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Review

The Interventional Radiological Management of Cholangiocarcinoma

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The successful management of cholangiocarcinoma requires the collaboration of several clinical disciplines. Modern imaging can demonstrate the liver and the surrounding structures in exquisite detail. Complete surgical resection offers the only potential for cure. The judgement of whether resection is feasible requires precise staging of the tumour. Unfortunately, in most cases, imaging delineates an advanced and inoperable tumour, requiring non-surgical palliative treatment, usually by means of endoscopic or percutaneous radiological techniques. The management of hilar lesions can be problematic requiring substantial experience and skill. Hatzidakis A. and Adam A. (2003). *Clinical Radiology* **58**, 91–96.

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INTRODUCTION

Cholangiocarcinomas are relatively rare tumours with an autopsy incidence of 0.5–2% and 4500 new cases annually in the U.S.A. [1,2]. The incidence increases with age, with most tumours occurring in between 50 and 70 years, more commonly in men [2]. Predisposing factors include primary sclerosing cholangitis, hepatolithiasis, ulcerative colitis, biliary parasites, specific oncogenes and congenital malformations, such as choledochal cysts [2–4].

Histologically, the vast majority of cholangiocarcinomas are adenocarcinomas and they are topographically differentiated as intra- and extrahepatic [3]. Intrahepatic lesions are classified according to the macroscopic types, as mass-forming, periductal-infiltrating and intraductal, whereas extrahepatic tumours are divided as hilar and distal [3,5]. Intrahepatic tumours do not usually cause extensive bile duct dilatation, so jaundice, as a primary symptom, is rare. They can present as a large peripheral mass, a cystic lesion or an intraductal tumour with segmental bile duct dilatation [3,5]. Extrahepatic tumours usually present with obstructive jaundice due to obstruction at the hilum at common bile duct (CBD) level [3]. Up to two-thirds of all cholangiocarcinomas are located at or near the hilum [3].

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DIAGNOSTIC IMAGING

Current imaging techniques effectively evaluate the location and extent of the tumour, permitting accurate staging [6]. Ultrasonography, computed tomography (CT) and magnetic resonance imaging [MRI; including magnetic resonance cholangio-pancreatography (MRCP)] can provide valuable information about the extent of the tumour, the level of the obstruction, metastatic disease and infiltration or encasement of vascular structures [3,7]. The decision whether the tumour is resectable is based on the imaging information and the result of any biopsies taken.

SURGICAL TREATMENT

The best chance of cure is offered by complete surgical resection with negative margins and restoration of biliary–enteric continuity [3,8]. Resectability criteria are based on tumour extension, vascular involvement, distant metastases, the presence of liver cirrhosis and dysfunction, portal hypertension

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and the general condition of the patient [3,9]. Cholangiocarcinomas are resectable if vascular and biliary ductal involvement is limited to one lobe of the liver and if there is no extrahepatic disease in patients who are fit for surgery. Extended right hepatic resection is possible in some patients with involvement of the quadrate lobe.

In patients in whom the proportion of the liver to be resected is substantial, it may be useful to carry out embolization of the appropriate branch of the portal vein, in order to achieve atrophy of the lobe to be resected. Compensatory hypertrophy of the remaining parenchyma at the same time will minimize the risk of post-operative liver failure [5].

If pre-operative investigations do not definitively demonstrate an irresectable tumour, surgical exploration can be performed. Some surgeons advocate the use of staging laparoscopy in order to avoid exploratory laparotomy [10]. Hilar tumours present a challenge to surgeons because of their proximity to the portal vein, hepatic arteries and liver parenchyma. Nevertheless, a large Japanese study reported resectability rates as high as 80% for patients treated by combined bile duct and liver resection with caudate lobectomy [11]. Other centres report much lower rates of 10–56% [12–14]. In many cases, tumours thought to be resectable are shown to be irresectable at the time of surgery, so that only a palliative surgical bypass is performed [3,8]. If curative resection is not possible, surgical, endoscopic or percutaneous methods of palliation can be used [3,10]. Palliative surgical bypass has a procedure-related mortality of 13.6%, an overall 30-day mortality of 7% for all types of lesions and, in patients with hilar tumours, a post-operative complication rate of approximately 20% [13,15].

Curative resection of hilar tumours is associated with an operative mortality rate of 5–7% and a post-operative complication rate of 22% [3,13]. The median survival after resection of hilar cholangiocarcinoma is 27–59 months [3,8], with 5- and 10-year survival rates ranging between 0–56% and 0–18%, respectively [8,16]. Other authors report a lower overall median survival rate of 14–19 months [14,17]. Hilar tumours of Bismuth types I and II (Table 1) have a relatively better 5-year survival rate (14–33%) in comparison to type III and IV tumours (0–25%) [12]. Survival is lower if there is local lymph node involvement, but it still remains longer than for the unresectable patients [8]. The management of patients with hilar tumours is decided according to local expertise and is based on a number of factors, including age, performance status, other comorbid conditions, location of the tumour and resectability criteria [16]. The 5-year survival rate after curative resection of distal extrahepatic tumours varies between 0 and 39% (mean 25%) [16]. Peripheral cholangiocarcinomas show a post-resection median survival of about 18 months [18].

Table 1 – The Bismuth classification of biliary strictures

Type	Description
Type I	Stricture of the common bile duct, at least 2 cm distal to the bifurcation
Type II	Stricture involving the proximal common hepatic duct
Type III	Stricture involving the confluence of the left and right main bile ducts but with remaining communication between the two lobes of the liver
Type IV	Stricture involving the confluence of the left and right main bile ducts with lack of communication between the two lobes of the liver

ADJUVANT TREATMENT

The benefit of external-beam radiotherapy or intra-arterial local chemotherapy is uncertain [14,19–21]. Pre-operative treatment using external-beam irradiation in combination with bolus 5-Fluorouracil (5-FU) chemotherapy, followed by brachytherapy plus protracted venous infusion of 5-FU, may increase the survival rate [22]. Also, Ir192 brachytherapy may restrict tumour spread [22]. Other authors believe that intraluminal brachytherapy does not provide any advantage compared with external-beam irradiation [23].

Photodynamic therapy is a safe, minimally invasive palliative therapy which can be effective in reducing malignant stenosis [24]. It also seems to lead to a significant decrease in serum bilirubin, longer survival and improved quality of life in patients with non-resectable Bismuth type III and IV tumours [25].

ENDOSCOPIC TREATMENT

Endoscopic biliary drainage with stent placement is a widely used method of palliation [26]. Endoscopic retrograde cholangio-pancreatography (ERCP) has several advantages over percutaneous transhepatic cholangiography (PTC) in distal CBD lesions. Use of ERCP provides direct inspection of the duodenum and the papilla, can help to differentiate malignant from benign causes, and allows cannulation of the stricture [27]. Cytological samples can be easily obtained, with subsequent placement of a plastic stent to relieve the patient's jaundice [27,28].

If endoscopic stent placement fails, percutaneous transhepatic biliary drainage (PTBD) or a combined endoscopic-radiological procedure can be performed [26]. Failure of endoscopic drainage may be due to anatomical alterations, a periampullary diverticulum, duodenal obstruction by adjacent tumour, failure to cannulate the biliary tree, or inability to advance the guidewire or push a stent through the stricture [26]. Nevertheless, plastic stents are inserted successfully in approximately 90–95% of patients. The procedure is more often successful in patients with distal rather than proximal lesions [26,27]. Endoscopic management for proximal bile duct strictures has a lower overall success rate than percutaneous treatment (19 vs 97%) with comparable complication rates (26 vs 25%). There is only a single study that reported a much higher endoscopic success rate (81–89%) compared with that for the percutaneous approach (57–83%) [29].

PERCUTANEOUS TREATMENT

Many authors favour the percutaneous approach over the endoscopic approach for the palliation of patients with malignant hilar biliary obstruction because the percutaneous

technique provides better demonstration of the proximal extent of the tumour and allows easier placement of drainage catheters [14]. Endoscopic stent insertion is often successful in type I hilar tumours, but the percutaneous route is preferable in type II–IV lesions [27,29,30]. Endoscopic stent placement is particularly problematic in type III and IV strictures in which successful drainage is achieved in only 15% of patients [31]. Nevertheless, there is one report of successful endoscopic plastic stent placement in 100% of patients with type III and IV tumours, followed by stent exchange every 4 months [32]. The palliative management of hilar lesions is strongly dependent on individual expertise.

Percutaneous transhepatic transluminal forceps biopsy is a safe technique, which is easy to perform through an existing track, producing a diagnostic result in 71% of cases [33]. Percutaneous cholangioscopic endoluminal forceps biopsy has a sensitivity of 89%, and is appropriate even for very small intraductal lesions [34]. Placement of metallic stents does not preclude subsequent biopsy. Therefore, the requirement for histology is not in itself a contraindication to the placement of metallic endoprostheses.

Plastic Stents

Most endoscopists use plastic stents to achieve biliary drainage [26]. Plastic devices should be used in preference to metallic endoprostheses in patients being drained percutaneously when a definitive diagnosis of malignancy has not been made or when there is extensive malignant infiltration of the duodenum [30]. However, metallic stents are generally preferable to plastic devices for percutaneous drainage, especially if the tumour is quite advanced and considered unresectable. Such stents can be placed as a one-stage procedure. In patients in whom metallic stents protruding into the duodenum have become occluded, patency can often be restored by endoscopic insertion of a plastic endoprosthesis.

Plastic Stent Types

A large number of different types of plastic endoprostheses, such as Carey-Coons and Miller stents, are available. Plastic stents usually become occluded because of bile encrustation. The frequency of occlusion is inversely proportional to the size of the stent lumen. However, large-diameter tracks are necessary for transhepatic placement of large-calibre plastic stents, increasing patient discomfort and the risk of haemobilia. Such devices are usually inserted in two stages, increasing the patient's stay in hospital and the accompanying costs [30].

Metallic Stents

Metallic stents have revolutionized the interventional radiological management of patients with malignant obstructive jaundice. They can be inserted in a single-stage procedure in most patients, minimizing hospital stay and reducing the associated costs, even though the cost of metallic stents is significantly higher than that for plastic stents [35,36]. Patients with life expectancy of more than 3 months are particularly good candidates for an expandable metallic stent [26,37], but it is difficult to predict which patients are likely to survive to stent exchange [27]. The main disadvantage of metallic endoprostheses is that they cannot be removed [37]. Therefore, staging and resectability should be determined before stent placement, as this could compromise subsequent surgery [30].

Metallic Stent Types

The majority of metallic stents used are self-expandable devices, such as the Wallstent (Boston Scientific, Watertown, MA, U.S.A.) and the Zilver stent (Cook, Bloomington, IN, U.S.A.). Dilatation of the stricture prior to stent deployment may be helpful. Balloon-expandable stents are infrequently used in the biliary system, because their relatively high rigidity is a significant disadvantage, especially when they have to be deployed along a curve, which is very frequently necessary in patients with hilar lesions [30].

Stenting Procedure

After percutaneous cannulation of the bile ducts and passing a hydrophilic guidewire across the obstructing lesion, the stricture can be carefully dilated with an 8–10 mm balloon. This allows easier passage of the stent delivery catheter and accelerates full expansion of the metallic stent. The proximal end of the stent should be placed in a peripheral intrahepatic duct, in order to minimize the risk of occlusion by tumour overgrowth. The distal part of the stent should protrude about 1 cm into the duodenum to allow easy endoscopic access, in case it is needed for the restoration of patency of occluded stents [30].

In patients with hilar tumours obstructing both the left and right hepatic ducts, bilateral stent insertion is usually indicated. If the contralateral duct system is not opacified during percutaneous cholangiography, it may be sufficient to drain a single lobe, particularly if staging CT/MRI demonstrates atrophy of the non-opacified lobe of the liver. However, if the patient's jaundice fails to resolve, or if there is infection of the contralateral lobe, bilateral drainage should be carried out. Deployment of two stents can be achieved either through a single transhepatic tract or by using two separate punctures to gain access to each lobe. The latter arrangement is preferable as parallel deployment of two metallic stents allows easier recanalization in cases of obstruction [30].

Non-surgical Complications

Complications of percutaneous treatment include cholangitis (5–6.5%), haemorrhage (2%), bile leakage (<2%), abscess and catheter dislodgment [29,30,38]. Minor complications are seen in 10–23% of cases, while the incidence of major complications ranges from 2.3 to 20.8%. Most complications are related to the transhepatic puncture rather than the stent placement [38]. Endoscopic complications include all the abovementioned ones, plus acute pancreatitis and bowel perforation [29]. Aggressive guidewire and catheter manipulations, as well as vigorous filling of multiple undrained segments with contrast medium during cholangiography, can cause cholangitis and septicaemia, especially if stent insertion is

unsuccessful [39,40]. Incomplete biliary drainage after ERCP leads to cholangitis in up to 87% of patients [39]. Septicaemia may be caused by bacteria, already present in obstructed ducts, which enter the bloodstream during the procedure because of the already high biliary pressure, which rises even further following injection of contrast medium [39].

Management of Cholangitis

When imaging studies suggest obstruction proximal to the distal third of the extrahepatic bile duct, percutaneous drainage is the preferred method of palliation as it is much more likely to be completed successfully than endoscopic drainage. This avoids the risk of septicaemia due to a failed attempt at endoscopic stent insertion [29]. If PTC demonstrates biliary obstruction, it is desirable that drainage is carried out in order to prevent cholangitis and sepsis [26]. However, PTC does not contaminate the bile ducts with enteric flora, as ERCP does, and is less likely to lead to sepsis [29]. Late complications due to non-obstructive cholangitis have been reported in 3% of patients [41]. Ensuring that the stent extends through the sphincter of Oddi minimizes the risk of late non-obstructive cholangitis and reduces post-procedural morbidity [42]. Stent-related complications include malpositioning, migration, inadequate expansion, failure of release of the stent, duodenal erosion or perforation when the stent protrudes too much into the bowel, and stent occlusion. The 30-day mortality is 6–39%, depending on the patient's general condition, the tumour stage and the therapeutic method used, whereas the procedure-related mortality ranges between 0.8 and 3.4% [30,41,43–46].

Pre-operative Biliary Drainage

Endoscopic stents inserted pre-operatively may increase the incidence of bile contamination and lead to a higher post-operative infection rate [47]. Except for patients with acute cholangitis, in whom emergency drainage is mandatory, pre-operative biliary drainage is not indicated in lower bile duct obstruction [48]. Some authors have reported that pre-operative PTBD reduces the incidence of post-operative sepsis, bleeding and renal failure [49,50]. However, several prospective, randomized trials have shown that pre-operative PTBD has no effect on mortality, morbidity or duration of hospitalization [51–53].

Stenting Results and Stent Patency

Metallic stents can be inserted successfully in up to 100% of patients [43]. Survival after metallic stent placement has been reported as ranging between 93 and 420 days, depending on patient population, tumour location and stage [30]. In bifurcation tumours, the longest survival rate has been observed in patients in whom both lobes have been drained. The shortest survival rate has been observed in those with cholangiographic opacification of both lobes but drainage of only one lobe [34,54,55].

Stent occlusion is usually caused by tumour overgrowth (2.4–16%) and less frequently by tumour ingrowth (2.4–7%) or bile encrustation. This condition may cause jaundice and cholangitis, and should be managed by insertion of a new endoprosthesis to relieve the obstruction [26]. Plastic stents become occluded after 3–6 months with an average patency of 126 days in comparison with a patency of 273 days for metallic self-expandable stents [26,56]. The use of metallic stents reduces hospital stay and minimizes costs [56].

The patency of metallic endoprostheses at 25 and 50 weeks in patients with CBD obstruction is 74 and 59%, respectively, and 62 and 47%, respectively, in patients with hilar obstruction [41]. The 12-month patency is 46% for hilar and 89% for non-hilar obstructions, with an overall 12-month survival of 35% [45]. The re-intervention rate is 18–19.2% after a mean period of 5.9 months [30,41]. In a prospective, randomized trial comparing percutaneously placed metallic stents with plastic stents in patients with malignant tumours at the hilum of the liver, metallic stents were found to have higher technical success, and patency rates were found to be more cost-effective than with plastic stents [57].

Covered metallic stents offer no significant improvement in patency in comparison with uncovered stents [58,59]. Stent occlusion due to encrustation of bile is uncommon, because of the large stent diameter. Covered stents prevent tumour ingrowth, but overgrowth remains a problem. If the covering membrane is damaged, ingrowth is possible through the tear. The stent cover can be damaged during deployment or through physical and mechanical factors, such as increasing pressure from the tumour on the covering membrane or corrosion due to reflux of duodenal and gastric juices [58]. The frequency of occlusion due to tumour overgrowth can be minimized by peripheral stent placement, but this may not be possible with covered stents as it may lead to the inadvertent occlusion of intrahepatic side branches [58]. Nevertheless, the possible future role of impregnated stents has yet to be determined. Cystic or pancreatic duct obstruction by covered stents does not usually result in cholecystitis or pancreatitis.

SUMMARY

The management of patients with cholangiocarcinoma presents great challenges for several medical disciplines. It requires a high degree of expertise in diagnostic imaging techniques, as well as endoscopic, interventional radiological and surgical skills. A dedicated team approach is essential. Early diagnosis and accurate staging is the key to reaching the correct decision regarding the resectability of the tumour. If resection is not possible, an endoscopic approach should be used for palliation of distal lesions, with percutaneous intervention reserved for endoscopic failures. However, in hilar lesions, interventional radiological palliation is the method of choice.

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