Successful resection of huge hepatocellular carcinoma with inferior vena cava thrombus after downsizing by three-dimensional conformal radiation therapy and transarterial chemoembolization

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Summary We report a successfully managed case of locally far-advanced hepatocellular carcinoma (HCC) by preoperative downsizing by transarterial chemoembolization (TACE) and three-dimensional conformal radiation therapy (3D-CRT), with subsequent surgical resection. A 35-year-old man was referred to our hospital with right huge HCC in May, 2006. The laboratory data were normal except for elevated aspartate transaminase 100 U/L (0–38), alanine transaminase 54 U/L (0–44), and α-fetoprotein 32 ng/mL (1–8). A computed tomography scan of the liver revealed a 20-cm right side huge HCC with inferior vena cava tumor thrombus (IVC-TT) and a second 2-cm HCC in segment III. TACE was performed on the right HCC with 20 mg of doxorubicin (Adriamycin), mixed with 10 mL of lipiodol and gelfoam. 3D-CRT was followed by 60 Gy (3 Gy/fraction) over 4 weeks. The posttreatment computed tomography scan showed significant shrinkage of the right tumor and IVC-TT. The tumors with the concomitant IVC-TT were surgically removed 6 weeks later.
1. Introduction

Medical history data obtained from patients with hepatocellular carcinoma (HCC) and major vascular invasion reveal a median survival time of 9–12 weeks. The optimal treatment for patients with HCC and major vascular invasion remains controversial. We report a successfully managed case of far-advanced HCC by preoperative transarterial chemoembolization (TACE), three-dimensional conformal radiation therapy (3D-CRT), and then surgical resection.

2. Case report

A 35-year-old man complaining of right upper abdominal pain visited a neighboring hospital, and was diagnosed to have a single right-sided huge HCC. He was a chronic hepatitis B carrier. He was then referred to our hospital for further treatment in May, 2006. Physical examination revealed a nontender, firm hepatomegaly, palpable 2 cm below the costal margin. Laboratory data consisted of a total bilirubin of 0.69 mg/dL (0–1.3); aspartate transaminase, 100 U/L (0–38); alanine transaminase, 60 U/L (0–44); albumin, 3.9 g/dL (3.5–5.0); international normalized ratio, 1.02; and alpha-fetoprotein, 32 ng/mL (1–8). The indocyanine green 15-minute retention test was 4.2%. The patient’s Eastern Cooperative Oncology Group performance status was 1. A triphasic computed tomography (CT) scan showed a 20-cm HCC occupying the entire right lobe with a tumor thrombus extending into the right hepatic vein and the inferior vena cava and a second 2-cm HCC in segment III (Figure 1). Surgery was considered infeasible because of the inadequate estimated remnant liver volume (<40% of standard liver volume). Angiography of the celiac trunk showed a huge hypervascular stain in the right lobe, compatible with HCC, and tumor invasion into the right hepatic vein. Hence TACE was performed on the right HCC with 20 mg of doxorubicin (Adriamycin), mixed with 10 mL of lipiodol and gelfoam. Subsequently both the main tumor and the inferior vena cava tumor thrombus (IVC-TT) were targeted by 3D-CRT (Elekta Precise SLi, Crawley, United Kingdom) 2 weeks after TACE. The daily fraction size was 3.0 Gy, given 5 days per week for 4 weeks, to a cumulative dose of 60 Gy (Figure 2). A triphasic CT scan 3 weeks after 3D-CRT showed shrinkage of the main tumor from 20 cm to 14 cm in diameter. The IVC-TT also shrunk significantly (Figure 3). Six weeks after 3D-CRT, the patient underwent an extended right hepatectomy with partial diaphragm resection by the anterior approach, an inferior vena cava thrombectomy via the right hepatic vein and a left partial hepatectomy (Figure 4). Hepatic parenchymal transection was performed with a Cavitron ultrasonic aspirator and bipolar electrocautery under intermittent inflow control using the Pringle maneuver (15-minute occlusion and 5-minute declamping). The transection time was 140 minutes and the operative blood loss was 400 mL. He did not receive any blood transfusion perioperatively. Two weeks after surgery, the patient was discharged without any complications. From the macroscopic findings of the resected specimen, the right hepatic vein was filled with a tumor thrombus. Histologically, necrosis was recognized in 95% of the main tumor, in 30% of the left tumor and in 100% of the IVC-TT. The juxta-inferior vena cava hepatic veins were not invaded by any malignant cells and the resection margins were clear. The patient died of leukemia 3 years after the operation.

Figure 1  Pretreatment liver CT. (A) The arterial phase showed a huge right lobe HCC and a small left lobe HCC (arrow); (B) the delayed phase showed a tumor thrombus in the inferior vena cava (arrow); (C) reconstructed coronal view of the portal venous phase showed the longest axis of right lobe HCC about 20 cm in diameter, and tumor thrombus in the right hepatic vein (arrow). CT = computed tomography; HCC = hepatocellular carcinoma.
3. Discussion

Vascular invasion is a critical prognostic factor for patients with HCC. Previous articles from the literature have reported that the median survival time of patients with major vascular invasion is 9–12 weeks if left untreated. To improve the dismal prognosis, various treatments have been applied to patients with advanced HCC. Pawlik and colleagues reported results from a multicenter study which suggested that patients with HCC and major vascular invasion derived survival benefit from surgical resection, with an overall 5-year survival rate of 10%.

TACE has been shown to improve survival compared with supportive care in recent meta-analyses. Although TACE has been frequently used in the treatment of unresectable HCC, its limitations are also well known, especially in large tumors. Previous studies have suggested a benefit of combining radiation therapy (RT) and TACE in patients with advanced HCC.

Historically, RT has played a minor role in the management of patients with unresectable liver cancer, primarily because of the low tolerance of the whole liver to RT. However, recent advances have allowed the safe delivery of higher dose external beam RT to liver tumors, such as advanced imaging to improve tumor definition, three-dimensional radiation planning techniques to deliver high doses that conform tightly to the tumor, image-guided radiotherapy to localize the tumor at the time of treatment, tumor immobilization and organ tracking to account for organ motion due to breathing, and improved knowledge of the partial volume tolerance of the liver to radiation. These advances have revived RT as an additional treatment option in primary liver malignancies.

The resected specimen in our case showed 95% necrosis in the main tumor while the left sided tumor, which did not receive any downsizing treatment, only showed 30% tumor necrosis attributed to the natural tumor biology. The fact that the main tumor received both TACE and RT makes the causative factor for tumor shrinkage and necrosis difficult. However, the IVC-TT showed 100% necrosis with significant shrinkage after RT. Furthermore, microscopic examination of the irradiated non-tumor liver tissue showed sinusoidal lining cell injury causing so-called veno-occlusive disease in the microcirculation. This effect might block tumor angiogenesis and be responsible for tumor shrinkage. These facts have led us to believe that RT was the main causative factor for downsizing and tumor necrosis.

The anterior approach is the preferred technique for extended right-sided hepatic resection for large HCC. This is because of the challenging right side liver mobilization with an increased risk of tumor rupture and higher blood loss associated with the classic approach. Our blood loss was limited to 400 mL with no need for transfusion because of this approach. Furthermore, we resected a part of the right diaphragm to limit the risk for tumor spillage and blood loss.

The patient died of leukemia 3 years postoperatively. Whether this was linked to RT remains controversial but secondary cancers induced by RT have become a clinically significant issue. This increase in risk has to be balanced...
against the generally high spontaneous cancer risk in these individuals and the benefits accruing from radiotherapy.

It is concluded that preoperative treatment with 3D-CRT combined with TACE has a potential role in downsizing large HCC with induced tumor necrosis, thereby facilitating radical resection without additional surgical risks.

References


Figure 4  (A) There were diffuse black spots on the irradiated right lobe liver; (B) anterior approach extended right hepatectomy was performed. The inferior vena cava tumor thrombus (arrow) was removed via the right hepatic vein; (C) the tumor in segment III was removed by a left partial hepatectomy; (D) the right tumor was 14 cm in diameter and macroscopically almost necrotic.