Treatment option for patients who are unsuitable for or progress on TACE

Jae Youn Cheong

Department of Gastroenterology
Ajou University School of Medicine, Suwon, South Korea
Liver cancer is the sixth most common cancer globally (both sexes)\(^1\)

Over 700,000 new cases of liver cancer are diagnosed worldwide each year,\(^1\) including
- Eastern Asia: 470,000\(^1\)
- Japan: 39,000\(^1\)
- Europe: 58,000\(^1\)
- United States: 21,000\(^1\)

Liver cancer is the third leading cause of cancer-related mortality,\(^1\) and is the leading cause of death in cirrhotic patients

The incidence of HCC is increasing globally\(^2\)

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AASLD guidelines

Stage 0
PST 0, Child–Pugh A

Very early stage (0)
1 HCC < 2 cm
Carcinoma in situ

Early stage (A)
1 HCC or 3 nodules < 3 cm, PST 0

Intermediate stage (B)
Multinodular, PST 0

Advanced stage (C)
Portal invasion, N1, M1, PST 1–2

End stage (D)
PST > 2, Child–Pugh C

HCC

Resection
Liver transplantation
PEI/RFA
TACE
Sorafenib
Symptomatic treatment (20%)
Survival < 3 months

Curative treatments (30%)
5-year survival (40–70%)
Palliative treatments (50%)
Median survival 11–20 months

APASL guidelines

HCC

Confined to the liver
Main portal vein patent

Resectable

Yes

Resection/RFA (for < 3 cm HCC)

Solitary tumor ≤ 5 cm ≤ 3 tumors ≤ 3 cm
No venous invasion

Child–Pugh A

Local ablation

Child–Pugh B

Transplantation

Child–Pugh C

TACE

Extrahepatic metastasis
Main portal vein tumor thrombus

Child–Pugh A/B

Sorafenib or systemic therapy trial

Child–Pugh C

Tumor > 5 cm > 3 tumors
Invasion of hepatic / portal vein branches

Child–Pugh A/B

Supportive care

Child–Pugh C

Management of intermediate HCC
TACE is the standard of care for intermediate-stage HCC patients

TACE in intermediate HCC

- Treatment modalities: very heterogeneous
  - drug, embolic material used
  - selectivity, retreatment schedule
- Inclusion/exclusion criteria: heterogeneous
- Results of TACE: heterogeneous
  - 7 randomized controlled studies
  - only 2 positive studies
  - meta-analysis: positive

But, meta-analyses also concluded other treatment options that were as effective as, if not superior to, TACE in unresectable HCC

**TACE is the standard of care for intermediate-stage HCC patients**

**TAE/TACE vs best supportive care: meta-analysis**

<table>
<thead>
<tr>
<th>Author, journal, year</th>
<th>Patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors treatment</th>
<th>Favors control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, Gastroenterology, 1998</td>
<td>63</td>
<td></td>
<td>0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>GETCH, NEJM, 1995</td>
<td>96</td>
<td></td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Bruix, Hepatology, 1998</td>
<td>80</td>
<td></td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Pelletier, J Hepatol, 1998</td>
<td>73</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lo, Hepatology, 2002</td>
<td>79</td>
<td></td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Llovet, Lancet, 2002</td>
<td>112</td>
<td></td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Overall</td>
<td>503</td>
<td></td>
<td>0.01</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Heterogeneity p = 0.14

\[ z = -2.3 \]

\[ p = 0.017 \]

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경동맥화학색전술: 권고사항

1. 근치적 치료가 불가능한 간세포암중 중 주혈관 침습이나 간외 전이가 없는 경우에 TACE 치료는 생존율을 향상시킨다. (증거순위 I)

2. 수술적 절제술이나 국소 치료술이 어려운 경우 TACE를 효과적인 치료법으로 시행할 수 있다. (증거순위 II-1)

3. 간문맥침습이 있는 간세포암중 중 잔존 간기능이 좋고 간 내 종양이 국소적인 경우 선택적 TACE를 시행할 수 있다. (증거순위 II-3)

4. TACE로 불완전한 효과가 예상되는 간세포암중에서는 경피적 알코올 주입술(증거순위 II-3), 고주파 열치료술(증거순위 I), 및 방사선치료 (증거순위 III) 병용치료를 고려한다.

5. 임상적 시도중인 치료술들은 아직 기존의 표준적 치료들과 대조연구가 없고 분석 가능한 대상 환자 수가 적어, 표준적 치료 대상이 되는 간세포암중 환자들에게 일반적으로 적용되지 않는다. (증거순위 II)

2009 간세포암중 진료 가이드라인, 대한간암연구회, 국립암센터
Antitumour treatment

Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: Available evidence and expert opinion on the use of transarterial chemoembolization

J.-L. Raoul a,⁎, B. Sangro b,c, A. Forner d, V. Mazzaferro e, F. Piscaglia f, L. Bolondi f, R. Lencioni g

a Department of Medical Oncology, Centre E. Marquis, INSERM U991 and Rennes University, CS4429, 35042 Rennes, France
b Liver Unit, Clinica Universitaria de Navarra, Pamplona 31008, Spain
c Centro de Investigacion Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Avenida Pio XII, 36, Pamplona 31008, Spain
d Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clinic Barcelona, IDIBAPS, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), University of Barcelona, Barcelona, Spain
e National Cancer Institute, IRCCS Foundation, Via Venezian 1, 20133 Milan, Italy
f Department of Digestive Disease and Internal Medicine, S. Orsola – Malpighi General and University Hospital, Via Albertoni 15, Bologna 40138, Italy
g Pisa University School of Medicine, Cisanello Hospital, Building No. 30C, Suite 197, Via Paradisa 2, IT 56124 Pisa, Italy
### Factors associated with outcomes with cTACE

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Associated with positive survival outcomes</th>
<th>Associated with negative survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 0$^{39,66}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh A (or B)$^{26,28,30,37,42,45,49,51,53,56,57,60,69}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$-FP ($\leq$200 ng/mL)$^{23,32,43,49,51,59,110}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good liver function$^{23,29,34,42}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg-negative$^{58}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender$^{45}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High pre-treatment albumin ($&gt;35$ g/L)$^{23,43}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin ($\leq$34 g/L)$^{31,71,72}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of ascites$^{31,63,72,87}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$-FP level ($\geq$400 ng/mL)$^{72}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin $&gt;30$ mg/L$^{54,63,72}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly$^{20}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO performance status 1–4$^{20}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of cirrhosis$^{73}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLIP $\geq$2 and MELD $\geq$10$^{41}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age $&gt; 60$ years$^{54}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Factors associated with outcomes with cTACE

<table>
<thead>
<tr>
<th>Disease (HCC) presentation characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with positive survival outcomes</td>
<td>Associated with negative survival outcomes</td>
</tr>
<tr>
<td>Okuda I (or II)(^{15,23,30,45,51-53,59})</td>
<td>(\geq 3) liver lesions(^{63,87})</td>
</tr>
<tr>
<td>TNM stage I(^{33})</td>
<td>Diameter main tumour (\geq 5/\geq 6.5/\geq 10) cm(^{20,35,39,54,64,70-72,75,87})</td>
</tr>
<tr>
<td>Hypervascular disease(^{27,30,32,44})</td>
<td>Tumour type (multinodular or diffuse)(^{35,50,62,65,70,87})</td>
</tr>
<tr>
<td>Unifocal disease(^{22,24,30,45,47})</td>
<td>High pre-treatment VEGF ((&gt;49.5) ng/L/(&gt;240) pg/L)(^{38,67,68,75})</td>
</tr>
<tr>
<td>Tumour size (\leq 5) cm(^{15,30,32,61,74})</td>
<td>Bilobar tumour(^{87})</td>
</tr>
<tr>
<td>Unibilobar(^{30,60})</td>
<td>EHS(^{46})</td>
</tr>
<tr>
<td>No PVT(^{15,30,36,55,57}) or EHS(^{29,37})</td>
<td>PVT(^{31,46,87})</td>
</tr>
<tr>
<td>Non-recurrent disease(^{60})</td>
<td></td>
</tr>
<tr>
<td>Intact capsule(^{57})</td>
<td></td>
</tr>
<tr>
<td>No. of tumours (\leq 5)(^{32,45,47,57})</td>
<td></td>
</tr>
<tr>
<td>Unifocal disease(^{22,24,30,45,47})</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic(^{29,37})</td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with outcomes with cTACE

<table>
<thead>
<tr>
<th>Treatment characteristics</th>
<th>Associated with positive survival outcomes</th>
<th>Associated with negative survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective (segmental or sub-segmental)(^{21,24})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employ (&gt;1) embolization(^{51})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple TACE sessions(^{21,26,30,48})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar embolization (vs. super selective)(^{24})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Absolute and relative contraindication to cTACE

**Absolute contraindications**

- Decompensated cirrhosis (Child-Pugh B ≥ 8) including:
  - Jaundice
  - Clinical encephalopathy
  - Refractory ascites
  - Hepatorenal syndrome
- Extensive tumour with massive replacement of both entire lobes
- Severely reduced portal vein flow (e.g. non-tumoural portal vein occlusion or hepatofugal blood flow)
- Technical contraindications to hepatic intra-arterial treatment, e.g. untreatable arteriovenous fistula
- Renal insufficiency (creatinine ≥ 2 mg/dL or creatinine clearance < 30 mL/min)

Absolute and relative contraindication to cTACE

Relative contraindications

- Tumour size ≥ 10 cm
- Comorbidities involving compromised organ function:
  - Active cardiovascular disease\(^a\)
  - Active lung disease\(^b\)
- Untreated varices at high risk of bleeding
- Bile-duct occlusion or incompetent papilla due to stent or surgery

\(^a\) Active cardiovascular disease includes those diseases caused by underlying atherosclerosis (e.g. aortic aneurysm, cerebrovascular accident, congestive heart failure, angina pectoris, coronary artery disease, recent myocardial infarction, severe peripheral vascular disease, large aortic or hepatic arterial aneurysm).

\(^b\) Clinically active disease that requires oxygen support or multiple drug treatment.
Multiple cycles of cTACE: Impact on survival and tolerability

- The main reasons that patients discontinue cTACE are due to TACE-related adverse events and liver decompensation, and not tumor progression.

<table>
<thead>
<tr>
<th>Regular cTACE (^a)</th>
<th>On-demand cTACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>More cycles</td>
<td>Fewer cycles</td>
</tr>
<tr>
<td>More liver damage</td>
<td>Less liver damage</td>
</tr>
<tr>
<td>More complications</td>
<td>Fewer complications</td>
</tr>
<tr>
<td>Shorter intervals</td>
<td>Longer intervals</td>
</tr>
<tr>
<td>More disruptive to patient's quality of life</td>
<td>Better patient quality of life</td>
</tr>
<tr>
<td>Lack of patient selection</td>
<td>Restricted to patients who are likely to benefit from repeated treatment</td>
</tr>
<tr>
<td>Additional adverse effects may outweigh survival benefits</td>
<td>Other treatments may be more appropriate in certain patients</td>
</tr>
</tbody>
</table>

- To our knowledge, there are at least two studies with regular cTACE that have had positive outcomes.

- One optimal strategy for delivering TACE and maintaining quality of life may be to use repetition on-demand, with longer intervals between treatments, rather than regular repetition.

Initial CT-2011.2.5

- M/49 HCC, B-viral LC, Child Pugh A
- AFP 2279 ng/mL, PIVKA-II >2000 mAU/mL
After 1\textsuperscript{st} TACE-2011.2.24

- Child Pugh A, AFP 868 ng/mL
Unresolved issue in Korean population
After 2nd TACE-2011.3.31

- Child Pugh B, bilirubin 2.1 mg/dL
- 2011.4.22 sorafenib 400mg → 2011.5.6 sorafenib 중단
- 2011.5.23 Expire
Original article

Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: A systematic review and meta-analysis

Mao-Bin Meng a,b,1, Yao-Li Cui c,1, You Lu a,d, Bin She b, Yan Chen b, Yong-Song Guan d, Rui-Ming Zhang b,*

a Division of Thoracic Cancer, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China
b Department of Integrated Traditional Chinese and Western Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China
c Center of Infectious disease, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China
d State Key Laboratory of Biotherapy, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

n=1476 (5 RCT + 12 NRCT)
TACE in combination with RT vs TACE alone

- TACE+RT, compared with TACE alone, significantly improved the survival and the tumor response
- Serious adverse events were not increased exception for total bilirubin level
Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma


Abstract: Purpose: In order to determine the effect of additional radiotherapy (RT) after an incomplete transcatheter arterial chemoembolization (TACE) in an unresectable hepatocellular carcinoma (HCC), the treatment results of patients receiving TACE plus RT were analyzed and compared with those treated with TACE alone. Materials and methods: One hundred and five patients with an unresectable HCC were treated with TACE from January 1992 to December 2002. In 73 of these patients, the TACE was incomplete. Among them, TACE was repeatedly performed in 35 patients (TACE group), and the remaining 38 patients were also treated with local RT (TACERT group). The patients were either in stage III or IVA, Eastern Cooperative Oncology Group 2 or less, and Child–Pugh class A or B. The average frequency of TACE prior to RT was 2 and the RT was started within 7–10 days after the TACE. Results: The 2-year survival rate was significantly higher in the TACERT than in the TACE group (36.8% vs. 14.3%, P = 0.001). According to the tumor size, the 2-year survival rates in the TACERT and TACE groups were 63% vs. 42% in 5–7 cm (P = 0.22), 50% vs. 0% in 8–10 cm (P = 0.03), and 17% vs. 0% in larger than 10 cm (P = 0.0002) respectively. Conclusion: There was a significantly improved survival rate in the TACERT group of unresectable HCC patients than in the TACE group, particularly in case of tumors ≥8 cm in diameter. Therefore, RT in addition to TACE is strongly recommended for patients with an unresectable HCC.
Intraarterial infusion chemotherapy

Survival benefits of intra-arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with portal vein tumor thrombosis

Jae Youn Cheong\textsuperscript{a}, Kee Myung Lee\textsuperscript{a}, Sung Won Cho\textsuperscript{a,\*}, Je Hwan Won\textsuperscript{b},
Jai Keun Kim\textsuperscript{b}, Hee Jung Wang\textsuperscript{c}, Ki Baik Hahn\textsuperscript{a}, Jin Hong Kim\textsuperscript{a}

Fig. 1. Cumulative survival curves according to treatment modalities: (⋯⋯) conservative treatment; (---) systemic chemotherapy; (—) IA infusion chemotherapy.
Intraarterial infusion chemotherapy

A randomized comparative study of high-dose and low-dose hepatic arterial infusion chemotherapy for intractable, advanced hepatocellular carcinoma

Hyun Young Woo · Si Hyun Bae · Jun Yong Park · Kwang Hyub Han · Ho Jong Chun · Byung Gil Choi · Hyeon U. Im · Jong Young Choi · Seung Kew Yoon · Jae Youn Cheong · Sung Won Cho · Byoung Kuk Jang · Jae Seok Hwang · Sang Gyune Kim · Young Seok Kim · Yeon Seok Seo · Hyung Joon Yim · Soon Ho Um · Korean Liver Cancer Study Group

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Abstract

Purpose Hepatic arterial infusion chemotherapy (HAIC) has been reported to be effective in patients with advanced hepatocellular carcinoma (HCC).

Methods In this multicenter, prospective, open-labeled, clinical trial, we randomly assigned 68 patients with advanced HCC to receive either low-dose \( [n = 32, \text{5-fluorouracil (FU)}, 170 \text{mg/m}^2 \text{and cisplatin, 7 mg/m}^2 \text{on days 1–5}] \) or high-dose HAIC \( [n = 36, \text{5-FU}, 500 \text{mg/m}^2 \text{on days 1–3 and cisplatin, 60 mg/m}^2 \text{on day 2}] \) every 4 weeks via an implantable port system.

Results A total of 207 cycles of HAIC was given to the 68 patients. Overall, 6 patients (8.8%) achieved a partial response and 21 patients (30.9%) had stable disease. The objective response rate \((\text{CR} + \text{PR})\) was significantly improved in the high-dose group compared to the low-dose group \((16.7\% \text{ vs. } 0\%, P = 0.024)\). The median time to disease progression and overall survival were slightly prolonged in the high-dose group compared to the low-dose group \((\text{median survival, 193 vs. 153 days; } P = 0.108; \text{median time to disease progression, 145 vs. 90 days; } P = 0.095)\). Multivariate analysis showed that tumor response to treatment \([P = 0.007, \text{RR 2.27 (95\% CI, 1.248–4.132)}]\) was the only factor associated with overall survival. All adverse events were tolerable and successfully managed in both treatment groups.

Conclusions Both HAIC regimens are safe and effective in patients with advanced HCC. High-dose HAIC achieves a better tumor response compared to low-dose HAIC.
# Systemic chemotherapy for HCC

<table>
<thead>
<tr>
<th>연구자</th>
<th>약제</th>
<th>치료반응률 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sciarrino et al, 1985</td>
<td>Doxorubicin</td>
<td>0</td>
</tr>
<tr>
<td>Chlebowski et al, 1987</td>
<td>Doxorubicin</td>
<td>11</td>
</tr>
<tr>
<td>Falkson et al, 1984</td>
<td>Doxorubicin+5-FU+ methy-CCNU</td>
<td>15</td>
</tr>
<tr>
<td>Melia et al, 1983</td>
<td>VP-16</td>
<td>18</td>
</tr>
<tr>
<td>Falkson et al, 1987</td>
<td>Cisplatin</td>
<td>17</td>
</tr>
<tr>
<td>Patt et al, 2003</td>
<td>5-FU+interferon</td>
<td>18</td>
</tr>
<tr>
<td>Patt et al, 1999</td>
<td>5-FU + inteferon + Cisplatin + Doxorubicin</td>
<td>20</td>
</tr>
<tr>
<td>Okada et al, 1999</td>
<td>Cisplatin, Mitosantrone+5-FU</td>
<td>33</td>
</tr>
</tbody>
</table>
Recommendations

18. TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (level I).

19. Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function (level I).
21. **Radioembolization with Yttrium90-labeled glass beads has been shown to induce extensive tumour necrosis with acceptable safety profile. However, there no studies demonstrating an impact on survival and hence, its value in the clinical setting has not been established and cannot be recommended as standard therapy for advanced HCC outside clinical trials (level II).**

22. **Systemic or selective intra-arterial chemotherapy is not recommended and should not be used as standard of care (level II).**
Sorafenib may be a possible alternative for HCC patients not suitable for TACE

SHARP exploratory sub-analysis shows a trend of survival benefit in patients without vascular invasion / extrahepatic spread and in intermediate HCC patients


*Intermediate pts=BCLC B pts in SHARP trial
Sorafenib may be a possible alternative for HCC patients not suitable for TACE

Asia-Pacific exploratory sub-analysis shows a trend of survival benefit in patients without vascular invasion/extrahepatic spread

Tak W-J, et al. EASL 2009, Copenhagen, Denmark.
Bruix J, et al. ASCO 2009, Orlando, FL, USA.
Suggested treatment algorithm for TACE in patients with HCC

Patient/disease characteristics

No PVT or EHS

Child-Pugh A or B

Absolute or relative

CI to TACE

First TACE

CT or MRI

Second TACE

CT or MRI

Liver deterioration

Major complications

Unfit for TACE

Consider sorafenib

Disease control (CR, PR, SD)

Disease progression

New lesion

Growth of existing lesion

Consider retreatment with TACE?

Follow-up 3 months

Summary (1)

• TACE is the current standard of care for intermediate-stage HCC
  – however, a significant percentage of intermediate-stage patients are not candidates for TACE by strict criteria\textsuperscript{1,2}

• Patient and treatment characteristics most often associated with positive and negative survival outcomes with cTACE should be considered in the management of intermediate-stage HCC

Summary (2)

• Exploratory subset analyses from the SHARP$^3$ and Asia–Pacific$^4$ trials have suggested sorafenib shows a trend of survival benefit in

  – Intermediate-stage patients (BCLC B stage)$^5$
  – patients without vascular invasion / extrahepatic spread$^6$
  – patients previously treated with TACE$^7,8$

• Updated AASLD guidelines recommend sorafenib as first-line option in patients with intermediate HCC who cannot benefit from TACE or fail TACE, and still have preserved liver function$^9$

• Sorafenib may be treatment option in HCC patients who have either failed TACE or are unsuitable for TACE