original article

Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma

W. Weder[1†], R. A. Stahel[2*†], J. Bernhard[3,8], S. Bodis[4], P. Vogt[5], P. Ballabeni[3], D. Lardinois[6], D. Betticher[7], R. Schmid[8], R. Stupp[9], H. B. Ris[10], M. Jermann[2], W. Mingrone[11], A. D. Roth[12] & A. Spiliopoulos[13]
On behalf of the Swiss Group for Clinical Cancer Research

[1]Department of Thoracic Surgery; [2]Clinic and Poliklinik for Oncology, University Hospital, University Hospital Zurich, Zurich; [3]Swiss Group for Clinical Cancer Research (SAKK), Bern; [4]Institute for Radio-Oncology, Kantonsspital Aarau, Aarau; [5]Institute of Pathology; [6]Department of Thoracic Surgery, University Hospital, University Hospital Zurich, Zurich; [7]Department of Medicine, Hospital of Fribourg, Fribourg; [8]Clinic and Policlinic for Thoracic Surgery, Inselspital Bern, Bern; [9]Centre Pluridisciplinaire d'Oncologie; [10]Service de chirurgie thoracique, Centre Hospitalier Universitaire Vaudois, Lausanne; [11]Zentrum für Onkologie, Kantonsspital Aarau, Aarau; [12]Département de Chirurgie Oncochirurgie; [13]Unité Chirurgie Thorac, University Hospital Geneva, Genève, Switzerland

Background: The aim of this multicenter trial was to prospectively evaluate neo-adjuvant chemotherapy followed by extrapleural pneumonectomy (EPP) and radiotherapy, including quality of life as outcome.

Patients and methods: Eligible patients had malignant pleural mesothelioma of all histological types, World Health Organization performance status of zero to two and clinical stage T1–T3, N0–2, M0 disease considered completely resectable. Neo-adjuvant chemotherapy consisted of three cycles of cisplatin and gemcitabine followed by EPP. Postoperative radiotherapy was considered for all patients.

Results: In all, 58 of 61 patients completed three cycles of neo-adjuvant chemotherapy. Forty-five patients (74%) underwent EPP and in 37 patients (61%) the resection was complete. Postoperative radiotherapy was initiated in 36 patients. The median survival of all patients was 19.8 months [95% confidence interval (CI) 14.6–24.5]. For the 45 patients undergoing EPP, the median survival was 23 months (95% CI 16.6–32.9). Psychological distress showed minor variations over time with distress above the cut-off score indicating no morbidity with 82% (N = 36) at baseline and 76% (N = 26) at 3 months after surgery (P = 0.5).

Conclusions: The observed rate of operability is promising. A median survival of 23 months for patients undergoing EPP compares favourably with the survival reported from single center studies of upfront surgery. This approach was not associated with an increase in psychological distress.

Key words: extrapleural pneumonectomy, malignant pleural mesothelioma, neo-adjuvant chemotherapy, quality of life

introduction

In Europe, the incidence of malignant pleural mesothelioma (MPM) is continuing to rise with a peak of the epidemic expected around the year 2015 [1–3]. In the past, there was a tendency to associate MPM with a sense of hopelessness and specific oncologic care was not offered to many patients. This situation has changed recently with evidence that chemotherapy palliates symptoms [4, 5] and the demonstration of a survival benefit with the addition of the folate antagonists pemetrexed or raltitrexed to cisplatin [6, 7].

The role of surgery for earlier stages of pleural MPM continues to be a matter of debate [8]. Extrapleural pneumonectomy (EPP) in combination with adjuvant chemotherapy is, however, the only procedure which has been associated with long-term survival and even cure in selected patients. The largest published experience with this procedure in conjunction with adjuvant chemotherapy and radiotherapy has been published by the group at the Brigham's Hospital in Boston, MA. An update from this group included 183 patients intended for the trimodality approach [9]. The median survival in the 176 patients alive after surgery was 19 months and the estimated 2- and 5-year survival was 38% and 15%, respectively. The perioperative mortality of EPP was reported to be up to 31% in an initial series [10]; however, with more experience and better preoperative management, the mortality has decreased to between 3.4 and 6.8% [11–13].

Correspondence to: Dr R. A. Stahel, Clinic and Policlinic of Oncology, University Hospital, CH-8091 Zurich, Switzerland. Tel: +41-44-634-2871; Fax: +41-44-634-2872; E-mail: rolf.stahel@usz.ch

[†]Both authors contributed equally to this manuscript.

The difficulty in providing adjuvant therapy after EPP led us to carry out a pilot study at the University Hospital of Zürich with a neo-adjuvant approach using the best documented combination chemotherapy at that time [14]. Nineteen patients with potentially resectable mesothelioma were treated with three cycles cisplatin and gemcitabine [15]. The response rate was 32% and 16 patients underwent EPP with no perioperative mortality and the median survival of all patients was 23 months. The aim of this trial SAKK 17/00 was to prospectively evaluate neo-adjuvant chemotherapy followed by EPP with or without radiotherapy in a multicenter setting in Switzerland.

patients and methods

trial design
The original trial design was an optimal two-stage design for the primary endpoint of operability after chemotherapy with the original target sample size of 30 patients An operability rate of 50% or less is considered as unworthy, while a rate of at least 80% is considered as promising for further investigation. After confirming operability on 11 of 13 patients in stage I, the sample size was increased to 61 patients to address questions regarding the patients' quality of life (QoL), with psychological distress as the primary endpoint. The trial was approved by the appropriate local ethics committees and Swissmedic.

eligibility criteria
Patients were eligible for the trial if they had a histologically confirmed diagnosis of MPM, including all subtypes and clinical T1–T3, N0–2, M0 disease considered to be completely resectable as evaluated by a thoracic oncology tumor board including a thoracic surgeon [16]. Mediastinoscopy was carried out in all patients to exclude N3 disease. The choice to include patients with N2 disease and sarcomatous histology was based on the patient selection made in our pilot study [15]. Other requirements included a World Health Organization performance status (PS) of zero to two, a serum creatinine within normal limits, no major organ dysfunction, no history of other malignancies, a calculated postoperative forced expiratory volume in one second (FEV1) >40% of predicted value, and a written informed consent. Patients were not eligible if they had had prior pleurectomy or lung resection (except small biopsies for diagnostic purposes) or contraindications to surgery or prior chemotherapy.

chemotherapy
Neo-adjuvant 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, given every 28 days. Dose modification was mandated as follows: Cisplatin was to be reduced to 50% for a serum creatinine >120 μmol/l and omitted for a serum creatinine >150 μmol/l. The dose of gemcitabine was to be reduced to 75% for a neutrophil count <1.5 g/l or a platelet count <100 g/l and omitted for a neutrophil count <1.0 g/l or a platelet count <75 g/l.

surgery
All patients were scheduled to undergo EPP. Reasons for inoperability were a predicted postoperative FEV1 <40%, based on immediate preoperative spirometry and lung perfusion scan or unresectability due to tumor progression documented on chest computed tomography scan after chemotherapy. The EPP was defined as an en bloc resection of the entire pleura, lungs, ipsilateral diaphragm and pericardium as described previously [15]. The ipsilateral peritracheal, infracarinal and perioesophageal lymph nodes were resected. Additionally, the port sites of the previous thoracoscopy and drain channels were resected.

Patients found to have a multilevel invasion of the chest wall or mediastinal structures at thoracotomy were not resected.

The surgeons participating in this trial needed to have an experience of at least 15 EPP carried out in the last 5 years.

radiotherapy
Radiotherapy was recommended to areas of obvious incomplete resection and to high-risk areas as defined by the surgeon, such as the sinus phrenicocostalis and sites of surgical incisions. Clips were to be placed at areas of high risk and simulation of patients were to include consultation with the thoracic surgeon and radiotherapy was limited to the clipped area with a margin of 2–5 cm dependent on anatomical site and breath dependent mobility. Radiation was to start within 8 weeks after surgery. The radiotherapy dose recommended was 60 Gy in 2-Gy daily fraction 5 times per week for residual macroscopic disease and 50 Gy in 2-Gy daily fraction 5 times per week for high-risk areas. If not radically resected, port-site incisions were to be irradiated with a single dose of 1 × 8 Gy.

quality of life
QoL was assessed at registration, day 1 of cycle 3, and 1, 3 and 6 months after surgery with the Rotterdam Symptom Checklist (RSCL) [17]. The RSCL is a cancer-specific questionnaire consisting of subscales for physical symptom distress, psychological distress, activity impairment and an overall evaluation of QoL. Due to feasibility problems, the item 'decreased sexual interest' was replaced by 'chest pain' (at the end of the symptom list) and included in the physical symptom subscale. 'Change in weight' was added as single item in the same response format.

The amended sample size was calculated to assess changes from baseline to 3 months after surgery, with the psychological distress scale (seven items) as the primary endpoint. According to the recommendation of the RSCL manual, a cut-off raw score of ≥15 was defined to detect probable cases of psychological or psychiatric morbidity. To detect an improvement of 20% in the proportion of 'cases' versus 'non cases' with 90% power and an α of 0.05 (one-sided), 53 patients were needed. Assuming missing data in 15% of all patients a total sample of N = 61 was defined. If on a form ≥4 of these items were not answered, the distress score for this assessment was considered as missing. If ≤3 items were not answered, the missing values were replaced by the mean value of the answered items of this assessment. The rate of patients below or above the cut-off was calculated for the assessments at baseline and at 3 months after surgery and compared with the one-sided exact McNemar's test. The other items and scales were analyzed descriptively. To facilitate comparison with other studies, the raw scores of all items and scales were transformed to a standardized scale with values from 0 (worst QoL condition) to 100 (best condition). For all items and scales, we considered a change of ≥8 points as clinically significant [18].

results

Sixty-one patients with MPM, 57 male and four female, entered the trial from July 2000 to June 2003. The median age was 59 years (range: 44–72). PS was zero in 37 patients, one in 23 patients and two in one patient. Forty-two patients had epithelial, 14 patients mixed and three patients sarcomatous type of mesothelioma diagnosed at trial entry, while in two the subtype of mesothelioma could not be ascertained. The combination of clinical T and mediastinoscopically determined N stage is given in Table 1.

Fifty-eight patients have completed the prescribed three cycles of chemotherapy. Two patients went off-treatment after one cycle because of progressive disease and one patient refused

Table 1. Combinations of T and N stages (frequency of patients)

T stage	N stage				Total
	0	1	2	×	
1	10	1	3	0	14
1a	1	0	0	0	1
1b	1	1	0	0	2
2	26	5	2	1	34
3	7	1	2	0	10
Total	45	8	7	1	61

Figure 1. Survival time of all 61 patients by intent to treat analysis as estimated by the Kaplan–Meier method (broken lines: 95% confidence interval) (A) and survival according to histological type (epithelial: N = 38 versus sarcomatoid or mixed: N = 19) (B).

further treatment after two cycles. The incidence of grade 3 or 4 toxicity in 178 documented cycles were as follows: nausea and vomiting 6%, other gastrointestinal toxic effects 1%, myalgia 2% and dyspnea 1%, leucopenia 15% and thrombocytopenia 6%.

In all, 45 of 61 patients underwent EPP after neo-adjuvant chemotherapy. The operability rate was thus 74%. All but one of the operated patients underwent surgery within 6 weeks of completion of the chemotherapy. In 37 patients, the tumor was completely resectable as determined by the surgeon and pathologist (R0 or R1) and in eight patients macroscopical tumor was left behind (R2). The resectability rate was therefore 61%. The reasons for nonoperability in the 16 patients were as follows: tumor progression or withdrawal of consent before completion of neo-adjuvant chemotherapy (three patients), tumor progression at time of completion of neo-adjuvant chemotherapy (five patients), intraoperative decision because of doubtful resectability (four patients), decrease in PS (two patients) and tumor infiltration of the chest wall and myocardial infarction (one patient each). After initial refusal for surgery, one patient finally agreed to be operated 4 months after chemotherapy and thus was considered in this analysis.

Major postoperative complications occurred in 16 (35%) of the patients undergoing EPP. Mortality was 2.2% with one in-hospital death in an obese patient with diabetes due to respiratory infection and subsequent multi-organ failure. Other major complications included respiratory infection (five patients), chylothorax (two patients), bleeding, necessitating reoperation (two patients), bronchial insufficiency (two patients), as well as thrombosis, myocardial infarction, pneumothorax and laryngeal nerve palsy (one patient each). Supraventricular arrhythmias occurred in 11 patients.

The 45 operative specimens after EPP were examined for the presence of necrosis. Tissue necrosis between 10 and 50% or >50% was observed one in each specimen.

Radiotherapy after EPP was administered in 36 of 45 patients. Only in 24 patients radiotherapy was initiated within the 8 weeks postoperatively, however. In six patients additional protocol deviations were necessary because of deteriorating condition or infection (four patients), tumor recurrence (one patient) and radiation pneumonitis (one patient). There were no grade 3–4 acute and long-term toxic effects.

With a median follow-up of 46 months the estimated median survival for all 61 patients entering the trial was 19.8 months [95% confidence interval (CI) 14.6–24.5] from the start of chemotherapy (Figure 1A).

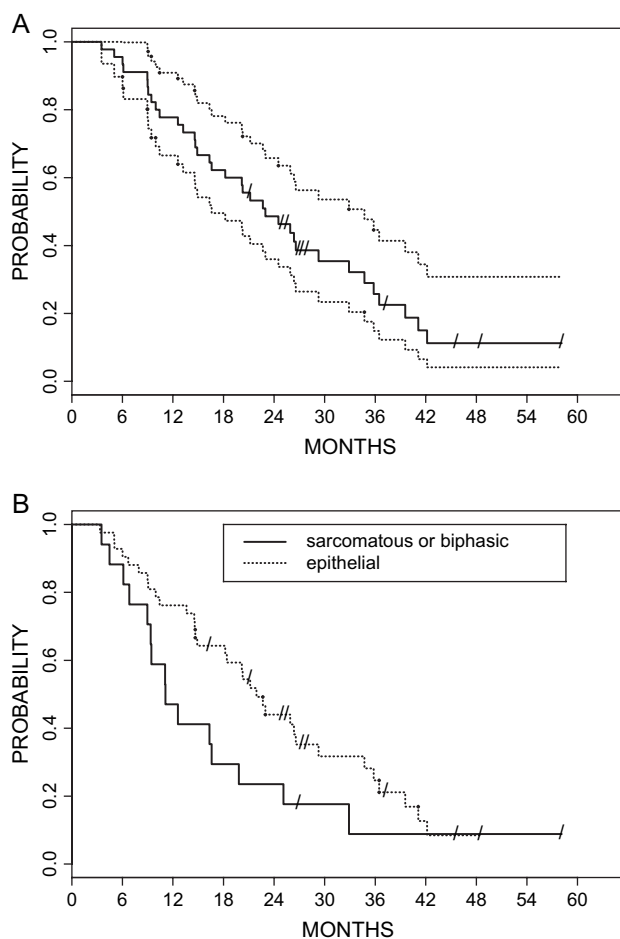For the 45 patients undergoing EPP the estimated median survival was 23 months (95% CI 16.6–32.9) (Figure 2A).

Tumor recurrence after EPP has been observed in 38 patients with a median time to recurrence of 13.5 months (95% CI 10.2–18.8) (Figure 2B).

Operated patients with epithelial tumors tended to have a better survival than patients with sarcomatoid and mixed tumors with median survival of 21.9 months (95% CI 14.9–29.3) versus 11.1 months (95% CI 9–19.8, log-rank $P = 0.259$) (Figure 1B). When the European Organisation for Research and Treatment of Cancer prognostic score [19] was applied to our dataset, survival was 17.4 (range: 3.5–45.6+) months for the high-risk group and 26.3 (range: 5.0–58.1+) months for the low-risk group.

QoL data based on the RSCL was available in all but one patient at baseline and from 93% (57 patients) at cycle 3. Compliance after surgery remained high with RSCL available at months 1, 3 and 6 after surgery in 86% (N = 38), 93% (N = 40) and 94% (N = 36) of operated patients, respectively. In the following section, varying numbers for a given QoL variable and assessment time point are due to missing items on the received forms. Overall, the operated cases showed a tendency towards worse baseline scores than the nonoperated cases (Table 2). Among the four global QoL domains, psychological
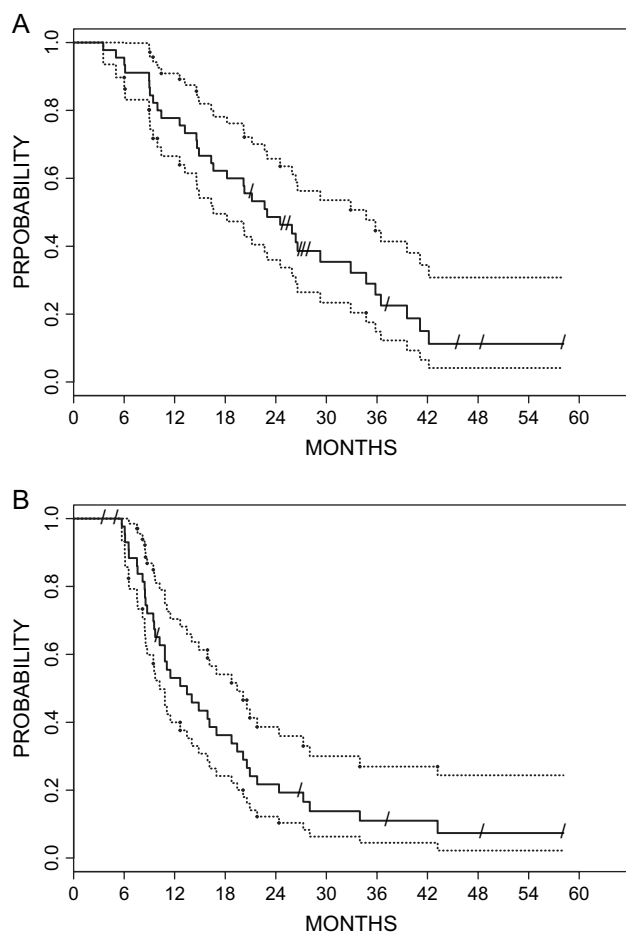
Figure 2. Survival (A) and time to recurrence (B) of the 45 patients undergoing extrapleural peumonectomy (broken lines: 95% confidence interval).

Table 2. Baseline quality-of-life scores

	Operated patients		Nonoperated patients	
	N	Median[a] (25%–75% quartile range)	N	Median[a] (25%–75% quartile range)
Dimension scores				
Psychological distress	44	77.8 (66.7–85.7)	13	81.0 (71.4–98.2)
Physical symptom distress	44	89.9 (84.8–92.8)	13	92.4 (89.9–95.7)
Activities of daily living	44	100.0 (87.5–100.0)	13	100.0 (95.8–100.0)
Overall quality of life	44	83.3 (66.7–83.3)	12	83.3 (83.3–83.3)
Symptom scores				
Tiredness	44	66.7 (66.7–100.0)	13	66.7 (66.7–100)
Shortness of breath	44	66.7 (66.7–100.0)	13	100.0 (66.7–100.0)
Change in weight	43	100.0 (66.7–100.0)	13	100.0 (66.7–100.0)
Chest pain	44	66.7 (66.7–100.0)	13	100.0 (66.7–100.0)

[a]Scores range from 0 to 100, with higher scores indicating a better condition.

distress was most impaired. It showed only minor variation over time (Figure 3A). The rates of operated patients with distress cut-off score indicating no morbidity showed a nonsignificant decline from 82% (36 of 44 patients with a QoL form) at baseline to 76% (26 of 34) at 3 months after surgery (McNemar's exact test for the 34 patients with both QoL forms: $P = 0.4$). Six patients with a baseline score above the cut-off indicated distress below the cut-off at 3 months after surgery; four patients with baseline distress below the cut-off indicated a score above the cut-off at 3 months after surgery.

Physical symptom distress showed the expected worsening at 1 (N = 34, median change = −16.7) and 3 months (N = 34, median change = −11.6) after surgery, followed by a recovery to a level close to baseline at 6 months after surgery (N = 30, median change = −4.3). Activity level was high at baseline and exhibited a similar pattern, with a considerable deterioration at 1 month after surgery (N = 33, median change = −54.2) and recovery close to baseline at 6 months (N = 30, median change = −4.5). Overall QoL was less impaired after surgery, though it did not reach the baseline level 6 months thereafter (N = 30, median change = −8.3) (Figures 3B, C and D).

Patients indicated tiredness, shortness of breath and chest pain was likewise strong at baseline (Table 2). Chest pain

was worse at 1 month after surgery (N = 34, median change = −16.7) and improved to baseline at 6 months after surgery. Tiredness and shortness of breath showed the same impairment at 1 and 3 months after surgery (both N = 34, median changes = −33.3), followed by a recovery back to baseline level. Patients perceived a change in weight at 3 months after surgery (N = 33, median change = −33.3), followed by a recovery to baseline values (Figures 4A–D).

discussion

In our initial trial design, a rate of operability of 80% would constitute a promising outcome warranting further exploration of this approach. Based on an intention-to-treat analysis the operability rate was 74%, and 64% of patients were judged to be macroscopically completely resected by the surgeon. The operatibilty and resectabilty rate might be partially dependent on the effect of induction, chemotherapy the major determination, however, is the stage of the disease at study entry and the willingness of the surgeon to accept macroscopic incompleteness after the EPP. These results, however, come close to our high expectation set forth at the onset of the trial. We are aware that the resectability rate might have been influenced by several factors, including patient selection, the effect of chemotherapy, the experience of the surgical team and the willingness to accept a higher risk with the combined modality approach.

In regard to survival, the results or this multicenter trial do not substantially differ from those of our single-center pilot study with—by intent to treat analysis—a median median survival of 19.8 months (95% CI 14.6–24.5) and a median survival of 23 months (95% CI 16.6–32.9). They compare favorably with the results of the trimodality approach with adjuvant chemotherapy of the group at Brigham's Hospital [9]. While the published results so far are indicative that radical
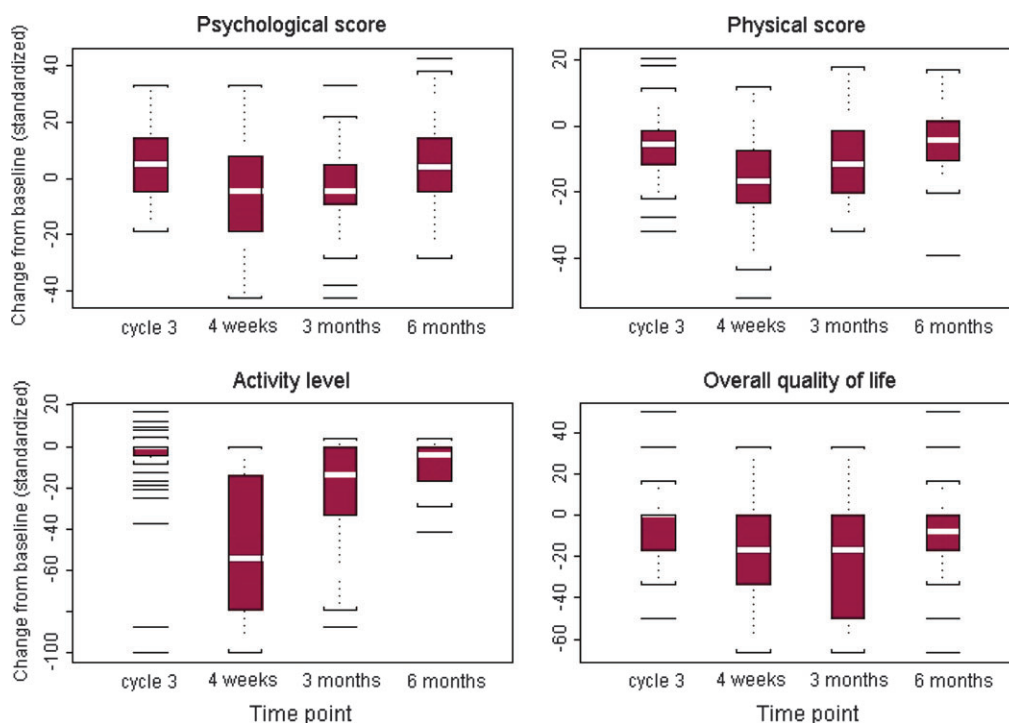
Figure 3. Qualitly-of-life analysis with changes in (A) psychological distress, (B) physical symptom distress, (C) activity level and (D) overall quality of life from baseline (standardized scores; range: 0–100) after three cycles of chemotherapy and 4 weeks, 3 months and 6 months after surgery. Higher change scores indicate an improvement (median changes: white bars).
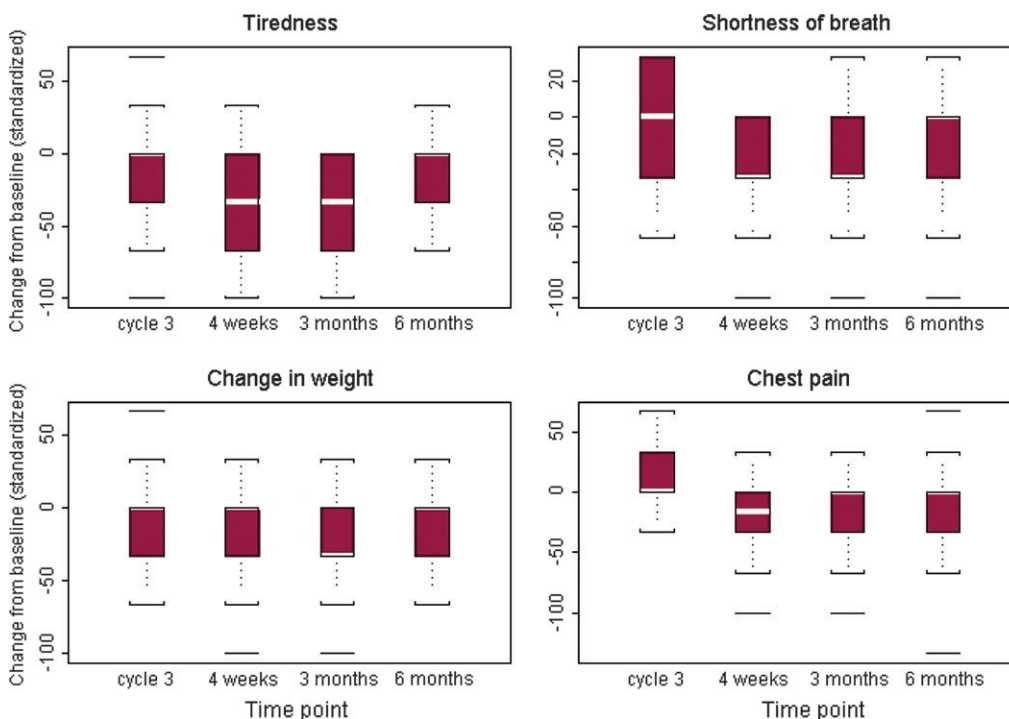

Figure 4. Analysis of major symptoms with changes in (A) tiredness, (B) shortness of breath, (C) weight change and (D) chest pain from baseline (standardized scores) after three cycles of chemotherapy and 4 weeks, 3 months and 6 months after surgery. Higher change scores indicate an improvement (median changes: white bars).

surgery may indeed be associated with a longer survival as compared with chemotherapy alone, final proof of this concept will only come from a randomized trial.

The criteria for selecting patients for EPP remain a matter of debate. Our trial did not exclude patients with unfavorable characteristics such as N2 disease and sarcomatous histology

based on the fact that long-term survival—although at a lower level—has also been reported in these circumstances by others [9] and in our pilot study [15]. We also included patients with radiological T3 disease, if the extent of chest wall invasion was such that the thoracic surgeon deemed a resection possible. Based on cancer registry data, the incidence of newly diagnosed patients with MPM in Switzerland during the years of the trial was 137 cases per year [20]. Considering that peak age-specific incidence is >70 years, we estimate that at least 15% of patients <70 years with newly diagnosed MPM took part of this trial.

The response rate of MPM to cisplatin and gemcitabine has been reported to range between 16 and 47% [14, 21, 22] and was 32% in our previous neo-adjuvant trial [15]. Because of the inherent difficulties to assess responses, we, however, elected not to determine radiological response in our trial. The response to cisplatin and pemetrexed has been reported to be 41% in advanced MPM [6] and most groups are now exploring this combination in a neo-adjuvant approach.

Our perioperative or in-hospital mortality was 2.2% which compares favorably with other reports of EPP without neo-adjuvant chemotherapy [11–13]. Resection after chemotherapy is technically more demanding due to a scarring reaction at the dissection plane and patients are more susceptible to general complications such as infections, acute respiratory distress syndrome and others [23]. We observed as major surgical complications arrhythmias in 35% followed by respiratory tract infections in 10% and bleeding, chylothorax and bronchial stump insufficiency in 4% each. All could be treated successfully. Thus, while EPP after chemotherapy is a demanding procedure, it can be carried out with an acceptable mortality and morbidity, but should be reserved for dedicated centers.

Within the observation period, tumor recurrence after EPP has occurred in 84% of patients with a median time to recurrence of 13.5 months. Radiotherapy can be effective for local palliation and has been indicated to be of benefit for the prevention of malignant seeding after invasive diagnostic procedures [24, 25], however, this recently come in doubts by another report [26]. Relapse in the ipsilateral hemithorax after EPP has remained a major problem, despite the fact that adjuvant radiotherapy has been part of trimodality therapy since its inception [27]. A phase II trial from the Memorial Sloan-Kettering Cancer Center of postoperative radiotherapy in high doses indicated a decrease in the local failure rate to 6% without apparent impact on survival [28]. Intensity-modulated radiotherapy after EPP has been intensively investigated by the M.D. Anderson group [29, 30] and appears also promising in reducing the rate of local relapse. Whether high doses of intensity-modulated or conformal radiotherapy are feasible and provide better local control after EPP in a neo-adjuvant setting is uncertain [31] and currently under investigation by our group.

In previous MPM trials, QoL endpoints were related to chemotherapy effects [4, 6, 7, 32, 33]. We investigated QoL across the whole trimodality treatment and hypothesized an improvement of psychological distress at 3 months after surgery. Psychological distress was most impaired among the four global QoL dimensions. It showed only minor variation over time despite the aggressiveness of the therapeutic approach and a full recovery after a period of 6 months which was longer than expected. Roughly every fourth to fifth patient indicated psychological morbidity, pointing towards the importance of supportive care interventions. Physical symptoms and activity showed the expected worsening after surgery, followed by a recovery back to baseline level.

While combination chemotherapy with a platin compound and a folate antagonist is the recommended treatment of patients with advanced disease, our results indicate that patients with potentially operable MPM can be offered the benefit of a more radical multimodality approach including neo-adjuvant chemotherapy and EPP without major long-term impairment on their QoL, if the treatment is carried out by an experienced team.

acknowledgements

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