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Stereotactic body radiation therapy for liver metastasis – The linac-based Greater Poland Cancer Centre practice

Magdalena Fundowicz[a,*], *Marta Adamczyk*[b], *Anna Kołodziej-Dybaś*[c]

[a] *Radiotherapy Ward I, Greater Poland Cancer Centre, Poznan, Poland*
[b] *Department of Medical Physics, Greater Poland Cancer Centre, Poznan, Poland*
[c] *Department of Radiotherapy, Greater Poland Cancer Centre, Poznan, Poland*

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ABSTRACT

Aim: The main purpose of this work is to give a technical description and present the properties of the liver SBRT protocol implemented in the Greater Poland Cancer Centre (GPCC) in Poznan, Poland.
Background: Stereotactic body radiation therapy (SBRT) for liver metastasis is a non-invasive therapeutic option which enables irradiation of a small target in the body with a high dose.
Materials and methods: This study presents details of our linac-based liver SBRT protocol. Special emphasis has been placed on fiducial implantation, patient preparation (CT scanning, immobilization), treatment planning, and its implementation.
Results: The liver SBRT treatment course implemented in the GPCC consists of three fractions to deliver a total of 45 Gy. Fraction delivery details with description of patient positioning (localization of liver metastasis) are presented below.
Conclusions: The literature validation of the assumptions concerning the steps of the GPCC linac-based liver SBRT procedure show their potential for an effective and patient friendly implementation.

1. Background

Most of the cancers: colorectal, breast, kidney, lung, pancreas cancers, often present solitary metastasis or oligometastases in the liver. A surgical resection provides a long term survival in approximately 30% of patients with the colorectal carcinoma liver metastases, but only a limited (10–25%) percentage of patients is amenable to surgery. Non-surgical ablation methods include cryotherapy, laser-induced interstitial thermotherapy, and radiofrequency ablation which is the most frequently used method. Stereotactic body radiation therapy (SBRT) is a non-invasive therapeutic option, which enables irradiation of a small target in the body with a high dose.[1–4] The use of SBRT is rapidly increasing.[5–8]

* *Corresponding author at*: Radiotherapy Ward I, Greater Poland Cancer Centre, 15th Garbary Street, 61-866 Poznan, Poland.
E-mail address: Magdalena.fundowicz@wco.pl (M. Fundowicz).
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2. Aim

The aim of the study is to present the SBRT treatment for liver metastases using a conventional linear accelerator.

3. Materials and methods

At the Greater Poland Cancer Centre (GPCC), for the SBRT purposes, we classify patients into those with metastases in one organ (liver metastases); those with a histopathologically proven colorectal adenocarcinoma; those after a radical resection of the primary tumor; inoperable; or those with a recurrence after an operation on the liver. The maximum accepted diameter of the largest metastasis is 6 cm. If two lesions of metastases are close to each other, the maximum diameter is greater (up to 8–9 cm with the lesions contoured as one connected target). One to four metastases are accepted while a tumor is visible on CT scans.

The patient should have status 2 WHO/ECOG; chemotherapy is allowed before and after the study treatment, but the last chemotherapy must be within one month before the SBRT.

Exclusion criteria: an uncontrolled extrahepatic disease and an uncontrolled primary cancer, a liver cirrhosis.

Before the treatment begins, all patients are discussed at a meeting of a multidisciplinary team consisting of surgeons, medical oncologists, radiation therapists, radiologists and hepatologists. At the GPCC, preparation for the stereotactic treatment starts by conducting an operation. For the treatment, internal fiducial markers are implanted near the liver tumor to allow monitoring the tumor movement during the treatment. While the fiducial markers are typically implanted under CT-guidance or ultrasound guidance, at the GPCC the fiducial markers are implanted during the operation. The tumor at the time of treatment may turn out to be larger than estimated through CT or ultrasound examinations. The surgeon or radiation oncologist visually implants 2–4 fiducial markers in healthy tissues, in a strategic, non-planer geometric relationship among one another. The operator can observe the tumor, measure it if necessary, and can easily observe the distance between the tumor and the healthy tissue. The implantation process becomes easier than the one conducted through the CT guidance. A CT scan treatment planning with contrast and slice thickness of 3 mm is conducted about ten to fourteen days after the fiducial placement. An appropriate preparation for the SBRT treatment is started by forming the vacuum pillow on which the patient is positioned frameless in a standard supine position, the patient's arms are abducted alongside the head, and knee support is utilized.[9,10] The CT images are acquired at 3 mm slice spacing in different breathing conditions:

- free shallow breathing for planning purpose[10,11];
- deep breathing while maintaining position;
- free shallow breathing with contrast enhancement.[10]

All CT scans are transferred to the Eclipse V.10.0 Treatment Planning System (Varian Medical Systems, Palo Alto, California, USA). A gross tumor volume (GTV) and organs at risk (OARs) are delineated by a physician on the free breathing CT scan.[10,30] The gross tumor volume is considered to be identical with the clinical target volume (CTV) and expanded by 5 mm margin (the exception being by 10 mm in the cranio-caudal direction) to create the planning target volume (PTV)[11–13] for the respiratory motion observed at the time of simulation. The OARs may include healthy organs (liver for which the PTV volume is subtracted, kidneys, spinal cord, stomach, esophagus, bowel, heart). The dose delivered to the organs is presented in Table 1. Dose constraints to OARs are adopted to the clinical protocol as proposed by the International Liver Tumor Group.[31,32]

Table 1 – Dose constraints to organs at risk.

Organ at risk	Dose constraint
Liver (healthy) (liver-PTV)	$D_{700\,ml} < 15$ Gy
Kidneys (both)	$D_{35\%} < 15$ Gy for kidneys volume (sum of both kidneys) $D_{50\%} < 15$ Gy for the kidney receiving the highest dose
Spinal cord	$D_{max} < 18$ Gy
Stomach	$D_{1CC} < 21$ Gy
Esophagus	$D_{1CC} < 21$ Gy
Bowel	$D_{1CC} < 21$ Gy
Heart	$D_{1CC} < 30$ Gy
Duodenum	$D_{1CC} < 21$ Gy

$D_{700\,ml}$ – dose received by 700 ml of the analyzed organ.
$D_{X\%}$ – dose delivered to x% of the analyzed organ.
D_{1CC} – dose delivered to 1cc of the analyzed organ.

According to numerous literature findings, the dose is normalized to prescribe 100% of the dose to the mean GTV. At the same time, jaws and a multileaf collimator (MLC) should be adopted and fitted to encompass the GTV and PTV volumes by at least 95% and 67% isodose, respectively.[13,26,33]

In our treatment protocol (the liver SBRT), we use 15 Gy in 3 fractions (the total dose 45 Gy).[9] The protocol assumes that the treatment plan is prepared by a three dimensional conventional conformal radiotherapy technique with 6 MV photons and the dose rate of 600 MU/min. A dosimetric calculation is conducted using the Anisotropic Analytical Algorithm with heterogeneity correction.[14–16]

The geometry of the plan should be proposed taking into account the tumor size, medical location, boundary, and vasculature projection in the treated area.[17,30] To enhance dose homogeneity, field weighting and wedges can be used.

At the GPCC, we use the Varian environment: the Eclipse v. 10.0 Treatment Planning System. The patients are treated in a Clinac 2300CD linear accelerator with the On-board Imager, OBI and 120 Millennium MLC with 0.5 cm width in the isocenter.[9]

4. Results

In our SBRT protocol three fractions are delivered according to two proposed schemes: irradiation every second day with the treatment starting on Monday; or the treatment starting on Tuesday and ending on Monday. Both schemes are applied in different cancer centers with three dose fractions delivered in one week (Erasmus). The total course of the SBRT is completed

within 14 days[12,31] and each isocenter is treated within 8 days with each fraction having been delivered.[12] Before each session, a system of wall mounted alignment lasers is used for initial, daily positioning of the patient. For each fraction, the set-up is performed using co-registration between the kV cone beam CT scans (CBCT) and the planning CT scans[18–20] to determine the actual position of the target (fiducial markers based verification). After making a CBCT based shift, the kV imaging is taken to confirm the position of the tumor (localization of the fiducial markers position). In our protocol, the patient set-up is repeated after the first half of the treatment to correct a possible intra-fraction movement and after the daily fraction to observe the final tumor position.[9]

During and after the treatment, the side effects are generally mild. Observed toxicities range from grade 1 to 2 in the CTCAE v.4 (Common Terminology Criteria for Adverse Events). The most common acute toxicities include nausea, vomiting, gastritis, and an abdominal or chest wall pain.[21,25,27]

Now, we start the liver SBRT with 4D CT planning and the treatment on the CyberKnife.

5. Discussion

In the last few years, the SBRT has been used as a non-invasive, loco-regional treatment for many primary and secondary tumors with promising results[25] Some retrospective[16,17] and some prospective[14,22–24] studies have investigated the efficacy of the SBRT in the treatment of liver metastases from various primary tumors. In general, patients with up to four metastases, and with the maximum diameter of the largest metastasis of no more than 40 mm, are selected for the SBRT treatment.[28] However, some authors describe treatment procedures performed for 110-mm hepatic metastasis[3,15] that are also applicable to patients with metastases in two organs. The SBRT requires a highly precise dose planning and delivery. In the simulation phase, the patient is immobilized with a personalized vacuum pillow. An abdominal compression device should be used to reduce the organ motion related to the respiratory excursion.[34] A contrast-free computed tomography (CT) scan and a three-phase contrast-enhanced CT scan are acquired. The potential of dealing with tumor motion in the SBRT is improved by the introduction of a 4-dimensional CT (4D CT) imaging. This imaging tool is widely used to accurately compensate for exhalation and inhalation.[11] The 4D CT scan enables contouring for the internal target volume while incorporating the tumor motion, as it is visualized throughout the breathing cycle. Without the CT, which enables to achieve 4D scanning or eventually ultra-slow scanning, we prepare the reconstruction in different modes, which, after registration, gives us the information about the tumor expansion in different breathing conditions.[9] In the CyberKnife, before each treatment, the Xsight spine positioning is performed to check the body alignment and to verify possible fiducials migration.[11] Without the CyberKnife, the guidance on the basis of images obtained using the CT scanners in the treatment room (the helical MV CT or the kV cone-beam CT scanners) enables to guide and monitor the fraction treatment. Similar to the CyberKnife Synchrony, fiducials are recommended for CBCT positioning. Unfortunately, due to a poor image contrast between the tumor and the liver tissues, without fiducials, a tumor-based match between planning and the pre-treatment CTs is unfeasible[9,11] Worm et al.[11] in their study report that using the CT-guidance helps prevent critical errors connected with initial tumor positioning and ensure a proper radiation delivery exactly to the target. In clinics without a fiducial implantation, the bony landmarks fusion for the liver SBRT pre-treatment verification is the most commonly used procedure. Unfortunately, due to the independent movement between the liver and bones[11], such a set-up procedure introduces another source of uncertainty during irradiation, which must be taken into account while applying the CTV-to-PTV margin.

The prescription doses generally range from 30 to 60 Gy in 3 fractions, although a publication describes a phase II trial where a higher prescription dose of 75 Gy in 3 fractions was delivered.[23] According to the SBRT assumptions, the highest dose per fraction (from 5.0 Gy up to 25.0 Gy)[10,12,28] is delivered to small target volumes. Even if the highest scheme of dose per fraction is used, all literature reports underline that if a dose reduction is needed, based on acceptable location of a tumor close to the OARs (esophagus, stomach, bowel and kidneys), a lower dose level for the target is to be chosen. When there is more than one metastasis, it is acceptable to choose a lower dose level for the target which is located near the critical structure and a higher dose level for the non-critical targets.[13,15] Schefer et al.[12] enrolled 16 patients with liver metastases in a phase I trial. They reported that it was possible to increase the radiation dose to 60 Gy in three fractions without any toxicity,[22,29] and the local control rate was 93% in the first year after the SBRT. Hoyer et al.[13] published results of a Danish phase II study of the liver metastases treated with the total dose of 45 Gy in three fractions. The local control rates after 1 and 2 years after the SBRT were 89% and 79%, respectively. Kavanagh at al.[21] reported an actuarial local control rate of 93% after 18 months.

Most studies showed a low toxicity profile with a ≥G3 toxicity rate of 1–10% and the incidence of the radiation-induced liver disease (RILD) of less than 1%. In phase II trial by Scorsetti et al.[23] on 61 patients, no RILD was observed using a dose constraint allowing no more than 700 mL of the uninvolved liver to receive 15 Gy or greater in 3 fractions. The most common G2 toxicities included a transient hepatic transaminase increase approximately 3 months after the SBRT[13,14]; and gastrointestinal, soft-tissue complications related to lesions close to the duodenum, bowel, skin and ribs.

Good selection criteria for patients with liver metastases who are candidates for SBRT remain a controversial topic. A multidisciplinary tumor board discussion is recommended before each qualification. For discussion purposes, candidates for SBRT can be divided into three categories: suitable, cautionary and unsuitable patients.[23,34] Selection criteria may be based on: the lesion number, the lesion diameter, the distance from the OARs, the liver function and patients' conditions.

6. Conclusions

The goal of the SBRT is to deliver a high dose to the target, thereby providing better local tumor control while limiting

the dose to the surrounding healthy tissue, thereby potentially decreasing the chances of complication. For the patients, implanting fiducial markers during the operation is a safer, relatively painless method. As our treatment approach is based on the SBRT delivery with no motion restrictive external immobilization, breathing instructions and frequent online imaging cannot be neglected. Due to the mentioned capability of delivering various doses with different equipment, the literature validation of our liver SBRT protocol finds it suitable for patients with liver metastases, and highlights its potential for an effective and patient friendly delivery.

Conflict of interest

None declared.

Financial disclosure

None declared.

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