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

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Shortened Title

Analysis of HCC SBRT Dose Prescription Method using UTCP Model

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Declarations

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Not Applicable.

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Authors' contributions

MLC was responsible for research design, data collection, data analysis and manuscript writing. MWK was responsible for data analysis and manuscript editing. ATC was responsible for research guidance and supervision

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Abstract

Background: This work was to establish an uncomplicated tumour control probability (UTCP) model using Hepatocellular Carcinoma Stereotactic Body Radiation Therapy (HCC SBRT) clinical data in our institution. The model was then used to analyze the treatment outcome of the current dose prescription method and to seek the opportunity for improvement.

Methods: A tumour 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 (NTCP) model based on the study by Dawson et al. The authors investigated the dependence of maximum achievable UTCP on tumor mean biological effective dose (BED) at various ratio between tumour mean biological effective dose (BED) and normal liver mean BED (T/N BED ratios). A new term uncomplicated tumour 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 BED ratio was achieved.

Results: The UTCE of the HCC SBRT patients based on the current dose prescription method was found to be 0.90±0.08. 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 NTCP value smaller than 5 %.

Conclusion: The treatment outcome 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 treatment outcome.

Keywords: SBRT, VMAT, HCC, TCP, NTCP, UTCP

Background

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 radiotherapy (SBRT) is considered as an alternative. With the use of modern radiotherapy techniques such as intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT), 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 70–100%. [2-5].

There had been some institutions reporting existence of dose-response relationship for their Hepatocellular carcinoma (HCC) patients receiving stereotactic body radiotherapy (SBRT) [6-8]. However, the authors of a recent HyTEC organ-specific paper claimed that they did not find evidence of dose-response relationship for primary liver tumour 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 was explored. A tumour control probability (TCP) model [18,19] was fitted with local clinical data and combined with Dawson's liver normal tissue complication probability (NTCP) model [20-22] to form an uncomplicated tumour control probability (UTCP) model [10,11]. In order to facilitate the analysis of UTCP, a new term, uncomplicated tumour control efficiency (UTCE), was introduced.

Since normal liver is the major critical organ for radiation treatment of HCC patients, tumour-to-normal uptake ratio is commonly used to determine the dose to HCC patients in 90Y microspheres treatments to limit the radiation side effect to normal liver [12,13]. The authors made use of a similar concept in this study. By investigating the dependence of maximum achievable UTCP and UTCE on the ratio between tumour mean biological effective dose (BED) and normal liver mean BED (T/N BED ratio), it was found that the original dose prescription protocol used for the population cohort was very safe and conservative. It is possible to improve the treatment outcome by using a more aggressive prescription scheme. Finally, a new dose prescription scheme was proposed to achieve a higher UTCE for HCC SBRT. The new scheme aimed to escalate the prescription dose, based on the T/N BED ratio, to achieve a higher control rates. However, verification based on clinical samples is required in the future.

Methods

Patient Selection

Records of HCC patients 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 prior to the start of SBRT. Patients who underwent additional concurrent therapy or previous RT were excluded from the study. The number of lesions in a patient was limited to 1-2. No limit was placed on the size of the target lesions.

Table 1. Characteristics of HCC SBRT patients in this study.

Age (years)	71 (48-86)
Gender	
Male	42 (82%)
Female	9 (18%)
BCLC Staging	
A	30 (59%)
B	19 (37%)
C	2 (4%)
Tumour Volume (cc)	63.8 (12.8 - 390.1)
PTV margin from GTV (mm)	5.4 (5-10)
Number of lesions	1 - 2
Number of fractions	5
Prescription dose (Gy)	40.3 (27.5 - 50)
Tumour mean dose (Gy)	45.3 (28.6 - 59.1)
Biologically effective dose (BED) (Gy)	94.0 (46.3 - 131.8)

Median follow up (month)	10.4

Treatment Planning Techniques

The HCC SBRT were delivered using Truebeam (Varian Medical Systems, Palo Alto, USA) flattening filter free (FFF) mode via volumetric modulated arc therapy (VMAT). The diaphragm, lipiodol or fiducial markers were used as surrogates for the tumours. 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 (ITV) was generated as a union of Gross Tumor Volume (GTV) of all phases of four-dimensional computed tomography (4DCT). The Planning Target Volume (PTV) was generated by adding 5-10 mm margin to the ITV. The treatment plans were generated using Eclipse Treatment Planning System version 13.6 (Varian Medical Systems, Palo Alto, USA). Anisotropic Analytical Algorithm (AAA) 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 (Table 2) [14]. 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 organs dose constraints, following RTOG 1112, were listed in Table 3. Follow-up data typically included Computed Tomography/Magnetic Resonance (CT/MR) scan-based measurements of tumour size and measurements of a-fetoprotein (AFP) biomarkers. Local control was defined as less than 20 % increase in diameter of tumours [15]. An end point of 6-month was chosen for our dose response relation analysis in this study.

Table 2. The RTOG 1112 HCC SBRT dose prescription method.

Allowed Mean Liver Dose (MLD) in Gy	Planned Prescription Dose in Gy	If the maximum allowed mean liver dose (MLD) is exceeded at this planned dose
13	50	Reduce to 45 Gy and re-evaluate
15	45	Reduce to 40 Gy and re-evaluate
15	40	Reduce to 35 Gy and re-evaluate
15.5	35	Reduce to 30 Gy and re-evaluate
16	30	Reduce to 27.5 Gy and re-evaluate
17	27.5	Ineligible

121

122 **Table 3. The organs dose constraints.**

Organs at risk	Dose limit (Gy)
Liver	See Table 2
Spinal cord	$D_{0.5cc} < 25Gy$
Kidneys	$D_{mean} < 10Gy$
Heart	$D_{30cc} < 30Gy$
Great vessels	$D_{0.5cc} < 60Gy$

Skin	$D_{0.5cc}$ < 32Gy
Gallbladder	$D_{0.5cc}$ < 55Gy
Common bile duct	$D_{0.5cc}$ < 50Gy
Chest wall	$D_{0.5cc}$ < 50Gy
Stomach	$D_{0.5cc}$ < 30Gy, D_{5cc} < 25Gy
Duodenum	$D_{0.5cc}$ < 30Gy, D_{5cc} < 25Gy
Bowels	$D_{0.5cc}$ < 30Gy, D_{5cc} < 25Gy
Esophagus	$D_{0.5cc}$ < 32Gy

123

124 Statistical Analysis for Factors Affecting Tumor Local Control

125 Univariate analysis for local control was carried out using log-rank test. All factors having p values less than 0.1 were
126 subjected to multivariate analysis using Cox proportional hazards regression model with backward conditional stepwise
127 approach to find out the independent significant factors that affects the local control. The statistical analyses were
128 performed using SPSS Statistics version 17.0 (SPSS, Inc., Chicago, IL, USA). The analyses showed that tumour mean BED was
129 a prognostic factor of HCC SBRT tumour control.

130

Tumor Control Probability (TCP) Model

The dose volume histograms (DVH) of the HCC SBRT patients were extracted from the Eclipse version 13.6 (Varian Oncology systems, Palo Alto, CA). The physical dose was converted into biologically effective dose (BED) [16,17] with α/β ratio of 10 using the Eq. (1). The DVHs in BED were used to calculate the mean dose of the HCC tumours for the patients.

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

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 calculated tumour mean BED was then used for modeling of tumor control probability (TCP) using a logistic function [18,19] in Eq. (2),

$$\mathrm{p_i} = \mathrm{TCP_i} = \frac{1}{1+\left(\frac{\mathrm{D_{50}}}{\mathrm{D_i}}\right)^{\mathrm{k}}} \quad (2)$$

Where p_i was the tumour control probability (TCP) for patient i, D_{50} was the BED that led to 50% tumour control probability, D_i was the mean BED to the tumour of patient i and k was a parameter that controlled the slope of the TCP curve.

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

$$l = \sum_{\mathrm{i}} \log\left(\mathrm{p_i}^{\mathrm{R_i}}(1-\mathrm{p_i})^{(1-\mathrm{R_i})}\right) \quad (3)$$

148 Where p_i was the tumour control probability (TCP) for patient i, R_i was the control of tumour of patient i. If the tumuor had

149 no signs of progression within 6 months, then R_i was equal to 1. Otherwise, R_i was equal to 0.

150

151 Tumour volume was not included as an input parameter of our TCP model because the tumour dose prescription scheme

152 currently used in our institution was based on liver mean dose, which was related to tumour volume. Therefore, the tumour

153 mean BED and tumour volume were dependent on each other.

154

155 Normal Tissue Complication Probability (NTCP) Model

156 A complication of the liver was defined as RTOG Grade3 or higher radiation-induced liver disease (RILD) [20]. Due to the

157 limited number of RILD incidences in our institution to fit our own NTCP model, one of the most commonly used NTCP

158 model for liver, the Lyman Kutcher Burman (LKB) model fitted by Dawson et. al., was used in this study as shown in Eq. (4)

159 [20-22].

160 $$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx \quad (4)$$

161 Where

162 $$\mathrm{t} = \frac{\mathrm{D} - \mathrm{TD}_{50}(v)}{m \cdot \mathrm{TD}_{50}(v)} \quad (5)$$

163 $$\mathrm{TD}_{50}(v) = \mathrm{TD}_{50}(1) \cdot v^{-n} \quad (6)$$

164

An α/β ratio of 2.5 for normal tissue was used in BED calculation [22]. $\mathrm{TD}_{50}(1)$ was the tolerance dose for a homogeneous irradiation to an organ which would result in 50 % risk of complication, while $\mathrm{TD}_{50}(v)$ was the tolerance dose of a homogeneous irradiation to a partial volume *v* of an organ. $\mathrm{TD}_{50}(1)$, n and m were 39.8, 0.97 and 0.12 respectively in the study by Dawson et. al. [20]. This model was used to calculate the NTCP in this study.

Uncomplicated Tumor Control Probability (UTCP) Model

Uncomplicated tumour control probability (UTCP) is one of the most common measure of therapeutic gain [10,11,25,26]. It was defined as:

$$\mathrm{UTCP} = \mathrm{TCP} \cdot (1 - \mathrm{NTCP}) \tag{7}$$

The fitted TCP model of our institution and the NTCP model based on Dawson et. al. would be used to form a UTCP model for evaluation of treatment outcome. The variation of the treatment outcome with tumour mean BED, as well as with the ratio between tumour mean BED and normal liver mean BED (T/N BED ratio) were analysed. The T/N BED ratio was defined as:

$$\mathrm{T/N\ BED\ ratio} = \frac{\mathrm{Tumour\ mean\ BED\ (Gy)}}{\mathrm{Normal\ Liver\ mean\ BED\ (Gy)}} \tag{8}$$

A similar concept had been used to describe uptake of radiopharmaceutical in liver [12,13]. However, BED dose ratio was used instead of radiopharmaceutical uptake ratio in this study. The value of this BED dose ratio depends on the size the tumour and its location inside the liver as demonstrated in Fig 1. For example, a small planning target volume (PTV) located at the peripheral of the liver will lead to a lower normal liver mean BED and a higher T/N BED ratio resulting in a higher

183 UTCP, while a large PTV near the center of the liver will lead to a higher normal liver mean BED and a lower T/N BED ratio

184 resulting in a lower UTCP.

185

186 **Fig 1. Effect of PTV size and location on liver mean dose.** (a) For the same PTV mean dose, the normal liver mean dose

187 should be smaller if the PTV volume is smaller (the case on the right hand side). (b) For the same PTV mean dose, the normal

188 liver mean dose should be smaller if the PTV was located at a more peripheral region (the case on the right hand side).

189

190 Uncomplicated Tumour Control Efficiency (UTCE)

191 To facilitate the analysis of the UTCP of current dose prescription scheme, a new concept of Uncomplicated Tumour Control

192 Efficiency (UTCE) was introduced:

193 $$\mathrm{UTCE} = \frac{\mathrm{UTCP}}{\mathrm{Max\ UTCP\ achievable}} \quad (9)$$

194 The value of UTCE had to be between 0 and 1. A UTCE value of 1 implied that the theoretical maximum UTCP of the

195 corresponding T/N BED ratio was achieved.

196

197 Results

198 TCP model

199 The fitted TCP model using local clinical data was shown in Fig 2. The bins have different number of patients.

Bin1 (>110 Gy_{BED}): 19 patients

Bin2 (85 – 110 Gy_{BED}): 11 patients

Bin3 (70 – 85 Gy_{BED}): 11 patients

Bin4 (<70 Gy_{BED}): 10 patients

The error bars represent 2 standard deviation of the distribution of the BED with respect to the mean BED of the bin. The fitted value of D_{50} was found to be 72.3 Gy_{BED} with the 95% confidence interval between 59.6Gy_{BED} and 86.7Gy_{BED}. The fitted k value was found to be 3.46 with the 95% confidence interval between 1.63 and 5.70. Lausch et. al. reported a 2Gy Equivalent D_{50} of 53Gy (63.6Gy_{BED}) for a 6-month TCP model [7]. Jang et. al. reported a 3-fraction D_{50} of 34.9Gy (75.5Gy_{BED}) for a 2-year TCP model [8]. Our result representing a 5-fraction D_{50} was found to be more comparable to the one reported for the 3-fraction D_{50} studies.

Fig 2. TCP model of HCC SBRT fitted with local clinical data.

UTCP model

A UTCP Model of HCC SBRT was formed by combining TCP Model fitted based on local clinical data and NTCP model of Dawson et al for different tumor mean BED to normal liver mean BED ratio (T/N BED ratio) in Fig 3. The optimal tumour mean BED and the theoretical achievable maximum UTCP value with T/N BED ratio were shown in Fig 4 and Fig 5 respectively.

It was observed that the values of the optimal tumour mean BED increased almost linearly with the T/N BED ratio in Fig 4. From Fig 5, it was shown that the higher the T/N BED ratio, the higher the maximum UTCP could be achieved with an optimal tumour mean BED. The maximum UTCP was close to 1 when T/N BED ratio was 5, compared to 0.24 when T/N BED ratio was 1.

Fig 3. UTCP model of HCC SBRT formed by combining the TCP model of local clinical data and the NTCP model of Dawson et al.

Fig 4. Tumor mean BED to achieve maximum UTCP versus T/N BED ratio.

Fig 5. Maximum UTCP achievable versus T/N BED ratio.

The tumour mean BED of the patients who were prescribed according to RTOG 1112 mean liver dose prescription method (Table 2) [14] were compared to the optimal tumour mean BED to achieve maximum UTCP (Fig 6). For T/N BED ratio less than 2.9, the actual tumour mean BED correlated the optimal tumour mean BED with Pearson correlation coefficient of 0.962. When the T/N BED ratio approached 2.9, the prescription dose reached the highest level by following the RTOG 1112 method. As a result, the tumour mean BED did not increase anymore with further increase in T/N BED ratio greater than 2.9, indicating that the actual given mean doses to the tumour were lower than the optimum values. Fig 7 illustrated the comparison between the UTCP of the patients with the maximum UTCP achievable. It can be observed that the estimated UTCP of the patients were in general lower than the maximum achievable values especially when T/N BED ratios greater

than 2.9. Fig 8 showed the plot of UTCE versus T/N BED ratio for the HCC SBRT cases in our institution, where the average UTCE was 0.90±0.08. This implied that there was a potential to improve the treatment outcome for this group of patients by further increasing the prescription dose such that the UTCE could be closer to one.

Fig 6. Tumor mean BED versus T/N BED ratio for HCC SBRT local cases.

Fig 7. UTCP versus T/N BED ratio for HCC SBRT local cases.

Fig 8. UTCE versus T/N BED ratio for HCC SBRT local cases.

Discussion

A likely reason that the HyTEC Liver TCP paper [9] did not find evidence of dose-response relationship for primary liver tumour might be the incomplete reporting of results in the published literature to enable data pooling, as emphasized in the lessons of QUANTEC [23,24]. In particular, there were not many reported prescriptions substantially below $100Gy_{BED}$, and very few of them were as low as $60Gy_{BED}$ like we had (Fig 2). The tumour mean dose and tumour control outcome per patient, as well as mean liver dose and liver toxicity outcome per patient in this study were shown in S1 Table in an additional file.

UTCP had been used in other investigations together with parameters such as quality adjusted life years (QALY) to predict

the overall outcome of the different treatment plans [25]. It had been applied to other SBRT evaluations such as non-small cell lung cancer [26]. 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.

Current dose prescription protocol based on RTOG1112 were evaluated using the UTCP model built from local clinical cases with the NTCP model proposed by Dawson et al to assess if maximum theoretical UTCP had been achieved and if there were any room for dose escalation. For cases with T/N BED ratio greater than 2.9, most of the cases already reached the highest level of dose prescription following the RTOG 1112 scheme (100Gy_{BED} corresponding to 50 Gy physical dose). Therefore, there was no more increase in the tumour mean BED with further increase in the T/N BED ratio above the value of 2.9 in Fig 6. The prescription BED seemed to be far below the values to achieve optimal UTCP.

In order to achieve higher UTCP values, the prescription dose was increased using a new dose prescription scheme in Table 4. For T/N BED ratio between 2.1 and 3.7, the prescription dose was the optimal dose to achieve maximum UTCP (Fig 4). For T/N BED ratio less than 2.1, the optimal dose that achieved maximum UTCP would lead to NTCP greater than 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 T/N BED ratio less than 2.1 (Fig 9). For T/N BED ratio larger than 3.7, a maximum dose was also set at 170 Gy_{BED} (corresponding to about 70 Gy physical dose) such that it resulted in at least 95% TCP. The TCP curve entered a relatively flat region for dose larger than 170 Gy_{BED} and the increase in TCP is less than 0.1% per Gy_{BED}.

Table 4. Proposed HCC SBRT dose prescription method

T/N BED Ratio	Prescription Dose (Gy_{BED})
< 2.1	Max dose such that NTCP = 5%
2.1 – 3.7	Dose to achieve optimal UTCP (Fig 4)
> 3.7	170 Gy_{BED}

*Remarks: Dose should be reduced if dose limits of organs at risk were exceeded

Fig 9. NTCP versus T/N BED ratio using the new prescription dose scheme.

The new prescribed doses of 51 patients following the rules in Table 4 were compared with the original dose scheme under RTOG1112. It was found that the increase in tumour mean BED ranged from 1% to 44%. In general, higher T/N BED ratio resulted in a higher percentage increase of tumour mean BED (Fig 10). It was because the cases with low T/N BED ratio usually had higher normal liver mean BED, limiting the potential to increase dose prescription. Also, the higher T/N BED ratio cases were originally limited by the RTOG 1112 highest dose prescription level of 50Gy, which was far from the optimal prescription dose to achieve theoretical maximum UTCP. With the new prescription dose scheme, the prescription dose could be increased up to 70 Gy (corresponding to 170 Gy_{BED}).

Fig 10. Percentage increase in tumor mean BED using the new dose prescription scheme.

Interestingly, the percentage increase in TCP versus T/N BED ratio (range from 1% to 54%) in Fig 11 showed a different pattern when compared with the percentage increase in tumor mean BED versus T/N BED ratio in Fig 10 under the new dose prescription scheme. The lower T/N BED ratio resulted in a higher percentage increase in TCP (Fig 11). It was because the dose prescriptions were generally low for low T/N BED ratio cases due to limitation by normal liver mean BED. The TCP curve was steep at low dose range in Fig 2 and therefore a relatively small increase in tumour BED could lead to a large increase in TCP. Finally, the UTCE of the cases using the new scheme was calculated and shown in Fig 12. The results were very close to one except those with T/N BED less than 2.1 due to the limit of 5% NTCP under the new dose prescription scheme (Fig 9). The average UTCE of the 51 cases using the new dose scheme was boosted up to 0.99±0.03, comparing to 0.90±0.08 of the RTOG 1112 dose prescription scheme.

Fig 11. Percentage increase in TCP using the new dose prescription scheme.

Fig 12. UTCE versus T/N BED ratio using the new prescription dose scheme.

Limitations

The TCP model used to combine with NTCP model for UTCP model generation in this study was based on local clinical data

of 51 cases with less than 1-year median follow-up time, targeting for an end point of 6-month local control only. Local control for 1 year or more could be achieved if more clinical data with longer follow-up time was available. This could improve the credibility of the model and enrich our understanding on the clinical outcome of HCC SBRT.

In addition, NTCP of organs at risk (OAR) other than normal liver was not included in deriving the UTCP model in this study. A more comprehensive UTCP model could be developed to include the NTCP of other OARs in future study. Also, the effect of patient movement and setup error was not considered in this study. In addition, Dawson's NTCP data which was used in present study, was derived from another patient cohort. The NTCP predicted may or may not be entirely homogenous with our own patient cohort. Further clinical study would be required to verify this in the future.

Conclusion

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 for the targeted T/N BED ratios. It was suggested that there could be a potential to increase the current planned 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.

List of Abbreviations

4DCT: Four-dimensional computed tomography

AAA: Anisotropic analytical algorithm

BCLC: Barcelona Clinic Liver Cancer

BED: Biologically effective dose

CT: Computed tomography

DVH: Dose volume histogram

FFF: Flattening filter free

GTV: Gross tumor volume

HCC: Hepatocellular Carcinoma

ITV: Internal target volume

LKB: Lyman-Kutcher-Burman

MR: Magnetic Resonance

NTCP: Normal tissue complication probability

PTV: Planning target volume

RILD: Radiation-induced liver damage

RTOG: Radiation Therapy Oncology Group

SBRT: Stereotactic body radiotherapy

TCP: Tumor control probability

TD: Tolerance dose

T/N: Tumour to normal tissue

UTCE: uncomplicated tumor control efficiency

UTCP: uncomplicated tumor control probability

References

1. Yang JD, Hainaut P, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16(10):589-604.
2. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e447–53.
3. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26: 657–64.
4. Huang WY, Jen YM, Lee MS, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2012; 84:355–61.

5. Price TR, Perkins SM, Sandrasegaran K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. Cancer 2012;118:3191–8.

6. Park HC, Seong J, Han KH, et al. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2002; 54:150–5.

7. Lausch A, Sinclair K, Lock M, et al. Determination and comparison of radiotherapy dose responses for hepatocellular carcinoma and metastatic colorectal liver tumours. Br J Radiol. 2013; 86:20130147.

8. Jang WI, Kim MS, Bae SH, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. Radiat Oncol 2013; 8:250.

9. Ohri N, Tomé W, Méndez Romero A, et al. Local Control After Stereotactic Body Radiation Therapy for Liver Tumors, Int J Radiat Oncol Biol Phys 2018; S0360-3016(17)34525-X.

10. Holthusen H. Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen and deren Nutzanwendung zur Verhütung von Schäden [Experiences on the tolerability limit for X-rays and practical application for the prevention of damage]. Strahlentherapie. 1936;57:254–269.

11. Agren A, Brahme A, Turesson I. Optimization of uncomplicated control for head and neck tumors. Int J Radiat Oncol Biol Phys. 1990;19(4):1077–85.

12. Lau WY, Leung TW, Ho S, et al. Diagnostic pharmaco-scintigraphy with hepatic intra-arterial technetium-99m macroaggregated albumin in the determination of tumour to non-tumour uptake ratio in hepatocellular carcinoma. Br J Radiol 1994; 67:136–139.

13. Ho S, Lau WY, Leung TW, et al. Tumour-to-normal uptake ratio of 90Y microspheres in hepatic cancer assessed with 99Tcm macroaggregated albumin. Br J Radiol. 1997;70(836):823-828.

14. Clinicaltrials.gov identifier NCT01730937. Accessed July 17, 2020.

15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

16. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989; 62:679–94.

17. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21:109–122.

18. Goiten M, Schultheiss TE. Strategies for treating possible tumor extension: some theoretical considerations. Int J Radiat Oncol Biol Phys 1985; 11:1519–28.

19. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer 2011; 117:4060–9.

20. Dawson LA, Normolle D, Balter JM, et al. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002; 53:810–821.

21. Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl 1985; 8:S13–S19.

22. Dawson LA, Eccles C, Craig T. Individualized Image Guided Iso-NTCP based Liver Cancer SBRT. Acta Oncol 2006; 45:856–864.

23. Deasy JO, Bentzen SM, Jackson A, et al. Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S151-4.

24. Jackson A, Marks LB, Bentzen SM, et al. The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S155-60.

25. Chaikh A, Docquière N, Bondiau PY, et al. Impact of dose calculation models on radiotherapy outcomes and quality adjusted life years for lung cancer treatment: do we need to measure radiotherapy outcomes to tune the radiobiological parameters of a normal tissue complication probability model? Transl Lung Cancer Res. 2016;5(6):673-680.

26. Lu JY, Lin PX, Huang BT. Calculating the individualized fraction regime in stereotactic body radiotherapy for non-small cell lung cancer based on uncomplicated tumor control probability function. Radiat Oncol. 2019;14(1):111.

Additional Files

Filename: Additional File 1.docx

File format: Microsoft Word (.docx)

Title: S1 Table

Description: GTV mean BED, control outcome, liver-GTV mean BED and toxicity outcome per patient. (1=yes, 0 = no)

Figures

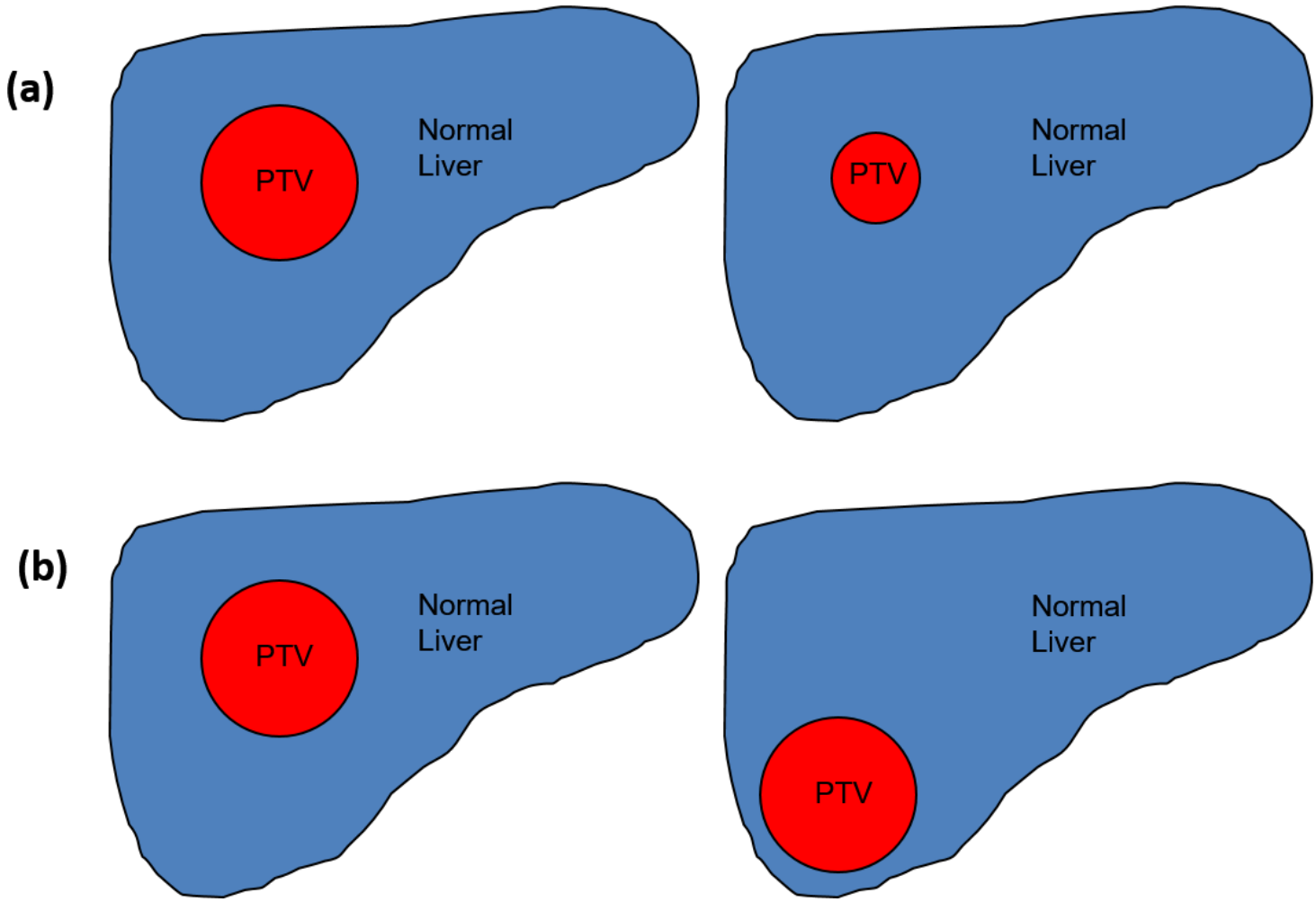

Figure 1

Effect of PTV size and location on liver mean dose. (a) For the same PTV mean dose, the normal liver mean dose should be smaller if the PTV volume is smaller (the case on the right hand side). (b) For the same PTV mean dose, the normal liver mean dose should be smaller if the PTV was located at a more peripheral region (the case on the right hand side).

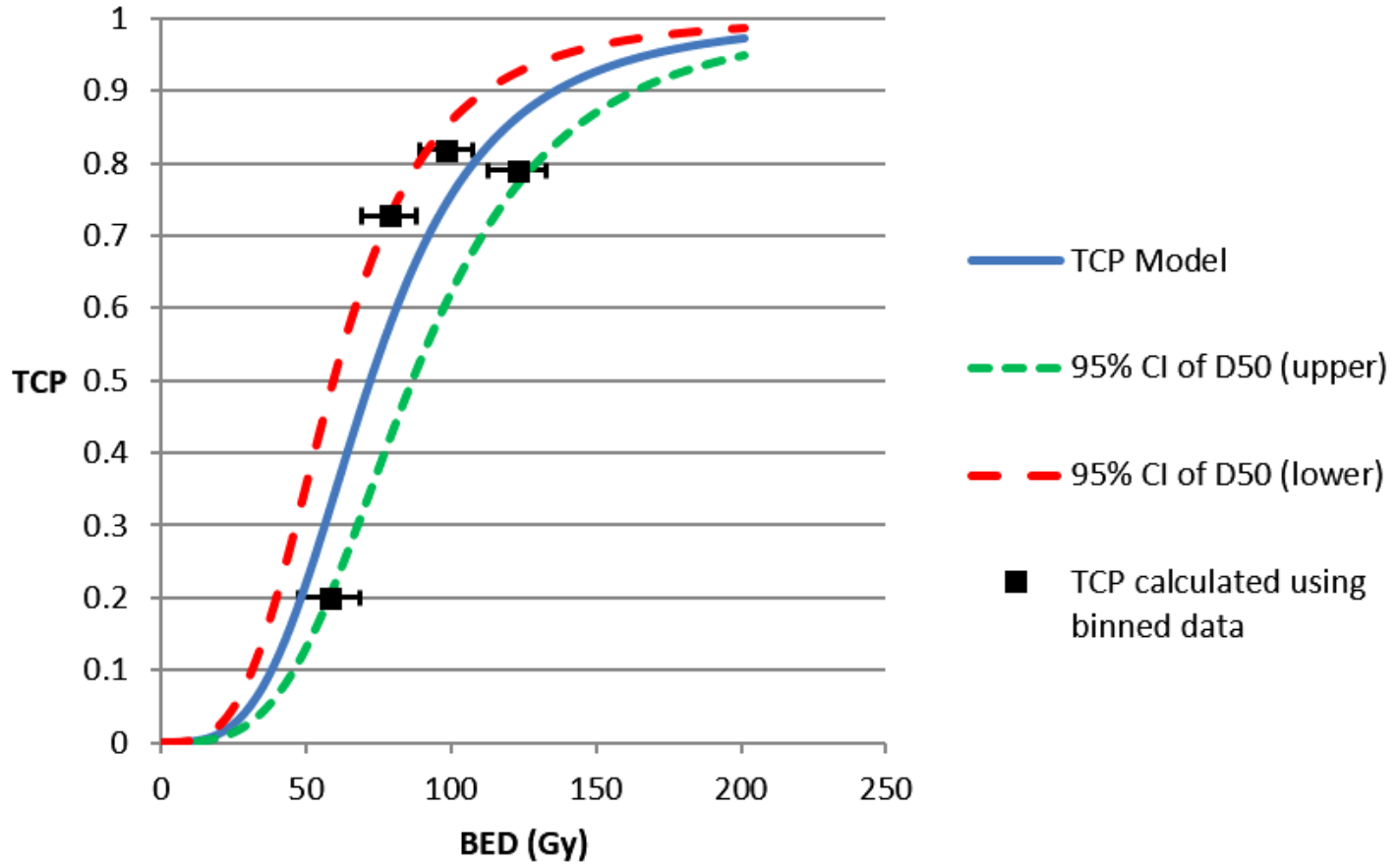

Figure 2

TCP model of HCC SBRT fitted with local clinical data.

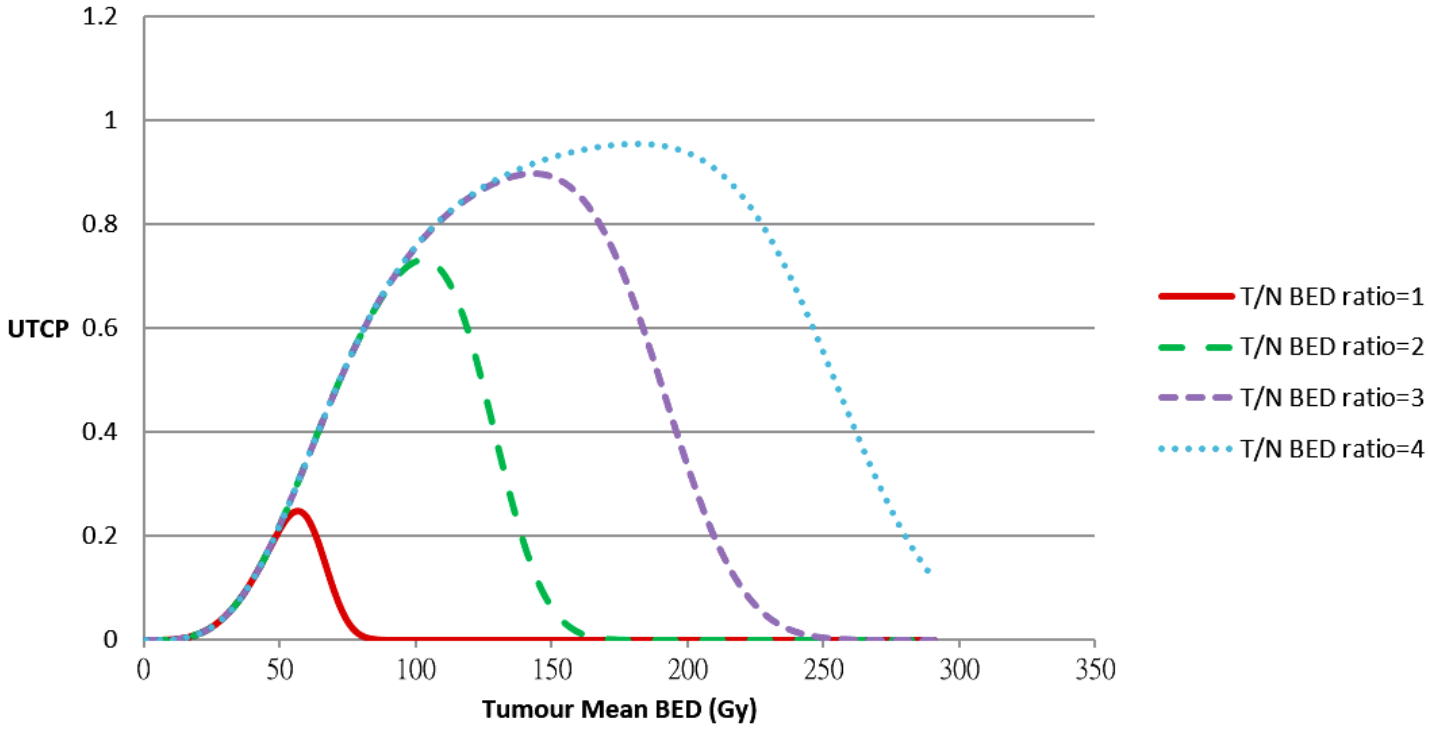

Figure 3

UTCP model of HCC SBRT formed by combining the TCP model of local clinical data and the NTCP model of Dawson et al.

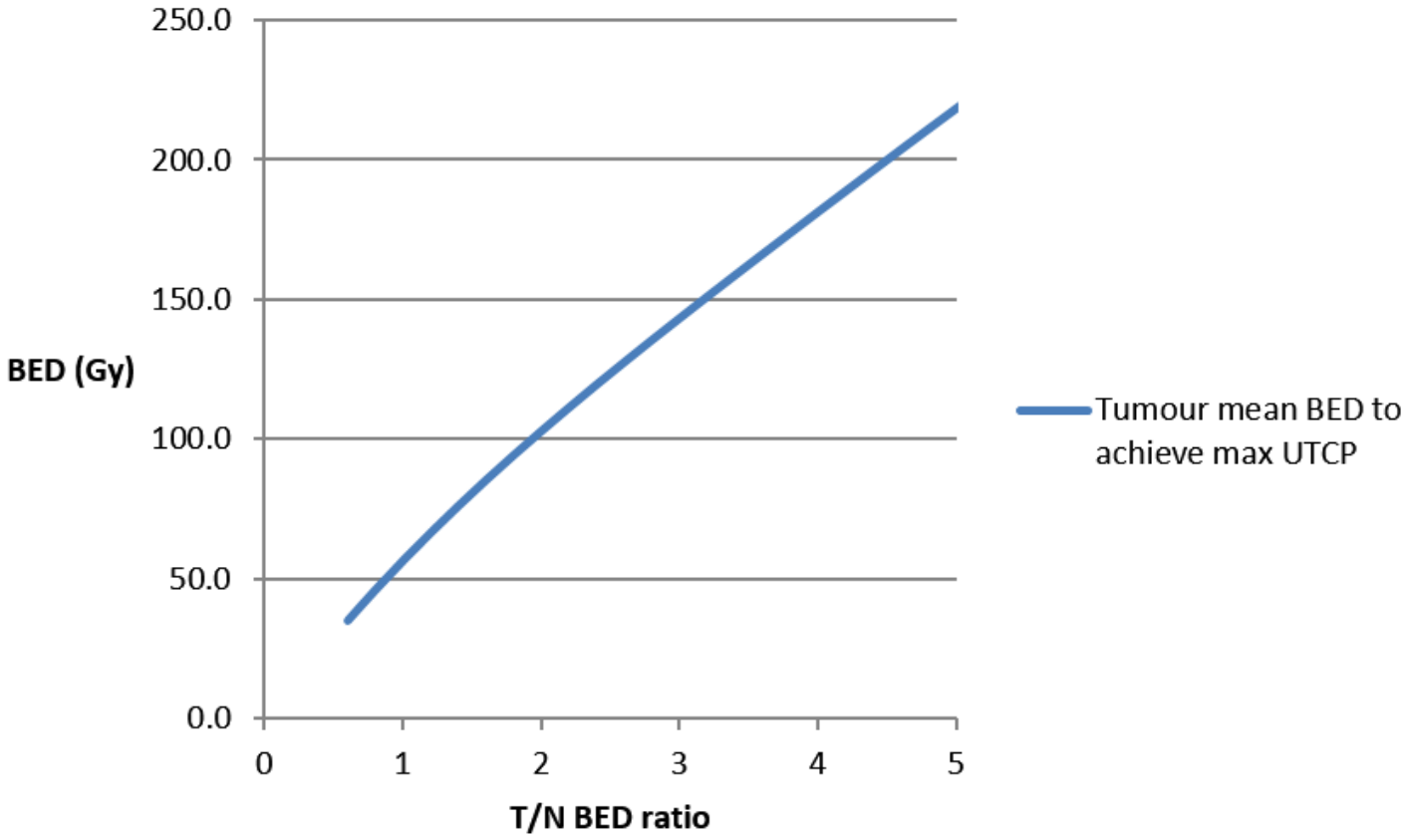

Figure 4

Tumor mean BED to achieve maximum UTCP versus T/N BED ratio.

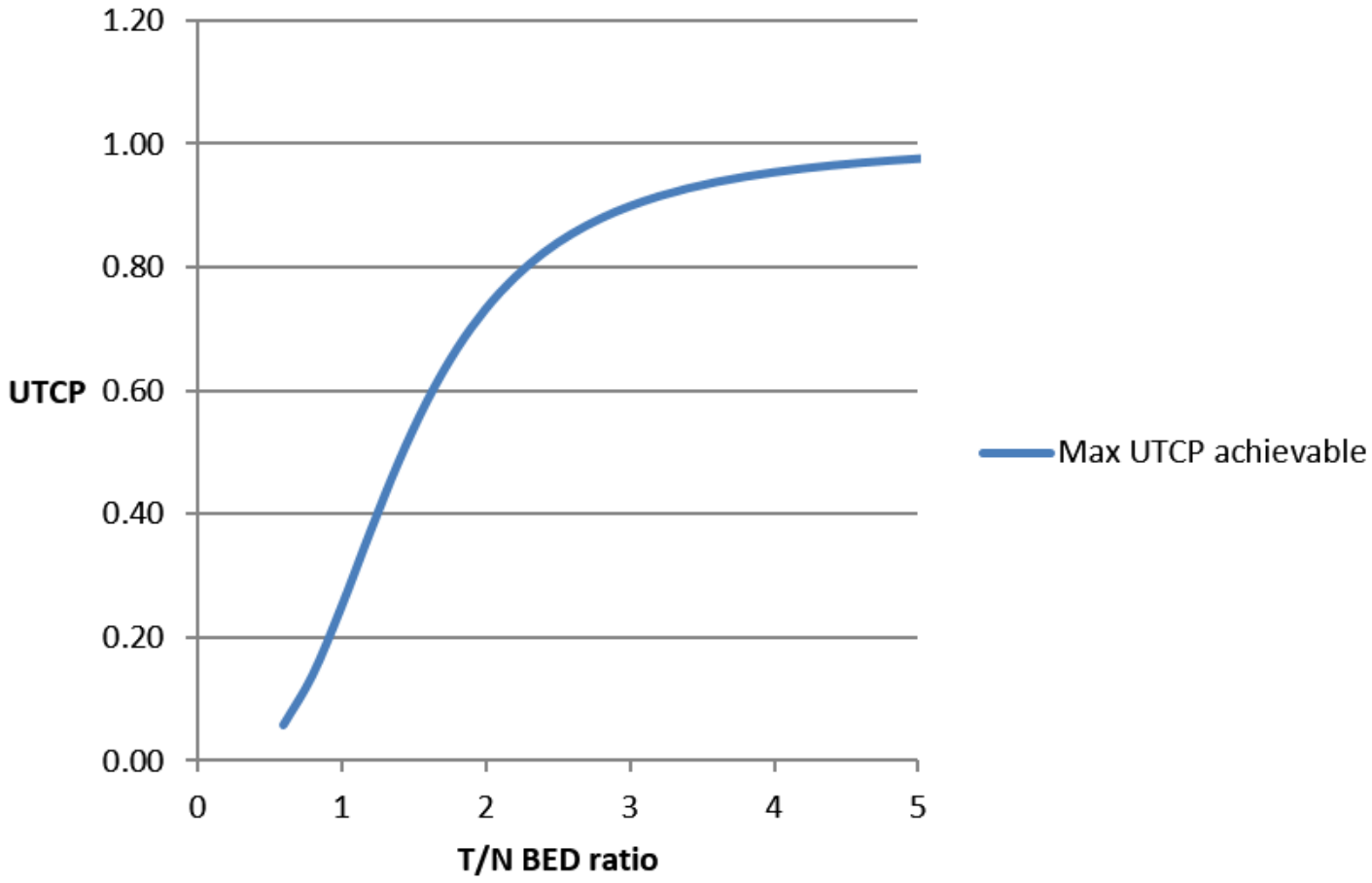

Figure 5

Maximum UTCP achievable versus T/N BED ratio.

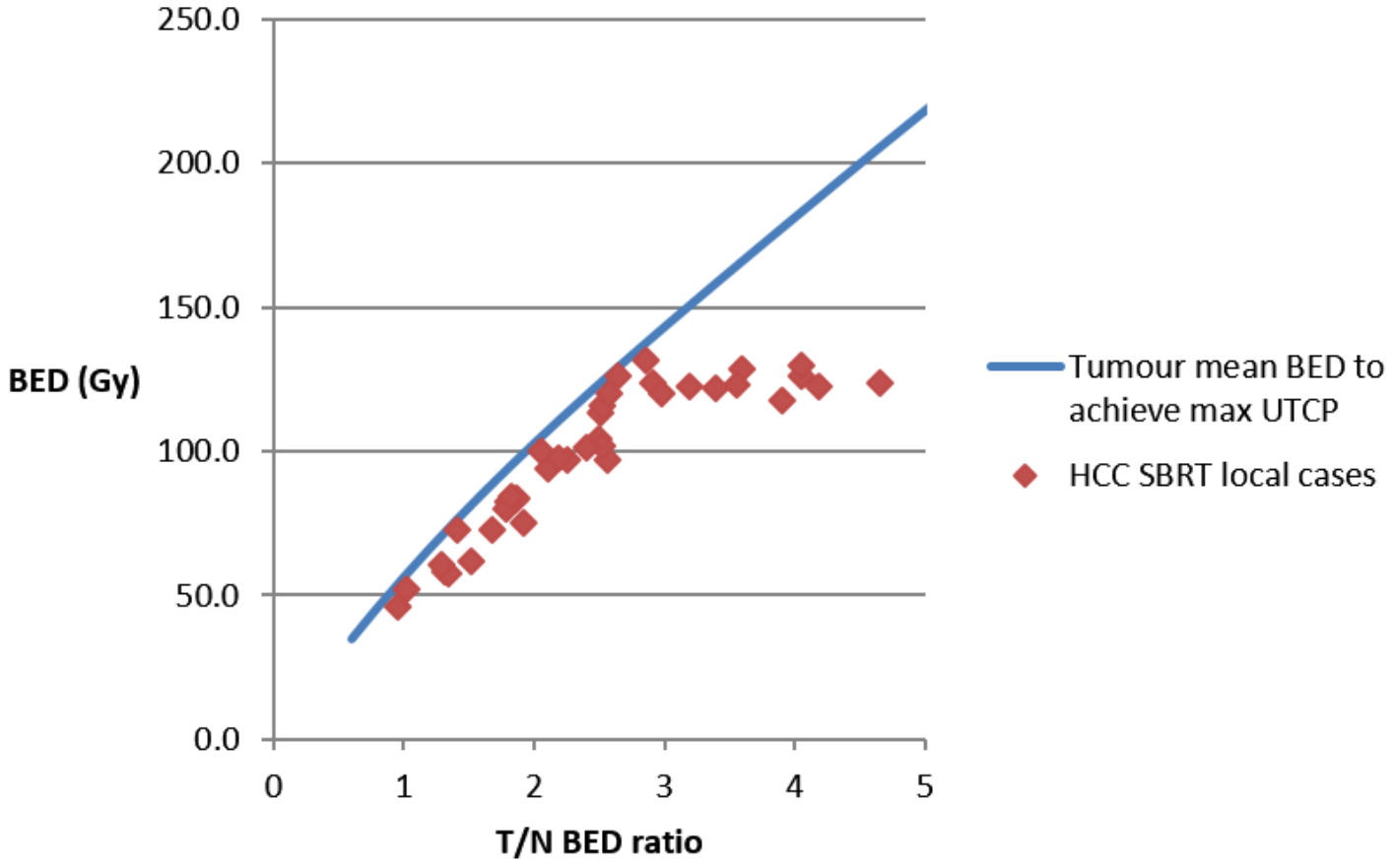

Figure 6

Tumor mean BED versus T/N BED ratio for HCC SBRT local cases.

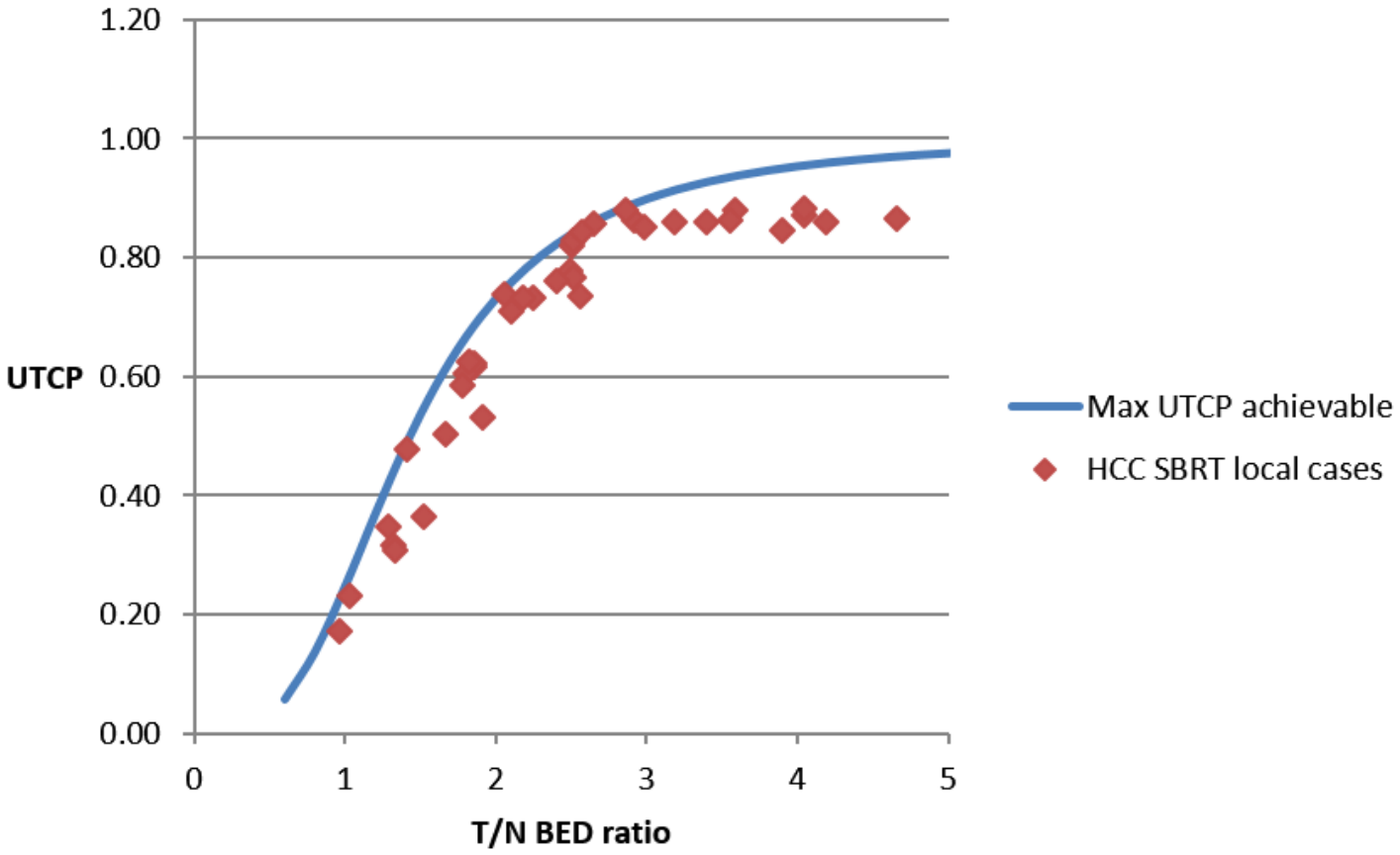

Figure 7

UTCP versus T/N BED ratio for HCC SBRT local cases.

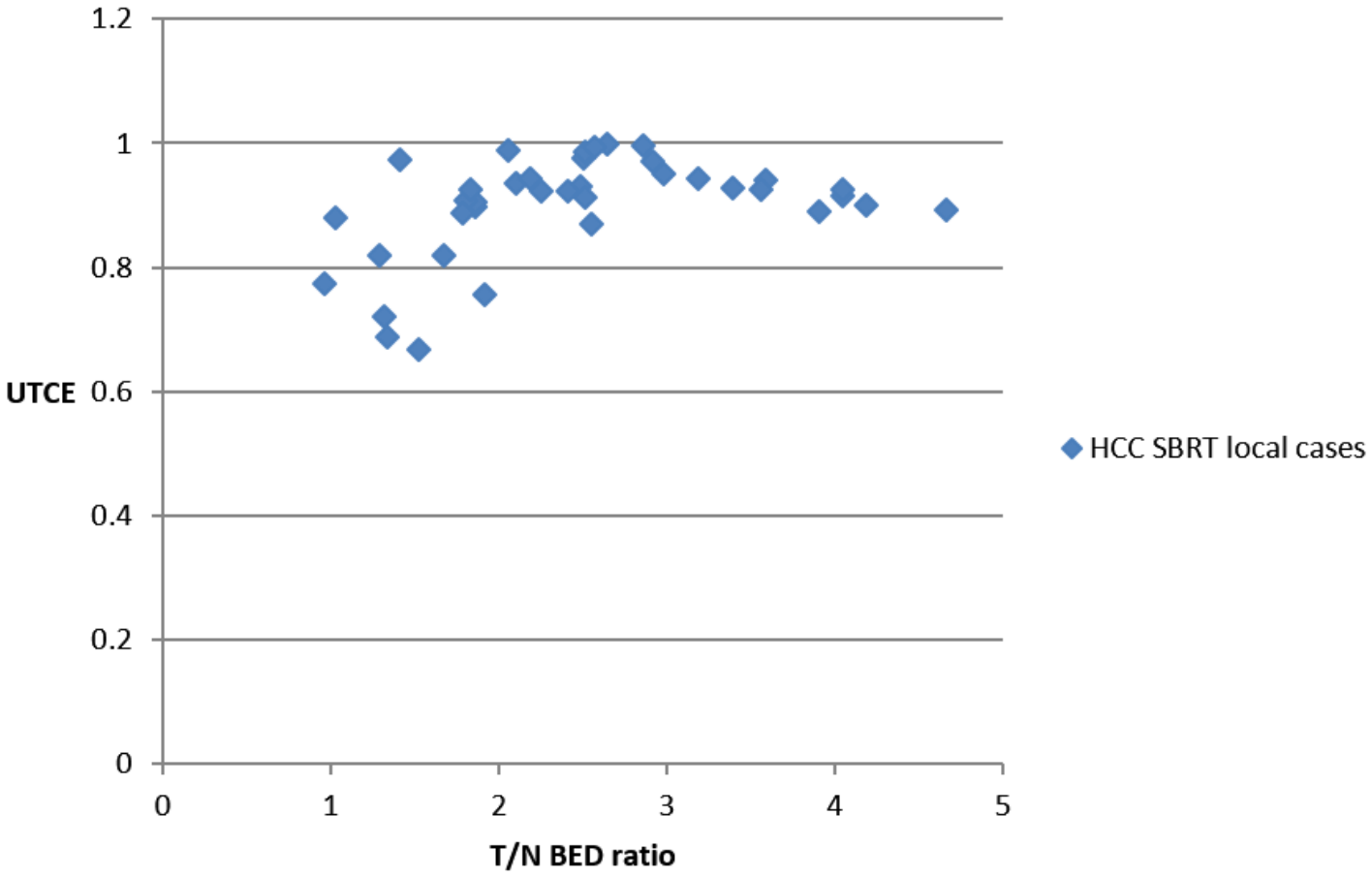

Figure 8

UTCE versus T/N BED ratio for HCC SBRT local cases.

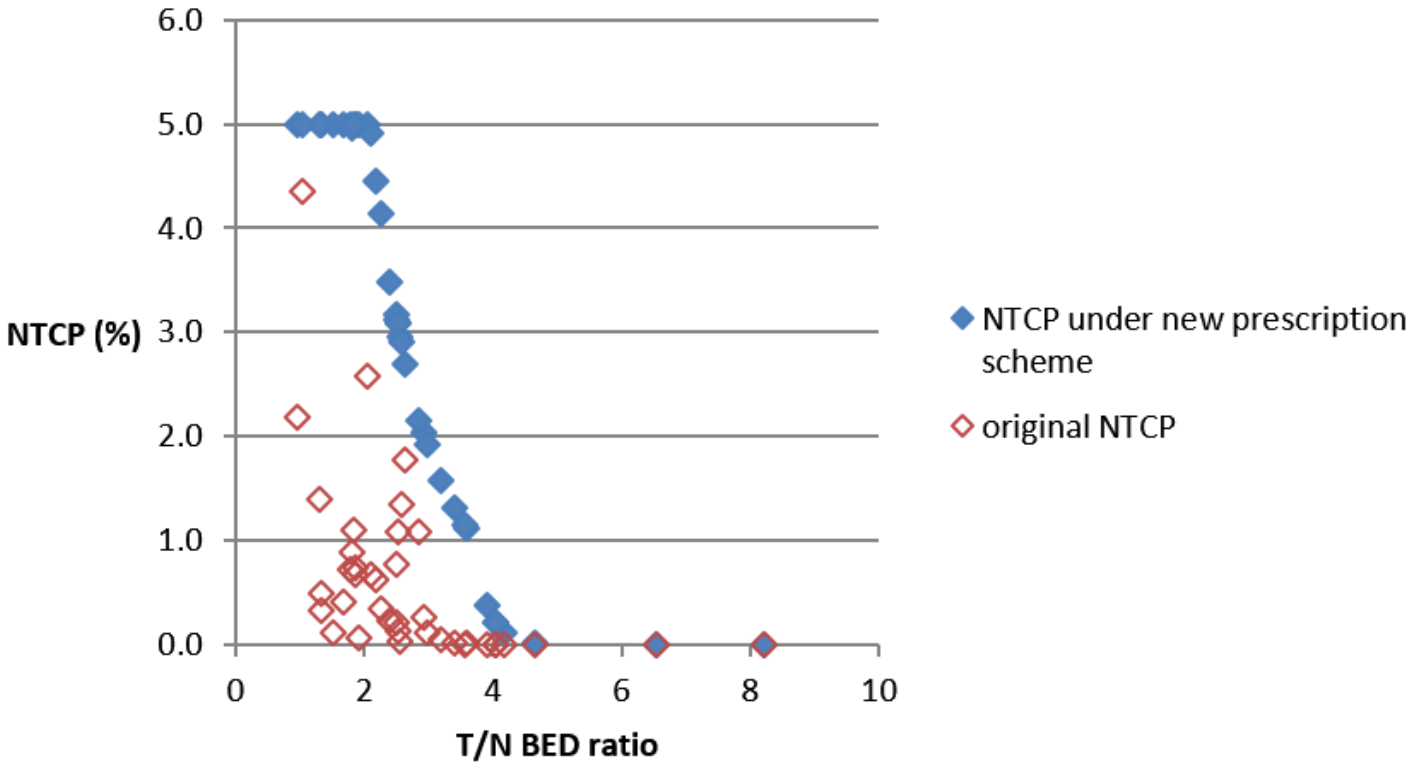

Figure 9

NTCP versus T/N BED ratio using the new prescription dose scheme.

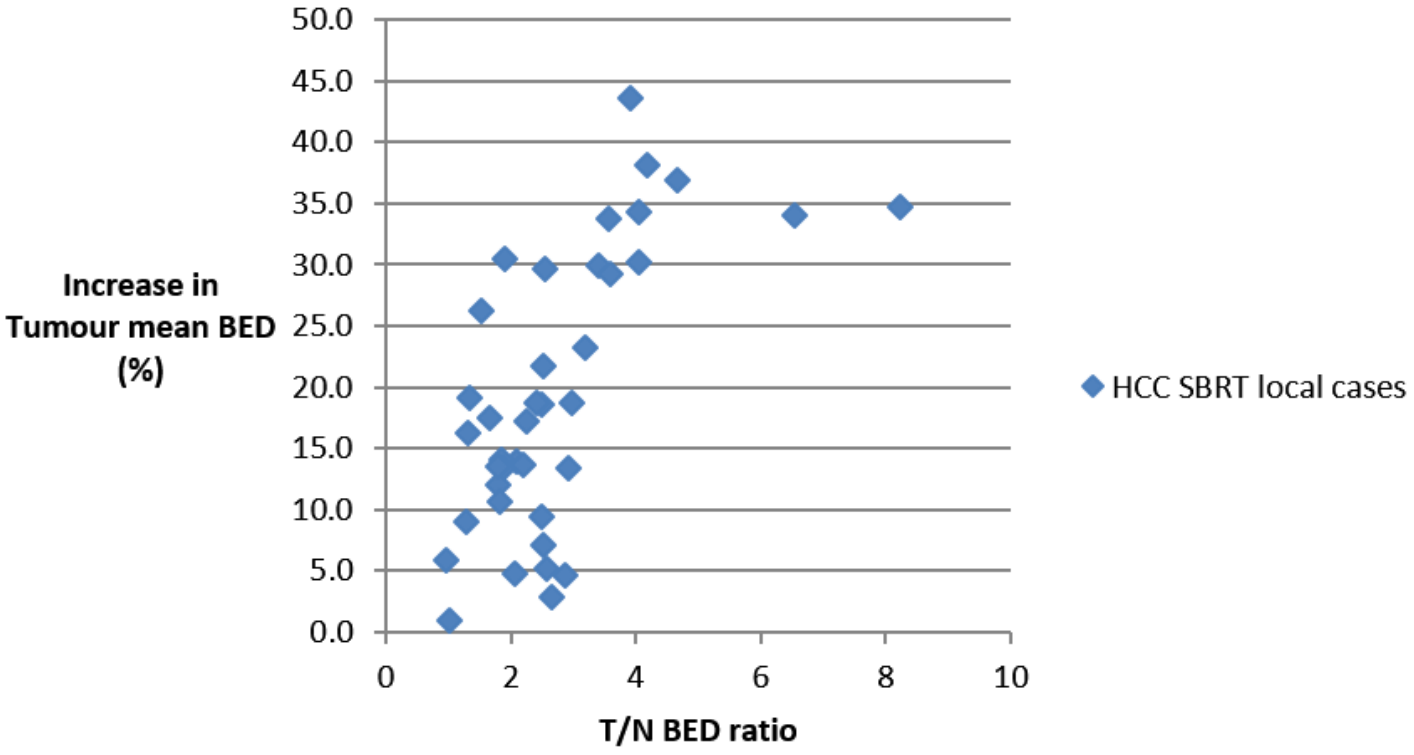

Figure 10

Percentage increase in tumor mean BED using the new dose prescription scheme.

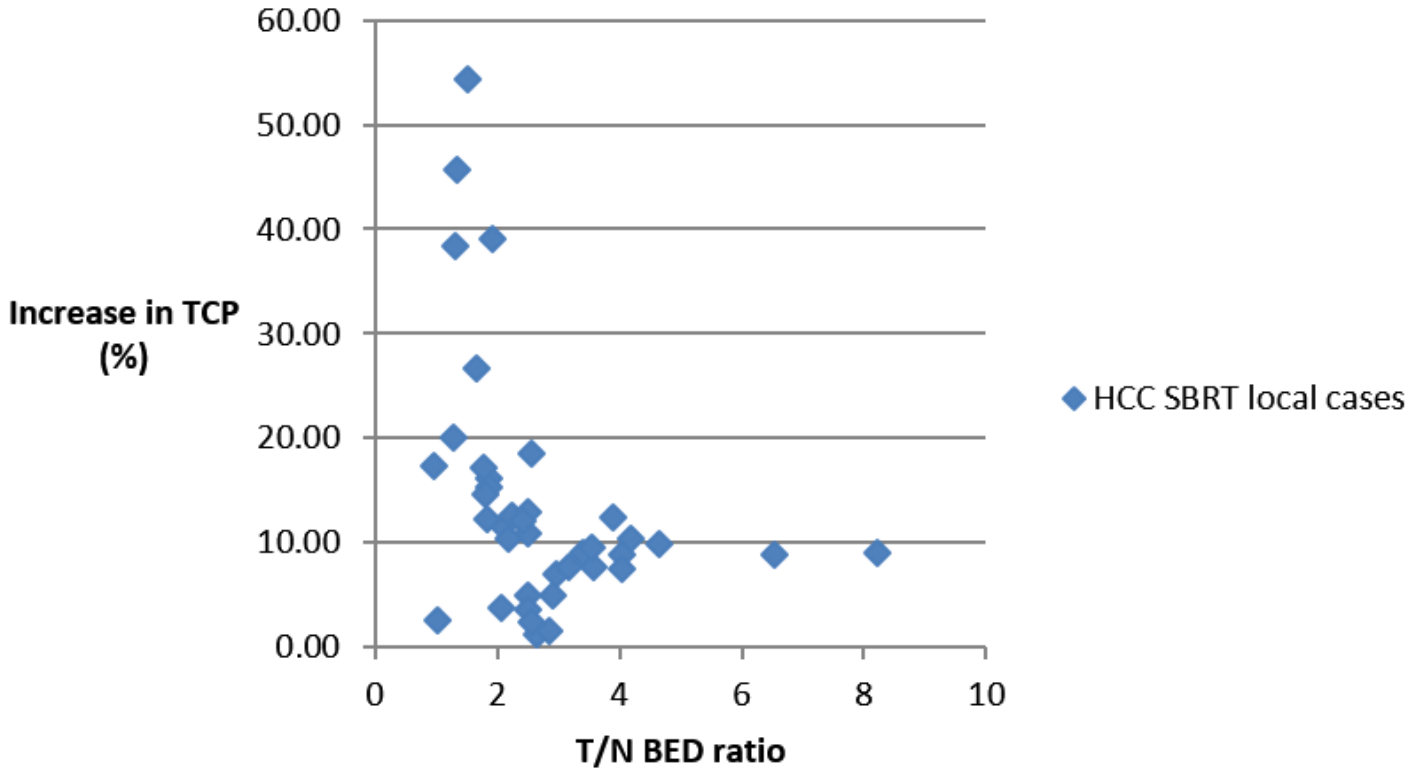

Figure 11

Percentage increase in TCP using the new dose prescription scheme.

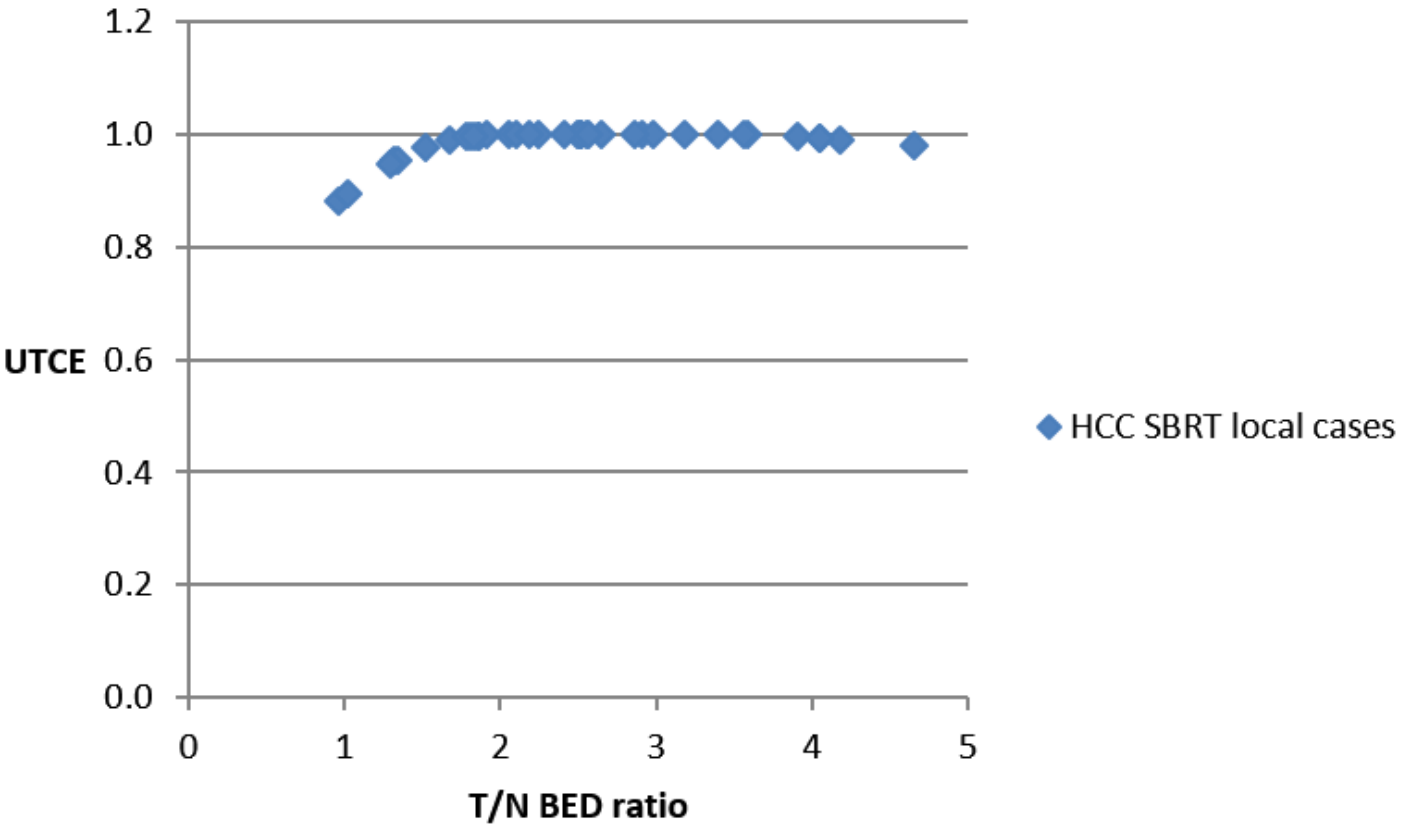

Figure 12

UTCE versus T/N BED ratio using the new prescription dose scheme.

Supplementary Files

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