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Relation	

An overview of stereotactic body radiation therapy for hepatocellular carcinoma

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Abstract

Introduction: According to several guidelines, stereotactic body radiation therapy (SBRT) for early hepatocellular carcinoma (HCC) can be considered an alternative to other modalities, such as resection, radiofrequency ablation (RFA), and transarterial chemoembolization (TACE), or when these therapies have failed or are contraindicated. This article reviews the current status of SBRT for treatment of HCC.

Areas covered: From the results of many retrospective reports, SBRT is a promising modality with an excellent local control of almost 90% at 2-3 years and acceptable toxicities. Currently there are no randomised trials to compare SBRT and other modalities, such as resection, RFA, and TACE, but many retrospective reports and propensity score matching have showed that SBRT is comparable to the different modalities. Repeated SBRT for intra-hepatic recurrent HCC also resulted in high local control with safety and satisfactory overall survival, which were comparable to those of other curative local treatments

Expert opinion: Despite the good results of SBRT, the conclusions of the comparisons of SBRT and other modalities are still controversial. Further studies, including randomised phase III studies to define that patients are more suitable for each curative local treatment, are needed.

Keywords

stereotactic body radiotherapy (SBRT), hepatocellular carcinoma (HCC), resection, radiofrequency ablation (RFA), transarterial chemoembolisation (TACE)

Article highlights

- According to several guidelines, SBRT can be considered an alternative to ablation/embolization or when these therapies have failed or are contraindicated.
- Promising results of SBRT have been reported in early HCC, with high local control (LC) rates that generally range from 70-100% at 2-3 years and overall survival rates that range from 60-70%.
- The most frequent adverse effects were generally mild, and associated with liver injury, such as the elevation of total bilirubin and transaminase and the decrease of platelets and ascites. Gastrointestinal toxicities, central biliary tract stenosis, and portal vein thrombosis should be evaluated as low incident toxicities.
- For evaluation after SBRT, residual early arterial enhancement disappeared within 6 months in most cases. An early assessment within 3 months may result in a misleading response evaluation.
- Currently there are no randomised trials to compare SBRT and other modalities, such as resection, RFA, and TACE, but many retrospective reports and propensity score matching reports, for the comparison of the different modalities, have been published. Compared to TACE, SBRT could improve LC. Compared to RFA and resection, the results are still controversial.
- Combining SBRT and immune checkpoint inhibitor has showed promising data.

1. Introduction: Current status of SBRT for HCC

Liver cancer is the second leading cause of cancer-related death worldwide, despite being ranked sixth in incidence [1]. Hepatocellular carcinoma (HCC) is the most common pathological diagnosis for liver cancer patients. According to the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy, resection, transplantation, and ablation, such as radiofrequency ablation (RFA), are recommended as the first-line treatments for early-stage hepatocellular carcinoma (HCC) [2]. However, because of underlying cirrhosis or the presence of multifocal tumours arising from viral infection, only about 38% of patients who were initially diagnosed with HCC were eligible for resection [3]. Compared to resection, RFA produces comparable local control (LC) but is less invasive and easily repeated [4]. However, it is limited by ultrasonographically invisible HCCs or tumours located near large vessels and in deep layers of the liver. Transarterial chemoembolisation (TACE) is often indicated for patients with HCC unfit for resection or RFA, regardless of tumour size, location, or number [5, 6]. However, it offers less LC than resection or RFA [3]. Promising results of stereotactic body radiotherapy (SBRT) have been reported in early HCC, with high LC rates that generally range from 70-100% at 2-3 years and overall survival (OS) rates that range from 60-70% [7-15]. However, SBRT is not considered to be a curative treatment under several treatment guidelines due to sparse evidence, and it is usually not indicated for first-line treatment of localised HCCs [2, 16, 17]. According to several guidelines, SBRT can be considered as an alternative to other modalities, such as resection, radiofrequency ablation, and transarterial chemoembolisation [2, 16].

2. SBRT for HCC

2.1 Patient eligibility

According to the general eligibility criteria in several reports [7-15], typically suitable patients include the following: 1) primary nodular HCC that has been pathologically proven or clinically diagnosed based on typical enhancement patterns on either dynamic CT, dynamic MRI, or perflubutane-enhanced ultrasound; 2) less than three HCC nodules, each up to 50 mm in diameter without extrahepatic metastases; 3) inoperability because of poor general condition or surgery refusal; 4) unsuitability for RFA because of tumour location (on the liver surface has a particularly high risk of pneumothorax, and near the porta hepatis), tumour invisibility on ultrasonography, bleeding tendencies, or refusal of RFA; 5) a Child-Pugh score of A or B; 6) an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2;7) appropriate organ functions, and so on. Patients were usually excluded if they suffer from uncontrolled ascites, tumours located close to the bowel, oesophageal varices with a high risk of bleeding, severe infection, coexisting cancers, interstitial pneumonitis, pulmonary fibrosis, severe emphysema, or psychiatric disease. Patients with a prior history of radiotherapy at the same site and pregnant patients were also excluded.

2.2 Treatment procedure

SBRT was performed via three-dimensional conformal radiotherapy (3D-CRT) or volumetric modulated arc therapy (VMAT) with respiratory motion management, such as the breath-hold technique, abdominal compression, respiratory gating, or tumour tracking. Verification using several image guidance methods is essential for SBRT. The gross tumour volume (GTV) is defined as the volume of the primary tumour on dynamic CT or MRI. The clinical target volume (CTV) is usually equated to the GTV, in many institutions. In several institutions, CTV is expanded from the GTV by the addition of a 2-5 mm margin. The internal target volume (ITV) depends on the respiratory motion management strategy at each institution, such as free breath or abdominal compression using 4DCT [9, 11, 14], breath-hold technique [10], and tumour tracking [8]. The planning target volume (PTV) also depends on

the set-up management strategy at each institution and is usually added to the ITV with a 3-5mm margin.

As shown in Table 1, various dose-fraction schedules, usually 24-60 Gy in 3-6 fractions, were used in previous reports [7-15]. The dose is either prescribed to isocentre or maximum dose (isocentre prescription) or to a surrounding isodose (usually 60-80% of the maximum dose) covering 95-100% of the PTV (volume prescription). Compared to isocentre prescriptions, volume prescriptions have a dosimetric advantage of a steep dose gradient within the PTV, which leads to tight conformity with a steep and isotropic dose fall-off and high dose delivery to the PTV (Figure 1). Jang et al. compared several dose-fraction schedules of SBRT, such as >54 Gy, 45-54 Gy, and <45 Gy in 3 fractions, using converting the biologically equivalent dose (BED) between different fractionations for patients with HCC. Higher dose-fractions (>54 Gy) improved the 2-year LC and OS, significantly (the doses of >54, 45–54, and <45 Gy were 100%/71%, 78%/64%, and 64%/30%, respectively, $p = 0.009$ in LC/$p < 0.001$ in OS) [17]. Despite using BED, higher doses may improve treatment results, but there is no clear evidence about the optimal dose-fraction schedule of SBRT for HCC. Further investigation will be needed.

Dose constraints for the planning organ at risk volume, such as liver, stomach, and small bowel were described in quantitative analyses of normal tissue effects in the clinic (QUANTEC) [18, 19]. According to the consensus at the Asia-Pacific Primary Liver Cancer Expert meeting, a dose constraint of >700 mL of normal liver is received <15 Gy in three to five fractions is important [20]

2.3 Outcomes of SBRT

Table 1 shows several retrospective and prospective results of SBRT for HCC, with an excellent LC of almost 90% at 2-3 years. A recent meta-analysis of 32 published studies involving 1950 HCC patients who underwent SBRT, showed that 3-year OS and LC were

48.3% and 83.9%, respectively, and severe complications rarely occurred [21]. Prognostic factors were tumour size for both OS and LC, and a marginal radiation dose for LC. Kimura et al. reported the results of the multicentre prospective study of SBRT for untreated solitary HCC [15]. A total of 35 naïve patients who were unfit for resection or RFA underwent SBRT with 40 Gy in 5 fractions. The 3-year OS was 77.7%, which was superior to the expected 3-year OS of 70% with a 50% threshold, and the 3-year LC rates were 90.0%. These results could be a landmark to compare with the results of other first-line treatments.

2.4 Toxicities of SBRT

The adverse effects of SBRT are generally mild. Table 1 shows the incidence of toxicities ≥ grade 3, ranged from 2.4 to 30%, in several reports. The most frequent adverse effects were associated with liver injury, such as the elevation of total bilirubin and transaminase and the decrease of platelets and ascites. Radiation-induced liver disease (RILD) is a well-known phenomenon which involves anicteric hepatomegaly, ascites, and elevated alkaline phosphatase and is sometimes fatal after conventional radiation therapy [22]. RILD has been divided into two subtypes, “classic”, as described above, and “non-classic”, which is not fatal and applies to the SBRT area. For the determination of the feasibility of SBRT, it is very important to evaluate background liver function. An association between pre-treatment CTP scores and the development of liver toxicity has been observed in several other studies [9, 10, 23]. XXX reported that the incidence of grade ≥3 toxicity was higher in CTP class B than in class A ($p = 0.0127$) in 65 patients [10]. Lasley et al. reported that although there was no critical liver dose-volume constraint correlated with toxicity for CTP class A patients, CTP class B patients experiencing grade 3 or 4 liver toxicity had significantly higher mean liver dose, higher dose to one-third normal liver, and larger volumes of liver receiving low doses, such as 2.5 to 15 Gy in 2.5-Gy increments [23]. From these results, more severe dose constraints could be needed for patients with CTP class B.

Gastrointestinal (GI) toxicities have been reported by several authors [13, 24]. Kang et al. reported that 5 (10.5%) of 47 patients experienced more than G3 GI toxicity, including grade 4 gastric ulcer perforation in 2 patients (4.3%). They concluded that pre-existing gastro-duodenal disease with cirrhosis was a significant risk factor, because in patients with liver cirrhosis, portal hypertension probably affects the gastrointestinal mucosal defensive and healing mechanisms, whereas liver cirrhosis increases GI toxicity. Bae et al. suggested that the maximum max point dose of the GI tract is a valuable predictor of severe GI toxicities [24]. In general, it is recommended that the target proximity to the luminal GI tract should be more that 2 cm from the tumour. Central liver toxicities, such as central biliary tract (CBT) stenosis and portal vein (PV) thrombosis, have been also reported [25-27]. Eriguchi et al. reported that only 2 patients (3.6% in 55 patients) experienced asymptomatic bile and concluded that SBRT for liver tumours adjacent to the CBT was feasible with minimal biliary toxicity [25]. However, Toesca et al. reported that Grade 3 ≥ CBT stenoses were observed in 7 patients (17.5% of 40 patients) and recommended the limiting dose of CBT to $V_{BED10}40 <$ 37 cc and $V_{BED10}30 < 45$ cc [26]. Takahashi et al. reported that Grade 3 ≥ PV thrombi were observed in 3 patients (4.8% in 63 patients), and concluded that PV thrombosis may be necessary to be considered in patients with a higher Child-Pugh class, with higher doses received to 2% of the PV volume [27].

3. Evaluation method of SBRT

For the evaluation of SBRT, various methods, such as the response evaluation criteria in cancer of the liver (RECICL) [28], the Modified Response Evaluation Criteria in Solid Tumors (mRECIST), [29] and dynamic CT with or without tumour enhancement [30] have been used to evaluate tumour response. However, there are cases that are difficult to evaluate the treatment effects. We evaluated four pattern types of dynamic CT appearance of tumour

responses after SBRT in 59 patients with 67 tumours; type 1, continuous lipiodol accumulation without early arterial enhancement (26 lesions, 38.8%); type 2, residual early arterial enhancement within 3 months after SBRT (17 lesions, 25.3%); type 3, residual early arterial enhancement more than 3 months after SBRT (19 lesions, 28.4%); and type 4, shrinking low-density area without early arterial enhancement (five lesions, 7.5%) [31]. From the results, which residual early arterial enhancement disappeared within 6 months in most cases, we concluded that early assessment, within 3 months, may result in a misleading response evaluation. Figure 2 shows the case of the residual early arterial enhancement over 6 months. Mendiratta-Lala et al. reported the radiology-pathology response correlation in 10 patients with successful response (defined as >90% necrosis on explant pathology or declining alfa-fetoprotein to normalization within 1 year after SBRT without other treatment). Four of 10 lesions had persistent central arterial hyperenhancement 3 to 12 months after SBRT, and persistent wash-out was common up to 12 months (9 of 10) in CT or MRI follow-up [32]. They also reported MRI evaluation of HCC after SBRT in 62 patients and post-SBRT arterial phase hyperenhancement was observed in 39 patients (58%) [33]. Mastrocostas et al. suggested that imaging before 3 months post-SBRT may underestimate the response [34], and standard response assessment such as mRECIST should be used with caution, particularly in the early phases after SBRT [32-34]. Validated guidelines for the imaging assessment of post-SBRT tumour response are warranted by further evaluation.

4. Comparison with the other modalities

Currently there are no randomised trials to compare SBRT and other modalities, such as resection, RFA, and TACE, but many retrospective reports and propensity score matching (PSM) reports, for the comparison of the different modalities, have been published.

4.1 The comparison with TACE

Huo et al. reported a meta-analysis of 25 articles from several databases, such as Medline, PubMed, and others to compare TACE alone and TACE plus radiation therapy, including SBRT, retrospectively [35]. The pooled median survival for TACE plus radiation therapy (RT) was significantly better than that for TACE alone (22.7 months vs 13.5 months; $p < .001$, respectively). The benefits of TACE plus RT continuously increased for 2-, 3-, 4-, and 5-year survivals. Sapir et al. compared TACE (84 patients with 114 lesions) and SBRT (125 patients with 173 lesions) using PSM for 1 to 2 HCCs [36]. The 2-year LC was 91% for SBRT and 23% for TACE (hazard ratio 66.5, $p < .001$), and grade ≥3 toxicity occurred after 13% and 8% of TACE and SBRT treatments, respectively ($p = 0.05$). They concluded that SBRT is a safe alternative to TACE and provides better LC, with no observed difference in OS. Many patients underwent SBRT combined with TACE, because there are several theoretical advantages of the combination with TACE, such as tumour shrinkage, remaining lipiodol as a target for image-guided radiotherapy, and enhanced sensitivity to irradiation. However, the effectiveness of the combination with TACE is still unknown. For small HCCs, there were no significant differences between both groups in 2-year OS and LC, retrospectively (OS; 78.6% in SBRT alone vs, 80.3% in SBRT+TACE, $p = 0.6583$, LC; 95.4% in SBRT alone vs, 98.5% in SBRT+TACE, $p = 0.4239$) [37]. In contrast, for large HCCs >5 cm, 5-year OS of SBRT+TACE was significantly better than that of SBRT alone, retrospectively (46.9% in SBRT+TACE vs 32.9% in SBRT alone, $p = 0.047$). The authors concluded that SBRT+TACE may be an effective option for large HCCs > 5cm [38].

4.2 The comparison with RFA

Wahl et al. reported the retrospective comparison of RFA (161 patients with 249 lesions) and SBRT (63 patients with 83 lesions), the endpoint of this study was freedom from local progression (FFLP) [39]. In univariable analysis, treatment modality (RFA vs SBRT) was

associated with local progression (hazard ratio = 2.63, p = 0.016), in particular, for tumours ≥2 cm, there was decreased FFLP for RFA compared to SBRT (HR, 3.35; p = 0.025). Hara et al. compared the outcomes of RFA and SBRT for early-stage HCCs using a PSM of 106 patients, and the 3-year OSs for RFA and SBRT were comparable (69.1% and 70.4%, respectively; p = 0.86) [40]. Additionally, Rajyaguru et al. compared RFA (3684 patients) and SBRT (296 patients) from the National Cancer Database for stage I-II HCC [41]. After PSM, 5-year OS was 29.8% in the RFA vs 19.3% in the SBRT (p = 0.001). This study suggested that treatment with RFA yields superior survival compared to SBRT for nonsurgically managed patients with stage I or II HCCs. However, several investigators commented that this report has several critical limitations, such as selection bias.

4.3 The comparison with resection

Recently, a comparison of resection and SBRT has been reported. Su et al. compared with resection (35 patients) and SBRT (82 patients) for 1-2 HCCs ≤5 cm and Child-Pugh A cirrhosis [42]. After PSM, 5-year OS was 69.2% in the resection group vs 74.3% in the SBRT group (p = 0.405) with a similarity of hepatotoxicity and local effects between the 2 groups. They concluded that SBRT has an advantage over resection by being less invasive. Additionally, Nakano et al. compared resection (254 patients) and SBRT (27 patients) for 1-3 HCCs ≤3 cm using PSM [43]. The 5-year OS was 75.2% in resection and 47.8% in SBRT (p = 0.0149). They concluded that although SBRT may be an effective alternative treatment for inoperable patients with early HCC, resection should be considered as the first-line treatment for patients deemed eligible for surgery.

5. Repeated SBRT -Comparison with the other modalities in recurrent tumours-

Because of multifocal nature, according to a Japanese survey, 29% and 87% of patients with HCC experience intrahepatic recurrence within 2 years following the first treatment and for all follow-up durations, respectively [44]. Therefore, repeated locoregional therapies play an important role in the clinical setting. In principle, the treatment strategy for patients with recurrent HCC following local therapies such as resection or RFA should be designed to follow the same criteria used for treating HCC at the initial onset [45]. In particular, repeated resection is considered a feasible option [46, 47]. However, this is often offered to highly selected patients and contraindicated in most cases. In these highly selected patients, based on an assessment of 22 studies of 1125 patients with a median age of 61 years, the median OS was 52 months (range, 22–66 months), and the 3- and 5-year OS rates after repeated hepatectomy were 69% (range, 41–88%) and 52% (range, 22–83%), respectively [48]. Repeated RFA is another treatment option for these patients. Survival following RFA is comparable to that following surgical resection [49]. Sun et al. reported that RFA conferred a shorter hospital stay and relatively low treatment-related morbidity and achieved similar OS to that by repeated resection; the estimated 3- and 5-year OS rates from the date of treatment of the first recurrence were 82.7% and 56.4% in the repeated resection group and 77.2% and 52.6% in the RFA group, respectively ($p = 0.89$) [50]. Rossi et al. reported the high repeatability of RFA with safety to control for intrahepatic recurrences [51]. They retrospectively analysed a prospective series of 706 patients with 859 HCCs who underwent RFA, and overall, there were 877 episodes of recurrence (1–8 per patient); 577 (65.8%) of these patients underwent RFA that achieved complete responses in 557 (96.5%) patients with no procedure-related deaths. The 3- and 5-year OS rates after repeated RFA were 67.0% and 40.1%, respectively.

Accordingly, repeated SBRT has also been required frequently. However, given the concerns of RILD, the efficacy and safety of repeated SBRT has not been established. Our experience of 24 patients with 53 tumours who underwent repeated SBRT [≥2 courses (median 2 times; range, 2–4 times)] showed that 3-year OS and LC rates were 75% and 97.4%, respectively [52]. The frequency of grade 3 toxicities such as transaminase elevation, decreased platelet count, and ascites were observed in 4 patients (16.7 %) in the first course and 5 patients (20.8 %) in the second course or beyond. Repeated SBRT for intra-hepatic recurrent HCC resulted in high local control with safety and satisfactory OS, which were comparable to those of other curative local treatments, as described above. SBRT is important for treating intra-hepatic recurrent HCC.

6. SBRT as a bridging therapy to transplantation

Liver transplantation **(**LT) is the first treatment choice for patients who meet the Milan criteria; single tumours less than 5 cm or ≤3 nodules ≤3 cm [2]. Theoretically, LT can cure not only the tumour but also the underlying cirrhosis. There are two scenarios in bridging therapy to LT such as neo-adjuvant treatment, which minimizes tumour progression while the patient is waiting for LT, and down-staging policies, which down-stages patients' tumours to within Milan criteria limits. Locoregional therapies, including SBRT, can be considered bridging therapies. Table 2 summarizes treatment results of SBRT as a bridging therapy [53-57]. Number of patients was not as many and rate of patients with CP class A was not as high. Several dose-fraction schedules were used, but they were not high compared to usual SBRT. OS and disease-free survival ranged from 70 to100%, and drop-off rate ranged from 10 to 30%. Sapisochin et al. reported the safety and efficacy of SBRT (n = 36) in an intention-to-treat analysis compared to TACE (n=99) and RFA (n = 244) as a

bridge therapy [58]. The drop-out rate was similar between groups (16.7% in SBRT group vs. 20.2% in TACE group and 16.8% in RFA group, p = 0.7). Five-year OS after LT was also similar between groups (75% in SBRT group vs. 69% in TACE group and 73% in RFA group, p = 0.7). Therefore, the patients who received SBRT were generally not candidates for TACE or RFA because of poor liver function, the incidence of impairment of liver function was significantly higher in the SBRT group than that in the TACE and RFA groups (38.9% in SBRT group vs. 19.4% in TACE group and 13% in RFA group, p = 0.001). They concluded that SBRT can be safely utilized as a bridge to LT in patients with HCC as an alternative to conventional bridging therapies.

According to the results of these reports, SBRT is effective as a bridge therapy. However, there are several problems to solve, such as the ideal dose-fraction schedule, the optimal timing, the number of lesions which should be treated, and others."

7. Conclusion

Despite good results of SBRT including repeated SBRT, the conclusions of the comparisons of SBRT and other modalities, such as resection, RFA and TACE, are still controversial. Further studies, including randomised phase III studies to define which patients are more suitable for each curative local treatment, are needed.

8. Expert opinion

8.1 A comparison of SBRT and other modalities for naïve patients

As described above, the conclusions of the comparisons of SBRT and other modalities are still a controversial issue. The results of SBRT have been influenced by several factors. One

of the factors is that many patients whose treatment was combined with TACE were involved. Another factor is that most studies included patients who have received previous treatments, such as resection, RFA, and TACE. Because of these factors, OSs of published SBRT series may have been compromised. In particular, inclusion of many non-naïve patients in the SBRT series may have misled these comparisons. Table 3 shows the results compared to the results of other modalities as a first-line treatment [3, 15, 59-62]. The 3-year OSs and recurrence-free survivals (RFS) ranged from approximately 75-90% and 60% in surgery to 70-75% and 30-50% in RFA, respectively [3,59-62]. Three-year intra-hepatic recurrence-free rate (IHRF) was 40% in RFA [62]. Our data [15] found a 3-year OS and IHRF of 77.7% and 60.4%, respectively [15]. From these results of naïve patients, OS after SBRT was excellent, despite patients being unfit for resection and RFA. Although further studies, including a randomised phase III study to define which patients are more suitable for each curative local treatment, are needed for SBRT to be listed as one of the recommended local treatment options for early-stage HCC in the guidelines.

8.2 Five-year view

Most controversial is the combination of radiation therapy with immune checkpoint inhibitor (ICI). Local radiation therapy can produce immune-mediated systemic responses and induce an "abscopal effect". Radiation, combined with checkpoint blockade immunotherapy, increases tumour cell susceptibility to immune-mediated cell death [63]. Kim et al. reported that the level of soluble programmed cell death ligand-1 (sPD-L1) in HCC patients treated with radiotherapy, including SBRT, was significantly increased. In addition, the sPD-L1 level continuously increased in the SBRT group compared to the conventional radiation therapy group. This suggests that SBRT might be better than conventional fractionated RT for combined use with immune checkpoint inhibitors [64]. In a clinical setting, Tang et al. reported a phase I trial testing SBRT with cytotoxic T lymphocyte antigen 4 (CTLA-4) and

ipilimumab for patients with metastatic solid tumours of the liver or lung refractory to standard therapies. They concluded that combining SBRT and ipilimumab was safe with a 10% partial response in non-irradiated lesions, and irradiation to the liver produced greater T-cell activation than did irradiation to the lung [65]. The most interesting clinical question is whether ICI can reduce intra-hepatic recurrence, lymph node, and distant metastasis after SBRT, for early-stage HCC. Several more studies are ongoing, and these results are expected in the near future.

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Figure Legends

Fig. 1. Typical dose distribution of volume prescription

Prescribed dose (40 Gy) covered 95% of PTV, and the maximum dose was 143% of the prescribed dose (70% isodose).

Fig. 2. A case of persistent early arterial enhancement over 6 months.

Dynamic computed tomographic appearance of tumor responses (arterial phase). (A) Dose distribution (48 Gy/4 fractions). (B) Before stereotactic body radiotherapy (SBRT), early arterial enhancement is visible (red arrow). (C) After two and (D) after 6 months, early arterial enhancement is more evident than before stereotactic body radiotherapy (red arrow). (E) After 11 months, enhancement remains, although the tumor is shrinking (red arrow).

Fig. 1

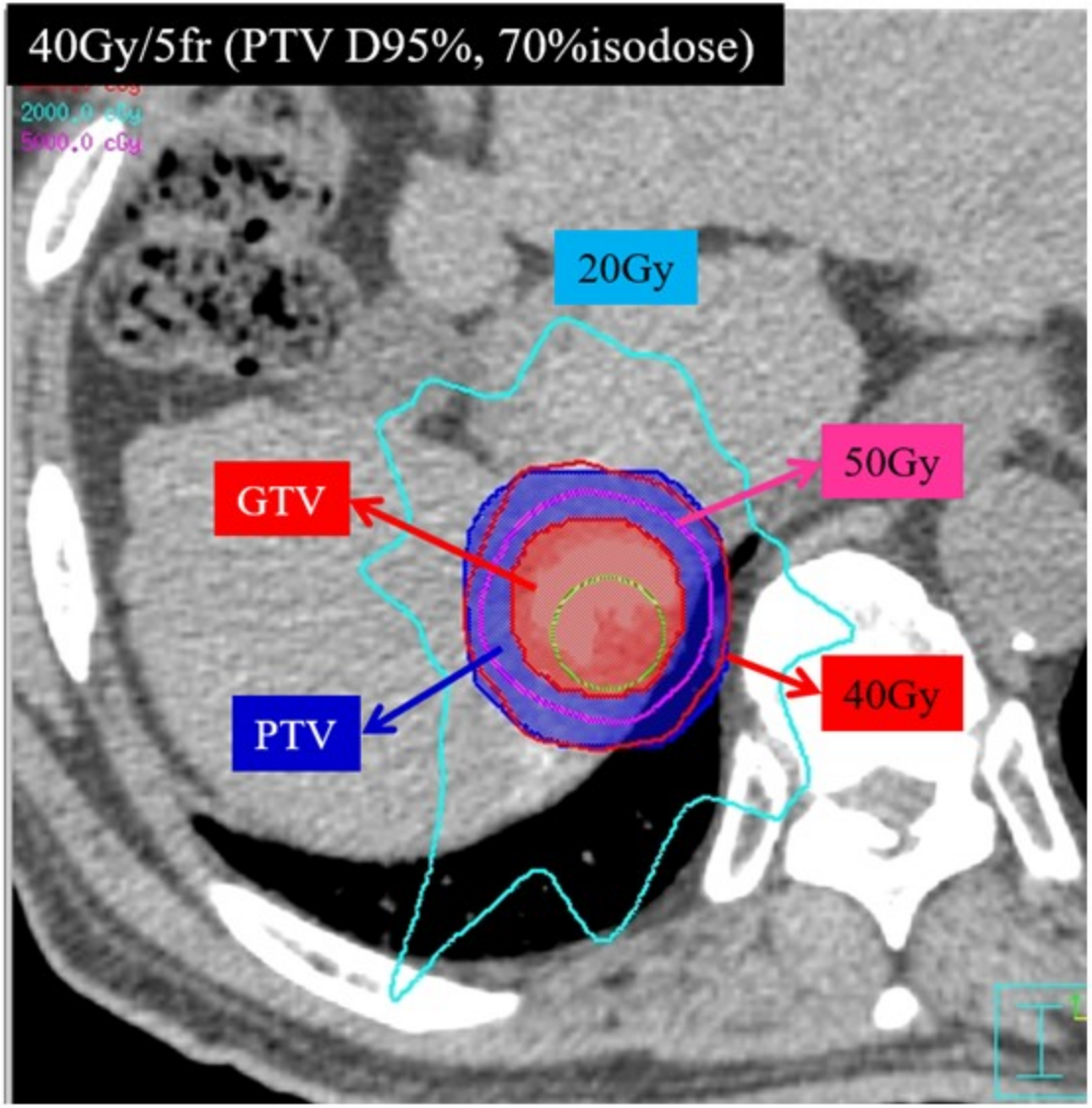
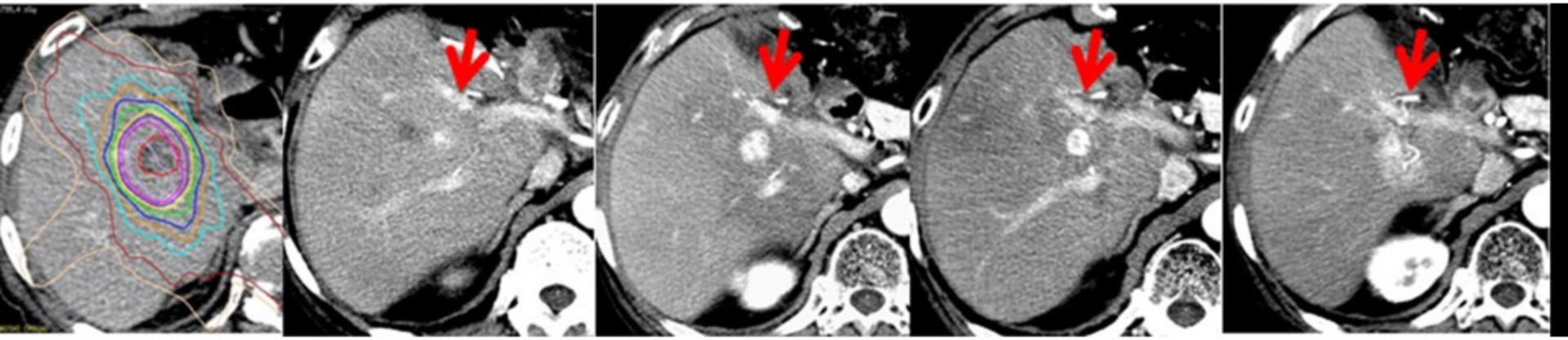


Fig. 2



(A) Dose distribution (B) Before (C) After 2 months (D) After 6 months (E) After 11 months