Extrahepatic Bile Duct Cancer: A Review

RUSSELL G. POSTIER, MD
ROBERT A. RANKIN, MD
G. RAINNEY WILLIAMS, MD

Extrahepatic bile duct cancer causes death in most cases by bile duct obstruction. Effective means of achieving bile duct drainage are now available and have increased our ability to extend palliation and increase chances for cure in these patients.

Extrahepatic bile duct cancer is uncommon and is often misdiagnosed and inadequately treated. Even when treatment is optimal, the disease is associated with significant morbidity and mortality. Better understanding of the major causes of morbidity and newer surgical techniques for long-term internal biliary tract decompression have resulted in improved results and have prompted this review.

History

In 1840, Durand-Fardel first reported an extrahepatic bile duct cancer in man and, 38 years later, Schueppel described hepatic duct carcinoma. In 1940, Stewart and associates reviewed the world literature up to 1936 and were able to find 104 cases with history and microscopic study sufficient to establish the diagnosis of cancer of the extrahepatic bile ducts. Sako, et al, in 1957, reported an additional 570 cases gleaned from the world literature from 1935 to 1954.

The operative history of bile duct cancer begins with Hesper, who, on June 28, 1892, opened and closed a patient with a cancer of the confluence of the bile ducts. The second operation for bile duct cancer, a cholecystostomy, was performed on the same patient by Hesper two days later. This patient died eight days after his first operation.

Since that time, other methods of operative treatment have been described. Total excision of a proximal bile duct cancer with inser-
tion of a radium implant was first reported by Walters and Olson in 1935.4 Pancreaticoduodenectomy for pancreatic carcinoma was first performed by Whipple in 1935 and subsequently was used in treating distal bile duct cancer.5 Transhepatic stenting, described by Goetze in 1951, was used in the 1960s by Prad-eri as palliative treatment of bile duct cancer.6,7

Epidemiology
Cancer of the bile ducts is present in approximately 0.5% of patients coming to autopsy.3 The average age at diagnosis is 59.2 years with a range of 20 to 89 years. The male to female ratio is 3:2.4 Although the etiology is unknown, several interesting associations have been noted. Gallstones are found in 20% to 57% of patients with bile duct cancer, numbers higher than those in a comparable age group without bile duct tumors.5,8 Ulcerative colitis is associated with an increased incidence of cancer of the bile ducts. In a review of 200 patients with ulcerative colitis at the Johns Hopkins Hospital, 2 had associated bile duct cancer.9 Conversely, of 103 patients with bile duct cancer in a report by Ross, et al, from the Lahey Clinic, 8 had associated ulcerative colitis.10 The concurrence of ulcerative colitis and bile duct cancer appears to be greater than would occur by chance, and the risk of bile duct cancer in patients with ulcerative colitis does not appear to be affected by proctocolectomy.9

Choledochal cysts are associated with a 9% to 24% incidence of bile duct carcinoma. Patients with choledochal cysts who develop bile duct cancer tend to do so at an earlier age than those without choledochal cysts.11,12

There are also reports of an association between bile duct cancer and colon cancer, familial polyposis, and biliary papillomas, but these occurrences are probably coincidental.10,13,14

Pathology
The pathological classification of bile duct cancers is not well standardized and, as a result, the literature contains numerous heterogeneous and inconsistent classifications. A simple way to group these tumors is based on their gross and microscopic appearance. By gross appearance, tumors can be divided into three categories: nodular, infiltrating, and papillary. The importance of the macroscopic characteristics of the tumors is emphasized in the Japanese report of Todoroki, et al. Four of 23 patients studied had papillary tumors, all of which were amenable to surgical resection; all patients were alive and free of disease at 30 to 62 months after surgery.15 Tumors are placed in four descriptive histologic categories: adenocarcinoma, infiltrating scirrhus carcinoma, papillary adenocarcinoma, and anaplastic carcinoma, each of which can be further categorized as well differentiated, moderately well differentiated, and poorly differentiated.16

The anatomic location of bile duct tumors has been emphasized as important in both treatment and prognosis and is divided into three areas: (1) the upper region, including the left and right hepatic ducts, their confluence, and the proximal common hepatic duct; (2) the common hepatic and common bile duct in the region of the cystic duct; and (3) the distal common bile duct above the ampulla of vater. The relative frequency with which tumors occupied these locations was studied by Sako in a series of 500 site-specified lesions. One hundred twenty-six were in the upper portion, 171 in the middle portion, and 203 in the lower portion.8

Clinical Presentation
The clinical presentation of carcinoma of the bile ducts has been defined in several series. The Cleveland Clinic series is representative, and findings from it are summarized. Jaundice was the most common clinical finding and occurred in 89% of the patients. Hepatomegaly occurred in 59%. Weight loss of greater than 10 pounds occurred in 53% of the patients. Pain, located in the epigastrium or right upper quadrant, occurred in 39%. The gallbladder was palpable in only 4% of the patients. Only 10% of the patients had fever or chills attributable to cholangitis, making this a relatively rare finding. Laboratory findings of note are those of obstructive jaundice. Elevated alkaline phosphatase and bilirubin levels were present in greater than 95% of the cases. Decreased serum albumin level was seen in 50% of the cases. A prolonged prothrombin time, usually correctable with vitamin K, was found in approximately one-third of the cases.

Diagnosis
Careful history, physical examination, and liver enzyme measurements will usually support the presumptive diagnosis of obstructive jaundice. Further studies are required to de-
Extrahepatic (continued)

tive choledochoenterostomy should be carried out with or without gastroenterostomy, depending on the degree of duodenal invasion. In selected patients, pancreaticoduodenectomy may be preferable for palliation since the operative mortality rate for both bypass and pancreaticoduodenectomy is approximately 5% to 10%.20

Mid-Duct Tumors (Common bile duct near cystic duct take-off). Tumors of the middle portion of the bile ducts, if small and resectable, may be treated by local excision and hepaticojjunostomy if adequate margins can be obtained distally. This is particularly appropriate for the sclerosing carcinoma initially

Gallstones are found in 20% to 57% of patients with bile duct cancer.

emphasized by Altemeier, et al, in 1957.21 This tumor is easily overlooked because it is not a bulky lesion. Any mid- or proximal duct stenosing lesion should be biopsied during surgery to ensure that this rather innocuous-appearing lesion is not overlooked. If adequate distal margins cannot be obtained, pancreaticoduodenectomy should be carried out.22,23 For unresectable lesions, transection of the common hepatic duct above the lesion with hepaticojjunostomy, usually with transhepatic stenting, should be performed.24 Examination of frozen sections may be necessary to define upper extension of the tumor.

Proximal Tumors (Hepatic duct at its bifurcation, or left or right hepatic duct). Proximal bile duct cancers have long been recognized as being different from the more distally placed tumors with regard to rate of growth and propensity to early metastasis. Credit for this recognition is generally given to Gerald Klatskin because of his detailed study of 13 cases reported in the American Journal of Medicine in 1965.24 However, Stewart, Lieber, and Morgan, in the Archives of Surgery in 1940, reported 48 cases of proximal bile duct cancer in which the disease was still localized

with subsets in the latter

tonsils have a moss condensate in the middle and bile into the ac

parenchyma would be indicated.

Y-tubed as the lin

migration of their sludge

Th overcoun for tr

by Smi
dilatation of th

fluoroscopic distal e

through transhe

for pati

cannot be t

It may b

each heq

OKLAHOMA STATE MEDICAL ASSOCIATION
without metastases at the time of death and subsequent autopsy in 54%. The cause of death in the majority of their patients was not metastatic disease or direct invasion of other structures, but unrelated biliary tract obstruction. They stated, "Generally speaking, then, symptoms appear early, the neoplasm is slow growing and metastases occur late... Early diagnosis and early operation while the patient's condition is not yet critical yield vastly more satisfactory results... Although the surgeon has a limited field in which to work, in a number of cases cited resection of the primary neoplasm followed by re-establishment of biliary flow by implantation of the hepatic duct into the gastrointestinal tract was satisfactorily accomplished."  

From this and many reports since, it is apparent that the potential for long-term palliation existed if techniques were developed that would allow for long-term biliary drainage. There also existed the potential for cure if more radical resections were employed. T-tube or Y-tube intubation of these tumors was attempted as palliation with variable success, primarily limited by the tendency for these tubes to migrate into the distal biliary tree, as well as their propensity to become occluded by biliary sludge.

These problems were at least partially overcome by the development of the technique for transhepatic stenting suggested by Goetz in 1951 and Praderi in 1961, and popularized by Smith in 1964. This technique allows for dilation of the tumor from below and placement of a silastic tube with side holes through the tumor into the peripheral bile duct, through the liver parenchyma, and out through the skin. The lower end of the stent is either placed in the distal common bile duct or brought into a Roux-en-Y loop of jejunum which is anastomosed end-to-side into the bile duct below the tumor. This allows for long-term decompression of the biliary tree with a firm but relatively inert tube which can be changed as needed over a guidewire under fluoroscopic control. Others have brought the distal end of the stent out the jejunal loop and through the skin as a U-tube. Placement of transhepatic stents is the procedure of choice for patients with locally unresectable tumors or tumors with nodal or liver metastases which cannot be encompassed in an en bloc resection. It may be preferable to pass two tubes, one into each hepatic duct, if this is done. There is some evidence that radiotherapy given by external beam and iridium seeds placed within the lumen of the transhepatic stents add significantly to the length of survival.

In rare cases, scarring from previous surgery or masses of nodes will make dissection of the porta hepatis difficult and dangerous enough to preclude dilation of the tumor and passage of transhepatic stents from below. In such cases the Longmire procedure can be used to establish biliary drainage. This procedure will normally allow the return of liver function test results to near normal even if only the left lobe of the liver is drained. A modification of the Longmire procedure (percutaneous placement of a catheter into the peripheral portion of the left hepatic duct to facilitate operative location of this duct) has been developed which decreases the technical difficulty of the procedure.

Another technique for management of these cases is cholangiojejunostomy between the bile duct in segment III, identified just to the left of the falciform ligament, and a Roux-en-Y jejunal limb. This technique, described by Bismuth and Corlette, is advocated by Malt and appears to be an alternative to the Longmire procedure.

As greater experience has developed and more radical approaches have been tried, more localized tumors high in the porta hepatitis have been found to be resectable for potential cure. Usually a core of liver tissue is excised in the porta hepatitis surrounding the right and left hepatic ducts, with care taken to avoid the portal vein branches. The common bile duct is then transected below the tumor with the distal duct ligated. Using upward traction on the proximal end of the transected bile duct, the bile duct with tumor is dissected proximally to a point above the uppermost extent of tumor in each hepatic duct and transected. Each hepatic duct is then anastomosed to a single Roux-en-Y jejunal loop using a transhepatic stent. Postoperative external beam radiotherapy, as well as iridium seeds placed within the stents, can be used in an at-
Extrahepatic (continued)

tempt to further increase the chance for cure or long-term palliation. As experience has increased with both palliative and potentially curative operations for proximal bile duct cancer, the operative mortality rate has fallen to under 5%. 20

Prognosis

The outlook for this once uniformly fatal disease is now improved and depends on the anatomic location, extent of local spread, and gross and microscopic appearance of the tumor. For distally placed tumors, the 5-year survival rate after pancreaticoduodenectomy for cure is approximately 30%, with an average survival time of 3.2 years. For this same group of patients, in whom resectable disease is present but who underwent only bypass, the 5-year survival rate is 0 and the mean survival time is 1.4 years.20

For patients with tumors of the middle portion of the bile ducts who are resected for cure, the 5-year survival rate is about 31%. One patient in Longmire's series died of intra-pancreatic recurrence 11 years after resection for cure; thus, 5-year survival rates with this disease probably do not indicate cures. Average length of survival in this group of patients with locally unresectable disease who undergo palliative bypass is less than 1 year.23

The results of therapy for proximal bile duct tumors are clearly improving. In Stewart's 1940 study, the overall mean survival time of this group of patients was 4.6 months, with the patients who were operated surviving 7.6 months.2 In Klatskin's study, 12 of 13 patients died of their disease; the mean survival time was 15.5 months. All those who died did so as a result of hepatocellular failure.24 In Cameron and Broe's recent review of the Johns Hopkins experience with 25 patients, the mean survival time (with 10 patients still alive) is 16.5 months. In 32% of their patients, all gross tumor was removed at operation, allowing for potential cure. External radiotherapy combined with internal iridium seeds was used in most cases.26 Long-term survival after palliative intubation of these tumors with transhepatic stents is not uncommon, with some authors reporting patients alive more than 5 years after surgery.27 The key element in palliative therapy is adequate biliary decompression, which is best accomplished with transhepatic stenting of both the right and left ductal system.

Summary

Extrahepatic bile duct cancer is a relatively uncommon disease that, in the majority of cases, results in death by biliary tract obstruction. The operative approach to these lesions is difficult and demanding but can result in significant palliation in most cases and a potential for cure in many.

References

21. Altemeier WA, Gall JA, Zinzinger MM, Hazworth PJ: Staining of carci-

Oklahoma State Medical Association
of the abdominal not pa-
dest of ur-
ety of uc-
ig-

Russell G. Postier, MD, Department of Surgery, University of Oklahoma Health Sciences Center, PO Box 26307, Everett Building, Room 2005, Oklahoma City, Oklahoma 73126.

This is a valuable little work worth more than its price to the busy practitioner.

Appendicitis and Diseases of the Vermiform Appendix. By Howard A. Kelly, M.D., with 215 original illustrations, some in colors and three lithographical plates. This is a handsome octavo volume of over 500 pages, published by J. B. Lippincott Company, Philadelphia. Price, cloth $6.00 net.

This work is a compact resume dwelling with especial care on the practical side of the subject of Appendicitis and other diseases of that useless organ. The book treats of the Etiology, Pathology, the differential diagnosis, the treatment before operation and the post-operation treatment and in fact almost anything that the reader cares to know about the subject. The illustrations are the very best that can be made, and the book taken as a whole is one of the most useful of modern books.

—Journal of the Oklahoma State Medical Association April 1909