Diagnostic and Interventional Imaging (2019) **100**, 39—46

ORIGINAL ARTICLE / *Cancer Imaging*

Clinical utility of one month imaging following selective internal radiation therapy

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KEYWORDS
Selective internal radiation therapy (SIRT);
Transarterial radioembolization;
Hepatocellular carcinoma;
Metastatic liver disease;
Treatment strategy

Abstract
Purpose: The goal of this retrospective review was to determine the clinical relevance of one-month post-treatment imaging in the selective internal radiation therapy (SIRT) patient population by reporting the incidence of change in clinical management.
Materials and methods: Between January 2012 and January 2016, 85 patients underwent 109 SIRT treatments for either primary or secondary hepatic malignancies. There were 59 men and 26 women with a mean age of 62.4 years (range: 39—89 years). Patients' medical records were retrospectively reviewed for procedural, historical, laboratory and imaging information. The imaging study was considered to have changed patients' clinical management if it resulted in the addition of a new procedure, canceling of a planned procedure or change in systemic therapy.
Results: The one-month post-treatment imaging findings led to management changes in 10 of 109 (9.2%) of treatments. When evaluated by cancer type, 2/61 (3.3%) hepatocellular carcinoma (HCC) treatments had management changed while 8/48 (16.7%) non-HCC treatments underwent management change ($P = 0.03$). This difference was also significant at multivariate analysis ($P = 0.03$; odds ratio: 0.17 [0.03—082]).
Conclusion: Management is rarely changed by one-month post-SIRT imaging in patients with HCC and thus is likely unwarranted. Conversely, in non-HCC patients, one month post-SIRT imaging led to a significant percentage of clinical management changes suggesting that one month imaging in this setting is likely warranted.

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https://doi.org/10.1016/j.diii.2018.07.005

Since its introduction approximately 20 years ago, selective internal radiation therapy (SIRT) has been found to be effective in the treatment of primary and secondary hepatic tumors [1—6]. The mechanism of treatment for SIRT is different than other locoregional therapies (LRT) of the liver. While transarterial chemoembolization (TACE) disrupts blood flow and delivers high dose local chemotherapy [7] and ablation induces coagulative necrosis through thermal injury [8], SIRT induces tumor death through high-energy beta-emission radiation [9]. This unique method of tumor treatment results in vastly different post-treatment imaging patterns compared with the other LRT. This difference can present an interpretative problem regarding tumor response on short-term follow up imaging post-SIRT [8,10].

Tumor response following LRT is evaluated by non-invasive imaging, typically using contrast enhanced multidetector computed tomography (CT), contrast enhanced magnetic resonance imaging (MRI), contrast enhanced ultrasound, or positron emission tomography (PET) CT, where degree of tumor contrast enhancement/radionuclide uptake, or the lack there of, serves as a surrogate for tumor response [11—13]. The goal of imaging has historically been to determine the extent of tumor response from LRT. However, post-therapy imaging should also detail any possible treatment related complication as well as tumor progression either within the liver or external to the liver that may alter patient management.

Because of the different mechanisms of tumor treatment by LRT, compared with the cytotoxic effects from standard systemic chemotherapy, new functional grading systems to assess for tumor response were devised, including the modified response evaluation criteria in solid tumors (mRECIST) and European Association for Study of the Liver (EASL) criteria [11,12]. When explicitly monitoring hepatocellular carcinoma (HCC) response post LRT, both of these grading systems use arterial hyperenhancement to correlate with residual, viable tumor while the lack of enhancement corresponds to tumor necrosis on multiphasic contrast enhanced CT or MRI [11]. While early imaging with multiphasic, contrast enhanced studies reliably reflect tumor response for TACE or ablation, the early imaging findings for SIRT are challenging to interpret and the determination of the presence or absence of disease cannot be made consistently [14,15]. Treatment effect is more reliably determined on imaging at 90 days following SIRT [14,15]. However, imaging at one-month post-SIRT is still frequently performed. This raises the question as to whether or not imaging at one month following SIRT is clinically warranted.

The goal of this retrospective review was to determine the clinical relevance of one-month post-treatment imaging in the SIRT patient population by reporting the incidence of change in clinical management.

Materials and methods

Patients

Institutional review board approval was obtained for this study, which conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained for each procedure. All patients who underwent SIRT between January 2012 and January 2016 at a single academic center were retrospectively reviewed. Patients who were lost to follow up prior to one month imaging, or had their first post-treatment imaging greater than 60 days after treatment were excluded. Fig. 1 demonstrates patient inclusion/exclusion, in total 100 patients underwent 130 SIRT treatments. Fifteen patients, who underwent 21 treatments, were excluded, because they were lost to follow up prior to one month imaging (10 patients) or the initial follow up imaging occurred greater than 60 days after SIRT (5 patients). The remaining 85 patients who underwent 109 treatments form this study's patient population. The cohort included 61 treatments in 50 patients for HCC and 48 treatments in 35 patients with non-HCC malignancies. The mean patient age was 62.4 years (range: 39.4—89.9 years) with 69.4% (59/85) men and 30.6% (26/85) women.

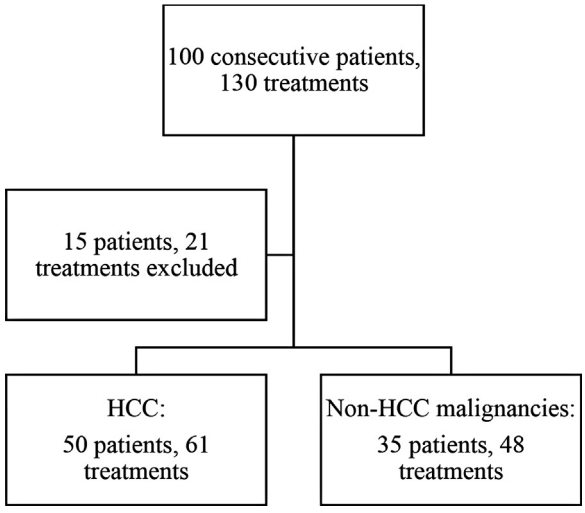

Figure 1. Flow diagram of patients treated with selective internal radiation therapy (SIRT) between 1/1/2012 and 8/1/2016 at a single academic institution. HCC: hepatocellular carcinoma.

Procedure

All patients underwent mapping followed by yttrium 90 (90Y) delivery in accordance with previously published techniques [1—6]. Patients were treated with either glass (TheraSphere®, BTG, London, United Kingdom) or resin (SIR-spheres, Sirtex Medical, New South Wales, Australia) at the discretion of the treating interventional radiologist. SIRT treatment variables including glass versus resin spheres and the dose of 90Y delivered were documented. The treatment zone (right or left lobe, single segment, greater than one segment but less than a lobe, or lobe plus one segment) was recorded.

Outcomes

The patients' electronic medical records were retrospectively reviewed to determine the type of cancer treated and whether or not there was untreated disease outside of the treatment zone (either intra- or extrahepatic). For patients with HCC, the underlying etiology of liver disease was recorded. HCC was diagnosed by accepted imaging standards [16] or biopsy while all other malignancies were diagnosed

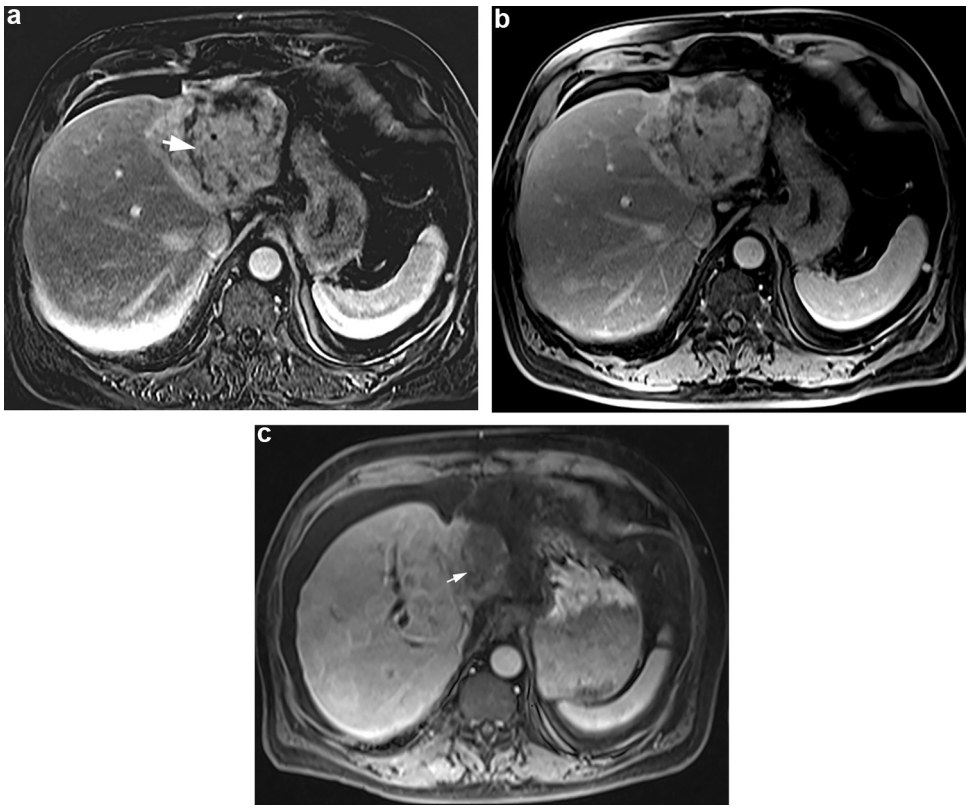

Figure 2. 66-year-old man with a large segment 4a hepatocellular carcinoma treated with selective internal radiation therapy (SIRT). a: arrow points to the lesion prior to treatment on subtracted contrast-enhanced T1-weighted magnetic resonance imaging (MRI) study; b: arrow points to diffuse enhancement on T1-weighted contrast-enhanced MRI one month following SIRT; c: follow-up contrast-enhanced T1-weighted MRI at 9 months shows no residual disease with complete response and associated necrosis (arrow).

by biopsy. Prior treatment histories were also reviewed including whether or not the patients had received prior systemic chemotherapy, external beam radiation, hepatic resection, TACE, or ablation. For those with metastatic disease, whether or not the primary tumor had been resected was noted. The model for end stage liver disease (MELD) [17] and Child Pugh scores at the time of SIRT were documented as were the alpha fetoprotein (AFP), creatinine, total bilirubin, albumin and international normalized ratio (INR). The number of lesions, largest lesion diameter and presence of portal vein invasion were also evaluated on the preprocedural imaging study and recorded.

The imaging modality used for both pretreatment and post-treatment was recorded as were the days between pre and post-treatment imaging. The days between SIRT and post-treatment imaging were noted as well. Fludeoxyglucose (^{18}F) was utilized as a tracer for all patients who underwent PET CT. Finally, whether or not additional liver lesions, new extrahepatic disease, or a treatment complication was identified on one month post-treatment imaging was documented (Figs. 2 and 3).

The primary outcome of treatment plan change was determined to have occurred if imaging resulted in the addition of a new procedure, canceling of a planned procedure, or change in systemic therapy. If a new lesion was found in an area, which was already scheduled for future treatment, this was not considered to have changed management.

All CT and MRI studies were conducted in accordance to the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) guidelines [16]. For all imaging studies, the report of the initial interpreting radiologist as well as an independent, retrospective review by an abdominal radiologist with 5 years' experience (T.S.) was performed. In case of difference in interpretation, the two interpretations were reconciled between the initially reporting radiologist and the study radiologist.

Statistical analysis

SAS (Cary, NC) was used for statistical analysis. *P* values were calculated using generalized estimating equation (GEE) in the form of logistic and multinomial regression to account for the within patient correlation. For sample sizes less than or equal to 5, Fisher's exact test was used. Variables with *P* values ≤ 0.1 at univariate analysis were included in the logistic regression multivariate analysis. A *P* value < 0.05 was considered to indicate statistically significant difference. All continuous variables were reported as mean $\pm$ standard deviation (SD), unless specified otherwise.

Results

A new lesion was found on one month post-treatment imaging in 13/109 treatments (11.9%). Three of these 13 treatments had hepatic lesions identified in a region that was scheduled to be subsequently treated. Therefore, the one-month post-treatment imaging changed management

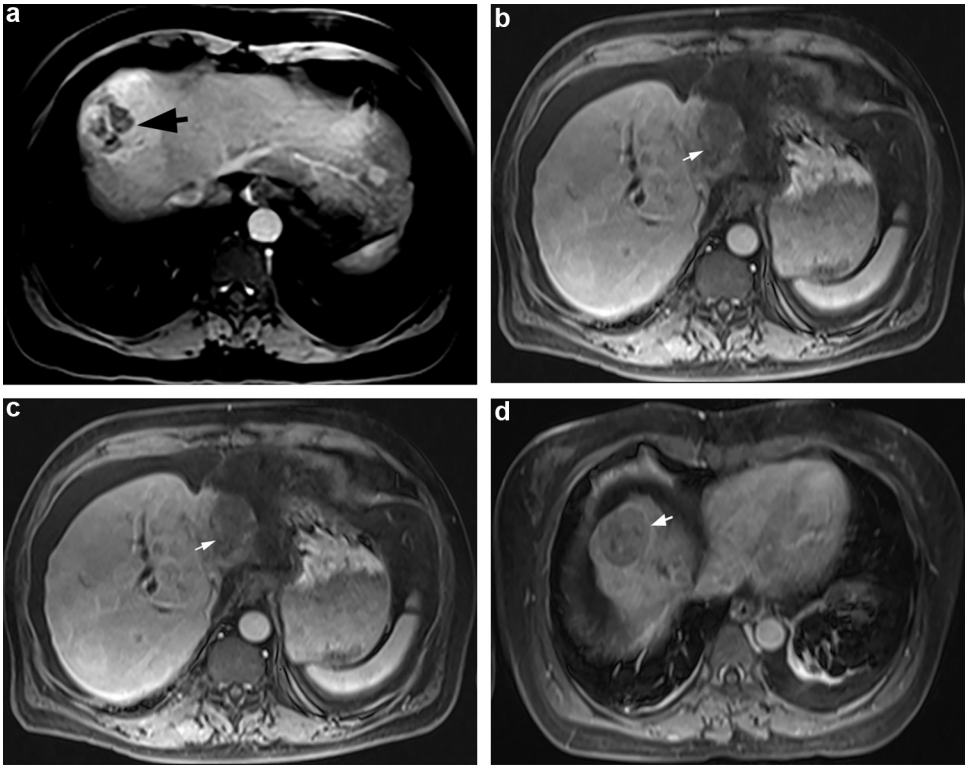

Figure 3. 58-year-old man with hepatocellular carcinoma of segment 7 treated with selective internal radiation therapy (SIRT). a: arrow points to the lesion on pretreatment contrast-enhanced T1-weighted magnetic resonance imaging (MRI) study; b: one month post imaging shows diffuse enhancement (arrow) of the treatment zone of unknown significance, similar to Fig. 2b on contrast-enhanced T1-weighted MRI; c and d: 3 month contrast enhanced T1 MRI in arterial (c) and portal venous (d) phases demonstrates clear residual disease (arrow).

in 10 treatments (10/109, 9.2%). Of these 10, 5 (50%) developed new intrahepatic tumor in an area, which had not been previously scheduled for therapy, 1 (10%) developed extrahepatic metastases, and 4 (40%) developed both new intra- and extrahepatic lesions. The cancer types treated are listed in Table 1 and pre- and post-treatment imaging modalities are listed in Table 2. Of the 18 treatments which had a preprocedural CT, 15 were non-HCC malignancies and 3 were HCC, while of the 8 treatments with post-procedural CTs 7 were non-HCC malignancies and 1 was HCC. All treatments with pre- (11) or post-(4) PET CT examination were non-HCC malignancies.

Univariate analysis

When divided as HCC versus non-HCC disease, management was changed in 2 of 61 (3.3%) HCC patients and 8 of 48 (16.7%) non-HCC patients. This difference was statistically significant ($P = 0.03$). Colorectal cancer (CRC) was the largest cohort in the non-HCC malignancy group with treatment change occurring in 3/22 (13.6%) treatments. There was no statistical difference in change in treatment outcomes when comparing CRC treatments to HCC treatments, or to the remaining non-HCC treatments ($P > 0.05$ for both). One patient (1/85, 1.1%) had radiation cholecystitis, given the imaging appearance and clinical symptoms, which was treated conservatively. As the treatment plan was unaffected, this patient was not one of the 10 who met the primary endpoint.

Table 1 Cancer types treated in 85 patients who underwent selective internal radiation therapy (SIRT).

Cancer types	Number of treatments performed
Hepatocellular carcinoma	61
Non-hepatocellular carcinoma malignancies	48
Colorectal cancer	22
Neuroendocrine	5
Renal cell carcinoma	3
Leiomyosarcoma	2
Cholangiocarcinoma	2
Choroidal melanoma	2
Lung cancer	2
Endometrial cancer	2
Medullary thyroid cancer	2
Breast cancer	2
Pancreatic adenocarcinoma	1
Esophageal cancer	1
Melanoma	1
Spindle cell sarcoma	1

The baseline characteristics prior to each treatment are given in Table 2. There was no significant difference in the creatinine, albumin and total bilirubin serum levels, INR, MELD or Child Pugh score between those patients who had a management change and those who did not ($P > 0.05$).

Table 2 Baseline and treatment characteristics.

Variable	Management change($n=10$)	No management change ($n=99$)	P value
Creatinine (mg/dL)	0.78 ± 0.21 [0.43—1.06]	0.9 ± 0.63 [0.51—6.66]	0.17
Total Bilirubin (mg/dL)	0.84 ± 0.54 [0.3—2.1]	0.95 ± 0.72 [0.1—3.7]	0.54
INR	1.13 ± 0.15 [0.96—1.46)	1.12 ± 0.16 [0.9—1.86]	0.46
Albumin (g/dL)	3.25 ± 0.46 [2.6—3.9]	3.33 ± 0.45 [1.9—4.4]	0.53
MELD score	8.4 ± 1.65 [7—11]	8.74 ± 2.72[6—22]	0.85
Child Pugh score	6.2 ± 0.92 [5—8]	6.17 ± 1.25 [5—10]	0.43
AFP prior to treatment	3105 ± 2612 [1257—4952]	1265 ± 5577 [2.6—40,635]	0.36
AFP following treatment	1598 ± 400 [1215—1881]	324.5 ± 942 [6.4—5233]	0.16
Pretreatment imaging modality			0.20
MRI	5 (50%)	75 (75.8%)	
CT	5 (50%)	13 (13.1%)	
PET CT	0 (0%)	11 (11.1%)	
Post-treatment imaging			0.88
MRI	9 (90%)	88 (88.9%)	
CT	1 (10%)	7 (7.1%)	
PET CT	0 (0%)	4 (4.0%)	
Size of largest tumor (cm)	8.23 ± 5.06 [1.8—17]	5.21 cm ± 4.14 [1—25]	0.19
Type of SIRT			0.85
Glass spheres	3 (10%)	35 (35.4%)	
Resin spheres	7 (70%)	64 (64.7%)	
History of prior TACE	4 (40%)	33 (33.3%)	0.78
History of prior ablation	1 (10%)	11 (11.1%)	0.99
History of prior resection			
Hepatic resection	2 (2.0%)	1 (1%)	0.42
Primary tumor resection	5 (50%)	28 (28.2%)	0.81
Prior chemotherapy	7 (70%)	35 (35.4%)	0.08
Disease outside treatment zone			0.10
Intrahepatic	2 (20%)	27 (27.3%)	
Extrahepatic	4 (40%)	10 (10.1%)	
Portal vein thrombosis	1 (10%)	11 (11.1%)	0.60
Number of lesions treated			0.19
1	3 (30%)	37 (37.3%)	
2	2 (20%)	21 (21.2%)	
3	1 (10%)	15 (15.2%)	
4	0 (0%)	6 (6%)	
5	0 (0%)	3 (3%)	
> 5	4 (40%)	17 (17.2%)	

Note results are presented as n (%) or mean ± standard deviation; numbers in brackets are ranges. AFP: alphafetoprotein; MELD: model for end-stage liver disease, INR: international normalized ratio, MRI: magnetic resonance imaging, CT: computed tomography, PET: positron emission tomography, SIRT: selective internal radiation therapy, TACE: transarterial chemoembolization, ⁝ untreated disease refers to untreated by SIRT.

The characteristics of the treatments are presented in Table 2. The treatment zone, use of glass or resin 90Y and presence of portal vein thrombosis, were all insignificant factors $P > 0.05$ when comparing those patients who had a management change and those who did not. Similarly, having undergone prior TACE, ablation, hepatic resection, or external beam radiation were not statistically significant $P > 0.05$. The mean SIRT radiation dose for those who had their management changed was 33.64 ± 9.5 (SD) mCi (range: 19—49.2 mCi), while for those without change had a dose of 40.32 mCi ± 30.0 (SD) mCi (range: 5.8—217.1 mCi) ($P = 0.13$). Patients who had undergone prior chemotherapy, 42/48 (87.5%) of the non-HCC cohort and 0/61 (0%) of the HCC cohort, were not statistically significantly different between the management change and non-management change cohorts ($P = 0.08$). No significant differences were found in groups with disease outside of the treatment zone (either intra- or extrahepatic) ($P > 0.05$), or with respect to lesion number or diameter of largest lesion treated ($P > 0.05$). Neither the etiology for the liver disease in the HCC patient nor the prior resection of the patient's primary tumor for metastatic disease proved to be significant ($P > 0.05$).

The average time between SIRT and the first imaging study was 32.9 ± 9.9 (SD) days (range: 13—45 days) in those patients with management change and 33.01 ± 10.5 (SD) days (range: 14—60 days) in those without ($P = 0.84$). There was no significant difference ($P = 0.85$) between the average time between pre and post-treatment imaging studies

comparing the management change cohort of 76.7 ± 18.6 (SD) days (range: 42—96 days) versus the 80 ± 31.7 (SD) days (range: 31—172 days) in the cohort without management change.

Multivariate analysis

At multivariate analysis, patients with HCC remained significantly less likely to have management changed based on one month imaging when compared to non-HCC malignancies ($P = 0.03$; odds ratio (*OR*): 0.17 [95%CI: 0.03—082]). Having received prior chemotherapy was found to be significantly associated with experiencing a change of management ($P = 0.04$; *OR*: 4.34 [95%CI: 1.08—17.50]).

Discussion

SIRT has become a mainstay for treatment of both HCC and metastatic disease to the liver [1—6]. Unlike TACE and ablation, SIRT induces tumor death via intra-arterial delivery of beta radiation [9]. Another difference is the lack of reliable tumor response determination at one month post-treatment imaging, a determination traditionally made with the other LRT [11,12]. Because tumor response cannot be reliably determined at one-month, the only remaining reason to image at this time point is if it will affect the treatment course. This raises the question as to whether there is any clinical utility of imaging SIRT patients at one month.

SIRT induces diffuse and prolonged enhancement within the treatment zone due to both edema and radiation effect which can easily be confused for residual disease or disease progression [8,18]. A frequently cited study reporting specifically on SIRT found that when using necrosis, an imaging grading system defined by the authors as lack of enhancement, analogous to the currently used mRECIST and EASL criteria, treatment response could be determined in a mean of 30 days [19]. While certainly the presence of some treatment response is commonly identified at 30 days following SIRT, this post-treatment response is frequently visualized as patchy enhancement around the edge of, or within, areas of necrosis [14,15]. Unfortunately, the presence of such enhancement has a poor positive predictive value for residual tumor when seen within 90 days of treatment [14,15]. Thus answering the clinically critical question of whether or not residual disease is present is not routinely possible.

A recent survey of Society of Interventional Radiology (SIR) members found that imaging follow up after SIRT was preferred at one month by 26 of 74 (35%) responders, while 32 of 74 (43%) preferred the first imaging to be obtained at three months [19]. These results differ from the nearly two thirds of responders who preferred one month follow up post-treatment for conventional TACE, drug eluting bead TACE and bland embolization 63% (54/86), 64% (53/83) and 64% (50/78) respectively [20]. These findings may reflect the difficulty with determining the level of treatment response at one month imaging following SIRT as compared to TACE.

The present study demonstrates that the one month, imaging findings were significant enough to trigger a management change in 10 of 109 cases (9.2%). An imaging study, which significantly alters management in nearly 1 out of 10 patients, would arguably be of meaningful value. However, when the treatment groups were divided into HCC and non-HCC cohorts, imaging was found to be clinically significant in 2 of 61 HCC treatments (3.2%) and 8 of 48 non-HCC treatments (16.7%), a statistically significant difference ($P = 0.03$) which remained on multivariate analysis [$P = 0.03$; odds ratio (*OR*) 0.17 (0.03—082)]. These findings would suggest that patients with HCC are very unlikely to receive clinical benefit from one month imaging. On the other hand, the percentage of clinically significant imaging studies within the non-HCC cohort would likely support the use of one month imaging.

The difference in clinical relevance seen between the HCC and non-HCC cohort may be due to the systemic nature of the disease in the non-HCC cohort. Another possible explanation is the fact that the majority of the non-HCC patients had received prior treatment. This may have led to sub selection of a more aggressive tumor strain. This theory may be further suggested by the statistical significance of having received prior chemotherapy on multivariate analysis. However, this finding must be interpreted with caution given the high percentage (87.5%) of non-HCC patients who had received prior chemotherapy as compared to HCC patients (0%).

Another possible argument for performing one month imaging is to detect post-SIRT complications. The most common adverse events are increases in hepatic related laboratory markers (liver function tests) and abdominal pain [21—23], both of which are managed conservatively. Imaging does not play a role with the diagnosis or treatment of these adverse events. More dreaded complications from non-target embolization to other portions of the abdomen such as the stomach and gallbladder have been rarely reported [21—23]. The present study found one complication, giving an overall extrahepatic complication rate of 0.9% consistent with previously reported complication rates [21—23]. The case of radiation cholecystitis was diagnosed with a combination of one month imaging and clinical symptomatology. It was successfully treated with supportive care and the patient did not reach the primary endpoint of management change. Also, this patient was symptomatic, a dependable feature of previously reported extrahepatic complications [21—23]. This suggests that the likelihood of a significant adverse event being clinically silent but apparent on imaging is quite low. Therefore, it does not seem reasonable to subject patients to the increased cost, both monetary and patient time as well as possible radiation exposure, of imaging at one month to search for complications unless the patient is clinically symptomatic.

Of note, the presence of disease outside of the treatment zone, either intra- or extrahepatic, was not found to be a significant predictor of clinical relevance. Several prior authors have found that an association between the presences of extrahepatic disease and poorer overall survival [24,25], while other authors have found that the presence of extrahepatic disease in chemorefractory metastatic patients treated with SIRT does not significantly influence overall survival [21]. The lack of significance of this variable may relate to the relatively short time period between pre- and post-treatment imaging (73.8 days). This relatively short time frame may result in the inability to perceive significant changes in disease burden due to imaging modality limitations.

No clear superiority of one imaging modality for pre- and post-treatment imaging has been established. Each imaging modality provides its own advantages and disadvantages. CT has excellent spatial resolution, MRI provides superior contrast resolution, and PET CT affords physiologic information [26]. Given the in-ability to reliably determine tumor response in the short term following SIRT, multiple authors have attempted to either find a new technique or to try to improve current methods. Perhaps, the most promising additional technique currently is diffusion-weighted (DWI) MRI [27—31]. Some authors have been able to show encouraging results in predicting tumor response at one month using DWI [27,28]. However, others have shown no differences when compared to other tumor response assessment methods such as EASL and an inability of DWI to accurately predict pathologic response [29,30]. While this area continues to be of interest, the variety of DWI techniques and disparity in results suggest it is not yet ready for everyday clinical use in this setting [31]. Thus, although DWI MRI is routinely used in our post-SIRT patients, its importance remains to be determined.

This study has several limitations, including its single institution data accumulation and the study's retrospective nature. The heterogeneity of the non-HCC patients also limits the ability to assess the validity of findings in individual cancer types. However, this variability also reflects a realistic clinical practice. There is also variation in the modalities used in both the pre- and post-treatment phases. A reproducibility study was also not undertaken for the primary findings, although, studies were reviewed by at least two diagnostic radiologists. Finally, this study lacks post-treatment pathologic correlation.

In conclusion, in this study, patients who undergo treatment of HCC with SIRT rarely gain clinically relevant data from their one-month post-treatment imaging, suggesting it is not warranted. Conversely, those with non-HCC disease are significantly more likely to gain clinically relevant information from one month post-treatment imaging and it is likely warranted in this population.

Disclosure of interest

The authors declare that they have no competing interest.

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