Prevention of bile duct cancer in primary sclerosing cholangitis

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Summary

Patients with primary sclerosing cholangitis (PSC) have a substantial predisposition to develop bile duct carcinoma. The mechanism is still unclear but the observation that patients with chronic Clonorchis sinensis infection are also prone to cholangiocarcinoma suggests a role for long standing inflammation. However, there is still no effective medical therapy which can halt the progression of the disease or prevent the development of cholangiocarcinoma. The only effective treatment for advanced PSC is orthotopic liver transplantation (OLT) which in the absence of cholangiocarcinoma has a 5 year survival of 89%. Patients with cholangiocarcinoma who undergo liver transplantation have a high risk of recurrence and a dramatically worse survival. Therefore, the identification of patients with a sufficient deterioration in liver function to warrant OLT before they develop cholangiocarcinoma remains a central goal in the management of PSC.

Ideally, screening patients with PSC would allow the identification of those with dysplastic change in the biliary epithelia before the development of overt carcinoma. However, although serum tumour markers such as CA 19.9 and CEA can be of value in aiding the diagnosis of cholangiocarcinoma in PSC there is currently no evidence that they are helpful in identifying those patients with premalignant changes of the biliary epithelia who would benefit from surgery. There are also no genetic markers to identify those at particular risk of malignant change. A recent report has suggested that regular biliary cytology sampling to detect dysplasia can predict the development of cholangiocarcinoma. However, regular instrumentation of the biliary tree to obtain cytology is unlikely to be widely adopted.

Key words: Child-Pugh classification, cholangiocarcinoma, cytology, dysplasia, liver transplantation, primary sclerosing cholangitis

Introduction

PSC is a progressive, chronic biliary disorder of unknown aetiology and is clinically characterised by multiple, fibrosing, inflammatory strictures of the intrahepatic and extrahepatic bile ducts. Clinical features include fatigue, pruritus and jaundice, and the diagnosis is supported by a cholestatic biochemical profile, characteristic liver histology, and typical cholangiographic features, with irregularity and beading of the intrahepatic or extrahepatic bile ducts [1, 2]. It occurs most commonly in young men and is frequently associated with inflammatory bowel disease IBD, usually chronic ulcerative colitis.

PSC was considered rare only 15 years ago [3] but increased clinical awareness and the introduction of endoscopic retrograde cholangiography to visualise the biliary tree has led to more cases being identified [4, 5]. The prevalence of PSC in the United States has been estimated to be 1 to 6 per 100,000 based on the prevalence of IBD [6] but the true prevalence in this population is not known. An epidemiological study in a defined Norwegian population found the mean annual incidence of PSC was 1.3 per 100,000 with a prevalence of 8.5 per 100,000 [7]. Although the prevalence may be lower in southern Europe because a Spanish epidemiological study over a 5 year period found the point prevalence to be between 0.78 to 2.24 cases per million [8].

Prognosis and natural history of PSC

Several studies have begun to address prognostic variables and the natural history of PSC, which is generally recognised to be slowly progressive, leading to long-term complications of chronic cholestasis, portal hypertension and biliary cirrhosis. Most patients are symptomatic at presentation, although symptoms do not relate to histological stage [9]. The median survival time from diagnosis to death is around 12 years [10, 11], although it is significantly longer if the patient is asymptomatic [11]. Patients with IBD are also reported to have a better prognosis, 71.8% 10 year survival, compared with 60% for patients without, although duration of IBD and colectomy do not influence survival [12].

Currently, there is no medical treatment that effectively halts the progression of the disease or improves survival [13]. Orthotopic liver transplantation remains the only definitive treatment for patients with end-stage PSC and it is therefore vital to identify individual patients with a poor prognosis and determine the optimal time for liver transplantation.

Serum bilirubin concentration, histological stage on liver biopsy, age, and the presence of splenomegaly have consistently been shown to be independent predictors of a high risk of dying [10, 11, 14-16]. Based on these prognostic variables, three mathematical models have been developed to predict survival of patients with PSC early in the course...
of the disease [10, 11, 15]. Of these, the Mayo disease-specific prognostic model has gained wide acceptance and is used to counsel patients, stratify participants in therapeutic trials, and decide on the timing of liver transplantation [15]. Recently, Shetty and colleagues proposed that the Child-Pugh classification could be used as an alternative to the Mayo disease-specific model [17]. They found the Child-Pugh score to be a powerful predictor of survival in PSC, the 7-year survival for Child-Pugh Class A, B, and C being 89.8%, 68%, and 24.9%, respectively. The Mayo disease-specific model risk score did not significantly enhance the predictive ability of the Child-Pugh score. The Child-Pugh classification is far simpler to calculate than the Mayo risk score and does not rely on invasive investigation. However, confirmation of the applicability in other populations is required before it will gain full acceptance as a prognostic index in PSC.

At cholangiography, intrahepatic duct strictures, which were high-grade (>75% narrowing) or diffuse (>25% of the ducts), were found to be indicators of a poor prognosis and were more predictive of an adverse outcome than the presence extrahepatic duct disease [18]. High-grade intrahepatic duct strictures have been confirmed to carry a poor prognosis [19].

Risk of developing bile duct cancer

Patients with PSC have a substantial risk of developing malignant tumours of the bile duct epithelium, most commonly cholangiocarcinoma but gallbladder carcinoma is also seen. In a Swedish population-based cohort of 125 patients with a verified diagnosis of PSC the cumulative risk of developing cholangiocarcinoma was found to be 11.2% over the 10 years after diagnosis [12]. In other large studies, the risk of cholangiocarcinoma ranged from 6.3% [10] to 14% [16]. The differences in reported risk probably relate to length of follow up, stage at diagnosis and under-recognition in studies with low autopsy rates. The risk of cholangiocarcinoma is not influenced by sex or duration of IBD [12] but patients with PSC and IBD complicated by colorectal neoplasia have a significantly higher risk of developing cholangiocarcinoma compared to patients having PSC and IBD alone [20]. Smoking is strongly identified as a risk factor for developing cholangiocarcinoma in patients with PSC [21].

Pathogenesis of malignant bile duct change

An understanding of the mechanism of malignant change in the biliary epithelia in PSC is lacking. The association of cholangiocarcinoma with several other aetiological factors including congenital choledochal cyst, liver fluke infestations (Clonorchis sinensis and Opisthorchis viverrini), hepatolithiasis and exposure to Thorotrast suggests that chronic inflammation plays a role. Chronic proliferative cholangitis, characterised by proliferation of the epithelial lining, is frequently seen in these conditions and biliary epithelial dysplasia is found in these duct lesions. It is not known whether biliary dysplasia is a premalignant lesion in PSC but bile duct dysplasia is frequently found in patients with PSC and cholangiocarcinoma in the nontumour liver tissue at sites distant to the tumour [21]. These areas often contain carinoembryonic antigen (CEA) positive epithelial atypia and carcinoma in situ [22]. Biliary dysplasia has been reported to predate the development of cholangiocarcinoma in a patient with PSC by 18 months [23], suggesting that it is a facet of the neoplastic change.

The "gastric type" MUCS6 apomucin is frequently expressed in cholangiocarcinoma, suggesting that biliary epithelial cells gain a gastric apomucin phenotype during carcinogenesis [24]. These changes are also seen in biliary epithelial dysplasia, further supporting the view that this is a premalignant lesion. In addition, c-erbB-2 immunoreactivity may be a marker for malignant transformation in PSC [25, 26], although this has not been a universal finding [27]. Accumulation of p53 protein was found in 78.5% of cholangiocarcinomas and, in 50% of patients, p53 protein accumulation was detected in biliary tissue separate from the main tumour [28]. In another study, mutation of the p53 gene was frequently seen in cholangiocarcinoma, irrespective of the aetiology [29].

Screening for cholangiocarcinoma

In a case control study of patients with hepatobiliary malignancy complicating PSC, clinical and biochemical parameters of patients with and without carcinoma did not differ during the year leading up to cancer diagnosis [21]. Specifically, evaluation of biochemical data did not indicate a more rapid deterioration among cancer patients. The duration of IBD and PSC, extra- and intrahepatic distribution of PSC, previous surgical and medical treatments did not differ between the two groups [21]. Carbohydrate antigen 19-9 (CA19-9) is a sialylated lacto-N-fucopentase II epitope related to the Lewis blood group antigen. A serum CA 19-9 value greater than 100 U/ml predicted the presence of cholangiocarcinoma in PSC with a sensitivity of 89%, and specificity of 86% [30]. An index of two serum tumour markers [CA19-9 + \( \text{CEA} \times 40 \) >400] had a positive predictive value of 100% and specificity of 100% but the sensitivity of this index was only 67% [31]. Although useful in confirming a diagnosis of cholangiocarcinoma, serum tumour markers have not been shown to predict the development of biliary malignancy and no correlation between elevated serum CA19-9 and bile duct dysplasia was noted [32]. Increased levels of CEA can be detected in the bile of patients with cholangiocarcinoma [33]. Monitoring these levels may have a role in screening for the development of cholangiocarcinoma in PSC.

K-ras mutations have been detected in stool specimens from patients with cholangiocarcinoma [34]. Although, K-ras mutations occur less frequently in cholangiocarcinoma than in other gastrointestinal malignancies. When cholangiograms from patients with both PSC and cholangiocarcinoma were compared with those from patients
with PSC alone, marked dilatation of ducts or ductal segments (100% vs. 24%) and the appearance of a polypoid mass, measuring 1 cm or greater in diameter, (46% vs. 7%) were common findings in the patients with malignancy [35]. On serial cholangiograms, progressive stricture formation or progressive ductal dilatation also indicated cholangiocarcinoma [35]. More recently, positron emission tomography (PET), using the radiolabeled tracer [18F]Fluoro-2-deoxy-D-glucose (a glucose analogue that accumulates in malignant tumours), was found to detect small cholangiocarcinomas in patients with PSC with high sensitivity and specificity [36]. However, there is currently no evidence that imaging techniques can predict the development of bile duct malignancy in PSC.

Using the Mayo disease-specific natural history model to calculate risk score, all patients with cholangiocarcinoma were found to have a risk score above 4 [37], although there was no correlation between the risk score (above 4) and the incidence of tumour. The regular scoring of patients using the Mayo model has been suggested, and transplantation referral for transplantation recommended at scores above 4. However, the cohort of patients with risk scores around 4 has a relatively good predicted prognosis at just under 70% survival at 5 years with medical treatment alone. It remains to be determined whether early referral for transplantation, which will increase the number of tumour free candidates, will improve the overall outcome given that the transplant procedure carries a mortality itself.

**Prognosis of cholangiocarcinoma**

Cholangiocarcinoma still has a poor prognosis and the majority of patients diagnosed with this tumour will die within 4 months without treatment. Surgical resection offers the only chance of cure but in the past surgery was often only palliative associated with a median survival of only 13 months [38]. The overall 5-year survival after surgery was around 16%, although new aggressive surgical approaches to obtain curative resections have resulted in a better prognosis with a 5-year survival around 26% [39]. The role of adjuvant chemotherapy and radiotherapy remains unclear [40].

**Liver transplantation**

The results of liver transplantation in patients with PSC are excellent and the quality of life is markedly improved. Liver transplantation is now the therapy of choice for patients with end-stage PSC. In a European study, actuarial patient survival rate 5 years after transplantation was greater than that expected from prognostic models (89% versus 31%) [41]. Similar results were reported from Pittsburgh, where at five years, the actuarial survival with liver transplantation was 73% compared with 28% expected from the Mayo disease-specific model [42]. Liver transplantation not only significantly improved the survival of those patients classified as high risk by the Mayo model but also those calculated to have a low mortality with medical treatment [42], reinforcing the need for early transplant assessment in patients with PSC. Although the optimal timing of liver transplantation has still yet to be defined ideally, Wiesner and colleagues have recommended that patients with PSC be considered for liver transplantation if they have (1) a Mayo risk score of > 4.8 in whom malignancy is ruled out, (2) cirrhosis and complications of portal hypertension such as variceal bleeding, refractory ascites, or encephalopathy, or (3) disabling symptoms such as fatigue, pruritus, or recurrent bacterial cholangitis [43].

Cholangiocarcinoma has generally been considered to be a poor indication for liver transplantation due to a high recurrence rate, even when the tumour was found incidentally at the time of transplantation. More recently, a small incidental cholangiocarcinoma, defined as a tumour < 1 cm in size that was discovered at the time of pathologic sectioning of the explanted liver, was found not to adversely affect patient survival [44]. In selected patients, survival rates for 1, 3, and 5 years after transplantation were 60%, 32%, and 25%, respectively [45]. Multivariate analysis revealed that pTNM stage 0, 1, and II, negative lymph node, and negative surgical margins were good prognostic factors and for these patients 1, 3, and 5 year survivals were 80%, 73%, and 73%, respectively [45]. Overall, there was still a tumour recurrence rate of 59%, even in this selected population [45].

**Conclusions**

The development of cholangiocarcinoma in a patient with PSC remains a devastating complication. The prevention of this tumour currently relies on the early referral of patients with PSC to a liver transplant unit, in order to identify patients who warrant transplantation prior to the development of malignancy. Smoking may be a risk factor for the development of cholangiocarcinoma in PSC but it remains to be determined whether stopping smoking will reduce the risk. Markers that will accurately predict the development of bile duct malignancy in an individual with PSC have not yet been identified. Dysplasia of biliary epithelia in PSC may herald the development of malignancy. If further studies confirm bile duct dysplasia is a premalignant lesion, then its detection before the development of cholangiocarcinoma will become a priority in PSC. Patients found to have bile duct dysplasia should then benefit from early liver transplantation. Accurate non-invasive imaging detection, or serum or stool markers of bile duct dysplasia will be more quickly and more widely adopted than tests which rely on repeated bile duct cannulation or liver biopsy.

**References**

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