Abstract. Background/Aim: This study aimed to clarify the efficacy of anatomical hepatectomy in patients with preserved liver function. Patients and Methods: We compared the clinicopathology of the anatomical hepatectomy (AH) group (n=264) with that of the non-anatomical hepatectomy (NAH) group (n=85) and evaluated favorable conditions of anatomical hepatectomy for patients with HCC with an indocyanine green 15-minute retention rate of less than 30%. Results: There was no significant difference between the two groups in five-year disease-free survival. However, disease-free survival of the AH group was significantly better than that of the NAH group when patients had T1 tumors, tumors without intrahepatic metastasis, tumors located within one subsegment, or serum alpha feto-protein less than 100 ng/dl (p=0.015, p=0.009, p=0.046 and p=0.036, respectively). Anatomical hepatectomy was an independent favorable prognostic factor by multivariate analysis taking into consideration clinical factors, which could be clarified pre- or intraoperatively (p=0.003). Conclusion: Anatomical hepatectomy should be performed for HCC patients with HCC with preserved liver function.

Most patients with hepatocellular carcinoma (HCC) develop new HCCs synchronously or metachronously, even after receiving treatment for the first lesion (1, 2). While the cumulative postoperative five-year survival rates for HCC have been reported to be 37%-65% (3, 4), the cumulative postoperative five-year disease-free survival rates for HCC range from 4% to 24.0% (5, 6). Among all cases that recur after surgery, approximately 90% recur in the residual liver. There are two patterns of HCC recurrence in the residual liver: intrahepatic metastasis from the primary tumor, and multicentric occurrence (i.e. second primary). It is very important to reduce the risk of intrahepatic recurrence in order to allow for a good prognosis. Most intrahepatic metastases develop multiple or diffuse recurrence within two years after resection of the primary tumor.

Anatomical hepatectomy involves the complete removal of a liver segment or sub-segment that receives blood through the segmental or sub-segmental portal vein, respectively (7). Theoretically, performing anatomical hepatectomy is the best way to prevent intrahepatic metastasis occurring via vascular invasion. In two recent meta-analyses (8, 9), the efficacy of anatomical resection was reported. However, these reports were retrospective studies that included patients with HCC from various backgrounds, clinical stages and liver functions. Moreover, patients with HCC with indocyanine green 15-minute retention rates (ICG-R15) of more than 29% were also included in the analysis. Such patients are not candidates for subsegmentectomy, which includes anatomical resection of a minimum extent of the liver, according to Makuuchi et al.’s criteria (10).

ICG is a tricarbocyanine dye that is completely and exclusively removed by the liver and excreted into the bile following intravenous injection. Previously, the normal ICG-R15 has been reported to be less than 15% (11, 12). The ICG clearance test was developed to assess the function of the liver and has been suggested to be a potential predictor of an HCC patient’s suitability for hepatic resection. Therefore, a comparison should be made between anatomical and non-anatomical resection in HCC patients who are candidates for subsegmentectomy.

The purpose of this study was to clarify the efficacy of anatomical hepatectomy in patients with HCC with ICG-R15 of less than 30%.
Patients and Methods

Between April 1980 and August 2011, 572 patients with HCC underwent primary hepatic resection at the Department of Surgery, Division of Digestive Surgery, Kyoto Prefectural University of Medicine, Japan. Clinicopathological data, including prognosis, were available for 423 patients who underwent curative resection for HCC. Among them, 349 patients with ICG-R15 of less than 30% were analyzed in this study. Curative resection was defined here as the complete removal of a macroscopic tumor that is not exposed on the cut surface.

Two hundred and sixty-four patients who underwent anatomical hepatectomy (AH group) were clinicopathologically compared with patients who underwent non-anatomical hepatectomy (n=85) (NAH group). We also evaluated favorable conditions of anatomical hepatectomy for patients using subset and multivariate analyses. To compare the efficacy of both operative procedures, we primarily evaluated postoperative disease-free survival (DFS).

ICG retention tests were performed as follows: after fasting, the patient was injected with 0.5 mg/kg (body weight) of ICG intravenously, and serial blood samples were drawn at 5, 10 and 15 min after injection. After processing the samples, the ICG-R15 was obtained as a percentage.

Anatomical hepatectomy was defined here as the removal of a Couinaud's hepatic segment (sub-segment) (13) or segments confined by tumor-bearing portal tributaries. Clinically, we resected the liver along the demarcation line appearing after occlusion of the portal vein and hepatic artery in hemihepatectomy and segmentectomy or after injection of dye into the portal vein feeding the tumor-bearing segment or subsegment using intraoperative ultrasound guidance in cases of anatomic segmentectomy or subsegmentectomy. Limited resection or enucleation smaller than Couinaud's segment (subsegment) was defined as a nonanatomical resection.

All resected liver specimens were cut at a thickness of approximately 5 mm, and microscopic sections were viewed after staining with hematoxylin and eosin. Pathological diagnosis and classification of the resected HCC tissues were carried out according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (14). The tumors were staged using the...
Follow-up. The patients were followed up using hepatic ultrasonography, computed tomography and assessment of the levels of serum alpha-fetoprotein (AFP) and levels of serum protein induced by vitamin K absence II every three to six months. DFS was defined as the interval between surgery and the date of diagnosis of the first recurrence or the last follow-up. Overall survival (OS) was defined as the interval between surgery and the date of death caused by HCC recurrence or the last follow-up. The median follow-up duration was 62 months (range: 3-269 months).

Statistics. The statistical analysis was carried out using the Mann Whitney U-test for unpaired observations and the chi-square test for the frequency of various attributes among groups. DFS was estimated according to the Kaplan Meier method and checked for statistical significance with the Wilcoxon and log-rank tests. Risk factors for extrahepatic metastasis were estimated using a logistic regression analysis. A Cox’s hazard proportional analysis was performed to identify the risk factors of postoperative survival. Differences with a p-value less than 0.05 were considered to be significant.

Results

Clinicopathological features. Regarding host-related factors, the AH group had significantly lower serum bilirubin levels and ICG retention rates than the NAH group. Regarding tumor-related factors, infiltrative large tumors located beyond one subsegment with venous invasion and intrahepatic metastasis were significantly more common in the AH group than in the NAH group. Regarding treatment-related factors, significantly more curative limited resections with a surgical margin of less than 10 mm and hepatectomy without preoperative transarterial chemoembolization (TAE) or blood transfusions were performed in the NAH group than in the AH group (all p<0.01) (Table I).

Regarding perioperative data of the hepatic resection cases performed since 2000, the amount of operative blood loss in the AH group was greater than that observed in the NAH group (p<0.05) (Table II). However, there were no significant differences in the morbidity or length of hospital stay between the two groups.

There were no significant differences in recurrence patterns between the two groups (Table III).

Feasible conditions for anatomic hepatectomy for HCC. There were no significant differences between the AH (36.9 and 67.3%) and NAH (31.0 and 81.2%) groups in 5-year DFS and OS (Figure 1). However, subset analyses revealed that the DFS of the AH group was significantly better than that of the NAH group when the patients had UICC T1(15) tumors, tumors without intrahepatic metastasis, tumors located within one sub-segment, or an AFP of less than 100 ng/dl and underwent anatomical hepatectomy (p=0.015, p=0.009, p=0.046 and p=0.036, respectively) (Figure 2).

Significance of anatomic hepatectomy as a prognostic factor. Among all patients with an ICG-R15 of less than 30%, anatomical hepatectomy was found to be an independent favorable prognostic factor according to a multivariate analysis taking into consideration 12 other clinical factors, namely the serum bilirubin and AFP levels, hepatitis B antigen infection, the presence or absence of cirrhosis, tumor size, involvement, gross type, the presence or absence of venous infiltration, intrahepatic metastasis, the use of blood transfusions, the length of the surgical margin, curability and the methods of hepatectomy assessed pre- or intraoperatively. In addition to anatomical resection, decreases in the tumor size, non-cirrhotic liver and simple nodular gross type, i.e. simple nodular and simple nodular with extragrowth, were found to be independent favorable factors of DFS. Although increased serum total bilirubin levels were a favorable factor, all data were less than 2.0 mg/dl, except for those observed in HCC patients with bile duct infiltration or familial hyperbilirubinemia (Table IV).

Discussion

The HCC treatment guidelines have been established based on scientific evidence (16, 17). The treatment algorithms included in the guidelines are very useful when considering strategies for treating HCC. The prognosis of HCC is thought to depend primarily on tumor- and host-related factors, not on treatment-related factors and the guidelines reflect this fact. Under the Japanese guidelines, having HCCs with fewer than three nodules measuring <3 cm diameter is a condition
for which several possible surgical treatments and image-guided non-surgical therapies are recommended, including percutaneous ethanol injection therapy, microcoagulation therapy and radiofrequency ablation (16). However, there are no conclusions regarding whether surgery or image-guided non-surgical therapy is better for HCC in such situations because liver function varies in these patients.

Regarding surgery, the significance of anatomical hepatectomy for HCC remains controversial. Huang et al. (18) showed no differences in prognosis between anatomical and limited resection among patients with HCC with cirrhosis. Tanaka et al. (19) and Dahiya et al. (20) suggested that there are no survival benefits for patients with HCC treated with anatomical resection compared with major hepatectomy. In contrast, Arii et al. (21) and Hasegawa et al. (22) reported that patients with HCC who undergo anatomical resection have higher recurrence-free survival rates than those who undergo non-anatomical resection. Recently, favorable reports of anatomical resection have increased under some conditions. Eguchi et al. (23) recommended anatomical subsegmentectomy for HCCs measuring 2 to 5 cm in size. Yamazaki et al. (24) also showed the superiority of anatomical resection for histologically-advanced single HCCs ranging from 2 to 5 cm in diameter. Sawada et al. (25) maintained that anatomical resection is effective for small HCCs measuring less than 2 cm if the patient has a good liver function. Kamiyama et al. (26) indicated that anatomical resection is feasible for patients with HCC who meet the Milan criteria. Furthermore, the two meta-analyses described above reported that anatomical resection was effective to improve the postoperative prognosis of patients with HCC (8, 9).

Summarizing these data, anatomical resection has no efficacy for patients with advanced HCC or those with liver dysfunction. In advanced cases, micrometastasis of the primary tumor may develop beyond the anatomical extent of the lesion. Moreover, the patient’s liver function can limit the resection extent and prognosis more than differences in hepatectomy.
methods. It is impossible to perform anatomic wide hepatectomy (i.e., Hr>H hepatectomy) (27) in such patients with liver dysfunction. These are some of the reasons why anatomical resection has no efficacy for patients with advanced HCC or those with liver dysfunction. In our series including only patients with HCC indicated for anatomical resection, anatomical resection was found to be superior to non-anatomical resection in these patients with T1 UICC tumors or tumors located within one subsegment that were not in advanced stages. Moreover, for intrahepatic metastasis-negative patients or patients with an AFP of less than 100 ng/dl, anatomical resection improved the DFS more significantly than did non-anatomical resection. Theoretically, we can understand that anatomical resection achieves good results under these conditions. Anatomical resection means complete removal of a segment or subsegment with microvenous tumor thrombi that have developed histological intrahepatic metastases through the segmental or subsegmental portal vein. AFP is also a surrogate marker of tumor size and infiltration. Anatomical resection can control tumors located within a segment or subsegment. Nanashima et al. (28) reported that the survival of patients with HCC with Vp1 or Vv1 according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (14) was significantly better with anatomical resection than non-anatomical resection. However, all data described above were obtained from retrospective studies of heterogeneous populations.

Whether anatomical resection or limited resection is selected is based primarily on the liver function in most institutes in accordance with Makuuchi et al.'s criteria (10), i.e., the presence or absence of ascites, the serum total bilirubin levels and an ICG-R15 (10). Patients with HCC with
undergo limited (nonanatomical) resection, and it is impossible to perform anatomical resection in patients with serum total bilirubin levels above 1.0 mg/dl or ICG-R15 above 29%. Therefore, when we compare the prognosis of patients with HCC who undergo anatomical resection versus those who undergo non-anatomical resection, we must analyze patients with ICG-R15 of less than 30%. However, in our series, among the patients who had a relatively good liver function, the heterogeneity of the patients’ backgrounds could not be avoided. As a result, there were no overall significant differences in prognosis between the AH and NAH groups. Therefore, we performed a multivariate analysis using all patients. Anatomic hepatectomy was found to be the only independent favorable surgical prognostic factor, which was thought to be the most reliable result of this study.

There are reports that anatomical resection causes more blood loss and has a longer operative time than nonanatomical resection (24, 26, 29). In our series analyzing patients who have undergone hepatectomy since 2000, the amount of blood loss in the AH group was more than that observed in the NAH group. However, there were no significant differences in mortality, morbidity, operative time or length of hospital stay between the two groups. Although anatomical resection may bring a perioperative burden to both surgeons and patients, the priority of treatment of HCC should be in obtaining a good prognosis for the patient. Therefore, surgeons must improve their liver resection skills to be able to perform anatomical resection with less blood loss.

The limitation of this study is that it was a retrospective one. Only randomized control studies using patients with similar backgrounds can clarify whether anatomical or non-anatomical resection is more effective for HCC.

In conclusion, anatomical hepatectomy improves the DFS of patients with relatively early-stage HCC who are able to undergo anatomical resection, i.e. patients with ICG-R15 of less than 30%. This procedure should therefore be performed as skillfully as possible.

Conflicts of Interest

There are no conflicts of interest to disclose.

References


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