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A M E R I C A N C O L L E G E O F
 **C H E S T**
P H Y S I C I A N S

Cytoreductive Surgery and Intraoperative Hyperthermic Intrathoracic Chemotherapy in Patients With Malignant Pleural Mesothelioma or Pleural Metastases of Thymoma*

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Study objectives: No established curative treatment is available for pleural thymoma metastases and malignant pleural mesothelioma (MPM). Recently, peritoneal malignancies have been treated by cytoreductive surgery and intraoperative hyperthermic intracavitary perfusion chemotherapy (HIPEC). We investigated the feasibility and safety of this multimodality treatment in the thoracic cavity.

Design: Patients with pleural thymoma metastases or early-stage MPM were enrolled in a feasibility study. Morbidity, recurrence, and survival rates were recorded.

Setting: The Netherlands Cancer Institute.

Patients: Three patients with pleural thymoma metastases and 11 patients with pleural mesothelioma were treated.

Interventions: Cytoreductive surgery and intraoperative hyperthermic intrathoracic perfusion chemotherapy (HITHOC) with cisplatin and adriamycin were performed. The mesothelioma patients received adjuvant radiotherapy on the thoracotomy wound and drainage tracts.

Measurements and results: Morbidity and mortality rates were 47% and 0%, respectively. Reoperation was necessary in four cases. Severe chemotherapy-related complications were not observed. A solitary mediastinal and a contralateral pleural thymoma recurrence were successfully treated by radiotherapy and a contralateral HITHOC procedure. All thymoma patients were alive and free of disease after a mean follow-up period of 18 months. After a mean follow-up period of 7.4 months, nine mesothelioma patients are alive. Two mesothelioma patients died of contralateral pleural and peritoneal recurrent disease, while one patient is alive with locoregional recurrence.

Conclusions: Cytoreductive surgery and HITHOC with cisplatin and adriamycin is feasible in patients with pleural thymoma metastases and early-stage MPM, and is associated with acceptable morbidity rates. Early data on locoregional disease control are encouraging, and a phase II study will be conducted. (CHEST 2002; 121:480-487)

Key words: cytoreductive; hyperthermia; intrapleural chemotherapy; intrathoracic chemotherapy; malignant mesothelioma; pleural malignancy; surgery; thymoma; thymic carcinoma

Abbreviations: HITHOC = hyperthermic intrathoracic perfusion chemotherapy; MMC = mytomycin-C; MPM = malignant pleural mesothelioma

Intracavitary chemotherapy is based on the dose-response relation of cytostatic drugs, meaning that increased concentrations of cytostatic agents lead to

increased tumor cell kill. Infusion of the drug into the cavity will lead to increased exposure of tumor cells adjacent to its surface, while systemic concentrations will remain below toxic levels due to the limited absorption of the drug from the cavity, resulting in limited systemic side effects.¹ Prerequisites for effective intracavitary chemotherapy are the absence of tumor outside the cavity and the surgical removal of all macroscopic tumor, as the penetration of most drugs is limited to a few millimeters.^{2,3} To improve the efficacy of chemotherapy, it can be combined with regional hyperthermia.⁴ Based on

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these principles, intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery has been used in the treatment of primary and secondary peritoneal malignancies.⁵⁻¹¹ Results of this treatment in patients with peritoneal mesothelioma were promising.⁹⁻¹¹ The experience with this treatment modality in the thoracic cavity is still limited.¹²⁻¹⁶

Recurrence of thymoma is frequently confined to the pleural cavities opened during the primary surgery, presumably as a result of peroperative seeding. In the stage of pleural dissemination, no curative therapy is known.¹⁷ In several phase II studies, systemic chemotherapy has been reported to be of temporary success. Aggressive multimodality treatment seems have better results.¹⁸⁻²⁰

For patients with malignant pleural mesothelioma (MPM), median survival time is < 1 year, despite the fact that this malignant disease is, at diagnosis, usually confined to the pleural cavity.^{21,22} Systemic metastatic disease is a relatively late phenomenon. Malignant mesothelioma remains a uniformly fatal disease, and best supportive care continues to be the standard treatment.²³ In limited-stage MPM (stage I), a number of locoregional treatment strategies have been tested. Surgery (limited excision or pleuropneumectomy) only or in conjunction with radiotherapy or photodynamic therapy has been applied with some success in phase I or phase II studies.²⁴⁻²⁶ In stage II and III disease, a variety of systemic cytostatic regimens have been tested, demonstrating limited response rates.^{26,27} Dose-escalated chemotherapeutic regimens may offer some advantage, whereas multidrug chemotherapy has not shown any benefit over single-agent therapy.²⁶⁻²⁸

During the last years, the Netherlands Cancer Institute has gained ample experience in both hyperthermic intraoperative intraperitoneal chemotherapy^{3,5-8} and locoregional treatment of MPM with surgery and photodynamic therapy.²⁴⁻²⁶ The latter multimodality treatment was abandoned because of the high morbidity rate observed (unpublished data). Against this background, the feasibility and toxicity of cytoreductive surgery and intraoperative hyperthermic intrathoracic perfusion chemotherapy (HITHOC) was studied in patients with stage I MPM and pleural thymoma recurrence.

MATERIALS AND METHODS

Patient Selection

General inclusion criteria for patients with MPM or pleural thymoma patients were as follows: (1) adequate pulmonary function to allow thoracotomy and eventual pneumonectomy estimated by lung function measurement, spirometry, and nu-

clear pulmonary ventilation and perfusion scan; (2) adequate cardiac function examined by nuclear ejection fraction measurement and cardiac ultrasonography; (3) performance status 0 or 1 (Eastern Cooperative Oncology Group/World Health Organization); (4) normal blood cell count and biochemical renal and liver function test results; (5) age \leq 70 years; and (6) written informed consent. Patients with signs of distant metastases, mediastinal involvement, and infiltration of vertebra, mediastinal vascular structures, or trachea at preoperative evaluation were excluded. When tumor progression was observed during systemic chemotherapy (cisplatin and/or adriamycin), this patient was also considered not suitable for intrathoracic chemotherapy with the same agents.

Disease-related inclusion criteria for thymoma were as follows: (1) primary tumor histologically proven to be thymoma, (2) disease limited to one pleural cavity on CT or MRI of chest and upper abdomen, and (3) technically resectable pleural metastases. Patients with MPM were enrolled when (1) MPM was histologically proven and confirmed by the Dutch mesothelioma panel, (2) the disease was determined as stage I (TNM staging according to the International Mesothelioma Interest Group) based on CT or MRI of chest and upper abdomen, (3) lymph node biopsy results at mediastinoscopy were negative, (4) respiratory movements were symmetrical, and (5) the lesions were deemed technically operable with potential preservation of the adjacent lung.

Surgical Aspects

With the patient in a lateral position, under general and thoracic epidural anesthesia and with a double-lumen endotracheal tube, a posterolateral thoracotomy through the fifth intercostal space was performed. Extrapleural dissection, between chest wall, diaphragm and mediastinum on one side and parietal pleura on the other side, was continued until the hilar structures were free. Subsequently, the thickened pleural sheets were removed from underlying healthy tissue, either visceral pleura or pulmonary parenchyma. After this decortication, the viability of the remaining lung was assessed. When the damage to the lung was too extensive, a pneumonectomy was performed. Small tumor nodules on the diaphragm and pericardium were evaporated by coagulation, while larger or invasive deposits required partial resection of the diaphragm and pericardium. When the diaphragm was accidentally opened or after limited diaphragmatic resection, the defect was left open to permit exposure of its margins and the subphrenic area to the chemotherapeutic agent.

Perfusion Chemotherapy

After completion of cytoreductive surgery, the perfusion system was set up. One Tenckhoff inflow catheter (Curl Cath; Quinton; Bothell, WA) was placed centrally in the thoracic cavity, and three silicone outflow catheters (Dura-Sil; Biometrix Ltd; Jerusalem, Israel) were placed in the pleural cavity top, posterior diaphragm sinus, and anterior diaphragm sinus, respectively. Temperature sensors (Mon-a-therm; Mallinckrodt Medical; St. Louis, MO) were attached to the inflow and outflow catheters and to the pump system, immediate after the heat exchanger. The core temperature was measured by a probe in the proximal esophagus. The outflow catheters were connected through connection tubes containing filters (blood transfusion filters; Pall Corporation; East Hills, NY) to a reservoir with filter (Safe II Filtered Cardiomy Reservoir; Polystan; Copenhagen, Denmark). The reservoir was connected to a roller pump (Polystan) and subsequently to a heat exchanger (Baxter; Uden, the Netherlands), from where the perfusate returned back to the patient

through the inflow catheter (Fig 1). Afterwards, a watertight continuous locking suture leaving at the highest point a small opening for the introduction of the catheters closed the skin.

The thoracic cavity was perfused at a speed of approximately 1 L/min with isotonic dialysis fluid (Dianeal PD1; Baxter). During perfusion, the contralateral lung was separately ventilated. The ipsilateral lung, when left *in situ*, was inflated at a pressure of 15 cm H₂O with oxygen, keeping the lung semi-inflated. This allowed sufficient space between parietal and visceral pleura for adequate perfusion, but limited possible toxicity of cytostatic drugs to lung parenchyma. After stabilization of the system with homogenous intrathoracic temperature distribution of 40°C to 41°C, adriamycin (15 to 25 mg/m²) and cisplatin (80 mg/m²; 50 mg/m² only in the first case) were added to the system. Perfusion was continued for 90 min. At the completion of perfusion the inflow and outflow catheters and temperature probes were removed.

Postperfusion Surgery

Diaphragm defects were closed by sutures or a Marlex mesh graft (Bard Vascular Systems; Haverhill, MA), whereas large pericardium defects were closed by a Vicryl mesh graft (Ethicon Endo-Surgery, Inc; Sycamore, OH). When the lung could be preserved, thoracic drains with mild suction drainage (15 cm H₂O) were placed in the apex and dorsal sinus. After pneumonectomy, one closed thoracic drain was left behind. The thoracic wall was closed in the regular way.

Morbidity

Intraoperative and postoperative complications, mortality rates, and duration of the procedure and hospital stay were noted.

Postoperative chemotherapy-related complications were recorded according to the World Health Organization toxicity scale.

Adjuvant Radiotherapy

Patients with MPM received external radiotherapy to the thoracotomy scar and the drainage tracts to reduce the risk on recurrence in thoracotomy wound and drainage tracts after postoperative recovery and complete wound healing. Starting at 6 weeks, but not later than 3 months, after the HITHOC procedure, 8 Gy was administered three times, with an interval between the fractions of 7 days.

Follow-up

Patients were routinely seen 6 weeks and 3 months after discharge and further on at 3-month intervals for 2 years and afterwards at 6-month intervals until 5 years. CT scans of the thorax and upper abdomen were made 3 months after discharge and later at 6-month intervals. When indicated, other diagnostic tests could be ordered. Time to recurrence, site of recurrence, and survival rate were noted.

RESULTS

Patient Characteristics

From June 1998 until August 2000, three patients with pleural thymoma metastases underwent cytoreductive surgery followed by HITHOC. One patient with a cortical thymoma and myasthenia gravis pre-

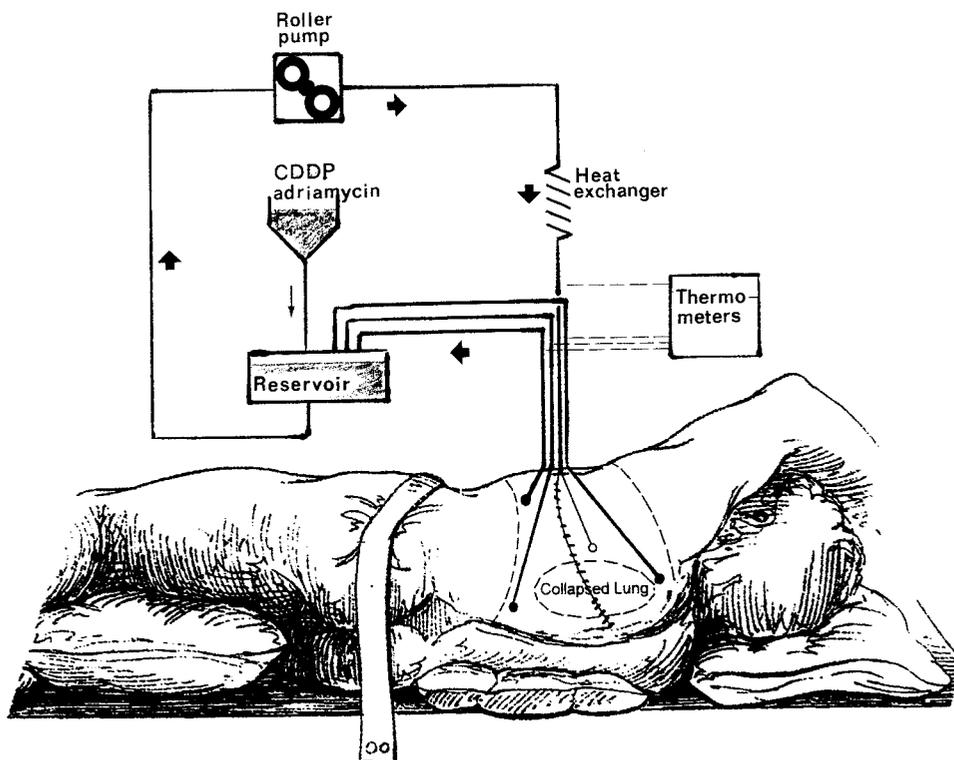


FIGURE 1. Schematic overview of the intraoperative HITHOC circuit. CDDP = cisplatin.

sented during follow-up examination with contralateral pleural metastases and was treated with the same approach at the contralateral side. Histologic examination of the other two primary tumors revealed a well-differentiated thymus carcinoma and a cortical thymoma with a small focus of well-differentiated thymus carcinoma. Eight patients with MPM were included in the study from January 2000 until March 2001. All but one patient were occupationally exposed to asbestos. Eight patients had a diffuse malignant epithelial mesothelioma, whereas histology of three patients revealed a mixed type of diffuse malignant mesothelioma. The patient characteristics are summarized in Table 1.

Previous Treatment

The patients with pleural thymoma metastases had undergone prior resection of their primary tumor. Patient 3 received adjuvant radiotherapy because of a histologically incomplete resection. Pleural metastases occurred 1, 3, 4, and 5 years after this resection. Patient 1 demonstrated a partial response after systemic chemotherapy with ifosfamide, cisplatin, and etoposide, whereas patient 2 had relapsed after a complete response on systemic chemotherapy with

adriamycin, cisplatin, vincristin, and cyclophosphamide. None of the MPM patients were previously treated.

Surgical Procedures

Although preoperative evaluation had suggested that the ipsilateral lung could be preserved, pneumonectomy was necessary in four patients with MPM, because of significant infiltration in the lung parenchyma (Table 1). In one patient with thymoma, preoperative evaluation had demonstrated that the ipsilateral lung contributed only 2 to 3% in lung ventilation and perfusion after resection of a large primary tumor and extensive vascular reconstructive surgery for involvement of the large upper-mediastinal vessels. Resection of this hardly functional lung was performed. The pericardium was opened or partially resected during the cytoreductive surgery in eight cases, five times in left-sided procedures and three times in right-sided procedures. In 10 patients, the diaphragm was opened or partially resected because of infiltration. In one patient, a Marlex mesh graft was used for diaphragm reconstruction. Estimated blood loss varied from 0.4 to 1.8 L (average 1.2 L) in thymoma patients and from 1.0 to 3.9 L

Table 1—Treatment of Pleural Thymoma Metastases and MPM by Cytoreductive Surgery and Intraoperative HITHOC*

Disease/ Patient No.	Sex/Age, yr	Side	Pneumonectomy	Pericardium Opened	Cisplatin/ adriamycin dose, mg/m ²	Complications	Hospital Stay, d	Recurrence Site/ Interval/Therapy	Outcome/ Follow-up, mo
Pleural thymoma metastases									
1	F/63	Right	No	No	50/15	Nephrotoxicity†	15	Local/20 mo/RT → CR	NED/31
2	F/32	Right	No	No	80/20	None	11	Left pleural/13 mo/HITHOC	
3	F/59	Right	Yes	No	80/25	Wound dehiscence‡	17	No	NED/18 NED/5
MPM									
4	M/59	Right	No	No	80/20	None	18	Left pleural/4 mo/no	DOD/8
5	M/54	Right	No	Yes	80/25	None§	17	Peritoneal/6 mo/no	DOD/7
6	M/38	Left	No	Yes	80/25	Sinus tachycardia†	16	Left hilus/7 mo/systemic chemotherapy, progressive disease	AWD/10
7	M/66	Left	No	Yes	80/25	Atrial fibrillation†	19	No	NED/8
8	M/66	Right	No	No	80/25	n. rec. paresis left	15	No	NED/6
9	M/53	Left	Yes	No	80/25	No	12	No	NED/6
10	M/45	Right	Yes	Yes	80/25	No	16	No	NED/5
11	M/66	Left	Yes	No	80/25	Diaphragm rupture‡	11	No	NED/4
12	M/61	Right	No	Yes	80/30	No	15	No	NED/3
13	M/52	Left	No	Yes	80/30	Diaphragm rupture‡	24	No	NED/3
14	M/57	Left	Yes	Yes	80/30	Chylous effusion‡	35	No	NED/2

*M = male; F = female; n. rec paresis = paresis of the recurrent laryngeal nerve after mediastinoscopy; RT → CR = radiotherapy (17 × 3Gy) for local recurrence with complete response; DOD = death of disease; AWD = alive with disease; NED = no evidence of disease.

†Transient, grade 2.

‡Reoperation necessary.

§Operated on 4 month postoperatively for bronchocutaneous fistula with empyema.

||After mediastinoscopy.

(average 2.0 L) in MPM patients. For the entire group of patients, the average amount was 1.8 L.

Peroperative and Postoperative Staging

Seven of the 11 MPM patients, who were all preoperatively determined as stage I, appeared to have actually stage II disease. They appeared to have confluent visceral pleural tumor involvement with or without extension into the underlying pulmonary parenchyma or the diaphragmatic muscle. Histologic examination did not reveal lymph node metastases.

Perfusion Characteristics

The volume needed to fill the perfusion circuit varied from 2 to 5 L, while the thoracic cavity contained 1.1 to 4.5 L of this perfusate. The highest volumes had to be administered after pneumonectomy, although thoracic cavities with a partially collapsed lung harbored up to 3.6 L of perfusate. After an average of 19 min (variation, 10 to 30 min) the perfusate was adequately warmed up ($> 40^{\circ}\text{C}$) to administer the chemotherapeutic agents. This period tended to be shorter after pneumonectomy. During perfusion chemotherapy, the maximal temperatures of the perfusate immediately after passing the heat exchanger, at the inflow and at the outflow catheters, were 41.0 to 42.6°C , 40.9 to 42.5°C , and 40.6 to 41.8°C , respectively. The maximal core temperature varied between 38.0°C and 39.4°C . There did not seem to be a relation between the highest values and whether pneumonectomy was performed.

Duration of the Procedure

The duration of the procedure, including the time needed to install the perfusion circuit and the perfusion time, varied from 4.25 h to 8.30 h (mean, 6.08 h). This procedure was shorter for pleural thymoma metastases than for MPM (mean, 4.10 h vs 6.31 h).

Morbidity

Complications are summarized in Table 1. After staging mediastinoscopy, permanent paresis of the left recurrent laryngeal nerve developed in one patient (Table 1). His voice improved significantly after speech therapy. No hematologic toxicity was observed. The degree of postoperative nausea and vomiting was comparable to that observed after major thoracic surgery without synchronous chemotherapy. In conclusion, the 30-day post-HITHOC complication rate was 47%. There was no treatment-related mortality.

Duration of Hospital Stay

Postoperatively, patients remained for an average period of 3 days in the ICU. The mean and median hospital stays were 17 days and 16 days, respectively. The mean period was longer for MPM patients than for thymoma patients (18 days vs 14 days).

Follow-up

The follow-up period varied from 2 to 31 months, with mean and median periods of 9.6 months and 6 months, respectively (Table 1). The mean follow-up period for thymoma patients was 18 months, whereas this period averaged 7.5 months for MPM patients. The patient who underwent twice a HITHOC procedure for bilateral pleural thymoma metastases was unavailable for follow-up after movement from the Netherlands, 18 months after her first HITHOC. Outcome is summarized in Table 1. In conclusion, locoregional, contralateral pleural, and overall recurrence rates were 13%, 13%, and 33%, respectively, whereas the overall and disease-free survival rate were 85% and 78%, respectively.

DISCUSSION

Simple instillation of chemotherapeutic agents in the pleural cavity has been implemented in the treatment of primary and secondary pleural malignancy. Some studies^{28,29} investigated the feasibility and efficacy of cisplatin-based intrapleural chemotherapy as primary treatment for malignant pleural effusion. Although feasible and pharmacokinetically favorable, this approach appeared to be inferior to administration of existing sclerosing agents in control of pleural effusion. To our knowledge, no experience in instillation intrapleural chemotherapy for pleural thymoma metastases has been reported. In a single-center study, primary treatment of MPM by intrapleural administration of adriamycin was associated with an average survival rate of 25 months.³⁰ In inoperable MPM, intrapleural administration of cisplatin has been successfully used as a palliative treatment.³¹ Limited surgery with postoperative intrapleural instillation of chemotherapeutic agents, with or without other adjuvant therapy, was studied in MPM patients by the American Lung Cancer Study Group and others.³²⁻³⁶ The results were not as promising as expected. The median survival rates after this multimodality treatment varied from 11.5 to 17 months.

The penetration depth of intracavitary chemotherapy into the tumor is limited to a few millimeters.^{2,3} Therefore, surgical tumor removal, leaving only microscopic or very small tumor deposits behind, has to

precede this chemotherapy. Similar to the peritoneal cavity, intraoperative intrathoracic perfusion chemotherapy provides probably more optimal, homogeneous exposure of the chemotherapeutic agents to the entire involved surface, compared to the simple installation chemotherapy.^{37,38} For the above reasons, better results are expected from application of intrathoracic chemotherapy intraoperatively.

An important aspect of intraoperative intracavitary chemotherapy is the limited duration of treatment. This means that only drugs with direct cytotoxic activity can be used, such as mitomycin-C (MMC), cisplatin, and adriamycin. To improve the efficacy of chemotherapy, it can be combined with intracavitary hyperthermia, which has the advantage of selectivity, as the penetration of heat is limited to a few millimeters below the cavitory surface, avoiding increased systemic toxicity.⁴ Hyperthermia is cytotoxic and has a synergistic cytotoxic effect and enhances drug uptake in local tissue for several drugs, including MMC, adriamycin, and cisplatin, both in experimental and in clinical settings.^{4,13,39,40} Cisplatin and adriamycin appear to be the most effective drugs in systemic chemotherapy for thymoma. Responses are observed in 50 to 90% of cases, with complete responses in up to 30% of cases. The median duration of response is approximately 1 year only. Median survival of thymoma patients with pleural metastases is reported between 17 months and 67 months after systemic chemotherapy.^{18–20,41} In stage II and III MPM, cisplatin, adriamycin, MMC, gemcitabine, and antimetabolites appear to be the most active drugs. The latter are the most effective, but these agents are not suitable for our intrapleural application due to the limited time of exposure.^{26,27} In two of the three patients with thymoma metastases, a response on systemic multidrug chemotherapy including cisplatin with or without adriamycin was observed before inclusion in this trial. Since both MPM and thymoma are relatively sensitive to adriamycin and cisplatin, it was chosen to use these agents in this treatment approach.

In studies on intraoperative intrathoracic perfusion chemotherapy with cisplatin, the ratios of the maximal concentration in perfusate to that in plasma were reported up to 100 for total cisplatin and up to 555 for free cisplatin, whereas of the ratio of regional to systemic platinum exposure varied from 32 to 88, depending on the extent of the operation performed.^{12–14} In another study,¹³ a higher regional to systemic cisplatin exposure ratio was seen after pleuropneumectomy than after pleurectomy and decortication of the lung, supporting the hypothesis that the lung plays an important role in cisplatin absorption. The ratio of local tissue to perfusate platinum concentrations tended to be higher after hyperthermic rather than normothermic perfusion chemotherapy.¹³ In reported HITHOC studies and

studies on intrapleural instillation chemotherapy, a dose of 90 to 200 mg/m² of cisplatin has been used.^{12–14,29,31,33–35} Because of the combination with adriamycin, we used a dose reduction to 50 mg/m² of cisplatin in the first case. Although a transient mild nephrotoxicity occurred, we considered a dose of 80 mg/m² of cisplatin as safe when perioperative hydration should be improved in the following patients. With this higher dose, cisplatin-related complications were not observed.

In an experimental model, congestive heart failure, fibrous adhesions, and tissue necrosis engaging the pleura, diaphragm, and lung were observed after a single intrapleural administration of adriamycin, especially using higher doses.⁴² The recommended total dose for intrapleural administration of adriamycin and its analogs for treatment of malignant pleural effusion is 40 to 60 mg.³⁶ In hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma, 15 mg/m² of adriamycin in combination with 50 mg/m² of cisplatin was administered in a series of 33 patients without toxicity necessitating dose reduction.¹¹ Since there is no experience in hyperthermic pleural perfusion chemotherapy with adriamycin, its known direct toxic effect to the heart, laying adjacent to or even in the perfused space, when the pericardium is opened, and the combination with cisplatin, we started our study with a dose of 15 mg/m². In the absence of severe cardiotoxicity we increased our dose gradually to 30 mg/m².

A multivariate analysis⁴³ of a large series of patients demonstrated that survival after extrapleural pneumonectomy was equal to that after pleurectomy and decortication of the lung in mesothelioma patients. Since pleuropneumectomy is traditionally associated with significant morbidity and pleurectomy with decortication of the lung followed by intrathoracic chemotherapy has been demonstrated to be feasible,^{32,34} the study was designed to preserve the lung. Although preoperative evaluation revealed stage I disease in MPM patients, 7 of the 11 patients perioperatively were actually found to have stage II disease, emphasizing the difficulty in adequate non-operative staging of this disease.⁴⁴ In one case of MPM, decortication of the lung led to prolonged air leakage to the thoracic drains and delayed air fistula to the thoracic cavity and skin with empyema. In the following cases with significant diffuse involvement of the visceral pleura and/or infiltration of the lung parenchyma, we were more inclined to abandon the attempt to preserve the lung in favor of pneumonectomy. Decrease in operative mortality after pleuropneumectomy in a large series,⁴⁵ mainly due to improvement of surgical technique and perioperative management, and the above-mentioned pharmacokinetic advantages of this proce-

ture¹³ justify our diminished intention to treat patients with extensive pleural disease by lung-preserving surgery. In this series, resection of the involved lung had to be performed in four patients. The higher blood loss and the longer operative duration reflect the more extensive procedures in MPM patients compared to surgery performed for pleural thymoma metastases.

Postoperatively, radiotherapy was applied to the thoracotomy wound and drainage tracts in MPM patients, because it has been demonstrated that it reduces the chance on development of implantation metastases.⁴⁶ No such recurrences have been observed in our series, whereas no radiotherapy-related complications occurred.

Whereas now ample experience exists in combining hyperthermia and intracavitary chemotherapy in the abdomen,⁵⁻¹¹ there is hardly any experience in the chest.¹²⁻¹⁴ In two reported series, intrapleural perfusion hyperthermochemotherapy was performed without resection of the pleural lesions,^{12,14} whereas in other studies this treatment modality was used as an adjuvant treatment after resection of the macroscopic lesions.¹³⁻¹⁶ Malignancies managed by this approach included MPM (13 patients),^{13,15} pleural disseminated lung (17 patients),¹² gastric (2 patients),¹⁴ breast (1 patient),¹² and thymic carcinoma (1 patient),¹⁶ and osteosarcoma (1 patient),¹² whereas in 2 patients pleural metastases of undefined adenocarcinoma were treated.¹⁵ In most patients, only cisplatin was used,^{12,13,15,16} where other drugs administered intrapleurally included mitomycin (4 patients),¹⁵ mitomycin, and etoposide in combination with cisplatin (2 patients).¹⁴

Morbidity rates in the reported small series varied from 0 to 60%.¹²⁻¹⁵ Complications reported in the 35 cases reported included transient, mild, probably cisplatin-related nephrotoxicity (3 patients),^{13,16} transient pulmonary infiltrates (2 patients),¹² wound infection (1 patient),¹³ diaphragmatic prosthesis displacement (1 patient),¹³ prolonged air leakage (1 patient),¹⁵ and pleural clotting (1 patient).¹⁵ None of the patients died because of a treatment-related cause. Postoperative complications occurred in 47% of our patients and are summarized in Table 1. No severe cardiotoxicity was seen in the postoperative period; grade 2 cardiac complications were observed in patients who had pericardium partially resected, allowing direct contact of adriamycin to the heart muscle. In six other patients in whom the pericardium was opened during surgery, no cardiotoxicity was observed. Hematologic toxicity and other chemotherapy-related morbidity were not noted.

In a series of 19 mainly lung cancer patients with pleural dissemination and/or effusion who underwent HITHOC without resection of pleural disease, results

suggested improvement of survival by this approach compared to a nonrandomized control group who did not receive this regional chemotherapy perfusion.¹² The single reported patient who underwent surgery and HITHOC for pleural thymoma dissemination was alive 16 months after treatment without evidence of recurrence.¹⁶ Another study¹⁵ reported pleural recurrence in two of the three MPM patients treated by this approach, while one of these patients and the third patient had systemic metastases develop. Also, in the patients with pleural adenocarcinoma metastases, pleural recurrence occurred. In our series with a limited follow-up period, locoregional disease control was obtained by this multimodality treatment in 87% of cases. One MPM patient died of peritoneal recurrence. Partial diaphragmatic resection with subsequent spread of malignant cells to the peritoneal cavity is the assumed cause of this event, despite the fact that closure of the defect was postponed until after perfusion chemotherapy. In nine other patients in whom the diaphragm was opened, no evidence of peritoneal recurrence was noted until the time of this analysis. Analogous to pseudomyxoma peritonei, where it is the most important risk factor for pleural recurrence,³⁷ opening the diaphragm is probably a significant risk factor for postoperative peritoneal recurrence in patients with MPM.

CONCLUSION

Surgical cytoreduction and HITHOC seems to be an attractive approach to primary and secondary pleural neoplasms. This regional treatment using cisplatin and adriamycin is feasible in patients with pleural metastases of thymoma and early-stage MPM and is associated with an acceptable morbidity rate. This therapeutic approach might provide an improved locoregional disease control. The promising results of this feasibility study have prompted us to extend the inclusion of patients to a proper phase II study in the Netherlands Cancer Institute.

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