REVIEW

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Computed tomography imaging assessment of postexternal beam radiation changes of the liver

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Radiation is being used for patients with primary and secondary liver cancers, as a rapidly evolving treatment. However, postradiation imaging changes of the liver are not well understood and therefore challenging to interpret. Distinguishing normal radiation changes from residual or recurrent disease is difficult. Size and contrast enhancement have been used to guide interpretation and clinical recommendations, but normal radiation changes can make interpretation difficult and are not accounted for in available guidelines. Knowledge of dose- and time-dependent changes in addition to imaging findings, such as morphological and enhancement patterns, provides useful differentiating parameters. This paper reviews recent studies using computed tomography that can guide interpretation and help differentiate tumor from benign changes after external beam radiation.

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Primary and metastatic liver cancer is a disease entity with a poor prognosis and a growing incidence [1]. Therefore, research for new agents and methods to combat this disease is a priority. Despite important advances, such as sorafenib and Y90, overall outcomes in patients with liver cancer remain dismal [2]. There is growing evidence that external beam radiation provides favorable local control and drives improvement in primary clinical outcomes [3,4]. In addition, the availability of highly conformal delivery techniques and the resulting improvement in treatment safety and tolerability have led to increasing use of radiation for liver cancer [5,6]. Therefore, the need for accurate image interpretation postradiation is also becoming more pressing. Patients and caregivers rely on this interpretation for prognosis; researchers rely on accurate outcome analysis for objective evaluation of new treatments; and clinicians rely on these interpretations for medical decision-making. However, radiation often results in complex benign radiographic changes that make interpretation difficult. Standard parameters, such as size and contrast enhancement, are fundamentally altered and can be unreliable in radiated liver. Therefore, additional criteria that describe systematic, therapy related, normal changes are required to correctly interpret images postradiation [7]. Important work in this area has revealed that certain changes and patterns can be categorized; reports can be standardized; and different types of radiation regimens result in predictable changes to normal tissues, which can be clinically useful. This article provides an evidence-based review and approach to computed tomography image interpretation following radiation therapy to the liver.

KEYWORDS

• hepatocellular carcinoma
• radiation therapy/
radiotherapy • stereotactic
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Size & enhancement

Unidimensional anatomical size has been the standard parameter and has been codified in the Response Evaluation Criteria in Solid Tumours (RECIST) criteria [8]. Originally developed in the mid-1990s, RECIST provided a standardized and well-accepted mean to communicate clinically important end points such as objective response and time to progression. These end points allow comparison of different types of treatments; anatomical size assessment alone has been instrumental in allowing Phase II screening trials of new agents/techniques [9] that subsequently lead to these agents being used as standard of care in many disease sites. However, there is growing evidence that in many disease sites and for many newer agents, RECIST is insufficient [10]. This includes studies in liver such as the study by Forner *et al.* in 55 hepatocellular carcinoma (HCC) patients, RECIST failed to provide important clinical information and missed all complete remissions in prospective evaluation [11]. Changes to RECIST have addressed evolving data in HCC with the inclusion of burden of disease parameters with the RECIST 1.1 update [12] and, in 2013, the inclusion of contrast parameters with the modified RECIST (mRECIST) criteria [13].

There are several reasons that using the parameter of size alone may not be useful after radiation. Radiation techniques require treatment beyond the tumor itself. This margin around the tumor accounts for motion of the patient during treatment, set-up variations and tumor motion. The margin for motion is particularly relevant in disease sites such as liver where the tumor can move as much as 2 cm with respiration [14]. Radiation treatments in the past have been very standardized and, often, the region irradiated could be easily assessed due to straight edges and geometric shapes (Figure 1A). However, modern treatments can be quite complex in terms of shape and dose delivered at various locations. This makes delineation of a tumor edge versus a radiation edge very difficult (Figure 1B).

Indeed, the available data suggest that size is not sufficiently predictive of clinical outcome unless lesions are very large (>6–10 cm) and assessed after sufficient time has passed (>6–12 months). In the classic paper by Price *et al.* [15], 26 patients with unresectable HCC awaiting transplant were treated with radiation. Patients had up to three lesions and had

well compensated cirrhosis. This study found little change in size in the first 3 months. In fact, radiology reports sometimes suggested an increase in size; yet, response rates for small lesions was over 90 and 60–70% for lesions up to 6 cm at 12 months. Many liver treatments result in necrosis as opposed to decrease in size. Therefore, size may not be practical for most patients and their caregivers due to a lack of clinical predictive accuracy at appropriate decision time points.

Rate of growth prior to radiation compared with postradiation may also be an important use of size assessments. As radiation impacts may take months to be revealed, growth rates may provide interim assessments. The study by Brook *et al.* provides insight into growth kinetics and recurrence [16]. Sixty-eight patients with primary and secondary liver cancers were followed for 5.6 months. Complete responses were seen in 11% of HCCs and 4% of metastases. Assessment for change in size demonstrated a drop in volume for the first 4 months and then the rate of growth slows or stabilizes. The nonenhancing portion increased until the third month and then stabilized. Increases in the size of the necrotic region beyond 3 months were suggestive of recurrence. However, parameters beyond size are still required as the variability of these size changes is significant.

As size alone is insufficient to provide adequate interpretation of images, the parameter of enhancement was added as a means to determine the presence of an active tumor versus benign changes such as necrosis and cirrhosis. EASL (European Association for Study of the Liver), WHO and mRECIST criteria (Table 1) were developed to take advantage of the additional information produced by differential contrast uptake [12,17]. This primarily relates to HCC. Multiple clinical and pathological studies confirm the value of enhancement in nonexternal beam radiation modalities [18,19]. This includes recent investigations in biologic chemotherapy. These new agents act by interfering with angiogenesis resulting in necrosis. Previously included in size criteria, the newer criteria account for necrosis and exclude these regions from tumor measurements. Some studies have confirmed the usefulness of these criteria for yttrium radiation [20,21], but radiological studies have failed to demonstrate a similar value in external beam radiation. Studies have concluded that mRECIST is

Figure 1. Radiation planning and postradiation changes. (A & B) A 45-year-old woman who received radiotherapy for cholangiocarcinoma with recognizable margins. Arterial phase scan (A) demonstrates slightly heterogeneous attenuation of the liver parenchyma. The portal venous phase scan (B) demonstrates clear definition of the hypo-enhanced radiation field (arrowheads) surrounding the mass (arrow). (C & D) A 49-year-old woman who has undergone stereotactic body radiotherapy of metastasis with less defined effect of radiation treatment. (C) With planning target volume surrounding the metastatic hypoattenuated lesion at the center. (D) Follow-up postcontrast computed tomography demonstrates areas of hypoattenuation corresponding to radiation plan (arrowheads) with shrunk mass at the center (arrow).

useful for correlation with prognosis and as a framework for clinical trial design, but should not be used for routine clinical practice due to its inaccuracy in estimating viable tumor

correctly [22,23]. This may be due to the problem of halo formation postradiation where a normal rim of enhancement develops around the region irradiated.

Table 1. Comparison of current hepatocellular carcinoma guidelines.			
Response status	EASL	RECIST 1.1	mRECIST
Complete response	Disappearance of any intratumoral arterial enhancement in all measurable arterially enhancing liver lesions	Disappearance of all target lesions (up to two measurable liver lesions)	Disappearance of any intratumoral arterial enhancement in all target lesions (up to two measurable liver lesions)
Partial response	At least a 50% decrease in the sum of the product of bidimensional diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the greatest unidimensional diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of unidimensional diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	An increase of at least 25% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
EASL: European Association for Study of the Liver; mRECIST: Modified RECIST; RECIST: Response Evaluation Criteria in Solid Tumor.			

Halos

We define halos as peritumoral hypervascular response seen postradiation (Figure 2A). In several studies of primary and secondary liver cancers, this abnormal enhancement was seen in all radiated patients by 6 months [6,16]. This enhancement makes measuring size difficult as the halo is often ill defined (Figure 2B), often increases in size and, in many cases, represents normal postradiation change. Pathologic assessment has shown this region to contain fibrosis with embedded bile ductules, regenerating hepatocytes and fibroblasts consistent with radiation effects alone [16]. If we apply the criteria that utilize enhancement, such as mRECIST and EASL, do we include this region of enhancement? Is there a means to distinguish normal radiation-induced enhancement from disease? Based on four primary studies [24–26], three types of normal radiation enhancement patterns have been identified based on postradiation change studies of both primary and secondary carcinomas [25]. This understanding is important as these enhancement patterns may be misinterpreted by standard criteria as progression. This pseudoprogression is well known outside the radiation specialty. The pseudoprogression is similar to well-known effects such as ipilimumab lymphocyte infiltration and blush in melanoma, tamoxifen blush in breast cancer and the temozolamide enhancement in glioma. These changes occur as a function of time and dose (Table 2 &

Figure 3A–E). Halo enhancement appears by 3 months and peaks at 6 months. Awareness of these three types of radiation change provides a tool to help differentiate a normal halo from a recurrence or progression of disease. Type I reaction occurs within 3 months of treatment and at a median of 1.8 months. A hypodense region is noted on the portal venous phase and an isodense region is noted on the delayed phase. Liver veins are not displaced in the irradiated region as opposed to a tumor region. Type II occurs at 3–6 months. Similar to type I, a hypodense region is seen in the portal venous phase, but this type is differentiated by a hyperdense region in the delayed phase. Finally, after 6 months, type III reaction is characterized by isodense or hyperdense portal venous phase and a hyperdense delayed phase. The pathologic hypothesis or rationale for these changes has been attributed to small vessel damage and obstruction following radiation. Immediately following radiation, this results in congestion and the delayed enhancement resulting in edema and hypodensity. Then acute veno-occlusive disease occurs with the sinusoids receiving contrast later than the normal liver. Furthermore, the contrast is cleared later due to central vein occlusion. This is thought to be the pathologic reason for the hypodense portal phase and then late enhancement in the delayed phase for the type II reaction. In type III, there is distortion of the liver architecture resulting in central and efferent veins being replaced with

Figure 2. Well-defined versus ill-defined postradiation halos. (A) Poststereotactic body radiation therapy with well-defined hypervascular halo surrounding a treated metastatic colon cancer lesion (arrow heads). (B) In contrast, note an ill-defined heterogeneous halo of enhancement (arrow heads) surrounding a treated hypodense metastatic cholangiocarcinoma.

narrowed vessels that take on contrast early and fail to drain well in later phases. This results in the hyperdense regions seen in the portal venous and delayed phases [27].

Having an awareness of these normal changes, one can distinguish normal halos from recurrence (Box 1). A strong clue to suggest an abnormal reaction is if the enhancement does wash out on the delayed phase (Figure 4). Normal sustained enhancement is present in essentially all patients with only 1.6% of patients in the Park series demonstrating washout in the delayed phase [28]. Clearly, this may not apply to more cirrhotic patients as most of the studies were comprised primarily of Child–Pugh A patients. Child–Pugh B patients have poor blood flow in both the portal and venous systems and, therefore, may not demonstrate the enhancement patterns described. Another clue suggesting tumor recurrence or progression is that lesions tend to have a lower density than a radiation reaction

plus compresses or displaces vessels [25,26]. A final tip is that the normal halo may increase in size and density until 6 months. Therefore, increasing enhancement may not mean recurrence during this period; however, beyond 6 months an increasing halo may be indicative of disease [5].

These three types of changes can help distinguish normal halos from recurrence. They were identified over a decade ago and since then there has been dramatic changes in the way radiation is provided. In particular, higher doses have been possible with improved image guidance, and with greater understanding of radiation toxicity limits and radiobiologic guidance. Has this impacted on how we understand these three reactions? More recent studies suggest that these reactions may not progress sequentially and, depending on dose, patients may start at a higher level or present more or less typically. For example, we believe that type II reaction is seen more commonly with higher doses and

Table 2. Characteristic changes postradiation in primary and secondary hepatic cancers.		
Type of radiation reaction	Portal venous phase	Delayed phase
Type I: occurs within 3 months (median: 1.8 months)	Hypodense (liver veins not displaced)	Isodense
Type II: 3–6 months	Hypodense	Hyperdense
Type III: after 6 months	Isodense/hyperdense	Hyperdense

Figure 3. Three types of postradiation halos. (A & B) Type I halo: portal venous phase computed tomography (CT) of the liver, approximately 1 month after stereotactic body radiotherapy, demonstrates a hypoenhancing halo surrounding a small metastasis, marked by a fiducial marker (arrow) (A). The halo becomes isodense to the rest of the liver parenchyma on delayed phase image (arrow) (B). (C & D) Type II halo: portal venous phase CT of the liver demonstrates a hyperdense halo surrounding treated lesion (arrow) (C). The halo becomes hypodense compared with the rest of the liver parenchyma on delayed phase image (arrow) (D). (E & F) Type III halo: portal venous phase CT of the liver demonstrates a hyperdense halo surrounding treated lesion (arrow) (E). The halo becomes hypodense compared with the rest of the liver parenchyma on delayed phase image (arrow) (F). (C & D) Reprinted with permission from [26].

increased fractions. At higher stereotactic body radiotherapy (SBRT) doses, the type I reaction may not be seen as patients present with type II reactions almost immediately. There appears to be a linear, time-independent, 7 HU decrease in normal liver density with dose escalation resulting in a wider and more prominent hypodense region (0.65 HU decrease per 5 Gy) at the treated area [29,30]. The Colorado group also demonstrated that there may be a threshold of

30–35 Gy for hepatic injury. In other words, at lower doses there may be no halo, so if a halo is present after lower dose radiation, the caveat is that one must suspect recurrence.

Lobulated enhancement

Improved understanding of size and enhancement changes over time and dose have resulted in useful guidelines and categorizations. However, these size and enhancement tools are not used

routinely as they are not sufficient to help clinicians confidently assess radiation changes. The reason is that there is a great heterogeneity in patients treated with radiation; subgroup analysis is often not possible due to small case numbers. Most patients who receive SBRT are highly pretreated and do not show internal enhancement at recurrence. Indeed, a group of researchers from Indiana University have demonstrated that conversely the lack (vs presence) of enhancement may be the best method to determine response in HCC [15,17]. Furthermore, the width and regularity of the halo vary depending on the shape and dose of the irradiated field. So, one can be fooled by standard and current tools such as mRECIST. An intriguing new concept, called lobulated enhancement (LE) [31], may provide some additional clues when differentiating and predicting risk of tumor progression. Developed in Lille, France, this change is defined as an irregular, thick (>1 mm) and distinct peripheral enhancement with more than or equal to three lobulations (Figure 5) [32]. These lobulations, similar to petals of a daisy, seem to be highly predictive of progression. The study is based on only 46 metastatic liver patients treated with SBRT, but produced remarkable

Box 1. Differentiating normal enhancement and recurrence.

Tumor/recurrence

- If enhancement post-'conventional radiation' (<35 Gy equivalent), then this is not normal and may be cancer
- Tumor lower density than radiation reaction
- Vessels are compressed or displaced by tumor

Normal halo

- Lack of washout on delayed phase (primary clue)
- Radiation shape and area (e.g., geometric or arc base)
- Shrinkage of hypodensity

performance results. The median time to LE was 3.2 months. In combination with RECIST criteria, LE appeared before size-based progression. Sensitivity for progression was 89% and the specificity was 100%. The positive predictive value was 100% and the negative predictive value was 95.3%. Furthermore, radiologists assessed LE independently demonstrating a concordance of 97.9% suggesting this concept may be easily and consistently identified. Caveats include that there has been no external validation of this concept; has only been investigated in the

Figure 4. A 61-year-old man with pancreatoblastoma, metastatic to the right chest wall and liver. Note arterial enhancement surrounding the fiducial marker at the area of radiation treatment (arrowheads) (A) with washout, as demonstrated by hypodensity on delayed phase image (arrowheads) (B), compatible with disease recurrence.

metastatic setting; and the radiation was the less commonly used Cyberknife. This concept may not be applicable to infiltrative HCC patients with cirrhosis who often present with lobulations or poorly delineated conglomerations. In addition, patients presenting with lobulations were excluded from this study and comparison to mRECIST was not performed. However, this seems to be a very intriguing concept with very high test performance.

Future perspective

Radiation for liver lesions is a rapidly evolving therapeutic modality. Standardization in image interpretation has not been achieved [5] and the available data suggest that postradiation imaging changes may vary by technique, regimen and dose. Furthermore, the value of complementary imaging techniques, especially MRI and PET, may provide critical additional information to help distinguish benign from pathologic changes [33]. Active research in areas such as diffusion-weighted imaging suggests incorporation of these parameters provides clinically meaningful predictive information [34,35]. However, these techniques are not universally available, and controversy exists as to their utility [5]. Similarly, functional imaging has limitations due to normal uptake in radiated tissue caused by inflammation and regeneration. Further development and validation of these promising approaches is warranted. Another promising new technology

is hybrid PET/MRI platforms that combines the detailed morphologic and functional data derived from MRI with metabolic/functional data from PET to increase the overall sensitivity and specificity of restaging. As conformal external beam and stereotactic radiation treatment emerges as an effective option in the management of neoplastic disease of the liver, it will be increasingly important to analyze postradiation effects on imaging in a more systematic manner. This will allow for a more structured and uniform reporting of postradiation imaging hopefully leading to more informed clinical decision-making which could, in turn, drive improved outcomes in liver cancer.

Conclusion

Primary and secondary liver cancers are growing in incidence and have a high morbidity and mortality burden. Stereotactic body radiotherapy is an effective ablative technique and is often utilized in the management of liver tumors. Therefore, the need to reliably interpret postradiation changes in diagnostic imaging of the liver is of pressing importance. Few systematic criteria have been described to aid in discriminating benign from pathologic findings in livers treated with conformal radiotherapy techniques. We have summarized imaging findings characteristic of radiated liver parenchyma and described emerging techniques for imaging postradiation changes in the liver.

Figure 5. A 52-year-old patient with metastatic colorectal cancer to the liver, who underwent stereotactic body radiotherapy. Mass appears as a heterogeneous hypo-enhancing lesion before radiation (A). Note the marginal lobulated enhancement surrounding the mass (arrowheads) with overall increase in size of the mass 2 months following radiation (B). Later image demonstrates further increase in size and appearance of satellite lesions (C).

Data sharing

Dataset is available from the corresponding author at Michael.Lock@lhsc.on.ca.

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EXECUTIVE SUMMARY

- Radiation for liver is evolving. Therefore, our understanding and assessment for postradiation changes are evolving.

Important parameters to assess

- Size: alone, this parameter is insufficient until lesions are quite large and normal postradiation liver changes can result in erroneous measurements.
- Shape: normal radiation changes result in a dose-dependent decrease in density which makes interpretation difficult. Tumor density is lower than a radiation reaction normally. Vessel compression or displacement is usually indicative of tumor. Other problems such as cirrhosis, radiation intensity modulation and radiation beam shapes may further complicate interpretation.
- Halo: differentiating the three types of rim enhancement over time is critical. Lack of washout of the contrast in the delayed phase is the primary clue that the enhancement is normal.
- Lobulated enhancement (LE): defined as an irregular, thick (more than 1 mm) and distinct peripheral enhancement with more than or equal to three lobulations. It has a positive predictive value of 100% and a negative predictive value of 95.3% but may not be applicable to infiltrative hepatocellular carcinoma patients with cirrhosis.
- Predictable normal postradiation changes: nonenhancing areas may represent necrosis and increase in size until 3 months. Enhancing areas increase up to 6 months. Changes beyond this may represent abnormal changes and have been correlated with outcome.

Clinical end point questions

- First, for overall survival, progression on the 2–3-month image is sufficient to provide information that the prognosis is poor [36].
- Second, the best time to assess for maximum response is at 12 months for both complete remission and partial remission. If there is insufficient response at this point, additional treatment needs to be considered.
- Last, the assessment at 6–9 months may provide the earliest point to predict for progression and need for further treatment [31]. This period is likely the best time to assess for the success or failure of radiation.

Approach to distinguishing tumor from normal postradiation changes [32]

- If a lesion is shrinking, received a dose higher than 35 Gy and has a thin halo, then the lesion is considered controlled. Note that at lower doses (<35 Gy), there should be no halo.
- If a lesion is stable or increasing, one must account for expected changes at specific milestones (3 and 6 months since radiation) and assess for LE. If there is no LE, consider the disease to be controlled.
- However, if there is LE, then early local recurrence must be strongly considered.

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