Therapeutic procedures in liver metastases: Conventional and future measures

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1. Background

Resection of liver metastases from colorectal carcinoma (CRC) is associated with 5-year survival rates of 30–40%, with the possibility of cure, even in the absence of systemic therapy. This demonstration of a local therapy improving outcomes for ‘oligo-metastatic’ CRC is well accepted. Long-term survivors have also been reported following resection of liver metastases from sarcoma, renal-cell carcinoma, breast cancer and melanoma, with 5-year survival rates of 23–36% in a series of non-CRC liver metastases. Resection of neuroendocrine liver metastases has also been associated with favourable survival.

Stereotactic body radiation therapy (SBRT) is an attractive option for patients with liver metastases. Liver SBRT requires a planning computed tomography (CT) simulation scan with intravenous (IV) contrast for target definition. Multimodal imaging with contrast-enhanced magnetic resonance imaging (MRI) or positron emission tomography (PET) may improve target delineation. Breathing-related liver motion should be assessed by respiratory-correlated (or 4D) CT, cine-MRI or 2D kV fluoroscopy to determine appropriate planning target volume (PTV) margins. Highly conformal dose distributions are desirable using multiple beams or arcs in coplanar or non-coplanar geometries. The nominal prescribed dose should reflect the isodose that encompasses the PTV (or 95% of the PTV) with hotspots within the PTV. Immobilization of the liver using controlled breath holds, shallow breathing, abdominal compression and gating of the RT (radiation therapy) beam during specified phases of the respiratory cycle, medications and tumour tracking of implanted fiducial markers may help reduce the adverse effects of breathing motion. Image-guided RT (IGRT) based on orthogonal imaging, ultrasound or volumetric imaging such as MV or kV cone beam CT, is required at every fraction in order to reduce PTV margins for setup uncertainty. MR IGRT is an area of active research that may benefit patients requiring liver SBRT.

Advantages of SBRT include increased convenience for patients. Furthermore, there are preclinical data demonstrating dose-per-fraction effects (e.g. endothelial and immune effects), with a threshold of approximately 8 Gray (Gy). Clinical experience in SBRT for liver metastases is rapidly increasing.

2. Methods

Updated results from Princess Margaret Cancer Centre phase I/II studies of SBRT for liver metastases are presented, as well as a review of previously published SBRT studies and consensus statements of radiation therapy for liver metastases.

3. Results

In our centre in Toronto, a phase I/II study of individualised IGRT-guided SBRT was conducted in 107 patients with 172 unresectable or medically inoperable liver metastases from CRC, breast cancer or other primary sites [1]. The median tumour volume was 75 ml. Extrahepatic disease was present in 40 patients (43%), and 75% had received prior systemic therapy. Patients were treated with six-fraction SBRT (median dose 42 Gy, range 24–48 Gy). No radiation-induced liver toxicity was observed. Median survival was 18.1 months. The presence of extrahepatic disease was associated with worse survival. Prognostic factors for improved local control included breast primary site, dose and tumour volume. Some patients with CRC or breast cancer liver metastases are alive with no progressive disease more than 5 years post-SBRT.

In a subset of patients from the Toronto cohort with unresectable liver metastases who had kV cone-beam CT scans at each fraction, the cone-beam CTs were used in combination with deformable image registration to deter-

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http://dx.doi.org/10.1016/j.ejcsup.2013.07.060
mine the accumulated delivered dose (versus the prescribed dose). Accumulated minimum doses to the GTV (gross tumour volume) of <35 Gy, 35–45 Gy and >45 Gy, in six fractions were associated with 18-month local control of 33%, 55% and 83%, respectively. The dose–response relationship was steeper for accumulated dose compared with prescribed dose.

Most published SBRT studies have prescribed doses in the range 30–60 Gy in 1–6 fractions, for ≤5 metastases, with maximal tumour size ≤6 cm. CRC liver metastases are the most frequent tumour type. However, an increasing number of patients with liver metastases from breast and lung cancer are being included in recent SBRT series. In the published series, survival rates have been better than those expected following systemic therapy alone. Toxicity is uncommon as long as enough uninvolved liver can be spared from radiation therapy (e.g. >700 ml receiving 15 Gy in three fractions or mean liver dose <18 Gy in six fractions). Local control of the irradiated liver metastases at 1 year ranges from 67% to 100%. The median survival of patients treated with SBRT ranges from 18 to 37 months, with the best outcomes seen in a more recent series. A dose response has been observed in most series, with an increased chance of sustained local control (80–90% at 2 years) when doses >42 Gy in three fractions are used. Local control is also improved in patients with metastases <3 cm in maximal size and in breast cancer metastases compared to colorectal cancer metastases.

In a pooled analysis of SBRT for CRC metastases [2], dose was the only significant prognostic factor for local control and extra-hepatic disease and local recurrence were associated with impaired survival. A dose of 48–51 Gy in three fractions was estimated to be associated with a 1-year local control rate of 90%.

An international subcommittee – with members from the American Society for Radiation Oncology (ASTRO), the European Society for Therapeutic Radiology and Oncology (ESTRO), the Canadian Association of Radiation Oncology (CARO) and the Trans-Tasman Radiation Oncology Group (TROG) – led by Hoyer et al [3] developed a consensus statement of liver metastases radiation therapy. Ideal candidates for SBRT were described as patients with good performance status (ECOG 0–1), possessing adequate hepatic function, with no extrahepatic disease, having ideally ≤5 liver metastases and an uninvolved liver volume ≥700 ml. As outcomes are best following higher-dose SBRT, most suitable patients include those with a focal distribution of metastases, at least 1 cm from luminal gastrointestinal organs. Breast cancer metastases appear more sensitive than CRC metastases. The consensus statement described uncommon toxicity in the liver, with increased risk in patients re-irradiated and/or with prior liver disease. Luminal gastrointestinal toxicity and chest wall and rib fractures have also occasionally been seen. Of note, the consensus statement briefly reviewed non-SBRT methods of delivering high-dose radiation therapy to liver metastases, including conformal radiation therapy, selective internal radiation therapy (e.g. hepatic arterial delivery of yttrium) and interstitial or intraluminal brachytherapy. In addition, patients with diffuse symptomatic liver metastases were highlighted as a population largely understudied, in whom low-dose palliative whole-liver radiation therapy may be of benefit. In a pilot study of 20 patients with symptoms from diffuse liver metastases at the Princess Margaret Cancer Centre, approximately 50% of the patients had a patient-reported benefit in pain or discomfort at 1 month following 8 Gy in one fraction. Based on this, a phase III study of simple palliative radiation therapy compared to best supportive care is planned (HE.1, through the National Cancer Institute of Canada Clinical Trials Group).

4. Conclusions

SBRT is a promising treatment for patients with focal ‘oligo’ liver metastases. The most suitable patients with liver metastases are those with three or fewer metastatic tumours, each ≤6 cm, with no extrahepatic disease and with metastases at least 2 cm from the luminal gastrointestinal tissues. More research is required regarding optimal dose-per-fraction and mechanisms, as well as the most appropriate patient selection.

Conflict of interest statement

I have received research grants from Elekta and Bayer in the past 5 years.

Acknowledgements

This research was funded in part by NCIC/Canadian Cancer Society, ASCO CDA, Princess Margaret Cancer Centre Foundation Gerry Ruby Fund and Department of Radiation Oncology Academic Enrichment Fund. These sponsors had no involvement in the research design, analysis or publication.

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