

# Tomotherapy after Pleurectomy/Decortication or Biopsy for Malignant Pleural Mesothelioma Allows the Delivery of High Dose of Radiation in Patients with Intact Lung

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**Introduction:** This study aimed to assess the safety of high doses of radiation delivered with tomotherapy to the intact lung after radical pleurectomy/decortication or biopsy for malignant pleural mesothelioma (MPM).

**Methods:** Twenty-eight patients were enrolled in this prospective study and underwent adjuvant or definitive tomotherapy after radical pleurectomy/decortication ( $n = 20$ ) or pleural biopsy ( $n = 8$ ) for MPM. The dose prescribed to the planning target volume, defined as the entire hemithorax, including chest-wall incisions and drain sites and excluding the intact lung, was 50 Gy delivered in 25 fractions. All patients underwent fluorodeoxyglucose-positron emission tomography for staging after surgery. Any fluorodeoxyglucose-avid areas or regions of particular concern for residual disease were given a simultaneous boost of radiotherapy to 60 Gy. Specific lung dosimetric parameters were reported. Toxicity was graded using the modified Common Toxicity Criteria version 3.0.

**Results:** The median follow-up was of 19 months (range, 6–29 months). Five patients (17.8%) experienced severe respiratory symptoms corresponding to grade 2 pneumonitis in three cases, and grade 3 pneumonitis in two cases. No fatal respiratory toxicity was reported. Controlateral lung V5 was strongly correlated with the risk of pneumonitis. Patients who developed grade 2 and 3 pneumonitis had a higher controlateral lung V5 (mean V5=32%) than those without pneumonitis (mean V5=17%) ( $p=0.002$ ). Other two grade 3 toxicities were registered: one severe pain to the chest wall, and one severe thrombocytopenia.

**Conclusions:** Tomotherapy allows the safe delivery of high dose of radiation to the hemithorax of MPM patients with intact lung.

**Key Words:** Malignant pleural mesothelioma, Radiotherapy, Pneumonitis, Pleurectomy/decortication.

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Malignant pleural mesothelioma (MPM) is an aggressive tumor of the pleura, mainly related to asbestos exposure. Extrapleural pneumonectomy (EPP) represents a highly invasive surgical option, consisting of an en bloc removal of the lung, visceral and parietal pleura, hemipericardium, and diaphragm.<sup>1</sup> Therefore, EPP has fallen out of favor among some surgeons, given the severe perioperative stress, the noticeable complication rate, and the long-term decrease in performance status. Radical pleurectomy/decortication (P/D) is a lung-sparing surgery for MPM, which represents a cytoreductive treatment option with the aim to remove all gross disease and to achieve macroscopic complete resection.<sup>2</sup> 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 both procedures in most cases, residual disease is possibly left behind, and adjuvant radiation therapy emerges as the therapeutic strategy that is advocated.

Although it has been shown that it is feasible to deliver high-radiation doses with intensity-modulated radiotherapy (IMRT) after EPP,<sup>3</sup> the use of adjuvant hemithoracic irradiation after radical P/D is limited because of the difficulty of irradiating such a large target volume to high-radiation doses without exceeding the tolerance of the adjacent normal tissues, especially the ipsilateral intact lung.<sup>4</sup>

Helical tomotherapy is a novel technique that allows the delivering of image-guided IMRT by using a dynamic delivery in which gantry, treatment couch, and multileaf collimator leaves are all in motion during treatment, resulting in a highly conformal radiation-dose distribution.<sup>5</sup>

We used helical tomotherapy to deliver high radiation doses in MPM patients who underwent lung-sparing surgery, including radical P/D or biopsy. In this article we report dosimetric results and toxicity, with the purpose of assessing the safety of tomotherapy in MPM patients with intact lung.

## 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 January 2009 and June 2011, thirty-five patients were treated with radical P/D or had a pleural biopsy for an MPM, and underwent adjuvant or definitive radiotherapy. Seven patients were excluded from the study because they were being treated with palliative radiation doses. The analysis was then conducted on 28 patients.

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 case of pathological N1–2 disease. Thoracotomy scars were also included in the CTV. Particular attention was directed 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. Boost gross tumor volume was defined together with the nuclear physician, for a better interpretation of PET imaging. Planning target volume (PTV) was delineated by uniform margins of 5 mm around the CTV. Normal tissue organs including liver, heart, esophagus, kidneys, ipsilateral and contralateral lung, gastrointestinal tract, and spinal cord were also contoured. A dummy structure, representing the central part of the treated lung, was also defined, helping optimization of planning. This is defined as the lung parenchyma located more than 2 cm internal to the pleural surface (Fig. 1).

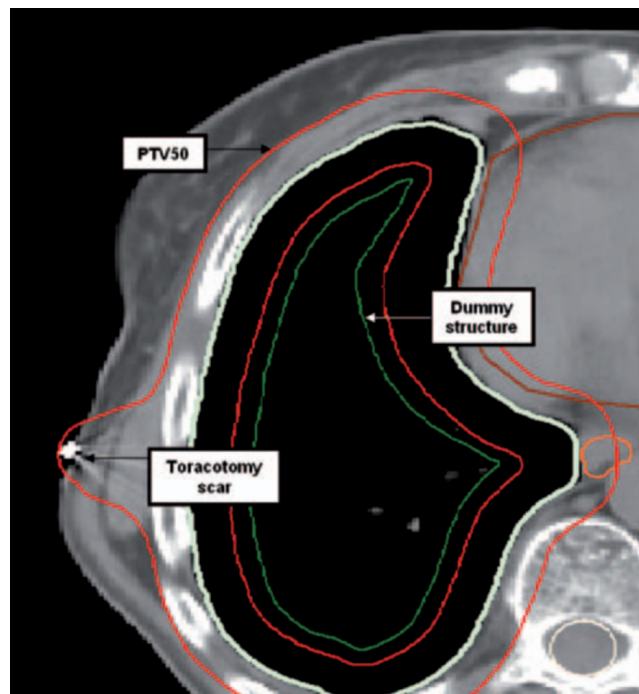
The dose prescribed to the PTV was 50 Gy delivered in 25 fractions (2 Gy/fraction). Any fluorodeoxyglucose-avid areas or regions of particular concern for residual disease were given a simultaneous boost of radiotherapy to 60 Gy (2.4 Gy/fraction). Radiotherapy boost was delivered in 25 patients.

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 less than 45 Gy; ipsilateral and contralateral kidney V25 (percentage of kidney volume receiving 25 Gy) less than 40% and V10 less than 10%, respectively; liver V30 less than 40%; contralateral mean lung dose less than 7 Gy; dummy structure mean dose less than 36 Gy. No specific dosimetric constraints were required for ipsilateral lung or total lung.

Dose-volume histograms were generated for all relevant structures for each of the 28 plans. Specific metrics were chosen to report dosimetric data in terms of dose distribution to the organs at risk.

Treatment was delivered once a day, five fractions weekly. All patients were treated by helical tomotherapy, a novel technique that allows the delivering of image-guided IMRT, resulting in a highly conformal radiation dose delivered. A megavolt CT-scan was also performed daily for each patient to image-guide the radiation treatment. All patients were administered inhalation steroids (Budesonide) during all the radiation course and antibiotics (Amoxicillin-Clavulanate) for 14 days (days 10–24), preventively.

Patients were seen weekly during the radiotherapy course, and then at regular intervals to determine the presence



**FIGURE 1.** Planning target volume includes all areas of pre-operative pleural surfaces and thoracotomy scars. A dummy structure, representing the central part of the treated lung, is also delineated, helping optimization of planning. This is defined as the lung parenchyma located more than 2 cm internal to the pleural surface.

of symptoms. Physicians evaluated clinical symptoms by Common Toxicity Criteria of Adverse Events, version 3.0. Dosimetric parameters from the subgroups with and without grade 2 or greater pulmonary toxicity were compared using a two-tailed Student's *t* test; statistical significance was claimed for *p* value less than 0.05.

## RESULTS

Patients and tumor characteristics are listed in Table 1. Twenty 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, and mediastinal lymph adenectomy. Eight patients underwent pleural biopsy only. Twenty-seven patients received systemic chemotherapy, usually with the combination of pemetrexed and cisplatin. Of these, four patients received neoadjuvant chemotherapy before surgery, 17 received adjuvant chemotherapy, and six received both neoadjuvant and adjuvant chemotherapy. The treatment profile is represented in Figure 2. Radiation was delivered 6 to 8 weeks after surgery or 4 weeks after completion of adjuvant chemotherapy.

The median follow-up was of 19 months (range, 6–29 months). All patients had a minimum follow-up of 6 months and were assessable for acute radiotherapy-related toxicity.

There were no treatment interruptions because of toxicity. All patients completed the radiotherapy course having received the planned dose. All patients experienced grade 1/2 nausea/vomiting, and 12 (43%) developed grade 1/2 fatigue.

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