PET-Guided Dose Escalation Tomotherapy in Malignant Pleural Mesothelioma

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Purpose: To test the feasibility of salvage radiotherapy using PET-guided helical tomotherapy in patients with progressive malignant pleural mesothelioma (MPM).

Patients and Methods: A group of 12 consecutive MPM patients was treated with 56 Gy/25 fractions to the planning target volume (PTV); FDG-PET/CT simulation was always performed to include all positive lymph nodes and MPM infiltrations. Subsequently, a second group of 12 consecutive patients was treated with the same dose to the whole pleura adding a simultaneous integrated boost of 62.5 Gy to the FDG-PET/CT positive areas (BTV).

Results: Good dosimetric results were obtained in both groups. No grade 3 (RTOG/EORTC) acute or late toxicities were reported in the first group, while 3 cases of grade 3 late pneumonitis were registered in the second group: the duration of symptoms was 2–10 weeks. Median overall survival was 8 months (1.2–50.5 months) and 20 months (4.3–33.8 months) from the beginning of radiotherapy, for groups I and II, respectively (p = 0.19). A significant impact on local relapse from radiotherapy was seen (median time to local relapse: 8 vs 17 months; 1-year local relapse-free rate: 16% vs 81%, p = 0.003).

Conclusions: The results of this pilot study support the planning of a phase III study of combined sequential chemoradiotherapy with dose escalation to BTV in patients not able to undergo resection.

Key words: Helical tomotherapy · Malignant pleural mesothelioma · IGRT · PET imaging
Introduction

There is no clear consensus on the optimal treatment of malignant pleural mesothelioma (MPM), a multifocal or extensive disease on the pleural surface at the time of detection. Despite the lack of controlled/randomized trials using combined treatments, the so-called trimodality therapy (extrapleural pneumonectomy + adjuvant chemotherapy + radiotherapy) has been adopted as the standard of care, based on a number of institutional experiences claiming improved outcome compared to the surgery alone approach [18, 30, 32, 36]. However, due to advanced disease at the time of diagnosis, most patients are considered to be unresectable [29, 36, 39] and are generally candidates for chemotherapy or palliative treatment.

The role of radiotherapy has not yet been clearly assessed but its impact has been claimed for the trimodality therapy [8, 25, 27, 28, 38], suggesting that more aggressive local treatment with high radiation doses could provide some benefit. Recent developments in the field of intensity-modulated and image-guided radiotherapy have led radiation oncologists to reconsider the role of radiotherapy, also for unresectable patients [1], thanks to the greatly improved possibility of closely tailoring the dose distribution around the target [26, 34, 35].

Based on these considerations, a feasibility study using high-dose image-guided tomotherapy was conducted at our institute in unresectable patients.

Materials and Methods

Study Design

A two-step nonrandomized, dose escalation pilot study was performed with the aim of achieving good palliation in progressive disease (PD) patients. The patients included were not previously irradiated on the ipsilateral pleura/lung and showed CT/PET progression/relapse after the previous treatments (surgery and/or chemotherapy). Written informed consent was obtained from all treated patients.

In the first step (May 2006–November 2007), 12 consecutive MPM patients with PD were treated. The optimal total dose, dose per fraction, and timing have not yet been defined for MPM patients, although there is some hope of improving local control by treatment acceleration. MPM cell line radiosensitivity presents $\alpha/\beta$ values varying from 4–28 Gy [19] with some evidence of a very high proliferation rate especially in the most aggressive tumors. For this reason, and in order to reduce the hospitalization time, a moderately hypofractionated regimen was chosen; the median prescribed dose to the planning target volume (PTV) was 56 Gy in 25 fractions (2.24 Gy/fraction) [13], approximately equivalent to a 2 Gy equivalent dose (EQD2) around 60 Gy, which is generally considered appropriate in many institutions.

Subsequently, 12 additional consecutive patients were treated with simultaneous integrated boost (SIB) dose escalation during the period March 2008–April 2009. The dose prescription was 56 Gy in 25 fractions to the PTV, while concomitantly delivering 62.5 Gy to the PET-positive subvolumes (named biological target volume, BTV). Thus, the BTV could receive an EQD2 up to approximately 70 Gy.

Patients’ Characteristics

The main patients’ characteristics are shown in Table 1; the two groups (no-SIB and SIB) were quite homogeneous. The following surgeries were performed: 1 extrapleural pneumonectomy, 4 pleurectomy/decortication, and 7 biopsy/talc pleurodesis in the no-SIB group, and 7 pleurectomy/decortication and 5 biopsy/talc pleurodesis in the SIB group. In the no-SIB group, 10 patients received perimetrexed-based chemotherapy, 1 patient received gemcitabine–cisplatin, and 1 patient with a previous gastrointestinal stromal tumor (GIST), in treatment for...