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Original article

Clinical impact of combined transarterial chemoembolization and radiotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: An external validation study

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ABSTRACT

Purpose: To evaluate the relationship between portal vein tumor thrombosis (PVTT) response and clinical outcomes in patients with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization followed by radiotherapy (TACE-RT).

Materials and methods: The study enrolled 329 patients in the training set and 179 patients in the validation set. All patients who were treated with TACE-RT from 2002 to 2008 and satisfied the inclusion criteria were enrolled in the study. The median follow-up period was 11.7 months (range, 1.6-108.6) in the training set and 11.9 months (range, 1.7–105.1) in the validation set.

Results: After TACE-RT, PVTT response was complete or partial in 32 (9.7%) and 134 (40.7%) patients of the training set and in 18 (10.1%) and 96 (53.6%) patients in the validation set, respectively. Failure to obtain PVTT response was significantly related with elevated post-treatment Child-Pugh score ($P < 0.001$). Furthermore, progression-free survival was significantly related with PVTT response ($P < 0.001$, hazard ratio 0.33, 95% confidence interval 0.25–0.42) in multivariate analysis. In receiver-operating characteristics analysis of 1-year progression prediction, the PVTT response showed an area under the curve of 0.74. Most of the findings were successfully reproduced in the independent external validation set.

Conclusions: Positive PVTT response was closely associated with favorable clinical outcomes. The PVTT response to TACE-RT reduces metastasis and makes it possible to maintain normal liver function and achieve longer survival.

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Primary liver cancer is the second leading cause of cancer-related death, and hepatocellular carcinoma (HCC) accounts for approximately 70–90% of primary liver cancers occurring worldwide [1]. Portal vein tumor thrombosis (PVTT) is recognized as a common accompanying manifestation, with reported rates of approximately 30–40% in patients with advanced HCC [2]. Several reports have described its role as one of the most important dismal prognostic indicators in these patients [3,4].

Although sorafenib is generally accepted as a standard of care for the treatment of advanced HCC, the objective response rate is somewhat disappointing at 2–5% [5,6]. Furthermore, median time to progression was only 2.8 months in a study of the Asia–Pacific region.

There is no widely accepted local modality as standard treatment; trans-arterial chemoembolization (TACE) followed by radiotherapy (RT) has shown encouraging survival as well as a favorable local response rate [7–9]. In many studies significant survival prolongation was reported in responders after TACE followed by RT (TACE-RT) compared with non-responders [7–12].

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A positive response after treatment is one of the most important and best-known determinants of prognosis in many oncologic fields, including HCC. In particular, considering the fact that PVTT is the main prognostic factor, a PVTT response might be the most important factor for improving the clinical outcomes of advanced HCC. However, the effect of the PVTT response on survival prolongation is poorly understood. Comparison of clinical outcomes according to the PVTT response after TACE-RT may provide an explanation for this relationship. Increasing RT application using higher conformal RT techniques, like stereotactic ablative RT (SABR) or particle beam RT, may be further emphasized in the present situation. Moreover, further treatment might be modified according to the response pattern based on more precise information on the effect of TACE-RT on PVTT.

Based on this background, the authors conducted the present analysis with an independent external validation study to evaluate the relationship between PVTT response and clinical outcomes in HCC patients with PVTT treated with TACE-RT.

Materials and methods

Patients and methods

The present study was conducted in HCC patients with main and/or first branch PVTT who were treated with TACE followed by three-dimensional conformal RT (3D-CRT) from August 2002 to September 2008 at Asan Medical Center. The diagnosis of HCC was based on guidelines proposed by the American Association for the Study of Liver Diseases (AASLD), and PVTT was confirmed by using dynamic contrast enhanced multi-phase computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, or angiography. On the contrast-enhanced CT or MRI, PVTT was identified by the presence of intraluminal filling defect of portal vein adjacent to the primary tumor on portal phase with contrast enhancement of inner side of the filling defect on arterial phase. We categorized the thrombi as main PVTT if thrombi were located in the bilateral first branches and the main trunk. Tumor size was defined as the length of the longest diameter of the primary tumor with PVTT. Patients with PVTT below the first branch were excluded to maintain homogeneity of the study because other local treatment modalities can be considered when PVTT is confined to only small branches. Other exclusion criteria were as follows: (1) distant metastasis before initiation of RT, (2) Eastern Cooperative Oncology Group performance status $\geqslant 3$, (3) poor liver function of Child-Pugh class C, (4) uncontrollable ascites or hepatic encephalopathy, (5) combined treatment with intra-arterial chemotherapy, (6) presence of double primary malignancies, and (7) planned RT was not completed. Patients for whom it was not possible to evaluate the response at 4–12 weeks after the completion of RT were also excluded from the analysis.

The detailed TACE and RT procedures were described in our previous study [8]. RT was started at 2–3 weeks after TACE or TACI (transarterial chemoinfusion), and every effort was made to encompass the tumor invading the portal vein as much as possible; if this could not be achieved, partial tumor and PVTT with margin was determined as the target. The clinical target volume (CTV) was regarded the same as gross tumor volume (GTV) defined by dynamic enhanced CT or MRI. For daily set-up of variation and respiratory movement of the liver, the planning target volume was determined using 1–2 cm margin from CTV. To reduce the uncertainty of respiratory motion, fluoroscopy as well as planning CT was checked in simulation with shallow-breathing in both sets. GTVs were determined by dynamic enhanced lesion, and they tried to encompass the entire tumor and PVTT as possible. The dose per fraction was 2 to 5 Gy at 5 fractions per week. The total dose was determined by the volume of normal liver receiving >50% of the prescription dose is maintained under 50%, and the maximum dose to the stomach or duodenum was limited to 36 Gy with 3 Gy or 44 Gy with 2 Gy fraction.

The next session of TACE was routinely planned for 6–8 weeks after completion of RT, and TACE continued until the viable intrahepatic tumor completely disappeared in patients with preserved hepatic function.

Patients were examined at least once a week during RT and then followed up 1 month after completion of RT. Thereafter, follow up was continued at 2- to 3-month intervals. The RT response was determined with dynamic contrast enhanced multi-phase liver CT scans 4–12 weeks after completion of treatment. To evaluate the effect of RT on PVTT with respect to overall clinical outcome, evaluation of RT response focused only on PVTT. In the evaluation of PVTT response, the greatest perpendicular diameter of the tumor thrombus was calculated and compared with the initial value as described previously [8]. Objective response was calculated as the combined number of patients with complete response and partial response. Adverse events were scored using the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0).

For external validation of the findings we used an independent external cohort of HCC patients with PVTT who satisfied the present inclusion criteria and received TACE-RT at Samsung Medical Center during the same period as the training set from August 2002 to September 2008. The procedure of TACE and RT used in the validation set was reported in another published article [11], and additional treatment, mostly TACE, was added on demand after TACE-RT.

The present study was approved with permission by the institutional review boards of both Asan Medical Center (IRB No. 2015-0264) and Samsung Medical Center (IRB No. 2015-03-073). Informed consent was waived because of the retrospective nature of the study.

Statistical analysis

Intrahepatic metastasis-free survival (IHMFS), distant metastasis-free survival (DMFS), progression-free survival (PFS), and overall survival (OS) were estimated using the Kaplan–Meier method. OS, IHMFS, DMFS, and PFS were measured from the date of the start of RT to the date of a patient's death, the last follow-up examination, or the date that an event developed, respectively. In univariate survival analyses, the log-rank test was used to evaluate differences. Potential prognostic variables that showed statistical significance in univariate analysis were used to perform multivariate analysis with the Cox proportional hazards model using the Schoenfeld residuals method. Correlation between PVTT response and other variables was evaluated using the chi-square test or Fisher's exact test. Receiver-operating characteristic (ROC) curves were drawn to evaluate the status of diseases whether they progressed or not at 1 year from the date of starting RT according to the prognostic factors that had statistical significance in multivariate analysis, and area under the curve (AUC) with 95% confidence interval (CI) was used to evaluate the power of prognostic factors. ROC curves were drawn and evaluated with the external validation set. All statistical analysis was performed using SPSS Statistics version 21.0 (Asan Medical Center) and version 22.0 (Samsung Medical Center) software for Windows (IBM, Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

Results

During the study period, 440 patients with HCC who had PVTT were treated with TACE-RT at Asan Medical Center. Among them, a

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