Liver Resection for Hepatocellular Carcinoma ≤3 cm: Results of an Italian Multicenter Study on 588 Patients

Felice Giuliante, MD, Francesco Ardito, MD, Antonio D Pinna, MD, Gerardo Sarno, MD, Stefano M Giulini, MD, Giorgio Ercolani, MD, Nazario Portolani, MD, Guido Torzilli, MD, Matteo Donadon, MD, Luca Aldrighetti, MD, Carlo Pulitanò, MD, Alfredo Guglielmi, MD, Andrea Ruzzenente, MD, Lorenzo Capussotti, MD, Alessandro Ferrero, MD, Fulvio Calise, MD, Vincenzo Scuderi, MD, Bruno Federico, MSc, Gennaro Nuzzo, MD

BACKGROUND: The best treatment for patients with small hepatocellular carcinoma (S-HCC) is still controversial. The aim of this study was to evaluate operative and long-term results after liver resection (LR) for S-HCC, defined as tumor ≤3 cm.

STUDY DESIGN: Retrospective multicenter study of 588 LRs for S-HCC from 8 Italian hepatobiliary surgery units (years 1992 to 2008). Primary outcomes included operative risk. Logistic regression analysis was used to evaluate risk factors for postoperative mortality. Secondary outcomes were overall survival (OS) and disease-free survival (DFS), estimated by the Kaplan-Meier method.

RESULTS: Postoperative mortality was 1.9%, morbidity was 35.7% (major morbidity 7.3%), and blood transfusion rate was 13.8%. Child-Pugh class B and blood transfusions were associated with higher postoperative mortality. Rates of microvascular invasion and microsatellite nodules were 37.0% and 23.1%. After a median follow-up of 38.4 months, 5- and 10-year OS rates were 52.8% and 20.3%, with DFS of 32.4% and 21.7%. Local recurrence rate was 1.4%. Between the years 2000 and 2008, 5-year OS was significantly higher than that between the years 1992 and 1999 (61.9% vs 42.6%; $p < 0.001$). In multivariable analysis, Child-Pugh class B, portal hypertension, and microsatellite lesions were independently associated with poor OS. Microsatellite lesion was the only variable independently associated with poor DFS.

CONCLUSIONS: Liver resection for S-HCC has improved over the years, with decreased operative risk. Long-term survival after LR has increased. Despite small tumor size, rates of microsatellite nodules and microvascular invasion are not negligible. Presence of microsatellite lesions was the only variable identified as being associated with poor both OS and DFS. (J Am Coll Surg 2012;215: 244–254. © 2012 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and the third most common cause of cancer mortality.[1] Although the majority of cases are still found in Asia and Africa, recent studies have shown that the incidence and mortality rates of HCC are increasing in North America and Europe.[2,3] The frequency of detection of early HCC is increasing due to wide diffusion of surveillance programs in high-risk patients[4] and advances in imaging techniques.[5]

There is still not a precise, widely accepted definition for early or small HCC. Various criteria for size for small HCC have been reported, for example, ≤2 cm (the so-called "very early HCC"),[4,6] ≤3 cm,[7,8] ≤4 cm,[9,10] or HCC within

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From the University Hospital Agostino Gemelli, Catholic University of the Sacred Heart, Rome (Giuliante, Ardito, Sarno, Nuzzo), Sant'Orsola Malpighi University Hospital, Bologna University, Bologna (Pinna, Ercolani), Spedali Civili University Hospital, Brescia University, Brescia (Giulini, Portolani), Istituto Clinico Humanitas, Milan University, Milan (Torzilli, Donadon), Scientific Institute Hospital San Raffaele, Vita-Salute San Raffaele University, Milan (Aldrighetti, Pulitanò), Gian Battista Rossi University Hospital, Verona University, Verona (Guglielmi, Ruzzenente), Ospedale Mauriziano Umberto I, Turin (Capussotti, Ferrero), Antonio Cardarelli Hospital, Naples (Calise, Scuderi), and Department of Health and Sport Sciences, University of Cassino, Cassino (Federico), Italy.

Correspondence address: Felice Giuliante, MD, Hepato-Biliary Surgery Unit, Department of Surgery, Catholic University of the Sacred Heart, Rome, University Hospital "Agostino Gemelli" Largo Agostino Gemelli, 8, I-00168 Rome, Italy. email: fgiuliante@tm.unicatt.it

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Abbreviations and Acronyms

DFS = disease-free survival
HCC = hepatocellular carcinoma
LR = liver resection
mVI = microvascular invasion
OS = overall survival
S-HCC = small hepatocellular carcinoma

the Milan criteria, that is, ≤3 nodules ≤3 cm or a single nodule of ≤5 cm.[11]

The best treatment for patients with small HCC (S-HCC) remains controversial because different therapeutic options are theoretically available with curative intent, such as liver transplantation, liver resection (LR), and ablative techniques. Liver resection is considered as a potentially curative treatment modality for patients with S-HCC and well-preserved liver function.[11-14] Perioperative morbidity and mortality are considered major disadvantages of LR. During the last few years, several improvements related to more accurate preoperative selection of patients, development of surgical techniques, and better postoperative management have reduced the perioperative risk of LR.[15-23] Data coming from recent large Western series on the results of LR in patients with early HCC are not available. The aim of this study was to evaluate current safety and effectiveness of LR for HCC ≤3 cm on the basis of a large cohort of patients collected in Italian specialized centers of liver surgery.

METHODS

Between January 1992 and December 2008, five hundred and eighty-eight consecutive patients who underwent curative LR for HCC ≤3 cm were retrospectively identified from prospectively maintained databases in 8 high-volume Italian hepatobiliary surgery centers. Hepatocellular carcinoma ≤3 cm in diameter without radiologic evidence of macrovascular invasion and extrahepatic metastasis were included. The 3-cm size cut-off was obtained from the Guidelines of Japan Cancer Study Group.[7] All patients had preoperative data on viral serologic testing for hepatitis, laboratory assessment of liver function, transabdominal ultrasonography, and abdominal CT or MR. All patients included in this study presented with underlying liver disease (presence of fibrosis or cirrhosis at final pathology). Patients with normal liver were excluded from this analysis.

Liver resections were defined according to the International Hepato-Pancreato-Biliary Association terminology derived from Couinaud's classification.[24] Anatomical or nonanatomical LRs were performed according to the extent and location of the tumor, hepatic function, and the preference of the surgeon. Intraoperative ultrasonography was routinely performed to confirm the characteristics of the HCC, to study the relationship with vascular and biliary structures, to evaluate the remnant liver for additional tumors, and to guide the resection.

The following data were collected for each patient: demographics, underlying hepatitis, blood biochemistry, serum α-fetoprotein, preoperative liver function status (assessment of Child-Pugh classification and Model for End-Stage Liver Disease score), evaluation of portal hypertension (assessment of esophageal varices, platelet count $<100{,}000/mm^3$, splenomegaly), tumor characteristics (size and number), operative details (type of liver resection, intraoperative blood transfusion requirement), histopathologic findings of the resected tumors (tumor grade, microvascular invasion [mVI], microsatellite lesions, width of surgical margin). Microsatellite lesions were defined as tumors surrounding the main tumor with multiple other satellite nodules or small solitary tumors located near the main tumor that are histologically similar or less differentiated than the main tumor.[25] The surgical resection margin was defined as the shortest distance from the edge of the tumor to the line of transection detected by histologic examination in the resected specimen fixed with formalin. Early and late results included postoperative (within 30 days) mortality and morbidity and 5- and 10-year overall and disease-free survival (DFS) rates. Postoperative mortality was defined as occurrence of death within 30 days after surgery. Postoperative morbidity was defined according to the Clavien classification of surgical complications.[26]

Data have been also analyzed by dividing the study in 2 periods (1992 to 1999 and 2000 to 2008). Patients were also stratified according to the early HCC score reported previously by Nathan and colleagues.[27] Because not all of these clinical background items were available, the numbers for some of the items reported here do not equal the total numbers of patients. All patients were followed up by the same surgical team who operated on them. The protocol of surveillance included liver function tests, serum α-fetoprotein level, ultrasonography, or CT every 3 to 4 months. Diagnosis of recurrence was based on an increased serum α-fetoprotein and typical imaging findings at ultrasonography, contrast-enhanced CT scan, or MR. Local recurrence was defined as recurrence at the margin of resection.

Outcomes assessment was completed by December 2009, one year after inclusion of the last patient.