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Cold-plasma coagulation in the treatment of malignant pleural mesothelioma: results of a combined approach

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Abstract

Malignant pleural mesothelioma is on a continuous rise throughout the Western countries. It is associated with asbestos fibre exposition in the past. Surgical approaches include extrapleural pneumonectomy and pleurectomy/decortication (P/D). We investigated the feasability of the implementation of cold-plasma coagulation (CPC) on the pleura, pericardium and diaphragm into an established therapeutic algorithm consisting of P/D and hyperthermic intrathoracal chemoperfusion (HITHOC) therapy. The underlying rationale was the prevention of cardiotoxic effects during HITHOC as well as accidental translocation of malignant cells to the abdomen. CPC was done as part of a multimodal therapy in stage III mesothelioma patients. Histologic examinations of pleural excisates after CPC were done. The patients were followed up in three-month intervals. Neither parenchymal fistulas, nor cardiotoxic effects were observed. The histologic examination of the pleural excisates showed complete predictable necrosis. Moreover, until now (median time after operation 1 year) no relapse of the disease was observed. CPC proved to be a safe technique when used on the pleura, pericardium and diaphragm. We consider our trial as a pilot-study. To evaluate potential survival benefits using this technique larger trials are mandatory.

Keywords: Malignant pleural mesothelioma; Cold-plasma coagulation; Hyperthermic intrathoracic chemoperfusion

1. Introduction

Malignant pleural mesothelioma (MPM) is associated with asbestos exposure. Due to the widespread use of asbestos fibres throughout the world in the past decades the incidence of the disease is on a continuous rise with an expected peak at the year 2015 [1, 2]. Until now all therapeutic approaches are strictly palliative, although encouraging results of surgical and non-surgical therapy with a profound prolongation of median survival were published during the last years [3–5].

Extrapleural pneumonectomy (EPP) is considered the most radical surgical approach leading to a complete removal of local tumor masses and an associated median survival of up to 38 months. EPP is limited to only very few carefully selected patients matching very restrictive selection criteria [6].

In several trials, pleurectomy and decortication (P/D) combined with hyperthermic intrathoracic chemoperfusion (HITHOC) led to comparable or even superior results compared to EPP [6, 7].

P/D in combination with HITHOC has therapeutic limitations, because of potential side effects of a radical pleurectomy at the diaphragma and the pericardium. Potential adverse events include direct cardiotoxic effects at the myocardium and small defects of the diaphragma leading to potential tumor cell translocation to the abdomen and consecutively abdominal recurrence of malignant mesothelioma.

We, therefore, introduced the use of cold-plasma coagulation (CPC) for tumor destruction at the pericardium and the diaphragma. This technique is strictly limited to superficial layers and accomplishes a predictable depth and area of necrosis. This article deals with the results of the first eight patients operated with the new therapeutic approach.

2. Materials and methods

The patient population in this study comprises eight patients, that were diagnosed with a pleural mesothelioma stage III, after asbestos fiber exposition. During informed consent a special focus was on the implementation of CPC into the operation. The data were analyzed retrospectively. Statistical analysis was omitted, because of the small number of patients and short follow-up.

2.1. Selection of patients

The patients had to have a diagnosis of MPM. Further inclusion criteria were as follows:

a. adequate pulmonary function to allow the operation, preoperative check-up included lung function measurement and spirometry
b. adequate cardiac function measured by echocardiography and ergometry
c. performance score of 0–2, according to the Eastern Oncology Cooperative Group

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d. normal blood count
e. written informed consent.

2.2. Operative procedure

The patient was placed in lateral position. An anterolateral thoracotomy was done. A complete parietal pleurectomy was done combined with a visceral pleurectomy, where feasible. CPC of the parietal pleura was used on the diaphragm and the pericardium. We used the CPC 1500 System of Soering GmbH, Quickborn, Germany.

2.3. Cold-plasma coagulation

CPC is realized by the generation of HF-energy by a HF-generator. The energy is transmitted contactless via the metal tip of a handpiece through ionized helium-gas to the tissue. Simultaneously, helium-gas is transported to the handpiece and pours out from a jet at the end of the handpiece. The activation of the handpiece produces a plasma discharge at the metal tip that is visible as a faint luminescent ionization. During this process, the number of ionized gas-molecules is on a constant rise. The temperature of the plasmastream is growing. A very low HF-energy is conducted through the tissue and ends up from the patients' surface at the earthed pole of the generator. The radical reduction of the HF-energy prevents the destruction by electric energy in deeper layers. The underlying rationale for this therapeutic approach was to reduce the probability of complications resulting from alloplastic reconstruction of the pericardium and the diaphragm.

2.4. Hyperthermic intrathoracic chemoperfusion therapy

A ThermoChem® 1000 System was used to establish a continuous thoracic perfusion. Perfusion was done via one inflow and three outflow catheters. We used doxorubicin (15 mg/m^2) and cisplatin (100 mg/m^2) as cytotoxic agents. Perfusion was done for 1 h at a temperature between 40 °C and 41 °C.

2.5. Adjuvant radio-chemotherapy

All patients received radiation therapy to the thoracotomy- and drainage-sites to prevent cutaneous metastases. The adjuvant chemotherapy was given by cooperating oncologists, the patients received different therapeutic regimes all including pemetrexed.

2.6. Follow-up

Patients were routinely followed-up, initially six weeks after discharge and then every three months until now. Computed tomography (CT) scans of the thorax and abdomen were done every three months in the first postoperative year.

3. Results

3.1. Patient characteristics

The average age of our eight patients was 72 years with a range of 72–76 years. All patients were male and had multiple expositions to asbestos fibers. The presentation was with a stage III disease in all cases (Fig. 1). No patient had distant metastatic disease. N2 metastases were detectable in two cases. Distant metastatic disease was excluded by abdominal- and chest-CT, head-CT and bone scans. A PET–CT-scan was not done. All patients were substantially reduced in their ability of undertaking the activities of daily life due to profound shortness of breath, because of pleural effusions. No patient had previous operative or chemotherapeutic treatment. One patient was on anti-platelet therapy with aspirin. The histology at presentation was epitheliomorph in two cases, while it was of mixed type in six cases. The ECOG performance status was 1 in three cases and it was 2 in five cases.

3.2. Therapeutic procedure

Average operation time was 255 min with a range of 125–310 min. All operations resulted in a completeness of cytoreduction score (CCS) of 0–1. During perfusion therapy, the temperature was never below the predefined level of 40 °C (Table 1).

3.3. Morbidity and mortality

Adverse events are summarized in Table 2. One bleeding complication of minor extent was treated in one patient with the transfusion of three packs of erythrocytes. The patient with prior anti-platelet therapy had major bleeding resulting in a hematothorax that required re-thoracotomy and the evacuation of the hematoma. After the re-operation the patient was stable, no further complications occurred and the patient was discharged on postoperative day 10.

We had no perioperative or postoperative 90-day mortality. One patient had a temporary elevation of the serum-creatinin levels up to 250 mg/dl. This patient had slightly elevated retention parameters before the operation. The values for kidney function returned to baseline at the 14th postoperative day. No hematologic toxicities after the intrathoracic chemotherapy were observed. Postoperative nausea and vomiting were comparable to other major thoracic

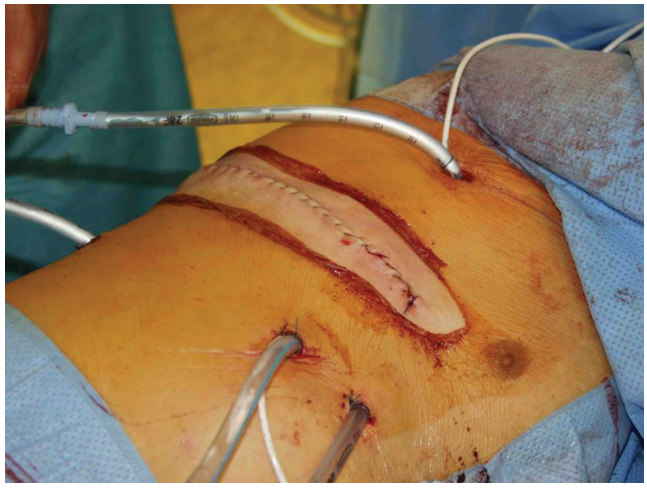

Fig. 1. Clinical image before establishment of perfusion cycle.

Table 1
Excerpt from the chemoperfusion-protocol

Time	Flow (l/min)	Heatex-changer (°C)	Water bath (°C)	Patient (°C)	Inflow	Outflow	Dorsal	mmHg
15:20	0.7	42.1	42.8	34.5	41.5	40.4	40.2	40
15:30	Administration of cisplatin and doxorubicin							
15:30	0.8	41.9	42.8	34.7	41.4	40.5	40.1	40
15:40	1.0	41.3	41.8	34.9	40.9	40.7	40.6	40
15:50	1.0	41.1	41.7	35.1	40.8	40.2	40.5	40
16:00	1.0	41.0	41.8	35.3	40.8	40.4	40.5	40
16:10	1.0	41.1	41.8	35.8	40.9	40.3	40.4	40
16:20	1.0	41.1	41.8	35.8	40.9	40.5	40.4	40

Pressure, temperature and flow were constant. The possibility to obtain intra-operative quality control is of major importance. Three temperature probes were placed adjacent to the in- and out-flow catheters.

Table 2
Adverse events that were detected during the study

Adverse event	*n*
Elevation of creatinine	1/8
Leukopenia	0/8
Fever	4/8
Elevation of C-reactive protein	4/8
Hemorrhage	2/8
Deep venous thrombosis	0/8

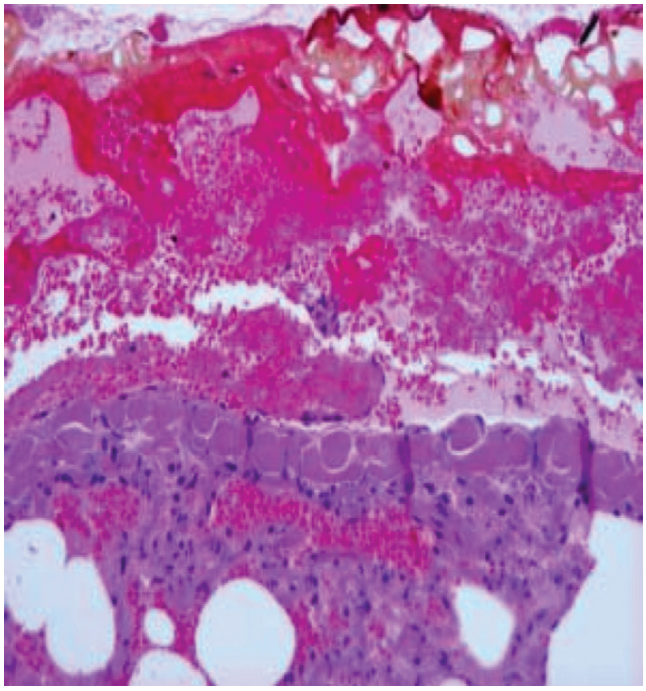

Fig. 2. Lung resectat after CPC with 25 W necrosis depth 0.5 mm.

surgery interventions. Also, no clinical signs of deep-vein thrombosis were apparent.

3.4. Hospital stay

The average hospital stay was 15 days with a range of 12–23 days. Average postoperative ICU-stay was three days with a range of 1–6 days.

3.5. Follow-up

The longest follow-up period is 12 months. Until now, neither pleural effusions nor a progress of the disease were detected in any of the surviving patients. One patient with stage III disease died at postoperative month ten, due to cardio-pulmonary failure. This accounts for an overall mortality of 14.3%. All remaining patients are satisfied with the operative results and consider their quality of life to have significantly improved.

3.6. Cold-plasma coagulation

The application of CPC to the parietal and visceral pleura was done without technical problems. The average time of application was 25 min with a range of 15–46 min. The histologic examinations of representative pleural excisates of different origin before and after CPC were not able to detect vital tumor cells after coagulation.

3.7. Adjuvant therapy

Patients were treated by co-operating oncologists. All patients received pemetrexed as a systemic chemotherapy. All patients received prophylactic radiation therapy to the chest wall and the former drainage sites to prevent new mesothelioma formation in the operation sites. Until now, no chest wall tumor recurrence was detected.

3.8. Quality of life

The patients were interviewed via telephone in regular intervals, postoperatively. The patients described initial postoperative fatigue that lasted for about 3–4 weeks. All patients considered their quality of life to have significantly improved, most important, due to the absence of pleural effusions and shortness of breath.

4. Discussion

The main goals of multi-modal therapy of pleural mesothelioma are prevention of pleural effusions, improvement of quality of life, prevention of disease progress and prolongation of patient survival [8].

A careful review of the results of different therapeutic approaches of the international literature was done. A combination of cytoreductive surgery and hyperthermic

chemoperfusion of the thorax seemed to be the best therapeutic option for patients with pleural mesothelioma stage III [6, 7]. Our therapeutic approach of a combined therapy with cytoreductive surgery and HITHOC followed by a systemic chemotherapy with permetrexed in most cases is supported by recent publications [9]. It was shown that the patients have an average survival of up to 39 months [9], which is significantly superior to a therapeutic approach of only systemic chemotherapy with permetrexed and a platin-based chemotherapy and best supportive care. This approach led to a median survival of 13.2 months compared to best supportive care with 9.3 months [10].

The main therapeutic goal of our intervention was the destruction of all macroscopically visible tumor masses. We implemented the use of CPC in our standard operative procedure before the background of the need to maintain optimal local tumor control at the pericardium and the diaphragm without the need to resect these anatomical structures. Doxorubicin used for perfusion is highly cardiotoxic. A direct contact of the drug with the myocardium therefore had to be omitted.

We decided against the use of HF-current or Argon-Beamer coagulation because of the potential side effect of uncontrollable thermo necrosis.

Until now only few investigational or congress-reports demonstrated the application of CPC on human or animal surfaces. We established the use of the CPC-technique in peritonectomy and heated intraperitoneal chemotherapy (HIPEC) procedures in 35 patients. Furthermore, we included experimental results of the application of CPC on the pulmonary surface of pigs and humans into our considerations. The results showed a predictable depth of necrosis dependent from the generator power on the pulmonary surface and the heart (Fig. 2). The results are in press and will be published in 2010. It could be argued that the use of this technique without preceding clinical expertise is possibly inefficient, exposing the patient to an increased risk of disease progression/early relapse.

The advantage of CPC with a localized superficial thermonecrosis was discussed afore the background of a possible survival of vital tumor cells in deeper layers.

Pleural mesothelioma characteristically develops tumor nodules and plaques with a superficial spread on the parietal and visceral pleura. In stage three multiple tuberous tumor formations are detected on the visceral and parietal pleura.

Histological examinations of pleural excisates treated with CPC demonstrated a predictable depth of necrosis dependent from the generator power. We took samples from the visceral and parietal pleura and also from the surface of the diaphragma and the pericardium. There was no standardized number or origin of the samples. The thermonecrosis was predictable in all localizations. Furthermore, we were unable to detect vital tumor cells in deeper layers of the pleural and subpleural space. Large tumor nodules were surgically resected, the small remnants where then treated with CPC. The application of CPC was introduced as part of a multidisciplinary concept for the treatment of pleural mesothelioma.

After the demonstration of the safety and absence of major adverse events of the technique, we consider our results as partial proof of concept.

Naturally, a scientific evaluation of a new therapeutic approach can only be done by a direct comparison of two therapeutic options that proved acceptable long-term results. We, therefore, argue for the design and realization of a multi-center trial comparing multi-modal therapy with cytoreduction, CPC, HITHOC and palliative chemotherapy with palliative chemotherapy alone. Such a trial was designed by our institution and is currently under review of the sponsoring governmental and industrial partners. Because of the expected peak of the incidence for pleural mesothelioma in the years 2015 and later such a trial is of remarkable importance.

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