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ORIGINAL ARTICLE

Metastatic lymph nodes in hilar cholangiocarcinoma: does size matter?

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Abstract

Aim: To determine the diagnostic efficacy of the size criteria for the detection of metastatic lymph nodes (LN) in patients with hilar cholangiocarcinoma (HCCA).

Introduction: LN metastasis is one of the most significant independent prognostic factors in patients with HCCA. Presently, in spite of the well known lack of sensitivity and specificity, one of the most used clinical criteria for nodal metastases is LN size.

Methods: Pathological slides of 147 patients who had undergone exploration for HCCA were assessed. The size (maximum and short axis diameter) of each single node was retrieved from the pathology report or measured from a section on the glass slide using a stereo microscope and a calibrated ruler integrated in the software. When a metastatic lesion was detected, the proportion of the lesion in relation to LN size was estimated.

Results: Out of 147 patients, 645 LN were retrieved and measured. In all, 106 nodes (16%) showed evidence of metastasis. The proportion of positive nodes was 8% in nodes <5 mm and 37% in nodes >30 mm. Ten per cent of LN smaller than 10 mm were positive, whereas only 23% of LN larger than 10 mm were metastastically involved. No clear cut-off point could be found. Similar results were found for the short axis diameter. In 50% of positive LN, the metastatic lesion accounted for 10% or less of the LN size.

Conclusion: No cut-off point could be determined for accurately predicting nodal involvement. Therefore, imaging studies should not rely on LN size when assessing nodal involvement.

Keywords

cholangiocarcinoma < liver, radiological imaging/intervention < cholangiocarcinoma, pathology < cholangiocarcinoma, staging, lymph nodes

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Introduction

The incidence of nodal involvement in resected specimens of patients with hilar cholangiocarcinoma (HCCA) has been reported to range from 30% to more than 50%.[1–3] Lymph node (LN) metastasis is one of the most significant independent prognostic factors in patients with HCCA[4–10]. HCCA patients with nodal involvement beyond the hepatoduodenal ligament are currently considered unresectable.[11,12] Hence, correct preoperative and operative assessment of LN status is of crucial importance. Presently, in spite of the well known lack of sensitivity and specificity, one of the most used clinical criteria for nodal metastases is LN size. Moreover, the sizes of the maximum diameter or the short-axis diameter are commonly measured. Although enlarged regional LN on imaging studies are usually interpreted as metastases, there is no data which supports this interpretation. In addition, most patients with HCCA present with jaundice and in many cases with cholangitis. Consequently, LN size may also be

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increased as a result of local inflammation and infection, further impeding the correct assessment of nodal status.

A number of studies have addressed the accuracy of several imaging techniques, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)[13–16] for LN staging in HCCA. Unfortunately, these studies have a major drawback, because they correlate nodal positivity on a patient basis, rather than on a nodal basis. In other words, these studies correlate patients with a positive LN on imaging to patients with a positive LN during laparotomy. This carries two important limitations. First, it is difficult to determine whether the suspicious node on imaging corresponds to the positive node found during laparotomy. Second, there often is a delay between imaging and surgery, and LN size may alter during this delay and hamper accurate measurements of LN size by CT.

Therefore, the aim of the present study was to evaluate the association between LN size and the presence of metastasis in patients with HCCA measuring LN size using (low power) microscopical examination. The proportional size of the metastatic lesion within positive nodes was also evaluated.

Materials and methods

Patients

Histological slides of 147 patients who had undergone exploration for HCCA with at least one LN available were assessed. Laparotomies were performed from 1992 through to 2010. Patients who were found to be unresectable during laparotomy were also included, once at least one lymph node was histologically analysed. In all, 147 patients underwent exploration, of whom 100 patients underwent a resection. Out of the 47 unresectable patients, 160 LN were assessed, of which 54 (34%) were tumour positive. In these patients only suspicious (large) LN were assessed, as a complete lymphadenectomy was not useful, owing to unresectability. In 100 resected patients, 485 LN were retrieved, of which 52 (10.7%) were tumour positive. Patients and operation characteristics are shown in Table 1.

Table 1 Characteristics of hilar cholangiocarcinoma (HCCA) patients who underwent a laparotomy from 1992 through to 2010

	Patients (n = 147)	
Patient details		
Male	94	(64)
Female	53	(36)
Age (median)	25–78	(62)
Bismuth–Corlette classification		
Type 1 or 2	38	(26)
Type 3a	57	(38)
Type 3b	32	(22)
Type 4	20	(14)
Resection performed		
Yes	100	(68)
No	47	(32)
LN		
Total	645	(100)
Negative LN	539	(84)
Positive LN	106	(16)
N0 patients	93	(63)
N1 patients	54	(37)
Average LN evaluated per patient	4.4	
Size in mm. (mean)	11.3	

LN, lymph node.

Lymph nodes

In the first years of this study (until 2000), LN were not routinely harvested and only suspicious LN were removed and assessed. In the last decade a complete lymphadenectomy of the hepatoduodenal ligament was routinely performed, which was extended along the common hepatic artery until the celiac axis. Isolated LN were sent to the pathology department or dissected from the specimen by the pathologist according to a standardized protocol. Biopsies of LN were excluded, and only complete LN were assessed. The specimens were fixed in 5% formaldehyde and embedded in paraffin. Grossly enlarged LN that could not be embedded in one single block were measured before processing and recorded in the pathology report. The size (maximum diameter and short-axis diameter) of each single node was retrieved from the report or measured from the pathological section on the glass slide. The separation of individual LN in clusters of para-aortic LN was difficult macroscopically, however, microscopically these LN could well be distinguished from each other. Images of the histological sections were acquired with a stereo microscope (model M165 FC; Leica Microsystems, Wetzlar, Germany) equipped with a 1.0 × Planapo objective and a digital camera (model DFC 425C, Leica). The maximum diameter of the LN was measured offline using a calibrated ruler integrated in the software (Leica Application Suite) (Fig. 1). All LN were microscopically re-evaluated for the presence of metastasis; this analysis was carried out by an experienced hepatobiliary pathologist (F.Jt.K.). When a metastatic lesion was detected, the proportion of the metastatic lesion in relation to the LN was estimated and recorded.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (version 16.0.2.1; SPSS Inc., Chicago, IL, USA). Continuous data were compared using an independent sample t-test, and are expressed as means ± SD. Frequencies were analysed using the χ^2 test. A receiver-operating characteristic (ROC) curve analysis was performed. All statistical tests were two-tailed, and were evaluated at the 5% level of significance.