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High dose irradiation after pleurectomy/decortication or biopsy for pleural mesothelioma treatment

Radiothérapie à doses élevées après pleurectomie/décortication ou biopsie pour la prise en charge du mésothéliome pleural

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ABSTRACT

Purpose. – The role played by radiation therapy after pleurectomy/decortication or surgical biopsy in malignant pleural mesothelioma is uncertain. We treated patients with accelerated hypofractionated radiotherapy using helical tomotherapy and intensity-modulated arc therapy in an attempt to keep lung toxicity to a minimum. The present study reports the feasibility and toxicity of this approach.
Material and Methods. – Between 2008 and 2012, 36 patients with malignant pleural mesothelioma underwent accelerated hypofractionated radiotherapy to the hemithorax after pleurectomy/decortication (19 patients) or biopsy (17 patients). The prescription dose was 25 Gy in five fractions over 5 consecutive days.
Results. – We observed three patients with G3 pneumonitis, five cases of grade 2 dyspnea and six cases of grade 2 cough. The median follow-up was 37 months (range: 3–54 months). The median overall survival for patients who underwent pleurectomy/decortication followed by radiotherapy was 21.6 months [95% confidence interval (95% CI): 15.5–24.1] compared to 19.4 months for patients not submitted to surgery.
Conclusion. – Treatment of intact lung with pleural intensity-modulated arc irradiation in malignant pleural mesothelioma patients with malignant pleural mesothelioma proved safe and feasible, with an acceptable rate of pneumonitis. Survival rates were encouraging for both biopsy-only and pleurectomy/decortication groups. We are currently conducting a phase II dose escalation trial in a similar patient setting to prospectively evaluate the impact of radiotherapy on toxicity, disease-free survival and overall survival.

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RÉSUMÉ

Objectif de l'étude. – Le rôle joué par la radiothérapie après la pleurectomie/décortication ou par la biopsie chirurgicale dans le mésothéliome pleural malin est incertain. Nous avons pris en charge les patients par une tomothérapie hélicoïdale ou une arcthérapie modulée hypofractionnée afin de réduire la toxicité pulmonaire au minimum. Le présent article rapporte la faisabilité et la toxicité de cette approche.

Matériel et méthode. – Entre 2008 et 2012, 36 patients atteints de mésothéliome pleural malin ont reçu une radiothérapie hypofractionnée accélérée de l'hémithorax après une pleurectomie/décortication (19 patients) ou une biopsie (17 patients). La dose prescrite était de 25 Gy en cinq fractions et 5 jours consécutifs.

Résultats. – Nous avons observé trois pneumonies de grade 3, cinq dyspnées de grade 2 et six toux de grade 2. La durée médiane de survie a été de 37 mois (extrêmes : 3–54 mois). La durée médiane de survie globale après pleurectomie/décortication suivie d'une radiothérapie était de 21,6 mois (intervalle de confiance à 95 % : 15,5–24,1) comparativement à 19,4 mois en l'absence d'intervention chirurgicale.

Conclusion. – L'arcthérapie modulée des poumons intacts chez les patients atteints de mésothéliome pleural malin s'est avérée sûre et réalisable, avec un taux acceptable de pneumonies. Les taux de survie ont été encourageants, tant après pleurectomie/décortication que biopsie. Nous menons actuellement une étude de phase II à doses croissantes dans un contexte similaire afin d'évaluer l'impact de la radiothérapie sur la toxicité, la survie sans récidive ainsi que sur la survie globale.

1. Introduction

Malignant pleural mesothelioma is a relatively rare malignancy associated with previous exposure to asbestos, chrysotile, amosite or crocidolite [1]. It can develop even decades after exposure to asbestos fibres [2], but the median survival time after diagnosis is less than 12 months [3,4]. Incidence of malignant pleural mesothelioma in Europe, currently around 18 cases per million, is increasing and is likely to reach its peak in the next few decades [5,6].

Malignant pleural mesothelioma originates from the lining of the pleural cavity and has a strong propensity to propagate (locoregional progression and distant metastases). As the most common site of treatment failure is the ipsilateral hemithorax, optimizing local control provides the best opportunity for long-term survival. Two kinds of surgery are performed for mesothelioma: extrapleural pneumonectomy and pleurectomy/decortication [7,8]. After EPP, adjuvant hemithorax radiotherapy to the chest cavity has been shown to improve local control and survival [9]. Intensity-modulated radiation therapy, in particular, intensity modulated arc therapy would appear to be the most effective adjuvant treatment [10–13]. Recently, the practice of extrapleural pneumonectomy has waned, mainly because it is burdened by higher morbidity and mortality than pleurectomy/decortication [14–17]. Results from the MARS trial, albeit much debated, confirmed the high morbidity associated with radical surgery in the form of extrapleural pneumonectomy, the authors concluding that this kind of surgery as part of trimodality therapy offers no benefit and possibly even harms patients [18]. In a recent retrospective study of 663 patients submitted to surgical resection, Flores et al. reported a higher survival rate for patients submitted to pleurectomy/decortication rather than extrapleural pneumonectomy on the basis of stage, histology, gender, and multimodality therapy [hazard ratio (HR) 1.4 for EPP, $P < 0.001$] [19]. Cao et al. published a meta-analysis in which they demonstrated that perioperative mortality (2.9 vs. 6.8%, $P = 0.02$) and morbidity (27.9 vs. 62.0%, $P = 0.0001$) were significantly lower in patients who underwent extended pleurectomy/decortication than for those submitted to extrapleural pneumonectomy. They also underlined that patients undergoing pleurectomy/decortication were more amenable to additional therapy than extrapleural pneumonectomy patients [20]. Luckratz et al. also reported that pleurectomy/decortication and postoperative adjuvant therapy resulted in longer survival than extrapleural pneumonectomy and adjuvant treatment [21].

Pleurectomy/decortication involves resection of the parietal and visceral pleurae, pericardium and, when necessary, the diaphragm, but spares the entire lung in opposite with extrapleural pneumonectomy. The goal of this extended surgical procedure is to achieve cytoreduction and complete macroscopic resection. Although the majority of centres that study and treat malignant pleural mesothelioma in Europe, North America and Japan now perform pleurectomy/decortication with curative intent, the role of radiation therapy after this procedure has yet to be defined [15,16,22]. Local control remains the primary objective and radiotherapy is a challenge because of the risk of pneumonitis in the intact lung. There are no specific clinical data to support the use of adjuvant radiation therapy after pleurectomy/decortication or definitive radiation therapy after biopsy-based diagnosis for patients not amenable to surgery. However, recent publications on intensity-modulated radiotherapy and conventional fractionation after pleurectomy/decortication or biopsy have shown the feasibility and acceptable toxicity profile of the treatment [23,24,33].

We present a retrospective analysis of accelerated, hypofractionated, intensity-modulated arc therapy using tomotherapy for malignant pleural mesothelioma following pleurectomy/decortication or diagnostic biopsy.

2. Materials and Methods

A total of 36 patients with biopsy-proven malignant pleural mesothelioma underwent tomotherapy (TomoTherapy Inc., Madison, WI, USA) at our institute between January 2008 and August 2012. Of these, 15 patients had undergone occupational exposure to asbestos and were ex-smokers, six had undergone exposure to asbestos, and four were ex-smokers. Seventeen patients underwent radiotherapy after biopsy and 19 after pleurectomy/decortication. All patients with a histologically proven diagnosis of malignant pleural mesothelioma, age 85 years old or less, FEV1 over 50%, life expectancy over 6 months, Karnofsky index 70–100, and normal organ and bone marrow function were included in the study. Exclusion criteria were as follows: presence of metastases, respiratory failure in oxygen, prior thoracic radiotherapy; interstitial pneumopathy, active pneumonia, presence of fissural disease,

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