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.[1] 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.[2] 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,[3] 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.[4]

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.[5]

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 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.

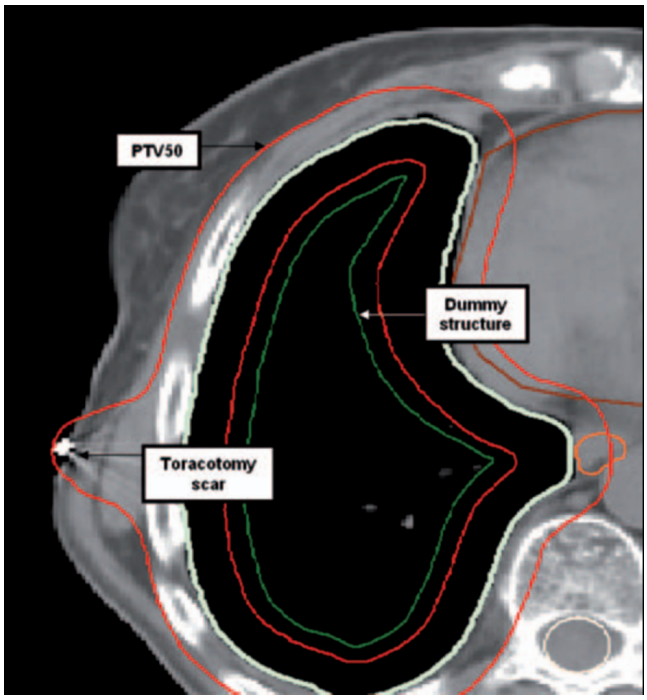

FIGURE 1. Planning target volume includes all areas of preoperative pleural surfaces and thoracotomy scars. A dummy structure, representing the central part of the treated lung, is also delineated, helping optimization of planning. This is defined as the lung parenchyma located more than 2 cm internal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

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 grade1/2 fatigue.

TABLE 1. Patient and Tumor Characteristics (n=28)

Age Median (yr)	**68 (44–83)**
Sex	
Male	25
Female	3
Performance status	
0–1	17
2	11
Laterality	
Right	16
Left	12
Surgery	
P/D	20
Biopsy	8
Histology	
Hepitelioid	25
Nonhepitelioid	3
Stage	
I	4
II	6
III	17
IV (T4)	1
Nodal status	
N0	22
N 1-2	6
Preradiotherapy PFT (mean values)	
FEV1, predicted (%)	74
DLCO, predicted (%)	67

PFT, pulmonary function test; P/D, pleurectomy/decortication; FEV1, forced expiratory volume in the first second; DLCO, diffusion capacity of the lung for carbon monoxide.

Five of the 28 patients (17.8%) experienced severe respiratory symptoms within 5 months after the completion of radiotherapy, corresponding to grade 2 pneumonitis in three cases, and grade 3 pneumonitis in two cases. No fatal respiratory toxicity was reported.

Contralateral lung V5 was strongly correlated with the risk of pneumonitis. Patients who developed grade 2 and 3 pneumonitis had a higher contralateral lung V5 (mean V5=32%) than those without pneumonitis (mean V5=17%) (p = 0.02). Other significant dosimetric parameters for total lung, contralateral lung, treated lung, and central portion of the treated lung (dummy structure) are reported in Table 2. Two other grade 3 toxicities were registered—one patient experienced a severe pain to the chest wall, which required narcotics administration, and one patient developed a severe thrombocytopenia. There were no cases of grade 3 esophagitis. No rib fractures were documented. Relevant normal tissue dosimetric data are reported in Table 3.

DISCUSSION

We 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. This treatment resulted in a well-tolerated regimen: only two of the 28 patients (7%) developed a grade 3 pneumonitis within 5 months after the completion of the radiation therapy course, and no fatal pneumonitis was reported.

This low toxicity profile might be explained by the dosimetric data obtained. Two robust predictors of radiation pneumonitis are mean lung dose (MLD) and lung V20 (the volume of normal lung exceeding 20 Gy).[6,7] In general, MLD values of less than 20 Gy and lung V20 values of less than 37% produce acceptable rates of pneumonitis after radiation therapy for non–small-cell lung cancer. The median MLD and median lung V20 reported in our study were 20 Gy and 37%, respectively.

In our series, patients who developed grade 2 and 3 pneumonitis had a higher contralateral lung V5 (median V5=32%) compared with those without pneumonitis (median V5=17%). These data confirm the importance of the low dose of radiation in the pathogenesis of radiation pneumonitis. These results support the hypothesis that the lung volume completely spared from irradiation determines the risk of radiation pneumonitis.[8] The importance of low doses of radiation delivered to the contralateral (remaining) lung has been emphasized in recently published articles. The study by Allen et al.[9] reported that six of the 13 patients who underwent EPP after hemithoracic IMRT developed grade 5 pneumonitis. The most likely explanation for this increased pulmonary toxicity was the dose–volume effects of the IMRT on the contralateral lung, even though it was unclear which of the various lung dose–volume histograms metrics, including lung V5, best predicted for pneumonitis. The M.D. Anderson Cancer Center experience showed that patients who developed fatal pneumonitis had higher MLD, lung V20 and V5 than those patients without pneumonitis.[10] Even if with a small sample size, the Duke University study reported a higher lung V5 in patients who developed lung toxicity.[11] It must be noted that all these studies found dosimetric parameters correlating with pneumonitis in MPM patients who underwent EPP after hemithoracic IMRT. Our study is the first one to determine the crucial role of low doses of radiation to the contralateral lung in MPM, who underwent lung-sparing surgery, including radical P/D and biopsy, after hemithoracic radiotherapy.

The feasibility of treating the intact lung with pleural IMRT was recently reported by the researchers of the Memorial Sloan-Kettering Cancer Center.[12] Thirty-six MPM patients were treated with a median radiation dose of 46.8 Gy (range, 41.4–50.4 Gy). Seven patients (20%) experienced grade 3 or worse pneumonitis (including a possible toxicity-related death). This toxicity profile is therefore comparable with that reported in our study, although we delivered higher radiation doses to the hemithorax (minimum radiation dose of 50 Gy).

Steroids and antibiotics were administered to all treated patients. Antimicrobial prophylaxis might be able to prevent bacterial pneumonia in patients who may have an hypoventilation of the treated lung and limitation of cough reflex because of opioid analgesics, although steroids are administered with an anti-inflammatory intent. Whether this approach can

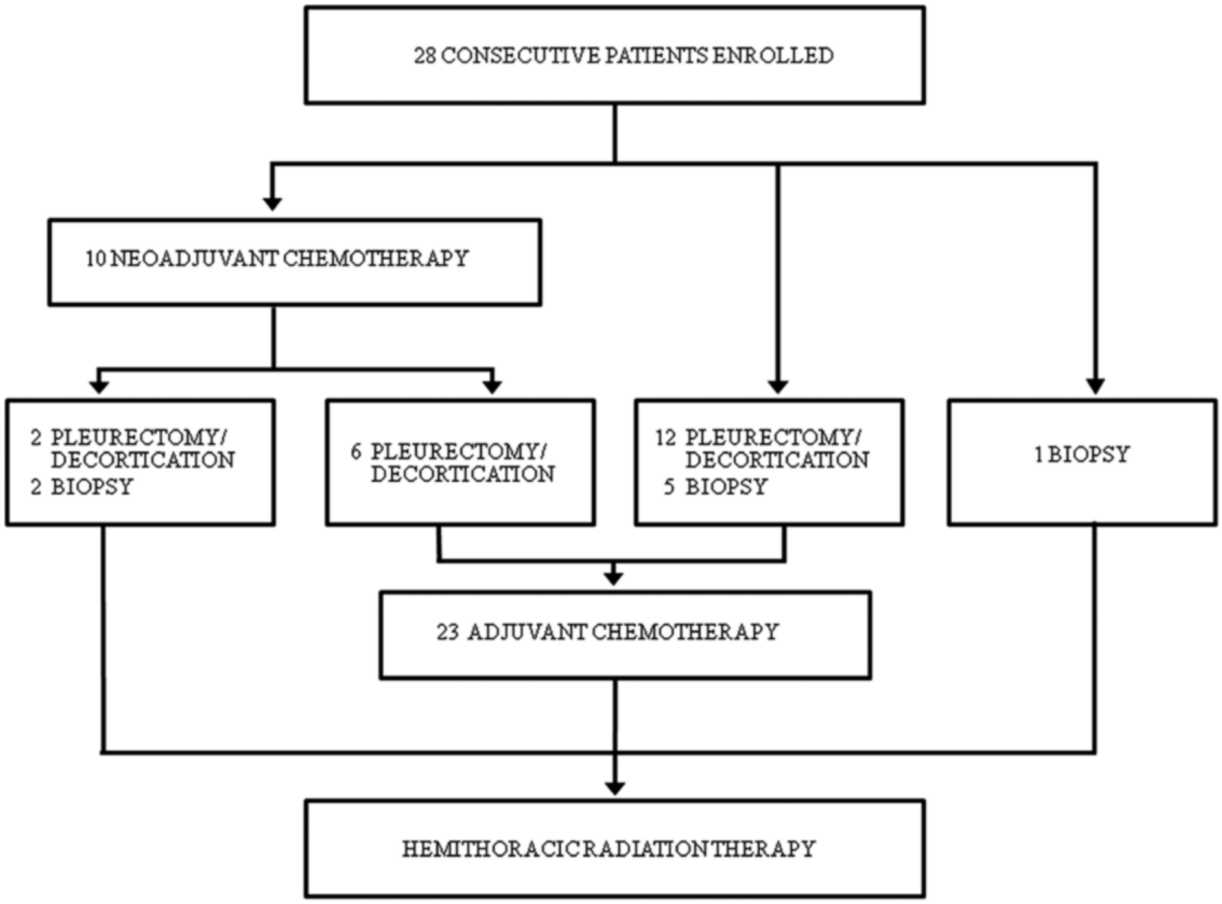

FIGURE 2. Treatment profile.

TABLE 2. Dosimetric Parameters (Mean Values) and Clinical Pneumonitis

	CP (−)(n=23)	CP (+)(n=5)	p
Treated lung			
V13	100%	100%	n.s.
V20	97%	97%	n.s.
V30	88%	88%	n.s.
Mean dose	46 Gy	46 Gy	n.s.
Contralateral lung			
V5	17%	33%	0.02
Mean dose	4 Gy	5 Gy	n.s.
Total lung (treated + contralateral)			
V13	38%	40%	n.s.
V20	36%	38%	n.s.
V30	33%	34%	n.s.
Mean dose	20 Gy	21 Gy	n.s.
Central portion of the treated lung (dummy structure)			
V20	90%	90%	n.s.
V30	59%	54%	n.s.
Mean dose	33 Gy	33 Gy	n.s.

V5, V13, V20, V30 indicates the normal tissue volume receiving more than 5, 13, 20 and 30 Gy, respectively. CP, clinical pneumonitis; n.s., not significant.

TABLE 3. Relevant Normal Tissue Dosimetric Data (Mean Values)

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	26%
Contralateral kidney	
V15	51%

prevent possible acute respiratory symptoms cannot be demonstrated, but detrimental effects are unlikely.

Our study has some limitations. First, although the median age was 68 years, the majority of the treated patients had a good performance status, and this could explain why the proposed radiation treatment was well tolerated. Second, the small sample size might have underestimated the rate of other severe complications.

In conclusion, we have shown that helical tomotherapy allows the safe delivery of high doses of radiation to the

hemithorax of MPM patients with intact lung. The question whether this therapeutic strategy might have a prognostic impact remains to be answered. Clinical outcome in terms of local control and survival will be reported with longer follow-up.

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