



Internal Radiation for Bile Duct Cancer

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The clinical course of 27 patients with bile duct cancer who received intraductal exposure to ^{192}Ir was reviewed. All patients exhibited evidence of biliary obstruction prior to diagnosis of cancer and all underwent intubation for relief of obstruction either by surgical or radiologic methods. The patients then received either internal irradiation alone or the combination of internal plus external irradiation. The patients lived an average of 11.5 months following internal irradiation and 13.5 months following diagnosis. Patients who received both internal and external irradiation lived longer than those who received internal irradiation alone. The 3 patients who had resection of their primary tumors lived longer than the group as a whole. All patients continued episodes of mild or severe cholangitis following irradiation. The heterogeneity of patient material, pretreatment methods, and lack of controls preclude any statement concerning effectiveness of radiation therapy for bile duct cancer. A few patients may benefit from the therapy, and use of irradiation techniques as an adjuvant modality is worth continued investigation; however, while internal irradiation for local control of proximal bile duct tumors remains theoretically attractive, there remains little evidence of its efficacy.

Extrahepatic bile duct cancer exhibits several characteristics which set it apart from other intraabdominal adenocarcinomas. The tumor mass usually remains small throughout the course of the disease and infrequently spreads to other anatomic sites. It commonly extends directly along bile ducts by intramural invasion but infrequently metastasizes extensively to the liver, lung, bone, peritoneal surfaces, and other locations. Bile duct cancer kills by producing biliary obstruction, which leads to liver failure, sepsis, hemorrhage, or some combination of the three.

While bile duct cancers are usually small, slow growing, and anatomically confined, the surgical treatment of this carcinoma produces surprisingly few 5-year survivors. The overall 5-year survival rate is about 20%, and is considerably less [1] for proximal or hilar tumors. The principal reason for this is the failure to achieve local control, particularly for hilar tumors with involvement of secondary or tertiary hepatic duct radicals. Local recurrence is a problem even after resection of all gross tumor or after liver transplantation. Because surgical treatment frequently failed to accomplish either local control or cure of

bile duct cancer, several years ago it seemed reasonable to use internal irradiation either alone or in combination with external radiation therapy to see if this modality might enhance the quality or quantity of life of victims of bile duct cancer. This article is an analysis of those patients with this tumor who received internal irradiation at our institutions since it was first proposed.

Methods

We reviewed the hospital records of patients with bile duct cancer whose treatment included internal exposure to ^{192}Ir , either alone or in combination with surgical excision administered at Duke University Medical Center or Durham Veterans Administration, Durham, North Carolina, or University of Virginia Medical Center, Charlottesville, Virginia, U.S.A. between 1980 and 1986. All patients received iridium 3,000-5,000 rads via biliary tubes according to the method described by Herskovic et al. [2] (Figs. 1, 2). External radiation was also administered to the liver in most patients in doses ranging from 3,000 to 4,500 rads. Patient follow-up was 100%.

Material

In all, 27 patients with bile duct cancer received intraductal exposure to iridium since 1980. Seventeen patients were treated at Duke University Medical Center, at University of Virginia, and at the Durham Veterans Administration Hospital. Eighteen patients were female and 9 were male, ranging in age from 38 to 84 years.

All patients except 2 who received irradiation had exhibited abdominal pain, nausea, and jaundice leading to the diagnosis and treatment of bile duct cancer. Four patients had previously undergone cholecystectomy a period of years prior to diagnosis of bile duct cancer. One patient also previously had a sphincteroplasty. Eighteen of the 27 patients had been operated on or received a percutaneous biliary tube immediately prior to referral to our institutions for further therapy. Thirteen of the 16 had the diagnosis of extrahepatic bile duct cancer established by biopsy at laparotomy or percutaneous aspiration cytology prior to referral. Pathology or cytopathology of all patients were either confirmed or initially diagnosed at our institutions. Twelve patients had the diagnosis of carcinoma established by percu-

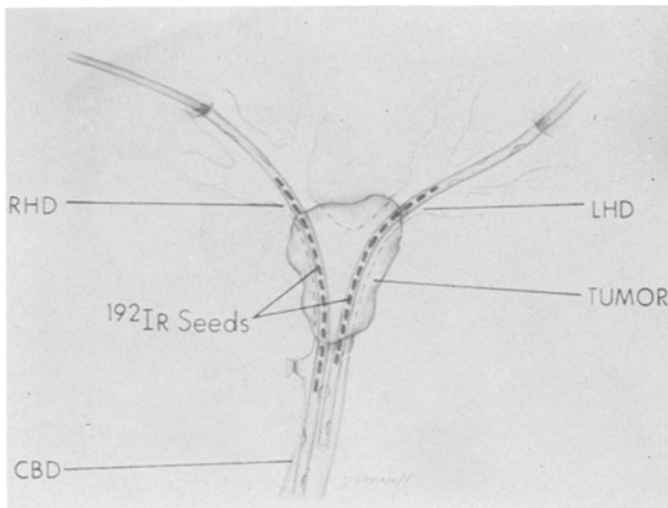


Fig. 1. Schematic diagram of placement of ^{192}Ir seeds for bile duct cancer located at the bifurcation of the ducts using bilateral transhepatic tubes. RHD = right hepatic duct, LHD = left hepatic duct, CBD = common bile duct.

taneous needle aspiration, 3 by examination of the biliary tube aspirate, and 1 by examination of samples obtained during endoscopic cannulation of the bile duct.

All 27 patients had transhepatic stents placed percutaneously by radiologic or surgical methods prior to radiation therapy. Four patients were referred with t-tubes in place; after placement of transhepatic stents, the t-tubes were removed in 3 of these 4 patients. Twenty-one patients were jaundiced at the time of application of radiation therapy.

Twenty-three of 27 patients had the common hepatic duct or one or both lobar ducts involved with tumor, demonstrated by transhepatic cholangiography. Three patients had lesions in the distal common duct and 1 patient initially had a lesion at the hepatic duct bifurcation, which was successfully treated with irradiation, and subsequently had a recurrence or second primary lesion in the distal duct. Resection was accomplished in 3 patients prior to irradiation. In all other patients the lesions were deemed unresectable by the operating surgeon or after review of the transhepatic cholangiograms and/or arteriography. Six patients did not undergo surgery either because of the extent of disease or associated medical problems or both. Two patients who had had both surgery and irradiation also underwent chemotherapy consisting of 5-fluorouracil, adriamycin, and mitomycin C according to the regimen of Harvey et al. [3].

Results

Twenty-one of 27 patients were jaundiced at the time of application of radiation therapy. All had some relief of jaundice and/or pruritis following transhepatic intubation. The patients lived an average of 13.5 months (range 2–58 months) from the time of diagnosis until death. At the time of last follow-up, 24 patients were dead and 2 were living. Internal radiation was administered an average of 2 months (range 1–10 months) after diagnosis. The patient who had internal radiation given 10 months after diagnosis had undergone resection of her tumor

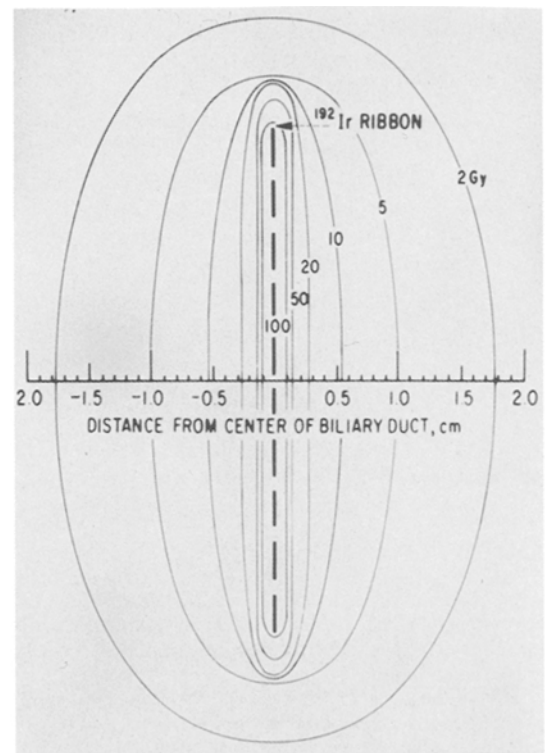


Fig. 2. Diagram depicting the area of transmission of the radiation from the tube, with 90% of the radioactivity occurring within 0.5 cm radius of the source. ^{192}Ir = $^{192}\text{Iridium}$.

and returned with a large supraclavicular lymph node that contained tumor as well as multiple other nodules documented by computed tomography. Irradiation was administered because of extensive local recurrence as well. She lived for 5 more months as an outpatient.

Patients lived an average of 11.5 months (range 1–58 months) following internal irradiation. Five of the patients did not receive external irradiation, i.e., received internal irradiation only. Those patients who received internal irradiation only lived an average of 3.6 months compared to 14.3 months for the patients who received internal plus external irradiation. The internal irradiation only group lived an average of 6.4 months from the time of diagnosis until death compared to 15.5 months for the combined radiation group. Six patients did not undergo any kind of surgical procedure. These lived 1, 1, 4, 4, 9, and 16 months from the time of internal irradiation until death, with an average survival of 5.8 months compared to 14.1 months for the rest of the group. One patient received irradiation of a proximal tumor which completely disappeared on computed tomographic scan and cholangiogram but developed a recurrence or second primary in the distal duct. This lesion also responded to internal irradiation although the patient lived only 16 months from the time of initial irradiation.

At some point during follow-up, all patients had fever and symptoms attributed to cholangitis. Twenty-one of the 27 patients had episodes following irradiation of severe cholangitis, suggesting septicemia. Four patients had severe hemobilia with 2 requiring blood transfusions near the terminal stage of their illness. Nine patients had evidence of small or large

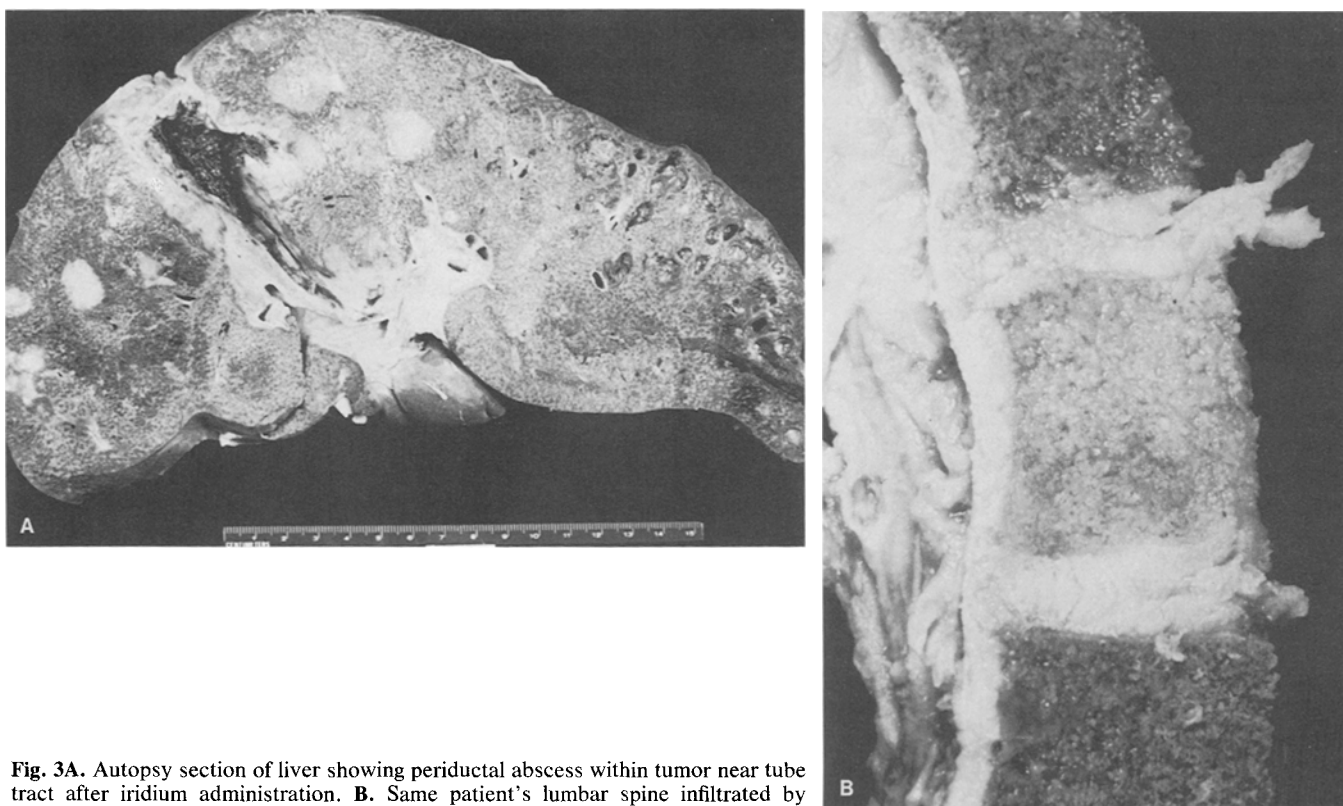


Fig. 3A. Autopsy section of liver showing periductal abscess within tumor near tube tract after iridium administration. **B.** Same patient's lumbar spine infiltrated by metastatic bile duct cancer.

periductal abscesses and tumor near the location of the iridium implant (Fig. 3). The most serious complication was a subhepatic abscess and choledochoduodenal fistula. That patient died of septicemia due to multiple hepatic abscesses and a necrotic subhepatic activity was confirmed at autopsy. The 2 patients who received chemotherapy died within 1 month of drug administration.

The 3 patients who had their tumors resected lived for 8, 15, and 53 months postoperatively. One resected patient mentioned above received irradiation 10 months after resection after evidence of local recurrence. The other 2 patients received internal radiation soon after surgery. The 2 patients who are living both have persistent or recurrent hepatic disease.

Discussion

Although extrahepatic bile duct cancer occurs relatively infrequently in North America, it comprises a significant portion of biliary disease in other parts of the world, particularly Asia. Nonetheless, physicians and surgeons who treat jaundiced patients will undoubtedly encounter bile duct cancer. In the United States, 1–2 of every 200 biliary operations involves extrahepatic ductal cancer. Jaundice remains the principal clinical manifestation of bile duct cancer, and its diagnosis should be considered in any jaundiced patient, particularly in the elderly. Ultrasound examination disclosing unequivocal intrahepatic bile duct dilatation and no evidence of extrahepatic dilatation suggests malignant obstruction of the proximal ducts. Percutaneous transhepatic cholangiography is generally recom-

mended because it accurately detects and localizes extrahepatic bile duct cancer. In addition, percutaneous cholangiography and, more recently, endoscopic techniques offer the option of internal drainage using placement of an internal drain through the obstruction into the duodenum. Curative resection of these tumors is uncommon but surgery offers the only chance at cure and removal of all gross tumor probably provides the longest survival. Local recurrence, however, is the rule, causing repeated episodes of cholangitis ultimately leading to liver failure, sepsis, hemorrhage, and death.

In 1981, Herskovic et al. [2] introduced intraductal ^{192}Ir as a therapeutic approach for bile duct cancer. Iridium emits radiation of such intensity that it penetrates only approximately 0.5 mm from the source into surrounding tissues. The iridium wire can be positioned through a percutaneous ductal tube into the region of the tumor. This technique has been modified using the technique of Karani et al. [4]. This therapy is generally well tolerated and produces minimal short- or long-term side effects. Other methods of irradiation have also been used including external beam and intraoperative electron therapy.

Two reasonable strategies exist for the application of radiation to bile duct cancer. One is for this to be the primary therapeutic modality of tumor ablation in patients who have surgically unresectable disease or who are otherwise unfit for surgery. The second is as an adjuvant to surgical excision. The average survival following use of internal irradiation in this study was only slightly more than 11 months. The patients who had internal irradiation combined with external beam irradiation lived over 10 months longer than those who had internal

Table 1. ¹⁹²Iridium therapy for bile duct cancer: A review of the literature.

Reference	No. of patients	Internal radiation	External radiation	Results
Herskovic et al. [2], 1981	6	5,000 rads	–	Tumor disappeared in 1, tumor reduction in 5.
Chitwood et al. [12], 1982	10	5,000 rads	3,000–5,000 rads	5 alive 1–12 mo after radiation, 5 died after 3–4 months
Fletcher et al. [11], 1983	19 (1 gallbladder cancer)	4,470 rads (mean)	–	9 alive, mean survival 11 mo (range 4–38)
Mornex et al. [14], 1984	7	10–60 Gy	20–50 Gy (4 patients)	4 alive, mean survival 8.2 mo (range 1–19)
Buskirk et al. [15], 1984	5	2,000–2,500 rads	4,500–5,000 rads	? 4 alive (may have had intraoperative radiation)
Johnson et al. [13], 1985	7	3,100–10,647 Gy	4,000–5,500 Gy	3 alive, mean survival 8.3 mo
Karani et al. [4], 1985	30 (23 histologically proven)	4,000–5,000 Gy	–	11 alive, mean survival 16.8 mo (range 1–66)
Present series, 1987	27	3,000–5,000 rads	3,000–5,000 rads (21 patients)	2 alive, mean survival 11.5 mo (range 1–58)

irradiation only. The patients who lived longest were those who had radiation therapy given in conjunction with surgical resection. This report contains no control subjects and it is clear that the decision to administer radiation was highly individualized according to the amount of tumor, degree of obstruction, and the patient's clinical condition. It is therefore impossible to evaluate with certainty the role of radiation therapy in this group of patients. All of the patients except 3 had proximal or hilar adenocarcinoma of the extrahepatic bile ducts and therefore represented a poor prognostic group because of that tumor location. Tompkins et al. [5] reported a median survival of 8.9 months for their group of patients with cancers in the upper third of the bile duct who were treated by excision, stenting, or biopsy alone, without radiation therapy. Therefore, no difference in survival or, at the most, several months, was seen between these groups of patients.

At present, no definite evidence exists to suggest efficacy of radiation therapy for bile duct cancer. External beam treatment [6] suffers the drawback that surrounding normal tissues may be injured in an effort to administer tumor site dosage. One of the first reports on this appeared in 1973 and describes 4 patients who survived 17 months following cobalt therapy [7]. More recently, reports, including one from Japan, documented shorter survival. Hishikawa et al. [8] treated 25 patients who had a mean survival of 9.2 months, although 1 patient was alive 6.5 years following irradiation. Nineteen of those patients underwent percutaneous transhepatic drainage, 3 underwent t-tube stenting, and 3 had no intubation. The 1 long-term survivor did not have pathologic documentation of the tumor. Fogel and Weissberg [9] reported a 5-year survival rate of 6% in an experience with 34 patients with a median survival of 11 months. Todoroki et al. [10] reported 5 patients treated with intraoperative radiation with the average survival of 9.5 months and 2 patients reported living 16 and 18 months following treatment.

The principal advantage of ¹⁹²iridium therapy is that it can be given with low morbidity and relatively little inconvenience to the patient. The principal deterrent to enthusiastic application of this therapy is the lack of evidence of efficacy. Only a modest, if any, increase in survival has been documented using this modality (Table 1). Fletcher et al. [11] and Chitwood et al. [12] reported some early clinical results of this therapy. Fletcher et

al. described 8 patients aged 28–67 years and 6 were alive an average of 12 months after therapy (range 2–23 months). Two had died 6 and 22 months following therapy. None of these patients underwent external beam therapy and all had received tumor stenting. Chitwood et al. reported 10 patients who received iridium with or without external beam irradiation and saw several long-term survivors, which seemed encouraging. Several more recent reports have also suggested a modest increase in survival. Johnson et al. [13] treated 7 patients with common hepatic duct tumors aged 41–82 years with a combination of external and internal irradiation. External dosage ranged from 2,100 to 5,400 rads and internal iridium ranged from 3,100 to 6,012 rads. They reported survivals ranging from 7 to 30 months and 3 patients were alive at the time of their report. Mean survival was 15.4 months. Mornex et al. [14] similarly treated patients with a combination of external and internal irradiation and 4 of their 7 patients were living at the time of the report with an observed survival of 1.5–23 months.

Buskirk et al. [15], Mayo Clinic, Rochester, Minnesota, U.S.A., treated 16 patients with extrahepatic bile duct cancer with external irradiation. Five received transcatheter iridium and 2 underwent intraoperative electron therapy. Five of the 16 patients were alive at the time of the report and the median survival was 18 months. Four of the 5 patients treated with transcatheter iridium or intraoperative therapy were without evidence of disease. Local failure was documented in only 1 of the 7 patients. The authors concluded that radiation may permit local regional control of bile duct cancer although it was not clear whether survival was enhanced.

Karani et al. [4] treated 30 patients with hilar bile duct cancer with internal biliary drainage and iridium between 1978 and 1984. Positive histologic confirmation of the tumor was obtained in 23 of the patients. Four thousand to 5,000 cGy was given over a 48-hour period. Twenty-one patients survived more than 1 year and 5 survived more than 2 years. The overall mean survival was 16.8 months with a range of 1–66 months. Mean survival was 19.1 months in a selected group of 23 patients with positive histology. Nineteen patients had died from effects of local tumor progression in this study. It was implied that none of the patients underwent even an attempt at resection so that a more favorable group of patients might be included in this review.

Evident from the present review were the 3 patients who

underwent resection and who lived longer than the rest of the group as a whole. Each of these patients developed widespread metastatic disease prior to death (Fig. 3). This was in contrast to most of the other patients whose disease was confined principally to the bile duct system. Based on this observation and our review of all the patients with bile duct cancer, we propose the following outline for treatment of patients with hilar bile duct cancer. If the patients are deemed fit for surgery, one must ask whether the lesion can be removed. This question was studied in detail using cholangiography, arteriography, portography, and computed tomographic scanning; the predictability of resectability of hilar carcinoma was high but not infallible [12, 16]. One must therefore conclude that the ultimate test for surgical resectability remains an attempt at surgical resection. Unfortunately, this approach remains inefficient because resectability rates for hilar carcinoma remain low, in the range of 20–30%. The use of radiation therapy as an adjunct to surgical excision of extrahepatic bile duct carcinoma remains theoretically appealing but, unfortunately, convincing evidence of the efficacy of this therapy is also lacking.

In the present report as well as the others, the heterogeneity of patient material, treatment methods, and lack of controls preclude any statement concerning effectiveness of radiation therapy for bile duct cancer. The natural history of the disease with transhepatic stenting is highly variable although most patients succumb in a relatively short period of time, usually months. A few patients may live as long as 2 years with stenting alone and further confound the evaluation of the various forms of therapy.

Résumé

L'évolution clinique de 27 malades atteints de cancer biliaire qui furent traités par irradiation intra-canalair avec de l'iridium¹⁹² a été analysée. Tous les malades présentaient un ictère par obstruction avant que fut porté le diagnostic de cancer et tous furent traités par intubation pour agir sur l'obstruction soit par des méthodes chirurgicales, soit par des méthodes radiologiques. Les malades alors furent traités par irradiation interne ou par l'association d'irradiation interne et d'irradiation externe. La durée de survie fut en moyenne de 11.5 mois après irradiation interne et de 13.5 mois après le diagnostic. Les malades qui furent traités par irradiation interne et externe vécurent plus longtemps que ceux traités par irradiation interne isolée. Les 3 malades dont la tumeur avait été résectionnée survécurent plus longtemps que les autres. Après irradiation tous les malades présentèrent des épisodes modérés ou sévères d'angiocholite. Le caractère hétérogène du groupe de malades, les diverses méthodes pré-thérapeutiques et le défaut d'un contrôle rigoureux ne permettent pas de définir la réelle efficacité de l'irradiation pour traiter le cancer biliaire. Quelques malades peuvent tirer quelque bénéfice de l'irradiation et les différentes techniques de ce traitement complémentaire méritent d'être encore étudiées. Cependant, si l'irradiation interne pour traiter les tumeurs du segment supérieur de l'arbre biliaire reste attirante, son efficacité n'est pas évidente.

Resumen

La evolución clínica de 27 pacientes con cáncer de la vía biliar que recibieron exposición intraductal a iridio¹⁹² fue revisada.

La totalidad de los pacientes exhibía evidencia de obstrucción biliar con anterioridad al diagnóstico de cáncer y todos fueron sometidos a intubación para el manejo de la obstrucción por métodos quirúrgicos o radiológicos. Los pacientes recibieron luego irradiación interna sólo, o la combinación de irradiación interna y externa. La supervivencia promedio fue de 11.5 meses a partir de la irradiación interna y de 13.5 meses a partir del diagnóstico. Los pacientes que recibieron irradiación interna y externa sobrevivieron por un tiempo mayor que los que recibieron irradiación interna solamente. Los 3 pacientes que tuvieron resección de sus tumores primarios sobrevivieron más que el grupo en total. Todos los pacientes presentaron episodios continuados de colangitis leve o severa después de la irradiación. La heterogeneidad del material clínico, la variedad de los métodos pretratamiento, y la falta de controles impide un pronunciamiento relativo a la eficacia de la radioterapia en el cáncer biliar. Unos pocos pacientes pueden beneficiarse de la terapia, y el uso de técnicas de irradiación como modalidad adyuvante debe ser motivo de continuada investigación. Sin embargo, aunque la irradiación interna como modalidad de control local de los tumores de los canales biliares proximales continúa siendo teóricamente atractiva, existe poca evidencia sobre su eficacia.

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