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Proton boost in liver cancer

Risk-adapted simultaneous integrated boost-proton beam therapy (SIB-PBT) for advanced hepatocellular carcinoma with tumour vascular thrombosis

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ABSTRACT

Purpose: To evaluate clinical effectiveness and safety of simultaneous integrated boost-proton beam therapy (SIB-PBT) in hepatocellular carcinoma (HCC) patients with tumour vascular thrombosis (TVT).

Material and methods: Forty-one HCC patients with TVT underwent SIB-PBT using three dose-fractionation schemes: if gross tumour volume <1 cm ($n = 27$), 1–1.9 cm ($n = 7$), and ⩾2 cm ($n = 7$) from gastrointestinal structures, 50 GyE (EQD2, 62.5 GyE_{10}), 60 Gy (EQD2, 80 GyE_{10}), 66 Gy (EQD2, 91.3 GyE_{10}), respectively, in 10 fractions was prescribed to planning target volume 1 (PTV1), and 30 GyE (EQD2, 32.5 GyE_{10}) in 10 fractions was prescribed to PTV2.

Results: Overall, treatment was well tolerated, with no grade toxicity ⩾3. Median overall survival (OS) was 34.4 months and 2-year local progression-free survival (LPFS), relapse free survival (RFS), and OS rates were 88.1%, 25%, and 51.1%, respectively. Patients treated with EQD2 of ⩾80 GyE_{10} tended to show better TVT response (92.8% vs. 55.5%, $p = 0.002$) 2-year LPFS (92.9% vs. 82.5%, $p = 0.463$), RFS (28.8% vs. 19%, $p = 0.545$), and OS (58.4% vs. 46.8%, $p = 0.428$) rates than those with EQD2 of <80 GyE_{10}. Multivariate analysis showed that TVT response and Child Pugh classification were independent prognostic factors for OS.

Conclusions: SIB-PBT is feasible and promising for HCC patients with TVT.

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Tumour vascular thrombosis (TVT), particularly in the portal vein, hepatic vein, and inferior vena cava, is a common accompanying manifestation of hepatocellular carcinoma (HCC), occurring in 30–50% of HCC patients, and HCC patients with TVT have an extremely poor prognosis, with median survival time of 2 to 4 months if left untreated. Moreover, treatment options have been limited for patients with HCC and TVT. For example, transcatheter arterial chemoembolisation (TACE) may be safe for selected advanced HCC patients with TVT, but its efficacy has remained unsatisfactory. Various intra-arterial and systemic chemotherapeutic agents have been tried in selected patients, but none has shown a survival benefit. Recently, sorafenib, an oral multikinase inhibitor, has shown modest prolongation of survival (about 2–3 months) in advanced HCC patients with/without TVT, but is unlikely to cure without local tumour control by local treatment modalities [1,2]. Thus, less invasive and more effective local treatments have been needed in HCC patients with TVT.

Technological innovations in the field of radiotherapy (RT) planning and delivery have made possible the conformal delivery of radical radiation to the tumour, while sparing the normal tissues. Various RT techniques, such as three-dimensional conformal RT (CRT), intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and proton beam therapy (PBT), have been attempted in treating HCC with or without TVT and have shown favourable clinical outcomes [3–12]. More recently, the development of SBRT, a technique minimising RT dose to adjacent normal tissues by delivering high dose of RT in a small number of fractions with high precision, has generated further promise for RT for HCC [3,13,14]. Moreover, due to the distinct physical characteristics of proton beams and the Bragg peak in allowing deposition of high doses of radiation within the target and the lack of an exit dose outside the target, the role of charged particle therapy, including PBT, has been actively investigated [15,16] and, in recent meta-analysis [17], survival rates for charged particle therapy was higher than those for CRT, but similar to those for SBRT, and toxicity tends

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to be lower for charged particle therapy compared to CRT and SBRT. Although choosing an appropriate RT modality in HCC patients with TVT is difficult due to their poor hepatic reserve resulting from decreased portal blood flow and underlying liver cirrhosis (LC) as well as closeness to radiosensitive organs (i.e., gastrointestinal structures), conceptually, PBT can exploit the potential advantages of an accelerated form of RT known as simultaneous integrated boost (SIB) in which different doses can be delivered to different targets at the same time. That is, a higher dose can be delivered to the tumour volume, while a lower dose is delivered simultaneously to close areas of surrounding normal tissue (i.e., gastrointestinal structures). This accelerated hypofractionated RT can create a potential improvement in the therapeutic ratio compared with conventional fractionated RT due to less repair of radiation damage of surrounding normal tissues, such as gastrointestinal structures, and shortened overall treatment time. Based on this background, patients with HCC with TVT have been treated at our institution by RT using the SIB-PBT technique since June 2012. This study was designed to retrospectively analyse the clinical outcomes of SIB-PBT in these patients and to evaluate the clinical effectiveness and safety of this method.

Materials and methods

Patients

Between June 2012 and February 2015, a total of 46 HCC patients with TVT underwent SIB-PBT. Of those, all but five patients received PBT for TVT alone, 41 patients received SIB-PBT for both TVT and primary tumour and included in this study. HCC was diagnosed by pathologic confirmation ($n = 15$) or on the basis of radiologic findings plus serum alpha-fetoprotein (AFP) concentrations $\geqslant$200 ng/mL ($n = 26$) in accordance with the guidelines of the Korean Liver Cancer Study Group and the National Cancer Center [18]. TVT was confirmed as a filling defect on dynamic contrast-enhanced imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), and/or angiography, with the occlusion of the portal vein, hepatic vein, and inferior vena cava. HCCs were classified according to the 2010 American Joint Committee on Cancer (AJCC) staging system and liver function was classified according to Child–Pugh classification. The study was performed in accordance with the guidelines of our institutional review board, which waived the requirement for informed consent due to the retrospective nature of the study.

Pretreatment evaluation and treatment

All patients underwent blood tests, including measurements of blood cell counts, liver and renal function tests, titres of hepatitis B and C virus (HBV and HCV), and AFP. Abdominal dynamic contrast-enhanced CT and/or MRI was used to evaluate the extent of HCC and TVT. For RT planning, patients underwent CT simulation in a supine position with arms above the head and immobilised using an arm-up holder to improve setup reproducibility. Contrast-enhanced four-dimensional (4D) CT images were acquired with 2.5-mm slice thickness under shallow respiration using a 4D CT simulator (Light-Speed RT; GE Healthcare, Waukesha, WI, USA). During the 4D CT scan, the respiration signals of the patients were monitored by a real-time position management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA). The acquired CT images were reconstructed in 10 equally spaced respiratory phases and in the post-processing stage maximum intensity projection (MIP), minimum intensity projection (MinIP), and average intensity projection (AIP) CT images were reconstructed using exhalation (gated) phases (30% of total respiratory cycle) on an Advantage workstation (Version 4.3, GE Healthcare, Milwaukee, WI, USA). All 4D CT images were transferred to the Eclipse treatment planning system (Version 8.1; Varian Medical System, Palo Alto, CA, USA), and the contours for targets and organs at risk (OARs) were delineated in AIP-CT images during the exhalation (gated) phases. Fig. 1 illustrates the definition of target volumes. The gross tumour volume (GTV) included all detectable primary tumours as determined by contrast-enhanced AIP-CT images during the exhalation phase and the clinical target volume (CTV) was regarded as GTV [3,19–21]. The gated internal target volume (ITV) was obtained by summing the GTVs in each CT image during the exhalation phases. The planning target volume 2 (PTV2) included the ITV plus 5–7 mm margins in all directions and PTV1 included the PTV2 minus overlapping volume of PTV2 and 10-mm expanded volume of gastrointestinal structures to avoid gastrointestinal toxicity (Fig. 1A–C). SIB-PBT planning was undergone using two coplanar or non-coplanar beams of 230 MeV protons (Proteus 235; Ion Beam Applications, S.A., Louvain-la-Neuve, Belgium) to cover the PTV2 and one beam to cover the PTV1. The beam energy and spread-out Bragg peak, defined as the distance between the distal and proximal 90% points of the maximum dose value, were fine-tuned so that the at least 95% of the PTV was encompassed by 100% of the prescribed dose and the proximal, distal, border smoothing, smearing and aperture margins for proton beams using the double scattering mode to PTV were set to 5–7 mm each. The beam weights of the plan were optimised to minimise the maximal dose within the target volume and OARs and the dose was calculated for the target volume and OARs with heterogeneity corrections and expressed in Gray equivalents [GyE = proton physical dose (in Gray) $\times$ relative biologic effectiveness (1.1)]. The treatment was designed so that at least 95% of the PTV1 and 2 would receive 100% of each prescribed dose and the equivalent dose in 2 Gy fraction (EQD2, GyE_{10} or GyE_3), was calculated using a linear quadratic model with α/β ratios of 10 and 3 for acute and late effects on tumour and OARs, respectively. Three SIB-PBT dose-fractionation schemes were designed, depending on the closeness of gastrointestinal structures: (1) in the patients with GTV <1 cm from gastrointestinal structures ($n = 27$), the prescribed doses to PTV1 and PTV2 were 50 GyE (EQD2, 62.5 GyE_{10}) and 30 GyE (EQD2, 32.5 GyE_{10}) in 10 fractions, five fractions/week, respectively; (2) in the patients with GTV within 1–1.9 cm from gastrointestinal structures ($n = 7$), the prescribed doses to PTV1 and PTV2 were 60 GyE (EQD2, 80 GyE_{10}) and 30 GyE in 10 fractions, respectively; and (3) in the patients with GTV $\geqslant$2 cm from gastrointestinal structures ($n = 7$), PTV1 and PTV2 were identical and the prescribed dose of PTV1 was 66 GyE (EQD2, 91.3 GyE_{10}) in 10 fractions (Fig. 1A–C). The details of the normal tissue constraints have been described previously [5,22–24]: the maximum dose to the spinal cord could not exceed 27 GyE; the relative volumes of the total and remaining normal liver that received doses of 27 GyE ($_{TL}V27$ and $_{RNL}V27$) were below 60% and 50%, respectively; the absolute volumes of the oesophagus and stomach that received at least 37 GyE were $\leqslant$2 cm^3; and the absolute volumes of the small and large bowel that received at least 35 GyE were $\leqslant$2 cm^3. At each treatment fraction, digital orthogonal fluoroscopy was used to position patient and to verify the isocentre, and irradiation was done during the exhalation phase using RPM system.

Follow-up and statistical considerations

Patients were assessed weekly during SIB-PBT and after completion of SIB-PBT at 1 month, then every 2–3 months for the first 2 years and every 6 months thereafter. Follow-up evaluations consisted of a physical examination, a complete blood count, liver-function testing, chest radiography, and liver dynamic contrast-enhanced CT or MRI. TVT in right and left lobar branches and main