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ORIGINAL ARTICLE

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Relapse pattern and second-line treatment following multimodality treatment for malignant pleural mesothelioma†

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Abstract

OBJECTIVES: To analyse the relapse pattern and influence of second-line treatment after recurrence of malignant pleural mesothelioma (MPM) in patients who had previously undergone multimodality treatment.

METHODS: Between September 1999 and December 2013, 136 patients underwent macroscopic complete resection (MCR) by extrapleural pneumonectomy after induction chemotherapy for MPM. We analysed 106 patients who presented with recurrent disease until October 2014. Data were retrieved from our mesothelioma database, with additional information regarding precise localization gathered by reviewing the imaging and medical records.

RESULTS: The overall recurrence rate was 78% (106/136 patients). The median freedom from recurrence was 9 months after surgery [95% confidence interval (95% CI) 7–10]. Local recurrence only was observed in 33 patients (31%), distant metastases only in 27 patients (26%) and simultaneous distant and local recurrence in 46 patients (43%). Local recurrence was observed significantly less frequently in patients having received adjuvant radiotherapy (19 vs 47%, $P = 0.003$), but there was no significant impact on overall survival (OS) [radiation: 22 months (95% CI 19–24); no-radiation: 23 months (95% CI 18–27), $P = 0.6$]. The median OS was 22 months (95% CI 21–24), median post-recurrence survival (PRS) was 7 months (95% CI 5–9) and patients with local recurrence only survived significantly longer (12 months, 95% CI 8–16) compared with patients with distant recurrence only (5 months, 95% CI 2–8) or distant plus local relapse (6 months, 95% CI 3–9; $P = 0.04$). A total of 78 patients received a second-line therapy after tumour recurrence: chemotherapy ($n = 48$), local radiotherapy ($n = 9$), surgery ($n = 10$) or a combination thereof ($n = 11$). Patients undergoing second-line treatment survived significantly longer compared with patients not receiving therapy ($P < 0.0005$). The median PRS after surgery was significantly longer than that of patients receiving chemo-, radio- or chemo-radiotherapy ($P = 0.04$).

CONCLUSIONS: Local recurrence of MPM remains the most frequent type of relapse even after multimodality treatment including MCR. In the present cohort, active treatment seems beneficial to the patient since surgical excision of local tumour relapse has good long-term outcome in selected patients. Thus, second-line treatment may prolong PRS; however, these results need to be confirmed in a prospective manner.

Keywords: Malignant pleural mesothelioma • Local recurrence • Distant failure • Second-line therapy • Multimodality treatment

INTRODUCTION

Currently, most centres specialized in the treatment of patients with malignant pleural mesothelioma (MPM) approach this disease with multimodality treatment including macroscopic complete resection (MCR) by either extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) [1–5]. However, rates of local and distant failure are high and appear early in the course of the disease [6, 7]. Little is known about the precise pattern of relapse after multimodality treatment including EPP [7–11] and even fewer data exist on the clinically most relevant question of how the course of the disease can be influenced by implementing a second line treatment after recurrence.

In this retrospective analysis of a large cohort having undergone induction chemotherapy followed by EPP, we wished to address two major points of interest: first, a description of the precise relapse pattern; and second, the impact of a second treatment on post-recurrence survival (PRS).

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MATERIALS AND METHODS

We performed a retrospective analysis on a mesothelioma database comprising data collected on MPM patients referred to our institution between March 1999 and July 2014, having been treated with a multimodality protocol and then presented with tumour recurrence. Local ethics committee approval was granted for retrospective analysis of this mesothelioma database (StV 29-2009, EK-ZH 2012-0094).

Multimodality treatment concept

Decisions regarding treatment were taken by an interdisciplinary tumour board consisting of thoracic surgeons, oncologists, radiation oncologists, respirologists and radiologists. All patients received induction chemotherapy; platinum/gemcitabine was used before implementing platinum/pemetrexed. Eligibility for multimodality treatment included biopsy-proven MPM (of any histological subtype) at clinical stage T1–3 N0–2 M0, and anticipated complete resectability by EPP as assessed by an experienced thoracic surgeon.

MCR was achieved by EPP in all cases. As described previously, standard EPP was performed within 6 weeks of completing the final cycle of chemotherapy [12]. In total, 59 patients received adjuvant radiotherapy after EPP, 10 of which were treated within the SAKK 17/04 protocol [13]. High-risk zones were defined either by the operating surgeon or according to the SAKK 17/04 protocol. Over the course of the study, different techniques of radiotherapy [3D conformal radiotherapy, $n = 41$; intensity-modulated radiation therapy (IMRT), $n = 9$; unknown, $n = 9$] and doses (median 50 Gy, range: 13–60) were applied.

Diagnosis and treatment of recurrence

Patients were followed up in outpatient clinics on a regular basis with serial computed tomography (CT) scan or positron emission tomography (PET)/CT every 4–6 months. Patient data, including time and gross location of recurrence, were recorded prospectively in our mesothelioma database. The precise location of recurrence was determined by reviewing chest CT or PET/CT scans and patient records.

Local recurrence was defined as tumour recurrence at the ipsilateral hemithorax, including the chest wall, diaphragm, pericardium, ipsilateral mediastinal lymph nodes as well as axillary, sub- and supraclavicular lymph nodes. Distant recurrence was further divided into recurrence at the contralateral hemithorax (with the same subgroups at the ipsilateral hemithorax), in the abdomen or at other distant locations.

Decisions regarding second-line treatment were taken by an interdisciplinary tumour board considering the patient's performance status and the presence of symptoms of disease progression, the location of recurrence and initial response to chemotherapy.

Statistical analysis

Overall survival (OS) was calculated as the time between the first cycle of chemotherapy and death. PRS was calculated as the time between recurrence and time point of death. Patients without an event were censored at the time of last follow-up. Freedom from recurrence (FFR) was calculated as the time between EPP and diagnosis of tumour relapse. The Kaplan–Meier method was used to estimate the FFR, OS and PRS. The log-rank test was used to test for significant differences between groups. Numbers are shown as median plus 95% confidence interval (95% CI) unless otherwise stated.

A stepwise Cox regression was used to test the independence of FFR from different factors. This analysis included all factors that were significant in the Kaplan–Meier analysis.

Fisher's exact test was used to compare categorical variables. A *P*-value below 0.05 was considered as statistically significant.

All statistical analyses were performed using the SPSS software package (IBM Corp., Released 2013; IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA).

RESULTS

Between July 1999 and August 2013, 405 patients with MPM were referred to our institution. Of these, 214 were eligible for multimodality treatment and 140 finally underwent induction chemotherapy and EPP.

Of the 136 patients analysed for recurrent disease, 108 (79%) were indeed found to have recurrent disease, whereas 24 (18%) had no tumour relapse during the observation period (until October 2014); 4 patients (3%) were lost to follow-up. The median follow-up was 22 months (range: 6–121); 106 (78%) patients had sufficient information to localize tumour recurrence accurately as well as second-line treatment. See Table 1 for patients' characteristics.

Tumour relapse was diagnosed by serial imaging (CT, PET/CT or MRI) in 69 patients (65%), by pathological confirmation in 33 cases (31%) [via tissue biopsy in 18 patients (17%) or fine needle aspiration with cytology in 15 patients (14%)], by clinical presentation in 3 patients (3%) and by autopsy in 1 patient (1%). Overall, with additional tissue biopsies taken at later points in some cases, a total of 31 biopsies were available for 27 patients. Comparing histotype at the initial diagnosis and at the time of recurrence, 3

Table 1: Patient characteristics

Age at surgery (years), median (range)	61 (36–72)
Number of patients, *n* (%)	106 (100)
Gender, *n* (%)	
Male	93 (88)
Female	13 (12)
Pathological IMIG stage, *n* (%)	
I	7 (7)
II	22 (21)
III	66 (62)
IV	11 (10)
Histology, *n* (%)	
Epithelioid	68 (64)
Biphasic	36 (34)
Sarcomatoid	2 (2)
Induction chemotherapy, *n* (%)	
Platinum/gemcitabine	41 (39)
Platinum/pemetrexed	65 (61)
Adjuvant radiotherapy, *n* (%)	
No	47 (44)
Yes	59 (56)

patients showed a transformation from an epithelioid to a biphasic and 1 patient from a biphasic to an epithelioid histotype.

Relapse pattern

The median FFR was 9 months after EPP (95% CI: 7–10) and did not differ significantly between different sites of recurrence: local recurrence occurred at a median of only 9 months (95% CI 8–10), distant recurrence only at 11 months (95% CI 6–17) and simultaneous local and distant relapse at 9 months (95% CI 6–11) ($P = 0.7$).

Tumour recurrence was local only in 33 patients (31%), the site of relapse was distant only in 27 patients (26%) and local as well as distant (both) in 46 patients (43%). The ipsilateral hemithorax was the most frequent site of recurrence (79 patients, 75%) followed by the abdomen (53 patients, 50%) and the contralateral hemithorax (39 patients, 37%); for details see Table 2.

The distribution of tumour recurrence according to IMIG stage is shown in Figure 1; the relative percentage of local relapse tended to be higher at lower IMIG stages, whereas contralateral hemithorax and abdominal manifestations were more frequent at higher IMIG stages.

FFR was prolonged significantly for lower compared with higher IMIG stages [IMIG stage I ($n = 7$): median FFR 19 months (95% CI 0–38); II ($n = 22$): 13 months (6–20); III ($n = 66$): 8 months (7–9); IV ($n = 11$): 8 months (4–12); $P = 0.001$; Fig. 2A] and also dependent on mediastinal lymph node involvement at the time point of EPP [pN0 ($n = 62$): 11 months (95% CI 8–14); combined pN1 and pN2 ($n = 44$): 7 months (95% CI 6–9); $P = 0.002$; Fig. 2B]; moreover, FFR was significantly longer in patients who underwent induction chemotherapy with platinum/gemcitabine [$n = 41$; 12 months (95% CI 9–14)] compared with those having received platinum/pemetrexed [$n = 65$; 8 months (95% CI: 8–9) $P = 0.01$; Fig. 2C]. Differences in FFR did not depend on the response to induction chemotherapy according to modified RECIST criteria [14] [partial response ($n = 25$): 11 months (9–13); stable disease ($n = 26$): 8 months (7–10); progressive disease ($n = 18$): 8 months (6–10); $P = 0.2$] or on histotype [epithelioid ($n = 64$): 9 months (8–11); non-epithelioid ($n = 38$): 8 months (6–10); $P = 0.3$]. After multivariate analysis in a Cox regression model, pathological IMIG stage remained a prognostic factor for prolonged FFR ($P = 0.001$).

Table 2: Exact location of recurrence

	Number of patients ($n = 106$)	Percentage of all patients
Ipsilateral hemithorax		
Total	79	75
Neopleura	26	25
Chest wall	53	50
Ipsilateral mediastinal LN	20	19
Axillary, sub- and supraclavicular LN	12	11
Diaphragm	9	8
Pericardium	7	7
Distant failure		
Total	73	69
Contralateral hemithorax		
Total	39	37
Pleura	26	25
Chest wall	2	2
Intrapulmonary	20	19
Mediastinal LN	7	7
Axillary, sub- and supraclavicular LN	3	3
Diaphragm	3	3
Pericardium	3	3
Abdomen		
Total	53	50
Peritoneum	33	31
Liver	8	8
Kidney	1	1
Adrenal gland	3	3
Spleen	1	1
Mesentery	3	3
Abdominal LN	16	15
Other distant		
Total	11	10
Muscle	2	2
Bone	6	6
Cervical LN	2	2

LN: lymph node.

Impact of adjuvant radiotherapy after extrapleural pneumonectomy

Fifty-nine (56%) patients received adjuvant radiotherapy after induction chemotherapy and EPP. Morbidity after adjuvant radiotherapy included nausea, vomiting and weight loss in 25 patients, radiation dermatitis in 9 patients, oesophagitis in 4 patients and was not documented in 18 patients.

Patients who underwent hemithoracic radiotherapy presented with significantly less loco-regional recurrence (radiation: 11 patients, 19%; no-radiation: 22 patients, 47%; $P = 0.003$). However, distant metastases occurred more frequently only in the radiation group (radiation: 21 patients, 36%; no-radiation: 6 patients, 13%; $P = 0.008$), and simultaneous distant and local relapse was present in equal proportion (radiation: 27 patients, 46%; no-radiation: 19 patients, 40%; $P = 0.7$; Fig. 3). FFR did not differ significantly between the radiation group ($n = 59$) and the no-radiation group ($n = 47$), with a median of 11 months (95% CI 7–15) and 9 months (95% CI 8–9), respectively ($P = 0.3$; Fig. 2D). OS was similar for both groups [radiation: 22 months (95% CI 19–24); no-radiation: 23 months (95% CI 18–27), $P = 0.6$].

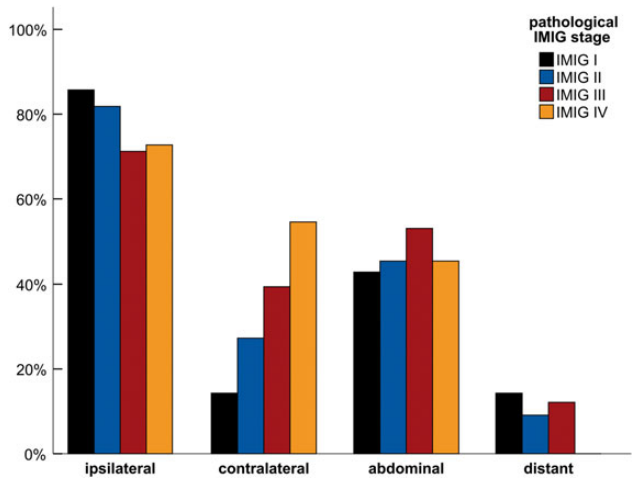

Figure 1: Relapse pattern depending on pathological IMIG stage.

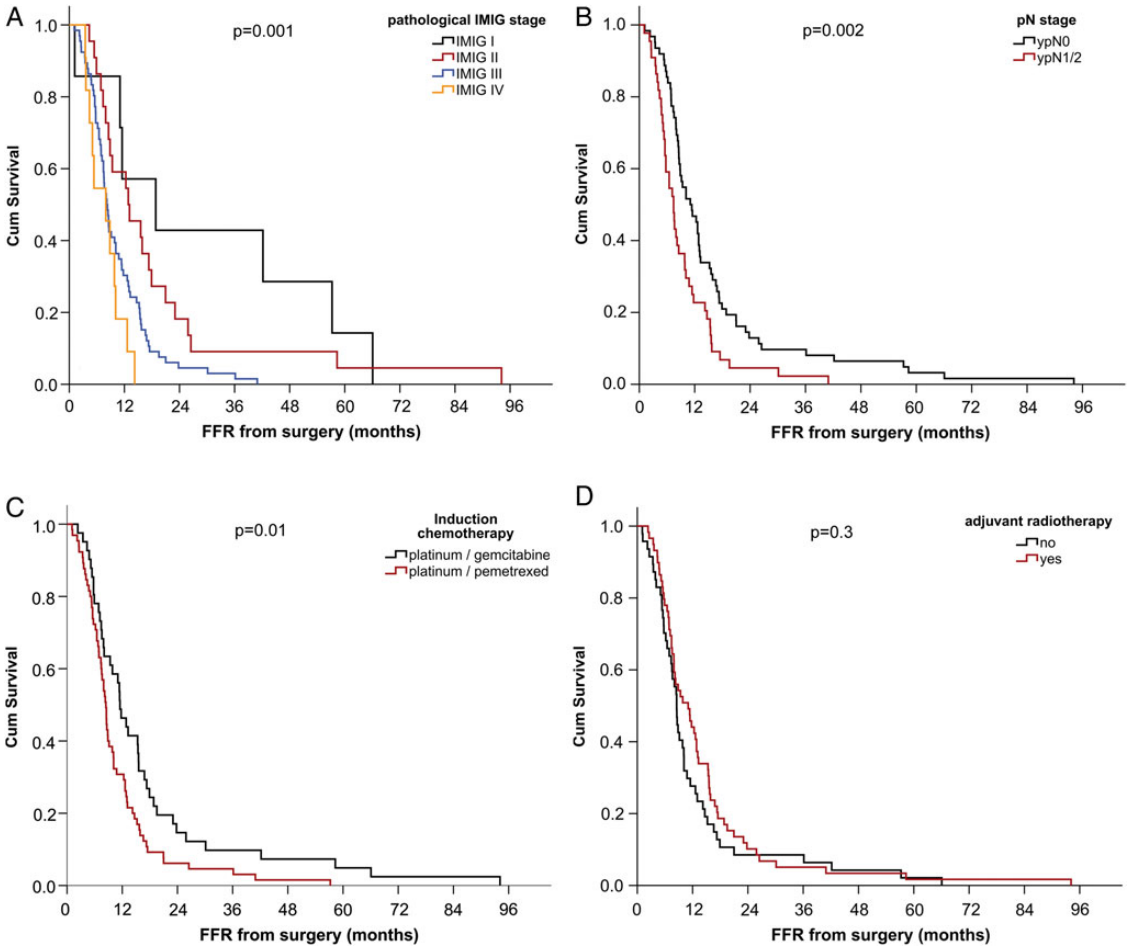

Figure 2: Freedom from recurrence (median 95% CI) as a factor of: (**A**) pathological IMIG stage: I (n = 7): 19 months (95% CI 0–38); II (n = 22): 13 months (95% CI 6–20); III (n = 66): 8 months (95% CI 7–9); IV (n = 11): 8 months (95% CI 4–12); P = 0.001. (**B**) Pathological N stage: pN0 (n = 62): 11 months (95% CI 8–14); pN1/2 (n = 44): 7 months (95% CI 6–9); P = 0.002. (**C**) Induction chemotherapy: platinum/gemcitabine (n = 41): 12 months (95% CI 9–14); platinum/pemetrexed (n = 65): 8 months (95% CI 8–9); P = 0.01. (**D**) Adjuvant radiotherapy: no (n = 47): 9 months (95% CI 8–9); yes (n = 59): 11 months (95% CI 7–15); P = 0.3. FFR: freedom from recurrence; 95% CI: 95% confidence interval.

Long-term oncological outcomes

Median OS for all patients was 22 months (95% CI 20–24; 4 cases censored). Median PRS was 7 months (95% CI 5–9; 4 cases censored). PRS was significantly longer for patients with local recurrence only (12 months, 95% CI 8–16) compared with patients presenting with distant metastases only (5 months, 95% CI 2–8) or simultaneous distant and local relapse (6 months, 95% CI 3–9; P = 0.04; Fig. 4A).

Second-line treatment

Seventy-eight patients (74%) received a second-line treatment, whereas 28 patients (26%) did not; reasons for not receiving a second treatment included refusal in 7 patients, a 'wait-and-see' strategy in 2 patients, poor physical status in 8 patients, death before treatment could be administered in 5 patients and were unknown in 6 patients. Therapy included chemotherapy (n = 55, 71%), local radiotherapy (n = 18, 23%) and redo surgery (n = 16, 21%); 67 patients (86%) received a single treatment modality and 11 patients (14%) received a combination of two different modalities (Table 3). PRS was significantly longer in patients receiving second-line treatment after tumour relapse compared with those not receiving any treatment [10 months (95% CI 8–11) vs 2 months (95% CI 0–5), P < 0.0005; Fig. 4B].

A redo surgery was performed in 16 patients; 9 had resection of soft tissue metastases at the ipsilateral chest wall, 4 had extended chest wall resections and 3 had contralateral partial pleurectomy either alone, in combination with pericardial fenestration or with lung wedge resection and axillary lymphadenectomy. The patient who underwent contralateral pleurectomy had a complicated postoperative course with sick sinus syndrome and systemic inflammatory response syndrome and died on postoperative day 8 after withdrawal of treatment because of poor prognosis. One other patient who underwent contralateral pleurectomy and pericardial fenestration died 12 days after the operation due to treatment withdrawal due to worsening overall condition. For details of combinations of different modalities, see Table 3. There was no significant difference in PRS between these groups, but the group of patients who underwent redo surgery had a significantly longer median PRS compared with those having received other types of second-line therapy and those who received no therapy at all (P < 0.0005; Fig. 4C).

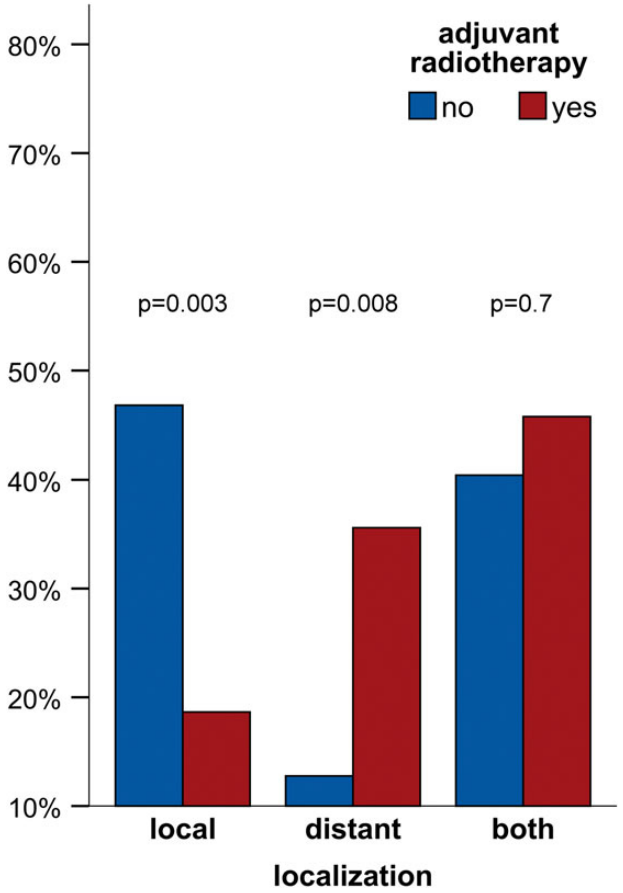

Figure 3: Adjuvant radiotherapy and localization of recurrence: local only (yes: $n = 11$, 19%; no: $n = 22$, 47%; $P = 0.003$); distant only (yes: $n = 21$, 36%; no = 6, 13%; $P = 0.008$) and both (yes: $n = 27$, 46%; no = 19, 40%; $P = 0.7$).

A second-line chemotherapy was administered in 55 patients with a median of four cycles (range: 1–21); 33 patients (64%) received a platinum compound combined with pemetrexed, 9 (17%) received platinum and gemcitabine and 10 (19%) were administered a monotherapy (vinorelbine: 3, pemetrexed: 1, gemcitabine: 2, carboplatin: 4). Adverse reactions of the second chemotherapy included haematological toxicity ($n = 14$, grade 3: 11 patients, grade 4: 1 patient), upper respiratory infections in 3 patients and renal toxicity in 2 patients. Twelve patients had a second chemotherapy without any adverse reaction, and data on toxicity were missing for 10 patients.

Eighteen patients received a second-line radiotherapy (3 patients had IMRT) with a median dose of 50 Gr (range: 20–60). Nine patients had radiation only, 5 had combined radio-chemotherapy and 4 had local radiotherapy of the resection margins after surgery. Adverse reactions to second radiotherapy included radiation dermatitis ($n = 4$), and grade 2 pneumonitis and grade 2 oesophagitis in 1 patient each. No adverse reactions were documented in 5 patients and information about adverse reactions was missing in 5 patients.

Patients receiving second chemotherapy alone, second radiotherapy alone or combined radio-chemotherapy had a similar PRS ($P = 0.3$) but a significantly longer PRS, compared with those patients who had not received a second treatment ($P < 0.0005$; Fig. 4D).

DISCUSSION

This retrospective analysis addressed two questions of high clinical relevance that arise after failure of multimodality treatment for MPM: first, the pattern of recurrence itself, and secondly, the impact of different second-line treatment modalities on PRS.

We analysed data from a large cohort of patients having undergone EPP after induction chemotherapy with detailed information on recurrence. We found that the site of first tumour recurrence seems to correlate with the initial tumour stage, with a trend to more contralateral and abdominal recurrences in higher IMIG stages as has been reported earlier [8]. Not surprisingly, FFR also decreased significantly for higher IMIG stages and for lymph node involvement at the time point of EPP. This is likely due to the increased biological aggressiveness of MPM in higher tumour stages or to the fact that the disease has already progressed more than appreciated with clinical staging given the limited representation of imaging tools in MPM. Moreover, FFR was prolonged significantly in patients who had undergone induction chemotherapy with platinum/gemcitabine, but was not significant in a multivariate analysis. Pathological IMIG stage was the only independent prognosticator for prolonged FFR.

Improved local control after hemithoracic radiotherapy has been described earlier [10, 15]. In our cohort, 59 patients (56%) received adjuvant radiation and the incidence of local tumour recurrence was reduced significantly but without significant influence on OS, which is in line with results from our multicenter randomized controlled trial (MC RCT) of the SAKK 17/04 protocol [13]. Successful local control did not seem to further influence the natural course of the disease which progressed to distant failure. It has already been suggested that better local control cannot improve survival because no highly effective systemic therapy to tackle distant metastasis is available [6]. However, those who have a local failure alone and who can be treated again successfully may benefit from longer OS.

The overall rate of recurrent disease was 79%, which is comparable to the 75% overall recurrence rate published recently by Baldini *et al.* [8]. Our recurrence rates for the abdomen (50 vs 53%), contralateral hemithorax and distant metastasis (11 vs 7%) resemble Baldini *et al.*'s data almost exactly [8]. As in their cohort, the ipsilateral hemithorax was the most frequent site of recurrence, with 75% of all recurrences (31% had local recurrence only and 43% local in combination with distant failure). The 72% local recurrence rate published by Baldini *et al.* [8] and our present results are among the highest rates published; previous reports claimed rates of between 9 and 41% [8, 11]. The reasons for this inconsistency in previously reported recurrence rates and our particularly high recurrence rates are numerous: differences in patient selection, varying treatment modalities as well as length and especially interval and tools for follow-up. At our institution, for example, 4–6 monthly chest and upper abdomen CT or PET/CT scan has long been routine for follow-up; therefore, many asymptomatic patients are diagnosed earlier with recurrent disease. Clearly, with a 4–6 monthly interval of imaging, the described FFR with a median of 9 months can also only be an approximation. However, local recurrence remains an eminent problem in the treatment of MPM and represents a good point of application for novel treatment approaches such as intracavitary chemotherapy in the form of a solution or loaded to a fibrin carrier, photodynamic therapy and others [16–18].

Despite the high local failure rate in our report, OS from induction chemotherapy was 22 months (95% CI 20–24) and compares

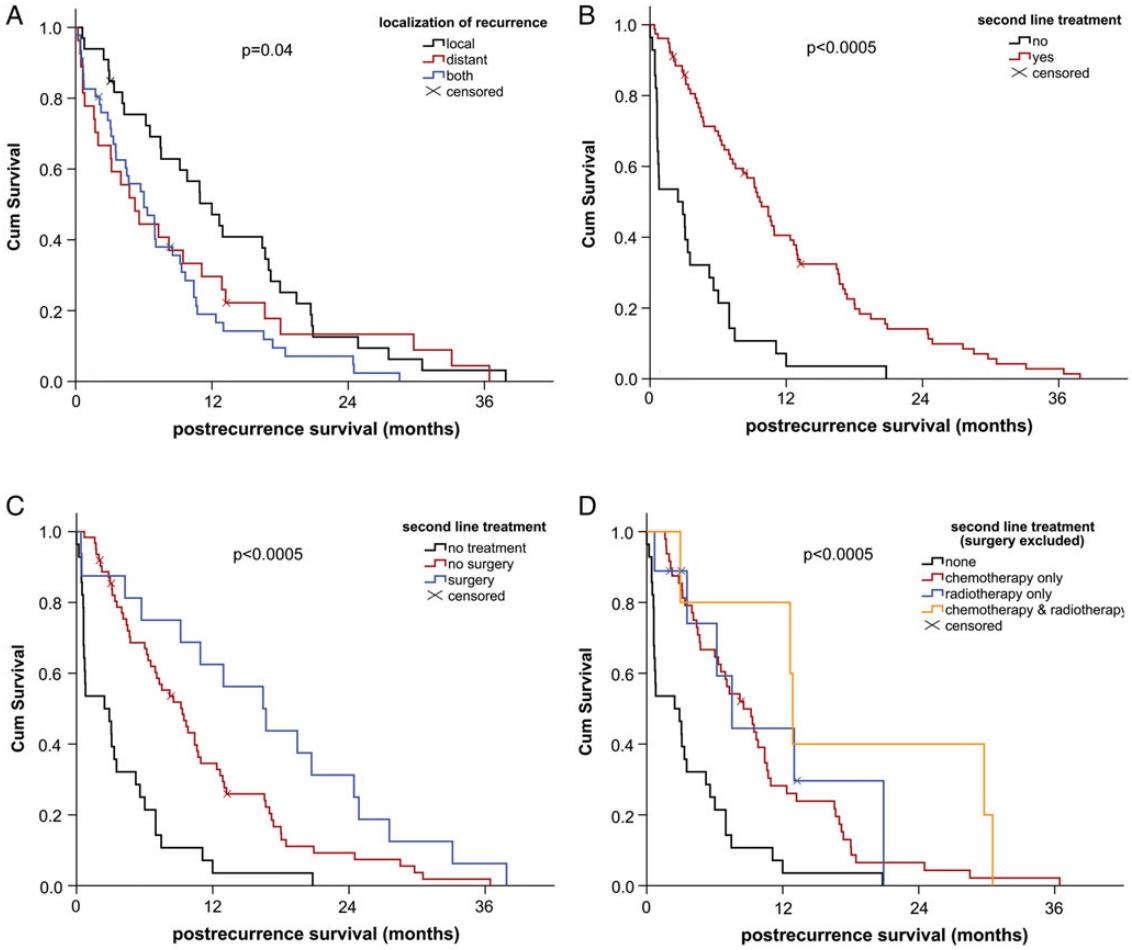

Figure 4: Post-recurrence survival [median (95% CI)] depending on: (**A**) localization of tumour recurrence: local ($n = 33$, 1 censored): 12 months (95% CI 8–16); distant ($n = 27$, 1 censored): 5 months (95% CI 2–8); both ($n = 46$, 2 censored): 6 months (95% CI 3–9); $P = 0.04$. Second treatment: (**B**) any kind of second treatment after recurrent disease [$n = 78$, 4 censored; 10 months (95% CI 8–11) vs no second treatment ($n = 28$, none censored; 2 months, 95% CI 0–5; $P < 0.0005$]. (**C**) Second surgery ($n = 16$, none censored; 16 months, 95% CI 9–24) vs other modality of second treatment ($n = 62$, 4 censored; 9 months, 95% CI 7–12) vs no treatment ($n = 28$, none censored; 2 months, 95% CI 0–5; $P < 0.0005$). (**D**) Second chemotherapy only ($n = 48$, 1 censored; 9 months, 95% CI 6–11), second radiotherapy only ($n = 9$, 3 censored; 8 months, 95% CI 4–11) and combined radio-chemotherapy ($n = 5$, none censored; 13 months, 95% CI 12–13; $P = 0.3$) vs no treatment ($n = 28$, none censored; 2 months, 95% CI 0–5; $P < 0.0005$). PRS: post-recurrence survival; 95% CI: 95% confidence interval.

Table 3: Second-line treatment modalities after recurrence and impact on PRS

	One modality, *n* (%) (*n* = 67)			Combination of two modalities, *n* (%) (*n* = 11)			No therapy (*n* = 28)
	Surgery (*n* = 10)	CTX (*n* = 48)	RTX (*n* = 9)	Surgery and CTX (*n* = 2)	Surgery and RTX (*n* = 4)	Chemo and RTX (*n* = 5)	
Localization							
Local only, *n* = 35	6 (18)	8 (24)	4 (12)	2 (6)	3 (9)	3 (9)	7 (22)
Distant, *n* = 71	4 (5)	40 (55)	5 (7)	0	1 (1)	2 (3)	21 (29)
OSR							
Month (95% CI)	11 (5–17)	9 (6–11)	8 (4–11)	16 (–)	17 (0–36)	13 (12–13)	2 (0–5)

The distribution of therapies differed significantly depending on the localization of tumour relapse ($P = 0.001$).
CTX: chemotherapy; RTX: radiotherapy; PRS: post-recurrence survival.

favourably to the current literature [19], of course taking into account that this is a selected patient series.

PRS depended significantly on the location of recurrence: patients experiencing local recurrence only had significantly better PRS compared with those presenting with distant only or both distant and local failure. It has been hypothesized previously that local recurrence may have a less deleterious effect on prognosis compared with distant metastasis [20]. One possible

explanation is that recurrence at the contralateral hemithorax and the abdomen represents only an expanded stage of local recurrence rather than true distant failure, and that the worse prognosis accompanied with recurrence at these locations derives from the later stage of the disease.

A progressive transformation from an epithelioid to a biphasic histotype was observed in 3 of the 31 patients with available tumour tissue. Little is known about the prognostic influence of a progression at the cellular level at the time of recurrence; however, the epithelial-to-mesenchymal transition has previously been shown to influence prognosis negatively [21]. The one case with a transformation from biphasic to epithelioid histotype most likely represents the limited diagnostic yield of conventional histology; therefore, further examination using molecular pathology is needed to determine the molecular behaviour of recurrent MPM and the prognostic effect of progressive transformation.

The impact of a second-line treatment for recurrent MPM after initial multimodality treatment has so far been described by only one other study; a subset of 12 patients previously having undergone multimodality treatment tended to have a longer PRS (median 13 months) compared with those not having had a second treatment ($n = 30$, 6 months); however, this result was not statistically significant [22].

The extent to which different second-line therapies influence PRS has, to our knowledge, never been described before: patients who did not receive a second therapy presented with significantly reduced OS compared with those with a second treatment both as a whole group and also in comparison with each subgroup of different modalities and their combination. Most likely, this represents a selection bias as those not having received a second treatment may either have not qualified because of poor performance status or may have died before treatment could be administered. The additional effect of a second treatment cannot be abstracted from our data set as patient-related data as well as information about the indication for a second treatment are incomplete.

However, our data show astonishing long-term outcomes after recurrence. A second, localized tumour excision was accompanied by a good median OS of 16 months (95% CI 9–24) after relapse. One other study described second surgery in 8 cases of localized solid mass recurrence with a similar median survival of 14.5 months (range 6–29) [23]; a second, larger, study including 47 patients with recurrent disease after initial multimodality management also concluded that chest wall resection is a safe and effective option in patients with localized recurrence [24]. The good survival in our cohort may be explained by the large proportion of patients with only soft tissue recurrence at the incision site, likely representing implantation metastases, and by the requirement of good physical condition to undergo surgery. However, patients having had extended resections were included in the analysis and a subgroup analysis did not reveal any significant difference between soft tissue resections compared with extended resections ($P = 0.5$). Nonetheless, 2 of the 3 patients who underwent contralateral pleurectomy died in the early postoperative course due to treatment withdrawal because of worsening condition and poor prognosis. Contralateral pleurectomy is therefore a high-risk procedure that cannot be recommended for patients with contralateral recurrence of MPM. For ipsilateral recurrence, however, surgery combined with radiotherapy seems to achieve the best outcomes and should be considered in patients fit enough for surgery.

Patients having received a second-line chemotherapy showed shorter OS compared with those receiving different modalities of second treatment, which very likely represents the higher distribution of distant failure in this group with a related worse general prognosis. To our knowledge, there are no data on second-line chemotherapy for progression of mesothelioma after multimodality treatment. However, one retrospective multicentre analysis of 181 patients who had received prior chemotherapy alone concluded that a re-challenge with pemetrexed combined with a platinum compound appeared to be a feasible option [25]. We agree that patients with distant failure and acceptable performance status who responded with stable disease or partial response to induction platinum/pemetrexed chemotherapy should be treated with a re-challenge; alternatively, vinorelbine is a good compound with less toxicity associated with better tolerance.

We are aware of several limitations of our study including the retrospective design of the analysis and the selection bias for the different treatment modalities. The actual effect of a second treatment can therefore not be proved in this highly selective setting; however, we feel that this is still an important and unique set of data that should encourage the community not only to collect data on the effect of the treatment of recurrent mesothelioma but also to seek universal criteria for the indication of such a second treatment. Moreover, quality-of-life data were not assessed for the whole cohort, thus we decided to exclude these data from the analysis. Furthermore, we did not include our patient cohort undergoing P/D—currently, the favoured MCR technique in earlier IMIG stages due to several studies suggesting OS data similar to EPP despite earlier local recurrence [6]. Indeed, in recent years, P/D has become the method of choice also in our institution as, whenever MCR is technically feasible, we try to preserve the lung. However, the 15 patients who had undergone P/D at our institution within the same time period were excluded from this analysis because of the small numbers and the inability to match according to tumour stage. Briefly, 11 (73%) of those had recurrence, and a preliminary analysis resembled differences in the pattern of failure described earlier [6]. Local-only recurrence after P/D was more frequent compared with EPP (64 vs 31%). On the other hand, distant failure was significantly more frequent after EPP (69 vs 36%; data not shown).

In conclusion, the major site of tumour recurrence even after EPP in the multimodality treatment setting remains the ipsilateral hemithorax. Adjuvant radiotherapy may reduce the frequency of local recurrence, but has no influence on OS. Local recurrence only has a better prognosis compared with distant relapse; adjuvant intracavitary treatment concepts may help to further reduce these high local recurrence rates. Second-line treatment after recurrence is feasible with acceptable morbidity rates and may lead to satisfactory long-term oncological outcomes in selected patient groups, with repeating surgery with or without radiotherapy presenting the most favourable outcomes. Contralateral pleurectomy is not recommended due to unpredictable outcomes; however, because of the risk of selection bias, the results concerning the actual effect of a second treatment have to be confirmed by further prospective investigation including definition of patient selection criteria and considering quality of life in addition to patient survival to assess the optimal second-line treatment for recurrent MPM.

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APPENDIX. CONFERENCE DISCUSSION

Dr M. de Perrot *(Toronto, Canada)*: This is a study on something important that we don't look at carefully enough, I think: the site and the timing of recurrence. I just have one question which is related to the local control with postop radiation. You are showing that there is less local recurrence if you give adjuvant radiation.

Dr Kostron: Yes, that is true, we could see a significantly reduced frequency of local recurrence.

Dr de Perrot: The question is regarding your clinical trial, the multicentre randomized trial, where the difference did not come out. The data you are presenting is from a single centre institution. Do you think it is the quality of the radiation, or what do you think is the cause?

Dr Kostron: I don't think it is the quality of our radiation that is working better, but it is a specific subgroup of the SAKK 1704 study. The results are the same regarding the overall survival; however, the local recurrence was reduced and I cannot tell you the precise reasons. I cannot say.

Dr de Perrot: And the other question concerns the pathology issue. Did you see any difference between the initial pathology on the explanted extrapleural specimen and the type of pathology at the time of recurrence?

Dr Kostron: That is a very good question. Unfortunately we didn't take a look at this specifically, but we will definitely do so in the future.

Dr D. Sugarbaker *(Baylor, TX, USA)*: A couple of questions. The first is, we published a paper about a year or so ago in the Journal of Thoracic and Cardiovascular Surgery (Dr. Burt was the first author) looking at a large number of patients who presented with isolated ipsilateral chest recurrence. We found that in those patients, the time from surgery to recurrence resection was then the second half, if you will, of the overall median survival. So if they had 18 months then you resected them, they usually got about another 18 months, and these were all epithelial patients, for the most part. Going along with the same question that we just heard, do you have a feeling as to whether subsequent resection is more valuable in epithelial versus mixed tumours?

Dr Kostron: Unfortunately we have only 16 patients, I think you had 47, so we did not take a specific look, because the groups were already small and very heterogeneous, so there was no sense in doing so. But it's a very interesting question indeed.

Dr Sugarbaker: Well, I think the nice thing that you point out is that locoregional recurrence, particularly ipsilateral chest, does remain one of the principal obstacles to long-term survival. So I think that treatment such as intraoperative radiotherapy, which was tried at Memorial some years ago, or intraoperative HITEC chemotherapy, now with new regimens that we are using in Houston at Baylor, these strategies focused on ipsilateral chest and abdominal recurrence and I think are really where we need, as a surgical community, to focus. I also like the idea that you are continuing to use the words macroscopic complete resection, because that is really the ultimate goal whether it is to be a pleurectomy or EPP.