Liver directed therapy in incurable mCRC: When and how? Radio- or Chemoembolization

Session XXI: Liver and peritoneal metastases
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Disclosures

Sirtex Medical: - Advisory Boards / speaker
- Research funding
- Co-CI of FOXFIRE Phase III study

Merck Serono; Pfizer: - Research funding; Trials CI & PI

Advisory Boards / speaker: Sanofi Aventis / Regeneron; Merck Serono KGA Roche; Bayer; Celgene; Lily: Servier; Array

Research funding: - CRUK; MRC; BRC-Imperial; NIHR

Limitations and unmet needs of systemic (chemotherapy) strategies

- **More ..& More Systemic** Chemotherapy / Biologicals
  - Quadruplets: 4 agent combinations now being used in CRC (e.g. TRIBE etc)
    - Toxicity ; QOL; Cost
    - ? increase CR's and durability :
      - Historically a failed strategy
      - Deeper and quicker responses desirable
    - ? Paradox to approaches with de-escalation / Treatment Holidays
    - Combination biological era will make 3+ or 4+ platforms difficult to build on

Possible Synergistic Strategies for "eradicating" Liver Tumours - 1

- **Direct Tumour targeting = visually targeted**
- **– Interventional (needles)**
  - **Intraoperatively or Radiologically**

  - **Thermal Ablation RFA** (Cryo-ablation)
  - **Microwave** : Quicker
  - **Nanoknife – Irreversible electroporation (IRE)**
    - designed to avoid damaging endothelial cells and blood vessels
    - Damage appears Pro-apototic with little inflammation ?

many others are and will be developed!

Possible Synergistic Strategies for "eradicating" Liver Tumours - 2

- **Direct Tumour targeting – External**
- **= <u>Visually targeted</u> Radiologically**

  –HIFU : High-intensity focussed ultrasound

  –**External Beam Radiotherapy**
  –SBRT/ Highly conformal / IMRT / IMGRT
  –Cyberknife
  –Protons (Carbon)

Possible Synergistic Strategies for "eradicating" Liver Tumours - 3

- **Liver targeted via loco-regional Vascular supply - Organ targeted (Regional) Treatment**

a) Cytotoxic agents delivered to higher concentration

– Hepatic Arterial Infusion (HAI) or Portal vein
  - 5FU / FUDR / Oxaliplatin & Combinations

b) Embolization (Bland / TAE) inducing ischemia and infarction

a+b) cTACE dTACE,

-Drug eluting Beads: Irinotecan (**Debiri**)/ Adriamycin
  – combines embolization with chemotherapy

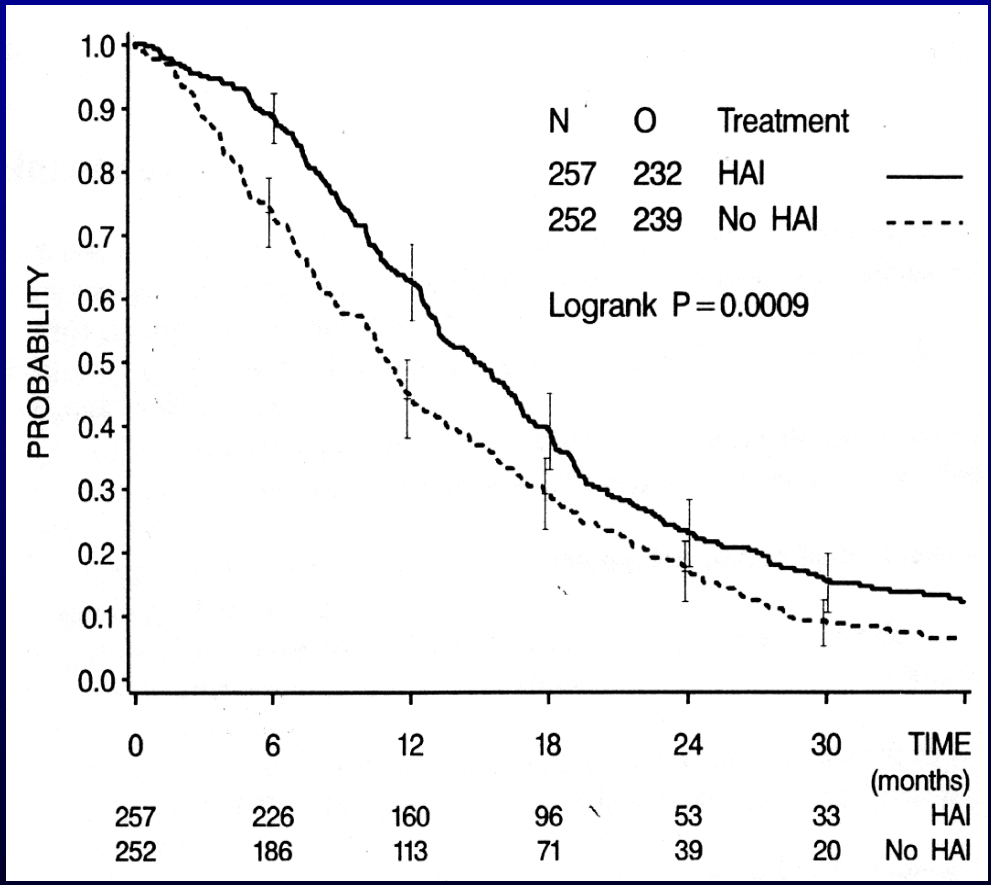
c) Selective internal radiation (SIRT)
  - Brachytherapy / TARE / radioembolization
  - HAI Y90 resin versus glass spheres

Hepatic Arterial Infusion Therapy Meta Analysis (FP Era)

- Meta analysis of six randomized trials for survival

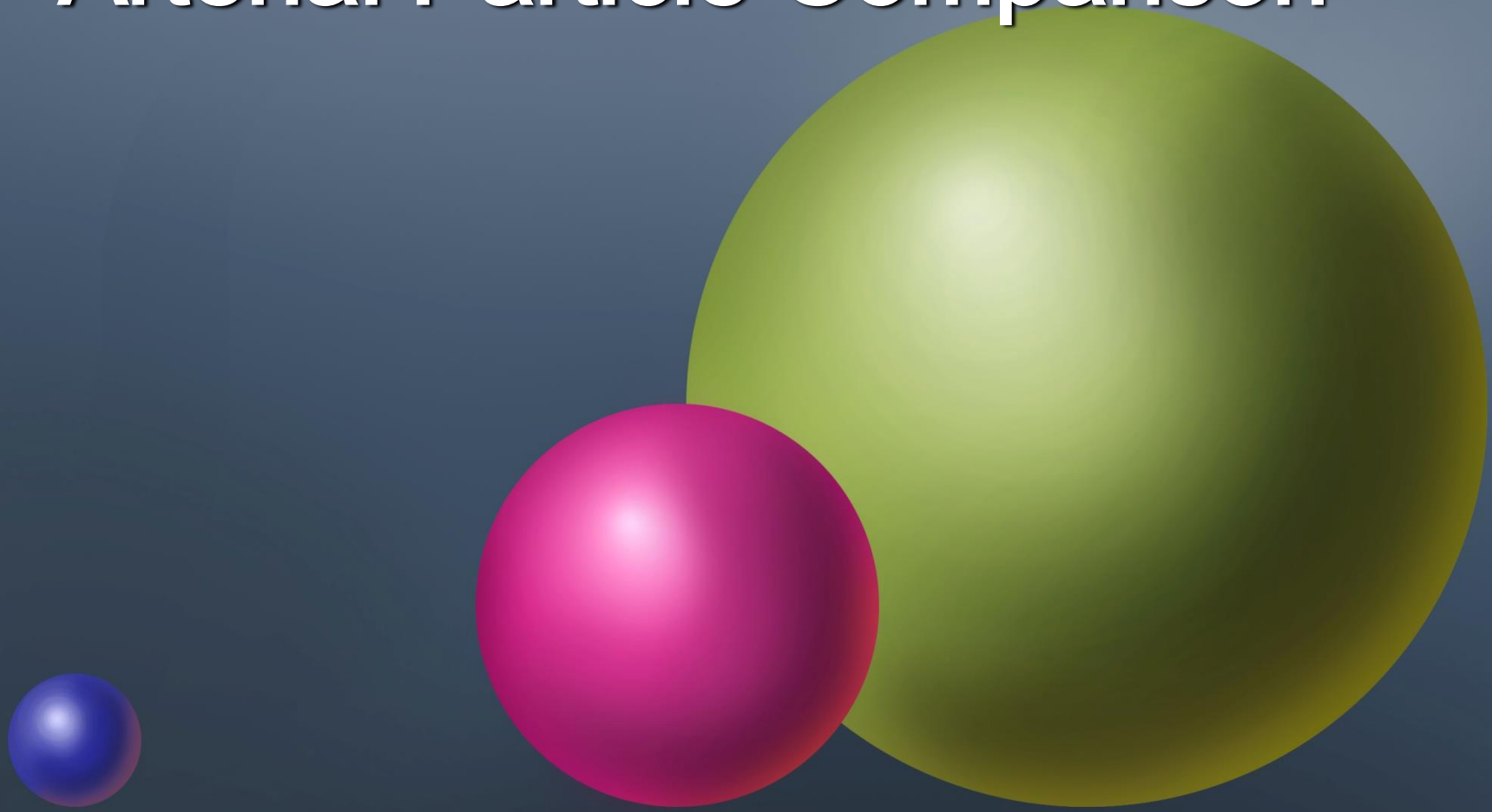
- Statistically significant improved response rate
  - 41% versus 14% ($p<10^{-10}$)

- Statistically significant survival advantage
  - 14.5 months versus 10.1 months p=0.0009



Meta-analysis group, J Natl Cancer Inst. 1996; 6;88(5):252-8

Arterial Particle Comparison



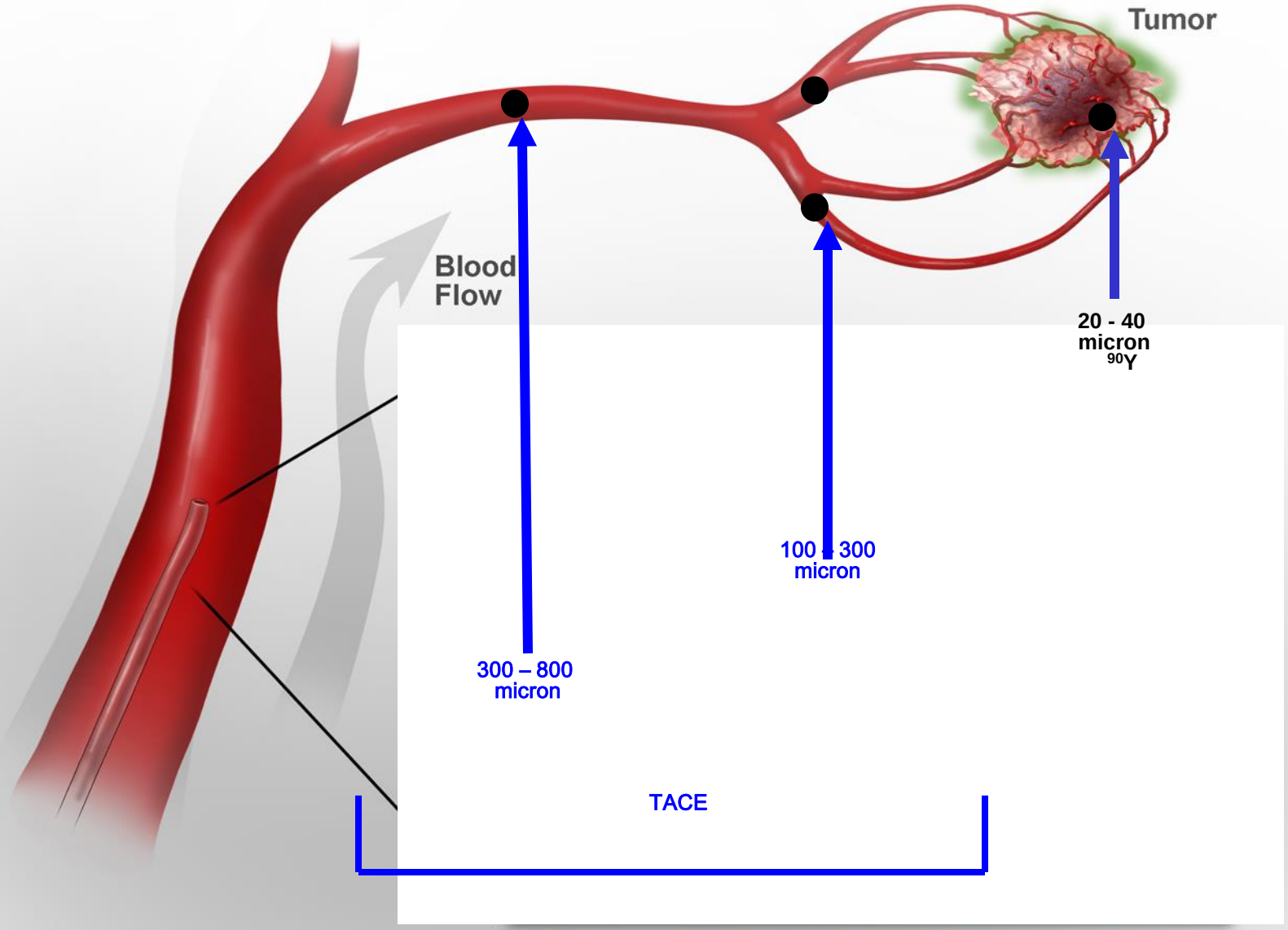
^{90}Y-microspheres
25-35 microns

TAE, TACE and Drug Eluting Beads
100-700 microns

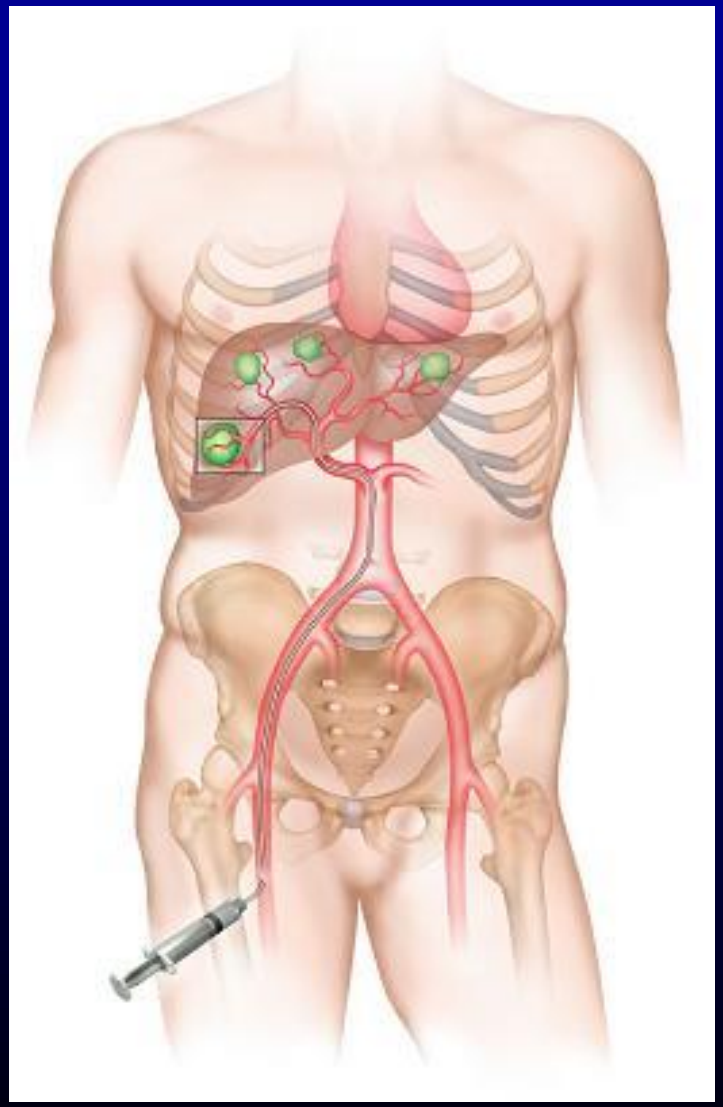
GOAL: implant tumor

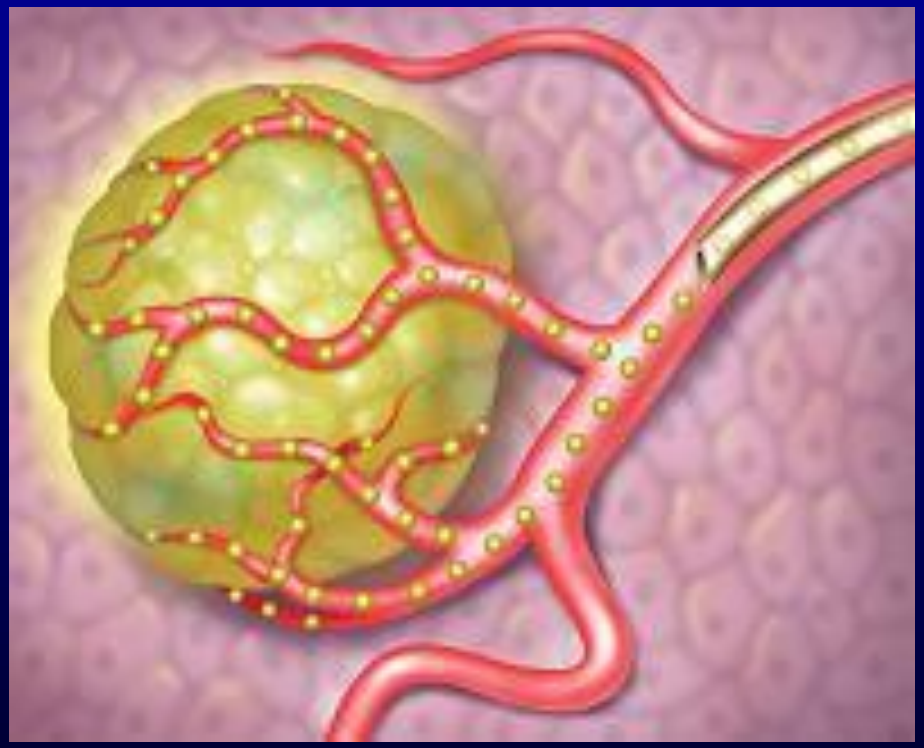
GOAL: block all blood to tumor

Morgan, Kennedy, Lewington et al. *Nature Reviews in Clinical Oncology* October 2010

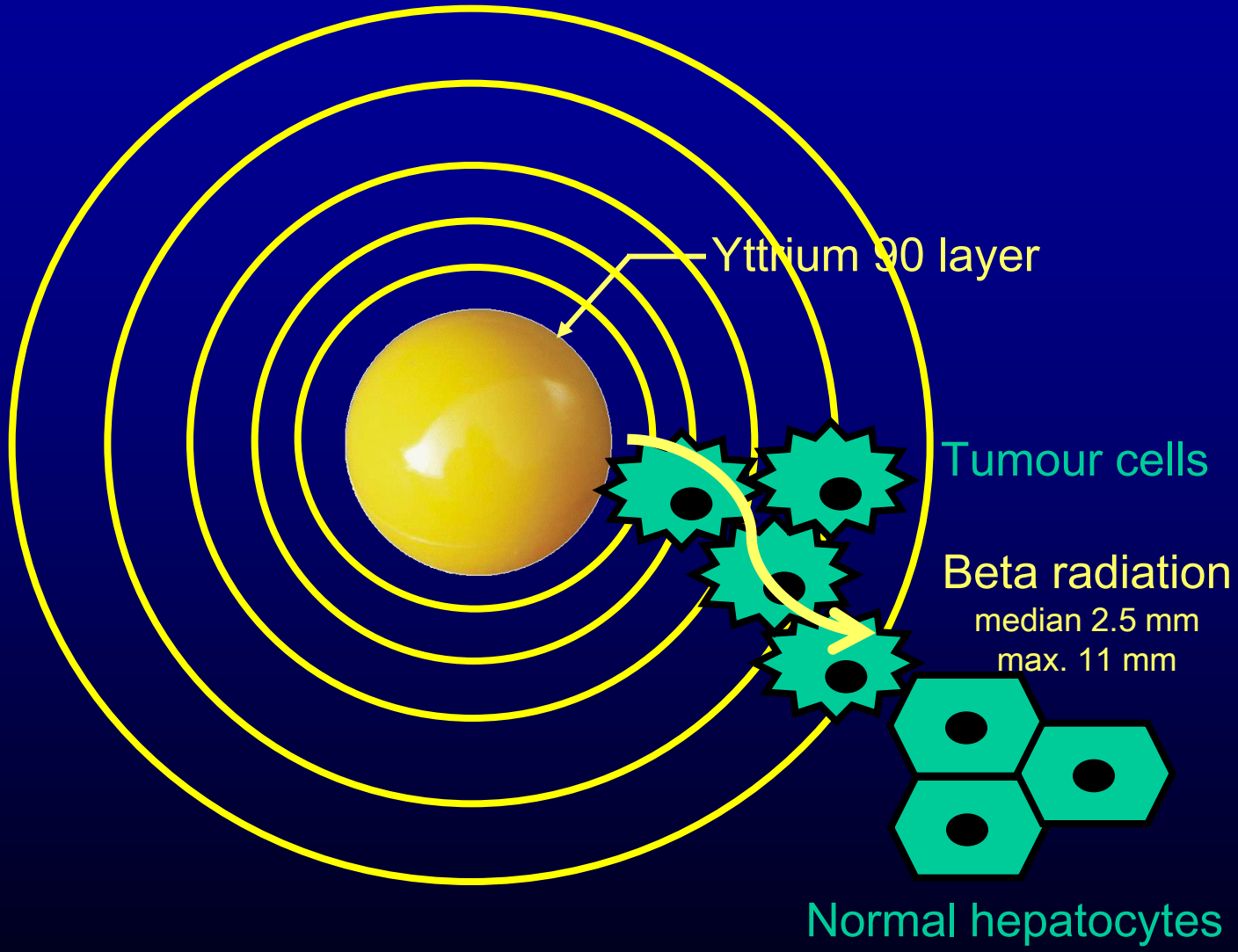


Radioembolization/SIRT
Yttrium 90 resin SIR-Spheres



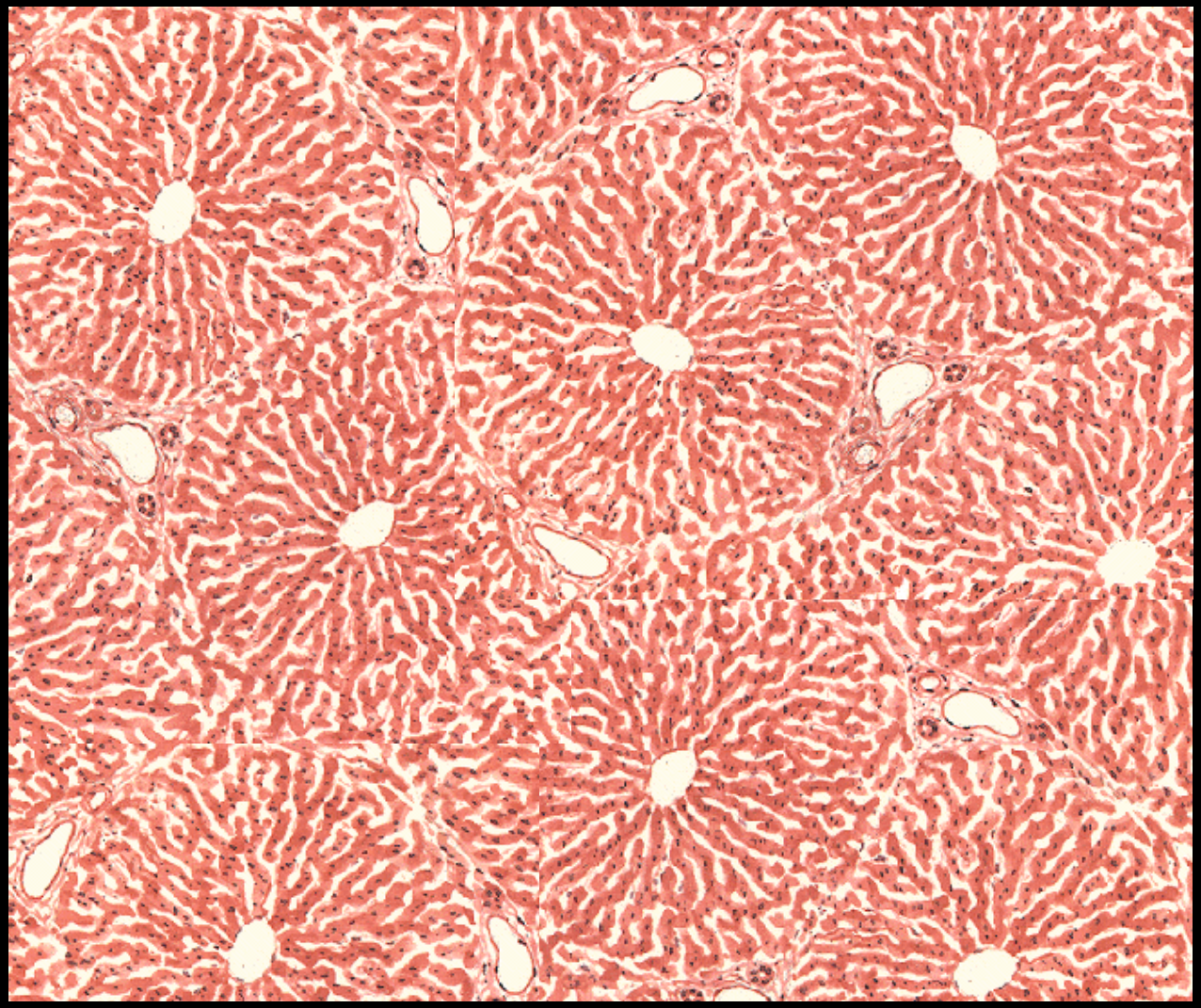


Y90 resin SIR-Spheres®



Seza Gulec

Hepatic Structural Targeting



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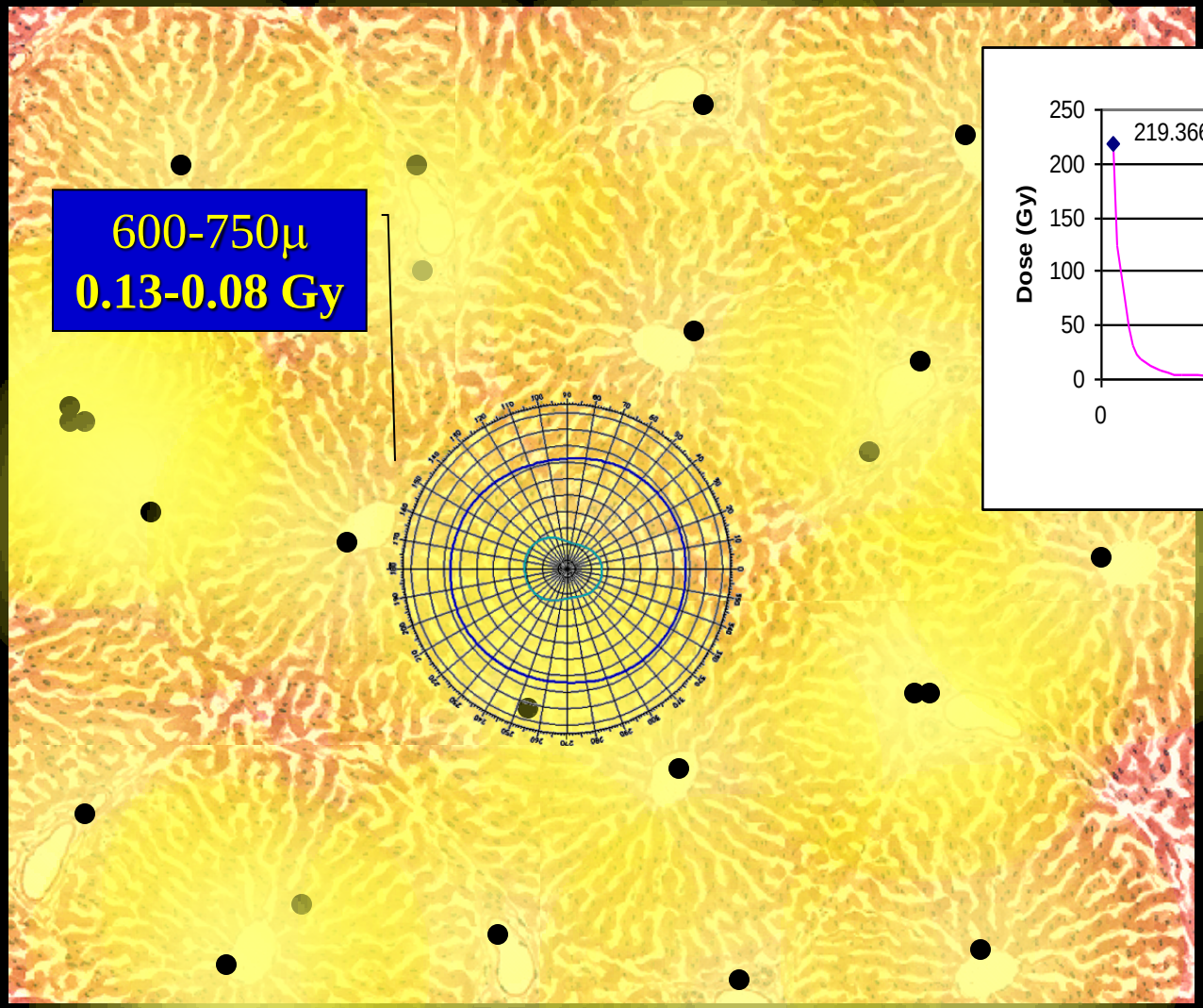
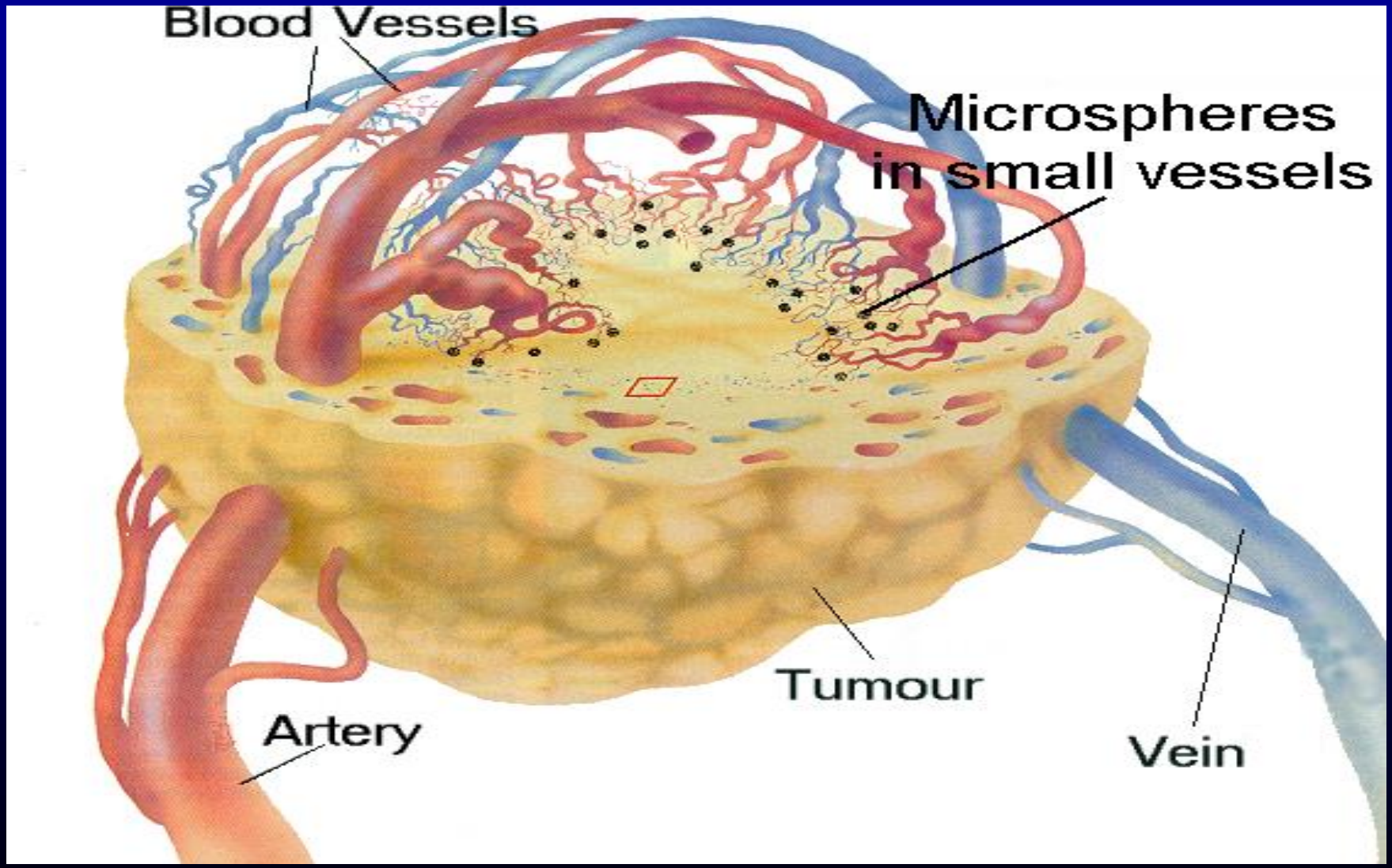
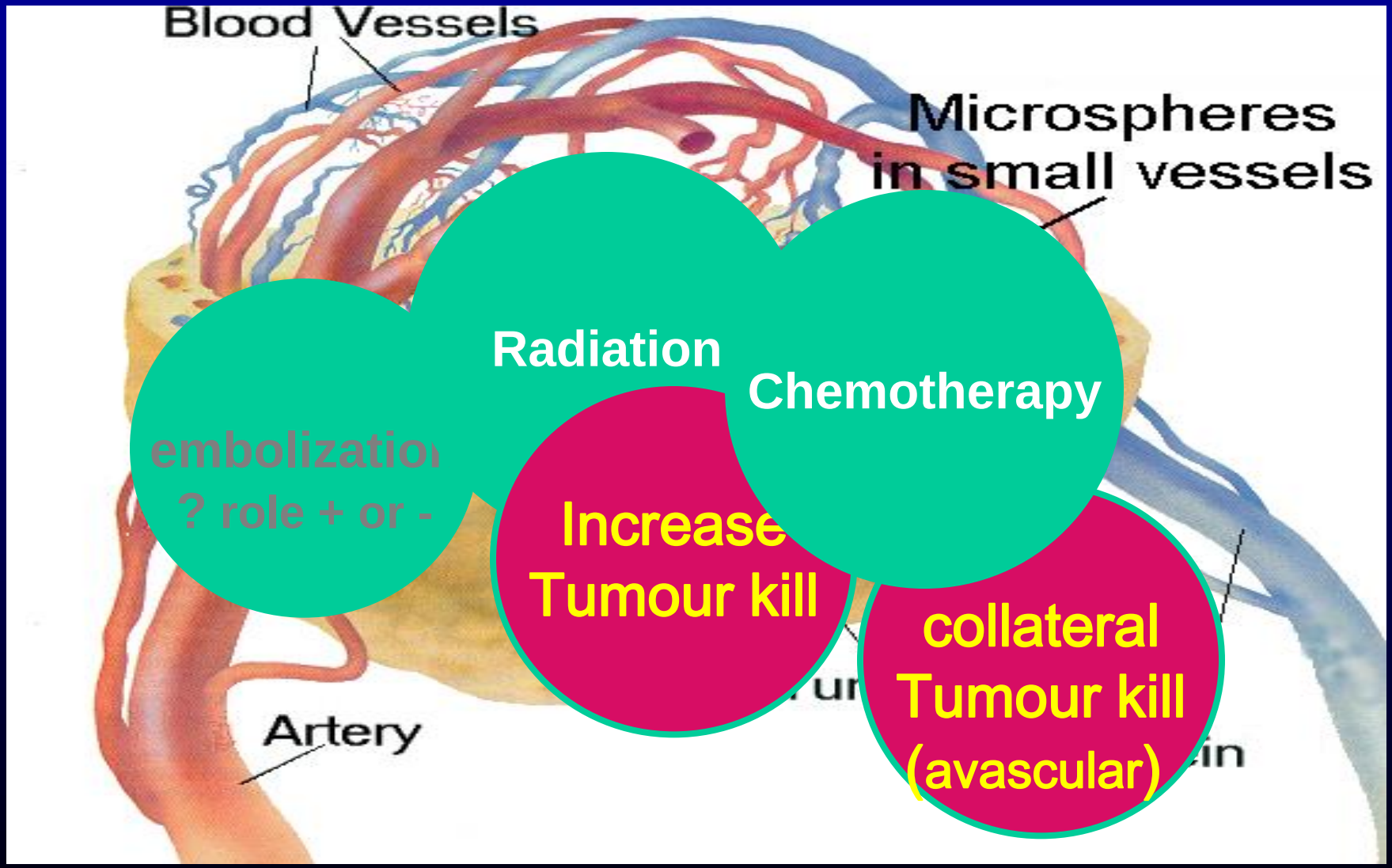


DISTRIBUTION OVERLAPS or CROSS-FIRE (collateral) EFFECT

Further synergy with radiosensitising systemic chemotherapy should increase collateral kill



Further synergy with radiosensitising systemic chemotherapy should increase collateral kill



Clinical Trials Evidence of integrating Embolic technologies with (standard of care) chemotherapy in mCRC:

- Lack of level one evidence until recently
  - Many small studies showing “benefit”
    - response rates
    - Reporting Standards !

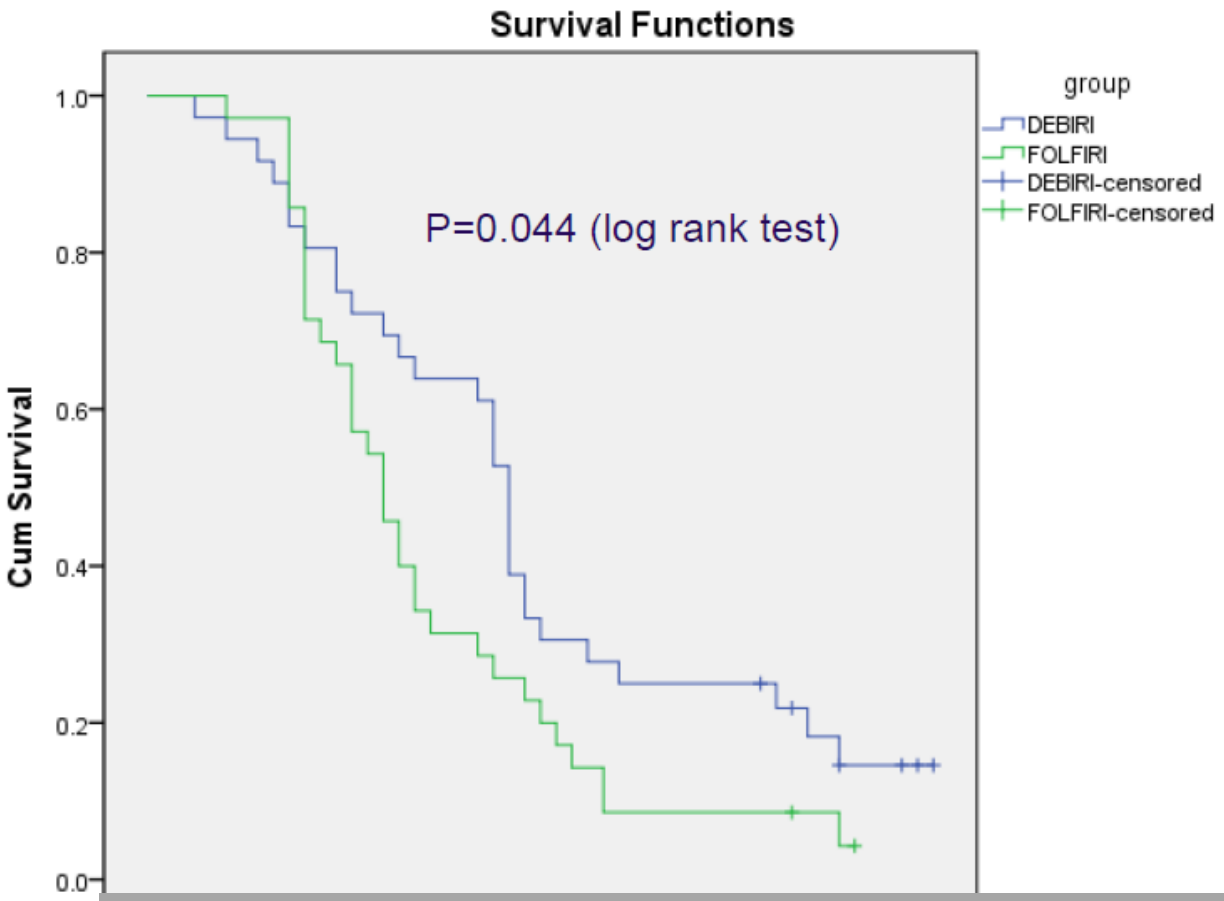
Randomised Chemoembolization studies in CRC

First-line setting

- Martin R *et al.* Cancer. 2015 Oct 15;121(20):3649-58. doi: 10.1002
- Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis

- NO Survival curves shown NO Significant PFS / OS benefit?
- The intention-to-treat population comprised 70 patients
- 30 patients randomly assigned to the FOLFOX-DEBIRI arm and 30 patients randomly assigned to the FOLFOX/bevacizumab
- *overall response rate was significantly greater in the FOLFOX-DEBIRI arm versus the FOLFOX/bevacizumab arm at 2 (78% vs 54%, P = .02), 4 (95% vs 70%, P = .03), and 6 months (76% vs 60%, P = .05)*

DEBIRI vs FOLFIRI (2nd/3rd Line)

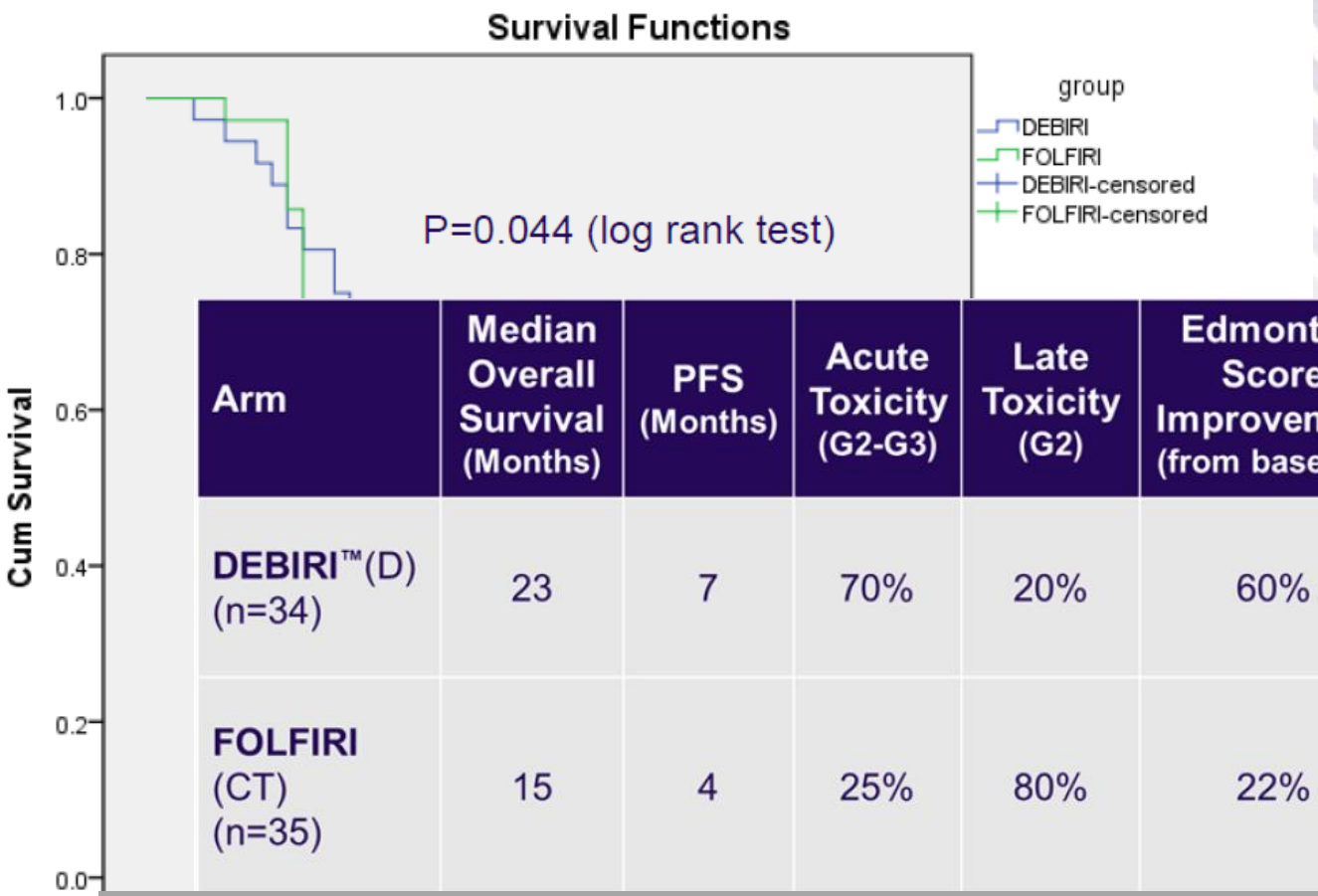


Six months of treatment (2-week cycle) with FOLFOX/ bevacizumab, can cost €90,000 in Europe

($120,000)

adapted from courtesy Stefan Pluntke ESSEN

DEBIRI vs FOLFIRI (2nd/3rd Line)



Arm	Median Overall Survival (Months)	PFS (Months)	Acute Toxicity (G2-G3)	Late Toxicity (G2)	Edmonton Score Improvement (from baseline)	Cost per Patient (Euros)
DEBIRI™(D) (n=34)	23	7	70%	20%	60%	7,000 (2 D)
FOLFIRI (CT) (n=35)	15	4	25%	80%	22%	24,000 (8 CT)

Six months of treatment (2-week cycle) with FOLFOX/ bevacizumab, can cost €90,000 in Europe

($120,000)

adapted from courtesy Stefan Pluntke ESSEN

Rationale for first-line Chemotherapy+SIRT in mCRC

First-line setting

- RCT of FUDR HAC *vs.* FUDR HAC + SIRT showed improved Time to Liver Progression (HR: nr, *p*=0.001) [2]
- Randomised phase II trial of 5FU/LV *vs.* 5FU/LV + SIRT showed improved Overall Survival (HR: 0.33, *p*=0.025) [3]
- Phase I study of FOLFOX4 + SIRT [4]

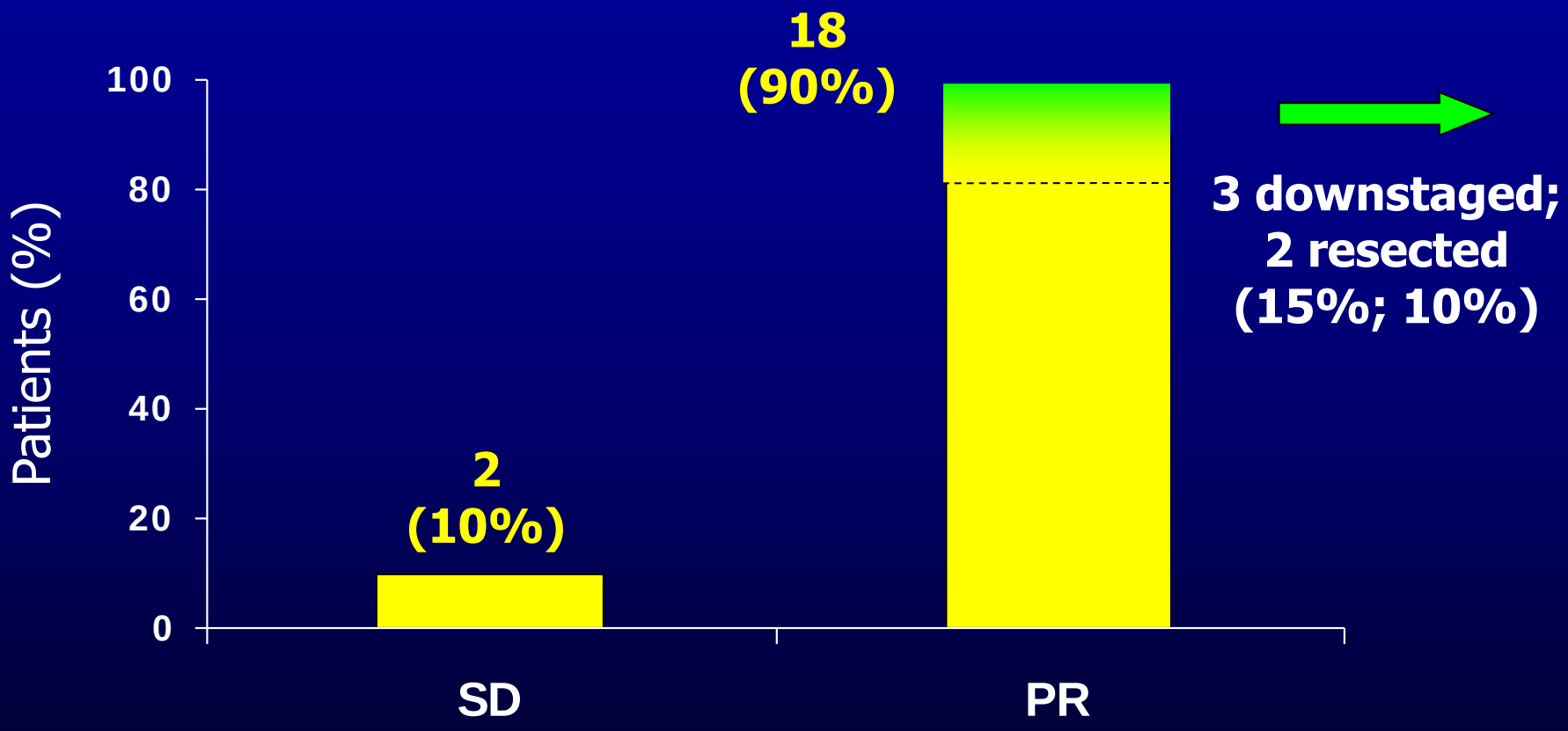
– Oxaliplatin MTD = 60 mg/m^2 for Cycles 1 – 3; Grade 3/4 neutropenia was the DLT

Chemotherapy refractory setting

- RCT of 5FU *vs*. 5FU + SIRT showed improved Time to Liver Progression (HR: 0.38, p=0.003) [5] – led to inclusion in current ESMO guidelines

1. Using SIR-Spheres® Y-90 resin microspheres, Sirtex Medical Limited, Sydney, Australia.
2. Gray *et al. Ann Oncol* 2001;**12**:1711–20.
3. Van Hazel *et al. J Surg Oncol* 2004;**88**:78–85.
4. Sharma *et al. J Clin Oncol* 2007;**25**:1099–106.
5. Hendlisz *et al. J Clin Oncol* 2010;**28**:3687–94.

Y90 resin SIR-Spheres + FOLFOX4 in mCRC: Response Rate by RECIST Criteria

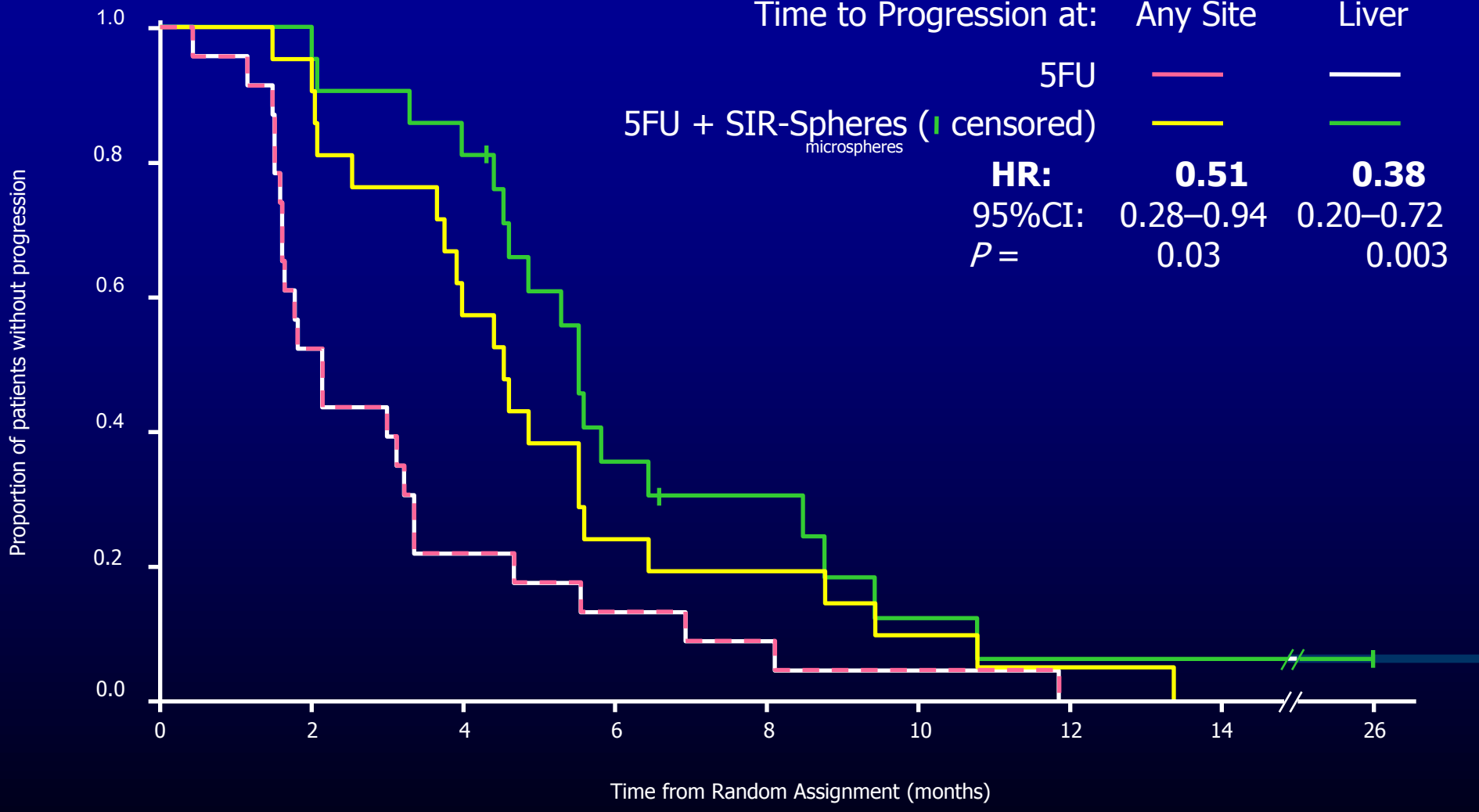


Comparative Phase III trial RECIST response FOLFOX4: 32–59%

Sharma RA *et al*. *J Clin Oncol* 2007; **25**: 1099–1106.
Kalofonos H *et al*. *Ann Oncol* 2005; **16**: 869–877. Tournigand C *et al*. *J Clin Oncol* 2006; **24**: 394–400.

SIR-Spheres + 5FU in mCRC Salvage Therapy: Primary Endpoint – Time to Liver Progression

Phase IIIR Belgian Multicentre



Hendlisz A *et al*. *J Clin Oncol* 2010; **28**: 3687–3694.

SIRFLOX: Randomized trial comparing first-line mFOLFOX6 ± bevacizumab *versus* mFOLFOX6 ± bevacizumab + selective internal radiation therapy (SIRT) in patients with metastatic colorectal cancer (mCRC) – analysis by presence or absence of extra-hepatic metastases and bevacizumab treatment

Guy A. van Hazel [(1)], Volker Heinemann, Navesh K. Sharma, Michael P. N. Findlay, Jens Ricke, Marc Peeters, David Perez, Bridget Robinson, Andrew Strickland, Tom Ferguson, Javier Rodrigez, Hendrik Kroening, Ido Wolf, Vinod Ganju, Euan Walpole, Eveline Boucher, Thomas Tichler, Val Gebski, Mark Van Buskirk, Peter Gibbs, on behalf of the SIRFLOX Study Group

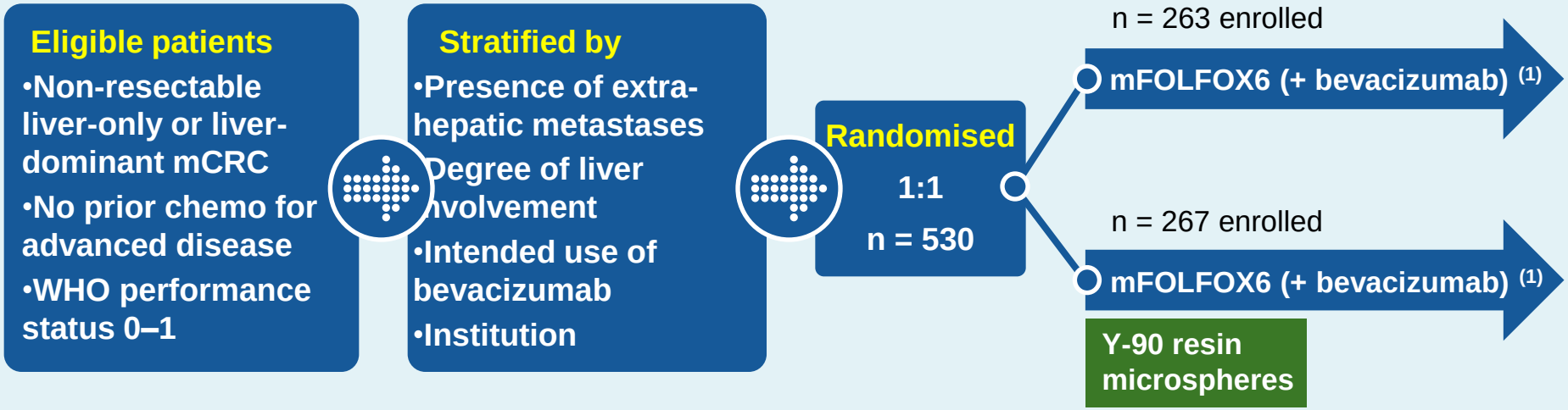
[(1)] **University of Western Australia, Perth, Western Australia, Australia**; Comprehensive Cancer Center, Ludwig-Maximilian-University of Munich, Germany; University of Maryland Medical Center, Baltimore, MD; Cancer Trials New Zealand, Auckland, New Zealand; University Clinic Magdeburg, Magdeburg, Germany; Antwerp University Hospital, Belgium; Dunedin Hospital, Dunedin, New Zealand ; Christchurch Hospital, Christchurch, New Zealand; Monash Medical Centre, Bentleigh, East Victoria, Australia; Royal Perth Hospital, Perth, Western Australia, Australia; Clinica Universitaria de Navarra, Pamplona, Spain; Schwerpunktpraxis of Haematology & Oncology, Magdeburg, Germany; Sheba Medical Centre, Tel-Hashomer, Israel; Frankston Private Hospital Peninsula Oncology Centre, Frankston, Victoria, Australia; Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; Centre Eugéne Marquis, Hopital de Jour, Rennes, France; Shaare-Zedek Medical Center, Jerusalem, Israel; NHMRC Clinical Trials Centre, Camperdown, New South Wales, Australia; Data Reduction LLC, Chester, NJ; Royal Melbourne Hospital, Melbourne, Victoria, Australia.

SIRflox

Study Design

Prospective open-label RCT

Primary endpoint: Progression-Free Survival (PFS) in the ITT population by independent central imaging



1. Bevacizumab allowed at investigator's discretion, per institutional practice

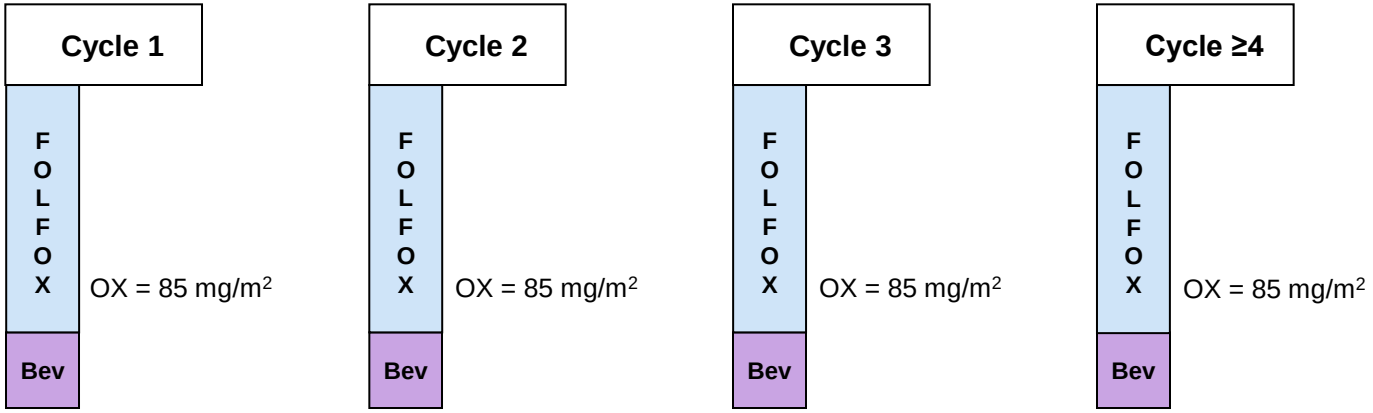
Secondary endpoints:

- PFS in the liver
- Tumour response rate in the liver
- Tumour response rate at any site (RECIST 1.0)
- Hepatic resection rate
- Toxicity & safety (NCI CTCAEv3.0)
- Health-related quality of life
- Overall survival, in a pre-planned combined analysis

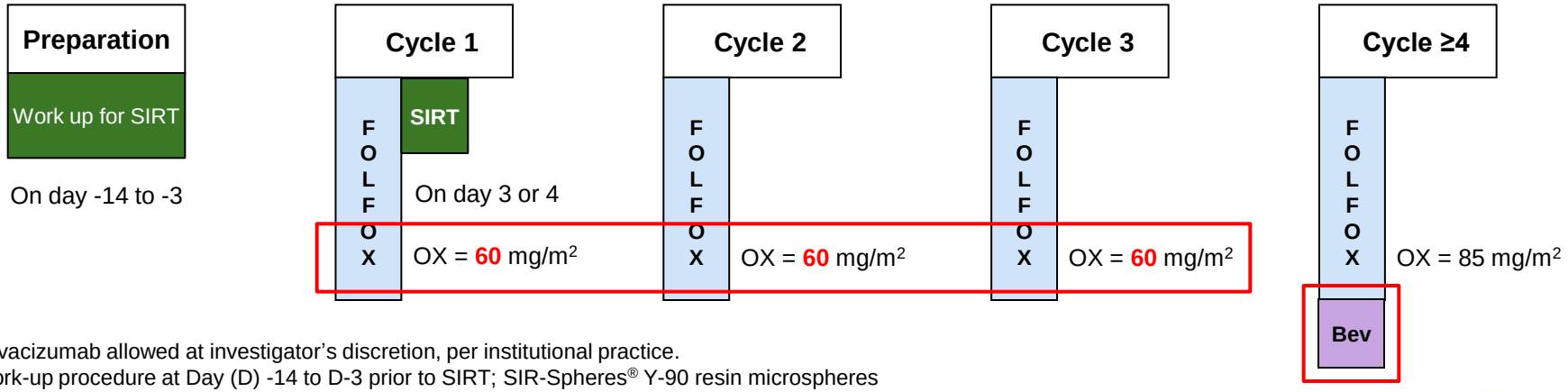
SIRflox

Treatment Schedule

Control arm: mFOLFOX6 (+ bevacizumab) (1)



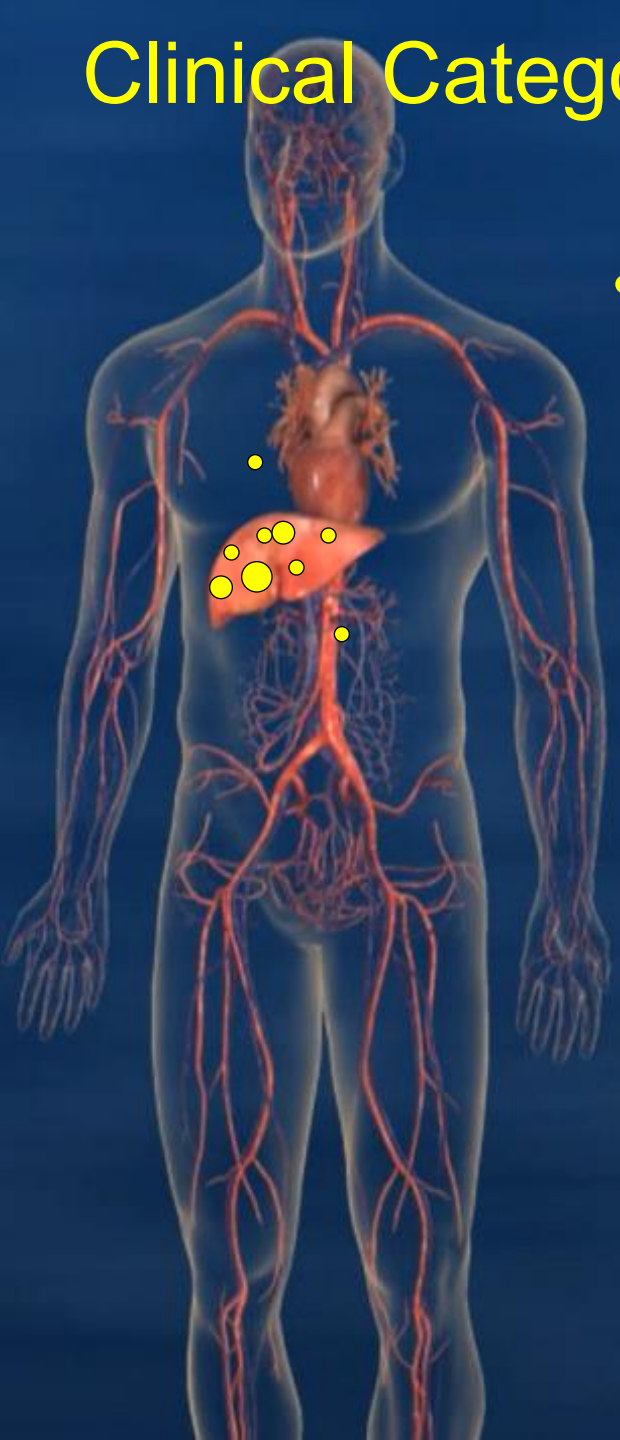
Treatment arm: mFOLFOX6 (+ bevacizumab) (1) + SIRT (2)



1. Bevacizumab allowed at investigator's discretion, per institutional practice.
2. Work-up procedure at Day (D) -14 to D-3 prior to SIRT; SIR-Spheres® Y-90 resin microspheres administered on either D3 or D4, of either Cycle 1 or Cycle 2.

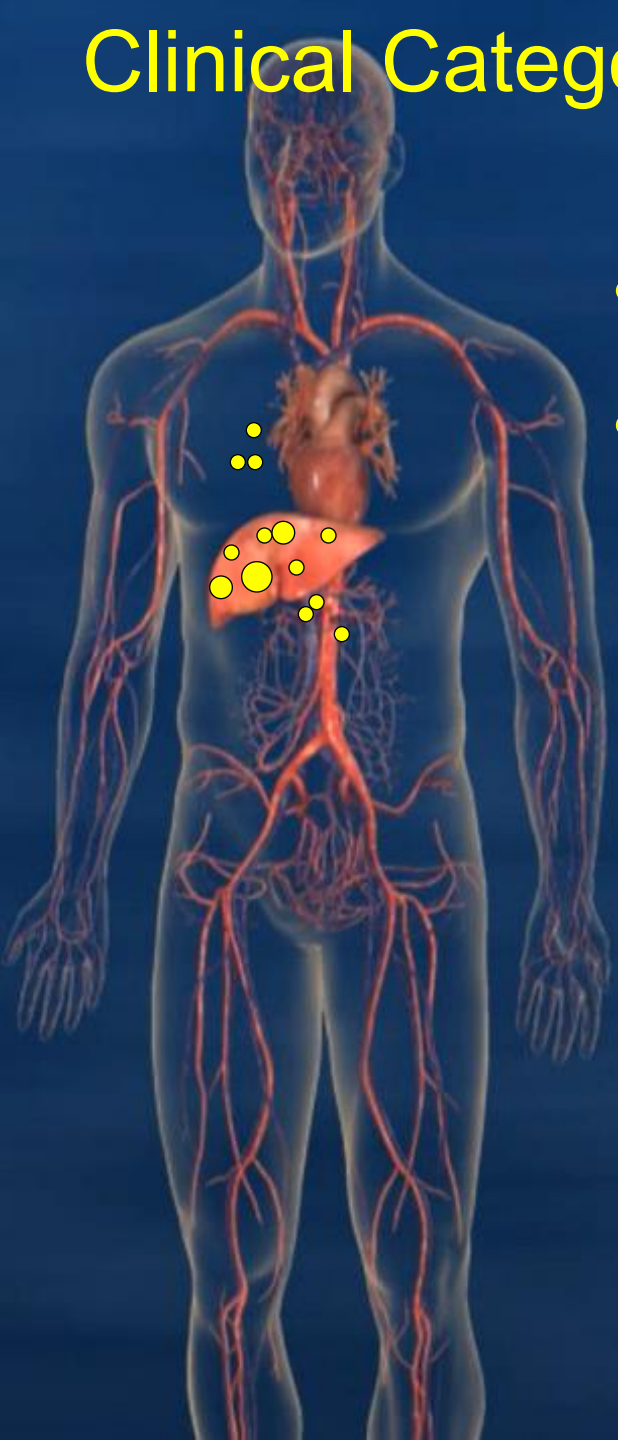
SIRflox

Clinical Categories of CRC Liver Metastases



- 4+ liver metastases ; Bilobar
  - "potentially operable" …..but Not Converted
- no *major* systemic disease
  - Randomised surgical trials in this sub-group are *lacking*
  - no consensus of what / who is 'potentially operable' and prediction of convertability
  - These patients invariably also have extra-hepatic disease

Clinical Categories of CRC Liver Metastases



- commonest / worst:
- Systemic disease – 'incurable'

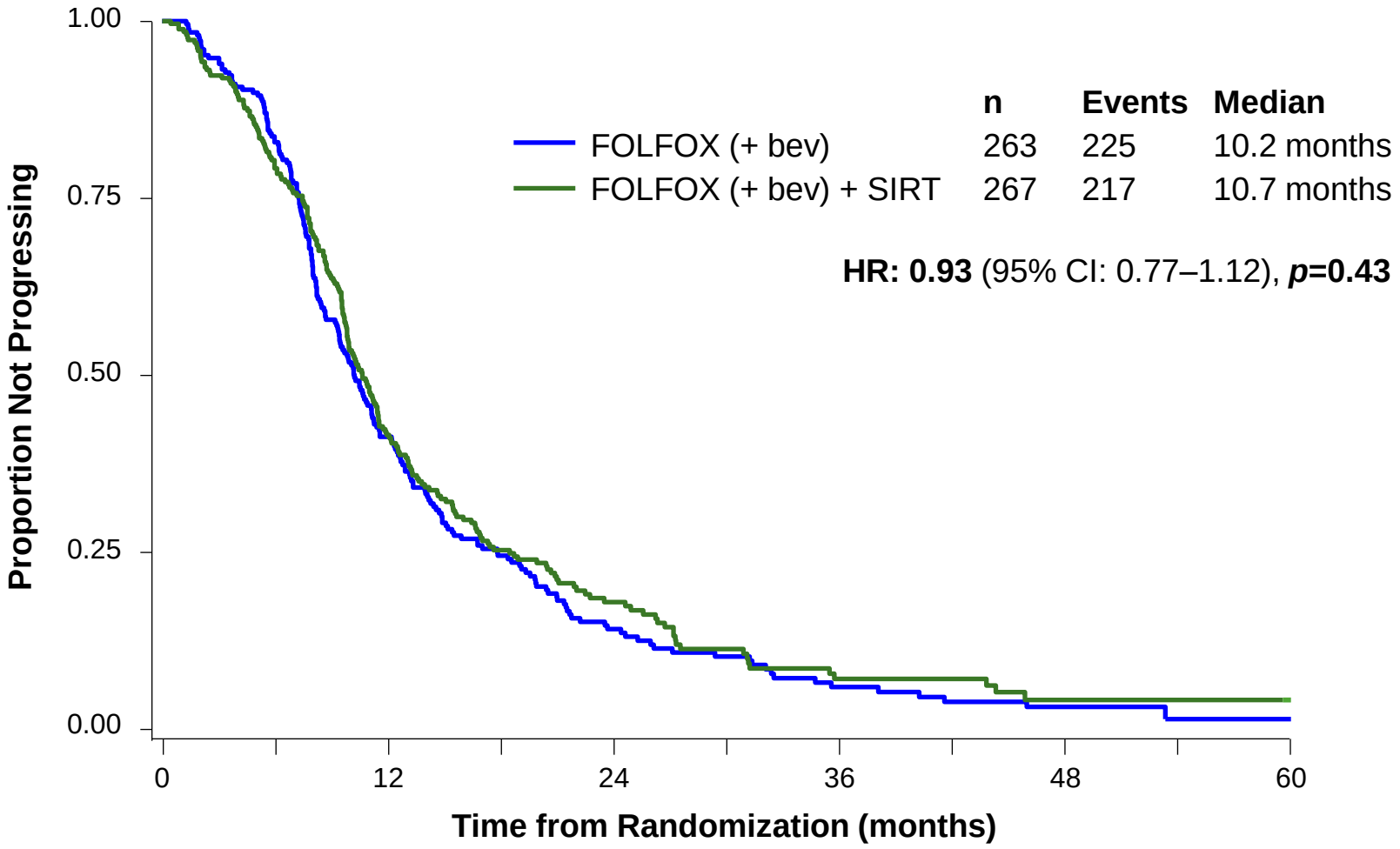
  + liver metastases

- **Median Overall Survival**
  18-25mths unselected

  ** plus* 5-7.5 mths Selected
  (KRAS/ NRAS wt)

- *Minus* ~5 mths? (BRAF mt)

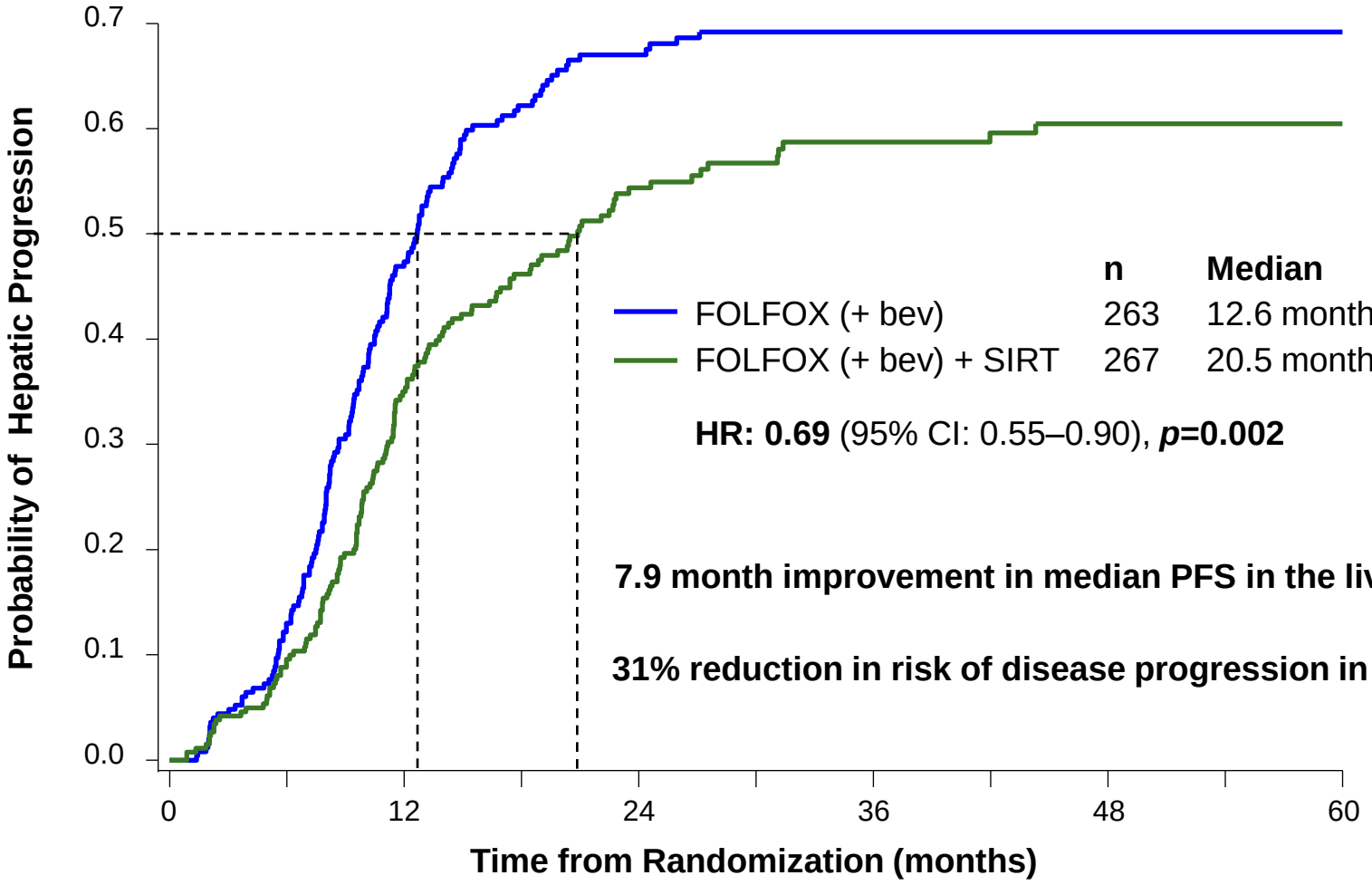
Progression-Free Survival at Any Site



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

SIRflox

PFS in the Liver:
Cumulative Incidence of Liver Progression



Number at risk						
FOLFOX (+ bev)	263	96	29	9	5	2
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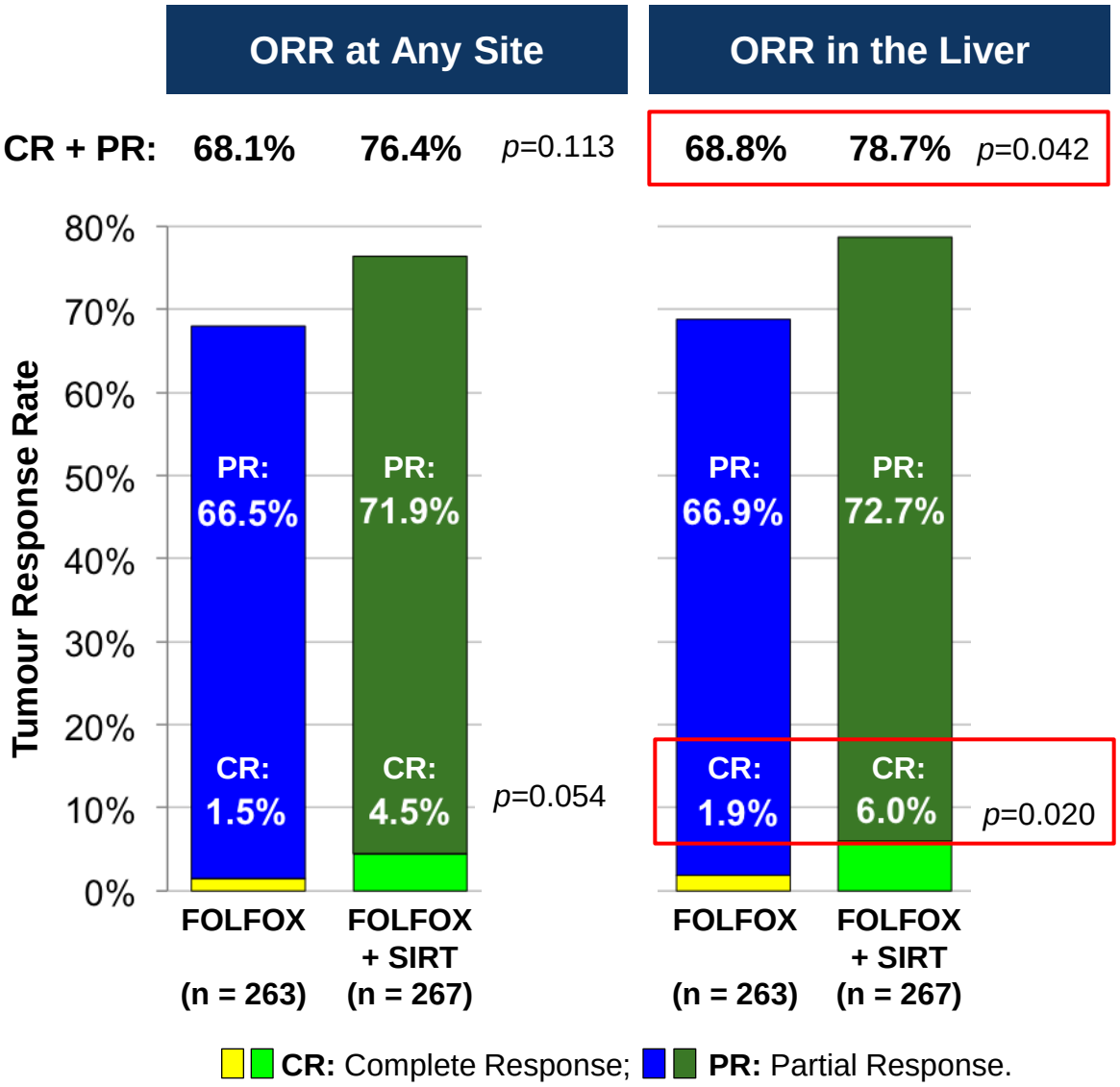
SIRflox

Objective Response Rate (ORR) by RECIST v1.0



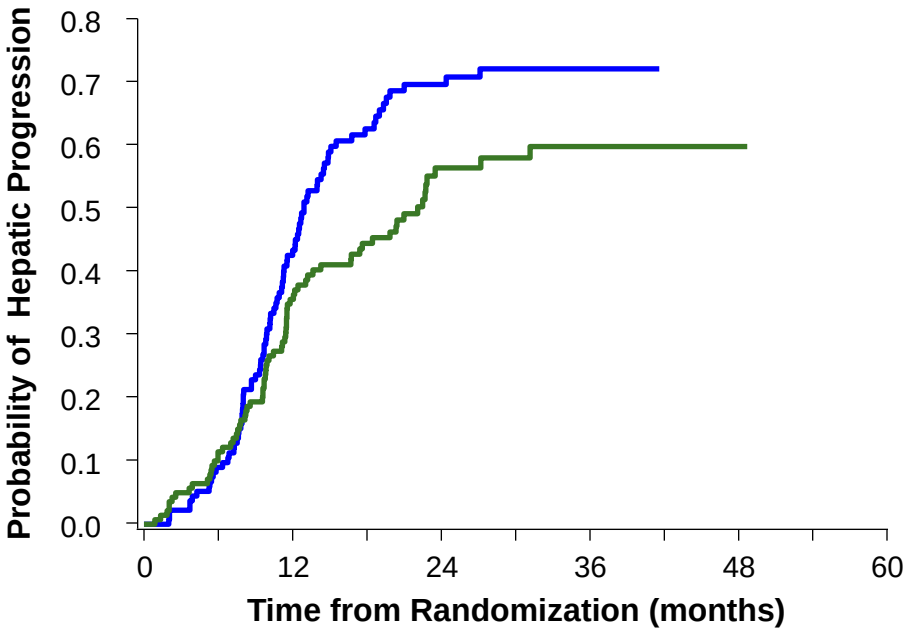
SIRflox

PFS in the Liver: Cumulative Incidence of Liver Progression Stratified by ITT for Bevacizumab or No Bevacizumab

Patients with ITT for bevacizumab

	N	Median	p-value
FOLFOX + bev	147	12.7 months	p=0.018
FOLFOX + bev + SIRT	145	21.0 months	

HR: 0.69 (95% CI: 0.50–0.94)

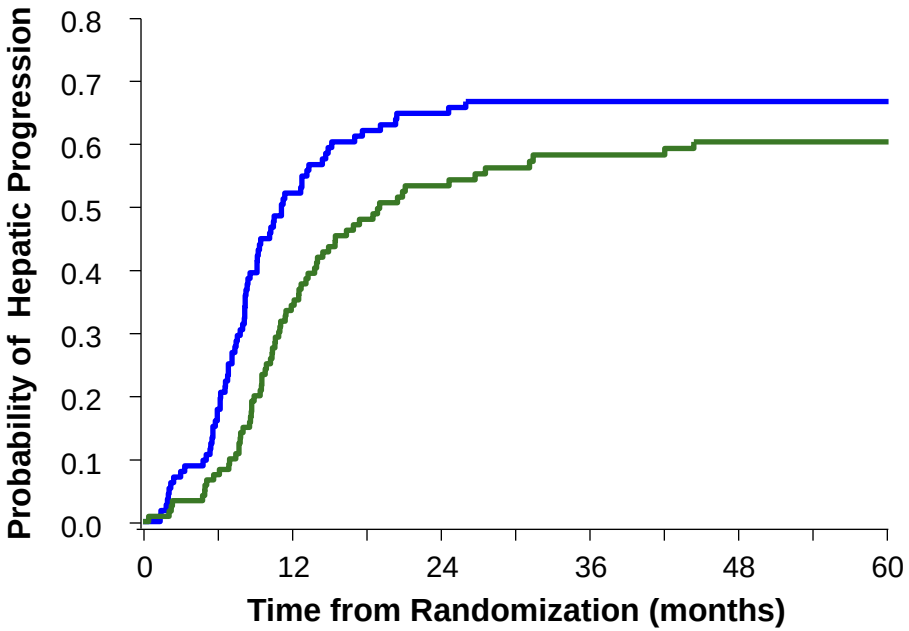


n at risk						
FOLFOX + bev	147	56	13	3	0	
FOLFOX + bev + SIRT	145	57	13	5	1	

Patients with ITT for no bevacizumab

	N	Median	p-value
FOLFOX	116	10.6 months	p=0.028
FOLFOX + SIRT	122	18.9 months	

HR: 0.69 (95% CI: 0.50–0.96)



FOLFOX	116	40	17	9	5	2
FOLFOX + SIRT	122	50	21	7	4	2

SIRflox

Structure for the OS analysis; (1020 patients)

Overall survival : > 1020 patients

The SIRFLOX Study

SIR-Spheres® + FOLFOX *versus* FOLFOX Alone (with or without bevacizumab) in Patients with Unresectable Liver Metastases from Colorectal Cancer

Randomised controlled study evaluating SIR-Spheres microspheres in combination with FOLFOX chemotherapy *vs.* FOLFOX chemotherapy alone for the first-line treatment of unresectable liver-only or liver-predominant colorectal cancer metastases.

- PFS
- **532 patients**

The FOXFIRE Trial

Can Selective Internal Radiotherapy to Liver Metastases Improve Overall Survival for Patients Treated with OxMdG Chemotherapy as First-Line Treatment of Metastatic Colorectal Cancer?

Randomised controlled trial evaluating SIR-Spheres microspheres in combination with OxMdG chemotherapy *vs.* OxMdG chemotherapy alone for the first-line treatment of unresectable liver-only or liver-predominant colorectal cancer metastases.

- OS in combination with SIRFLOX
- **364** patients

FOXFIRE Global

- OS in combination with SIRFLOX and FOXFIRE
- **~ 100 + patients**

Yttrium-90 glass microspheres studies

PARAMETER	STOP-HCC	EPOCH	YES-P
STUDY DESIGN	Phase III	Phase III	Phase III
PATIENT POPULATION	Unresectable HCC	mCRC to the liver who have failed 1st line chemotherapy	Unresectable HCC patients with portal vein thrombosis
PRINCIPAL INVESTIGATOR	Riad Salem, MD Northwestern, Chicago, US	Mary Mulcahy, MD Northwestern, Chicago, US	Vincent Mazzaferro, MD Istituto Nazionale dei Tumori, Milan, Italy Riad Salem, MD Northwestern, Chicago, US
CONTROL ARM	Kinase Inhibitor	Second-line Chemotherapy	Kinase Inhibitor
TREATMENT ARM	TheraSphere® + Kinase Inhibitor	TheraSphere® + Second-line Chemotherapy	TheraSphere®
ENDPOINTS	Efficacy, Safety	Efficacy, Safety	Efficacy, Safety
LOCATION	Worldwide	Worldwide	Worldwide
# SITES	40	30	24
# PATIENTS	~400	~350	~350

SIRT *vs.* TACE – key differences[1]

Table 4. Toxicity and Complications

Variable	Radioembolization (n = 38)	Chemoembolization (n = 35)	*P* Value
Hospitalization after index procedure			
Mean initial hospital stay (days) ± SEM	0.05 ± 0.04	2.0 ± 0.34	< .001
Extended initial hospitalization (>2 days) (%)	0	7 (20)	.01
30-day rehospitalization (%)	5 (13.2)	7 (20)	NS
Mean rehospitalization (days) ± SEM	3.6 ± 0.6	7.9 ± 1.7	.03
Mean total hospitalization (days) ± SEM	0.5 ± 0.2	3.5 ± 0.7	< .001
Complication rates (%)			
Any complications (minor or major)	10 (26.3)	17 (48.6)	.05
Postembolization syndrome	19 (50)	17 (48.6)	.02
Expected side effects*	16 (42.1)	8 (22.9)	
Minor complication†	1 (2.6)	2 (5.7)	
Major complication‡	1 (2.6)	7 (20)	
Other minor complications			
Rash	1 (2.6)	0	NS
Other major complications	7 (18.4)	8 (22.9)	NS
30-day all-cause mortality	0	3 (8.6)	.07
Gastrointestinal hemorrhage	2 (5.3)	0	NS
Hepatic dysfunction	5 (10.5)	3 (8.6)	NS
Cytopenia	0	0	NS
Other	0	2 (5.7)	NS

NS = nonsignificant; SEM = standard error of the mean.
* No additional physician visits required.
† Observation but no significant treatment required.
‡ Hospitalization and treatment required.

1.Lance C, McLennan G, Obuchowski N et al. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. Journal of Vascular and Interventional Radiology 2011; 22: 1697–1705.

SIRT *vs. D*-TACE costs

Treatment	Treatment cost/patient (€)
SIRT using SIR-Spheres microspheres	17,390[1] (UK) 15,942[4] (Italy)
DEBDOX / DEBIRI	18,615[2] (UK) 13,600[3] (Spain)

[1]Bester L, Wasan H, Sangro B *et al.* Selective internal radiotherapy (SIRT) using resin yttrium-90 microspheres for chemotherapy-8refractory metastatic colorectal cancer: A UK cost-effectiveness analysis. Value in Health 2013;16:A413; 1 GBP=1.18576€, mid-market rate assessed Dec 17 2013.
[2]Average number of treatments per patient: 3.4.
[3]Average number of treatments per patient: 3.4.
[4]Cosimelli M, Golfieri R, Pennington B, Sennfält K. Selective internal radiotherapy (SIRT) using resin yttrium-90 resin microspheres for chemotherapy-refractory metastatic colorectal cancer: An Italian cost-effectiveness analysis. Value in Health 2013;16:A409.

Conclusions

- Non-chemotherapeutic approaches to liver metastases complement ‘’standard of care’’ pathways with increasing evidence of clinical benefit
  - they also complement de-escalation strategies
- “loco-regional” radiotherapy can be safely be integrated into the therapeutics standard options for treating inoperable liver dominant mCRC
  - Evidence is emerging on clinical benefit of integrating “debulking strategies” (“deeper response” / ETS)
    But the “value” of Organ control in OS terms is still to be understood
- Phase 3 trials with QOL and safety will determine the exact role of all the new strategies in inoperable liver-dominant mCRC

Thank You !

Questions