Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma

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ABSTRACT

Objective: We have previously described patterns of failure after extrapleural pneumonectomy and multimodality therapy for malignant pleural mesothelioma and sought to update our results with a larger cohort of recent patients.

Methods: A total of 169 patients underwent extrapleural pneumonectomy without preoperative chemotherapy between 2001 and 2010. Data for treatment, recurrence, and survival were determined from medical records. A thoracic radiologist reviewed postoperative computed tomography or positron emission tomography computed tomography scans to determine sites of recurrence. Time to recurrence was estimated by the Kaplan–Meier method. Rates were compared using the Fisher exact test.

Results: The median age of patients was 62 years. Histology on final pathology was epithelial for 104 patients (62%) and nonepithelial for 65 patients (38%). A total of 132 patients (78%) received heated intraoperative chemotherapy; 77 patients (45%) received adjuvant chemotherapy, and 71 patients (42%) received adjuvant radiation therapy. Most chemotherapy regimens included platinum or pemetrexed. Median radiation therapy dose was 54 Gy. Among 158 evaluable patients, a recurrence developed in 118 (75%). Median follow-up was 83 months, median time to recurrence was 13.1 months, and median survival was 15 months. Sites of first recurrence were in the ipsilateral hemithorax or mediastinum for 54% of patients, in the abdomen for 39% of patients, in the contralateral hemithorax for 28% of patients, and in other distant sites for 5% of patients. Some patients had simultaneous recurrences in multiple sites.

Conclusions: The most common site of recurrence after extrapleural pneumonectomy and planned multimodality therapy remains the ipsilateral hemithorax (including mediastinum), and true distant failure (other than the abdomen or contralateral hemithorax) remains unusual. The distribution of recurrences is strikingly similar to our prior report. (J Thorac Cardiovasc Surg 2015;149:1374-81)

Site of Failure	N	% of all Patients (n=158)	% of all Failures (n=118)	% of all Failures from 1997 report (n=49)[10]
Ipsilateral Hemithorax +/or Mediastinum (Local Failure)	85	54%	72%	67%
Abdomen	62	39%	53%	50%
Contralateral Hemithorax	45	28%	38%	33%
Distant	8	5%	7%	8%

Sites of first failure for 158 patients in current cohort compared with previous cohort.

Central Message

Most common site of failure after EPP, heated intra-operative CT, systemic CT, and RT remains the ipsilateral hemithorax.

Perspective

The most common site of recurrence after EPP and planned multimodality therapy remains the ipsilateral hemithorax and true distant failure (other than abdomen or contralateral hemithorax) remains unusual. The distribution of recurrences is strikingly similar to our previous report and highlights the need for aggressive adjunctive therapies that would be best tested on prospective multicenter trials.

See Editorial Commentary page 1382.

Malignant pleural mesothelioma (MPM) is a rare but aggressive disease with poor prognosis. Median survival ranges from 7 months with supportive care to 12 months with chemotherapy, and perhaps longer with multimodality therapy including various combinations of surgery, radiation, and chemotherapy.[1-6] There are numerous potential local and systemic treatment strategies for MPM, including extrapleural pneumonectomy (EPP), pleurectomy/decortication, hemithoracic radiation therapy (RT), intracavitary and intravenous chemotherapy, photodynamic therapy, and novel targeted therapies. The optimal treatment approaches for various clinical scenarios of

Abbreviations and Acronyms
CHT = contralateral hemithorax
CI   = confidence interval
CT   = computed tomography
EPP = extrapleural pneumonectomy
EPT = electron-photon technique
HIOC = heated intraoperative chemotherapy
IHT = ipsilateral hemithorax
IMRT = intensity-modulated radiation therapy
MCR = macroscopic complete resection
MPM = malignant pleural mesothelioma
PET = positron emission tomography
RT   = radiation therapy

MPM have not been determined and are the subjects of active debate.[7-9] However, it is clear that local control for disease confined to the ipsilateral hemithorax (IHT) is a major challenge, and for this reason, at Brigham and Women's Hospital and Dana-Farber Cancer Institute, we have pursued multimodality therapies including EPP for patients with localized node-negative MPM, nonsarcomatoid histology, and good performance status.

Understanding the specific patterns of failure after treatment strategies helps inform decisions regarding where to direct subsequent treatment efforts. In 1997, we reported patterns of failure for 49 patients after EPP, adjuvant chemotherapy (cyclophosphamide, doxorubicin, and cisplatin), and 2-dimensional RT.[10] We found the most common site of failure was in the IHT, followed by failures in the abdomen, contralateral hemithorax (CHT), and, less frequently, in other distant sites. Since 1999, we have added heated intraoperative chemotherapy (HIOC) to our regimen in an attempt to augment local and abdominal control.[11-13] In addition, the introduction of pemetrexed has established for the first time a standard-of-care regimen for intravenous chemotherapy.[2] Another change is the routine availability of computed tomography (CT) scans for preoperative staging and post-treatment surveillance, which has improved both patient selection for surgery and detection of recurrent disease. Our practice also has incorporated specialist radiographic review. In the current analysis, we evaluate a separate and larger cohort of patients treated with intended multimodality therapy in the HIOC and pemetrexed era (between 2001 and 2010) to determine to what degree the patterns of failure have been affected by the evolution of MPM management since our prior analysis. Our group has recently described perioperative morbidity and mortality and overall survival for patients with epithelial MPM treated with EPP since 1988.[14] Although some of the patients in the current cohort were included in the former report, the current report describes different outcomes, namely, patterns of failure for patients treated

in the modern era, and is the first from Brigham and Women's Hospital and Dana-Farber Cancer Institute to describe recurrence patterns since 1997.

MATERIALS AND METHODS

A total of 447 patients who underwent EPP for MPM between 2001 and 2010 were identified from the Brigham and Women's Hospital International Mesothelioma Program Patient Data Registry. Unlike many institutions that use treatment strategies offering all patients neoadjuvant chemotherapy before resection, our strategy has been to treat eligible patients with initial surgery except in cases of mediastinoscopy-proven nodal involvement. For this reason, we have excluded patients treated with initial chemotherapy from the current analysis because they comprise a distinct cohort with poorer prognosis because of advanced stage at presentation. With institutional review board approval, records were reviewed to identify eligible patients who underwent macroscopic complete resection (MCR) by EPP at Brigham and Women's Hospital, who did not receive preoperative chemotherapy, and for whom a preoperative chest CT scan was available. A total of 169 patients met these criteria and constitute the study cohort.

After our prior experience with trimodality therapy, the intention-to-treat strategy during this study era was EPP with HIOC and subsequent evaluation for adjuvant chemotherapy and RT. Adjuvant chemotherapy or RT was recommended at the discretion of the treating oncologists and based on factors such as patient performance status, relative concerns of potential cumulative toxicity, and patient choice. EPP involved MCR achieved by en bloc resection of the lung, parietal pleura, ipsilateral pericardium, and ipsilateral diaphragm. Limited resection was also performed for previous biopsy, chest tube sites, or areas of localized gross tumor. Further details of the EPP technique have been reported.[15] HIOC entailed intraoperative instillation into the ipsilateral chest and abdomen of heated cisplatin with or without gemcitabine. HIOC was delivered on 1 of 2 treatment protocols active during the study time period or off protocol using protocol-established safe and effective dose and administration parameters. These parameters included MCR followed by cisplatin 175 to 225 mg/m^2 for a 1-hour lavage at 42°C with sodium thiosulfate rescue and with or without amifostine protection.[12,13] Reasons that some patients did not receive HIOC included ineligibility related to renal function, complete blood count or other factors, lack of an available spot on protocol because of a waiting period, and patient refusal. Adjuvant therapy was initiated 6 to 12 weeks postoperatively. Systemic chemotherapy agents typically included cisplatin, pemetrexed, or both given every 3 weeks. Adjuvant RT to the hemithorax was delivered using previously described techniques, including a matched electron-photon technique (EPT) during the earlier years of the study period and intensity-modulated RT (IMRT) during the later years.[16,17] Some patients treated at outside institutions received other 3-dimensional conformal RT techniques. Follow-up was typically a physical examination and chest CT or positron emission tomography (PET)/CT scan every 3 to 4 months for the first 3 years and every 6 months, thereafter.

Central review of all preoperative CT scans and all available postoperative studies (mostly CT scans and PET/CT scans) was performed by a dedicated thoracic radiologist (R.R.G.) to determine sites of recurrence. All sites of first recurrence were recorded and categorized as involving the IHT or mediastinum (local), CHT, abdomen, or other distant sites. Recurrence was scored as present if detected on imaging or physical examination. Biopsy or cytology confirmation was performed for many cases, but was not required in an effort to avoid under-reporting recurrences.

Recurrence-free interval was calculated as the time from surgery to first radiographic recurrence or biopsy determination of recurrence, with censoring on the date of the most recent study if recurrence was not demonstrated or the patient was subsequently lost to follow-up, or on the date of death if death from another cause (other than mesothelioma) was documented. Local recurrence-free survival was calculated as the time from surgery to the time of local recurrence, with censoring at the time

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of other sites of recurrence, death, or on the most recent contact date. Disease-free survival was calculated as the time from surgery to the time of any recurrence or death, with censoring for living patients on the most recent evaluation date. Overall survival was calculated as the time from surgery to the time of death from any cause, with censoring for living patients and those lost to follow-up on the most recent contact date. Kaplan–Meier survival function estimates were calculated and compared using the log-rank statistic. Proportions were compared using the Fisher exact test. Cox regression was performed to assess time to local recurrence and local recurrence-free survival, controlling for nonepithelial histology and use of RT, HIOC, and adjuvant chemotherapy.

RESULTS
Preoperative Staging

All patients had preoperative chest CT scans as a criterion for inclusion in this study cohort. Magnetic resonance imaging was consistently used to evaluate chest wall and diaphragmatic invasion except when precluded by metallic implants or claustrophobia (156/169 patients; 92%). Mediastinoscopy was routinely performed after pemetrexed-cisplatin became established as the first standard of care chemotherapy in 2004 (133/136 cohort patients; 98%), but had been infrequently used before that time (2/33; 6%). Coincident with the addition of mediastinoscopy to the standard preoperative evaluation, PET/CT imaging became more readily available and was also incorporated into the standard workup to rule out extrathoracic metastasis (123/136; 90% after 2004 vs 9/33; 27% before 2004).

Clinical and Treatment Characteristics

Patient, tumor, and treatment characteristics are shown in Table 1. Median age was 62 years (range, 37-79 years), and there were 136 men (80%) and 33 women (20%). Histologic subtype on initial pathology was epithelioid or biphasic for all patients, but on final pathology (at the time of EPP) was epithelioid for 104 patients (62%), biphasic for 60 patients (36%), sarcomatoid for 4 patients (2%), and desmoplastic for 1 patient (1%). All patients underwent EPP, and 132 patients (78%) received HIOC. A total of 77 patients (46%) received adjuvant chemotherapy; 85% of regimens included cisplatin, 79% contained pemetrexed, and 46% contained both. Seventy-one patients (42%) received RT with a median dose of 54 Gy (range, 30-60.4 Gy). The RT technique was EPT for 31 patients (44%), IMRT for 21 patients (30%), and other 3-dimensional conformal techniques for 8 patients (11%).

Outcomes and Patterns of Failure

A total of 156 patients are deceased, and 13 patients are alive with a median follow-up of 83 months (range, 58-107 months). Median overall survival among all 169 patients was 15.0 months. Detailed recurrence evaluation was not available for 11 patients (2 patients had recurrence, but the specific location of recurrence was not known, and 9

TABLE 1. Patient, tumor, and treatment characteristics for 169 patients with malignant pleural mesothelioma who underwent extrapleural pneumonectomy and adjuvant therapy

Age	Median, 62 y (range, 37-79 y)
Gender	
Men	136 (80%)
Women	33 (20%)
Side of disease	
Right	84 (50%)
Left	85 (50%)
Pathologic AJCC stage	
I	4 (2%)
II	25 (15%)
III	89 (53%)
IV	51 (30%)
pT classification	
T0	1 (1%)
T1	4 (2%)
T2	39 (23%)
T3	74 (44%)
T4	51 (30%)
pN classification	
N0	86 (51%)
N1	31 (18%)
N2	52 (31%)
Histology by final pathology	
Epithelial	104 (62%)
Biphasic	60 (36%)
Sarcomatoid	4 (2%)
Desmoplastic	1 (1%)
Surgery	
EPP	169 (100%)
Adjuvant therapy	
HIOC	47 (28%)
HIOC, CTX	26 (15%)
HIOC, RT	21 (12%)
HIOC, CTX, RT	38 (22%)
CTX, RT	6 (4%)
CTX	7 (4%)
RT	6 (4%)
None	18 (11%)

AJCC, American Joint Committee on Cancer; *EPP*, extrapleural pneumonectomy; *HIOC*, heated intraoperative chemotherapy; *CTX*, chemotherapy; *RT*, radiotherapy.

patients died perioperatively before evaluation for recurrence). Among 158 patients who were evaluable for recurrence, 118 had documented recurrence (75%), with a median time to any recurrence of 13.1 months and median time to local recurrence of 18 months from the date of surgery. Actuarial 3-year local recurrence-free survival was 17% (95% confidence interval [CI], 11-23), disease-free survival was 16% (95% CI, 10-21), and overall survival was 23% (95% CI, 17-30).

Sites of first failure are depicted in Table 2. Some patients had recurrence in multiple locations. A total of 85 patients (54%) had initial failure in sites that included the IHT or mediastinum (local failure), 62 patients (39%) had initial

TABLE 2. Sites of first failure among 158 patients evaluable for recurrence: Some patients had failures in more than 1 site

Site of failure	N	% of all patients (n = 158)	% of all failures (n = 118)	% of all failures from 1997 report (n = 49)[10]
IHT +/or mediastinum (local failure)	85	54	72	67
Abdomen	62	39	53	50
CHT	45	28	38	33
Distant	8	5	7	8

IHT, Ipsilateral hemithorax; *CHT*, contralateral hemithorax.

failure in the abdomen, 45 patients (28%) had initial failure in the CHT, and 8 patients (5%) had initial failure in other distant sites. The proportions of patients experiencing initial recurrence in the mediastinum, abdomen, or distant sites increased with pathologic stage, whereas the proportions recurring in the ipsilateral or CHT were consistent across stages (Figure 1). Detailed local recurrence rates were 47% in the IHT, 27% in the mediastinum, and 15% in the IHT or mediastinum only (without other sites of recurrence). Among all failures, 72% were local in the IHT or mediastinum, 53% were in the abdomen, 38% were in the CHT, and 7% were in other distant sites.

Specific sites of first recurrence are shown in Table 3. The most common sites of recurrence within each site were as follows. For the IHT, 71% of recurrences were as a chest wall mass and 29% were neopleural thickening or mass. For the mediastinum, 70% were lymphadenopathy and 28% were as a soft tissue mass (that did not clearly represent lymphadenopathy.) For the abdomen, 31% were ascites, 27% were retroperitoneal adenopathy, and 24% were an abdominal mass. For the CHT, 49% were lung nodules and 49% were pleural effusions. The other distant sites included bone for 88%, soft tissue for 13%, and brain for 13%.

Patients who received RT experienced a lower rate of local failure (in the IHT or mediastinum). Crude local recurrence was 39% (27/70) among patients who received RT compared with 66% (58/88) among those who did not receive RT (P = .01), and actuarial 3-year local recurrence rate was 47% (95% CI, 31-63) among patients who received RT compared with 82% (72%-92%) among those who did not (P < .0001). Adjuvant RT was also associated with significantly longer time to local recurrence and local recurrence-free survival when correcting for histology, HIOC, and adjuvant chemotherapy (Table 4).

DISCUSSION

Our report from 1997 described patterns of failure after EPP and adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy and 2-dimensional conformal RT.[10] Although there remains no clear current standard of care, our more recent treatment approach has consisted of a revised intention-to-treat strategy consisting of EPP, HIOC, and adjuvant pemetrexed-based chemotherapy and 3-dimensional RT or IMRT. In this updated series, we sought to determine whether our revised approach was associated with a change in the patterns of failure. We have demonstrated that for the current series of 169 patients treated with EPP between 2001 and 2010, recurrent disease developed in 75% of patients. The pattern of recurrence was local for 54% of patients, in the abdomen for 39% of patients, in the CHT for 28% of patients, and in other
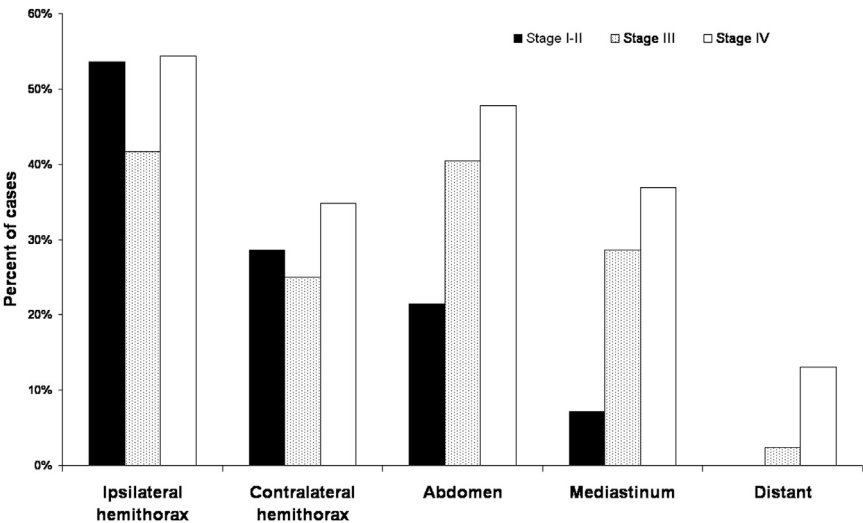

FIGURE 1. Percentage of patients with first site of recurrence in IHT, CHT, abdomen, and mediastinum according to the American Joint Committee on Cancer stage.

TABLE 3. Detailed sites of first failures among 158 evaluable patients: Some patients had failures in more than 1 site

Site	N	(% of failures in that site)
IHT (all failures)	75	
Chest wall mass	53	71
Neo-pleural thickening or mass	22	29
Lymphadenopathy	7	9
Pericardial thickening	4	5
Mediastinum (all failures)	43	
Lymphadenopathy	30	70
Soft tissue mass	12	28
Pericardial	5	12
Abdomen (all failures)	62	
Ascites	19	31
Retroperitoneal adenopathy	17	27
Abdominal mass NOS	15	24
Liver	12	19
Peritoneal mass	11	18
Abdominal wall mass	11	18
Mesenteric mass	7	11
Omental mass	7	11
CHT (all failures)	45	
Lung nodules	22	49
Pleural effusion	22	49
Pleural thickening or mass	6	13
Lymphadenopathy	3	7
Other distant sites (all failures)	8	
Bone	7	88
Soft tissue	1	13
Brain	1	13

IHT, Ipsilateral hemithorax; *NOS*, not otherwise specified; *CHT*, contralateral hemithorax.

distant sites for 5% of patients. Despite the changes in treatment approach, the relative distribution of recurrence sites is almost identical to that of our prior series (Table 2).[10] In the current series, 72% of recurrences were local compared with 67% for our prior series; 53% were in the abdomen compared with 50% previously; 38% were in the CHT compared with 33% previously; and 7% were in other distant sites compared with 8% previously.

The observed relationship of recurrence location to stage generates hypotheses relevant to therapeutic strategy. IHT

TABLE 4. Multivariate analysis of time to local recurrence and local recurrence-free survival

	Time to local recurrence HR (95% CI)	Local recurrence-free survival HR (95% CI)
Non-epithelioid histology	2.2 (1.4-3.5)	1.6 (1.2-2.3)
HIOC	0.7 (0.4-1.1)	0.7 (0.5-1.0)
CTX	0.7 (0.5-1.1)	0.7 (0.5-1.0)
RT	0.3 (0.2-0.5)	0.4 (0.3-0.6)

HR, Hazard ratio; *CI*, confidence interval; *HIOC*, heated intraoperative chemotherapy; *CTX*, chemotherapy; *RT*, radiation therapy.

remains the most common recurrence site independent of stage, likely representing regrowth of microscopic tumor not completely eradicated by treatment. Mediastinal, abdominal, and distant recurrence were observed more commonly with increasing stage, consistent with potential tumor erosion through diaphragm or pericardium or micro-metastases disseminated via vascular or lymphatic routes that would presumably be more common with later stage tumors. The stage independence of apparent recurrence in the CHT suggests the possibility that some cases (particularly early stage) may represent new primary pleural disease.

As shown in Table 5, reports in the literature for local recurrence rates after EPP and RT (with or without neoadjuvant or adjuvant chemotherapy) range from 9% to 41%.[3-6,10,18-26] One series reported a 2-year actuarial local recurrence rate of 53%.[24] It is difficult to compare recurrence rates across series for many reasons. The case mixes no doubt vary significantly in terms of other relevant factors, such as selection of patients for combined modality treatment, stage of disease, mesothelioma histology, margin status, reported results for intent to treat with multiple modalities versus for patients who actually received all treatments, length of follow-up, frequency of surveillance imaging, surgical expertise, chemotherapy agents, and RT technique. In addition, most of the reported rates are crude rates rather than actuarial rates, further rendering comparison difficult. Nonetheless, the majority of publications demonstrate high local recurrence rates.

The crude local recurrence rate for patients treated with EPP and RT in the current series was 39%, which is among the highest reported. There are several potential explanations for this. A dedicated thoracic radiologist re-reviewed all post-treatment imaging to score recurrences. It is likely that many recurrences were asymptomatic, detected by imaging alone, and would not have been appreciated in earlier cohorts before the widespread use of CT and PET/CT for surveillance. In addition, the follow-up period in the current report is more than twice as long as most other series, allowing more time for recurrences to be detected. Last, there has been a learning curve in the evolution of adjuvant hemithoracic RT techniques. In the 2-dimensional RT planning era (before the availability of 3-dimensional CT planning), the approach at our institution was to deliver moderate dose RT, which consisted of 30 Gy to the hemithorax, 40 Gy to the mediastinum, and a boost dose to focal areas of concern to 54 Gy. The crude local failure rate with this approach was 50%, which is not surprising given that 30 Gy is likely an insufficient dose to achieve local control.[18] In 2003, we started using high-dose EPT as developed at Memorial Sloan-Kettering Cancer Center.[16] EPT delivers a higher dose of 54 Gy to the hemithorax and 39.6 Gy to the mediastinum; however, the technique results in some under-dosing at matched areas. In 2007, we reported a local recurrence rate with this approach of 27%, and an updated

TABLE 5. Patterns of failure after extrapleural pneumonectomy and radiation therapy (with or without neoadjuvant or adjuvant chemotherapy) for malignant pleural mesothelioma from several institutions

	No. treated with EPP	No. treated with EPP and RT	Treatment	RT technique	% with recurrence	LR %	Isolated LR %	DR %
Current series	169	71* (42%)	EPP, HIOC, CTX, RT	44% EPT, 30% IMRT, 11% other	75	39	15	53
Baldini and colleagues[10]	46*	35 (76%)	EPP, CTX, RT	2D-RT	54	35	13	41
Gupta and colleagues[19]	86	78* (91%)	EPP, RT	EPT	74	41	19	55
Buduhan and colleagues[22]	46	38* (83%)	CTX, EPP, RT	63% EBRT, 37% IMRT	63	32	18	45
Gomez and colleagues[6]	136	86* (64%)	EPP, RT	IMRT	62	16	2	59
de Perrot and colleagues[3]	45	30* (67%)	CTX, EPP, RT	IMRT 3D-CRT	53	17	17	37
Tonoli and colleagues[25]	56	56* (100%)	EPP, RT, CTX	89% IMRT 7% 3D-CRT 4% HT	30	9	9	23
Krug and colleagues[4]	57*	40 (70%)	CTX, EPP, RT	EPT IMRT	40	19	14	26
Rea and colleagues[20]	17*	15 (88%)	CTX, EPP, RT	EPT	77	35	NS	65
Patel and colleagues[24]	30*	30* (100%)	EPP, RT, CTX	IMRT	73	33	13	60
van Sandick and colleagues[23]	15*	15* (100%)	EPP, RT	IMRT	73	33	9	67
Van Schil and colleagues[5]	42	37* (88%)	CTX, EPP, RT	3D-CRT	NS	16	NS	27

EPP, Extrapleural pneumonectomy; *RT*, radiation therapy; *LR*, local recurrence; *DR*, distant recurrence (including abdomen and CHT); *HIOC*, heated intraoperative chemotherapy; *CTX*, chemotherapy; *IMRT*, intensity-modulated radiation therapy; *2D-RT*, 2-dimensional radiation therapy; *EPT*, electron-photon technique; *EBRT*, external beam radiation therapy; *3D-CRT*, 3-dimensional conformal radiation therapy; *HT*, helical tomotherapy; *NS*, not stated. *Patient cohort for reported recurrence results.

review of 34 patients treated with EPT has shown a local recurrence rate of 41% with the majority of recurrences occurring under blocks or at match lines in under-dosed areas.[18,27] Investigators from Memorial Sloan-Kettering Cancer Center have reported local failure rates with EPT of 18% to 37%.[16,26] Furthermore, the RT community has learned the importance of adequately extending the inferior border of the hemithoracic field to avoid "marginal misses" related to unappreciated extension of the pleura into the upper abdomen.[16,18] In 2003, investigators from MD Anderson Cancer Center were the first to describe an IMRT technique that enables delivery of a high dose (50 Gy) to the entirety of the complex IHT volume.[17] This IMRT technique appears to provide superior target coverage compared with prior techniques and should be associated with improved hemithoracic control rates.[17,28] Only 13% of the current cohort received IMRT, which may be another explanation for the high local recurrence rate in this series. The early experience of IMRT at our institution resulted in unanticipated and unacceptable pulmonary toxicity, and for that reason, post-EPP IMRT treatment was suspended.[29] More recently, other groups have demonstrated improved safety profiles with IMRT, and this approach should be reconsidered in future treatment strategies.[6,24,30]

Study Limitations

There are several limitations of this retrospective report. Although the intention to treat included evaluation for adjuvant chemotherapy and RT, the actual delivery of these modalities was highly variable. This was not due to a random or individualized treatment approach, but is a reflection of reality and the difficulties of safely delivering adjuvant therapies after aggressive surgery. Furthermore, because only the more fit patients typically were able to receive adjunctive treatments, it was not possible to assess the relative impact on the patterns of failure of adjuvant RT or chemotherapy compared with EPP alone. The analyses of local failure end points for patients treated with and without RT were provided for interest and to generate hypotheses for future trials. We acknowledge that formal conclusions cannot be drawn from these comparisons. Furthermore, not all of the recurrences were histologically confirmed. Chest x-ray was the prior standard follow-up modality for our earlier report, whereas the current series used CT or PET scans and specialized radiology review. As a result, many asymptomatic areas were detected and scored as recurrent disease, potentially inflating the recurrence numbers compared with other reports.

CONCLUSIONS

It is disappointing that our updated results failed to show a change in the patterns of failure after multimodality therapy with HIOC, pemetrexed-based chemotherapy, and more sophisticated RT, but others have similarly reported disappointing outcomes. MPM remains an aggressive disease that poses many treatment challenges. Careful study of large cohorts of patients managed with a standard

intent to treat holds the only hope for progress. For patients with good performance status and localized disease, we believe that prolonged disease-free survival can be achieved only with aggressive local measures. We continue to support the role of surgery (EPP or pleurectomy/decortication as indicated to achieve MCR) for these patients.[9,31] The optimal combination of therapies as adjuncts to surgery remains under active investigation. Given that the predominant pattern of failure remains local, implementation of postoperative hemithoracic RT is worthy of further study. However, the RT target volume is complex, in proximity to several radiosensitive critical organs, and early experiences with IMRT were associated with high fatality rates.[21,29,32,33] More recent reports have demonstrated acceptable toxicity profiles for IMRT after EPP, but this approach is best used at experienced high-volume centers, and preferably on treatment protocols.[6,24,30] Alternatively, preoperative hemithoracic RT using hypo-fractionated IMRT is another option. Preliminary results for this technique are promising with respect to both efficacy and tolerability.[34] Reports for intraoperative adjuncts such as HIOC and photodynamic therapy have shown suggestions of improved disease control in certain patient subpopulations, and these modalities are worthy of further investigation.[13,35] HIOC is safe and feasible after EPP, and with the discovery of more effective agents, local delivery in the context of minimal residual disease may represent an effective paradigm to enhance local control. Last, integration of neoadjuvant or adjuvant intravenous chemotherapy or new targeted agents is also warranted. Because there may be interactions between these various adjunctive treatment modalities, aggressive multimodality regimens are best tested on thoughtfully designed, institutional review board–approved protocols, and patients should be enrolled in prospective multicenter trials when feasible.

Conflict of Interest Statement

David E. Kozono reports consulting fees from Genzyme/Sanofi. Raymond H. Mak reports consulting fees for Boehringer-Ingelheim, Inc and equity ownership in Celgene. Raphael Bueno reports consulting fees for Myriad Genetics, Inc, Novartis Inst. Biomedical Research, Verastem, Inc Study 1, Verastem, Inc Study 2, Castle Biosciences, Meso Study, Castle Biosciences, Esoph Study Genentech Inc, Siemens Medical Solutions, Inc and Exosome Diagnostics, Inc. All other authors have nothing to disclose with regard to commercial support.

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