Stereotactic body radiotherapy for liver metastases

By Hans T. Chung, MD, FRCPC, Radiation Oncology, Odette Cancer Centre

HOT SPOT

Surgical resection remains the standard of care for liver metastases. For unresectable lesions, stereotactic body radiotherapy (SBRT) is rapidly emerging as an attractive option. As compared to radiofrequency ablation (RFA), another form of nonsurgical local treatment, SBRT is completely non-invasive. Unlike conventional radiotherapy, the objectives of SBRT are to escalate the dose to the target lesion and, thus, improve local control while limiting dose to nearby critical structures, reducing the risk of complications. The fundamental prerequisites for optimal delivery of SBRT are the ability to precisely localize the target lesion(s); accounting for tumour motion due to respiration; generating a treatment plan to deliver highly conformal radiation to the target volume with a sharp dose gradient to maximize liver sparing; and image guidance at the time of radiation delivery.

Background

- Recently, two pivotal prospective studies reported the safety and efficacy of SBRT for liver metastases.
- In the Princess Margaret Hospital study, 70 patients were enrolled in a phase 1 study to evaluate the safety and efficacy of a six-fraction regimen. The radiation dose was individualized based on the volume of irradiated liver, and corresponding risk of radiation-induced liver disease (Lee et al., 2009).
  - Acute toxicities: Among grade 3 toxicities, two patients had elevation of liver enzymes, two had gastritis and two had nausea. Among grade 2 toxicities, 12 (18%) patients had elevation of liver enzymes, five (7%) had gastritis, 12 (18%) had lethargy, four (6%) had nausea, and three (4%) had liver pain.
  - No dose-limiting toxicities or radiation-induced liver disease was observed.
  - Late toxicities: one grade 4 duodenal bleed; one grade 5 malignant small bowel obstruction due to tumour progression and invasion into duodenum; one grade 4 small bowel obstruction through an abdominal hernia; and two grade 2 non-traumatic rib fractures.
  - Local control at one year was 71%.
- In a multi-institutional phase I/II study from the U.S., 47 patients from seven centres received 60 Gy in three fractions. Based on surgical literature, the protocol specified that at least 700 cc of normal liver should receive less than 15 Gy (Rusthoven et al., 2009).
  - No radiation-induced liver disease, grade 4–5 toxicities or bleeding/thrombotic complications observed with subsequent bevacizumab. One patient had grade 3 soft tissue toxicity with skin breakdown in the anterior abdomen. Grade ≥3 toxicity was 2%.
  - Local control was 95% and 92% at 1y and 2y, respectively. In subset analyses, lesions with maximum diameter of 3 cm or less had a 2y local control rate of 100%, compared to 77% for lesions greater than 3 cm.
- Acute side effects may include fatigue, nausea, vomiting, dysphagia, loss of appetite, fever and chills.
- Potential late complications include radiation-induced liver disease, ascites, stomach or duodenal ulcer, elevated liver function tests, bowel obstruction, gastrointestinal bleeds, rib fracture and biliary sclerosis. The risk of any of the above grade ≥3 late complications is less than 5%.

Eligibility

- 1–3 liver metastases from any solid tumour except a germ cell tumour or lymphoma.
- Inoperable or medically unsuitable for resection.
- Maximum tumour diameter ≤ 6 cm
- ≥ 800 mL liver uninvolved by tumour, Childs-Pugh A.
- KPS ≥ 60%, life expectancy ≥ 3 mths.
- No evidence of progressive or untreated gross extrahepatic disease.
- Hemoglobin ≥ 90; neutrophil ≥ 1.5; PLT ≥ 80; INR ≤ 1.3; AST/ALT ≤ 6x ULN; bilirubin < 3x ULN; Cr ≤ 200.
- No chemo 2 wks before to 4 wks after SBRT.

Patient set-up

- Different techniques to address tumour motion have been described, but they can be broadly divided into *motion-restrictive* and *motion-compensating* approaches. The former includes techniques that limit respiratory motion, such as abdominal compression devices or breath holding, which is used at the Odette Cancer Centre. The latter includes techniques that account for respiratory motion, such as respiratory gating or real-time tumour tracking.
- Patients undergo planning CT scans with contrast, which are often fused with the diagnostic scans to facilitate tumour delineation. Many centres, including the Odette Cancer Centre, use 4D-CT scans, which can assess anatomy changes with respiration.

Target definition and dosimetry

- Target volumes and organs at risks (i.e., kidneys, liver, spinal cord, chest wall, stomach, heart) are contoured by the radiation oncologists.
- A radiation plan is then generated using pre-established dose-constraints to organs at risk (see Figure 1). No consensus prescription dose has been made, but the majority of studies have used 30-60 Gy in at least two fractions. At the Odette Cancer Centre, we prescribe 60 Gy in six fractions.

Positional verification on treatment day

- For every treatment, the patient is immobilized in the same manner as the planning CT scan. An onboard x-ray volumetric imaging system (i.e., cone-beam CT scan) scans the patient. These scans are compared with the planning CT scan to check for positional differences. Any differences are corrected before starting treatment**.** This whole process is repeated for all six fractions.

References

Lee, M.T., Kim, J.J., Dinniwell, R., et al. (2009). Phase I study of individualized stereotactic body radiotherapy of liver metastases. **J Clin Oncol, 27**(10), 1585–1591.

Rusthoven, K.E., Kavanagh, B.D., Cardenes, H., et al. (2009). Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. **J Clin Oncol, 27,** 1572–1578.

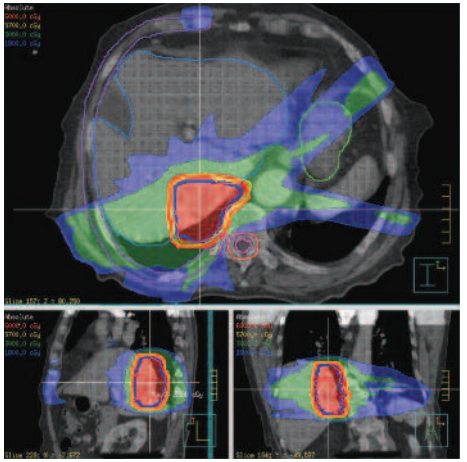

Figure 1.

Surgical resection of colorectal liver metastases: An update

By Calvin H.L. Law, MD, MPH, FRCSC, Hepatobiliary, Pancreatic and Gastrointestinal Surgical Oncology, The Edmond Odette Cancer Centre at Sunnybrook Health Sciences Centre, Associate Professor of Surgery, University of Toronto

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- Surgical resection for colorectal liver metastases has evolved from a novel therapy for a minority of colorectal cancer patients to at least a therapeutic consideration in the multidisciplinary management in nearly all patients, as well as an emerging endpoint for evaluating the efficacy of many chemotherapeutic regimens against metastatic colorectal cancer.
- The main developments in advancing surgical treatment for liver metastases have been: (i) better and more detailed imaging; (ii) more effective chemotherapy; (iii) pre-operative methods to optimize liver capacity for surgery such as portal vein embolization; and (iv) newer surgical tools and techniques that allow for novel methods of liver sparing and minimally invasive surgery.
- All patients coming to the Odette Cancer Centre with liver metastases usually undergo the following approach: (i) a team-based evaluation (radiology, pathology, medical, radiation and surgical oncology) to determine the patient's cancer risk profile (i.e., likelihood of more cancer elsewhere); (ii) full image-based mapping of all liver metastases, as well as staging the chest, abdomen and pelvis; (iii) discussion regarding the role of peri-operative chemotherapy; (iv) balancing all other non-surgical treatment options; and (v) determining the time for surgical resection.
- A way to understand how surgery fits in the therapeutic plan for patients with colorectal liver metastases is to sort the patients as follows: (i) patients who present with small volume liver metastases and are immediately surgically operable; (ii) patients who present with operable liver metastases, but have a higher risk for recurrence profile; (iii) patients who present with liver metastases that represent a challenge to surgical resection.
- For the patient with a ***small volume liver metastases and immediately surgically operable***:
  - chemotherapy can be given either before (pre-op chemo) and after surgery, or else simply after surgery (pseudo adjuvant chemo)—this is determined by a team approach that incorporates the evaluation of multiple factors including overall disease risk of recurrence and patient considerations.
- For patients ***who are operable, but have a higher risk for recurrence profile***:
  - chemotherapy is often given before surgery here—this allows for (i) determination of the biological efficacy of the chemotherapy; (ii) monitoring of other higher risk sites for cancer recurrence; and (iii) final determination for suitability for surgery.
  - ideally, a maximum of three months of chemotherapy is given preoperatively, with only stability of overall staging and/or any response in the liver metastases being the criteria for surgical resection.
  - 4 to 8 weeks between the last cycle of chemotherapy (eight weeks for those on bevacizumab) and surgery allows for enough time to clear most of the detrimental effects of chemotherapy that may affect surgical outcomes.
- For patients who present with ***liver metastases that represent a challenge to surgical resection:***
  - the most effective chemotherapy is considered up-front in order to allow for a decrease in the size of the liver metastases (conversion therapy)—this is continued until such time that a surgical resection can be considered. This is referred to as "downstaging" or "conversion".
- If the liver is not of a sufficient size to allow for surgery, we can redirect blood flow using a portal vein embolization technique that will force the planned remaining side of the liver to grow before surgical resection.
- Patients with liver metastases along with other sites of disease such as the lung are not immediately ruled out for surgical resection—their cases are discussed in a team format and using surgery on multiple sites is a consideration.
- In summary, patients who present with colorectal liver metastases have a wider gamut of options available now than ever before. The key to treatment is to be considered by a multidisciplinary team for combination therapy and to be aware of the rich variety of options available.

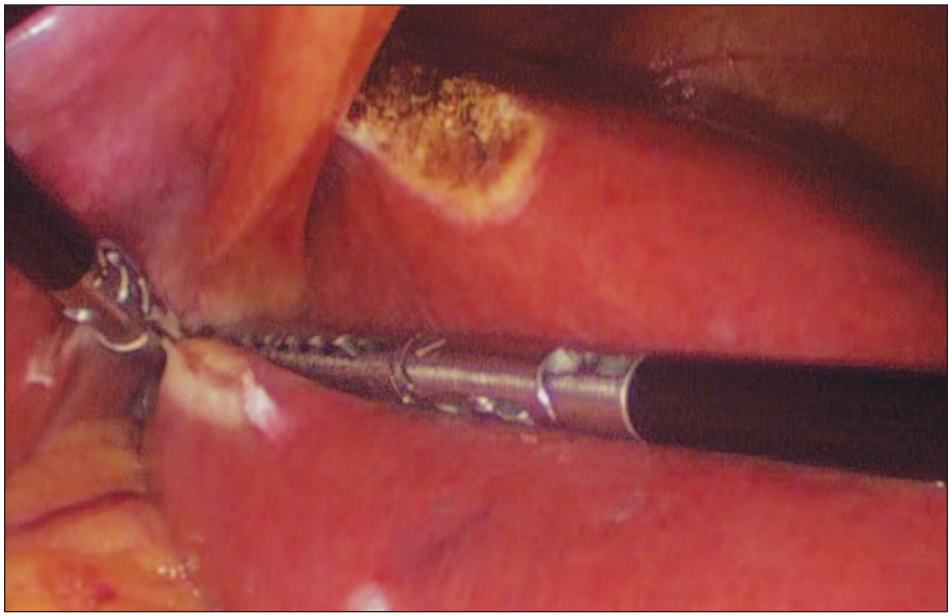

Figure 1: Laparoscopic resection of colorectal liver metastases using a novel collagen sealing technique developed at Sunnybrook.

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