

Solitary Liver Lesions of Indeterminate Malignancy – Outcome Following Surgical Resection

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Abstract. *Background:* Well-differentiated hepatocellular carcinoma (HCC) may resemble benign liver lesions on initial diagnostic work-up. The validity of surgical resection for preoperatively unclear liver lesions was investigated in this study. *Patients and Methods:* We conducted a retrospective analysis of 483 patients subjected to liver resection over a 15-year period. *Results:* Forty-five patients (9%) were considered to have presented with indeterminate solitary lesions. There were 18 cases of HCC (40%) and 27 cases (60%) of benign lesions, most commonly focal nodular hyperplasia (n=18). Patients with HCC had a higher median age as compared to patients with benign pathology (67 vs. 55 years; $p=0.002$) and the median tumor size was larger (85 vs. 30 mm; $p=0.007$). Major complications (Clavien grade III or higher) occurred in three cases (7%) and there was no in-hospital mortality. *Conclusion:* The results favor an aggressive approach, i.e. surgical intervention, to patients presenting with indeterminate solitary liver tumors due to the high likelihood of an underlying HCC.

Hepatocellular carcinoma (HCC) is the fifth most frequent malignancy worldwide. It accounts for approximately 748,000 new cases annually, ranking third amongst cancer-related deaths (1). Established risk factors for HCC are hepatitis B and C virus infections, alcohol-induced liver disease and non-alcoholic fatty liver disease. HCC evolves through a multistep carcinogenic process, involving gene mutations, gene amplifications, chromosomal alterations, and epigenetic modifications (2). Several signaling pathways are consistently reported to be disrupted in HCC. These include for example RAS-RAF-MEK, phosphoinositide-3-kinase

(PI3K)/Akt/mammalian target of rapamycin (mTOR), wntless (Wnt), insulin-like growth factor receptor 1 (IGF1R), hepatocyte growth factor (HGF)/c-MET, vascular endothelial growth factor (VEGF), epithelial growth factor receptor (EGFR), and platelet-derived growth factor (PDGF) (2, 3). Sorafenib, a multikinase inhibitor with proven activity against RAF, VEGF and PDGF, has been shown to prolong survival of patients with advanced HCC (4, 5).

Non-malignant liver tumors are increasingly being detected due to the frequent use of sensitive imaging studies, and they may still sometimes be difficult to differentiate from well-differentiated HCC, despite improvements in preoperative imaging and general diagnostic work-up. The most common benign liver lesion is hemangioma (6). Autopsy reports describe this benign vascular tumor to be present in 3-20% of cases (7). Patients are usually asymptomatic, however, large hemangiomas (>10 cm diameter) can cause abdominal discomfort or other symptoms (8). Focal nodular hyperplasia (FNH) ranks second in terms of incidence among benign lesions, followed by adenomas, cysts and abscesses (7).

In liver surgery, more precise surgical techniques and better control of, e.g. operative hemorrhage, has led to fewer complications such as bile leakage, bleeding and liver failure. Hospital mortality rates have decreased from 10% in the 1980s to <1% in recent studies (9-12). The indication for liver resection has steadily increased to include more high-risk patients (11). Definitions on what is considered as an adequate remnant liver function are, however, being constantly re-evaluated. Although liver resection is generally a safe procedure, the indications for surgery must be appropriate in order to avoid unnecessary interventions. One unanswered question is whether surgical resection should be performed in case of indeterminate liver lesion, i.e. when malignancy cannot be fully ruled-out preoperatively. To our knowledge, this is the first study to estimate the incidence of well-differentiated HCC amongst liver lesions where malignancy cannot be ruled out after initial imaging, blood sampling and biopsy. A comparison of clinical features between malignant and non-malignant cases is also attempted.

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Key Words: Indeterminate liver tumor, hepatocellular carcinoma, benign lesion, liver resection, diagnosis.

Patients and Methods

A retrospective study was conducted after approval from the local Human Ethics Committee. A total of 483 patients undergoing liver resection at the Department of Surgery, Skåne University Hospital, Lund, Sweden, between January 1995 and November 2009, were selected. Consideration for resection included anatomically resectable disease without evidence of extrahepatic spread or gross vascular invasion of *e.g.* the portal vein or the inferior caval vein. Child-Pugh class C status remained a contraindication for surgery. Resection was performed with Cavitron Ultrasonic Surgical Aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) in the majority of cases or Helix Hydro-Jet® (Erbe Elektromedizin GmbH, Tuebingen, Germany).

For the purposes of this study, an indeterminate liver lesion was defined by preoperative suspicion of HCC with inconclusive imaging and biopsy findings; alpha-fetoprotein (AFP) levels <200 ng/ml (13); and no previous patient history of chronic viral hepatitis (B or C). Thus, 366 resected cases were excluded, being metastases from colorectal cancer (n=278), other malignancies including cholangiocarcinoma and non-colorectal metastatic disease (n=86) and trauma (n=2). Among the remaining 117 cases, the indications for surgery were evaluated and 72 cases were subsequently excluded; 34 cases because of a history of extrahepatic malignancy; 18 because the diagnosis of a benign lesion was made preoperatively and resection was due to symptoms, risk of bleeding or malignant transformation; 9 because the diagnosis of HCC was made preoperatively without doubts; 8 because of AFP levels >200 ng/ml; and 3 because of a history of chronic viral hepatitis (1 with hepatitis B and 2 with hepatitis C). The final study population included 45 patients, who underwent liver resection to rule-out HCC, potentially suspected but not verified. For each patient, information regarding age, sex, preoperative AFP level, tumor size and postoperative complications were recorded. All complications were graded according to a previously validated classification (Clavien-Dindo) (14).

Statistical analysis. Values are expressed as median and range unless otherwise stated. The Mann-Whitney *U*-test was used for continuous variables. For categorical data, the Chi-Square test was used. Differences of *p*<0.05 were considered to be statically significant. Analyses were performed using the SPSS computer software (SPSS version 19; IBM Corp., Somers, NY, USA).

Results

During the 15-year study period, 45 patients (9%) with indeterminate lesions were seen at our department. There were 29 women and 16 men, and the median age was 57 (25-84) years.

HCC was detected in 18 (40%) of the patients after final histopathological evaluation of the surgical specimens. The remaining 27 patients (60%) had benign pathology, including FNH (n=18), adenoma (n=6), hemangioma (n=2), and a fibrotic lesion (n=1). Comparisons of preoperative characteristics between malignant and benign cases are shown in Table I. No significant differences were observed in gender or AFP levels. The median age of the HCC group was significantly higher than that seen in the group with benign

Table I. Preoperative characteristics predicting malignancy.

Variables	HCC (n=18)	Benign (n=27)	<i>p</i> -Value
Male: Female	8:10	8:19	0.309
Age (years)	67 (45-84)	55 (25-73)	0.002
AFP (ng/ml)	4 (1-104)	5 (1-83)	0.389
Tumor size (mm)	85 (6-250)	30 (5-100)	0.007

HCC: Hepatocellular carcinoma; AFP, alpha-fetoprotein.

lesions (67 vs. 55 years; *p*=0.002). The median tumor size was significantly larger in the HCC group (85 vs. 30 mm; *p*=0.007).

Postoperative complications occurred in 19 patients (42%); ten in the HCC group and nine in the group with benign tumors (*p*=0.139). Out of these, three were classified as major, requiring either surgical, radiological or endoscopic intervention (Clavien grade III) or intensive care (Clavien grade IV). Included herein were an intra-abdominal hematoma requiring drainage (one patient), respiratory failure necessitating intubation (one patient) and cardiac failure with hemodynamic instability requiring intensive care (one patient). All major complications occurred in the HCC group. No perioperative death was noted.

Discussion

Despite improvements in imaging techniques, it may occasionally be difficult to preoperatively assess the true nature of a primary, solitary liver tumor. Of all the indeterminate liver lesions, 40% were ultimately found to be HCC in the present analysis. By comparing preoperative results between HCC and benign lesions, we found that age was higher and tumor size increased in the HCC group. The current series was different from previous ones in several aspects. Firstly, only cases with a preoperative suspicion of a potential malignancy but with inconclusive findings on imaging and biopsy were included. Secondly, we did not select patients with underlying chronic hepatitis. Thirdly, only well-differentiated HCC and benign lesions were chosen, as the real difficulty lies in distinguishing benign lesions from well-differentiated HCC. In one study, 58% of patients with liver incidentaloma were ultimately found to harbor malignant tumors (15). Notably, this study included a high percentage of patients with hepatitis B and malignancies other than HCC, for example cholangiocarcinoma. Other studies have reported a malignancy rate amongst liver incidentalomas in the range of 19-37% (16, 17).

The diagnosis of HCC can be performed on the basis of typical findings on four-phase multidetector computed-tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) with arterial enhancement and delayed washout (18, 19). In our study, at least two dynamic

studies (contrast-enhanced ultrasound, CT or MRI) were used for each patient prior to surgical resection. Although a high level of AFP is not an accurate screening test, an AFP level above 200 ng/ml combined with a focal liver lesion is considered to be diagnostic of HCC (13). Biopsy is suggested when imaging findings are inconclusive, or for lesions in non-cirrhotic livers.

The sensitivity and specificity of imaging modalities in the surgical population are typically lower than those observed in the general population. This could be because of selection bias, where more atypical cases are selected for surgery (20). The design of previous studies that evaluated the diagnostic capacity of imaging methods often exclude atypical cases and include those with an HCC already diagnosed by imaging or by biopsy (21). Therefore, the incidence of “indeterminate” lesions reported here may be higher than previously reported. The role of fine-needle aspiration (FNA) biopsy of liver tumors is debated, mainly because of the increased risk of tumor seeding. The incidence of needle-tract tumor seeding in HCC is estimated to be 2.7% in total, or 0.9% per year (22). Furthermore, FNA biopsy has been associated with a false-negative rate of 30% (21). Efforts have been made to refine the diagnostic criteria using biomarker panels, but so far results are not sufficiently accurate (23-26).

FNH is a rare benign liver tumor that is caused by a congenital arterial malformation leading to hepatocellular hyperplasia. We noted a high proportion of FNH amongst indeterminate lesions. FNH has a hypervascular pattern and may present with atypical features, with some cases bearing close resemblance to HCC (27). Hemangiomas are generally easier to distinguish from other lesions with conventional imaging, but a rapid-filling hemangioma may present without the appearance of a peripheral nodular enhancement in the arterial phase of the CT scan and thus render definite diagnosis difficult (28). FNA biopsy is not recommended given the risk of hemangioma rupture, as well as the low diagnostic yield (29).

The main limitation of the present study is its retrospective nature. Furthermore, several assumptions had to be made *a priori*. We made the assumption that the cases with a preoperative suspicion of malignancy were found among the patients with a final diagnosis of HCC or a benign lesion. The preferred method would have been to start with the indication for surgery as the primary selection criteria, but this information was not available for all cases. We also made the assumption that patients with a primary tumor in an organ other than the liver were operated on the indication of possible metastases.

In conclusion, we have shown that indeterminate liver lesions are associated with a high risk of being HCC. Increased age and tumor size are associated with a higher likelihood of a malignant finding. As the safety of the liver resection *per se* is acceptable, we propose an aggressive

surgical strategy for patients presenting with liver lesions of uncertain malignancy when initial diagnostic work-up is inconclusive. With the gradual improvement at least of imaging modalities, the percentage of uncertain lesions hopefully will be reduced.

Conflict of interest

The Authors declare no conflict of interest.

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