NCCN Guidelines® Update: Locoregional Treatment Approaches for Hepatocellular Carcinoma

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Locoregional Therapy in the Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma most commonly occurs in the setting of underlying liver disease.

30-50% Hep B

Hepatitis B,C  Alcohol, NASH  Hemochromatosis  Biliary cirrhosis, 1AT def, Autoimmune hepatitis etc

Cirrhosis

HCC

Hepatocellular carcinoma is a global problem; the 5th most common cause of cancer worldwide and the 3rd leading cause of cancer related death.


Thein H et al. CMAJ v3(2) Apr-Jun 2015 PMID 26389099
Hepatocellular carcinoma is a global problem; the 5th most common cause of cancer worldwide and the 3rd leading cause of cancer related death.

1-3 tumors < 3 cm
Multi-focal > 3 cm
Liver dominant
Extrahepatic dz
Vascular invasion

Resection
Transplantation
Ablation
Arterially directed therapy
+/- ablation
Chemotherapy
Chemotherapy
Arterially directed therapy?
Ablation is potentially curative for accessible tumors < 3 cm in size and up to 3 in number.
Ablation is potentially curative for accessible tumors < 3 cm in size and up to 3 in number
There are 4 RCTs and several NRCTs comparing RFA and surgical resection in the treatment of small HCC.

For lesions < 3 cm overall survival at 1, 3, 5 years is no different.

+ Less transfusion
+ Shorter hospital stay
- Limited by tumor location

+Lower rate of local recurrence
+Better long-term disease-free
-Increase risk of complications

Feng K et al. J. Hepatol 2013 57:794-802
Lu et al. Zhonghua 2006 86(10):801-805
Randomized controlled trials comparing RFA to resection for HCC < 3 cm show no difference in 1, 3 & 4 year survival

Non-randomized controlled trials show significant benefit to resection probably due to patient selection bias
For resectable tumors, resection or transplant is preferred if feasible.

Ablation may also be curative for HCC < 3 cm.
Arterially directed therapies to the liver are possible due to the dual nature of hepatic blood supply

Bland embolization (TAE, HAE)
Bland embolization (TAE, HAE)
Bland embolization (TAE, HAE)

Transarterial chemoembolization (TACE)
Transarterial chemoembolization (TACE)

Embolization with drug eluting beads (DEB)
Embolization with drug eluting beads (DEB)
Embolization with drug eluting beads (DEB)

Radio “embolization” with Y90 (RAE)
Radio "embolization" with Y90 (RAE)
No additional treatment 6/2012-1/2014

1/2014

Two randomized controlled trials showing embolization has a survival advantage compared to best supportive care.

[Diagram showing the trial results and patient outcomes, with 903 patients registered, 791 excluded, and 112 randomized.]

Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial.

[Reference: journal citation provided]
Two randomized controlled trials showing embolization has a survival advantage compared to best supportive care.

OS at 3 years in TACE vs supportive care 29 vs 17%

279 newly diagnosed HCC

80 pts randomized

40 TACE (cisplatin, ethiodol, gelatin sponge)

199 excluded: liver function, performance status, MPV thrombosis

40 patients Symptomatic treatment

OS at 3 years in TACE vs supportive care 26 vs 3%
Two randomized controlled trials showing embolization has a survival advantage compared to best supportive care.

OS at 3 years in TACE vs supportive care 26 vs 3%

Combination of arterially directed therapy and ablation is recommended when there are 1-3 tumors 3-5 cm
Figure 3: Cumulative (a) overall survival curves for subgroup analysis of patients with tumors measuring 2.1–5.0 cm. Curves show (b) overall and (c) recurrence-free survival for patients treated with sequential TACE, RF ablation, and RF ablation alone.
For unresectable tumors > 3 cm in patients with preserved liver function, treatment with arterially directed therapy is recommended.

The choice of which arterially directed therapy is based on local expertise.

Combination arterially directed therapy and ablation may be used to treat tumors 3-5 cm.
Locoregional therapy for HCC

- Ablation alone may be curative for small HCC < 3 cm
- Arterially directed therapies are recommended for unresectable lesions > 3 cm
  - TAE/HAE, TACE, DEB, RAE
  - Specific treatment usually dictated by local expertise
- Combination arterially directed therapy and ablation is recommended for patients with 1-3 tumors 3-5 cm
- Sorafenib is reserved for residual/recurrent tumor not amenable to additional local therapy
PRINCIPLES OF LOCOREGIONAL THERAPY

All patients with HCC should be evaluated for potential curative therapies (resection, transplantation, and for small lesions, ablative strategies). Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies. These are broadly categorized into ablation and arterially directed therapies.

Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):
- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.
- Sorafenib should not be used as adjuvant therapy post-ablation.

PRINCIPLES OF LOCOREGIONAL THERAPY

Arterially Directed Therapies:
- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.
- Arterially directed therapies include transarterial bland embolization (TAE), chemoembolization (transarterial chemoembolization [TACE]) and TACE with drug-eluting beads (DEB-TACE), and radioembolization (RE) with yttrium-90 microspheres.
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed. RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.
- Arterially directed therapies are relatively contraindicated in patients with main portal vein thrombosis and Child-Pugh Class C.
- The angiographic endpoint of embolization may be chosen by the treating physician.
- Sorafenib may be appropriate following arterially directed therapies in patients with adequate liver function once bilirubin returns to baseline if there is evidence of residual/recurrent tumor not amenable to additional local therapies. The safety and efficacy of the use of sorafenib concomitantly with arterially directed therapies has not been associated with significant benefit in two randomized trials; other randomized phase III trials are ongoing to further investigate combination approaches.
Updates on Local-Regional Therapy for Hepatocellular Carcinoma: External Beam Radiation

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Radiation Oncology
Associate Professor
Stanford University

Basics of Radiobiology

Therapeutic Ratio

\[ TR = \frac{\text{prob tumor control}}{\text{prob toxicity}} \]

Optimize Ther Ratio

\[ TR_B \gg TR_A \text{ and } TR_C \]
Terms and Definitions

- EBRT – external beam radiotherapy
  - Radiation that comes from a machine into the patient
  - Photons or electrons, protons, heavy ions

- 3D CRT – 3D conformal RT
  - CT-based planning using uniform beams to treat a target

- IMRT – intensity modulated radiotherapy
  - Advanced conformal radiation using non-uniform beam intensities to shape the dose around critical structures
3D RT vs IMRT

- SBRT – stereotactic body radiotherapy
  - SABR – stereotactic ablative radiotherapy
  - High doses of radiation (8-25 Gy/day), usually with IMRT, delivered in ≤5 fractions
  - Ablative compared with conventional fractionation (2 Gy/day)

- IGRT – image guided radiotherapy
  - Any of the above using kV imaging to ensure target alignment
What’s in a name?
Liver Radiotherapy

- Historically not used due to concerns of toxicity of liver radiation
  - 1965 paper from Stanford first described radiation hepatitis
- RT primarily reserved for palliation
- Development of 3-D radiation and recognition that partial liver volumes could tolerate higher doses of radiation (>30 Gy) lead to expanded use of liver radiotherapy

Take home points about radiation

- Radiation is non-invasive
- No such thing as “too big,” though smaller is easier than bigger
- Can treat multiple tumors
- Dose can be adjusted based on size and location of critical structures
- Tumor thrombus is not a contraindication for treatment
- Caution about combining radiation with radioembolization
Combination of EBRT and Transarterial Chemoembolization (TACE)

- TACE with EBRT for salvage
- TACE combined with EBRT to treat the whole tumor
- TACE combined with EBRT to treat portal vein tumor thrombus
PVTT

Baseline

3 mos

12 mos
Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma

Guo World J Gastroenterol 2003

- HCC ≥ 5 cm, 22% with PVTT
- 76 pts – EBRT and TACE
- 89 pts – TACE alone
- ORR – 47% vs 28%, p<0.05

A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus

Zeng IJROBP 2005

- PVTT or IVC thrombus
- 44 pts – EBRT and TACE
- 73 pts – TACE alone
- 18 pts – Surgery alone
- 23 pts – No therapy
- 34% CR of PVTT or IVCT with EBRT

Studies using EBRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Tumor Size (range)</th>
<th>PVT (%)</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al</td>
<td>8.5 cm (4-13)</td>
<td>15 (33)</td>
<td>45</td>
<td>TACE + 50.4 Gy</td>
<td>6 (13)</td>
<td>35 (78)</td>
<td>4 (9)</td>
<td>23</td>
</tr>
<tr>
<td>Mendez et al</td>
<td>6 (3)</td>
<td>54</td>
<td>10</td>
<td>TACE + 52-60 Gy</td>
<td>3 (6)</td>
<td>38 (70)</td>
<td>13 (24)</td>
<td>20</td>
</tr>
<tr>
<td>Seong et al</td>
<td>7.2 cm (6-12)</td>
<td>80 (51)</td>
<td>158</td>
<td>TACE + 64-2-7.9 Gy</td>
<td>1 (1)</td>
<td>105 (67)</td>
<td>41 (26)</td>
<td>10</td>
</tr>
<tr>
<td>Guo et al</td>
<td>10.2 cm (6-13)</td>
<td>22 (11)</td>
<td>107</td>
<td>TACE + 25-55 Gy</td>
<td>6 (6)</td>
<td>46 (43)</td>
<td>42 (39)</td>
<td>18</td>
</tr>
</tbody>
</table>

Studies using EBRT with TACE

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Tumor Size (range)</th>
<th>PVT (%)</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>Median Survival (months)</th>
</tr>
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<tbody>
<tr>
<td>Li et al</td>
<td>8.5 cm (4-13)</td>
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<td>TACE + 50.4 Gy</td>
<td>6 (13)</td>
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</tr>
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</table>

Feng and Ben-Josef Sem Radiat Oncol 2011
Potential Advantages of SABR/SBRT

- Improvement in local control
- Shorter course of treatment
  - Allows integration with more intensive systemic chemotherapy
  - Patient convenience
- Cost effective
- QOL

Model for Radiation Cell Killing
Stereotactic Body Radiotherapy (SBRT)
Stereotactic Ablative Radiotherapy (SABR)

1990 2000 2010
First report of SBRT (1994)
First clinical report of lung and liver SBRT (1998)
First reports of SBRT for pancreas (2004)

HCC SBRT Reports

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lesions</th>
<th>SBRT</th>
<th>PTV</th>
<th>% Childs A/B</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibarra (2012)</td>
<td>32</td>
<td>21-HCC 11 - IHC</td>
<td>43</td>
<td>30-37.5 Gy/3, 22 Gy/1 47 Gy/10</td>
<td>GTV + 3-5mm or 7-10(mm)</td>
</tr>
<tr>
<td>Andolino (2011)</td>
<td>60</td>
<td>71</td>
<td>30-48 Gy/3 – CPA 40 Gy/5 - CPB</td>
<td>GTV + 5axial, 10sup-inf</td>
<td>60/40</td>
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<tr>
<td>PMH</td>
<td>41</td>
<td>31 HCC 10 IHC</td>
<td>Variable, NTCP-based Median 6 Gy x 6</td>
<td>GTV+8mm+margin PTVprimary = GTV+5+mm</td>
<td>100/0</td>
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<tr>
<td>Choi (2008)</td>
<td>31</td>
<td>32</td>
<td>30-39 Gy/3</td>
<td>GTV + 5 mm</td>
<td>84/16</td>
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<tr>
<td>Seo (2010)</td>
<td>38</td>
<td>47</td>
<td>30-57 Gy/3</td>
<td>ITV + 2 mm axial, 4 mm sup-inf</td>
<td>89/8</td>
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<tr>
<td>Japan (Takeda)</td>
<td>16</td>
<td>16</td>
<td>20-50 Gy in 5-8 fractions</td>
<td>ITV + 5-10 mm</td>
<td>88/12</td>
</tr>
</tbody>
</table>
Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma

- 102 patients from 2 prospective trials
- All with Child Pugh A
- 38% with HBV, 38% with HCV, 25% with EtOH
- Median GTV 117 cc
- 54% with vascular tumor thrombus
- Dose – 36 Gy (24-54) in 6 fractions

Bujold JCO 2013

1-year Local control 87%

Tumor volume not significant for LC

Overall survival

Bujold JCO 2013
224 patients with inoperable HCC treated with:
- RFA – 161 patients 249 tumors
- SBRT – 63 patients 83 tumors

SBRT dose range 27-60 Gy
- 3 fractions – median 30 Gy
- 5 fractions – median 50 Gy

Freedom from local progression
- Absence of disease progression within or at PTV margin or ablation zone
- Tumors requiring multiple RFAs for residual disease not counted as failure until after all tumor successfully treated

1-year FFLP
- RFA – 84%
- SBRT – 97%

2-year FFLP
- RFA – 80%
- SBRT – 84%
FFLP by size

Wahl JCO 2015

<2 cm
P=0.15

≥2 cm
P=0.025

Favors SBRT

Wahl JCO 2015
RADIATION THERAPY ONCOLOGY GROUP

RTOG 1112

Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma

SCHEMA

<table>
<thead>
<tr>
<th>Registration</th>
<th>STRATIFY</th>
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<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B vs. C vs. other</td>
<td></td>
</tr>
<tr>
<td>North American site vs. Non-North American site</td>
<td></td>
</tr>
<tr>
<td>HCC volume/liver volume (&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomize</th>
<th>Arm 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily sorafenib</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomize</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBRT alone (27.5 Gy – 50 Gy in 5 fractions) Followed by Sorafenib alone daily</td>
<td></td>
</tr>
</tbody>
</table>

https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=13150

International HCC SBRT Trial

Residual or recurrent disease following TACE

Randomized (stratified by tumor size ≤ 3 cm vs > 3 cm)

80 patients

TACE

80 patients

SABR 15 Gy x 3 = 45 Gy or 8-10 Gy x 5 – 40-50 Gy with tissue constraints met, see Section 5.3.4.

Crossover between arms allowed at progression (patients followed on-study after crossover)

Follow up for 18 months Follow up for 3 years for survival only

Total sample size: 160
Proton vs photon

Toxicities

- Classic radiation induced liver disease (RILD)
  - Typically occurs 6 weeks (4-12 weeks) after radiation
  - Clinical – anicteric ascites, hepatomegaly, and 2 X increase in alk phos
  - Pathologic – veno-occlusive disease due to fibrin and collagen deposition within sinusoidal vessels and central veins → vascular congestion → hypoxia/death of centrilobular hepatocytes → hepatic atrophy and dysfunction
Nonclassic RILD

- Non-classic RILD - ≥5 X increase in transaminases – suggesting direct damage to hepatocytes
  - 10/12 patients in Taiwan series had non-classic RILD
  - All patients were carriers of HCV or HBV

Liver Tolerance

- Child Pugh A cirrhosis appear to have good tolerance to radiation
- Child Pugh B cirrhosis appear to have reduced tolerance to radiation
  - Reduced dose and strict adherence to dose constraints required
- Child Pugh C cirrhosis – little to no data on liver tolerance
  - In general RT should be avoided
Worse tolerance of Child B than Child A

Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma

- Showed that Child A livers could be safely treated up to 48 Gy at 16 Gy/fraction
- 2/6 patients with Child B developed dose limiting toxicity
- Dose de-escalated to 40 Gy at 8 Gy/fraction

Cardenes et al, Clin Tranl Oncol 2010

Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy

No association of liver dosimetry with toxicity in Child A patients
Higher liver dosimetry seen in patients with toxicity in Child B patients

<table>
<thead>
<tr>
<th>Maximal dose to normal volume in CPC-B patients</th>
<th>Normal volume receiving dose without hepatic toxicity</th>
<th>Normal volume receiving dose with grade III/IV hepatic toxicity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15 Gy</td>
<td>1053.1 mL</td>
<td>1515.9 mL</td>
<td>.0396</td>
</tr>
<tr>
<td>&gt;12.5 Gy</td>
<td>946.1 mL</td>
<td>1432.0 mL</td>
<td>.0254</td>
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<tr>
<td>≤10 Gy</td>
<td>797.8 mL</td>
<td>1293.0 mL</td>
<td>.0132</td>
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<tr>
<td>&gt;7.5 Gy</td>
<td>625.9 mL</td>
<td>1149.7 mL</td>
<td>.0041</td>
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<tr>
<td>≤5 Gy</td>
<td>480.8 mL</td>
<td>1024.1 mL</td>
<td>.0015</td>
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<tr>
<td>&gt;2.5 Gy</td>
<td>304.9 mL</td>
<td>810.8 mL</td>
<td>.0011</td>
</tr>
</tbody>
</table>

CPC-B, Child-Pugh class B.

Lasley PRO 2015
Caution: \textit{HBV reactivation}

- Reported after conventional RT for HCC
- Consider in differential diagnosis of radiation-induced liver disease in high risk pt
- Antiviral therapy likely reduces risk
  - Figure at right:
    - Group I antiviral therapy
    - Group II none

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Comparison of HBV reactivation rates between Group I and Group II.}
\end{figure}

Center for Liver Cancer, South Korea

\textit{Courtesy of B. Kavanagh}

Don't confuse post-radiation change with recurrence

\begin{table}
\centering
\begin{tabular}{c|c|c|c}
\hline
Type & Pre & Art & PV \\
\hline
A & Iso & Iso & Iso \\
\hline
B & Low & Iso & Iso \\
\hline
C & Low & Iso & High or High \\
\hline
\end{tabular}
\caption{Types of post-radiation changes.}
\end{table}

Sanuki-Fujimoto Br J Rad 2010
Conclusions

- EBRT is an important and effective treatment option for HCC
- Improvements in technology have allowed safe delivery of ablative doses of radiation with excellent control rates
- Further studies and ideally randomized trials with other liver-directed therapies are needed in the overall treatment algorithm for HCC
- Need better understanding of liver tolerance to optimize dose fractionation