Radiation in the treatment of liver cancer

A review of the literature

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Radiation therapy (RT) is a newly evolving option in the treatment of both primary and metastatic liver cancer. To understand how RT can be applied to liver cancer and potential future directions of treatments, a review of the literature was performed.

INTRODUCTION & GENERAL TREATMENT OVERVIEW

PRIMARY LIVER CANCER

Primary liver cancer is the fastest growing cancer in Canada, with the incidence rate increasing by almost 4% per year in males and 3% per year in females since 1970, and is the third most common cause of cancer death worldwide.¹ The most common type of primary liver cancer is hepatocellular carcinoma (HCC), accounting for approximately 72% of cases.¹ Hepatitis B and C viruses (HBV and HCV) are known to be oncogenic¹ and it is possible that some of the increase in the rates of liver cancer in North America is a result of increased immigration from countries where HBV is endemic;² however, half of all cases of HCC in North America are not related to HBV or HCV.³ Other risk factors include alcohol,⁴ obesity,⁵ diabetes,⁶ smoking⁷ and genetic risk factors such as hemochromatosis and alpha1-antitrypsin deficiency.⁸ Primary liver cancer is one of the deadliest cancers, with a 20% five-year survival.¹

The only treatments of liver cancer currently considered potentially curative are resection, transplantation,⁹ transarterial chemoembolization (TACE)¹⁰ and radiofrequency ablation (RFA).^{1,11} In 2008, a chemotherapeutic agent, sorafenib, was shown to be tolerable and effective in a select group of patients.¹² Patients with very early-stage primary liver cancer are typically treated with surgical resection, resulting in a 90% five-year survival rate.¹⁴ Resection can also be used in patients with early-stage disease and good liver function (Child-Pugh A),¹ resulting in a 50% five-year survival rate; however, these patients still have a 70% recurrence rate.¹⁵ Resection is not an option for patients with early-stage disease and poor liver function, so they are often treated with liver transplantation,¹ resulting in a 70% five-year survival rate and a recurrence rate of less than 15%;¹⁵ unfortunately, the wait time for such a surgery is typically very long. Other patients with early-stage disease for whom surgery is not possible due to the location of the tumour can be treated with RFA,¹ which has similar survival rates to resection.¹⁶ TACE is often used to treat intermediate-stage liver cancer and has been shown to improve survival by 20 to 25%,¹⁴ with the best results occurring when there is no macrovascular involvement^{10,17} and a tumour size less than 10 cm.¹⁸ Those with advanced disease are typically not treated actively,¹ the exception being the relatively uncommon case where the patient retains good liver function and sorafenib may be used.¹⁴ Two randomized controlled trials with

sorafenib have shown that median survival is improved by two to three months.¹²

LIVER METASTASES

The most common causes of secondary hepatic malignancy are colorectal carcinoma, breast carcinoma, melanoma and neuroendocrine tumours.¹⁵ The 5-year overall survival with unresectable liver metastases from colorectal cancer is less than 2% when treated with chemotherapy.¹⁵ If local therapy, such as surgical resection or RFA, is possible, survival increases to between 33 to 58%¹⁹⁻²¹ and 17 to 55%¹⁵ respectively. Therefore, resection and preservation of a minimal functional remnant of liver is recommended.²¹ If the tumours are originally unresectable, it is sometimes possible to use chemotherapy to shrink the tumours to a resectable size or away from critical structures such as blood vessels.¹⁵

NOVEL TREATMENT METHODS FOR LIVER CANCER

Many novel approaches to improving survival in both primary and secondary liver cancer have been investigated. Radioembolization, the delivery of radioactive particles to a tumour via the bloodstream, has shown limited success in causing tumour necrosis, thereby improving survival.²² Biodegradable microspheres full of a chemotherapeutic agent may also be used and this technique has been shown to be safer than traditional chemotherapy in patients with liver disease; however, there is no evidence to date that it improves survival compared to other traditional treatment options.²³ Another approach has been to use radiotherapy, a treatment frequently employed for cancers in other locations, but, for reasons described below, it has only recently been used with curative intent in patients with liver cancer. Radiation is appealing as it is non-invasive and has been shown to be effective in the primary cancers that commonly metastasize to the liver. Furthermore, it has been shown to improve survival in patients who cannot receive other therapies due to complications such as portal vein thrombosis.²⁴

LIVER TOXICITY IN RADIOTHERAPY

Irradiating the liver can lead to radiation-induced liver disease (RILD) even at low doses. A whole-liver tolerance dose has been set at a maximum of 30 Gy in separate 2 Gy fractions, a dose which results in a 5% risk of liver failure 5 years after treatment.²⁵ RILD is potentially life-threatening and in the past has limited the role of radiation in liver cancer to mostly palliative.²⁶⁻²⁹ This risk of RILD increases if the patient has established poor liver function due to cirrhosis or the cancer itself.^{28,30} Malignant lesions of the liver typically require greater than 75 Gy for adequate treatment³¹ and, therefore, treatment of these lesions with radiation poses a very high risk of

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RILD. Since the liver has regenerative properties, it is possible to irradiate a portion of the liver, rather than the entire organ, thereby decreasing the risk of RILD;^{32,33} however, until recently the technology required to locate the tumour within the liver and to apply radiation to that limited area has not been available.

TECHNICAL ADVANCES WHICH ALLOW FOR RADIOTHERAPY WITH CURATIVE INTENT

IMAGING METHODS

Recent advancements have allowed the use of radiation in liver cancer with curative intent. New imaging techniques can better localize the tumour within the liver, allowing for high doses to be applied to a small area around the focal lesion and limiting the risk of RILD to less than 5%.³⁴⁻³⁸ These include the use of contrast-enhanced computed tomography (CT)³⁹ as well as combined imaging techniques such as CT with magnetic resonance imaging (MRI) or positron emission tomography (PET) to better define tumour boundaries.^{40,41} Further, imaging can now be performed in the treatment room, using technology such as cone beam CT to allow for visualization of the liver immediately before or during treatment.⁴⁵

MOTION INCORPORATING METHODS

Methods for reducing or accounting for liver motion can be applied during imaging to improve the quality of the image or during treatment to allow for more precise delivery. During breathing, the liver moves on average 15.5 mm in the craniocaudal direction, 10 mm in the anteroposterior direction and 7.5 mm in the mediolateral direction.⁴⁶ It is recommended that treatment planning account for any motion greater than 5 mm.⁴⁷ This can be done by three methods: reducing motion through abdominal compression, eliminating motion through breath holding or incorporating motion through gating or tracking of surrogate markers.⁴⁵ Abdominal compression requires the patient to voluntarily breathe shallowly while the abdomen is mechanically compressed,⁴⁵ and can reduce liver motion by approximately 7 mm.⁴⁸ Eliminating motion through breath-holding is most reproducible if patients hold their breath at the exhale position⁴⁵ and has an interfraction variability of 2.2 mm +/- 2.0 mm.^{49,50} Incorporating motion into treatment is currently the focus of extensive research as it reduces the burden on the patient.⁴⁵ Relevant techniques include gating, where the radiation beam is only turned on when the tumour is in a specific position, and tracking, where the beam is moved according to the position of the tumour. Both require tracking the position of the tumour with either an external marker placed on the patient's chest, or a fiducial marker placed within the patient's liver.⁵¹

DOSE DELIVERY METHODS

Advances in methods of delivering radiation have also allowed for more precise dose delivery. Conformal RT (CRT), intensity-modulated RT (IMRT) and stereotactic ablative RT (SABR) have allowed for a higher dose to be delivered to a focal tumour even while a lower dose is delivered to the surrounding liver and other normal structures.⁵²⁻⁵⁴ CRT utilizes multiple beams to sculpt

the dose to conform to the shape of tumours. IMRT advances this technique by using computer algorithms to enable even more accurate placement of radiation dose within the tumour. SABR uses image guidance and increased dose per treatment fraction to ablate tumours. Studies have shown that the most important predictor of survival for liver cancer is radiation dose.³¹ Treating a tumour with more than 75 Gy overall has been shown to increase mean survival from 14.9 months to 23.9 months in HCC;³¹ however, no randomized trials have been performed to date.

COMBINATION TREATMENT METHODS

A further technique is to combine other treatment modalities with RT. The most common treatment used in such a combination is TACE.⁵⁵⁻⁵⁹ Studies have found that it is sometimes possible to shrink the tumour using TACE, then irradiate the smaller liver volume.³¹ A higher overall survival rate has been found with the combination of radiation and TACE versus TACE alone (11.7 compared to 4.7 months median overall survival).⁶⁰

CONCLUSIONS AND FUTURE DIRECTIONS

Despite statistically significant mortality improvements in primary and secondary liver cancer as a result of the above, the overall outcome for a large proportion of patients remains poor. Major advancements in radiation technology have resulted in better motion control, tumour localization, understanding of radiobiological toxicity and radiation delivery. Case series data suggests that this has translated into improved local control and survival. These early studies have suggested particular roles for radiation that require additional investigation, including the role of radiation in patients (1) with larger lesions when combined with TACE, (2) being bridged to transplant, (3) with portal vein thrombosis and (4) undergoing palliation.

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