Original Article

Prognosticators of hepatocellular carcinoma with intrahepatic vascular invasion

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ABSTRACT

Objective: The prognosis of intrahepatic vascular invasion, including unilateral or main portal vein tumor thrombosis (PVTT) and hepatic vein thrombosis, is still poor. Many patients with intrahepatic vascular invasions never receive radiotherapy (RT). In recent years, more conformal RT techniques such as intensity-modulated RT (IMRT) have been developed and applied to treat other cancers and have significantly improved treatment results and decreased side effects. The purpose of this study is to evaluate the treatment results in patients with intrahepatic vascular invasion and explore the role of IMRT in these treatments. Materials and Methods: There were a total of 73 patients with newly diagnosed AJCC stage IIIB hepatocellular carcinoma (HCC), with either PVTT or hepatic vein thrombosis between 2007 and 2015 in our hospital. IMRT was used for all patients who received RT. Prognostic factors, including treatment modalities, liver function, and comorbidities, were analyzed using univariate and multivariate analysis with the Cox model. Survival time was analyzed using the Kaplan–Meier method. Results: The longest follow-up time was 45.3 months. The median age was 67 years. Univariate analyses indicated that IMRT, transarterial chemoembolization (TACE), target therapy (sorafenib), tumor size, Child-Pugh class, and ascites were significantly associated with overall survival (OS). In multivariate analysis, IMRT (hazard ratio [HR], 0.495; P = 0.019), sorafenib (HR, 0.340; P = 0.013), tumor size (HR, 2.085; P = 0.020), and Child-Pugh class (P = 0.004) were independent prognostic predictors for patients with intrahepatic vessel invasion, but TACE and ascites were not. The outcomes of patients who had different treatment modalities were significantly different (P < 0.001). Patients who received IMRT with TACE had the best outcomes. Patients who received an RT dose above 5400 cGy had better outcomes than those who with a dose below 5400 cGy, although the results were not significantly different (P = 0.248). Conclusion: IMRT is an important treatment component for patients with intrahepatic vascular invasion. Combined treatment modalities, such as IMRT with TACE, could improve the outcomes of HCC patients with intrahepatic vessel invasion.

KEYWORDS: Hepatic vein thrombosis, Hepatocellular carcinoma, Portal vein thrombosis, Prognosticators, Radiotherapy, Transarterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer in the world and the third most common cause of cancer-related deaths in men [1]. Partial heptectomy, liver transplantation, and local ablative treatments provide potentially curative therapy for HCC. However, only a minority (20%–25%) of HCC patients can be managed with curative treatment [2]. The prognosis of HCC is extremely poor in patients with advanced disease. Although several factors contribute to this poor prognosis, major vascular invasion, i.e., portal vein tumor thrombosis (PVTT) or hepatic vein tumor thrombosis (HVTT), is one of the most important factors [3].

About 8%–26% of HCC patients have main portal vein obstruction [4,5]. PVTT can lead to serious complications,
such as portal vein hypertension, rupture of esophageal and rectal varices, ascites, and ischemic liver damage. Patients with advanced HCC with PVTT have a particularly grave prognosis [6]. The previous study showed that the median survival time of patients who have HCC with PVTT is 2–3 months if no treatment is received [7].

The incidence of HVTT ranges from 1.4% to 4.9% [8,9]. Compared with PVTT, little is known about HVTT due to its relatively low incidence [9]. Patients with both HVTT and PVTT have a worse prognosis than those with HVTT alone, due to the high risk of intrahepatic metastasis and portal hypertension complications [10].

In locally advanced HCCs, radiotherapy (RT) has been used to relieve obstruction and improve portal blood flow if the tumor invades the biliary tree or portal vein [11]. RT techniques for the treatment of HCC have evolved substantially over the past decades. Delivery of radiation has become more precise, which has enabled higher doses of radiation to tumors while saving the normal liver parenchyma [12]. RT has also been used in combination with transarterial chemoembolization (TACE) for intermediate stage tumors.

In this study, we retrospectively analyzed the prognostic factors of stage IIIB HCC patients with either PVTT or HVTT. We also examined the outcomes of patients who were treated with combined intensity-modulated RT (IMRT) and TACE compared with TACE alone, IMRT alone, and supportive care alone.

MATERIALS AND METHODS

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan (B10404010). The procedures we followed were in accordance with both the ethical standards of the Institutional Review Board of our institution and with the Helsinki Declaration. Informed written consent was waived because the study was a retrospective data analysis.

Patients

Between January 1, 2007, and December 31, 2015, a total of 73 patients with newly diagnosed AJCC stage IIIB HCC who had an initial diagnosis of either PVTT or HVTT were retrospectively enrolled into the study. All patients were evaluated with a baseline history and physical examination, serum laboratory tests, including baseline liver function tests, and computed tomography or magnetic resonance imaging scan of the abdomen and pelvis.

Treatment modality

The treatment strategies adopted by physicians, patients, and their families were recorded, which included TACE alone, RT alone, both RT and TACE, and supportive care alone.

IMRT was carried out using an inverse planning system in all patients who received RT. The prescribed doses delivered by external beam RT were at least 45 Gy, ranging from 45 to 70 Gy. Conventional RT fractionation was given, namely, 3–4.5 Gy per day, 5 days per week for 2–4 weeks, with a total of 11–20 fractions. The biologically effective dose (BED) ranged from 58.5 Gy\textsubscript{10} to 84.5 Gy\textsubscript{10}.

Measurements of endpoint and covariates

The primary dependent variable in the study was overall survival (OS), which was calculated from the date of diagnosis to the past follow-up or death. Factors which could possibly affect OS were adjusted accordingly. These independent variables included gender, age, cancer treatment modalities received, Barcelona clinic liver cancer (BCLC) stage, initial Child-Pugh score, largest tumor size, PVTT status, HVTT status, hepatitis serological condition, liver cirrhosis, ascites, and comorbidities including diabetes mellitus (DM), hypertension (HTN), stroke, and chronic kidney disease (CKD) [Table 1]. Cancer treatment modalities for these stage IIIB patients included RT alone, TACE alone, TACE and RT, and best supportive care only.

Statistical analysis

We used commercial statistical software (SPSS version 17.0; SPSS Inc., Chicago, IL, USA) to conduct statistical analyses. The Kaplan–Meier method was used for survival analysis. The difference between survival curves was determined using the log-rank test. The Cox regression model was used in the univariate analysis to identify significant prognostic factors. Only those statistically significant variables in univariate analysis were included in multivariate analysis using the Cox regression model. All tests were two-tailed and considered to be statistically significant when \( P < 0.05 \).

RESULTS

The longest follow-up time was 45.3 months. The first, median, and third quartile follow-up times were 1, 4, and 8.23 months, respectively. The relatively short follow-up time was mainly due to the poor prognosis and short survival time of these stage AJCC stage IIIB patients. The cumulative 6-month, 1-year, 2-year, and 3-year OS rates were 35.6%, 17.8%, 8.9%, and 8.9%, respectively and the median survival for all patients was 4 months.

The first, median, and third quartile ages of all these HCC patients in our hospital were 56.5, 67, and 75.5 years old, respectively; the oldest patient was 92 years old. This was a relatively older age distribution for HCC patients, compared with the rest of Taiwan, which may be due to population aging problems in Chiayi county. A total of 76.7% of patients were male. Most patients (39 patients, 53.4%) received only the best supportive care without TACE or RT. A total of 16, 11, and 7 patients received RT alone, TACE alone, and both TACE and RT, respectively. A total of 40 (54.8%) cases were Child-Pugh class B, followed by 21 (28.8%) cases with Child-Pugh class A. Only 12 (16.4%) cases were classified class C based on initial clinical and laboratory evaluation. In 54 patients (74%), the tumors were larger than 5 cm.

Intrahepatic vein invasion was classified according to the criteria of the liver cancer study group of Japan as portal tumor invasion involving first-order branches or the main trunk of the portal vein, or as tumor invasion involving first-order branches of the hepatic vein. Seventy patients had PVTT (95.9%), and eleven patients had HVTT (15.1%). Forty of the PVTT patients
Table 1: Patient characteristics \((n=73)\)

| Variable                           | Without RT \((n=50)\), \(n\%\) | With RT \((n=23)\), \(n\%\) | \(P\) |
|------------------------------------|----------------------------------|--------------------------------|-------|
| Gender                             |                                 |                                |       |
| Male                               | 36  72.0%                        | 20  87.0%                      | 0.16  |
| Female                             | 14  28.0%                        | 3  13.0%                       |       |
| Age                                |                                 |                                |       |
| <65                                | 15  30.0%                        | 13  56.5%                      | 0.07  |
| ≥65–<75                            | 19  38.0%                        | 7  30.4%                       |       |
| ≥75                                | 16  32.0%                        | 3  13.0%                       |       |
| BCLC stage                         |                                 |                                |       |
| C                                  | 40  80.0%                        | 22  95.7%                      | 0.08  |
| D                                  | 10  20.0%                        | 1  4.3%                        |       |
| Child Pugh Score                   |                                 |                                |       |
| Class A                            | 12  24.0%                        | 9  39.1%                       | 0.28  |
| Class B                            | 28  56.0%                        | 12  52.2%                      |       |
| Class C                            | 10  20.0%                        | 2  8.7%                        |       |
| Tumor Size                         |                                 |                                |       |
| <5cm                               | 11  22.0%                        | 8  34.8%                       | 0.25  |
| ≥5cm                               | 39  78.0%                        | 15  65.2%                      |       |
| Portal Vein Thrombosis             |                                 |                                |       |
| (-)                                | 1  2.0%                          | 2  8.7%                        | 0.18  |
| (+)                                | 49  98.0%                        | 21  91.3%                      |       |
| Main                               | 23  46.9%                        | 7  33.3%                       | 0.29  |
| Right or Left Branch               | 26  53.1%                        | 14  66.7%                      |       |
| Hepatic Vein Thrombosis            |                                 |                                |       |
| (-)                                | 45  90.0%                        | 17  73.9%                      | 0.07  |
| (+)                                | 5  10.0%                         | 6  26.1%                       |       |
| TACE                               |                                 |                                |       |
| (-)                                | 39  78.0%                        | 16  69.6%                      | 0.44  |
| (+)                                | 11  22.0%                        | 7  30.4%                       |       |
| Sorafenib                          |                                 |                                |       |
| (+)                                | 46  92.0%                        | 16  69.6%                      | 0.01  |
| (+)                                | 4  8.0%                          | 7  30.4%                       |       |
| Hepatitis                          |                                 |                                |       |
| (-)                                | 14  28.0%                        | 8  34.8%                       | 0.09  |
| HBV                                | 15  30.0%                        | 12  52.2%                      |       |
| HCV                                | 17  34.0%                        | 2  8.7%                        |       |
| HBV and HCV                        | 4  8.0%                          | 1  4.3%                        |       |
| Liver Cirrhosis                    |                                 |                                |       |
| (-)                                | 13  26.0%                        | 5  21.7%                       | 0.69  |
| (+)                                | 37  74.0%                        | 18  78.3%                      |       |
| Ascites                            |                                 |                                |       |
| (-)                                | 12  24.0%                        | 11  47.8%                      | 0.04  |
| (+)                                | 38  76.0%                        | 12  52.2%                      |       |
| Diabetes Mellitus                  |                                 |                                |       |
| (-)                                | 29  58.0%                        | 17  73.9%                      | 0.19  |
| (+)                                | 21  42.0%                        | 6  26.1%                       |       |
| Hypertension                       |                                 |                                |       |
| (-)                                | 22  44.0%                        | 15  65.2%                      | 0.09  |
| (+)                                | 28  56.0%                        | 8  34.8%                       |       |
| Stroke                             |                                 |                                |       |
| (-)                                | 49  98.0%                        | 22  95.7%                      | 0.57  |
| (+)                                | 1  2.0%                          | 1  4.3%                        |       |
| Chronic Kidney Disease             |                                 |                                |       |
| (-)                                | 48  96.0%                        | 21  91.3%                      | 0.41  |
| (+)                                | 2  4.0%                          | 2  8.7%                        |       |

IMRT: Intensity-modulated radiation therapy; HCC: hepatocellular carcinoma; RT: radiotherapy; TACE: transcatheter arterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer staging system; HBV: hepatitis B virus; HCV: hepatitis C virus; IMRT was used in all patients
had an invasion of the first-order branch of the portal vein, and 30 patients had main trunk invasion. A total of 51 patients had hepatitis. Among them, 27, 19, and 5 patients had hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and concurrent HBV/HCV hepatitis, respectively. A total of 55 patients had liver cirrhosis (75.3%), and 50 patients had ascites. No patients received resection surgery. Eleven patients received sorafenib.

A comparison of patient characteristics (including age groups, liver functional reserve status, tumor factors, treatment modalities, and comorbidity) between patients with and without IMRT is shown in Table 1. These two groups were not significantly different except for sorafenib use and ascites which were then incorporated into univariate and multivariate analysis for adjustment and exploration of effects on prognosis [Tables 2 and 3].

Patients who were in BCLC stage C had significantly better outcomes than those in stage D [Figure 1a, \( P < 0.001 \)]. Patients who had better liver function reserves had significantly better outcomes [Figure 1b, \( P < 0.001 \)]. The outcomes of patients with only first-order branch portal vein invasion were not significantly different than those with main trunk invasion [Figure 1c, \( P = 0.847 \)]. The outcomes of patients with different treatment modalities were significantly different [Figure 2, \( P < 0.001 \)]. Patients who received IMRT combined with TACE had the best outcomes. Patients who received IMRT with TACE had nonsignificantly better outcomes than those with IMRT alone or TACE alone with one year OS rate being 42.9%, 31.3%, 18.2%,
respectively [Figure 2, P = 0.242 and 0.240]. The outcomes of patients who received IMRT alone were not significantly different than those with TACE alone (P = 0.714). Patients who received IMRT with TACE, IMRT alone, or TACE alone, all had better outcomes than those with supportive care only, with significant results (P = 0.002, 0.001, and 0.010, respectively).

For patients who received IMRT, the first, median, and third quartile survival times were 4, 8, and 18.9 months, respectively. Patients who received IMRT doses above 5400 cGy had better outcomes than those with doses below 5400 cGy, but the results were not significantly different [Figure 3, P = 0.248].

Univariate analyses indicated that IMRT, TACE, sorafenib, tumor size, Child-Pugh class, and the presence of ascites were significantly associated with OS [Table 2]. On multivariate analysis [Table 3], IMRT (hazard ratio [HR], 0.495; 95% CI, 0.276–0.889; P = 0.019), sorafenib (HR, 0.340; 95% CI, 0.145–0.800; p, 0.013), tumor Size (HR, 2.085; 95% CI, 1.125–3.865; P = 0.020), and Child-Pugh class (p, 0.004), were independent prognostic predictors. TACE and ascites were not.

Gender, age, tumor size, HVTT, viral hepatitis, liver cirrhosis, ascites, comorbidities, including DM, HTN, stroke, and CKD were all found not to affect OS after multivariate analysis.

**DISCUSSION**

In this study, we reviewed the preliminary treatment results of patients with clinical AJCC stage III B HCC, who were treated with different modalities at our hospital. The survival rate of our stage IIIB patients was relatively low because most of them did not receive any active treatment but only best supportive care. The reasons for this included long distances from care facilities, poor family support (many patients lived alone), and relatively old age (77.6% of patients were over 60 years old).

All treatment strategy decisions were made by a multidisciplinary cancer team of gastroenterologists, pathologists, radiologists, hepatobiliary surgeons, radiation oncologists, medical oncologists, and registered dietitians. However, patients and families may refuse suggested strategies such as RT or TACE due to the above reasons. In addition, oncologists can tailor treatment for patients living alone or with poor family support to avoid harmful side effects [13]. Relatives also play an important role in the care of cancer patients and their presence may even prolong survival [14]. In this retrospective study, 63.3% stage IIIB patients did not receive definite treatment but only best supportive are.

Table 2: Univariate analysis of patient-, treatment-, and dosimetry-related variables

| Variable | Univariate Analysis |   |   |
|----------|---------------------|---|---|
| Gender (Male, ref.) | 0.732 | 0.405-1.323 | 0.732 |
| Age | 0.840 |   |   |
| <65 (ref.) | 1 | - | - |
| ≥65--<75 | 0.908 | 0.516-1.599 | 0.739 |
| ≥75 | 1.099 | 0.597-2.021 | 0.762 |
| IMRT (no IMRT, ref.) | 0.405 | 0.233-0.704 | 0.001* |
| TACE (no TACE, ref.) | 0.472 | 0.260-0.858 | 0.014* |
| Sorafenib (no sorafenib, ref.) | 0.270 | 0.120-0.608 | 0.002* |
| Tumor Size (<5 cm, ref.) | 2.285 | 1.266-4.123 | 0.006* |
| Hepatic Vein Tumor Thrombosis (without, ref.) | 0.629 | 0.310-1.275 | 0.198 |
| Portal Vein Tumor Thrombosis (without, ref.) | 3.057 | 0.743-12.572 | 0.121 |
| Child Pugh Class | 0.001* |   |   |
| Class A (ref.) | 1 | - | - |
| Class B | 2.767 | 1.485-5.155 | 0.001* |
| Class C | 5.902 | 2.589-13.455 | 0.000* |
| HBV (without, ref.) | 0.875 | 0.538-1.423 | 0.237 |
| HCV (without, ref.) | 1.093 | 0.655-1.826 | 0.733 |
| Liver Cirrhosis (without, ref.) | 0.863 | 0.496-1.501 | 0.601 |
| Ascites (without, ref.) | 2.266 | 1.276-4.025 | 0.005* |
| Diabetes Mellitus (without, ref.) | 0.99 | 0.597-1.641 | 0.969 |
| Hypertension (without, ref.) | 0.988 | 0.609-1.604 | 0.961 |
| Stroke (without, ref.) | 1.871 | 0.451-7.762 | 0.388 |
| Chronic Kidney Disease (without, ref.) | 0.639 | 0.231-1.763 | 0.135 |

*P<0.05; HR, hazard ratio; CI: confidence interval; ref: reference; IMRT: intensity-modulated radiotherapy; TACE: transcatheter arterial chemoembolization; HBV: hepatitis B virus; HCV: hepatitis C virus

Table 3: Multivariate analysis of patient-, treatment-, and dosimetry-related variables

| Variable | Multivariate Analysis |   |   |
|----------|---------------------|---|---|
| IMRT (no IMRT, ref.) | 0.495 | 0.276-0.889 | 0.019* |
| TACE (no TACE, ref.) | 0.556 | 0.290-1.068 | 0.078 |
| Sorafenib (no sorafenib, ref.) | 0.340 | 0.145-0.800 | 0.013* |
| Tumor Size (<5 cm, ref.) | 2.085 | 1.125-3.865 | 0.020* |
| Child Pugh Class | 0.004* |   |   |
| Class A (ref.) | 1 | - | - |
| Class B | 2.137 | 1.116-4.089 | 0.022* |
| Class C | 4.360 | 1.821-10.440 | 0.001* |
| Ascites (without, ref.) | 1.396 | 0.768-2.539 | 0.274 |

*P<0.05; HR, hazard ratio; CI: Confidence interval; ref: reference; IMRT: intensity-modulated radiotherapy; TACE: transcatheter arterial chemoembolization

**Figure 3:** The cumulative 6-month, 1-year, 2-year, and 3-year overall survival rates and median survival for intensity-modulated radiotherapy doses above 5400 cGy were 70%, 50%, 30%, and 30%, and 6.83 months, and for doses below 5400 cGy, were 53.8%, 23.1%, 11.5%, and censored, and 8.57 months.
The study results showed that the outcomes of different treatment modalities for patients with intrahepatic vessel invasion were significantly different ($P < 0.001$). Previous limitation for RT treatment of HCC was that the radiation tolerance of the liver was far less than the therapeutic radiation dose, i.e., low therapeutic ratio [15]. However, recent RT technological developments have enabled more successful treatment of HCC by delivering a substantial dose of radiation to the tumor and avoiding peripheral normal liver tissue. Now, the improved efficacy of RT is more widely understood and increasing numbers of institutions have adopted local RT for advanced HCC [16]. In this study, patients who received RT alone had significantly better outcomes than those with best supportive care only ($P = 0.01$).

Culleton et al. reported a median survival of 7.9 months for HCC patients with PVTT and Child-Pugh class B to C, treated by stereotactic body RT with median dose 30 Gy in 6 fractions [17]. In this study, patients with daily dose of 3–4.5 Gy had a median survival of 8 months.

RT has also been used to treat PVTT with good outcomes [18,19]. Lee et al. performed RT with a BED of 39 Gy$_{eq}$ to 70.2 Gy$_{eq}$. Their study showed a dose-response relation with response rates for a BED $<58$ Gy$_{eq}$ and $\geq58$ Gy$_{eq}$ of 20% and 54.6%, respectively ($P = 0.034$) [18]. The study results showed that a BED $\geq63.7$ Gy$_{eq}$ ($\geq54$ Gy) resulted in nonsignificantly better outcomes than a BED $<63.7$ Gy$_{eq}$, with 1 year OS rate of 50% and 23.1%, respectively ($P = 0.248$).

Higher doses of RT could result in a higher response rate for large tumors. In our treatment experience, the prescribed doses can be increased from 45 to 70 cGy without significant radiation-induced liver disease. In this study, all patients received RT using the IMRT technique. A previous study showed that IMRT significantly reduced the probability of complications in normal tissue, compared with three-dimensional conformal RT (3DCRT) [20]. Simultaneous integrated boost-intensity modulated RT has also been shown effective for advanced HCC [21].

Advances in 3D conformal techniques for treatment planning have allowed RT to be a complement to incomplete TACE [22-24]. Conversely, Lu et al. compared 3DCRT followed by 2–3 series of TACE to TACE alone and found that combined treatment significantly improved clinical outcomes in patients with HCC and PVTT (mean survival time 13.0 vs. 9.0 months) [25]. A literature review showed that most combined therapy studies were 3DCRT/IMRT with TACE. Our study showed results of purely IMRT with TACE and found that clinical outcomes combining IMRT and TACE were the best, followed by IMRT alone, and TACE alone, with supportive care alone being the worst. Consistent with a previous 3DCRT study, our study reported that patients who received IMRT with TACE, and TACE alone had mean survivals of 17.8 and 8.5 months, respectively.

The prognosis of untreated HCC is grave despite improved supportive treatment. Yeung et al. reported on 106 Chinese patients with HCC who were not amenable to curative treatment and were managed symptomatically [6]. The overall median survival was 3 months, with Okuda stages I, II, and III of 5.1, 2.7, and 1.0 months, respectively ($P < 0.05$). In our study, patients who received best supportive care only had a mean survival of 2.3 months. Previous studies have shown that individuals in rural areas have trouble accessing palliative care due to shortages of health care professionals as well as transportation issues imposed by geography [26].

**Study strengths**

This study had several strengths. First, image examination results were available, including hepatic vein invasion status, and first-degree or main trunk PVTT. This study incorporated this image information into univariate and multivariate analysis to find significant prognosticators. Second, this study focused on AJCC clinical stage IIIB patients who all had intrahepatic vessel invasion. This study design could decrease the bias of cancer stage diversity.

**Study limitations**

Our study also had several limitations. First, the number of patients with AJCC stage IIIB was small, although the results still reached statistical significance. With respect to future work, a larger sample size would be helpful, as would a longer longitudinal study. Second, this was a retrospective review study rather than a prospective randomized controlled trial, although many variates had been adjusted. Further investigation is warranted. Third, this study lacked information on sociodemographic characteristics, such as socioeconomic status.

**CONCLUSION**

IMRT is an important treatment component in intrahepatic vascular invasion patients. Combined treatment modalities, such as IMRT with TACE, could improve the outcomes of HCC patients with intrahepatic vessel invasion. Action is needed to improve family support with social support networks and improve access to medical services, to encourage patients and their families to receive active treatment.

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**Conflicts of interest**

There is no conflict of interest.

**REFERENCES**

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, et al. Hepatectomy for hepatocellular carcinoma: Toward zero hospital deaths. Ann Surg 1999;229:322-30.
3. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20:1527-36.
4. Bismuth H, Morino M, Sherlock D, Castaing D, Miglietta C, Cauquil P, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. Am J Surg 1992;163:387-94.
5. Yamada R, Sato M, Kawabata M, Nakatsu H, Nakamura K, Takashima S, et al. Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 1983;148:397-401.
6. Yeung YP, Lo CM, Liu CL, Wong BC, Fan ST, Wong J, et al. Natural
history of untreated nonsurgical hepatocellular carcinoma. Am J Gastroenterol 2005;100:1995-2004.

7. Fujii T, Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Kosuge T, et al. Hepatocellular carcinoma with portal tumor thrombus: Analysis of factors determining prognosis. Jpn J Clin Oncol 1993;23:105-9.

8. Kim HC, Lee JH, Chung JW, Kang B, Yoon JH, Kim YJ, et al. Transarterial chemoembolization with additional cisplatin infusion for hepatocellular carcinoma invading the hepatic vein. J Vasc Interv Radiol 2013;24:274-83.

9. Kokudo T, Hasegawa K, Yamamoto S, Shindoh J, Takemura N, Aoki T, et al. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. J Hepatol 2014;61:583-8.

10. Ikai I, Yamaoka Y, Yamamoto Y, Ozaki N, Sakai Y, Satoh S, et al. Surgical intervention for patients with stage IV-A hepatocellular carcinoma without lymph node metastasis: Proposal as a standard therapy. Ann Surg 1998;227:433-9.

11. Han KH, Seong J, Kim JK, Ahn SH, Lee DY, Chon CY, et al. Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. Cancer 2008;113:995-1003.

12. Seong J. Challenge and hope in radiotherapy of hepatocellular carcinoma. Yonsei Med J 2009;50:601-12.

13. Cavalli-Björkman N, Glimelius B, Strang P. Equal cancer treatment regardless of education level and family support? A qualitative study of oncologists’ decision-making. BMJ Open 2012;2 pii: e001248.

14. Leng JI, Xu YZ, Dong JH. Efficacy of transarterial chemoembolization for hepatocellular carcinoma with portal vein thrombosis: A meta-analysis. ANZ J Surg 2016;86:816-20.

15. Lawrence TS, Robertson JM, Ansher MS, Jirtle RL, Ensminger WD, Fajardo LF, et al. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237-48.

16. Dawson LA, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol 2000;18:2210-8.

17. Culleton S, Jiang H, Haddad CR, Kim J, Brierley J, Brade A, et al. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. Radiother Oncol 2014;111:412-7.

18. Kim DY, Park W, Lim DH, Lee JH, Yoo BC, Paik SW, et al. Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma. Cancer 2005;103:2419-26.

19. Nakagawa K, Yamashita H, Shiraishi K, Nakamura N, Tago M, Igaki H, et al. Radiation therapy for portal venous invasion by hepatocellular carcinoma. World J Gastroenterol 2005;11:7237-41.

20. Cheng JC, Wu JK, Huang CM, Liu HS, Huang DY, Tsai SY, et al. Dosimetric analysis and comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy for patients with hepatocellular carcinoma and radiation-induced liver disease. Int J Radiat Oncol Biol Phys 2003;56:229-34.

21. Kim TH, Park JW, Kim YJ, Kim BH, Woo SM, Moon SH, et al. Simultaneous integrated boost-intensity modulated radiation therapy for inoperable hepatocellular carcinoma. Strahlenther Onkol 2014;190:882-90.

22. Li B, Yu J, Wang L, Li C, Zhou T, Zhai L, et al. Study of local three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for patients with stage III hepatocellular carcinoma. Am J Clin Oncol 2003;26:e92-9.

23. Mornex F, Girard N, Beziat C, Kubas A, Khodri M, Trepo C, et al. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies – Mature results of the French Phase II RTF-1 trial. Int J Radiat Oncol Biol Phys 2006;66:1152-8.

24. Shim SJ, Seong J, Han KH, Chon CY, Suh CO, Lee JT, et al. Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma. Liver Int 2005;25:1189-96.

25. Lu DH, Fei ZL, Zhou JP, Hu ZT, Hao WS. A comparison between three-dimensional conformal radiotherapy combined with interventional treatment and interventional treatment alone for hepatocellular carcinoma with portal vein tumour thrombosis. J Med Imaging Radiother Oncol 2015;59:109-14.

26. Wilson DM, Justice C, Sheps S, Thomas R, Reid P, Leibovici K, et al. Planning and providing end-of-life care in rural areas. J Rural Health 2006;22:174-81.