

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2022 March 16; 14(3): 106-190



MINIREVIEWS

- 106 Role of intraluminal brachytherapy in palliation of biliary obstruction in cholangiocarcinoma: A brief review
Khosla D, Zaheer S, Gupta R, Madan R, Goyal S, Kumar N, Kapoor R
- 113 Endoscopic management of difficult laterally spreading tumors in colorectum
Castillo-Regalado E, Uchima H

ORIGINAL ARTICLE

Retrospective Cohort Study

- 129 Endoscopic ultrasound-guided through-the-needle microforceps biopsy and needle-based confocal laser-endomicroscopy increase detection of potentially malignant pancreatic cystic lesions: A single-center study
Robles-Medrand C, Olmos JJ, Puga-Tejada M, Oleas R, Baquerizo-Burgos J, Arevalo-Mora M, Del Valle Zavala R, Nebel JA, Calle Loffredo D, Pitanga-Lukashok H

Observational Study

- 142 Ergonomics of gastrointestinal endoscopies: Musculoskeletal injury among endoscopy physicians, nurses, and technicians
Shah SZ, Rehman ST, Khan A, Hussain MM, Ali M, Sarwar S, Abid S
- 153 SARS-CoV-2 in inflammatory bowel disease population: Antibodies, disease and correlation with therapy
Conti CB, Mainardi E, Soro S, Testa S, De Silvestri A, Drago A, Cereatti F, Grassia R

SYSTEMATIC REVIEWS

- 163 Endoscopic management and outcome of non-variceal bleeding in patients with liver cirrhosis: A systematic review
Demetiou G, Augoustaki A, Kalaitzakis E

CASE REPORT

- 176 Mucosa-associated lymphoid tissue lymphoma in the terminal ileum: A case report
de Figueiredo VLP, Ribeiro IB, de Moura DTH, Oliveira CC, de Moura EGH
- 183 Z-per-oral endoscopic myotomy as definitive prevention of a bleeding ulcer in Zenker's diverticulum: A case report
Krutsri C, Hiranyatheeb P, Sumritpradit P, Singhatas P, Choikrua P

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Clement LK Chia, FRCS (Ed), Assistant Professor, Consultant, Department of General Surgery, Khoo Teck Puat Hospital, Singapore 768828, Singapore. chia.clement.lk@ktph.com.sg

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (WJGE, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

INDEXING/ABSTRACTING

The WJGE is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for WJGE as 0.36.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Xu Guo, Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

LAUNCH DATE

October 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee, Joo Young Cho

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5190/editorialboard.htm>

PUBLICATION DATE

March 16, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Role of intraluminal brachytherapy in palliation of biliary obstruction in cholangiocarcinoma: A brief review

Divya Khosla, Samreen Zaheer, Rahul Gupta, Renu Madan, Shikha Goyal, Narendra Kumar, Rakesh Kapoor

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Ricci AD, Italy;
Tabibian JH, United States

Received: May 30, 2021

Peer-review started: May 30, 2021

First decision: October 18, 2021

Revised: November 24, 2021

Accepted: February 25, 2022

Article in press: February 25, 2022

Published online: March 16, 2022



Divya Khosla, Samreen Zaheer, Renu Madan, Shikha Goyal, Narendra Kumar, Rakesh Kapoor, Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, U.T., India

Rahul Gupta, Department of Gastroenterology and Hepatology, Shalby Multispeciality Hospital, Mohali 160062, Punjab, India

Corresponding author: Divya Khosla, MD, Associate Professor, Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Room No. 4, Radiotherapy Office, Ground Floor, Sector 12, Chandigarh 160012, U.T., India.

dr_divya_khosla@yahoo.com

Abstract

Surgery is the only curative treatment for cholangiocarcinoma. However, most patients present with advanced disease, and hence are unresectable. Thus, the intent of treatment shifts from curative to palliative in the majority of cases. Biliary drainage with intraluminal brachytherapy is an effective means of relieving the malignant biliary obstruction. In this review, we discuss the role of brachytherapy in the palliation of obstructive symptoms in extrahepatic cholangiocarcinoma.

Key Words: Biliary tract; Cholangiocarcinoma; Extrahepatic; Intraluminal brachytherapy

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Intraluminal brachytherapy (ILBT) is an effective means for palliation of biliary obstruction in patients with cholangiocarcinoma. It delivers a high dose of radiation to the tumor but spares surrounding normal tissues, thus avoiding many of the side effects seen with external beam radiation. The high dose *per* fraction in ILBT can have an ablative effect on the tumor and can lead to better symptom control and quality of life. ILBT, when combined with these drainage procedures, improves the stent patency rates by inhibiting tumor ingrowth.

Citation: Khosla D, Zaheer S, Gupta R, Madan R, Goyal S, Kumar N, Kapoor R. Role of intraluminal brachytherapy in palliation of biliary obstruction in cholangiocarcinoma: A brief review. *World J Gastrointest Endosc* 2022; 14(3): 106-112

URL: <https://www.wjgnet.com/1948-5190/full/v14/i3/106.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v14.i3.106>

INTRODUCTION

Biliary tract carcinomas, also known as cholangiocarcinomas, may be intrahepatic or extrahepatic. Intrahepatic cholangiocarcinomas arise from the biliary duct epithelium within the liver parenchyma. Extrahepatic cholangiocarcinomas include hilar and distal cholangiocarcinomas. Among these variants, the hilar variety, also known as Klatskin tumor, is the most common. It arises at the junction of the right and the left hepatic ducts.

The Asian population is more susceptible to developing bile duct carcinomas. The disease is more frequently seen in Thailand, India, Japan, and Korea. The incidence varies from 0.3 to 6 *per* lakh population[1]. Surgery is the only curative treatment. However, the disease is resectable only in a minority of the cases. Biliary obstruction is common and results in symptoms such as jaundice, intense pruritis, or pain abdomen. The various means of palliation include biliary drainage procedures, which may be endoscopic or percutaneous, external beam radiation therapy (EBRT), palliative chemotherapy, and intraluminal brachytherapy (ILBT) with or without EBRT.

CLINICAL FEATURES AND PATHOLOGY

Cholangiocarcinoma is a disease of the elderly, mostly affecting those more than 60 years of age. It is seen more commonly in males as compared to females. The risk factors include parasitic infection by organisms such as *Clonorchis sinensis* and *Opisthorchis viverrini*, biliary stones, and smoking. Primary sclerosing cholangitis and hepatitis C are the other risk factors. Primary sclerosing cholangitis with or without cholangitis is the commonest risk factor in Western countries[2].

In the early stages, the patient is usually asymptomatic. The signs and symptoms are non-specific. These may include pain abdomen, fever, jaundice, loss of weight, loss of appetite, generalized itching, and other features of biliary obstruction. Distant metastasis is fairly common[3]. Most of the patients present with either locally advanced or metastatic disease.

Cholangiocarcinomas are histologically adenocarcinomas in 95% of cases[2]. These can be well-differentiated, moderately differentiated, or poorly differentiated[4].

DIAGNOSTIC WORK-UP

Ultrasonography (USG) is the baseline investigation done whenever a biliary obstruction is suspected. It may reveal dilated biliary channels, any mass, or the presence of gallstones. Contrast-enhanced computed tomography (CECT) is the standard imaging tool, especially for staging and preoperative assessment. The delayed scans are useful for diagnosing intrahepatic cholangiocarcinomas which may show contrast enhancement on delayed scans due to abundant fibrous stroma[5-7]. However, CECT may not show the true longitudinal extent of perihilar cholangiocarcinoma[8]. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) is considered the imaging modality of choice. It allows the assessment of the entire biliary tree as well as the vascular anatomy[9].

Cancer antigen (CA) 19-9, carcinoembryonic antigen (CEA), and CA-125 are the non-specific tumor markers, which may help in establishing the diagnosis[10]. Tissue diagnosis is essential before a patient can be given chemotherapy or radiotherapy. This may be quite challenging, especially if the patient has primary sclerosing cholangitis or biliary strictures. The biopsy samples, collected by endoscopic imaging and tissue sampling, are usually inadequate for molecular typing. In this setting, liquid biopsy holds promise. It is mainly based on circulating free DNA and circulating tumour DNA[11]. Cholangiocarcinomas exhibit specific RNA profiles in extra-cellular vesicles in a patient's serum and urine. It is one of the promising liquid biopsy markers[12].

MANAGEMENT

Surgery is the only curative treatment for cholangiocarcinomas. The disease is resectable in only 10%-15% of the patients[13,14]. The low resection rates may be due to invasion of the hepatic artery or portal

vein, lymph node involvement, or the invasion of the adjacent structures. Some patients may present with peritoneal or distant metastasis, so are inoperable, and need to be managed with palliative intent. Operative mortality has been reported to be 5%-10% in some studies[14-16]. The 5-year survival rates after surgery are 9%-18% for proximal bile duct lesions and 20%-30% for distal bile duct lesions[2]. Although phase 2 studies and some retrospective studies suggest the advantage of adding adjuvant therapy, there are no phase 3 studies to support this[17-20].

Bonet Beltrán *et al*[21] did a systematic review and meta-analysis in patients with extrahepatic bile duct cancer. The authors reported a significant benefit of adjuvant radiation, especially in patients with extrahepatic cholangiocarcinoma. This benefit was seen in terms of improved overall survival[21].

Sahai *et al*[22] reviewed the literature on the role of radiation in adjuvant, neoadjuvant, definitive, and palliative settings. They concluded that stenting with palliative radiotherapy, either external or brachytherapy, improves the stent patency rates and survival in unresectable cholangiocarcinoma[22].

There is no definite consensus on the role of adjuvant chemotherapy. The studies have reported variable results. A retrospective study on patients with hilar cholangiocarcinoma showed a significant improvement in survival in those who received adjuvant chemotherapy[23]. The greatest benefit of adjuvant chemotherapy is seen in those with lymph node positive or resection margin positive status [24]. After the BILCAP study, capecitabine is considered to be the standard treatment for biliary tract cancers in the adjuvant setting[25].

Neoadjuvant therapy has been explored in cholangiocarcinoma with the aim to achieve negative surgical margins and improve survival rates. Nelson *et al*[26] conducted a study in patients diagnosed with extra-hepatic cholangiocarcinoma. These patients received neoadjuvant chemo-radiotherapy with 5-fluorouracil and EBRT with or without brachytherapy. They reported a R0 resection rate of 91.7% [26]. Similar results have been reported by Jung *et al*[27] and Sumiyoshi *et al*[28].

Novel treatment options are opening the doors of a new world. There is increasing interest in the use of targeted therapy and immunotherapy. Targeted therapies have demonstrated a role in mainly intrahepatic cholangiocarcinoma[29]. Fibroblast growth factor receptor (FGFR) aberrations and isocitrate dehydrogenase (IDH) mutations based therapy hold promise[30,31].

There are several ongoing trials on immunotherapy in advanced biliary tract cancers. Although monotherapy with immune check-point inhibitors or their combination with other anti-cancer agents shows only modest survival advantages and efficacy, there is a need to test these patients for deficiency in mismatch repair proteins (dMMR), high microsatellite instability (MSI-H), increased tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) expression[32,33].

Due to low resectability, the goal of treatment is palliation in most of the patients. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) are the initial procedures that may be used to relieve biliary obstruction resulting from cholangiocarcinoma. These procedures are only palliative with a median survival of around 6 mo[34]. This article provides a concise overview of the role of ILBT in the palliation of biliary obstruction. Biliary drainage, which is done either endoscopically or percutaneously, can palliate symptoms, but ILBT can decrease the tumor size and delay the tumor ingrowth.

ROLE OF BRACHYTHERAPY

ILBT can be used in cholangiocarcinomas with both palliative and curative intent. With curative intent, it can be used following chemoradiotherapy to escalate the tumor dose and thus increase the local control[35]. The main indication in the palliative setting is to relieve the biliary obstruction. The mechanism may be *via* preventing stent re-occlusion, which may occur due to tumor ingrowth[36,37].

When ILBT is combined with EBRT, usually 30-40 Gy are delivered *via* EBRT and 15-20 Gy in 2-3 fractions *via* high dose rate (HDR) brachytherapy. When pulsed dose rate brachytherapy (PDR) is used in the combined modality setting, a single course of 20 Gy is usually prescribed[3]. In the palliative setting, the HDR ILBT dose is usually 15-20 Gy in 3-4 Gy/fraction. When PDR brachytherapy is used, 1 or 2 fractions of 20-40 Gy may be prescribed[3].

ILBT techniques, dose, and response

ILBT can be performed using ERCP or PTBD. Whenever possible, percutaneous transhepatic technique is preferred. It is reported that when PTBD is combined with ILBT, the median survival time increases [38,39]. The feasibility of ILBT is better with PTBD. Lesions in the right and left hepatic duct, as well as the common bile duct, can be easily assessed. Before PTBD, imaging is done to know the exact site and extent of the obstruction. It can be assessed *via* USG, CT, or MRI. First, percutaneous transhepatic cholangiography is performed followed by biliary decompression. ILBT catheters are inserted when serum bilirubin levels decrease and the patient stabilizes. Jain *et al*[40] performed ILBT when the serum bilirubin levels decreased to 2 mg% or fell to 50% of the baseline. Other inclusion criteria reported by them included Eastern Cooperative Oncology Group (ECOG) performance status 0-2; absence of fever, signs of cholangitis, or any evidence of distant metastasis[40]. Aggarwal *et al*[34] did ILBT after biliary drainage *via* PTBD when the serum bilirubin levels were below 5 mg% [34]. They did PTBD under USG

Table 1 Some studies in which brachytherapy has been used with palliative intent

No.	No of patients	Diagnosis	PTBD	EBRT	Dose of ILBT	Survival	Stent patency	Ref.
1	18	Malignant biliary obstruction	Yes	-	16 Gy in 2 fractions	8.27 mo (median survival)	-	Aggarwal <i>et al</i> [34]
2	48	Bile duct and pancreatic cancer	Yes	-	25 pulses of 0.8 Gy hourly (total dose of 20 Gy PDR)	11.2 mo for bile duct carcinoma	-	Skowronek <i>et al</i> [36]
3	32	Non resectable biliary malignancy	Yes	-	5 Gy in 6 fractions	358 d in Klatskin-tumour	418 d	Bruha <i>et al</i> [37]
4	22	Malignant biliary obstruction	Yes	Yes	15-31 Gy (mean 25 Gy)	22.6 mo	19.5 mo	Eschelman <i>et al</i> [39]
5	12	Malignant obstructive jaundice	Yes	Yes (6 patients)	10-14 Gy	-	9.8 mo	Jain <i>et al</i> [40]
6	34	Malignant obstructive jaundice	Yes	-	14-21 Gy in 3-4 fractions	9.4 mo	12.6 mo	Chen <i>et al</i> [43]
7	14	Bile duct cancers	Yes	Yes (5 patients)	10 Gy, 2 fractions of 2.5 Gy 6 h apart for 2 d	6.5 mo (median survival)	-	Mayer <i>et al</i> [44]
8	8	Malignant obstruction of bile duct	Yes	-	2 fractions of 10 Gy each	7.5 mo	6.9 mo	Kocak <i>et al</i> [45]

PTBD: Percutaneous transhepatic biliary drainage; EBRT: External beam radiation therapy; ILBT: Intraluminal brachytherapy.

and fluoroscopic guidance. After biliary decompression, an internal-external drainage tube was inserted and left in place for 7-10 d to allow bilirubin levels to fall and the patient's general condition to improve. When ILBT was performed, the external-internal catheter was replaced with brachytherapy catheter. Its tip was placed 1.5-2 cm beyond the distal end of the stricture. These patients received a dose of 8 Gy in 2 fractions at an interval of 1 wk *via* HDR brachytherapy. Various brachytherapy doses and schedules are described in the literature. Jain *et al* [40] used a dose of 10-14 Gy at 1 cm from the central axis of the source, which was delivered *via* HDR microselectron [40].

Deufel *et al* [41] have described the HDR brachytherapy in patients with cholangiocarcinoma *via* a nasobiliary route [41]. They did the procedure using an 8.5 Fr or 10 Fr nasobiliary catheter inserted *via* ERCP technique. This was followed by insertion of a 4.7 Fr treatment catheter into the nasobiliary catheter. The dose schedules described are a single fraction of 9.3 Gy or fractionated regime using four fractions of 4 Gy delivered twice a day. For patients who are suitable for liver transplantation after neoadjuvant chemoradiation, the minimally invasive nasobiliary approach may be preferred as there is a higher risk of tumor seeding with transhepatic technique [42]. However, the nasobiliary route is technically more difficult and may not be preferred in the palliative setting.

Bruha *et al* [37] in their study on cholangiocarcinoma patients with malignant obstructive jaundice treated by HDR ILBT, showed that the mean stent patency was 418 d [37]. Jain *et al* [40] reported a mean stent patency duration of 9.4 mo in patients with cholangiocarcinoma treated by PTBD and ILBT [40].

Chen *et al* [43] showed a similar trend in their study. The stent patency rate in patients who underwent ILBT with PTBD was 45%. However, this rate was just 21% in the group of patients who had only stent placement. The dose of ILBT used was 14-21 Gy in 3-4 fractions. The duration of stent patency was also significantly greater in the ILBT group [43].

Aggarwal *et al* [34] reported an improvement in symptoms such as fatiguability, nausea, vomiting, pain, icterus, pruritis, dyspnea, insomnia, and loss of appetite after palliation with PTBD combined with ILBT [34]. Mayer *et al* [44] reported symptomatic improvement in pruritis and jaundice in all their patients with unresectable bile duct malignancy after biliary decompression with PTBD followed by ILBT. The dose of brachytherapy in their study was 2.5 Gy in 2 fractions *per* day for a total dose of 10 Gy. However, five of their patients also received EBRT [44]. Few of the studies in which brachytherapy has been used with palliative intent, mainly to relieve biliary obstruction, are presented in Table 1.

Complications

The most frequent complication of ILBT is cholangitis [45]. Other side effects of PTBD combined with ILBT include nausea, vomiting, and gastroduodenal ulceration [34].

Limitations

ILBT is not used frequently due to the lack of availability and expertise and patient's moribund condition due to disease. Also, there is paucity of literature, and a lack of survival benefit. But in patients with malignant biliary obstruction, it can be used as an adjunct to systemic therapies. It can be

used as an adjunct to biliary drainage in the palliative setting.

CONCLUSION

ILBT offers an effective means of palliating biliary obstruction in patients with cholangiocarcinoma. The article focuses mainly on the role of ILBT in the palliation of malignant biliary obstruction. ILBT delivers a high dose of radiation to the tumor with sparing of surrounding normal tissues, thus avoiding many of the side effects seen with external beam radiation. The high dose *per fraction* in ILBT can have an ablative effect on the tumor and can lead to better symptom control and quality of life. The transhepatic approach is preferred over the endoscopic technique as ILBT is easier to perform when combined with PTBD as compared to ERCP. ILBT, when combined with these drainage procedures, improves the stent patency rates by inhibiting tumor ingrowth. There is a need for prospective studies to compare the quality of life and outcome in such patients using ILBT.

FOOTNOTES

Author contributions: Khosla D contributed to conceptualization and manuscript preparation, writing, and editing and was responsible for the integrity of the article; Zaheer S and Gupta R contributed to literature search and manuscript writing and editing; Madan R contributed to literature search; Goyal S contributed to manuscript editing; Kumar N and Kapoor R reviewed and approved the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest in the preparation of the manuscript.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Divya Khosla 0000-0002-7912-115X; Samreen Zaheer 0000-0002-9769-8593; Rahul Gupta 0000-0002-5775-0959; Renu Madan 0000-0002-6649-4328; Shikha Goyal 0000-0002-9972-6682; Narendra Kumar 0000-0002-3755-8900; Rakesh Kapoor 0000-0003-3789-1591.

S-Editor: Fan JR

L-Editor: Wang TQ

P-Editor: Fan JR

REFERENCES

- 1 Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpino G, Andersen JB, Braconi C, Calvisi DF, Perugorria MJ, Fabris L, Boulter L, Macias RIR, Gaudio E, Alvaro D, Gradilone SA, Strazzabosco M, Marziani M, Coulouarn C, Fouassier L, Raggi C, Invernizzi P, Mertens JC, Moncsek A, Rizvi S, Heimbach J, Koerkamp BG, Bruix J, Forner A, Bridgewater J, Valle JW, Gores GJ. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 557-588 [PMID: 32606456 DOI: 10.1038/s41575-020-0310-z]
- 2 Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Thursz MR, Wasan H; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut* 2002; **51** Suppl 6: VI1-VI9 [PMID: 12376491 DOI: 10.1136/gut.51.suppl_6.vi1]
- 3 Skowronek J, Zwierzchowski G. Brachytherapy in the treatment of bile duct cancer - a tough challenge. *J Contemp Brachytherapy* 2017; **9**: 187-195 [PMID: 28533809 DOI: 10.5114/jcb.2017.66893]
- 4 Chung YE, Kim MJ, Park YN, Choi JY, Pyo JY, Kim YC, Cho HJ, Kim KA, Choi SY. Varying appearances of cholangiocarcinoma: radiologic-pathologic correlation. *Radiographics* 2009; **29**: 683-700 [PMID: 19448110 DOI: 10.1148/rg.293085729]
- 5 Kim SA, Lee JM, Lee KB, Kim SH, Yoon SH, Han JK, Choi BI. Intrahepatic mass-forming cholangiocarcinomas: enhancement patterns at multiphasic CT, with special emphasis on arterial enhancement pattern--correlation with clinicopathologic findings. *Radiology* 2011; **260**: 148-157 [PMID: 21474703 DOI: 10.1148/radiol.11101777]
- 6 Kim SJ, Lee JM, Han JK, Kim KH, Lee JY, Choi BI. Peripheral mass-forming cholangiocarcinoma in cirrhotic liver. *AJR Am J Roentgenol* 2007; **189**: 1428-1434 [PMID: 18029881 DOI: 10.2214/AJR.07.2484]
- 7 Lacomis JM, Baron RL, Oliver JH 3rd, Nalesnik MA, Federle MP. Cholangiocarcinoma: delayed CT contrast enhancement patterns. *Radiology* 1997; **203**: 98-104 [PMID: 9122423 DOI: 10.1148/radiology.203.1.9122423]
- 8 Vilgrain V. Staging cholangiocarcinoma by imaging studies. *HPB (Oxford)* 2008; **10**: 106-109 [PMID: 18773065 DOI: 10.1007/s12089-008-9000-0]

- 10.1080/13651820801992617]
- 9 **Mahajan MS**, Moorthy S, Karumathil SP, Rajeshkannan R, Pothera R. Hilar cholangiocarcinoma: Cross sectional evaluation of disease spectrum. *Indian J Radiol Imaging* 2015; **25**: 184-192 [PMID: [25969643](#) DOI: [10.4103/0971-3026.155871](#)]
- 10 **Blechacz B**, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 512-522 [PMID: [21808282](#) DOI: [10.1038/nrgastro.2011.131](#)]
- 11 **Rizzo A**, Ricci AD, Tavolari S, Brandi G. Circulating Tumor DNA in Biliary Tract Cancer: Current Evidence and Future Perspectives. *Cancer Genomics Proteomics* 2020; **17**: 441-452 [PMID: [32859625](#) DOI: [10.21873/cgp.20203](#)]
- 12 **Lapitz A**, Arbelaiz A, O'Rourke CJ, Lavin JL, Casta A, Ibarra C, Jimeno JP, Santos-Laso A, Izquierdo-Sanchez L, Krawczyk M, Perugorria MJ, Jimenez-Aguero R, Sanchez-Campos A, Riaño I, González E, Lammert F, Marziani M, Macías RIR, Marin JJG, Karlsen TH, Bujanda L, Falcón-Pérez JM, Andersen JB, Aransay AM, Rodrigues PM, Banalles JM. Patients with Cholangiocarcinoma Present Specific RNA Profiles in Serum and Urine Extracellular Vesicles Mirroring the Tumor Expression: Novel Liquid Biopsy Biomarkers for Disease Diagnosis. *Cells* 2020; **9** [PMID: [32183400](#) DOI: [10.3390/cells9030721](#)]
- 13 **Baer HU**, Stain SC, Dennison AR, Eggers B, Blumgart LH. Improvements in survival by aggressive resections of hilar cholangiocarcinoma. *Ann Surg* 1993; **217**: 20-27 [PMID: [8380975](#) DOI: [10.1097/0000658-199301000-00005](#)]
- 14 **Hadjis NS**, Blenkarn JI, Alexander N, Benjamin IS, Blumgart LH. Outcome of radical surgery in hilar cholangiocarcinoma. *Surgery* 1990; **107**: 597-604 [PMID: [2162082](#)]
- 15 **Nagorney DM**, Donohue JH, Farnell MB, Schleck CD, Ilstrup DM. Outcomes after curative resections of cholangiocarcinoma. *Arch Surg* 1993; **128**: 871-7; discussion 877 [PMID: [8393652](#) DOI: [10.1001/archsurg.1993.01420200045008](#)]
- 16 **Chung C**, Bautista N, O'Connell TX. Prognosis and treatment of bile duct carcinoma. *Am Surg* 1998; **64**: 921-925 [PMID: [9764692](#)]
- 17 **Jarnagin WR**, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, Wagman R, Blumgart LH, Fong Y. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer* 2003; **98**: 1689-1700 [PMID: [14534886](#) DOI: [10.1002/cncr.11699](#)]
- 18 **Cheng Q**, Luo X, Zhang B, Jiang X, Yi B, Wu M. Predictive factors for prognosis of hilar cholangiocarcinoma: postresection radiotherapy improves survival. *Eur J Surg Oncol* 2007; **33**: 202-207 [PMID: [17088040](#) DOI: [10.1016/j.ejso.2006.09.033](#)]
- 19 **Kim TH**, Han SS, Park SJ, Lee WJ, Woo SM, Moon SH, Yoo T, Kim SS, Kim SH, Hong EK, Kim DY, Park JW. Role of adjuvant chemoradiotherapy for resected extrahepatic biliary tract cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**: e853-e859 [PMID: [21497455](#) DOI: [10.1016/j.ijrobp.2010.12.019](#)]
- 20 **Todoroki T**, Ohara K, Kawamoto T, Koike N, Yoshida S, Kashiwagi H, Otsuka M, Fukao K. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. *Int J Radiat Oncol Biol Phys* 2000; **46**: 581-587 [PMID: [10701737](#) DOI: [10.1016/s0360-3016\(99\)00472-1](#)]
- 21 **Bonet Beltrán M**, Allal AS, Gich I, Solé JM, Carrió I. Is adjuvant radiotherapy needed after curative resection of extrahepatic biliary tract cancers? *Cancer Treat Rev* 2012; **38**: 111-119 [PMID: [21652148](#) DOI: [10.1016/j.ctrv.2011.05.003](#)]
- 22 **Sahai P**, Kumar S. External radiotherapy and brachytherapy in the management of extrahepatic and intrahepatic cholangiocarcinoma: available evidence. *Br J Radiol* 2017; **90**: 20170061 [PMID: [28466653](#) DOI: [10.1259/bjr.20170061](#)]
- 23 **Yubin L**, Chihua F, Zhixiang J, Jinrui O, Zixian L, Jianghua Z, Ye L, Haosheng J, Chaomin L. Surgical management and prognostic factors of hilar cholangiocarcinoma: experience with 115 cases in China. *Ann Surg Oncol* 2008; **15**: 2113-2119 [PMID: [18546046](#) DOI: [10.1245/s10434-008-9932-z](#)]
- 24 **Horgan AM**, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012; **30**: 1934-1940 [PMID: [22529261](#) DOI: [10.1200/JCO.2011.40.5381](#)]
- 25 **Rizzo A**, Brandi G. BILCAP trial and adjuvant capecitabine in resectable biliary tract cancer: reflections on a standard of care. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 483-485 [PMID: [33307876](#) DOI: [10.1080/17474124.2021.1864325](#)]
- 26 **Nelson JW**, Ghafoori AP, Willett CG, Tyler DS, Pappas TN, Clary BM, Hurwitz HI, Bendell JC, Morse MA, Clough RW, Czito BG. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2009; **73**: 148-153 [PMID: [18805651](#) DOI: [10.1016/j.ijrobp.2008.07.008](#)]
- 27 **Jung JH**, Lee HJ, Lee HS, Jo JH, Cho IR, Chung MJ, Park JY, Park SW, Song SY, Bang S. Benefit of neoadjuvant concurrent chemoradiotherapy for locally advanced perihilar cholangiocarcinoma. *World J Gastroenterol* 2017; **23**: 3301-3308 [PMID: [28566890](#) DOI: [10.3748/wjg.v23.i18.3301](#)]
- 28 **Sumiyoshi T**, Shima Y, Okabayashi T, Negoro Y, Shimada Y, Iwata J, Matsumoto M, Hata Y, Noda Y, Sui K, Sueda T. Chemoradiotherapy for Initially Unresectable Locally Advanced Cholangiocarcinoma. *World J Surg* 2018; **42**: 2910-2918 [PMID: [29511872](#) DOI: [10.1007/s00268-018-4558-1](#)]
- 29 **Xie C**, McGrath NA, Monge Bonilla C, Fu J. Systemic treatment options for advanced biliary tract carcinoma. *J Gastroenterol* 2020; **55**: 944-957 [PMID: [32748173](#) DOI: [10.1007/s00535-020-01712-9](#)]
- 30 **Abou-Alfa GK**, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DV, Borad MJ, Bridgewater J, Harris WP, Murphy AG, Oh DY, Whisenant J, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Fan B, Wu B, Chamberlain CX, Jiang L, Gliser C, Pandya SS, Valle JW, Zhu AX. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 796-807 [PMID: [32416072](#) DOI: [10.1016/S1470-2045\(20\)30157-1](#)]
- 31 **Abou-Alfa GK**, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, Oh DY, Dotan E, Catenacci DV, Van Cutsem E, Ji T, Lihou CF, Zhen H, Féliz L, Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2020; **21**: 671-684 [PMID: [32203698](#) DOI: [10.1016/S1470-2045\(20\)30109-1](#)]
- 32 **Rizzo A**, Ricci AD, Brandi G. Recent advances of immunotherapy for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 527-536 [PMID: [33215952](#) DOI: [10.1080/17474124.2021.1853527](#)]

- 33 **Rizzo A**, Ricci AD, Brandi G. PD-L1, TMB, MSI, and Other Predictors of Response to Immune Checkpoint Inhibitors in Biliary Tract Cancer. *Cancers (Basel)* 2021; **13** [PMID: [33535621](#) DOI: [10.3390/cancers13030558](#)]
- 34 **Aggarwal R**, Patel FD, Kapoor R, Kang M, Kumar P, Chander Sharma S. Evaluation of high-dose-rate intraluminal brachytherapy by percutaneous transhepatic biliary drainage in the palliative management of malignant biliary obstruction--a pilot study. *Brachytherapy* 2013; **12**: 162-170 [PMID: [23186613](#) DOI: [10.1016/j.brachy.2012.06.002](#)]
- 35 **Simmons DT**, Baron TH, Petersen BT, Gostout CJ, Haddock MG, Gores GJ, Yeakel PD, Topazian MD, Levy MJ. A novel endoscopic approach to brachytherapy in the management of Hilar cholangiocarcinoma. *Am J Gastroenterol* 2006; **101**: 1792-1796 [PMID: [16780552](#) DOI: [10.1111/j.1572-0241.2006.00700.x](#)]
- 36 **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 Brachytherapy* 2009; **1**: 97-104 [PMID: [27795719](#)]
- 37 **Bruha R**, Petrtyl J, Kubecova M, Marecek Z, Dufek V, Urbanek P, Kodadova J, Chodounsky Z. Intraluminal brachytherapy and selfexpandable stents in nonresectable biliary malignancies--the question of long-term palliation. *Hepatogastroenterology* 2001; **48**: 631-637 [PMID: [11462891](#)]
- 38 **Mahe M**, Romestaing P, Talon B, Ardiet JM, Salerno N, Sentenac I, Gerard JP. Radiation therapy in extrahepatic bile duct carcinoma. *Radiation Oncol* 1991; **21**: 121-127 [PMID: [1866463](#) DOI: [10.1016/0167-8140\(91\)90084-t](#)]
- 39 **Eschelman DJ**, Shapiro MJ, Bonn J, Sullivan KL, Alden ME, Hovsepian DM, Gardiner GA Jr. Malignant biliary duct obstruction: long-term experience with Gianturco stents and combined-modality radiation therapy. *Radiology* 1996; **200**: 717-724 [PMID: [8756921](#) DOI: [10.1148/radiology.200.3.8756921](#)]
- 40 **Jain S**, Kataria T, Bisht SS, Gupta D, Vikraman S, Baijal S, Sud R. Malignant obstructive jaundice - brachytherapy as a tool for palliation. *J Contemp Brachytherapy* 2013; **5**: 83-88 [PMID: [23878552](#) DOI: [10.5114/jcb.2013.35563](#)]
- 41 **Deufel CL**, Furutani KM, Dahl RA, Grams MP, McLemore LB, Hallemeier CL, Neben-Wittich M, Martenson JA, Haddock MG. Technique for the administration of high-dose-rate brachytherapy to the bile duct using a nasobiliary catheter. *Brachytherapy* 2018; **17**: 718-725 [PMID: [29776892](#) DOI: [10.1016/j.brachy.2018.03.006](#)]
- 42 **Lin H**, Li S, Liu X. The safety and efficacy of nasobiliary drainage versus biliary stenting in malignant biliary obstruction: A systematic review and meta-analysis. *Medicine (Baltimore)* 2016; **95**: e5253 [PMID: [27861347](#) DOI: [10.1097/MD.0000000000005253](#)]
- 43 **Chen Y**, Wang XL, Yan ZP, Cheng JM, Wang JH, Gong GQ, Qian S, Luo JJ, Liu QX. HDR-192Ir intraluminal brachytherapy in treatment of malignant obstructive jaundice. *World J Gastroenterol* 2004; **10**: 3506-3510 [PMID: [15526374](#) DOI: [10.3748/wjg.v10.i23.3506](#)]
- 44 **Mayer R**, Stranzl H, Prettenhofer U, Quehenberger F, Stüchlschweiger G, Winkler P, Hackl A. Palliative treatment of unresectable bile duct tumours. *Acta Med Austriaca* 2003; **30**: 10-12 [PMID: [12558559](#) DOI: [10.1046/j.1563-2571.2003.02049.x](#)]
- 45 **Kocak Z**, Ozkan H, Adli M, Garipagaoglu M, Kurtman C, Cakmak A. Intraluminal brachytherapy with metallic stenting in the palliative treatment of malignant obstruction of the bile duct. *Radiat Med* 2005; **23**: 200-207 [PMID: [15940068](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

