Colangiocarcinoma intra-epatico: Trattamenti intra-arteriosi

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Intrahepatic cholangiocarcinoma (ICC) is the second most common (15%) primary liver cancer after hepatocellular carcinoma (HCC), with a rate of about 2.1/100,000 people per year in western countries.

Long established risk factors for CCA: hepatobiliary flukes, PSC, biliary tract cysts, epatolithiasis.

More recently recognized risk factors for iCCA are similar to those known for HCC: cirrhosis, chronic hepatitis B and C and alcohol.

The prevalence of these risk factors is much lower for iCCA than for HCC.
CLASSIFICATION

- The classification of the disease is based on the anatomic location: intra and extrahepatic cholangiocarcinoma.

- Intrahepatic cholangiocarcinoma (ICC) constitutes no more than 5–15% of all cases.

- The prognosis of the disease is dismal and surgical resection is the only curative treatment option with five-year survival rates varying from 14% to 40% (unspecific clinical symptoms and central localization).

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Anderson CD et al. Oncologist. 004;9:43-57
Surgical resection is the mainstay for treatment of iCCA. Unfortunately, only about 20–40% of ICCs are diagnosed at a stage which meets the criteria for curative resection. Moreover, curative-intent surgery is mainly limited by the high recurrence rate of this cancer.

If untreated, unresectable ICCs have a median survival of less than 8 months which can be increased to approximately 12 months with systemic chemotherapy (gemcitabine and cisplatin).
Over the last decade, the use of image-guided loco-regional therapies (LRT) as a palliative option in unresectable ICC has become increasingly accepted among multidisciplinary teams that manage this subset of liver cancer patients.

Intra-arterial therapies (IAT) are the most commonly used approaches for the treatment of ICC.

Embolic materials and/or chemotherapeutic agents or internal radiation can be delivered directly to the tumor with high doses within the tumor tissue while significantly reducing its systemic distribution.

Most commonly used IAT: HAI/TACI, C-TACE, DEB-TACE and TARE.

The current management of cholangiocarcinoma: A comparison of current guidelines

Yulong Cai¹², Nansheng Cheng¹, Hui Ye¹, Fuyu Li¹, Peipei Song³*, Wei Tang¹²

Table 1. Current guidelines on cholangiocarcinoma

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Approach</th>
<th>Content</th>
<th>Tumor</th>
<th>Evaluation measures</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN Guideline (2016)</td>
<td>Expert panel</td>
<td>D&amp;T + E + F</td>
<td>CC, GBC, HCC</td>
<td>Consensus categories</td>
<td>(14)</td>
</tr>
<tr>
<td>SEOM Guideline (2015)</td>
<td>Literature analysis</td>
<td>D&amp;T + E</td>
<td>CC, GBC</td>
<td>Evidence categories and recommendation grades</td>
<td>(13)</td>
</tr>
<tr>
<td>Japanese Guideline (2014)</td>
<td>Expert panel</td>
<td>D&amp;T + E</td>
<td>CC, GBC, AC</td>
<td>Evidence categories and recommendation grades</td>
<td>(18)</td>
</tr>
<tr>
<td>Chinese Guideline 1 (2014)</td>
<td>Expert panel</td>
<td>D&amp;T + E</td>
<td>CC</td>
<td>Evidence categories and recommendation grades</td>
<td>(16)</td>
</tr>
<tr>
<td>BSG Guideline (2012)</td>
<td>Expert panel</td>
<td>D&amp;T + E + F</td>
<td>CC</td>
<td>Evidence categories and recommendation grades</td>
<td>(15)</td>
</tr>
<tr>
<td>Asia-Pacific Guideline (2013)</td>
<td>Expert panel</td>
<td>D&amp;T + E</td>
<td>pCC</td>
<td>Evidence categories and recommendation grades</td>
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<td>Chinese Guideline 2 (2013)</td>
<td>Expert panel</td>
<td>D&amp;T</td>
<td>pCC</td>
<td>Evidence categories and recommendation grades</td>
<td>(17)</td>
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<tr>
<td>BSG Guideline (2012)</td>
<td>Literature analysis</td>
<td>D&amp;T + E + F</td>
<td>CC</td>
<td>Evidence categories and recommendation grades</td>
<td>(11)</td>
</tr>
<tr>
<td>Italian Guideline (2010)</td>
<td>Expert panel</td>
<td>D&amp;T + E</td>
<td>CC</td>
<td>Evidence categories and recommendation grades</td>
<td>(12)</td>
</tr>
</tbody>
</table>

D&T, diagnosis and treatment; E, epidemiology; F, follow up; CC, cholangiocarcinoma; pCC, perihilar cholangiocarcinoma; iCC, intrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma; AC, ampullary carcinoma; HCC, hepatocellular carcinoma.
Figure 2. The treatment algorithm in current guidelines for cholangiocarcinoma. *Major hepatectomy with small FLR volume or insufficient liver function. PVE, portal vein embolization; LT, liver transplantation; GC, Gemcitabine/cisplatin combination.
Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma

John Bridgewater¹, Peter R. Galle², Shahid A. Khan³, Josep M. Llovet⁴,⁵, Joong-Won Park⁶, Tushar Patel⁷, Timothy M. Pawlik⁸, Gregory J. Gores⁵,*

Recommendations

- The 7th edition of the AJCC/UICCA staging schema is currently the preferred staging system for resected ICCA
  Recommendation B1

Table 3. TNM definition according to the new chapter of intrahepatic cholangiocarcinoma

<table>
<thead>
<tr>
<th>Primary tumors (T)</th>
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<tr>
<td>TX</td>
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<tr>
<td>T0</td>
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<tr>
<td>Tis</td>
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<tr>
<td>T1</td>
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<tr>
<td>T2a</td>
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<td>T2b</td>
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<td>T3</td>
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<td>T4</td>
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</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
</tr>
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<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
</tbody>
</table>

Distant metastasis (M)

| M0 | No distant metastasis |
| N1 | Distant metastasis |
Fig. 3. A suggested treatment algorithm for patients with iCCA. These are standard of practice recommendations. Larger and appropriate studies are required to provide evidence for standard of care guidelines.
Hepatic arterial infusion chemotherapy, through an implanted port system (HAI), represents a loco-regional approach that administers a continuous infusion of drug directly into the liver.

The greatest experience with HAI has been in patients with colorectal liver metastases. Several studies have demonstrated the efficacy of HAI with significantly higher response rates, less toxicity and a potential survival benefit compared to systemic chemotherapy alone.

By contrast, experience with HAI in primary liver cancers is much more limited.
Phase I/II Study of Hepatic Arterial Infusion Chemotherapy With Gemcitabine in Patients With Unresectable Intrahepatic Cholangiocarcinoma (JIVROSG-0301)

Yoshitaka Inaba, MD,* Yasuaki Arai, MD,† Hidekazu Yamaura, MD,* Yozo Sato, MD,* Mina Najima, MD,* Takeshi Aramaki, MD,‡ Miyuki Sone, MD,§ Takashi Kumada, MD,¶ Noboru Tanigawa, MD,¶ Hiroshi Anai, MD,** Tetsuya Yoshioka, MD,†† and Masafumi Ikeda, MD,‡‡ for Japan Interventional Radiology in Oncology Study Group (JIVROSG)

- 11 patients with unresectable ICC were treated with infusion of fluorouracil combined with a variety of other agents (doxorubicin, mitomycin C, cisplatin).
- Mean survival of 26 months.
- Tanaka et al reported the most favorable survival outcomes in the literature for patients with unresectable ICC, despite a patient cohort that included 63% (7/11) with extrahepatic disease.

- 25 patients were enrolled from May 2004 to November 2006.
- Histologically confirmed ICC.
- Not responder to other chemotherapy.
- ECOG 2 or less.
- Median survival: 340 days.
- The disease control rate and MST were acceptable, but, considering that the implanted catheter-port system was required for HAI as a painful procedure, it cannot be claimed that this protocol has an advantage over systemic treatment.
Unresectable Intrahepatic Cholangiocarcinoma: Systemic Plus Hepatic Arterial Infusion Chemotherapy is Associated with Longer Survival Compared to Systemic Chemotherapy Alone

Ioannis T. Konstantinidis, MD1, Bas Groot Koerkamp, MD1, Richard K.G. Do, MD2, Mithat Gonen, PhD3, Yuman Fong, MD1, Peter J. Allen, MD1, Michael I. D’Angelica, MD1, T. Peter Kingham, MD1, Ronald P. DeMatteo, MD1, David S. Klimstra, MD4, Nancy E. Kemeny, MD5, and William R. Jarnagin, MD1

- HAI (methotrexate and 5-fluorouracil) was administered to 110 patients. 56 patients received concomitant (dex)
- Between 1/2000 and 8/2012, 525 patients with ICC were evaluated. 167 with unresectable disease confined to the liver were enrolled: 74 (SYS) and 93 (HAI + SYS).
- Patients with ICC had a higher response rate (53.8%) compared with those with HCC (25%).
- One patient with ICC responded sufficiently to undergo resection.
- The median survival in the combined group was longer compared to patients who received SYS alone (30.8 months vs 18.4 months).
- Eight patients who initially presented with unresectable tumors responded enough to undergo complete resection and had a median overall survival of 37 months (range=10.4 – 92.3 months).
Conventional TACE is the most commonly used intra-arterial modality in unresectable ICC.

During cTACE, an emulsion of chemotherapeutics and an oil-based contrast agent (Ethiodol or Lipiodol) is injected into the tumor-supplying branches, followed by the administration of an embolizing agent.

The most commonly used drug combination in the US and Europe consists of doxorubicin, cisplatin and mitomycin-C, but gemcitabine has also been used.

TACE is tolerated well by the majority of patients without major adverse events.

Most studies that investigate clinical outcomes in ICC treated with cTACE are retrospective and do not use a standardized procedure protocol. However, the available literature suggests potential survival benefits in patients with unresectable lesions.
A retrospective analysis included 15 patients treated with cTACE using mitomycin-c (10 mg) for 59 treatment sessions over a period of six years. The patients were diagnosed with inoperable ICC with a mean tumor diameter of 10.8±4.6 cm and multifocal disease in seven patients. Previous treatments were reported for seven patients including liver resection (n=1, 6.7%), RFA (n=2, 13.3%) and systemic chemotherapy (n=4, 26.7%). One patient (6.7%) had liver cirrhosis, however, Child Pugh score was A in 14 (93.3%) and B in one patient (6.7%). Median OS of 16.3 months.
C-TACE

Chemoembolization of Intrahepatic Cholangiocarcinoma With Cisplatinum, Doxorubicin, Mitomycin C, Ethiodol, and Polyvinyl Alcohol

A 2-Center Study

Matthew V. Klefer, BA; Marissa Albert, BA, MSc; Madeline McNally, MD; Mary Robertson, RN; Weijing Sun, MD; Douglas Fraker, MD; Kim Othoff, MD; Kathleen Christians, MD; Sam Pappas, MD; William Rilling, MD; and Michael C. Soulen, MD

- Retrospective analysis included 62 patients Treated with conventional TACE (cisplatin, doxorubicin, and mitomycin C)
- Eighteen patients (29%) had received prior conventional chemotherapy, and 7% had prior liver resection
- Eighteen patients (29%) had extrahepatic disease
- 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 OS for the entire cohort 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)
Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma

S.-Y. Park¹, J.H. Kim²,*, H.-J. Yoon³, I.-S. Lee³, H.-K. Yoon³, K.-P. Kim⁴

Compared cTACE (n=72) with symptomatic supportive therapy (n=83) in the palliative treatment of 155 patients with unresectable ICC.

Extrahepatic disease was found in 39 patients (54%) of the TACE cohort and in 50 patients (60%) of the supportive care group.

Median OS in the TACE group (12.2 months) compared to the supportive treatment group (3.3 months).

Prospective trials included 115 patients with unresectable ICC treated with TACE from 1999 to 2010.

TACE regimens varied, mitomycin-C, gemcitabine, both mitomycin-C and gemcitabine and cisplatin.

Patients with Child-Pugh class C liver disease or extrahepatic disease were excluded.

Hypervascular tumors were present in 62 patients (54%).

Median survival was 13 months from initial chemoembolization.

No significant survival difference was observed between TACE regimens.

Tumor vascularity was identified as a positive prognostic indicator, among other factors.
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.

Multiple DEB platforms are available that have been used to deliver both doxorubicin and oxaliplatin and irinotecan chemotherapy regimens.

Only a few series to date have investigated DEB-TACE therapy in the treatment of ICC.
DEB-TACE

Cardiovasc Intervent Radiol (2009) 8

OEM-TACE: A New Therapeutic Approach in Unresectable Intrahepatic Cholangiocarcinoma

Guido Poggi · A. Amatu · B. Montagna · P. Quaretti · C. Minoia · C. Sottani · L. Villani · B. Tagliaferri · F. Sottoteti · O. Rossi · E. Pozzi · F. Zappoli · A. Riccardi · G. Bernardo

- Small retrospective comparative study including 11 patients who underwent TACE with DC Beads (Biocompatibles UK, Surrey, UK) loaded with doxorubicin.
- Small retrospective comparative study including 9 patients treated with oxaliplatin-preloaded (50 mg) microspheres (HepaSpheres, Biosphere Medical, France) combined with systemic chemotherapy (oxaliplatin and gemcitabine).
- These patients were compared to a retrospectively acquired group of eleven patients, who were treated with chemotherapy (FOLFOX) only.
- With one exception, Child Pugh class B and C as well as extrahepatic disease were exclusion factors in both groups.
- The median OS after DEB-TACE and chemotherapy was 30 months compared to 12.7 months for chemotherapy alone.
A prospectively designed multi-institutional review included 24 patients with unresectable ICC total of 42 DEB-TACE sessions.

The DEB-TACE regimen using DC/LC Beads (Biocompatibles, Farnham, UK) consisted of doxorubicin (150 mg) and irinotecan (75 mg; range, 40–100 mg) and was combined with systemic chemotherapy in eight patients (33.3%).

The median OS was 17.5 months.

Three patients (12.5%) were converted to surgical resection postprocedurally.

DEBIRI (irinotecan 200 mg; DC/LC Beads, Biocompatibles/BTG, UK; n = 26).

cTACE (mitomycin-c 15 mg; gelfoam; n = 10).

Compared to cTACE and systemic chemotherapy, DEBIRI revealed prolonged median OS (5.7 vs. 11.7 months).

The median OS was 17.5 months.

Three patients (12.5%) were converted to surgical resection postprocedurally.
Y-90

• Y90-RE is a form of selective internal radiation therapy (SIRT). The concept consists of the intra-arterial delivery of small embolic particles (20–40 μm) containing the radionucleotide Y90, that emits β-radiation. Y90-RE allows maximization of treatment efficacy while sparing the healthy liver parenchyma from radiation-induced injury.

• Currently, two major devices are available: glass-based microspheres (TheraSphere, MDS, Nordion, Ottawa, Ontario, Canada) and resin-based microspheres (SIR-Sphere, Sirtex, New South Wales, Australia).

• Given the small size and the severe radiation potency of Y90-particles, complications may derive from unintended extrahepatic deployment of the payload.

• All patients must be subjected to shunt evaluation using technetium-99 macroagglutinated albumin (Tc-MAA), SPECT and angiographic imaging.

Hoffmann RT et al. Cardiovasc Intervent Radiol 2012;35:105-16
Mouli S et al. J Vasc Interv Radiol 2013;24:1227-34
Treatment of Unresectable Cholangiocarcinoma Using Yttrium-90 Microspheres

Results From a Pilot Study

Saad M. Ibrahim

25 patients with histologically confirmed ICC underwent resin-based 90Y radioembolization for unresectable ICC between January 2004 and May 2009. (Follow-up available for 22 patients), according to the WHO Criteria, a partial response (PR) in 6 patients (27%), stable disease (SD) in 15 patients (68%), and disease progression in one patient (5%), and according to the EASL Criteria, a complete response in two lesions (9%) and a PR in 17 lesions (77%).

Survival was significantly correlated to two factors: peripheral tumor type (vs infiltrative; p = 0.004) and an ECOG performance status of 0 (vs 1 and 2; p < 0.001).

The median survival of patients with peripheral versus infiltrative tumors was 31.8 and 5.7 months, respectively.

The median survival for patients with and without portal vein thrombosis was 5.7 and 31.8 months, respectively.

The median survival was significantly prolonged in patients with ECOG performance status 0 than in those with status 1 and 2 (31.8 vs 6.1 and 1 month, respectively, p < 0.0001).
Y-90 Radioembolization for Intrahepatic Cholangiocarcinoma: Safety, Response, and Survival Analysis


- The series of 33 patients expands upon the prior report by Ibrahim.
- Including forty-six patients who were treated with Y90 radioembolization at a single institution from July 2003 to May 2011, median OS was 9.8 months.
- Survival and TTP were significantly prolonged in patients with ECOG 0 versus ECOG 1 or 2 (median OS: 25.6, 10, and 5.1 months, respectively; TTP: 17.5, 6.9, and 2.4 months, respectively), in those with a tumor burden ≤25% (OS: 26.7 vs 6 months; TTP: 17.5 vs 2.3 months) or in those with tumor response (PR or SD vs progressive disease; OS: 35.5, 17.7 vs 5.7 months, respectively; TTP: 31.9, 9.8 vs 2.5 months, respectively).
Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis

D.P. Al-Adra a, R.S. Gill a, S.J. Axford b, X. Shi c, N. Kneteman a, S.-S. Liau d,∗

a Department of Surgery, University of Alberta, Edmonton, AB, Canada
b St. George’s University, University Centre, Grenada, West Indies
C Center for the Advancement of Minimally Invasive Surgery, Royal Alexandra Hospital, Edmonton, AB, Canada
d Hepatopancreato-biliary Surgical Unit, University Department of Surgery, Addenbrooke’s Hospital, University of Cambridge, United Kingdom

Y-90

• Showed benefits with chemotherapy and clinical outcomes of stage B/C treated with Y-90-TARE are comparable to resectable ICC
• 22 patients with severe HLA – control group treated with CIS-GEM
• Median progression-free survival after TARE of 10.3 months
• Longer progression-free survival with chemotherapy was associated with respectively 20.0 versus 8.8 months (p = 0.001)

chemotherapy prior to or during the treatment
Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study

Cristina Mosconi¹, Anne Giulia Gramenzi², Salvatore Ascanio¹, Alberta Cappelli¹, Matteo Renzulli¹, Cinzia Pettinato³, Giovanni Brandi⁴, Fabio Monari⁵, Alessandro Cucchetti⁶, Franco Trevisani² and Rita Golferi¹

- 23 patients between 2010-2015.
- The overall median survival was 17.9 months.
- Longer survival in naive patients as compared with patients in whom TARE was preceded by other treatments.
### TABLE 1. Summary of Individual Studies Selected for Meta-Analysis of HAT Outcomes for Unresectable ICC

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Sample</th>
<th>Study design</th>
<th>Treatment regimen</th>
<th>EHD%</th>
<th>RECIST response (CR + PR)</th>
<th>Median survival (months)</th>
<th>Toxicities</th>
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<td><strong>HAI</strong></td>
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<tr>
<td>Tanaka et al. (2002) [22]</td>
<td>11 PC</td>
<td>5-FU, Doxorubicin, MMC, Ciaplatin</td>
<td>36.4</td>
<td>7</td>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
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<td>Jumaglu et al. (2009) [23]</td>
<td>26 PC</td>
<td>FUDR</td>
<td>0</td>
<td>14</td>
<td>31</td>
<td>6</td>
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<tr>
<td>Inaba et al. (2011) [24]</td>
<td>25 PC</td>
<td>Gemcitabine</td>
<td>36</td>
<td>3</td>
<td>11.3</td>
<td>12</td>
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<tr>
<td>Burger et al. (2005) [25]</td>
<td>17 PC</td>
<td>Ciaplatin + MMC + Doxorubicin</td>
<td>29.4</td>
<td>NR</td>
<td>23&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td></td>
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<tr>
<td><strong>TACE</strong></td>
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<tr>
<td>Herber et al. (2007) [26]</td>
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<td>MMC</td>
<td>0</td>
<td>1</td>
<td>16.3</td>
<td>2</td>
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<tr>
<td>Gusani et al. (2008) [27]</td>
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<td>Gemcitabine, Ciaplatin Oxaliplatin</td>
<td>45.2</td>
<td>0</td>
<td>9.1</td>
<td>7</td>
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<tr>
<td>Shitara et al. (2008) [28]</td>
<td>20 RS</td>
<td>MMC</td>
<td>85</td>
<td>10</td>
<td>14.1</td>
<td>7</td>
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<tr>
<td>Andrasina et al. (2010) [29]</td>
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<td>Ciaplatin</td>
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<td>NR</td>
<td>25.2&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Park et al. (2011) [30]</td>
<td>72 RS</td>
<td>5-FU + Ciaplatin</td>
<td>54.2</td>
<td>15</td>
<td>12.2&lt;sup&gt;c,d&lt;/sup&gt;</td>
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<tr>
<td>Kietzer et al. (2011) [31]</td>
<td>62 PC</td>
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<td>30.6</td>
<td>2</td>
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<td>Kuhlmann et al. (2012) [31]</td>
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<td>MMC</td>
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<tr>
<td>Halappar et al. (2012) [32]</td>
<td>29 RS</td>
<td>Ciaplatin + MMC + Doxorubicin</td>
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<td>NR</td>
<td>16&lt;sup&gt;c,d&lt;/sup&gt;</td>
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<td>Vogt et al. (2012) [33]</td>
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<td>MMC, Gemcitabine, Ciaplatin</td>
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<td>10</td>
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<tr>
<td>Scheuermann et al. (2013) [34]</td>
<td>32 RS</td>
<td>MMC</td>
<td>0</td>
<td>NR</td>
<td>11</td>
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<tr>
<td><strong>DEB-TACE</strong></td>
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<tr>
<td>Aliberti et al. (2008) [35]</td>
<td>11 PC</td>
<td>Doxorubicin DEB</td>
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<td>Kuhlmann et al. (2012) [31]</td>
<td>26 PC</td>
<td>Irinotecan DEB</td>
<td>42.3</td>
<td>1</td>
<td>11.7</td>
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<tr>
<td><strong>Y90</strong></td>
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<tr>
<td>Ibahim et al. (2008) [36]</td>
<td>24 PC</td>
<td>Y-90</td>
<td>33.3</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14.9</td>
<td>5</td>
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<td>Huang et al. (2011) [38]</td>
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<td>Y-90</td>
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<td>5</td>
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<td>Hoffmann et al. (2012) [39]</td>
<td>33 RS</td>
<td>Y-90</td>
<td>24.2</td>
<td>12</td>
<td>22</td>
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<tr>
<td>Ruff et al. (2013) [40]</td>
<td>19 PC</td>
<td>Y-90</td>
<td>57.9</td>
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<td>11.5</td>
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</tbody>
</table>

HAT, hepatic artery based therapy; ICC, intrahepatic cholangiocarcinoma; HAI, hepatic arterial infusion; TACE, transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead TACE; Y90, Yttrium<sup>90</sup> radioembolization; EHD, extra hepatic disease; CR, complete response to therapy; PR, partial response to therapy; PC, prospective cohort study; RC, retrospective study; NR, not reported; 5-FU, 5-fluorouracil; MMC, mitomycin C; FUDR, flouxuridine.

<sup>a</sup>NCI/WHO Grade III/IV Toxicities.

<sup>b</sup>Represents mean survival as median survival was not reported in the group.

<sup>c</sup>Survival calculated from the date of diagnosis.

<sup>d</sup>Treatment naive group (therefore, date of diagnosis was assumed as date of initiation of HAT for the purpose of analysis).

<sup>e</sup>World Health Organization Tumor Response Criteria.
The overall median survival across the four strategies was 14.5 months confirming a beneficial effect. The results, however, must be interpreted cautiously due to the potential selection bias across the treatment groups. No standardized chemotherapeutic drug or schedule. HAI involves the implantation of a chemoinfusion pump or port which may predispose patients to a greater set of risks when compared with other intra-arterial strategies.

**TABLE III. Results of Meta-analysis of Median Overall Survival and Tumor Response by Recist Criteria Using Random Effects Model for Unresectable ICC Treated With HAT**

<table>
<thead>
<tr>
<th></th>
<th>HAI (95% CI)</th>
<th>TACE (95% CI)</th>
<th>DEB-TACE (95% CI)</th>
<th>Y-90 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative median OS</td>
<td>22.8 (9.8–35.8)</td>
<td>12.4 (10.9–13.9)</td>
<td>12.3 (11.0–13.5)</td>
<td>13.9 (9.5–18.3)</td>
</tr>
<tr>
<td>RECIST tumor response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete/partial response</td>
<td>56.9 (41.0–72.8)</td>
<td>17.3 (6.8–27.8)</td>
<td>—</td>
<td>27.4 (17.4–37.5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>42.2 (17.1–67.2)</td>
<td>46.9 (35.5–58.4)</td>
<td>61.5 (42.8–80.2)</td>
<td>54.8 (45.2–56.7)</td>
</tr>
</tbody>
</table>

HAT, hepatic artery based therapy; ICC, intrahepatic cholangiocarcinoma; HAI, hepatic arterial infusion; TACE, transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead TACE; Y-90, Yttrium⁹⁰ radioembolization.
**GUIDELINES**

**The dark side of the guidelines**

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**Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma**

John Bridgewater, Peter J. Galle, Shahid A. Khan, Joep M. Usser1, Joong-Won Park, Tushar Patel, Timothy M. Pawlik, Gregory J. Gores2

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**GUIDELINES**

**LINEE GUIDA TUMORI DELLE VIE BILIARI**

<table>
<thead>
<tr>
<th>Grado di raccomandazione SIGN</th>
<th>Raccomandazione Clinica</th>
<th>Forza della raccomandazione clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>TACE e TARE hanno dimostrato effetto antinumorale in pazienti con iCCA, con tossicità clinicamente accettabile pertanto possono essere prese in considerazione come opzione terapeutica, ma ulteriori trials clinici sono necessari per stabilirne il ruolo in questo contesto clinico</td>
<td>Positiva debole (481-483)</td>
</tr>
</tbody>
</table>

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**SIRCCA–Study**

Prospective randomised controlled Phase II study evaluating SIR-Spheres® Y-90 resin microspheres chemotherapy versus CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic cholangiocarcinoma (SIRCCA)

**Eligible patients with unresectable intrahepatic cholangiocarcinoma (ICC)**

- Extra-hepatic disease
- Cirrhosis
- Unilobar vs. bi-lobar intended treatment
- Albumin <35g/L vs. ≥35g/L
- ECOG Status

**Randomise 1:1 N = 160**

**Protocol still DRAFT**

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**Recommendations**

- There are no established first-line local-regional therapeutic options for patients with non-resectable iCCA
  - Recommendation B1
- EBRT cannot be recommended as standard therapy for patients with unresectable iCCA. Additional clinical trials of single, combination or adjuvant therapy are needed to establish its role in this population
  - Recommendation B2
- TACE and TARE have shown anti-tumor effects with acceptable toxicities in patients with iCCA but require further examination in appropriately designed clinical trials and therefore cannot be recommended as standard therapy for patients with unresectable iCCA
  - Recommendation B2
- TACI is not recommended for management of patients with unresectable iCCA
  - Recommendation C2
- Ablation approaches may be considered for small, single lesions <3 cm if surgery is not an option, but additional clinical trials are needed to establish its role in this population
  - Recommendation C2

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**Suggestions for future studies**

Randomized controlled trials are recommended to establish first-line local-regional treatment options for patients with unresectable iCCA

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2nd Interventional Radiologist under 40 Meeting

*Interventional Oncology*
Conclusion

• ICC still represents a complex and heterogeneous scenario in which no evidence-based algorithms of care exist. A similar to HCC diagnostic and therapeutic algorithm is recommended for ICC.

• Despite the lack of randomized controlled trials, current literature indicates evidence in support of the use of LRT for patients with unresectable ICC.

• In particular, IAT have proven feasible, safe and effective in inducing local tumor response. Moreover current clinical evidence suggests survival benefits for IAT over systemic chemotherapy and the ability of downstaging tumors until eligible to resection.

• A multidisciplinary team of experts is necessary to ensure the best patient selection and to obtain optimal results; this is possible only in tertiary level centers having certified expertise, after thorough training of the staff.
Grazie per l’attenzione