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Original article

Respiratory-gated bilateral pulmonary radiotherapy for Ewing's sarcoma and nephroblastoma in children and young adults: Dosimetric and clinical feasibility studies

Asservissement respiratoire lors d'une radiothérapie pulmonaire bilatérale pour le sarcome d'Ewing ou le néphroblastome chez des enfants et jeunes adultes : études dosimétrique et clinique de faisabilité

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ABSTRACT

Purpose. – Bilateral pulmonary radiotherapy in children and young adults aims to reduce the recurrence of lung metastases. The radiation field includes liver tissue, which is sensitive to even low radiation doses. We investigated the feasibility of respiratory gating radiotherapy using voluntary deep inspiration breath hold and its toxicity in these patients.
Patients and method. – A retrospective clinical review was conducted for all patients who had undergone bilateral pulmonary radiotherapy, with or without deep inspiration breath hold, treated in our institution between October 1999 and May 2012. A dosimetric study was conducted on seven consecutive children using 4D-scan data on free-breathing and a SpiroDyn'RX-system-scan on deep inspiration breath hold. A radiation treatment of 20 Gy was simulated.
Results. – Concerning the clinical study, seven patients of mean age 11.9 years (range: 4.9–21.1 years) were treated with free-breathing and ten patients of mean age 15.6 years (range: 8.6–19.7 years) were treated with deep inspiration breath hold for mainly Ewing sarcoma and nephroblastoma. Within six months of radiotherapy, all patients experienced mild liver toxicity (grade 1 or 2 altered levels of alanine/aspartate aminotransferase [$n = 8$ of 9] or cholestasis [$n = 1$ of 9]), which resolved completely with no difference between deep inspiration breath hold and free-breathing technique. Over a median follow-up of 2.6 years (range: 0.1–9.3 years), four patients died from disease progression (mean 1.5 years post-radiotherapy [range: 1.1–1.6 years]) and three experienced grade III–V lung toxicity. Concerning the dosimetric study, the irradiated liver volume was significantly lower with deep inspiration breath hold than free-breathing, for each isodose (V5: 73.80% versus 86.74%, $P < 0.05$; V20: 5.70% versus 26.44%, $P < 0.05$).
Conclusions. – The dosimetric data of respiratory-gated bilateral pulmonary radiotherapy showed a significantly spare of normal liver tissue. Clinical data showed that this technique is feasible even in young children. However, no liver toxicity difference between deep inspiration breath hold and free-breathing was shown.

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RÉSUMÉ

Objectif de l'étude. – La radiothérapie pulmonaire bilatérale vise chez les enfants et les jeunes adultes à réduire la récidive des métastases pulmonaires. Une partie du tissu hépatique situé à proximité est incluse dans le volume irradié. Or ce tissu est sensible au rayonnement ionisant dès de faibles doses. Nous avons étudié la faisabilité d'un traitement par asservissement respiratoire selon la technique de blocage en inspiration profonde volontaire et sa toxicité chez ces patients.

Patients et méthode. – Une étude clinique rétrospective a été réalisée pour tous les patients qui avaient eu une radiothérapie pulmonaire bilatérale, avec ou sans blocage en inspiration profonde volontaire, dans notre institution entre octobre 1999 et mai 2012. Une étude dosimétrique, avec une dose de 20 Gy, a été menée sur sept enfants consécutifs à l'aide de données obtenues par scanographie quadridimensionnelle en respiration libre et par scanographie en inspiration profonde volontaire bloquée avec le système SpiroDyn'RX.

Résultats. – En ce qui concerne l'étude clinique, sept patients d'âge moyen 11,9 ans (4,9–21,1 ans) ont été traités en respiration libre et dix patients de moyenne d'âge de 15,6 ans (8,6–19,7 ans) ont été traités en inspiration profonde volontaire bloquée, principalement pour des sarcomes d'Ewing et des néphroblastomes. Dans les six mois de la radiothérapie, tous les patients ont connu une légère toxicité hépatique (de grade 1 ou 2, avec des dosages perturbés de transaminases [ALAT/ASAT ; $n = 8$ sur 9] ou des cholestases [$n = 1$ sur 9]), avec une normalisation complète sans différence entre inspiration profonde volontaire bloquée et respiration libre. Au cours d'un suivi médian de 2,6 ans (0,1–9,3 ans), quatre patients sont décédés de progression de la maladie et trois ont souffert de toxicité pulmonaire de grade III–V (1,5 ans après la radiothérapie en moyenne [1,1–1,6 ans]). En ce qui concerne l'étude dosimétrique, le volume du foie irradié était significativement plus faible en inspiration profonde volontaire bloquée qu'en respiration libre, pour chacune des isodoses (volume recevant 5 Gy [V5] : 73,80 % contre 86,74 %, $p < 0,05$; volume recevant 20 Gy [V20] : 5,70 % contre 26,44 %, $p < 0,05$).

Conclusions. – L'analyse des données dosimétriques d'une radiothérapie pulmonaire bilatérale en inspiration profonde volontaire bloquée a significativement montré une meilleure protection du tissu hépatique. Celle des données cliniques a montré que cette technique est envisageable, même chez les jeunes enfants. Cependant, aucune différence de toxicité hépatique entre l'inspiration profonde volontaire bloquée et la respiration libre n'a été montrée.

1. Introduction

Bilateral pulmonary radiotherapy (14 to 20 Gy) is indicated in association to other treatments in children and young adults with nephroblastoma, Ewing sarcoma (EuroEwing protocol), and stage IV Hodgkin lymphoma with the objective of decreasing the recurrence of lung metastases. The principal toxicity is respiratory with an increased risk of fibrosis, infection, and impaired respiratory function (in 50% of subjects) with increasing dose [1,2]. Other possible sequelae include underdevelopment of the thorax, mammary hypoplasia in girls treated before puberty, and cardiac toxicity [3]. Another organ partly exposed in bilateral pulmonary radiotherapy is the liver. Several data have been published concerning the tolerance of the adult liver to radiotherapy but very few concerning the tolerance of the paediatric liver [4–6]. Acute liver toxicity was infrequently observed in a study of 61 children undergoing radiotherapy involving the liver [7]. Patients with grade 1 or 2 acute liver toxicity had greater organ volumes exposed to radiation doses 10 Gy than patients without toxicity. Late severe hepatic sequelae (grade 3 or worse) are extremely rare (< 1%) after radiotherapy as illustrated by the German RISK cohort of 1392 children, of whom 216 had received at least some radiation to the liver [8]. Secondary hepatic cancers have also been described in the literature, though these are uncommon [9].

Similarly to pulmonary, pericardiac or peridiaphragmatic tumours, bilateral pulmonary radiotherapy is affected by respiratory motion. Substantial movements may occur in craniocaudal, lateral and anterior–posterior directions [10]. Depending of the phases or the respiratory cycle, the diaphragm can remain highly convex or become almost horizontal. This results in greater difficulty in tumour contouring on 3D-scans and in tumour targeting during treatment [11,12]. As a result, the margin around the target is increased and/or adjacent tissues may be exposed to high radiation doses. In the case of bilateral pulmonary radiotherapy, care is needed to encompass the entire clinical target volume, including the pleural cavities. Several CT-image acquisition and treatment methods take tumour motion into account, and can be used to improve the quality of target volume contours, treatment planning, and treatment. They include placing safety margins around the gross tumour volume during free-breathing, immobilizing the target volume during radiation delivery, synchronizing radiation delivery with the respiratory cycle, and real-time tumour tracking. Respiratory gating radiotherapy using voluntary deep inspiration breath hold is a reproducible technique that helps spare organs at risk [13]. Paediatric use of an active breathing control device significantly spared the heart and lungs in Hodgkin's lymphoma without affecting the breasts and thyroid [14].

Taking into account these two facts, our aim was to optimize the clinical target volume and spare healthy tissue to reduce toxicity. We hypothesized that lung immobilization during deep inspiration breath hold might help spare the liver in children and young adults undergoing bilateral pulmonary radiotherapy. We thus performed a dosimetric study to compare liver exposure on deep inspiration breath hold and on free-breathing radiotherapy followed by a retrospective clinical study.

2. Patients and methods

2.1. Respiratory gating radiotherapy using voluntary deep inspiration breath hold

We used the Spirodyn'RX respiratory gating system (Muret, France) to acquire CT-scans during deep inspiration breath hold at a predetermined amplitude. The gating system comprised a