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Comparative study of the calculated risk of radiation-induced cancer after photon- and proton-beam based radiosurgery of liver metastases

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ABSTRACT

Introduction: The potential of proton therapy to improve the sparing of the healthy tissue has been demonstrated in several studies. However, even small doses delivered to the organs at risk (OAR) may induce long-term detriments after radiotherapy. In this study, we investigated the possibility to reduce the risk of radiation-induced secondary cancers with intensity modulated proton therapy (IMPT), when used for radiosurgery of liver metastases.

Material and methods: Ten patients, previously treated for liver metastases with photon-beam based stereotactic body radiation therapy (SBRT) were retrospectively planned for radiosurgery with IMPT. A treatment plan comparison was then performed in terms of calculated risk of radiation-induced secondary cancer. The risks were estimated using two distinct models (Dasu et al., 2005; Schneider et al., 2005, 2009). The plans were compared pairwise with a two-sided Wilcoxon signed-rank test with a significance level of 0.05.

Results: Reduced risks for induction of fatal and other types of cancers were estimated for the IMPT plans ($p < 0.05$) with the Dasu et al. model. Using the Schneider et al. model, lower risks for carcinoma-induction with IMPT were estimated for the skin, lungs, healthy part of the liver, esophagus and the remaining part of the body ($p < 0.05$). The risk of observing sarcomas in the bone was also reduced with IMPT ($p < 0.05$).

Conclusion: The findings of this study indicate that the risks of radiation-induced secondary cancers after radiosurgery of liver metastases may be reduced, if IMPT is used instead of photon-beam based SBRT.

1. Introduction

Proton-beam therapy (PBT) is an emerging form of radiotherapy (RT) used for cancer treatment. A reduction in the number of observed long-term side effects can be expected after proton beam radiotherapy [1–4], due to the decreased integral doses delivered to the risk organs [5]. The reduced risks of inducing secondary malignancies have also been stated as a rationale for the implementation of proton beams in the clinic. This advantage has been emphasized mainly for the radiotherapy of paediatric patients [6–8]. However, in the last decades, advances in cancer diagnostics as well as in systemic treatment options, in combination with a variety of local treatment modalities, have led to increasing survival rates and life expectancy, even for patients receiving RT late in life. This makes the incidence of cancer induction after RT pertinent also for adult RT patients [9,10].

The frequency of radiation-induced cancer in human tissues, after total body exposures with low doses of ionizing radiation, has been determined in different epidemiological studies [11–14]. However, these studies involve doses (<100 mSv) which are lower than those used in RT, for which the dose-response can be described with the linear non-threshold (LNT) model. It is well-known that the LNT model overestimates the risks for higher doses, as it does not account for cell kill which decreases the cancer risk [15,16]. Different dose-response models, valid for all doses, have been proposed [15–18]. These models predict a linear increase of risk with dose in the low dose region. At higher doses, some models predict an exponential decrease of the risk with increasing doses. Other models assume risk saturation at high doses. Due to the fact that the estimated cancer-risk depends on

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the dose heterogeneity across the irradiated organ and on the type of tissue irradiated, these factors should be included in the risk estimation.

A photon-based radiosurgery technique called stereotactic body radiation therapy (SBRT) has been developed, with which high lethal doses can be delivered to targets in the liver with low toxicity. It has been suggested that hypofractionated RT could reduce the frequency of radiation-induced secondary cancers, compared to conventionally fractionated RT [19]. The age at the time of treatment is in general high for patients receiving radiosurgery of liver metastases [20]. However, a large fraction of the patients treated have been found to be long-term survivors [20–22], which has made the late side effects more relevant.

Radiosurgery implemented with proton beams have been proposed for the treatment of liver metastases. Dosimetric studies, comparing photon- and proton-beam therapy for the treatment of oligo-metastases in the liver [22–24] have reported that the doses given to normal tissues can be reduced with PBT. This is in particular the case for the doses given to the normal part of the liver, the main OAR in radiation therapy of malignancies in the liver.

In a recent dosimetric study of radiosurgery of liver metastases, involving patients included in the present study [24], the OARs were found to be better spared from irradiation with low and intermediate doses with the intensity modulated proton therapy (IMPT) technique. However, stochastic effects which lead to cancer induction may occur at all dose levels [25]. Therefore, to be able to compare the risk of radiation-induced cancer, produced with different RT modalities, the risks need to be quantified with the suggested radiation-risk models. The aim of this study was to use radiobiological models to investigate the potential of IMPT to reduce the risk of inducing secondary malignancies after radiosurgery of liver metastases.

2. Material and methods

2.1. Patient selection and treatment planning

Ten patients diagnosed with liver metastases from primary colorectal cancer were included in this study (median age of 77 years and range 66 – 89 years). These patients were treated with photon-based SBRT at the Department of Oncology and Pathology at Karolinska University Hospital and were selected based on the tumour size and location within the liver (Table 1), as representative cases for this patient group. A summary of the treatment characteristics is also shown in Table 1.

The planning computed tomography (CT) image sets consisted of 3.0 mm thick slices. The dose calculations, carried out as part of the treatment planning, were based on patient-composition data from regular free-breathing CT studies. The ITV concept was used to take the target motion into consideration in the planning. The CTV to ITV expansion margins were determined using 4D-CT studies. The ITV to PTV margins were set to 5 mm in the transversal direction and 10 mm in the cranio-caudal direction. Two distinct SBRT treatment techniques were used to create the photon plans, the static-field three-dimensional conformal radiotherapy (3D-CRT) technique (7 patients) and the volumetric modulated arc therapy (VMAT) technique (3 patients). VMAT was used to treat the patients with large target volumes (patients 3 and 6) or when critical structures were located close to the target (patient 8), (Table 1). These photon plans, used for the actual treatments, were used as reference plans in the comparison with the prepared IMPT plans. The stereotactic frame, used for patient immobilization, was assigned the Hounsfield unit of air in the planning CT study used for the IMPT planning in order to avoid uncertainties specific for the proton dose calculation.

A two-field IMPT technique was used to retrospectively plan all the patients. The planning objective was set to achieve a similar PTV dose coverage as with the original photon plans. In these plans, the periphery of the PTV received 100% of the prescribed dose and in the center of the target volume, where presumably the more radio-resistant cells were located, doses in the range from 145% to 160% of the prescribed dose were allowed. The healthy part of the liver was identified as the most critical OAR. Other OARs considered were the skin, kidneys, lungs, esophagus, bone and spinal cord. Direct irradiations through the spinal cord and the right kidney were avoided in the IMPT planning. The assessment of risk for treatment-induced secondary malignancies was also performed for the remaining tissues (the part of the body encompassed by the CT study that was not delineated as OARs), referred to as "other-solid".

The treatment planning was performed with the Eclipse treatment planning system (TPS) (Varian Medical Systems, Palo Alto, California, version 11.0.42). Photon beams of energy 6 MV, produced by a Varian (Varian Medical Systems, Palo Alto, California) linear accelerator, were used for the photon-beam therapy planning. The proton-beam data was taken from a facility with an IBA cyclotron (Ion Beam Applications S.A., Louvain-La-Neuve, Belgium) with initial proton energies varying between 60 and 230 MeV. A generic relative biologic effectiveness (RBE) value of 1.1 was assumed for the proton beams.

2.2. Estimation of the risk for radiation-induced secondary cancer

The cancer-risk calculations were performed using data extracted from the dose-volume histograms (DVHs) generated in the treatment planning process. The estimation of the risk for radiation-induced secondary malignancies following radiotherapy was performed using two distinct calculation models. One of these models, the competition model (competition between mutation induction and cell kill), was first proposed by UNSCEAR [17] and later adapted by Dasu et al. [15] to account for both treatment dose fractionation and dose heterogeneity within the OARs. The other model, proposed by Schneider and co-authors [16,18], is based

Table 1
Patient setup and description of the photon-beam treatment.

Patient #	Modality (photon SBRT)	Fractionation	Abdominal pressure	PTV (cm^3)	Target location
1	Static fields	15 Gy x 3	Yes	59.6	Central-peripheral
2	Static fields	17 Gy x 3	Yes	73.1	Superior
3	VMAT	8 Gy x 7	No	332.3	Posterior/whole liver extent axially
4	Static fields	8 Gy x 5	Yes	302.6	Central/whole liver extent axially
5	Static fields	7 Gy x 8	No	66.4	Central-periphery
6	VMAT	7 Gy x 8	No	294.1	Central-superior
7	Static fields	15 Gy x 3	No	18.6	Central-periphery
8	VMAT	7 Gy x 8	Yes	78.6	Superior
9	Static fields	17 Gy x 3	No	30.2	Central
10	Static fields	15 Gy x 3	No	72.3	Central

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