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CLINICAL INVESTIGATION **Liver**

IMPACT FACTORS FOR MICROINVASION IN INTRAHEPATIC CHOLANGIOCARCINOMA: A POSSIBLE SYSTEM FOR DEFINING CLINICAL TARGET VOLUME

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Purpose: To quantify microscopic invasion of intrahepatic cholangiocarcinoma (IHC) into nontumor tissue and define the gross tumor volume (GTV)-to-clinical target volume (CTV) expansion necessary for radiotherapy.
Methods and Materials: One-hundred IHC patients undergoing radical resection from January 2004 to July 2008 were enrolled in this study. Pathologic and clinical data including maximum tumor diameter, tumor boundary type, TNM stage, histologic grade, tumor markers, and liver enzymes were reviewed. The distance of microinvasion from the tumor boundary was measured by microscopy. The contraction coefficient for tumor measurements in radiographs and slide-mounted tissue was calculated. SPSS15.0 was used for statistical analysis.
Results: Sixty-five patients (65%) exhibited tumor microinvasions. Microinvasions ranged from 0.4–8 mm, with 96% of patients having a microinvasion distance ≤6 mm measured on slide. The radiograph-to-slide contraction coefficient was 82.1%. The degree of microinvasion was correlated with tumor boundary type, TNM stage, histologic grade, and serum levels of carbohydrate antigen 19-9, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase and alkaline phosphatase. To define CTV accurately, we devised a scoring system based on combination of these factors. According to this system, a score ≤1.5 is associated with 96.1% sensitivity in detecting patients with a microextension ≤4.9 mm in radiographs, whereas a score ≥2 has a 95.1% sensitivity in detecting microextension ≤7.9 mm measured on radiograph.
Conclusions: Patients with a score ≤1.5 and ≥2 require a radiographic GTV-to-CTV expansions of 4.9 and 7.9 mm, respectively, to encompass >95% of microinvasions. © 2010 Elsevier Inc.

Intrahepatic cholangiocarcinoma, Pathologic characteristics, Microinvasion, Clinical target volume, Conformal radiotherapy.

INTRODUCTION

Intrahepatic cholangiocarcinoma (IHC), which arises from the intrahepatic bile duct epithelium, is the second most common primary liver malignancy. In the past 3 decades, the incidence of IHC and the mortality rates associated with this disease have increased worldwide (1). Because IHC is difficult to diagnose at an early stage and extends diffusely, most patients have unresectable tumors at clinical presentation, with median survival being less than 5 months (2, 3). External beam radiotherapy (EBRT) has been reported to benefit unresectable IHC (4–6). We have previously found that, in a study of 45 patients with unresectable IHC (22 with EBRT and 23 without EBRT), EBRT appeared to improve the prognosis of unresectable IHC (6).

Technologic advances in EBRT have made three-dimensional conformal radiotherapy (3-DCRT) a feasible option in routine clinical practice. The accuracy in differentiating cancerous tissue from normal tissue is increasingly important in optimizing the benefits of 3-DCRT while minimizing potential adverse effects to normal tissue. The gross tumor volume (GTV) is the visible tumor. The clinical target volume (CTV) includes the GTV and is defined as the volume of tissue that has a significant probability of containing microscopic tumor extensions (subclinical disease). Determination of the CTV is one of the greatest challenges for radiotherapists because none of the currently available imaging techniques allows for direct detection of microinvasion. Radiotherapists have investigated the microextension of

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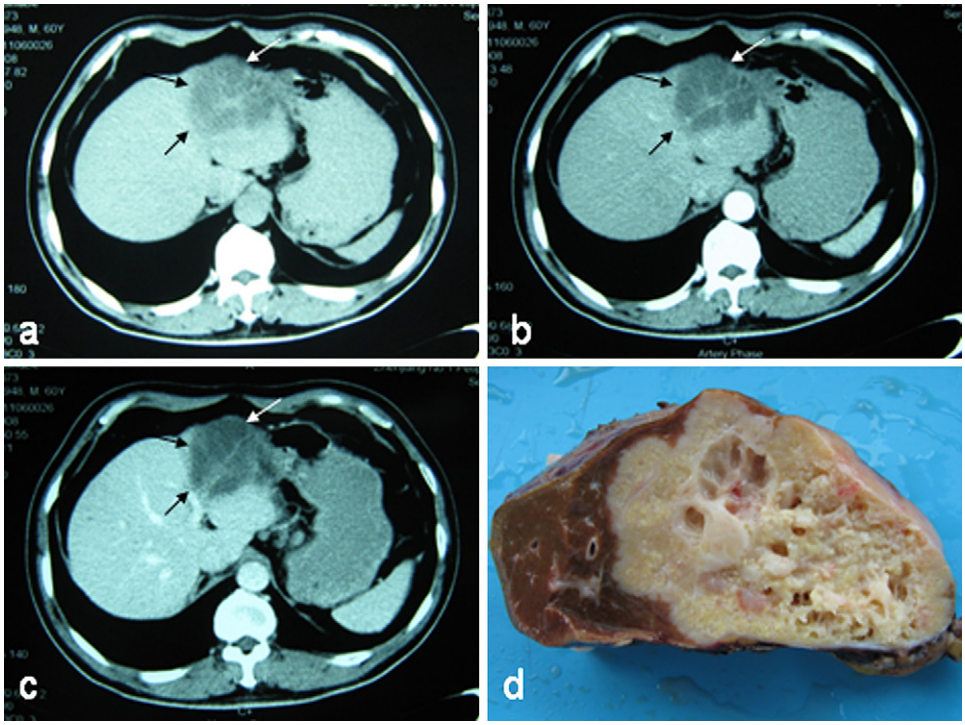

Fig. 1. (a) Plain CT scan showing an intrahepatic cholangiocarcinoma that appeared as a low density area and had a regular and distinct boundary. (b and c) CT scans performed with contrast enhancement during the arterial and portal venous phases showing a tumor with a distinct boundary. (d) A surgical specimen containing a white-colored tumor with a distinct boundary.

non–small cell lung cancer, prostate carcinoma, and hepatocellular carcinoma. However, few studies have investigated the radiotherapy of unresectable IHC because of the low morbidity of this disease. Recent publications have failed to detect the extension from the GTV to the CTV (7, 8), and others have defined the CTV as the GTV along with a margin of ≥1 cm (6, 9–11) or 0.8 cm (12). However, no study has analyzed IHC microextension and provided a system for determining GTV-to-CTV expansion in cases of unresectable IHC to be treated with EBRT. The aim of this study was to perform histological quantification of IHC microextension and to define CTV as precisely as possible.

METHODS AND MATERIALS

Between January 2004 and July 2008, 321 IHC patients underwent radical surgical resection or exploratory laparotomy at the Liver Cancer Institute, Zhongshan Hospital. Patient selection was based on the following criteria: patients must have undergone a radical resection at our hospital and received a pathologic diagnosis of IHC (combined hepatocellular-cholangiocarcinoma were excluded). The normal liver tissue must have had at least a 1-cm margin extending beyond the tumor boundary so that the microinvasion could be observed properly. Patients were excluded if satellite nodules were detected during the preoperative radiograph or laparotomy. Patients should have not received any treatment for the primary solitary lesion and should have had complete clinical data, including tumor information and laboratory values.

After radical resection, the surgical specimens were analyzed by surgeons to determine the boundary type and maximum diameter. Next, the surgical specimens were placed in phosphate-buffered saline with 10% formalin fixative by the operating room staff and submitted to the department of pathology. Resected specimens that had yet not been placed in formalin fixative are hereafter referred to as surgical specimens. Those that had been placed are referred to as pathology specimens. All specimens were sectioned into 1.5- × 1.0- × 0.4-cm slices, dehydrated, and embedded in paraffin. Tissue blocks were then prepared for routine histologic examination, and 5-μm sections were stained with hematoxylin and eosin (H&E) for light microscopy. Two hundred eighty-seven slides from these specimens were reviewed. To avoid variations between observations, a single pathologist (J.Y.) assessed all the specimens and identified microscopic evidence of microextension and histological grade.

On each histologic slide, tumor margins were assessed on the cut surface of gross findings and then marked with an indelible marker pen. Microinvasion was defined as extension of the tumor through the marked margin. Microinvasion was analyzed by light microscopy (Olympus BX 40; Olympus, Tokyo, Japan) at a low-power magnification (×40) to identify the boundary between the tumor tissue and normal liver tissue; these observations were confirmed by examination at a higher magnification (×100 or ×400). On each slide, the maximum distance of normal liver around the periphery of the tumor was also determined using a micrometer eyepiece. If two or more microinvasions were observed, the longest invasive distance was recorded.

Routine examination

The preoperative evaluation included a medical history and physical examination, complete blood count, liver function tests, alpha-fetoprotein (AFP) levels, carcinoembryonic antigen (CEA) levels, carbohydrate antigen 19-9 (CA19-9) levels, chest X-ray, abdominal