Transarterial Therapies for the Treatment of Intrahepatic Cholangiocarcinoma

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Abstract

Keywords

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► outcomes

Cholangiocarcinoma, whether arising from the intrahepatic or extrahepatic biliary system, is a rare but devastating malignancy. Prognosis is poor, with 5-year overall survival <5% including patients undergoing surgery. Resection is the only curative treatment; however, only ∼30% of patients present at a resectable stage, and intrahepatic recurrence is common even after complete resection. This article discusses the current role of transarterial therapies in the treatment of intrahepatic cholangiocarcinoma.

Objectives: Upon completion of this article, the reader will be able to discuss the role of chemoembolization and radioembolization in the treatment of intrahepatic cholangiocarcinoma.

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Cholangiocarcinoma, whether arising from the intrahepatic or extrahepatic biliary system, is a rare but devastating malignancy. Prognosis is poor, with 5-year overall survival rates <5% including patients undergoing surgery.[1–3] Resection is the only curative treatment; however, only ∼30% of patients present at a resectable stage, and intrahepatic recurrence is common even after complete resection.[4,5] Survival, therefore, remains low even for postoperative patients, ranging from 8% to 47% at 5 years.[1] It is also appropriate to recognize that the epidemiology, management, and prognosis of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) differ, such that they must be considered separately when evaluating new treatment strategies.

More than 90% of cholangiocarcinomas are adenocarcinomas, and most tumors arise at the bifurcation of the hepatic ducts (Klatskin tumors) or from the common bile duct; ICC therefore constitutes only 5 to 10% of all cholangiocarcinomas.[1] Cancers of the biliary tract can be classified by a variety of means. The most frequently used staging systems include the American Joint Committee on Cancer (AJCC)/International Union Against Cancer and a Japanese staging system.[6,7] The AJCC system has been criticized for failing to consider hepatocellular carcinoma (HCC) and cholangiocarcinoma separately; the seventh and most recent edition now addresses this issue.[6,8]

In the United States, the incidence of ICC is rising, and patients with ICC tend to present at a later stage than those with ECC (the incidence of which is actually decreasing).[3] These factors underscore the importance of refining and improving nonsurgical treatment modalities in the treatment of ICC. The scope of this review is limited to the treatment of intrahepatic cholangiocarcinoma, with a focus on intraarterial liver-directed therapies.

Traditional palliative approaches to ICC include biliary decompression, systemic chemotherapy, and external radiation therapy, with symptom control and improved quality of life the primary treatment goals. The effectiveness of these modalities is limited. In fact, a standard chemotherapy regimen was not uniformly established until a recent 410-patient phase 3 trial identified the combination of cisplatin and

gemcitabine as superior to gemcitabine alone (median overall survival of 11.7 months compared with 8.1 months, respectively).[9] However, only 80 patients (20%) in this trial had intrahepatic tumors. In another study, combination therapy with gemcitabine and oxaliplatin has also been reported with favorable results (with ICC representing 45% of the cohort).[10]

Evidence supporting the use of external radiation therapy in unresectable ICC is limited, with many prior studies addressing ECC or gallbladder carcinoma. A series including 46 patients with ICC using high-dose conformal radiation therapy demonstrated a median survival of 13.3 months; however, patients also received concurrent continuous infusion of floxuridine via implanted arterial ports as part of the treatment regimen.[11] More recently, stereotactic body radiotherapy was used in 26 patients with Klatskin tumors and one patient with ICC, resulting in an overall median survival of 10.6 months. However, six patients developed duodenal ulceration, all severely symptomatic requiring transfusion and/or hospitalization, and three patients developed duodenal stenosis, two of whom required endoscopic dilation.[12]

Percutaneous tumor ablation including radiofrequency and microwave ablation have also been reported, but they have a limited role in advanced ICC because these therapies are suited to small peripheral tumors.[13–17]

Intra-arterial therapies primarily consist of chemotherapy-based modalities including conventional transcatheter arterial chemoembolization (TACE), transcatheter arterial chemoinfusion (TACI), or drug-eluding bead transcatheter arterial chemoembolization (DEB-TACE). More recently, intra-arterial brachytherapy in the form of yttrium-90 (^{90}Y) radioembolization has been reported in ICC, complementing an increasing experience with ^{90}Y in HCC and hepatic tumors in general.

Intra-Arterial Liver-Directed Therapies

Transcatheter Arterial Chemoembolization
Chemoembolization strategies use high-dose chemotherapy delivered in a selective manner to hypervascular liver tumors via catheter injection from the hepatic artery, followed by
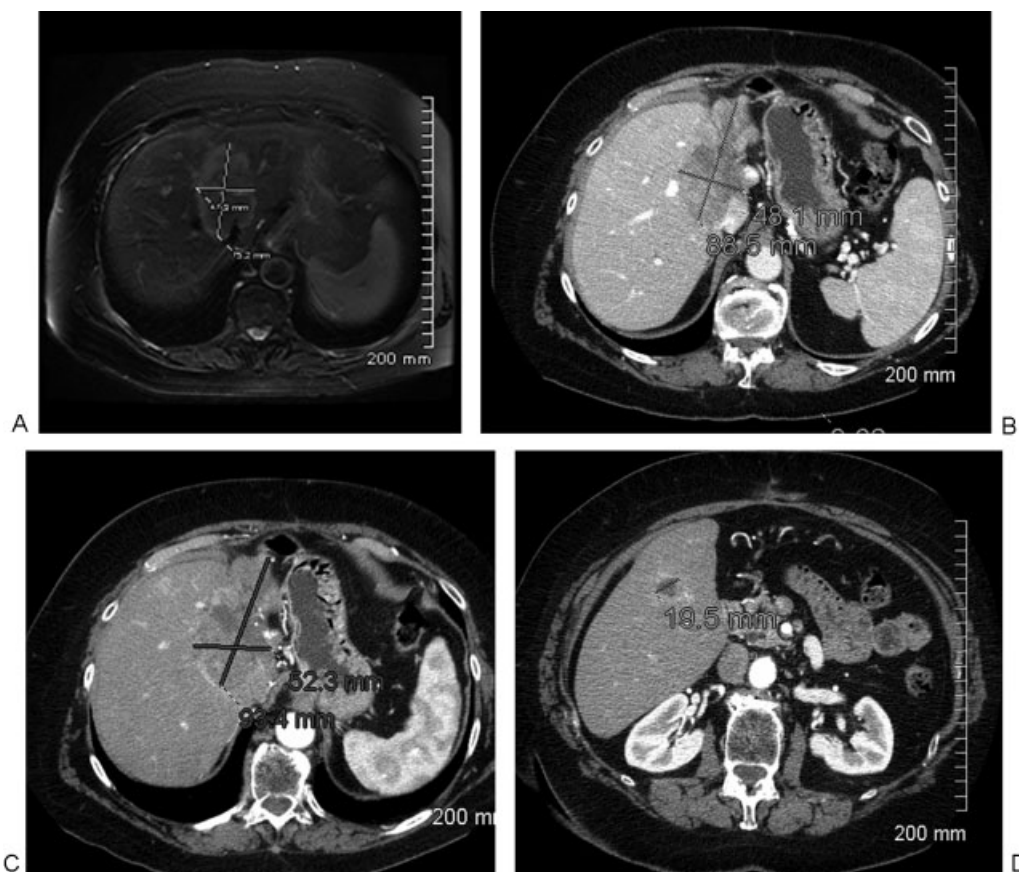
Figure 1 (A) A 73-year-old woman with a large heterogeneous lesion in the central aspect of the liver underwent ultrasound-guided biopsy that confirmed cholangiocarcinoma, followed by conventional chemoembolization. (B) After three transcatheter arterial chemoembolization (TACE) sessions performed over 6 months, the mass had not progressed in size, and there is atrophy of the left lobe. TACE was performed with cisplatin 100 mg, doxorubicin 50 mg, and mitomycin-C 10 mg. (C) Imaging performed ~18 months after the initial chemoembolization demonstrates relative stability of the dominant lesion in the central aspect of the liver. The patient had undergone three TACE sessions and two drug-eluding bead (DEB)-TACE sessions at this point; DEB-TACE was performed with LC Beads loaded with doxorubicin 50 mg. (D) Imaging at 18 months demonstrates new peripherally enhancing low attenuation lesions (one shown on representative computed tomography scan), consistent with intrahepatic metastases and disease progression.

Table 1 Current Series of Transcatheter Arterial Chemoembolization/Transcatheter Arterial Chemoinfusion in the Treatment of Intrahepatic Cholangiocarcinoma

Investigators	Chemotherapy type	No. of patients	Patient factors		Median survival[a] (mo)
			Extrahepatic disease (%)	Prior systemic chemotherapy (%)	
Burger et al	Cisplatin (cis), doxorubicin, mitomycin-C	17	Excluded	35	23
Gusani et al	Gemcitabine (gem), Gem then cis, Gem then oxali, Gem plus cis	42	45	NA	Overall: 9.1 Gem plus cis: 13.8
Kim et al	TACI (n = 13), TACE (n = 21), TACE and TACI (n = 15); using cisplatin	49	51	NA	Overall: 12 Hypervascular tumors: 15
Kiefer et al	Cisplatin, doxorubicin, and mitomycin-C	62	31	29	15
Vogl et al	Varied, including mitomycin-C, gemcitabine, and cisplatin	115	Excluded	NA	13

Abbreviations: NA, not applicable; TACE, transcatheter arterial chemoembolization; TACI, transcatheter arterial chemoinfusion.
[a]From time of first TACE/TACI treatment.

delivery of an embolic agent (►**Fig. 1**). Highly vascular liver tumors derive a disproportionate fraction of their blood supply from the hepatic artery, such that high doses of chemotherapy can be safely administered even in the presence of compromised liver function. Chemoembolization experience derives primarily from the treatment of HCC, with two seminal randomized trials in 2002 demonstrating a survival benefit following TACE.[18,19] Several series have subsequently assessed its use in the treatment of ICC (►**Table 1**).

One of the earliest series by Burger et al included 17 patients treated between 1995 and 2004, using a conventional TACE regimen consisting of cisplatin, doxorubicin, and mitomycin-C, followed by embolization with polyvinyl alcohol (PVA) or Embosphere particles (Biosphere Medical, Rockland, MA), although three treatment sessions varied from this protocol.[20] Only six patients had received prior chemotherapy. Liver function was generally preserved (15 of 17 Child-Pugh class A), as well as performance status (PS) (14 of 17 Eastern Cooperative Oncology Group [ECOG] PS <2). Patients underwent a median of two TACE sessions. All tumors were hypervascular; an angiographic blush was seen during all treatment sessions. Median overall survival was 23 months. Two patients were deemed to have resectable disease following TACE.

A series by Gusani et al included 42 patients treated with TACE from 2001 to 2007. Several regimens were used including gemcitabine alone (n = 18), gemcitabine followed by cisplatin (n = 2), gemcitabine followed by oxaliplatin (n = 4), and gemcitabine and cisplatin in combination (n = 14).[21] Patients with ECOG PS >1 were excluded. Extrahepatic disease was present in 45% of patients. Patients underwent a median of 3.5 TACE sessions. Median survival for the entire cohort was 9.1 months, with combination gemcitabine-cisplatin TACE showing improved survival over gemcitabine alone (13.8 versus 6.3 months, respectively; $p = 0.0005$).

Kim et al reported 49 patients treated with chemoinfusion and chemoembolization strategies; 13 patients received cisplatin infusion only, 21 patients received chemoembolization (the addition of Gelfoam embolization; Upjohn, Kalamazoo, MI), and 15 patients underwent both TACI and TACE.[22] Patients with Child-Pugh class C liver disease were excluded, although 10 patients (20%) had cirrhosis. Extrahepatic disease was present in 25 patients (51%). Hypervascular tumors were observed in 36 patients (73%), defined as visible tumor blush at angiography. Patients underwent a mean of three treatment sessions. Median survival was 24 months from time of diagnosis, and 12 months from the initial TACI or TACE session. Comparison of survival among patients treated with either TACI or TACE was not assessed. Patients with hypervascular tumors had a median survival of 15 months, compared with 5 months for patients with hypovascular tumors ($p < 0.001$).

Kiefer et al treated 62 patients with conventional TACE (cisplatin, doxorubicin, and mitomycin-C infusion followed by PVA embolization).[23] These patients had either ICC (n = 37) or intrahepatic adenocarcinoma of unknown primary (n = 25), considered most likely to be ICC. Eighteen patients (29%) had received prior chemotherapy, and 7 patients (11%) had prior liver resection. Extrahepatic disease was present in 19 patients (31%); however, the extrahepatic disease burden was deemed minimal. One patient had an ECOG PS of 2; the remainder of the cohort had ECOG PS 0 to 1. Patients underwent a mean of 2.7 TACE sessions. Median survival was 20 months from time of diagnosis, and 15 months from initial chemoembolization. Patients having received prior systemic chemotherapy survived longer than those who did not (28 months versus 16 months; $p = 0.02$).

In the largest series to date, Vogl et al treated 115 patients with unresectable cholangiocarcinoma from 1999 to 2010.[24] TACE regimens varied, with 24 patients receiving mitomycin-C, 8 patients receiving gemcitabine, 54 patients receiving both mitomycin-C and gemcitabine, and 29 patients receiving

Table 2 Current Series of Drug-Eluting Beads-Transcatheter Arterial Chemoembolization in the Treatment of Intrahepatic Cholangiocarcinoma

Investigators	Device	No. of patients	Patient factors		Median survival[a] (mo)
			Extrahepatic disease	Prior systemic chemotherapy	
Aliberti et al	Doxorubicin/DC beads	11	NA	NA	13
Poggi et al	Oxaliplatin/HepaSphere	9	Excluded	NA	30
Kuhlmann et al	Irinotecan/DC/LC beads	26	~40%	~20%	11.7

Abbreviation: NA, not applicable.
[a]From time of first drug-eluting beads-transcatheter arterial chemoembolization treatment.

mitomycin-C, gemcitabine, and cisplatin. Patients with Child-Pugh class C liver disease or extrahepatic disease were excluded. Patients received at least three TACE sessions, using stable disease after two treatment sessions or progressive disease as end points for treatment. Hypervascular tumors were present in 62 patients (54%), defined as those with tumor vessels clearly identified at angiography and lipiodol being confined solely to the site of the intended lesion on posttreatment noncontrast computed tomography. Median survival was 13 months from initial chemoembolization. No significant survival difference was observed between TACE regimens ($p = 0.28$). Tumor vascularity was identified as a positive prognostic indicator, among other factors.

Drug-Eluting Bead Chemoembolization

Drug-eluting bead (DEB) therapy consists of highly absorbent microspheres mixed with high doses of chemotherapy, prior to hepatic arterial delivery similar to conventional TACE procedures. With DEB-TACE, more favorable dose delivery and reduced systemic toxicity have been achieved in animal models and in patients with hepatocellular carcinoma when compared with conventional chemoembolization.[25–27] Multiple DEB platforms are available that have been used to deliver both doxorubicin and oxaliplatin chemotherapy regimens; only a few series to date have investigated DEB-TACE therapy in the treatment of ICC (►**Table 2**).

Aliberti et al were the first to report 11 patients who underwent TACE with DC Beads (Biocompatibles UK, Surrey, UK) loaded with doxorubicin.[28] All patients in this series had received prior systemic chemotherapy and/or hepatic resection. Patient characteristics, such as severity of liver disease, presence of extrahepatic disease, and tumor vascularity, were not described. A median of three treatment sessions was performed. Median survival was 13 months following the first DEB-TACE session.

Another small series by Poggi et al reported nine patients treated with microspheres (HepaSphere, Biosphere Medical, Roissy CDG Cedex, France) mixed with oxaliplatin, followed by systemic chemotherapy (oxaliplatin and gemcitabine).[29] Patients who received DEB-TACE were compared with a historical control receiving only systemic chemotherapy. Only one patient in the systemic chemotherapy arm had Child-Pugh class B liver disease; patients in both arms other-

wise had class A liver disease. Furthermore, extrahepatic disease was used as an exclusion criteria. With this in mind, an impressive median survival of 30 months was observed in the DEB-TACE arm, compared with 12.7 months for systemic chemotherapy alone ($p = 0.004$).

More recently, Kuhlmann et al compared treatment of 26 patients with unresectable cholangiocarcinoma with irinotecan-eluting PVA microspheres (DC/LC Bead, Biocompatibles, Farnham, UK) to 10 patients treated with conventional TACE (mitomycin and Gelfoam).[30] Comparison was also made with 31 patients treated with systemic chemotherapy only, consisting of gemcitabine and oxaliplatin.[10] Approximately 20% of patients in the chemoembolization arms had received prior systemic chemotherapy. Median overall survival was 11.7 months in the DEB-TACE group, 5.7 months in the conventional TACE group, and 11.0 months in the systemic chemotherapy group. Precise comparison between these groups is difficult, however, because the primary tumor site varied substantially between the groups, with 55% of tumors either extrahepatic or confined to the gallbladder in the systemic chemotherapy arm, compared with ~90% of tumors located within intrahepatic bile ducts in the chemoembolization arms. Extrahepatic disease was present in ~40% of patients treated with chemoembolization; 90% of patients treated with systemic chemotherapy had extrahepatic disease.

Yttrium-90 Radioembolization

Yttrium-90 (^{90}Y) radioembolization is a form of internal radiation consisting of the delivery of 20- to 40-μm particles via the hepatic artery; the ^{90}Y microspheres are taken up preferentially by hypervascular liver tumors, which then emit β-radiation. Higher local radiation doses are achievable compared with external radiation therapy; typically a target dose of 120 Gy is delivered (►**Fig. 2**). When tumors are bilobar, separate lobar treatments can be performed, separated by 4 weeks. Two devices are currently available including glass microspheres (TheraSphere, MDS Nordion, Ottawa, Ontario, Canada) and resin microspheres (SIR-Sphere, Sirtex, New South Wales, Australia).[31] As a newer technique, less data are available for ^{90}Y radioembolization compared with other intra-arterial therapies such as TACE (►**Table 3**).

In the first series to report ^{90}Y radioembolization, Ibrahim et al treated 24 patients with glass-based ^{90}Y microspheres

Figure 2 (A) A 59-year-old woman with intrahepatic cholangiocarcinoma, demonstrated by a large hypoattenuating mass in the right lobe of the liver. (B) Selective angiography of the right hepatic artery demonstrating significant tumor blush in the right lobe. Subsequently, ^{90}Y radioembolization was performed to a target dose of 120 Gy with the TheraSphere device. (C) Computed tomography (CT) scan performed 1 month after radioembolization demonstrates decreased size of the primary tumor and areas of decreased attenuation within the mass, indicative of central tumor necrosis. (D) CT scan performed at 6 months after radioembolization demonstrates a progressive decrease in the size of the primary tumor.

(TheraSphere).[32] Patients generally received one to two ^{90}Y treatments; sessions were separated by 30 to 60 days when bilobar disease necessitated multiple treatments. Seven patients (29%) had received prior systemic chemotherapy, and extrahepatic metastases were present in eight patients (33%). Bilobar disease was present in 16 patients (67%). Overall median survival was 14.9 months from the time of the first ^{90}Y session.

Saxena et al reported 25 patients treated with the resin-based ^{90}Y microspheres (SIR-Sphere).[33] Median survival was 9.3 months from the first treatment, and 20.4 months from tissue diagnosis. Compared with the study of Ibrahim et al, more patients had received prior systemic chemotherapy (17

patients, 68%) and had extrahepatic disease (12 patients, 48%). The 1-, 2-, and 3-year overall survival rates were 40%, 27%, and 13%, respectively.

Hoffmann et al treated 33 patients with resin-based ^{90}Y microspheres.[34] In this series, eight patients (24%) had extrahepatic disease; however, this was more strictly defined compared with other series as stable abdominal lymph nodes. Nine patients (27%) had ECOG PS 2; the remainder of the cohort was ECOG PS 0 to 1. Prior treatment included systemic chemotherapy in 27 patients (79%) and hepatic resection in 12 patients (36%). Five patients had received prior liver-directed therapy in the form of radiofrequency ablation or TACE. Patients had been diagnosed, on average, 21 months

Table 3 Current Series of [90]Y Radioembolization Treatment of Intrahepatic Cholangiocarcinoma

Investigators	Device	No. of patients	Patient factors		Median survival[a] (months)
			Extrahepatic disease (%)	Prior systemic chemotherapy (%)	
Ibrahim et al	Glass microspheres	24	33	29	14.9
Saxena et al	Resin microspheres	25	48	68	9.3
Hoffman et al	Resin microspheres	33	24	79	22

[a]From time of first ^{90}Y treatment.

prior to treatment with ^{90}Y microspheres. Tumors were bilobar in 21 patients (64%). Median overall survival was 22 months after the first ^{90}Y treatment and 43.7 months after initial diagnosis. Good performance status was associated with improved survival (29.4, 10, and 5.1 months for patients with ECOG PS 0, 1, and 2, respectively; $p < 0.001$).

Conclusion

Cholangiocarcinoma represents a spectrum of rare biliary tract cancers with an increasing incidence of ICC. The disease overall carries a poor prognosis, and most patients with ICC are unresectable at presentation. Several treatment options exist for unresectable ICC, with liver-directed therapies representing a favorable approach for palliative treatment given their targeted nature. Many series describing intra-arterial approaches have been reported, however, patient demographics vary substantially between studies, making exact comparison difficult. Prospective and/or randomized trials are difficult to perform due to the rarity of the disease. However, response rates and survival for ICC appear to be higher for liver-directed therapies than those reported with modern combination chemotherapy regimens. Future studies should strive to analyze the various subgroups of cholangiocarcinoma independently, principally ICC and ECC, such that useful comparisons can be made between liver-directed therapy, systemic therapy, and combined approaches.

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