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

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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 *et 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 TD5 =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
declared 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 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.

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Footnote

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References