

# World Journal of *Gastrointestinal Endoscopy*

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



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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.

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**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

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<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



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### 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

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**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 fatigability, 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.

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**S-Editor:** Fan JR

**L-Editor:** Wang TQ

**P-Editor:** Fan JR

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