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LETTER TO THE EDITOR

Bullet fragment fiducials in stereotactic body radiotherapy as a bridge to transplant for hepatocellular carcinoma

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To the Editor:

Hepatocellular carcinoma (HCC) is the third most frequent cause of cancer death worldwide [1]. While surgical resection and orthotopic liver transplantation (OLT) are potentially curative, most patients are ineligible for resection due to advanced presentation, and many wait years for donor organ availability [2]. Stereotactic body radiation therapy (SBRT) is emerging as a safe and effective treatment for inoperable HCC, especially as a 'bridge' to transplant [3]. Fiducial marker placement, an important part of SBRT delivery, may not be tolerated in some patients and alternatives to percutaneous fiducial placement are limited [4].

Here, we report the successful use of residual bullets as fiducials for SBRT in a HCC patient needing bridging therapy before OLT.

Case

A 54-year-old man with history of alcoholism and Hepatitis C-related cirrhosis (Child–Pugh B) presented with a new 15 mm enhancing lesion consistent with cT1N0M0 HCC on imaging. He underwent transarterial chemoembolization (TACE), but was not eligible for liver transplant due to active amphetamine abuse. Subsequent MRI seven years later demonstrated residual HCC in segment 2/3. Transarterial bead embolization (TABE) was initially planned and then aborted after discovery of significant arteriovenous shunting, a relative contraindication [5]. Multidisciplinary tumor board recommended SBRT.

Imaging demonstrated a nodular atrophic liver with a 20.3 × 16.4 mm arterially enhancing lesion with washout and capsule (stage T2, Figure 1) as well as a large amount of intra-abdominal ascites and right pleural effusion. He had Child–Pugh C liver disease and Model for End-Stage Liver Disease (MELD) score of 19. Previous gunshot injuries were evidenced by numerous bullet fragments in his abdomen.

A 4D CT simulation was performed to determine the range of motion of the tumor, monitor breathing patterns, and determine imaging parameters to maximize image quality for tumor delineation and radiation therapy treatment planning (Figure 2).

MRI was fused to assist with internal target volume (ITV) delineation. The ITV was expanded 5 mm radially and 7 mm superiorly/inferiorly to create a planning target volume (PTV). Fiducial placement was contraindicated given the patient's hepatic dysfunction and potential coagulopathy. Instead, bullet fragments from prior gunshot wounds embedded in his liver were used as fiducials to determine target area range of motion for gating during delivery (Figure 3). The patient received 35 Gy in 5 fractions and tolerated therapy well despite fatigue and persistent ascites. He underwent ultrasound-guided intraperitoneal drainage of his ascites 7 d before simulation.

Six weeks after SBRT, he acutely decompensated with new occlusive bland thrombi in the main and left portal veins. His MELD score was 30–34. He was then deemed eligible for transplantation as he had been sober for 14 months. Eight weeks after completing SBRT, he underwent OLT from a cadaveric donor. Previous gunshot wounds had created dense inflammation with adhesions around the liver, rendering the explant difficult.

Explant pathology showed moderately differentiated HCC staged ypT1NX with negative margins—a solitary 2.0 cm lesion confined to the liver without vascular invasion. There was marked cholestasis, ballooning degeneration and cirrhosis in the background liver parenchyma. The tumor was composed of moderately differentiated HCC with ballooned tumor cells having abundant Mallory hyaline and bile production (Figure 4), consistent with the 'steatohepatitic' variant of hepatocellular carcinoma. Although no necrosis was seen, bands of fibrosis were present in regions of the tumor (Figure 4(B)), representing radiation treatment effect of more poorly differentiated tumor.

Interval CT scans show no evidence of recurrence or metastatic disease within the abdomen post-transplant and the patient is currently doing well.

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Discussion

This case report demonstrates the role of liver SBRT as a bridge to transplant in a patient with HCC, the utilization of internal fiducials (bullet fragments in this case) and the successful outcomes of OLT for those with past substance abuse.

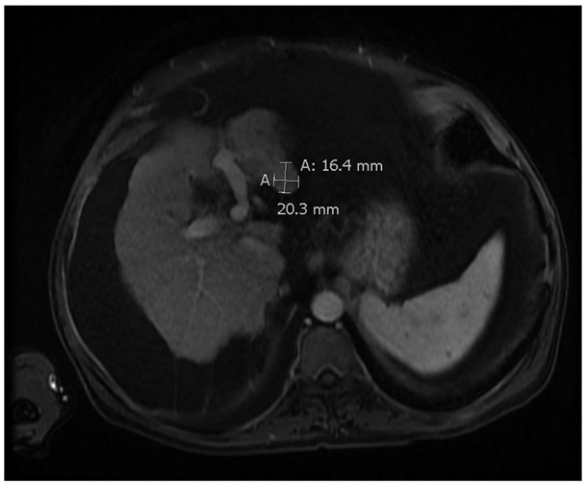

Figure 1. Axial T1 contrast-enhanced MRI showing nodular liver with residual tumor.

SBRT is an effective therapy for inoperable HCC, with a 1-year and 2-year local control rate of up to 70–90% and 64%, respectively [3,6]. Furthermore, a recent study showed that for tumors $\geq$2 cm, SBRT resulted in higher 1-year freedom from local progression compared with radiofrequency ablation (97.4 and 83.8%) [6]. SBRT is also a good option for patients with significant arteriovenous (AV) shunting. Presence of these shunts, seen in up to 60% of patients with HCC [7], introduces risk of hepatic infarcts or pulmonary embolisms during TACE [8]. Since SBRT does not incorporate vascular based therapy, such patients are still eligible for SBRT.

SBRT can be a safe and effective bridging therapy to transplant in patients who are ineligible for other therapies [3]. In terms of efficacy, one study on SBRT in HCC patients prior to transplant showed no local progression at transplant or change in peri-operative morbidity [9]. Toxicities for most HCC patients after SBRT tend to be mild, including fatigue, elevated liver enzymes and leukopenia [3,6]. However, one group did note three cases of bland portal vein thrombosis (PVT) after SBRT in Child–Pugh class B

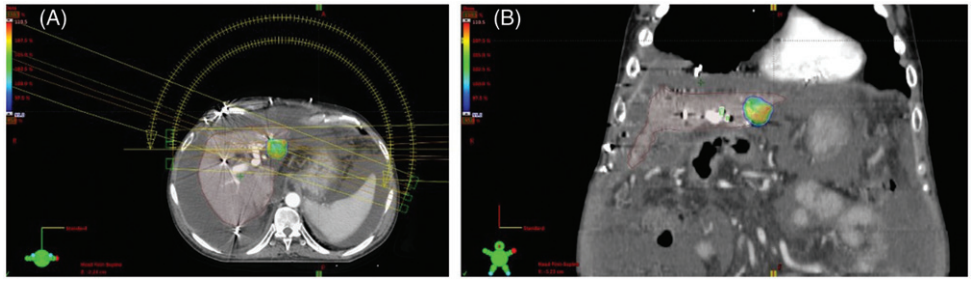

Figure 2. Planning 4D-CT with radiation dose plan. Axial (A) and coronal (B) views. Liver, outlined, surrounded by ascites. ITV is shaded in right liver lobe. Bullet fragments used as fiducials are shaded, just adjacent to ITV in coronal view. ITV: internal target volume.

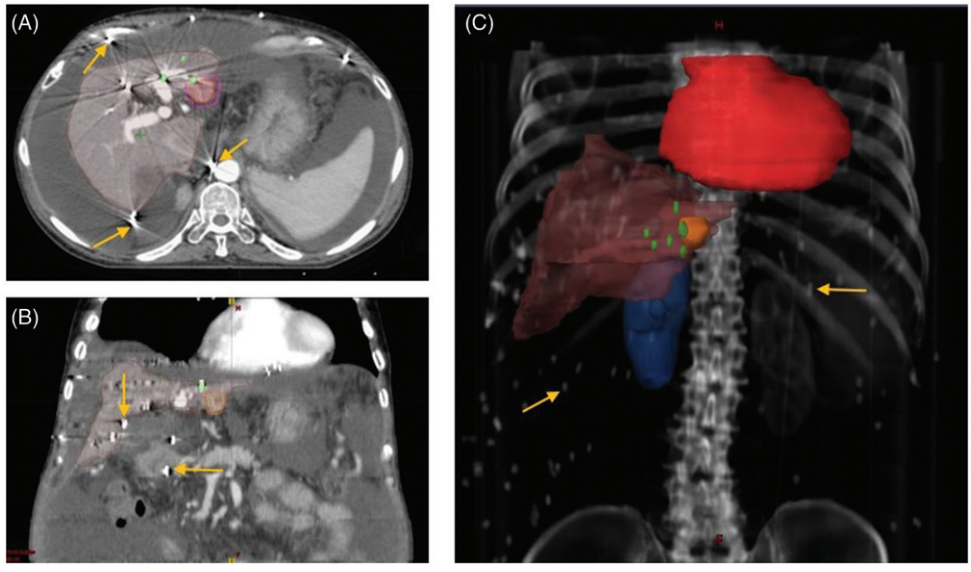

Figure 3. Bullet fragment fiducials used in SBRT planning. Transverse (A) and coronal (B) plane views of GTV and PTV, both outlined in right liver lobe. (C) 3D rendering highlights tumor location, 6 fiducials, liver, kidney, and heart. Arrows indicate examples bullet fragments not used for planning. GTV: gross tumor volume; PTV: planning target volume.

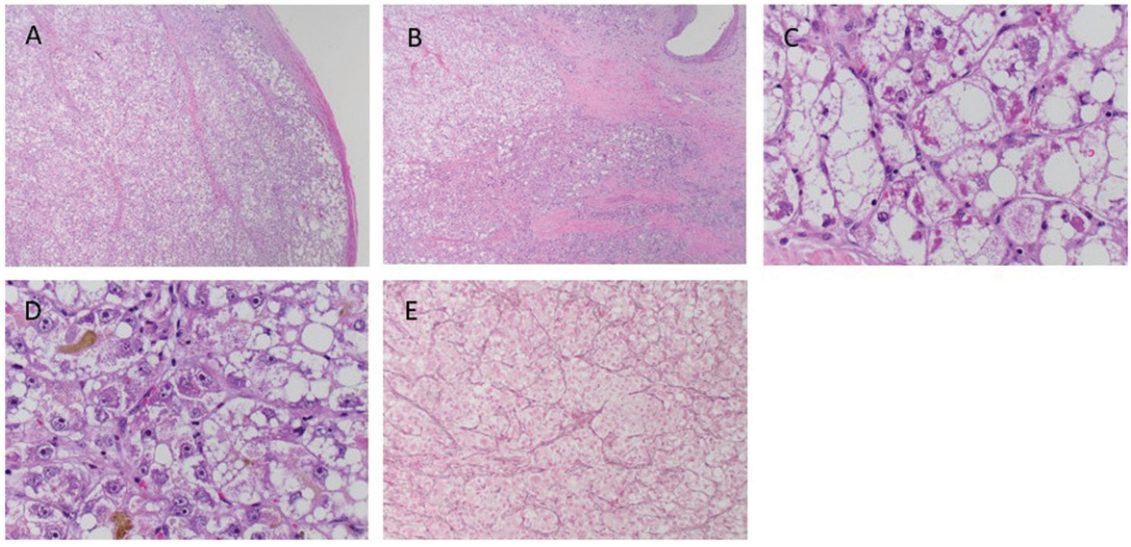

Figure 4. Liver explant histology. A) Subcapsular, 40x; B) Fibrosis, no necrosis, 40x; C) Mallory hyaline, ballooned hepatocytes and steatosis within the tumor, 400x; D) Bile production within the tumor, 400×; E) Loss of reticulin stain within the tumor, 100x.

patients [10]. In this case, the PVT was thought to be a natural sequela of the patient's cirrhosis, and not an adverse effect of treatment. The cumulative incidence of a new PVT after 5 years of cirrhosis is 10.7% [11], and can be attributed to venous stasis, thrombophilia or portal endotoxinaemia [12].

To facilitate SBRT planning, the use of fiducials is essential for motion management to decrease radiation to adjacent healthy tissue. Fiducial markers allow for superior guidance as compared to other surrogates of tumor position [13]. However, some patients may be ineligible for the placement procedure, and alternatives, such as ionized oil from prior TACE [14] or surgical clips [15] have been effective motion surrogates. In our case, remaining bullet fragments allowed for successful SBRT planning and delivery. Explant pathology of the treated liver tumor had patchy areas of fibrosis consistent with treatment effect.

Lastly, this case provides insight into the successful outcomes of OLT for those with prior substance abuse. This patient was not eligible for transplant due to active drug use. The United Network for Organ Sharing (UNOS) mandates a 6-month period of abstinence from illicit drugs and alcohol before patients can be listed as candidates for OLT [16]. This 6-month period is used as a predictor for long-term sobriety and compliance after OLT. The patient presented here has not tested positive for illicit drugs since becoming eligible for transplantation and has been compliant with his medication.

Conclusions

This case demonstrates the utility of liver SBRT as bridging therapy prior to transplant for HCC and the use of alternative fiducials for motion management in SBRT. Explant pathology shows tumor and treatment effect after SBRT. Utilizing alternative motion surrogates can enable successful delivery of SBRT in patients who would otherwise be ineligible for treatment.

Disclosure statement

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LETTER TO THE EDITOR

Metastatic melanoma in a 95 years old patient responding to treatment with talimogene laherparepvec followed by nivolumab

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Background

Talimogene laherparepvec (T-VEC) is an oncolytic virus derived from an attenuated recombinant type-1 herpes virus, genetically engineered to replicate preferentially within tumor cells. When injected directly into the tumor, it generates an antitumor immune response. This pro-immunogenic potential is orchestrated via lysis of tumor cells induced by the virus resulting in the release of tumor-associated antigens along with an enhanced expression of granulocyte macrophage colony-stimulating factor (GM-CSF) [1]. Nivolumab, a fully human immuno-globulin-4 (IgG-4) monoclonal antibody is approved as a single agent [2] and in combination with ipilimumab [3] for the treatment of metastatic melanoma. It is directed against the programed cell death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2. This checkpoint blockade culminates into the release of an immunogenic response within the tumor microenvironment mainly by impeding co-inhibitory signals on effector T cells and also lowering the activation threshold for an antigen directed T-cell response [4]. Promising outcomes from an early phase-1b study have been observed with the anti-PD-1 antibody pembrolizumab in combination with T-VEC for patients with metastatic melanoma [5]. However, no cases of T-VEC in combination with nivolumab have been reported to date.

Case presentation

A 92-year-old Caucasian female was diagnosed with melanoma after noticing a change in the size and character of a skin lesion on the right calf that had been present for 10 years. A punch biopsy of the lesion revealed a 2.20 mm thick, Clark's level IV solar lentiginous melanoma positive for S-100 and MART-1 by immunohistochemistry, with both radial and vertical growth phase present. Vascular invasion was present with positive margins. She underwent a wide local excision with split thickness graft for wound coverage. No sentinel node biopsy was performed due to her advanced age. She developed recurrent in-transit disease 18 months after her initial diagnosis and subsequently underwent isolated right leg limb infusion (LI) with melphalan/dactinomycin. The patient had a second progression 8 months later and underwent repeat LI. Positron emission tomography (PET) imaging 2 months after the second LI demonstrated numerous soft tissue areas of hypermetabolic activity in the right leg and a focus in the right groin likely representing malignant adenopathy. Biopsy of right inguinal nodes confirmed *BRAF*-negative metastatic melanoma. Repeat isolated right leg LI with melphalan/dactinomycin was performed along with right superficial inguinal lymph node dissection (2 of 14 nodes were positive for melanoma). Three months postlymph node dissection when she was 95 years old, progression was noted again, with increasing number and size of nodules in the right leg. Imaging of the brain was negative. Lactate dehydrogenase was within normal range. She was started on T-VEC, injecting <4 mL of 10^6 plaque-forming units (PFU)/mL in nodal/(sub)cutaneous lesions on day 1, then 10^8 PFU/mL on day 20 and every 2 weeks subsequently. Given her advanced age and previous limb infusion therapy, the number of treatments was predefined. She completed a total of six treatments after which it was decided to monitor

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