Short Communication

Evaluating dose constraints for radiation induced liver damage following magnetic resonance image guided Stereotactic Body radiotherapy

Poonam Yadav [a],[*],[1], Aleksandra Kuczmarska-Haas [a],[1], Hima Bindu Musunuru [b], Jacob Witt [a], Grace Blitzer [a], Peter Mahler [a], Michael F. Bassetti [a]

[a] Department of Human Oncology, University of Wisconsin Hospital and Clinics, United States
[b] Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

ABSTRACT

This study reports dose corresponding to visible radiation induced liver damage following Stereotactic Body Radiation Therapy (SBRT) for liver metastasis, and the optimal time for follow up scans using post radiation imaging. Diagnostic magnetic resonance scans of nine patients treated with liver SBRT using a 0.35 T MRI-guided radiotherapy system were analyzed. The dice coefficients between the region of visible liver damage and the delivered dose were calculated. A median dose of 35 Gy correlated most closely with the visible radiation induced liver damage. We compared scans over two to nine months and observed maximal dice coefficients at two to five months post radiation. We have presented a new method for developing treatment planning guidelines for liver SBRT.

1. Introduction

Radiotherapy is an essential tool in the treatment of primary and metastatic liver tumors. Recent advancements in imaging and focused target delivery have made Stereotactic Body Radiation Therapy (SBRT) a feasible treatment option for liver lesions. For patients with metastatic disease to the liver, multi-institutional data has shown that liver SBRT is highly effective, with 80–90% local control at two years [1,2]. SBRT can improve local control rates as compared to conventional radiation therapy by delivering a higher biological effective dose (BED) [3–5]. However, to prevent serious toxicities, it is imperative to constrain the dose to nearby organs at risk (OARs), particularly uninvolved liver. In order to avoid hepatic failure, treatment plans commonly constrain a volume of functional liver below a threshold dose (e.g. >700 cm^3 of liver <15 Gy) [1]. This guideline was derived from the surgical literature, where patients with normal Liver Function Tests (LFTs) can successfully have more than half of their liver resected [6,7].

Recently published results from the SABR-COMET and Gomez et al phase II randomized trials demonstrated that treating oligometastatic disease aggressively can improve patients' overall survival [8,9]. There is also evidence in colorectal cancer that patients with isolated liver metastases treated with surgical resection can experience long term survival [10]. SBRT can potentially be used in patients not eligible for surgical resection. Treatment planning dose constraints that are too conservative may potentially compromise a patient's local control or overall survival.

Diagnostic magnetic resonance imaging (MRI) is the preferred imaging technique for liver imaging due to its high level of soft tissue contrast, multiple sequences, and liver specific contrast agents compared to computed tomography (CT) [11]. MRI-guided radiotherapy (MRgRT) offers real time image guidance during gated treatment delivery [12]. This permits tracking the tumor volume during radiotherapy, allowing precise delivery of radiation dose and reduction of margin when expanding from the gross tumor volume (GTV).

In this study we retrospectively investigated the optimal isodose line for ^{60}Co MRI-guided SBRT plans that correlated with radiation induced liver damage and optimal follow up time using diagnostic MRI scans.

2. Materials and methods

Nine patients treated with five-fraction breath-hold ^{60}Co MRI-guided liver SBRT treatment for metastases were selected based on the

* Corresponding author at: Department of Human Oncology, The University of Wisconsin Hospital and Clinics, 600 Highland Avenue, Madison, WI 53792, United States.
  E-mail address: yadavphy@gmail.com (P. Yadav).
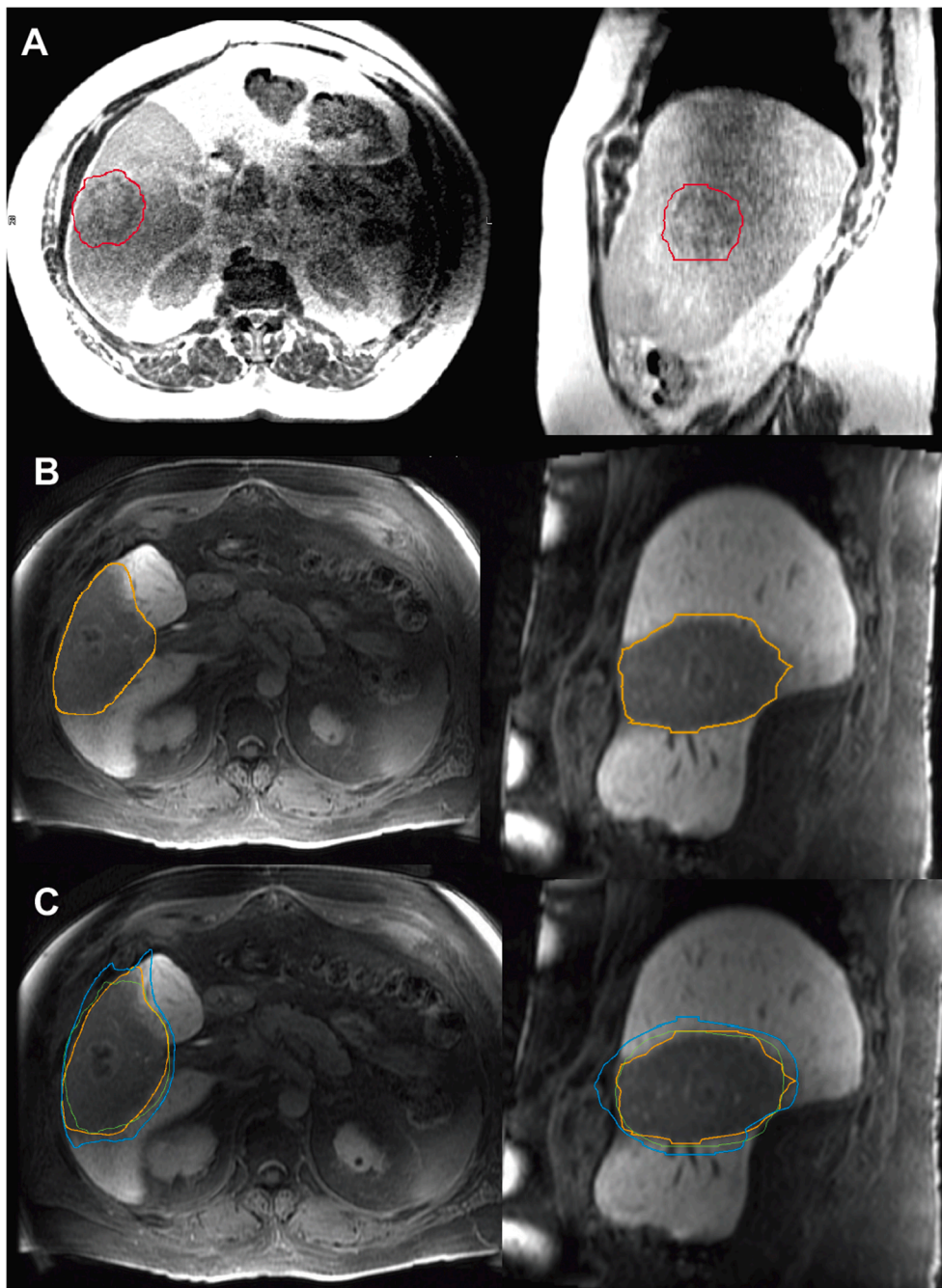[1] Co-primary authors.

Fig. 1. An example of (A) Planning target volume (red) treated with ^{60}Co MRI-guided SBRT plan, (B) radiation induced liver damage segmented in organ on diagnostic MR scan acquired 20 min post contrast administration and (C) Radiation isodose line corresponding to 35 Gy and 30 Gy are shown in green and blue color, displayed on diagnostic MR scan along with radiation induced liver damage contour. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

availability of follow up MRI scans. Patients ranged from 30 to 82 years of age. Primary disease sites included breast cancer (1), endometrioid adenocarcinoma (1), NSCLC (1), colorectal cancer (5), and pancreatic cancer (1). Lesions were treated to a total dose of 44–60 Gy in 5 fractions. Five of the patients considered for this study were previously treated with one of the following liver treatments: microwave ablation, cryoablation, partial hepatectomy, or Y90 liver treatment. Baseline MRIs were obtained <1 month prior to treatment. Follow up MRI scans were acquired at 1.6–6.6 months following ^{60}Co SBRT treatment completion. This study was approved by the Institutional Review Board of University of Wisconsin, Madison (WI).

For treatment, patients were simulated on the ViewRay cobalt MRIdian system (ViewRay Inc., Mountain View, CA) which consists of a ring gantry with three ^{60}Co heads positioned 120° apart and a 0.35 T MR scanner. This system acquires images as fast as 17 sec using the true fast imaging with steady state free precession (TRUFI) pulse sequence. Patients were scanned in the head first supine position with arms elevated using thoracic receiver surface coils to acquire 3 mm volumetric images. This study utilized Eovist (Bayer HealthCare Pharmaceuticals, USA) as MR contrast agent. It is gadolinium-based MR contrast agent and is often used for liver imaging. Both pre contrast and 20–25 min post contrast scans were acquired in breath hold phases. A similar setup but without coils, was used for CT simulation on Siemens Somatom Definition Edge (Somatom Definition Edge; Siemens Healthcare, Erlangen, Germany).

The simulation CT scans were deformably registered with the MR images to obtain electron density information for MRI based planning on a ViewRay treatment planning system. The median planning target volumes was 89 cm^3 with a range of 15–161 cm^3. The median GTV treated was 63 cm^3 (range, 6–103 cm^3). Median radiation induced liver damage volume was 261 cm^3 (range, 18–261 cm^3) on MR scans acquired
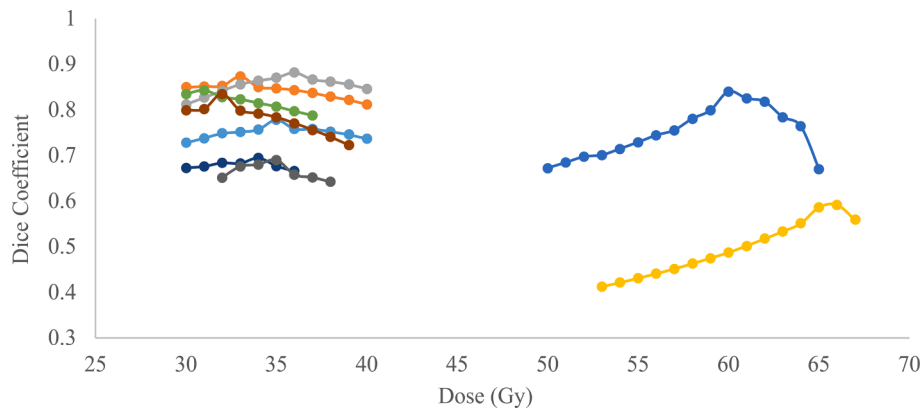
Fig. 2. Dice coefficient between the radiation induced liver damage region segmented by the radiation oncologist on follow up diagnostic MR scans and dose for nine patients. The peak of each curve indicates the highest dice coefficient.

2–5 months following treatment. The median liver volume on planning MR scans was 1863 cm^3 (range, 1219 cm^3–2771 cm^3).

For dose calculation using a Monte Carlo algorithm, a 0.2 cm grid size was used. The magnetic field was taken into consideration for optimization and final dose calculations. The MRIdian system uses a step and shoot intensity modulated radiation therapy (IMRT) technique to deliver the intended dose.

For better target visualization and setup, contrast was given prior to each fraction [13]. All patients were treated with a respiratory gated technique where GTV was used as the tracking structure. The beam was delivered as long as the tracking structure was within the pre-defined boundary, which was a uniform 3 mm expansion of the tracking structure. All patients treated with ^{60}Co MRgRT liver SBRT were imaged with post-treatment enhanced MRI scans. Follow up scans were acquired on 1.5 T GE diagnostic MR scanner (GE Healthcare, Waukesha, WI) using gradient echo T1 weighted LAVA sequence (response time: 6.0 ms, echo time: 2.42 ms, flip angle: 30°, slice thickness: 1.8 mm). Contrast was injected with a flow rate of 2 mL/s with a gadolinium dose of 0.05 mmol/kg of body weight in head first supine position with arms on sides.

All planning CT scans, follow up diagnostic MR scans, and dose data were exported to MIM (version 6.6.11, MIM Software Inc., Cleveland, OH). An experienced radiation oncologist contoured visible radiation induced liver damage on follow up diagnostic MR scans. Radiation induced liver damage was defined as areas of hypointensity on the follow-up T1 MRI, acquired 20 min following contrast administration. Finally, 10 Gy–70 Gy treatment isodose lines in increments of 1 Gy were transferred from the planning scans to the follow-up diagnostic MR scans. Sørensen–Dice coefficients (DC) were calculated using Matlab and the isodose lines with the highest DC were identified as relevant. In addition, the relationship between the time to follow up and isodose line corresponding to the areas of hypointensity was evaluated.

3. Results

An example of the treatment volume and radiation induced liver damage contour are shown in Fig. 1A and B. Mean dose to liver ranged between 4 Gy and 22 Gy with a median of 15 Gy. For all cases, a median 567 cm^3 of the liver volume received less than 15 Gy (range 432 cm^3–654 cm^3). Median liver volume receiving 30 Gy was 302 cm^3.

The isodose line of 35 Gy (range, 30 Gy-36 Gy, N = 6 patients) correlated with the highest DC (0.75–0.9), as shown in Fig. 1C. For the remaining three patients, the optimal DC was at higher isodose lines ranging from 45 Gy to 66 Gy. DC as a function of radiation dose is plotted for all the patients in Fig. 2. The ideal period for analyzing radiation induced liver damage in the presented dataset was between (90–145 days) and 30–35 Gy isodose lines corresponded to the liver damage during this period (see Supplementary materials Fig. S1 for

details). There were no late grade 2 liver toxicities.

4. Discussion

In this study, we investigated the utilization of diagnostic MRI to delineate change in treated liver post SBRT radiation induced liver damage. Highest DC for six patients was for a median dose of 35 Gy in five fractions, with a range of 30–36 Gy. In the three datasets where the results were not concordant, the follow up scans were acquired either earlier (<2 months following treatment) prior to development of radiation induced liver damage or later (>5 months), after radiation induced fibrosis caused contraction of the targeted lesion. Thus, it appears that our approach of correlating the liver damage region using dice coefficient can help in determining appropriate time for obtaining follow up scans.

In the studies that quantified radiation changes using either Hounsfield Unit differences on follow-up CT scans or intensity changes on follow up MRI scans, imaging changes were associated with lower isodose lines in the range of 25 Gy–42 Gy [14]. Takeda et al. [15] analyzed follow up CT scans and proposed using 30 Gy in 5 fractions as a threshold dose. In a study by Jung et al. [16] the relationship between radiation dose and focal liver damage was evaluated on follow up MRI scans of six patients treated with liver SBRT. The results of these studies are not significantly different from our findings. The treatment plans in these studies [14–16] were generated using 6 MV conventional linear accelerator. Patients selected for our study underwent gated treatment on ^{60}Co unit with onboard MRI scanner. Treatment plans for ^{60}Co are relatively accurate for establishing correlation between isodose lines and radiation induced liver damage due to larger penumbra when compared to the non-MRI guided radiation therapy system plans that have a much sharper dose gradient. Additionally, precise treatment setup reproducibility using MRI guidance minimized the risk of blurring of isodose lines between fractions. Breath-hold respiratory gating with real time MRI cine reduces the uncertainty associated with blurring of dose associated with internal target volume based dose delivery.

One limitation of this study is that there were a small number of evaluable patients. Future works could examine whether areas of radiation induced liver damage on post-treatment contrast enhanced MR is pathologically indicative of completely non-functioning liver versus poorly functioning liver that has the potential for repair. Patients with primary liver tumors were excluded as it is conceivable that in patients with underlying hepatic dysfunction, the "nonfunctional liver" isodose threshold may be different.

Future studies are needed to examine the relationship between dose specific radiological findings and hepatocyte function, perhaps as reflected in LFTs. An accurate understanding of pathophysiology of the remaining functioning liver is essential to establish an accurate liver

dose constraint that might facilitate safe SBRT dose-escalation while not increasing toxicity.

In conclusion, breath hold MRI-guided liver SBRT induces a well demarcated hypointense area of radiation damage on the early follow-up MRI scans. The workflow used in this study shows that the area of radiation induced liver damage correlated with a specific dose level which is higher than commonly used threshold dose constraints. This potentially indicates that current liver volumetric constraints may be too conservative. Further studies in larger patient cohorts are needed to determine the relationship between regions of radiation induced liver damage and corresponding dose level.

5. Funding statement

None.

6. Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2021.01.009.

References

[1] Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572–8. https://doi.org/10.1200/JCO.2008.19.6329.

[2] Rosenberg SA, Henke LE, Shaverdian N, Mittauer K, Wojcieszynski AP, Hullett CR, et al. A multi-institutional experience of MR-guided liver stereotactic body radiation therapy. Adv Radiat Oncol 2019;4:142–9. https://doi.org/10.1016/j.adro.2018.08.005.

[3] Mahadevan A, Blanck O, Lanciano R, Peddada A, Sundararaman S, D'Ambrosio D, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis – clinical outcomes from the international multi-institutional RSSearch(R) Patient Registry. Radiat Oncol 2018;13:26. https://doi.org/10.1186/s13014-018-0969-2.

[4] Kok END, Jansen EPM, Heeres BC, Kok NFM, Janssen T, van Werkhoven E, et al. High versus low dose stereotactic body radiation therapy for hepatic metastases. Clin Transl Radiat Oncol 2020;20:45–50. https://doi.org/10.1016/j.ctro.2019.11.004.

[5] Joo JH, Park JH, Kim JC, Yu CS, Lim SB, Park IJ, et al. Local control outcomes using stereotactic body radiation therapy for liver metastases from colorectal cancer. Int J Radiat Oncol Biol Phys 2017;99:876–83. https://doi.org/10.1016/j.ijrobp.2017.07.030.

[6] Rahnemai-Azar AA, Cloyd JM, Weber SM, Dillhoff M, Schmidt C, Winslow ER, et al. Update on liver failure following hepatic resection: strategies for prediction and avoidance of post-operative liver insufficiency. J Clin Transl Hepatol 2018;6: 97–104. https://dx.doi.org/10.14218%2FJCTH.2017.00060.

[7] Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512–9. https://doi.org/10.1067/msy.2000.105294.

[8] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393:2051–8. https://doi.org/10.1016/S0140-6736(18)32487-5.

[9] Gomez DR, Tang C, Zhang J, Blumenschein Jr GR, Hernandez M, Lee JJ, et al. Local consolidative therapy Vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. J Clin Oncol 2019;37:1558–65. https://dx.doi.org/10.1200%2FJCO.19.00201.

[10] Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575–80. https://doi.org/10.1200/JCO.2007.11.0833.

[11] Yadav P, Musunuru HB, Witt JS, Bassetti M, Bayouth J, Baschnagel AM. Dosimetric study for spine stereotactic body radiation therapy: magnetic resonance guided linear accelerator versus volumetric modulated arc therapy. Radiol Oncol 2019;53: 362–8. https://doi.org/10.2478/raon-2019-0042.

[12] Kim T, Park JC, Gach HM, Chun J, Mutic S. Technical Note: Real-time 3D MRI in the presence of motion for MRI-guided radiotherapy: 3D Dynamic keyhole imaging with super-resolution. Med Phys 2019;46:4631–8. https://doi.org/10.1002/mp.13748.

[13] Wojcieszynski AP, Rosenberg SA, Brower JV, Hullett CR, Geurts MW, Labby ZE, et al. Gadoxetate for direct tumor therapy and tracking with real-time MRI-guided stereotactic body radiation therapy of the liver. Radiother Oncol 2016;118:416–8. https://doi.org/10.1016/j.radonc.2015.10.024.

[14] Howells CC, Stinauer MA, Diot Q, Westerly DC, Schefter TE, Kavanagh BD, et al. Normal liver tissue density dose response in patients treated with stereotactic body radiation therapy for liver metastases. Int J Radiat Oncol Biol Phys 2012;84: e441–6. https://doi.org/10.1016/j.ijrobp.2012.04.041.

[15] Takeda A, Oku Y, Sanuki N, Kunieda E, Koike N, Aoki Y, et al. Dose volume histogram analysis of focal liver reaction in follow-up multiphasic CT following stereotactic body radiotherapy for small hepatocellular carcinoma. Radiother Oncol 2012;104:374–8. https://doi.org/10.1016/j.radonc.2011.12.008.

[16] Jung SH, Yu JI, Park HC, Lim DH, Han Y. A feasibility study evaluating the relationship between dose and focal liver reaction in stereotactic ablative radiotherapy for liver cancer based on intensity change of Gd-EOB-DTPA-enhanced magnetic resonance images. Radiat Oncol J 2016;34:64–75. https://dx.doi.org/10.3857%2Froj.2016.34.1.64.