Is preoperative histological diagnosis necessary for cholangiocarcinoma?

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Abstract

Surgery is currently the only curative treatment for patients with cholangiocarcinoma (CCA). Whether histological diagnosis of CCA is necessary before surgery is controversial. Fifteen percent of patients with suspected biliary malignancy who undergo surgery are found to have benign disease. Surgery is a major procedure with significant morbidity and mortality and alternative treatment is available for those known to have benign stenoses. The aim of this review was to determine whether any of the current diagnostic tests have sufficient sensitivity and specificity to identify patients with benign and malignant bile duct stenoses. A literature search was performed until July 2007 to obtain information from studies published in the previous 10 years. Only studies reporting an appropriate reference test (confirmation of malignancy by biopsy, confirmation of benign nature by histology following surgical excision, or at least 6 months of follow-up for all patients) were included for review. The diagnostic odds ratio was used to measure diagnostic performance. Forty-one references of 34 studies were included in this review. None of the studies used differential verification. Six studies used blinding of assessor. None of the diagnostic tests had sufficient diagnostic accuracy to reliably separate patients with benign from malignant biliary strictures. Differentiating benign from malignant bile strictures is an important aim. There is no trial evidence demonstrating benefit in obtaining a preoperative histological diagnosis of CCA. New methods are required for stricture assessment.

Key Words: Cholangiocarcinoma

Background

Cholangiocarcinoma (CCA) may arise from either the intrahepatic or extrahepatic bile duct, but typically arises at the bifurcation of the right and left hepatic ducts (Klatskin’s tumor) [1]. The incidence of CCA has increased by about 16-fold in the past three decades [2] and is currently 1.13 and 1.35 per 100,000 males and females in England and Wales [2]. Surgery is currently the only curative treatment for patients with CCA [1]. Whether histological diagnosis of CCA is necessary before surgery is controversial. The incidence of benign lesions in patients undergoing surgical resection with suspected bile duct malignancy is around 15% despite extensive preoperative assessment [3,4].

Effective treatment without surgery is available for patients with benign bile duct strictures who can be treated by progressive endoscopic balloon dilatation and stenting with success rates reported of 60% to 90% [5–9]. Surgical intervention remains available for those in whom endoscopic therapy is not possible or in whom it fails. As the treatment is radically different, it is important to establish the benign or malignant nature of bile duct strictures.

Biopsies taken preoperatively from the site of the bile duct stricture at endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or via cholangioscopy and examined histologically can reliably distinguish benign from malignant strictures [10–12]. However, taking biopsies of the biliary tract is not without risk. Tumor seeding after CCA biopsy is recognized, but has largely been reported after percutaneous transhepatic biliary drainage (PTBD) [13,14]. Tumor seeding after a single pass of a biopsy needle has been reported in hepatocellular carcinomas [13]. Partly
due to the risk of seeding, tumor biopsy in patients with potentially resectable CCA in current clinical guidelines is not recommended [1]. Other complications of biopsy include bleeding (4.2%), transient hemobilia and pain (12.5%) [15].

Current review

The current published literature has been reviewed to assess the ability of preoperative diagnostic tests available for the assessment of patients with bile duct strictures to differentiate benign from malignant strictures. Only studies in which an adequate reference test was used were included (confirmation of malignancy by biopsy, confirmation of benign nature by surgical excision biopsy, or at least 6 months of follow-up for all patients). The range of sensitivities and specificities was calculated for each diagnostic test. The diagnostic odds ratio (DOR) was then calculated for each modality of investigation by the method of Deeks [16]. Results are given in Table I.

Results

As indicated in Table I, there was a wide range of sensitivities between the diagnostic tests as well as a wide variation reported between different studies reporting the same investigation. Specificities ranged from 0% to 100%, again with a very wide variation between studies using the same diagnostic test. The best diagnostic odds ratio was seen for CT scan. For PSC, the highest DOR was seen in a study on PET scanning. However, two other studies on PET scanning showed poor DOR. None of the diagnostic modalities had consistently high accuracy for the investigation to be recommended as the diagnostic modality of choice, i.e. there is no Grade A recommendation (recommendation based on direct scientific fact) for any of the diagnostic modalities used.

Discussion

Assessment of the diagnostic tests evaluated in this analysis has focused solely on their ability to separate patients with benign from malignant biliary strictures. Clearly, these investigations provide information on many other aspects, including the stage of disease and whether a malignant bile duct stricture may be related to CCA rather than HCC, pancreatic Ca or metastatic nodal disease. The ability of the test to distinguish between the different malignancies of the biliary tract was not reported in the studies.

In patients with a malignant bile duct stricture, there is currently no evidence for the benefit of neoadjuvant therapy [40–42]. The decision to operate may therefore be unaltered by whether the malignant stricture is secondary to CCA, HCC, or pancreatic cancer. However, a preoperative diagnosis of metastatic disease would completely alter the treatment plan. The incidence of metastatic disease producing bile duct obstruction with features suggestive of bile duct cancer is 1% to 9% of biliary strictures [20,43].

The diagnostic tests assessed in this review carried a poor diagnostic ability. Histological assessment of biopsies from the stricture site has variable sensitivity (52% to 93%) [10–12,44,45], although it is highly specific [11,12,45]. The main reasons for the variable sensitivity of biopsies are: (a) the type of lesions (i.e. polypoid versus stenotic) and (b) the number of biopsies [46]. While a positive tissue diagnosis is confirmatory of cancer (high specificity) [11,12,45], a negative result does not rule out cancer. Surgical

Table I. Diagnostic performance.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Sensitivity (range)</th>
<th>Specificity (range)</th>
<th>Diagnostic odds ratio (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCP [17–19]</td>
<td>0.0 to 0.66</td>
<td>0.61 to 1</td>
<td>0 to 165</td>
</tr>
<tr>
<td>ERCP FNA [20]</td>
<td>0.45</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>EUS [21]</td>
<td>0.76</td>
<td>0.75</td>
<td>8</td>
</tr>
<tr>
<td>EUS FNA [22,23]</td>
<td>0.62 to 0.86</td>
<td>0.88 to 1</td>
<td>26 to 36</td>
</tr>
<tr>
<td>IDUS [21,24,25]</td>
<td>0.89 to 0.91</td>
<td>0.5 to 0.93</td>
<td>7 to 90</td>
</tr>
<tr>
<td>Cholangioscopy [18,19]</td>
<td>0.92 to 1</td>
<td>0.51 to 0.91</td>
<td>8 to 786</td>
</tr>
<tr>
<td>Brush cytology (ERCP) [20,26,27]</td>
<td>0.2 to 0.85</td>
<td>0.67 to 1</td>
<td>4 to 59</td>
</tr>
<tr>
<td>Bile cytology (PTC) [24,28]</td>
<td>0.43 to 0.64</td>
<td>0.93 to 1</td>
<td>16 to 35</td>
</tr>
<tr>
<td>DNA ploidy [17,26,29]</td>
<td>0.29 to 0.85</td>
<td>0.91 to 1</td>
<td>3 to 75</td>
</tr>
<tr>
<td>Molecular markers in brush cytology [30,31]</td>
<td>0.17 to 1</td>
<td>0.79 to 1</td>
<td>3 to 31</td>
</tr>
<tr>
<td>Molecular markers in bile [32]</td>
<td>0.33 to 0.67</td>
<td>1</td>
<td>7 to 23</td>
</tr>
<tr>
<td>Serum Ca 19–9 [17,33]</td>
<td>0.54 to 1</td>
<td>0.4 to 0.9</td>
<td>2 to 14</td>
</tr>
<tr>
<td>Serum CEA [17]</td>
<td>0.56</td>
<td>0.89</td>
<td>9</td>
</tr>
<tr>
<td>Biliary Ca 19–9 [17]</td>
<td>0.46</td>
<td>0.70</td>
<td>2</td>
</tr>
<tr>
<td>Biliary CEA [17]</td>
<td>0.58</td>
<td>0.8</td>
<td>6</td>
</tr>
<tr>
<td>CT scan [34,35]</td>
<td>0.94 to 1</td>
<td>0.83 to 0.92</td>
<td>54 to 192</td>
</tr>
<tr>
<td>MRCP [36]</td>
<td>1</td>
<td>0.14</td>
<td>Not available</td>
</tr>
<tr>
<td>PET scan [37–39]</td>
<td>0.5 to 1</td>
<td>0 to 1</td>
<td>1 to 247</td>
</tr>
</tbody>
</table>

CT = computed tomogram, DNA = deoxyribonucleic acid, ERCP = endoscopic retrograde cholangiopancreatography, EUS = endoscopic ultrasound, FNA = fine-needle aspiration, IDUS = intraductal sonography, PET = positron emission tomography, PTC = percutaneous transhepatic cholangiography.
excision would therefore be the best option for a lesion highly suspicious of a cancer on radiology with a negative tissue diagnosis.

New techniques are clearly required to improve our ability to detect and determine the nature of a biliary tract cancer in patients presenting with a bile duct stricture. Optical coherence tomography (OCT or optical biopsy) is a method similar to intraductal ultrasound but uses infrared light rather than sound to provide the image [47]. It provides tissue architecture which could previously be obtained only by conventional biopsy [47]. Preliminary results suggest that the addition of OCT improves the diagnostic accuracy of biliary brushings [48]. Magnetic resonance spectroscopy (MRS) provides non-invasive information on phospholipid metabolism [49]. The levels of phosphatidyl choline in bile are lower in cancer patients compared to controls [49]. Further assessment of whether this can be used for diagnostic purposes is necessary.

The use of a DNA microarray for gene profiling using a set of genes common to many malignancies has been reported with a variety of cancer types [50] and may lead to detection of a cancer type from blood without the need for a histological diagnosis [51].

**Conclusions**

- None of the currently available tests (including histological examination of biopsy specimens) can reliably distinguish benign from malignant biliary strictures.
- The evidence for the diagnostic ability of the tests is based on case-control or cohort studies with high risk of bias.
- There is currently no evidence to support routine histological examination for the diagnosis of CCA.
- Randomized controlled trials assessing the need for routine histological diagnosis in the preoperative diagnosis of CCA should follow the consort statement [52] and be adequately powered.
- Based on detecting a 10% reduction in the requirement for unnecessary surgery, sample size calculation (performed using statistical software StatsDirect version 2.6.7) revealed that for $\alpha = 0.05$ (two tailed) and a statistical power of 0.8 at least 282 patients would be needed. This is feasible only as a multicentric trial.

**References**


[19] Tischendorf JJW, Kru¨ger M, Trautwein C, et al. Cholangioscopy (MRC) provides non-invasive information on phospholipid metabolism [49]. The use of a DNA microarray for gene profiling using a set of genes common to many malignancies has been reported with a variety of cancer types [50] and may lead to detection of a cancer type from blood without the need for a histological diagnosis [51].


