Uitgangsvraag 6: Wat is de plaats van stereotactische radiotherapiebehandeling (SBRT) bij HCC patiënten?

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Lin C-S 2006 [1]	• Prospective controlled trial • Funding/CoI: partly supported by CY Foundation for Advancement of Education, Sciences, and Medicine; conflicts of interest not reported • Setting: single centre, Taiwan • Sample size: N=43 • Duration: inclusion from 3/2002-11/2004	• Eligibility criteria: ○ Patients with unresectable HCC accompanied by tumour thrombosis in the portal trunk and/or bilateral main portal vein branches • *A priori* patient characteristics: ○ 7 patients received surgery before diagnosis of PVTT ○ 18 patients received TACE before diagnosis of PVTT ○ 6 patients had distant metastases ○ Median age: 57y ○ HBV: N=31; HCV: N=14 • Group comparability: no significant differences (SBRT vs. 3DCRT) ○ Male: 77% vs. 81% ○ Mean age: 59.5 vs. 54.0y ○ Child-Pugh A: 32% vs. 24%	SBRT (Elekta), 45 Gy in fractions of 3 Gy 3x/week for 5 weeks (N=22) vs. 3D-conformal radiotherapy , 45 Gy in fractions of 1.8 Gy 5x/week for 5 weeks (N=21)	• Response (ITT, N=43): ○ CR: 0% vs. 5% ○ PR: 27% vs. 19% ○ SD: 9% vs. 5% • Survival and mortality: ○ Median survival (evaluable patients only, N= 14): 6.0 vs. 6.7 months (p=0.911) ○ Death before response evaluation: 64% vs. 71%	• No separate safety results for SBRT	Level of evidence: B • No randomization • No blinding • Completion of RT: 41% vs. 33%. Treatment interruptions by cancer death or poor performance status • Response evaluated within 3 months after completion of RT • Median follow-up: 2.5 maanden

Case series

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Andolino 2011 [2]	• Retrospective • Funding/CoI: no conflicts declared • Setting: single centre, US • Sample size: N=60 • Duration: 2005-2009	• Patients with HCC confined to the liver at the time of treatment • Age: 59y • Male: 82% • HCV: 50%; HBV: 13% • Child-Pugh A: 60% • Median diameter: 3.1 cm • 6 patients received prior	SBRT (Elekta): • Child-Pugh A: 48 Gy in 3 fractions • Child-Pugh B: 40 Gy in 5 fractions	• Response: ○ CR: 30% ○ PR: 40% ○ SD: 25% • Survival: ○ Median OS: 44.4 months ○ Median PFS: 20.4 months ○ 2-year OS: 67% ○ 2-year PFS: 48%	• Grade 3/4 toxicity: ○ Liver enzymes/ hyperbilirubinemia: N=10 (17%) ○ Thrombocytopenia: N=10 (17%) ○ Elevated INR: N=2 (7%) ○ Hypoalbuminemia:	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 27 months

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		TACE • 23 patients proceeded to OLT (time to transplant 7 months)			N=7 (12%)	
Cardenes 2010 [3]	• Prospective, phase I • Funding/CoI: no conflicts declared • Setting: single university centre, US • Sample size: N=17 • Duration: 3/2005-8/2007	• Patients with HCC, Child-Pugh A or B, ECOG performance status 0-2, >18y, and minimum life expectancy 3 months; no candidate for resection; solitary tumour ≤ 6 cm, or up to 3 lesions with the sum of the diameters ≤ 6 cm; no evidence of progressive or untreated gross extrahepatic disease • Median age: 61y • Male: 94% • HCV: 53%; HBV: 12% • Child-Pugh A: 35% • Median diameter: 4 cm • Prior therapy: 23.5% • 6 patients proceeded to OLT	SBRT (Elekta): escalation in dose; maximum dose: • Child-Pugh A: 48 Gy in 3 fractions • Child-Pugh B: 40 Gy in 5 fractions	• Response (16 evaluable patients): ○ CR: 25% ○ PR: 56% ○ SD: 19% • Survival: ○ 1-year OS: 75% ○ 2-year OS: 60%	• Grade 3/4 toxicity: ○ AST: N=3 (18%) ○ Hyperbilirubinemia: N=4 (18%) ○ Thrombocytopenia: N=4 (24%) ○ Elevated INR: N=1 (6%) ○ Hypoalbuminemia: N=1 (6%) ○ Leukopenia: N=1 (6%)	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 24 months • All patients potentially included in Price TR 2011
Yang 2010 [4]	• RCT • Funding/CoI: support from National Natural Science Foundation of China (no. 30872975) • Setting: single university centre, China • Sample size: N=40, of which 20 received SBRT • Duration: 8/2004-5/2007	• Patients with HCC without extrahepatic metastasis, Child-Pugh A or B, ECOG-score 0-2, no previous RT, single lesion • Median age: 53y • Male: 75% • Child-Pugh A: 60% • Median diameter: 3.2 cm	SBRT (OUR company): 5x5 Gy for 2 weeks	• Response: ○ CR: 20% ○ PR: 50% ○ SD: 30% • Survival: ○ Median OS: 20 months ○ 1-year OS: 70% ○ 1-year DFS: 65%	• Grade 3/4 toxicity: N=0	Level of evidence: C • RCT comparing SBRT with SBRT and rAd-p53; results of SBRT arm are included here • Consecutive patients • Median follow-up: 35 months
Kwon 2010 [5]	• Retrospective • Funding/CoI: no conflicts declared • Setting: single university centre, South-Korea • Sample size: N=42 • Duration: 3/2004-5/2007	• Patients with HCC without extrahepatic metastasis, tumour volume ≤ 100 cc, inoperable or inaccessible for local treatment • Mean age: 60.1y • Male: 76% • HCV: 17%; HBV: 69% • Child-Pugh A: 90% • Median tumour volume: 15.4 cc • Previous TACE: 26%	SBRT (CyberKnife): median total dose 33 Gy (range 30-39), in 3 fractions on consecutive days	• Response: ○ CR: 60% ○ PR: 26% ○ SD: 14% • Survival: ○ 1-year OS: 92.9% ○ 3-year OS: 58.6% ○ 1-year PFS: 72% ○ 3-year PFS: 68% ○ Median PFS: 15.4 months	• Grade 3/4 toxicity: ○ Liver failure: N=1 (2%)	Level of evidence: C • Includes 31 patients from Choi BO, BMC Cancer 2008 • Unclear if consecutive patients • Median follow-up: 28.7 months
Seo 2010 [6]	• Retrospective analysis	• Patients with a single HCC ±	SBRT (CyberKnife):	• Response:	• Grade 3/4 toxicity:	Level of evidence: C

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	of prospective database • Funding/CoI: supported by Nuclear Research Development Program of Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean government • Setting: single university centre, South-Korea • Sample size: N=38 • Duration: 3/2003-4/2008	daughter nodule, < 10 cm, ECOG 0-1, no extrahepatic metastases, unresectable • Median age: 61y • Male: 63% • Child-Pugh A: 89% • Median tumour volume: 40.5 cc • Previous TACE: 100%	dose depending on tumour volume • <50 ml: 39-57 Gy • 50-100: 36-51 Gy • 100-300: 33-51 Gy • 300-500: 40-44 Gy	○ CR: 3% ○ PR: 61% ○ SD: 29% ○ PD: 8% • Survival: ○ Median OS: 32 months ○ 1-year OS: 68.4% ○ 2-year OS: 61.4% ○ 3-year OS: 42.1% ○ 1-year local PFS: 78.5% ○ 2-year local PFS: 66.4% ○ 1-year disease PFS: 46.4% ○ 2-year disease PFS: 37.5%	○ Soft tissue toxicity: N=1 (3%)	• Unclear if consecutive patients • Median follow-up: 15 months
Tse 2008 [7]	• Prospective, phase I • Funding/CoI: 1 author received research funding from Elekta Oncology Systems • Setting: single university centre, Canada • Sample size: N=41, of wich 31 with HCC • Duration: 8/2003-3/2006	• Patients with unresectable HCC, >18y,Child-Pugh A, KI at least 60% • Median age: 66y • Male: 77% • HCV: 39%; HBV: 42% • Child-Pugh A: 100% • Median tumour volume: 173 cm^3 • Previous treatment: 61%	SBRT (Elekta): dose escalation, 6 fractions in 2 weeks	• Response: not separated for HCC • Survival: ○ Median OS: 11.7 months ○ 1-year OS: 48%	• Grade 3/4 toxicity: ○ Liver enzymes: N=8 (26%) ○ Hyperbilirubinemia: N=2 (6%) ○ Thrombocytopenia: N=1 (3%) ○ Lethargy: N=1 (3%) ○ Nausea: N=3 (10%)	Level of evidence: C • Unclear if consecutive patients • 1 patient excluded after start of treatment, 1 patients had no 3-month follow-up data because of death • Median follow-up: 17.6 months
Price 2011 [8]	• Prospective, phase 2 • Funding/CoI: no conflicts or support declared • Setting: single university centre, US • Sample size: N=26 • Duration: 3/2005-6/2008	• Patients with unresectable HCC, solitary tumour ≤ 6 cm or up to 3 lesions with sum of diameter ≤ 6 cm, Child-Pugh A/B, no ascites • Median age: 60y • Male: 88% • HCV: 58%; HBV: 12% • Child-Pugh A: 54% • Previous treatment: 27%	SBRT (Elekta): • Child-Pugh A: 48 Gy in 3 fractions • Child-Pugh B: 40 Gy in 5 fractions	• Response: ○ CR: 15% ○ PR: 58% ○ SD: 27% • Survival: ○ 1-year OS: 77% ○ 2-year OS: 60%		Level of evidence: C • Unclear if consecutive patients • Median follow-up: 13 months • Overlap with Cardenes 2010?
Louis 2010 [9]	• Retrospective • Funding/CoI: not reported • Setting: single university centre, Belgium • Sample size: N=25 • Duration: not reported	• Patients with a single HCC lesion, ECOG 0-2, Child-Pugh A/B • Mean age: 70y • Male: 76% • Alcoholic cirrhosis: 80% • Child-Pugh A: 88% • Median diameter: 4.5 cm	SBRT (CyberKnife): 45 Gy in 3 fractions of 15 Gy	• Response (14 evaluable patients): ○ CR: 57% ○ PR: 29% ○ PD: 7% • Survival: ○ 1-year OS: 79% ○ 2-year OS: 52% ○ Median DFS: 15.8 months	• Grade 3/4 toxicity: ○ Hepatic toxicity: N=1 (5%) ○ Hepatic pain: N=1 (5%) ○ Gastroduodenal ulcer: N=1 (5%) ○ Late toxicity (after 9 months): N=2	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 12.7 months

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		• Previous treatment: 36%			(10%)	
Choi 2006 [10]	• Retrospective • Funding/CoI: not reported • Setting: single university centre, South-Korea • Sample size: N=20 • Duration: 7/1999-6/2002	• Patients with a solitary HCC nodule, no extrahepatic metastasis, Child Pugh A/B, ECOG 0-2, no previous RT • Median age: 59y • Male: 80% • Child-Pugh A: 75% • Median tumour volume: 25.2 cc • Previous TACE: 60%	SBRT, total dose of 50 Gy (3-5x 5-10 Gy/week for 2 weeks)	• Response: ○ CR: 20% ○ PR: 60% • Survival: ○ Median OS: 22 months ○ 1-year OS: 70.0% ○ 2-year OS: 43.1% ○ Median DFS: 19 months ○ 1-year DFS: 65.0% ○ 2-year DFS: 32.5%	• Grade 3/4 toxicity: N=0	Level of evidence: C • Consecutive patients • Median follow-up: 23 months
Chan 2011 [11]	• Retrospective • Funding/CoI: not reported • Setting: single centre, Hong Kong • Sample size: N=16 • Duration: 5/2000-11/2004	• Patients with a intrahepatic HCC, irresectable or not suitable for local treatment • Median age: 58y • Male: 94% • HBV: 81% • Child-Pugh A: 75% • Median diameter: 3 cm	SBRT (ExacTRA): 10x4.5 Gy	• Response: ○ CR: 13% ○ PR: 19% ○ SD: 31% ○ PD: 6% • Survival: ○ Median OS: 23 months ○ 1-year OS: 62% ○ 3-year OS: 28%	• Grade 3/4 toxicity: ○ 1 death due to radiation-induced liver disease ○ ALT: N=1 (6%) ○ Liver pain: N=1 (6%)	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 24 months
Takeda 2008 [12]	• Retrospective • Funding/CoI: not reported • Setting: single centre, Japan • Sample size: N=16 • Duration: 12/2002-9/2004	• Patients with a HCC not previously treated with ablation therapy • Median age: 69y • Male: 88% • HCV: 75%; HBV: 13% • Child-Pugh A: 88% • Median tumour volume: 13.6 cm^3 • Previous TACE: 88%	SBRT, total dose of 35-50 Gy in 5-7 fractions over 5-9 days	• Response: ○ CR: 50% ○ SD: 44% • Survival: ○ All patients alive at the end of 612 days follow-up ○ 1-year RFS: 100% ○ 2-year RFS: 90%	• Grade 3/4 toxicity: not explicitly mentioned	Level of evidence: C • Unclear if consecutive patients • Mean follow-up: 612 days
Mendez Romero 2006 [13]	• Retrospective • Funding/CoI: no conflicts declared • Setting: single centre, The Netherlands • Sample size: N=25, of which 8 with HCC • Duration: 10/2002-6/2006	• Patients with a HCC confined to the liver, not eligible for surgery or other local treatment, Child Pugh A/B, maximum size 7 cm, maximum of 3 lesions • Child-Pugh A: 63% • Other characteristics not provided separately for HCC	SBRT (Elekta), 3x10-12.5 Gy or 5x5 Gy	• Local control rate: ○ 1-year: 75% • Survival: ○ 1-year OS: 75% ○ 2-year OS: 40%	• Grade 3/4 toxicity: not provided separately for HCC	Level of evidence: C • Unclear if consecutive patients • Maximum follow-up: 22 months
Goyal 2010 [14]	• Retrospective • Funding/CoI: not reported • Setting: single university centre, US • Sample size: N=17, of	• Patients with an unresectable HCC, life expectancy of at least 12 weeks • Mean age: 62.7y • Male: 67 % • Mean tumour diameter:	SBRT (CyberKnife)	• No local failure • Distant recurrence: 33% • Response: ○ CR: 0% ○ PR: 83% ○ SD: 17%	• 1 patient with gastric ulcer	Level of evidence: C • Consecutive patients • Mean follow-up: 10 months

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	which 6 with HCC • Duration: 10/2007-5/2009	9.3 cm				
Iwata 2010 [15]	• Prospective • Funding/CoI: no conflicts declared • Setting: single centre, Japan • Sample size: N=18, of which 6 with HCC • Duration: 2/2008-10/2009	• Patients with an inoperable HCC, WHO performance status 0-2, tumour diameter maximum 5 cm, Child-Pugh A/B • Characteristics not provided separately for HCC	SBRT: • Child-Pugh A: 55 Gy in 10 fractions • Child-Pugh B: 50 Gy in 10 fractions	• Local control: ○ 1-year: 100% • Survival: ○ 1-year DFS: 78%	• Grade 3/4 toxicity: not provided separately for HCC	Level of evidence: C • Unclear if consecutive patients • Median follow-up:
Shin 2010 [16]	• Unclear design • Funding/CoI: not reported • Setting: single university centre, South-Korea • Sample size: N=6 • Duration: 3/2003-3/2008	• Patients with a single HCC with/without daughter nodule, longest diameter > 12 cm or target volume > 1000 mL, inoperable, failure to respond to TACE, ECOG 0-1, Child-Pugh A, no extrahepatic metastases • Median age: 48.5y • HBV: 50% • Child-Pugh A: 100% • Previous TACE: 100%	SBRT (CyberKnife): 32-40 Gy in 4 fractions	• Response: ○ PR: 67% ○ SD: 17% ○ PD: 17% • Survival: ○ Median OS: 10 months ○ Median PFS: 6 months	• Grade 3/4 toxicity: ○ Liver enzymes: N=1 (17%)	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 25.9 months
Sanuki-Fujimoto 2010 [17]	• Retrospective • Funding/CoI: not reported • Setting: single centre, Japan • Sample size: N=47 • Duration: 3/2005-7/2008	• Patients with a solitary HCC ≤ 4 cm, inoperable, percutaneous ablative therapy not feasible, Child-Pugh A/B • Median age: 71y • HBV: 4%; HCV 74% • Child-Pugh A: 87% • Previous TACE: 100%	SBRT, 30-40 Gy in 5 fractions over 5-9 days	• Response: ○ CR: 72% ○ PR: 14%	•	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 18.1 months

Abbreviations: 3DCRT: 3D-conformal radiotherapy; ALT: alanine transaminase; AST: aspartate aminotransferase; CoI: conflicts of interest; CR: complete resonse; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; Gy: Gray; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; INR: international normalized ratio; KI: Karnofsky index; OLT: orthotopic liver transplantation; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; PVTT: portal vein tumour thrombosis; RFS: recurrence-free survival; RT: radiotherapy; SBRT: stereotactic body radiotherapy; SD: stable disease; TACE: transarterial chemo-embolisation.