SIRT in malignant liver lesions

Inaugural Malaysian Nuclear Medicine Conference

September 2018

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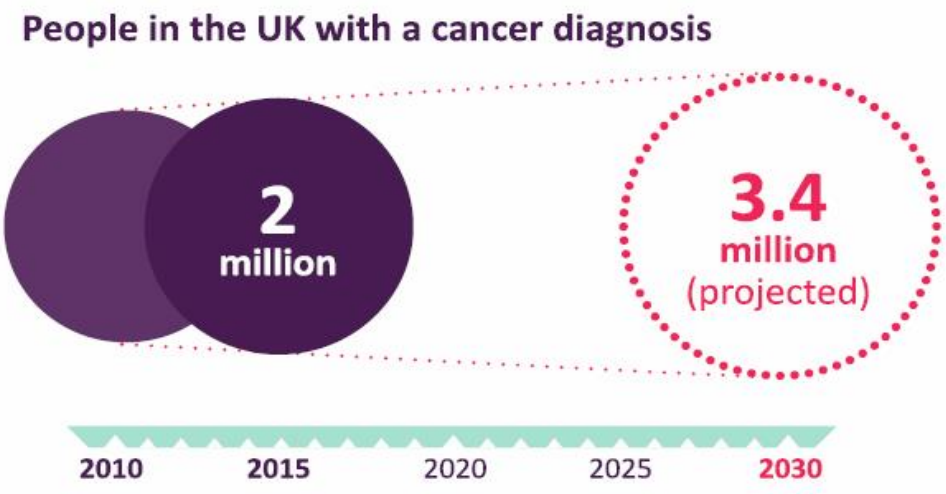
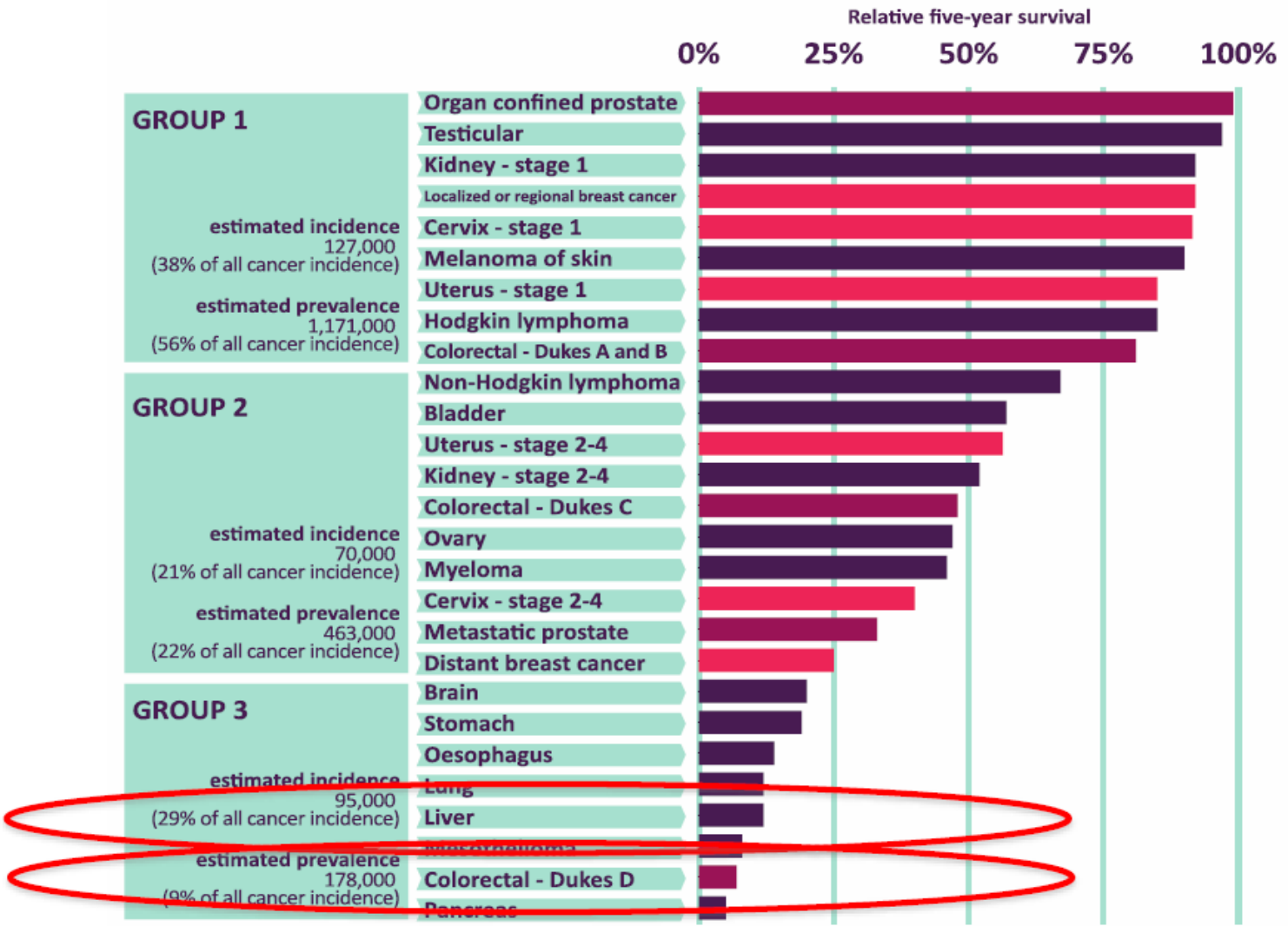
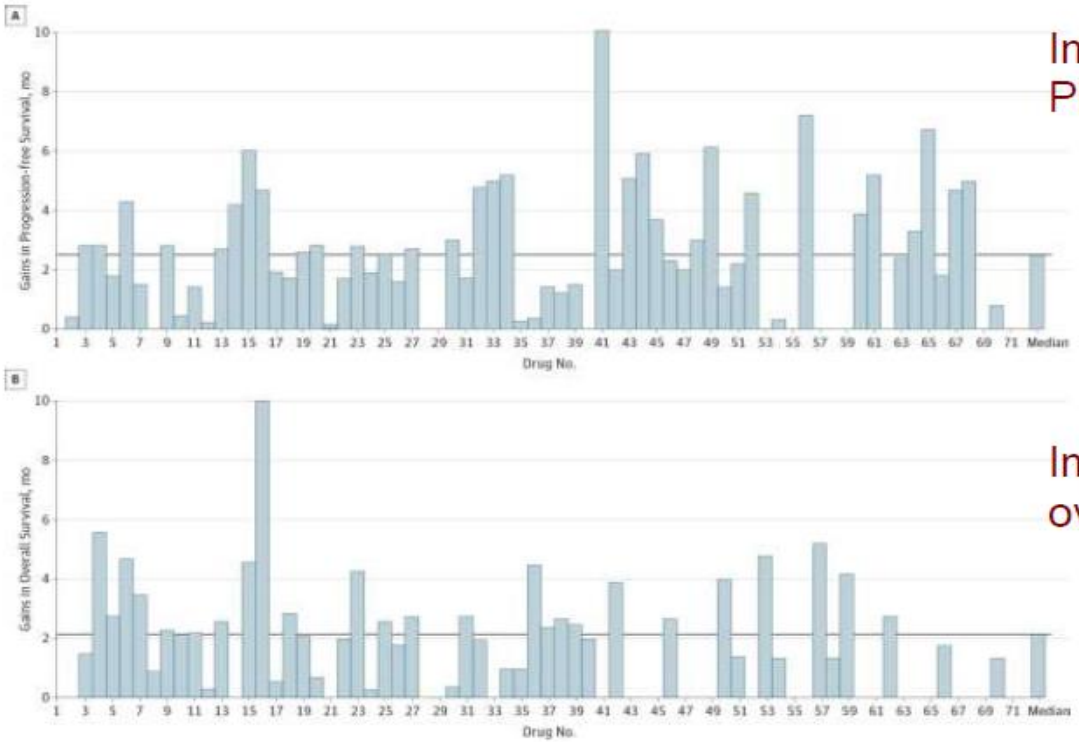
1 in 2 people in the UK will get cancer

Category: Press release 4 February 2015 Cancer Research UK




Relative five-year survival
0%
25%
50%
75%
100%
GROUP 1
estimated incidence
127,000
(38% of all cancer incidence)
estimated prevalence
1,171,000
(56% of all cancer incidence)
Organ confined prostate
Testicular
Kidney - stage 1
Localized or regional breast cancer
Cervix - stage 1
Melanoma of skin
Uterus - stage 1
Hodgkin lymphoma
Colorectal - Dukes A and B
GROUP 2
estimated incidence
70,000
(21% of all cancer incidence)
estimated prevalence
463,000
(22% of all cancer incidence)
Non-Hodgkin lymphoma
Bladder
Uterus - stage 2-4
Kidney - stage 2-4
Colorectal - Dukes C
Ovary
Myeloma
Cervix - stage 2-4
Metastatic prostate
Distant breast cancer
GROUP 3
estimated incidence
95,000
(29% of all cancer incidence)
estimated prevalence
178,000
(9% of all cancer incidence)
Brain
Stomach
Oesophagus
Liver
Colorectal - Dukes D

71 drugs for all solid cancers approved by the FDA from 2002 to 2014



Improvement in median PFS = 2.5 months

Improvement in median overall survival = 2.1 months

Fojo T et al. *JAMA Otolaryngol Head Neck Surg*. 2014; 140: 1225-1236

Interventional oncology (IO)

- Rapidly growing subspeciality – radiology/oncology/minimally invasive surgery
- Potentially curative image guided treatment, complex multidisciplinary care
- Aims to develop disease modifying treatment options beyond conventional surgical and oncological therapies
- Evidence dominated by single arm studies, not sufficient to change clinical practice uniformly across health care systems
- Limited data on cost effectiveness and PROMS

Interventional oncology (IO)

- IR techniques used in diagnosis, treatment or palliation of patients with cancer
- Examples of disease modifying procedures:
  - image guided ablation
  - image guided brachytherapy
  - bland/chemo embolisation
  - isolated perfusion chemotherapy
  - selective internal radiation therapy (SIRT)

Liver disease

- Liver metastases are the commonest form of malignant liver disease
- Associated with poor prognosis
- Most frequently from primary colorectal cancer (20%)
- Primary liver tumours eg. HCC, cholangioCa less common in Europe
- Surgical resection is treatment of choice, 5 yr OS – 50%
- Only 20% of patients with liver metastases are candidates for surgical resection

Liver disease

- For unresectable disease, non-surgical approaches include systemic chemotherapy
- Chemotherapy has proven survival benefits
- Chemotherapy associated with toxicity, short duration and poor response rates, with poor clinical outcomes
- More effective non-surgical liver directed therapeutic strategies required
- Local vs systemic therapy should improve efficacy and reduce systemic toxicity
- Liver directed therapies include RFA, TAE, TACE, SABR and SIRT/TARE

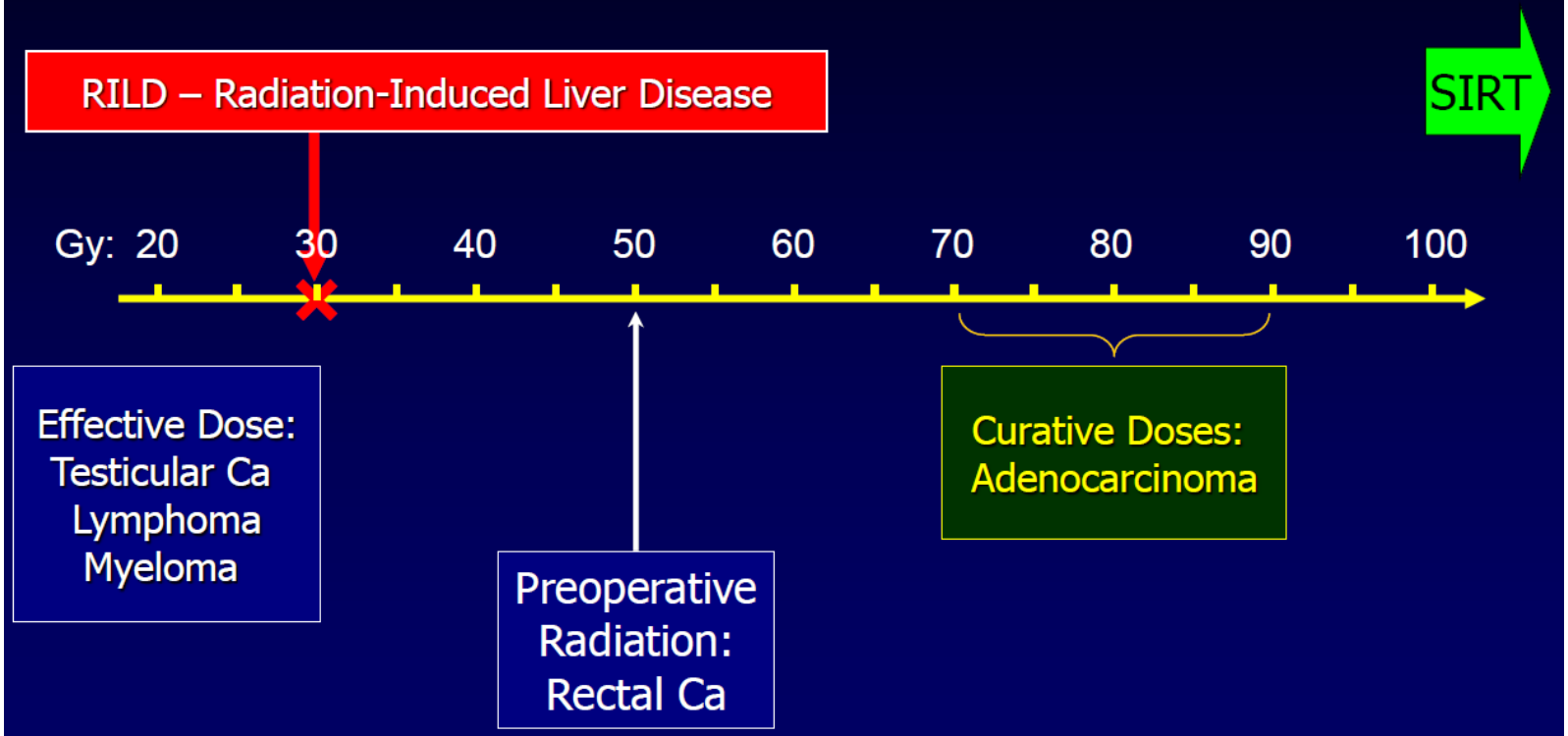
Selective internal radiation therapy (SIRT)

- For primary liver malignancy (mainly HCC) and liver metastases (mainly CRC)
- Other malignancies include cholangiocarcinoma, breast and NET metastases
- Not yet included in liver management guidelines as RCT outcomes awaited
- EASL guidelines recommend:
  - TACE for intermediate stage HCC
  - Sorafenib for advanced stage HCC

Concept of SIRT

- Also known as radioembolization (TARE), hepatic artery brachytherapy
- Delivery of radioactive substance into tumour vascular supply (common/left/right hepatic artery) via intra-arterial catheter
- Liver tumours derive >80% blood supply from hepatic artery
- Selectively deliver very high radiation doses to liver tumours, whilst minimising radiation dose to normal liver parenchyma
- Achieves tumouricidal doses of radiation (>100 Gy)

Liver Tolerance & Tumour Sensitivity to Radiation



Kennedy A, Coldwell D, Nutting C *et al.* Pathology and microdosimetry in human livers after ^{90}Y-microspheres. *Int J Rad Oncol Biol Phys* 2004; **60**(5): 1520–1533.

Overview of SIRT Technique

- **2 stage process**
- **Work-up procedure:**

- Transfemoral angiogram to access hepatic arterial vasculature and identify tumour feeding vessels

- Prophylactic occlusion of extra-hepatic vessels eg GDA, right gastric etc.

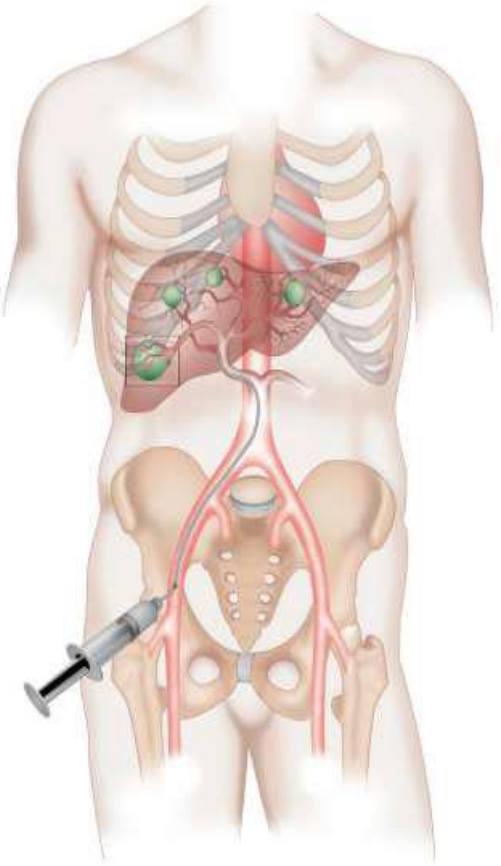
- 99mTc-MAA administration + gamma camera SPECT +/- CT to assess lung shunt, hepatic & extra-hepatic uptake

- **Treatment procedure** 1-3 weeks later:

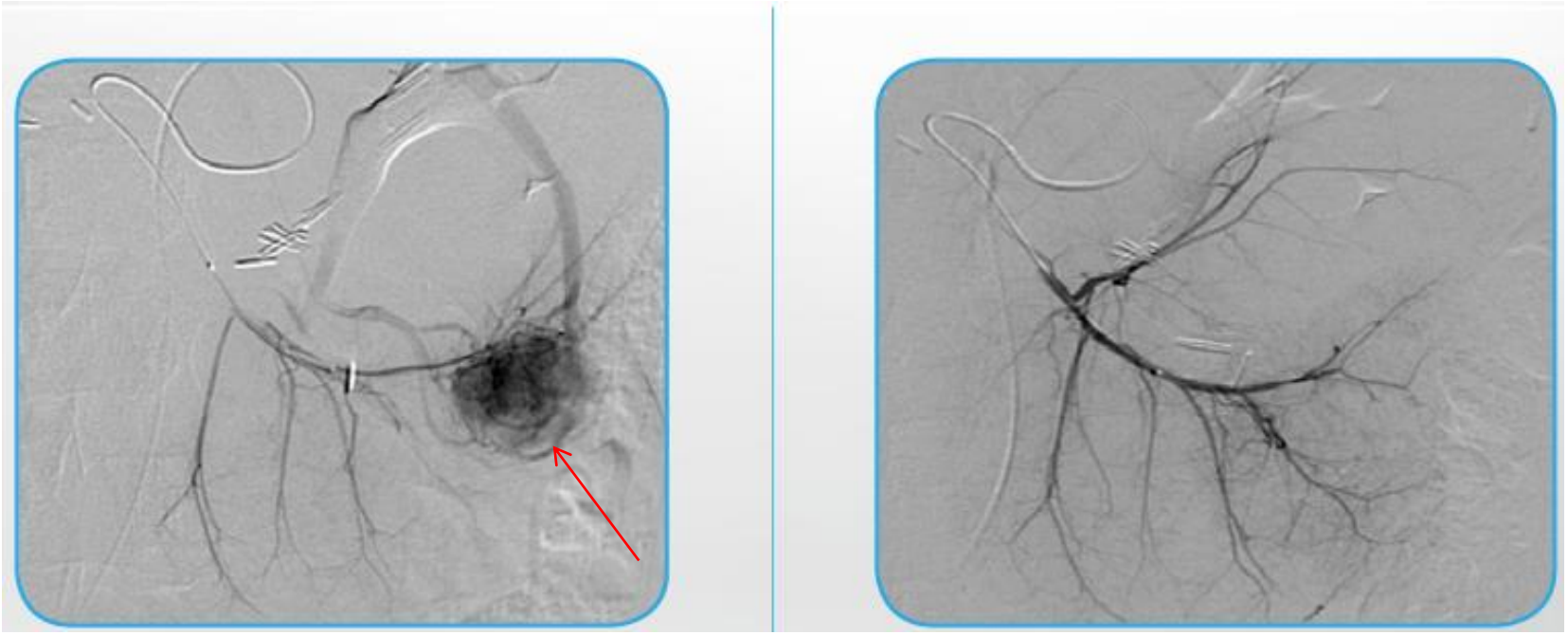
- Reassessment of vascular anatomy

- Delivery of 90Y-microspheres treatment

- Planar +/- SPECT CT images to confirm adequacy of treatment



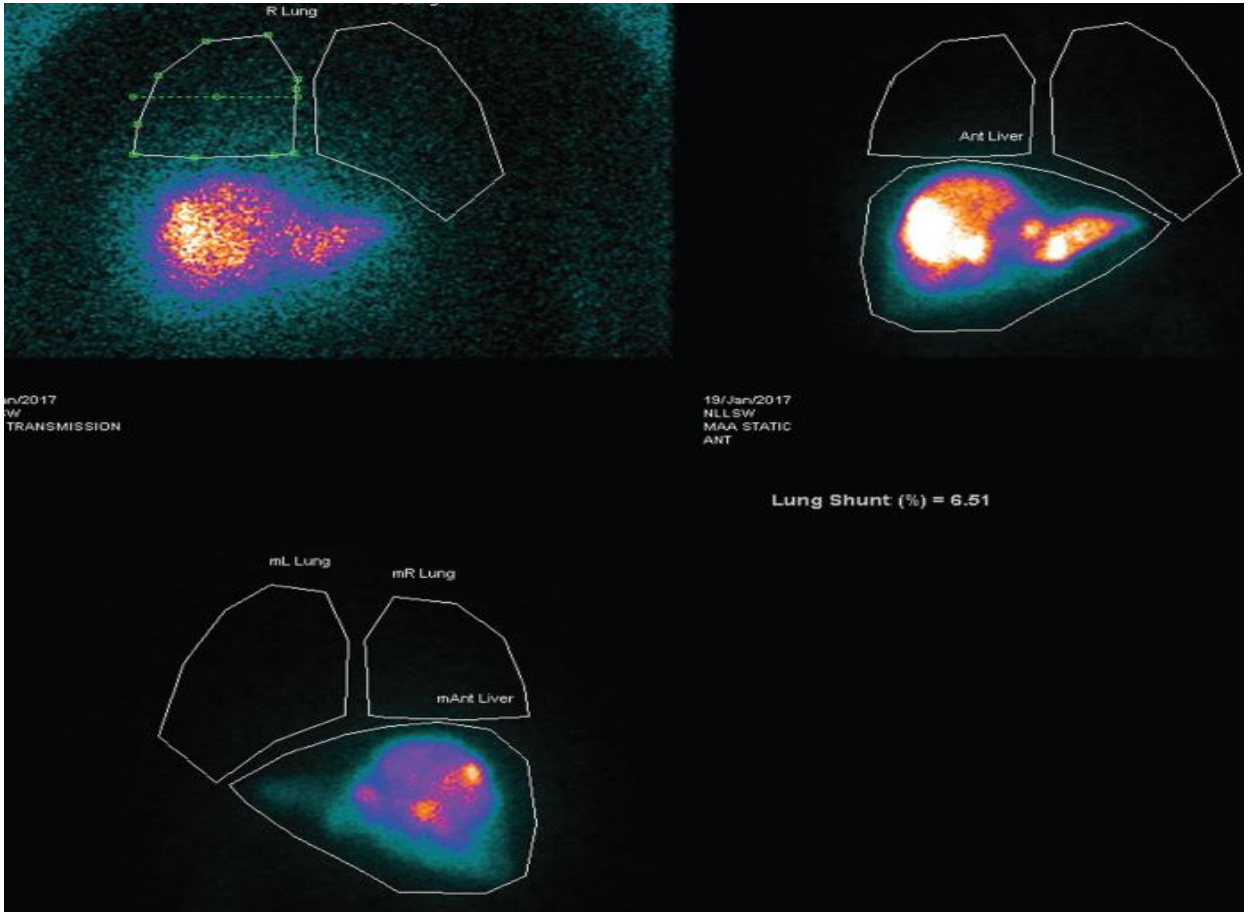
Angiography



Pre SIRT

Post SIRT

^{99m}Tc-MAA study and lung shunt calculation



^{99m}Tc-MAA study extra-hepatic uptake

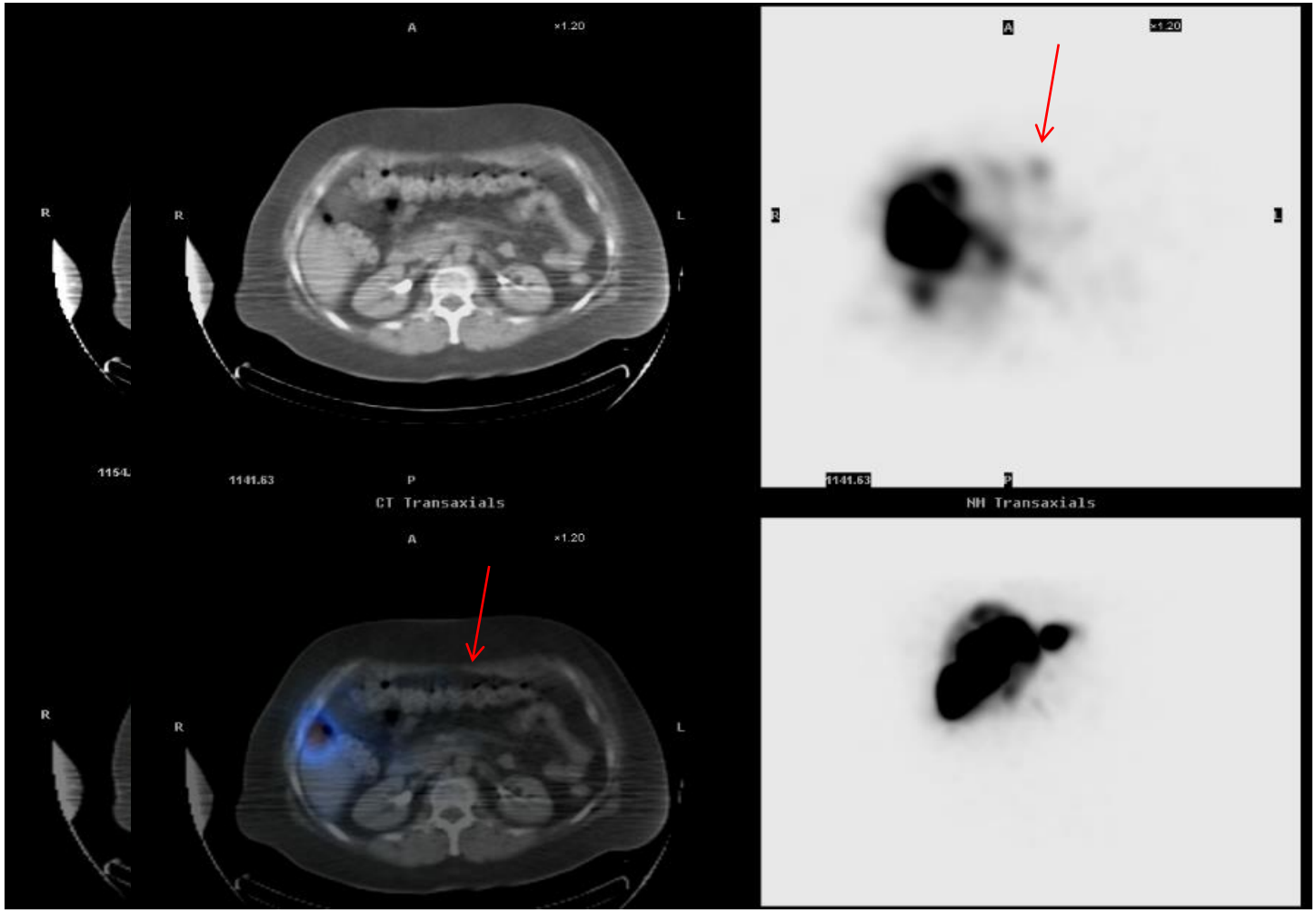
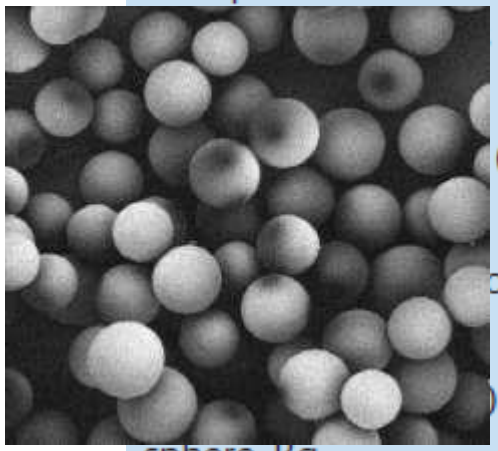
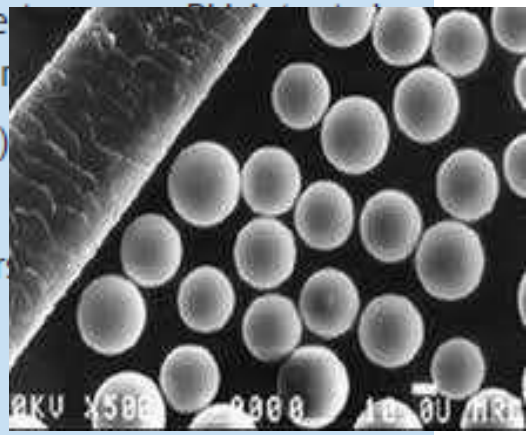


Table 1. Properties of compounds used in selective internal radiation therapy

	TheraSpheres	SIR-Spheres	QuiremSpheres
Size, μm	20–30	20–60	20–50
Isotope	Yttrium-90 in matrix	Yttrium-90 adsorbe resin su	Holmium-166
	(β)	beta (β)	
	ours	64 hour	
sphere, Bq		50	
Number of particles	~1–8×10^6	~40–80×10^6	33×10^6
Angiographic monitoring	No	Necessary (potential reflux)	Necessary (potential reflux)



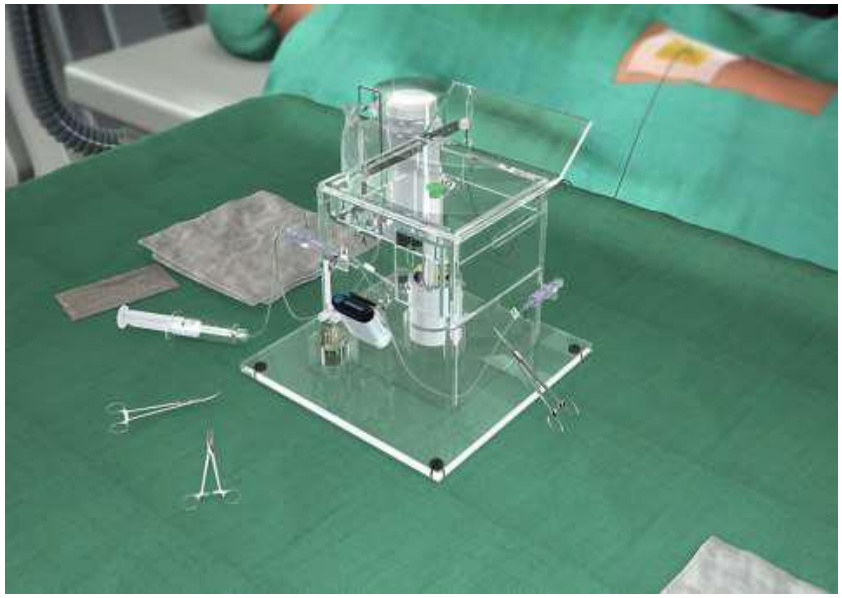


SIRT delivery techniques

	Theraspheres	SIR-spheres
Flushing agent	Saline	5% dextrose
Flushing technique	2 x 20 ml flush	Sandwich technique
Imaging	No fluoroscopy	Intermittent fluoroscopy
Dose vials	Patient specific	Decanted from standard 3GBq activity
Radiopharmacy input	Not required	Dispensing
Treatment plan	Fixed treatment	Administration flexibility

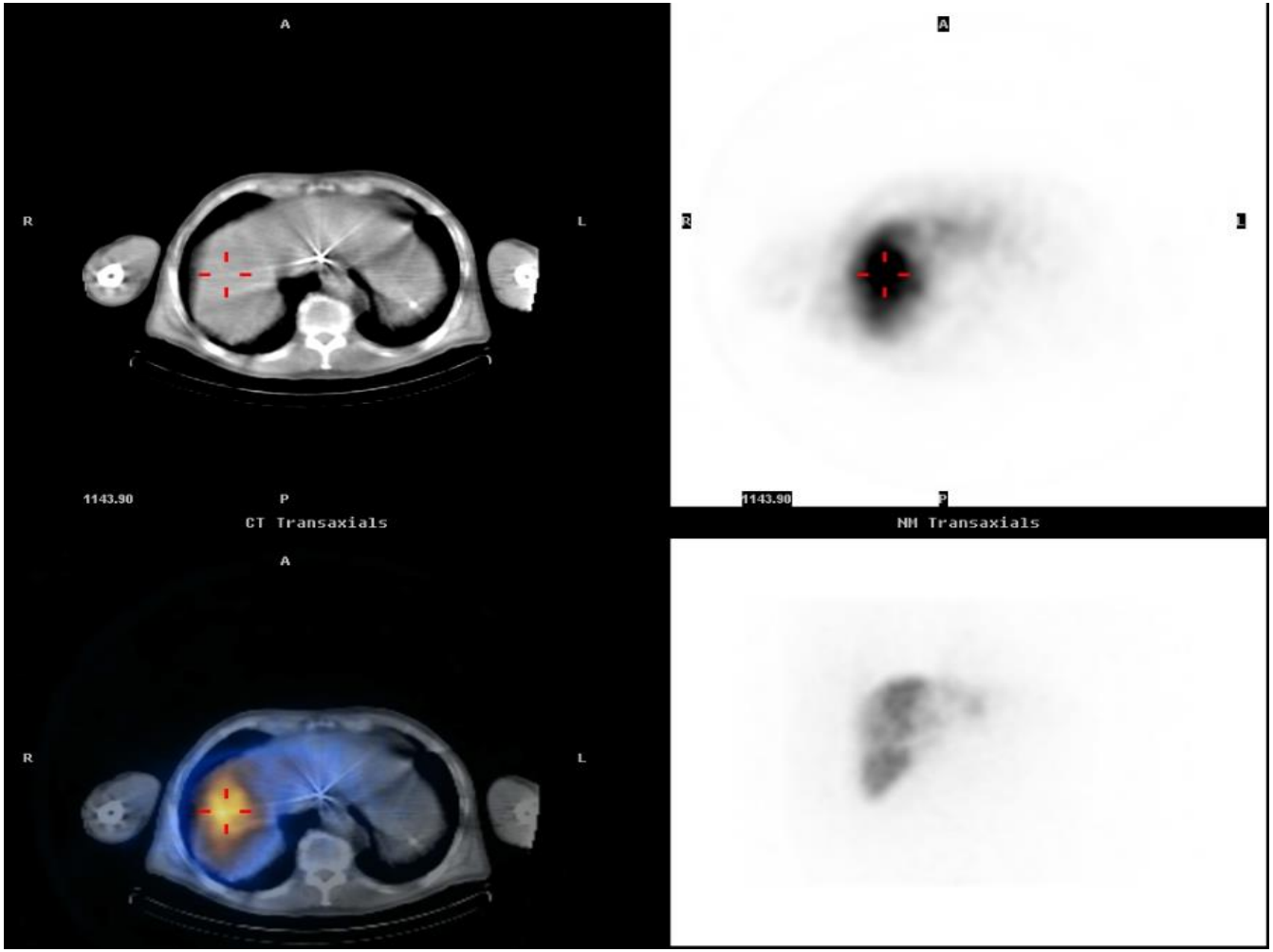
SIRT delivery systems

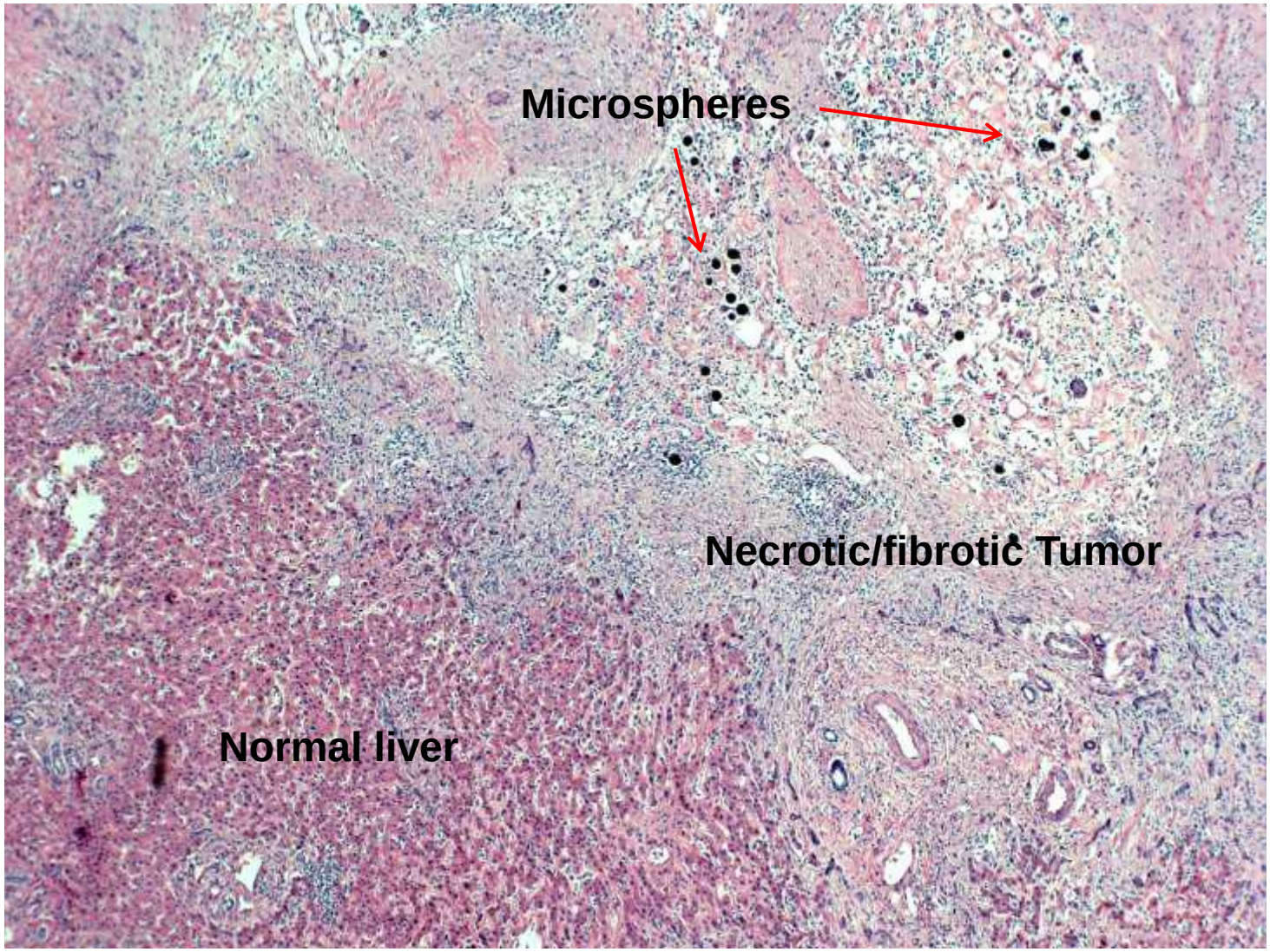
Theraspheres



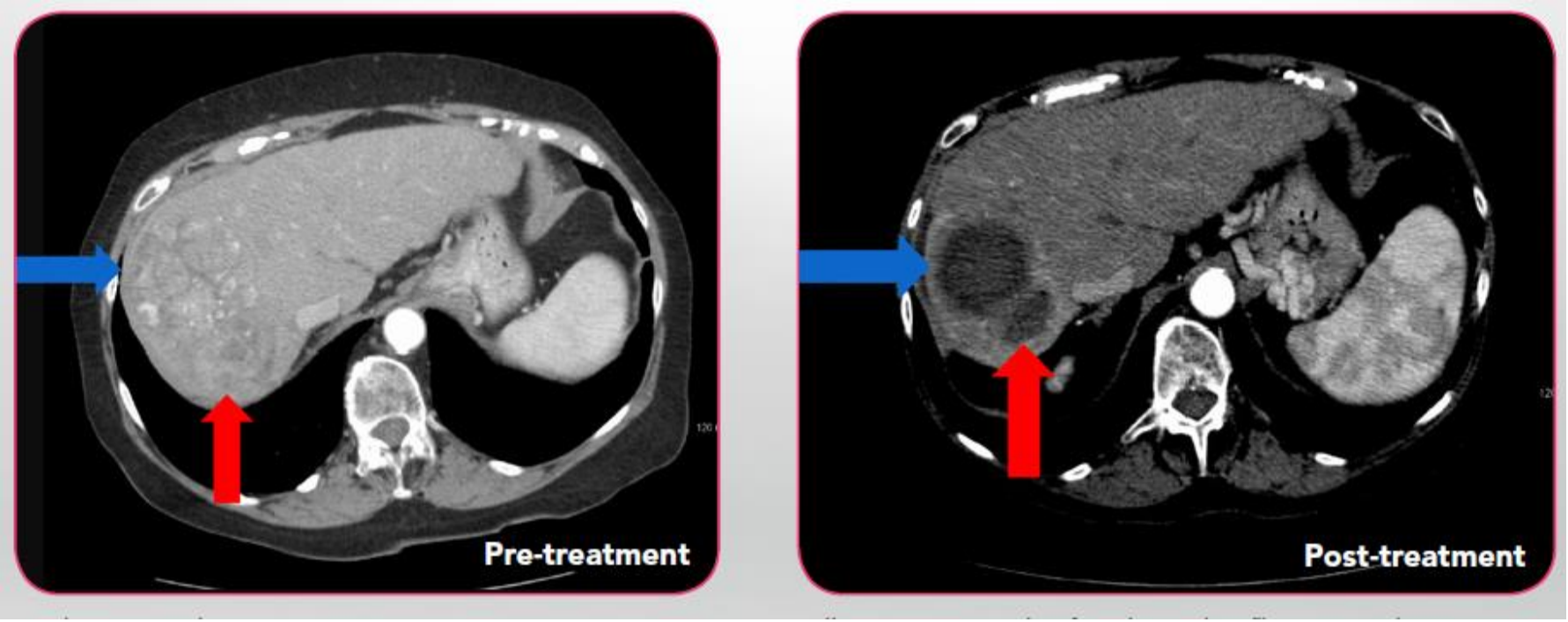
SIR-spheres

Post SIRT Bremsstrahlung imaging




Microspheres
Necrotic/fibrotic Tumor
Normal liver

CT liver



Pre SIRT

Post SIRT

SIRT in metastatic colorectal cancer

Journal of Surgical Oncology 2004;88:78–85

Randomised Phase 2 Trial of SIR-Spheres® Plus Fluorouracil/Leucovorin Chemotherapy Versus Fluorouracil/Leucovorin Chemotherapy Alone in Advanced Colorectal Cancer

GUY VAN HAZEL,[1,2] ANTHONY BLACKWELL,[2] JAMES ANDERSON,[3] DAVID PRICE,[3] PAUL MOROZ,[3] GEOFF BOWER,[1] GIUSEPPE CARDACI,[1] AND BRUCE GRAY[1]*
[1]Mount Hospital, Western Australia, Australia
[2]Sir Charles Gairdner Hospital, Western Australia, Australia
[3]Greenslopes Hospital, Queensland, Australia

First line setting

- Improved OS
  - HR 0.33
  - P <0.05

VOLUME 28 · NUMBER 23 · AUGUST 10 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or With Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy

Alain Hendlisz, Marc Van den Eynde, Marc Peeters, Geert Maleux, Bieke Lambert, Jaarke Vannoote, Katrien De Keukeleire, Chris Verslype, Luc Defreyne, Eric Van Cutsem, Philippe Delatte, Thierry Delaunoit, Nicola Personeni, Marianne Paesmans, Jean-Luc Van Laethem, and Patrick Flamen

Chemorefractory setting

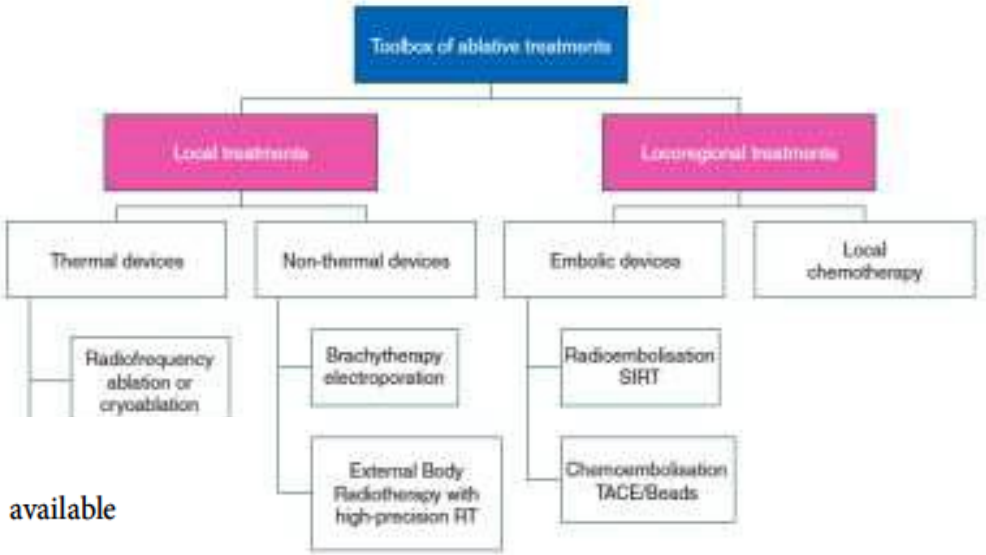
- Improved TTP
  - HR 0.38
  - P <0.05

ESMO Guidelines 2016

Annals of Oncology 0: 1–38, 2016
doi:10.1093/annonc/mdw235

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

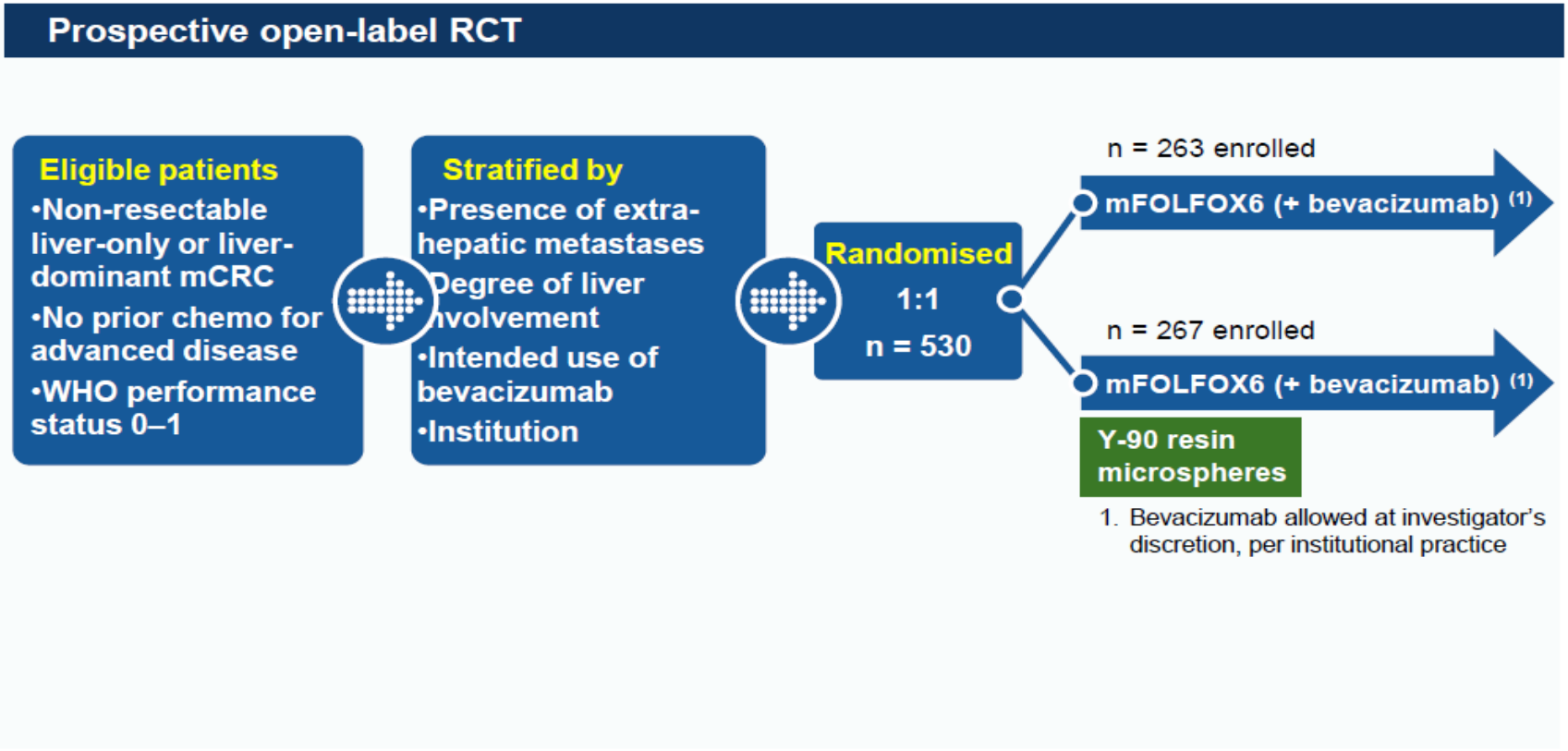
E. Van Cutsem[1*], A. Cervantes[2], R. Adam[3], A. Sobrero
Aguilar[7], A. Bardelli[8], A. Benson[9], G. Bodoky[10], F. Ciar
J.-Y. Douillard[14], M. Ducreux[15], A. Falcone[16,17], A. Grot
V. Heinemann[21], P. Hoff[22], C.-H. Köhne[23], R. Labianca
K. Muro[28], N. Normanno[29], P. Österlund[30,31], W. J. G.
G. Pentheroudakis[34], P. Pfeiffer[35], T. J. Price[36], C. Punt
W. Scheithauer[41], H. J. Schmoll[42], J. Tabernero[43], J. T
T. Yoshino[45], A. Zaanan[25] & D. Arnold[46]



recommendation 16: embolisation.

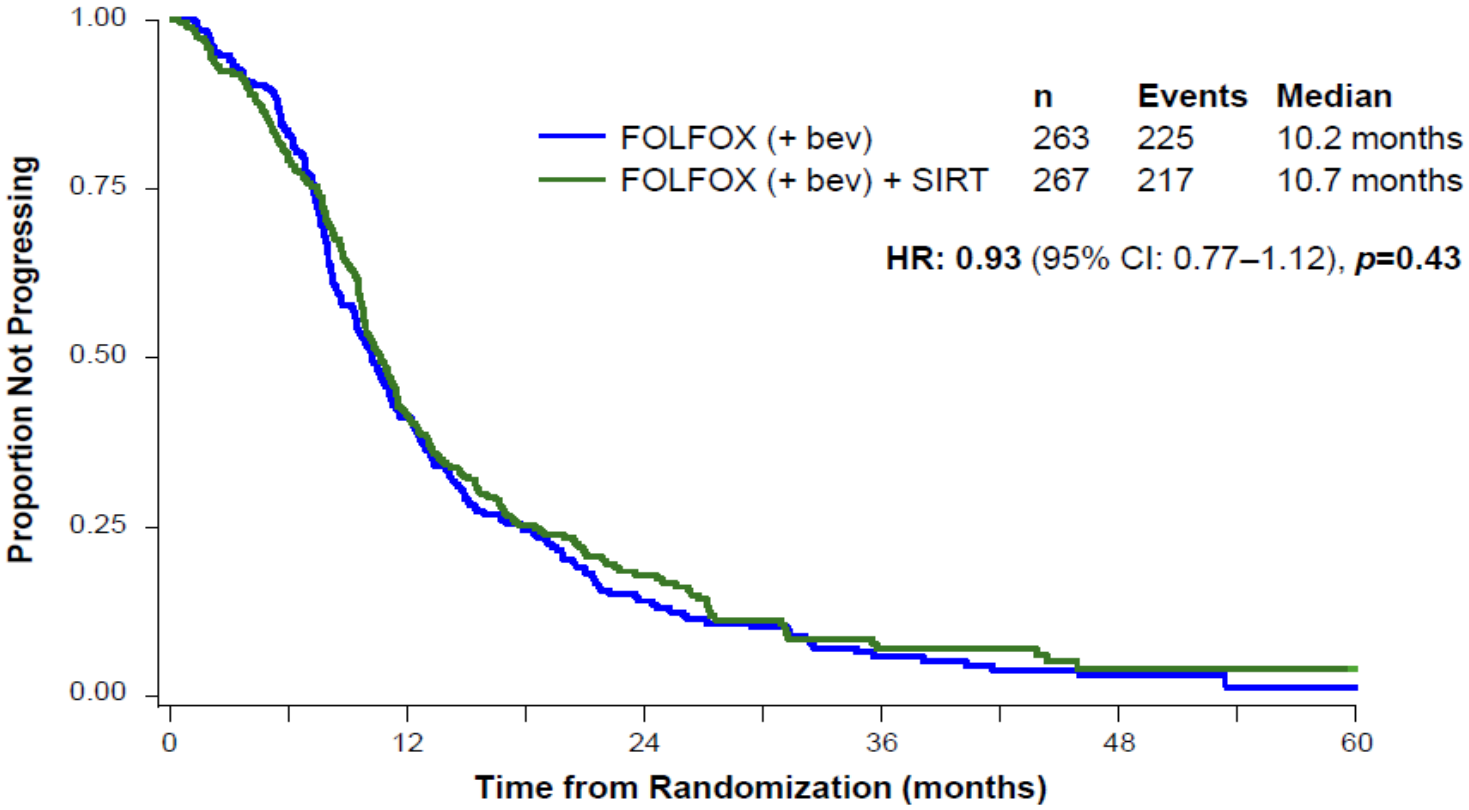
- For patients with liver-limited disease failing the available chemotherapeutic options
  - Radioembolisation with yttrium-90 microspheres should be considered [II, B].
  - Chemoembolisation may be also considered as a treatment option [IV, B].
- Radioembolisation (and chemoembolisation) of CLM in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials.

SIRFLOX Study Design



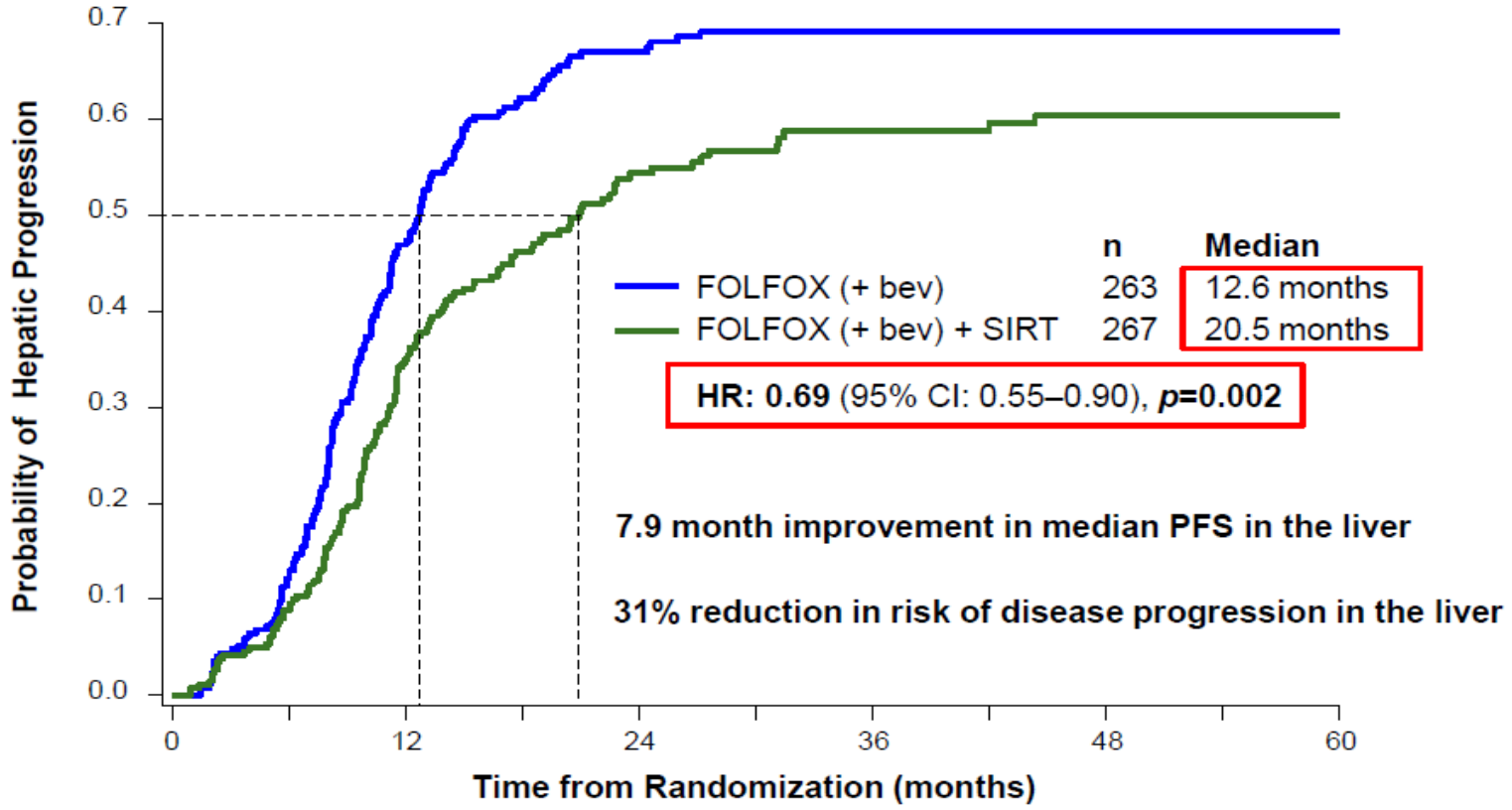
Gibbs P *et al. Presented at 2015 ASCO Annual Meeting; J Clin Oncol* 2015; **33** (Suppl): Abs 3502

Progression-Free Survival at Any Site



Gibbs P *et al. Presented at 2015 ASCO Annual Meeting; J Clin Oncol* 2015; **33** (Suppl): Abs 3502

PFS in the Liver:
Cumulative Incidence of Liver Progression



Number at risk						
FOLFOX (+ bev)	263	96	29	9	5	2
FOLFOX (+ bev) + SIRT	267	106	33	11	5	2

Gibbs P *et al. Presented at 2015 ASCO Annual Meeting; J Clin Oncol* 2015; **33** (Suppl): Abs 3502

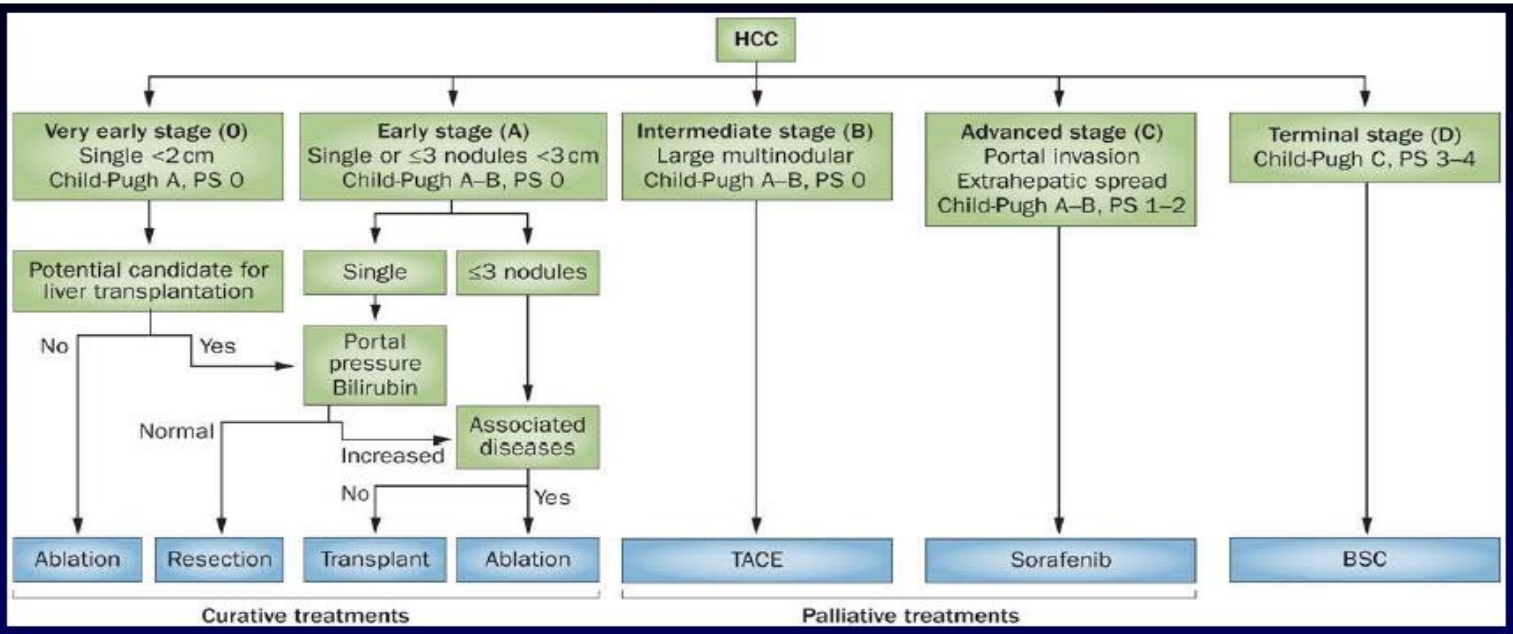
Grade ≥3 Adverse Events in SIRFLOX

	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

SIRFLOX is the first of three RCTs designed for a combined analysis of Overall Survival

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

BCLC staging and treatment strategy



3-40 %	Target:20%	Target:40%	Target: 10%
Median OS >60mo; 5-yr survival:40-17%	OS; 20 mo (45-14)	OS: 11 ML (6-14)	OS: 3mo

Forner, A. *et al.* (2014) Treatment of intermediate-stage hepatocellular carcinoma *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2014.122

nature REVIEWS CLINICAL ONCOLOGY

SIRT in HCC

Liver INTERNATIONAL

Liver International ISSN 1478-3223

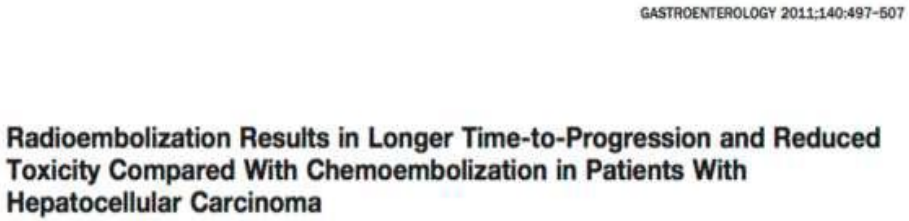
CANCER

A comparison of survival in patients with hepatocellular carcinoma and portal vein invasion treated by radioembolization or sorafenib

Manuel A. de la Torre[1], Juan Buades-Mateu[1], Pedro A. de la Rosa[2], Alberto Lué[3], Francisco J. Bustamante[4], María T. Serrano[3], Milagros Testillano[4], Sara Lorente[3], Juan I. Arenas[5], Cristina Gil[4], Mercedes Iñarrairaegui[1,6] and Bruno Sangro[1,6]

1 Liver Unit, Clínica Universidad de Navarra, Pamplona, Spain
2 Preventive Medicine, Complejo Hospitalario de Navarra, Pamplona, Spain
3 Gastroenterology and Hepatology, Hospital Clínico Universitario Lozano Blesa, Instituto de Investigación Sanitaria de Aragón (IIS Aragón), Zaragoza, Spain
4 Liver Unit, Hospital Universitario Cruces, Baracaldo, Spain
5 Gastroenterology and Hepatology, Hospital Universitario Donostia, San Sebastian, Spain
6 Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Pamplona, Spain

Liver Int. 2016; 36: 1206–1212. DOI: 10.1111/liv.13098



GASTROENTEROLOGY 2011;140:497–507

Radioembolization Results in Longer Time-to-Progression and Reduced Toxicity Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

Retrospective series

- PVT
- Resin microspheres
- SIRT or sorafenib
- OS: 8.8 vs. 5.4 mo, p=0.047

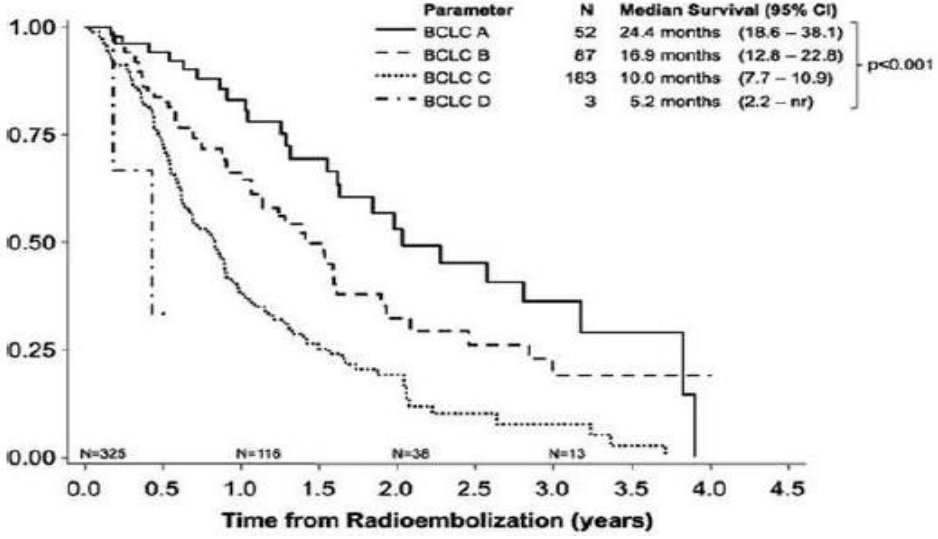
Non randomised study

Comparison with TACE

- n = 245
- Glass microspheres
- Earlier stage disease (>80% BCLC A/B)
- TTP 13.3 vs. 8.4 mo p=0.46
- No difference in OS

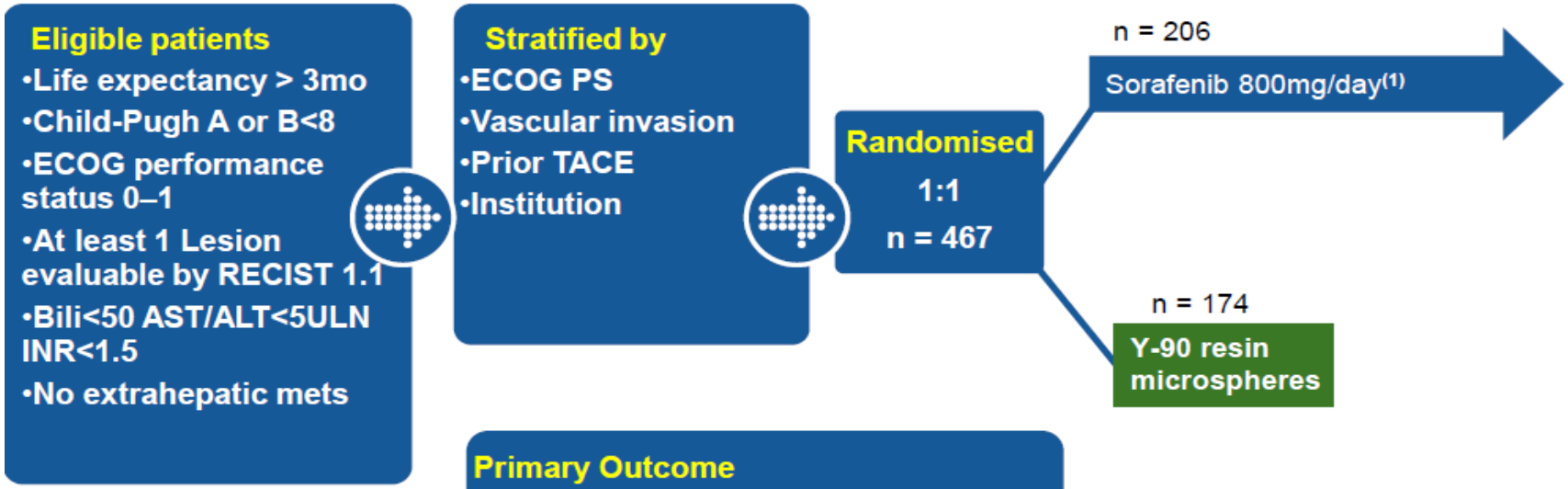
Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation

Bruno Sangro,[1] Livio Carpanese,[2] Roberto Cianni,[3] Rita Golfieri,[4] Daniele Gasparini,[5] Samer Ezziddin,[6] Philipp M. Paprottka,[7] Francesco Fiore,[8] Mark Van Buskirk,[9] Jose Ignacio Bilbao,[10] Giuseppe Maria Ettorre,[11] Rita Salvatori,[12] Emanuela Giampalma,[4] Onelio Geatti,[13] Kai Wilhelm,[14] Ralf Thorsten Hoffmann,[7] Francesco Izzo,[15] Mercedes Iñarrairaegui,[1] Carlo Ludovico Maini,[16] Carlo Urigo,[3] Alberta Cappelli,[17] Alessandro Vit,[5] Hojjat Ahmadzadehfar,[6] Tobias Franz Jakobs,[7] and Secondo Lastoria,[18] on behalf of the European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY)



SARAH Study Design

Prospective Open-label RCT 25 centers in France



Primary Outcome
OS

Secondary outcomes
- PFS
- Hepatic vs. extrahepatic progression
- Tumour response rate (RECIST 1.1)
- Tolerance
- QOL

Vilgrain V *et al. Presented at 2017 International liver congress EASL Meeting; Amsterdam*

SARAH Study Design

Prospective Open-label RCT 25 centers in France

Primary Outcome: OS

No survival difference between groups

ITT Population (n=459):
SIRT OS 8mo
SOR OS 9.9mo
P=0.18

Per protocol population (n=380):
SIRT OS 9.9mo
SOR 9.9mo
P=0.92

Secondary Outcome: PFS

No difference

ITT (n=459):
SIRT 4.1mo
SOR 3.7mo
P=0.76

Per Protocol (n=380)
SIRT 4.3mo
SOR 3.7mo
P=0.77

Secondary Outcome: Tumour response rate

Response better in SIRT group

19%vs. 11.6% p=0.042

Secondary Outcome: QOL

Better in SIRT group
EOTRC QLQ30

Vilgrain V *et al. Presented at 2017 International liver congress EASL Meeting; Amsterdam*

TOLERANCE AND SAFETY

Treatment-related AES	SIRT	Sorafenib
All	1297	2837
Grade 3-5	230	411

Treatment–related AE's were significantly lower in SIRT Group

Treatment-related AES	SIRT n (G3-5)	Sorafenib n (G3-5)
Fatigue	94 (20)	140 (41)
Wt loss	14 (0)	46 (6)
Infection	9 (3)	23 (9)
Alopeia	0 (0)	35 (0)
Hand foot syndrome	1 (1)	45 (12)
Pruritis	7 (1)	19 (1)
Diarrhoea	29 (3)	146 (30)
Abdominal Pain	46 (6)	63 (14)
Hypertension	6 (0)	26 (6)

SIRT future directions in HCC

	Population	Design	Sample size	Primary endpoint	Secondary endpoint
SARAH	BCLC A after failure BCLC B & C Child A to B7 ECOG 0-1	sorafenib vs SIRT	460	OS	PFS QoL Health economics
SIRVENIB	BCLC B & C Child A to B7 ECOG 0-1	sorafenib vs SIRT	360	OS	PFS QoL Health economics
STOP-HCC	BCLC B & C Child A to B7 ECOG 0-1	sorafenib vs sorafenib + SIRT	390	OS	PFS QoL
SORAMIC	BCLC B & C Child A to B7 ECOG 0-1	sorafenib vs sorafenib + SIRT	375	OS	PFS QoL

Other studies

- **EPOCH** – Phase III trial evaluating 2nd line Theraspheres treatment in patients with CRC liver metastases who failed 1st line chemotherapy
- **SIRCCA** – Phase II trial evaluating SIRTEX + standard chemo (CIS-GEM) vs chemo as 1st line treatment in unresectable intrahepatic cholangiocarcinoma

PAPER POINTS

INSTITUTIONAL DECISION TO ADOPT Y90 AS PRIMARY TREATMENT FOR HCC INFORMED BY A 1,000-PATIENT 15-YEAR EXPERIENCE

Riad Salem, Ahmed Gabr , Ahsun Riaz, Ronald Mora, Rehan Ali, Michael Abecassis, Ryan Hickey, Laura Kulik, Daniel Ganger, Steven Flamm, Rohl Atassi, Bassel Atassi, Kent Sato, Al B Benson, Mary F Mulcahy, Nadine Abouchaleh, Ali Al Asadi, Kush Desai, Bartley Thornburg, Michael Vouche, Ali Habib, Juan Calcedo, Frank H Miller, Vahid Yaghmai, Joseph R Kalinl, Samdeep Mouli, Robert J Lewandowski. Hepatology 2017; [Impact Factor: 13.246 (2016)]

HIGHLIGHTS

Positive outcomes following TheraSphere® treatment in 1000 patients over 15 years led the Northwestern University, Chicago to adopt TARE with TheraSphere® as a first line transarterial locoregional therapy (LRT) for patients with HCC limited to the liver.

BACKGROUND AND OBJECTIVE

- Y90 (TheraSphere®) transarterial radioembolization (TARE) is a transarterial locoregional therapy (LRT) for hepatocellular carcinoma (HCC).
- Objective: Summarise a cumulative 15 year - 1000 patients experience of TheraSphere® to various BCLC stages.

METHOD

- Study time: December 1, 2003 and March 31, 2017 - 1000 patients with HCC treated with TheraSphere® as part of a prospective cohort study (the largest single centre cohort conducted).
- Standard pre-treatment angiography and To-99m MAA - TheraSphere® target dose was 120 Gy for lobar infusions. Practice changed in time with the application of radiation segmentectomy and lobectomy and target doses were modified to >190 (potentially curative ablative dose) and 150 Gy, respectively. Median dose per treatment was 119 Gy.
- Total TheraSphere® treatments = 1577 (median 1- range 1-8).
- Follow-up: 4-6 week scans and subsequently at 2-3 month intervals.

Baseline characteristics	
ECOG	0 (56%); 1 (40%); 2 (4%)
Child-Pugh Class	A (51%); B (45%); C (4%)
BCLC	A (26%); B (15%); C (54%); D (4%)

- Outcomes were stratified by baseline Child-Pugh (CP) class, United Network for Organ Sharing (UNOS) and Barcelona Clinic Liver Cancer (BCLC) staging systems.
- OS outcomes were reported using censoring and intention-to-treat methodologies.

RESULTS

- Survival for BCLC stages A-C patients treated with Y90 (47, 25 and 15 months, respectively) compares favourably with survival expectations of BCLC A (36-50 months), BCLC B (18-26 months) and BCLC C (11 months) cited by EASL-EORTC guidelines.
- Properly selected BCLC D patients may benefit from selective TheraSphere® followed by liver transplantation.
- Overall, 49 (5%) patients developed new grade 3/4 albumin toxicities, 110 (11%) showed grade 3/4 bilirubin toxicities for all CP classes. No patient developed radiation pneumonitis or gastritis.

SIRT at UHS Nuclear Medicine Department

- SIRT service introduced in Jan 2009
  - ^{90}Yttrium-resin-microspheres (SIRTEX) since Jan 2009
  - ^{90}Yttrium-glass-microspheres (Theraspheres) since July 2015
  - 1 of 10 SIRT centres in England since 2013

Conclusions

- SIRT is used for primary and secondary liver cancers
- Most patients with liver metastases are unsuitable for liver resection
- Multidisciplinary treatment involving NM, IR & oncology
- Targeted intra-arterial delivery of radioactive (usually ^{90}Y) labelled microspheres to the liver
- Two part procedure is reasonably well tolerated with minimal side effects
- Established clinical benefit
- Growing evidence about safety and efficacy in chemorefractory patients