvant chemotherapy using cisplatin + gemcitabine followed by EPP in a pilot study [8] and after promising results, the Schweizer Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) performed a nationwide, multicentre phase II trial [10]. Currently, patients receive cisplatin + pemetrexed as neoadjuvant chemotherapy before EPP.

2.2. Interventions

Neoadjuvant chemotherapy consisted of three cycles of cisplatin 80 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 administered every 28 days or, since March 2003, of cisplatin 80 mg/m^2 on day 1 and pemetrexed 500 mg/m^2 on day 1 administered every 21 days. Tumour response was assessed by computed tomography (CT) using unidimensional measurement of the pleural thickness perpendicular to the chest wall and guidelines according to the modified Response Evaluation Criteria in Solid Tumours (RECIST) [11]. Patients were considered to be resectable when there were no obvious signs for widespread chest wall invasion (resectable chest wall lesions were accepted) or obvious infiltration of mediastinal structures as the aorta, heart, spine or oesophagus according to the CT scan performed after neoadjuvant chemotherapy. *Surgery* was performed within 6 weeks after completion of the last injection of chemotherapy (day 15 of the third cycle). The procedure included a complete EPP with resection of the ipsilateral pericardium and the ipsilateral diaphragm. It was performed via extended anterolateral thoracotomy throughout the bed of the 6th rib, which was occasionally resected. If resection in the posterior costodiaphragmatical angle was difficult, a second lateral thoracotomy two intercostal spaces lower was carried out. Previous trocar sites for thoracoscopic biopsy were excised. Dissection plane of EPP was between parietal pleura and endothoracic fascia. The mediastinal pleura was bluntly dissected down towards the hilar structures, and the pericardium was opened widely. Vessels and main bronchus were closed using stapling devices. Radical mediastinal lymphadenectomy was performed. The diaphragm was completely resected at its insertion site at the thoracic wall without opening of the peritoneum. It was reconstructed with a Mersilene mesh (Mersilene; Ethicon, Inc, Sommerville, NJ, USA). Equine xenopericard patch (Supple Peri-guard Synovis Surgical Innovations; St Paul, MN, USA) was used for pericardium reconstruction. If localized chest wall infiltration occurred, this region was excised en bloc with the pleuropneumonectomy specimen. Patients with multilevel thoracic wall invasion were excluded from radical resection and herewith from analysis. Final pathological staging was carried out following the TNM staging system [12]. *Radiotherapy* was performed according to definite tumour stage (histologically confirmed local infiltration beyond the endothoracic fascia) and if high-risk zone of resection was defined by the operating surgeon. Patients received three-dimensional conformal radiotherapy using a 6-MV linear accelerator equipped with a multileaf collimator. If multilevel high-risk situation of residual disease was given, a radiation dose of 30 Gy to the ipsilateral hemithorax and a boost dose of 20 Gy to the area of highest risk was performed (fractionation schedule 2 Gy/day, five times a week). Radiation treatment was delivered with two equally weighted, opposed anterioposterior–posterioanterior fields, and critical organ structures were shielded with multileaf collimators. Patients with a single high-risk area received involved-field radiotherapy of 45–60 Gy (fractionation 1.8–2 Gy/day, five times a week).

Since May 2005, five patients were treated with intensity-modulated radiotherapy receiving in clinical target volume 1 (=field of surgery including the entire preoperative pleural and pulmonary structures) 45–46 Gy and in clinical target volume 2 (=risk of residual postoperative microscopic disease or the area of highest risk for intrathoracic relapse) a total dose of 55.9–56.2 Gy.

2.3. Analysis of data

All consecutive patients who underwent EPP after neoadjuvant chemotherapy in our centre were retrospectively analyzed for the incidence and management of postoperative complications. Postoperative complications within the hospital stay were defined as complications directly related to surgery such as major bleeding with necessity of revision, bronchopleural fistula, postpneumonectomy-empyema, patch failure, chylothorax or as general complications including adult respiratory distress syndrome (ARDS), pneumonia, atrial fibrillation (AF), myocardial infarction, deep vein thrombosis or pulmonary embolism. Vocal cord paralysis, Horner syndrome and seroma were documented. The retrospective data were collected from medical records archived in our data management program KISIM Version 4.785.

Statistical analysis was carried out using the software package SPSS for Windows, version 11, SPSS Inc. Data are given in total number and percentages. Binary logistic regression analysis and if possible multivariate analysis was performed in order to define odds ratios and 95% confidence interval for the incidence of postoperative complications, bronchopleural fistula and postpneumonectomy-empyema. The prognostic factors analyzed were sex, age, side of operation, weight loss, smoking, exposure to asbestos,

substance of chemotherapy (cisplatin + gemcitabine vs cisplatin + pemetrexed), EORTC-score (European Organization for Research and Treatment of Cancer-classification) and duration of surgery. The EORTC-score was calculated as follows [13]: (0.55)a + (0.6)b + (0.52)c + (0.67)d + (0.6)e

(a) if WBC $> 8.3 \times 10^9$ l^{-1};
(b) if ECOG performance status 1 and 2;
(c) if histology is probable;
(d) if sarcomatoid histology;
(e) if male gender.

Between 1st May 1999 and 15th August 2005, 63 patients (92% male) underwent EPP after completion of three cycles neoadjuvant chemotherapy (39 on the right and 24 on the left side). The median age was 57 years (37; 69) at the time of surgery. Fifty-one patients (81%) were symptomatic in terms of dyspnoea, 30 patients (48%) suffered from chest pain and weight loss (more than 10% bodyweight) occurred in 25 cases (40%). Asbestos exposure was identified in 43 patients (68%) and 27 patients (42%) presented a history of more than 10 pack years smoking. Patient's characteristics are listed in Table 1.

Diagnosis was confirmed in 58 patients (92%) via thoracoscopy, the remaining five patients underwent a small thoracotomy. In 36 cases (57%), talc pleurodesis was performed during the same intervention. Mediastinal lymph node status was assessed via mediastinoscopy in 51 patients (81%) and 8 patients were staged N2 after mediastinoscopy.

After staging procedures, 47 patients (75%) received three cycles of the combination cisplatin + gemcitabine as neoadjuvant chemotherapy and, since March 2003, 16 patients (25%) received the combination cisplatin + pemetrexed. Side effects were observed in 68% of the cases ($n = 43$), whereas nausea or emesis ($n = 27$) were the most frequent, followed by neurological ($n = 13$) and haematological ($n = 7$) complications. In the subsequent CT scan, progressive disease was diagnosed in 11 patients (17%), in 32 cases (51%) no change was observed and in 20 patients (32%) partial response could be determined.

Table 1
Patient's characteristics

	Number of patients (%)
ECOG-PS	
0	36 (57)
1	21 (33)
2	6 (10)
pTNM stage	
pT1	9
pT2	36
pT3	18
pT4	
pN0	43
pN1	9
pN2	11
Histology	
Epitheloid	44
Mixed	17
Sarcomatoid	2

ECOG-PS: The Eastern Cooperative Oncology Group-Performance Status.

3. Results

Between 1st May 1999 and 15th August 2005, 63 patients (92% male) underwent EPP after completion of three cycles of neoadjuvant chemotherapy. It was performed in a median operation time of 355 min (240–490 min). Intraoperative complications occurred in seven cases (11%): two injuries of the spleen capsule requiring splenectomy in one case. Three patients presented abnormal bleeding tendency during operation leading in one case to perioperative transfusion of five erythrocyte concentrates and four fresh frozen plasmas. Two patients suffered from intraoperative cardiac arrhythmia.

The median cumulative ICU stay was 4 days (1–31 days), whereas patients stayed on average 1.5 times (SD 0.9) in ICU. The median duration of hospital stay was 15 days (6–39 days). Two patients died in hospital or within the first 30 days after operation (in-hospital- and 30-days mortality 3.2%). One patient (obese with a diabetes mellitus) succumbed to septic multiorgan failure due to pneumonia on the seventh postoperative day and the other patient died from a pulmonary embolism at day 4.

Postoperative complications related to the operation occurred in 39 cases (62%) (Fig. 1). Surgery-related complications occurred in 22 patients (35%): 5 patients (7.9%) presented a chylothorax, 2 of which had to be reoperated for surgical closure of thoracic duct. The other three patients were successfully treated with parenteral alimentation. Ten patients (15.8%) developed postpneumonectomy-empyema, all except for three on the right side. In six cases, bronchopleural fistula was diagnosed without exception after right-sided EPP. These patients with postpneumonectomy-empyema required reoperation with radical debridement and packing of the pleural cavity with povidone–iodine-soaked towels (dilution 1:10). This procedure was repeated in 2-day intervals until macroscopical disappearance of the infection. In case of proven bronchopleural fistula, omentoplasty was performed in two cases and muscle flap technique in four cases (three times serratus anterior muscle, once latissimus dorsi muscle). Finally, the pleural space was obliterated with antibiotic solution (1 l NaCl 0.9% mixed with 2.2 g amoxicilline/clavulanic acid, 0.3 g netilmicin and 1 g vancomycin) as described previously [14]. With this concept, we were able to manage successfully all empyemas and the chest was closed within 8 days.

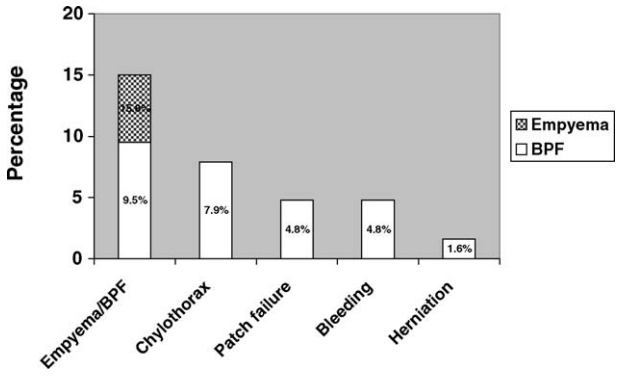

Fig. 1. Surgery related postoperative complications. BPF: bronchopleural fistula. Data are given in percentage.

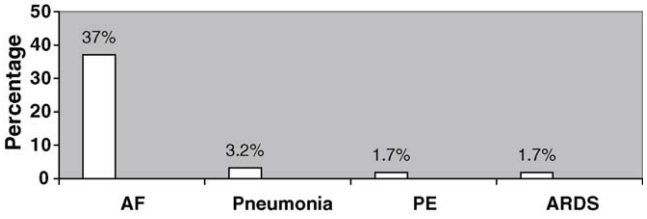

Fig. 2. General postoperative complications. AF: atrial fibrillation, PE: pulmonary embolism, ARDS: adult respiratory distress syndrome. Data are given in percentage.

Other surgery-related complications were cardiac herniation ($n = 2$) due to dehiscence of the patch or restriction of cardiac output due to constrictive patch ($n = 1$) and gastric herniation after dehiscence of the diaphragmatic reconstruction ($n = 1$). Altogether, 19 patients had to be reoperated for surgical complications (30.2%), 3 of them because of bleeding complications. Submuscular seromas were observed in 11 cases (17.5%). Horner syndrome ($n = 5$) and vocal cord paralysis ($n = 2$) were sequellaes of radical resection because of direct involvement of the nerve.

The most frequent complication was atrial fibrillation with 23 cases (37%). Twenty-two patients received amiodarone (cordarone) medication for successful medical conversion of heart-rhythm, one patient converted spontaneously. One patient developed ARDS 2 days after operation but fully recovered after prolonged intubation. Other complications are summarized in Fig. 2.

Univariate analysis of the incidence of postoperative complications, bronchopleural fistula- and postpneumonectomy-empyema rate showed that neither age, weight loss, smoking, asbestos exposure, chemotherapy (cisplatin + gemcitabine vs cisplatin + pemetrexed) nor side of operation were significantly influencing factors (Table 2). The EORTC-score showed a significant impact on the incidence of postoperative complications: per 1 point increase in EORTC-score, the incidence increased by factor 4.5 ($p = 0.03$). A tendency that women developed less complications than men ($p = 0.08$) was observed but this effect is questionable because of the low number of women in the sample size ($n = 5$). Likewise the duration of operation as a continuous variable tended to significantly influence the incidence of postoperative complications ($p = 0.07$), which was equally observed for the incidence of postpneumonectomy-empyema ($p = 0.07$). This effect was not observed for patients developing BPF. BPF always occurred after right-sided pneumonectomies. It was striking that all six patients received the combination cisplatin plus gemcitabine, but the numbers in the cisplatin–pemetrexed treated patients might be too small.

Table 2
Prognostic factors for the incidence of postoperative complications

	OR	95% CI	p
Sex (female vs male)	0.1	0.01; 1.3	0.08
Age at diagnosis	0.9	0.9; 1.1	ns
Side of operation (left vs right)	0.4	0.2; 1.3	ns
Weight loss (yes vs no)	0.7	0.2; 1.9	ns
Smoking (yes vs no)	1.1	0.4; 3.1	ns
Chemotherapy (cisplatin + pemetrexed vs cisplatin + gemcitabine)	0.4	0.1; 1.7	ns
Duration of operation	1	0.99; 1.01	0.07
EORTC-prognostic score	4.5	1.2; 17.3	0.03

EORTC-score: European Organization for Research and Treatment of Cancer-classification. p-value < 0.05 were statistically significant. OR: odds ratio, 95% CI: confidence interval.

4. Discussion

These data report our experience with 63 cases of EPP performed after induction chemotherapy. The results demonstrate that the mortality rate of 3.2% is relatively low and compares favourably to series of EPP without previous neoadjuvant chemotherapy. The mortality rate is lower than after pneumonectomy alone with, e.g. 6.2% in a large multicentre, prospective series of 569 pneumonectomies from the Lung Cancer Study Group [15]. Postoperative morbidity remains high with 62% but is comparable to other centres' complication rate with 60.4% reporting about 328 EPP for MPM without induction chemotherapy in a time period of 20 years [4]. Also, mortality in this series after application of adjuvant chemotherapy with rates of 3.4% is comparable to our results after neoadjuvant chemotherapy. The relatively low mortality rate in comparison to a high morbidity rate shows that complications can be managed in a multidisciplinary approach.

Overall postpneumonectomy-empyema rate was 15.8% and the most serious postoperative complication. It was caused in 60% by bronchopleural fistulas on the right side. The fact that the last empyema occurred in February 2002 seems to confirm that our preventive concept of irrigation of the thoracic cavity with a povidone–iodine solution diluted 1:10 with NaCl 0.9% at the end of the operation might be important. Perioperative prophylactic antibiotic regimen with amoxicillin for 5 days was applied routinely in all patients. Sugarbaker et al. [4] even used prophylactic triple intravenous chemotherapy for 5 days with cefazolin, levofloxacin and metronidazole for reasons of the prosthetic material used.

The rate of bronchopleural fistula (9.5%) seems to be very high in comparison to the literature (2.4%; 6.7%) [4,7], and might be associated in our series with the concept of neoadjuvant chemotherapy. It is well documented that in an analogous manner, patients with lung cancer present increased morbidity and mortality after neoadjuvant chemotherapy [12]. An important factor for prophylaxis is a short bronchial stump in order to prevent blind end for secretion retention. This was aimed in all our procedures and a long stump was never the reason for the fistula. The other important point is avoidance of devascularization during preparation. This is difficult to respect during EPP since the radicality of the procedure together with mediastinal lymph node dissection automatically causes some sort of devascularization. Some groups routinely cover the bronchial stump with a parathymic-pericardial fat pad based on a proximal pedicle and fixed with a suture [4]. To our experience coverage of the bronchial stump with vascularized intrathoracic tissue is difficult particularly on the right side for reasons of lacking material when radical resection was performed. The only possible prophylactic coverage needs

the transposition of the omentum or a muscle flap. We do not perform this routinely as a prophylaxis since it would increase the surgical trauma unnecessarily in 90% of the patients. Additionally, we observed that patients with MPM have very often only thin intercostal muscles due to the underlying disease that is associated with kachexy. Furthermore, we have experienced that a postpneumonectomy-empyema even in the presence of BPF can be treated successfully.

Another reason might be drainage duration of the thoracic cavity, which remains a point of discussion. As the 24—28 Charrière tube serves as a monitor for bleeding, we remove it within the first 48 h the latest. Clampage is performed and opened once every 8 h for investigation of bleeding or for compensation of mediastinal shift in cases of excessive fluid production. Other groups insist on leaving in the drain for approximately 3 days allowing removal of fluid of the operated hemithorax for balancing the chest [4,7]. On the other side, the drain can be a potential danger for contamination along the drain to the inside of the thoracic cavity.

But not only prophylaxis, management of bronchopleural fistula and postpneumonectomy-empyema also varies among different centres ranging from bronchoscopical sealing of small fistulas, open closure of the bronchial stump, debridement of the pleural cavity to tube thoracostomy alone, Clagett window, obliteration of the pleural space with antibiotic solution (Clagett procedure) [16] or vascularized tissue or even thoracoplasty [17] with success rates up to 90%. Our closed chest management with stepwise radical debridement of the pleural cavity and packing with povidone—iodine-soaked dressings plus coverage of the bronchial stump if bronchopleural fistula, and finally, instillation of antibiotic solution [14] was 100% successful in terms of mortality and control of infection. This might be due to aggressive resection of the necrotic tissue in a standardized and repeated manner allowing consequent purgation of the pleural space. We were not obliged to remove the pericardial patch or the mersilene mesh for diaphragmatic reconstruction.

The second most common surgical complication was chylothorax with 7.9% of the patients, which was also observed by other groups in a relatively high percentage (6.7%) [7]. This is probably due to aggressive resection along the thoracic aorta and the inferior mediastinum. A prophylactic measure can be clipping of the lymphatic vessels to assure lymphostasis or ligating the thoracic duct near the diaphragm. However, the lymph vessels are often not identifiable during surgery. If chylothorax occurs, conservative treatment with parenteral nutrition is the first step. When chylus secretion exceeds 500 ml after 5 days, reoperation is recommended [18]. We performed open closure of the thoracic duct in all cases of revision. If the leakage cannot be identified, mass ligature of the tissues containing the thoracic duct above the diaphragm or below the aortic arch is recommended [19]. We always packed the thoracic cavity with povidone—iodine soaked dressings at the end of the reoperation. They were removed after 48 h with the intention to prevent empyema and to enable us to ensure sealing.

Failure of the pericardial-patch occurred in 4.7%. The patients suffered from cardiac herniation in two cases within the first hours after operation. In one case, persistent orthostatic hypotension was caused by a too tightly sutured patch and became finally apparent 15 days postoperatively. These complications are fully avoidable with the appropriate surgical technique. It is recommended to start the sutures of the pericardial patch in the deepest and most difficult part and to ensure that the stitches are set in the remaining pericardium and not in the loose tissue of the posterior mediastinum.

Another complication related to technical problems was a gastric herniation due to dehiscence of the diaphragmatic patch. This complication rate of 1.7% is particularly lower than reported in the literature (8.1%) [7] although we perform complete resection of the diaphragm for radicality reason. It is recommended to leave a rim of the diaphragmatic crus around the oesophagus for stability at the hiatus, but there are no oncologic data supporting one or other technique [4]. Since this event, all marlex meshes were fixed with stitches around all the ribs, which avoided another herniation.

Bleeding complications became rare with the routine application of argon beamer technique for haemostasis and is comparable to the one reported in the literature [7].

Non-technical complications were atrial fibrillation (AF) in most cases. The reported percentage of 37% is comparable to AF rates observed by other groups (17%, 24% and 44%) [4,7,20]. In a multivariate analysis of patients undergoing thoracic surgery, significant variables for the incidence of atrial fibrillation were male sex, age over 50 years, congestive heart failure, history of arrhythmias and history of peripheral vascular disease [21]. But nevertheless, prophylactic strategies are currently not recommended.

In conclusion, EPP after neoadjuvant chemotherapy can be performed with a low mortality but complications are still frequent even if they can be successfully managed. This relatively high incidence of complications reflects the magnitude of this procedure. It was obvious for us that there is a learning curve although not provable in this data analysis. By an increasing number of operations performed by the same team, many of the complications are either avoidable or treatable in a very early phase. An interesting approach would be anticipation of the known complications; therefore, we wanted to perform a multivariate regression analysis in order to define independent prognostic factors.

Surprisingly, age does not significantly influence the incidence of postoperative complications. The side of operation did not influence the overall complication rate although bronchopleural fistula was observed only after right-sided EPP ($p = 0.07$). According to our results, the EORTC-score seems to be a prognostic factor for prediction of postoperative complications. However, this factor was demonstrated to be the only influencing one, so that multivariate analysis was not performed. This might be feasible in the future with a higher number of patients so that independent factors for postoperative complications may be defined. Inclusion of this knowledge in the algorithm of decision for EPP indication might help in selecting patients and therefore improve short-term outcome.

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Appendix A. Conference discussion

Mr B. Keogh (*Birmingham, United Kingdom*): You have shown a very good mortality rate, but it seems as though the price that you pay for that is a significant amount of postoperative morbidity. Do you have an obvious and easy explanation for the high incidence of empyemas?

Dr Opitz: Dr Sugarbaker reported in the postgraduate course an empyema rate of 3% only. It might be possible that our empyema rate is higher due to the fact that patients received neoadjuvant chemotherapy. And as to date we have the largest series of patients undergoing neoadjuvant chemotherapy followed by extrapleural pneumonectomy, we don't have any comparison.

Dr M. Orringer (*Ann Arbor, USA*): There still remains controversy on the other side of the water if this major undertaking is justified in most patients with mesothelioma. Despite David Sugarbaker's enthusiasm and the tremendous work that he and you and your colleagues have done in this area, this is an enormous price to pay for a disease that for most of our patients translates to 12–14 months of survival. A right-sided empyema and bronchopleural fistula is just a horrendous complication for somebody to put up with in the last months of life.

You say that the bronchopleural fistula was managed. How about the empyema? Did they have an open window (Eloesser procedure)? Did they have the chest closed and filled with antibiotics (Clagett procedure)? Did the patients and their families spend the rest of their time caring for a huge open chest wound? What would the survival have been had the patients received only chemoradiation therapy and no resection? Would it have been any less traumatic for the patient? Again, I compliment you on a tremendous paper. Thank you very much.

Dr Opitz: As to your first comment concerning morbidity, we agree, morbidity rates of 60% are high. But taking into account the overall results of our multicenter national study, we observed that quality of life within the first 3 months after operation did not deteriorate. Despite the reported morbidity, the procedure is justified since most complications can be treated successfully and quality of life is re-established. The median survival time is almost 2 years and better than reported in any series. Concerning your question to the empyema, we did not perform any Clagett window. We apply a radical debridement in 2-day intervals and fill the pleural cavity with povidone–iodine soaked dressings. This procedure is repeated three times and the thoracic cavity is finally closed after filling with an antibiotic solution. With this treatment, we were able to control infection in every case.

Dr J. Benfield (*Los Angeles, USA*): I would like to follow up on Dr Orringer's comment about quality of life. In my experience with patients with malignant mesotheliomas, they unfortunately have a miserable quality of life despite everything we do and try. I noted in your presentation that you had a significant incidence of objective remission based on the induction chemotherapy. This suggests the possibility that chemotherapy might eventually become primary therapy with resection as adjunctive treatment. Do you and your colleagues think there is a place, or perhaps there will be a place, for random prospective studies of nonoperative therapy (with operation as an adjunct, if needed) versus induction therapy plus extrapleural pneumonectomy?

Dr Opitz: We don't have plans for that at the moment, no.

Dr Benfield: I gather you don't anticipate that there will be a place for that in the future. Let me be on record to say that I think there will be a place for that in the future.

Dr G. Leschber (*Berlin, Germany*): Dr Sugarbaker yesterday told us that he always covers this stump with some tissue. What is your experience? Do you have any strategy to cover the right-sided stump, bronchial stump?

Dr Opitz: After radical extrapleural pneumonectomy we never find local viable tissue to cover the bronchial stump. An intercostal muscle flap after EPP is often thin. Other groups cover the stump with an extrathoracic muscle flap or with aomentoplasty. But we do not perform this since it would be unnecessary in 80%.

Dr B. Passlick (*Freiburg, Germany*): I think that this is the largest series of patients who were treated neoadjuvantly with this disease. So I would like to know what was the tumor response to the neo-adjuvant treatment? Do you have any data on the histological specimen of the primary tumor and also on the lymph nodes? Was there any tumor regression or was it without any reaction after the neoadjuvant treatment?

Dr Opitz: The majority of tumor specimen show a response of less than 10% necrosis and only in 5% the tumor is necrotic in up to 90%.

Dr W. Weder (*Zurich, Switzerland*): I would like to answer to Dr Benfield that there is a randomized trial activated in England which is called the MARS trial, and investigate the role of surgery after induction chemotherapy in a randomized fashion.