Successful treatment of primary renal lymphoma using image guided helical tomotherapy

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Purpose: *To describe a clinical pilot case of renal lymphoma successfully treated using helical tomotherapy, and to evaluate alternative hypofractionated treatment schedules and their potential applicability to future cases of renal cell carcinoma (RCC).*

Patients and methods: *An 82-year-old female patient with a large right perinephric mass encircling the lower pole of the right kidney was treated on the Hi-ART unit (TomoTherapy Inc. Madison, WI, USA) with daily pretreatment megavoltage CT imaging. Gross tumor volumes (GTVs) were outlined on every MVCT study. The Planned Adaptive software was used for calculation of dosimetric parameters for both the target and organs at risk (OARs). In response to observed GTV regression, a hypothetical anatomy changes adjusted plan was generated and analyzed. Six alternative treatment schedules were investigated: 48 Gy in 4 and 3 fractions, and 60 Gy in 30, 5, 4 and 3 fractions, as possible clinical scenarios for RCC. Normal tissue complication probability (NTCP) and tumor control probability (TCP) values were estimated for each scenario in the study.*

Results: *During 30 days, the GTV was reduced by 50.6%. The smaller GTV and the reduced planning target volume (PTV) margins from 15 mm to 10 mm after 12 fractions would allow for a decrease of the planned mean liver and spinal cord dose by 3.8 Gy and 4 Gy, respectively. Improvements to portions of the colon include a 3.3 Gy and 9.2 Gy reduction in planned mean dose to the descending and ascending colons, respectively. NTCP and TCP estimates have shown that hypofractionated treatment schedules provide a much higher probability of local control, but the risk of tissue complication rises simultaneously. For this particular case, hypofractionation would not be suitable due to the potential adverse affects brought on to the liver.*

Conclusions: *Caution should be observed in high dose hypofractionated radiotherapy in right sided, whole kidney carcinoma due to increased risk of liver complication. The accelerated treatment may however be justified by the significantly higher TCP rates for left sided kidney cases. Further investigation of small renal tumors is needed to evaluate control rates, vasculopathy, and residual normal function.*

Key Words: helical tomotherapy, renal lymphoma, adaptive radiotherapy

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Introduction

Renal involvement in patients suffering from lymphoma is commonly detected using computed tomography (CT) scanning.[1] The clinical existence of primary renal lymphoma has been disputed due to the absence of lymphatic tissue in the kidneys.[2-4] Despite this fact, primary renal lymphoma must be considered when dealing with unexplained kidney masses and

symptoms.[1] Renal cell carcinoma (RCC) is a much more common disease afflicting the kidney. Although it has been traditionally considered a radioresistant carcinoma and has been historically treated using surgery, external radiation modalities such as high dose per fraction, conformal and stereotactic radiotherapy have been used as alternative or preoperative treatment options in recent years.[5-7] To our knowledge no cases of renal lymphoma or RCC have been reported using helical tomotherapy (HT) (TomoTherapy, Inc., Madison, WI).

HT is composed of a 6 MV linear accelerator mounted on a ring gantry, which rotates around a continuously translating patient. This configuration allows beams to enter the body from many angles, enabling precise targeting of tumors and improved avoidance of healthy tissue.[8] Beam intensity is dynamically modulated by a 64 leaf binary collimator. In addition to delivering highly conformal radiation dose distributions, HT unit is equipped with xenon detectors designed to obtain megavoltage computed tomography (MVCT) image studies of the patient prior to treatment.[8] Radiation therapists coregister these MVCT scans with a planning stage kilovoltage CT (kVCT) study in order to position the patient correctly thereby minimizing setup error. Pretreatment MVCT imaging provides enough soft tissue contrast to reliably delineate organs and lesions, enabling clinicians to monitor interfraction variations in patient anatomy. This type of image guidance becomes especially crucial when treating sites where interfractional motion is common and critical organs are in close vicinity.

Planned Adaptive software (TomoTherapy, Inc., Madison, WI) provides a possibility to verify the radiation delivery for any given treatment fraction. The program calculates dose distribution using the fluence sinogram and MVCT study and compares it with the planned one. Setup errors and anatomy changes lead to discrepancies in the delivered dose distribution over the course of treatment. If significant variations exist between the planned and verified dose distributions, an adaptive plan may be created in order to make corrections. Plan adaptation is accomplished by manually adjusting the contours to reflect the observed anatomy on the MVCT study followed by optimization of planned dose distribution.

Tumor response has reportedly varied in the case of RCC undergoing radiotherapy with different fractionation schemes. Wersäll et al retrospectively evaluated 58 patients with RCC (primary tumors and metastases) treated using stereotactic radiotherapy for response rates, local control rates and side effects. The most common dose/fractionation schedules used were 8, 10, and 15 Gy in 4, 4, and 3 fractions, respectively, delivered within approximately 1 week. Biological effective dose (BED) for these cases (converted to equivalent 2 Gy per fraction doses and assuming an α/β value of 10) would be 9.6, 13.1 and 30.5 Gy, respectively. Complete remission was observed in 30% of cases, 22% had > 50% regression, and 38% had either partial (< 50%) or no volume reduction. Only three cases of reoccurrence (90%-98% local control) were reported. Side effects were reported as being generally mild.[5] Beitler et al treated nine patients with nonmetastatic RCC to 40 Gy in 5 fractions, delivered over a median of 15 days (BED: 132 Gy), using conformal external radiation therapy. Only four patients, each with tumors ≤ 3.4 cm in largest dimension and clinically negative nodes remained alive for a follow up 48 months later.[6] In 2007, Ponsky et al reported their experience of radiosurgical treatment of RCC. Patients received 16 Gy in 4 fractions (BED: 27.4 Gy) and subsequently evaluated. No adverse events, no acute toxicities or changes in normal renal function were reported in any patients.[7] Based on these studies, there is a need for dose escalation for increased tumor control.

The aim of this study is to report a clinical pilot case of renal lymphoma treated to a conventional dose of 40 Gy in 20 fractions (BED: 48 Gy) using HT in which both the contralateral kidney and spinal cord were successfully spared. Possible advantage of plan modification in response to tumor shrinkage is investigated. Alternative hypofractionated treatment schedules are presented and their applicability to RCC is explored.

Methods and materials

An 82-year-old female patient (with a history of total remission from breast cancer diagnosed in 1990) was presented in 2006 with symptomatic nonHodgkin's lymphoma of the right kidney, proved to be inoperable by biopsy. The patient did not receive any chemotherapy and it was decided to give radiotherapy only. A diagnostic kVCT study, Figure 1a, was performed 12 days before the start of treatment on a helical CT scanner (Philips Brilliance Big Bore, 3 mm slice thickness). The radiation oncologist outlined the gross tumor volume (GTV) and the following sensitive structures using the Pinnacle treatment planning system (Pinnacle^3 version 8.0d; Philips, Fitchburg, WI): liver, spinal cord, and left kidney. All critical structures were assumed to be solid organs for dosimetric purposes. The GTV was delineated with the intention of including the whole kidney with a large right perinephric mass encircling the lower pole, and extending inferior to it. The PTV was created by a 15 mm 3D isotropic margin around the GTV including a 5 mm margin to encompass the

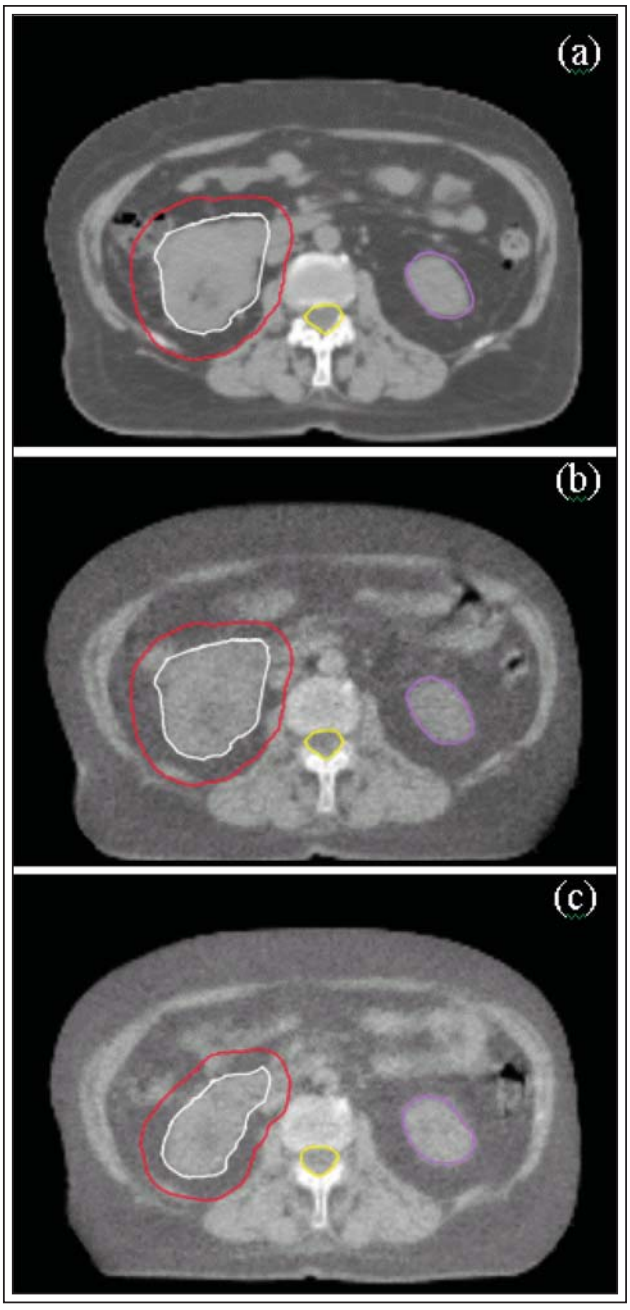

Figure 1. (a) kVCT image taken 12 days before treatment began. (b) MVCT image acquired prior to 1st fraction and (c) 20th fraction. GTV (white), PTV (red), left kidney (purple) and spinal cord (yellow) are outlined. Long term GTV volume regression is seen.

microscopic disease and create the clinical target volume (CTV) plus 10 mm margin to account for the expected intrafractional motion as well as setup uncertainties. Initial recorded volume of the GTV was 388.1 cm^3. A dose of 40 Gy was prescribed to the PTV and delivered in 20 fractions over 4 weeks.

Helical tomotherapy planning

CT and structure datasets were transferred to the Tomotherapy Hi-ART planning station (version 2.2.2, Tomotherapy Inc., Madison, WI) using the DICOM RT protocol. HT controls dose delivery using three parameters: fan beam thickness, pitch and modulation factor, described in detail elsewhere.[9] In this study, all plans were set with a field width of 5.02 cm. Pitch and maximum modulation factor were set for all fractionation schemes due to HT unit specification to achieve a gantry rotation period of less than a minute. The dose calculation grid was approximately 4 × 4 × 3 mm^3. Optimization was guided using precedence, importance, and penalty factor parameters. Coverage of 95% of the PTV was set as the optimization target in each plan, fixed by corresponding normalization. Desired dosimetric constraints on OARs were D_{Max} for the spinal cord (30 Gy), D_{Max} to the liver (40 Gy) as well as D_{Max} for the left kidney (10 Gy). About 200 iterations were used in the optimization procedure for each plan, with the total planning time ranging from 2 to 12 hours, depending upon the pitch. The HT plan based on the initial anatomy (plan 1: pitch 0.243, modulation factor 4.0, expected beam on time 495.8 s per fraction) was approved for treatment.

Hypothetical plan modification after 12 fractions

Due to observed tumor shrinkage first seen on the pretreatment MVCT studies, the oncologist requested to explore the possibility of the plan modification. The patient was subject to another kVCT study 12 fractions into treatment. Existing structure contours were manually adjusted according to the observed anatomy. The subclinical microscopic disease was deemed sterilized after delivery of 24 Gy,[10-12] so that the CTV was assumed to be equal to the current GTV. The PTV margin was redefined as a 10 mm isotropic 3D margin around the GTV = the CTV. This modified plan (plan 2: pitch 0.243, modulation factor 4.0, expected beam on time 459.5 s per fraction) was evaluated to develop guidelines for the future.

Delineation of structures

MVCT studies, Figures 1b and 1c, were acquired preceding each treatment. GTV, PTV and OAR contours were manually adjusted on the HT planning station using Planned Adaptive in order to assess any volumetric or dosimetric variations due to changes in patient anatomy. Absolute volume of the GTV as well as calculated D_{95} and D_5 for the PTV were recorded. D_{Max} for the liver, left kidney and spinal cord were also tabulated. To assess the interobserver contouring uncertainty, contour

adaptation was twice repeated to include both the largest and smallest observable GTV volumes on the 1st, 10th and 20th fractions. Interpolation of volumetric discrepancies between these days was assumed to be linear.

For the purpose of this case report, the radiation oncologist retrospectively delineated the small bowel, stomach, as well as the ascending, descending and transverse colon regions on the original kVCT study. The original plan was regenerated using the original optimization parameters in order to have these additional structures included in the dose volume histogram (DVH).

Hypofractionated planning study

The successful sparing of this patient's spinal cord and contralateral kidney has given us confidence in HT as a possible treatment option for future cases of RCC. A hypofractionated treatment schedule of 3 to 5 fractions delivered within a week would be desirable, similar to hypofractionated nonsmall cell lung cancer cases. A planning study has been done to test the feasibility of six possible treatment schedules, summarized in Table 1.

Normal tissue complication probability

Normal tissue complication probability (NTCP) calculations are a convenient way to assess the impact of treatment on OARs. The phenomenological set of equations based on the Lyman model:[13]

$$NTCP(D) = \frac{1}{\sqrt{2\pi}} \int^{(D-TD_{50}(v))/(m\cdot TD_{50}(v))} e^{\frac{-x^2}{2}} dx,$$

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n} \qquad (1)$$

was used for this purpose. Clinically and experimentally derived estimates of parameters m, n and TD_{50} used by the Lyman model have been published, and in this report those reported by Burman et al were used.[14] NTCP of the contralateral kidney, liver, spinal cord, stomach, small bowel as well as ascending, descending and transverse colon regions were determined for each plan.[14] Representation of dose fractionation effects is provided by either the linear quadratic equation (BED) in the case of standard fractionation schedules (2 Gy per fraction) or by the isoeffective dose equation (LQED2) for 2-Gy fractions in the case of hypofractionated schedules.[15,16]

$$BED(j) = D(j)\left(1 + \frac{d(j)}{\alpha/\beta}\right) \qquad (2)$$

$$LQED2(j) = D(j) \cdot \frac{d(j) + (\alpha/\beta)}{2 + (\alpha/\beta)} \qquad (3)$$

The estimates of α/β used by equations (2) and (3) were taken from several sources.[15,17-21] Dose volume histograms (DVH) were reduced to an equivalent partial irradiation of a volume fraction, V_{eff}, to the maximum calculated dose, D_{max}, using the following algorithm:[22]

$$V_{eff} = \sum v_i \left(\frac{D_i}{D_{max}}\right)^{1/n} \qquad (4)$$

where v_i is a volume fraction receiving a dose between $D_i - \Delta$ and $D_i + \Delta$. The n value refers to the dependence of NTCP on irradiated volume. Values of n near unity imply a strong volume dependence.

Tumor control probability

A logistic dose response curve was assumed for the TCP calculations.[23] The LQED2 equation, corrected for the overall treatment time, T, was used.[24]

$$TCP(D) = \left(1 + \left(\frac{D_{50}}{EQD_{2,T}}\right)^{4\gamma}\right)^{-1} \qquad (5)$$

$$EQD_{2,T} = LQED2(j) + (T_{Ref} - T) \cdot D_{Prolif} \qquad (6)$$

TABLE 1. **Summary of tomotherapy plans**

Plan #	Treatment schedule	Pitch	Maximum modulation factor	Expected beam on time (s)
1	40 Gy in 20 fractions	0.243	4.0	495.8
2	40 Gy in 20 fractions	0.243	4.0	459.5
3	48 Gy in 4 fractions	0.095	4.0	2846.6
4	48 Gy in 3 fractions	0.086	4.0	2324.9
5	60 Gy in 30 fractions	0.078	3.0	933.9
6	60 Gy in 5 fractions	0.078	3.0	3414.5
7	60 Gy in 4 fractions	0.078	3.0	3525.5
8	60 Gy in 3 fractions	0.078	3.0	3627.8

TABLE 2. **Parameters used for calculation of NTCP[12,14-18]**

Organ	α/β	n	m	TD_{50}
Colon	3.1-5[a] 8-9[b] 9-13[c]	0.17	0.11	55
Kidney	1.6	0.7	0.1	28
Liver	2.0	0.32	0.15	40
Stomach	7-10	0.15	0.16	55
Spinal cord	3.3	0.05	0.175	66.5
Small bowel	3.9	0.15	0.14	65

[a]late reaction: weight loss
[b]early reaction: clones
[c]early reaction: weight loss

D_{50} is the required dose to achieve 50% TCP and γ is the normalized slope of the radiation response curve at D_{50}. For these calculations, D_{50} was taken as 70 Gy and γ as 2.0.[21] An α/β ratio of 10 was assumed for the tumor.[18] T_{Ref} was taken as 21 days since accelerated repopulation was assumed to start after 3 weeks.[24] The daily recovered dose, D_{Prolif}, was assumed to be 0 (no repopulation) prior to 21 days, and 0.6 Gy/day after 3 weeks.[25] Limitations in the TCP calculations are recognized; therefore the TCP calculations were only taken as estimations and served mainly to compare the various plans of this study. All NTCP and TCP parameters are listed in Table 2.

Results and discussion

Treatment of renal lymphoma

Original plan 1 was used for complete course (20 fractions) of radiation therapy. MVCT studies were coregistered with planning kVCT using the spinal cord as reference in order to ensure it was being spared. Alignment was not done with respect to the GTV since sufficiently large PTV margins had been defined to account for intra and interfractional motion. Sparing of the contralateral kidney and spinal cord were of the highest priority. The patient was also asked to eat a light breakfast prior to treatment fractions, ensuring that stomach volume was minimal. A food laden stomach will expand in the inferior direction, making it prone to receive excess radiation. A follow up CT scan 18 months post treatment confirmed complete remission (no recurrence or metastases) with no normal tissue complications.

Relative changes in GTV volume over the course of treatment are presented in Figure 2. In this case study, a modified plan (plan 2) was generated with reduced PTV margin in response to tumor regression to explore possible advantage of such modification for future treatment. Hypothetical hypofractionated treatment schedules (plans 3 to 8) for future cases of RCC were generated and evaluated using NTCP and TCP. DVH analysis comparing each hypothetical plan in this report to actually delivered plan 1 is shown in Figure 3. The usage of daily image guidance to this particular case is evaluated.

Organs at risk

Sensitive structure dose constraints were met for the spinal cord in plans 1 and 2, due to lower prescription dose. Spinal cord D_{max} was recorded as 31.2 Gy and 42.9 Gy in plans 3-4 and 5-8, respectively. Contralateral kidney dose constraints were met in plans 2-4, due to reduced PTV margins. D_{max} was 11.1 Gy in plan 1, and 13.9 Gy in plans 5-8. Desired liver constraints were achieved in plan 2 only. Plan 1 had a D_{max} of 41.3 Gy, in plan 3-4 it was 51.3 Gy, and in plans 4-6 it was 64.3 Gy. These increasing values are a result of the small percentage of liver that overlapped the PTV, which was prescribed higher doses in the hypofractionated plans.

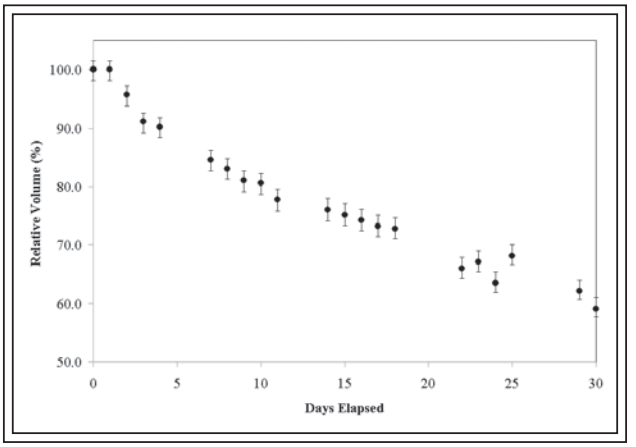

Figure 2. Relative GTV volume recorded over the course of treatment.

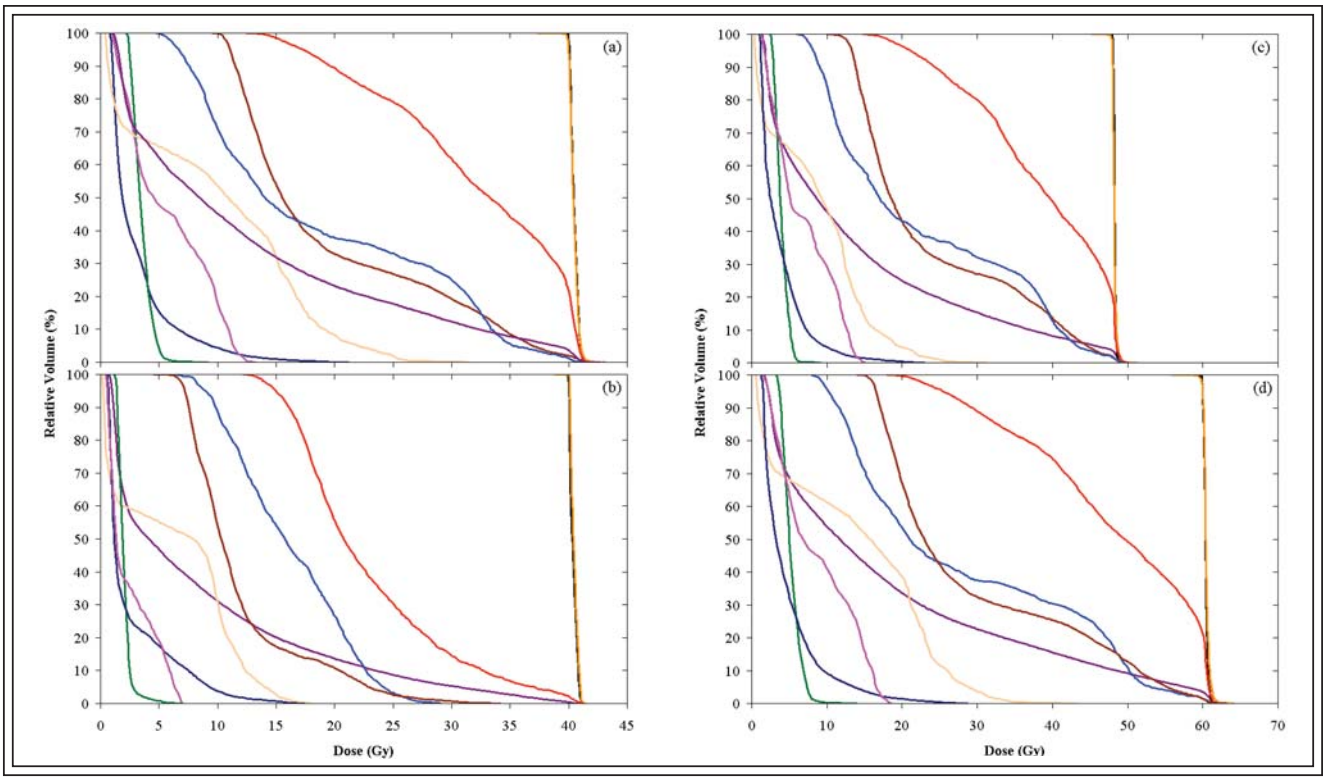

Figure 3. Dose volume histograms of a) plan 1, b) plan 2, c) plan 3-4 and d) plans 5-8. Color code: GTV (black), PTV (orange), liver (violet), left kidney (green), spinal cord (tan), ascending colon (red), descending colon (pink), transverse colon (blue), stomach (dark blue) and small bowel (brown).

Ideally the maximum dose delivered to the stomach, small bowel and colon would be at most 35 Gy. In all plans except 2 the ascending and transverse portions of the colon as well as the small bowel were planned to receive the prescription maximum dose due to their slight overlap with the PTV. In plan 2, the PTV margins were reduced and as a result no longer overlapped with either the transverse colon or small bowel. Only the ascending colon still received more than 35 Gy. In all plans, the desired dose constraints for the stomach and descending colon were met. Table 3 summarizes these results.

Expected effect of plan modification due to tumor shrinkage

By lesion shrinkage due to irradiation and the margin decrease from 15 mm to 10 mm, the PTV was reduced from 1316.8 cm^3 to 507.2 cm^3 in plan 2. This decrease in size meant both less radiation needed to fulfill the prescription dose and a decrease in the amount of PTV overlap with nearby OARs. The effects of the latter are clearly seen through improvements in the small bowel and the transverse colon, where the planned maximum doses are reduced from 41.5 Gy and 41.1 Gy to 32.9 Gy and 28.4 Gy, respectively. Had the

TABLE 3. **Summary of maximum dose (in Gy) to organs at risk**

Plan	Liver	Spinal cord	Left kidney	Stomach	Small bowel	Ascending colon	Descending colon	Transverse colon
1	42.0	31.5	9.1	21.1	43.0	41.6	13.1	41.2
2	40.9	18.0	6.7	17.3	34.0	41.3	6.9	29.0
3-4	51.3	31.2	9.0	22.9	45.0	50.1	15.0	49.7
5-8	64.3	42.9	13.9	28.9	63.3	62.5	18.7	61.5

modified plan been in effect for the final 8 fractions, small bowel D_{max} could have been reduced by 2.7 Gy, and transverse colon D_{max} by 3.8 Gy. Additional significant gains include the planned mean dose to the spinal cord, which is lowered from 10.0 Gy to 6.2 Gy, the planned ascending colon mean dose is reduced from 31.9 Gy to 22.7 Gy and the liver's planned mean dose decreased from 12.5 Gy to 8.5 Gy. If plan 2 is applied to the final 8 fractions, mean doses to the spinal cord, ascending colon and liver are down by 1.1 Gy, 2.8 Gy and 1.2 Gy, respectively. Planned mean dose to the descending colon would be reduced from 5.7 Gy to 2.4 Gy.

NTCP and TCP

NTCP and TCP results are shown in Table 4. In plans 1, 2 and 5 (standard fractionation) all NTCP values were found to be less than 1%, with the exception of the ascending colon. On the kVCT study there was a significant amount of overlap of this portion of the colon with the PTV, which caused it to receive large dose. The probability of early weight loss (irradiated atrophy in the region of the ascending colon receiving the highest dose) was estimated to be between 0.5% and 2% for these plans. Probability of late weight loss was found to range 15%-64% in plans 1 and 2, and 4%-19% in plan 5. The probability ranges are based on the calculations using the smallest and largest α/β values shown in Table 2. The hypofractionated schedules under assessment (plans 3, 4 and 6-8) had much higher NTCP values for liver, ascending and transverse colon, small bowel and spinal cord. Given that the ipsilateral kidney was on the right side of the body, it came into close proximity to the liver, effectively giving it clinically unacceptable amounts of radiation. On the other hand, the contralateral kidney received little radiation and had 0% NTCP. From these

TABLE 4. **NTCP and TCP estimates**

Plan #	Treatment schedule	Liver	Left kidney	Spinal cord	Small bowel	Stomach	TCP
1,2	40 Gy in 20 fractions	0.4%	0%	0.2%	0.5%	0%	0.6%
3	48 Gy in 4 fractions	100%	0%	3.8%	100%	0%	88.2%
4	48 Gy in 3 fractions	100%	0%	19.4%	100%	0%	96.0%
5	60 Gy in 30 fractions	11.3%	0%	0%	0.1%	0%	5.1%
6	60 Gy in 5 fractions	100%	0%	57.1%	100%	0%	97.4%
7	60 Gy in 4 fractions	100%	0%	86.4%	100%	0%	99.0%
8	60 Gy in 3 fractions	100%	0%	99.8%	100%	0%	99.8%

Plan #	Descending colon			Ascending colon			Transverse colon		
	Early weight loss	Late weight loss	Clones	Early weight loss	Late weight loss	Clones	Early weight loss	Late weight loss	Clones
1,2	0%	0%	0%	0.8%-2.2%	15.3%-63.8%	2.2%-3.1%	0%	0.2%-2.2%	0%
3	0%	0%	0%	98.7%-100%	100%	100%	34.3%-77.6%	100%	77.6%-88.4%
4	0%	0%	0%	100%	100%	100%	81.7% 99.4%	100%	99.4%-99.9%
5	0%	0%	0%	0.3%-0.7%	3.7%-19.0%	0.7%-0.9%	0%	0%-0.2%	0%
6	0%	0%	0%	100%	100%	100%	94.4%-99.9%	100%	99.9%-100%
7	0%	0%	0%	100%	100%	100%	99.8%-100%	100%	100%
8	0%	0%	0%	100%	100%	100%	100%	100%	100%

observations, one can predict that hypofractionated treatment would not be acceptable for a case such as this due to liver complications, however for a patient whose left kidney is affected, this type of treatment may be suitable. The higher NTCP values to certain organs may be justifiable by improved TCP values. In the conventional treatment schedules, TCP is estimated to be no higher than 5%, while in the hypofractionated cases control rates of 86% and 99% are predicted for 48 Gy and 60 Gy prescription doses, respectively.

Tumor regression

A total of 20 MVCT imaging studies were acquired over the span of 30 days. During that period of time, there was a 50.6% measured volume reduction in the GTV. Mean volume change per day was -2.53% ± 3.72%, with a range of -9.42% to 7.35% change per day. Rate of tumor regression was generally consistent, with no periods of accelerated decreasing. This reduction rate is quite high relative to several studies done on tumor regression in the case of non small cell lung cancer (NSCLC) patients. For example, in a study of 17 NSCLC patients, Woodford et al observed a mean tumor change per day of -0.79% ± 0.36%, with a range of 0.24%-1.65% decrease per day.[26] Similarly, Kupelian et al recorded a mean decrease of 1.2% in a study of 10 lung tumors.[27] The kidney is a clearly visible organ on CT images, and delineating the GTV was in general easier than contouring lung tumors. Often the tumors affecting the lung are embedded within the mediastinum, and their differentiation from normal soft tissue is difficult in MVCT studies.[28]

Conclusions

The successful treatment of this pilot case of renal lymphoma has given us confidence in the treatment of renal cell cancer using HT. The use of hypofractionated treatment schedules has been ruled out for cases in which the right kidney is affected due to high probability of liver complication. Left kidney diseases may be considered however, and would benefit from the significantly higher TCP rates. More planning should be done on a larger patient database in order to better establish the benefits and downfalls of hypo-fractionated treatment schedules. Further investigation of small renal tumors with partial kidney irradiation should be done, in order to evaluate control rates, vasculopathy, and residual normal function. Additional study into patients with tumors in a solitary kidney is needed as well. □

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