REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY XXX (2016) XXX–XXX

Available online at www.sciencedirect.com

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journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Institutional experience in the treatment of colorectal liver metastases with stereotactic body radiation therapy

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ARTICLE INFO

Article history:
Received 3 November 2015
Received in revised form
10 July 2016
Accepted 11 October 2016
Available online xxx

Keywords:
Colorectal
Metastases
Liver
Stereotactic body radiation therapy

ABSTRACT

Aim: To investigate whether the impact of dose escalation in our patient population represented an improvement in local control without increasing treatment related toxicity.

Materials and methods: A cohort of consecutive patients with colorectal liver metastases treated with stereotactic body radiation therapy (SBRT) between December 2002 and December 2013 were eligible for this study. Inclusion criteria were a Karnofsky performance status ≥80% and, according to the multidisciplinary tumor board, ineligibility for surgery or radiofrequency ablation. Exclusion criteria were a lesion size >6 cm, more than 3 metastases, and treatment delivered with other fractionation scheme than 3 times 12.5 Gy or 16.75 Gy prescribed at the 65–67% isodose. To analyze local control, CT or MRI scans were acquired during follow-up. Toxicity was scored using the Common Toxicity Criteria Adverse Events v4.0.

Results: A total of 40 patients with 55 colorectal liver metastases were included in this study. We delivered 37.5 Gy to 32 lesions, and 50.25 Gy to 23 lesions. Median follow-up was 26 and 25 months for these two groups. Local control at 2 and 3 years was 74 and 66% in the low dose group while 90 and 81% was reached in the high dose group. No significant difference in local control between the two dose fractionation schemes could be found. Grade 3 toxicity was limited and was not increased in the high dose group.

Conclusions: SBRT for colorectal liver metastases offers a high chance of local control at long term. High irradiation doses may contribute to enhance this effect without increasing toxicity.

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http://dx.doi.org/10.1016/j.rpor.2016.10.003
1507-1367/

1. Background

Liver metastases develop in up to 70% of patients with colorectal cancer. Resection is the 'golden standard' treatment with reported median survival of 44 months and 34–40% of patients being alive at 5 years.[1] Because most of the patients are not eligible for surgery, other nonsurgical ablation techniques are used, with radiofrequency ablation (RFA) being the most widely applied treatment modality. Several factors have been described to impact the success rate of RFA. A tumor size >3 cm has been identified as a predictor of a higher relapse rate.[2] The location of the tumors within the liver is also an important factor; in particular tumors adjacent to large hepatic vessels present a unique problem due to the cooling effect provided by the blood flowing through them.[2] Location near the portal vein pedicles is also associated with increased complications because RFA in this area can cause injury to the main bile duct resulting in biliary stricture.[2] Retrospective RFA series for colorectal liver metastases have shown site recurrence rates of 9–42% for percutaneous RFA and 5–14% for open RFA with median survival of 36 months.[3,4] For patients not eligible for RFA, stereotactic body radiation therapy (SBRT) offers the possibility to deliver potent biological doses to limited volumes of the liver in a few fractions. High local control rates at 2 years of 74–91% and median survival of 34 months have been reported after SBRT for colorectal liver metastases.[5,6]

A few studies have assessed the role of dose escalation on the clinical outcomes after SBRT for liver metastases. In 2006 Wulf et al. found a significant improvement in 2 year local control (82 vs. 58%) with 12–12.5 Gy in 3 fractions or 26 Gy in 1 fraction vs. 30 Gy in 3 fractions.[7] No severe toxicity was observed. Later on, in a multi-institutional phase I/II study, Rusthoven et al. evaluated the efficacy and tolerability of high dose SBRT.[8] The dose was safely escalated from 36 till 60 Gy delivered in 3 fractions with 2 year local control rate of 92%. Only one patient experienced grade III (soft tissue) toxicity. Rule et al. studied three dose-escalation cohorts and showed a significant difference in local control between 60 Gy in 5 fractions vs. 30 Gy in 3 fractions.[9] No patient experienced grade III or higher toxicity. Regardless of the above mentioned results, Vautravers-Dewas and colleagues did not find a significant difference in local control between 40 Gy in 4 fractions and 45 Gy in 3 for their cohort treated with SBRT.[10]

In 2010, our group reported a 2-year local control of 74% for patients with colorectal liver metastases treated mainly with 37.5 Gy in 3 fractions.[5] Later on, and based on published data, the dose was escalated to 50.25 Gy also delivered in 3 fractions. This retrospective study investigated whether the increase in dose represented an improvement in local control without raising the treatment associated toxicity in our patient population.

2. Materials and methods

2.1. Design

This study was designed as a retrospective, observational, and single institution. It was performed in accordance with the code of ethics of the Helsinki declaration and approved by the Ethical Committee of Erasmus Medical Center (MEC-2015-029).

2.2. Population

All consecutive patients treated in our department between December 2002 and December 2013 were considered candidates for this study. Patients should fulfill the following criteria: diagnose of colorectal liver metastases, not eligible for surgery or radiofrequency ablation (RFA) according to the multidisciplinary tumor board, and a Karnofsky performance score of at least 80%. If extrahepatic disease was present, it had to be limited and potentially treatable with local therapies. Exclusion criteria for this study included: a tumor diameter >6 cm, more than 3 metastases per patient, and dose fractionation scheme other than 3 times 12.5 Gy or 16.75 Gy delivered at the 65–67% isodose.

2.3. Endpoints

Primary endpoints of this study were the assessment of local control and toxicity. Local control was defined as no in field progression during follow-up on CT or MR imaging. Toxicity was scored with the Common Toxicity Criteria (CTC) of the National Cancer Institute v 4.0. Secondary endpoint was overall survival. Factors related to local control were also investigated, including age, gender, and size and number of metastases.

2.4. Treatment preparation and delivery

Between 2002 and 2011 patients were positioned in a stereotactic body frame (Elekta Oncology Systems, Stockholm, Sweden) with abdominal compression to reduce respiratory tumor motion for planning and treatment purposes. Three computed tomography (CT) scans per patient were acquired; one in the arterial phase and one in the venous phase for tumor definition, and one large-volume non-enhanced scan for dose planning. Details about this procedure have been reported earlier.[5,11–13] From 2011, only one large contrast enhanced planning CT in the venous phase was acquired. The tumor delineations have always been reviewed by an experienced radiologist. The boundary of the metastasis was considered the border or contrast enhancement.

Since 2005, we have been implanting fiducial markers in the vicinity of the tumor to assess the respiratory motion of the area where the tumor is located. Initially the motion was measured with video fluoroscopy registrations and later on with a reconstruction of 4DCT registrations.[14,15]

No margin between gross target volume and clinical target volume was used. Planning target volume (PTV) margins were initially based on the Karolinska experience.[16,17] With the introduction of fiducial markers, margins were individualized based on an in-house developed margin recipe that was used to calculate required PTV margin for each patient individually. The margin recipe takes as input the treatment technique (e.g. tracking or non-tracking), the amplitude of the respiratory-induced motion, and the distance between the center-off-mass of the marker configuration and the center of the tumor.[15] For conventional linac based treatments

Please cite this article in press as: Méndez Romero A, et al. Institutional experience in the treatment of colorectal liver metastases with stereotactic body radiation therapy. *Rep Pract Oncol Radiother* (2016), http://dx.doi.org/10.1016/j.rpor.2016.10.003