Evolving development of multi-parametric normal tissue complication probability model for liver radiotherapy

Chiao-Ling Tsai[1,2], Jason Chia-Hsien Cheng[1,2,3]

[1]Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [2]Graduate Institute of Clinical Medicine, [3]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan

Correspondence to: Jason Chia-Hsien Cheng. Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan. Email: jasoncheng@ntu.edu.tw.

Comment on: El Naqa I, Johansson A, Owen D, *et al.* Modeling of Normal Tissue Complications Using Imaging and Biomarkers After Radiation Therapy for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2018;100:335-43.

The dosimetry model of normal tissue complication probability (NTCP) has been investigated for decades. Incorporation of imaging parameters and biomarkers into NTCP is a must in this modern era. El Naqa and colleagues developed a novel NTCP model with the incorporation of imaging and cytokine biomarkers for patients with hepatocellular carcinoma (HCC) undergoing radiotherapy (RT) (1). They defined the changes in albumin-bilirubin (ALBI) and Child-Pugh (C-P) score, and higher than grade 3 liver enzyme changes as clinical endpoints for radiation-induced liver disease (RILD). The changes in local dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) portal venous perfusion before, during, and one month after RT were used as imaging biomarkers. Four inflammatory cytokines including transforming growth factor beta (TGF-β1), eotaxin (CCL11), hepatic growth factor (HGF), and CD40 ligand were investigated as cytokine biomarkers, but only TGF-β1 and eotaxin showed the impact on the defined endpoints. Of note, their patients included 76% of them treated with stereotactic body RT (SBRT) and 24% treated with conventional RT. The timing of developing RILD after RT may differ between SBRT and conventional RT (2). Besides, some commonly reported cytokines after liver RT, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and many others were not analyzed in the study. The investigation on the specific cytokines related to radiation injury is also a potential issue.

The pathological features of liver after RT

The ALBI grade has recently been proposed to predict prognosis in HCC patients, and the C-P score has long been the most important prognosticator for HCC and used in assessing the baseline liver function. El Naqa's novel NTCP model is the first one to adopt ALBI and C-P score as part of the endpoints for evaluating liver injury after RT. In fact, the liver enzyme changes at one month after completion of RT might not be adequate for RILD detection. The C-P score and ALBI changes are not totally representative of both classic and non-classic RILD. Instead, the endpoints for SBRT should be a combination of enzymatic change, C-P score, and platelet count.

The occurrence of RILD is a time-dependent event. RILD typically occurs 4–8 weeks after the completion of conventional RT. RILD has also been described as early as two weeks and as late as seven months after RT in some reports. The pathological changes of liver after excessive radiation damage can be divided into acute, subacute, and chronic phases. In the acute phase (<3 months post-RT), massive portal and systemic venous congestion, fibrin thrombi within sinusoids, perisinusoidal hemorrhages, reactive hyperemia, atrophy, and degeneration of hepatocytes are widely observed around the centrilobular areas of the hepatic acinus. In the subacute phase (3–6 months post-RT), obstruction of sublobular veins is overlapped upon the acute-phase findings. In the chronic phase (>6 months post-RT), moderate elastosis in the

walls of the central veins and mild elastosis in the walls of perivenular sinusoids cause occlusion of the central veins (3). According to the pathogenesis, RILD is classified into classic and non-classic types. Classic RILD involves veno-occlusive disease (VOD) and obliteration of the central veins of the hepatic lobules, retrograde congestion, and secondary hepatocyte necrosis. Non-classic RILD is associated with hepatocyte loss and dysfunction accompanied by hepatic sinusoidal endothelial death caused by reactivation of viral hepatitis (4). Sanuki *et al.* retrospectively evaluated the impact of liver toxicity on prognosis after SBRT in 194 HCC patients (2). They identified three criteria associated with death from liver failure within 12 months: (I) ≥ grade 3 transaminases elevation, (II) C-P score ≥8, and (III) ≥ grade 3 thrombocytopenia. Elevated alkaline phosphatase (ALP) which is a marker of classic RILD, was not prognostic.

Cytokine changes after liver RT

Many studies have reported that cytokine levels are associated with the HCC response to RT (5). El Naqa's novel NTCP model is the pioneer model to incorporate the cytokines into the prediction of RILD. However, the cytokines selected by El Napa *et al.* may not be comprehensively representative of RILD. The cytokine levels examined in only 50% of patients treated with SBRT is insufficient to characterize the whole group. Following an injury to the liver parenchyma, the production of growth factors and other cytokines has been involved in the pathogenesis of RILD, such as TGF-β, TNF-α, and IL-6. TGF-β is known to stimulate fibroblasts that would migrate to the regions of hepatic injury and cause collagen deposition (5). TNF-α produced by Kupffer cells is shown to sensitize hepatocytes to radiation *in vitro* and cause the centrilobular atrophic process seen in patients with VOD (6). In hepatitis B virus (HBV) carriers, the bystander effect induced by IL-6 from irradiated endothelial cell reactivates HBV and aggravates RILD (7).

Prediction model for liver dysfunction after RT

The data collected by El Napa *et al.* is complete with the detailed patient profile. In El Naqa's study, 85% of the patients in the SBRT group and 67% in the conventional group presented with liver cirrhosis while receiving RT. The pre-existing liver disease would confound the predicting power of RILD. This important factor, unfortunately, was not included in their NTCP model.

Lyman's NTCP, a three-parameter model, has become the most widely used model in clinical practice (8). In 1991, Emami *at al.* established the tolerant RT dose to partial liver and other organs with the individualized endpoints (9). Later, Burman *et al.* fitted the tolerance values developed by Emami *et al.* into the Lyman model. After adjusting the parameters to make the probability curve pass through a 50- and 5-percent complication points, liver came with the parameters of n=0.32, m=0.15, and TD_{50} =40 Gy (10). Meanwhile, Steel and Peacock analyzed tumor radiosensitivity in term of cell killing based on the linear-quadratic (LQ) equation which fits only in low-dose region (11). In 2010, the Steering Committee defined Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) which summaries the dose, volume, and outcome information for many organs (12). The liver is an organ in parallel, the risk of RILD is dependent on the volume irradiated. The liver constraints reviewed from the QUANTEC are mean liver dose less than 28 Gy if pre-existing liver disease and less than 30–32 Gy if no pre-existing liver disease when treated with convention fractionation of RT. In addition, mean liver dose less than 13–20 Gy or more than 700 mL normal liver volume receiving less than 15 Gy is recommended when treated with hypofractionated RT or SBRT (13).

Functional images for RILD

State-of-the-art method of DCE-MRI can provide quantitative insights into liver function. El Naqa's novel NTCP model is the first model to integrate quantitative image information into the prediction of liver injury after RT. The timing of DCE-MRI scans acquired at 2 weeks before RT, during RT, and 1 month after RT might not be perfect to represent liver function change of possibly latent RILD. The image changes of RILD may progress for several months, and other image modalities may also play a potential role in showing the liver changes after RT.

After RT to part of the liver, the irradiated hepatic parenchyma shows hypo-attenuation on unenhanced computed tomography (CT) and hyper-attenuation on contrast-enhanced CT. DCE CT or MRI may be used to measure microcirculation and tumor angiogenesis. Kimura *et al.* used DCE-CT to classify patterns of liver parenchyma after RT as type 1, hyperdensity in all enhanced phases; type 2, hypodensity in the arterial and portal venous phases; and type 3, isodensity in all enhanced phases. Type 1 is observed in the normal irradiated liver. Half of types

S122

Tsai and Cheng. Novel NTCP model for HCC RILD

2 and 3 patients with C-P class A reverted to type 1. After 3–6 months, C-P class B is a significant predictor of a type 3 appearance (14). Superparamagnetic iron oxide (SPIO) MRI may be one of the most sensitive images to visualize early phase of focal liver injury (15). Damaged Kupffer cells after RT is accompanied with a functional decrease in their phagocytic capacity for SPIO. SPIO MRI can visualize focal liver injury earlier than hepatocyte-specific gadolinium agents such as gadoxetate disodium [gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)] and gadobenate disodium [gadobenate dimeglumine (Gd-BOPTA)] which are used to identify HCC and liver metastasis (16). Technetium-99m galactosyl human serum albumin (99mTc-GSA) binds specifically to asialoglycoprotein receptors (ASGPR) on the hepatocellular membrane. The combination of single photon emission computed tomography (SPECT) with 99mTc-GSA could aid in assessing functional liver function (FLV) in patients with hepatic dysfunction. Shirai *et al.* recommended the evaluation of the FLV distribution before RT in HCC patients with portal vein tumor thrombus (PVTT). The existence of dysfunctional liver volume could serve as a kind of natural spacer in planning liver-sparing dosimetry to minimize RT-induced liver dysfunction (17).

Conclusions

HCC is one of the most challenging cancers for RT due to the susceptibility to RILD. The existing virus hepatitis, cirrhosis, and underlying liver disease are involved in liver function change after RT. With the advances in RT technology, high-dose RT can be delivered accurately to a confined target and provide a promising outcome in patients with HCC. However, traditional models to predict RT complication are based on standard fractionations, and a useful RILD model to aid modern fractionated RT or SBRT with the integrated functional images and translational materials is needed. Nonetheless, a good agreement of the parameters to fit the generalized model is ambiguous. As the quotation from George E. P. Box, the British statistician, who died in 2013, he very aptly pointed out the significance of model risk by saying: "*Essentially, all models are wrong, but some are useful (Box & Draper, 2007)*." Although several problems are encountered, more studies are needed to integrate functional imaging parameters and potential biomarkers to predict liver injury after conventional RT and SBRT.

References

1. El Naqa I, Johansson A, Owen D, et al. Modeling of Normal Tissue Complications Using Imaging and Biomarkers After Radiation Therapy for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2018;100:335-43.
2. Sanuki N, Takeda A, Oku Y, et al. Influence of liver toxicities on prognosis after stereotactic body radiation therapy for hepatocellular carcinoma. Hepatol Res 2015;45:540-7.
3. Takamatsu S, Kozaka K, Kobayashi S, et al. Pathology and images of radiation-induced hepatitis: a review article. Jpn J Radiol 2018;36:241-56.
4. Cheng JC, Wu JK, Huang CM, et al. Radiation-induced liver disease after radiotherapy for hepatocellular carcinoma: clinical manifestation and dosimetric

description. Radiother Oncol 2002;63:41-5.

5. Anscher MS, Crocker IR, Jirtle RL. Transforming growth factor-beta 1 expression in irradiated liver. Radiat Res 1990;122:77-85.

6. Christiansen H, Saile B, Neubauer-Saile K, et al. Irradiation leads to susceptibility of hepatocytes to TNF-alpha mediated apoptosis. Radiother Oncol 2004;72:291-6.

7. Chou CH, Chen PJ, Lee PH, et al. Radiation-induced hepatitis B virus reactivation in liver mediated by the bystander effect from irradiated endothelial cells. Clin Cancer Res 2007;13:851-7.

8. Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl 1985;8:S13-9.

9. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.

10. Burman C, Kutcher GJ, Emami B, et al. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123-35.

11. Steel GG, Peacock JH. Why are some human tumours more radiosensitive than others? Radiother Oncol 1989;15:63-72.

12. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys 2010;76:S3-9.

13. Marks LB, Yorke ED, Jackson A, et al. Use of Normal Tissue Complication Probability Models in the Clinic. Int J Radiat Oncol Biol Phys 2010;76:S10-9.

14. Kimura T, Takahashi S, Takahashi I, et al. The Time Course of Dynamic Computed Tomographic Appearance of Radiation Injury to the Cirrhotic Liver Following Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma. PLoS One 2015;10:e0125231.

15. Clement O, Muhler A, Vexler VS, et al. Evaluation of radiation-induced liver injury with MR imaging: comparison of hepatocellular and reticuloendothelial contrast agents. Radiology 1992;185:163-8.

16. Ruhl R, Ludemann L, Czarnecka A, et al. Radiobiological restrictions and tolerance doses of repeated single-fraction hdr-irradiation of intersecting small liver volumes for recurrent hepatic metastases. Radiat Oncol 2010;5:44.

17. Shirai S, Sato M, Noda Y, et al. Distribution of functional liver volume in hepatocellular carcinoma patients with portal vein tumor thrombus in the 1st branch and main trunk using single photon emission computed tomography-application to radiation therapy. Cancers (Basel) 2011;3:4114-26.