Detection of New Tumors by Intraoperative Ultrasonography During Repeated Hepatic Resections for Hepatocellular Carcinoma

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Objective: To evaluate the efficacy of intraoperative (IO) ultrasonography (US) as compared with other imaging modalities on the primary and repeated hepatectomies for hepatocellular carcinoma.

Design: Retrospective study.

Setting: University hospital.


Main Outcome Measures: New tumors detected by IOUS at the primary and second hepatectomies were analyzed. The long-term outcomes were also studied.

Results: Intraoperative US sensitivity was the highest. The detection rate by each imaging modality slightly but uniformly decreased at the second hepatectomy. Intraoperative US detected 56 new tumors in 30 cases (7.0%) at the primary hepatectomy and 13 new tumors in 8 cases (7.3%) at the second hepatectomy. The mean±SD tumor sizes were 8.7±3.8 mm and 9.0±5.2 mm at the primary and second resections, respectively. The preoperative surgical plan was changed owing to the IOUS findings alone in 24 cases (5.6%) at the primary hepatectomy and in 7 cases (6.4%) at the second. Although recurrence was frequent in patients with new tumors at the primary hepatectomy, long-term survival after appropriate treatment for recurrence was similar to that of patients without new tumors.

Conclusions: Despite the recent progress in imaging modalities, IOUS is still the most sensitive. The same degree of precaution is necessary for new tumors when performing IOUS during repeated hepatectomy. Patients with new tumors are at high risk for recurrence, so regular follow-up is important to prolong survival.

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Since its development in the late 1970s, intraoperative (IO) ultrasonography (US) has been widely used in liver surgery. It is now an indispensable tool for final diagnostic imaging before the resection of primary and secondary liver tumors. During liver resection for hepatocellular carcinoma (HCC), IOUS detects new lesions in 13.1% to 30% of cases and the operative plan has to be changed according to the IOUS findings. It is well known that the rate of recurrence of HCCs is very high, and approximately 70% of patients develop cancer recurrence within 5 years after curative liver resection. For recurrent HCCs, repeated liver resection provides the best chance for a cure. This approach has recently been adopted routinely in cancer center hospitals. Intraoperative US is also actively used in repeated resections; however, to our knowledge, there have been no reports of the significance of IOUS in the setting of repeated liver resection.

In this study, we have evaluated the effect of IOUS on the treatment of 430 patients undergoing 555 primary and repeated hepatectomies for HCC and analyzed 69 new tumors detected by IOUS. The aim of the study was to address the following 3 important questions: (1) How often are new tumors detected by IOUS and the operative plans changed in the era of repeated resection for HCC? (2) What are the characteristics of new tumors (size, location, background)? and (3) How does detection of the new tumors affect the patient outcome after primary resection?

See Invited Critique at end of article

METHODS

From January 6, 1995, to December 26, 2002, 430 consecutive patients underwent 555 hepatic resections for the treatment of HCC at the...
University of Tokyo Hospital, Tokyo, Japan (primary [first] hepatectomy in 430 cases, second hepatectomy in 110 cases, third hepatectomy in 11 cases, and fourth hepatectomy in 4 cases). The primary and second hepatectomies were the subject of this study. There were 335 men and 95 women aged 13 to 83 years (median age, 63 years) (Table 1). Of these, 72 patients had positive findings for serum hepatitis B virus surface antigen and 281 patients had positive findings for hepatitis C virus antibody; 11 patients had positive findings for both; and 77 patients had negative findings for both. The histological diagnosis of the hepatic parenchyma was liver cirrhosis in 183 patients, liver fibrosis or chronic hepatitis in 184, and healthy liver in 63.

Preoperative imaging modalities included US, computed tomography (CT), lipiodol CT, angiography, and magnetic resonance imaging (MRI). Magnetic resonance imaging was optional because of the limited availability of slots, and it was ordered only when necessary as decided by attending physicians. All of the preoperative image data were reviewed by staff radiologists and the number, size, and location of the tumors were recorded. Imaging protocols for HCC were essentially the same during the study period. All of the patients underwent US examination (Aloka SSD 630 [1995-1998], SSD 2000 [1996-2002], SSD 5300 [2000-2002], SSD 6500 [2002]; Aloka Co, Tokyo) before and during the operation.

For IOUS, T-shaped linear- or miniconvex-type US probes were used at frequencies of both 5 MHz and 7.5 MHz. The whole liver was carefully scanned for new tumors. Intraoperative gross findings by inspection or palpation and IOUS findings were recorded. Hepatocellular carcinoma lesions that were not detected by preoperative imaging studies were noted as new tumors. All of the nodules or space occupying lesions first detected intraoperatively were defined as new nodules and included new tumors (HCC) and nonmalignant ones, which were not the subject of this study. New tumors detected by IOUS that were not palpable or visible were regarded as being identified by IOUS alone. Likewise, new tumors that were palpable but not visible were considered to be identified by palpation alone. New tumors that were not only palpable but also visible were considered visible. Operative procedures were selected by a combination of tumor location and liver function according to an algorithm proposed by Makuuchi et al. The operative approach was changed or extended as necessary to remove all of the new tumors (Table 2).

Patients were followed up at our outpatient clinic every month, and serum α-fetoprotein and des-γ-carboxy prothrombin levels were checked. Abdominal US was performed every 3 months and dynamic CT or MRI was performed every 6 months. When recurrent disease was found, appropriate treatments including repeated hepatectomy and transarterial chemotherapy were selected by the attending physicians.

To test the effect of new tumors on the patient outcome, overall and disease-free survival rates of the following subgroups were compared: subgroup S, 284 patients who had a single tumor with no new tumors; subgroup M, 112 patients with 2 tumors with no new tumors; and subgroup NT, 29 patients who had at least 1 new tumor. Five patients were excluded because of a poor follow-up record.

Fisher exact test was used to evaluate the difference in detection rates regarding primary HCC lesions according to imaging modalities between the first and second hepatectomies. Survival curves were calculated using the Kaplan-Meier method and compared with the results of the log-rank test. Statistical software (Abacus Concepts, Berkeley, California) was used for data analyses. A difference of P < .05 was considered statistically significant.

The overall complete detection rates of all of the primary HCC lesions by US, CT, lipiodol CT, angiography, MRI, and IOUS at the primary hepatectomy were 88.1%, 86.5%, 93.8%, 93.3%, 74.2%, and 97.7%, respectively. At the second hepatectomy, the detection rates were 81.8%, 83.6%, 93.1%, 84.3%, 72.7%, and 96.3% (Table 3). In Table 3, cases with multiple tumors of which not all were visual-
ized by a certain modality were judged negative. Intraoperative US could not visualize all of the primary tumors in 14 cases (2.6%), 10 at the primary hepatectomy and 4 at the second hepatectomy. There were 15 missed lesions by IOUS in total, all of which were smaller than 10 mm and 12 (80.0%) of which were no larger than 5 mm. Only 3 of 15 lesions were positive on lipiodol CT, and the others were incidentally found in the resected specimen. Intraoperative plan was changed secondary to the IOUS findings alone in 6.4% of patients (7 of 110 patients). The operation plan had to be changed in 24 cases (80.0%). Overall, the preoperative surgical plan was changed secondary to the IOUS findings alone in 5.6% of patients (24 of 430 patients).

The characteristics of the new tumors found at the second hepatectomy were essentially the same as those found at the primary hepatectomy (Table 5). The detection rate of new tumors was 7.0% (in 30 of 430 patients) and there was no significant difference between detection rates in patients with and without cirrhosis ($P = .08$, Fisher exact test). A total of 691 HCC lesions were found during 555 hepatic resections. Fifty-six new tumors were detected in 30 cases at the primary hepatectomy and 13 new tumors were detected in 8 cases at the second hepatectomy. Table 4 summarizes the characteristics of new tumors found at the primary hepatectomy. The detection rate of new tumors was 7.0% (in 30 of 430 patients) and there was no significant difference between detection rates in patients with and without cirrhosis ($P = .16$, Fisher exact test). The number of new tumors per patient ranged from 1 to 5 (average, 1.8 nodules). Only 7 new tumors (12.5%) were visible or palpable, and 49 (87.5%) of the new tumors were found only by IOUS. Of 30 cases with new tumors, the operation plan had to be changed in 24 cases (80.0%). Overall, the preoperative surgical plan was changed secondary to the IOUS findings alone in 5.6% of patients (24 of 430 patients).

The characteristics of the new tumors found at the second hepatectomy were essentially the same as those found at the primary hepatectomy (Table 5). The detection rate of new tumors was 7.3% (8 of 110 patients) and the number of tumors per patient ranged from 1 to 3 (average, 1.6 nodules). Only 2 new tumors (15.4%) were visible or palpable, and 49 (82.8%) of the new tumors were found only by IOUS. Of 8 cases with new tumors, the operation plan had to be changed in 7 cases (87.5%). Overall, the preoperative surgical plan was changed secondary to the IOUS findings alone in 6.4% of patients (7 of 110 patients).

Figure 1 compares the locations of primary tumors and new tumors at the primary hepatectomy in 30 cases that had new tumors. The pattern of tumor distribution according to Couinaud segments was similar between primary and new tumors, but the largest discrepancy was seen in segment 3. When the relative location of new tumor was analyzed, 12 of 24 new tumors (50.0%) were found in segment 3, compared with 18 of 66 primary tumors (27.3%) at the corresponding location ($P = .03$, Wilcoxon signed rank test). The decrease in the detection rate was the largest in US, from 88.1% to 81.8% ($P = .08$, Fisher exact test).

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patients with HCC, IOUS and IO macroscopic examination made it possible to discover another 56 new tumors in 30 cases (7.0%) at the primary hepatectomy. Of new tumors, 87.5% were detected by IOUS only. The incidence of new tumors at the second hepatectomy was essentially the same, 7.3% (8 of 110 patients). There were no significant differences in the characteristics of new tumors between those found at the first and second hepatectomies. Although this study covers a relatively long period of 8 years, imaging protocols for HCC were consistent in our institution. Ultrasonography and enhanced (dynamic) CT (or MRI for patients with allergy to iodine) were performed in all of the cases, and angiography plus lipiodolization followed by CT were done in 86.0% to 95.8% of the cases (Table 3).

Detection rates of primary tumors at the second hepatectomy by various imaging modalities decreased slightly but uniformly compared with those at the primary hepatectomy (Table 3). This may be owing to postoperative artifacts caused by deformities, scar formation, or adhesion in the remnant liver. The decrease in the US detection rate was the largest probably because ultrasonic energy is easily interfered with by deformity, scars, and gases in attached intestines, most of which can be avoided in the IOUS setting. However, the detection rate of new tumors was not increased at the second hepatectomy.

The significance of IOUS during hepatic resection has been discussed by a number of researchers. It is reported that the preoperatively planned surgical procedure had to be changed due to IOUS in 4.9% to 67% of cases.8,16-23 Jarnagin et al24 reported that findings of IOUS alone changed the planned operation in 7.2% of patients (8 of 111 patients) with liver tumors, most of which were colorectal metastases. Although the type of liver tumor was different, our study showed comparative effects of IOUS on surgical decision making during liver resection for HCC, 5.6% at the primary hepatectomy and

Our study demonstrates that the same degree of precaution is necessary for new tumors when performing IOUS during repeated hepatic resections for HCC. Among 430

Figure 1. Distribution of new tumors and primary tumors at the primary hepatectomy.

Figure 2. Size distribution of new tumors and primary tumors at the primary hepatectomy.

Figure 3. (A) The 3-year (5-year) disease-free survival rates of subgroups S, M, and NT were 77.9% (60.7%), 63.3% (48.4%), and 69.4% (56.6%), respectively. Long-term survival in subgroup S was significantly better than that in subgroup M (P=.02, Wilcoxon signed rank test). The survival outcome in subgroup NT appeared to be between those of the former 2 groups (Figure 3A). The 3-year (5-year) disease-free survival rates of subgroups S, M, and NT were 43.2% (30.5%), 28.3% (18.9%), and 6.9% (0%), respectively. Subgroup S showed the most favorable outcome, whereas subgroup NT showed the worst (P<.001, Wilcoxon signed rank test) (Figure 3B).

When the long-term outcomes of 29 cases with new tumors were analyzed according to the relative location of new tumors against primary tumors, overall survival after the primary hepatectomy in subgroup IS (n=12) was slightly better than that in subgroup OS (n=18), but it did not reach statistical significance (P=.20, Wilcoxon signed rank test). However, disease-free survival in subgroup IS was significantly favored to that in subgroup OS (P=.008, Wilcoxon signed rank test) (Figure 4).
The location of new tumors was thoroughly investigated. Because 60.0% of new tumors were found distant from the primary tumors outside the tumor-bearing sector, the whole liver should be carefully scanned by IOUS to look for new tumors. The pattern of segmental distribution inside the liver was not different between primary tumors and new tumors. The reason new tumors were relatively common in segment 3 is unclear, but this could be due to the flat shape of segment 3 or the effects of heartbeat and gas in the neighboring stomach or colon. Analyzing preoperative MRI, Cerwenka et al8 also reported that additional lesions were found intraoperatively more often in the left liver as compared with the right liver. They speculated that MRI problems caused by the heart and the stomach on the left side may be the reason.

The existence of new tumors did not affect long-term patient survival very much provided that new tumors were completely removed and recurrent tumors were appropriately treated (Figure 3A). The significant difference in overall survival between subgroups S and M was similar to the well-known significant difference in long-term survival between HCC cases with single and multiple tumors. According to the most recent nationwide survey in Japan, 5-year survival rates after curative resection for single and 2 HCC lesions were 56.5% and 45.0%, respectively (P < .001).26 The relatively favorable outcome in subgroup NT may be due to the small number of patients (n = 29) and successful rigorous treatment for recurrent tumors because the recurrence rate was high in this subgroup (Figure 3B). The existence of new tumors did have a significant effect on the recurrence rate, especially in subgroup OS (Figure 4). New tumors should be completely removed, and thorough, regular follow-up is mandatory to detect and treat recurrent tumors.

Although IOUS had the highest sensitivity for the detection of HCC lesions, it could not visualize all of the primary tumors in 14 cases (2.6%), 10 at the primary hepatectomy and 4 at the second hepatectomy. All of the lesions missed by IOUS were smaller than 10 mm and only 3 of them were positive on lipiodol CT. Further improvement in the detection rate of IOUS for liver nodules may be expected with the introduction of new US
contrast agents in the IOUS setting. Contrast-enhanced IOUS may also be useful in determining whether the new nodule is malignant.

In conclusion, IOUS is still the most sensitive preoperative imaging modality for HCCs. Its results altered the operative plans in 5.6% to 6.4% of cases despite the recent progress in imaging modalities. The same degree of precaution is necessary for new tumors when performing IOUS during repeated hepatic resections for HCCs. Patients with new tumors are at high risk for recurrence, so regular and thorough follow-up is important to prolong survival.

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