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Is There Any Evidence for a Role of Local Treatment in Cholangiocarcinoma?

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Keywords
Cholangiocarcinoma · Local therapy · Locoregional therapy · Intervention

Summary
Background: Most cholangiocarcinomas (CCA) are locally advanced and unresectable at the time of diagnosis. Currently, chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced biliary tract cancer. However, median overall survival is only approximately 1 year. As the hepatic tumor burden is the limiting factor for the prognosis of these patients, local tumor control is essential. **Methods:** We present and discuss the current evidence for such therapy options for patients with CCA. **Results:** Local and locoregional therapies have been shown to be well tolerated and can contribute to tumor control in the context of a comprehensive oncologic treatment strategy, and may prolong survival of patients with advanced CCA. Unfortunately, only few high-quality clinical trials are available. **Conclusion:** Randomized prospective clinical trials enrolling larger numbers of patients need to be carried out to elucidate the precise value of these treatments alone as well as in combination with systemic chemotherapy.

Schlüsselwörter
Cholangiozelluläres Karzinom · Lokale Therapie · Lokoregionale Therapie · Intervention

Zusammenfassung
Hintergrund: Das cholangiozelluläre Karzinom (CCA) ist zum Zeitpunkt der Diagnose meist lokal fortgeschritten und damit inoperabel. Derzeit ist die Kombination von Gemcitabin mit einem platinhaltigen Agens das empfohlene Erstlinienbehandlungsschema für das fortgeschrittene CCA. Dennoch beträgt das mediane Gesamtüberleben damit nur etwa 1 Jahr. Da die Lebertumorlast der limitierende Faktor für die Prognose dieser Patienten darstellt, ist eine lokale Tumorkontrolle essenziell. **Methoden:** Wir präsentieren und diskutieren die aktuelle Datenlage solcher Behandlungsoptionen für Patienten mit CCA. **Ergebnisse:** Lokale und lokoregionale Therapien haben eine gute Verträglichkeit und können zur Tumorkontrolle im Rahmen einer umfassenden onkologischen Behandlungsstrategie beitragen, die das Überleben von Patienten mit fortgeschrittenem CCA verlängern kann. Leider stehen derzeit nur wenige qualitativ hochwertige klinische Studien zur Verfügung. **Schlussfolgerung:** Um die genaue Wertigkeit solcher Behandlungen alleine sowie in Kombination mit systemischen Therapien beurteilen zu können, bedarf es der Durchführung prospektiv randomisierter klinischer Studien mit großen Patientenzahlen.

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Introduction

Cholangiocarcinoma (CCA) is the second most common primary liver cancer. In Western countries, the incidence is increasing, and currently up to 1/100,000 people are diagnosed with CCA per year [1]. CCA defines all tumors originating from bile duct epithelium, including intrahepatic CCA (ICC) and extrahepatic CCA (ECC), as well as gallbladder carcinoma. ECC can be divided into perihilar carcinoma and distal ECC. Radical resection is the only curative treatment option. However, in cases with potentially curative surgery, 5-year survival rates of only 25–30% are reported, indicating an unmet need for multimodal treatment strategies to improve the cure rate of patients with CCA [2]. In the palliative setting, the treatment intent is to extend life expectancy, relieve symptoms of obstructive jaundice, and improve quality of life. Subclinical or frank cholangitis is associated with increased morbidity and mortality, and endoscopic biliary drainage is an established procedure for palliation of unresectable malignant hilar biliary strictures. In metastatic disease, chemotherapy improves quality of life and survival, and gemcitabine with cisplatin represents the standard of care based on recently published phase II and III clinical trials [3]. However, all patients ultimately progress on this therapy, and hence clinical trials with new and better agents and innovative treatment strategies are essential to expand the existing treatment options for patients with CCA. Thus, minimally invasive treatment options are gaining attention, such as photodynamic therapy (PDT) which consists of a photosensitizing agent in combination with laser irradiation, intraductal and percutaneous radiofrequency ablation (RFA), and high-dose-rate brachytherapy (HDR-BT), as well as transarterial approaches such as hepatic arterial infusion (HAI) chemotherapy, transarterial chemoembolization (TACE), and ^{90}yttrium radioembolization (RE). Here, we present and discuss the current evidence for these local and locoregional therapy options for patients with CCA.

Therapy Options for Cholangiocarcinoma

Photodynamic Therapy

One of the mainstays in the treatment of CCA is to relief obstructive jaundice through placement of biliary stents, which has been shown to improve symptoms and prevent infectious complications such as cholangitis. To further improve local control in CCA, PDT has been first introduced as a treatment modality in 1991. PDT is based on the relatively specific accumulation of photosensitizers, such as porphyrins, in dysplastic or malignant cells (fig. 1). Approximately 24–48 h after administration, non-thermal laser light of appropriate wavelength activates the photosensitizer. Laser activation creates toxic oxygen radicals that induce microvascular disturbances and degradation of membranes and lysosomes of the malignant cells [4]. PDT can be subsequently repeated depending on local tumor control and re-obstruction. Up to date, evidence for the use of PDT in CCA is based on three published randomized trials, three meta-analyses, and several retrospective, mostly single-center reports [3, 5–8]. In the pivotal clinical trial by Ortner et al. [5], PDT led to significant improvement in quality of life and prolonged overall survival from 3.3 to 16.4 months in 20 patients compared to 19 controls treated with stenting alone. These data were confirmed in a subsequent study with 32 patients in whom PDT increased median survival from 7 to 21 months [6]. Subsequently, several retrospective studies added more evidence that PDT is superior to stenting alone in the treatment of non-resectable CCA. These observations were summarized in a recently published meta-analysis which included six studies with 170 patients who received PDT using similar administration techniques compared to placement of either plastic or metal stents alone [9]. In this meta-analysis, PDT was associated with a statistically significant increase in median survival, improvement in Karnofsky scores, and a trend for decline in serum bilirubin. In summary, evidence is still rather low, but these studies indicate that PDT is associated with a promising trend toward improved survival as well as improvement in quality of life compared to stenting alone despite the significant heterogeneity between the different groups and potential selection bias.

However, there is clear evidence for a significant survival benefit for CCA patients treated with a combination of gemcitabine and cisplatin chemotherapy based on a large phase III clinical trial [10]. Therefore, the value of PDT has to be considered in the context of state-of-the-art chemotherapy. In this regard, Talreja et al. [11] recently reported their outcome in 55 patients with unresectable CCA, who received either Photofrin®(porfimer sodium; Pinnacle Biologics, Inc., Bannockburn, IL, USA)-based PDT alone or in combination with chemotherapy and/or radiation between 2004 and 2010 [11]. 26 patients received chemotherapy and/or radiation therapy, whereas 29 patients were treated with PDT alone. In all patients, plastic stents were systematically placed following PDT. Median survival of patients treated with PDT alone was 190 days compared to 257 days for patients additionally receiving chemotherapy and/or radiation. Due to the small sample size, the difference in survival was not statistically significant. However, in line with this study, the not yet fully published Photostent-02 study revealed similar findings. In the UK Photostent-02 trial, 92 patients with confirmed CCA were randomized to receive PDT plus stenting or stenting alone. Overall survival was significantly reduced to 5.6 months for PDT plus stenting compared to 8.5 months for stenting alone (hazard ratio 1.8; $p = 0.027$). At this point, the reasons for the poor overall survival in the PDT group remain elusive. However, only 9 patients in the PDT/stenting arm compared to 19 patients in the stenting alone arm received subsequent chemotherapy. Overall survival was significantly improved among those who had chemotherapy

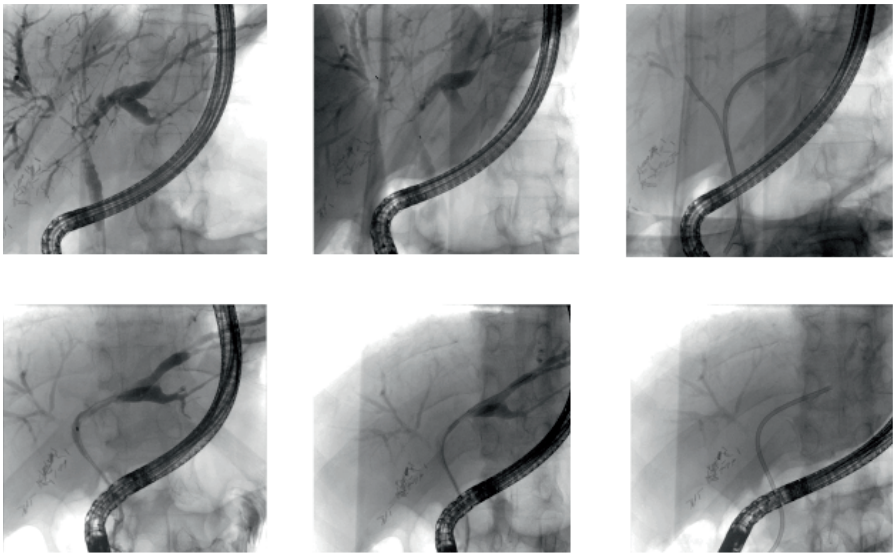

Fig. 1. Endoscopic images before, during, and after photodynamic therapy (PDT; top row) as well as endobiliary radiofrequency ablation (eRFA; bottom row). In 2012, an interruption of the contrast medium was seen at the right ductus hepaticus, which was treated with PDT and stent placement. In 2013, the tumor progressed into the left ductus hepaticus, which was subsequently treated with eRFA and stent placement.

compared with those who did not (11.1 vs. 4.8 months; p = 0.001), suggesting that lack of subsequent palliative chemotherapy may partly explain the detrimental effect in this trial [12]. Very recently, results of a phase II trial from Korea were published in which 43 patients with unresectable hilar CCA were randomly assigned to receive either PDT plus the oral fluoropyrimidine S-1 or PDT alone [13]. In this trial, PDT plus S-1 was associated with a significant improvement in overall survival (17 vs. 8 months; p = 0.005) and progression-free survival (10 vs. 2 months; p = 0.005) compared with PDT alone, strongly suggesting that effective tumor control with systemic chemotherapy is required in CCA.

Most trials suggest that PDT only induces minimal side effects, with the most frequently encountered adverse effect being phototoxicity to the skin. However, a significant number of patients, more than 50% in some reports [14], subsequently develop infectious complications such as cholangitis or hepatic abscesses due to stenting complications or as the result of necrosis associated with PDT. Infectious complications due to PDT may not only have direct consequences on survival but may also delay exposure to chemotherapy in CCA patients.

Together, these data indicate that PDT may be of value in highly selected patients. Additional prospective studies are clearly required to specifically analyze the impact of PDT on the morbidity and mortality of patients with CCA, specifically in the context of systemic chemotherapy. In the recently published guidelines for the treatment of CCA from the British Society of Gastroenterology, PDT is not recommended for routine use based on the most recent data [53].

Endobiliary Radiofrequency Ablation

One of the problems associated with PDT is related to its phototoxicity requiring patients to avoid exposure to sunlight for 4–6 weeks. Another innovative technique to ensure continued biliary drainage is endobiliary RFA (eRFA) (fig. 1). Percutaneous RFA has been previously employed in the treatment of ICC as discussed below. ECC, however, are mostly not amenable to percutaneous RFA treatment, and eRFA may be an attractive alternative. Similarly to percutaneously applied RFA, eRFA is a minimally invasive technique that uses high-frequency alternating current to heat tissue to the point of coagulation, leading to local tumor destruction over a length of approximately 2–3 cm. One of the first published studies included 21 patients with unresectable biliary obstruction due to pancreatic and biliary cancer [15]. Successful self-expandable metal stent placement was achieved in all patients following eRFA allowing initial biliary decompression in 21 patients. Moreover, 30-day stent patency was achieved in 20 patients, and at 90-day follow-up stent patency was preserved in 16 of 19 living patients. Subsequently, it was shown in 39 patients that eRFA may also be safely performed via the percutaneous transhepatic route with an over-the-wire technique [16]. In this study, all but 1 patient had patent stents at the time of last follow-up or death. Both series did not reveal any new unsuspected safety concerns. Together, the so far available evidence suggests that eRFA is safe and feasible and may prolong stent patency in patients with malignant biliary obstruction. Randomized clinical trials are now required to determine how eRFA can be integrated in the multimodal treatment of CCA.

Radiofrequency Ablation

Percutaneous image-guided RFA is a minimally invasive technique that uses high-frequency alternating current to heat tissue to the point of coagulation with the aim of local

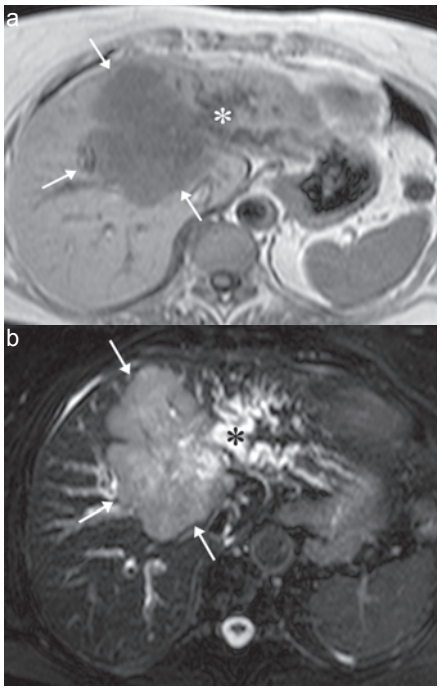

Fig. 2. a T1- and **b** T2-weighted magnetic resonance image of a 61-year-old woman with a centrally located intrahepatic cholangiocarcinoma (arrows) with preferentially left-sided cholestasis (asterisk).

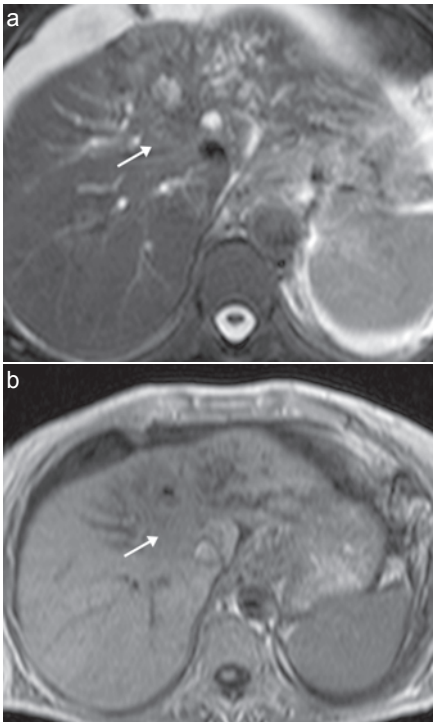

Fig. 4. A T1- and **B** T2-weighted magnetic resonance image 2 years and 1 month after high-dose-rate brachytherapy showing a marked decrease in tumor size (arrow) and regressive cholestasis.

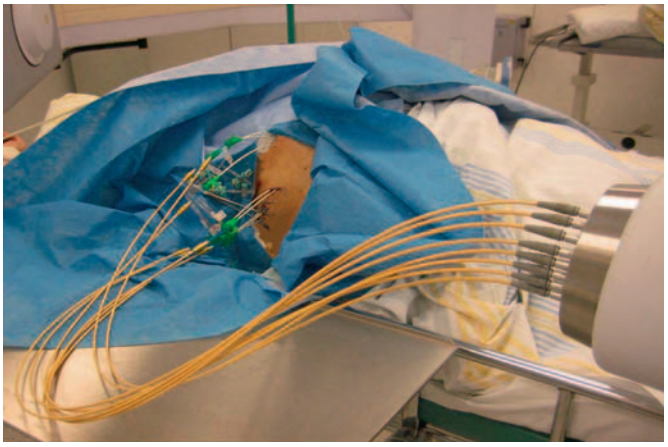

Fig. 3. Image of the patient with a total of 8 catheters placed intratumorally for high-dose-rate brachytherapy with a tumor-enclosing dose of 15 Gy. The closed-end brachytherapy catheters are already connected to the afterloader (microSelectron®; Nucleotron, Elekta, Stockholm, Sweden).

tumor destruction. RFA has been reported to be safe and effective in the local control of hepatic malignancies in patients considered unsuitable for surgical resection, regardless of tumor vascularity [17–19]. In a study including 13 patients with 17 primary ICC (10 tumors <3 cm, 5 tumors 3–5 cm, 2 tumors >5 cm) treated with RFA, local control was achieved in 88%. The median overall survival period was 38.5 months [20]. In the two treatment failures, the tumors were more than 5 cm in diameter. Thus, RFA may provide successful local tumor control in patients with intermediate (3–5 cm) or small (<3 cm) ICC.

High-Dose-Rate Brachytherapy

In HDR-BT, liver malignancies are treated by percutaneous placement of brachytherapy catheters under cross-sectional image guidance followed by a single intratumoral high-dose-rate irradiation with iridium-192 of typically 15–20 Gy using an afterloading technique (figs. 2–4) [21, 22]. This technique was established in 2002 and has been subsequently used with promising outcomes, e.g., in colorectal cancer metastases or hepatocellular carcinoma [23, 24]. HDR-BT has been proven valuable especially in those lesions unfavorable for RFA because of large diameters (up to 10–13 cm), complex shape, or closeness to central bile ducts or vessels [25]. Specifically in patients in whom RFA is not feasible owing to larger tumor size (>5 cm) or adjacent larger vessels which can cause convection of heat (cooling effect) during thermal ablation, possibly resulting in incomplete ablation, HDR-BT may be an alternative option [26]. As ICC regularly arises from larger bile ducts, which are adjacent to the major vessels, such a condition is encountered frequently in this tumor entity so that a considerable number of ICC lesions are not suitable for RFA.

Schnapauff et al. [21] evaluated outcomes after repeated interstitial HDR-BT (27 sessions) in 15 patients with unresectable ICC, who did not show extrahepatic metastasis and suffered from limited hepatic disease only. The median size of liver lesions was 5.25 cm (range 1–12 cm). Median local tumor control, including repeated local ablations, was 11 months with a median survival of 21 months after primary diagnosis. We have evaluated the clinical outcome in a total of 55 patients with unresectable ICC treated with a tailored therapeutic approach combining systemic with advanced image-guided local

or locoregional therapies such as RFA, HDR-BT, HAI chemotherapy, TACE, or RE, with the majority of patients (n = 45; 83%) being treated with HDR-BT (own submitted but yet unpublished data). 8 (15%) patients showed complete remission, 21 (38%) partial remission, 8 (15%) stable disease, and 18 (33%) progressive disease with a median overall survival of 33.1 months (95% confidence interval 16.5–49.8 months) from the time of first diagnosis. Remarkably, these results were comparable to those after surgical resection with curative intent with a median survival of 27–36 months [27–29].

Hepatic Arterial Infusion Chemotherapy

In HAI chemotherapy, the chemotherapeutic agent is delivered through a (micro-)catheter-port system into the hepatic artery and implanted via the common femoral artery as described elsewhere [30], which can be performed on an outpatient basis. This method minimizes systemic side effects (e.g. nausea and vomiting) and maximizes the chemotoxic effects of the drugs on the hepatic malignancy [31, 32]. The rationale to apply HAI chemotherapy to patients with CCA is strengthened by the high hepatic extraction on the first pass of some drugs that reach the bile canaliculi at high concentrations and by the finding that the blood supply of the upper biliary tree and gallbladder derives from the hepatic artery [33, 34]. There are only a few retrospective reports with small patient numbers published to date concerning the effectiveness of HAI chemotherapy in these rare tumors [35–37]. Among them, an analysis of 32 patients represents the largest trial, but a variety of biliary tract carcinomas (i.e., 17 patients with ICC and ECC and 15 patients with gallbladder carcinoma) were included. The HAI chemotherapy protocol consisted of a combination of 5-fluorouracil (5-FU), cisplatin, and folinic acid. In comparison to patients treated with supportive measures or with systemic chemotherapy alone, this regimen showed rather good activity and an improvement in survival. However, it was not a randomized prospective trial. Thus, any conclusions from these data are of limited value. In a phase II trial, 30 consecutive patients with advanced or metastatic biliary tumors were treated with epirubicin and cisplatin administered as a bolus into the hepatic artery on day 1, combined with systemic continuous infusion of 5-FU per day from day 1 to day 14, every 3 weeks [31, 38]. In this heterogenous patient group, the overall response rate was 40% including 1 complete response and 11 partial responses with a median patient survival of up to 13.2 months.

Transarterial Chemoembolization

TACE includes two therapeutic strategies to target solid tumors – the intra-arterial application of a chemotherapeutic drug combined with hepatic artery embolization. Severe systemic toxicity is limited because only about 15% of the agent administered appears in the periphery, resulting in a favorable side effect profile as compared with systemic chemotherapy. Conventional TACE has been studied as a palliative treatment option for CCA with protocols using lipiodol in combination with mitomycin C, gemcitabine, cisplatin, or doxorubicin. In a small study of 15 unresectable ICC who received palliative TACE with a mixture of lipiodol and mitomycin C, median survival was reported to be 16.3 months [39]. In a study by Vogl et al. [40], 115 patients were treated with a total of 819 TACE using different protocols (mitomycin C alone, gemcitabine alone, gemcitabine and mitomycin C or gemcitabine, mitomycin C and cisplatin), which resulted in a median overall survival of 13 months. Another trial investigated the effect of TACE using mitomycin C, doxorubicin, and cisplatin in 62 patients with ICC or adenocarcinoma of unknown primary reporting a median survival of 20 months from diagnosis and 15 months from the time of first TACE [41]. In a study conducted by Park et al. [42], 72 patients with untreated unresectable CCA received a cisplatin-based TACE as first-line therapy. Survival after diagnosis was measured and compared with that of patients who received supportive therapy only. Median survival was 12.2 months for the TACE group and 3.3 months for the supportive treatment group. Taken together, these studies showed a significant survival benefit for patients with CCA treated with TACE compared to patients who received best supportive care. However, no definite conclusions can be drawn from these data, since none of the studies were prospective comparative trials.

Drug-Eluting Bead TACE

Chemoembolization with drug-eluting beads (DEB) combines a controlled drug release from beads with a reduction in blood flow by embolization. In a small retrospective comparison of 9 patients who underwent DEB-TACE with oxaliplatin associated with systemic chemotherapy applying oxaliplatin and gemcitabine, overall survival was with 30 months significantly increased as compared to 12.7 months in a historical group of 11 patients treated with chemotherapy only [43]. Another small but prospective trial compared TACE with DEB loaded with doxorubicin (n = 11) with palliative care or systemic chemotherapy (n = 9) [44]. A response rate of 100% according to RECIST criteria was observed in the locoregional treatment group. Median survival was with 13 months significantly prolonged as compared to 7 months in patients who received palliative care or chemotherapy. DEB-TACE using beads containing irinotecan was investigated in another study of 26 patients with histologically proven ICC and compared retrospectively with conventional TACE with mitomycin C and to systemic chemotherapy with oxaliplatin and gemcitabine [45]. Local tumor control was achieved in 66% of patients receiving DEB-TACE that resulted in a median overall survival of 11.7 months compared with 5.7 months in patients treated with conventional TACE

and 11.0 months in patients receiving systemic chemotherapy. Despite the fact that the study was retrospective, DEB-TACE is feasible and may be more effective than conventional TACE in the treatment of ICC. However, again results of prospective trials are lacking. Thus, no definite conclusions ought to be drawn.

^{90}Yttrium Radioembolization

RE is another promising catheter-based liver-directed modality approved by the U.S. Food and Drug Administration for the treatment of patients with primary and metastatic liver cancer [46, 47]. For this interventional technique, microspheres of glass or resin, impregnated with the isotope ^{90}yttrium, are infused directly into the hepatic arteries where they become lodged within the tumor microvasculature so that the β-emissions from the isotope can irradiate the tumor. The mean tissue penetration is only 2.5 mm with a maximum range of 11 mm. Two preliminary studies with 24 and 25 patients have shown favorable initial results for RE, with an overall survival of 9.3 and 14.9 months, respectively [48, 49]. In another trial, 19 patients with unresectable ICC underwent a total of 24 RE [50]. Median survival from the time of diagnosis and first procedure in this population was 25.1 and 11.5 months, respectively. Hoffmann et al. [51] retrospectively investigated RE in 33 patients with unresectable ICC. Most of the patients were pretreated with different therapies. Response rates after 3 months were: partial response in 12 (36.4%) patients, stable disease in 17 (51.1%), and progressive disease in 5 (15.2%). Median overall survival was 22 months. In a large multi-institutional analysis of 198 patients, the effects of various intra-arterial therapies for advanced ICC were evaluated, with RE being applied in 46 patients [52]. Median overall survival in these patients was 11.3 months, which was comparable to conventional TACE, the locoregional therapy most frequently applied in this trial.

Conclusion

In metastatic disease, chemotherapy improves quality of life and survival, and gemcitabine with cisplatin represents the standard of care. However, all patients ultimately progress on this therapy, so clinical trials with new and better agents are essential to expand the existing treatment options for patients with biliary cancer. Local and locoregional therapies have been shown to be well tolerated and effective in the treatment of CCA, nevertheless their precise role needs to be evaluated in phase III prospective trials.

Disclosure Statement

The authors disclose that they have no conflicts of interest.

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