The dark side of the guidelines

2nd Interventional Radiologist under 40 Meeting

Interventional Oncology

8-10 Maggio 2017

Bologna

Società Medica Chirurgica - Palazzo dell'Archiginnasio

Colangiocarcinoma intra-epatico:

Trattamenti intra-arteriosi

Dott. Francesco Modestino

Unità Operativa Radiologia Malpighi
Azienda Ospedaliero-Universitaria di Bologna
Policlinico S. Orsola - Malpighi

EPIDEMIOLOGY

- 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.

Bridgewater J et al *J. Hepatol.* 2014;60, 1268–1289
Yang JD et al. *Am. J. Gastroenterol*. 2012;107, 1256–1262
Khan SA et al. *Lancet*. 2005;366:1303–1314
Palmer WC et al. *J Hepatol* . 2012;57:69–76

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).

Anderson CD et al. *Oncologist* . 004;9:43-57
Poultsides GA et al. *Surg Clin North Am 2010;90:817-37*
Tan JC et al. *Ann Surg Oncol 2008;15:600-8*

TREATMENT

- 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).

Tan JC et al. *Ann Surg Oncol.* 2008;15:600–608
Bridgewater J et al *J. Hepatol.* 2014;60, 1268–1289

LR-THERAPIES

- 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.

Burger I et al. *J Vasc Interv Radiol 2005;16:353-61*

Dodson RM et al. *J Am Coll Surg. 2013;217:736-750*

Review

DOI: 10.5582/bst.2016.01048

The current management of cholangiocarcinoma: A comparison of current guidelines

Yulong Cai[1,2], Nansheng Cheng[1], Hui Ye[1], Fuyu Li[1], Peipei Song[3,*], Wei Tang[1,2]

Table 1. Current guidelines on cholangiocarcinoma

Guidelines	Approach	Content	Tumor	Evaluation measures	*Ref.*
NCCN Guideline (*2016*)	Expert panel	D&T + E + F	CC, GBC, HCC	Consensus categories	(*14*)
SEOM Guideline (*2015*)	Literature analysis	D&T + E	CC, GBC	Evidence categories and recommendation grades	(*13*)
Japanese Guideline (*2014*)	Expert panel	D&T + E	CC, GBC, AC	Evidence categories and recommendation grades	(*18*)
Chinese Guideline 1 (*2014*)	Expert panel	D&T + E	CC	-	(*16*)
EASL Guideline (*2014*)	Expert panel	D&T + E	iCC	Evidence categories and recommendation grades	(*15*)
Asia-Pacific Guideline (*2013*)	Expert panel	D&T + E	pCC	Evidence categories and recommendation grades	(*19*)
Chinese Guideline 2 (*2013*)	Expert panel	D&T	pCC	Evidence categories and recommendation grades	(*17*)
BSG Guideline (*2012*)	Literature analysis	D&T + E + F	CC	Evidence categories and recommendation grades	(*11*)
Italian Guideline (*2010*)	Expert panel	D&T + E	CC	Evidence categories and recommendation grades	(*12*)

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.

GUIDELINES

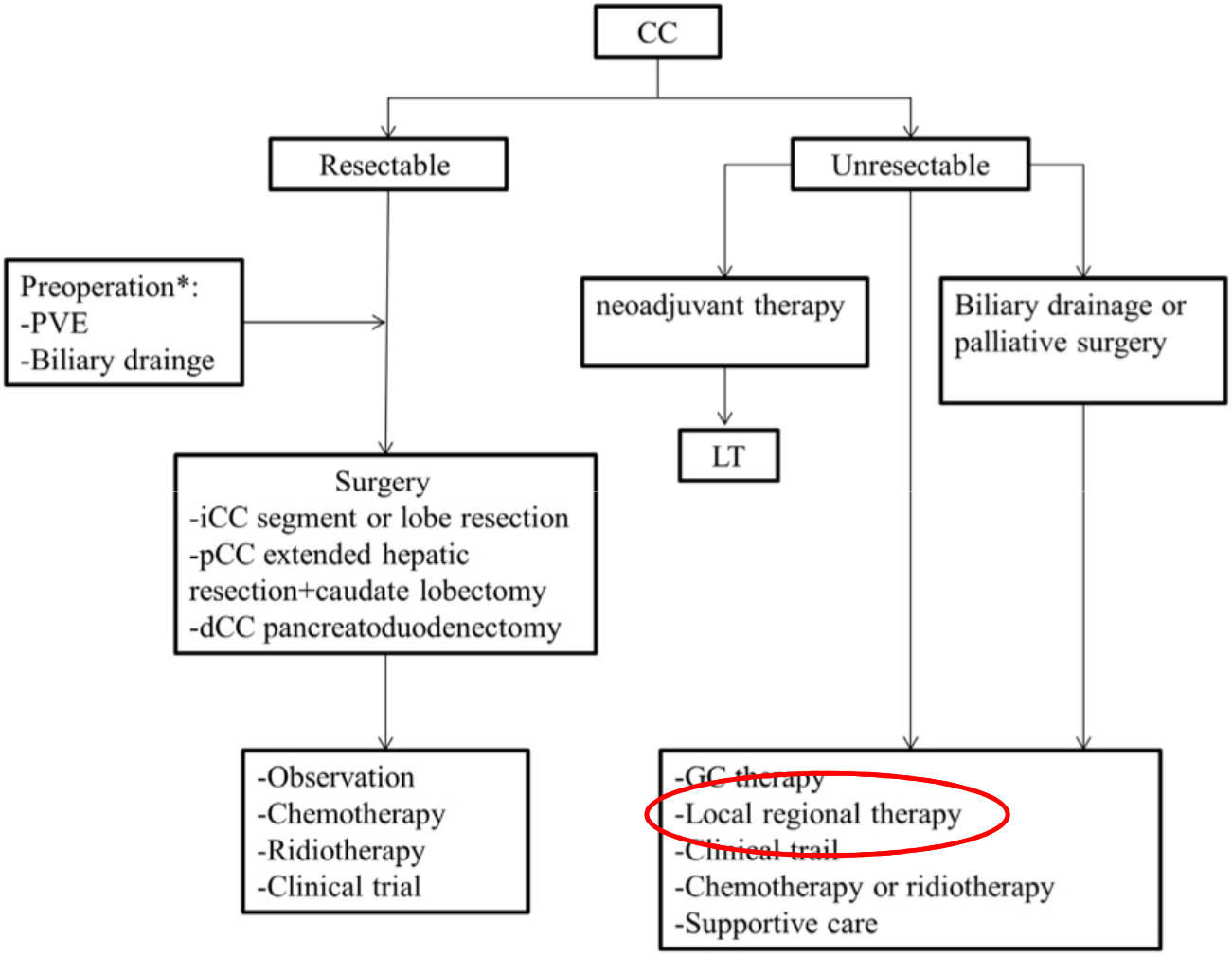

Figure 2. The treatment algorithm in current guidelines for cholangiocarcinoma. *Major hepatectomy with small FLR volume or insufficient liver function. PVE, portal vein embolization; LT, liver transplantation; GC, Gemcitabine/cisplatin combination.

GUIDELINES

Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma

John Bridgewater[1], Peter R. Galle[2], Shahid A. Khan[3], Josep M. Llovet[4,5], Joong-Won Park[6], Tushar Patel[7], Timothy M. Pawlik[8], Gregory J. Gores[9,*]

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

Primary tumors (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
T4	Tumor with periductal invasion
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
N1	Distant metastasis

Guidelines

EASL JOURNAL OF HEPATOLOGY

Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma

John Bridgewater[1], Peter R. Galle[2], Shahid A. Khan[3], Josep M. Llovet[4,5], Joong-Won Park[6], Tushar Patel[7], Timothy M. Pawlik[8], Gregory J. Gores[9,*]

GUIDELINES

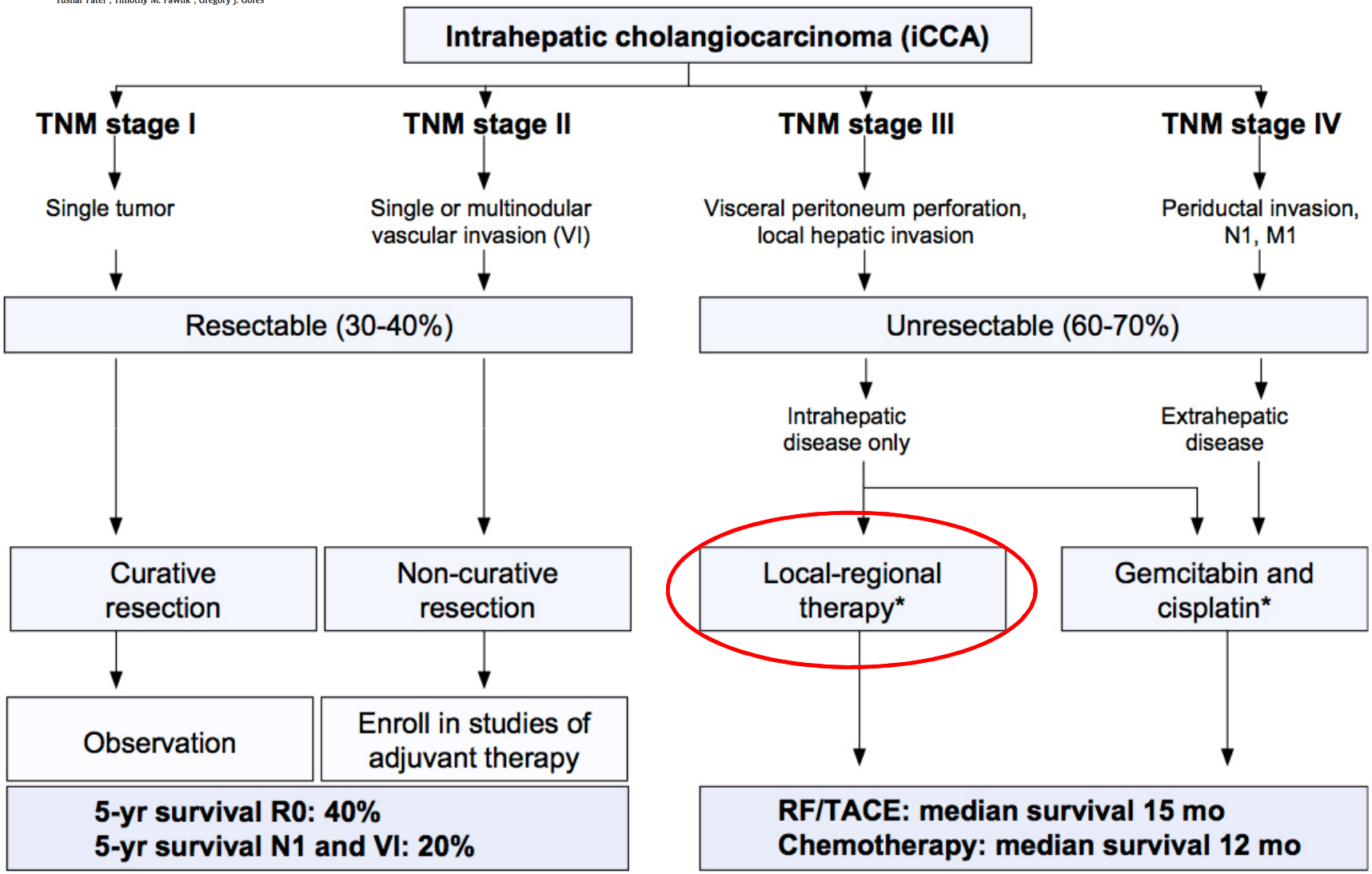

Fig. 3. A suggested treatment algorithm for patients with iCCA.* These are standard of practice recommendations. Larger and appropriate studies are required to provide evidence for standard of care guidelines.

HAI/TACI

- 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.

Sullivan RD et al. *N Engl J Med* .1964.270:321–7
House MG et al. *Annals of surgery*. 2011; 254(6):851–62
Yamashita T et al. *Oncology*. 2011; 81(5–6):281–90

HAI/TACI

American Journal of Clinical Oncology — ORIGINAL ARTICLE

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)

- 25 patients were enrolled from May 2004 to November 2006.
- Histologically confirmed ICC Not responder to other
- ECOG 2 or less
- Median survival of 340d
- The disease control rate and MST were acceptable, but considering that the implanted catheter-port system was required for HAI procedure, it cannot be claimed that this protocol has an advantage over systemic treatment.

- HAI via percutaneous implanted port system (femoral or subclavian access).
- 11 patients with unresectable ICC were treated with infusion of fluorouracil combined with a variety of other agents (doxorubicin, mitomycin C, cisplastin).
- Median survival of 26 months.
- Tanaka et al reported the most favorable outcome in the literature for patients with unresectable ICC, despite 1 patient was not included 63% (7/11) with extrahepatic disease.

HAI/TACI

Cancer. 2016 March 1; 122(5): 758–765. doi:10.1002/cncr.29824.

Unresectable Intrahepatic Cholangiocarcinoma: Systemic Plus Hepatic Arterial Infusion Chemotherapy is Associated with Longer Survival Compared to Systemic Chemotherapy Alone

Ioannis T. Konstantinidis, MD[1], Bas Groot Koerkamp, MD[1], Richard K.G. Do, MD[2], Mithat Gönen, PhD[3], Yuman Fong, MD[1], Peter J. Allen, MD[1], Michael I. D'Angelica, MD[1], T. Peter Kingham, MD[1], Ronald P. DeMatteo, MD[1], David S. Klimstra, MD[4], Nancy E. Kemeny, MD[5], and William R. Jarnagin, MD[1]

- Between 1/2000 and 8/2012, 325 patients with ICC were evaluated.
- Thirty-four unresectable patients (26 ICC and 8 HCC) were enrolled to receive HAI FUDR (n = 167) or systemic chemotherapy (n = 158).
- Patients with ICC had a higher response rate (53.8%) compared with those with HCC (25%).
- Overall survival in ICC responders was significantly longer compared to patients who received SYS alone (30.8 months vs. 18.4 months).
- The median survival was 29.5 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).

C-TACE

- 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.

Yamada R et al. *Osaka City Med J*. 1980;26:81-96
Kiefer MV et al. *Cancer*. 2011;117:1498-505
Cohen MJ et al *World J Gastroenterol*. 2013;19:2521-8
Hyder O et al. *Ann Surg Oncol*. 2013;20:3779-86

C-TACE

Cardiovasc Intervent Radiol (2007)

Transarterial Chemoembolization (TACE) for Inoperable Intrahepatic Cholangiocarcinoma

S. Herber · G. Otto · J. Schneider · N. Manzl · I. Kummer · S. Kanzler · A. Schuchmann · J. Thies · C. Düber · M. Pitton

- 17 patients treated between 1995 and 2004.
- Conventional TACE regimen consisting of cisplatin, doxorubicin, and mitomycin-C, followed by embolization with polyvinyl alcohol (PVA) or Embosphere particles (Biosphere Medical, Rockland, MA).
- Liver function was generally preserved (15 of 17 Child-Pugh class A), as well as (PS) (14 of 17 [ECOG] PS <2).
- Patients underwent a median of two TACE sessions.
- Median overall survival was 23 months.
- Two patients were deemed to have resectable disease following TACE.

- A retrospective analysis included 15 patients.
- Treatment with TACE 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

Cancer April 1, 2011 (2008)

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

A 2-Center Study

Matthew V. Kiefer, BA[1]; Marissa Albert, BA, MSc[1]; Madeline McNally, MD[2]; Mary Robertson, RN[2]; Weijing Sun, MD[3]; Douglas Fraker, MD[4]; Kim Olthoff, MD[5]; Kathleen Christians, MD[6]; Sam Pappas, MD[6]; William Rilling, MD[2]; and Michael C. Soulen, MD[1]

- Retrospective analysis included 62 patients Treated with conventional TACE (cisplatin, doxorubicin, and mitomycin C infusion followed by PVA embolization)
- Eighteen patients (29%) had received prior chemotherapy, and 7 patients (11%) had prior liver resection
- Extrahepatic disease was present in 19 patients (31%)
- 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

- A retrospective trial included a total of 42 patients
- cTACE with different regimens consisting of gemcitabine combined with or followed by cisplatin and oxaliplatin
- The median OS for the entire cohort was 9.1 months
- Patients with SD showed a median OS of 13.1 months compared to 6.9 months for patients with PD (P=0.017)

C-TACE

Clinical Radiology 66 (2011) (2012)

Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma

S.-Y. Park [a], J.H. Kim [a,*], H.-J. Yoon [a], I.-S. Lee [a], H.-K. Yoon [a], K.-P. Kim [b]

- Prospective trial (n=72) with symptomatic supportive therapy (n=83) in the palliative treatment of 155 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 dysfunction (14%) at the time of TACE were excluded.
- Hypervascular tumors were present in 62 patients (54%).
- Median survival was 15 months (12.2 months) compared to the supportive treatment group (3.3 months).
- No significant survival difference was observed between TACE regimens.
- Tumor vascularity was identified as a positive prognostic indicator, among other factors.

DEB-TACE

- 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.

Lewis AL et al. *J Vasc Interv Radiol* 006;17(8):1335–1343
Hong K et al. *Clin Cancer Res* 2006;12:2563-7
Varela M et al. *J Hepatol* 2007;46(3):474–481

DEB-TACE

Cardiovasc Intervent Radiol (2009)18)

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. Sottotetti · O. Rossi · E. Pozzi · F. Zappoli · A. Riccardi · G. Bernardo

- 11 patients were treated with DC Beads (Biocompatibles UK Ltd, Farnham, UK) loaded with doxorubicin.
- All patients had received previous systemic chemotherapy and/or hepatic resection.
- A median of three treatment sessions was performed.
- 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.

DEB-TACE

European Journal of Gastroenterology & Hepatology 2012

Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy

Jan B. Kuhlmann[a], Wulf Euringer[b], Hans C. Spangenberg[a], Matthias Breidert[d], [4], Hubert E. Blum[a], Jan Harder[c*] and Richard Fischer[a*]

- 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).
Systemic chemotherapy (gemcitabine and oxaliplatin; n=31)
Compared to cTACE and systemic chemotherapy, DEBIRI revealed prolonged median OS (5.7 vs. 11 vs. 11.7 months).

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.

Veeze-Kuijpers B et al. *Int J Radiat Oncol Biol Phys* 1990;18:63-7
Hoffmann RT et al. *Cardiovasc Intervent Radiol* 2012;35:105-16
Mouli S et al. *J Vasc Interv Radiol* 2013;24:1227-34

Y-90

CANCER October 15, 2008

Treatment of Unresectable Cholangiocarcinoma Using Yttrium-90 Microspheres

Results From a Pilot Study Saad M. Ibrahim

- 25 patients underwent yttrium-based 90 Y radioembolization for unresectable ICC between January 2004 and May 2009.
- 24 patients with histologically proven ICC.
- They showed (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%).
- Patients were assessed at 1 month and then at 3-month intervals after treatment.
- A median OS of 9.3 months.
- The median OS was 14.1 months from the time of the first treatment.
- 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).
- 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).
- The median survival for patients with and without portal vein thrombosis was 5.7 and 31.8 months, respectively
- The median survival of patients with peripheral versus infiltrative tumors was 31.8 and 5.7 months, respectively.

Y-90

J Vasc Interv Radiol. 2013 (2)

Yttrium-90 Radioembolization for Intrahepatic Cholangiocarcinoma: Safety, Response, and Survival Analysis

Samdeep Mouli[1], Khairuddin Memon[1], Talia Baker[2], Al B. Benson III[3], Mary F. Mulcahy[3], Ramona Gupta[1], Robert K. Ryu[1], Riad Salem[1,2,3], and Robert J. Lewandowski[1]

- The current study expands upon the prior report if ibrahim.
- Including forty-six patients with unresectable ICC who were treated with Y90 radioembolization at a single institution from July 2003 – May 2011.
- Survival and TTP were significantly prolonged in patients with ECOG 0 versus ECOG 1 or 2 (median OS: 29.4, 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).

- In a series of 33 patients
- A median OS of 22 months from the time of the first treatment.
- The median time to progression (TTP) was 9.8 months.
- Survival varied according to the presence of multifocal (5.7 vs 14.6 months), infiltrative (6.1 vs 15.6 months) or bilobar disease (10.9 vs 11.7 months).
- Five patients (11%) were downstaged to resection after treatment.

Y-90

EJSO 41 (2015) 120–127 www.ejso.com

CrossMark

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] Hepatopancreatobiliary Surgical Unit, University Department of Surgery, Addenbrooke's Hospital, University of Cambridge, United Kingdom

D,§

- Comprehensive review of the current studies and clinical outcomes of unresectable ICC treated with 90Y-TARE
- 12 studies with relevant data
- Median survival after TARE of 15.5 months
- Longer progression-free survival was observed when chemotherapy was given before 90Y-TARE, with respective median of 20.0 versus 8.8 months (p = 0.001)

- Showed that SIRT combined with chemotherapy is a promising strategy as first-line treatment for unresectable ICC
- 24 patients treated with SIRT – control group treated with CIS-GEM
- Median progression-free survival was 10.3 months
- However, the authors pointed out the heterogeneity of the study populations: all the studies reported chemotherapy was given before SIRT, but in some cases the patients had undergone systemic chemotherapy prior to or during the treatment

Y-90

Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study

Cristina Mosconi[*,1], Annagiulia Gramenzi[2], Salvatore Ascanio[1], Alberta Cappelli[1], Matteo Renzulli[1], Cinzia Pettinato[3], Giovanni Brandi[4], Fabio Monari[5], Alessandro Cucchetti[6], Franco Trevisani[2] and Rita Golfieri[1]

- 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.

Journal of Surgical Oncology 2015;111:213–220

TABLE I. Summary of Individual Studies Selected for Meta-Analysis of HAT Outcomes for Unresectable ICC

Author (year)	Sample	Study design	Treatment regimen	EHD%	RECIST response (CR + PR)	Median survival (months)	Toxicities[a]
HAI							
Tanaka et al. (2002) [22]	11	PC	5-FU, Doxorubicin, MMC, Cisplatin	36.4	7	26[b]	NR
Jarnagin et al. (2009) [23]	26	PC	FUDR	0	14	31	6
Inaba et al. (2011) [24]	25	PC	Gemcitabine	36	3	11.3	12
Burger et al. (2005) [25]	17	PC	Cisplatin + MMC + Doxorubicin	29.4	NR	23[c]	1
TACE							
Herber et al. (2007) [26]	15	RS	MMC	0	1	16.3	2
Gusani et al. (2008) [27]	42	RS	Gemcitabine, Cisplatin Oxaliplatin	45.2	0	9.1	7
Shitara et al. (2008) [28]	20	RS	MMC	85	10	14.1	7
Andrasina et al. (2010) [29]	17	PC	5-FU + Cisplatin	0	NR	25.2[c]	0
Park et al. (2011) [30]	72	RS	Cisplatin	54.2	15	12.2[c,d]	36
Kiefer et al. (2011) [31]	62	PC	Cisplatin + MMC + Doxorubicin	30.6	5	15	5
Kuhlman et al. (2012) [21]	10	PC	MMC	40	1	5.7	3
Halappa et al. (2012) [32]	29	RS	Cisplatin + MMC + Doxorubicin	NR	NR	16[c,d]	NR
Vogl et al. (2012) [33]	115	RS	MMC, Gemcitabine, Cisplatin	0	10	13	0
Scheuermann et al. (2013) [34]	32	RS	MMC	0	NR	11	NR
DEB-TACE							
Aliberti et al. (2008) [35]	11	PC	Doxorubicin DEB	NR	10	13	1
Kuhlman et al. (2012) [21]	26	PC	Irinotecan DEB	42.3	1	11.7	11
Y90							
Ibrahim et al. (2008) [36]	24	PC	Y-90	33.3	6[c]	14.9	5
Saxena et al. (2010) [37]	25	PC	Y-90	48	6	9.3	5
Haug et al. (2011) [38]	26	PC	Y-90	30.8	5	11.8	NR
Hoffmann et al. (2012) [39]	33	RS	Y-90	24.2	12	22	NR
Rafi et al. (2013) [40]	19	PC	Y-90	57.9	2	11.5	2

HAT, hepatic artery based therapy; ICC, intrahepatic cholangiocarcinoma; HAI, hepatic arterial infusion; TACE, transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead TACE; Y90, Yttrium^{90} 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, floxuridine.

[a]NCI/WHO Grade III/IV Toxicities.

[b]Represents mean survival as median survival was not reported in the group.

[c]Survival calculated from the date of diagnosis.

[d]Treatment naïve group (therefore, date of diagnosis was assumed as date of initiation of HAT for the purpose of analysis).

[e]World Health Organization Tumor Response Criteria.

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

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

HAT, hepatic artery based therapy; ICC, intrahepatic cholangiocarcinoma; HAI, hepatic arterial infusion; TACE, transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead TACE; Y-90, Yttrium^{90} radioembolization.

- 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

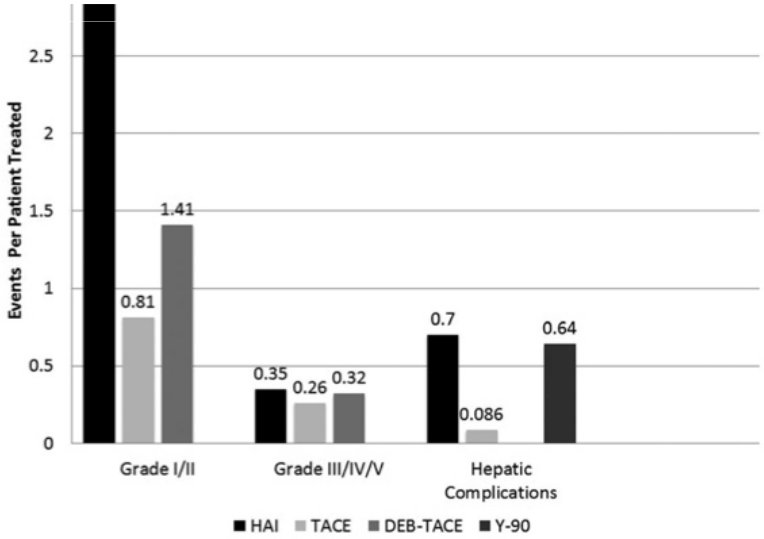

Fig. 6. Bar plots describing the distribution of complications across the three HAT strategies for unresectable ICC (events per patient treated). HAT, hepatic artery based therapy; ICC, intrahepatic cholangiocarcinoma; HAI, hepatic arterial infusion; TACE transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead TACE; Y-90 Yttrium^{90} radioembolization.

The dark side of the guidelines

Guidelines

EASL JOURNAL OF HEPATOLOGY

GUIDELINES

Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma

John Bridgewater[1], Peter R. Galle[2], Shahid A. Khan[3], Josep M. Llovet[4,5], Joong-Won Park[6], Tushar Patel[7], Timothy M. Pawlik[8], Gregory J. Gores[9,*]

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

Suggestions for future studies

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

LINEE GUIDA TUMORI DELLE VIE BILIARI

AIOM

Grado di raccomandazione SIGN	Raccomandazione Clinica	Forza della raccomandazione clinica
D	TACE e TARE hanno dimostrato effetto antitumorale 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	Positiva debole (481-483)

SIRCCA–Study

Eligible patients with unresectable intrahepatic cholangiocarcinoma (ICC)

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

Stratify:

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

Randomise 1:1 N = 160

- Systemic chemotherapy CIS + GEM
- SIR-Spheres followed by systemic chemotherapy CIS + GEM

Protocol still DRAFT

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