Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience†

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Abstract

OBJECTIVES: A combination of cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion (HITHOC) was performed for the treatment of primary and secondary pleural malignancies. We describe the perioperative management and our clinical experience.

METHODS: Between September 2008 and August 2011, eight patients with pleural manifestation of thymoma (Masaoka stage IVa) and eight patients with malignant pleural mesothelioma (MPM) were prospectively enrolled. Postoperative morbidity, recurrence and survival rates were analysed.

RESULTS: All the patients received multimodality therapy, including chemotherapy, radiation and surgical resection (pleurectomy/decortication) followed by the HITHOC procedure. Chemotherapy perfusion was performed with cisplatin (100–150 mg/m²) at 42°C for 1 h. Severe chemotherapy-related complications were not observed. Reoperation was necessary in two patients. There was no 30-day mortality. The median stay on the intensive care unit was 1 day, and the median duration of hospitalization was 15 days. Pleural recurrence of thymoma was evident in one thymoma patient 6 months after HITHOC. At mean follow-up of 22 months, seven thymoma patients (7/8; 88%) are alive without recurrence. Tumour progression was present in six mesothelioma patients (6/8; 75%). Four patients (50%) with MPM are alive, including two with no evidence of mesothelioma, and the median survival is 18 months.

CONCLUSIONS: Cytoreductive surgery in combination with HITHOC can be performed with acceptable morbidity and mortality rates in selected patients. Patients should be evaluated by an interdisciplinary team to determine their eligibility for this therapeutic alternative. Early clinical results may encourage the use of this surgical option to provide better local tumour control in a multimodality treatment setting.

Keywords: Thymoma • Pleural mesothelioma • Cytoreductive surgery • Hyperthermic perfusion • Multimodality treatment

INTRODUCTION

The optimal treatment of pleural malignancies in the contexts of malignant pleural mesothelioma (MPM) and advanced thymoma with pleural spread remains controversial. There exists no standard treatment regime with curative intention. MPM is a rare thoracic cancer associated with asbestos exposure that has an increasing incidence, with an expected peak around 2020 [1]. This tumour arises from the pleural surface (mesothelial cells) and involves invasive growth with infiltration of the lung, mediastinum and other adjacent organs or structures. Death is caused by loco-regional tumour extension in most cases, and patients with MPM usually have a poor prognosis, with a median survival time after diagnosis in the range of 6–12 months [2]. Current treatment options are based on a multimodality therapy regime involving induction chemotherapy, surgery and adjuvant chemotherapy in addition to radiotherapy [3].

The prognosis of locally advanced thymoma with pleural spread (Masaoka stage IVa) is also poor, and no standardized treatment has been established to date [4]. Limited data are available in the literature, but a multimodality approach can be used to decrease the recurrence rate and consequently improve the outcome [5].

For both MPM and stage IVa thymoma, complete surgical resection is essential for local tumour control [6, 7]. Radical surgical resection can be achieved by performing extrapleural
Pneumonectomy (EPP) with en bloc removal of the parietal and visceral pleura, lung, pericardium and diaphragm [8]. On the other hand, lung-sparing cytoreduction can be performed with pleurectomy/decortication (P/D) [9]. The type of surgery chosen should depend on the extent of the disease, patient comorbidities and the multimodality therapy planned [10]. However, surgery alone cannot achieve microscopically complete resection. Residual tumour cells will stay in the pleural cavity, enhancing local tumour recurrence. Therefore, cytoreductive surgery combined with adjuvant therapies, including intracavitary chemotherapy, has increasingly gained attention [11].

A multimodal approach consisting of cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion (HITHOC) has recently been developed, which might improve local tumour control and the prognosis of patients with pleural tumours [12]. Here, we present our perioperative management approach and clinical experience with this innovative surgical therapy in a multimodality setting.

PATIENTS AND METHODS

Patients and study design

This was an observational, prospective, single-centre study. From September 2008 to August 2011, a total of 16 patients with primary or secondary pleural malignancies, including MPM and pleural metastases of the thymoma (Masaoka stage IVa), were prospectively enrolled in this study at the University Medical Center Regensburg. All patients signed an informed consent form. Patients were recruited in an interdisciplinary thoracic oncology assessment involving thoracic surgeons, neurologists, oncologists, pulmonary specialists, radio- oncologists and radiologists. Patients who were considered for operative therapy with curative intention were included in this study group. Therefore, only patients whose pleural mesothelioma or thymoma was almost certainly completely resectable were included. Patients with preoperative renal insufficiency requiring renal replacement therapy and patients who were not considered to be operable because of impaired cardiopulmonary function were excluded. In addition, patients with evidence of contralateral tumour masses or peripheral metastases were excluded. Multimodality therapy was administered in all patients. Second-line treatments were administered when appropriate. All patients received cytoreductive surgery consisting of P/D to achieve macroscopic complete tumour resection. Therefore, parietal and visceral pleurectomy was performed to remove all gross tumour without or with (extended) resection of the diaphragm and/or the pericardium [9]. Immediately after cytoreduction, HITHOC perfusion with cisplatin was performed to destroy residual tumour cells and to achieve better local tumour control. All operations were performed by the same cardio-thoracic surgeon. All patients received a detailed preoperative history and physical examination to ensure functional operability. In addition, lung function testing (spirometry, blood gas analysis) was performed to detect adequate pulmonary function to allow thoracotomy and eventual partial or complete lung resection surgery. In patients aged older than 60 years or with a preoperative history of cardiac events, cardiac ultrasonography was performed. Preoperative staging consisted of conventional radiographs and a computed tomography (CT) scan of the chest with contrast agents in all patients. To clarify eventual contralateral or peritoneal mesothelioma invasion, 18-fluoro-deoxyglucose positron emission tomography (PET)-CT was used preoperatively. Flexible bronchoscopy combined with endobronchial ultrasound-guided transbronchial needle aspiration was used to exclude endobronchial tumour growth and mediastinal lymph node affection. Any suspected pleural mesothelioma diagnosis was confirmed by video-assisted thoracoscopy and histological examination. Beginning in October 2010, Cine-MR (magnetic resonance tomography) was performed in patients with invasive thymoma to obviate myocardial or great vessel infiltration.

The primary endpoint of this study was to determine the safety and feasibility of HITHOC with cisplatin immediately after P/D for curative treatment of malignant pleural tumours. Perioperative complications were noted. Secondary endpoints were postoperative morbidity and mortality during this combination therapy in a multimodality treatment setting with particular reference to renal function. Lengths of intensive care unit (ICU) and hospital stays were noted. Mid-term patient survival and disease-free interval were evaluated and documented. Descriptive statistics were calculated throughout the study.

Surgical technique

Macroscopic complete resection was the aim in all patients with primary and secondary pleural malignancies. Patients with Masaoka stage IVa thymoma primarily had radical thymectomy via median sternotomy, including the en bloc resection of the thymoma along with the thymic gland and perithymic fat tissue. When appropriate, the resection was extended to the pleura, pericardium, lung, great vessels and phrenic nerves.

For cytoreductive surgery of the pleura, the patient was placed in a lateral position with pneumatic boots, and posterolateral thoracotomy through the fifth intercostal space was the preferred approach. Where necessary, a second access thoracotomy was performed to ensure a complete resection of the tumour masses in the phrenicocostal recess or for partial resection of the diaphragm. After pleural exploration to score the tumour extent and confirm that resection seemed feasible an extrapleural dissection between the lung and tumour was performed. Subsequently, pleurectomy from the apex down to the diaphragm and from anterior to posterior was performed until the hilar structures were free. The visceral pleura was separated from the lung, and wedge resections of infiltrated parts of the lung were performed when appropriate. Larger air leakages were sutured. Where necessary, extended resections (partial or complete) of the pericardium, diaphragm or chest wall were made (extended P/D). Reconstruction was performed using polytetrafluoroethylene (PTFE) mesh (2 mm Dual Mesh, GORETEC, WL Gore and Associated, Flagstaff, USA) or Peri-Guard Repair Patch (durable autologous-like patch solutions). Chest tubes (28 F) were inserted and regular wound closure was performed before starting perfusion.

Chemotherapy perfusion

After completion of the surgical cytoreduction, the tubes were connected to the perfusion system (ThermoChem HT-1000), and the extracorporeal circulation was started. The perfusion system consisted of a roller pump, a reservoir and a heat exchanger. There were one (or two) inflow catheters placed apically in the anterior and posterior pleural cavity and two or three outflow...
Anaesthesiological management

All patients were under general, and in most cases thoracic epidural, anaesthesia. A double-lumen endotracheal tube was used to facilitate one-lung ventilation (OLV). Patient monitoring included invasive arterial blood pressure, central venous pressure and pulse oximetry. Blood gas samples were obtained routinely. The patients received prophylactic antibiotics peripherally (three doses of cefuroxime). During chemotherapy perfusion, OLV was performed on the contralateral lung, whereas the ipsilateral lung (side of operation) was only partially ventilated, or a continuous positive airway pressure with a PEEP of ≏5–10 mmHg was used to allow acceptable oxygenation and sufficient space between the chest wall and the pulmonary parenchyma. Because of hyperthermic lavage, the body’s core temperature was measured continuously rectally and oesophageally. If necessary, active external cooling was performed. Urinary output was controlled continuously. Extubation was preferred in all cases directly after surgery in the operation theatre. Postoperatively, all patients were transferred to the ICU and received standard monitoring. In all patients, the lengths of isolation and ICU stay were at least 24 h or longer if appropriate. The fluid contents of the drainages were depolluted separately. Prophylactic antibiotics were given for 1 week.

Follow-up

Survival was calculated from the date of resection and HITHOC. Patients were routinely observed 2 weeks and 3 months after hospital discharge and then at 6-month intervals in our department or at the outpatient hospital. Patients with thymoma were adjuvant treated and monitored by neurologists at the District Medical Center Regensburg. When necessary, further diagnostics were performed (CT, MRI, PET-CT). Follow-up for all patients was continued until either death or the end of April 2012. Time to recurrence, side of recurrence and overall survival were recorded.

RESULTS

Patient characteristics

Between September 2008 and August 2011, a total of 16 patients were prospectively enrolled in this trial. Patient characteristics and treatment regimes are summarized in Tables 1 and 2. There were 13 male and 3 female patients with a mean age of 56 years (median: 60 years; range: 25–72). Eight patients had histologically confirmed MPM (epithelial n = 7, biphasic-epithelial n = 1) without evidence of contralateral or peritoneal dissemination. Exposure to asbestos was evident in four MPM patients. All of the mesothelioma patients had previously been treated with combination chemotherapy consisting of cisplatin and pemetrexed. Thus, no complete pathological response was registered after induction chemotherapy.

Eight patients with pleural thymoma metastases (Masaoka stage IVa) were also included in the study sample (Fig. 1). Their WHO histological classifications were type B2 (n = 5) and type B3 (n = 3). In this sample, all but one patient with thymoma received neoadjuvant chemotherapy. Adjuvant chemotherapy and/or radiotherapy was utilized in each individual depending on the extent of the

Table 1: Characteristics of patients with MPM

<table>
<thead>
<tr>
<th>Gender/age (years)</th>
<th>Histology/side</th>
<th>Multimodality therapy</th>
<th>Cisplatin dose (mg/m²)</th>
<th>Complication</th>
<th>ICU-/hospital-stay (days)</th>
<th>Recurrence side/time interval (months)</th>
<th>Survival/follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/71</td>
<td>Epithelial/right</td>
<td>CT; Extended P/D (partial pericardium); CT + RT</td>
<td>100</td>
<td>No</td>
<td>1/10</td>
<td>Right/6</td>
<td>DOD/28</td>
</tr>
<tr>
<td>Male/69</td>
<td>Biphasic/right</td>
<td>CT; P/D; CT</td>
<td>100</td>
<td>No</td>
<td>1/17</td>
<td>Right/3</td>
<td>DOD/4</td>
</tr>
<tr>
<td>Male/72</td>
<td>Epithelial/left</td>
<td>CT; Extended P/D (partial pericardium); CT</td>
<td>100</td>
<td>Rupture of the diaphragm: reoperation</td>
<td>1/21</td>
<td>Left/9</td>
<td>DOD/27</td>
</tr>
<tr>
<td>Male/69</td>
<td>Epithelial/left</td>
<td>CT; P/D; CT + RT</td>
<td>100</td>
<td>No</td>
<td>1/21</td>
<td>Left/7</td>
<td>DOD/12</td>
</tr>
<tr>
<td>Male/60</td>
<td>Epithelial/left</td>
<td>CT; P/D; CT + RT</td>
<td>100</td>
<td>No</td>
<td>1/14</td>
<td>Left/16</td>
<td>AWD/21</td>
</tr>
<tr>
<td>Male/63</td>
<td>Epithelial/left</td>
<td>CT; P/D; CT</td>
<td>100</td>
<td>No</td>
<td>1/8</td>
<td>No</td>
<td>Alive/18</td>
</tr>
<tr>
<td>Female/58</td>
<td>Epithelial/left</td>
<td>CT; Extended P/D (partial pericardium)</td>
<td>100</td>
<td>No</td>
<td>1/11</td>
<td>No</td>
<td>Alive/13</td>
</tr>
<tr>
<td>Male/61</td>
<td>Epithelial/right</td>
<td>CT; Extended P/D (partial pericardium)</td>
<td>150</td>
<td>No</td>
<td>1/10</td>
<td>Right/3</td>
<td>AWD/16</td>
</tr>
</tbody>
</table>

Different therapies are listed in chronological order. AWD: alive with disease; CT: chemotherapy; DOD: dead of disease; P/D: pleurectomy/decortication; RT: radiotherapy.
disease and the patient’s overall condition and preference. Adjuvant chemotherapy was administered in six of eight (75%) patients with MPM with three patients receiving additional radiotherapy. Both patients who did not receive adjuvant therapy were in a reduced overall condition and were not suitable for chemotherapy (Table 1). In all, four of the thymoma patients obtained postoperative chemotherapy, and no patient needed radiotherapy. Finally, three thymoma patients without adjuvant chemotherapy had already undergone preoperative chemotherapy (Table 2).

**Operative data**

Patients with thymoma received prior radical thymectomy via median sternotomy, and combination therapy was administered in a secondary surgery. Four patients with initial-stage IVa thymoma underwent subsequent cytoreductive surgery with HITHOC after radical thymectomy (at 7, 20, 90 and 15 days, respectively). The time interval between the first and second operations depended on the patient’s overall condition. In one patient, the time interval was 90 days because extended surgical resections (wedge resection right lung and partial resection of the pericardium) were performed during primary thymectomy to achieve macroscopic complete resection. The other four patients had pleural recurrence of thymoma after previous radical thymectomy (25–36 months).

All patients underwent P/D ($n = 7$) or extended P/D ($n = 9$) followed by the HITHOC procedure (Figs 2 and 3). In 11 patients (69%), a second thoracotomy was performed in the seventh or eighth intercostal space to permit sufficient tumour resection in the basal pleural space. Intrathoracic chemotherapy perfusion was performed with cisplatin (100–150 mg/m$^2$) at 42°C for 1 h.
with 1.5 l/min pump flow. The cisplatin dose was increased to 150 mg/m² in the last two patients of the study. After an average of 25 min (range: 15–50 min), volume stabilization and optimal temperature of the circuit were achieved, and the chemotherapeutic agent was administered. There were no technical problems during the perfusion period. The overall median duration of the operation, including preparation of the perfusion circuit and perfusion time, was 275 min (range: 160–448 min).

Postoperative morbidity

Severe postoperative complications requiring surgical correction occurred in two patients. One mesothelioma patient underwent timely reoperation due to rupture of the diaphragm, with successful reconstruction (PTFE-Patch). One thymoma patient with a prolonged ICU stay (13 days) due to redo-thoracotomy, extensive tumour growth and impaired overall condition was readmitted to the ICU because of respiratory insufficiency, fulminant sepsis and haemothorax. Emergent operative revision with pneumonectomy had to be performed. One patient with extended resection after invasive pleural thymoma dissemination experienced subclavian and axillary vein thrombosis on the ipsilateral side of surgery. Severe chemotherapy-related complications were not observed including renal impairment due to renal toxicity of systemic cisplatin. The median length of stay on the ICU was 1 day (range: 1–13 days), and the overall median hospital stay was 15 days (range: 8–63 days). Timely extubation directly after surgery was performed in 14 patients (88%), whereas 2 patients needed mechanical ventilation (for 6 h and 2 days, respectively).

Outcome

There was no in-hospital mortality or death within 30 days after operation among all patients in this series. At the end of the study period (April), seven of eight (88%) thymoma patients were alive without evidence of recurrence, with a mean follow-up period of 22 months (range: 7–35 months; median survival 23 months). The first thymoma patient had ipsilateral pleural thymoma recurrence 6 months after multimodality therapy and was treated by systemic second-line chemotherapy. Death was documented 35 months after surgical therapy due to loco-regional tumour recurrence. After 13 months, one patient developed mediastinal thymoma recurrence and underwent successful reoperation with complete resection.

After a mean follow-up of 17.4 months (range: 13–28 months), four (50%) patients with MPM were alive. Overall median survival was 18 months. Tumour progression or recurrence was observed in six (75%) patients, two of whom remained alive at the end of the analysis. The initial site of recurrence in all mesothelioma patients was the ipsilateral haemithorax (100%). Median time to radiologically confirmed recurrence was 4.5 months (mean: 7.3 months; range: 3–16 months).

DISCUSSION

Current treatment strategies with curative intention for primary and secondary pleural malignancies are based on a multimodality approach consisting of induction chemotherapy, surgical resection, adjuvant chemotherapy and, in some cases, radiotherapy. Following the success of intraoperative hyperthermic chemotherapy with surgical cytoreduction for peritoneal malignancies, this combination technique has also been applied as part of multimodality treatment of malignant pleural tumours [12–14]. Cytoreductive surgery is a well-known term for surgical procedures in the treatment of pleural malignancies, as mentioned in the recent literature [11, 14]. In this series, we present our early clinical experience using this innovative multimodality treatment regime for patients with MPM or invasive thymoma with pleural dissemination. We investigated the safety and feasibility of this combination treatment regime in our institution with respect to morbidity and mortality. There was no postoperative mortality recognized. Reoperation was necessary in two cases, and the median stay on the ICU was one day and the overall median hospitalization was 15 days. Follow-up in patients with thymoma was encouraging, with all but one of the eight patients being alive without local recurrence (88%). Median survival of MPM patients was 18 months (50% are alive).

Nevertheless, there is no recognized curative treatment regime established for MPM to date, and median survival is often <12 months [15]. Combination chemotherapy with cisplatin and pemetrexed could significantly improve patient survival (12.1 months) compared with cisplatin alone (9.3 months) and represents the current therapeutic standard [16]. Whenever possible, complete surgical tumour resection (EPP) along with chemotherapy should be performed to further improve the outcome [17]. In the largest prospective multicenter study of multimodality therapy, mesothelioma patients received neoadjuvant pemetrexed/cisplatin, followed by EPP and haemothoracic radiation. Although the median survival was only 17 months, the 2-year survival rate was 37% [18]. However, EPP is an extremely radical procedure that is associated with significant morbidity, with serious postoperative complications developing in ~50% of patients. Mortality rates decreased over time from 33% to <5% in experienced centres [17]. In patients with limited cardiopulmonary reserve, effective cytoreduction is performed by extended P/D [19]. In a large retrospective analysis, patients who underwent EPP had a higher mortality (7 vs 4%) and a poorer overall survival compared with P/D (12 vs 16 months). Local recurrence is more common after P/D compared with EPP (65 vs 33%), whereas distant recurrences are more frequent after EPP (66 vs 35%) [10]. Hence, multimodality therapy appears more feasible in patients with P/D than EPP, with a median survival of 30
months [20]. Thus, overall survival might be improved in patients with less-aggressive resections. On the other hand, adjuvant hae- 

mithermic radiation-therapy to improve local tumour control is limited after P/D due to pneumonitis and fibrosis. However, to reduce local relapse after extended P/D, intraope-

rative hyperthermic perfusion with chemotherapeutic agents can be performed to provide homogeneous exposure to the involvement surface. Complete surgical cytoreduction, leaving only microscopic residual tumour cells, is absolutely required because the penetration depth of most drugs is limited to a few milli-

metres [21]. In addition, regional hyperthermia can improve the efficacy and penetration of the chemotherapeutic agent [13]. Cisplatin, alone or in combination (Adriamycin, doxorubicin), is the preferred agent for regional chemotherapy perfusion [14]. The intrapleural doses of cisplatin reported in the literature vary between 80 and 250 mg/m². There is no consensus about the optimal dosage. Richards et al. [19] suggest that higher doses of cisplatin (175–225 mg/m²) have a better impact on survival than lower doses (50–150 mg/m²). The maximum tolerable dose is 225 mg/m² cisplatin due to higher morbidity and mortality when this dose is exceeded. We began with a dosage of 100 mg/m² cisplatin (n = 14) and increased the dosage to a maximum of 150 mg/m² in the last two patients. We observed no severe chemotherapy-related complications, such as post-

operative renal insufficiency or haematological depression, in our study sample. However, to avoid major cisplatin-related complications due to systemic absorption causing renal toxicity, we do not anticipate increasing the dosage further. Thus, effective cytoprotective strategies are needed to ensure renal protection under high intracavitary dosages of cisplatin [22].

In two recent reports, morbidity after cytoreductive surgery (EPP and P/D) and HITHOC for mesothelioma patients ranged from 47 to 65% [11, 14]. However, our postoperative morbidity rate was significantly lower, with only three major complications (19%). Mortality varied from 0 to 11% after this combination therapy in a multimodality regime [14, 19]. These preliminary results were rather disappointing in patients with an aggressive treatment strategy. Despite these first results, current studies demonstrated acceptable median survival durations (13.1–26 months) for patients treated with EPP and HITHOC, depending on the cisplatin dosage and epithelial subtype (175–200 mg/m²) [22, 23].

Treatment of advanced thymoma (stage IVa) with pleural in-

volvement is a challenging situation and still a matter of debate. Although complete surgical resection plays a major role in a multidisciplinary approach, the exact choice of surgical procedure requires controversy [4, 5]. After induction chemotherapy, EPP can be performed safely in selected patients with extensive tumour masses and may improve survival due to local control [7]. To obviate pneumonectomy, P/D could be performed to respect residual pulmonary function. Because there seems to be diffuse microscopic invasion of the visceral pleura, consequent decortication has to be undertaken [24]. Nevertheless, loco-regional recurrence is the most common cause of death. Recently, cytoreductive surgery (P/D) in combina-

tion with HITHOC perfusion as additional therapy has been investigated as a way to provide better local disease control. Only two studies using a small cohort of patients confirm that this combination therapy is safe and feasible (0% mortality) while reporting promising survival rates (5-year survival rate 70%) [14, 25]. However, the technique may be associated with significant morbidity (20%) [25]. In line with these encouraging results, seven of our eight thymoma patients (88%) are still alive without evidence of recurrence, with a median survival of 23 months. Nevertheless, our current follow-up in thymoma patients may be still too short to give validated data regarding long-term survival. Except for one patient with sepsis, we observed no severe postoperative complications (12.5%).

Strengths and study limitations

This is a feasibility study concerning a multimodality therapy in combination with P/D and HITHOC with cisplatin in patients with MPM and advanced thymoma. Our perioperative manage-

ment and technical learning points are described. But our study suffers from some limitations. Its main limitations are the relatively small sample size, non-randomization, eventual patient selection bias and the slightly short follow-up, especially in patients with thymoma. Further randomized prospective multi-

centre trials are warranted to evaluate multimodality regimes in-

cluding P/D and HITHOC. Further investigations with respect to the combination of different chemotherapeutic agents and effective and safe dose are necessary. Therefore, the pharmacokinetics of cisplatin will be investigated in our department by measuring perfusate, serum and tissue levels.

CONCLUSION

In conclusion, cytoreductive surgery (P/D) in combination with 

HITHOC perfusion is feasible and can be performed with accept-

able morbidity and mortality rates in patients with pleural spread of thymoma and MPM. Patients should be evaluated by an interdisciplinary team in an experienced thoracic cancer centre to determine the eligibility for this therapeutic alternative. Extended P/D, preferably with complete macroscopic tumour resection, constitutes the mainstay of successful intrathoracic chemotherapy perfusion. Early clinical results may encourage the use of this new surgical option as an additional treatment tool to provide better local tumour control in a multimodality treatment setting including induction chemotherapy and adjuvant chemo-radiotherapy. Patients receiving higher doses of cisplatin may have a survival advantage. Future multicentre studies are needed.

Conflict of interest: none declared.

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