Radiation oncologist’s perspective: Providing survival benefit

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Department of Radiation Oncology
<table>
<thead>
<tr>
<th>Guideline</th>
<th>EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001 Barcelona-EASL consensus</td>
<td>No</td>
</tr>
<tr>
<td>2002 US NCCN guideline</td>
<td></td>
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<tr>
<td>2003 KLCSG-NCC guideline</td>
<td>Yes</td>
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<tr>
<td>2005 AASLD guideline</td>
<td>No*</td>
</tr>
<tr>
<td>2005 Japan guideline for evidence-based clinical practice</td>
<td>No†</td>
</tr>
<tr>
<td>2007 JSH guideline: consensus-based clinical practice manual</td>
<td>No</td>
</tr>
<tr>
<td>2008 US NCCN guideline</td>
<td>Yes</td>
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<tr>
<td>2009 KLCSG guideline</td>
<td>Yes</td>
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<tr>
<td>2010 AASLD</td>
<td>No</td>
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<td>2012 EASL-EORTC 2012</td>
<td>Yes</td>
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</tbody>
</table>

* Non-curative treatment: There are multiple other treatment modalities such as octreotide, interferon, external radiation, tamoxifen, or antiandrogenic therapy, but none have been shown to improve survival.

† For Child-Pugh C cases with vascular invasion or an extrahepatic lesion, palliative care is the basic treatment, including radiotherapy aimed at palliative pain removal.
Ablation (RFA etc.)
Emblization
RTx
Hepatocellular Carcinoma

**CLINICAL PRESENTATION**

**Unresectable**

- Inadequate hepatic reserve
- Tumor location
- Extensive liver tumor burden

**TREATMENT**

Evaluate whether patient is a candidate for transplant (See UNOS criteria under Surgical Assessment HCC-5)

- Refer to liver transplant center
- Consider bridge therapy as indicated

**SURVEILLANCE**

- Imaging every 3-6 mo for 2 y, then every 6-12 mo
- AFP, if initially elevated, every 3-6 mo for 2 y, then every 6-12 mo
- See relevant pathway (HCC-2 through HCC-7) if disease recurs

**Options:**

- Sorafenib (Child-Pugh Class A [category 1] or B) \(^{u,w,x}\)
  - Chemotherapy + RT only in the context of a clinical trial
  - Clinical trial
  - Locoregional therapy \(^{x,y}\)
  - RT (conformal or stereotactic) \(^{z}\) (category 2B)

**Supportive care**

**Systemic or intra-arterial chemotherapy in clinical trial**


\(^{v}\)Many transplant centers consider bridge therapy for transplant candidates. (See Discussion)

\(^{w}\)See Principles of Locoregional Therapy (HCC-C)

\(^{x}\)See Child-Pugh Score (HCC-A).

\(^{y}\)Order does not indicate preference with the exception of category 1 options which are listed first.


\(^{z}\)There are limited data to support the use of RT in this setting.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Chemoembolization and transcatheter therapies

- Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread (evidence 1iiA; recommendation 1A)
- The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events (evidence 1D; recommendation 2B)
- Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread (evidence 1iiA; recommendation 1B)
- Bland embolization is not recommended
- Internal radiation with $^{131}$I or $^{90}$Y glass beads has shown promising anti-tumoral results with a safe profile, but cannot be recommended as standard therapy. Further research trials are needed to establish a competitive efficacy role in this population (evidence 2A; recommendation 2B)
- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC (evidence 2A; recommendation 2B)
- External three-dimensional conformal radiotherapy is under investigation, and there is no evidence to support this therapeutic approach in the management of HCC (evidence 3A; recommendation 2C)
간세포암종 가이드라인 (2003)

간세포암종 진료 가이드라인 - 3

2003 간세포암종 진료 가이드라인 - 3
대한간암연구회, 국립암센터

일차 판단

• 간암병기
• Child-Pugh 등급

가이드라인

D1
간세포암종

D2
수술 가능

D2
결제 가능

검사

• ICG 검사
• 역동적 조영증강 MRI
• 빠른 스캔
• 흉부 CT
• 혈관조영술 염성 CT
• PET
• 용적측정

결제 가능

• 간소간기능 부족
• 간세포암종이 명확하지 않은 경우

치료 방침**

• 간결제술 (I)
• 경동맥화학요법 (TACE) (II)
• 국소치료술 (III)
• ± 간식

• 간세포암종 경동맥화학요법
• 경동맥화학요법
• 국소치료술
• ± 간식

• 간세포암종 경동맥화학요법
• 경동맥화학요법
• 국소치료술
• ± 간식

• 간세포암종 경동맥화학요법
• 경동맥화학요법
• 국소치료술
• ± 간식

• 간세포암종 경동맥화학요법
• 경동맥화학요법
• 국소치료술
• ± 간식

*경동맥화학요법(TACE)을 시행하는 경우 있음
**순위는 표기 순위를 뜻함. 숫자가 없는 것은 4등급(열점자료 1)
2003 간세포암중 진료 가이드라인

1. 절대적 비적응증
   ▶ 간기능 Child-Pugh C이면서 전 간의 다발성, 미만성 종양이며 수행상태 ECOG 활동도 3 이상

2. 상대적 비적응증
   ▶ 간기능 Child-pugh A,B이면서 전 간에 걸친 다발성, 미만성 종양
   ▶ 제한적 간외 전이
   ▶ 주변 장기, 외장간 등의 활동성 염증이나 궤양이 동반된 경우

3. 적응증
   ▶ 근치적 목적: 간기능 child-Pugh A,B이면서 종양이 전 간의 2/3 이하이고 간 외 전이가 없는 경우
   ▶ 완화 목적: 종양으로 인한 통증, 파열이 예상되는 종양, 간문맥 종양 혈전증, 종양으로 인한 담도폐색, 국소적 간외 전이 등
간절제술
간이식
고주파열치료
(± 경동맥화학색전술)
간암병기
Child-Pugh 등급
ECOG 수행능력

근치적치료

종양치료가능

선택검사
ICG 검사
뼈스캔
흉부 CT
혈관조영술
PET-CT
응적측정
위내시경

비근치적치료

임상적시도

Drug eluting bead-TACE
방사선색전술
HIFU
간동맥내 주입항암요법
세포독성화학요법
전이병소절제술

• 경동맥화학색전술
• 방사선치료 (II-I)
• 흉양화학요법)*
* Sorafenib (I)
세포독성화학요법 (III)

• 간절제술
• 간이식
• 고주파열치료
(± 경동맥화학색전술)

• 간암병기
• Child-Pugh 등급
• ECOG 수행능력

• 종양병기진행
• 간기능저하(Child-Pugh 등급 C)**
• 동반된 전신질환(ECOG >2)
• 동반된 전신질환

**간이식 고려 (I)
권고사항

1. 근치적 치료가 불가능한 간세포암중 중 주혈관 침범이나 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. 간문막침범이 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 II-2), 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).

권고사항

1. 간기능이 Child–Pugh 등급 A 또는 상위 B 등급이면서 종양이 전체 간부피의 2/3 이하인 경우 방사선치료를 시행할 수 있다(증거순위 II-3).
2. 간문맥 종양혈전증을 동반한 간세포암중에 방사선치료를 시행할 수 있다(증거순위 II-1).
3. 간세포암중의 원발암 및 전이암으로 인한 종상을 완화시키기 위해 방사선치료를 시행할 수 있다(증거순위 II-2).
수정전 권고사항 (방사선종양학과 제시안)

간세포암에서의 근치적 방사선치료의 적응증
1. 간기능이 Child-Pugh A 또는 B 이면서 종양이 전체 간부피의 2/3이하 이고, 간외전이가 없는 경우 근치적 목적의 방사선치료를 시행할 수 있다. (II-3).
2. 간문맥혈전증은 방사선치료가 효과적이다. (II-1).
3. 경동맥화학색전술 단독보다는 방사선치료와의 병합요법이 보다 효과적이다. (II-1)

간세포암에서의 고식적 방사선치료의 적응증
1. 경동맥화학색전술 후 재발성 간암에 대한 구제치료로서 고식적 목적의 방사선치료를 시행할 수 있다. (II-2)
2. 간암으로 인한 복부통증 등 증상완화를 목적으로 방사선치료를 시행할 수 있다. (III)
3. 황달 증상을 보이는 간암에 방사선치료를 시행할 수 있다. (II-2)
4. 종양으로 인한 동정맥단락에서 일차치료로 방사선치료를 시행하여 향후 TACE 등을 가능하게 할 수 있다. (III)
5. 복부 림프절 전이에 대해서 방사선치료의 시행으로 생존율의 향상을 기대할 수 있다. (II-2)
6. 뼈전이에 의한 통증이 있는 경우 방사선 치료로 증상완화를 이룰 수 있다. (II-3)
7. 뇌전이로 인한 신경학적 증상을 완화하기 위해 전뇌방사선치료가 효과적이다. (II-3)
8. 간암의 척수압박으로 인한 신경학적 증상을 완화하기 위해 방사선치료는 효과적이다. (III)
HCC

Stage 0
- PST 0, Child-Pugh A
  - Very early stage (0)
    - Single <2 cm, Carcinoma in situ
      - Single
      - Portal pressure/bilirubin
        - Increased
        - Associated diseases
          - Normal
          - No
          - Yes
            - Resection
            - Liver transplantation (CLT/LDLT)
            - RF/PEI

Stage A-C
- PST 0-2, Child-Pugh A-B
  - Early stage (A)
    - Single or 3 nodules ≤3 cm, PS 0
      - 3 nodules ≤3 cm
        - Associated diseases
          - Normal
          - No
          - Yes
            - RF/PEI
            - TACE

Stage D
- PST >2, Child-Pugh C*
  - Intermediate stage (B)
    - Multinodular, PS 0
  - Advanced stage (C)
    - Portal invasion, N1, M1, PS 1-2
  - Terminal stage (D)

Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%

Target: 20%
OS: 20 mo (45-14)

Target: 40%
OS: 11 mo (6-14)

Target: 10%
OS: <3 mo

Best supportive care
**Fig. 3.** Radiotherapy according to the Barcelona Clinic Liver Cancer stage. Inoperable, not feasible for curative treatment, or locally recurring hepatocellular carcinoma (HCC) can be managed using radiotherapy. Solitary tumors distant from the gastrointestinal tract and kidneys with a tumor volume <100 cm³ are eligible for stereotactic body radiotherapy (SBRT).

PST, performance status; PEI, percutaneous ethanol injection; RF, radiofrequency; TACE, transcatheter arterial embolization; CCRT, concurrent chemoradiotherapy; IA CTx, intraarterial chemotherapy.
Fig. 3. Radiotherapy according to the Barcelona Clinic Liver Cancer (BCLC) stage. Inoperable, not feasible for curative treatment, or locally recurring hepatocellular carcinoma (HCC) can be managed using radiotherapy. Solitary tumors distant from the gastrointestinal tract and kidneys with a tumor volume <100 cm³ are eligible for stereotactic body radiotherapy (SBRT). PST, performance status; PEI, percutaneous ethanol injection; RF, radiofrequency; TACE, transarterial chemotherapy; CCRT, concurrent chemoradiotherapy; iA CTx, intraarterial chemotherapy.
Early stage

M/59, T2N0

Initial
M/59, T2N0

Initial

SBRT (9 Gy x 4 fractions)

1 month

2 months

6 months

AFP (ng/mL)

Pre-SBRT: 4656
At finish: 3643
1 month: 92.2
2 months: 2.68
6 months: 1.63
Stereotactic Body Radiation Therapy for Inoperable Hepatocellular Carcinoma as a Local Salvage Treatment After Incomplete Transarterial Chemoembolization

Jin-Kyu Kang, MD¹; Mi-Sook Kim, MD, PhD¹; Chul Koo Cho, MD, PhD¹; Kwang Mo Yang, MD, PhD¹; Hyung Jun Yoo, MD¹; Jin Ho Kim, MD¹; Sun Hyun Bae, MD¹; Da Hoon Jung, MD¹; Kum Bae Kim¹; Dong Han Lee, PhD²; Chul Ju Han, MD³; Jin Kim, MD³; Su Cheol Park, MD³; and Young Han Kim, MD⁴

Figure 1. Kaplan-Meier survival outcomes after stereotactic body radiation therapy (SBRT) are illustrated.

Figure 3. The relation between the presence of a pre-existing gastrointestinal (GI) ulcer and stereotactic body radiation therapy (SBRT) related severe GI toxicity is illustrated. A pre-existing GI ulcer significantly affected SBRT-related severe GI toxicity (Fisher exact test).
Intermediate stage

Clinical Studies

Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma

Suh CO, Lee JT. Local radiotherapy as an effective tool in transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma.

Su Jung Shim¹, Jinsil Seong¹, Hyub Han², Chae Yoon Chon², Ok Suh¹ and Jong Tae Lee³

¹Departments of Radiation Oncology, Cancer Center, ²Internal Medicine, ³Radiology, Korea University College of Medicine, Seoul, Korea
TACE in combination with RT for unresectable HCC: A systematic review and meta-analysis

- Meng et al. (2009)
  *Radiotherapy and Oncology*
TACE → RTx
How many TACE??

Consensus Statements

27 The following situation should be regarded as TACE failure or refractory:
(a) Intrahepatic lesion.
   (i) **More than two** consecutive incomplete necrosis (depositions (<50%) of lipiodol) are seen by response evaluation CT within the treated tumors at the 4 weeks after adequately performed TACE.
   (ii) More than two consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT at the 4 weeks after adequately performed TACE.
(b) Appearance of vascular invasion.
(c) Appearance of extrahepatic spread – continuous elevation of tumor markers even though right after TACE.
(d) Tumor marker – continuous elevation of tumor markers even though right after TACE.

Consensus-Based Clinical Practice Guidelines Proposed by the Japan Society of Hepatology (JSH) 2010, Kudo et al.

For patients who show no response of the treated tumour after at least two **sessions** of TACE, other therapies, including systemic therapy with a targeted agent, could be considered as an alternative to further TACE cycles.

*Raoul et al. Cancer Tret Rev, 2011*
Advanced stage

# HCC (non-B, non-C), cT3N1M0, stage IVA

Huge marginal enhancing mass in Rt lobe of liver, Rt PVT (+) aortocaval, retrocaval space, porta LNE

s/p IA FL based definitive CCRT 50Gy/ 25 fx (2011.02.05-2011.03.04)
s/p IA FP #2 (2011.03.05-2011.06.08)
Initial AFP 4978 → 8.6
비근치적치료

- 경동맥화학색전술
- 방사선치료 (II-I)
- 항암화학요법)*
  * Sorafenib (I)
- 세포독성 화학요법 (III)

임상적시도

- Drug eluting bead-TACE
- 방사선색전술
- HIFU
- 간동맥내 주입항암요법
- 세포독성화학요법
- 전이 병소 절제술

- 양성자선치료

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HCC multidisciplinary conference

- Intermediate stage (B)
  - multinodular; PST 0

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

  - Portal invasion, N1, M1
    - No
      - Chemoembolization
    - Yes
      - Sorafenib

      - Incomplete, not feasible, non-responder, or recurred
        - TACE+RTx
        - CCRT → iA CTx
Initial Tx? Salvage Tx?

Multidisciplinary management
RADIOThERAPY PLUS TRANSarterial CHEMOEMBOLIZATION FOR HEPATOCellular CARCINOMA INVADING THE PORTAL VEIN: LONG-TERM PATIENT OUTCOMES

Sang Min Yoon, M.D., Young-Suk Lim, M.D., Hyung Jin Won, M.D., Jong Hoon Kim, M.D., Ph.D., Kang Mo Kim, M.D., Han Chu Lee, M.D., Young-Hwa Chung, M.D., Yung Sang Lee, M.D., Sung Gyu Lee, M.D., Jin-hong Park, M.D., and Dong Jin Suh, M.D.

Departments of *Radiation Oncology, †Gastroenterology, ‡Radiology, and §Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

- TACE + Ext. RTx
- Role of Salvage Tx.
CLINICAL STUDIES

A multicenter retrospective cohort study of practice patterns and clinical outcome on radiotherapy for hepatocellular carcinoma in Korea

Jinsil Seong¹,¹¹, Ik Jae Lee¹, Su Jung Shim¹, Do Hoon Lim², Tae Hyun Kim³, Jong Hoon Kim⁴, Hong Seok Jang⁵, Mi Sook Kim⁶, Eui Kyu Chie⁷, Jin Hee Kim⁸, Taek-Keun Nam⁹, Hyung Sik Lee¹⁰ and Chul Joo Han⁶,¹¹

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2 Sungkyunkwan University Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
3 National Cancer Center, Goyang, Korea
4 Asan Medical Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
5 Catholic University College of Medicine, Seoul, Korea
6 Korea Cancer Center Hospital, Seoul, Korea
7 Seoul National University College of Medicine, Seoul, Korea
8 Keimyung University College of Medicine, Daegu, Korea
9 Chonnam National University College of Medicine, Gwangju, Korea
10 Dong-A University College of Medicine, Busan, Korea
11 Korean Liver Cancer Study Association, Seoul, Korea

<table>
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<tr>
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<th>All (n = 398)</th>
<th>3D-CRT (n = 326)</th>
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<tbody>
<tr>
<td>TACI</td>
<td>54 (13.6)</td>
<td>25 (7.6)</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>10 (2.5)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Radiofrequency ablation</td>
<td>35 (8.8)</td>
<td>11 (3.3)</td>
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<tr>
<td>iA-chemotherapy</td>
<td>34 (8.5)</td>
<td>6 (2.0)</td>
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<tr>
<td>Surgery</td>
<td>25 (6.3)</td>
<td>10 (3.0)</td>
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<tr>
<td>Percutaneous ethanol injection</td>
<td>8 (2.0)</td>
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<td>Holmium</td>
<td>7 (1.8)</td>
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<td>33 (10.1)</td>
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Clinical factors related to treatment failure after hepatic arterial concurrent chemoradiotherapy for locally advanced HCC

Cha et al. Yonsei Univ. submitted.

### Risk factors of progression free survival - Multivariate analysis

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<thead>
<tr>
<th></th>
<th>Local failure</th>
<th>Distant failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infield</td>
<td>Intrahepatic-outfield</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI p</td>
<td>HR 95% CI p</td>
</tr>
<tr>
<td>Age, ≥50</td>
<td>0.742 0.360−1.531 0.420</td>
<td>0.853 0.480−1.518 0.589</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>1.036 0.431−2.493 0.937</td>
<td>0.878 0.426−1.810 0.724</td>
</tr>
<tr>
<td>Portal vein thrombosis, Yes</td>
<td>1.386 0.725−2.651 0.324</td>
<td>1.267 0.729−2.203 0.401</td>
</tr>
<tr>
<td>Pre-CCRT treatment history, Yes</td>
<td>2.190 1.132−4.235 <strong>0.020</strong></td>
<td>1.198 0.677−2.120 0.536</td>
</tr>
<tr>
<td>Pre-CCRT AFP (IU/mL), ≥200</td>
<td>0.444 0.096−2.048 0.298</td>
<td>1.045 0.231−4.726 0.954</td>
</tr>
<tr>
<td>Pre-CCRT PIVKA-II (mAU/mL), ≥60</td>
<td>0.742 0.250−2.207 0.592</td>
<td>1.422 0.423−4.784 0.569</td>
</tr>
<tr>
<td>Pre-CCRT AFP &amp; PIVKA-II</td>
<td>2.511 0.485−12.997 0.272</td>
<td>1.740 0.353−8.587 0.496</td>
</tr>
</tbody>
</table>
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골전이로 방사선치료 후 효과적인 고식적 치료로 장기간 추적 관찰 중인 간세포암 종 1예

Efficacy of External Beam Radiation Therapy in the Treatment of Bone Metastases: A Long Term Followed Up Case

김미선¹, 이익재¹, 이병춘², 이관식³
연세대학교 의과대학 간남세브란스병원 ¹방사선치료과, ²영상의학과, ³소화기내과

Mi Sun Kim, M.D.¹, Ik Jae Lee, M.D.¹, Kwang-Hun Lee, M.D.², Kwan Sik Lee, M.D.³
Department of Radiation Oncology, Radiology and Internal Medicine,
Gangnam Severance Hospital, Yonsei University Health System, Seoul, Korea
Factors we have to consider for Radiotherapy

→ Radiotherapy is locoregional Tx.
• Location
• Tumor volume
• Extrahepatic disease (Lymph node, portal vein thrombosis etc.)
• Normal liver volume
• Adjacent normal organ (stomach, duodenum, kidney....)
• Liver function (Child-Pugh’s class etc.)
• Tumor markers
• Biologic behavior (CTx response, indolent vs. rapid progression)
• Available radiotherapy modalities (SBRT, 3D-CRT, IMRT, gated RTx, Immobilization device etc.)
RADIOThERAPEUTIC PARAMETERS PREDICTIVE OF LIVER COMPLICATIONS INDUCED BY LIVER TUMOR RADIOTHERAPY

IK JAE LEE, M.D.,* JINSIL SEONG, M.D.,* SU JUNG SHIM, M.D.,* AND KWANG HYUB HAN, M.D.†

*Department of Radiation Oncology and †Yonsei Liver Cancer Clinic, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Table 4. Incidence of liver complications by $V_{50\%}$ of normal liver volume

<table>
<thead>
<tr>
<th>Fraction of normal liver treated ($V_{50%}$)</th>
<th>Nontumor liver volume (cc)</th>
<th>No. of patients (%)</th>
<th>RT dose, range (Gy)</th>
<th>RT dose, mean (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Michigan guideline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;33</td>
<td>1078.0 ± 410.8</td>
<td>3/27 (11.1%)</td>
<td>28.8–59.4</td>
<td>48.1</td>
</tr>
<tr>
<td>33–66</td>
<td>1075.0 ± 363.4</td>
<td>8/78 (10.3%)</td>
<td>30.6–54.0</td>
<td>45.1</td>
</tr>
<tr>
<td>&gt;66</td>
<td>856.7 ± 257.1</td>
<td>2/11 (18.2%)</td>
<td>30.6–45.0</td>
<td>42.2</td>
</tr>
<tr>
<td>Yonsei University guideline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>1205.7 ± 303.9</td>
<td>1/10 (10.0%)</td>
<td>28.8–59.4</td>
<td>49.5</td>
</tr>
<tr>
<td>25–49</td>
<td>1018.3 ± 402.0</td>
<td>7/58 (12.1%)</td>
<td>30.6–54.0</td>
<td>46.6</td>
</tr>
<tr>
<td>50–75</td>
<td>1009.4 ± 339.7</td>
<td>5/48 (10.4%)</td>
<td>30.6–45.0</td>
<td>43.4</td>
</tr>
<tr>
<td>&gt;75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RT = radiotherapy.

Table 6. Incidence of liver complication by hepatic functional status and tumor factor

<table>
<thead>
<tr>
<th>Hepatic functional status</th>
<th>No of patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RT ICG-R15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>7/56 (12.5)</td>
<td>0.779</td>
</tr>
<tr>
<td>10–40%</td>
<td>6/57 (10.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;40%</td>
<td>0/3 (−)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>9/114 (7.9)</td>
<td>0.044</td>
</tr>
<tr>
<td>B</td>
<td>4/17 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Tumor factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-RT AFP</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>8/70 (11.4)</td>
<td></td>
</tr>
<tr>
<td>≥1,000</td>
<td>3/36 (8.3)</td>
<td></td>
</tr>
<tr>
<td>PIVKA-II</td>
<td></td>
<td>0.432</td>
</tr>
<tr>
<td>≤40</td>
<td>0/5 (−)</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>5/45 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>No</td>
<td>6/66 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7/5 (10.8)</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 5: SUMMARY OF LIVER RADIATION TOLERANCES FROM LITERATURE REVIEW

<table>
<thead>
<tr>
<th>Study group</th>
<th>N</th>
<th>Diagnosis</th>
<th>Child-Pugh score</th>
<th>Child-Pugh score per fraction</th>
<th>Total liver dose</th>
<th>Factors associated with RLD</th>
<th>RLD (median)</th>
<th>Median liver dose</th>
<th>RLD (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh A</td>
<td>29</td>
<td>BCLC 1</td>
<td>31.5 mg/kg</td>
<td>30 Gy</td>
<td>60 Gy</td>
<td>30 Gy</td>
<td>15 Gy</td>
<td>15 Gy</td>
<td>15 Gy</td>
</tr>
<tr>
<td>Child-Pugh B</td>
<td>29</td>
<td>BCLC 1</td>
<td>31.5 mg/kg</td>
<td>30 Gy</td>
<td>60 Gy</td>
<td>30 Gy</td>
<td>15 Gy</td>
<td>15 Gy</td>
<td>15 Gy</td>
</tr>
<tr>
<td>Child-Pugh C</td>
<td>29</td>
<td>BCLC 1</td>
<td>31.5 mg/kg</td>
<td>30 Gy</td>
<td>60 Gy</td>
<td>30 Gy</td>
<td>15 Gy</td>
<td>15 Gy</td>
<td>15 Gy</td>
</tr>
</tbody>
</table>

### TABLE 6: RECOMMENDED RADIATION DOSE-VOLUMES TO NORMAL LIVER AND TOTAL LIVER

<table>
<thead>
<tr>
<th>Normal liver</th>
<th>Total liver</th>
<th>Constraint</th>
<th>Daily dose</th>
<th>Total liver dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 cm³</td>
<td>1.5 cm³</td>
<td>&lt;3 cm³</td>
<td>&lt;2 cm³</td>
<td>&lt;1 cm³</td>
</tr>
<tr>
<td>1.8 cm³</td>
<td>2.2 cm³</td>
<td>&lt;3.5 cm³</td>
<td>&lt;2.5 cm³</td>
<td>&lt;1.5 cm³</td>
</tr>
<tr>
<td>2.4 cm³</td>
<td>2.8 cm³</td>
<td>&lt;4 cm³</td>
<td>&lt;2.5 cm³</td>
<td>&lt;1.5 cm³</td>
</tr>
</tbody>
</table>

### TABLE 7: TRENDS AND PRACTICES IN DIAGNOSIS AND TREATMENT OF HEPATOCARCINOMA

- Incidence of hepatocellular carcinoma (HCC) has increased worldwide.
- Early detection through screening is crucial for improving survival.
- Combination therapies like chemotherapy, radiotherapy, and surgical resection are常用的 treatment options.
- Advances in imaging techniques have improved diagnosis accuracy.
- Liver transplantation is a viable option for selected patients.
Predictive Index for PVTT in Patients with HCC treated with RTx (PITH)

- Performance status (ECOG),
- Child-Pugh classification B or C,
- 10 cm or more of tumor size,
- multiplicity of the tumor
- main PVTT involvement, complete occlusion of portal flow
- lymph node metastasis.

Yu et al. JKMS 2011

Table 4. Comparison of survivals according to prognostic models

<table>
<thead>
<tr>
<th>Prognostic model</th>
<th>Group</th>
<th>Number (%)</th>
<th>Median (month)</th>
<th>Inter-quartile range (month)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLC</td>
<td>C</td>
<td>276 (96.1)</td>
<td>12.0</td>
<td>4.8-26.9</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>5 (3.9)</td>
<td>3.2</td>
<td>2.8-4.9</td>
<td></td>
</tr>
<tr>
<td>CLIP</td>
<td>1</td>
<td>42 (14.9)</td>
<td>15.0</td>
<td>9.1-24.6</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>102 (36.3)</td>
<td>13.6</td>
<td>4.8-50.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>55 (19.6)</td>
<td>10.9</td>
<td>5.6-27.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>47 (16.7)</td>
<td>6.3</td>
<td>4.2-23.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 + 6</td>
<td>35 (12.5)</td>
<td>5.9</td>
<td>3.8-12.0</td>
<td></td>
</tr>
<tr>
<td>Okuda</td>
<td>I</td>
<td>161 (57.3)</td>
<td>15.0</td>
<td>7.1-29.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>116 (41.3)</td>
<td>6.0</td>
<td>3.8-16.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>4 (1.4)</td>
<td>3.1</td>
<td>1.9-4.9</td>
<td></td>
</tr>
<tr>
<td>JIS</td>
<td>2</td>
<td>206 (73.3)</td>
<td>13.3</td>
<td>5.3-27.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>65 (23.1)</td>
<td>7.1</td>
<td>3.8-18.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>9 (3.2)</td>
<td>3.2</td>
<td>2.7-4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1 (0.4)</td>
<td>4.9</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>CUPI</td>
<td>Low</td>
<td>188 (66.9)</td>
<td>15.0</td>
<td>5.8-33.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>92 (32.7)</td>
<td>5.7</td>
<td>3.2-13.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1 (0.4)</td>
<td>2.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>PITH</td>
<td>Low</td>
<td>54 (19.2)</td>
<td>27.2</td>
<td>19.1-73.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Low intermediate</td>
<td>133 (47.3)</td>
<td>11.4</td>
<td>5.0-19.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High intermediate</td>
<td>76 (27.0)</td>
<td>6.4</td>
<td>4.4-16.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>18 (6.4)</td>
<td>3.3</td>
<td>3.0-5.3</td>
<td></td>
</tr>
</tbody>
</table>

BCLC, Barcelona Clinic Liver Cancer (BCLC) staging classification; CLIP, Cancer of the Liver Italian Program (CLIP) scoring system; JIS, Japan Integrated Staging (JIS) scoring system; CUPI, The Chinese University Prognostic Index; PITH, Predictive Index for portal vein tumor thrombosis of the hepatocellular carcinoma.
저는 어떤 치료를 받는 것이 가장 좋을까요?

양성자치료
3차원입체조형방사선치료
방사선수술, 사이버나이프
세기조절방사선치료, 랜프드아크, 트루빔, 노발리스, 토모테라피
Tumor dose (Gy)

No. of Fraction

Conventional RT

IMRT
Elekta Synergy, Varian Trilogy, Siemens Artiste, Helical Tomotherapy etc.

FSRT
Cyberknife, Novalis

SRS

IGRT

YONSEI UNIVERSITY MEDICAL CENTER
Selection of the Optimal Radiotherapy Technique for Locally Advanced Hepatocellular Carcinoma

Ik Jae Lee¹, Jinsil Seong¹*, Woong Sub Koom¹, Yong Bae Kim¹, Byeong Chul Jeon¹, Joo Ho Kim¹ and Kwang Hyub Han²

위치에 따라 다양한 방사선치료 계획이 세워짐.
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Eligibility Criteria for Different Radiation Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRT</td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>+++</td>
</tr>
<tr>
<td>3-6 cm</td>
<td>+++</td>
</tr>
<tr>
<td>6-10 cm</td>
<td>+++</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>++</td>
</tr>
<tr>
<td>Diffuse</td>
<td>0</td>
</tr>
<tr>
<td>High bleeding risk</td>
<td>++</td>
</tr>
<tr>
<td>Child-Pugh B</td>
<td>++</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>+++</td>
</tr>
<tr>
<td>Caudate lobe</td>
<td>+++</td>
</tr>
<tr>
<td>Target &lt;1 cm from GI tissues†</td>
<td>++</td>
</tr>
</tbody>
</table>

*Proton, protons or any other charged particle therapy.
†GI tissues, luminal gastrointestinal tissues (e.g., stomach, duodenum).

Abbreviations: CRT, conformal radiation therapy; SBRT, stereotactic radiation therapy; Brachy, brachytherapy; Yttrium-90, hepatic arterial yttrium-90.
Spectrum of in-room image-guidance technologies

- Ultrasound
- kV Radiographic
- Portal Imaging
- Markers (Active and Passive)
- CT “on rails”
- TomoTherapy
- MV CT
- Cone-beam CT
Spectrum of in-room image-guidance technologies
간세포암 환자에서의 방사선치료의 효과에 대한 짝을 이룬 관찰치 비교 분석 (Matched-pair analysis)

간암등록사업 자료 활용 연구 - 대한간암연구학회

세브란스병원
방사선치료
1134명

세브란스병원
치료료법
방사선치료
313명

무작위등록자료
치료료법
방사선치료
49명

무작위등록자료
전체 환자
4444명

세브란스병원
치료료법
방사선치료 제외
821명

방사선치료군
362명

무작위등록자료
치료료법
방사선치료 제외
4395명

Propensity 점수를 이용한
1:1 matched-pairing

방사선치료군
362명

대조군
362명

전체 생존율 비교분석 및 야군 분석
Trial design strategies and control groups

- **BCLC 0-A** (early HCC)
  - Standard of care: Resection, transplantation, percutaneous ablation
  - First line: Plaabebo vs. drug
  - Second line: TACE vs. TACE + drug/device

- **BCLC B** (intermediate HCC)
  - Standard of care: Chemoembolization-TACE
  - First line: TACE vs. TACE + drug/device
  - Second line: Plaabebo vs. drug

- **BCLC C** (advanced HCC)
  - Standard of care: Sorafenib
  - First line: Sorafenib vs. Sorafenib + drug
  - Second line: Plaabebo vs. drug

5. Summary of trial design strategies and control groups. Adapted from Llovet et al. [164].

Journal of Hepatology 2012 vol. 56 908–943

RTx ± Sorafenib
Sorafenib + RTx
CCRT ± Sorafenib
Phase II multicenter study of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma (KROG 12-02)

Radiation: Total stereotactic Body radiotherapy (SBRT) doses will be **60 Gy in 3 fractionations**. Patients receive 3 fractionations separated by >48 hours.

Target sample size: 71 institutes

PI: Kim, MS
RTOG 1112: Randomized Phase III Study of Sorafenib versus SBRT followed by Sorafenib in HCC

<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular involvement</td>
<td>Arm 1</td>
</tr>
<tr>
<td>(IVC, main portal vein/</td>
<td>Daily sorafenib</td>
</tr>
<tr>
<td>right or left main branch</td>
<td>Arm 2</td>
</tr>
<tr>
<td>portal vein vs. other</td>
<td>SBRT alone</td>
</tr>
<tr>
<td>vascular involvement vs.</td>
<td>(27.5 Gy – 50 Gy in 5 fractions)</td>
</tr>
<tr>
<td>none)</td>
<td>Followed by Sorafenib alone daily</td>
</tr>
<tr>
<td>Hepatitis B vs. C vs.</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td></td>
</tr>
<tr>
<td>North American site vs.</td>
<td></td>
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<tr>
<td>Non-North American site</td>
<td></td>
</tr>
<tr>
<td>HCC volume/liver volume</td>
<td></td>
</tr>
<tr>
<td>(&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td></td>
</tr>
</tbody>
</table>

- Patients
  - Unsuitable for resection or transplant or radiofrequency ablation (RFA)
  - Unsuitable for TACE or refractory to TACE
  - Barcelona Clinic Liver Cancer Stage (BCLC) Intermediate (B) or Advanced (C)
- LINAC-based, Cyberknife, or protons

RTOG Affiliated members in Korea: NCC, Severance hospital
In Evidence Based Medicine.....
Summary and Conclusions

• RT can be a useful therapy for tumors in various stages according to the BCLC system.
• Stage 0 or A → serve as a nonsurgical curative therapy.
• Stage B → combined with other treatments such as TACE
• Stage C → RT in combination treatment can prolong the survival time in selected patients who present locally advanced HCC associated with portal vein invasion but not distant metastasis.
• Stage D → RT can provide effective palliation.

• A variety of new RT machines are currently available. Although 3D-CRT has been the standard mode, it is highly recommended to use a precision RT technology involving intensity modulation as well as image-guided one.

• Further clinical study in the radiation treatment of HCC is necessary to confirm its role in multidisciplinary management of HCC.
내 이름을 경외하는 너희에게는 의로운 해가 떠올라서 치료하는 광선을 발하리니 너희가 나가서 외양간에서 나온 송아지 같이 뛰리라 말라기 4장 2절