The GEC ESTRO Handbook of Brachytherapy

SECOND EDITION

PART II: CLINICAL PRACTICE

28

Bile Duct Cancer

Janusz Skowronek

Editors

Erik Van Limbergen

Richard Pötter

Peter Hoskin

Dimos Baltas

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

28 Bile Duct Cancer

Janusz Skowronek

1. SUMMARY

Biliary tract cancer is a rare disease. Surgical resection offers the best chance for long-term survival, but the results are not satisfactory and local relapses are frequent. The majority of patients present with locally advanced or metastatic disease, which is not amenable to surgical resection, resulting in poor survival [1]. Adjuvant or definitive radiotherapy (RT) with or without chemotherapy is therefore used in many centers worldwide for better local control and with the expectation that it will have a favorable effect on survival. However, the lack of appropriate prospective trials, as well as the small size of the published series and their retrospective nature, has produced insufficient evidence for the best treatment for these patients [1].

The proportion of advanced cases affects the use of brachytherapy (BT) in treatment of bile duct cancers. Indications for brachytherapy include all malignant strictures of the bile duct which can be cannulated. Intraluminal brachytherapy (ILBT) is an important component in the multimodality approach to bile duct cancers. The objective of this treatment is to deliver a high local dose of radiation to the tumour while sparing surrounding healthy tissues. The treatment can be safely adapted for right and left hepatic duct as well as for common bile duct lesions.

Indications for BT can be summarized as follow:
1. BT as a palliative treatment - in order to facilitate the outflow of bile. For unresectable patients, the goal of treatment is prevention of locoregional disease progression to enhance quality of life and survival.
2. BT as a radical treatment: alone in small inoperable tumours or in combination with EBRT / chemotherapy in advanced disease for unresectable patients.
3. BT as an adjuvant treatment after subradical excision, maybe combined with EBRT.

2. INTRODUCTION

Bile duct cancer is a rare tumor in developed countries; there are approximately 10,000 new cases per year in United States. In 2015 in USA there are 10,910 estimated new gallbladder and other biliary cancer cases (4,990 – men, 5,920 – woman) resulting in death in 3,700 (men -1,660, woman - 2,040) [2].The 5-year overall survival (OS) rate is estimated at 5%-30%. In Japan there were 20,734 new cases diagnosed in 2007 [1]. In Poland (2011) there were 1207 gallbladder cancers and 627 bile ducts and ampulla of Vater cancers, respectively.

Biliary tract tumors have a higher incidence in Asia, particularly in Thailand, Korea, India, and Japan. It is one of the most common cancers in endemic areas of developing countries, as high as 87 per 100,000 people in northeast Thailand. Cholangiocarcinoma accounts for about 20% of the primary liver cancer in Western countries, and <10% in Asian nations that are endemic for HCC [3]. The major risk factor in Western countries is primary sclerosing cholangitis, which is closely associated with chronic inflammatory bowel disease, particularly ulcerative colitis. The risk of developing cholangiocarcinoma is higher in patients with primary sclerosing cholangitis, ulcerative colitis, and colonic neoplasms than in patients with primary sclerosing cholangitis and ulcerative colitis without colonic neoplasm. In Japan, patients with HCV infection have 1,000 times higher incidence than would be expected in the general population, and the accumulated rate of newly diagnosed cholangiocarcinoma is 1.6% at 5 years and 3.5% at 10 years. In Asia, chronic infections of the biliary tract and infestation by certain liver flukes, such as clonorchis sinensis and opisthorchis viverinni are associated with cholangiocarcinoma and hepatolithiasis.

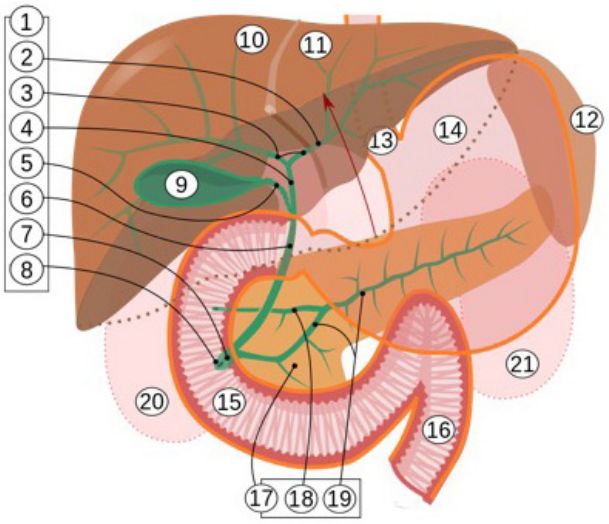

Fig. 28.1 (from: http://en.wikipedia.org/wiki/Ampulla_of_Vater)
Bile duct and pancreas:
1. Bile ducts: 2. Intrahepatic bile ducts; 3. Left and right hepatic ducts; 4. Common hepatic duct; 5. Cystic duct; 6. Common bile duct; 7. Ampulla of Vater; 8. Major duodenal papilla. 9. Gallbladder. 10-11. Right and left lobes of liver. 12. Spleen. 13. Esophagus. 14. Stomach. 15. Duodenum. 16. Jejunum. 17. Pancreas: 18. Accessory pancreatic duct; 19. Pancreatic duct. 20-21: Right and left kidneys

Hepatolithiasis itself is also a risk factor for cholangiocarcinoma; 5% to 10% of patients with intrahepatic stones develop this complication. Moreover, the combination of liver fluke infestation and nitrosamine exposure may explain the very high incidence of cholangiocarcinoma in northeast Thailand. Other risk factors, although rare, include congenital fibropolycystic disease of the biliary system such as choledochal cysts and Caroli's disease (cystic dilatation of intrahepatic bile ducts) [3].

The majority of bile duct carcinomas involve the hepatic duct bifurcation, the common hepatic duct, the cystic duct, and the ampulla (Fig. 28.1). Tumor can spread along the sinusoids and neoplastic destruction of normal cholangioles leads to the retention of bile around the margin of the tumor. Tumor emboli in the portal and hepatic veins are common and vascular invasion can occur in up to 90% of cases. Local relapses are frequent. The tumor may also metastasize to lungs, peritoneum and intra-peritoneal organs. Patients commonly present with obstructive jaundice.

Treatment options for bile duct cancer remain limited due to the large number of patients with advanced disease at the time of diagnosis [4-9]. Unresectable bile duct cancers are very difficult to treat with external beam therapy (EBRT) alone due to the proximity of adjacent normal organs and the high doses required to effectively irradiate these neoplasms [10-13]. The only curative treatment is radical surgical excision. However, because of the propensity of cholangiocarcinomas to invade the hepatic artery, portal vein and other vital structures this is only feasible in 10 to 15% of cases and is associated with an operative mortality of 5 to 10% [5,14,15]. Effective palliation is achieved by biliary decompression. This is carried out either surgically by using bypass procedures such as hepatojejunostomy or by endoscopic or percutaneous insertion of biliary endoprotheses [16,17]. For unresectable tumors, the purpose of treatment is to palliate symptoms such as obstructive jaundice, biliary tract infection, pain, and ascites.

Prognostic factors include tumor stage, tumor location, nodal involvement, and extent of resection. Tumor location in ampulla of Vater is associated with better prognosis compared to Klatskin tumors (intrahepatic, perihilar).

3. ANATOMICAL TOPOGRAPHY

The biliary tract includes tumors deriving from the epithelium in the gallbladder, as well as intrahepatic and extrahepatic biliary epithelium. Bile ducts include intrahepatic, perihilar and distal extrahepatic biliary tree. Gallbladder cancer is the most common cancer of the biliary tract and accounts for two thirds of these cancer patients, whereas bile duct cancer accounts for the remaining one-third [17].

The bile ducts originate within the liver, with the left and right hepatic ducts joining to form the common hepatic duct. At the origin of the cystic duct, it becomes the common bile duct. The cystic duct drains bile from the gallbladder into the common bile duct. The gallbladder is adjacent to the undersurface of the liver (Fig. 28.1).

There is a rich lymphatic network along the submucosa of bile ducts. The primary lymphatic drainage of the biliary tract is to the lymph nodes in the pericholedochal area, periportal region, hepatoduodenal ligament, common hepatic artery and pancreaticoduodenal groups [17,18].

4. PATHOLOGY

The majority of tumors are low grade cholangiocarcinomas. Cholangiocarcinomas arise from the epithelium of the biliary tract; the majority of them are adenocarcinomas. Other rare histologies include squamous cell carcinoma, mucoepidermoid carcinoma, cystadenocarcinoma, and carcinoid tumor. Grossly, three subtypes of cholangiocarcinomas are identified: sclerosing, nodular, and papillary [19,20]. Cholangiocarcinoma can be classified from well differentiated to undifferentiated.

Sclerosing tumors are characterized by an intense desmoplastic reaction. This type of tumor tends to invade the bile duct wall early, and as a result, is associated with low resectability and cure rates. Most cholangiocarcinomas are of this type [21]. In contrast, papillary histology has the most favorable prognosis [22].

5. WORK UP

The most common presenting symptoms of biliary tract cancer are caused by obstruction of the bile duct and include painless jaundice, clay-coloured stool, tea-coloured urine, and pruritus. Other signs and symptoms include abdominal pain, fever, general

malaise, abdominal distention, fullness, anorexia, and weight loss. Patients with extrahepatic tumour usually present with jaundice and tea-coloured urine. Patients with intrahepatic tumours are less likely to be jaundiced and more likely to present with abdominal symptoms [17].

Basic diagnostic tests include history and physical examination, laboratory studies (blood cell counts, blood chemistry with liver function studies, tumour markers: CA 19-9, CEA), standard imaging studies (computed tomography, ultrasonography, percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangio-pancreatography (ERCP)), optional imaging studies (endoscopic ultrasound, magnetic resonance cholangio-pancreatography (MRCP), dynamic contrast enhanced (DCE) computed tomography scan, arteriography).

There are no reliable screening methods. Early asymptomatic diagnosis is very rare; occasionally patients are diagnosed when levels of alkaline phosphatase and gamma-glutamyl transferase in screening blood work are elevated. Ultrasonography and CT are most frequently used as primary diagnostic methods.

6. INDICATIONS, CONTRA-INDICATIONS

Surgical excision of all detectable cancer along the biliary tract is associated with improvement in long-term survival. Patients with inoperable peri-hilar cholangiocarcinoma usually have obstructive jaundice and should be treated with endoscopic or percutaneous drainage and/or stent placement initially. EBRT alone rarely controls advanced disease. Combinations of EBRT, different schedules of chemotherapy and ILBT may relieve pain and contribute to biliary decompression, and sometimes achieve long-term survival [16]. Usually, a 1-2 weeks interval is planned between the completion of EBRT and BT. Investigators have had the broadest experience with 5-FU, which has response rates of approximately 14%. Single-agent activity has been noted with other drugs, such as adriamycin, but clinical results have been disappointing. Currently, no combination regimen has been proven sufficiently to become an established therapy. In some cases, combined chemotherapy and radiotherapy may delay the progression of cholangiocarcinomas and to provide the chance for liver transplant [23-25].

ILBT is an important component in the multimodality approach of bile duct cancers. The objective of this treatment is to deliver a high local dose of radiation to the tumour while sparing surrounding normal tissues. The treatment can be safely adapted for right and left hepatic duct as well as for common bile duct lesions.

Indications for BT include all malignant strictures of the bile duct which can be cannulised.

They can be summarized as follow:

1. BT as a palliative treatment - in order to facilitate the outflow of bile (irrespective of the size of the tumor, including large inoperable tumors with significant extraductal disease). For unresectable patients, the goal of treatment is prevention of locoregional disease progression to enhance quality of life and survival. In almost all cases such palliative treatment is recommended for Klatskin tumours. This group of indications occurs most frequently.
2. BT as a radical treatment: alone in small inoperable tumours or in combination with EBRT / chemotherapy in advanced disease for unresectable patients.
3. BT as an adjuvant treatment after subradical excision, maybe combined with EBRT.

Patients should be fit enough (WHO score 0-2 in individual cases) for the procedure and should have been reviewed to confirm that they are not suitable for resection. Combined treatment is possible in patients who are in reasonably good condition; it is usual to combine BT with EBRT [8,26-32]. Although the results available in the literature are somewhat contradictory with regard to the possible use of BT in a curative setting, some evidence indicates that BT can add something to improve results of the treatment of unresectable extrahepatic bile duct and pancreatic cancers if a proper subset of patients is identified and a rational and aggressive scheme of multimodality treatment is designed.

Until now, no prospective controlled trial including significant patient cohorts with enough statistical power has been conducted to determine the impact of BT on survival outcomes [33].

Contraindications:

1. Significant risk of radiation-induced severe complications in OARs;
2. Poor general condition (WHO score > 2).

7. TARGET VOLUME

The location and length of the stenotic bile duct tumor should be identified at PTC or ERCP or MRCP. In case of 2D planning for the Clinical Target Length (CTL) a 1-1.5 cm margin is taken proximally and distally from the visible stenosis. Using PTC or ERCP alone, no individual tumour and target depth can be defined, as extraductal disease can only be defined by additional sectional imaging (CT and MRI).

In case of 3D planning the gross tumor volume (GTV) is defined as any visible tumor by CT and/or MRI. Clinical target volume (CTV) may be defined as 1-1.5 cm margin from the GTV, along the bile duct, and to the target depth which needs to be determined (which may also include an adjacent lymph node). A planning target volume may be defined by adding a margin of 0.5 to 1 cm to the CTV (CTL).

8. TECHNIQUE

Usually, brachytherapy is delivered through a percutaneous transhepatic biliary drainage (PTBD) tube (PTC) placed under fluoroscopic guidance or through catheters placed in the tumor bed during surgery. The trans-duodenal endoscopic technique is used less frequently.

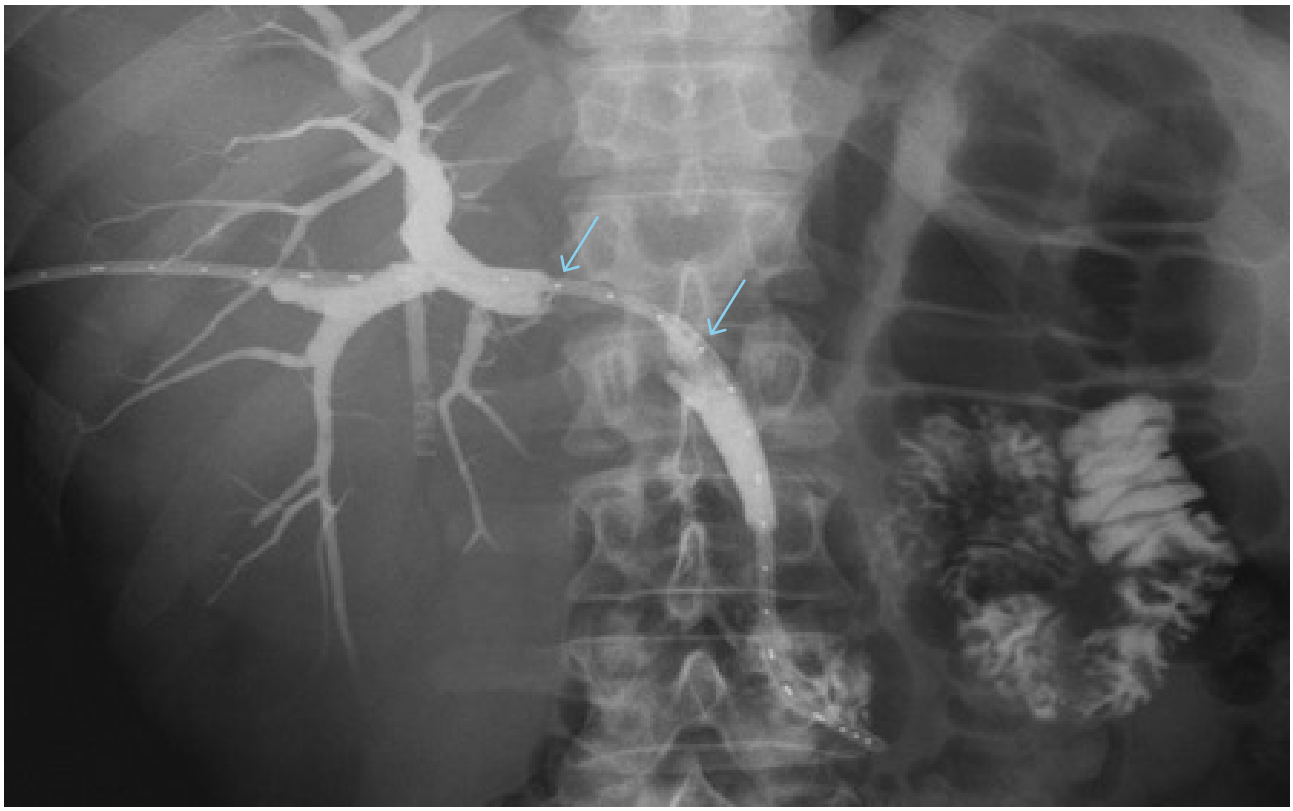

Fig. 28.2
Trans-hepatic approach based on a percutaneous trans-hepatic cholangiogram (PTC). Bile duct cancer, dilated common hepatic and right and left hepatic ducts with interruption of contrast filling (arrows) after cholangiography. 5 French brachytherapy catheter with radio-opaque marker wire introduced via the right hepatic duct passing through the stenosis and reaching the duodenum via the common bile duct.

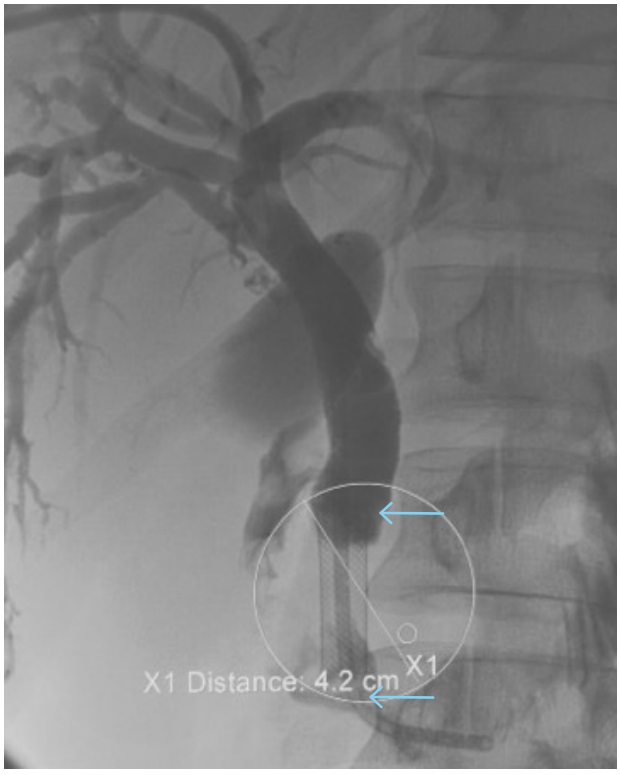

Fig. 28.3
Trans-hepatic approach based on a percutaneous trans-hepatic cholangiogram (PTC). Bile duct cancer with recurrence in the proximal common bile duct after insertion of a metallic stent (arrows), dilated bile ducts visible after cholangiography. Obturated part visible as a break.

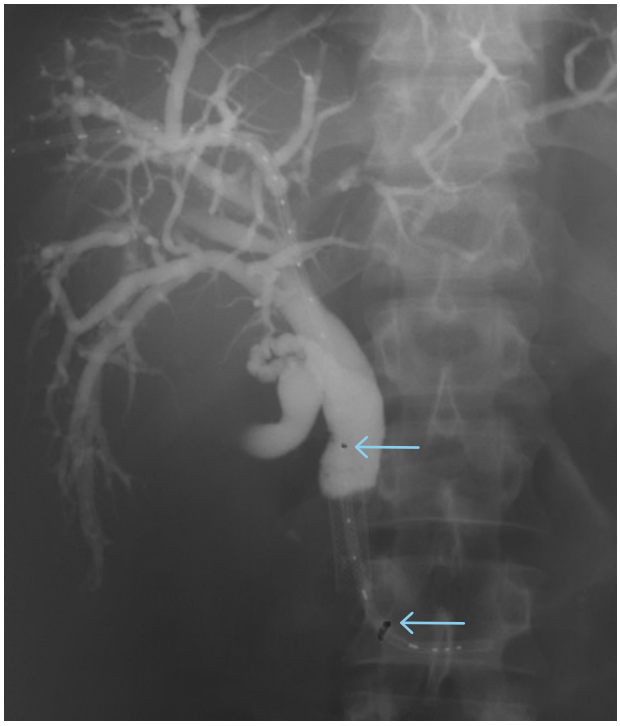

Fig. 28.4
Trans-hepatic approach based on a percutaneous trans-hepatic cholangiogram (PTC). Bile duct cancer with recurrence after insertion of stent, bile ducts visible after cholangiography, obturated part visible as a break, 5 French brachytherapy catheter with radio-opaque marker inside, irradiated length (arrows) is 5 cm (3 cm of obturated bile duct and a margin of 1 cm distally and proximally).

Trans-hepatic technique

Where possible it is best to use a percutaneous trans-hepatic technique which allows the passage of a catheter through the stricture. Cholangiography is performed and then radiographs with a dummy source in the catheter.

The transhepatic catheter placement during PTCA has the advantage of providing both internal drainage across the tumour and external drainage via the proximal end of the catheter. In the face of a refractory obstruction, BT to the proximal tumour may help open up the channel to the duodenum. This is nowadays the preferred approach in most cases [34]. Both, HDR and PDR BT are well tolerated and can be used.

The technique includes the following steps: 1. identifying the site and length of the malignant stricture by cholangiogram; 2. bilary drainage with minimum 10 French diameter; 3. inserting a BT blind-ended catheter through the biliary drainage 10 F catheter; 4. a marker wire is then passed into the brachytherapy catheter and orthogonal radiographs are obtained for computerized 2D dosimetry (or CT scans in case of 3D planning); 5. Treatment planning procedure.

Trans-duodenal endoscopic technique [35]

A less frequently used technique is a trans-duodenal endoscopic approach. Before the procedure endoscopic retrograde cholangiography (ERC) is performed to identify the site of the tumour, the length of bile duct involved and the extent of disease. ERCP is first performed and a sphincterotomy carried out to allow cannulation of the bile duct. A guidewire is then advanced through the malignant stricture and beyond. The endoscope is removed and then a naso-biliary tube threaded over the guidewire beyond the stricture into the biliary tree. The procedure is performed under fluoroscopy to check the position of the guidewire and the nasobiliary tube. The tube is finally taped to the patient's nose.

An afterloading catheter containing a radio-opaque marker wire is then passed through the naso-biliary tube under fluoroscopy and advanced through the lesion. The radio-opaque wire has markers at intervals which indicate where the radioactive source should be placed. Orthogonal radiographs or for 3D planning, CT are taken to confirm the position and to perform the dose calculation.

Loading the radioactive source into the catheter is similar to that described for the percutaneous trans-hepatic technique.

The naso-biliary catheter can be attached to a remote afterloading machine which will give a fraction of high dose rate BT (PDR-BT is not recommended because of the short tolerance of endoscopy). In this case, the dwell positions of the source must be programmed taking into account the measured distances from the localising radiographs.

9. TREATMENT PLANNING

2D planning

In the majority of cases 2D planning is still the usual method due to the palliative aim of the treatment and the poor condition of the majority of patients. Presence of jaundice may also be a resaon to shorten the planning process. X-ray images are taken directly during percutaneous trans-hepatic cholangiograpgy (PTC). In most cases an anterior-posterior X-ray is used. Clinical Target Length (CTL) is defined as a 1-1-5 cm margin taken proximally and distally from the visible stenosis which indicates the length of the GTV.

Dose specification for prescription and reporting is at 1 cm from the source axis.

3D planning

When using CT for 3D treatment planning 1 to 3 mm slice thickness is recommended with contrast to reconstruct the bile ducts and to visualize the gross tumor volume (GTV). The GTV is defined as any tumor visible through CT and/or MRI. Clinical target volume (CTV) is defined as 1 to 1.5 cm distance from the GTV in length (Clinical Target Length) along the bilde duct. Some distance may also be defined in depth indicating the Clinical Target Depth (orthogonal to the lumen axis). Potential lymphatic drainage areas may be considered, in particular along the porta hepatis and pancreaticoduodenal system. [36, 37]. However, treating nodal disease with brachytherapy is usually not possible. The planning target volume (PTV) is defined by adding in the longitudinal direction a margin of 1 cm both, distally and proximally to the CTV [25].

The dose-limiting surrounding organs (both for EBRT and BT) include the liver, pancreas, duodenum, small bowel, stomach, and spinal cord.

10. DOSE, DOSE RATE, FRACTIONATION

In patients who are in reasonably good condition, it is usual to combine bile duct BT with EBRT. Typically 30 to 40 Gy (2 Gy fractions) are delivered through EBRT to a volume which encompasses the porta hepatis, the common bile duct and regional nodes. For BT the dose commonly used is 15-20 Gy prescribed to the brachytherapy related PTV, generally over 2-3 treatments with HDR.

In the same group of patients radical PDR BT may be proposed with curative intent. After EBRT delivering 40 Gy a single dose of 20 Gy (pulses of 0.5 – 0.8 Gy every hour) is given. For monotherapy, when EBRT is not given, 2-3 fractions of 20 Gy (same schedule) are proposed [6].

After non radical resection 40-50 Gy in 2 -3 courses (PDR) can be applied (see 3D planning rules).

For palliative treatment 20 - 40 Gy in one or two courses are suggested. PDR BT is recommended for the trans-hepatic technique [8,11] at 10 mm from the source axis using 2D Planning or according to target depth using 3D Planning – see part 7.

When using HDR BT for palliative patients the dose commonly prescribed is 15-20 Gy at 10 mm depth in 3-4 fractions (4-5 Gy/fraction), generally over 2-3 applications.

Table 28.1
Results of combined EBRT and BT

Author	Number of patients	EBRT, dose	BT, number of fractions, fraction dose, method	Prescription depth	Results of treatment	Statistical analysis
Veeze-Kuijpers et al. [13]	42	30 Gy (15 fractions a 2 Gy), since 1985 – 40 Gy in 16 fractions of 2.5 Gy	^{192}Ir wire, 15 Gy/75 hours, 2 sessions (schedules changed for some patients)	dose prescribed at 10 mm	MS – 10 months, 15% of patients > 2 years	n.d.
Foo et al. [26]	24	50,4 Gy (median), 1.8 Gy/fraction	^{192}Ir seeds, 20 Gy (median)	BT – 20/24 dose prescribed at 10 mm, 2/24 – 5mm, 7.5 and 7,0 mm in 1/24 patient	MS – 12 months, (2 years) – 19 months (5 years) – 14 months	p=0.39
Fritz et al. [27]	30	30 – 45 Gy in 25 patients	HDR, 5 – 10 Gy fractions, total dose 20 – 45 Gy	dose prescribed at 10 mm	MS – 10 months, (2 yrs) – 18%, (5 yrs) – 8%	n.d.
Yoshioka et al. [33]	1. 153 2. 56	50 Gy (median), fractions 1.8 or 2.0 Gy	1. No 2. 18 Gy median (3 x 6 Gy fractions) HDR	2. 43/56 cases - dose prescribed at 10 mm, 4/56 – at 12 mm, 5/56 – at 5 mm	1. OS (2 yrs) – 40% DSS (2 yrs) – 41% LC (2 yrs) – 35% 2. OS (2 yrs) – 31% DSS (2 yrs) – 42% LC (2 yrs) – 65%	LC – p=0.094
Gonzalez et al. [40]	1. Group I – 41 (+ surgery), Group II – 19 (unresectable)	1. 45 Gy (median) 2. 48 Gy (median)	^{192}Ir wire 1. 10 Gy 2. 22 – 25 Gy	BT - dose prescribed at 10 mm	1. MS – 24 months 2. MS – 10.4 months	n.s.
Eschelmann et al. [43]	11	25 – 56 Gy, fractions 1.8-2.0 Gy	^{192}Ir wire 25 Gy (mean dose), 15 – 31 Gy	BT - dose prescribed at 10 mm	MS – 22.6 months	n.d.
Takamura et al. [44]	93	50 Gy, 25 fractions a 2 Gy	^{192}Ir wire 27 – 50 Gy (median 39.2)	BT - dose prescribed at 5 mm	MS 12 months OS (3yrs) 10% (5yrs) 4%	n.d.
Shin et al. [49]	1. 17 2.14	36 – 55 Gy (median 50.4)	1. No BT 2. 3 x 5 Gy HDR	BT - dose prescribed at 15 mm	1. RR – 53% 2. RR – 36% 1. MDC – 5 months 2. MDC – 9 months 1. OS (2 y) – 0% 2. OS (2 y) – 21%	RR – p>0.05 MDC – p=0.06 OS - p=0.015
Schleicher et al. [50]	1. 18 2. 12	median 30 Gy, 19 fractions a 1.6 Gy	1. No BT 2. median 40 Gy, 4 - 5 fractions, HDR	BT - dose prescribed at 5 mm	1. OS – 3.9 months 2.OS – 9.1 months	OS – p <0.05
Kamada et al. [51]	1. 42 2.103	. 40 – 50 Gy (median), fractions a 2.0-2.5 Gy	^{192}Ir wire 1. No BT 2. 25 Gy	BT - dose prescribed at 5 mm	1. MS – 4.3 months 2. MS – 9.3 months	n.d.
Ghafoori et al. [52]	1. 8 2. 23	30 – 62 Gy (median) – 45 Gy, fractions 1.8 to 3 Gy	^{192}Ir wire 1. Yes (median 25 Gy) 2. No BT	BT - dose prescribed at 5-10 mm	1. MS – (2 yrs) - 22 months (5 yrs) – 13 months 2. MS – (5 yrs) – 5 months	p=0,096

EBRT - external beam radiotherapy, BT – brachytherapy, HDR – high dose rate brachytherapy, LDR – low dose rate brachytherapy, RR – Recurrence Rate, MDC – Median Time to Tumor Recurrence, OS – Overall Survival, DSS - Disease-Specific Survival, MS – Median Survival; n.d. – no data, n.s. – no significant;

11. MONITORING

The most common complication is infection. Antibiotic prophylaxis should therefore be given before, during and after the procedure. BT does increase the risk of cholangitis and bleeding from inserting catheters into the biliary tract.

12. RESULTS

For patients with **unresectable** disease, many researchers have favoured EBRT with or without BT to prolong survival. In table 28.1 the patient cohorts are analysed groups are heterogeneous and small but there is a trend in these results. Most frequently overall median survival (OS) ranges from 10 to 15 months.

Improvement in survival was correlated with the use of BT with EBRT in some papers [10,38,39], but others have found no evident benefits [40].

A few studies have reported long-term survival for unresectable patients with the use of EBRT and BT boosts. EBRT, with or without BT, has also been reported to provide long-lasting palliation [41-43], including maintenance of stent patency for patients with locally advanced cancer [33,43-45]. Selection bias could have affected these results as well as the retrospective character of analysis.

In a recently published study by Yoshioka et al. [33] the results with BT on overall survival (OS), disease-specific survival (DSS), and local control (LC) were reported. The group comprised 209 patients, including 153 who underwent EBRT alone and 56 who received both BT and EBRT. It was concluded that in the treatment for unresectable biliary tract cancer, the addition of BT to EBRT has no impact on OS or DSS but is associated with better LC: the 2-year LC rates were 65% for the ILBT (+) group and 35% for the ILBT (-) group. Therefore, the role of BT should be assessed by measures other than survival benefit, for example benefit in toxicity, prolonged biliary tract patency decreasing the need for further palliative interventions, or benefit in quality of life.

Shinohara et al. [46] noted a survival benefit for BT in comparison between BT and no RT groups. T heir study cohort included not only unresectable but also postoperative patients. The median survival for patients treated with brachytherapy was 11 months (95% confidence interwal [CI] 9–13 months), compared with 4 months for patients who received no radiation ($p < 0.0001$).

A phase I/II dose escalation trial Included 18 patients with unresectable or subtotally resected extrahepatic biliary duct carcinoma who received 45 Gy EBRT with concurrent 5-FU chemotherapy and HDR brachytherapy, using either 1-, 2-, or 3-weekly fractions of 7 Gy. Median OS and 2-year survival rate was 12.2 months and 28%, respectively. Improved response was seen with increasing doses in the three groups (median survival 9 months vs. 12 months vs. 20 months) [47].

Chen et al. [48] evaluated the clinical effect on stent patency and patient survival in 34 patients with obstructive jaundice (14 treated with BT, 20 (group A) – control group (B)). HDR was used with 3 - 4 fractions of 4 - 7 Gy per fraction given every 3 - 6 days. Mean stent patency of group A (12.6 mo) was significantly longer than that of group B (8.3 mo) ($P<0.05$). There was a difference in the mean survival (9.4 months vs 6.0 months) between the two groups but this was not significant.

There are very few reports on BT monotherapy. Skowronek et al. published [8] results on 29 patients with bile duct cancer treated palliatively exclusively with PDR BT. In most cases 20 Gy using PDR BT was given (pulse 0.8 Gy every hour/at 1cm). In 19/29 (65,5%) cases clinical improvement with a decrease in jaundice was noted after 4 weeks. Median overall survival time (OS) for bile duct cancer patients was 11,2 months.

Taking into account the heterogeneity of the patient groups, different treatment indications and other uncontrolled factors, it is difficult to suggest improved survival for locally advanced patients receiving BT. The addition of BT to EBRT may be beneficial, achieving an increase in radiation dose to the primary tumour along the bile ducts, where the largest volume of gross disease exists.

13. ADVERSE SIDE EFFECTS

ILBT does increase the risk of cholangitis and bleeding due to inserting catheters into the biliary tract. As late complications bile duct stenosis or stricture are observed. The exact rate is unknown due to different cohorts of patients and treatment methods analyzed in published papers.

Acute complications of EBRT and ILBT include nausea, vomiting, and transient elevation of transaminase. These effects are usually mild and tolerable [3].

Late complications are associated with radiation dose to surrounding organs from EBRT. The most common complications are gastrointestinal bleeding, biliary bleeding, and duodenal stenosis. With external-beam doses of <55 Gy to the duodenum or stomach, the risk of severe gastrointestinal complications varies from 5% to 10%. At doses >55 Gy, one-third of patients develop severe problems [3].

14. KEY MESSAGES

- Brachytherapy has a potential benefit because it may enhance local control and prolong patency of the biliary tract, which may be associated with better QoL and also OS. Well-designed prospective trials should address the efficacy of brachytherapy.
- BT can be used as a palliative treatment to facilitate the flow of bile. For unresectable patients, the goal of treatment is prevention of locoregional disease progression to enhance survival and quality of life.
- BT can be applied as radical treatment alone in small inoperable tumours or in combination with EBRT with or without chemotherapy in advanced disease for unresectable patients.
- BT as adjuvant treatment alone after subradical excision may be combined with EBRT.

15. REFERENCES

1. Yoshioka Y, Ogawa K, Oikawa H et al. Factors influencing survival outcome for radiotherapy for biliary tract cancer: A multicenter retrospective study. *Radiother Oncol* 2014; 10: 546–552.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. *Ca Cancer J Clin* 2015;65:5–29.
3. Cheng SH, Huang AT. Liver and Hepatobiliary Tract - Chapter 57. In: *Perez and Brady's Principles and Practice of Radiation Oncology*, 5th Edition. Editors: Halperin, Edward C.; Perez, Carlos A.; Brady, Luther W. Lippincott Williams & Wilkins 2008.
4. Williams TM, Majithia L, Wang SJ et al. Defining the Role of Adjuvant Therapy: Cholangiocarcinoma and Gall Bladder Cancer. *Semin Radiat Oncol* 2014; 24: 94-104.
5. Baer HU, Stain SC, Dennison AR et al. Improvements in survival by aggressive resections of hilar cholangiocarcinoma. *Ann Surg* 1993; 217: 20-27.
6. Buskirk SJ, Gunderson LL, Adson MA et al. Analysis of failure following curative irradiation of gallbladder and extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1984; 10: 2013-2023.
7. Cameron JL, Pitt HA, Zinner MJ et al. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. *Am J Surg* 1990; 159: 91-97.
8. Skowronek J, Sowier A, Skrzywanek P. Trans-hepatic technique and intraluminal Pulsed Dose Rate (PDR-BT) brachytherapy in treatment of locally advanced bile duct and pancreas cancer. *J Contemp Brachyther* 2009; 1: 97-104.
9. Jabbour SK, Mulvihill D. Defining the Role of Adjuvant Therapy: Ampullary and Duodenal Adenocarcinoma. *Semin Radiat Oncol* 2014; 24: 85-93.
10. Fields JN, Emami B. Carcinoma of the extrahepatic biliary system - results of primary and adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 1987; 13: 331-338.
11. Skowronek J, Sowier A, Skrzywanek P. Intraluminal Pulsed Dose Rate (PDR) brachytherapy and trans-hepatic technique in treatment of locally advanced bile duct cancer – preliminary assessment. *Rep Pract Radioth Oncol* 2007; 2: 125 – 133.
12. Montemaggi P, Costamagna G, Dobelbower RR et al. Intraluminal brachytherapy (ILBT) in the treatment of pancreas and bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1995; 32: 437-443.
13. Veeze-Kuijpers B, Meerwaldt JH, Lameris JS et al. The role of radiotherapy in the treatment of bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1990; 18:63-67.
14. Hadjis NS, Blenkharn JI, Alexander N et al. Outcome of radical surgery in hilar cholangiocarcinoma. *Surgery* 1990; 107: 597-604.
15. Nagorney DM, Donohue JH, Faruell MB et al. Outcomes after curative resections of cholangiocarcinoma. *Arch Surg* 1993; 128: 871-879.
16. Adam A, Chetty N, Roddie M et al. Self-expandable stainless steel endoprostheses for treatment of malignant bile duct obstruction. *Am J Radiol* 1991; 156: 321-325.
17. Davids RHE, Groen AK, Rauws EAJ et al. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; 340: 1488-1492.
18. Shirabe K, Shimada M, Harimoto N et al. Intrahepatic cholangiocarcinoma: its mode of spreading and therapeutic modalities. *Surgery* 2002; 131: 159 - 164.
19. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* 1995; 75: 171 - 190.
20. Weinbren K, Mutum SS: Pathological aspects of cholangiocarcinoma. *J Pathol* 1983; 139:217 - 238.
21. Nakeeb A, Pitt HA, Sohn TA et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996; 224: 463 - 475.
22. Chung C, Bautista N, O'Connell TX: Prognosis and treatment of bile duct carcinoma. *Am Surg* 1998; 64: 921 - 925.
23. Minsky BD, Kemeny N, Armstrong JG et al. Extrahepatic biliary system cancer: an update of a combined modality approach. *Am J Clin Oncol* 1991; 14: 433 - 437.
24. Moerman CJ, Bueno-de-Mesquita HB: The epidemiology of gallbladder cancer: lifestyle related risk factors and limited surgical possibilities for prevention. *Hepatogastroenterology* 1999; 46: 1533 - 1539.
25. Morganti AG, Trodella L, Valentini V et al. Combined modality treatment in unresectable extrahepatic biliary carcinoma. *Int J Radiat Oncol Biol Phys* 2000; 46: 913 - 919.
26. Foo ML, Gunderson LL, Bender CE et al. External Radiation Therapy And Transcatheter Iridium In The Treatment Of Extrahepatic Bile Duct Carcinoma. *Int J Radiat Oncol Biol Phys* 1997; 39: 929 – 933.
27. Fritz E, Brambs H-J, Schraube E et al. Combined external beam radiotherapy and intraluminal high dose rate brachytherapy on bile duct carcinomas. *Int J Radiat Oncol Biol Phys* 1994; 29: 855-861.
28. Johnson DW, Safai C, Goffinet DR. Malignant obstructive jaundice: treatment with external-beam and intracavitary radiotherapy. *Int J Radiat Oncol Biol Phys* 1985; 11: 411- 416.
29. Fogel TD, Weissberg JB. The role of radiation therapy in carcinoma of the extrahepatic bile ducts. *Int J Radiat Oncol Biol Phys* 1984; 10: 2251-2258.
30. Gonzfilez DG, Gerard JR, Maners AW et al. Results of radiation therapy in carcinoma of the proximal bile duct (Klatskin tumor). *Sere Liver Dis* 1990; 10: 131-141.
31. Montemaggi P, Morganti AG, Dobelbower Jr RR et al. Role of Intraluminal Brachytherapy In Extrahepatic Bile Duct and Pancreatic Cancers: Is It Just for Palliation? *Radiology* 1996; 199: 861-866.
32. Dobelbowe, RR, Montemaggi P. Brachytherapy for pancreatic cancer: a review. *Hepatogastroenterology* 1996; 43:, 333-337.
33. Yoshioka Y, Ogawa K, Oikawa H et al. Impact of Intraluminal Brachytherapy on Survival Outcome for Radiation Therapy for Unresectable Biliary Tract Cancer: A Propensity-Score Matched-Pair Analysis. *Int J Radiation Oncol Biol Phys* 2014; 89: 822 – 829.
34. Yamaguchi K, Chijiiwa K, Saiki S, et al. Carcinoma of the extrahepatic bile duct: mode of spread and its prognostic implications. *Hepatogastroenterology* 1997; 44: 1256 - 1261.
35. Nori D, Parikh S, Sundararaman S, Heffernan M. Brachytherapy in the treatment of pancreas and bile duct cancer. In: Joslin CA, Flynn A, Hall EJ. Principles and Practice of Brachytherapy using afterloading systems. *Arnold, New York* 2001; 325 – 332.
36. Yoshida T, Aramaki M, Bandoh T, et al. Para-aortic lymph node metastasis in carcinoma of the distal bile duct. *Hepatogastroenterology* 1998; 45: 2388 – 2391.
37. Alden ME, Mohiuddin M. The impact of radiation dose in combined external beam and intraluminal Ir-192 brachytherapy for bile duct cancer. *Int J Radiat Oncol Biol Phys* 1994; 28: 945-951.
38. Ash D. Bile Duct Tumours - Chapter; 539-542. In: Gerbaulet A, Potter R, Mazeron J-J et al. (eds.) *The GEC ESTRO Handbook of Brachytherapy.* ESTRO: Brussels 2002.
39. Gerhards MF, van Gulik TM Gonzalez Gonzalez D et al. Results of postoperative radiotherapy for resectable hilar cholangiocarcinoma. *World J Surg* 2003; 27: 173-179.
40. Gonzalez Gonzalez D, Gouma D, Rauws E et al. Role of radiotherapy, in particular intraluminal brachytherapy, in the treatment of proximal bile duct carcinoma. *Ann Oncol* 1999;10:215-220.
41. Buskirk SJ, Gunderson LL, Schild S et al. Analysis of failure after curative irradiation of extrahepatic bile duct carcinoma. *Ann Surg* 1991; 215: 125-131.
42. Fritz P, Branbs H, Schraube P et al. Combined external beam radiotherapy in intraluminal high-dose-rate brachytherapy on bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1994; 29: 855-861.
43. Eschelman D, Shapiro M, Bonn J et al. Malignant biliary duct obstruction: Long-term experience with Gianturco stents and combined-modality radiation therapy. *Radiology* 1996; 200: 717-724.

44. Takamura A, Saito H, Kamada T et al. Intraluminal low-dose-rate 192Ir brachytherapy combined with external beam radiotherapy and biliary stenting for unresectable extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 2003; 57: 1357-1365.

45. Shinchi H, Takao S, Nishida H et al. Length and quality of survival following external beam radiotherapy combined with expandable metallic stent for unresectable hilar cholangiocarcinoma. *J Surg Oncol* 2000; 75: 89-94.

46. Shinohara ET, Guo M, Mitra N et al. Brachytherapy in the treatment of cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2010; 78: 722-728.

47. Lu JJ, Bains YS, Abdel-Wahab M et al. High-dose-rate remote after loading intracavitary brachytherapy for the treatment of extra hepatic biliary duct carcinoma. *Cancer* 2002; 8: 74-78.

48. Chen Y, Wang X-L, Yan Z-P et al. HDR-192Ir intraluminal brachytherapy in treatment of malignant obstructive jaundice. *World J Gastroenterol* 2004; 10: 3506-3510.

49. Shin HS, Seong J, Kim WC et al. Combination of external beam irradiation and high-dose-rate intraluminal brachytherapy for inoperable carcinoma of the extrahepatic bile ducts. *Int J Radiat Oncol Biol Phys* 2003; 57: 105–112.

50. Schleicher UM, Staatz G, Alzen G et al. Combined External Beam and Intraluminal Radiotherapy for Irresectable Klatskin Tumors. *Strahlenther Onkol* 2002; 178: 682–687.

51. Kamada T, Saitou H, Takamura A et al. The role of radiotherapy in the management of extrahepatic bile duct cancer: an analysis of 145 consecutive patients treated with intraluminal and/or external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 1996; 34: 767–774.

52. Ghafoori AP, Nelson JW, Willett CG et al. Radiotherapy in the treatment of patients with unresectable extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2011; 81: 654-659.

ACKNOWLEDGEMENTS
Thanks to Dan Ash as author of the chapter edition in 2002 and the editors for a thorough analysis and valuable comments.

AUTHOR
Janusz Skowronek, MD, PhD
Head of Brachytherapy Department,
Greater Poland Cancer Centre, Poznań,
Professor in Electroradiology Department,
Poznan University of Medical Sciences,
Poznań, Poland