

mCRC Liver directed therapy

– When and how?

Session XV: Liver and peritoneal metastases

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Disclosures in respect of this talk

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

Merck KGA: - Advisory Boards / speaker
 - Research funding

Sanofi Aventis; Merck KGA; Pfizer, Roche; Bayer :
 - Advisory Boards / speaker

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

Reality check, limitations &.....'unmet needs'

www.CartoonStock.com



"I do not think I'm God. God-like, yes, but not God."

*Liver surgery
can cure patients with
colorectal liver metastases...*

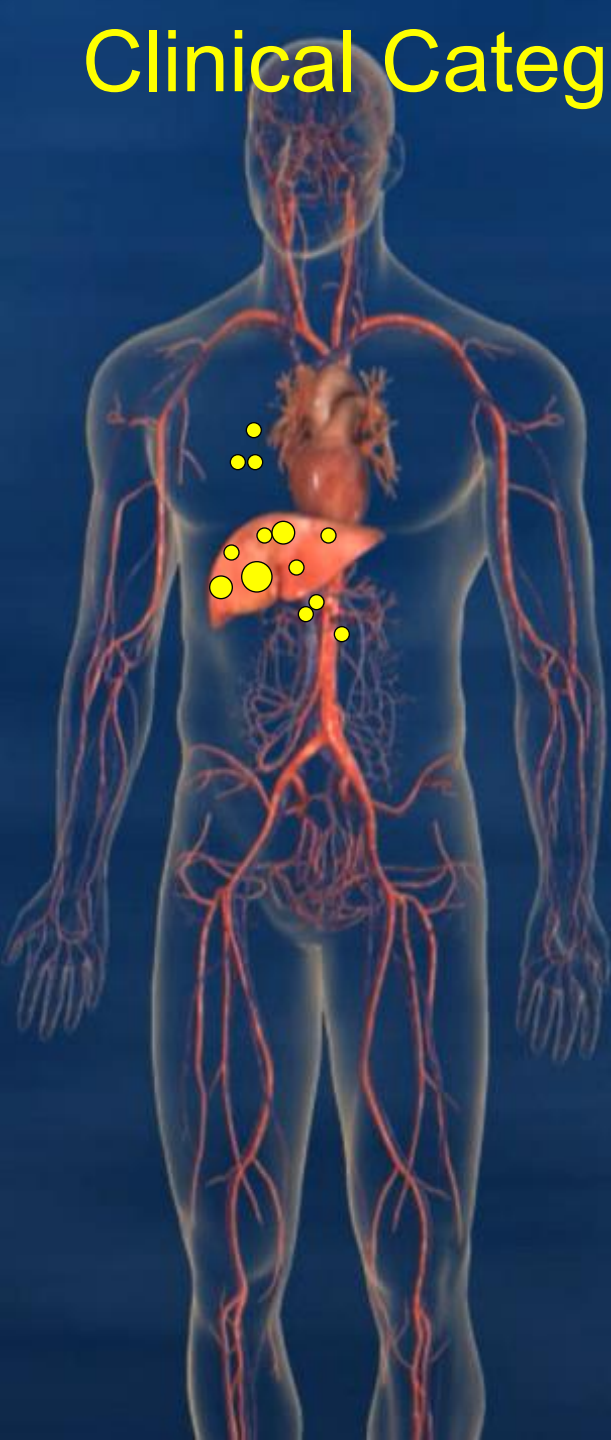
*What are our current
Benchmarks
(? level 1 evidence)*

Clinical Categories of CRC Liver Metastases?



- Cat A (Best): localised
 - < 3–4 liver metastases
 - Operable / surgical “cure”:*
 - Chemotherapy (FOLFOX) *then* Surgery
 - EORTC 40983 Intergroup
 - phase III study

Clinical Categories of CRC Liver Metastases?



- Cat C (commonest / worst) :
- Systemic disease – ‘incurable’
+ liver metastases

- Liver-only population (unselected) <13%
- R0 resection rate <6.5 % (?OS)

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

** plus 5-7.5 mths Selected*

(KRAS/ NRAS wt)

- *Minus 5 mths? (BRAF mt)*

Clinical Categories of CRC Liver Metastases?



- Cat B: 4+ liver mets
 - “potentially operable”
- no *obvious* systemic disease
 - Randomised surgical trials in this sub-group are lacking
 - no consensus of what / who is ‘potentially operable’
 - These patients invariably also have extra-hepatic disease
 - by definition worse than Category A
 - CELIM study
 - New-EPOC preliminary data not encouraging

Liver surgery can cure (5yr) some patients with colorectal liver metastases (only)

Resectable CRC liver metastases (>4): EORTC Intergroup phase III study 40983	5yrs OS	50%
Nordlinger <i>et al Lancet</i> 2008; 371(9617): 1007–1016 & <i>Lancet Oncol.</i> 2013 Nov;14(12):1208-15.	Disease Free	30%

‘Potentially’ Resectable CRC liver metastases : Prospective Studies in Molecular era

CELIM: Disease-free survival after R0 resection	5yr	OS	DFS
5+ metastases Kras-wt selected R0 resected		49%	8%
	Not R0 resected	16%	0%

*Liver surgery can cure (5yr)
some
patients with colorectal liver metastases*

Unselected CRC all-metastases : 5yrs OS 7%
SEER

Unselected CRC all-metastases : 5yrs OS 10-15%
Modern Trials population

*how do we increase this from a minority to
the majority?*

Possible Synergistic Strategies for “eradicating” Liver Tumours

- **More ..& More Systemic** Chemotherapy / Biologicals
 - Quadruplets: 4 agent combinations now being used in CRC (e.g. TRIBE etc)
 - Toxicity
 - ? increase CR's and durability : Historically a failed strategy
 - Paradox to approaches with de-escalation / Treatment Holidays
 - Combination biological era now dawning will make this difficult

Possible Synergistic Strategies for “eradicating” Liver Tumours

- Direct Tumour targeting (non-open or surgical)
- = Visually targeted – Interventional (needles)
 - Intraoperatively or Radiologically
 - Thermal Ablation RFA (Cryo-ablation)
 - Microwave : Quicker
 - Nanoknife (U/S) – 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!

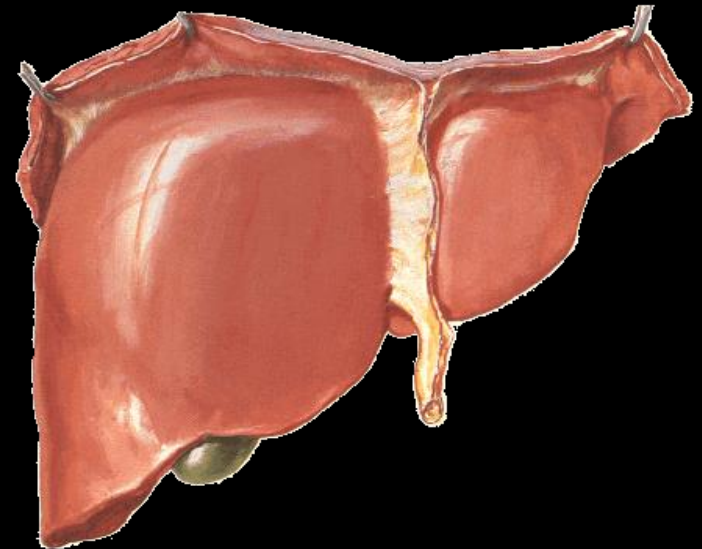
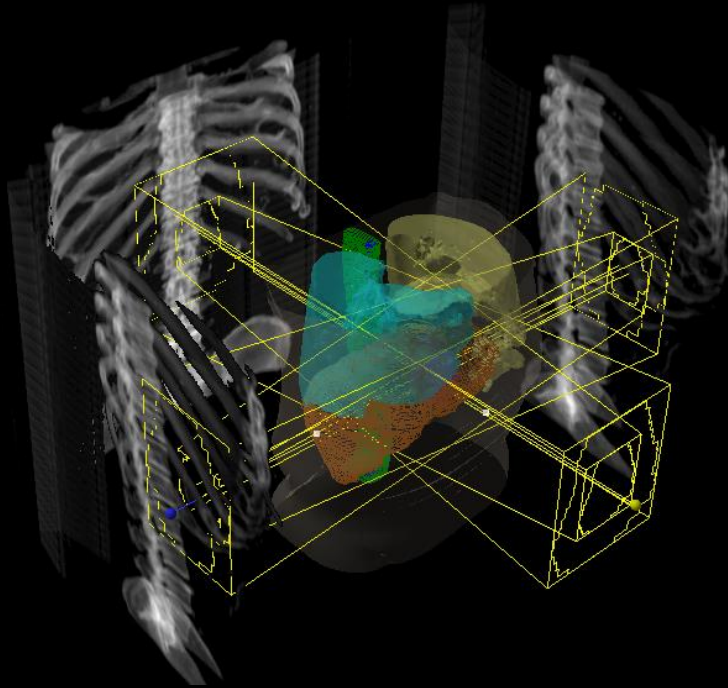
Possible Synergistic Strategies for “eradicating” Liver Tumours

- **Direct Tumour targeting – External**
- **= Visually targeted – Non-Interventional** (no needles)
 - Radiologically
 - HIFU : High-intensity focussed ultrasound
 - **External Beam Radiotherapy**
 - SBRT/ Highly conformal / IMRT / IMGRT
 - Cyberknife
 - Protons (Carbon)

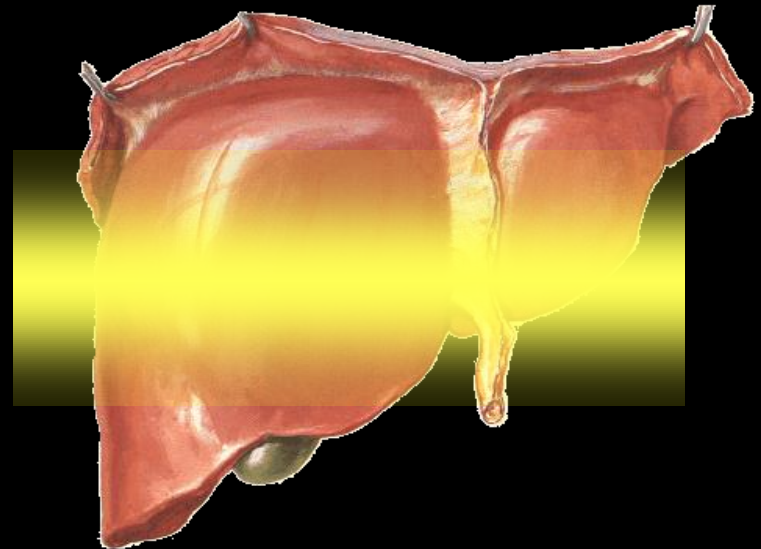
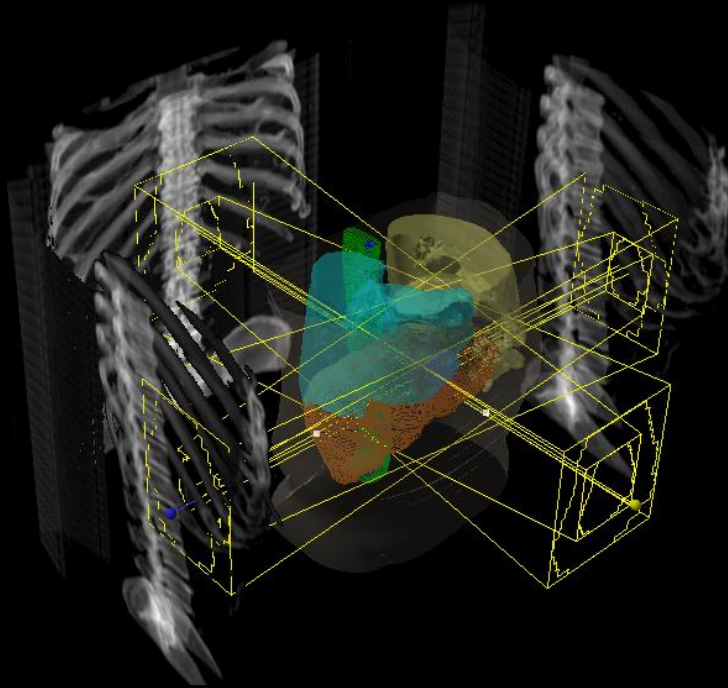
Possible Synergistic Strategies for “eradicating” Liver Tumours

- Direct Tumour targeting (e.g. external beam)
- = Visually targeted (no needles)
 - Radiological
 - Why would Visually targeted approaches improve outcomes compared to Liver surgery in advanced disease ?
 - will be suitable for select individual cases
 - HIFU
 - Extremity
 - SBRT
 - Cyberknife
 - Protons

Hepatic Structural Targetting, External Beam RT



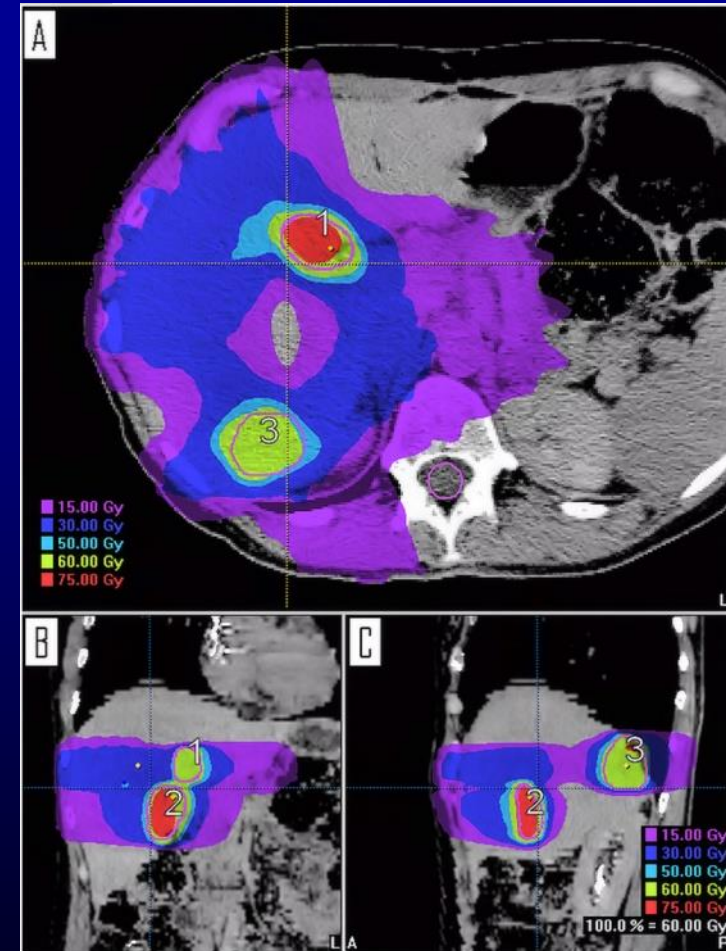
Hepatic Structural Targetting, External Beam RT



Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Scheffer

- Eligibility, n=46
 - 1-3 liver metastases
 - Solid tumors < 6cm
 - Liver and kidney function OK
 - Bili <3 mg/dL, alb > 2.5 g/dL
 - Liver enzymes <3xULN
 - No ascites
 - No systemic therapy within 14 days pre- or post-SBRT
- Dose escalation to 20 Gy x 3
- Image guidance and breathing motion management
- Liver doses:
 - > 700 cc had to receive < 15 Gy



Possible Synergistic Strategies for “eradicating” Liver Tumours

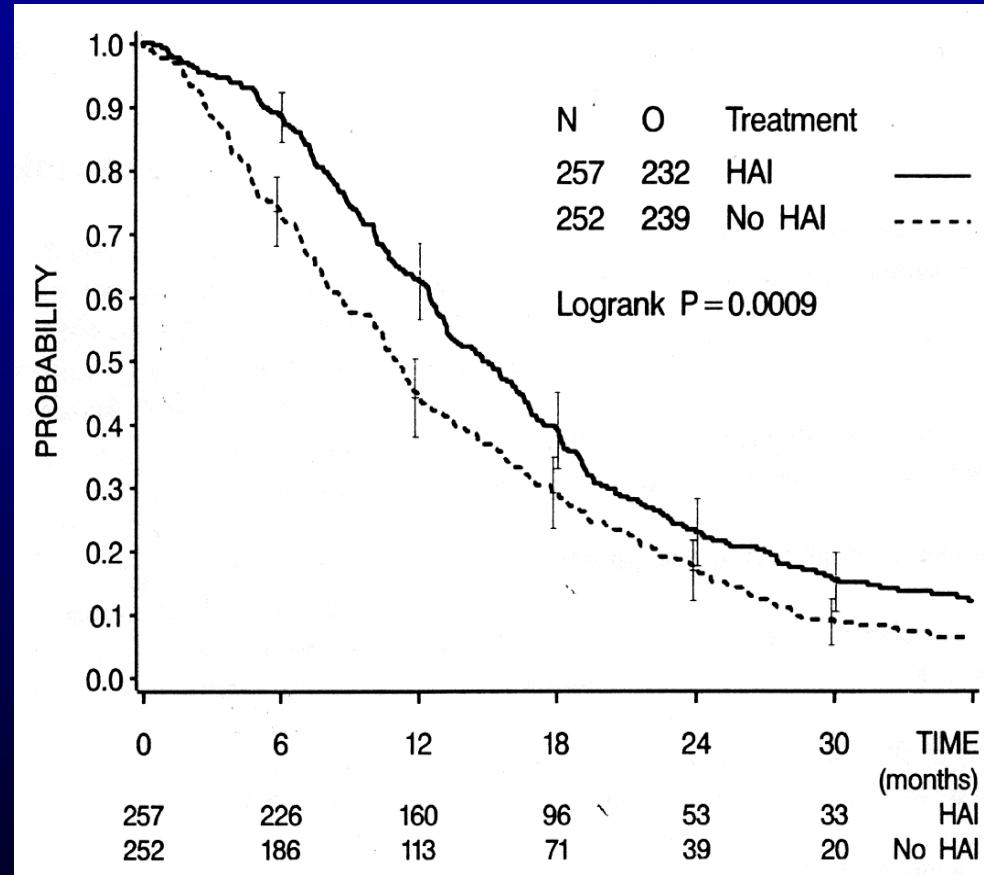
- **Liver targeted via loco-regional Vascular supply-Organ targeted**
 - Embolisation (Bland / TAE) inducing ischemia and infarction
 - Cytotoxic agents delivered to higher concentration
 - (HAI or Portal vein)
 - 5FU / FUDR
 - Oxaliplatin & Combinations
 - Drug eluting Beads: Irinotecan / Doxorubicin
 - combines embolisation
 - Selective internal radiation (SIRT) / Brachytherapy)
 - HAI Y90 resin V glass = radioembolisation

Hepatic Arterial Infusion Therapy Meta Analysis (FP Era)

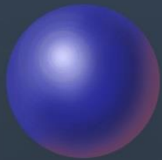
- Meta analysis of six randomized trials for survival

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

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

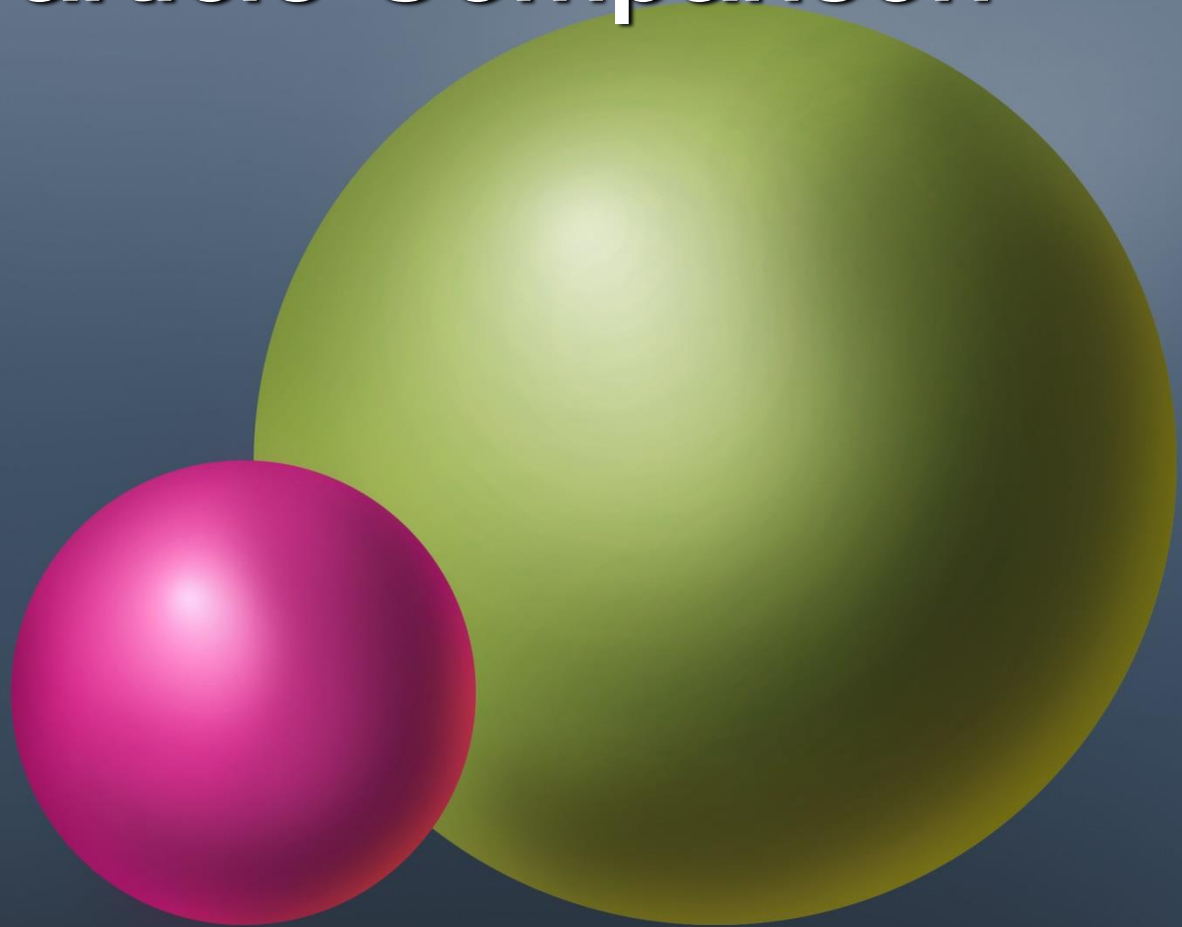


Arterial Particle Comparison



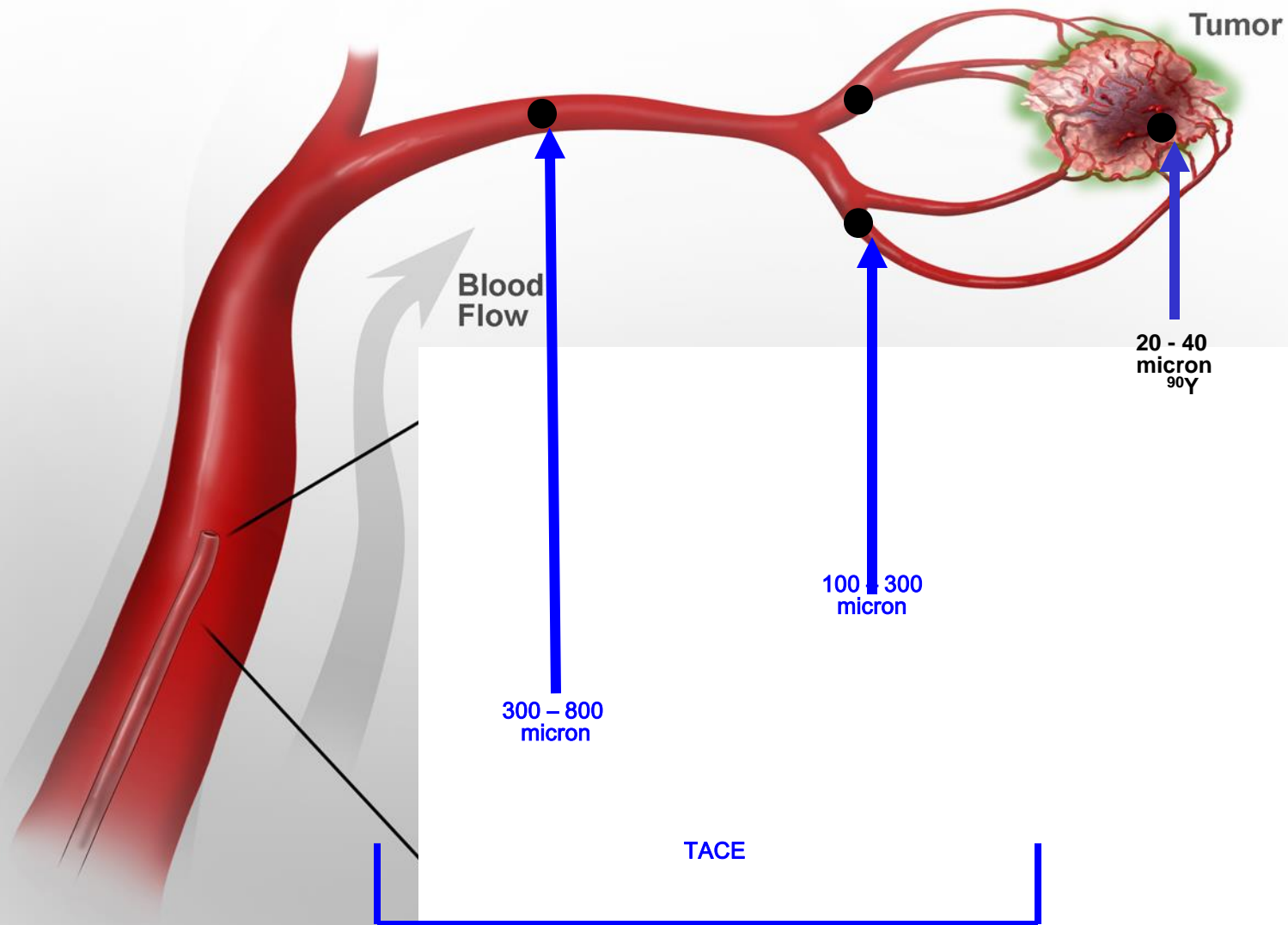
⁹⁰Y-microspheres
25-35 microns

GOAL: implant tumor

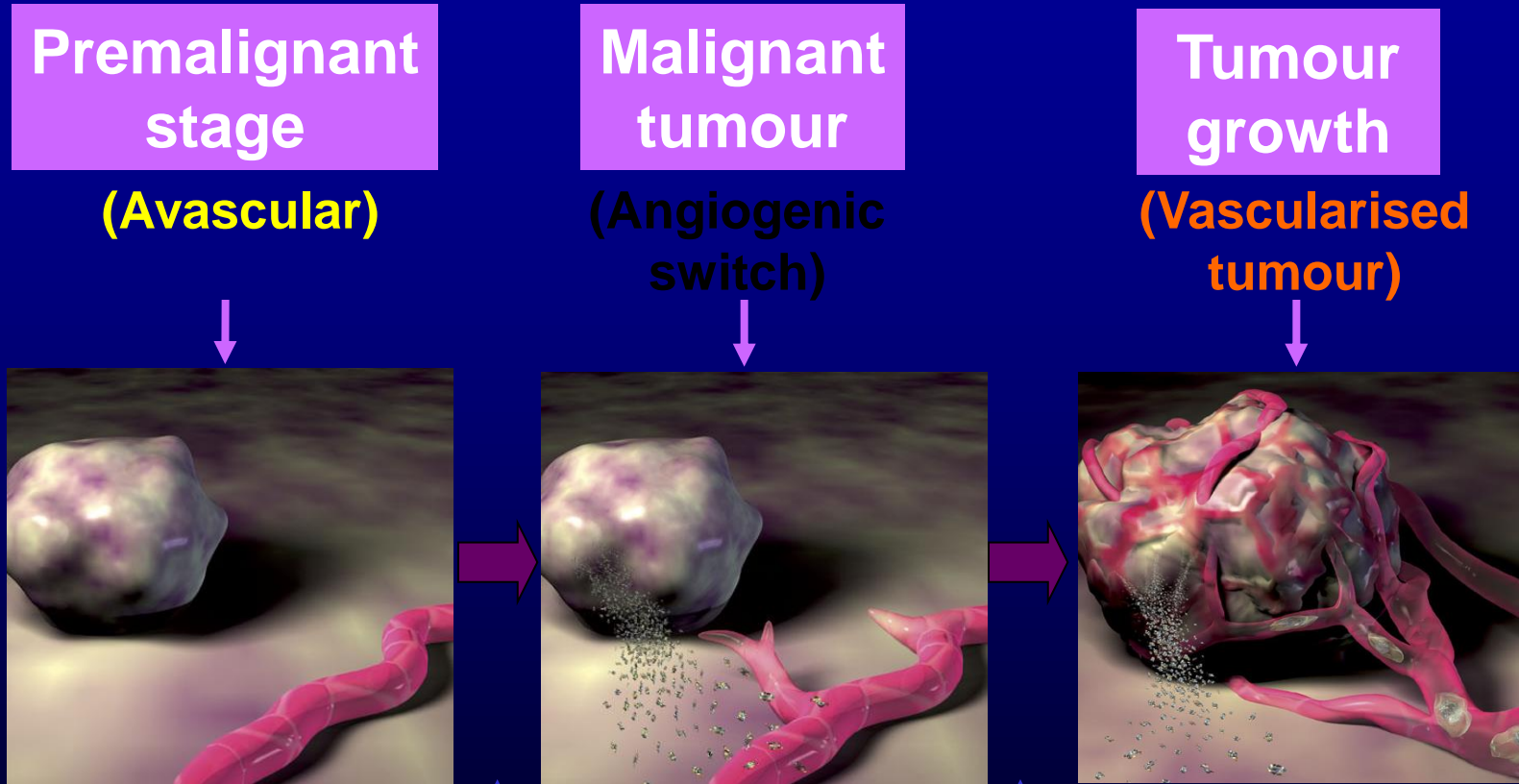


TAE, TACE and Drug Eluting Beads
100-700 microns

GOAL: block all blood to tumor

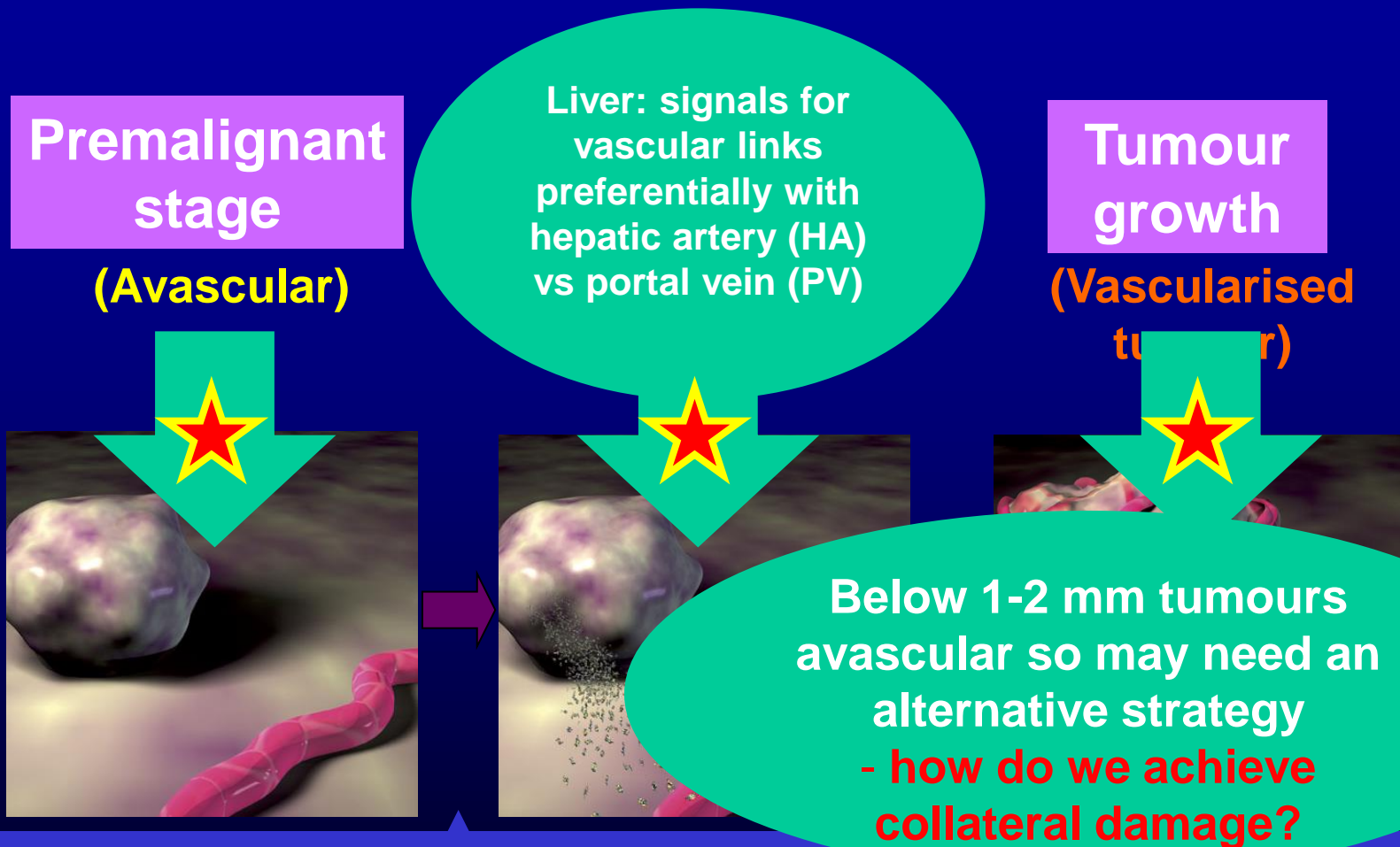


Angiogenesis is involved throughout tumour formation.....but micro-metastases remain avascular



Stages at which angiogenesis plays a role in tumour progression

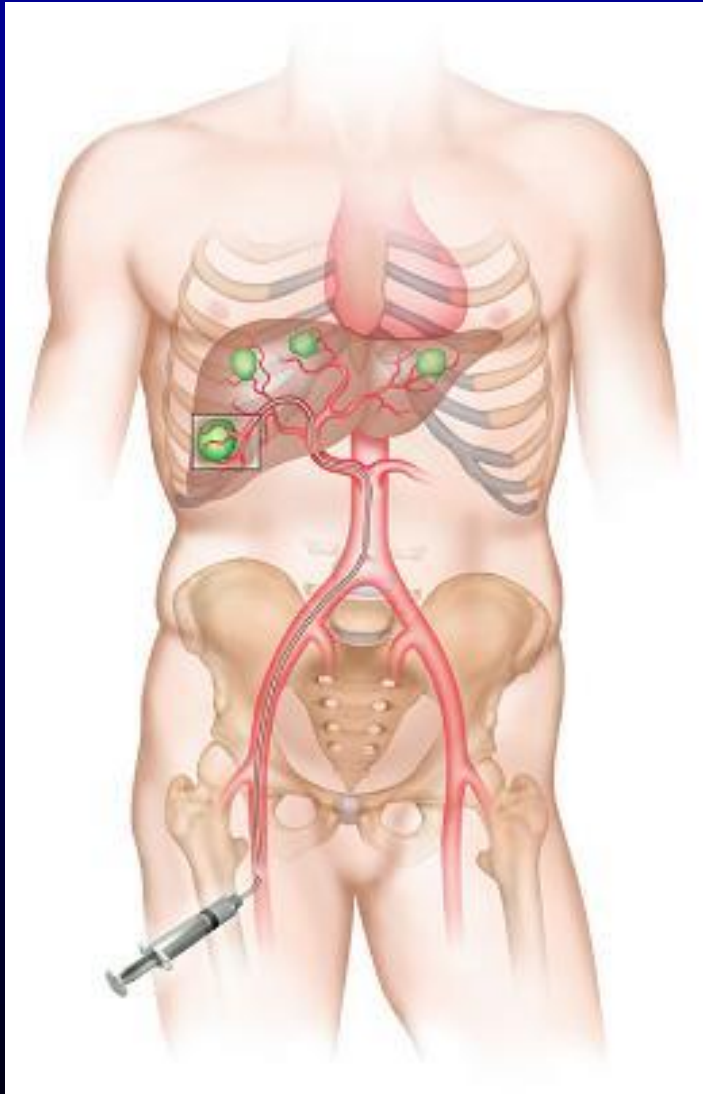
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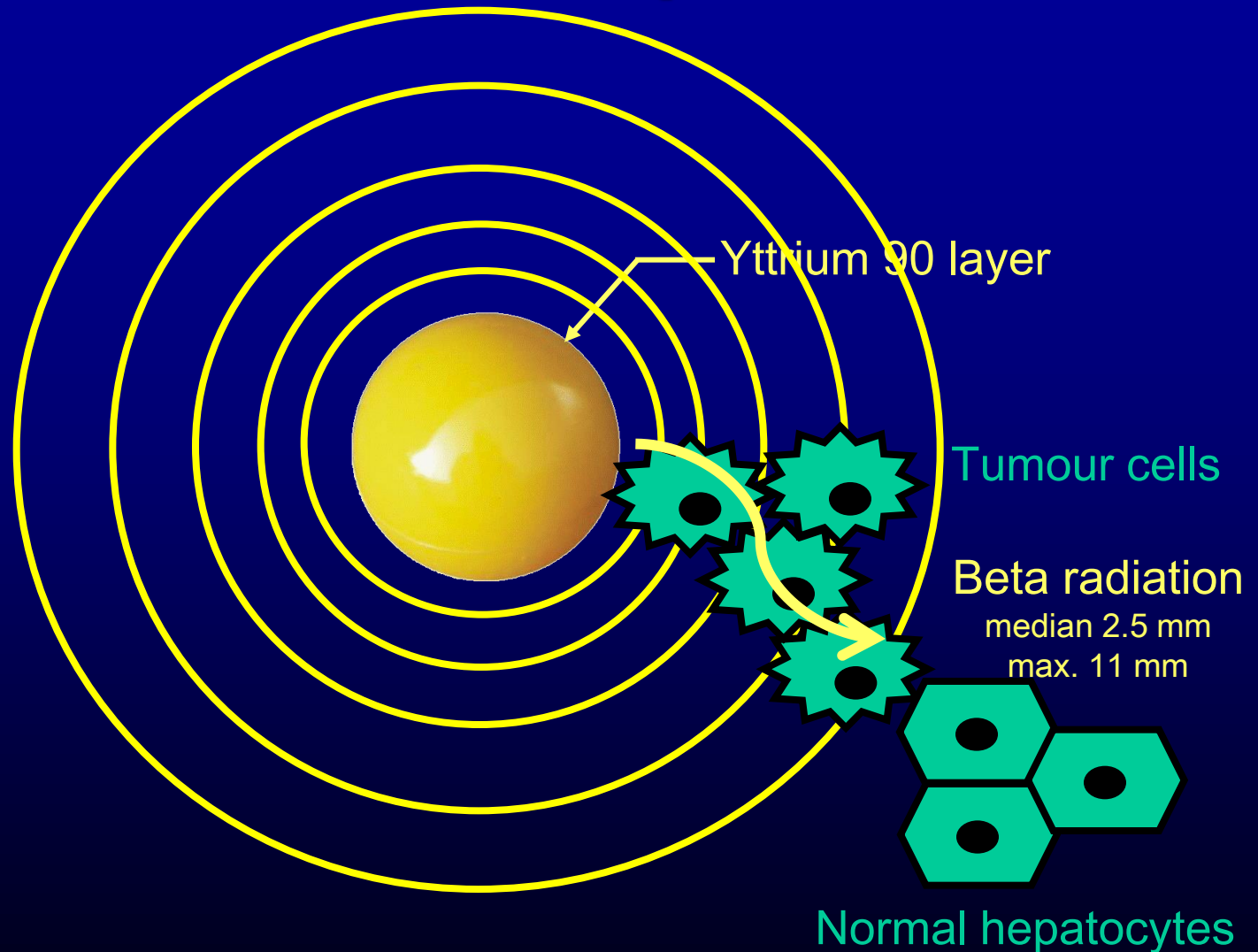
Stages at which angiogenesis plays a role in tumour progression

Radioembolization/SIRT

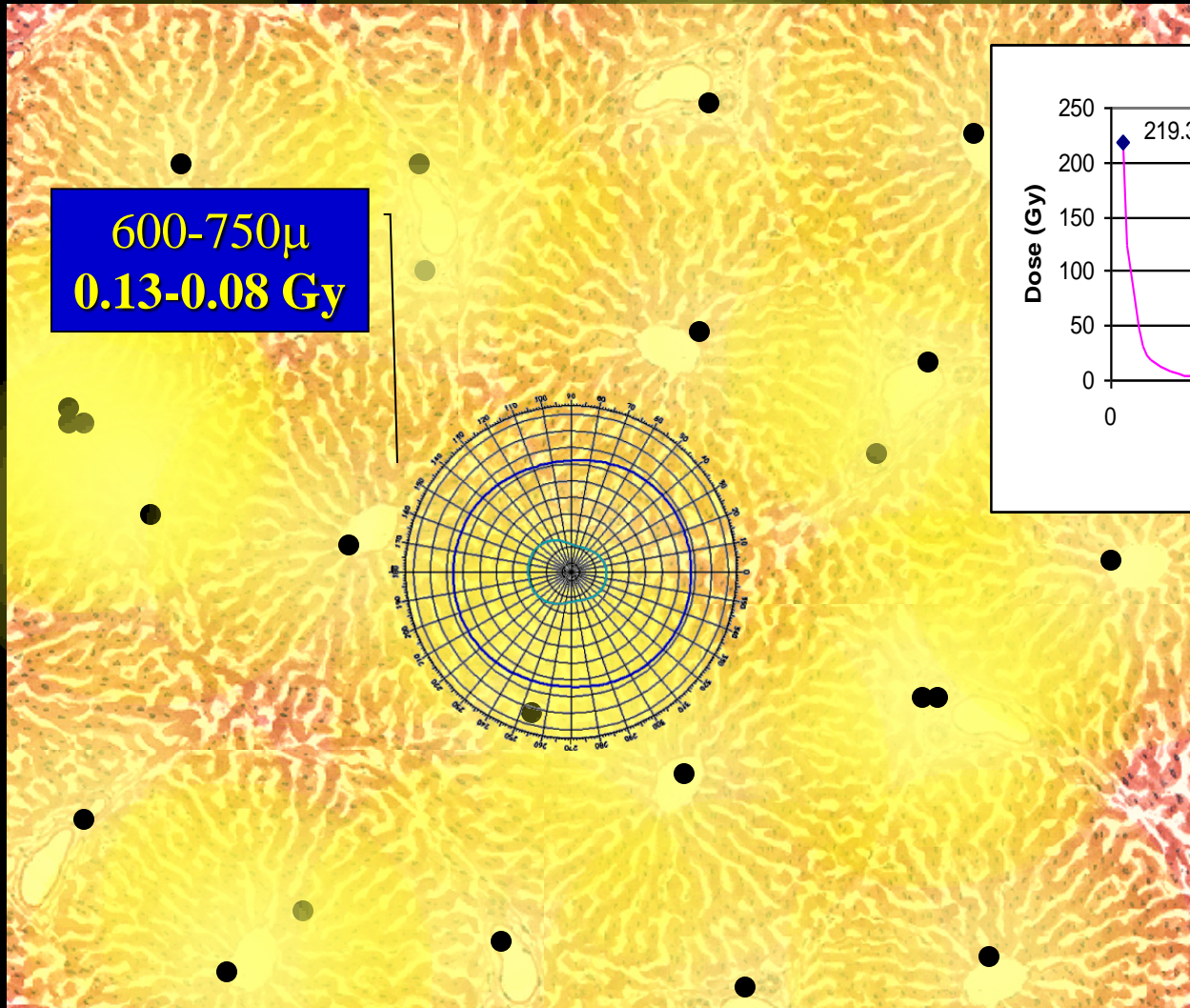
Yttrium 90 resin SIR-Spheres



Y90 resin SIR-Spheres®

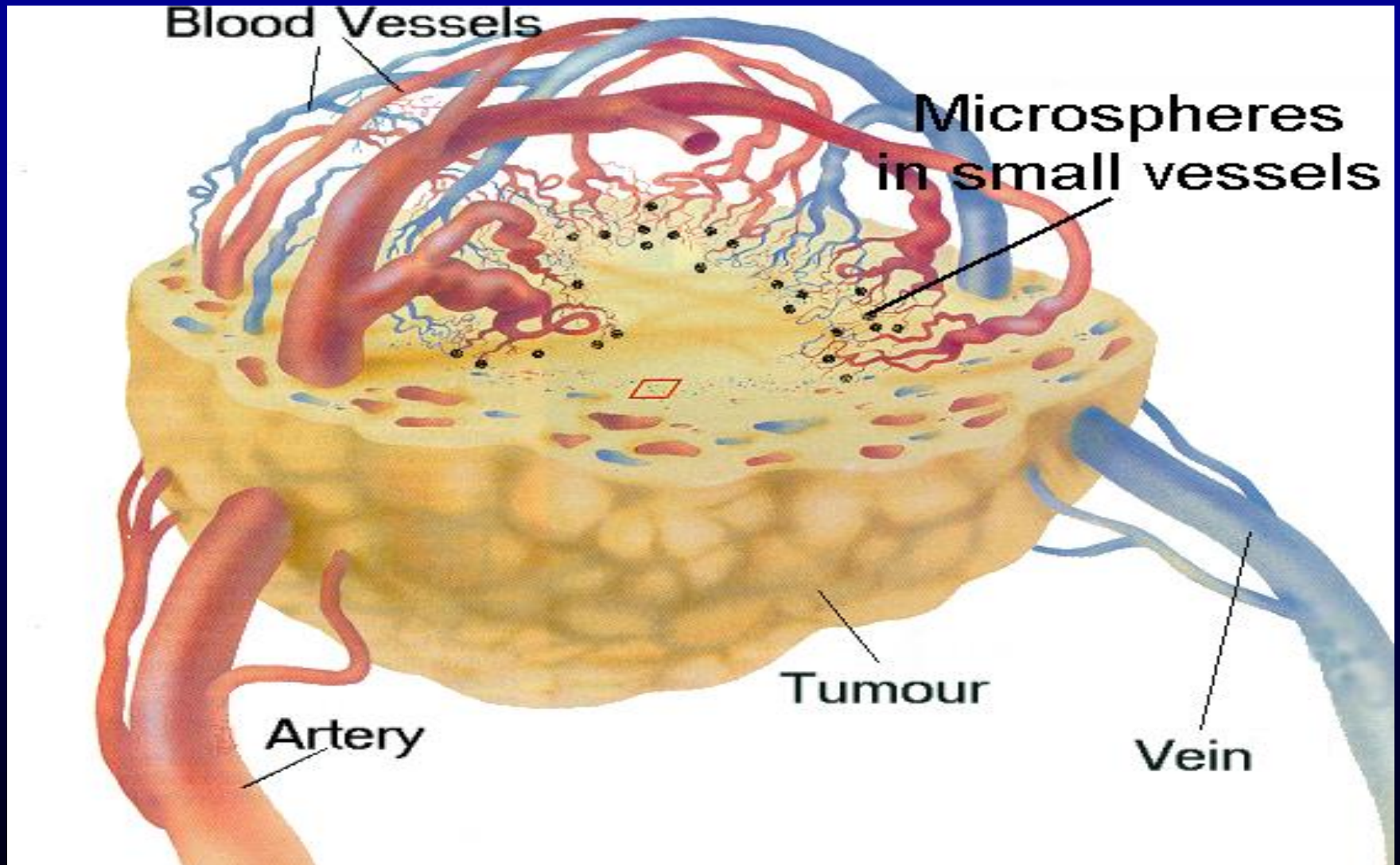


Hepatic Structural Targeting

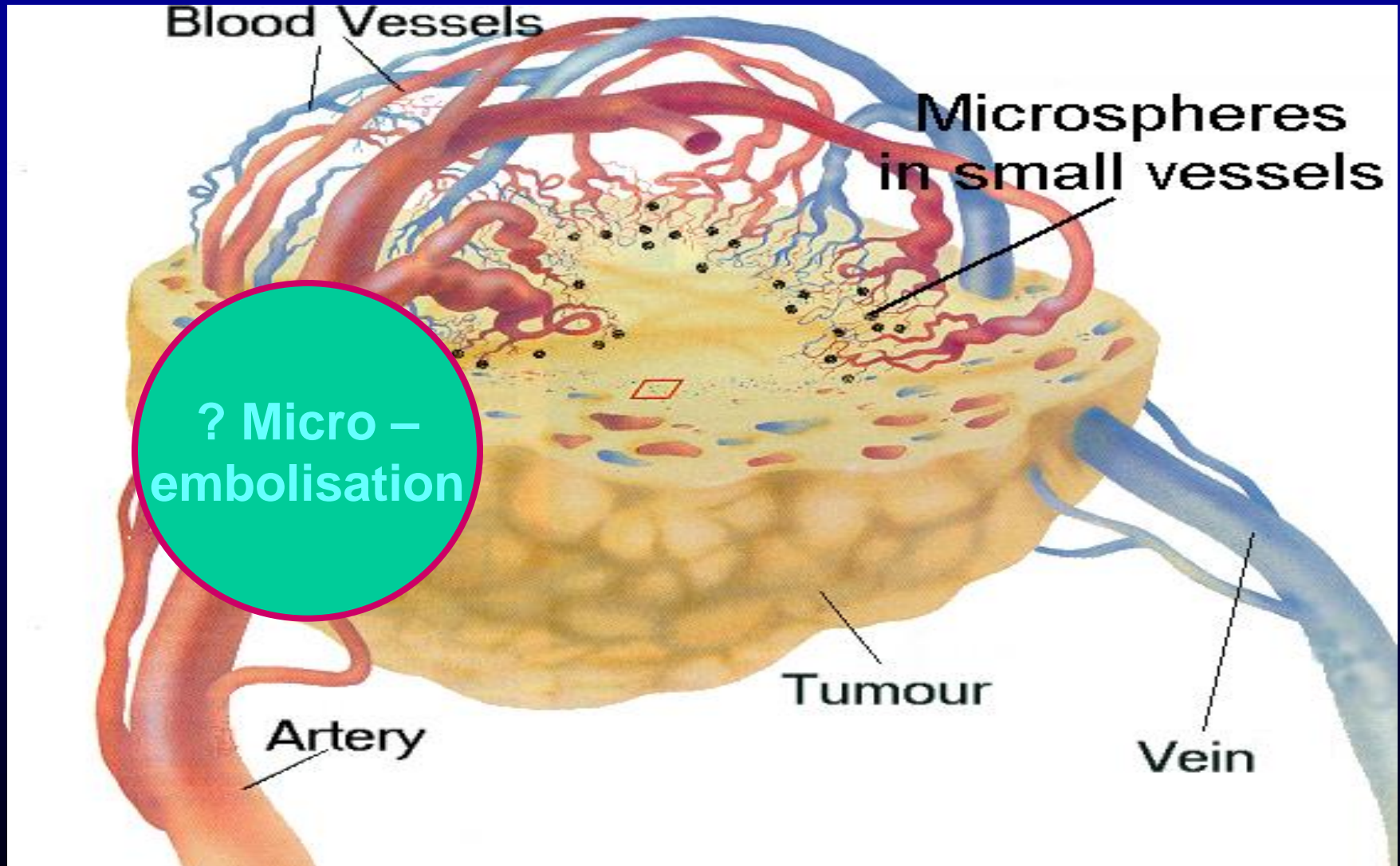


DISTRIBUTION OPTIMIZES CROSS-FIRE (collateral) EFFECT

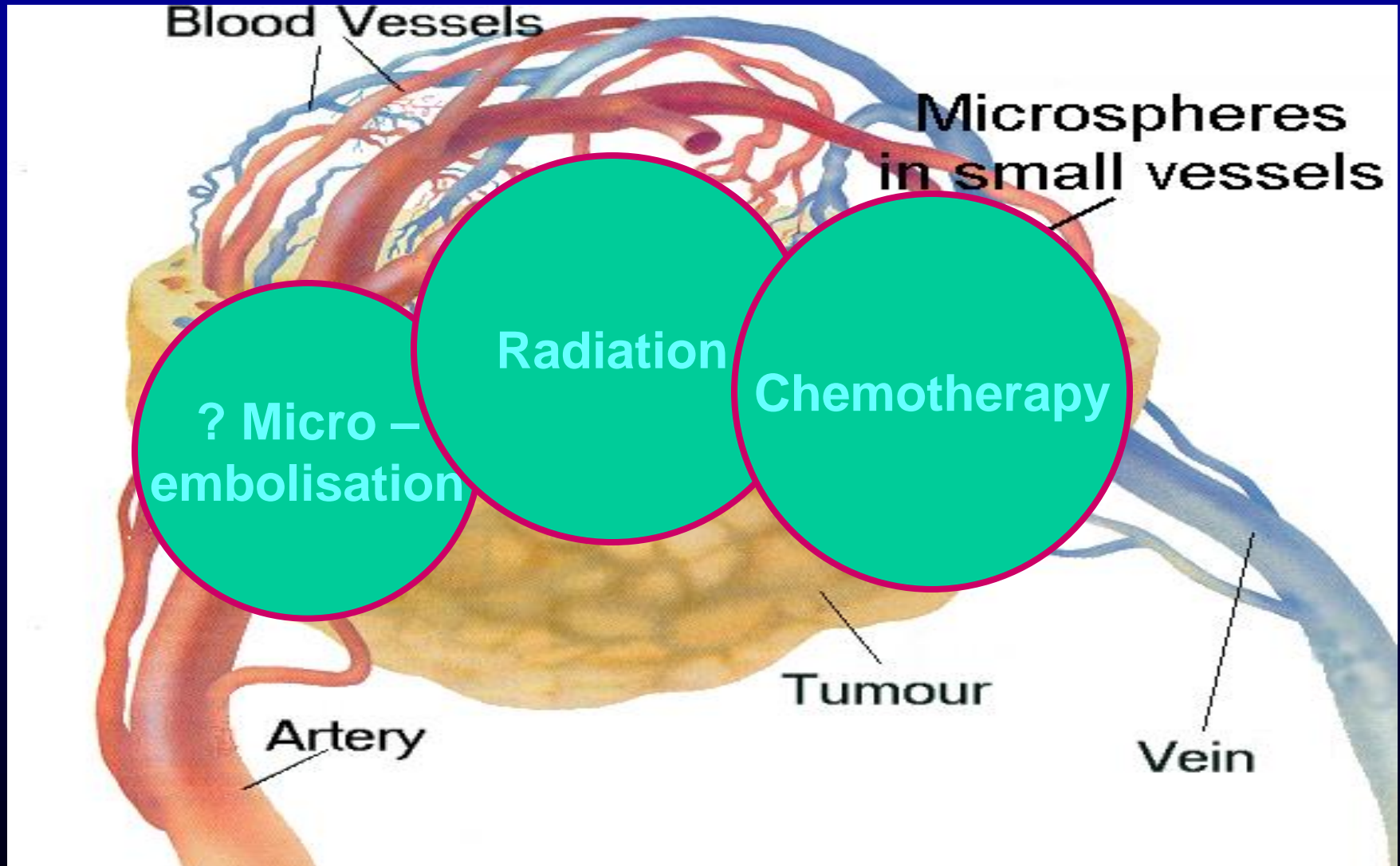
Potential synergy with radio-sensitising systemic chemotherapy could lead to collateral damage



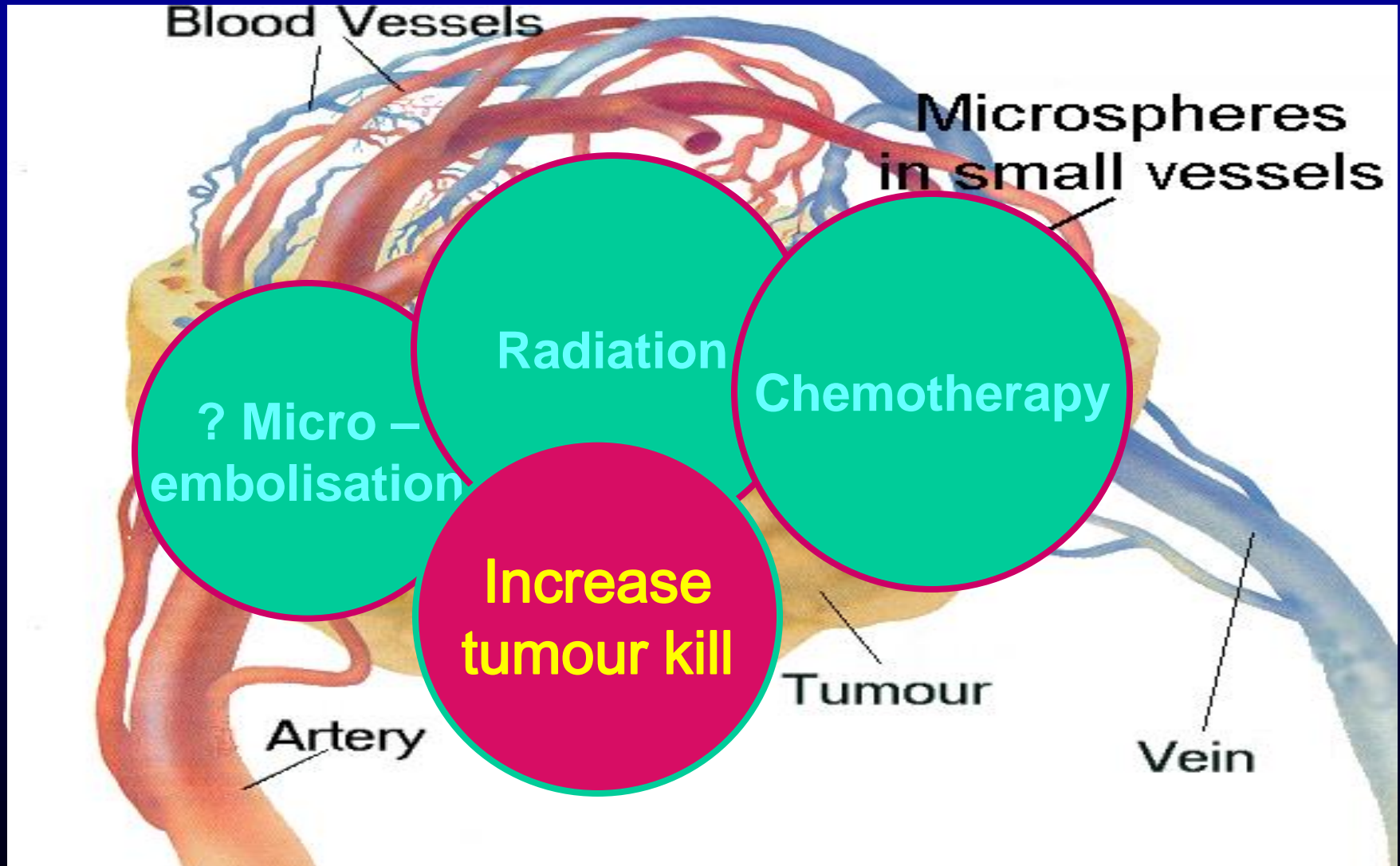
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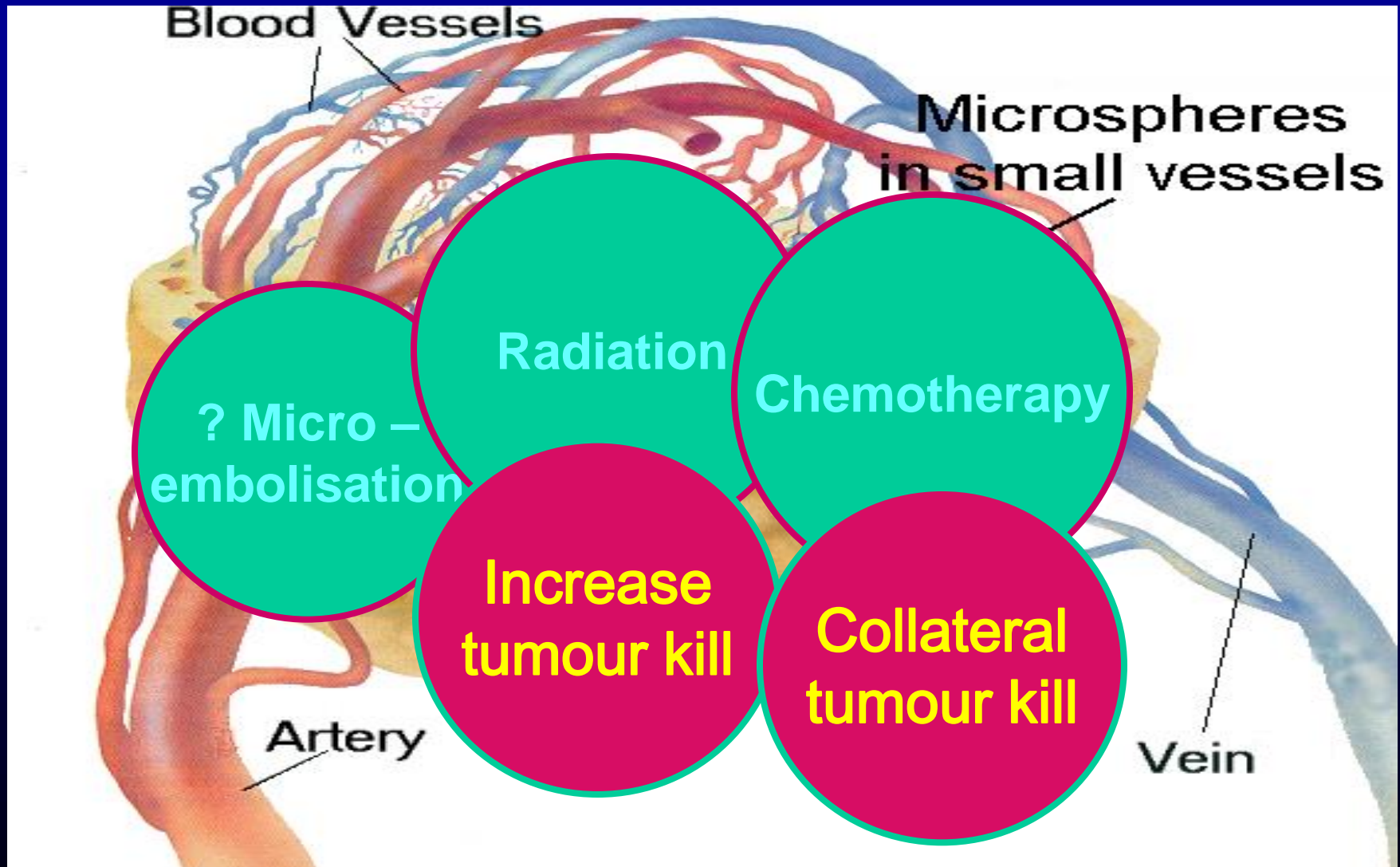
Potential synergy with radio-sensitising systemic chemotherapy could lead to collateral damage



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Potential synergy with radio-sensitising systemic chemotherapy could lead to collateral damage



Clinical Trials Evidence of integrating technologies with standard of care:

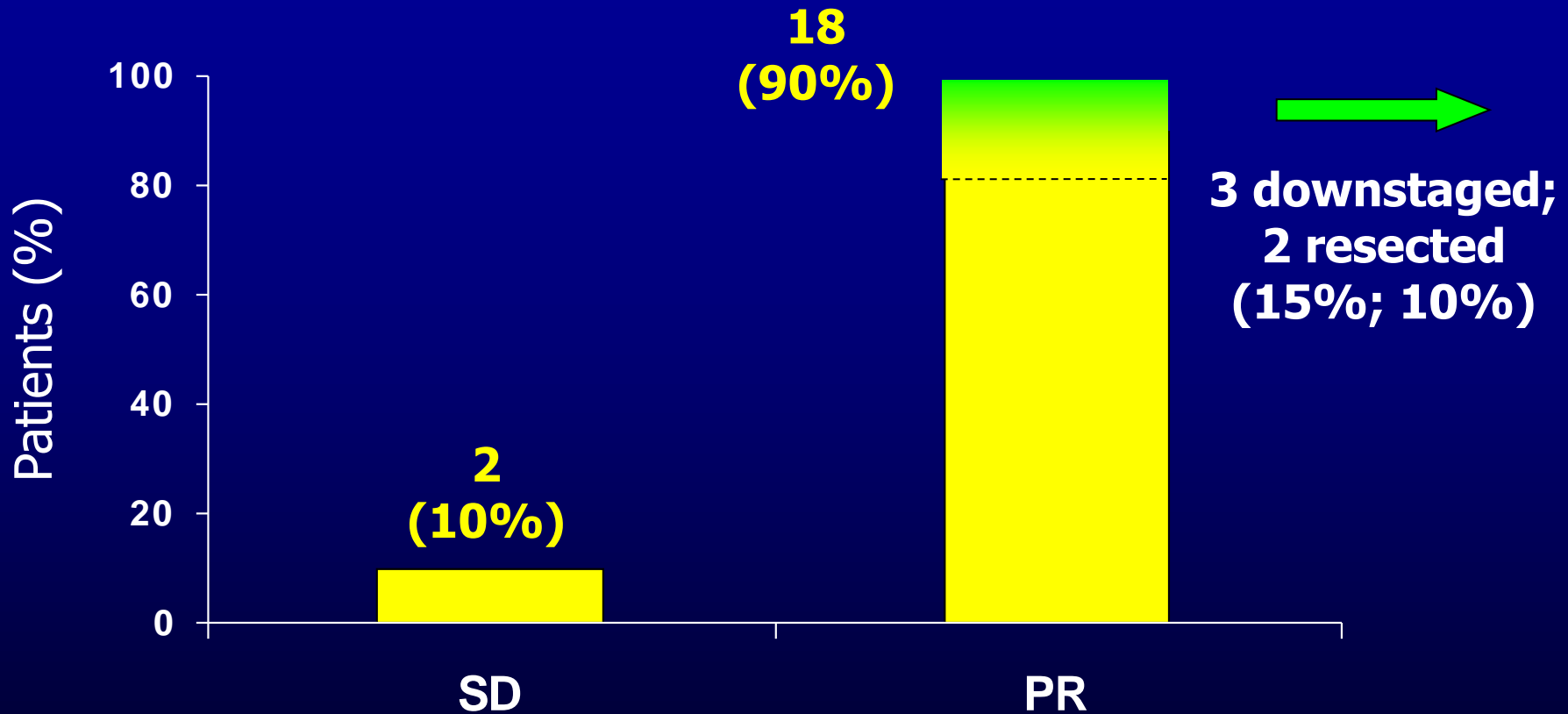
- Lack of level one evidence
 - Integrating with chemotherapy CRC standards
 - but is rapidly evolving

**EORTC intergroup randomized study 40004 (CLOCC)*
evaluating the benefit of radiofrequency ablation (RFA)
combined with chemotherapy (CT)
for *unresectable* CRC liver metastases**

- 60% had ≥ 4 Liver Mets
- median PFS
 - 16.8 months in the RFA + CT arm (95% CI, 11.7-22.1)
 - 9.9 months (9.3- 13.7) in the CT arm (p = 0.025)
- the 30-months OS rate was:
 - 61.7% (95% CI, 48.21-73.93) in the RFA +CT arm
 - 57.6% (44.07-70.39) in the CT arm.
- first study that prospectively investigates the efficacy of RFA in combination with Chemotherapy and suggests synergy.....
.....Even in palliation

*J Clin Oncol 28:15s, 2010 (suppl; abstr 3526)

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



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

Y90 resin SIR-Spheres + 5FU in mCRC Salvage Therapy: Phase IIIR

Eligible Patients

Liver-only mCRC,
PS 0–2, refractory to
chemotherapy

Stratify

- Institution
- Interval to progression on chemotherapy

Random Assignment

Arm A:

5FU protracted IV infusion
(300 mg/m² D1–14 q3w)

until progression

Y90 resin SIR-Spheres

Arm B:

Y90 resin SIR-Spheres
on Day 1 (D1) Cycle 1 (C1)

+

5FU protracted IV infusion
(225 mg/m² D1–14 C1
and 300 mg/m² D1–14
q3w thereafter)

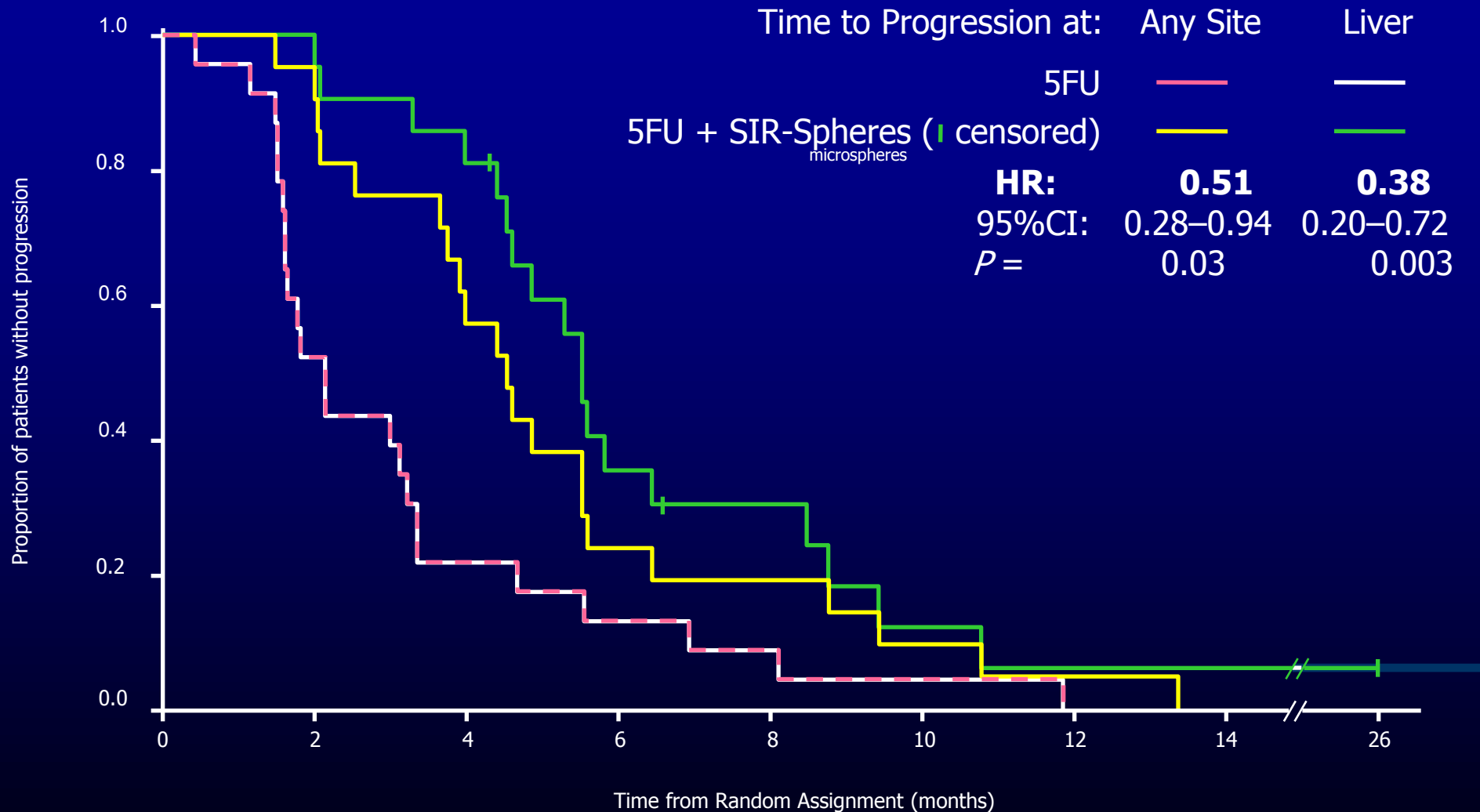
until progression

Eligible Patients

Liver-dominant mCRC,
PS 0–2

Salvage= failed all available therapies

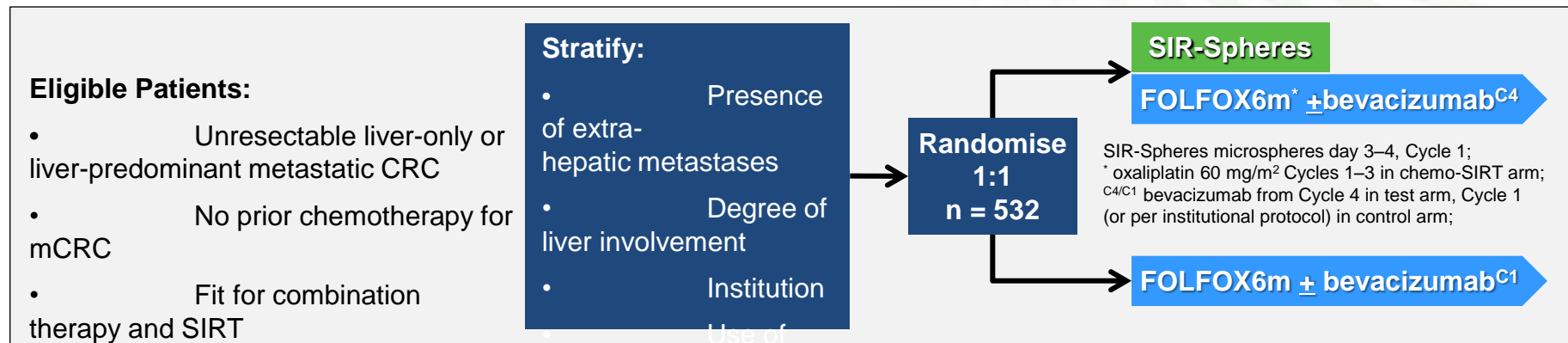
SIR-Spheres + 5FU in mCRC Salvage Therapy: Primary Endpoint – Time to Liver Progression



The SIRFLOX Study

To assess the efficacy and safety of adding targeted radiation (SIR-Spheres® microspheres) to standard-of-care systemic chemotherapy (FOLFOX6m \pm bevacizumab), compared to FOLFOX6m chemotherapy (\pm bevacizumab) alone as 1st-line therapy in patients with non-resectable colorectal liver metastases, with or without evidence of extra-hepatic metastases

Design: Prospective open-label, multi-centre, multi-national RCT



Primary endpoint: Progression-free survival (PFS)

Sponsor: Sirtex

PIs: Prof. Peter Gibbs; Prof. Guy van Hazel

Status: Completed recruitment April 2013

Secondary endpoints: PFS in liver
Overall survival
Response rate
Quality of life
Recurrence rate
Toxicity
Resection rate

Structure for the OS analysis; (Currently ~960 patients)

Overall survival : > 1020 patients

The S_{IR}FLOX Study

S_{IR}-Spheres[®] + FOLFOX *versus* FOLFOX Alone
(with or without bevacizumab) in Patients with
Unresectable Liver Metastases from Colorectal Cancer

Randomised controlled study evaluating S_{IR}-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**



- OS in combination with S_{IR}FLOX and FOXFIRE
- ~ **100 / 150 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?

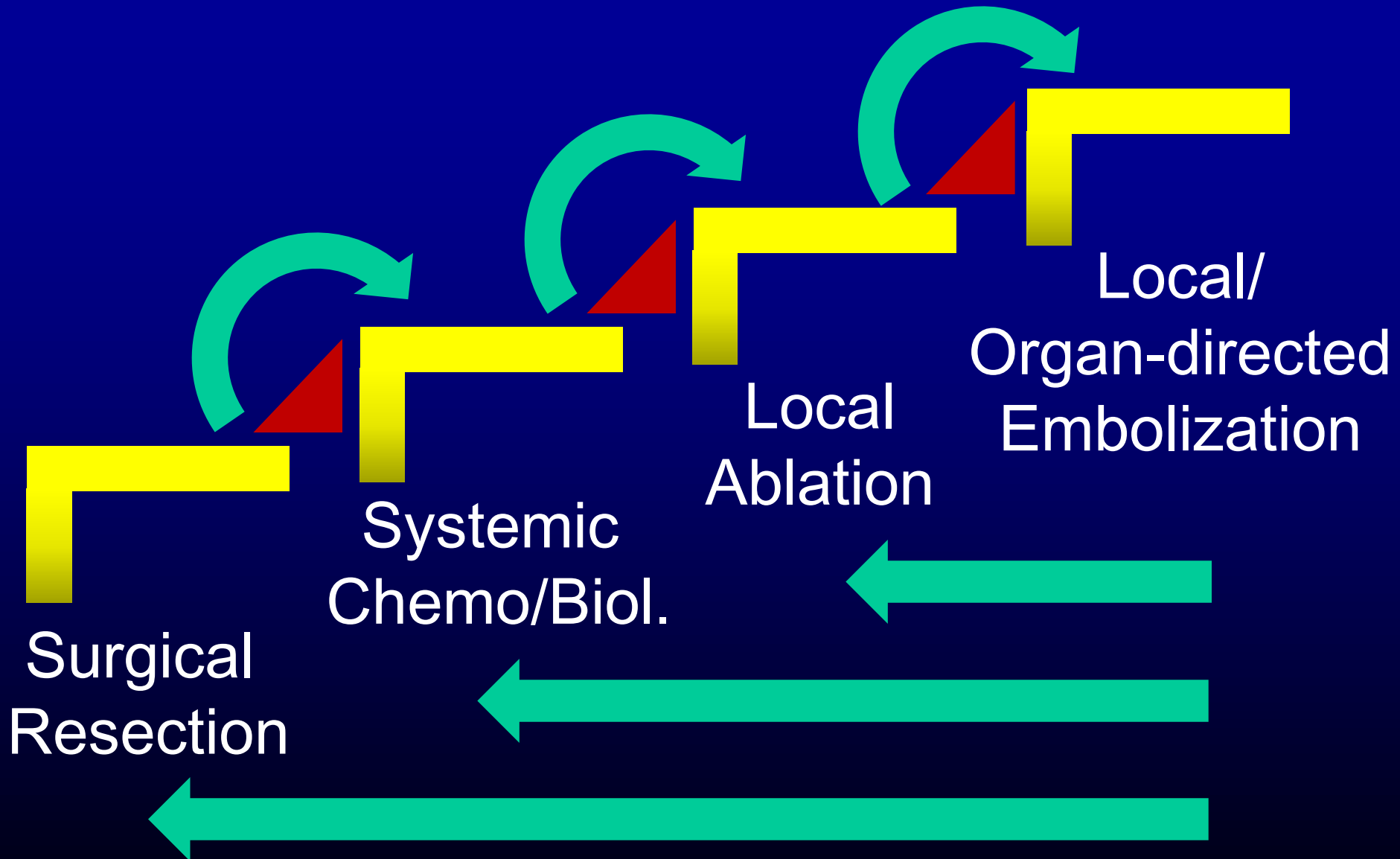
Randomised controlled trial evaluating S_{IR}-Spheres microspheres in combination with OxMdG chemotherapy vs. OxMdG chemotherapy alone for the first-line treatment of unresectable liver-only or liver-predominant colorectal cancer metastases.

- OS in combination with S_{IR}FLOX
- Up to 490 patients
- ~ **332 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

The loco-regional shuffle



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 to be added to the therapeutics options for treating inoperable liver dominant mCRC
 - Evidence is emerging on clinical benefit integrating “debulking strategies”
- 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