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Radical pleurectomy/decortication followed by high dose of radiation therapy for malignant pleural mesothelioma. Final results with long-term follow-up

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ABSTRACT

Purpose: We have previously shown the feasibility of delivering high doses of radiotherapy in malignant pleural mesothelioma (MPM) patients who underwent radical pleurectomy/decortication (P/D) or surgical biopsy. In this report, we present the long-term results of MPM patients treated with radical P/D followed by high doses of radiotherapy.
Methods and materials: Twenty consecutive MPM patients were enrolled in this prospective study and underwent radical P/D followed by high dose radiotherapy. The clinical target volume was defined as the entire hemithorax excluding the intact lung. The dose prescribed was 50 Gy in 25 fractions. Any FDG-avid areas or regions of particular concern for residual disease were given a simultaneous boost to 60 Gy. Nineteen patients received cisplatin/pemetrexed chemotherapy. Kaplan–Meier analysis was used to calculate rates of overall survival (OS), progression-free survival (PFS), and loco-regional control (LRC).
Results: The median follow-up was of 27 months. The median OS and PFS were 33 and 29 months, respectively. The median LRC was not reached. The Kaplan–Meier estimates of OS at 2 and 3 years were 70% and 49%, respectively. The estimates of PFS at 2 and 3 years were 65% and 46%, respectively. The estimates of LRC at 2 and 3 years were 68% and 59%, respectively. The predominant pattern of failure was distant: 7 patients developed distant metastases as the first site of relapse, whereas only 3 patients experienced an isolated loco-regional recurrence. No fatal toxicity was reported. Five Grades 2–3 pneumonitis were documented.
Conclusions: High dose radiation therapy following radical P/D led to excellent loco-regional control and survival results in MPM patients. A median OS of 33 months and a 3-year OS rate of 49% are among the best observed in recent studies, supporting the idea that this approach represents a concrete therapeutic option for malignant pleural mesothelioma.

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor of the pleura, mainly related to asbestos exposure [1]. Extrapleural pneumonectomy (EPP) is a fundamental component of the therapeutic approach, showing prolonged survival in patients with epithelioid histology [2,3]. EPP is a highly invasive surgical option consisting of an *en bloc* removal of the lung, visceral and parietal pleura, pericardium, and diaphragm [3]. Due to the severe perioperative stress, the noticeable complication rate and the long-term detrimental anatomical and functional effects, EPP fallen out of favour among some surgeons [4]. The Mesothelioma and Radical Surgery (MARS) trial compared the best medical therapy with or without EPP [5]; the findings concluded by the authors suggest

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that because of the high morbidity of EPP, it should be abandoned in the setting of trimodal therapy.

Radical pleurectomy/decortication (P/D) is a lung-sparing surgery for MPM, that represents a cytoreductive treatment option with the aim of removing all gross disease and achieving macroscopic complete resection [6]. This operation includes macroscopic removal of the parietal and visceral pleural layer, along with the pericardium and diaphragm if needed, yet sparing the underlying lung. After this surgical procedure, residual microscopic disease is possibly left behind, and adjuvant radiation therapy is a therapeutic strategy that has been advocated; however, its use has been limited due the difficulty of irradiating such a large target volume with high radiation doses without exceeding the tolerance of the adjacent normal tissues, especially the ipsilateral intact lung [7].

We have recently reported the toxicity results of a prospective study in which Tomotherapy was used to deliver radical doses of radiation to the hemithorax with the intact lung, after radical P/D or surgical staging for MPM. We documented that the treatment was well-tolerated, and we reported only 7% of Grade 3 radiation pneumonitis, and no fatal toxicity [8].

In the present paper we report the long-term survival of radical P/D followed by high doses of radiotherapy delivered to the hemithorax of MPM patients with intact lung.

2. Methods and materials

This prospective study was conducted with the approval of our Institutional Review Board, and written informed consent was obtained from all the patients. Between March 2009 and December 2010, 20 consecutive patients were treated with radical P/D for a MPM and underwent adjuvant radiotherapy. All patients underwent radical P/D, with the resection of the entire parietal and visceral pleura, along with portions of the pericardium and diaphragm if involved by tumor. All patients underwent also internal mammary and mediastinal lymphadenectomy, whereas intercostal lymph nodes were not routinely dissected. Patients with tumor diffusion to the interlobar pleura, or patients with metastatic disease (Stage IVB) were not included in this study. Patient who underwent neoadjuvant or adjuvant chemotherapy were included in the present trial. Chemotherapy was not a component of the study and was administered elsewhere in the majority of the cases. Patients who experienced tumor progression during or after chemotherapy were not referred for radiation therapy.

The radiation therapy technique was previously described in detail [8]. Briefly, the radiation oncologist drew the clinical target volume (CTV) from the lung apex to upper abdomen to include all areas of preoperative pleural surfaces. Interlobar pleura were not included in the CTV. Volumes also included the ipsilateral mediastinal lymph nodes in cases of pathological N1-2 disease. Thoracotomy scars were also included in the CTV. Particular attention was paid to defining the posterior/inferior extent of the CTV to include the insertion of the diaphragm, which was often in the vicinity of the L2 vertebral body. Medially, the CTV included the ipsilateral pericardium. Boost gross tumor volume was targeted on areas with positive margins or suspected residual disease, and foci of PET-uptake on the restaging PET/CT done before radiation therapy. Planning target volume (PTV) was delineated by uniform margins of 5 mm around the CTV.

The dose prescribed to the PTV was 50 Gy delivered in 25 fractions (2 Gy/fraction). Any FDG-avid areas or regions of particular concern for residual disease were given a simultaneous boost of radiotherapy to 60 Gy (2.4 Gy/fraction). Radiotherapy boost was delivered in 19 patients. All patients were treated by Helical Tomotherapy, a novel technique, which allows the delivering of image-guide intensity-modulated radiation therapy (IG-IMRT), resulting in a highly conformal radiation dose delivered [9]. A Megavolt CT-scan was also performed daily for each patient to image-guide the radiation treatment. Delivery quality assurance (DQA) was performed for all radiotherapy plans. DQA was performed with the Delta4 phantom, and clinical gamma criteria (3%/3 mm) were adopted [10].

Table 1
Relevant normal tissue dosimetric data (mean values).

Treated lung	
V20	96%
V30	87%
Mean dose	46 Gy
Contralateral lung	
V5	19%
Mean dose	4 Gy
Total lung (treated + contralateral)	
V20	36%
V30	32%
Mean dose	20 Gy
Spinal cord	
Maximum dose	39 Gy
Esophagus	
Mean dose	28 Gy
Liver	
V30 for right treated lung	38%
V30 for left treated lung	1%
Ipsilateral kidney	
V30	27%
Contralateral kidney	
V15	1%

The spinal cord, ipsilateral and contralateral kidney, contralateral lung and the dummy structure were the dose-limiting tissues. Specific dosimetric guidelines were the following: spinal cord maximum dose <45 Gy; ipsilateral and contralateral kidney V25 (percentage of kidney volume receiving 25 Gy) <40% and V10 < 10%, respectively; liver V30 < 40%; contralateral mean lung dose <7 Gy; dummy structure mean dose <36 Gy. No specific dosimetric constraints were required for ipsilateral lung or total lung. Dose-volume histograms (DVHs) were generated for all relevant structures for each of the 20 plans. Specific metrics were chosen to report dosimetric data in terms of dose distribution to the organs at risk (OAR) (Table 1).

Patients were seen weekly during the radiotherapy course, and then at regular intervals to determine the presence of symptoms. Physicians evaluated clinical symptoms by Common Terminology Criteria of Adverse Events, version 3.0. Loco-regional and distant relapses were assessed using PET/CT. Follow-up PET/CT scans were evaluated by a 20-year experienced radiologist in the field of oncologic imaging and nuclear medicine. Relapse was defined by an increase in the FDG standardized uptake value (SUV) or by the appearance of new FDG-avid lesions. Loco-regional control (LRC) was defined as the absence of relapse in all areas of preoperative pleural surfaces or in the regional lymph nodes. The study end-points were LRC, progression-free survival (PFS), and overall survival (OS), and were estimated by the Kaplan–Meier method, starting from the date of surgery until death or the last available follow-up examination. Patients who experienced tumor progression during or after chemotherapy were not referred for radiation therapy, and were not included in survival analysis.

3. Results

Patients and tumor characteristics are listed in Table 2. The majority of the patients were male (90%) and had a median age of 68