Role of Radiation Therapy in the management of Hepatocellular Carcinoma

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February 10 2023

Radiation effect on the liver

Direct and indirect mechanisms resulting in DSBs

Causes vascular injury ---- hypoperfusion, hypoxia and indirect cell death.

Immunostimulatory effects ---- immunogenic cell death.

A higher dose per fraction causes damage to the vascular endothelium, with consequent apoptosis and vascular leakage

Role of Radiation Therapy in the management of HCC

Neoadjuvant setting – bridge to transplant

SBRT in the definitive setting – Early Stage

Intermediate and advanced stage HCC (BCLC B/C)

SBRT/RT in the palliative setting

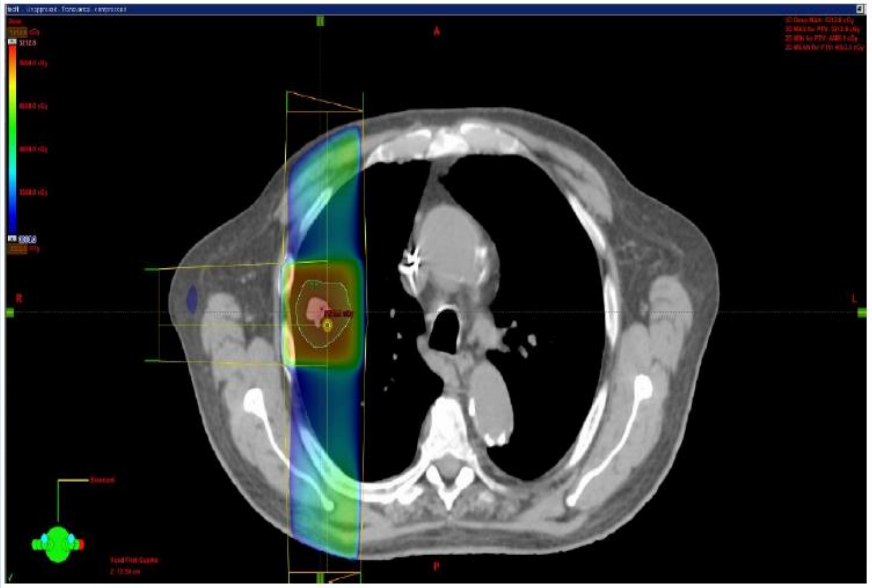
SBRT

- Highly conformal radiation treatment
- Use of multiple radiation beams that converge upon the target isocenter
- Spread out the entry radiation damage
- Punishing Radiation Target Dose
- Steep Radiation Gradients to Normal Tissue

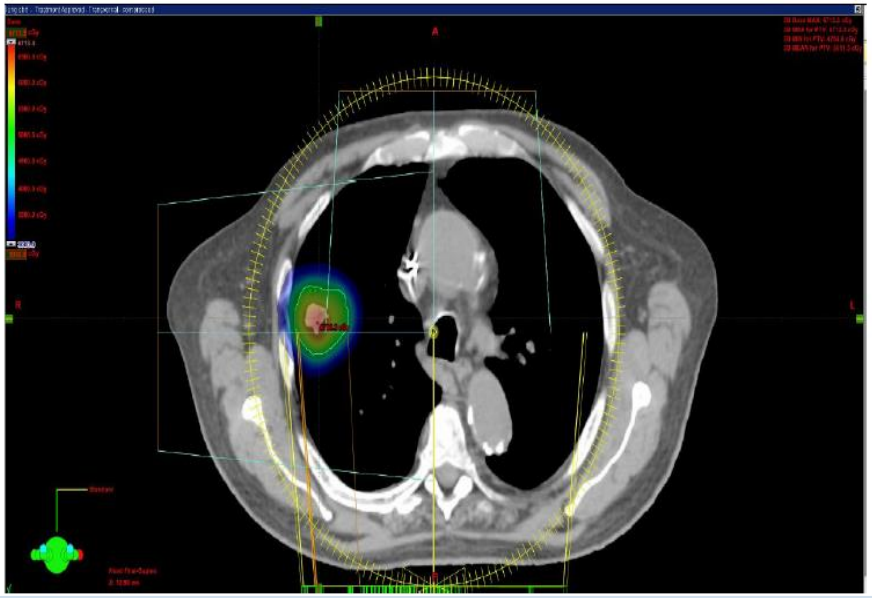
SBRT

- A high potent biological dose of radiation is delivered to the tumor
- Intended to ablate all cells within the target volume
- improving the cure rates for the tumor

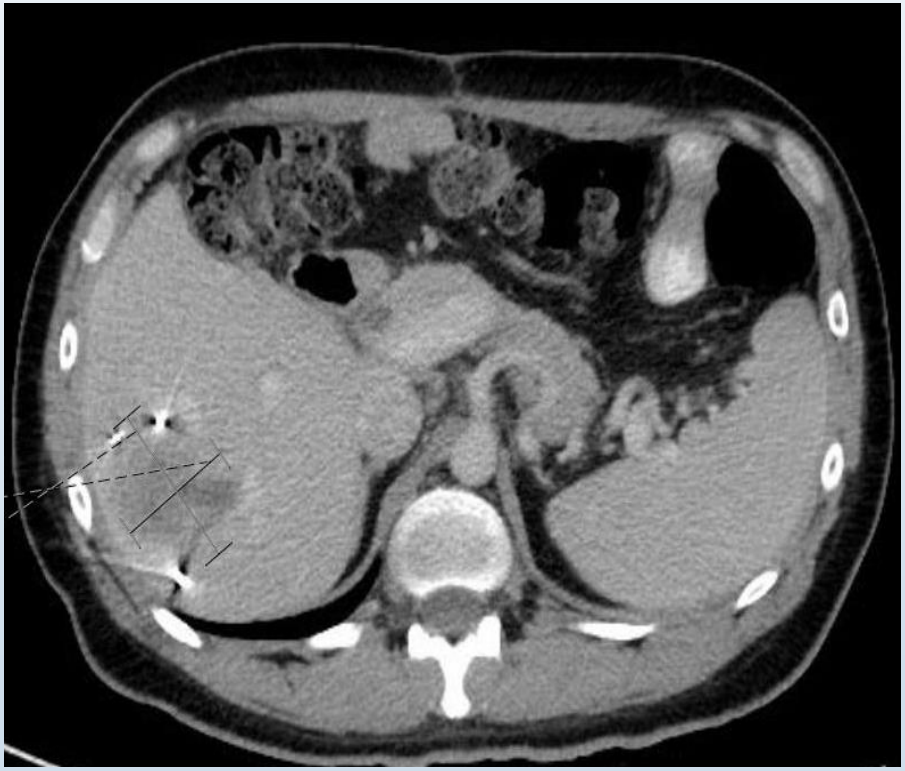
Conventional Dose Distribution

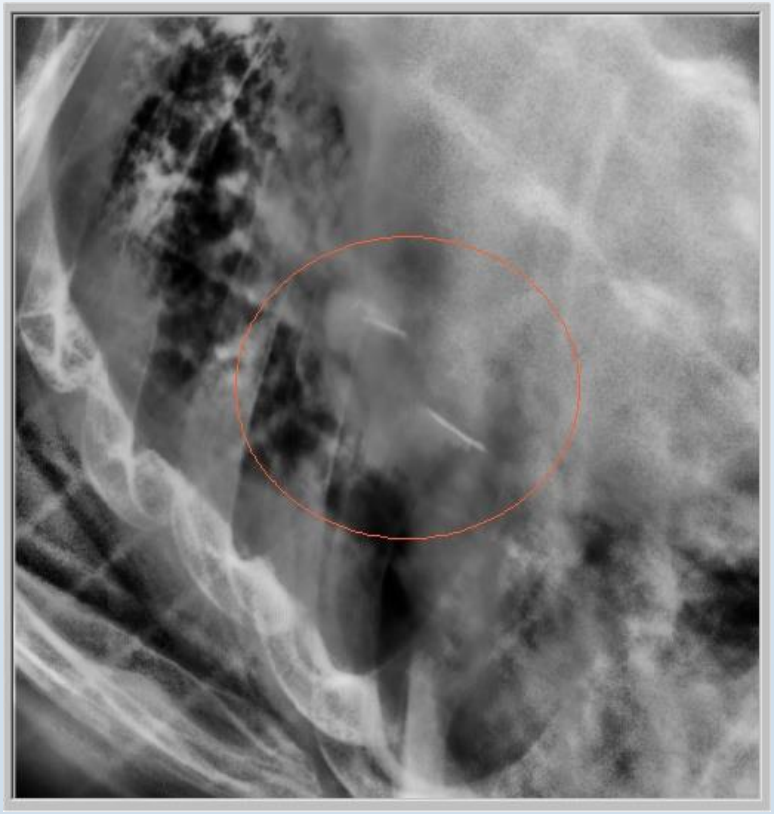


SBRT Dose Distribution

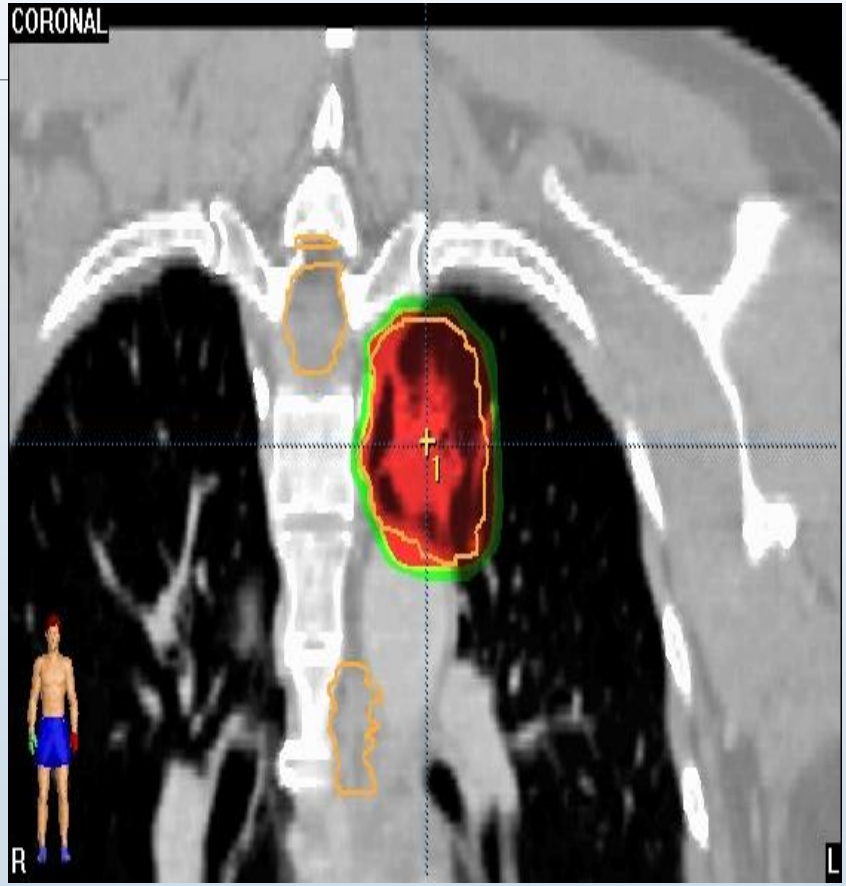


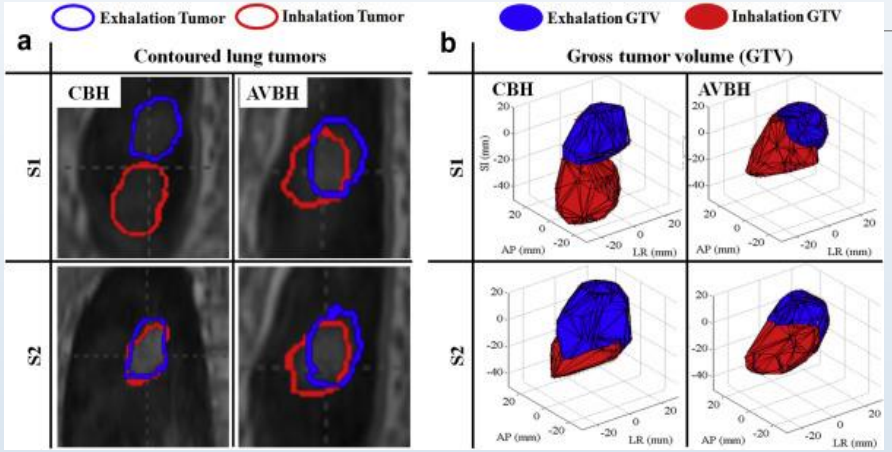
Breathing Motion

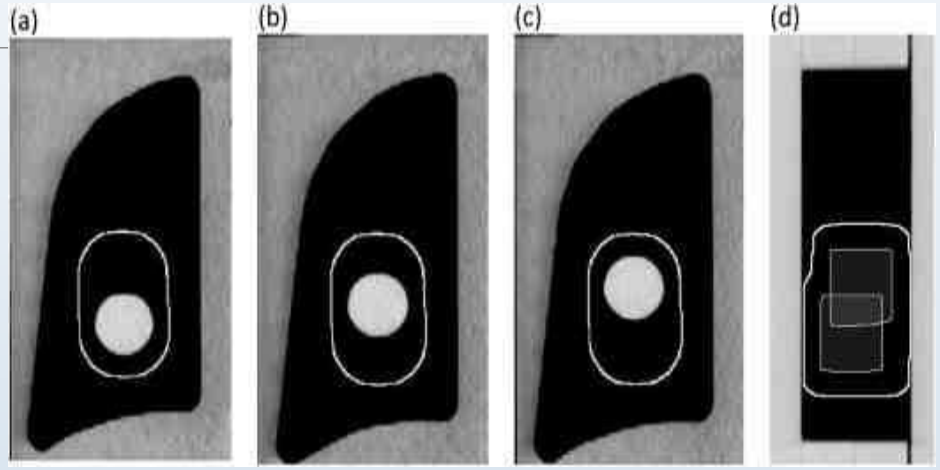




4DCT maps the target area over breathing cycle.







- ITV is contoured on MIP

Challenges in Targeting Liver Tumors

Low tolerance of liver to radiation

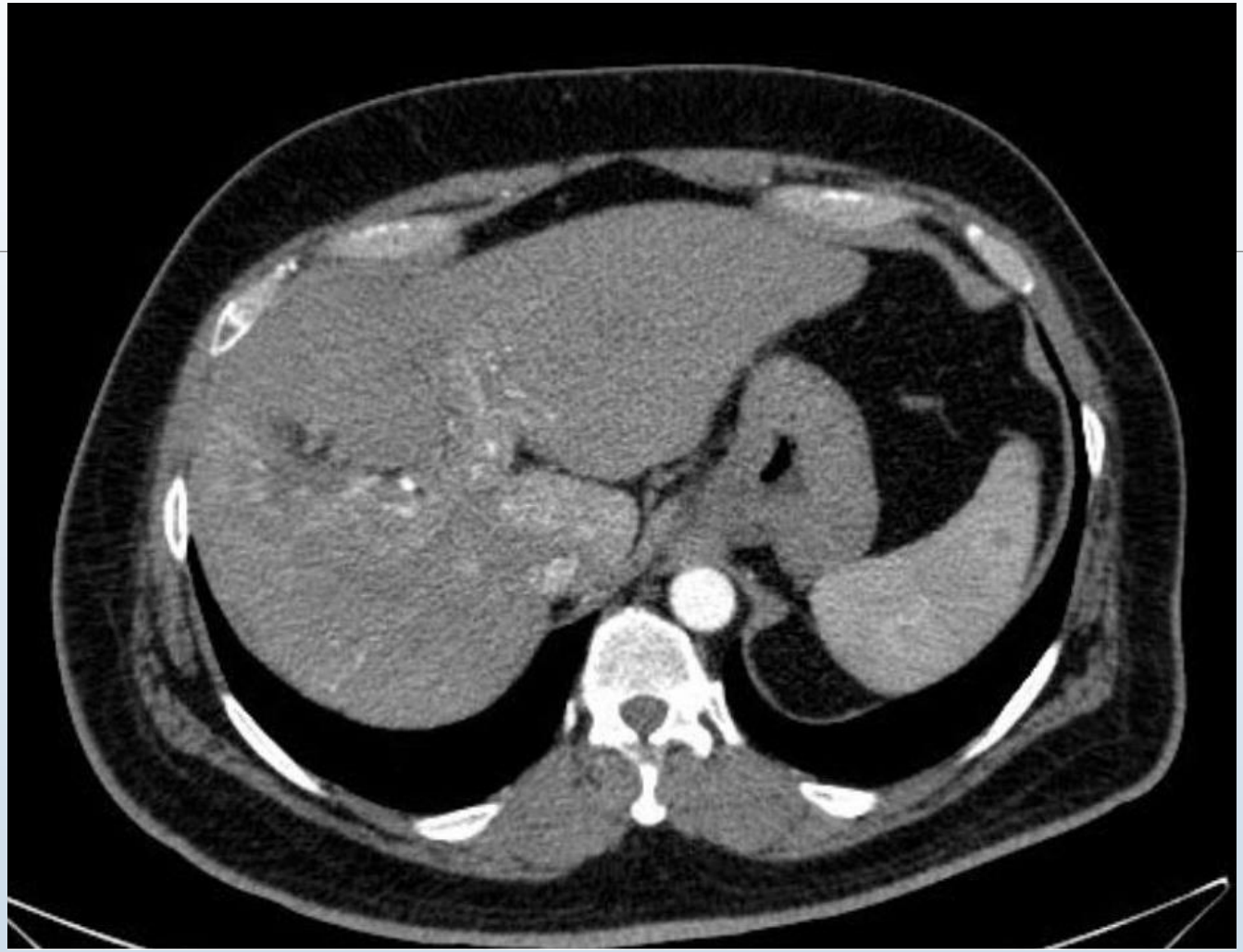
Limited visualization of the target

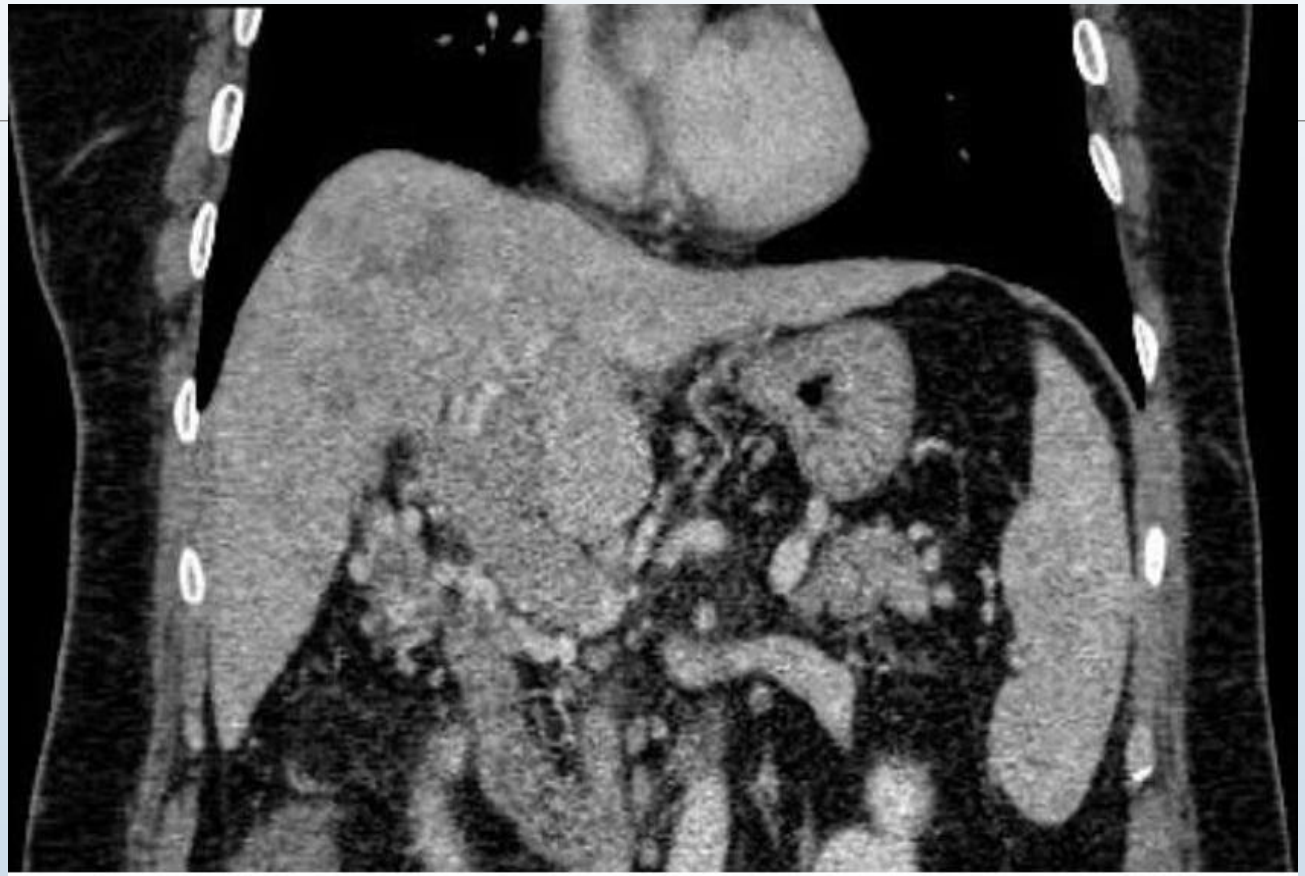
Liver deformation with respiration

Challenges in Targeting Liver Tumors

Changes in GI organ luminal filling

Interfraction target displacement with respect to bony anatomy





Study	Patient number	Quality/type of study	Indication/stage (BCLC)	Dose and fractionation	Follow up	Outcomes (LC/OS)	Toxicity (Grade 3 liver/GI)	Study conclusion
Kim *et al*., 2021[30]	72	Phase III randomised trial- Proton vs RFA	0-C	66Gy/10Fr (Protons)	51.6m	2y LC: 92.8% 2y OS: 91.7%	none	Proton beam therapy was non-inferior to RFA and was tolerable.
Yoon *et al*., 2020[31]	50	Prospective Phase II trial	0 and A (small HCC)	45 Gy/3#	47.8 m	5y LC: 97.1% 5y OS: 77.6%	4%	SBRT showed good results for ablation of small HCC with minimal toxicity.
Labrunie *et al*., 2020[32]	43	Prospective Phase II trial	A-C	45 Gy/3#	4 y	2y LC: 94% 2y OS: 69%	5%	LC and OS was promising in HCC treated with SBRT.
Jang *et al*., 2020[33]	65	Prospective Phase II trial	0-C	60 Gy/3#	41m	2y LC:97% 2y OS: 84%	2%	SBRT for HCC was well tolerated.
Park *et al*., 2020[34]	290	Prospective Phase II trial	0-A	30-60Gy/3#	38.2m	5y LC: 91.3% 5y OS: 44.9%	8.8%	SBRT is an ablative option for small HCC.
Mathew *et al*., 2020[35]	297	Retrospective	0-D	27-60Gy/3-6#	19.9m	3y LC: 87% 3y OS: 39%	16%	SBRT provides good LC and OS in HCC when it is unsuitable or refractory to other locoregional treatment.

Table 2. Summary of HCC Radiotherapy Studies in Order of Local Control at 2 Years.[a]

Study, Year	n	CP-B %	Median Tumor Diameter, cm	Dose (Range) /fx	BED Gy_{10}	EQD2	Dose-Prescription Point	1-Year OS	2-Year LC
Yamashita, 2015[24]	79	11%	2.7	48 Gy/4-10	71-106	59-88	D95% PTV	78%	64%
Bujold, 2013[7]	102	0%	9.9	24-54 Gy/6	34-103	28-86	D95% PTV modified based on effective liver volume irradiated	75%	74%
Bibault, 2013[25]	75	11%	3.7	40-45 Gy/3	72-85	60-71	80% IDL D95% PTV	79%	90%
Andolino, 2011[26]	60	40%	3.1	30-48 Gy/3	60-125	50-104	80% IDL	82%[b]	90%
Jung, 2013[27]	92	26%	2.5	45 Gy/3-4	96-113	80-94	85-90% IDL	87%	92% (3 years)
Sanuki, 2013[28]	185	15%	2.7	40 Gy/5	72	60	70-80% IDL	95%	93%
Yoon, 2013[29]	93	26%	2.0	45 Gy/3-4	96-113	80-94	D100% PTV	86%	95%[b]
Takeda, 2014[30]	63	16%	2.6	35-40 Gy/5	60-72	50-60	70-80% IDL	100%	95%
Huertas, 2015[31]	77	14%	2.4	45 Gy/3	113	94	80% IDL	82%	99%
Kimura, 2015[32]	65	14%	1.6	48 Gy/4	106	88	Isocenter	NR	100%
Jang, 2013[22]	108	10%	3.0	51 Gy/3	138	115	70-80% IDL D97% PTV	83%[b]	100%

Abbreviations: BED, biologically equivalent dose; CP, Child-Pugh; EQD2, equivalent dose is 2 Gy fractions; fx, fractions; HCC, hepatocellular carcinoma; IDL, isodose line; LC, local control; n, patient number; NR, not reported; OS, overall survival; PTV, planning target volume.

[a]Studies included were published between 2002 and 2017 with more than 50 patients with HCC and reporting 2-year local control.

[b]Estimated from survival curve.

Table 2. Summary of HCC Radiotherapy Studies in Order of Local Control at 2 Years.a

Published in: Stephanie K. Schaub; Pehr E. Hartvigson; Michael I. Lock; Morten Høyer; Thomas B. Brunner; Higinia R. Cardenes; Laura A. Dawson; Edward Y. Kim; Nina A. Mayr; Simon S. Lo; Smith Apisarnthanarax; *Technol Cancer Res Treat* 17, 1533033818790217.
DOI: 10.1177/1533033818790217

SBRT in neoadjuvant setting – bridge to transplant

The aim of local therapy in this setting is to prevent progression and downsize the tumour to maintain the eligibility for transplant.

The application of SBRT as bridging therapy is relatively new, with only a few institutional series reporting on its safety and efficacy.

One of the earliest reports, from the University of Toronto, demonstrated the safety of conformal radiation therapy (8.5-33 Gy in 1-6 fractions) as bridging therapy, with 5 of 10 patients undergoing transplant after radiation without complications.

Connor et al. treated 10 patients with SBRT (median 51 Gy in 3 fractions) before transplant, and 27% had a complete response, while the remaining 73% had a partial response or stable disease.

The median time to transplant was 113 days with no increase in postoperative morbidity. The overall survival (OS) and disease-free survival were 100% at 5 years.

SBRT in the definitive setting

Early-stage HCC (BCLC 0/A)

RFA is the recommended first-line treatment for HCC less than 3 cm, if unresectable or not suitable for transplant, with 3-year local control rates of over 90%.

The application of RFA is challenging in situations where the tumour is near vessels (heat sink effect) or the hilum or dome of the diaphragm (risk of complications), or if the tumour is large (resulting in incomplete ablation [2-60%] and poor outcomes).

SBRT provides reasonable local control and survival rates (3-year local control: 68-97% and 3-year survival: 39-84%) when RFA is contraindicated or in a recurrent setting post-RFA or TACE.

SBRT in the definitive setting

Early-stage HCC (BCLC 0/A)

A phase III randomised non-inferiority trial by Kim et al. compared PBT with RFA in recurrent HCC (n = 144) and found the 2-year local progression-free survival with PBT was non-inferior to RFA (92.8% for PBT vs. 83.2% for RFA).The 4-year survival was similar between the 2 arms.

Matthew et al. reported outcomes of 297 high-risk patients with HCC treated with SBRT from 2003 to 2016; patients were either not candidates for RFA/TACE or had recurrent/residual disease without vascular invasion after RFA/TACE(35). The 3-year OS rate was 39% with a 13% recurrence rate despite large tumours.

The toxicity was acceptable with Child-Pugh progression by 2 points at 3 months noted in 16% with no RILD. Even in treatment-naïve small HCC (1-3 cm)

Su et al. showed superior local control and progression-free survival with SBRT (n = 167) compared to TACE (n = 159) in 326 patients with inoperable BCLC-A stage HCC.

The meta-analysis by Pan et al. included 10 studies comparing SBRT with RFA in patients with treatment-naïve HCC and showed superior 1- and 3-year local control with SBRT.

Intermediate and advanced stage HCC (BCLC B/C)

Several retrospective and prospective series showed acceptable local control (2-year: 65-95%) and OS (2-year: 40-80%) rates with SBRT

Sapir et al. reported outcomes of a propensity score analysis of 209 patients with 1-2 tumours who underwent TACE (n = 84) or SBRT (n = 125).

The 2-year local control rate was superior with SBRT compared to TACE (91% vs. 23%, p <0.001), with similar survival rates (2-year OS 34.9% vs. 54.9 %, p = 0.21).

a propensity score analysis by Bettinger et al., comparing TACE with SBRT in HCC BCLC B/C, showed comparable 1-year local control (82.9% vs. 84.8%, p = 0.8) and 1 year OS (52.9% vs. 53.1%) rates.

Intermediate and advanced stage HCC (BCLC B/C)

A meta-analysis by Zhao et al. suggests higher response, local control, and survival rates with TACE and SBRT vs. SBRT alone.[78]

Randomised studies comparing TACE with TACE and SBRT in unresectable HCC are ongoing (NCT03895359 and NCT02794337).

While systemic therapy is standard of care for portal vein thrombosis (PVT), radiation therapy appears to provide sustained local control in a substantial proportion of patients. A randomised trial by Yoon et al. compared the combination of TACE and radiation with sorafenib in 90 patients with Child-Pugh A HCC with PVT and showed improved progression-free survival (86.7% vs. 34.3%; p <0.001), time to progression (31.0 vs. 11.7 weeks; p <0.001) and OS (55.0 vs. 43.0 weeks; p = 0.04) with TACE-RT.[45]

Munoz-Schuffenegger reported the long-term outcomes of 128 patients with HCC and PVT treated with SBRT in a single institution from 2003 to 2016.[79]

With a dose of 27-54 Gy in 5 fractions, 1-year local control was 87.4% and median OS was 18.3 months. The RTOG 1112 is a phase III trial comparing SBRT with sequential sorafenib vs. sorafenib alone, and the results are awaited (NCT01730937). A retrospective study by Bettinger et al. compared SBRT with sorafenib in advanced HCC (recurrent, metastatic, and advanced) in a propensity score analysis.[80]

SBRT showed improved median overall survival compared to sorafenib (17 vs. 9.6 months).

SBRT/RT in the palliative setting

The studies of whole liver radiation therapy indicate palliation with 20-30 Gy in 45-80% of cases.

In a phase II trial by Soliman et al., 21 patients with HCC were treated with 8 Gy in a single fraction to the whole liver or tumour.

At 1 month, 48% had symptom improvement with quality-of-life improvements in 21-29%.

Unresectable HCC

Until recently, minimal role for RT

Perceived radioresistance of HCC

Underlying liver dysfunction increased risk of liver toxicity

-Dose escalated RT

1-year local control ranged from 50-80%

SBRT for Primary Liver Tumors

41 patients with unresectable primary liver tumors

HCC = 31 (Childs-Pugh A) IHCC = 10

Dose (24 – 54 Gy) over 6 fractions(median = 36 Gy)

Dose dependent on volume of liver irradiated

Grade 3 elevation of LFT's in 5 patients (12%)

No RILD or treatment-related grade 4/5 toxicity

Dawson L, et. al., J Clin Oncol, 2008

SBRT for Primary Liver Tumors

1 year in-field LC = 65%

CR = 5%

PR = 44%

SD = 42%

Median OS:

HCC = 11.7 months, IHCC = 15 months

Dawson L, et. al., J Clin Oncol, 2008

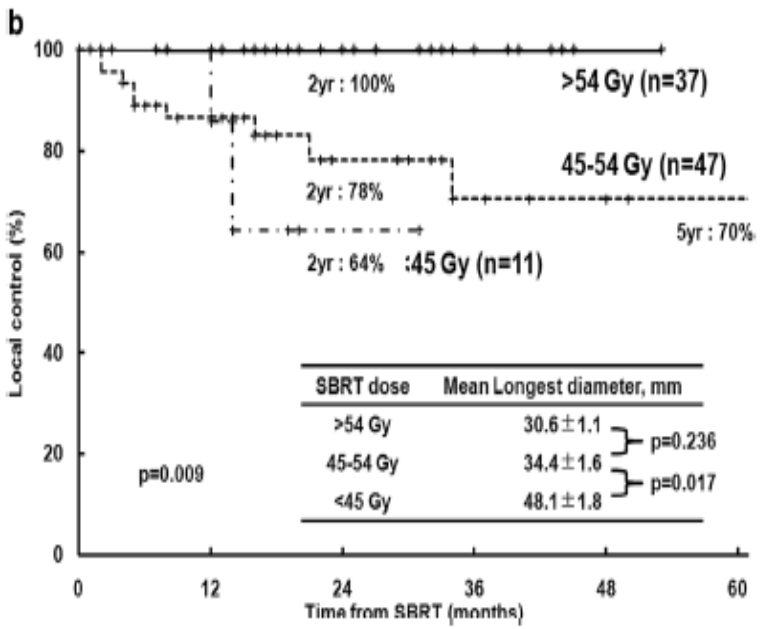
Jang et al. Radiation Oncology 2013, 8:250
http://www.ro-journal.com/content/8/1/250

RADIATION ONCOLOGY

RESEARCH Open Access

High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma

Won Il Jang[1], Mi-Sook Kim[1*], Sun Hyun Bae[2], Chul Koo Cho[1], Hyung Jun Yoo[1], Young Seok Seo[1], Jin-Kyu Kang[1], So Young Kim[3], Dong Han Lee[4], Chul Ju Han[5], Jin Kim[5], Su Cheol Park[5], Sang Bum Kim[6], Eung-Ho Cho[6] and Young Han Kim[7]



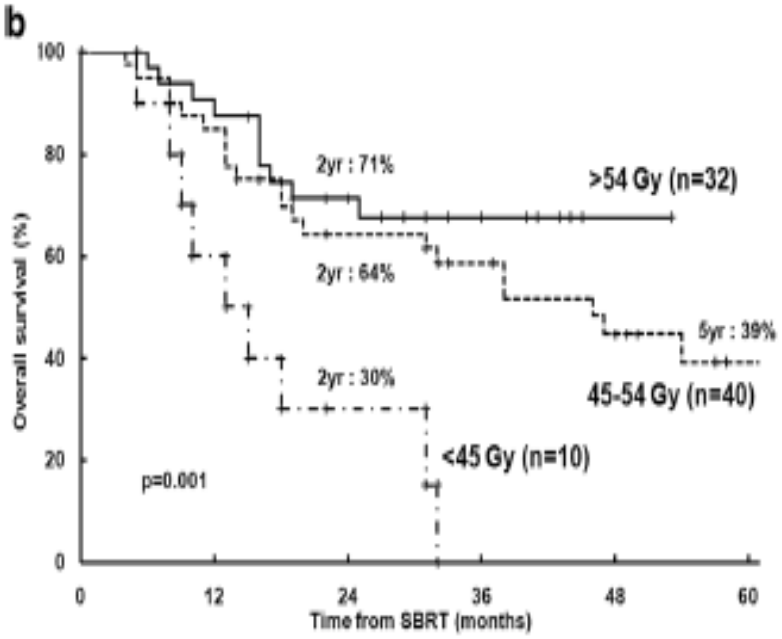
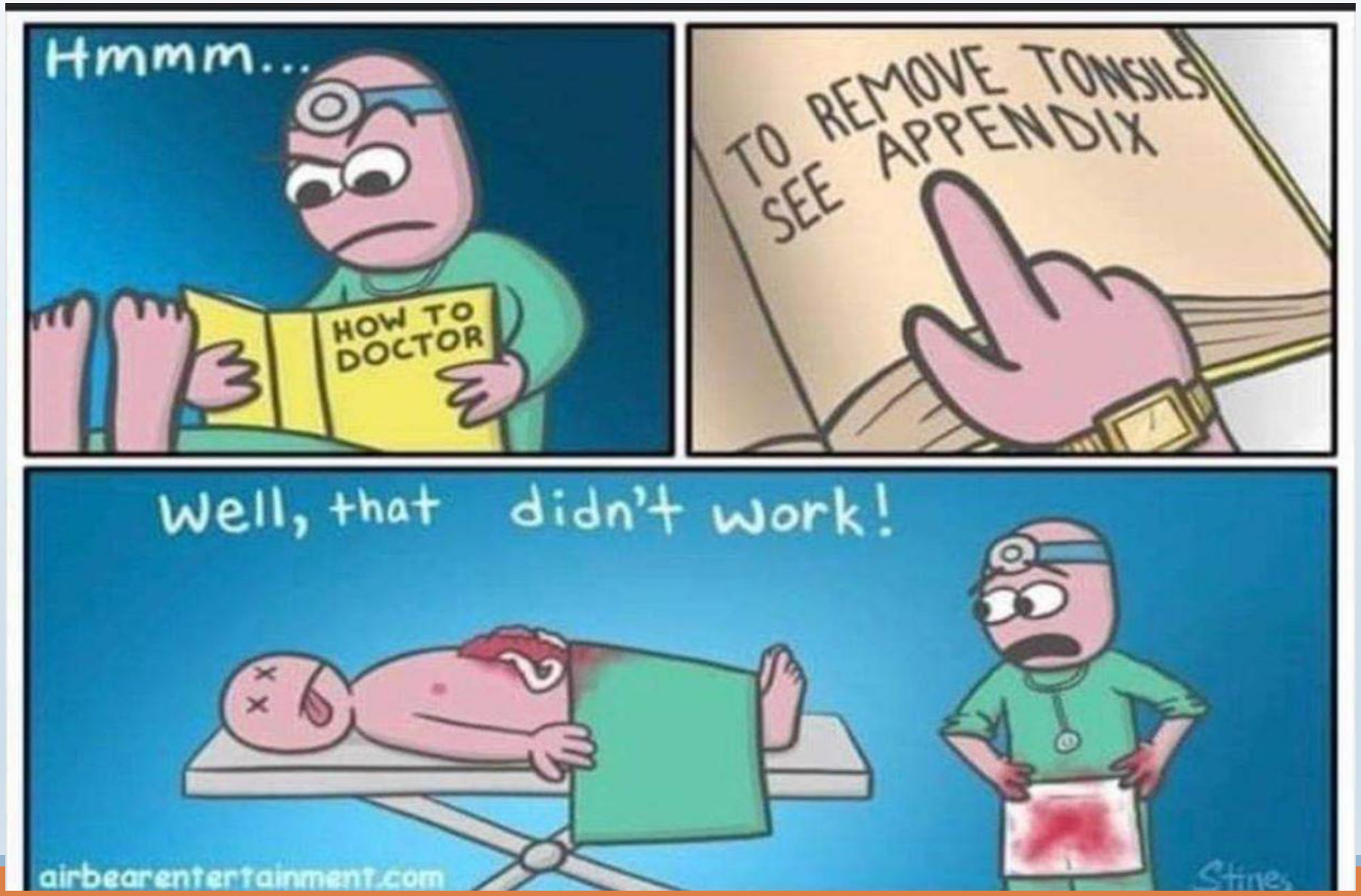
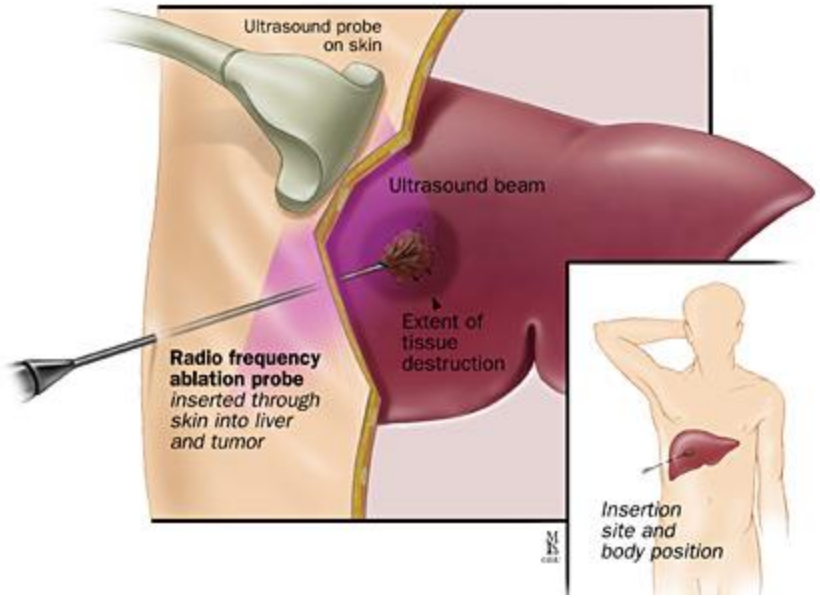
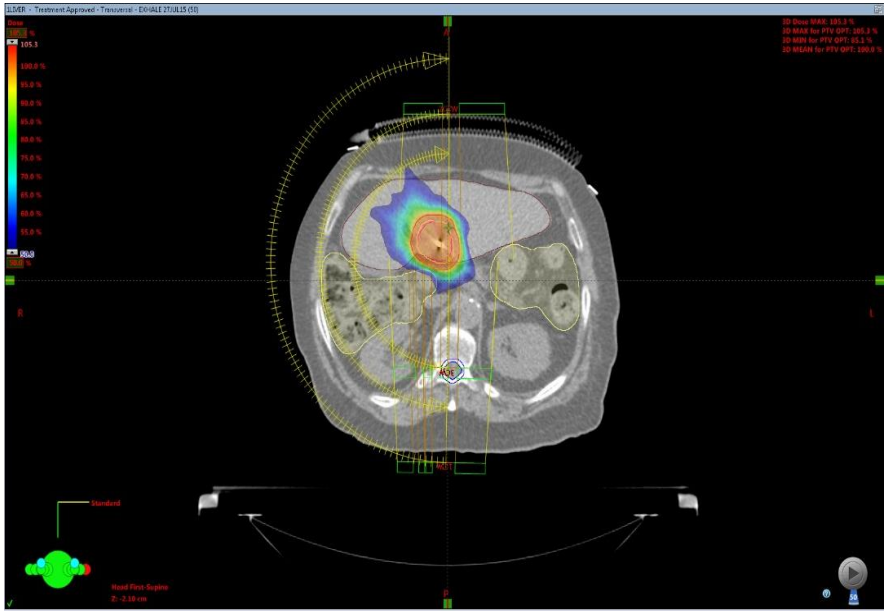


Figure 1 Local control from the time of the first stereotactic body radiotherapy (SBRT) treatment. (a) All lesions (n = 95); (b) By SBI dose. yr, year.


Hmmm...
HOW TO DOCTOR
TO REMOVE TONSILS SEE APPENDIX
Well, that didn't work!
airbearentertainment.com
Stines


Ultrasound probe on skin
Ultrasound beam
Extent of tissue destruction
Radio frequency ablation probe inserted through skin into liver and tumor
Insertion site and body position

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VOLUME 34 · NUMBER 5 · FEBRUARY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma

Daniel R. Wahl, Matthew H. Stenmark, Yebin Tao, Erqi L. Pollom, Elaine M. Caoili, Theodore S. Lawrence,

224 patients with inoperable, non-metastatic HCC

RFA (n = 161) to 249 tumors

or SBRT (n = 63) to 83 tumors

SBRT vs RFA for HCC

The SBRT group had :

-Lower pretreatment Child-Pugh scores (P = .003),

-Higher pretreatment alpha-fetoprotein levels (P = .04),

-Greater number of prior liver-directed treatments (P=.001).

One- and 2-year FFLP

RFA were 83.6% and 80.2%

SBRT 97.4% and 83.8% .

SBRT vs RFA for HCC

Tumor size predicted for FFLP in RFA but not with SBRT

For tumors>2 cm, there was decreased FFLP for RFA compared with SBRT (HR, 3.35; P = .025).

Acute grade 3+ complications

11% of RFA

5% SBRT treatments (P = .31).

SBRT vs RFA for HCC

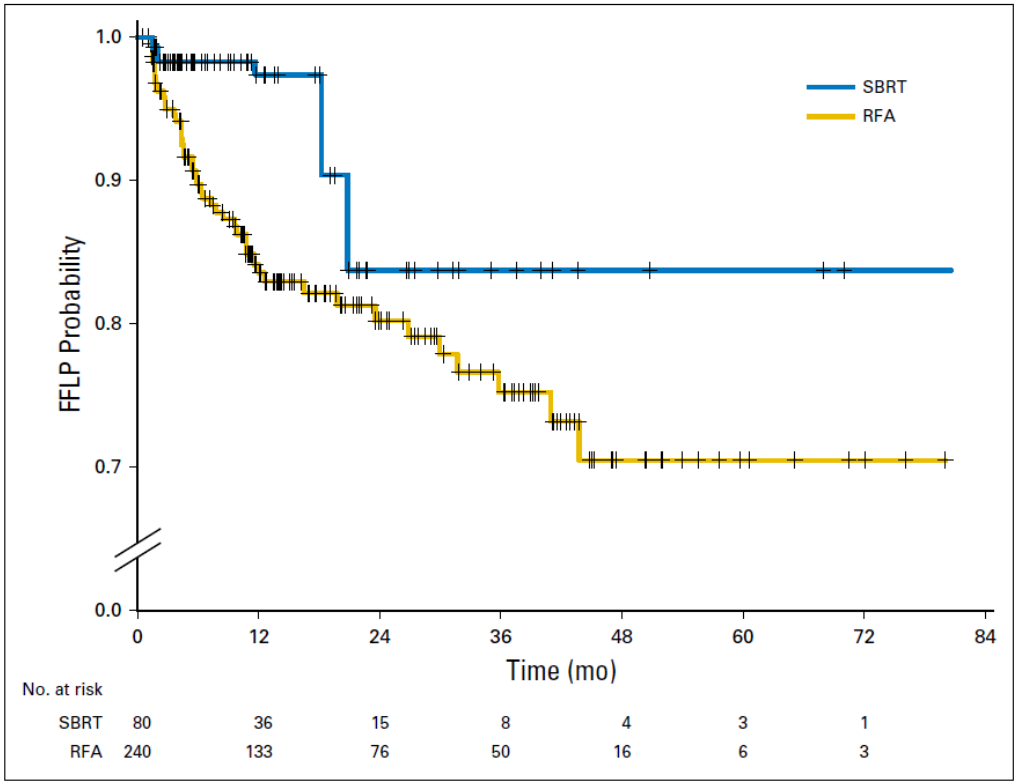
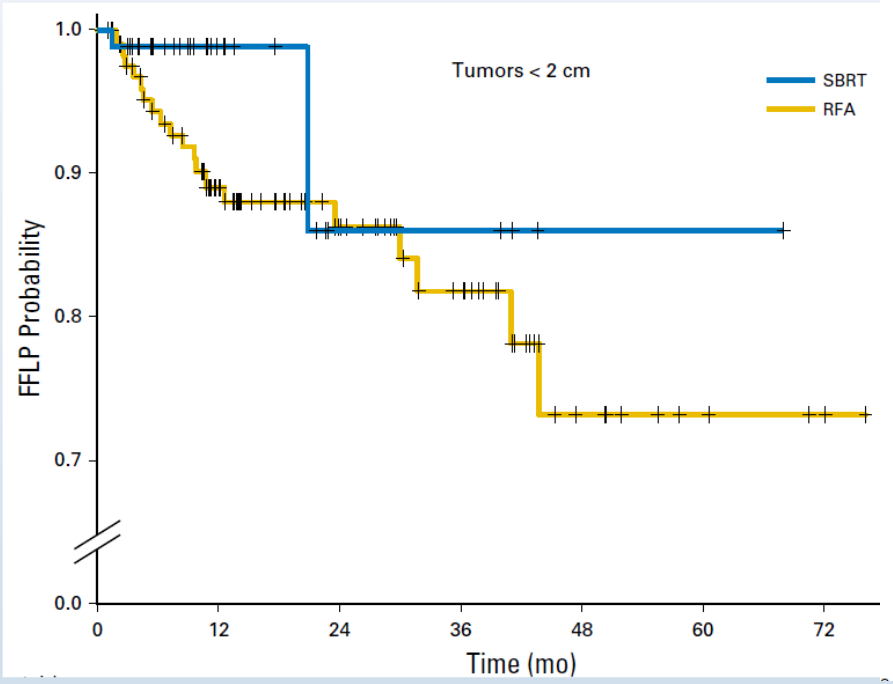
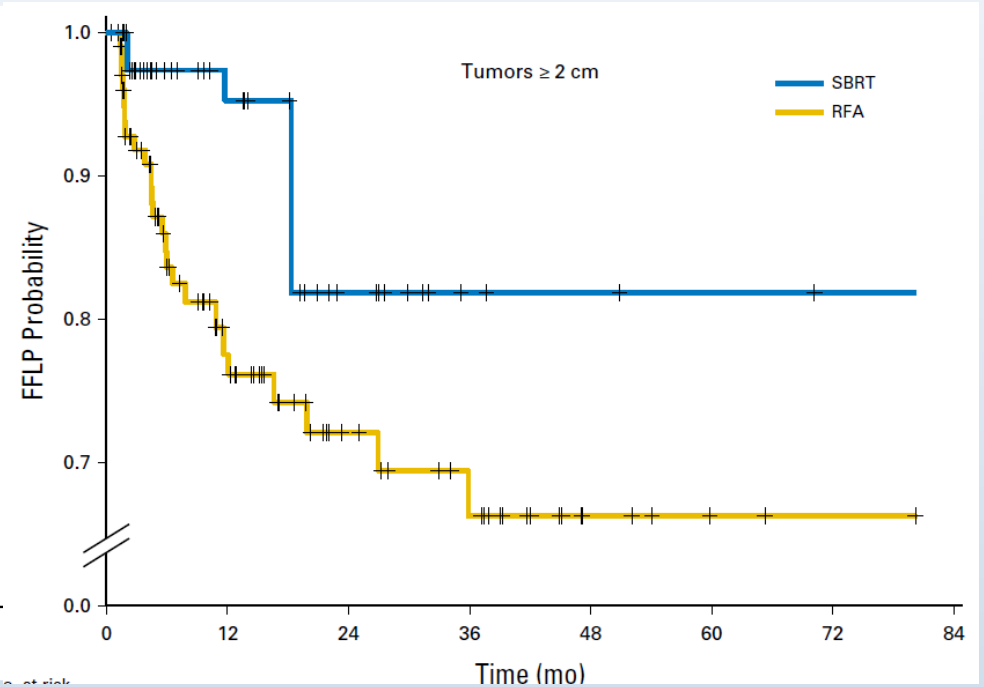


Fig 1. Freedom from local progression (FFLP) by treatment modality. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

SBRT vs RFA for HCC

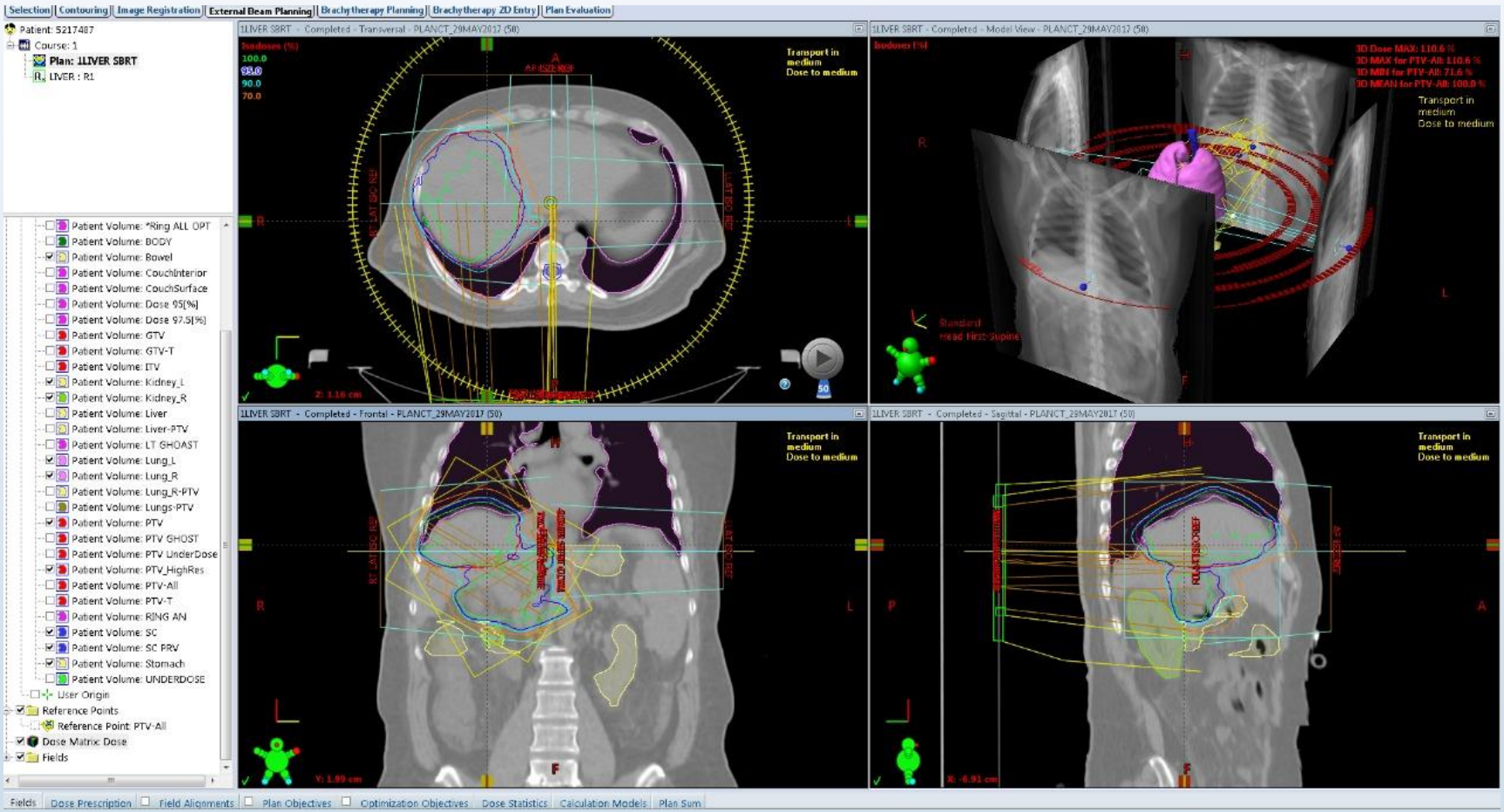





WHAT IS IT?
YOU SAID TO DO AN ABSTRACT
hildabastian.net


?
?


5217487
1
1LIVER SBRT
LIVER : R1
1LIVER SBRT - Completed - Transversal - PLANCT_29MAY2017 (50)
Dose
110.6
105.0 %
100.0 %
95.0 %
90.0 %
85.0 %
80.0 %
75.0 %
70.0 %
65.0 %
60.0 %
55.0 %
50.0
3D Dose MAX: 110.6 %
3D MAX for PTV-All: 110.6 %
3D MIN for PTV-All: 71.6 %
3D MEAN for PTV-All: 100.0 %
Transport in medium
Dose to medium
MR_5_13MAR2017
CT50
*PTV ALL OPT
*PTV LIVER OPT
*PTV T OPT
*RING
*Ring ALL OPT
BODY
Bowel
CouchInterior
CouchSurface
Dose 95[%]
Dose 97.5[%]
GTV
GTV-T
ITV
Kidney_L
Kidney_R
Liver
Liver-PTV
LT GHOAST
Lung_L
Lung_R
Lung_R-PTV
Lungs-PTV
PTV
PTV GHOST
PTV UnderDose
PTV_HighRes
PTV-All
PTV-T
RING AN
SC
SC PRV
Stomach
UNDERDOSE
Standard
Head First-Supine
Z: 1.50 cm


Selection
Contouring
Image Registration
External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
Patient: 5217487
Course: 1
Plan: 1LIVER SBRT
LIVER : R1
1LIVER SBRT - Completed - Transversal - PLANCT_29MAY2017 (50)
1LIVER SBRT - Completed - Model View - PLANCT_29MAY2017 (50)
1LIVER SBRT - Completed - Frontal - PLANCT_29MAY2017 (50)
1LIVER SBRT - Completed - Sagittal - PLANCT_29MAY2017 (50)
Isodoses (%)
100.0
95.0
90.0
70.0
Transport in medium
Dose to medium
3D Dose MAX: 110.6 %
3D MAX for PTV-All: 110.6 %
3D MIN for PTV-All: 71.6 %
3D MEAN for PTV-All: 100.0 %
Standard
Head First-Supine
Patient Volume: *Ring ALL OPT
Patient Volume: BODY
Patient Volume: Bowel
Patient Volume: CouchInterior
Patient Volume: CouchSurface
Patient Volume: Dose 95[%]
Patient Volume: Dose 97.5[%]
Patient Volume: GTV
Patient Volume: GTV-T
Patient Volume: ITV
Patient Volume: Kidney_L
Patient Volume: Kidney_R
Patient Volume: Liver
Patient Volume: Liver-PTV
Patient Volume: LT GHOAST
Patient Volume: Lung_L
Patient Volume: Lung_R
Patient Volume: Lung_R-PTV
Patient Volume: Lungs-PTV
Patient Volume: PTV
Patient Volume: PTV GHOST
Patient Volume: PTV UnderDose
Patient Volume: PTV_HighRes
Patient Volume: PTV-All
Patient Volume: PTV-T
Patient Volume: RING AN
Patient Volume: SC
Patient Volume: SC PRV
Patient Volume: Stomach
Patient Volume: UNDERDOSE
User Origin
Reference Points
Reference Point: PTV-All
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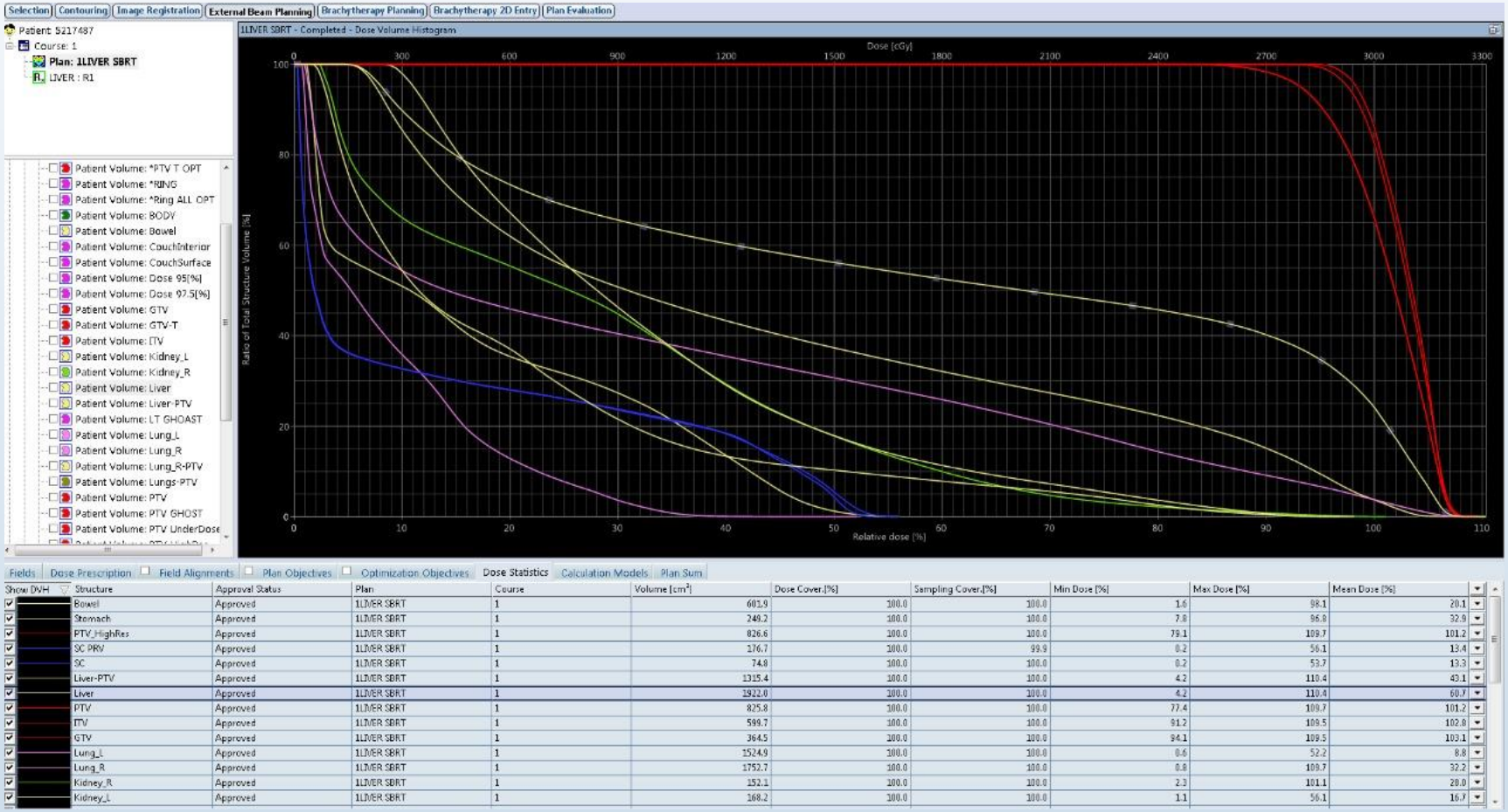
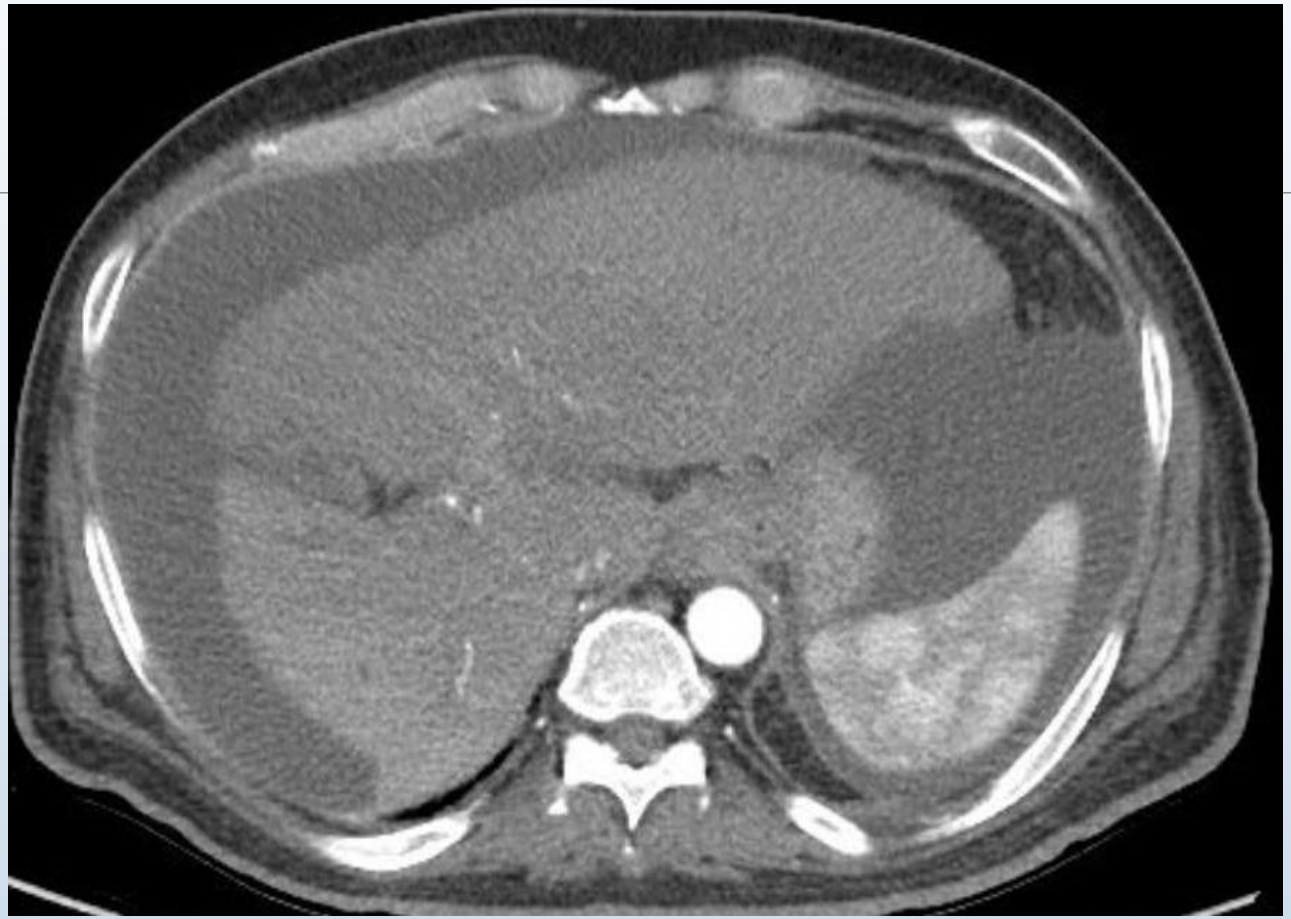
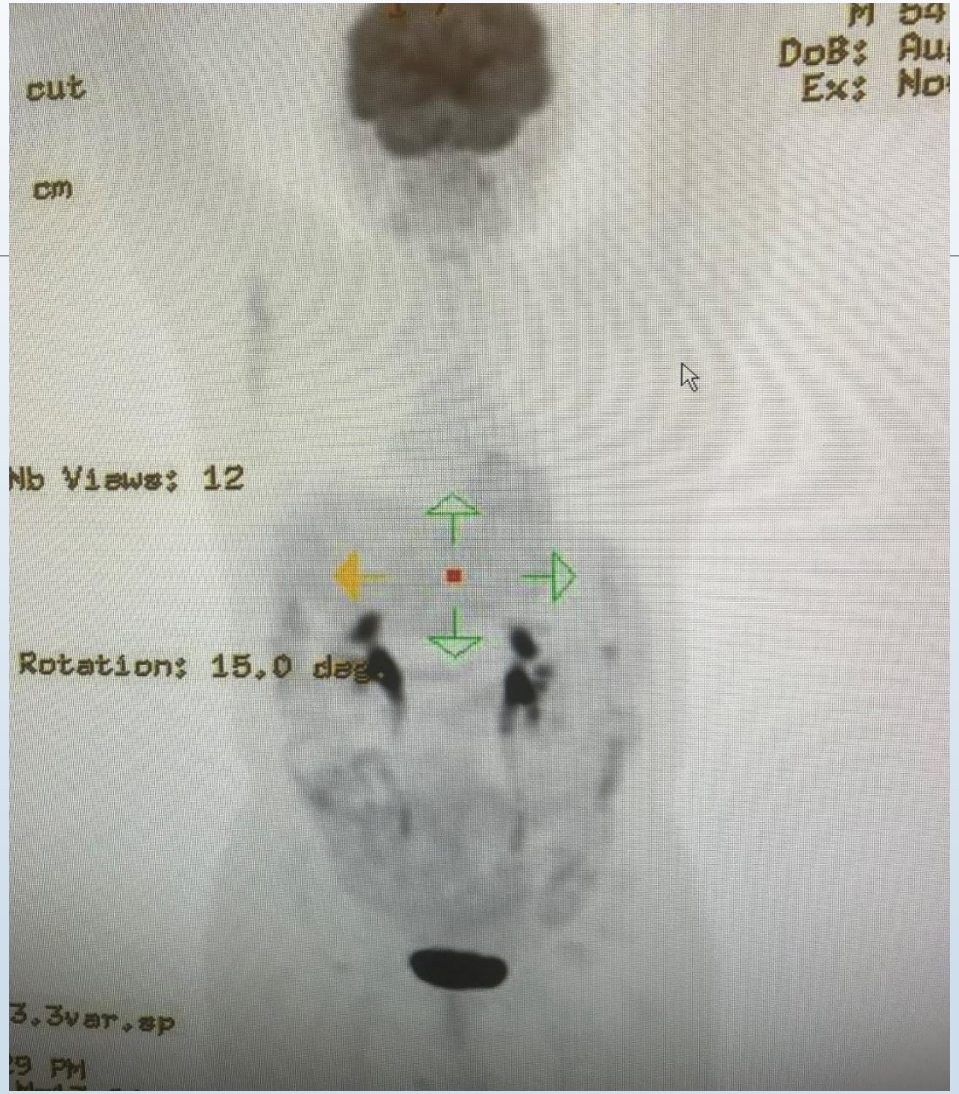
Dose Prescription
Field Alignments
Plan Objectives
Optimization Objectives
Dose Statistics
Calculation Models
Plan Sum



Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [%]	Max Dose [%]	Mean Dose [%]
☑	Bowel	Approved	1LIVER SBRT	1	601.9	100.0	100.0	1.6	98.1	20.1
☑	Stomach	Approved	1LIVER SBRT	1	249.2	100.0	100.0	7.8	96.8	32.9
☑	PTV_HighRes	Approved	1LIVER SBRT	1	826.6	100.0	100.0	79.1	109.7	101.2
☑	SC PRV	Approved	1LIVER SBRT	1	176.7	100.0	99.9	0.2	56.1	13.4
☑	SC	Approved	1LIVER SBRT	1	74.8	100.0	100.0	0.2	53.7	13.3
☑	Liver-PTV	Approved	1LIVER SBRT	1	1315.4	100.0	100.0	4.2	110.4	43.1
☑	Liver	Approved	1LIVER SBRT	1	1922.0	100.0	100.0	4.2	110.4	60.7
☑	PTV	Approved	1LIVER SBRT	1	825.8	100.0	100.0	77.4	109.7	101.2
☑	ITV	Approved	1LIVER SBRT	1	599.7	100.0	100.0	91.2	109.5	102.8
☑	GTV	Approved	1LIVER SBRT	1	364.5	100.0	100.0	94.1	109.5	103.1
☑	Lung_L	Approved	1LIVER SBRT	1	1524.9	100.0	100.0	0.6	52.2	8.8
☑	Lung_R	Approved	1LIVER SBRT	1	1752.7	100.0	100.0	0.8	109.7	32.2
☑	Kidney_R	Approved	1LIVER SBRT	1	152.1	100.0	100.0	2.3	101.1	28.0
☑	Kidney_L	Approved	1LIVER SBRT	1	168.2	100.0	100.0	1.1	56.1	16.7

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Radiotherapy and Oncology 145 (2020) 63–70

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

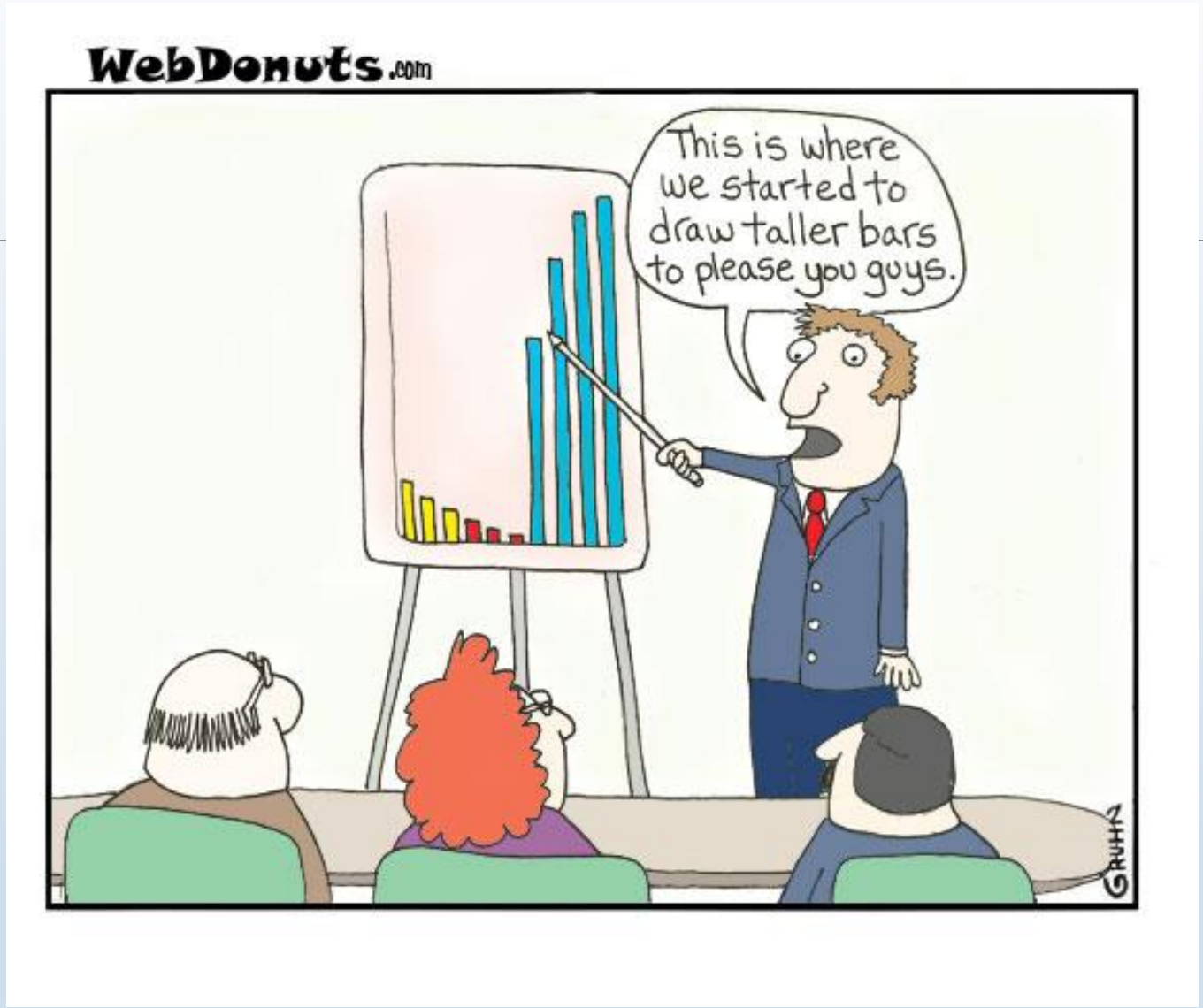
Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: Meta-analyses and a systematic review

Jeongshim Lee [a,b], In-Soo Shin [c], Won Sup Yoon [d], Woong Sub Koom [b], Chai Hong Rim [d,*]

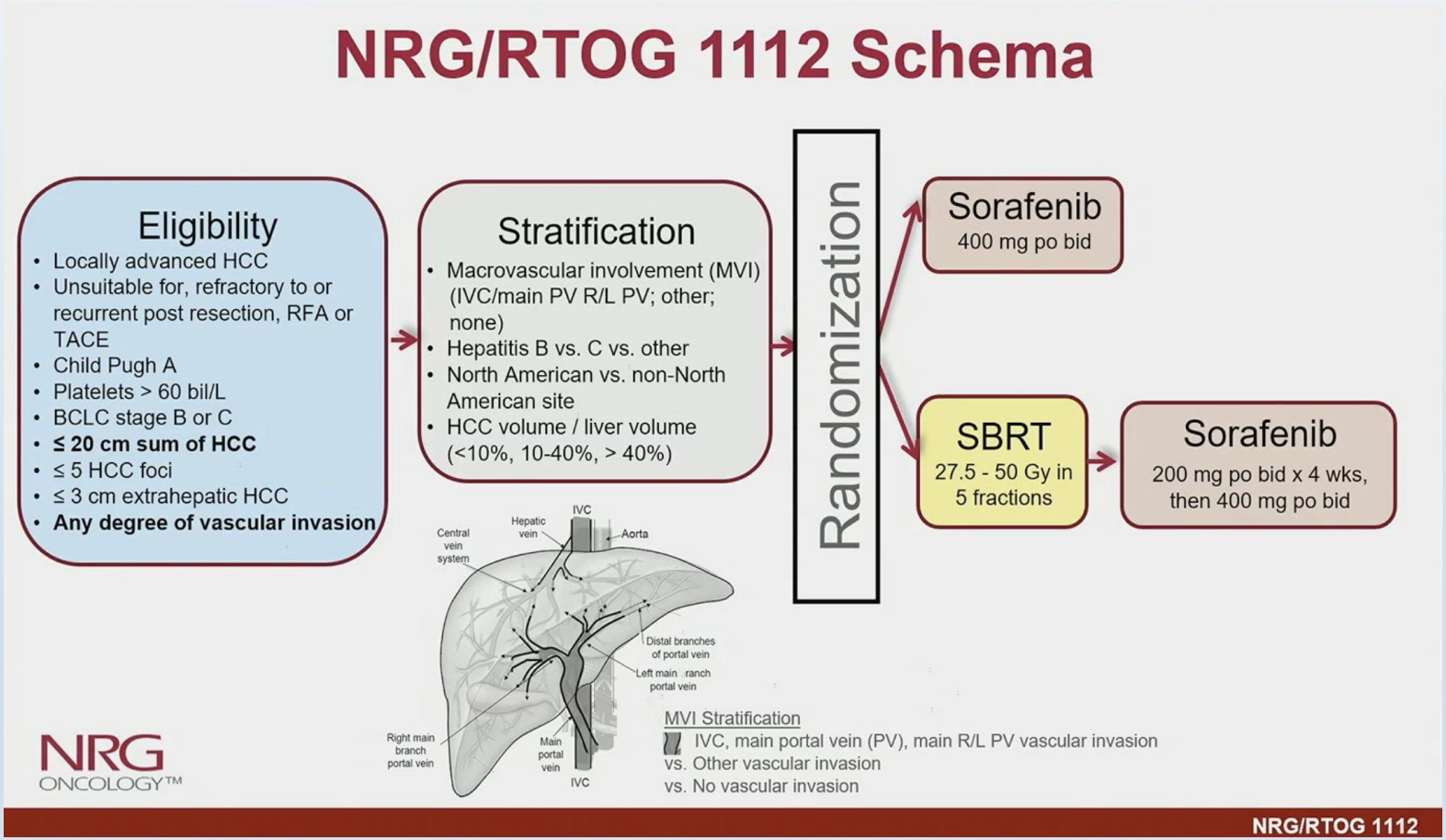
[a] Department of Radiation Oncology, Inha University Hospital, Inha University School of Medicine, Incheon; [b] Department of Radiation Oncology, Yonsei University College of Medicine, Seoul; [c] Department of Transdisciplinary Security, Dongguk University, Seoul; and [d] Department of Radiation Oncology, Ansan Hospital, Korea University Medical College, Ansan, Republic of Korea

Eleven studies involving 2238 patients were included

Pooled 2-year LC was higher with SBRT, including HCC and metastases studies. (83.8% vs. 71.8%, p =0.024).


WebDonuts.com
This is where we started to draw taller bars to please you guys.
GRUHN

NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937)



NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937)

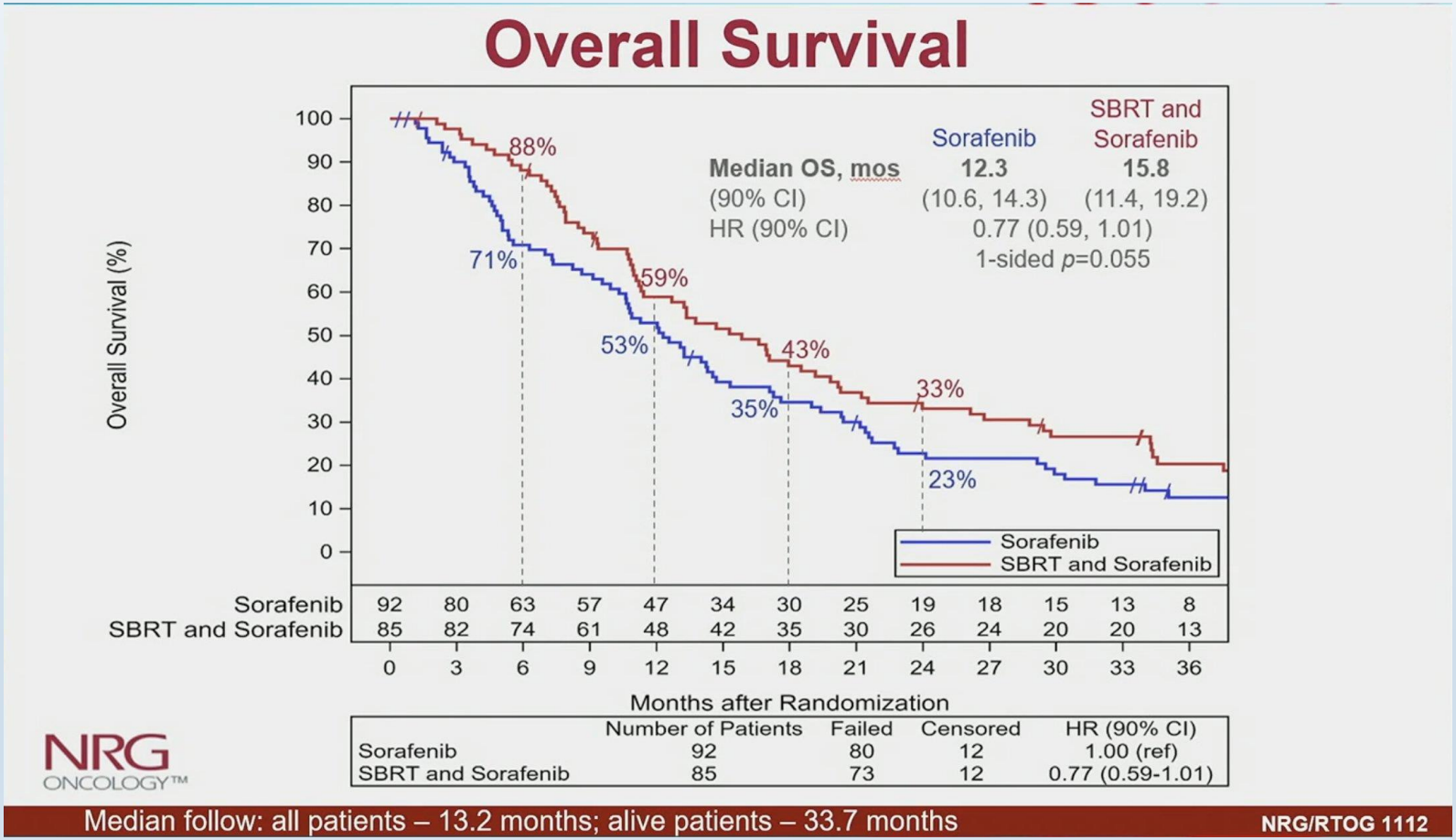
Of 193 patients accrued from April 2013 to March 2021 from 23 sites, 177 eligible patients were randomized to S (n=92) vs. SBRT/S (n=85).

Median age was 66 years (27-84); 41% had Hepatitis C and 19% had Hepatitis B or B/C.
The majority were stage BCLC C (82%),
with macrovascular invasion (74%).
4% had metastases.

Median follow-up for all and alive patients was 13.2 and 33.7 months, respectively.
With 153 OS events,

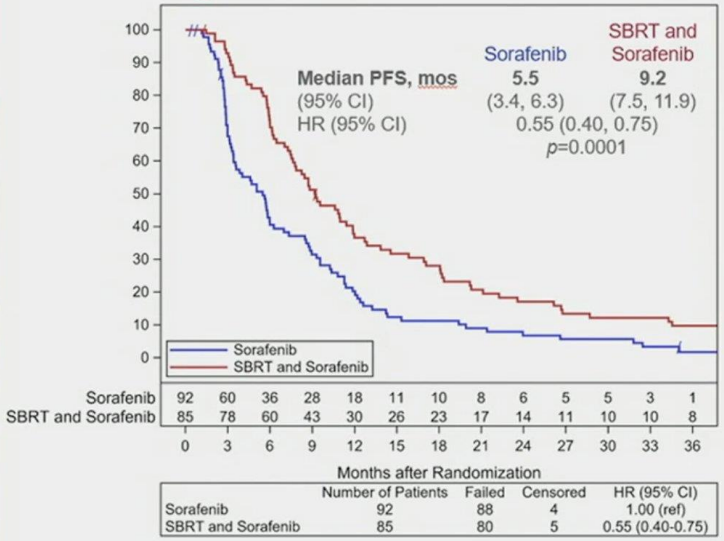
Treatment-related grade 3+ AEs were not significantly different (S - 42%, SBRT/S - 47%; p=0.52). There was one grade 5 treatment-related AE, in the S arm.

NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937)



NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937)

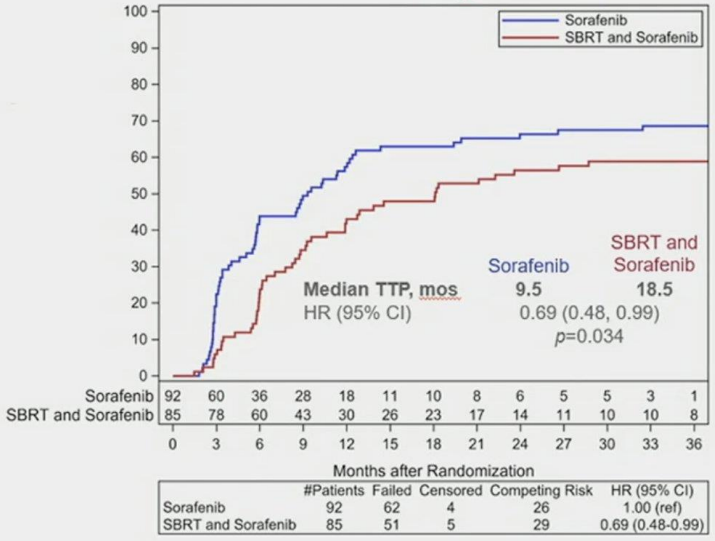
Progression-Free Survival



	Number of Patients	Failed	Censored	HR (95% CI)
Sorafenib	92	88	4	1.00 (ref)
SBRT and Sorafenib	85	80	5	0.55 (0.40-0.75)

Estimate (95% CI)	Sorafenib (n=92)	SBRT & Sorafenib (n=85)
6-month	41% (30%, 51%)	71% (62%, 81%)
12-month	20% (12%, 29%)	37% (26%, 43%)

Time to Progression



	#Patients	Failed	Censored	Competing Risk	HR (95% CI)
Sorafenib	92	62	4	26	1.00 (ref)
SBRT and Sorafenib	85	51	5	29	0.69 (0.48-0.99)

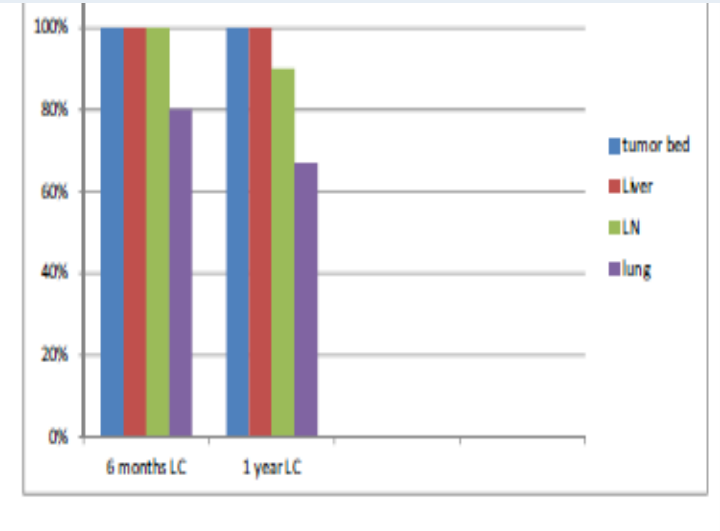
Estimate (95% CI)	Sorafenib (n=92)	SBRT & Sorafenib (n=85)
6-month	44% (33%, 54%)	23% (14%, 32%)
12-month	57% (46%, 67%)	43% (32%, 53%)

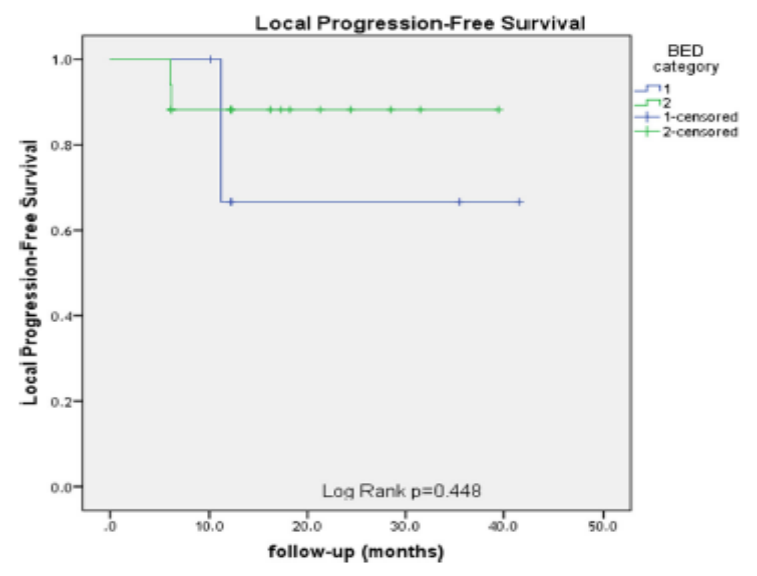
NRG ONCOLOGY™

TTP was estimated with cumulative incidence and arms compared using Gray's test

NRG/RTOG 1112

SBR for multiple sites





Alsuhaibani, A., et al. J Gastrointest Canc (2018).

Conclusion

•SBRT is applicable across BCLC stages (bridge to transplant, BCLC A, BCLC B, portal vein thrombosis) as an alternative treatment strategy to TACE/RFA, or in recurrent tumours as salvage therapy.

Treatment delivery is complicated and requires state-of-the-art treatment facilities

Take Home Message

SBRT has shown to be effective and safe in patients with HCC

SBRT local control rates :
91% (<5 cm tumors) and
74% (≥5 cm tumors) in a recent meta-analysis .

SBRT compensates for the limitations of RFA

phase III trials comparing SBRT with other modalities are ongoing


That's all Folks!