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# Integration of chemoembolization and radioembolization into multimodal treatment of cholangiocarcinoma



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Over the last decade radioembolization and transarterial chemoembolization have been shown to be effective in unresectable intrahepatic cholangiocellular carcinoma. Unfortunately, up to now the evidence is not high with most of the conclusions drawn from single center retrospective analyses with small sample sizes treated in the salvage situation. However, the results are promising and suggest a survival benefit in the treatment of unresectable cholangiocellular carcinoma, even in an advanced stage with extrahepatic disease. In the following, available results of the treatment of unresectable cholangiocellular carcinoma by radioembolization and transarterial chemoembolization will be summarized. Special attention will be given to prognostic factors and efficacy as measured by response criteria. The potential integration of these therapies into multimodal treatment concepts will be discussed with focus on the intensification of therapy and a staged concept of therapy.

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## Introduction

Peripheral or intrahepatic cholangiocellular carcinoma (ICC) is a rare but devastating neoplasm. Its incidence and mortality have been reported to be increasing worldwide [1]. Prognosis is poor, with a five-year survival below 5%, including resected patients. Surgical treatment currently represents the only potentially curative therapy, but unfortunately only 30% of patients are eligible for resection because of disease spread, anatomic conditions, inadequate hepatic reserve or limiting comorbidities. Unfortunately intrahepatic recurrence is common with a resulting survival rate of 8–47% at five years [2–4].

The median survival of patients with unresectable disease has been reported to be 6–12 months [5]. Although modern chemotherapy regimens have improved survival considerably, median survival is still less than one year. A recent larger-scale randomized phase III trial of systemic therapy were published, comparing ‘gemcitabine alone’ with ‘gemcitabine plus cisplatin’ in a heterogeneous group of 410 patients with locally advanced or metastatic cholangiocarcinoma, gall-bladder cancer, or ampullary cancer. In that study the gemcitabine–cisplatin combination resulted in a significantly prolonged median overall survival of 11.7 months, compared with 8.1 months in the gemcitabine monotherapy group [6].

However, due to the different epidemiology, treatment and prognosis of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) it is necessary to consider both entities separately, especially when evaluating new treatment strategies [7].

The scope of this review is limited to the treatment of ICC (with a focus on intraarterial liver-directed therapies).

Several palliative therapeutic options exist for patients with unresectable ICC. The goals of palliative therapy are to control local tumor growth, to relieve symptoms, and to improve and preserve quality of life. Thus, local ablative treatment options are gaining attention, as results from studies analyzing percutaneous tumor ablation and intraarterial therapies have been encouraging [8–11].

Being indicative for successful percutaneous tumor ablation, Kim and colleagues reported excellent results for 13 patients with 17 unresectable but small ICC which have been treated by RFA in an early tumor stage (8 stage I, 3 stage II, 1 IIIB and 1 stage IV according to UICC). Local control was successful in 88% at a median follow-up of 19.5 months. In the two treatment failures, the tumors were more than 5 cm in diameter. The median overall survival was 38.5 months. One out of 17 RFA interventions was complicated by a liver abscess [12]. RFA should be performed only in patients with intermediate (3–5 cm) or small (<3 cm) intrahepatic cholangiocarcinomas that are not located subcapsular or adjacent to liver hilum, common bile duct, hepatic bifurcation or in the immediate proximity to large intrahepatic vessels because otherwise it may result in insufficient ablations, which are associated with a poorer clinical outcome. Considering that ICC is usually diagnosed in an advanced stage, these restrictions usually preclude the application of RFA.

In such cases interstitial high-dose-rate brachytherapy (HDR-BT), which is employable almost independently from lesion size and location, implies a good option: a recently published study evaluated outcome after repeated HDR-BT in 15 patients with unresectable ICC. They were treated by using an Iridium-192 source in afterloading technique through CT-guided percutaneous placed catheters in 27 sessions. Patients did not show extrahepatic metastasis and suffered from limited hepatic disease only (<5 lesions) with liver lesions measuring up to 12 cm (median size 5.25 cm (range, 1–12)). Median survival after local ablation was 14 months and after primary diagnosis 21 months [11].

One of the major challenges is the treatment of patients who have maintained good performance status but present with extensive liver involvement – beyond or beside systemic chemotherapy. In this context, intraarterial therapies consisting of transcatheter arterial chemoinfusion (TACI), Y90-Radioembolization (RE) and conventional transarterial chemoembolization (cTACE) or drug-eluting bead transarterial chemoembolization (DEB-TACE) represent a promising approach. In the following, available results of the treatment of unresectable cholangiocellular carcinoma by RE and TACE will be summarized with special focus on patient and tumor characteristics, factors with influence on survival and response.

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