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Review Article

Stereotactic Body Radiation Therapy for Liver Cancer: A Review of the Technology

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ABSTRACT

Stereotactic body radiation therapy has been adopted in the treatment of liver cancer because of its highly conformal dose distribution when compared with other conventional approaches, and many studies have been published to report the positive clinical outcome associated with this technique. To achieve the precision needed to maintain or to improve the therapeutic ratio, various strategies are applied in different components in the stereotactic body radiation therapy process. Immobilization devices are used in minimizing geometric uncertainty induced by treatment positioning and internal organ motion. Along with a better definition of target by the integration of multimodality imaging, planning target volume margin to compensate for the uncertainty can be reduced to minimize inclusion of normal tissue in the treatment volume. In addition, sparing of normal tissue from irradiation is improved by the use of high precision treatment delivery technologies such as intensity-modulated radiotherapy or volumetric modulated arc therapy. Target localization before treatment delivery with image guidance enables reproduction of the patient's geometry for delivering the planned dose. The application of these advanced technologies contributes to the evolution of the role of radiation therapy in the treatment of liver cancer, making it an important radical or palliative treatment modality.

RÉSUMÉ

La radiothérapie stéréotaxique corporelle (RSC) a été adoptée dans le traitement du cancer du foie parce qu'elle permet une répartition de dose hautement conformée par rapport aux autres approches conventionnelles, et plusieurs études ont été publiées pour rapporter les résultats cliniques positifs associés à cette technique. Afin d'atteindre le degré de précision nécessaire pour maintenir ou améliorer le ratio thérapeutique, différentes stratégies sont appliquées aux différents composants du processus de RSC. Les dispositifs d'immobilisation sont utilisés pour minimiser l'incertitude géométrique induite par le positionnement du traitement et les déplacements des organes internes. Avec une meilleure définition de la cible grâce à l'intégration de l'imagerie multimodale, la marge prévue dans la planification du volume cible afin de compenser l'incertitude peut être réduite afin de minimiser l'inclusion de tissus sains dans le volume de traitement. De plus, la protection des tissus normaux contre l'irradiation est améliorée par le recours à des technologies d'administration du traitement de haute précision comme la radiothérapie conformationnelle avec modulation d'intensité(RCMI) ou l'arcthérapie avec modulation de volume (ATMV). La localisation de la cible avant le traitement avec guidage par l'image permet la reproduction de la géométrie du patient avant l'administration de la dose prévue. L'application de ces technologies avancées contribue à l'évolution du rôle de la radiothérapie dans le traitement du cancer du foie et en fait une modalité de traitement radical ou palliatif importante.

Keywords: Liver; stereotactic body radiation therapy; treatment planning; treatment delivery

Introduction

Primary liver cancers such as hepatocellular carcinoma are the fifth most commonly diagnosed cancer worldwide [1] and, according to Canadian Cancer Statistics 2013, the incidence rates in Canada continue to rise faster than other cancers [2]. Hepatic metastases are also common, for example, in up to half of colorectal cancer patients with a substantial portion confined to the liver [3]. Surgery has been the primary treatment modality for either primary or secondary liver cancer for selected group of patients with 5-year survival rates of 43%–47% [4, 5]. However, recurrence rates have also been reported to be upward of 50% at 5 years with surgery [4], and most patients are inoperable due to high tumour burden, tumour location, and poor liver function (eg, cirrhosis). Localized modalities such as radiofrequency ablation [6, 7], percutaneous ethanol injection [7], radioactive isotopes [8], and chemoembolization [9] can offer comparable outcomes to surgery, but they too each have unique contraindications.

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Systematic chemotherapy is generally ineffective for liver cancers [10].

External beam radiotherapy is a versatile treatment option for patients who are unsuitable for, or who have failed the modalities mentioned previously. Whole liver irradiation in doses of ~35 Gy in 2 Gy/fraction [11, 12] or a single 8 Gy fraction [13] has been offered to alleviate symptoms for patients with primary or metastatic liver disease. However, it has a limiting role in disease progression. Clinical studies have shown that local control is significantly improved when liver tumours receives >54 Gy [14], suggesting higher doses are beneficial. With the liver being a parallel functioning organ that can sustain focal damage without failure, partial liver irradiation is more tolerable with a $TD_{5/5}$ of 50 Gy and 35 Gy to one- third and two- thirds of the liver, respectively [15]. Radiobiological studies using normal tissue complication probability models have shown doses of >100 Gy in 2 Gy/fraction could theoretically be delivered to small liver volumes for an radiation induced liver disease (RILD) risk under 5% [16]. However, with the proximity of critical organs adjacent to the liver and the potential for large geometric variations, there is a challenge in delivering dose-escalated radiotherapy to the liver safely.

Stereotactic body radiation therapy (SBRT) has been adopted to treat lung, liver, and spine with its capability of delivering much higher dose than other conventional techniques. It is defined by the Canadian Association of Radiation Oncology task force as: ''the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extracranial body target with doses at least biologically equivalent to a radical course when given over a protracted conventionally (1.8–3.0 Gy/fraction) fractionated schedule.'' [17].

Advantages of hypofractionation over conventional radiotherapy are patient convenience and the potential to be more radiobiologically damaging. Multimodality target definition, highly conformal dose distributions, and daily online image guidance is used for liver SBRT. SBRT to tumours typically <5 cm treated with doses of 18–55 Gy/1–10 fractions has resulted in median survival rates of 14.5–28.6 months, with only rare instances of RILD and liver failure [18–23] and 1-year local control of up to 90% possible [24]. Low rates of other potentially serious SBRT toxicities can include gastrointestinal ulcerations or bleeding, rib fractures, and for primary cancers in particular, a decline in liver function, elevated liver enzymes, and transient biliary obstructions [18, 25, 26]. The purpose of this article was to review strategies and tools that are commonly used in minimizing geometric uncertainty and in generating highly conformal dose distributions for liver SBRT.

Methods and Materials

A literature review was conducted using Ovid Medline and Google Scholar in March 2014. Using a combination of the following keywords, peer-reviewed articles that detail the tools and technologies involved in SBRT and published in English were retrieved: Liver SBRT, target volume definition, liver SBRT immobilization, interfraction, and intrafraction motion. Additional articles were identified by handsearching the reference lists of the retrieved articles and using the ''cited by'' function in Ovid Medline and Google Scholar.

Information from various sources was then synthesized into the following categories:

- Mitigation of geometric uncertainties;
- Target volume and margin definition;
- Optimization of dose distribution;
- Optimization of treatment precision.

Strategies to Mitigate Geometric Uncertainties during Delivery

Immobilization can minimize setup variability and stabilize the patient position in the setting of SBRT. Lax et al first reported the use of stereotactic body frame with a vacuum pillow for treating malignancies in the abdomen, with Wulf et al demonstrating that the bony structure alignment had a median deviation of 0 mm compared with the initial plan and a standard deviation of <4 mm [27, 28]. However, the same study reported that motion of mobile soft tissue targets such as liver tumour poorly correlated with bony structures, and they had additional displacements of >5 mm in 33% of cases [28]. This work highlights that daily image guidance for liver SBRT should not rely on bony anatomy.

When liver motion induced by diaphragmatic movement is larger than 5 mm, it has been recommended that motion management strategies should be used to reduce the planning target volume (PTV) margin [29]. Active breathing control (ABC) is one of the strategies in restricting the tumour motion from breathing. The use of end-exhale breath hold has usually been adopted because of its higher inter- and intrafraction reproducibility of the diaphragm position when compared with end-inhale breath hold [30, 31]. However, comparable diaphragm reproducibility has also been demonstrated using end-inhale phase, and it is deemed to be more feasible in acquiring single breath-hold cone-beam computed tomography (CBCT) due to a longer breath-holding duration [32]. This also improves efficiency in treatment delivery with the capability of delivering more doses in a single breath hold. Whether the end-exhale or end-inhale phase is used, the maximum motion of the diaphragm in the superior–inferior direction was measured to be 2 mm [32, 33], facilitating a PTV margin reduction from a maximum of 30–9 mm [34]. Another study by Ten Haken et al estimated that eliminating the margin required for breathing motion would result in a 6%–7% increase in tumour control probability for the same risk of liver toxicity [35]. In addition to reducing inter- and intrafraction tumour motion, ABC can also improve the accuracy in volume delineation and the agreement between the planned and delivered dose of the delineated volume by reducing the motion artifact on CT [36]. Nevertheless, there are limitations to the use of ABC. In a study by Dawson et al,