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Scientific Article

Analysis of Hepatocellular Carcinoma Stereotactic Body Radiation Therapy Dose Prescription Method Using Uncomplicated Tumor Control Probability Model

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Abstract

Purpose: This work was to establish an uncomplicated tumor control probability (UTCP) model using hepatocellular carcinoma (HCC) stereotactic body radiation therapy (SBRT) clinical data in our institution. The model was then used to analyze the current dose prescription method and to seek the opportunity for improvement.

Methods and Materials: A tumor control probability (TCP) model was generated based on local clinical data using the maximum likelihood method. A UTCP model was then formed by combining the established TCP model with the normal tissue complication probability model based on the study by Dawson et al. The authors investigated the dependence of maximum achievable UTCP on planning target volume equivalent uniform dose (EUD) at various ratio between planning target volume EUD and normal liver EUD (T/N EUD ratios). A new term uncomplicated tumor control efficiency (UTCE) was also introduced to analyze the outcome. A UTCE value of 1 implied that the theoretical maximum UTCP for the corresponding T/N EUD ratio was achieved.

Results: The UTCE of the HCC SBRT patients based on the current dose prescription method was found to be 0.93 ± 0.05. It was found that the UTCE could be increased to 0.99 ± 0.03 by using a new dose prescription scheme, for which the UTCP could be maximized while keeping the normal tissue complication probability value smaller than 5%.

Conclusions: The dose prescription method of the current HCC SBRT in our institution was analyzed using a UTCP model established based on local clinical data. It was shown that there could be a potential to increase the prescription dose of HCC SBRT. A new dose prescription scheme was proposed to achieve better UTCP. Additional clinical trials would be required to validate the proposed dose prescription scheme in the future.

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related mortality in the world.[1] Surgical resection and liver transplantation are the standard treatments for HCC. However, not all HCC patients are eligible for surgery. Stereotactic body radiation therapy (SBRT) is considered as an alternative. With the use of modern radiation therapy techniques such as intensity modulated radiation therapy or volumetric modulated arc therapy, it is possible to deliver a highly conformal photon beam dose to the lesion, while minimizing the dose to the normal liver. SBRT involves the delivery of a precise and high intensity dose to treat the lesion with a small number of fractions. Several investigations have shown that the use of SBRT for the treatment of HCC resulted in high local control rates of 70% to 100%.[2-5]

There had been some institutions reporting existence of dose-response relationship for their HCC patients receiving SBRT.[6-8] However, the authors of a recent HyTEC organ-specific article claimed that they did not find evidence of dose-response relationship for primary liver tumor after qualitatively analyzing reported data from 13 institutions from different parts of the world.[9] This implied that the dose-response for HCC patients might vary among different regions and races so that a worldwide dose-response model may not fit all. Therefore, it was worthwhile for our institution to investigate the dose-response relationship for local HCC SBRT patients based on our own clinical data. In this study, the dose-response relationship for HCC SBRT patients in our institution would be investigated and the possibility for improving the current dose prescription scheme would be explored.

Methods and Materials

Local clinical data

Records of patients with HCC treated with SBRT at our institution from 2014 to 2017 were reviewed. Clinical data of 51 patients in our institution who received their first HCC SBRT were retrospectively analyzed (Table 1). Patients who had previous regional or systemic therapy were included in the analysis if their previous treatment concluded before the start of SBRT. Patients who underwent additional concurrent therapy or previous radiation therapy were excluded from the study. The number of lesions in a patient was limited to 1 to 2. No limit was placed on the size of the target lesions. Follow-up data typically included computed tomography/magnetic resonance (CT/MR) scan-based measurements of tumor size and

Table 1 Characteristics of HCC SBRT patients in this study

Characteristic	Data
Age (y)	70 (45-89)
Sex	
Male	39 (76%)
Female	12 (24%)
Barcelona Clinic Liver Cancer Staging	
A	30 (59%)
B	20 (39%)
C	1 (2%)
Tumor volume (mL)	78.0 (2.2-972.6)
PTV margin from GTV (mm)	5-10
No. of lesions	1-2
No. of fractions	5
*Prescription dose (Gy)	41.6 (27.5-50)
PTV mean dose (Gy)	45.8 (28.9-56.1)
Median follow-up (mo)	12.8

* Dose by which at least 95% of PTV volume was covered.
Abbreviations: GTV = gross tumor volume; HCC = hepatocellular carcinoma; PTV = planning target volume; SBRT = stereotactic body radiation therapy.

measurements of alpha-fetoprotein biomarkers. The follow-up frequency was every 4 to 8 weeks after SBRT. CT/MR scans were performed every 3 months after day 1 of SBRT. Local control was defined as less than 20% increase in diameter of tumors.[10] An endpoint of 6-month local control was chosen for our dose response relation analysis in this study. This study was approved by the Joint CUHK-NTEC Clinical Research Ethics Committee, Hong Kong (CREC Ref Number: 2020.506).

Treatment planning techniques

The HCC SBRT were delivered using Truebeam (Varian Medical Systems, Palo Alto, CA) flattening filter free mode via volumetric modulated arc therapy. The diaphragm, lipiodol, or fiducial markers were used as surrogates for the tumors. The amplitude of the movement of the surrogates was limited to less than 1 cm by either active breathing control or abdominal compressor. The internal target volume was generated as a union of gross tumor volume (GTV) of all phases of 4-dimensional computed tomography. The planning target volume (PTV) was generated by adding 5 to 10 mm margin to the internal target volume. The treatment plans were generated using Eclipse Treatment Planning System version 13.6 (Varian Medical Systems, Palo Alto, CA). Anisotropic Analytical Algorithm version 13.6.23 was used to perform dose calculation. The prescription dose ranged from 27.5 Gy to 50 Gy in 5

fractions depending on the normal liver (excluding all GTVs) mean dose, following the Radiation Therapy Oncology Group (RTOG) 1112 dose prescription approach.[11] For a typical treatment plan, the isodose line of 80% was used for dose prescription and the center of the GTV was boosted to around 100% isodose line. The dose constraints to organs at risk were also adopted following RTOG 1112.

Statistical analysis for factors affecting tumor local control

Univariate analysis for local control was carried out using log-rank test. All factors having P values $< .1$ were subjected to multivariate analysis using Cox proportional hazards regression model with backward conditional stepwise approach to find out the independent significant factors that affects the local control. The statistical analyses were performed using SPSS Statistics version 17.0 (SPSS, Inc, Chicago, IL).

Tumor control probability model

The local clinical data was used to fit a tumor control probability (TCP) model.[12,13] The dose volume histograms (DVH) of the HCC SBRT patients were extracted from the Eclipse treatment planning system. The physical dose was converted into biologically effective dose (BED)[14,15] with α/β ratio of 10 using the Eq. (1).

$$BED = Nd\left(1 + \frac{d}{\alpha/\beta}\right) \qquad (1)$$

Where N was the number of fractions, d was the dose per fraction, α and β were the linear and quadratic components of cell survival curve, respectively.

The DVHs in BED were used to calculate the PTV equivalent uniform dose (EUD)[16-18] for the patients using Eq. (2).

$$EUD = \left(\sum_i v_i \cdot D_i^a\right)^{\frac{1}{a}} \qquad (2)$$

Where v_i was the partial volume, D_i was the absorbed dose and a was the radiobiological parameter. Parameters v_i and D_i could be obtained using the BED-converted DVHs. Parameter a would be found during the fitting process of the TCP model.

The calculated PTV EUD then was used for modeling of TCP using a logistic function[12,13] in Eq. (3),

$$p_i = TCP_i = \frac{1}{1 + \left(\frac{D_{50}}{D_i}\right)^k} \qquad (3)$$

Where p_i was the TCP for patient i, D_{50} was the EUD that led to 50% tumor control probability, D_i was the PTV EUD of patient i and k was a parameter that controlled the slope of the TCP curve.

The TCP modeling was implemented using MATLAB 2019a in the present study (The MathWorks, Inc, Natick, MA). Maximum likelihood method was used to iteratively adjust the parameters of a in Eq. (2) and k and D_{50} in Eq. (3) such that maximum likelihood of the patient i is obtained in Eq. (4).

$$l = \sum_i \log\left(p_i^{R_i}(1 - p_i)^{(1-R_i)}\right) \qquad (4)$$

Where p_i was the TCP for patient i, R_i was the control of tumor of patient i. If the tumor had no signs of progression within 6 months, then R_i was equal to 1. Otherwise, R_i was equal to 0. Tumor volume was not included as an input parameter of our TCP model because the tumor dose prescription scheme currently used in our institution was based on liver mean dose, which was related to tumor volume. Therefore, the tumor dose and tumor volume were dependent on each other.

Normal tissue complication probability model

A complication of the liver was defined as RTOG grade 3 or higher radiation-induced liver disease.[19] Due to the limited number of radiation-induced liver disease incidences in our institution to fit our own normal tissue complication probability (NTCP) model, one of the most commonly used NTCP model for liver, the Lyman Kutcher Burman model fitted by Dawson et al, was used in this study as shown in Eq. (5).[19-21] An α/β ratio of 2.5 for normal tissue was used in BED calculation.[21]

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx \qquad (5)$$

Where

$$t = \frac{EUD - TD_{50}}{m \cdot TD_{50}} \qquad (6)$$

$$EUD = \left(\sum_i v_i \cdot D_i^{\frac{1}{n}}\right)^n \qquad (7)$$

EUD was the equivalent uniform dose of an organ. TD_{50} was the tolerance dose for a homogeneous irradiation to an organ which would result in 50% risk of complication. Parameter m determined the gradient of the dose response at TD_{50}. Parameter n determined the volume effect which related the tolerance doses of uniform whole organ irradiation to uniform partial organ irradiation. TD_{50}, n and m were 39.8, 0.97, and 0.12, respectively in the study by Dawson et al.[19]

Uncomplicated tumor control probability model

Uncomplicated tumor control probability (UTCP) is one of the most common measures of therapeutic gain.[22-25] It was defined as:

$$UTCP = TCP \cdot (1 - NTCP) \tag{8}$$

The fitted TCP model of our institution and the NTCP model based on Dawson et al would be used to form a UTCP model. The variation of UTCP with PTV EUD, as well as with the ratio between PTV EUD and normal liver EUD (T/N EUD ratio) were analyzed. The T/N EUD ratio was defined as:

$$T/N \; EUD \; ratio = \frac{PTV \; EUD \; (Gy)}{Normal \; Liver \; EUD \; (Gy)} \tag{9}$$

A similar concept had been used to describe uptake of radiopharmaceutical in liver.[26,27] However, EUD dose ratio was used instead of radiopharmaceutical uptake ratio in this study. The value of this EUD dose ratio depends on the size the tumor and its location inside the liver. For example, a small PTV located at the peripheral of the liver will lead to a lower normal liver EUD and a higher T/N EUD ratio resulting in a higher UTCP, while a large PTV near the center of the liver will lead to a higher normal liver EUD and a lower T/N EUD ratio resulting in a lower UTCP.

Uncomplicated tumor control efficiency

To facilitate the analysis of the UTCP of HCC SBRT plans using current dose prescription scheme, a new concept of UTCE was introduced:

$$UTCE = \frac{UTCP}{Max \; UTCP \; achievable} \tag{10}$$

The value of UTCE had to be between 0 and 1. A UTCE value of 1 implied that the theoretical maximum UTCP of the corresponding T/N EUD ratio was achieved.

Results

Statistical analysis for factors affecting tumor local control

The univariate and multivariate analyses showed that PTV mean dose was a prognostic factor of HCC SBRT tumor control (Appendix E1).
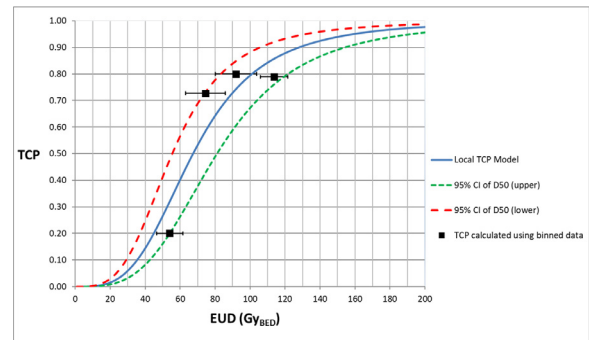

Fig. 1 Tumor control probability (TCP) model of hepatocellular carcinoma stereotactic body radiation therapy fitted with local clinical data. *Abbreviation*: EUD = equivalent uniform dose.

TCP model

The fitted TCP model using local clinical data was shown in Figure 1. The observed local control data were divided into 4 bins by equally dividing the dose range (45.3-118.6 Gy_{BED}) into 4 ranges. The TCP of each bin was calculated for comparison with the fitted TCP model. The error bars in Figure 1 represent 2 standard deviation of the distribution of the EUD for each bin.

The fitted value of a in Eq. (2) was −0.033 with the 95% confidence interval between −10.26 and $+\infty$. The fitted value of D_{50} was found to be 67.4 Gy_{BED} with the 95% confidence interval between 55.2 Gy_{BED} and 81.5 Gy_{BED}. The fitted value of k was found to be 3.42 with the 95% confidence interval between 1.58 and 5.67.

UTCP model

A UTCP model[22,23] of HCC SBRT was formed by combining TCP model fitted based on local clinical data and NTCP model of Dawson et al for different PTV EUD to normal liver EUD ratio (T/N EUD ratio). The optimal PTV EUD and the theoretical achievable maximum UTCP value with T/N EUD ratio are shown in Figures 2 and 3, respectively (see Appendix E2 for the derivation of optimal PTV EUD and theoretical achievable maximum UTCP for different T/N EUD ratio). It was observed that the values of the optimal PTV EUD increased almost linearly with the T/N EUD ratio in Figure 2. From Figure 3, it was shown that the higher the T/N EUD ratio, the higher the maximum UTCP could be achieved with an optimal PTV EUD. The maximum UTCP was close to 1 when T/N EUD ratio was 5, compared with 0.24 when T/N EUD ratio was 1.

The PTV EUD of the patients who were prescribed according to RTOG 1112 mean liver dose prescription method[11] were compared with the optimal PTV EUD to achieve maximum UTCP (Fig 2). For T/N EUD ratio
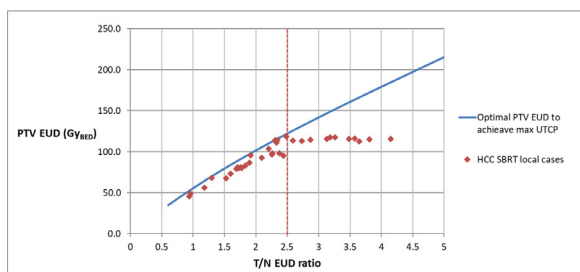
Fig. 2 Planning target volume (PTV) equivalent uniform dose (EUD) versus normal liver EUD (T/N EUD) ratio for hepatocellular carcinoma (HCC) stereotactic body radiation therapy (SBRT) local cases. The dotted line indicated the beginning of plateau region where the PTV EUD did not increase anymore with further increase in T/N EUD ratio.

Fig. 4 Uncomplicated tumor control probability (UTCP) versus normal liver equivalent uniform dose (T/N EUD) ratio using the new dose prescription scheme based on liver UTCP model compared with the original dose prescription scheme.

<2.5, the actual PTV EUD were much closer to the optimal PTV EUD, although still being underprescribed in general. The actual PTV EUD correlated to the optimal PTV EUD with Pearson correlation coefficient of 0.957. When the T/N EUD ratio approached 2.5, the prescription dose reached the highest level by following the RTOG 1112 method. As a result, the PTV EUD did not increase anymore with further increase in T/N EUD ratio >2.5, indicating that the actual given mean doses to the tumor were lower than the optimal values.

Figure 3 illustrates the comparison between the UTCP of the patients with the maximum UTCP achievable. The estimated UTCPs of the patients were in general lower than the maximum achievable values, especially when T/N EUD ratios were >2.5. Figure 4 shows the plot of UTCE versus T/N EUD ratio for the HCC SBRT cases in our institution, where the average UTCE was 0.93 ± 0.05. This implies that there was a potential to improve the dose prescription method for this group of patients such that the UTCE could be closer to one.

A new dose prescription scheme was proposed to achieve higher UTCP values. For a T/N EUD ratio between 1.9 and 3.5, the prescribed PTV EUD was the
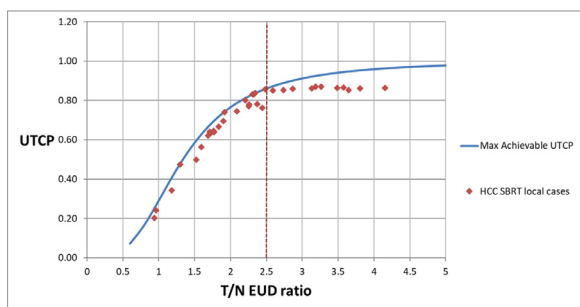
optimal EUD to achieve maximum UTCP. For a T/N EUD ratio <1.9, the optimal EUD that achieved maximum UTCP would lead to NTCP >5%, which was the maximum acceptable local tolerance of normal liver NTCP. Therefore, an iso-NTCP approach with NTCP equal to 5% was used for dose prescription for a T/N EUD ratio <1.9. For a T/N EUD ratio >3.5, a maximum EUD was also set at 160 Gy_{BED} (corresponding to about 68 Gy physical dose) such that it resulted in at least 95% TCP. The TCP curve entered a relatively flat region for dose larger than 160 Gy_{BED} and the increase in TCP was less than 0.1% per Gy_{BED}.

The patients were represcribed following the new prescription scheme to increase the overall UTCE and keep the liver NTCP within 5%. The PTV EUD and TCP under the new scheme were compared with that under the original RTOG 1112 prescription scheme. It was found that the change in PTV EUD ranged from −2.7% to 40.9%, and the change in TCP ranged from −4.6% to 15.3% (Fig 5). There was an average increase of 16.5% in PTV EUD and an average increase of 7.7% in TCP. The average UTCE of the new prescription scheme was

Fig. 3 Uncomplicated tumor control probability (UTCP) versus normal liver equivalent uniform dose (T/N EUD) ratio for hepatocellular carcinoma (HCC) stereotactic body radiation therapy (SBRT) local cases. The dotted line indicated the beginning of plateau region where the UTCP did not increase anymore with further increase in T/N EUD ratio.
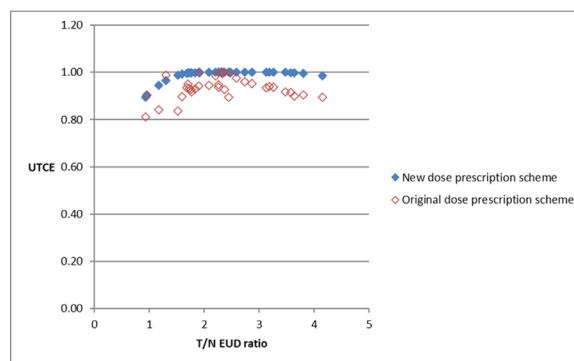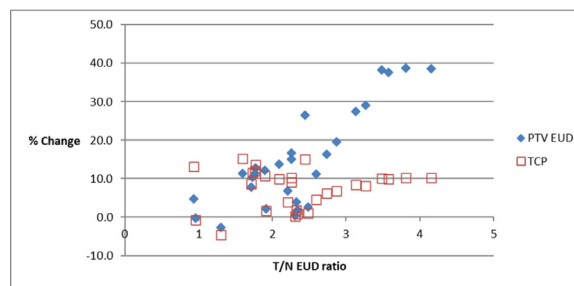

Fig 5 Percentage change in planning target volume (PTV) equivalent uniform dose (EUD) and TCP using the new dose prescription scheme based on liver uncomplicated tumor control probability model compared with the old dose prescription scheme following Radiation Therapy Oncology Group 1112.

increased to 0.99 ± 0.03 compared with 0.93 ± 0.05 of the original prescription scheme (Fig 4).

Discussion

UTCP had been used in other investigations together with parameters such as quality adjusted life years to predict the overall outcome of the different treatment plans.[24] It had been applied to other SBRT evaluations such as non-small cell lung cancer.[25] With its usefulness, building local UTCP model and using it to evaluate HCC SBRT treatments locally as well as to seek room for potential dose escalation were the purpose of this study.

A 6-month TCP model was fitted using local clinical cases and the fitted value of D_{50} was 67.4 Gy_{BED}. Lausch et al reported a 2 Gy Equivalent D_{50} of 53 Gy (63.6 Gy_{BED}) for a 6-month TCP model.[7] Jang et al reported a 3-fraction D_{50} of 34.9 Gy (75.5 Gy_{BED}) for a 2-year TCP model.[8] Our fitted value of D_{50} was found to be more comparable to the 6-month model of Lausch et al.

The fitted TCP model was then combined with the NTCP model proposed by Dawson et al to form the UTCP model to assess if maximum theoretical UTCP had been achieved under the current dose prescription protocol based on RTOG 1112 and to see whether there was any room for dose escalation. For cases with a T/N EUD ratio greater than 2.5, most of the cases already reached the highest level of dose prescription following the RTOG 1112 scheme (100 Gy_{BED} corresponding to 50 Gy physical dose). Therefore, there was no more increase in the PTV EUD with further increase in the T/N EUD ratio above the value of 2.5 in Figure 2. The prescription dose seemed to be far below the values to achieve optimal UTCP.

A new prescription scheme was proposed to increase the overall UTCE and keep the liver NTCP within 5%. Under the new prescription scheme, a higher T/N EUD ratio resulted in a higher percentage increase PTV EUD in general (Fig 5). It was because the cases with a low T/N EUD ratio usually had higher normal liver EUD, limiting the potential to increase dose prescription. Also, the higher T/N EUD ratio cases were originally limited by the RTOG 1112 highest dose prescription level of 50 Gy, which was far from the optimal prescription dose to achieve theoretical maximum UTCP.

The percentage increase in TCP versus T/N EUD ratio (range, -2.7% to 40.9%) showed a different pattern compared with the percentage increase in PTV EUD versus T/N EUD ratio under the new dose prescription schemes (Fig 5). The lower T/N EUD ratio resulted in a higher percentage increase in TCP. It was because the dose prescriptions were generally low for a low T/N EUD ratio cases due to normal liver dose limit. The TCP curve was steep at low dose range and therefore a relatively small increase in PTV EUD could lead to a large increase in

TCP. Two cases had a decrease in PTV EUD and TCP. This was because the original liver NTCP of these 2 cases were >5%. Therefore, the PTV EUD was decreased such that the liver NTCP was kept within 5%.

The UTCE of the cases using the new dose prescription schemes were closer to one than the original dose prescription scheme except those with T/N EUD ratio less than 1.9 owing to the limit of 5% NTCP. The average UTCE of the cases using the new dose schemes was boosted up to 0.99 ± 0.03, comparing to 0.93 ± 0.05 of the RTOG 1112 dose prescription scheme.

Conclusions

There was a dose-response relationship for the patients undergoing HCC SBRT in our institution. A TCP model fitted with clinical data of local HCC SBRT patients was combined with a published NTCP model to form a new UTCP model. Current dose prescription method used in our institution was analyzed using the newly established UTCP model to evaluate if theoretical maximum UTCP was achieved. It was suggested that there could be a potential to increase the current prescription dose for HCC SBRT to obtain higher UTCP. A new dose prescription scheme was proposed accordingly in this study and further clinical trials would be required to validate the proposed dose prescription scheme in the future.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.adro.2021.100739.

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