Interventional radiology and stereotactic radiotherapy

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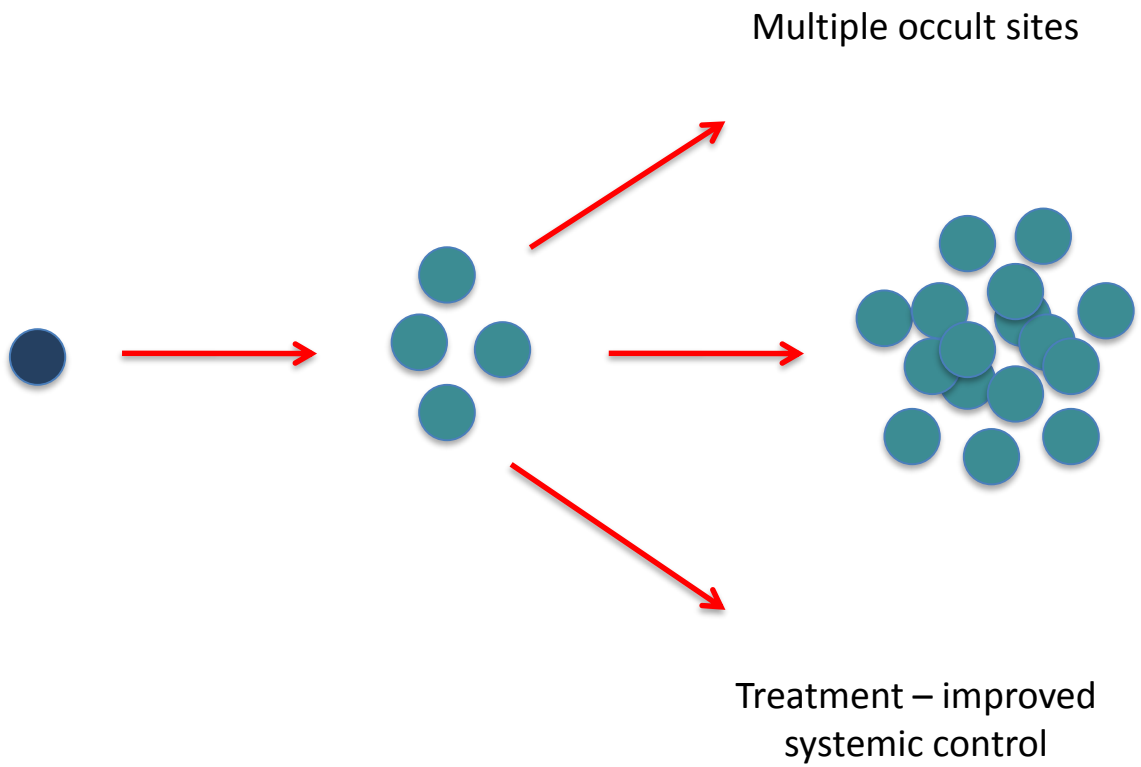
My Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer, AIS
- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca
- **Funding to attend meetings**: Roche, Merck Serono, Sanofi Aventis,
- **Research funding**: Roche, Merck Serono, Sanofi Aventis

Oligometasteses

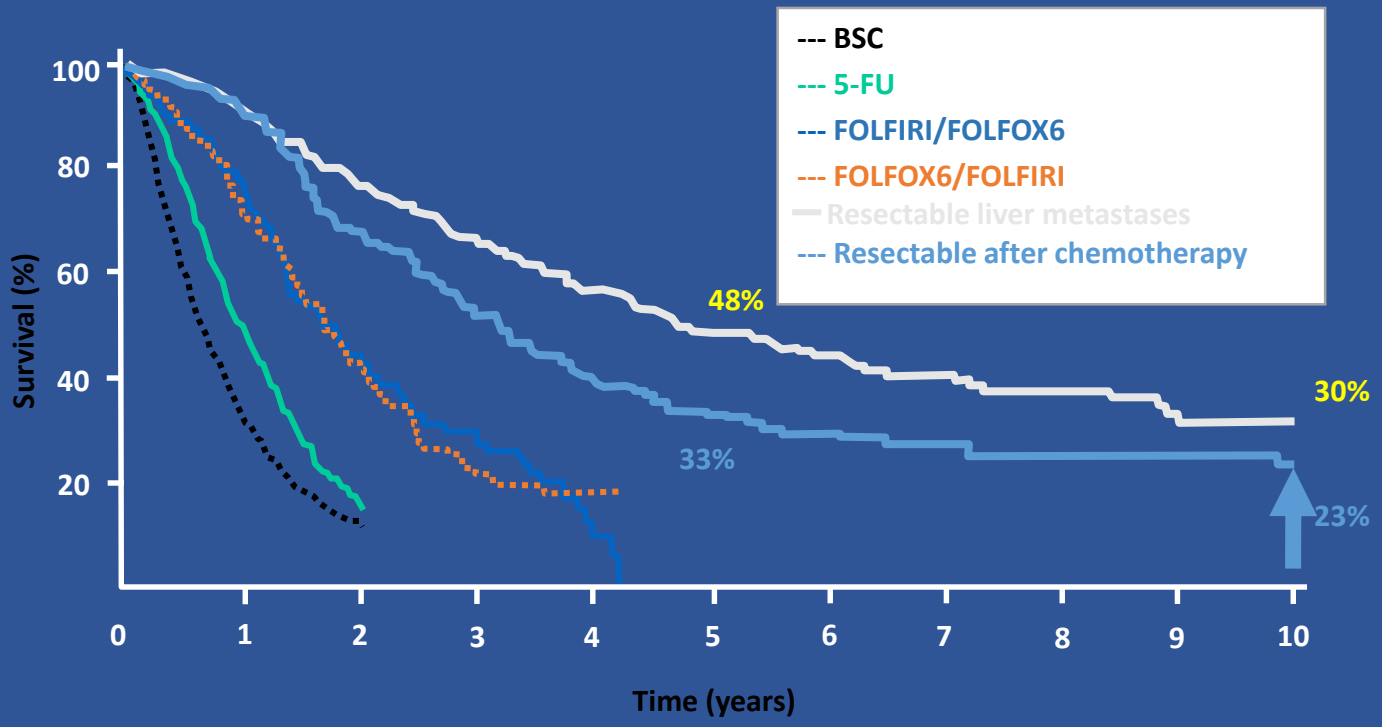


Oligometastases

- Local control of oligometastases may improve systemic control and prolonged survival via immune effects

- Stereotactic technique for extracranial sites, including the liver, lungs, nodes and spinal cord

Colorectal cancer exhibits an oligometastatic phenotype



Colon Cancer Collaborative Group. Br Med J 2000;321:521–522;
Tournigand C et al. J Clin Oncol 2004;22:229–237;
Adam R et al. Ann Surg 2004;240:644–658

Treatment options for Oligometastatic disease in mCRC

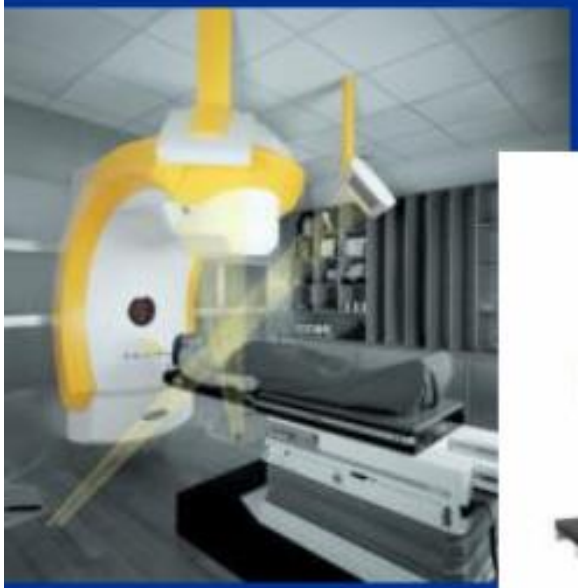
Site	Treatment Options
Liver	Surgery, RFA, TACE, SIRT, SBRT
Lung	Surgery, RFA, SBRT
Nodes	Surgery, CRT, SBRT
Brain	Surgery, RT, SBRT
Bone	RT, SBRT
Retreat after previous CRT	Surgery. SBRT

Principle 1

- Liver has a tolerance of only about 30 Gy if whole liver irradiated
- 30 Gy whole liver does not impact on survival
- Single lesions can be irradiated to high doses – but require about 70Gy for cure
- ie RT not feasible for diffuse disease

Technological Advances

- SBRT may be delivered through a variety of machines:
  - Linac-based SBRT (e.g. Novalis, Varian)
  - Cyberknife



mayo

Stereotactic body Radiotherapy (SBRT)

- **Delivery of a large dose of radiation to a lesion in a limited number of high dose treatments**

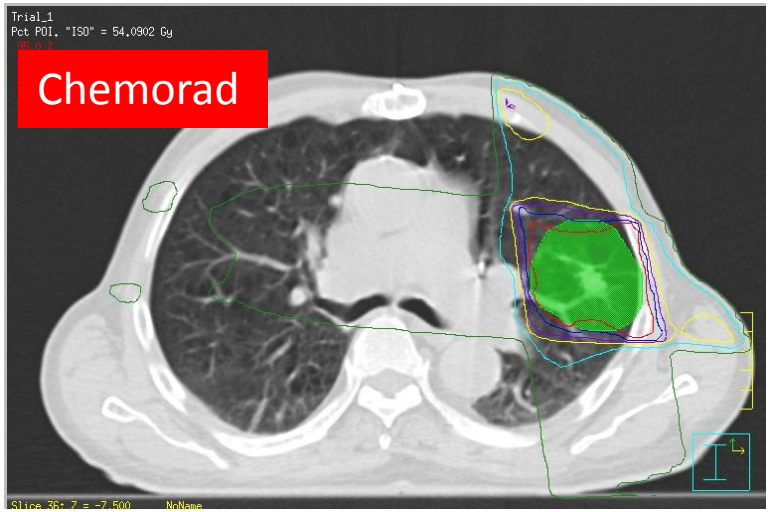
- Usually 5 or fewer fractions often 2-3

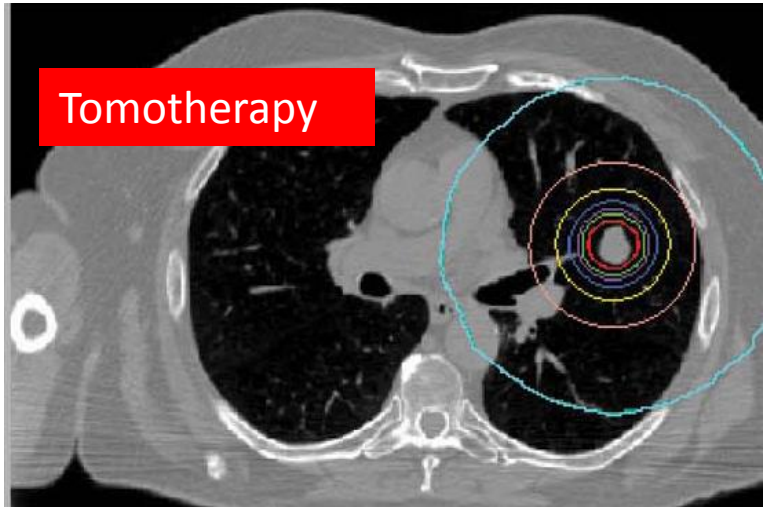
- **Multiple external beams are utilized**

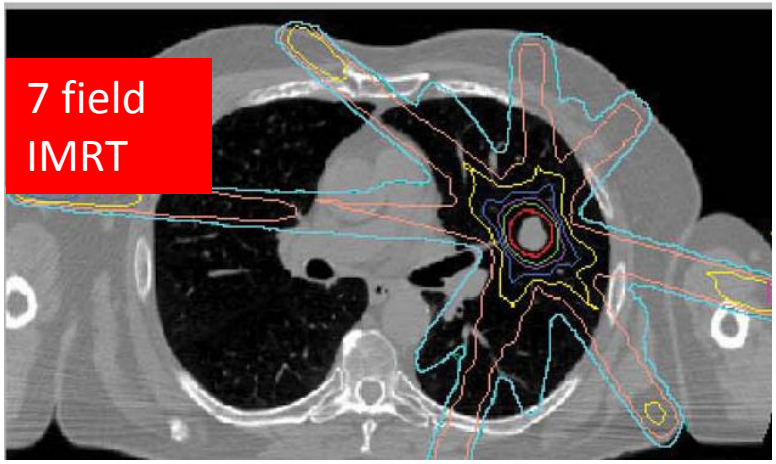
- precise, conformal dose distribution to the target
- relative sparing of the nearby normal tissues
- Allows for ablative doses to be delivered with acceptable toxicity in appropriately selected patients

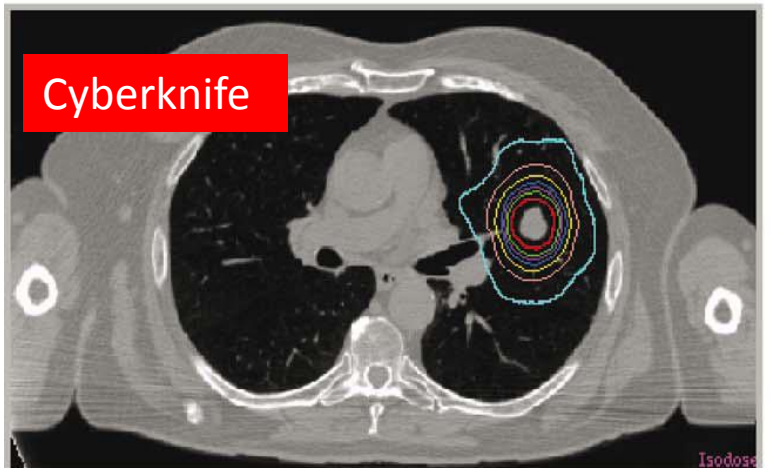
First Cyberknife in NHS in UK

CRT, tomo, IMRT (7field), CK









Stereotactic body Radiotherapy (SBRT)

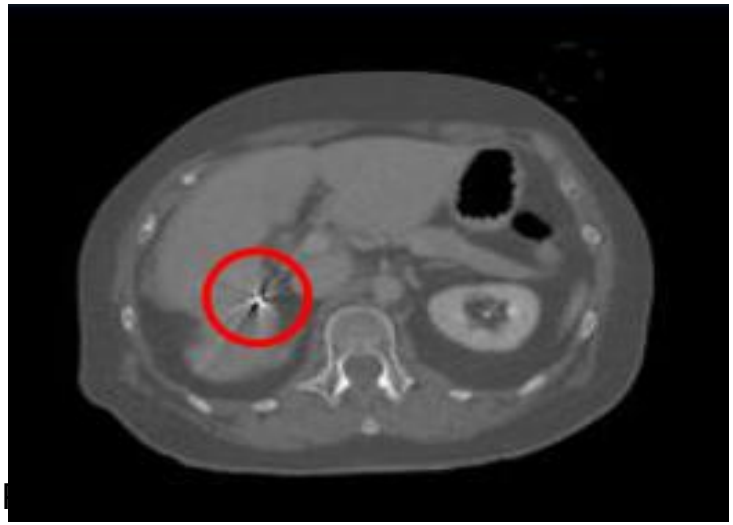
Extracranial sites are subject to movement from normal physiological processes

- Respiration
- Heartbeat
- Involuntary muscle contraction (e.g. GI tract)

Stereotactic body Radiotherapy (SBRT)

- Custom body cast with radiopaque markers (establishes coordinate system in 3-dimensional space)
- Implantation of markers internally (fiducials) for accurate tumour targeting
- Respiratory Gating ie turning the beam on & off in conjunction with the normal respiratory cycle
- breath-holding technique and

  direct abdominal compression



SBRT for mCRC

Author	Year	Pts	Lesions	LC (%)	OS (%)
Hoyer	2006	64	141	86 (2 yr)	38 (3yr) 13 (5yr)
Kang	2010	59	78	66 (3yr)	49(3yr)
Bae	2012	41	50	64	

Efficacy of SBRT for Liver Metastasis

Author	# of targets	Median follow up	Total Dose (Gy)	# of fractions	Local Control
Blomgren, 1995	21	9 mo	20-45	1-5	95%
Herfarth, 2001	60	6 mo	14-26	1	78%
Sato, 1998	23	10 mo	50-60	5-10	100%
Wulf, 2007	56	15 mo	28-37.5	3-4	1 yr: 92% 2 yr: 66%
Katz, 2007	174	14.5 mo	30-55	7-20	10 mo: 76% 20 mo: 57%
Lee, 2009	143	11 mo	30-60	6	1 yr: 71%
Rusthoven, 2009	63	16 mo	60	3	1 yr: 95% 2 yrs: 92%

Small studies with wide variety of fractionation schemes, but local control was excellent at 1 year (71-100%)

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Sci Rep. 2017; 7: 4866.
Published online 2017 Jul 7. doi: 10.1038/s41598-017-04978-x

PMCID: PMC5501824

Hypofractionated stereotactic radiation therapy activates the peripheral immune response in operable stage I non-small-cell lung cancer

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Abstract

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It has been reported that in patients with operable stage I non-small cell lung cancer (NSCLC), overall survival (OS) is better in those who undergo hypofractionated stereotactic radiation therapy (HSRT) than in those who undergo surgery. However, the reason that HSRT has a better OS has not been fully explored. Here, we analyzed reconstitution kinetics in immune cells in the peripheral blood of NSCLC patients after HSRT. We found that HSRT increased the frequency of total T cells, especially the proportion of $CD8^+$ T cells, but decreased the frequency of inhibitory Tregs. Intracellular staining showed that after HSRT, peripheral $CD8^+$ T cells were transformed into activated T cells, which express high levels of TNF-α, IFN-γ, granzyme B and IL-2. HSRT also increased the production of IL-2, TNF-α, and IFN-γ but down-regulated the production of TGF-β in $CD4^+$ T cells. The frequencies of naïve B cells and double-negative B cells were lower, while the proportions of MZ-like B cells, transitional B cells and plasmablast cells were higher after HSRT. Collectively, our results demonstrate that HSRT activates the peripheral immune response and indicate the dynamic variation in peripheral lymphocytes after HSRT, which is very important for optimizing combination treatments in clinical practice.

Radiotherapy can be curative

- not only by killing tumor cells
- and killing associated stromal and vascular cells,
- but also by inducing T cell immunity

- Treatment of advanced CT26 tumors by single high dose radiation leads to complete remission, and development of systemic long-term immunity that can be adoptively transferred by T cells

Filatenkov A, et al . Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions. Clin Cancer Res. 2015 Aug 15;21(16):3727-39

- If more diffuse liver metastases

Selective internal radiotherapy (SIRT)

- Percutaneous trans-arterial administration of micron-sized embolic particles containing a radioisotope
- Delivers high dose of RT to a small target volume

Yttrium-90

- 15-20 million resin spheres
- Pure beta emitter with a mean energy of 0.94 MeV, max 2.27
- 1 GBq (27 mCi) delivers a total absorbed dose of 50 Gy/kg
- Tissue penetration range mean 2.5mm, max 11 mm
- 2.67 days half life (≈64 hours)
- Following administration, 94% of the radiation is delivered in 11 days.

First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials

Harpreet S Wasan, Peter Gibbs*, Navesh K Sharma, Julien Taieb, Volker Heinemann, Jens Ricke, Marc Peeters, Michael Findlay, Andrew Weaver, Jamie Mills, Charles Wilson, Richard Adams, Anne Francis, Joanna Moschandreas, Pradeep S Virdee, Peter Dutton, Sharon Love, Val Gebski, Alastair Gray, FOXFIRE trial investigators†, SIRFLOX trial investigators†, FOXFIRE-Global trial investigators†, Guy van Hazel*, Ricky A Sharma**

Summary

Background Data suggest selective internal radiotherapy (SIRT) in third-line or subsequent therapy for metastatic colorectal cancer has clinical benefit in patients with colorectal liver metastases with liver-dominant disease after chemotherapy. The FOXFIRE, SIRFLOX, and FOXFIRE-Global randomised studies evaluated the efficacy of combining first-line chemotherapy with SIRT using yttrium-90 resin microspheres in patients with metastatic colorectal cancer with liver metastases. The studies were designed for combined analysis of overall survival.

Methods FOXFIRE, SIRFLOX, and FOXFIRE-Global were randomised, phase 3 trials done in hospitals and specialist liver centres in 14 countries worldwide (Australia, Belgium, France, Germany, Israel, Italy, New Zealand, Portugal, South Korea, Singapore, Spain, Taiwan, the UK, and the USA). Chemotherapy-naive patients with metastatic colorectal cancer (WHO performance status 0 or 1) with liver metastases not suitable for curative resection or ablation were randomly assigned (1:1) to either oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) or FOLFOX plus single treatment SIRT concurrent with cycle 1 or 2 of chemotherapy. In FOXFIRE, FOLFOX chemotherapy was OxMdG (oxaliplatin modified de Gramont chemotherapy; 85 mg/m² oxaliplatin infusion over 2 h, L-leucovorin 175 mg or D,L-leucovorin 350 mg infusion over 2 h, and 400 mg/m² bolus fluorouracil followed by a 2400 mg/m² continuous fluorouracil infusion over 46 h). In SIRFLOX and FOXFIRE-Global, FOLFOX chemotherapy was modified FOLFOX6 (85 mg/m² oxaliplatin infusion over 2 h, 200 mg leucovorin, and

Lancet Oncol 2017; 18: 1159–71

Published Online August 3, 2017 http://dx.doi.org/10.1016/S1470-2045(17)30457-6

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†Full list of members in the appendix

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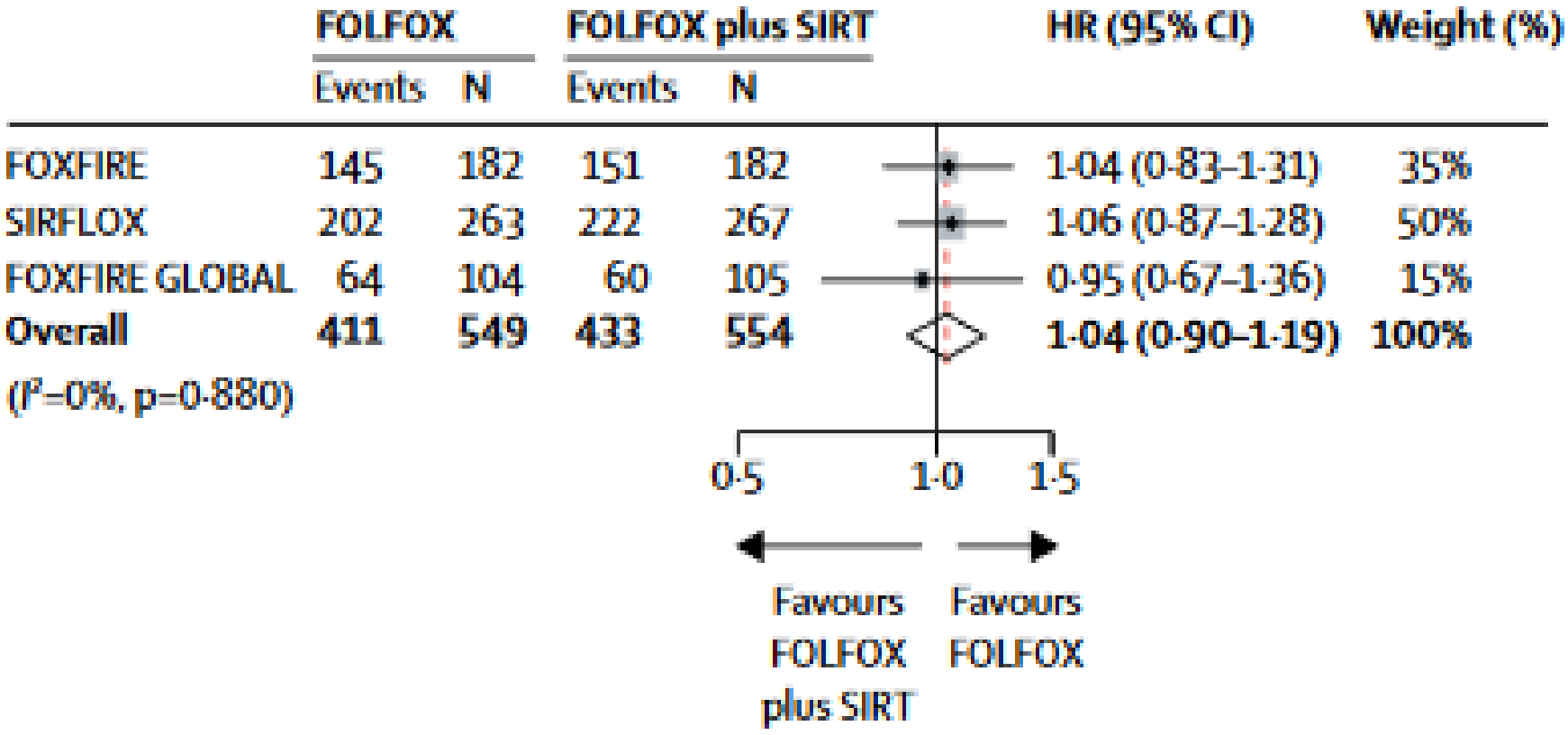

FOLFOX
FOLFOX plus SIRT
HR (95% CI)
Weight (%)
Events N Events N
FOXFIRE 145 182 151 182 1·04 (0·83–1·31) 35%
SIRFLOX 202 263 222 267 1·06 (0·87–1·28) 50%
FOXFIRE GLOBAL 64 104 60 105 0·95 (0·67–1·36) 15%
Overall 411 549 433 554 1·04 (0·90–1·19) 100%
(I²=0%, p=0·880)
0·5
1·0
1·5
Favours FOLFOX plus SIRT
Favours FOLFOX

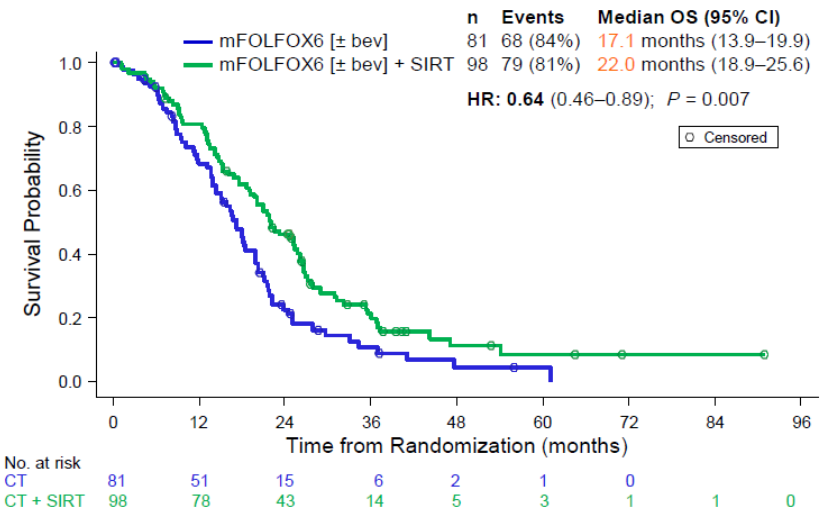
SIRT added to first-line FOLFOX in liver-only and liver-dominant CRC

- higher response
- Improved liver-specific PFS
- No improvement overall PFS
- No improvement overall survival

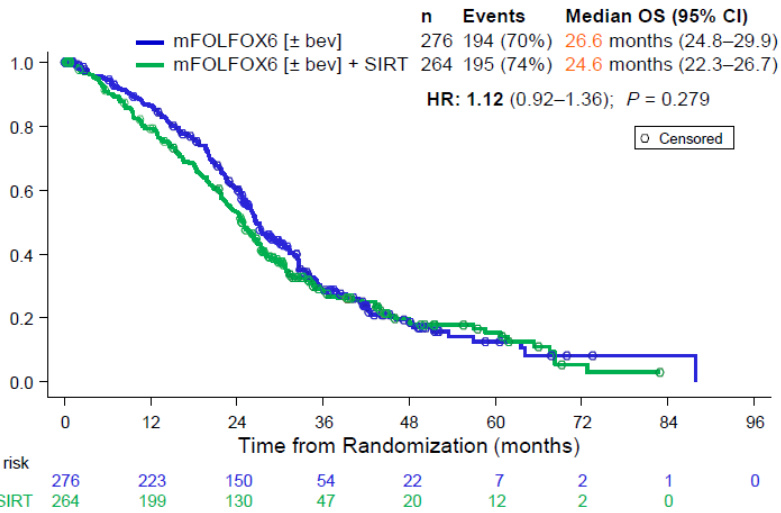
Wasan H, et al Lancet Oncology 2017.

Adding SIRT to 1st-line chemotherapy was associated with a statistically and clinically significant gain in OS for RSP patients, but not for LSP patients

Right-Sided Primary Tumours



Left-Sided Primary Tumours



Summary SBRT

- Numerous small studies
- Excellent 1 year local control (80% overall)
- Optimal dose and fractionation yet to be determined
- Late effects unknown as yet

- If local control approx. 25% don’t get more mets

Summary SIRT

- 3 small studies
- No clear benefit in DFS or OS