SBRT IN LIVER TUMOURS

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MOST COMMON LIVER TUMOURS

• LIVER CANCERS
  – Hepatocellular carcinoma (75-80% of all primary liver cancers)
  – Intrahepatic cholangiocarcinoma
  – Liver metastasis
HEPATOCELLULAR CARCINOMA
HCC INCIDENCE

• The incidence has tripled in USA in last four decades, and 2% increase in incidence is seen every year. [GLOBOCAN 2020]

• Its incidence varies across the globe, and has increased in USA and Europe and stable in Asia.

• HCC is the fifth most common cancer worldwide.

• Third most common cause of cancer death.
2.6% of newly diagnosed cancers in India are HCC – GLOBOCAN 2020

Close to 50000 new HCC are diagnosed every year in India

Incidence - About 0.7-7.5 per lakh in males and 0.2-2.2 per lakh in females

As per ICMR, the HCC cancer in India is increasing

ICMR 2014
Estimated number of new liver cancer cases in 2018 by International Agency for Research on Cancer (http://gco.iarc.fr/).
ETIOLOGY

• Hepatitis B and C
• Heavy alcohol use
• Obesity
• Diabetes
• Haemochromatosis
• Alpha-1 antitrypsin deficiency
• Mycotoxin exposure
• Aflatoxin exposure
Close to 18 staging systems made
Most commonly used is Barcelona Clinic Liver Cancer (BCLC) – most widely used

<table>
<thead>
<tr>
<th>BCLC categories</th>
<th>Parameters for categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Very early</td>
<td>• Tumour size</td>
</tr>
<tr>
<td>• Early</td>
<td>• Tumour burden</td>
</tr>
<tr>
<td>• Intermediate</td>
<td>• Liver function based on Child Pugh score</td>
</tr>
<tr>
<td>• Advanced</td>
<td>• Performance status</td>
</tr>
<tr>
<td>• terminal</td>
<td></td>
</tr>
</tbody>
</table>
BCLC Classification

Stage 0
PST 0, Child-Pugh A

Very early stage (0)
Single < 2 cm

Early stage (A)
Single nodule < 5 cm or 3 nodules < 3 cm

Intermediate stage (B)
Multi-nodular, PST 0

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

Stage A-C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Stage D
Okuda 3, PST>2 Child-Pugh C

Terminal stage (D)

Resection
Liver transplantation (CLT/LDLT)
PEI/RFA
Chemoembolization
Systemic treatment
Symptomatic treatment

Resection
Liver transplantation (CLT/LDLT)
PEI/RFA
Chemoembolization
Systemic treatment
Symptomatic treatment

Curative treatments
60% to 75% at 5 yrs
Randomized controlled trials
10% to 50% at 3 yrs
BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update

RECENT GUIDELIENS AS PER ESMO
NCCN Guidelines Version 1.2022
Hepatocellular Carcinoma

PRINCIPLES OF RADIATION THERAPY

External Beam Radiation Therapy:
• Treatment Modalities:  
  † EBRT is a treatment option for patients with unresectable disease, or for those who are medically inoperable due to comorbidity.
  † All tumors irrespective of the location may be amenable to radiation therapy (RT) (3D conformal RT (3D-CRT), intensity-modulated RT [IMRT], or stereotactic body RT [SBRT]). Image-guided RT (IGRT) is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.
  † Hypofractionation with photons\(^2\) or protons\(^2,3\) is an acceptable option for intrahepatic tumors, although treatment at centers with experience is recommended.
  † SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.
    † There is growing evidence for the usefulness of SBRT in the management of patients with HCC.\(^4,5\) SBRT can be considered as an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated.
    † SBRT (typically 3–5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver function. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.\(^6\) The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for these patients.\(^7,8\)
    † Proton beam therapy (PBT) may be appropriate in specific situations.\(^9,10\)
    † Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain, and extensive liver tumor burden.\(^11\)

• RT dosing\(^1\) depending on the ability to meet normal organ constraints and underlying liver function:
  † EBRT: SBRT or hypofractionation preferred
   ◊ SBRT: 30–50 Gy (typically in 3–5 fractions)\(^12\)
   ◊ Hypofractionation\(^2\)
     † 37.5–72 Gy in 10–15 fractions
     † Conventional fractionation:\(^13,14\)
       † 50–66 Gy in 25–33 fractions
PARAMETERS IN DECIDING TREATMENT

- **Patient Parameters**: age, comorbid conditions, performance status, liver disease etiology
- **Tumor Characteristics**: size, number, AFP, biomarkers
- **Histologic data**: differentiation, vascular invasion
- **Liver Function**: Child/MELD score, bilirubin, albumin
- **Complications**: ascites, encephalopathy
- **Portal hypertension
- **Organ availability for OLT
- **Financial constraints and access to care
BRIDGE TO TRANSPLANT

- Patients fit for transplant often have a long list of waiting for orthotopic liver transplant
- Bridge therapy is recommended
- Bridge therapy prevents disease progression while awaiting turn for orthotopic liver transplant
- Options are TACE, RFA, SBRT
COMPARISON OF MODALITIES

- Criteria for unsuitability for RFA – thrombocytopenia, arterial occlusion, biliary tree necrosis, tumour multifocality
- RFA not possible
  - Near vascular structures
  - Near organs like heart, bowel, stomach, biliary structures
- Ethanol - Not possible in areas with poor vascular access
- LC rate is lower than SBRT
- SBRT does not have these limitation, better LC rates
SBRT AS BRIDGE THERAPY

- SBRT give 70-100% radiographic LC and 5-8 months OS
- **MSKCC based study** – SBRT as bridge therapy –
  - 3 yr OS, DFS – 77%, 74%.
  - Pathological response 68%.
  - 29% showed worsened Child Pugh score before transplant
- As per a study, *(Sandroussi et al, Transpl Int 2010)*
  - Half patients need SBRT after TACE or RFA
  - Remaining half need SBRT due to unsuitability for TACE and RFA
  - With SBRT – significant reduction in AFP and radiologic tumour
  - Transplant average 157 days later
- **University of Indiana study** – 35% grade 3 toxicity (with those with poor baseline liver functions)
- Princess Margaret hospital – similar rates of success transplant, hospital stay, OS. Lower pCR – low dose, slow response to RT, variable time from bridge therapy to transplant
- Higher liver toxicity maybe due to poor liver functional status being posted for SBRT
- Ongoing trial at Lahey Clinic (TACE vs SBRT) (NCT02182687)
Early Stage Inoperable

Criteria for resection
- Size
- Number
- Location
- Normal liver reserve
- Medical fitness
- Limited extrahepatic disease

<5-10% are fit for resection due to disease status or comorbid conditions
Chemotherpay alone has OS of 12-14 months
Published trials establishing similar outcomes with SBRT as compared to other modalities, higher LC for larger tumours, good response even after multiple lines failure

Romero et al
University of Indiana – 82% LC
University of Michigan-2 yr LC -80%. 1 yr LC 97% for SBRT, 83% for RFA
Stereotactic Body Radiation Therapy (SBRT) in Hepatocellular Carcinoma

Horatio R. Thomas¹ · Mary Feng¹

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Abstract

Purpose of Review Hepatocellular carcinoma (HCC) is a rising cause of mortality and morbidity, and although surgical resection is the preferred curative local therapy, < 30% of patients are candidates at diagnosis. This review discusses SBRT as an option in a variety of clinical scenarios.

Recent Findings Multiple retrospective and prospective studies demonstrate that stereotactic body radiation therapy (SBRT) is an effective bridge for transplant candidates and local therapy for patients with inoperable early-, intermediate-, or advanced-stage disease. SBRT is associated with excellent local control, and it is well-tolerated despite study cohorts enriched with patients who failed prior therapies and had poor baseline liver function.

Summary Additional randomized control trials are needed to determine the ideal treatment regimen and patient selection for SBRT.

Table 1: Prospective phase I and II trials of SBRT for HCC with > 20 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>CP score/BCLC Stage</th>
<th>Prior treatment</th>
<th>Tumor size (range)</th>
<th>Number of lesions</th>
<th>Outcomes</th>
<th>Grade ≥ 3 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tse (2008)* [47]</td>
<td>31</td>
<td>CP A</td>
<td>BCLC A-C</td>
<td>TACE 6% RFA 13%</td>
<td>173 cc (9-1913)</td>
<td>≤3</td>
<td>1y-LC 65% 1y-OS 48%</td>
</tr>
<tr>
<td>Kang (2012) [48]</td>
<td>42</td>
<td>CP A-B</td>
<td>BCLC A-C</td>
<td>TACE 100%</td>
<td>2.9 cm (1-8)</td>
<td>NR</td>
<td>2y-LC 95% 2y-PFS 34%</td>
</tr>
<tr>
<td>Bujold (2013) [49]</td>
<td>102</td>
<td>CP A</td>
<td>BCLC A-C</td>
<td>TACE 22% RFA 34%</td>
<td>7.2 cm (1.4-23.1)</td>
<td>NR</td>
<td>1y-LC 97% 1y-medOS 17 mo</td>
</tr>
<tr>
<td>Lasley (2015) [46]</td>
<td>59</td>
<td>CP A-B</td>
<td>BCLC NR</td>
<td>TACE 10% Surgery 8%</td>
<td>33.6 cc (2-107)</td>
<td>NR</td>
<td>CP-A 3-y LC 91% CP-B 3-y PFS 48%</td>
</tr>
<tr>
<td>Takeda (2016) [50]</td>
<td>90</td>
<td>CP A-B</td>
<td>BCLC 0-C</td>
<td>TACE 28% RFA 3%</td>
<td>2.3 cm (1.0-4)</td>
<td>NR</td>
<td>3-y LC 96.3% 3-y OS 66.7%</td>
</tr>
<tr>
<td>Feng (2018)* [51]</td>
<td>69</td>
<td>CP A-B</td>
<td>BCLC NR</td>
<td>TACE 57%</td>
<td>2.4 cm (1.0-9.9)</td>
<td>≤2</td>
<td>2y-LC 95% 2y-OS 28%</td>
</tr>
<tr>
<td>Jang (2019) [52]</td>
<td>74</td>
<td>CP A-B</td>
<td>BCLC 0-C</td>
<td>None</td>
<td>2.8 cm (1.0-6.0)</td>
<td>1</td>
<td>1.5-y-LC 98%</td>
</tr>
</tbody>
</table>
INTERMEDIATE STAGE

- > 3 cm tumours OR multinodular (>3). Child Pugh A or B
- STAGE B not suitable for surgery
- **Newer 2022 update suggests assessment for transplant**
- Options are – RFA, TACE, SBRT, combination of both
- Grade 3 toxicity (MC – fatigue, loss of appetite, nausea)
  - TACE/TARE – 10-80%
  - SBRT – 5-30%
  - SBRT after 5 times TACE
  - 2 yr LC 94%, PFS 33.8%
- Need more data for combination therapy
ADVANCED STAGE AND VASCULAR INVASION (STAGE C)

- Stage C is defined by
  - Macroscopic vascular extension
  - Mild to moderate impairment of liver function or performance status
  - Extrahepatic extension

- Worse prognosis for
  - Decompensated liver cirrhosis
  - Portal hypertension due to portal vein thrombus

- Preferably treated with systemic therapy – sorafenib

- 1 yr OS 30-45%

- Hypofractionated EBRT permits recanalization of vessel in 15-33% and LC at 1 yr > 90%

- Phase III trial shows superiority of Atezolizumab with Bevacizumab in unresectable HCC.

Finn RS, NEJM 2020
• SBRT is good option for poor functional reserve or for vascular invasion

• Princess Margaret in 2008 treated 41 patients with a dose of 36Gy/6#. Median OS 11.7 months with PVT and 17.4 months without PVT

• Rusthoven 2009 — definitive RT for limited disease (1-3 hepatic lesions, <=6 cm). Dose escalation to 60Gy/3#
  – 1 year LC 95%
  – 2 yr LC 92%
  – 2 yr LC for < 3 cm - 100%
  – Median survival 20.5Gy
  – OS 30%
• MSKCC/Stanford treated primary liver tumours and metastasis
  – Dose escalation to 25Gy
  – Upto 5 cm
  – Single fraction SBRT
  – LF at 12 months – 23%
  – Median survival 28.6 months
  – 2 year OS 50.4%
  – Goodman K et al, IJROBP 2010
• *Dawson 2012* — Phase I study suggests sorafenib increases RT toxicity

• *Bujold 2014* — definitive for locally advanced disease, multiple lesions, largest upto 7.7 cm. 102 patients, 36Gy/6#. OS 17 months, LC 87%, grade 3+ toxicity 30%

• *Yamashita et al* evaluated 79 studies and concluded two important parameters affecting outcome of SBRT
  – BED more than or less than 100Gy
  – size more than or less than 3 cm (64% vs 85%)
# INCLUSION AND EXCLUSION CRITERIA FOR SBRT

<table>
<thead>
<tr>
<th>Selection Factor</th>
<th>Ideal Parameters for Liver SBRT</th>
<th>Exclusion Criteria Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient immobilization</td>
<td>Able to tolerate immobilization</td>
<td>Unable to tolerate immobilization</td>
</tr>
<tr>
<td>Imaging</td>
<td>Tumor clearly defined on triphasic enhanced CT or MRI (HCC) or contrast-enhanced CT or MRI or PET (metastases or CC)</td>
<td></td>
</tr>
<tr>
<td>Eligibility for other therapies</td>
<td>Ineligible for resection or other local therapies because of technical considerations or concerns of efficacy and/or toxicity</td>
<td></td>
</tr>
<tr>
<td>Liver function</td>
<td>Child–Pugh class A</td>
<td>Child–Pugh class C</td>
</tr>
<tr>
<td>Healthy liver volume</td>
<td>Ability to meet dose constraints</td>
<td>&lt;700 cm$^3$ remaining healthy liver volume</td>
</tr>
<tr>
<td>Tumor location</td>
<td>&gt;1 cm from critical OARs, such as bowel, diaphragm, chest wall, or central liver</td>
<td>&lt;5 mm from critical OARs</td>
</tr>
<tr>
<td>Great vessel involvement</td>
<td>May be involved</td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>1–3 lesions</td>
<td>Five or more intrahepatic lesions</td>
</tr>
<tr>
<td>Burden of extrahepatic disease</td>
<td>None</td>
<td>Uncontrolled or significant extrahepatic burden</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td>Very large tumours</td>
</tr>
</tbody>
</table>

Age and histology are not criteria for exclusion
POST TACE SBRT

- Retrospective study at University of AL (*Jocob et al 2015*)
- 161 patients, \(\geq 3\) cm HCC
- 124 patients TACE

<table>
<thead>
<tr>
<th></th>
<th>TACE</th>
<th>TACE+SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>124</td>
<td>37</td>
</tr>
<tr>
<td>LR ((P=0.04))</td>
<td>25.8%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Median OS ((P=0.02))</td>
<td>20 months</td>
<td>33 months</td>
</tr>
</tbody>
</table>

- *Su et al*, superior OS in TACE+SBRT versus SBRT alone
- TACE-SBRT combination had higher , START trial— *Yoon et al*
  - Radiologic response \((15\% \text{ vs } 1\% \text{ at } 24\, \text{weeks})\)
  - PFS\((84.7\% \text{ vs } 34.3\% \text{ at } 12\, \text{weeks})\)
  - Median OS\((55 \text{ vs } 43\, \text{weeks})\)
  - Time to progression \((31 \text{ vs } 11.7\, \text{weeks})\)
CURRENT PROTOCOL (RTOG1112)

- Randomized phase III study of sorafenib vs SBRT+sorafenib in HCC to assess effect on OS
- Patient population
  - Unsuitable for resection/transplant/RFA
  - Unsuitable or refractory to TACE
  - BCLC intermediat (B) or advanced (C)
PROTON BEAM THERAPY FOR LIVER SBRT

• Will help escalate dose
• Needs strict immobilisation and breath control
• Most proton centres do not have motion management
• Very few proton centres do liver SBRT due to it
• In a Danish study, protons halved the mean liver dose and spared 50% more normal liver volume at dose levels <15 Gy.

• Kim et al showed similar dose reduction to the liver with a considerable reduction in liver volume receiving 5 to 45 Gy.

• A University of Pennsylvania study by Gandhi et al showed that both tumor location and size were correlated with the dosimetric superiority of PBT-SBRT over photon-based SBRT.

• An interim analysis of a randomized trial testing PBT versus TACE in
  – 69 patients with inoperable HCC from Loma Linda
  – excellent control rates of 88
  – 2 yr PFS and OS of 48 and 58
  – Nonsignificant trend for improved LC and PFS in patients treated with PBT
Clinical Practice Guideline

External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline

Smith Apisarnthanarax, MD,*, Aisling Barry, MD, Minsong Cao, PhD, Brian Czito, MD, Ronald DeMatteo, MD, Mary Drinane, MD, Christopher L. Hallemeier, MD, Eugene J. Koay, MD, Jennifer Pursley, PhD, Jeffrey Meyer, MD, MS, Dawn Owen, MD, PhD, Jennifer Pursley, PhD

Abstract

Purpose: This guideline provides evidence-based recommendations for the indications and technique-dose of external beam radiation therapy (EBRT) in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC).

Methods: The American Society for Radiation Oncology convened a task force to address 5 key questions focused on the indications, techniques, and outcomes of EBRT in HCC and IHC. This guideline is intended to cover the definitive, consolidative, salvage, preoperative (including bridge to transplant), and adjuvant settings as well as palliative EBRT for symptomatic primary lesions. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: Strong recommendations are made for using EBRT as a potential first-line treatment in patients with liver-confined HCC who are not candidates for curative therapy, as consolidative therapy after incomplete response to liver-directed therapies, and as a salvage option for local recurrences. The guideline conditionally recommends EBRT for patients with liver-confined multifocal or unresectable HCC or those with macrovascular invasion, sequenced with systemic or catheter-based therapies. Palliative EBRT is conditionally recommended for symptomatic primary HCC and/or macrovascular tumor thrombi. EBRT is conditionally recommended as a bridge to transplant or before surgery in carefully selected patients.

For patients with unresectable IHC, consolidative EBRT with or without chemotherapy should be considered, typically after systemic therapy. Adjuvant EBRT is conditionally recommended for resected IHC with high-risk features. Selection of dose-fractionation regimen and technique should be based on disease extent, disease location, underlying liver function, and available technologies.

Conclusions: The task force has proposed recommendations to inform best clinical practices on the use of EBRT for HCC and IHC with strong emphasis on multidisciplinary care. Future studies should focus on further defining the role of EBRT in the context of liver-directed and systemic therapies and refining optimal regimens and techniques.

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**Table 3** EBRT in the definitive/nontransplant and palliative settings in HCC

<table>
<thead>
<tr>
<th>KQ1 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with liver-confined HCC who are <strong>not</strong> candidates for curative options (surgery or thermal ablation) and for whom catheter-based therapies are being considered, EBRT is recommended as a <strong>potential</strong> first-line single therapy option.</td>
<td>Strong</td>
<td>Moderate (25-36)</td>
</tr>
<tr>
<td>2. For patients with liver-confined multifocal and/or unresectable HCC, EBRT alone or sequenced with other catheter-based therapies* is <strong>conditionally</strong> recommended.</td>
<td>Conditional</td>
<td>Moderate (37-42)</td>
</tr>
<tr>
<td>3. For patients with liver-confined HCC who had an <strong>incomplete response</strong> to thermal ablation or catheter-based therapies, EBRT is recommended as a consolidative treatment option.</td>
<td>Strong</td>
<td>Moderate (38,40,43)</td>
</tr>
<tr>
<td>4. For patients with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies,** EBRT is recommended as a salvage treatment option.**</td>
<td>Strong</td>
<td>Low (25,35,44-46)</td>
</tr>
<tr>
<td>5. For patients with liver-confined HCC with <strong>macrovascular invasion,</strong> EBRT is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies.*</td>
<td>Conditional</td>
<td>Moderate (47-58)</td>
</tr>
<tr>
<td>6. For patients with symptomatic locally advanced and/or metastatic HCC, palliative hypofractionated EBRT directed to the liver and/or macrovascular tumor thrombus is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies.*</td>
<td>Conditional</td>
<td>Low (locally advanced HCC)</td>
</tr>
</tbody>
</table>

*Caution should be used when recommending EBRT after TARE until more data are available.

**Abbreviations:** EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; KQ = key question; TARE = transarterial radioembolization.

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**Figure 1** Algorithm for HCC: Liver confined, without macrovascular invasion.

**Figure 2** Algorithm for HCC: With macrovascular invasion.
Table 4  Neoadjuvant EBRT before surgery or OLT for HCC

<table>
<thead>
<tr>
<th>KQ2 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with HCC who are potential candidates for OLT, ultra- or moderately hypofractionated EBRT is conditionally recommended as a bridge to transplant or as a downstaging intervention.</td>
<td>Conditional</td>
<td>Low 38,42,72,77</td>
</tr>
<tr>
<td>2. For patients with HCC with portal vein tumor thrombus that are potentially resectable, neoadjuvant EBRT is conditionally recommended.</td>
<td>Conditional</td>
<td>Low 51,76,80</td>
</tr>
</tbody>
</table>

*Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinomas; KQ = key question; OLT = orthotopic liver transplantation.*

Table 5  EBRT technique and fractionation for HCC

<table>
<thead>
<tr>
<th>KQ3 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with liver-confined HCC, for whom EBRT is recommended, dose-escalated ultra- or moderately hypofractionated EBRT is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology (Table 6).</td>
<td>Strong</td>
<td>Moderate 24,30,31,32,34,36,40,43,77,88,90</td>
</tr>
<tr>
<td>2. For patients with HCC with macrovascular invasion for whom EBRT is delivered in combination with other catheter-based therapies, moderately hypofractionated EBRT is conditionally recommended (Table 6).</td>
<td>Conditional</td>
<td>Moderate 39,40,52,53,54,57,59,60,61,63,64,66,69</td>
</tr>
<tr>
<td>3. For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology.</td>
<td>Strong</td>
<td>Moderate 24,30,31,36,46,57,59,63,64,65,69</td>
</tr>
<tr>
<td>4. For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, respiratory motion management and daily image guidance are recommended.</td>
<td>Strong</td>
<td>Low 36,43,44,90,91</td>
</tr>
<tr>
<td>5. For patients with HCC, radiation dose to the liver minus the gross tumor volume should be evaluated and minimized to reduce the risk of radiation-induced liver disease (Table 7).</td>
<td>Strong</td>
<td>Moderate 41,65,85,95</td>
</tr>
</tbody>
</table>

*Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinomas; IMRT = intensity modulated radiation therapy; KQ = key question.*
Table 6  Recommended EBRT doses and fractionation for MCC and IHC*

<table>
<thead>
<tr>
<th>Fractionation Regimen</th>
<th>Total dose/fractionation</th>
<th>BED(_{10})</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncirrhotic (primarily IHC):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000-6000 cGy/3-5 fx</td>
<td>7200-18000 cGy</td>
<td></td>
<td>130</td>
</tr>
<tr>
<td>CP class A:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000-5000 cGy/3-5 fx</td>
<td>7200-12500 cGy</td>
<td>71.7,77,90,94,101</td>
<td></td>
</tr>
<tr>
<td>CP class B7:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000-4000 cGy/5 fx</td>
<td>4800-7200 cGy</td>
<td>16,30,68,94,101</td>
<td></td>
</tr>
<tr>
<td>4000-5400 cGy/6 fx</td>
<td>6700-10300 cGy</td>
<td>60,10</td>
<td></td>
</tr>
<tr>
<td>5000-6600 cGy/10 fx</td>
<td>7500-11100 cGy</td>
<td>57,92,95,93,103,112</td>
<td></td>
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<tr>
<td>Ultrahypofractionation</td>
<td></td>
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<tr>
<td>Moderate hypofractionation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4800 cGy/12 fx</td>
<td>6720 cGy</td>
<td></td>
<td>130</td>
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<tr>
<td>4500-6750 cGy/15 fx</td>
<td>5900-9800 cGy</td>
<td>43,96,101,102,112</td>
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<tr>
<td>6000 cGy/20 fx</td>
<td>7800 cGy</td>
<td>57</td>
<td></td>
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<tr>
<td>6600-7200 cGy/22 fx</td>
<td>8600-9600 cGy</td>
<td>57,95,112</td>
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<td>Standard fractionation</td>
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<tr>
<td>5940 cGy/28 fx</td>
<td>5947 cGy</td>
<td>13,4,13,9</td>
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<tr>
<td>6000 cGy/30 fx</td>
<td>7200 cGy</td>
<td>13,4,13,9</td>
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<tr>
<td>7700 cGy/35 fx</td>
<td>9400 cGy</td>
<td>13,4,13,9</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BED\(_{10}\) = biologically effective dose assuming an \(\alpha/\beta = 10\); CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

1. Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.
2. Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.
3. For IHC when combined with concurrent systemic therapy.
SBRT is the delivery of a radiation to an extracranial target

- high dose per fraction
- 1-5 fractions
- Multiple beams
- highly conformal dose distribution
- relative sparing of normal organs

For SBRT

- Strict immobilisation is of paramount importance
- Motion management helps reduce target volumes and sparing of OARs
BIOLOGIC RATIONALE FOR SBRT/HYPOFRACTIONATION

• High dose/fraction specific effects
  • Preclinical data
  • Threshold ~ 5-10 Gy/ fraction
• Postulated mechanisms of RT injury
  – Ablative direct cell kill
  – Endothelial target (Fuks)
    • Immune -RT increases tumor Ag-specific immune response ^*
    • Abscopal effect - Local therapy causes systemic response, Elusive in practice

• ^^ Park Rad Research 2012 ^ Lugade et al, J Immunology 2005;174:7516-7523
SCHEMATIC WORKFLOW FOR SBRT

Patient Evaluation
- History & Physical Exam
- Diagnostic Imaging
- Pathology & Laboratory Results
- Multidisciplinary Assessment

Simulation
- Fabrication of Immobilization Device
- Imaging in Treatment Position

Treatment Planning
- Contour Target & Normal Structures
- Selection of Treatment Technique
- Field Design
- Radiation Dose Calculation
- Critical Review of Dose Distribution

Treatment Delivery
- Position Patient in Immobilization Device
- Image Patient on Treatment Machine
- Adjust Patient Position or Beam Isocenter, as necessary
- Manage Intrafraction Motion
- Deliver Radiation

Quality Assurance

Optimization
IMAGING

• Triphasic CT scan (hepatic arterial, portal venous and delayed phase)
  – Preferable 1-1.35 mm slices
  – HCC appears hyperintense in arterial, hypodense in venous and delayed phase due to contrast washout.
  – Diagnostic scan should also include unenhanced phase

• Multiphase dynamic MRI
  – Better resolution of tumour than CT scan

• FED PET-CT —
  – Not adequate
  – Helps see change since diagnostic scan
  – Helps detect any small newer tumours

• Radiologist input needed to differentiate bland and tumour thrombus
MOTION MANAGEMENT

- Expected movements
  - Respiration – liver moves craniocaudal and axial
  - Heart beat
  - Organ filling and emptying
Respiratory Motion can be managed by

1) Free breathing with large margins to account for motion

2) ITV based to account for motion during respiration + setup - Encompassing motion – 4DCT, slow CT, multiple breathhold CT

3) ITV reduction **Motion restriction** –
   - deep inspiratory breath hold (active breath coordinator), abdominal compression (compression plate or belt-reduces motion by 12-13 mm- Berbecco et al 2007)

4) Selecting a section of ITV
   - real time position management (RPM)- selecting phases of respiration

5) **Treat time weighted average position with margin** (risky with chances of miss)

6) **Tumour tracking** – internal fiducials, cyberknife

Deep inspiration can overestimate the motion
MOTION MANAGEMENT

Can be categorised as

- **GANTRY-BASED SYSTEMS** use phase or amplitude gating via commercially available motion monitoring devices such as
  - DIBH
  - RPM
  - ANZAI
  - ABDOMINAL COMPRESSION
  - RESPONSE GATING™ ELEKTA

- **THE ROBOTIC ARM–BASED PLATFORM** such as CyberKnife (Accuray, Inc.) is the only system capable of respiratory tracking (Synchrony™)
  - Takes images every 10-30 sec to track fiducials
  - OR every 90 sec images track the synchrony vest
  - Patient breathes normally and images follow tumour motion in beam’s view
  - Multiple non coplanar beams (nodes)
Tumor Trailing for Liver SBRT on the MR-Linac

Martin Fast, PhD, Agustinus van de Schoot, PhD, Tessa van de Lindt, MSc, Casper Carbaat, Uulke van der Heide, PhD, and Jan-Jakob Sonke, PhD

Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

Received Feb 6, 2018. Accepted for publication Sep 10, 2018.

Summary
This study investigates tumor trailing for liver stereotactic body radiation therapy on the magnetic resonance linear accelerator platform. During tumor trailing, the beam aperture is continuously adjusted according to the most recent time-averaged tumor position. For a range of artificial and realistic liver baseline motions, simulated trailing restored the intended target dose while delivering up to 2 Gy/fraction more dose to the target than a conventional delivery. The dosimetric advantage of trailing was confirmed in a first proof-of-principle phantom experiment.

Purpose: Tumor trailing is a treatment delivery technique that continuously adjusts the beam aperture according to the last available time-averaged position of the target. This study investigates whether tumor trailing on a magnetic resonance (MR) linear accelerator (linac) can improve target coverage in liver stereotactic body radiation therapy (SBRT) in the case of baseline motion.

Methods and Materials: For 17 patients with oligometastatic liver disease, all-position SBRT treatment plans (3 × 20 Gy, 11-beam intensity modulated radiotherapy) were created using the Elekta Unity MR-Linac. Treatment was simulated using an in-house-developed delivery emulator. Respiratory motion was modulated as the superposition of periodic motion (patient-specific amplitude; 4-second period) and the following baseline motion scenarios: a continuous linear drift (0.5 mm/min). (2) a single shift halfway through treatment (10 mm), (3) a periodic drift (amplitude: 5 mm, period: 5 minutes), or (4) MR imaging—measured baseline drifts. Delivered dose was calculated under full consideration of the patient and machine motion interplay. In addition, trailing was experimentally validated on the MR-Linac using a programmable motion phantom.

Results: The average simulated delivery and beam-on times were 15.9 and 8.7 minutes, respectively. An imaging frequency of ≥1 Hz was deemed necessary for trailing. Trailing increased the median gross tumor volume D95% dose by 1.9 Gy (linear drift), 1.2 Gy (single shift), 0.7 Gy (periodic drift), and 0.5 to 1.5 Gy (measured drifts) per fraction, compared with a conventional delivery. In the phantom experiments, the 3%/2 mm local gamma pass rate nearly doubled to 98% when using trailing.

Conclusion: Tumor trailing on the MR-Linac restores target dose in liver SBRT in the case of baseline motion for the presented patient cohort. © 2018 Elsevier Inc. All rights reserved.

Original Article

Technical feasibility and clinical evaluation of 4D-MRI guided liver SBRT on the MR-linac

Author links open overlay panel T. N. van de Lindt, M. E. Nowee, T. Janssen, C. Schneider, P. Remeijer, V. W. J. van Pelt, A. Bagen, E. P. M. Jansen, J. J. Sonke

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Highlights
### Table 1 - Overview of the main published studies of SBRT for liver mets and the corresponding techniques used for immobilization, motion management and planning Imaging.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients number</th>
<th>Lesional patient</th>
<th>RT technique</th>
<th>Dose</th>
<th>Fractions</th>
<th>PTV definition</th>
<th>RT planning technique</th>
<th>PET/CT fusion</th>
<th>MRI fusion</th>
<th>Contention</th>
<th>Other immobilization technique</th>
<th>Motion management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosio</td>
<td>2009</td>
<td>27</td>
<td>N/A</td>
<td>Cyberknife</td>
<td>25–60</td>
<td>3</td>
<td>CT scan with contrast</td>
<td>No</td>
<td>N/A</td>
<td>Yes</td>
<td>IOMI 2</td>
<td>Synchrotron® system</td>
<td></td>
</tr>
<tr>
<td>Andrade@2</td>
<td>2015</td>
<td>74</td>
<td>1-4</td>
<td>30-35</td>
<td>3-5</td>
<td>3</td>
<td>CT scan with contrast</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Vacuoro drug</td>
<td>Free breathing</td>
<td></td>
</tr>
<tr>
<td>Dawson</td>
<td>2006</td>
<td>54</td>
<td>N/A</td>
<td>3D-CRT</td>
<td>24–53</td>
<td>6</td>
<td>CT scan with continual</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Breath-hold</td>
<td>Customized immobilization</td>
<td></td>
</tr>
<tr>
<td>Goodman</td>
<td>2010</td>
<td>19</td>
<td>N/A</td>
<td>Cyberknife</td>
<td>18–30</td>
<td>1</td>
<td>CT scan with contrast</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Alpha Cradle</td>
<td>Synchrotron® system</td>
<td></td>
</tr>
<tr>
<td>Kirsner</td>
<td>2001</td>
<td>37</td>
<td>1-4</td>
<td>14-26</td>
<td>1</td>
<td>3</td>
<td>CT scan with continual</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Free breathing</td>
<td>Abdominal compression</td>
<td></td>
</tr>
<tr>
<td>Hope</td>
<td>2006</td>
<td>44</td>
<td>1-5</td>
<td>3D-CRT</td>
<td>45</td>
<td>3</td>
<td>CT scan with contrast</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Vacuum couch</td>
<td>Free breathing</td>
<td></td>
</tr>
</tbody>
</table>

#### DIFFERENT SETUPS IN VARIOUS MACHINES

- Cyberknife
- 3D-CRT
- CT scan with contrast
- IOMI 2
- Vacuoro drug
- Breath-hold
- Alpha Cradle
- Customized immobilization
- Synchrotron® system
- Abdominal compression
- Free breathing
• 3-5 fiducials are needed
• Invasive procedure
• To be done 4-5 days prior to planning scan
• Most reliable for localisation
• Difficult in frail patients
• Mandatory for cyberknife
SIMULATION, MOTION MANAGEMENT

- POSITION – supine, hands above head
- LOCALISATION – fiducial/lipiodol from TACE/stent/indwelling catheters/ diaphragm
  Gold seed/grain fiducial is preferable to anchor/long fiducials – better target localisation, lesser artefacts
- Immobilisation using vacloc +/- body fix
- Using selected motion management technique – DIBH/RPM/compression plate etc
- Motion management –
  Deep inspiration breath hold scans are acquired for –
  1) arterial phase
  2) venous phase
  free breathing scans are acquired for –
  1) arterial phase end expiration
  2) venous phase end expiration
  3) 4D scan to account for all range of motion
- Slice thickness 1.25 mm
- At the time of treatment delivery - Image guidance for position verification is by cine imaging, 4 DCT, kV and MV imaging
TARGET DELINEATION

- Use all modalities – CT scan (arterial and venous phase), MRI, PET-CT
  - Mark the tumour (in both phases – arterial and venous)
  - Mark the enhancing tumour thrombus
  - Do not include bland thrombus
- CTV is not routinely made
- ITV is made depending on type of immobilisation
- PTV
  - 3 mm for DIBH with fiducials
  - 5-10 mm for free breathing
Fig. 1 – Coronal view of 4D CT (right side) and 4D PET CT (left side) in end expiratory (upper part) and end inspiratory (lower part) phases in a patient with liver met referred for SBRT. The respiratory cycle of the patient is divided in ten phases acquired for 4D CT and 4D PET CT. The volume is set by contouring each one of the ten phases and overlaps the contours to create an internal target volume. Only the end expiratory and end inspiratory phases of these ten phases are shown.
• **Inclue**
  – Bowel & duodenum
  – Esophagus
  – Stomach
  – Liver
  – Central hepatobiliary tract [cHBT]
  – Chest wall & ribs
  – Heart
  – Lungs
  – Kidneys
  – Spinal cord

• **PRV of the critical OARs is important**
SUBVOLUME FOR ADJACENT OAR

- SUBVOLUMES – for areas of overlap between PTV and PRV
DOSE PRESCRIPTION

- A threshold of 30 Gy EQD2 below which the impact of radiation is muted.
- Between approximately 53 and 84 Gy EQD2, the LC rates increase from 50% to 90%.
- Beyond 84 Gy, the degree of incremental LC improvement decreases while, depending on the anatomy, there is a continued incremental risk of toxicity.
DOSE PRESCRIPTION

• Ranges from 30-50Gy in 3-5 fractions
  – Depends on
  – number of lesions
  – size of lesions
  – location of lesions
  – OARs
  – residual liver
  – histology

• Resistant histologies need higher dose – melanoma, sarcoma, RCC, Kras mutant CRC – 48-49Gy/3#
### Table 6  Recommended EBRT doses and fractionation for HCC and IHC

<table>
<thead>
<tr>
<th>Fractionation Regimen</th>
<th>Total dose/fractionation</th>
<th>(\text{BED}_{10})</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noncirrhotic (primarily IHC):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4000-6000) cGy/3-5 fx</td>
<td></td>
<td>7200-18,000 cGy</td>
<td>110, 111</td>
</tr>
<tr>
<td><strong>CP class A:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4000-5000) cGy/3-5 fx</td>
<td></td>
<td>7200-12,500 cGy</td>
<td>24, 27, 28, 30, 34, 43, 44, 46, 86, 101, 111</td>
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<tr>
<td><strong>CP class B7:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3000-4000) cGy/5 fx</td>
<td></td>
<td>4800-7200 cGy</td>
<td>38, 39, 60, 94, 101</td>
</tr>
<tr>
<td>(4000-5400) cGy/6 fx</td>
<td></td>
<td>6700-10,500 cGy</td>
<td>65, 93</td>
</tr>
<tr>
<td>(5000-6600) cGy/10 fx</td>
<td></td>
<td>7500-11,000 cGy</td>
<td>57, 59, 83, 90, 100, 112</td>
</tr>
<tr>
<td><strong>Moderate hypofractionation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4800) cGy/12 fx</td>
<td></td>
<td>6720 cGy</td>
<td>110</td>
</tr>
<tr>
<td>(4500-6750) cGy/15 fx</td>
<td></td>
<td>5900-9800 cGy</td>
<td>42, 46, 50, 62, 80, 113, 114</td>
</tr>
<tr>
<td>(6000) cGy/20 fx</td>
<td></td>
<td>7800 cGy</td>
<td>57</td>
</tr>
<tr>
<td>(6600-7200) cGy/22 fx</td>
<td></td>
<td>8600-9600 cGy</td>
<td>57, 59, 112</td>
</tr>
<tr>
<td><strong>Standard fractionation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5040) cGy/28 fx</td>
<td></td>
<td>5947 cGy</td>
<td>114, 115</td>
</tr>
<tr>
<td>(6000) cGy/30 fx</td>
<td></td>
<td>7200 cGy</td>
<td>114, 115</td>
</tr>
<tr>
<td>(7700) cGy/35 fx</td>
<td></td>
<td>9400 cGy</td>
<td>58, 59</td>
</tr>
</tbody>
</table>

**Abbreviations:** \(\text{BED}_{10}\) = biologically effective dose assuming an \(\alpha/\beta = 10\); CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

\* Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.

\*\* Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.

\*\* For IHC when combined with concurrent systemic therapy.
• Dose selection as per Child Pugh score \([\text{phase I trial of university of Indiana and Colorado}]\)
  
  – Child Pugh A - 48Gy/3#
  
  – Child Pugh B max dose escalation 40Gy/5#
  
  – 1112 trail [NSABP, GOG & RTOG] adapts dose of 27.5Gy-50Gy in five fractions

Rational approach –

  – Child Pugh A –Peripheral - 45-48Gy/3#. Central [near OARs] – 30-50Gy/5#.
  
  – Child Pugh B – 25-40Gy/5#

• Ongoing trial by MGH & MF Anderson – hypofractionated 15 fractions upto 67.5Gy for peripheral tumours and 58.05Gy for central tumours
## OAR Tolerances

<table>
<thead>
<tr>
<th>Description</th>
<th>Constraint</th>
<th>3 fractions</th>
<th>5 fractions</th>
<th>Source</th>
<th>End point</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Optimal</td>
<td>Mandatory</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;22.2 Gy</td>
<td>–</td>
<td>&lt;35 Gy</td>
</tr>
<tr>
<td></td>
<td>D\text{1 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;33 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>D\text{5 cm}\textsuperscript{3}</td>
<td>–</td>
<td>&lt;16.5 Gy</td>
<td>–</td>
<td>&lt;25 Gy</td>
</tr>
<tr>
<td></td>
<td>D\text{9 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;15 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>D\text{10 cm}\textsuperscript{3}</td>
<td>–</td>
<td>&lt;11.4 Gy</td>
<td>–</td>
<td>&lt;25 Gy</td>
</tr>
<tr>
<td></td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;22.2 Gy</td>
<td>–</td>
<td>&lt;35 Gy</td>
</tr>
<tr>
<td>Stomach</td>
<td>D\text{5 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;25 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>D\text{10 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;12 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;25.2 Gy</td>
<td>–</td>
<td>&lt;35 Gy</td>
</tr>
<tr>
<td>Small bowel</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;25.2 Gy</td>
<td>–</td>
<td>&lt;35 Gy</td>
</tr>
<tr>
<td></td>
<td>D\text{5 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;30 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>D\text{10 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;17.7 Gy</td>
<td>–</td>
</tr>
<tr>
<td>Common bile duct</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;50 Gy</td>
<td>–</td>
<td>&lt;50 Gy</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;25.2 Gy</td>
<td>–</td>
<td>&lt;34 Gy (&lt;40 Gy for 8 fractions)</td>
</tr>
<tr>
<td></td>
<td>D\text{5 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;32 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>D\text{10 cm}\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;25 Gy</td>
<td>–</td>
</tr>
<tr>
<td>Large bowel</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;28.2 Gy</td>
<td>–</td>
<td>&lt;32 Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>&lt;28.2 Gy</td>
<td>–</td>
<td>&lt;32 Gy</td>
</tr>
<tr>
<td>Parallel gastrointestinal organs</td>
<td>D\text{Max} (0.5 cm\textsuperscript{3})</td>
<td>–</td>
<td>–</td>
<td>&lt;28.2 Gy</td>
<td>–</td>
</tr>
<tr>
<td>Normal liver (liver – gross tumour volume)</td>
<td>V\text{10 Gy}</td>
<td>–</td>
<td>–</td>
<td>&lt;70%</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Mean dose</td>
<td>–</td>
<td>–</td>
<td>&lt;13 Gy</td>
<td>–</td>
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<tr>
<td></td>
<td>D\text{50 Gy}</td>
<td>–</td>
<td>–</td>
<td>&lt;15 Gy</td>
<td>–</td>
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<tr>
<td></td>
<td>Dose to (\geq) 700 cm\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;19.2 Gy</td>
<td>–</td>
</tr>
<tr>
<td>Kidneys (individual and combined)</td>
<td>Mean dose</td>
<td>–</td>
<td>–</td>
<td>&lt;10 Gy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Dose to (\geq) 200 cm\textsuperscript{3}</td>
<td>–</td>
<td>–</td>
<td>&lt;16 Gy</td>
<td>–</td>
</tr>
<tr>
<td>If solitary kidney or if one kidney mean dose &gt;10 Gy</td>
<td>V\text{10 Gy}</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

D\text{Max} is the near-point maximum dose, defined in this case as D0.5 cm\textsuperscript{3}, which is the minimum dose to the 0.5 cm\textsuperscript{3} volume of the organ receiving the highest doses. D\text{1 cm}\textsuperscript{3}, D\text{5 cm}\textsuperscript{3}, D\text{9 cm}\textsuperscript{3}, D\text{10 cm}\textsuperscript{3} and D\text{50 cm}\textsuperscript{3} are the minimum doses to the specified volume of the organ (1 cm\textsuperscript{3}, 5 cm\textsuperscript{3}, etc.) that receive the highest doses. V\text{10 Gy} is the percentage volume of the organ receiving a dose of 10 Gy or higher.

Dose to \(\geq\) 700 cm\textsuperscript{3} and \(\geq\) 200 cm\textsuperscript{3} is the maximum dose to the specified volume of the organ (700 cm\textsuperscript{3}, 200 cm\textsuperscript{3}) that receives the lowest doses.

* If total kidney volume <200 cm\textsuperscript{3}, or treating renal or adrenal lesions, then total dose to contralateral kidney should be <16 Gy and aim to minimise spillage into ipsilateral kidney if possible.
<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Dose Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver—noncirrhotic</td>
<td>≥700 cm³ of uninvolved liver &lt;15 Gy (three fractions)</td>
</tr>
<tr>
<td></td>
<td>≥700 cm³ of uninvolved liver &lt;21 Gy (five fractions)</td>
</tr>
<tr>
<td>Liver—cirrhotic</td>
<td>Child–Pugh class A</td>
</tr>
<tr>
<td></td>
<td>≥700 cm³ of uninvolved liver &lt;15 Gy (in three or five fractions)</td>
</tr>
<tr>
<td></td>
<td>Mean liver dose &lt;15 Gy (in three or five fractions)</td>
</tr>
<tr>
<td></td>
<td>Child–Pugh class B</td>
</tr>
<tr>
<td></td>
<td>≥700 cm³ of uninvolved liver &lt;15 Gy (five fractions)</td>
</tr>
<tr>
<td></td>
<td>≥500 cm³ of uninvolved liver &lt;7 Gy (five fractions)</td>
</tr>
<tr>
<td></td>
<td>Mean liver dose &lt;10 Gy (in five fractions)</td>
</tr>
<tr>
<td>Central hepatobiliary tree</td>
<td>$V_{40} &lt; 37 \text{ cm}^3$ and $V_{30} &lt; 45 \text{ cm}^3$ (five fractions)</td>
</tr>
<tr>
<td>Heart</td>
<td>$D_{\text{mean}} &lt; 12 \text{ Gy}$, $V_{15} &lt; 10%$</td>
</tr>
<tr>
<td>Kidney</td>
<td>$V_5 &lt; 50%$, ipsilateral $V_{12.3\text{ Gy}} &lt; 130 \text{ cc}$</td>
</tr>
<tr>
<td>Chest wall</td>
<td>$V_{30} &lt; 30 \text{ cm}^3$ (recommended)</td>
</tr>
<tr>
<td>Ribs</td>
<td>$D_{2\text{mL}} &lt; 27 \text{ Gy}$ (recommended)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>$D_{\text{max}} &lt; 20 \text{ Gy}$ (three fractions)</td>
</tr>
<tr>
<td></td>
<td>$D_{\text{max}} &lt; 15 \text{ Gy}$ (three fractions)</td>
</tr>
</tbody>
</table>

- Diaphragm necrosis and pain is reported in liver SBRT, however no constraints or guidelines available for the same
- They present with scapular or abdominal pain, Most patients had a 3 fractions treatment
PLANNING

• Goal
  – D95- 100%
  – Global max 110-130-% but with in GTV
  – For critical OARs, dose coverage compromise is acceptable
• Push IDL as close to 95-100% as possible
• Dmax permissible -
• Avoid max dose outside PTV
• Linear accelerators use flattening filter free beams for a higher dose rate per min
• Cyberknife uses ray tracing algorithm
# Liver (HCC) SBRT Plan Evaluation Checklist [RTOG 1112]

<table>
<thead>
<tr>
<th>1. Name</th>
<th>UMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Diagnosis</td>
<td></td>
</tr>
<tr>
<td>3. Prior Treatment</td>
<td>TACE/TARE SURGERY RADIATION RFA SORAFENIB</td>
</tr>
<tr>
<td>4. Imaging Characteristics</td>
<td>SIZE CM NUMBER SEGMENTS</td>
</tr>
<tr>
<td></td>
<td>ENHANCEMENT PHASE THROMBOSIS TUMOR NON TUMOR</td>
</tr>
<tr>
<td>5. Motion Management</td>
<td></td>
</tr>
<tr>
<td>6. Number of Lesions</td>
<td>SERUM AEP</td>
</tr>
<tr>
<td>7. Child Score Points</td>
<td>1 2 3 TOTAL SCORE</td>
</tr>
<tr>
<td>BILIRUBIN mg/dl</td>
<td>&lt;2 2.5 3 A 5-6</td>
</tr>
<tr>
<td>ENCEPHALOPATHY</td>
<td>NIL GRADE 1-2 GRADE 3 B 7-9</td>
</tr>
<tr>
<td>ASCITES</td>
<td>NIL MILD TO MODERATE SEVERE C 10-15</td>
</tr>
<tr>
<td>ALBUMIN g/dl</td>
<td>&gt;2.5 2.0-2.5 &lt;2.0</td>
</tr>
<tr>
<td>INR/PROTHROMBIN TIME (SECONDS PROLONGED OVERCONTROL)</td>
<td>&lt;1.7/6 &lt;1.7-2.4</td>
</tr>
<tr>
<td>8. GTV_PR GTV_NODE GTV_FACE GTV_RFA GTV_VASCULAR</td>
<td></td>
</tr>
<tr>
<td>9. CTV GTV_a GTV_b GTV_c GTV_d GTV_e [NO MARGIN] PTV 6-10MM</td>
<td></td>
</tr>
<tr>
<td>10. Liver Volume</td>
<td>LIVER-GTV VOLUME LIVER-PTV VOLUME</td>
</tr>
<tr>
<td>11. Plan Type [3DCRT/VMAT/DG/IMRS]</td>
<td></td>
</tr>
<tr>
<td>12. Prescribed Marginal Isodose</td>
<td>BED</td>
</tr>
<tr>
<td>D_MAX</td>
<td></td>
</tr>
<tr>
<td>D95%</td>
<td></td>
</tr>
<tr>
<td>D100%</td>
<td></td>
</tr>
<tr>
<td>V95%</td>
<td></td>
</tr>
<tr>
<td>V100%</td>
<td></td>
</tr>
<tr>
<td>V120%</td>
<td></td>
</tr>
<tr>
<td>V130%</td>
<td></td>
</tr>
<tr>
<td>Distance Between 80% Isodose and 90% Isodose</td>
<td>[0-20mm]</td>
</tr>
<tr>
<td>Distance Between 80% Isodose and 90% Isodose</td>
<td>[0-20mm]</td>
</tr>
<tr>
<td>Conformity Index [IDEAL 1] Volume of Prescription Isodose/Volume of PTV</td>
<td></td>
</tr>
<tr>
<td>Homogeneity Index [Between 1.1-1.3] Max dose/Prescription dose</td>
<td></td>
</tr>
<tr>
<td>Gradient Index [Between 0.3-0.9] Radius of Prescription Isodose - Radius of Half Prescription Isodose</td>
<td></td>
</tr>
</tbody>
</table>

## Prescription Dose

<table>
<thead>
<tr>
<th>Prescription Dose</th>
<th>LIVER-GTV-L-700CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy</td>
<td>$\leq 2$ Gy</td>
</tr>
<tr>
<td>45 Gy</td>
<td>$\leq 2$ Gy</td>
</tr>
<tr>
<td>40 Gy</td>
<td>$\leq 2$ Gy</td>
</tr>
<tr>
<td>35 Gy</td>
<td>$\leq 2$ Gy</td>
</tr>
<tr>
<td>30 Gy</td>
<td>$\leq 2$ Gy</td>
</tr>
<tr>
<td>27 Gy</td>
<td>$\leq 2$ Gy</td>
</tr>
</tbody>
</table>

## Non Liver OAR Constraints

<table>
<thead>
<tr>
<th>Non Liver OAR Constraints</th>
<th>Needed</th>
<th>Acceptable</th>
<th>Unacceptable</th>
<th>Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Esophagus max (0.5CC)</td>
<td>$32$ Gy</td>
<td>$32$ but $\leq 34$ Gy</td>
<td>$\geq 34$ Gy</td>
<td></td>
</tr>
<tr>
<td>2. Stomach max (0.5CC)</td>
<td>$30$ Gy</td>
<td>$30$ but $\leq 32$ Gy</td>
<td>$\geq 34$ Gy</td>
<td></td>
</tr>
<tr>
<td>3. Duodenum max (0.5CC)</td>
<td>$30$ Gy</td>
<td>$30$ but $\leq 32$ Gy</td>
<td>$\geq 34$ Gy</td>
<td></td>
</tr>
<tr>
<td>4. Small bowel max (0.5CC)</td>
<td>$30$ Gy</td>
<td>$30$ but $\leq 32$ Gy</td>
<td>$\geq 34$ Gy</td>
<td></td>
</tr>
<tr>
<td>5. Large bowel max (0.5CC)</td>
<td>$32$ Gy</td>
<td>$32$ but $\leq 34$ Gy</td>
<td>$\geq 34$ Gy</td>
<td></td>
</tr>
<tr>
<td>6. Cord + Fossa max (0.5CC)</td>
<td>$25$ Gy</td>
<td>$25$ but $\leq 28$ Gy</td>
<td>$\geq 28$ Gy</td>
<td></td>
</tr>
<tr>
<td>7. Kidneys: Bilateral mean</td>
<td>$10$ Gy</td>
<td>$10$ but $\leq 12$ Gy</td>
<td>$\geq 12$ Gy</td>
<td></td>
</tr>
<tr>
<td>8. Chest wall (0.5CC)</td>
<td>$\leq 5$ Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Spleen (0.5CC)</td>
<td>$\leq 5$ Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. CED (0.5CC)</td>
<td>$\leq 5$ Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Skin (0.5CC)</td>
<td>$\leq 5$ Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Heart (0.5CC)</td>
<td>$\leq 5$ Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Great Vessel (0.5CC)</td>
<td>$\leq 5$ Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Credit – Dr. Kanhu Charan Patro**
CASE FROM ASTRO SITE

Dose Constraints

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>Max point dose (0.03cc)</td>
<td>≤32</td>
</tr>
<tr>
<td></td>
<td>&lt;5cc</td>
<td>≤18</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>Max point dose</td>
<td>&lt;35</td>
</tr>
<tr>
<td></td>
<td>&lt;5cc</td>
<td>19.5</td>
</tr>
<tr>
<td>Liver Uninvolved</td>
<td>V(liver)-V21 ≥700cc</td>
<td>&gt;700cc</td>
</tr>
<tr>
<td></td>
<td>Mean dose</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

- ITV 50Gy/5# - achieved V95 to 95%
- PTV 40Gy/5# - achieved V95 to 95%
TREATMENT DELIVERY

- First step is correct positioning with immobilisation and motion management
- Appropriately counsel and prepare the patient – depending on number of lesions and dose per fraction, 30-45 mins with motion management could be needed for the delivery
- Image acquisition as per plan prior to treatment, intra-fraction and post treatment
- Imaging could be planar (using gold fiducials), low dose CBCT scans
- Be alert and watch the patient
- Proper matching is mandatory
- Presence of radiation oncologist, physicist and RTT at the time of delivery is essential
RESPONSE ASSESSMENT

(1) optimal time for response assessment is at least 6 to 12 months after SBRT

(2) stability or decrease in lesion size is associated with successful local control

(3) arterial phase hyperenhancement may persist despite pathologic CR

(4) washout on delayed phases may persist after SBRT.

• If the RECIST, mRECIST, EASL, or LI-RADS TR v2017 criteria had been applied, many of these lesions would have been improperly categorized as treatment failures potentially leading to unnecessary additional therapies
FOLLOWUP/SURVEILLANCE-HCC

- TACE and TARE show complete necrosis by 4-6 weeks
- SBRT will show some change by 3-6 months and further improvement by 12 months
- High energy, triphasic, contrast enhanced CT scan or MRI
  - Can be obtained by 4 weeks or after 3 months (to allow radiation inflammation to settle)- this would be baseline
  - Then every 3-6 months for 2 years
  - After 2 years can be done every 6-12 months
  - *AASLD 2019 guideline*
- If any relevant findings, then further evaluated by AFP and other relevant tests
- Persistent enhancement should be followed up – since delayed response of HCC to SBRT is known
- A study reports complete response rate of 24% - 3 months, 67% at 6 months and 71% at 12 months. Few cases even beyond this
- Management of underlying liver disease
Fig. 1 Axial CT scans of the abdomen with contrast depicting stereotactic body radiation therapy (SBRT) to a solitary hepatocellular carcinoma (a) and the radiographic evolution of the lesion at 3 months (b) and 15 months (c) after treatment. The radiation dose gradient is represented by the colored lines in a. Red = 50 Gy (prescription dose), Orange = 40 Gy, Yellow = 30 Gy.
LOCAL CONTROL- HCC

- Large lesions – 45Gy/3-5 fractions – LC 51%
- Cardenes et al – 36-48Gy/3# for Child Pugh A and 40Gy/5# for Child Pugh B. at 2 years, LC 100%, OS 60%
- Bujold et al 24-53Gy/6# - 1 year LC 87%, CR – 11%
- Kang et al, SBRT post CR from TACE – 42-60Gy/3#. 38.3% had CR and 38.3% had PR. 2 year LC 94.6% and OS – 68.7%
- SBRT with protons gave 2 year LC of 74.8% and 74.1% for HCC and ICC.
- NRG-G1003 is evaluating protons versus photons.
- SBRT is proved superior to other modalities for unresectable HCC
<table>
<thead>
<tr>
<th>Study</th>
<th>Histology</th>
<th>Patients</th>
<th>Tumors</th>
<th>Mean/Median Tumor Volume (cm²)</th>
<th>Dose</th>
<th>Median Follow-Up (Months)</th>
<th>Grade ≥3 Toxicity</th>
<th>Local Control</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tse et al. (12)</td>
<td>HCC, CC</td>
<td>41</td>
<td>41</td>
<td>173</td>
<td>24-54 Gy in six fractions</td>
<td>17.6</td>
<td>12% liver</td>
<td>65% (1 year)</td>
<td>51% (1 year)</td>
</tr>
<tr>
<td>Cárdenes et al. (13)</td>
<td>HCC</td>
<td>17</td>
<td>25</td>
<td>34</td>
<td>36-48 Gy in three to five fractions</td>
<td>24</td>
<td>23.5% liver</td>
<td>100% (2 year)</td>
<td>60% (2 year)</td>
</tr>
<tr>
<td>Andolino et al. (14)</td>
<td>HCC</td>
<td>60</td>
<td>71</td>
<td>29</td>
<td>24-48 Gy in three to five fractions</td>
<td>27</td>
<td>0%</td>
<td>90% (2 year)</td>
<td>67% (2 year)</td>
</tr>
<tr>
<td>Kang et al. (15)</td>
<td>HCC</td>
<td>47</td>
<td>56</td>
<td>14.9</td>
<td>42-60 Gy in three fractions</td>
<td>17</td>
<td>6.4% GI</td>
<td>94.6% (2 year)</td>
<td>68.7% (2 year)</td>
</tr>
<tr>
<td>Bujold et al. (16)</td>
<td>HCC</td>
<td>102</td>
<td>&gt;162</td>
<td>117</td>
<td>24-54 Gy in six fractions</td>
<td>31.4</td>
<td>30% liver, chest wall</td>
<td>74% (2 year)</td>
<td>34% (2 year)</td>
</tr>
<tr>
<td>Bush et al. (17)</td>
<td>HCC</td>
<td>33</td>
<td>&gt;51</td>
<td>17.2</td>
<td>70.2 GyE in 15 fractions (protons)</td>
<td>28</td>
<td>N/A</td>
<td>88% (2 year)</td>
<td>59% (2 year)</td>
</tr>
<tr>
<td>Hong et al. (18)</td>
<td>HCC, CC</td>
<td>92</td>
<td>108</td>
<td>97</td>
<td>67.5 GyE in 15 fractions (protons)</td>
<td>19.5</td>
<td>1% liver, GI</td>
<td>94.4% (2 year)</td>
<td>63.2% HCC, 46.5% CC (2 year)</td>
</tr>
<tr>
<td>Herfarth et al. (19)</td>
<td>CRC, BC, CC, HCC, OC</td>
<td>37</td>
<td>60</td>
<td>10</td>
<td>14-26 Gy in one fraction</td>
<td>15.1</td>
<td>0%</td>
<td>68% (18 month)</td>
<td>25 months (median)</td>
</tr>
<tr>
<td>Hoyer et al. (20)</td>
<td>CRC</td>
<td>64</td>
<td>141</td>
<td>22.4</td>
<td>45 Gy in three fractions</td>
<td>51.6</td>
<td>16.3% chest wall, GI</td>
<td>86% (2 year)</td>
<td>13% (5 year)</td>
</tr>
<tr>
<td>Lee et al. (4)</td>
<td>CRC, BC, OC</td>
<td>68</td>
<td>143</td>
<td>75.2</td>
<td>27.7-60 Gy in six fractions</td>
<td>10.8</td>
<td>9% liver, GI</td>
<td>71% (1 year)</td>
<td>47% (18 month)</td>
</tr>
<tr>
<td>Rusthoven et al. (21)</td>
<td>CRC, LC, BC, HCC, OC</td>
<td>47</td>
<td>63</td>
<td>14.9</td>
<td>36-60 Gy in three fractions</td>
<td>16</td>
<td>2% chest wall</td>
<td>92% (2 year)</td>
<td>30% (2 year)</td>
</tr>
<tr>
<td>van der Pool et al. (22)</td>
<td>CRC</td>
<td>20</td>
<td>31</td>
<td>6.4</td>
<td>37.5-45 Gy in three fractions</td>
<td>26</td>
<td>10% liver</td>
<td>74% (2 year)</td>
<td>83% (2 year)</td>
</tr>
<tr>
<td>Goodman et al. (23)</td>
<td>CRC, CC, HCC, BC, OC</td>
<td>26</td>
<td>40</td>
<td>32.6</td>
<td>18-30 Gy in one fraction</td>
<td>17</td>
<td>0%</td>
<td>77% (1 year)</td>
<td>50.4% (2 year)</td>
</tr>
<tr>
<td>Scorsetti et al. (89)</td>
<td>CRC, BC, OC</td>
<td>61</td>
<td>76</td>
<td>18.6</td>
<td>52.5-75 Gy in three fractions</td>
<td>12</td>
<td>1.6% chest wall</td>
<td>90.6% (22 month)</td>
<td>83.5% (1 year)</td>
</tr>
</tbody>
</table>

BC, breast cancer; CC, cholangiocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; LC, lung cancer; N/A, not available; OC, other cancers.
• SBRT vs TACE-
  – LC 96.5% vs 47% at 1 year and 91% versus 23% at 2 years
  – 2 year LC 88% for RT and 45% for TACE
  – Freedom from hepatic progression at 1 year 56.5 % versus 36% at 2 years (27%-11%)

• Loma Linda University comparing proton RT with TACE

• BRIDGE TO TRANSPLANT
  – O’connor – 51Gy/3# followed by transplant - pCR in 27%, stable or partial response in others on histopathology in explant
  – Barry et al – 36Gy/6 # followed by transplant – 5 yr OS and DFS was 76% and 79% respectively
LOCAL CONTROL - ICC

• Mayo clinic – 55Gy/3-5# - one year DFS and OS – 31%, 73%
• O’Connor – 24Gy/3# - LC 75%, CR-25%, grade I toxicity-25%
• Sandler et al – 40Gy/5# - median time to progression and OS were 16.8 and 31.3 months with 77% grade 1-2 toxicity and 16% grade 3 or more toxicity
• SBRT also useful as bridge therapy prior to liver transplant
• 3 year LC for BED <80.5Gy and > 80.5Gy are 45% and 75%
LIVER METASTASIS
• Considering long survival of oligometastatic patients due to evolving systemic therapy – liver SBRT for oligometastasis is becoming increasingly important

• Liver mets from CRC – 5 year survival 50-60%
Image guided SBRT for multiple liver metastases with ExacTrac® Adaptive Gating

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Keywords:
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Liver metastases
Gating
ExacTrac

A B S T R A C T

Aim: To report the outcome and toxicity of sequential stereotactic body radiotherapy (SBRT) for multiple liver metastases in patients treated with ExacTrac Adaptive Gating.

Background: In selected patients with a limited number of liver metastases, SBRT has been evaluated as a safe and effective treatment, with minimal toxicity and high rates of local control.

Materials and methods: From April 2008 to October 2013, 21 patients with multiple (3–14) liver metastases (n = 101) were treated sequentially with SBRT at our institution. Maximum tumor diameter was 7.5 cm. Prior to treatment, internal markers were placed inside or near the tumor. CT or PET-CT simulation was used for the definition of gross tumor volume (GTV). Median planning target volume was 32.3 cc (3.6–139.3 cc). Treatment consisted of 3 fractions (12–20 Gy/fraction) or 5 fractions (10 Gy/fraction), prescribed to the 90–95% of the PTV volume. Daily intra-fraction image guidance was performed with ExacTrac Adaptive Gating. Regular follow-up included CT or PET-CT imaging.

Results: After a median of 23.2 months, the estimated local control rate was 94.4%, 80.6%, 65% and 65% after 1, 2, 3 and 4 years; the median overall survival was 62 months (95% CI 49.12–74.87) and the actuarial survival reached at 60 months was 57.6%. The univariate data analysis revealed that only primary histology other than colorectal adenocarcinoma was shown as an independent significant prognostic factor for local control (p = 0.022). Number of treated metastases did not modify significantly the overall survival (p = 0.51). No toxicity higher than G3 (1 patient with chest wall pain) and no radiation-induced liver disease were observed.
Conclusions

SBRT provides good OS and LC for metastatic liver lesions. Higher SBRT doses (BED₁₀ ≥ 100 Gy) and smaller tumor volumes (<40 cm³) are associated with improved LC and OS. Patients with liver metastases from CRC, breast and gynecological primary tumors tend to have better OS compared to lung and pancreatic primary tumor types, but this could be attributed to selection bias or differences in biology and use of systemic therapy. Future prospective trials assessing the impact of histology and dose with the combination of systemic and immune therapies are needed to help define the role for SBRT to improve outcomes.
FOLLOWUP/SURVEILLANCE-METASTASIS

• Single venous contrast CT scan of PET CT is adequate
• Frequency of follow up is same as HCC
• Adjacent liver parenchyma is hypodense
• Gradual response is known with persistent metabolic activity. SUV reduction to half by 3.6 months and SUV 2.6 by 7 months
• Usually have better liver health than HCC
LOCAL CONTROL- LIVER METASTASIS

- LC
  - 14-26Gy/1# - LC 68% at 18 months
  - 36-60Gy/3# - LC 92% at 2 years
  - Rusthoven et al – 2 year LC 100% for < 3cm and 77% for > 3 cm tumours.
    Scorcetti et al found equal control irrespective of size for 75Gy/3#

- Control rate depends on site of primary – Hoyer et al. found improved OS in patients with metachronous metastases or largest metastasis less than 35 mm (20). Rusthoven et al. reported worse median survival for tumors from the lung, ovaries, and noncolorectal gastrointestinal sites (12 months) versus breast, colorectal, renal, carcinoid, gastrointestinal stromal tumors, and sarcomas (32 months)
LIVER TOXICITY

• Hepatocytes are very sensitive to radiation. Toxicity is due to – fatigue, toxicity, gastritis, elevated liver enzymes
• But upto 75-80% of non cirrhotic liver removal can be done as per surgical literature. So average 2000 cc is liver volume and 1/4\{th}\  of it is around 500 cc, so 700 cc liver spared (means about 40%) is adequate buffer
• **classic RILD** is a syndrome of an acute triad of hepatomegaly, ascites, and elevated ALP followed by the development of anicteric ascites approximately 2 weeks to 4 months after hepatic irradiation described with conventional fractionation but has rarely been reported in SBRT studies.
• Constraints as per
  - Emami et al – 5% with 30Gy and 50% with 40 Gy whole liver RT at 1.8-2Gy/#
  - QUANTEC - <5% with 30-32Gy and higher risk with higher dose to whole liver RT at 1.8-2Gy/#
• **Nonclassic RILD** has emerged as a more commonly seen toxicity, described as a fivefold or higher increase in transaminase values, a decrease in liver function loosely defined as a 2-point or higher increase in CP score, reactivation of hepatitis, or any other toxicity not included in the classic RILD syndrome
• <700 ml liver gets 15Gy [university of Colorado] – they were the first to establish no RILD with this constraint
• 800 cc liver < 18Gy [son et al]
• Princess Margaret hospitale stablished grade 5 toxicity if constraint not met (median 18.1 Gy vs. 15.4 Gy, p = .02)
• Trial 1112 recommends liver mean dose 13-17Gy
<table>
<thead>
<tr>
<th>CTCAE v4.0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Loss of appetite</td>
<td>Decreased oral intake w/o weight change</td>
<td>Inadequate oral intake; tube feedings or TPN</td>
<td>Life threatening consequences</td>
<td>Death</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Mild</td>
<td>Moderate; causing difficulty with some ADLs</td>
<td>Severe; interfering with ADL</td>
<td>Disabling</td>
<td>Death</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Asymptomatic; Radiographic, endoscopic</td>
<td>Symptomatic</td>
<td>Symptomatic; tube feedings or TPN</td>
<td>Life-threatening; surgical intervention</td>
<td>Death</td>
</tr>
<tr>
<td>Liver Dysfunction</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life Threatening; disabling</td>
<td>Death</td>
</tr>
</tbody>
</table>
cHBT toxicity

- Osmundson et al established, cHBT toxicity
- Recommended to draw portal vein with 1.5 cm expansion
- Constraints V40 < 37 cc and V 30< 45cc
- cHBT toxicity associated more with primary liver tumour than with metastasis
• **STOMACH, DUODENUM, BOWEL**
  — Risk of perforation and ulceration
  — Dose constraints to these organs include $D_{\text{max}}$ less than 40 Gy, $V_{25}$ less than 9 mL, $V_{30}$ less than 5 mL, and $V_{35}$ less than 1 mL.
• **Heart** - $D_{\text{mean}}$ less than 12 Gy and $V_{15}$ less than 10%.
• **Kidneys** - kidney $V_5$ less than 50%.
• **Chest wall and ribs** - $V_{30}$ less than 30 mL, and ribs $D_{2\text{mL}}$ less than 27 Gy
• **Recent review by Pollom et al [check]**
TOXICITY

• Radiation induced liver disease (RILD) <1% (transient elevation of liver transaminases happens)
• Fatigue and loss of appetite worsens at 1 month and improves at 3 months
• For Child Pugh B – preferable to fractionate to five fractions
• Child Pugh class deterioration has been reported 3 months post SBRT – 29% at 3 months and 6% at 12 months (Bujold et al)
• Gastric perforation – for lesions close to bowel, higher with preexisting gastric ulcers (preferable to check with endoscopy prior to SBRT)
• Chest wall toxicity – grade 2 non traumatic rib fractures in two patients (reported at 0.5cc 51.8Gy and 66.2Gy in six fractions) – Lee et al
• Toxicity is enhanced by
  – Surgery, chemotherapy, stent, use of alcohol
  – Use of concurrent hypofractionation and immunotherapy (VEGF can enhance GI toxicity if used with SBRT)
  – Extensive chemotherapy use diminishes functional liver reserve (oxaliplatin – sinusoidal injury, irinotecan – steatohepatitis) – REMAIN ALERT WHILE SELECTING AND POSTING PATIENT FOR SBRT
  – Concurrent use of Sorafenib – interrupt for 2 weeks during SBRT
  – Watch for stent induced sepsis mimicking RILD
  – For cirrhotics and post chemo liver, DOSE CONSTRAINT 850cc< 15Gy
ongoing randomized trials investigating sorafenib with or without TACE (NCT01829035 and NCT01906216)

sorafenib with or without SBRT (NCT0173093 and RTOG 1112).

Trials for tremelimumab (monoclonal antibody against CTLA-4) for use with TACE, RFA, SBRT in HCC and biliary tract carcinomas (NCT01853618)

Trials to evaluate abscopal effect with use of immunotherapy with RT
THANKYOU