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Medical Physics Contribution:

Cumulative dose of radiation therapy of hepatocellular carcinoma patients and its deterministic relation to radiation-induced liver disease

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ABSTRACT

This study aimed to investigate the relationship between dose and radiation-induced liver disease (RILD) in patients with hepatocellular carcinoma (HCC) receiving 3-dimensional conformal radiotherapy (3DCRT). Twenty-three patients with HCC who received conventional fractionated 3DCRT, including 7 who were diagnosed with classic RILD, were enrolled in this retrospective investigation. Cone-beam computed tomography (CBCT) scans were acquired at the time of treatment for each patient. The beams from each patient's treatment plan were applied to each pretreatment CBCT (the modified CBCT or mCBCT) to construct the delivered dose distribution of the day considering inter-treatment anatomy changes. The daily doses were summed together with the help of deformable image registration (DIR) to obtain the adjusted cumulative dose ($D_{adjusted}$). The dose changes to the normal liver between the original planned dose (D_{plan}) and $D_{adjusted}$ were evaluated by V20, V30, V40, and the mean dose to normal liver (MDTNL). Univariate analysis was performed to identify the significant dose changes. Among the 23 patients, the liver V20, V30, V40, and MDTNL showed significant differences between D_{plan} and $D_{adjusted}$, with average values of these parameters increased by 4.1%, 4.7%, 4.5%, and 3.9 Gy, respectively ($p < 0.05$). The adjusted liver dose in 21 patients (91%) was higher than the planned value. For patients without and with RILD,the MDTNL was increased on average by 3.5 Gy and 4.7 Gy, and normal tissue complication

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probability (NTCP) increased on average by 2.8% and 7.5%, respectively. Our study found that the adjusted cumulative dose based on calculations using pretreatment mCBCT differs significantly from planned dose; the use of the dosimetric results of the initial plan was found to be less predictive of RILD as compared with $D_{adjusted}$. Determination of a reconstructed $D_{adjusted}$ using the mCBCT scans are more accurate in predicting RILD and has the potential to reduce the risk of RILD.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide.[1] Its prognosis remains poor worldwide, with 5-year survival below 20%.[2] The incidence of HCC varies significantly between countries. For example, in China it is the third leading cancer in males,[3] whereas in the United States it is the 10th leading cancer in males.[4] Advanced radiotherapy (RT), such as 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy, are increasingly used to treat HCC.[5-7] One of the most severe radiation-induced complications with hepatic radiation is radiation-induced liver disease (RILD),[8] which is related to the radiation dose to the liver.[9,10] RILD typically occurs 4 to 8 weeks after RT completion, with no effective way to manage the complication at present.[5] Because RILD can result in significant morbidity and mortality, measures to accurately predict and prevent RILD deserve special attention.

The liver is believed to be a typical parallel organ showing a strong correlation between the dose to the irradiated liver and RILD.[11] Cheng and coworkers, in their analysis of 68 patients with HCC and complete 3D dose-volume data, reported that mean hepatic dose was significantly higher in patients with RILD than in those without RILD (25.04 Gy *vs* 19.65 Gy, respectively, $p = 0.02$). Dawson *et al.* observed no case of RILD when mean dose to the normal liver (MDTNL) was below 31 Gy.[9] Subsequently, Liang *et al.*[12] concluded that a MDTNL of 23 Gy was tolerable for patients with HCC with Child-Pugh grade A cirrhosis treated with hypofractionated 3DCRT, and that keeping the MDTNL below this hepatic radiation tolerance in RT planning was significant for preventing RILD.

These studies have generally assumed that the planned MDTNL reflected accurately the dose that the liver actually received. Because of the highly deformable nature of liver and possible body weight or habitus changes during the course of treatment,[13,14] it is conceivable that the dose distribution delivered to the patient may vary from fraction to fraction.[15] Currently, adaptive RT[16,17] is a strategy to correct for dose distribution resulting from morphologic changes in patients' anatomy. Hansen *et al.*[18] emphasized that repeat scans and re-planning were essential to identify dose deviation and to ensure adequate target coverage and organs at risk (OAR) sparing. Nevertheless, the offline imaging does not reveal the anatomy immediately before each radiation fraction; therefore, it cannot document the accurate delivery of any re-planned dose distribution.

Cone-beam computed tomography (CBCT) provides volumetric images of a patient immediately before treatment delivery, providing the possibility for on-line or off-line image-guided dose reconstruction.[19-21] Currently, however, CBCT has large scatter radiation contamination, and the image quality suffers from the beam hardening effect,[22] resulting in inaccurate CT numbers. The CBCT values cannot be simply converted to electron densities and directly used for dose calculations because this might lead to dose errors of 5% or worse.[23] To obtain a more reliable relationship between the CT values (or Hounsfield units [HU]) of CBCT and relative electron density, Yang *et al.*[24] registered the CBCT scan with the fan-beam CT (FBCT) to map the FBCT HU numbers to the CBCT anatomy. This resulted in more accurate HU numbers and dose calculations.

The purpose of our current study was to investigate the relationship between dose and RILD in patients with HCC who received 3DCRT. For accurate dose reconstruction, we obtained a set of modified CBCT (mCBCT) images by deformedly registering the planning CT (pCT) and pretreatment CBCT for each patient. The planned dose (D_{plan}) and adjusted dose distribution ($D_{adjusted}$) were obtained for each patient. We then evaluated the difference between D_{plan} and $D_{adjusted}$, and their relationship with RILD.

Methods and Materials

Patient characteristics

Patients were selected based on the following criteria: (1) HCC with single lesion, and not treatable by surgery or percutaneous ablative therapies; (2) HCC confined to the liver without extrahepatic metastases; (3) prior irradiation with conventional fractionated 3DCRT; (4) Child-Pugh A liver function, no B or C; (5) 3DCRT dosimetric parameters and daily CBCT datasets available; and (6) follow-up data for tumor and RILD available.

A total of 23 patients with unresectable HCC undergoing 3DCRT, including 7 who were diagnosed with classic RILD, were enrolled in this study. Their median age was 57 years