

Selective internal radiotherapy for liver metastases from colorectal cancer

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Disclosures

Honoraria:

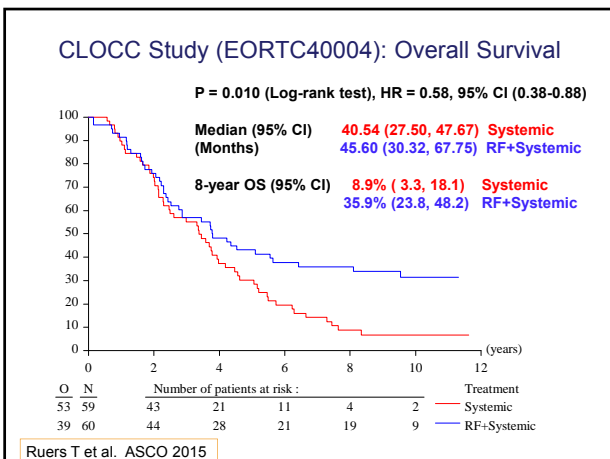
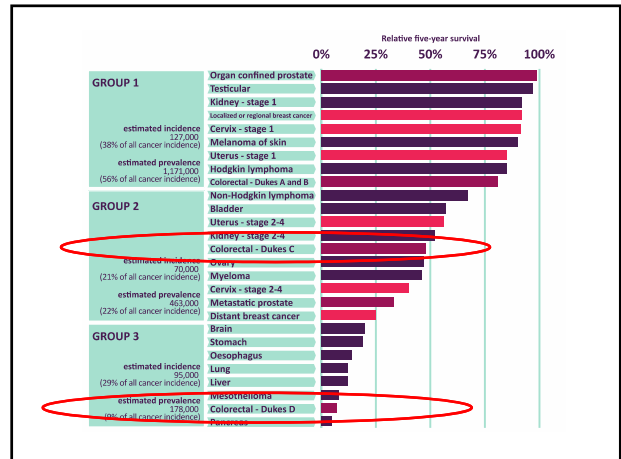
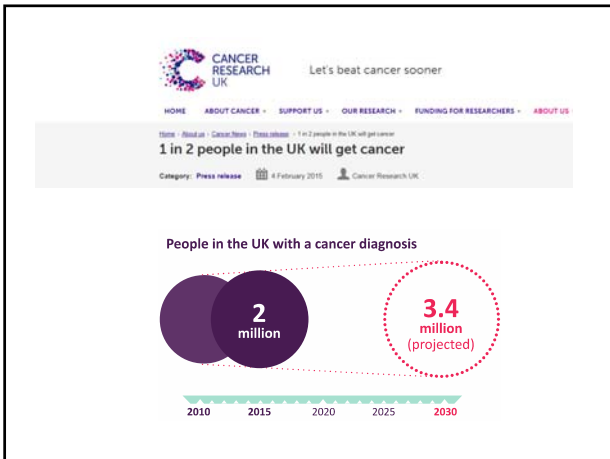
- Biocompatibles UK, Sirtex, Roche

Advisory Boards/Consultancy:

- Astra Zeneca, Vertex, Biocompatibles UK, Sirtex, Cancer Research Technology, Terumo, Affidea, Varian

Research Funding:

- Sirtex, BTG



Interventional Oncology

ALL CHANGE!

- Has always been about:
 - Supportive treatment, symptom relief
- Rapidly advancing new clinical specialism: Radiology + Oncology + Minimally Invasive Surgery
 - Potentially curative image-guided treatments
 - Challenging standard treatments
 - Complex multi-disciplinary care
 - Registry-based commissioning models

Franklin JM, Poston G, Sharma RA. *Nature Reviews Clinical Oncology* 20; 12: 93-104 (2015)

Liver-directed treatments to be considered by a Liver MDT, in addition to systemic therapy

Depends on number, distribution and exact position of each metastasis

<p>PAUCI-METASTATIC</p> <ul style="list-style-type: none"> • Surgery • Thermal ablation • SBRT • SIRT (segmental delivery) • Clinical trials of new technologies 	<p>POLY-METASTATIC</p> <ul style="list-style-type: none"> • The same • Clinical trials • SIRT
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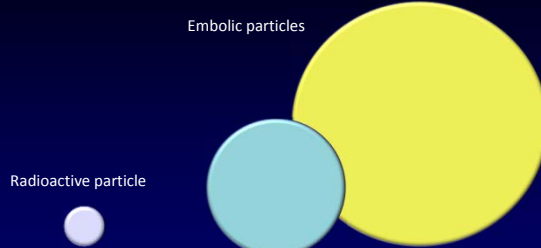
Tumorigenesis and Neoplastic Progression
Development of Arterial Blood Supply in Experimental Liver Metastases
Katalin Dezső,¹ Edina Bugyik,¹ Veronika Papp,¹ Viktória László,¹ Balázs Dóme,^{1†} József Tóvári,¹ József Timár,¹ Péter Nagy,² and Sándor Paku¹



Arterialised micrometastasis showing dilated arteriole as source of feeding branches

Metastasis supplied by dilated artery, significantly larger than the artery accompanying the portal vein

Microparticles Compared



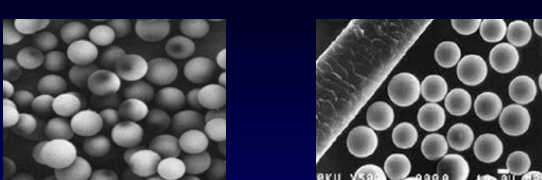
Embolic particles

Radioactive particle

⁹⁰Y-microspheres
20-35 microns

TAE, TACE and Drug Eluting Beads
75-700 microns

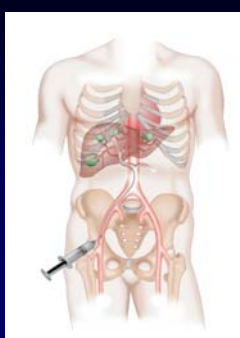
Resin and glass microspheres



- Mean diameter 20-35 µm
- Yttrium⁹⁰ = Beta 0.93 MeV
- 64 hour half life
- Tissue penetration: 2.5 mm mean
11 mm max

Overview of SIRT Technique

- Typically a 2-stage process:
- Work-up procedure:
 - Trans-femoral angio to access hepatic arterial vasculature and identify tumour feeding vessels
 - Prophylactic occlusion of extra-hepatic vessels
 - Injection of ^{99m}Tc-MAA /SPECT-CT and gamma camera to assess shunting
- Treatment procedure:
 - Up to 3 weeks later
 - Fluoroscopy and then delivery of Y90 microspheres dose
 - SPECT-CT or Y90-PET to confirm sites of activity



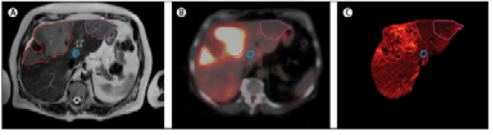
Yttrium-90 SIRT devices

TheraSphere [®]	Sir-Spheres [®]
BTG	Sirtex
Glass	Resin
Mean 20-30 µM	Mean 35 µM
Specific gravity 3.4	Specific gravity 1.6
High activity	Moderate activity
1.2 – 1.5 million per administration	20 – 40 million per administration

Articles

Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study

Maarten I J Smits, Johannes F W Nijzen, Maurice A A J van den Bosch, Manie G F H Lam, Maarten A D Vierge, Willem P T M Mali, Alfred D van der Schijf, Bernard A Zoonenborg



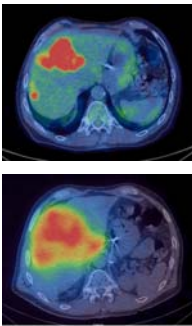
Lancet Oncol 2012,13:1025-1034



Delivery techniques

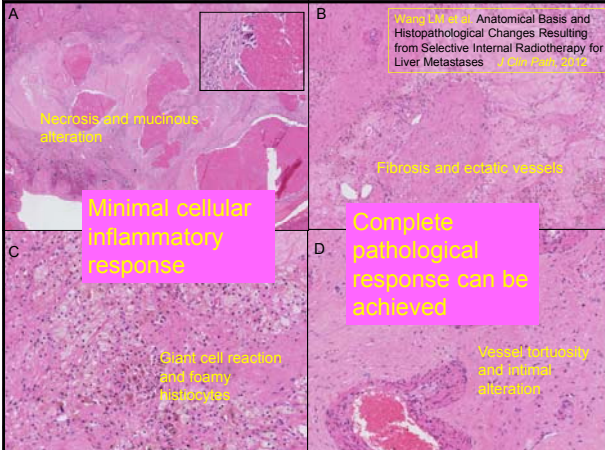
TheraSphere®	Sir-Spheres®
Saline	Glucose 5%
20 ml flush x2	Sandwich technique
No imaging	Intermittent fluoroscopy
Delivered in patient-specific dose vials	Decanted from standard 3 GBq activity
No radiopharmacy manipulation	Dispensed in radiopharmacy
Fixed treatment plan	Flexibility at administration

Segmental delivery of glass microspheres



FdG-PET scan of recurrent metastatic colorectal cancer

SPECT-CT 18 hours after yttrium-90 SIRT



Minimal cellular inflammatory response

Complete pathological response can be achieved

Wood LM et al. Anatomical Basis and Histopathological Changes Resulting from Selective Internal Radiotherapy for Liver Metastases. *J Clin Pathol* 2010

SIRT to treat Chemo-Refractory mCRC

Investigator	n	Treatment	ORR	SD	TTP/ [§] PFS	Survival
Hendlisz	44	SIRT + 5FU	10%	76%	5.5 / 4.5 mo	10.0 mo
		5FU > salvage with SIRT at PD	0%	35%	2.1 mo	7.3 mo
Rühl	29	SIRT	41%	17%	5.5 mo [§]	8.3 mo
		best supportive care (matched-pairs)	nr	nr	2.1 mo [§]	3.5 mo
Cosimelli	50	SIRT	24%	24%	4 mo [§]	12.6 mo
Jakobs	41 [†]	SIRT [†]	17%	61%	5.9 mo	10.5 mo
Cianni	41 [†]	SIRT	46%	36%	9.3 mo [§]	11.8 mo
Nace	51 [†]	SIRT	13%	64%	nr	10.2 mo
Kennedy	208 [†]	SIRT responders	36%	55%	7.2 mo	10.5 mo
		non-responders/controls	na	na	na	4.5 mo

Hendlisz et al. *J Clin Oncol* 2010; 28:3681-94. Rühl J et al. *Eur J Cancer Suppl* 2009; 7: 343 Abstr. 4071. Cosimelli et al. *Br J Cancer* 2010; 103:324-31. Jakobs et al. *J Vasc Interv Radiol* 2008; 19:1187-95. Cianni et al. *Cardiovasc Interv Radiol* 2009; 32:1179-86. Nace et al. *Int J Surg Oncol* 2011; ePub. Kennedy et al. *Int J Radiat Oncol Biol Phys* 2006; 65:412-25.



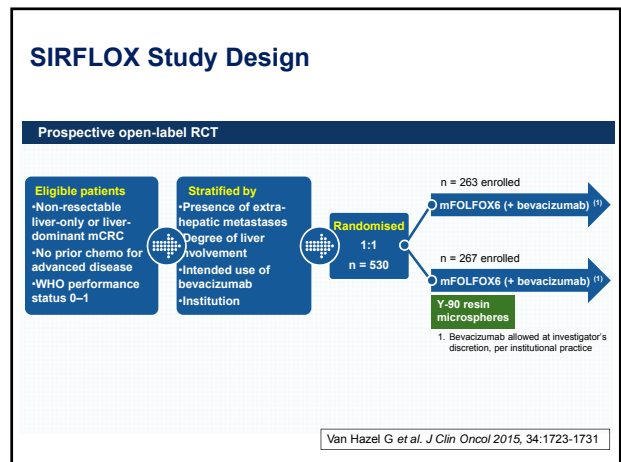
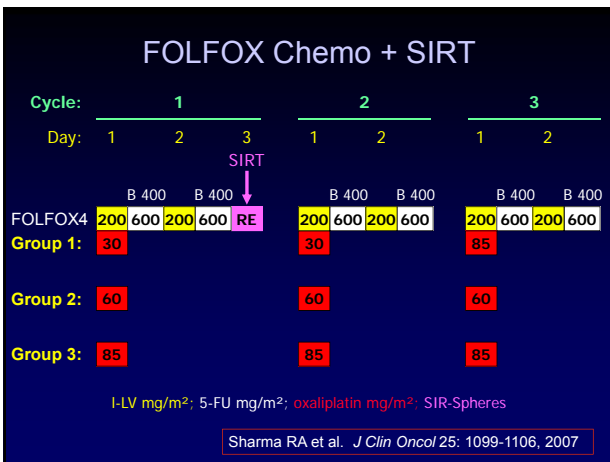
Patient selection for SIRT

PATIENT FACTORS

- Performance Status
- Liver Function Tests
- Previous hepatotoxic chemotherapy

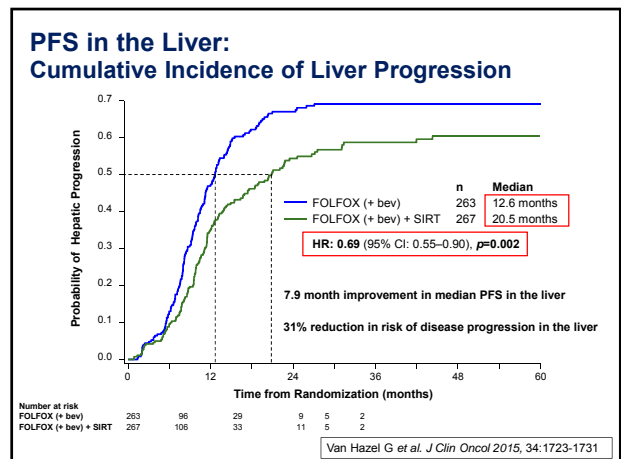
RADIOLOGICAL CRITERIA

- Percentage of liver replacement by tumour
- Rate of tumour progression
- Burden of extrahepatic disease



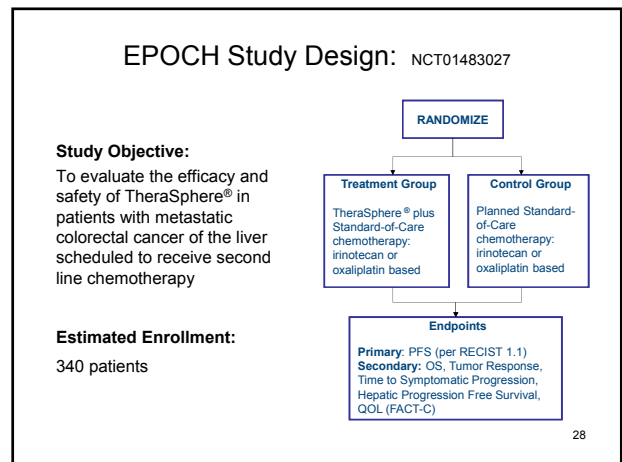
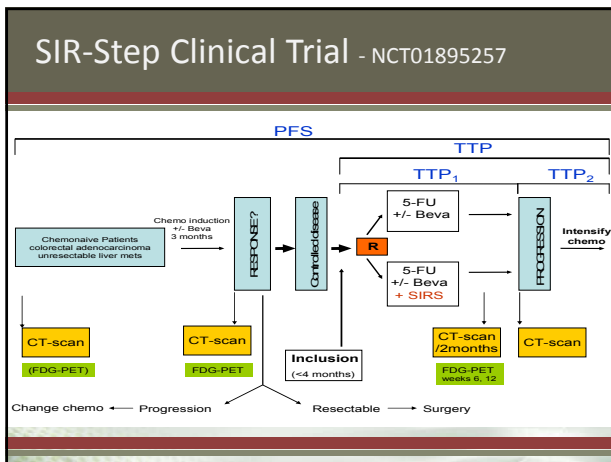
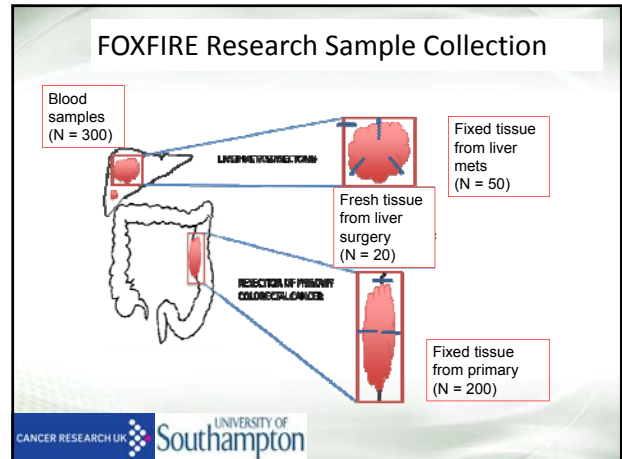
Grade ≥3 Adverse Events in SIRFLOX

	FOLFOX (+bev) (n = 270) Grade ≥3 (%)	FOLFOX (+bev) + SIRT (n = 246) Grade ≥3 (%)
All subjects	73.4	85.4
Chemotherapy-related events		
Neutropenia	28.5	40.7
Febrile neutropenia	1.9	6.1
Thrombocytopenia	2.6	9.7
Diarrhoea	8.9	7.3
Nausea and/or vomiting	4.1	8.1
SIRT-related events		
Gastric or duodenal ulcer	0	3.6
Ascites	0	2.8
Hepatic failure	0	1.2
Radiation hepatitis	0	0.8



Three studies designed for a combined analysis of Overall Survival, plus secondary endpoints

Study Name	Study Design	Geographic Region	Recruitment Completed	Patients Recruited	OS Data Expected
SIRFLOX	RCT	ANZ, EME, US	April 2013	530	ASCO 2017
FOXFIRE	RCT	UK	November 2014	364	
FOXFIRE Global	RCT	ANZ, AP, EME, US	January 2015	209	
Total accrual				1,103	



ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Durvalumab and Tremelimumab in Treating Patients With Microsatellite Stable Metastatic Colorectal Cancer to the Liver

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified December 2016 by City of Hope Medical Center

Sponsor:
City of Hope Medical Center

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
City of Hope Medical Center

ClinicalTrials.gov Identifier:
NCT03065002

First received: December 23, 2016
Last updated: NA
Last verified: December 2016
History: No changes posted

- Take home messages**
- Selective internal radiotherapy (SIRT) should be in patient pathways for chemo-refractory mCRC, and patient selection at highly specialist centres is appropriate
 - There is evidence SIRT can significantly improve control of liver metastases in the first-line setting; the impact on overall survival will be reported this year

