Radiotherapy and Oncology 113 (2014) 235–239

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Motion management in SBRT

Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer

Robbe Van den Begin, Benedikt Engels *, Thierry Gevaert, Michaël Duchateau, Koen Tournel, Dirk Verellen, Guy Storme, Mark De Ridder

Department of Radiotherapy, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Belgium

ARTICLE INFO

Article history:
Received 11 August 2014
Received in revised form 3 November 2014
Accepted 3 November 2014
Available online 28 November 2014

Keywords:
SBRT
Oligometastases
Colorectal cancer
Local control
Local failure
Motion management

ABSTRACT

Purpose: Stereotactic body radiotherapy (SBRT) in oligometastatic colorectal cancer (CRC) resulted in a disappointing 1-year local control rate of 54% in our experience. We aimed to determine the root cause(s).
Methods: 47 oligometastatic CRC patients were treated with SBRT by helical tomotherapy to a dose of 40 or 50 Gy in 10 fractions, without specific respiratory motion management and PTV-margins of 10–10–12 mm in all patients. The local recurrences (LRs) were delineated on diagnostic PET–CT scans and co-registered with initial planning CTs. LRs were classified as in-field or marginal with respect to the initial dose distribution, and predictors for LR were determined.
Results: Out of 105 irradiated metastases, LR modeling yielded 15 in-field and 15 marginal failures. Metastases in moving organs (liver and lung) exhibited a local control of 53% at 1-year (95% confidence interval (CI): 38–67%), compared to 79% for lymph nodes (95% CI: 32–95%). The first group exhibited a sixfold increased risk compared to the latter on multivariate analysis ($p = 0.01$).
Conclusions: The nature and locations of LR indicated that dose prescription and methodology were both inadequate for liver and lung metastases. This study demonstrates the need for individual respiratory motion management and a biological effective dose of >75 Gy.
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In general, overall survival (OS) in patients with metastatic colorectal cancer (CRC) has improved over the years [1]. This increases the interest in local therapies, especially for patients with a limited number of metastases, so called oligometastases [2]. For inoperable patients, there has been an expansion over the last decade in the use of stereotactic body radiotherapy (SBRT), a tailored delivery of high doses of radiation in a small number of fractions by a combination of high-conformal RT and rigorous localization of the target by image-guided RT (IGRT). In the eradication of liver- and lung metastases by properly conducted SBRT procedures, sustained local control (LC) and limited toxicity rates are reported by several authors [3–7], even to such an extent that surgery is challenged as a primary choice [8]. Our institution explored the use of SBRT by helical tomotherapy in two prospective phase II trials in patients with inoperable oligometastatic CRC [9,10]. Aiming at a broad applicability, thereby including patients with large and inconveniently located metastases, a dose of 40–50 Gy was delivered in 10 fractions. The reported 1-year LC rate of only 54% in both trials was unsatisfying, especially with the intensification of the dose to 50 Gy in the second trial [10]. To assess the causes of local treatment failure in those 2 trials, we now analyzed the origin of each local recurrence (LR). Recurrences originating in the gross tumor volume (GTV), called in-field LR, would suggest radioresistance to the delivered dose, whereas recurrences originating near the border of the GTV, called marginal LR, would indicate focal underdosage due to inadequacy in either determination and/or positioning of the planning target volume (PTV). Additionally, we evaluated the influence of patient-related factors on local treatment failure.

Materials and methods

Patient population

47 CRC patients with a radically resected primary tumor and five or less metastases were enrolled consecutively in 2 phase II trials between July 2008 and July 2011 (NCT00807313). Patients had to be considered inoperable by the localization, number or dimension of the metastases, medically unfit to undergo resection or refusing surgery. Patients who did not receive previous chemotherapy for metastatic disease had to be medically unfit to undergo systemic treatment or refusing chemotherapy.

* Corresponding author at: Department of Radiotherapy, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium.
E-mail address: benedikt.engels@gmail.com (B. Engels).

http://dx.doi.org/10.1016/j.radonc.2014.11.005
0167-8140/

[9,10]. Patient characteristics are summarized in Table 1. All patients signed a study-specific informed consent, which was reviewed and approved by the institutional ethics committee. No limitations were imposed on the localization or dimension of the metastases. In total, 105 metastases were irradiated, of which 52 metastases (in 23 patients) and 53 metastases (in 24 patients) received 10 × 4 Gy and 10 × 5 Gy, respectively. Metastases were located in lung (n = 39), liver (n = 25), lymph nodes (the latter located thoracic (n = 5) or abdominal/pelvic (n = 17)), remaining 19 metastases were found in soft tissue (n = 10), peritoneum (n = 7) and bone (n = 2).

Radiotherapy technique and IGRT procedure

All patients were treated with IMRT–IGRT using the Tomotherapy Hi-Art II System (Tomotherapy Inc., Madison, WI). For planning, a spiral free-breathing computed tomography (CT) with 3 mm slices was acquired in combination with ^{18}fluorodeoxyglucose-positron emission tomography (FDG-PET). No passive and/or active motion compensation techniques were applied, and no fiducials were used. Patients did also not receive any coaching during treatment. Contrast agent was given when appropriate. The anatomically defined tumor on CT was delineated as the GTV, no expansion to CTV was used. The GTV was expanded by 10, 10 and 12 mm for the anteroposterior, laterolateral and craniocaudal direction respectively, to create the planning target volume (PTV), which also had to encompass the visibly active volume (2.5 SUV contour) on PET. The planning goals were to deliver at least 95% of the prescribed dose to at least 95% of the PTV, while keeping the maximum dose below 105%. More detailed planning constraints were prescribed in previous publications [9,10]. For patient positioning during each treatment fraction, the integrated megavoltage (MV) CT scan of the treatment machine was co-registered with the planning kilovoltage CT scan, first based on bony anatomy, and in a second step adapted with soft tissue matching in case of metastases located outside the bone.

Table 1
Patient characteristics (n = 47).

		No. of patients	%
Sex	Male	28	60
	Female	19	40
Age (years)	Median	65 years	
	Range	45–91 years	
Karnofsky performance status	Median	80	
	Range	50–100	
Radiotherapy schedule	10 × 4 Gy	23 (52 lesions)	49
	10 × 5 Gy	24 (53 lesions)	51
Previous chemotherapy (number of lines)	0	14	30
	1	10	21
	2	17	37
	3	3	6
	4	3	6
Previous local therapy for metastases	No	20	43
	Yes	27	57
Number of metastases per patient	1	16	34
	2	14	30
	3	9	19
	4	6	13
	5	2	4
Gross tumor volume, per lesion (cc)	Median; mean	6.4; 19.4	
	Range	0.3–258	
Sum of gross tumor volumes, per patient (cc)	Median; mean	22.2; 43.4	
	Range	1–274 cc	
Number of involved sites	1	31	66
	2	12	25
	3	4	9
Follow-up (months)	Median	11 months	
	Range	3–18 months	

Follow-up and analysis of local recurrences

Patients were followed up by PET–CT every 3 months, starting 3 months after SBRT. 18 patients presented a LR at some point during follow-up, resulting in a disappointing 1-year LC rate (patient-based) of only 54% in both trials [9,10]. For the current analysis of these LRs, we considered each irradiated lesion as a different entity. For each local failure, an experienced radiation oncologist contoured the recurrent tumor volume (Vrecur) on the follow-up CT where the recurrence was detected, aided by the co-registered PET. As a next step, we performed a rigid co-registration of this CT-set with the initial planning CT, based on surrounding anatomical landmarks (e.g. bronchial tubes and blood vessels for lung metastases, liver borders and hepatic veins for liver metastases), and superimposed the radiation dose distribution of the planning CT on the follow-up CT. Intra- and inter-observer variability was checked by means of a second delineation of the Vrecur by the same observer >1 month later, and by a second observer, respectively. Contours were compared with the Dice similarity coefficient. The maximal value of the Dice similarity coefficient is 1 if the two contours overlap exactly and 0 if they do not intersect [11]. MIM 5.6.1 (MIM Software Inc., Cleveland, OH) was used for contouring and co-registration.

For modeling of the type of LR, we utilized a volumetric approach, custom in failure pattern analysis [12–15]. Dose–volume histograms (DVH) were calculated for the Vrecur by using a rigid overlay of the dose on the follow-up CT. LRs were then classified as "in-field" if 95% or more of Vrecur was located within the 95% isodose of the initial plan; "marginal," if 20% to 95% of Vrecur was within the 95% isodose; or "out-of-field," if less than 20% of the Vrecur was inside the 95% isodose (Fig. 1).

Statistical analysis

Types of local failures were compared with Fisher's Exact Test. Actuarial lesion-based LC was estimated by Kaplan–Meier analysis. Univariate analysis (UVA) by log-rank testing and multivariate analysis (MVA) by Cox proportional hazards regression model were used to evaluate association between patient-related factors and LC. The outcome of irradiated metastases in organs prone to respiratory motion, i.e. liver and lung, was compared to the other locations: lymph node, soft tissue and bone metastases. All statistical analyses were computed with SPSS 19 (IBM Corporation, Armonk, NY) and Prism 5 (GraphPad Software, San Diego, CA). A value of $p < 0.05$ indicated statistical significance.

Results

After a median follow-up of 10.6 months for a total of 105 irradiated metastases, a local failure occurred in 30 lesions (29%), of which 17 and 13 were in the group of 10 × 4 Gy and 10 × 5 Gy, respectively. The median time to local progression was 3.2 months for 10 × 4 Gy, as compared to 8 months for 10 × 5 Gy. We report a 1-year actuarial lesion-based LC of 59% (95% C.I. 41–73%) and 53% (95% C.I. 30–71%) for the metastases who received 10 × 4 Gy and 10 × 5 Gy, respectively (Fig. 2A) (p = 0.3).

Modeling of the LRs yielded 15 in-field and 15 marginal failures. In the 10 × 4 Gy group, 59% (n = 10) of the LRs were in-field and 41% (n = 7) marginal. Dose escalation to 10 × 5 Gy did not significantly reduce the in-field and/or marginal failures, reflected by