The Role of SBRT in the Management of HCC

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Disclosures

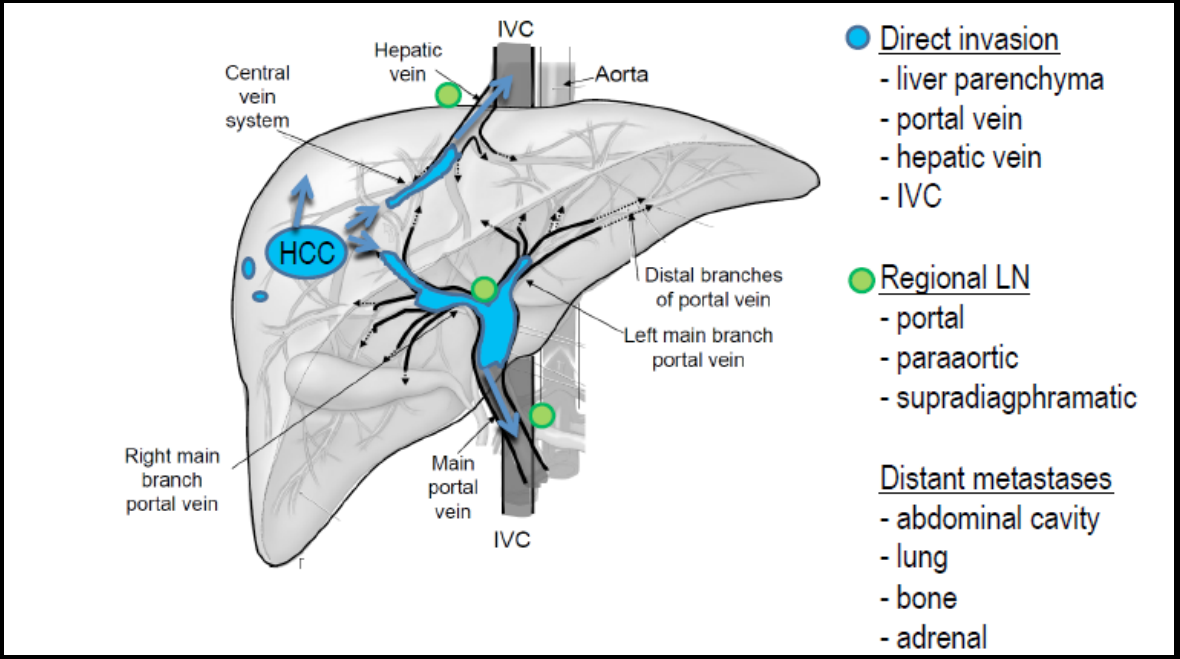
- Licensing agreement from Raysearch, paid to institution

- Advisory board: Merck ongoing
- Advisory board: SIRTEX 2016

- Research funding from Merck, paid to institution

HCC Patterns of Recurrence

- Most common recurrence pattern: hepatic / vascular
- Majority of patients die of hepatic HCC progression
  - Including patients with extrahepatic HCC[1]
  - Vascular invasion – a strong prognostic factor[2]
- Focal HCC, with or without vascular invasion, well suited for radiation therapy



1. Yoos JJ et al. PLoS One. 2014;9(11):e113926
2. Knox JJ et al. J Clin Oncol. 2015;3(16):1835–44

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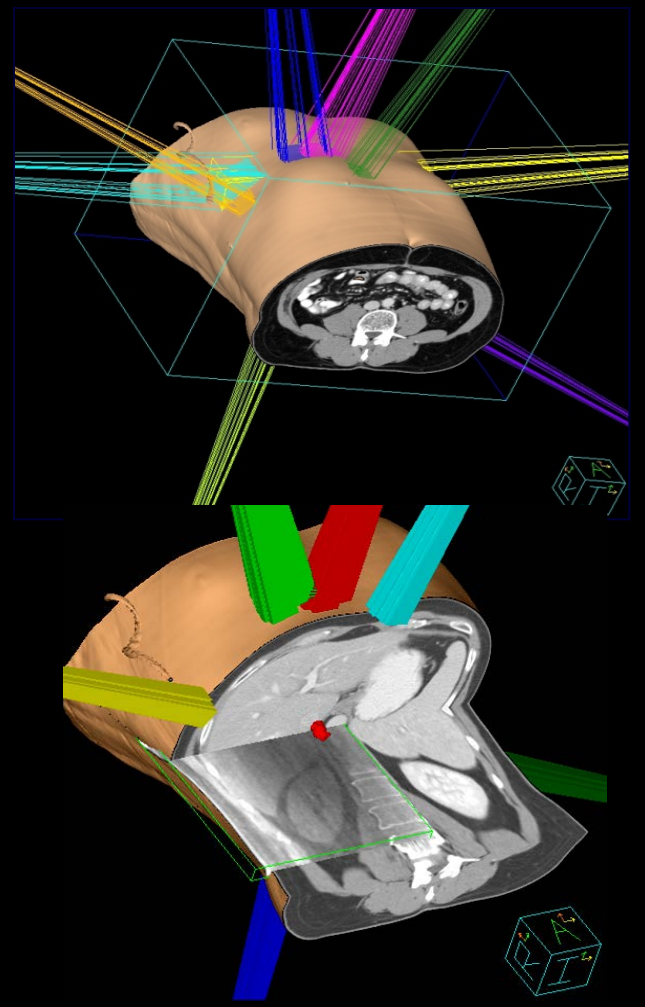
Stereotactic Body Radiotherapy, SBRT

- Very conformal dose distribution
- Highly potent doses
- High dose per fraction
- Motion management
- Image guidance (‘stereotactic’)
- Few number of fractions (~1-6)

  - Convenient, efficient, non-invasive
  - Widely available
  - SBRT techniques may be used for any fractionation



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Biologic Rationale for SBRT/Hypofractionation

- High dose/fraction specific effects
  - Preclinical data
  - Threshold ~ 5-8 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
* Finkelstein S, Timmerman R, et al. Clin Dev Immunol Nov 2011

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Korean HCC Guidelines

Topic	Recommendation
Transarterial chemoembolization and other transarterial treatments	1. TACE is recommended for patients with good performance status without major vascular invasion or extrahepatic spread who are ineligible for surgical resection, liver transplantation, RFA, or PEIT (A1). 2. TACE should be performed through tumor-feeding vessels using selective/superselective techniques to maximize antitumor activity and minimize hepatic damage (B1). 3. Chemoembolization using drug-eluting beads results in less systemic adverse events and has similar therapeutic efficacy compared with conventional TACE (B2). 4. In case of portal vein invasion, TACE can be considered for patients with localized tumor and well-preserved liver function (B2).
External-beam radiation therapy	1. EBRT can be performed in HCC patients if liver functions are Child-Pugh class A or superb B and the irradiated total liver volume receiving ≥ 30 Gy is ≤ 60% (B1). 2. EBRT can be considered for HCC patients ineligible for surgical resection, liver transplantation, RFA, PEIT, or TACE (C1). 3. EBRT can be considered for HCC patients who exhibit incomplete response to TACE when the dose-volume criteria in Recommendation 1 are met (B2). 4. EBRT can be considered for HCC patients with portal vein invasion when the dose-volume criteria in Recommendation 1 are met (C1). 5. EBRT is performed to alleviate symptoms caused by primary HCC or its metastases (B1).
Systemic therapies	1. Sorafenib is indicated for HCC patients with very well-preserved liver function (Child-Pugh class A), good performance status, and regional lymph node or extrahepatic spread or for patients with tumor progression on other therapies (A1). 2. Sorafenib is recommended for HCC patients with very well-preserved liver function (Child-Pugh class A), good performance status, and vascular invasion (A2). 3. Sorafenib is considered for HCC patients with liver function Child-Pugh class superb B and good performance status if the above conditions 1 and 2 are satisfied (B1). 4. Cytotoxic chemotherapy can be considered for HCC patients with advanced tumors who have with well-preserved liver function and, with good performance status, in whom sorafenib therapy has failed (C1). 5. Adjuvant TACE, sorafenib, or cytotoxic chemotherapy are not recommended for HCC patients treated with curative resection (B1).

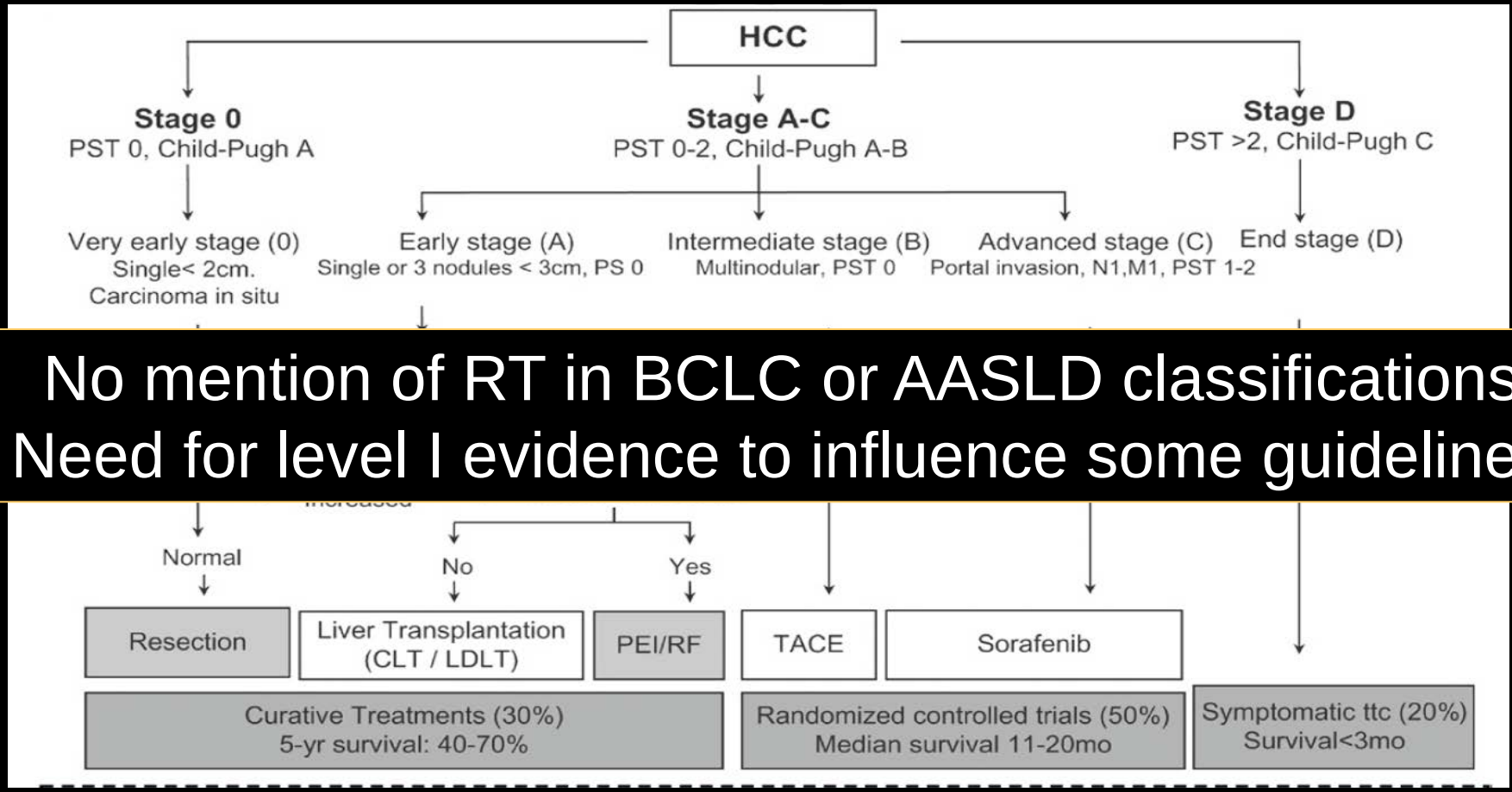
mUICC stage	Best option	Alternative option
I	Resection RFA	TACE PEIT EBRT
Single/≤ 2 cm/VI-		
II	Resection RFA (tumor size ≤ 3 cm)	TACE LT EBRT
Single/> 2 cm/VI-		
II	DDLT (within Milan criteria) TACE RFA (tumor number ≤ 3)	Resection LDLT PEIT (tumor number ≤ 3)
Multiple/≤ 2 cm/VI-		
II	TACE EBRT Sorafenib	Resection
Single/≤ 2 cm/VI+		
III	TACE LT (within Milan criteria) RFA (tumor number ≤ 3 and size ≤ 3 cm)	Resection
Multiple/> 2 cm/VI-		
III	TACE EBRT Sorafenib	Resection
Single/> 2 cm/VI+		
III	TACE Sorafenib	
Multiple/≤ 2 cm/VI+		
IVa	Sorafenib	TACE
Multiple/> 2 cm/VI+		
IVa	Sorafenib	EBRT TACE
Node+/no metastasis		
IVb	Sorafenib	TACE EBRT
Metastasis+		

KJR, KLCSG MCC Practice Guidelines, 2015

National Comprehensive Cancer Network (NCCN)

- Hepatocellular Carcinoma (OAO-B 17 of 32)
  - Stereotactic Body Radiation Therapy (SBRT)/Stereotactic Ablative Radiotherapy (SABR) should be considered for older patients, particularly those with comorbidities or compromised performance status, who may not be suitable for liver resection or transplantation. Because it is noninvasive, the successful completion rate of SBRT/SABR is high. Toxicity to treatment can be minimized by careful patient selection, appropriate radiation dosing, and optimized dosimetry to meet normal tissue constraints. Ideal patients are those with good liver function (Child Pugh Class A) and limited volume of disease.

HCC BCLC: Where RT Fits



No mention of RT in BCLC or AASLD classifications.
Need for level I evidence to influence some guidelines.

J Bruix & M Sherman

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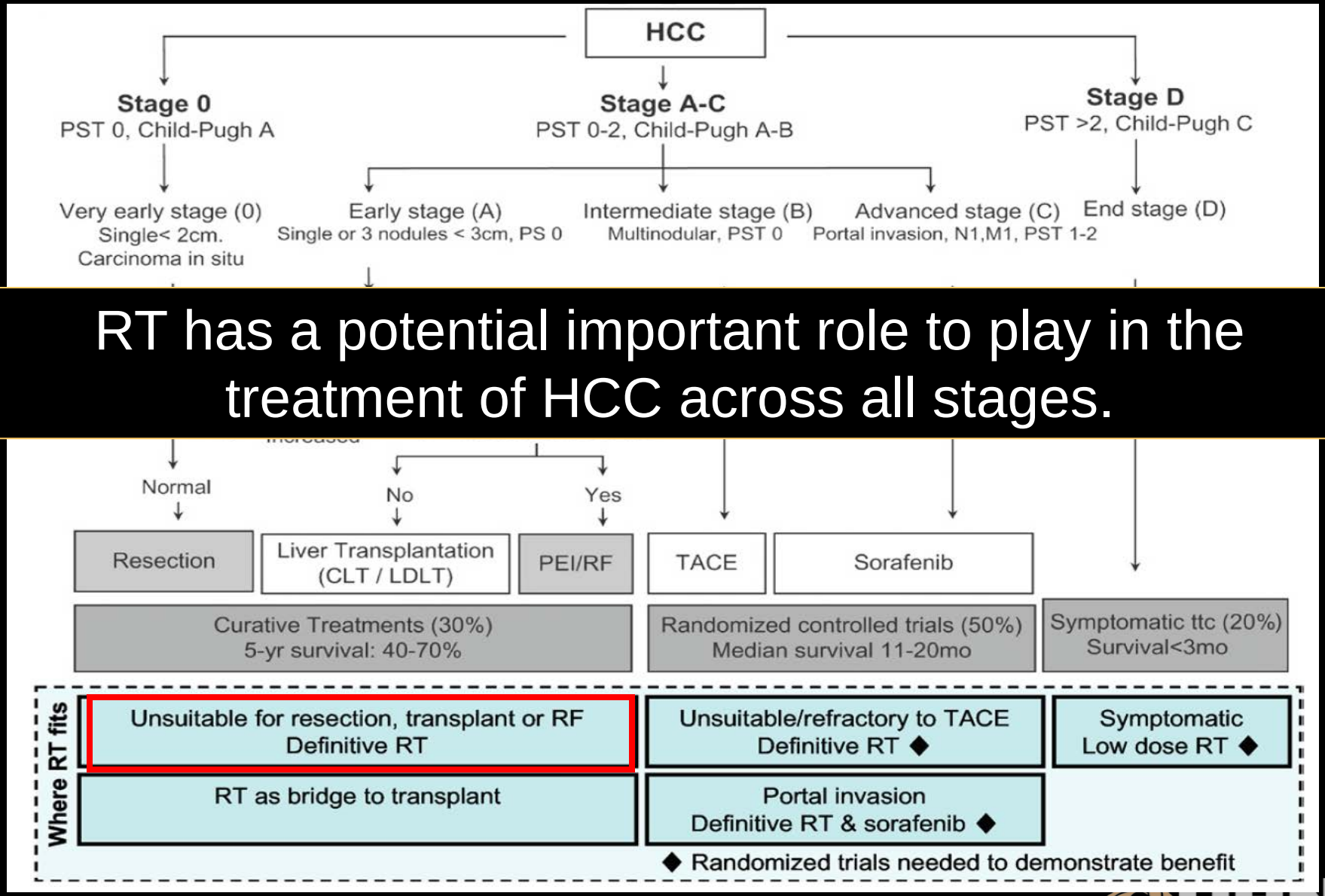
HCC BCLC: Where RT Fits



RT has a potential important role to play in the treatment of HCC across all stages.

Dawson LA et al. Semin Radiat Oncol. 2011;21:241

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Early stage HCC, unsuitable for standard curative therapies

- 78 year old lady with single HCC, Hep C
- Laparotomy
  - Resection aborted due to cirrhosis
  - Decompensation post-op
- 8 weeks post op
  - Improving, but not at baseline
  - PS 2, Child Pugh B8
  - Growing HCC (4.8 cm)

Barry, Wei, Knox, Dawson, JCO Grand Rounds, Jan 2016

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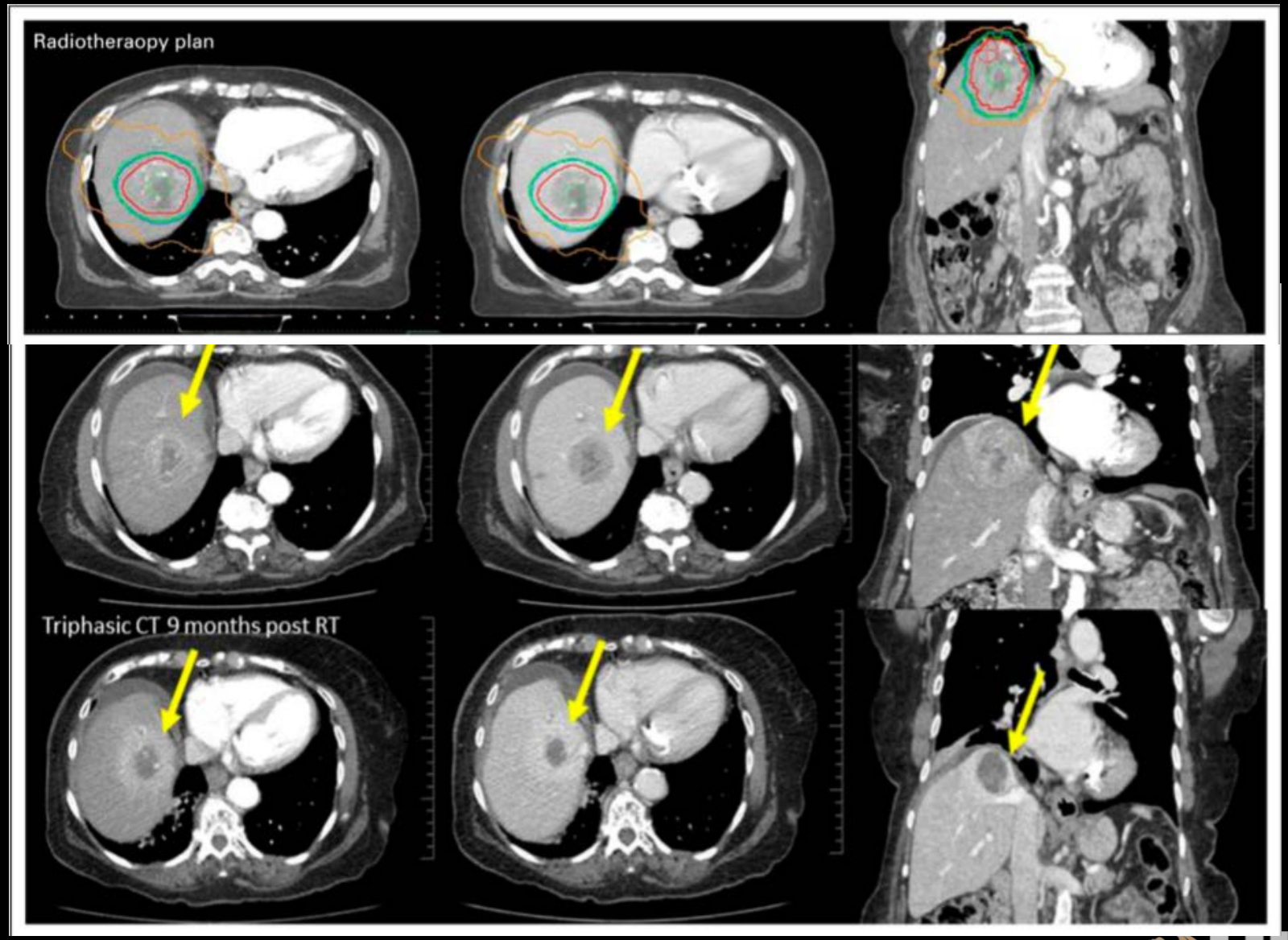
SBRT 45 Gy in 5 #: no progression at month 24



Barry, Wei, Knox, Dawson, JCO Grand Rounds, Jan 2016

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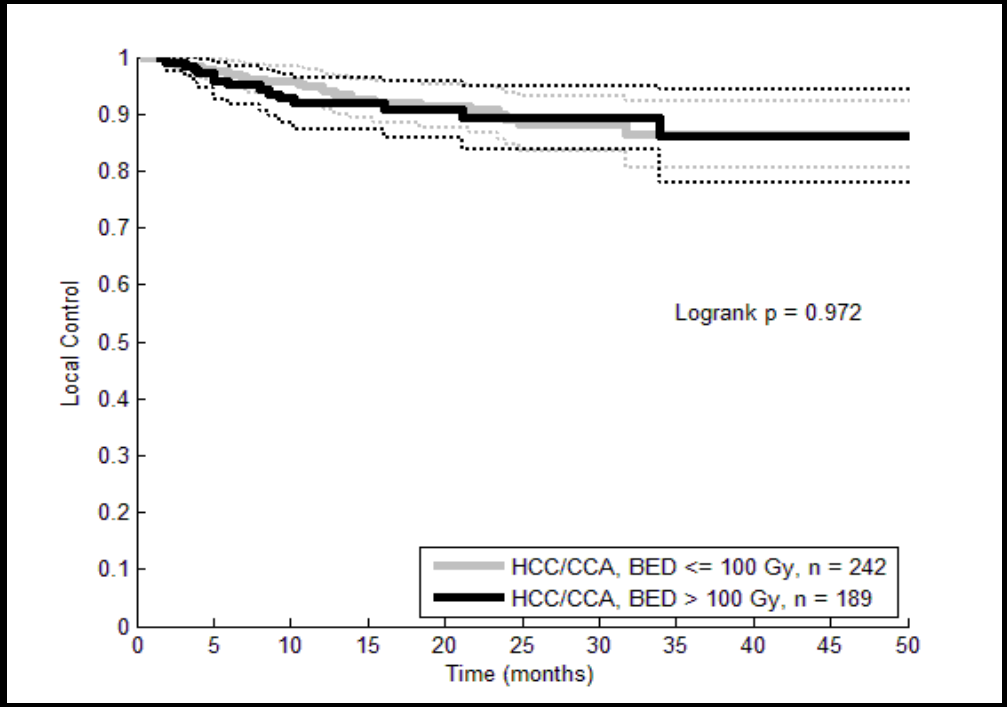
HCC is a RT sensitive tumor

- No dose response for HCC (33-54Gy in 3-5#)
- 3 year local control 86%



- Pooled analysis from 5 trials
- n = 431

AAPM Consensus TCP project, Ohir, Dawson, Tome

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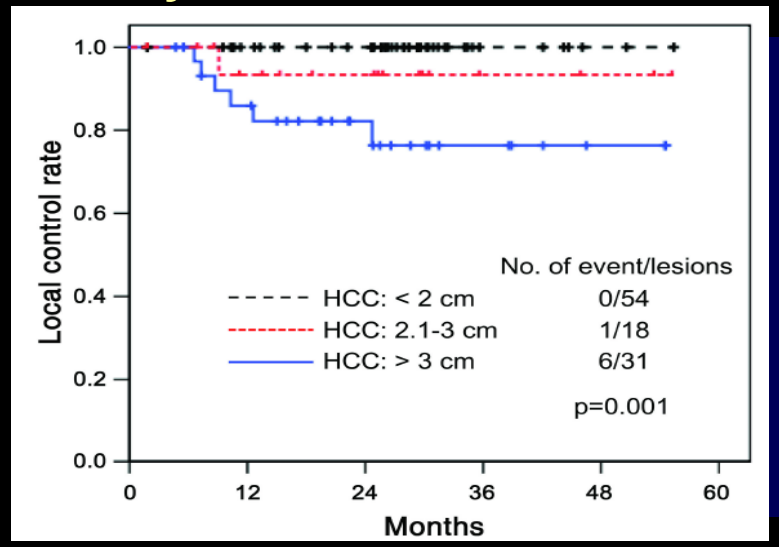
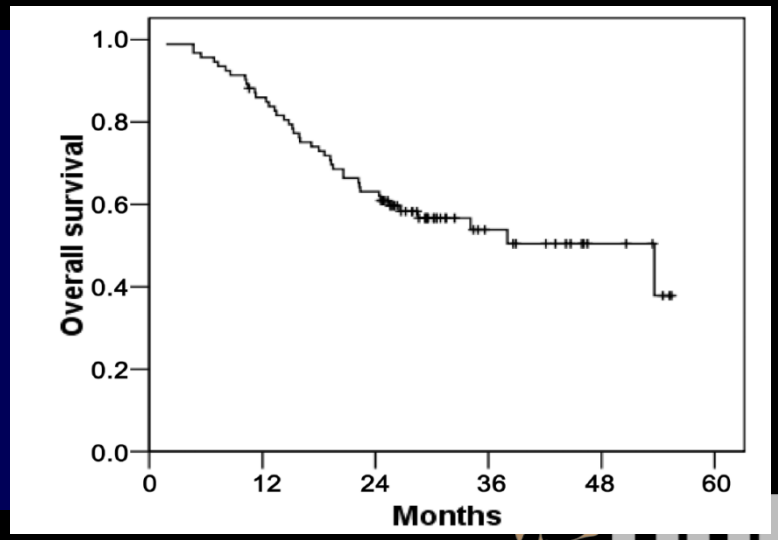
SBRT: Korean Registry

- N=93 HCC patients (26% CP B)
  - All refractory or unsuitable for TACE
- Dose: 30 - 40 Gy in 3- 4#
  - Size: median 2 cm (1-6 cm)
  - Improved local control for smaller tumors (100% < 2cm, 93% 2-3cm, 76% 3-6)
- Toxicity: Decline in CP score in 9.7% (gr 5, n=1 CP B pt)

3 yr local control 92%



3 yr survival 54%



Yoon, PLOS 2013

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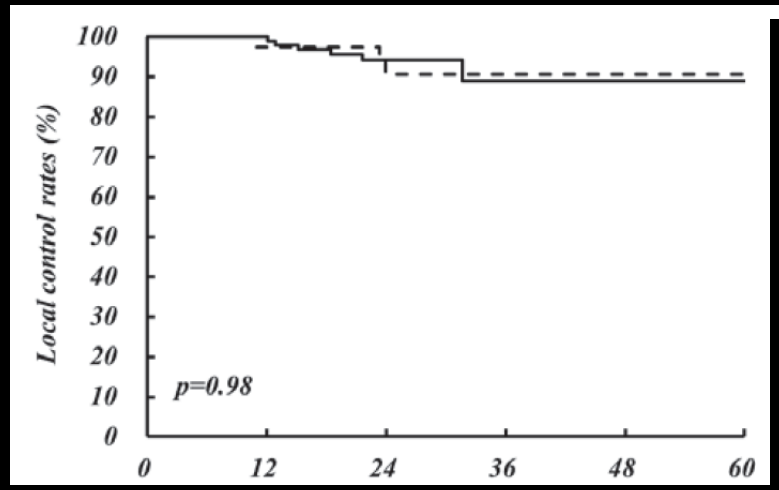
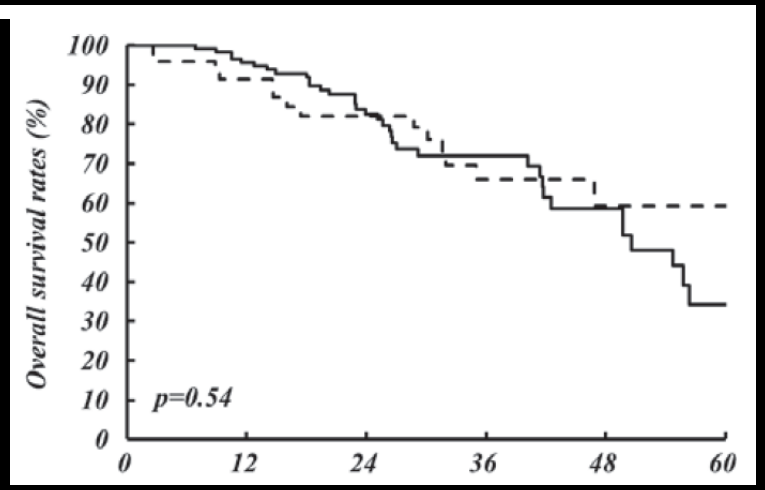
Japanese Retrospective Series-HCC SBRT

- N=221 (~84% T1) HCC patients (CP A:B=178:27)
  - 56–61% received TACE < 3 months prior to SBRT
- Dose: 40 Gy in 5#
  - 35 Gy: for CP B, and so < 20% liver ≥20Gy, n=48
  - Size: median 2.7 cm (35 Gy), 2.4 cm (40 Gy), max 5.0 cm
  - No sign. differences in outcomes for 35 vs 40 Gy
- Toxicity: Decline in CP score ~10% (gr 5, n=2 CP B pts)

3 yr local control 91% 3 yr survival 70%





Sanuki N et al. Acta Oncol. 2014;53(3):399–404

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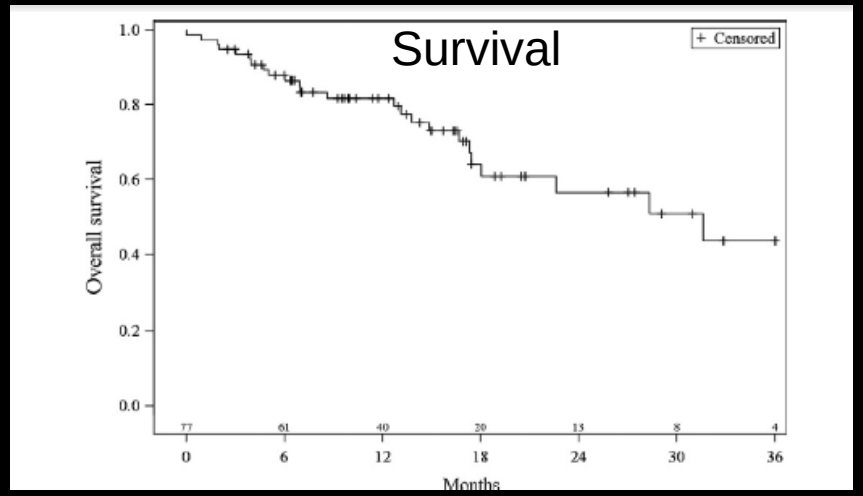
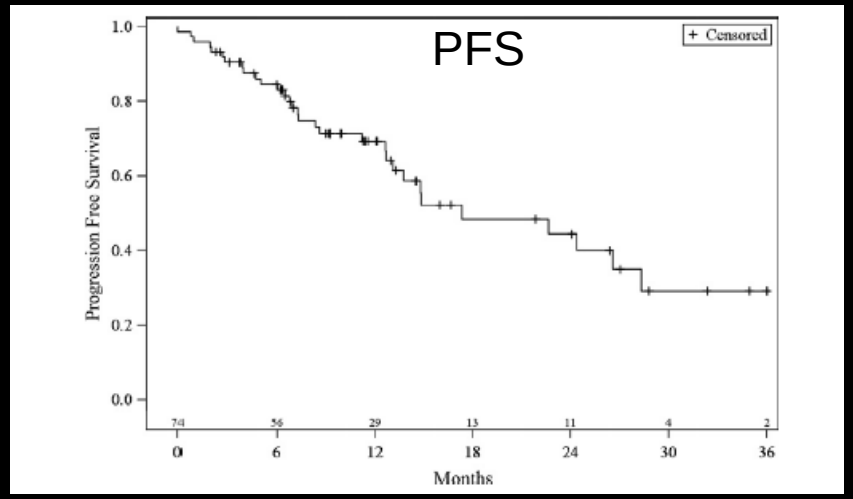
French Study: HCC SBRT

- N=77 (median size 2.4 cm)
- SBRT: 45 in 3 fractions
- Local control: 1 and 2 years 99%
- Survival: 1 and 2 years: 82% and 56%
  - CP B worse survival
- 8% with liver toxicity < 6 months





Huertas A et al. Radiother Oncol. 2015;115(2):211–6

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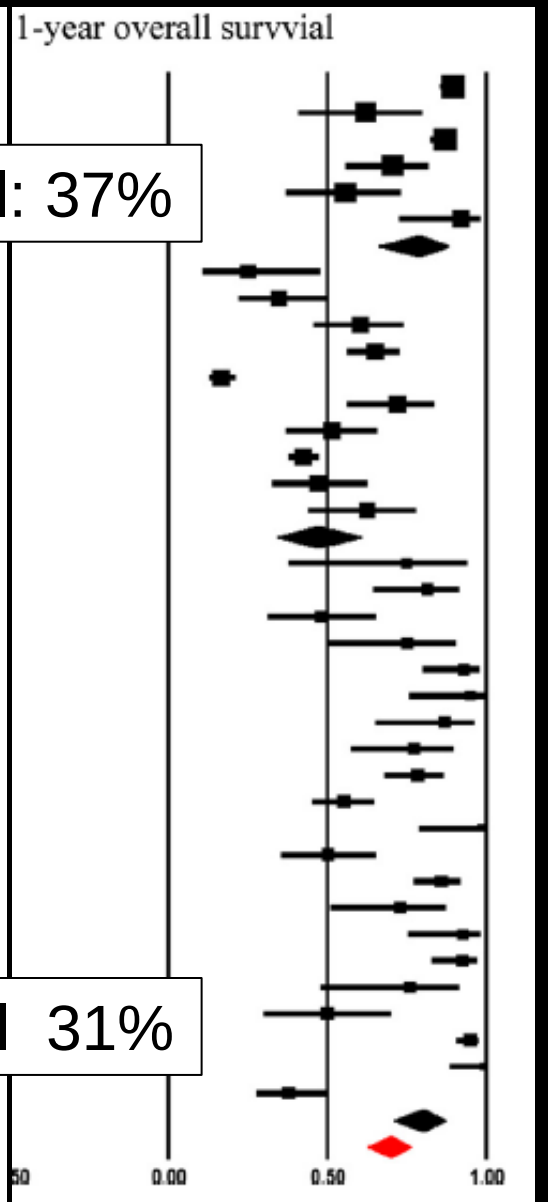
Meta-analysis (5204 patients)
1 Year Survival

		Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total
Nakayama/2009	CPT	0.895	0.856	0.924	11.714	0.000	285 / 318
Sugahara et al/2010	CPT	0.620	0.408	0.794	1.115	0.265	14 / 22
Mizumoto et al/2011	CPT	0.870	0.824	0.905	10.427	0.000	231 / 266
Nakayama et al/2							
Lee et al/2014							
Kato et al/2004							
	CPT	0.790	0.661	0.879	3.945	0.000	600 / 704
Ishikura et al/2001	CRT	0.250	0.108	0.478	-2.127	0.033	5 / 20
Zeng et al/2003	CRT	0.348	0.223	0.498	-1.984	0.047	15 / 44
Liu et al/2004	CRT	0.605	0.456	0.737	1.382	0.167	27 / 44
Liang et al/2005	CRT	0.650	0.564	0.728	3.341	0.001	83 / 128
Huang et al/2009	CRT	0.167	0.130	0.211	-10.822	0.000	54 / 326
Oh et al/2010	CRT	0.720	0.563	0.837	2.682	0.007	29 / 40
Rim et al/2012	CRT	0.515	0.372	0.656	0.201	0.841	23 / 45
Yoon et al/2012	CRT	0.425	0.378	0.473	-3.033	0.002	175 / 412
Fujino et al/2014	CRT	0.472	0.326	0.623	-0.358	0.720	19 / 41
Lu et al/2014	CRT	0.624	0.442	0.776	1.344	0.179	19 / 30
	CRT	0.470	0.340	0.604	-0.432	0.666	450 / 1130
Mendez Romero et al 2006	SBRT	0.750	0.377	0.937	1.346	0.178	6 / 8
Choi et al/2008	SBRT	0.814	0.642	0.914	3.249	0.001	26 / 32
Tse et al/2008	SBRT	0.480	0.313	0.651	-0.223	0.824	15 / 31
Cardenes et al/2010	SBRT	0.750	0.500	0.900	1.961	0.050	13 / 17
Kwon et al/2010	SBRT	0.929	0.801	0.977	4.280	0.000	39 / 42
Louis et al/2010	SBRT	0.950	0.759	0.991	3.209	0.001	24 / 25
Ibarra et al/2012	SBRT	0.870	0.652	0.960	2.930	0.003	18 / 21
Price et al/2012	SBRT	0.770	0.573	0.893	2.593	0.010	20 / 26
Bibault et al/2013	SBRT	0.785	0.678	0.864	4.608	0.000	59 / 75
Bujold et al.2013	SBRT	0.550	0.453	0.644	1.008	0.313	56 / 102
Honda et al/2013	SBRT	0.984	0.789	0.999	2.883	0.004	30 / 30
Xi et al /2013	SBRT	0.503	0.354	0.651	0.038	0.969	21 / 41
Yoon et al/2013	SBRT	0.860	0.774	0.917	6.074	0.000	80 / 93
Yuan et al/2013	SBRT	0.727	0.510	0.872	2.047	0.041	16 / 22
Honda et al 2014	SBRT	0.926	0.752	0.981	3.500	0.000	26 / 28
Kimura et al/2014	SBRT	0.923	0.828	0.968	5.339	0.000	60 / 65
Lo et al/2014	SBRT						
Que et al /2014	SBRT						
Sanuki et al/2014	SBRT						
Takeda et al 2014	SBRT						
Zhong et al/2014	SBRT	0.380	0.276	0.497	-2.016	0.044	27 / 72
	SBRT	0.802	0.706	0.872	5.259	0.000	796 / 1014
	Overal	0.697	0.624	0.761	4.995	0.000	1846 / 2848



Particle RT 5 year survival: 37%

SBRT 5 year survival 31%

Qi WX et al. Radiother Oncol. 2015;114(3):289–95

Meta-analysis (5204 patients)
≥ Grade 3 Toxicity

	Included study	Events	Total	Events rate (95%CI)	I^2	*p*
Acute toxicity						
Hepatic						
CPT	14	21	830	3.1% (1.3–7.6%)	73.8	–
SBRT	19	59	1164	4.9% (3.0–8.1%)	66.8	0.19
CRT	10	111	995	9.9% (6.0–16%)	75.1	0.014
Bone marrow						
CPT	14	40	805	5.1% (1.9–12.7%)	84.3	–
SBRT	11	23	644	4.9% (3.4–7.2%)	0	0.47
CRT	12	26	1015	6.1% (4.3–8.8%)	63.5	0.36
Overall						
CPT	16	68	1172	6.1% (2.8–12.6%)	83.8	–
SBRT	21	137	1221	9.6% (6.0–15.1%)	81.3	0.16
CRT	13	172	1023	20% (13.2–29.2%)	82.8	0.003
Late toxicity						
CPT	7	6	342	2.5% (1.3–4.9%)	0	–
SBRT	6	17	387	6.4% (4.0–10.1%)	50.6	0.011
CRT	5	11	293	6.9% (3.9–1.2%)	75.4	0.011

Qi WX et al. Radiother Oncol. 2015;114(3):289–95

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HCC: SBRT vs RFA

- 2004–2012: 224 patients with unresectable HCC treated with RFA or SBRT
  - 161 treated with RFA to 249 tumors
  - 63 treated with SBRT to 83 tumors

- Similar patients and outcomes

	RFA	SBRT
Failure from local progression (FFLP) 1 yr	84%	97%
FFLP 2 yr	80%	84%
Overall survival 1 yr	70%	74%
Gr 3+ toxicity	11%	5%

Wahl DR et al. J Clin Oncol. 2016;34(5):452–9

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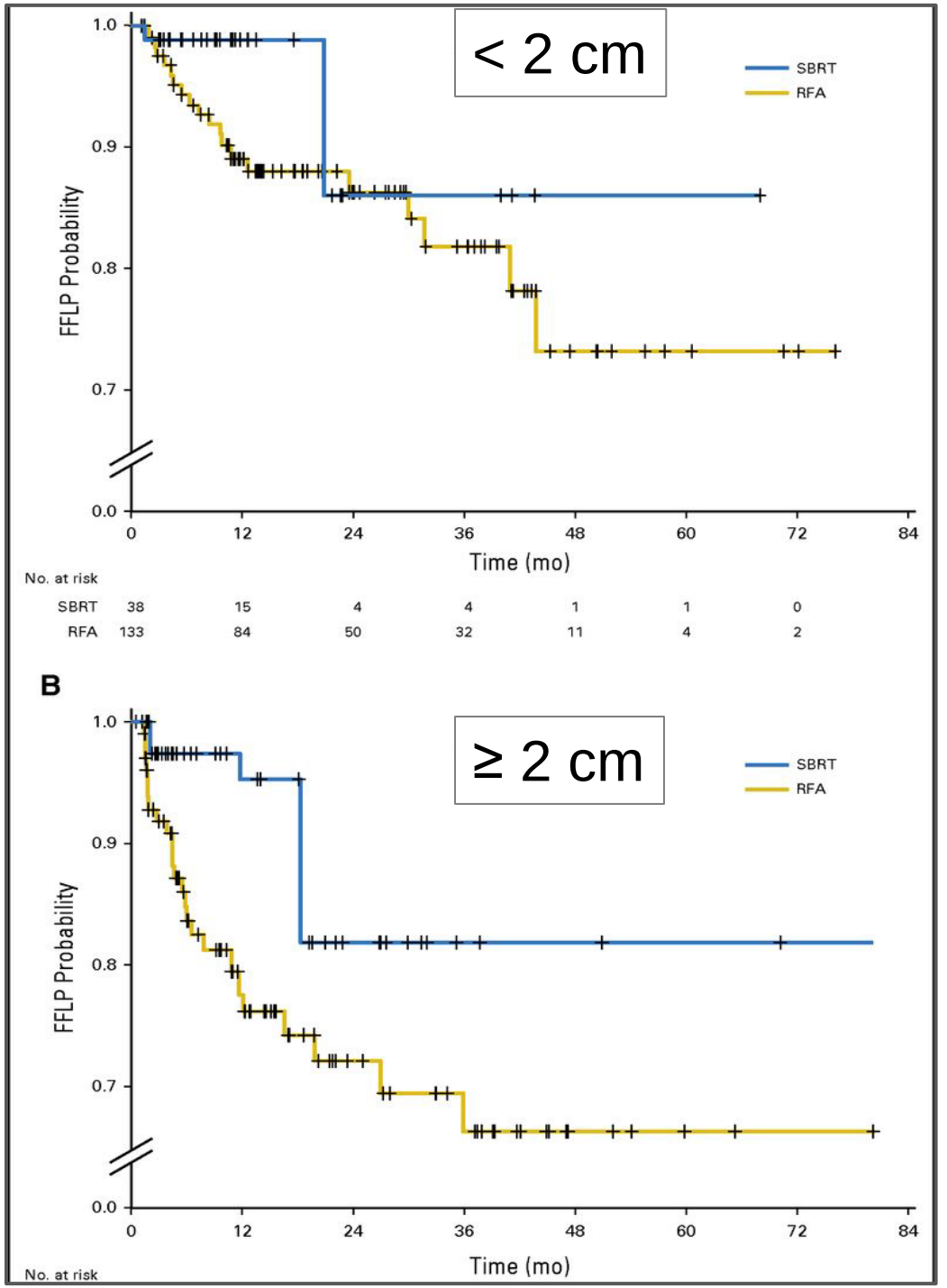
- Larger tumors less likely to be controlled by RFA
- No size dependency for SBRT

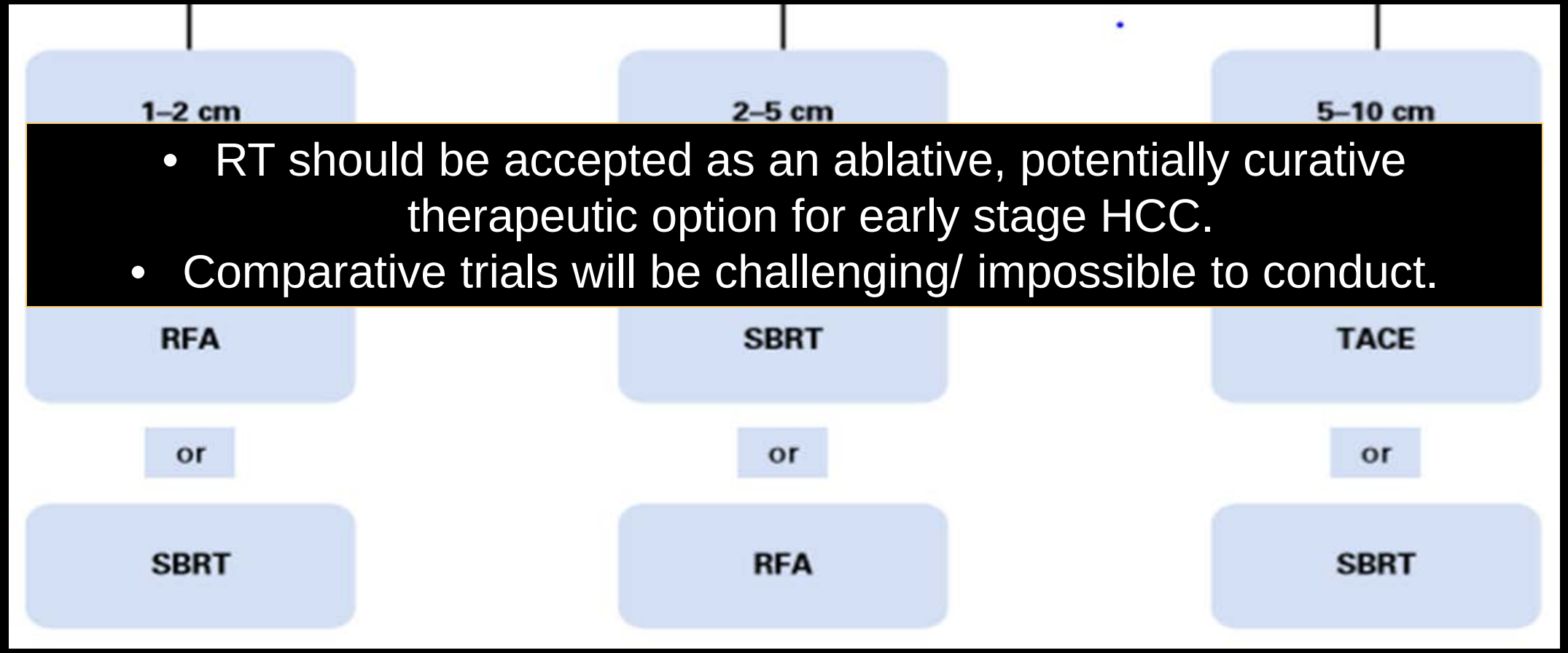


JOURNAL OF CLINICAL ONCOLOGY ASCO

Daniel R. Wahl et al. JCO doi:10.1200/JCO.2015.61.4925

SBRT is an effective therapeutic option for early stage HCC, unsuitable for resection or transplant

Proposed treatment algorithm for unresectable HCC



- RT should be accepted as an ablative, potentially curative therapeutic option for early stage HCC.
- Comparative trials will be challenging/ impossible to conduct.

Barry A et al. J Clin Oncol. 2016;34(5):404–8

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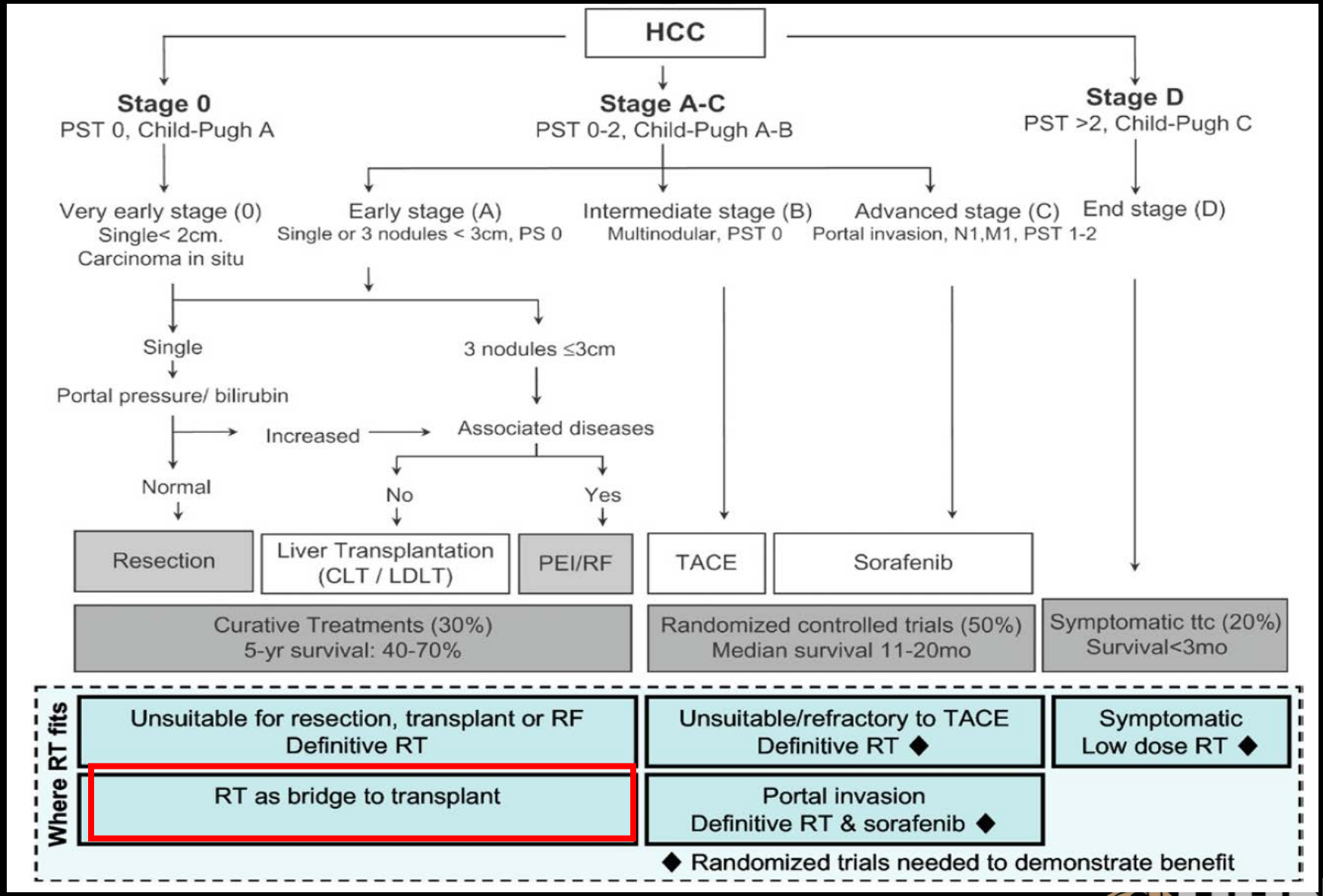
HCC BCLC: Where RT fits



Dawson LA et al. Semin Radiat Oncol. 2011;21:241

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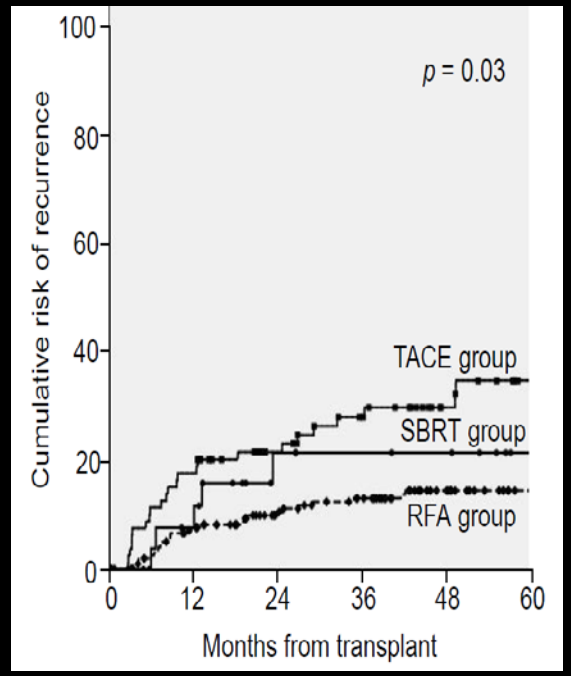
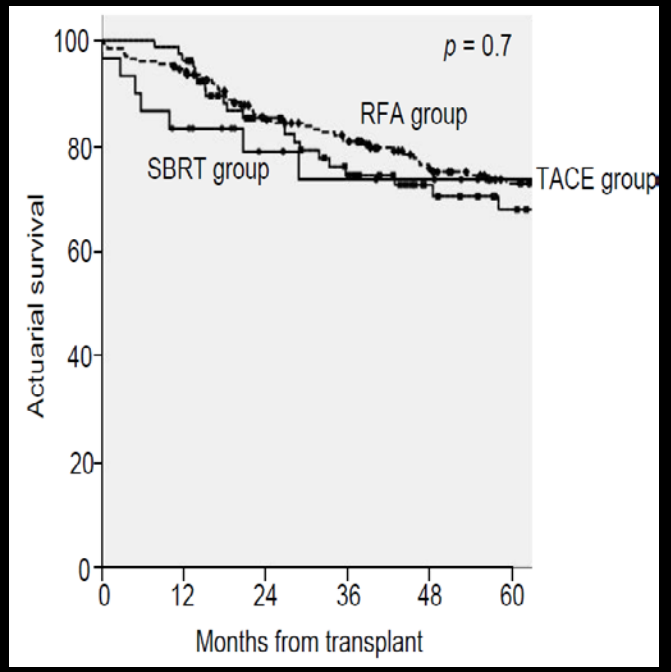
SBRT vs TACE & RFA: Bridge to Transplant

- Over 2007 – 2014, 406 / 594 (68%) HCC transplant patients received bridging therapies
  - RFA 60% , 88% within Milan
  - TACE 24% , 24% within Milan
  - SBRT 9% (if unsuitable for RFA or TACE) , 36% within Milan
    - 36 Gy in 6 fractions (quartile range 30 - 40Gy)

Recurrence



Actuarial survival



No increased toxicity at time of transplant

Sapisochin G., …, LA Dawson, D Grant, Hepatology.

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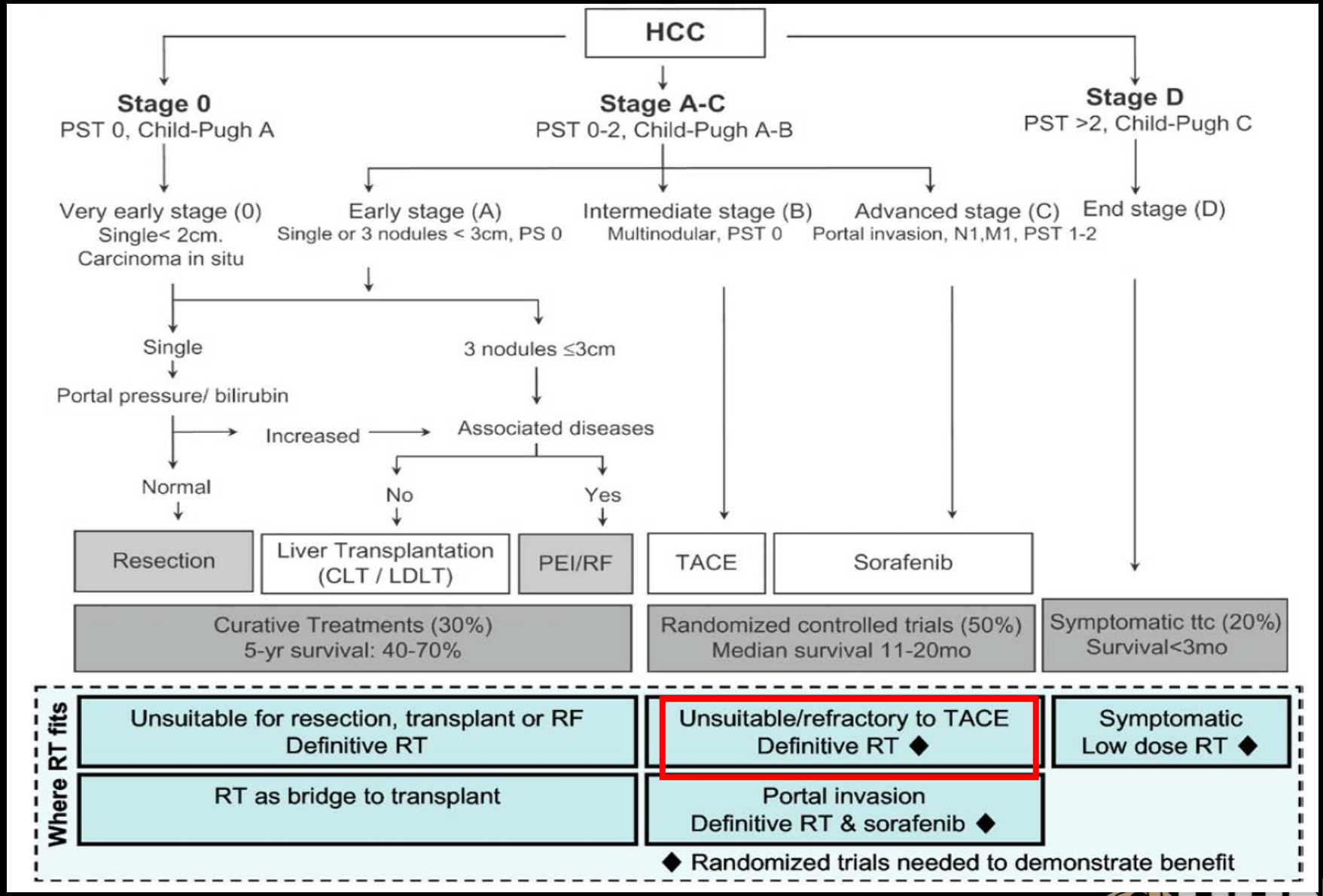
HCC BCLC: Where RT Fits



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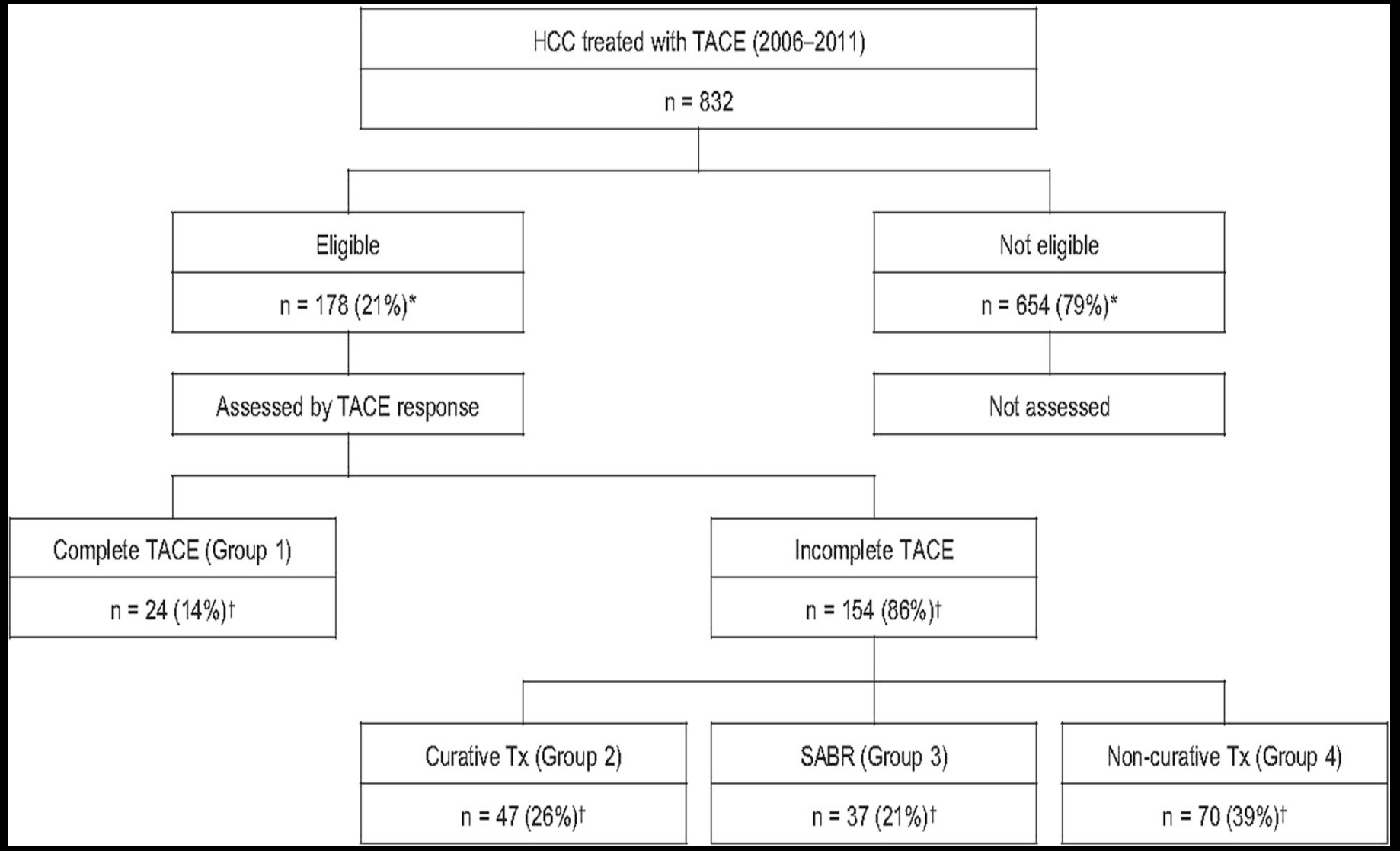
SBRT post TACE (Korea)



Paik, Radiation Oncology 2016

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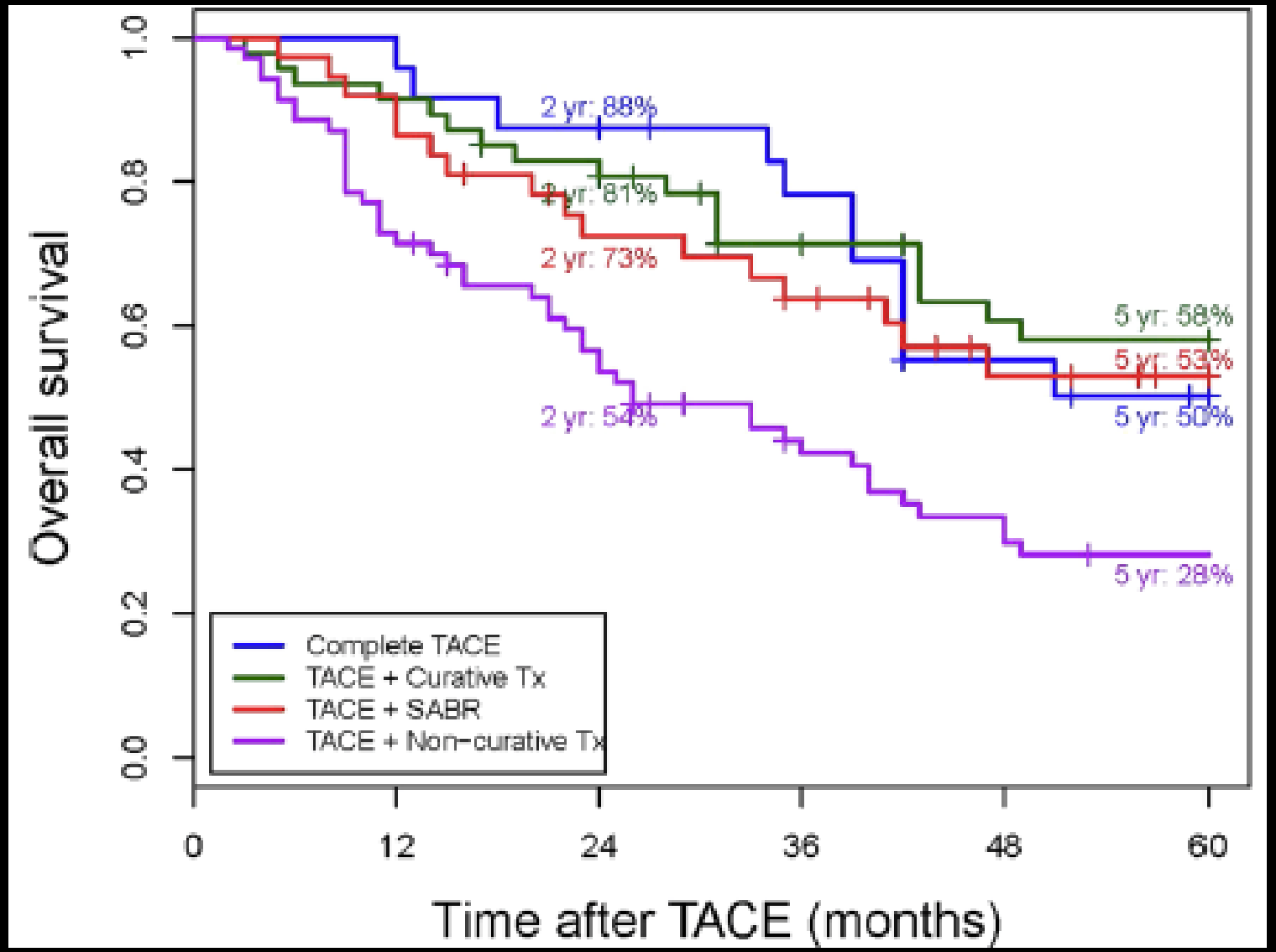
SBRT post TACE (Korea)



Paik EK et al. Radiat Oncol. 2016;11(1):22

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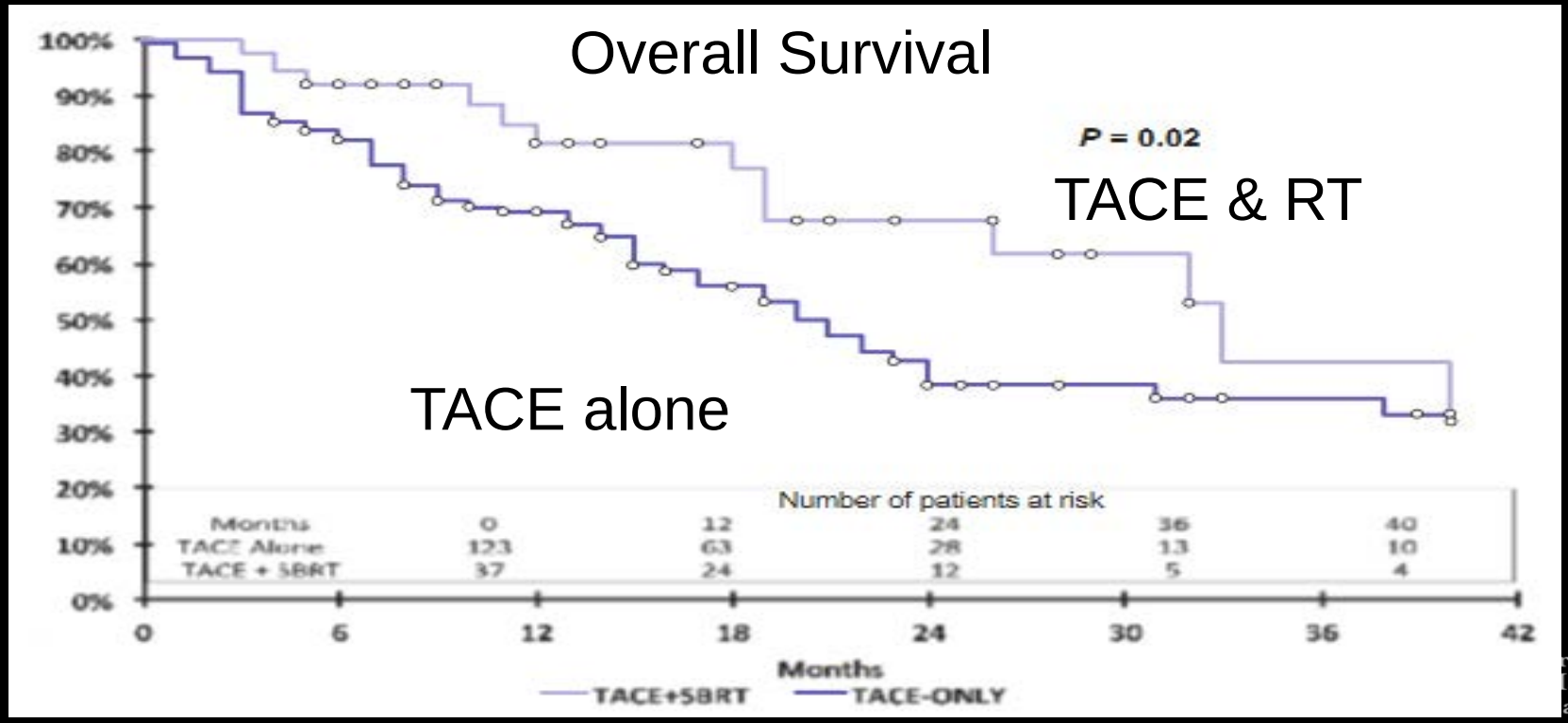
Alabama, Retrospective comparison of TACE +/- SBRT, for HCC > 3cm

Patients (161)	Local recurrence	Median survival
• 124 TACE	26%	20 mo
• 37 TACE & RT	11%	33 mo



Jacob, HBP 2015

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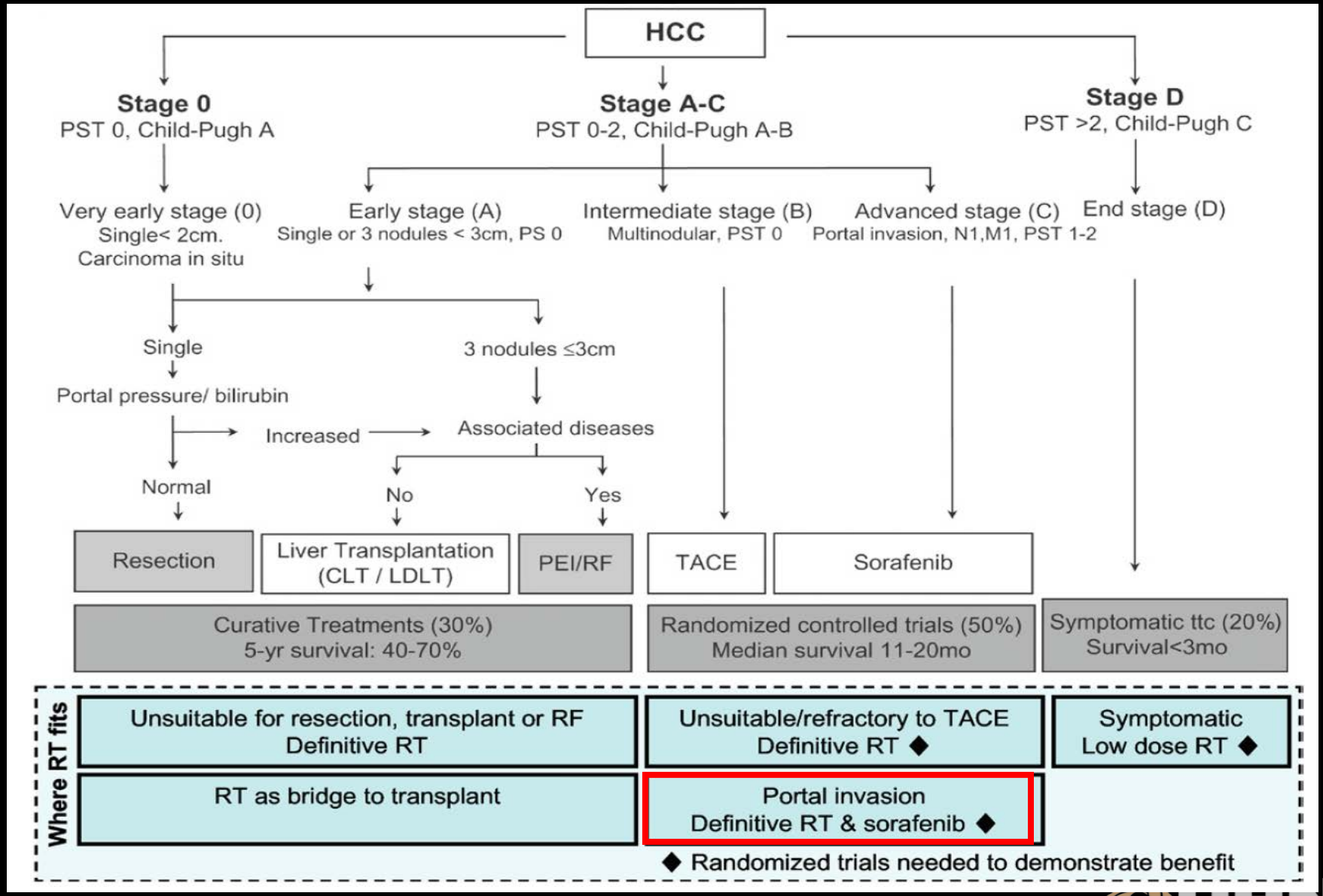
HCC BCLC: Where RT Fits



Dawson LA et al. Semin Radiat Oncol. 2011;21:241

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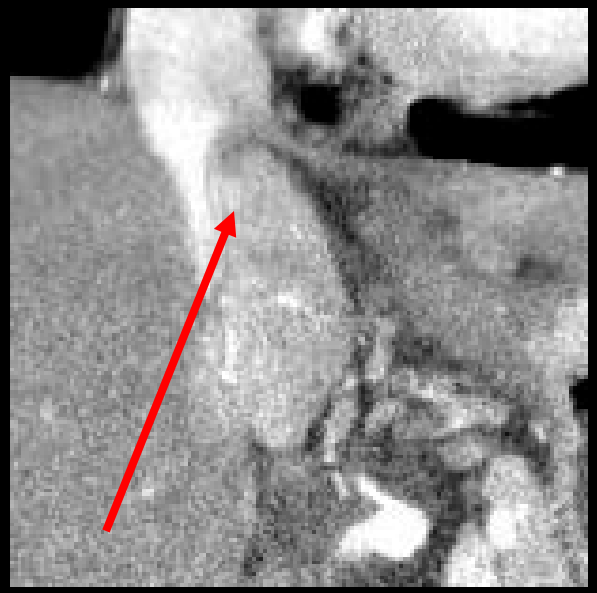
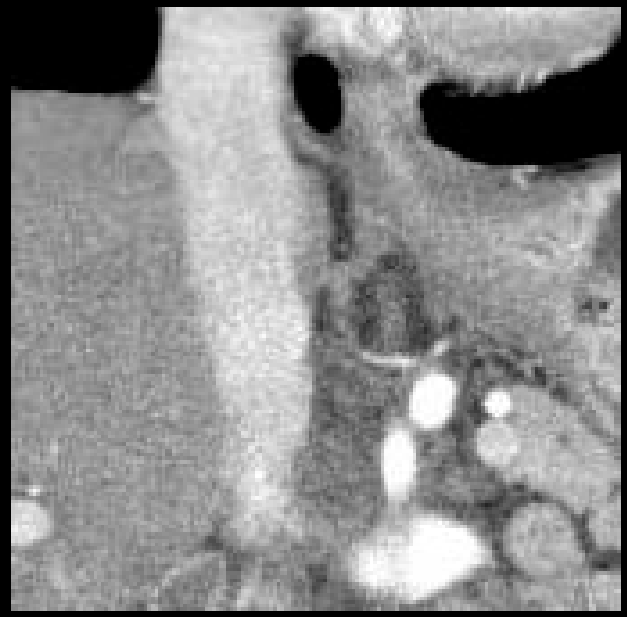
RT can effectively treat advanced HCC with main branch vascular invasion

Jan 2009
AFP 10,000



IVC HCC thrombus

Sept 2009
AFP 24



Complete response post RT

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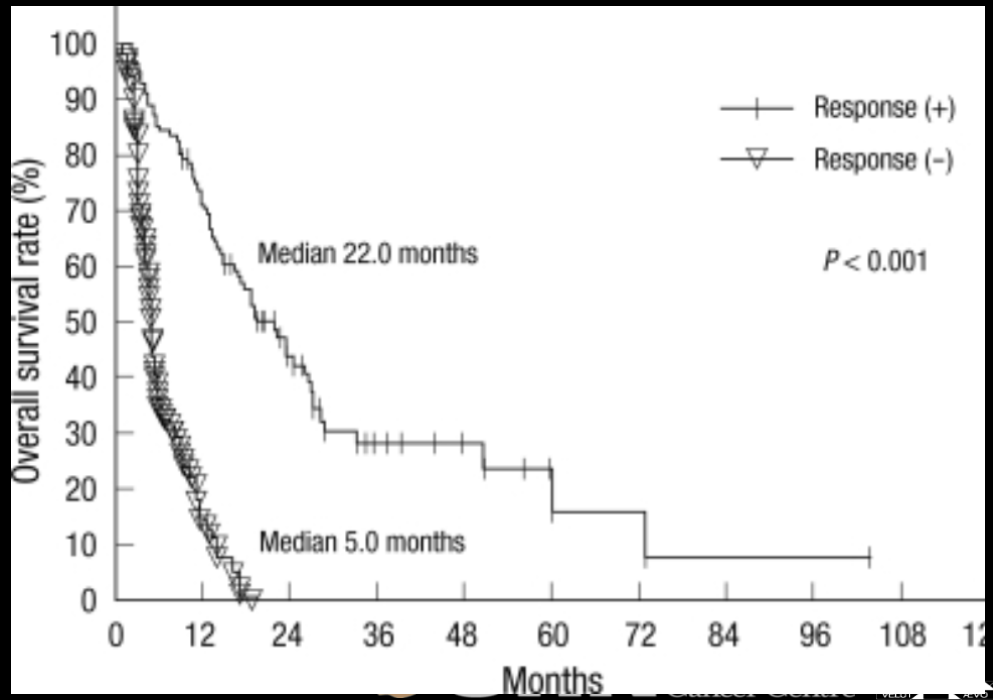
Korean series of HCC PVTT

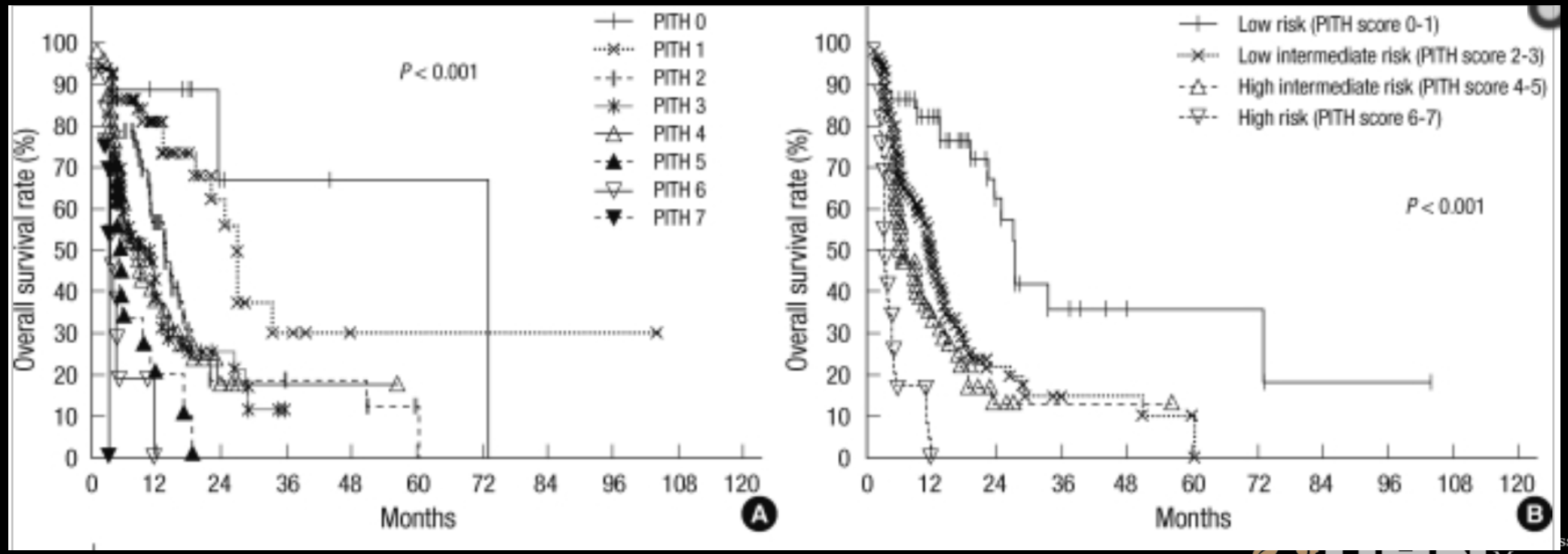
- Retrospective review of 281 patients with HCC PVTT treated with RT 1998- 2008
- 84% Child Pugh A
- RT 30 – 54 Gy, med fraction size 3 Gy/ #
- 50% PR
- 3% CR
- Median survival 11.6 mo
  - Responders 22.0 mo
  - Non responders 5.0 mo



Yu, Park et al. JKMS 28 (8), 10167-1022, 2011

Korean series of HCC PVTT, n=281

- Prognostic factors for overall survival on MVA:
  - ECOG performance status, CP
  - Degree of PVTT: main branch, complete occlusion
  - Tumor size, multiplicity, LN metastases
  - Response to RT



Yu, Park et al. JKMS 28 (8), 10167-1022, 2011

PMH Phase I/II HCC Study

- 102 HCC patients, unsuitable for transplant, resection, RFA or TACE

- Hep B: Hep C: alcohol 39%: 40%: 25%
- Prior therapies 50%
- Portal vein HCC thrombosis 55%
- Extrahepatic disease 12%
- Size: median 10 cm (2–43 cm)

- Median dose 36 Gy in 6# (7.5–54 Gy)
- 6 fractions, every other day

Bujold A et al. J Clin Oncol. 2013;31(13):1631-9

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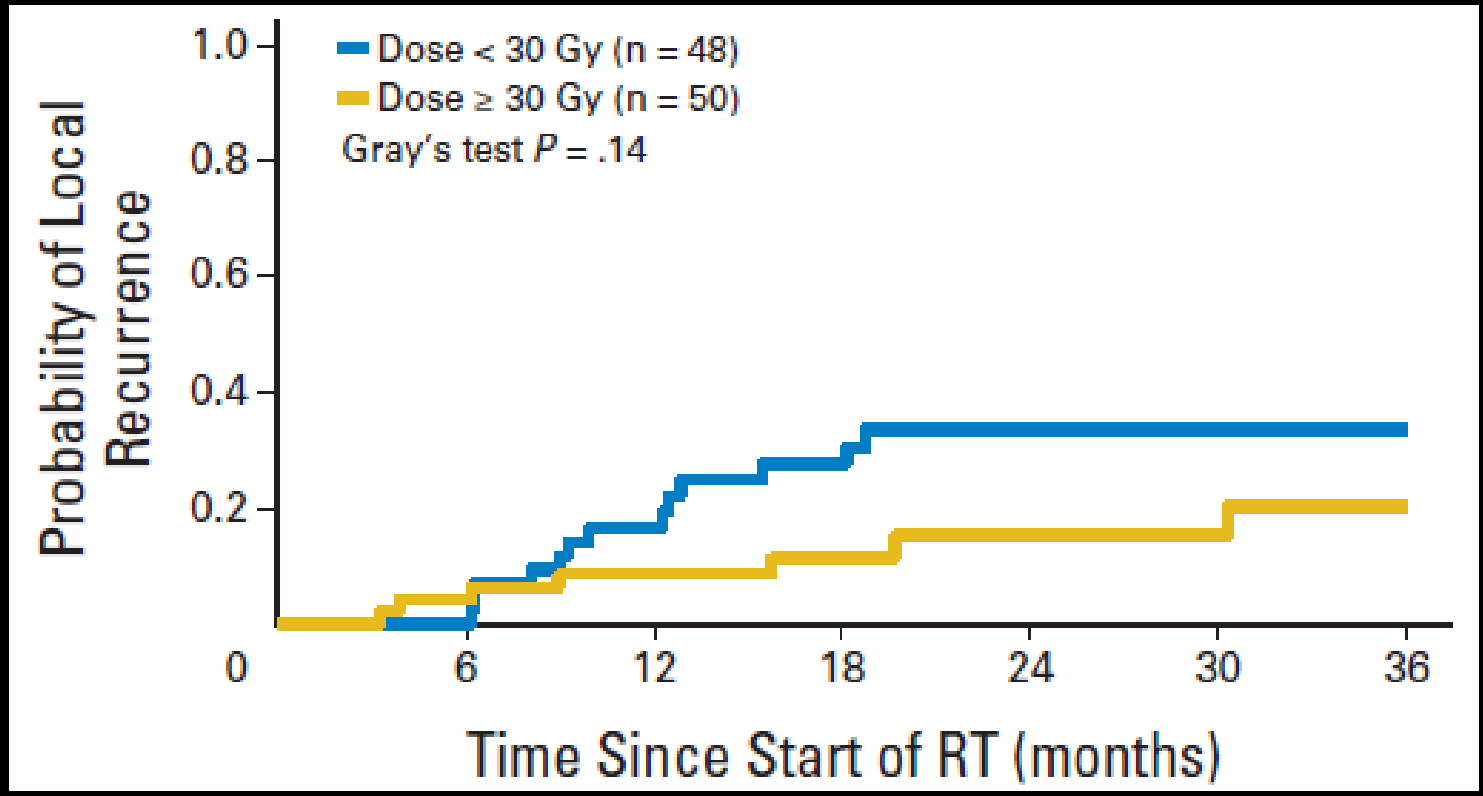
Local Control

- 1 year local control 87% (95% CI 78–93%)
- Dose response observed (> 30 Gy in 6 #)



Bujold A et al. J Clin Oncol. 2013;31(13):1631-9

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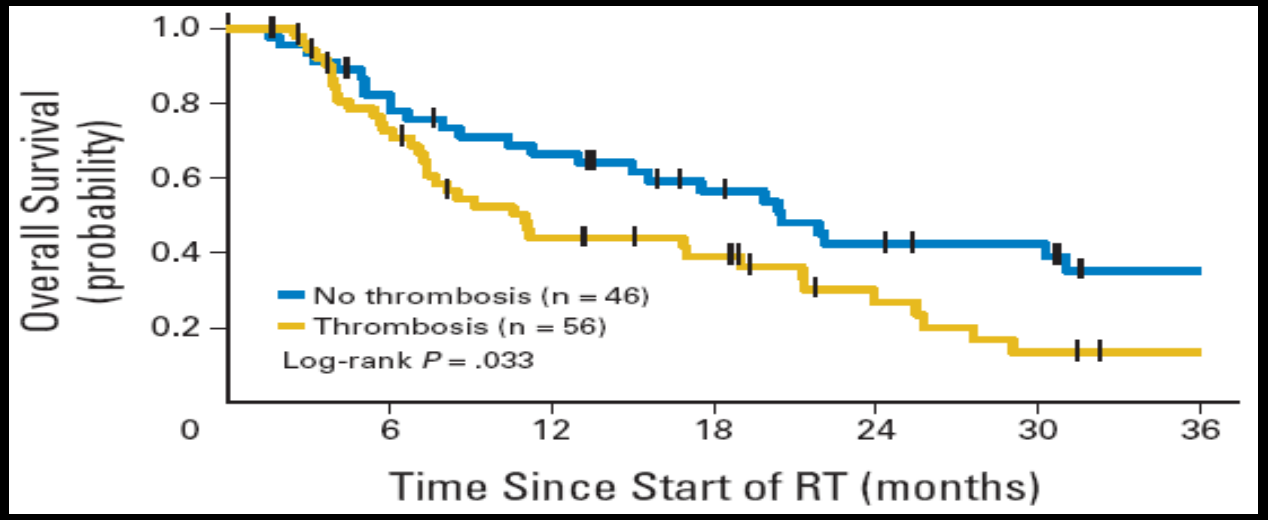
Survival

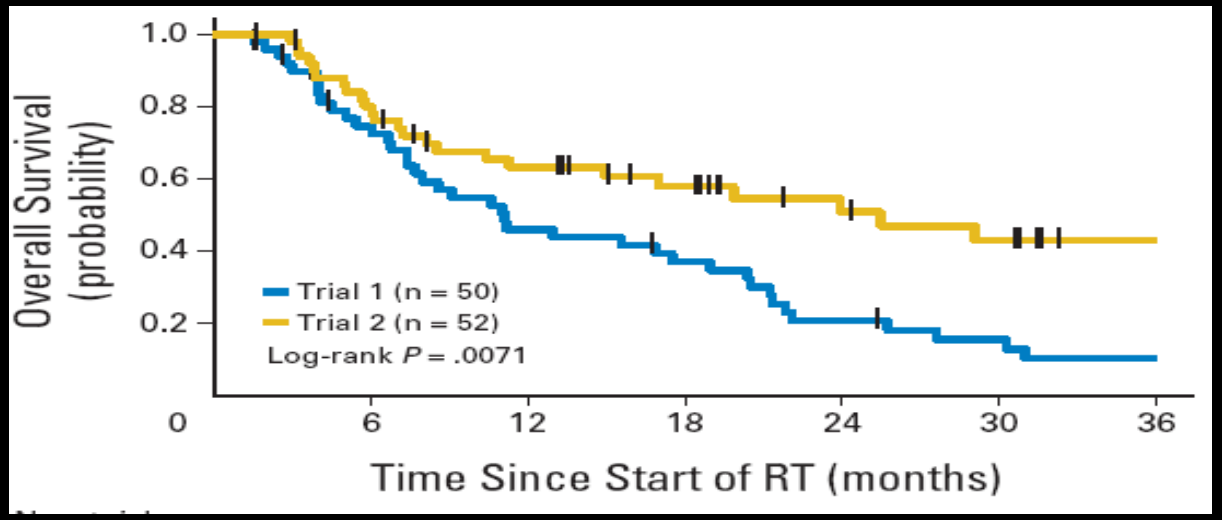
Median survival 17 months

Survival by thrombosis



	Median survival
No thrombosis	20.5 mo (95% CI 12.9, 36.9)
Thrombosis	11.0 mo (95% CI 11.3, NA)

Survival by trial



	Median survival
Trial 1	11.1 months (95% CI 7.4-19.0)
Trial 2	25.5 months (95% CI 11.3, NA)

Bujold, …Dawson, JCO April 2013

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Toronto Phase I HCC & Sorafenib

Strata I – Small HCC(s)

Liver volume irradiated: < 40%

Strata II – Large HCC

Liver volume irradiated: 40-60%

Ng, Brade, …Dawson, IJROBP 2016

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Ph I study Sorafenib and SBRT: Toxicity

- Strata I (Low Veff - < 40% liver volume)
  - 4 patients accrued at Dose Level 1 (200 mg bid)
    - All evaluable for DLT
    - *No dose limiting toxicity (DLT) observed*
    - Closed for slow accrual

- Strata II (High Veff – 40-60% liver volume)
  - 5 patients accrued at Dose Level 1 (200 mg bid)
    - 3 Evaluable for DLT
    - *2 DLT observed (GI Bleed, SBO)*
  - 7 patients accrued at Dose Level -1 (200 mg od)
    - 6 Evaluable for DLT
    - *1 DLT observed (Tumor rupture)*

Ng, Brade, …Dawson, IJROBP 2016

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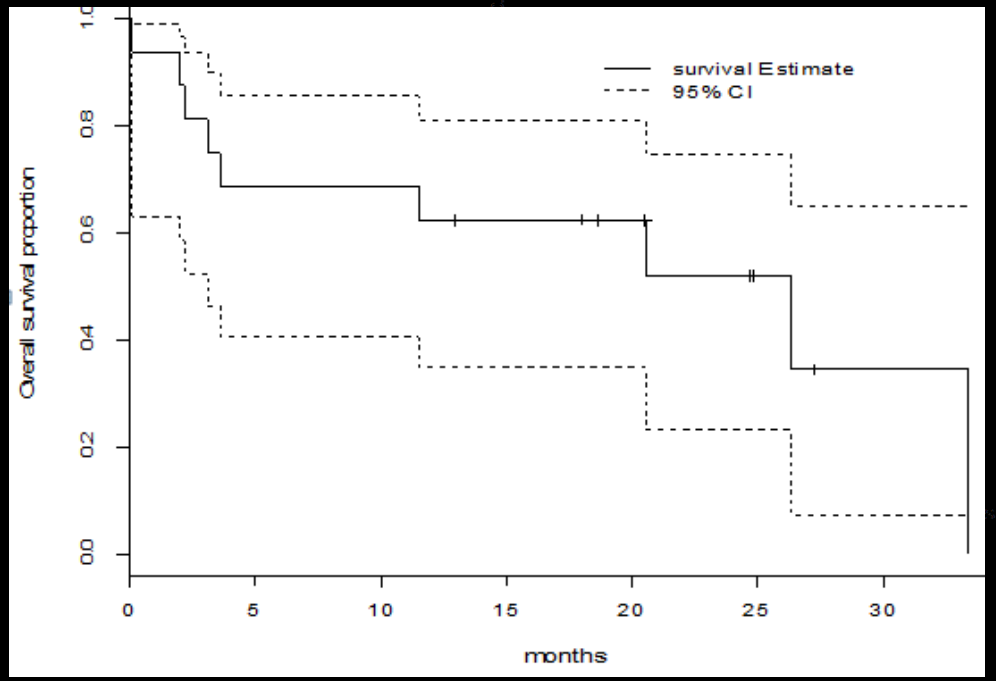
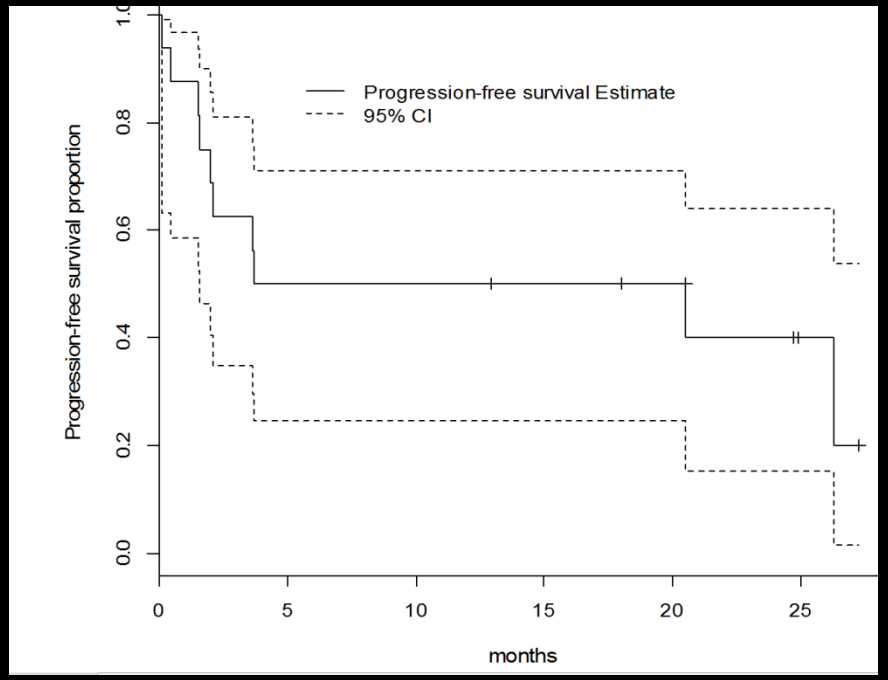
Ph I Study Sorafenib and SBRT
Overall Survival and PFS

Estimated median survival: 26.3 mo (3.1- not reached)



Estimated median PFS: 12.1 mo (1.6 – not reached)



Ng, Brade, …Dawson, IJROBP 2016

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RTOG 1112 Phase III Study

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

Randomized phase III study

Sample size: 368

Primary endpoint: overall survival (10.5 → 14.5 mo)

Radiation Therapy Oncology Group 2012. Clinical trial RTOG 1112..
https://www.rtog.org/Portals/0/RTOG%20Broadcasts/Attachments/1112

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RTOG1112 Key Eligibility

Inclusion Criteria

- Measureable HCC
- Unsuitable for or refractory to:
  - Surgery
  - RFA
  - TACE or DEB
- Child Pugh A
- BCLC B or C
- Platelets > 70 000 bil/L
- INR < 1.7
- Albumin ≥ 28 g/L
- AST, ALT < 6xULN
- Any degree of vascular invasion permitted, if otherwise eligible

Exclusion Criteria

- Prior Sorafenib > 60 days
- Prior abdominal RT or Y-90
- > 15 cm single HCC
- > 20 cm sum of max diameters
- > 5 discreet definite HCC
- Extrahepatic (EH) HCC > 3 cm
- HCC extension to stomach
- HCC extension to CBD
- Thrombolytic therapy < 28 days
- Bleeding < 60 days requiring transfusion

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Case
HCC with Vascular Invasion

- 57 year old male, background Hep B +ve diagnosed 20 years ago, on treatment with Tenofovir
- Diagnosed 8.4cm HCC in segment 5/8, and a 1cm HCC in segment 7, along with portal vein thrombus in the right anterior branch.
- Child Pugh A5 liver function.
- Planned for 35 Gy in 5 fraction SBRT on RTOG 1112 study
- ABC exhale breath hold
- PTV expansion 5mm

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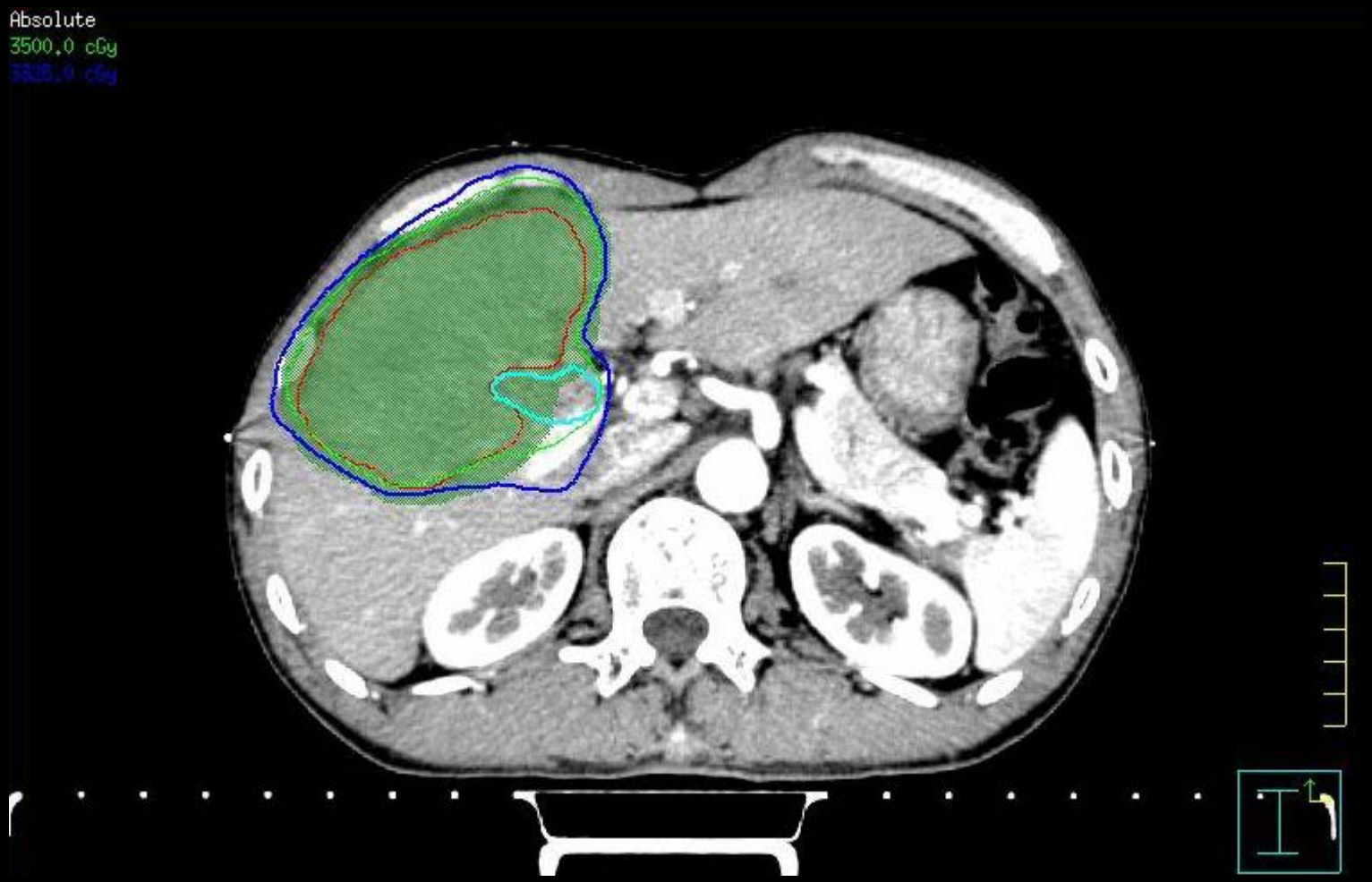
Case



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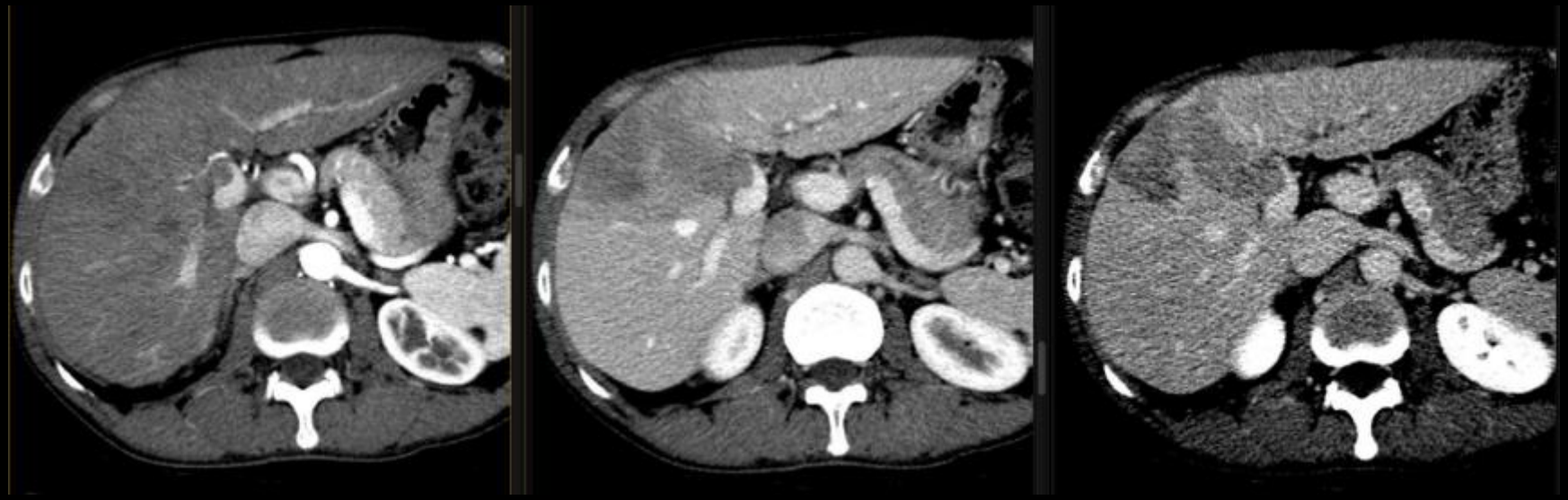
Case



baseline

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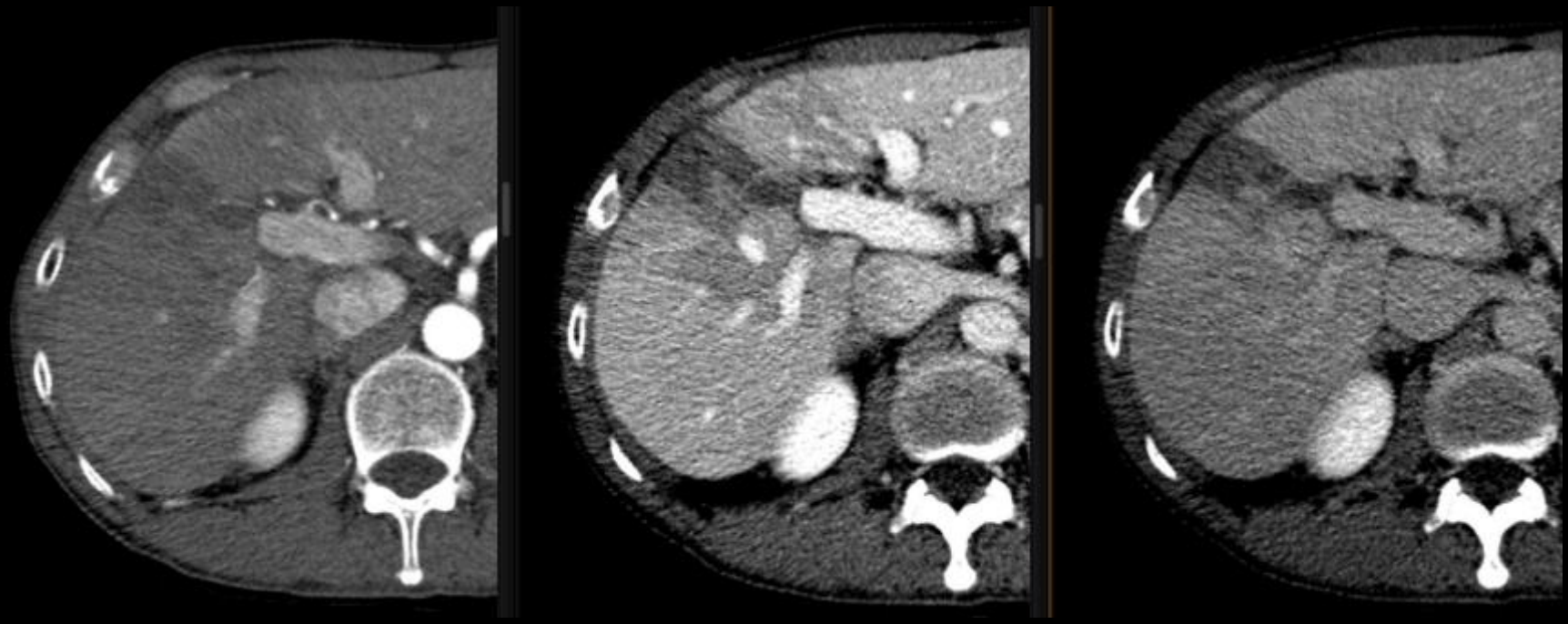
Case



3 months post SBRT

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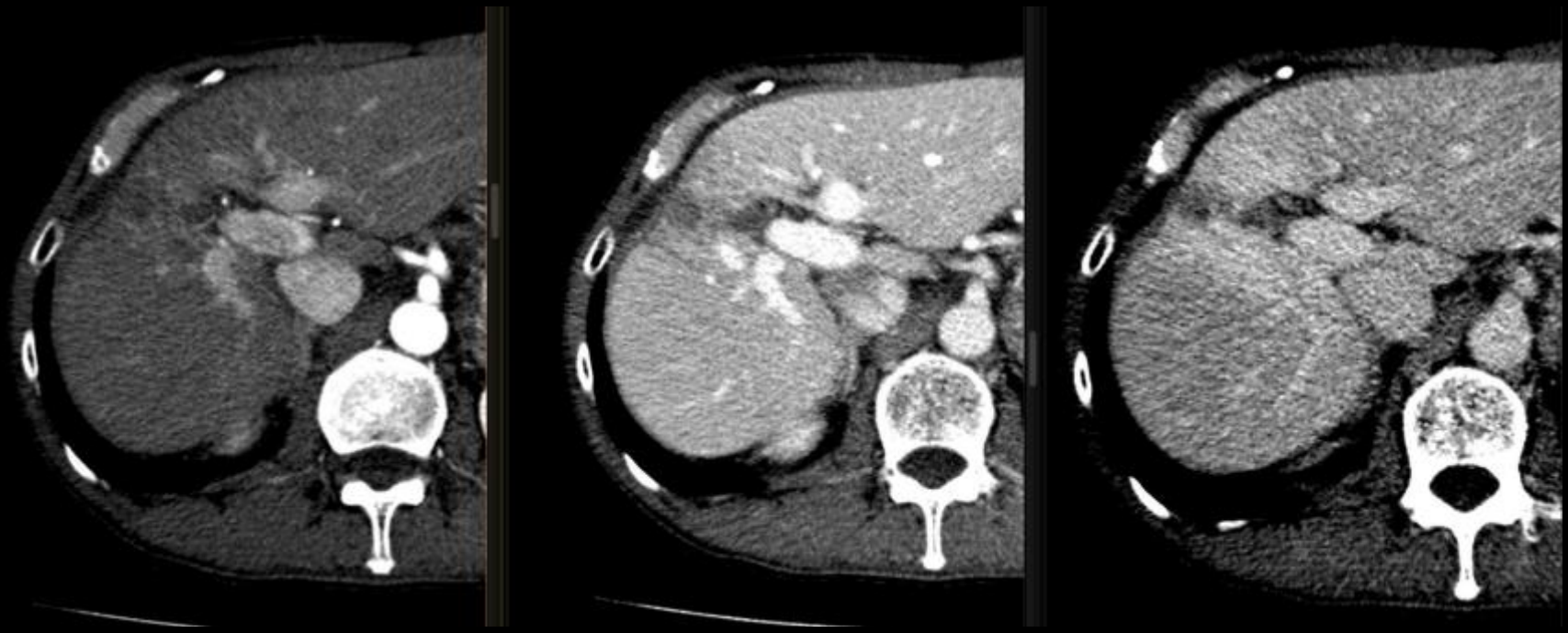
Case



18 months post SBRT

Sustained normalization of AFP at ~12 months

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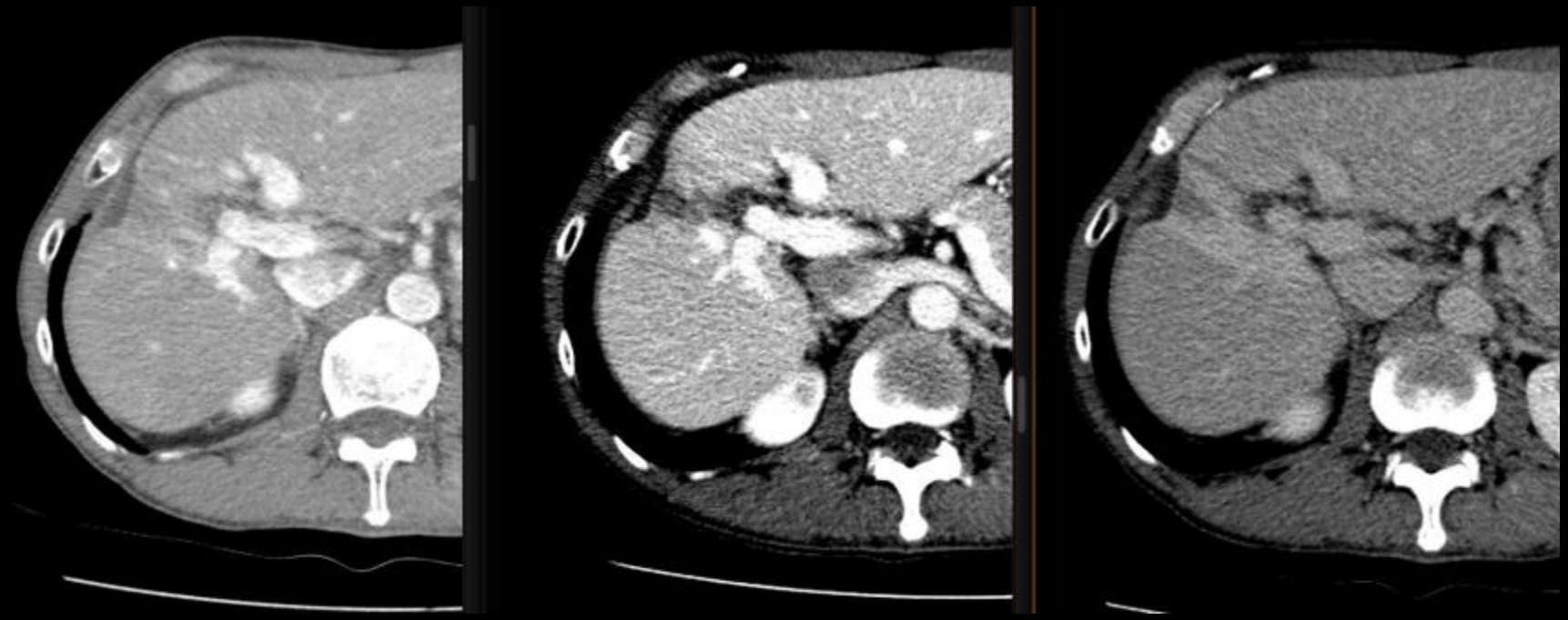
Case



36 months post SBRT

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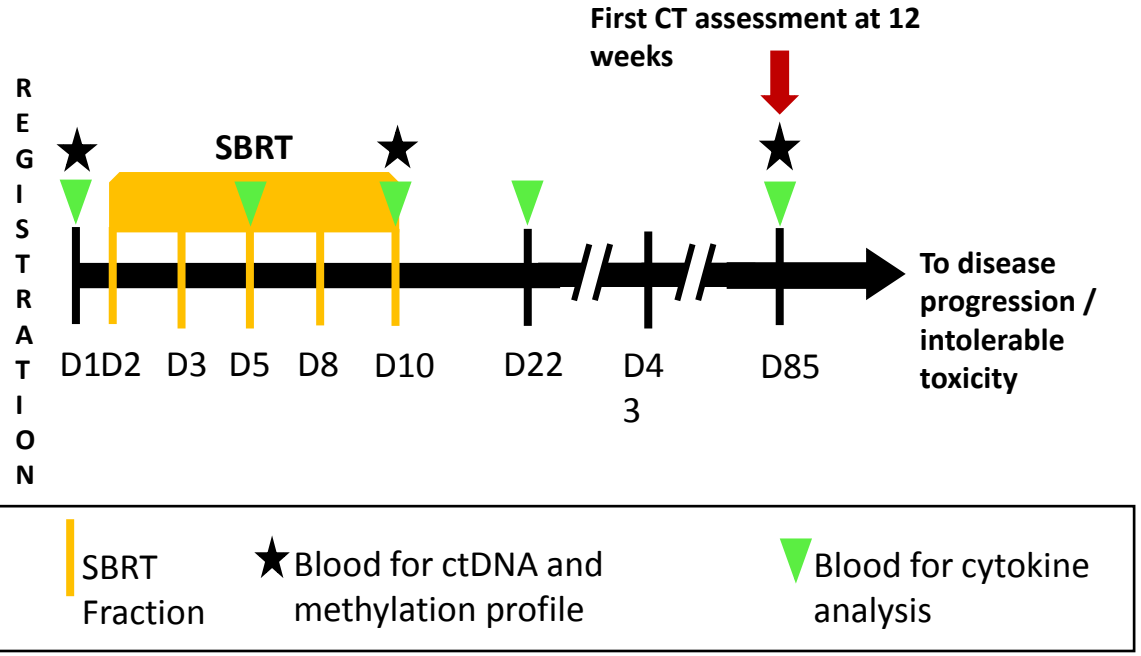
Planned Toronto Phase I Study: PEMRAD – Pembrolizumab + SBRT in HCC

-Advanced HCC post sorafenib, CP 5/6
-Disease amenable to SBRT
-Measurable disease by RECIST
-Fresh tissue biopsy for WES, RNAseq



- Single arm Investigator-initiated Phase II study, PI J Knox, L Dawson
- Primary endpoint is overall response (in-field plus systemic)
- Correlative components
- Aiming for 1st patient Summer 2017.

Conclusions

- HCC is a radiosensitive tumor
- RT has a role to play across all HCC stages
- SBRT is ready for prime time in selected HCC patients
  - SBRT outcomes best in CP A, small (< 8 cm) HCC
  - HCC with vascular invasion, if not suitable for other treatments

- There is a need for improved evidence regarding SBRT for HCC

- Randomized trials are ongoing
  - RTOG1112: Ph III study of SBRT for locally advanced HCC
  - Will benefit from international collaborations

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ASCO CDA, Canadian Cancer Society CIHR

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