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LETTER

Cytoreductive single-fraction stereotactic radiation therapy prior to living donor transplantation for inoperable liver-confined metastatic rectal cancer

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CASE REPORT

We report the case of a 51-year-old man who was initially diagnosed with a high rectal adenocarcinoma. He was treated with neoadjuvant chemoradiotherapy and proceeded to low anterior resection. Pathology showed ypT3N1c cancer with negative surgical margins. The tumor was microsatellite stable, with wild-type KRAS and BRAF status. He underwent adjuvant chemotherapy.

Three months after completion of chemotherapy he was found to have multiple bilobar hepatic lesions on surveillance imaging, without evidence for extrahepatic disease. Biopsy confirmed metastatic adenocarcinoma of colorectal origin. Subsequent management in the following months included further systemic therapy, liver metastasectomies, and hepatic arterial infusion chemotherapy. However, he developed a biliary stricture and it was deemed that clearance of the liver tumors could not be achieved by conventional surgical means. He was maintained on systemic therapy with FOLFIRI and panitumumab.

The patient was referred to our transplant clinic three years and nine months after initial diagnosis for consideration of liver transplantation as definitive management of inoperable metastatic disease confined to the liver on imaging. After evaluation by our multidisciplinary review committee, the patient was determined to be a candidate for living donor liver transplant. Repeat PET-CT (4 years and 4 months from original diagnosis) showed general stability of the multiple liver tumors, but interval growth of one dominant, FDG-avid, focus in segment VIII, measuring approximately 5.6 cm × 3.8 cm, resulting in an Oslo score of 2. There was an increase in the CEA levels as well in the preceding months. Small (sub-cm) lung nodules were present but not concerning for disease involvement.

Referral was made for evaluation for radiation therapy to treat this dominant mass prior to transplantation. At the time of evaluation, the patient's Eastern Cooperative Oncology Group (ECOG) performance status level was 1, Child Pugh Class A5. We offered the patient single-session stereotactic body radiotherapy (SBRT) to the dominant lesion. The other liver lesions were not targeted. During the treatment planning process the radiation oncologist and transplant surgeon reviewed the target region and tissues at risk. The liver hilum was identified

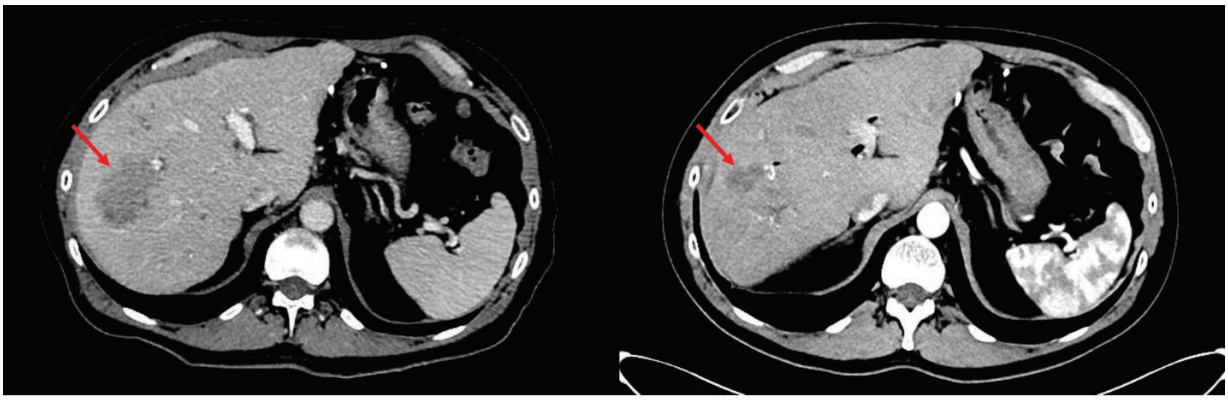

Figure 1. A) Targeted tumor (red arrow) from CT simulation scan B) CT scan appearance 2 months after SBRT (red arrow)

as an avoidance structure to limit radiation-induced fibrosis and possible attendant surgical challenges. The prescription dose was 18 Gy in a single fraction, utilizing volumetric modulated arc therapy with cone beam CT image guidance and active breathing coordinator (Elekta, Stockholm, Sweden) for motion management. Relevant dose metrics included a PTV D90 value of 18.3 Gy and a mean dose to the uninvolved liver (excluding the targeted tumor but inclusive of the other tumors) of 4.9 Gy. The D1cc dose to an expansion around the portal vein, serving as a surrogate for the liver hilum, was 5.1 Gy. The treatment was tolerated well. The CEA level drawn about 2 weeks prior to the radiation was 29.7 ng/mL. CEA 6 days after SBRT was 58.46 ng/mL, declining to 38.84 ng/mL and 13.47 ng/mL at about 3- and 5-weeks post-treatment, respectively. Repeat CT imaging at 2 months post-treatment showed a decrease in size of the treated lesion to 2.6 cm × 2.2 cm (Figure 1).

Three months after the radiation course the patient proceeded to orthotopic living donor liver transplantation with, now, an Oslo score of 0. The final CEA level prior to transplant was 5.86 ng/mL. Explant liver pathology revealed 6 lesions consistent with metastatic adenocarcinoma of colorectal origin, with approximately 60% necrosis in the irradiated tumor and 30-40% necrosis in the remaining lesions. He had an uncomplicated surgery and postoperative course and was discharged on postoperative day 6. CEA one week after surgery was 2.7 ng/mL. Follow-up at 3 months showed no clear evidence of new disease. There was interval enlargement of pre-existing lung nodules (largest: 8 mm), but notably the CEA level was stable at 2.8 ng/mL and there was no detectable circulating tumor DNA. As such, continued observation is planned.

DISCUSSION

Liver transplantation is indicated as a curative approach for selected patients with hepatocellular carcinoma (HCC). Liver-directed therapies such as embolization and thermal ablation are commonly used as bridging or downstaging treatments. Radiation therapy/SBRT has also been used as a bridging treatment in this setting.[1,2]

A less common but evolving indication for liver transplantation is in the setting of unresectable liver-confined colorectal cancer metastases.[3,4] Patient selection is key to the success of this approach. A recent publication by Dueland et al. reported median overall survival of 60.3 months in a study of 61 patients who underwent transplantation for unresectable liver-confined colorectal cancer metastases.[4] Multiple factors associated with a higher chance of posttransplant relapse (Oslo score) have been identified, including a preoperative maximum tumor diameter greater than 5.5 cm.[4] In the case described above, the maximum tumor diameter was 5.6 cm, subsequently shrinking to 2.6 cm in diameter after SBRT and prior to the surgery. Using single-fraction SBRT we were able to effectively control this lesion and also reduce the Oslo score. To the best of our knowledge, local therapies, including SBRT, have not been routinely applied in the peri-transplantation setting for this specific cancer indication. We considered it rational to apply the principles of bridging/downstaging in HCC transplantation to this situation.[1,2] Long-term impact on relapse risk needs further study.

Much higher single-fraction radiation doses have been delivered in the management of liver metastases, but our goal with this treatment course was safe and effective cytoreduction and not complete eradication of the targeted

focus.[5] Very high-dose irradiation may have complicated the primary curative treatment- liver transplantation- and thus been counterproductive. Also of note was the significant rise in the CEA level immediately (within one week) following the SBRT procedure, with rapid subsequent decline. This may be similar to the "CEA surge" that has been described in following chemotherapy for colorectal cancer.[6] This acute rise may be related to tumor cell death and lysis, and this phenomenon may be underappreciated following SBRT.

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