Interventional Oncology (IO)Treatment of Hepatic Metastatic Disease in 2023:

Y90 and Other Therapies

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CLI VASCULAR SPECIALISTS AND PALM VASCULAR CENTERS

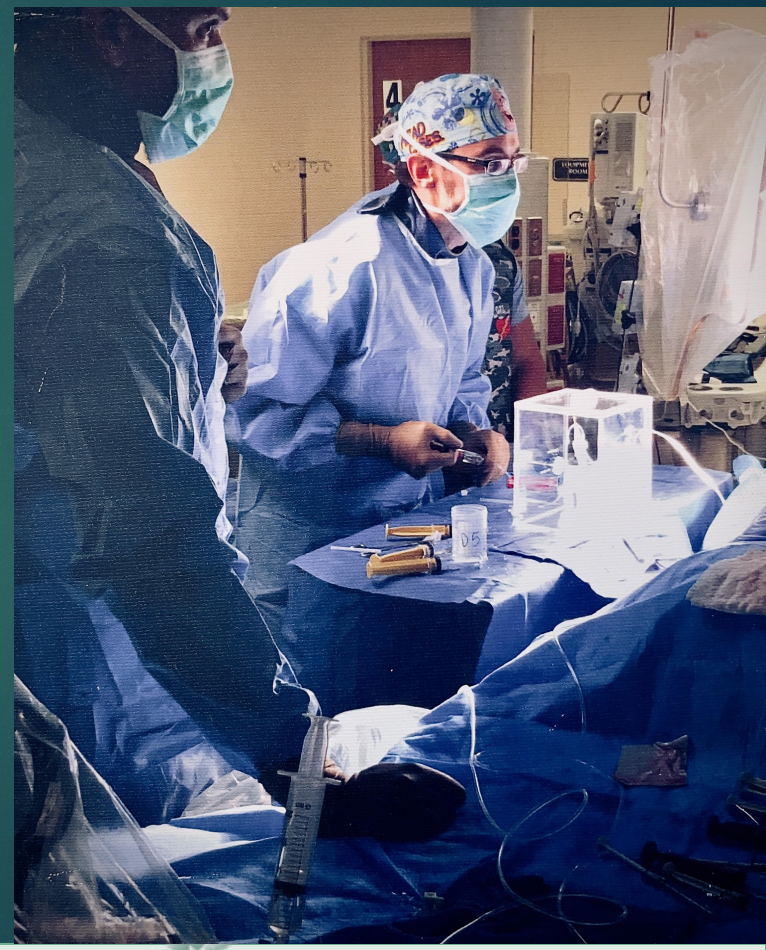
DELRAY BEACH, FL

Outline

- Role of IO in Your Practice
  - Imaging, Central access, Biopsy, Treatment
  - Ambulatory practice
- Background on Metastatic Hepatic Disease
- IO Treatment Modalities
  - Bland embolization, Chemoembolization, Radioembolization, Ablation (thermal, chemical)
- Radioembolization for Specific Metastatic Tumor Types
  - mCRC
  - mNET
  - Other

Role of IO (interventional Oncologist) in YOUR Practice

- Critical ally for imaging and longitudinal follow-up
- Standard referral pattern
  - Biopsy
  - Central Access
  - Drainage
- Higher level
  - Catheter-based oncological interventions
  - Thermal ablation
  - Pain and neurolysis
  - Most therapies *complimentary* to standard care



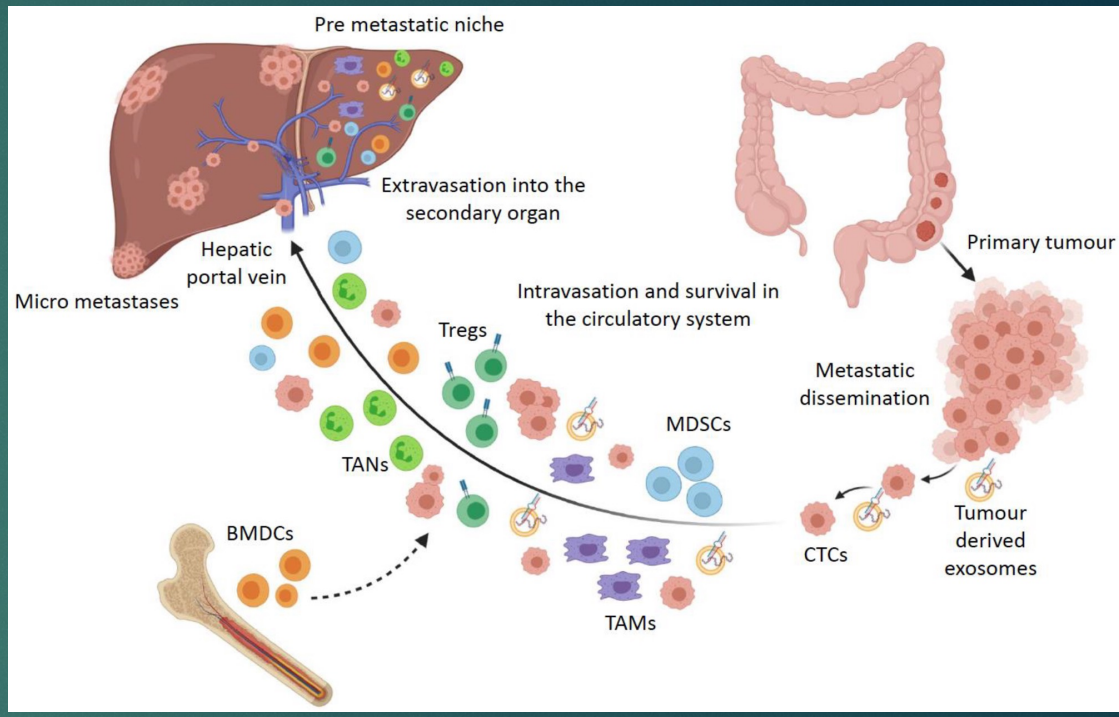
Ambulatory IO Practice

- Provide more one-one concierge care
- No associated hospitalization
- Improved patient satisfaction
- Increased throughput and decrease time to treatment

Hepatic Metastatic Disease

Hepatic Metastatic disease in Scope

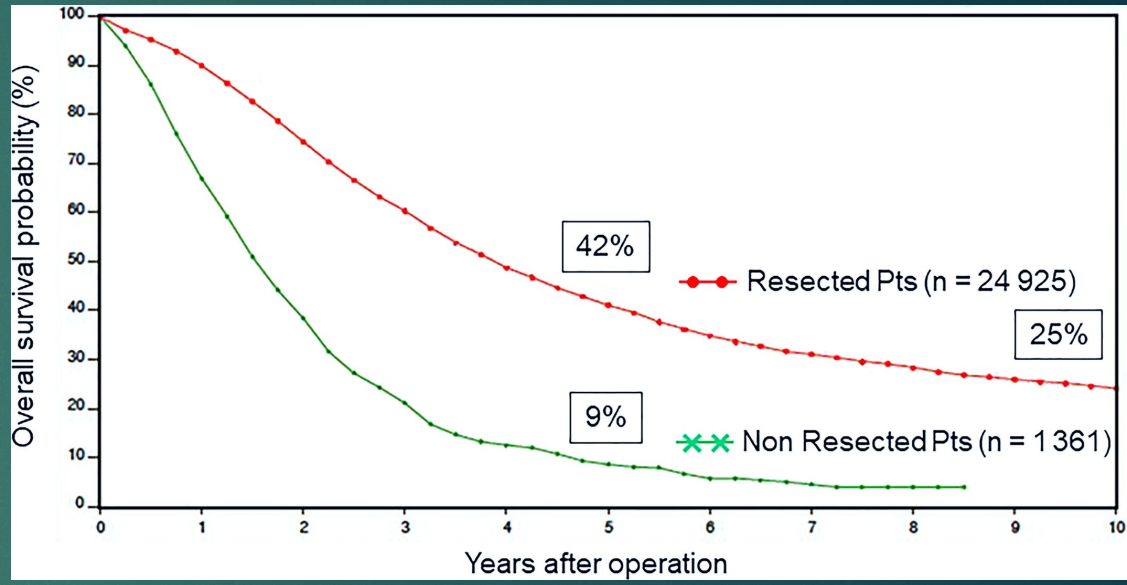
- A principal site for spread of distant mets
  - Vascularity & architecture -> prime for cancer cells
- Limited therapeutic options for hepatic malignancies[12]
  - HCC: ~41,210 new cases (27,980 M;13,230 F)
  - ~29,380 people (19,000 M; 10,380 F) die[30]
  - 5.14 % of cancer pts have synchronous liver mets (SEER Database of 2.4 million primary cancers)
  - Young: breast in women, CRC in men
  - Older: esophageal, gastric, small bowel, melanoma, bladder, lung, pancreatic NET and CRC
  - 1 year survival 15.1% with liver mets; 24% with non-hepatic mets[31]
- Cumulative liver toxicities common to chemos[23]
- Multidisciplinary approach[22] -> better outcomes



https://www.mdpi.com/ijms/ijms-22-02067/article_deploy/html/images/ijms-22-02067-g001.png

Goals of Treatment of Hepatic Metastases[5]

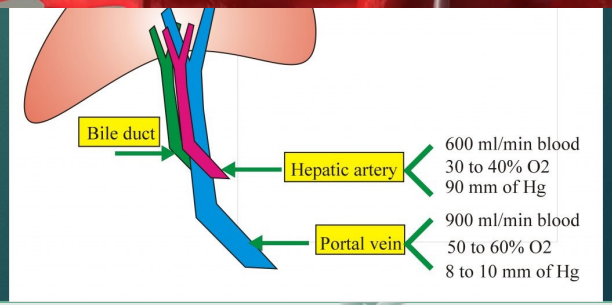
- Resection is gold standard for cure
  - 5 y OS survival ~25-44%, operative mortality ~0–6.6%.
  - mCRC resectable if R0 resection possible with ~20–25% of total liver volume
  - ~20% of patients with mets -> anatomic limitations, number, location, and extent of liver lesions, insufficient liver function, and comorbidities
- Local hepatic control may -> OS[10]
- Parallels taken from Milan Criteria and BCLC staging



Overall survival probability of patients with colorectal cancer liver metastases resected vs unresected[22]

What's special about the liver? Hepatic Circulation is Unique

- ~60-75% from portal venous system (gut drainage)
- ~25-40-% of perfusion from hepatic arterial system
- Met/1° hepatic malignancies derive *ALL* flow via vasotactic signalling and angioneogenesis from *hepatic arterial system*
- Tumors can be treated relatively aggressively via hepatic arteries -> preserving perfusion to normal liver parenchyma via portal
- No other organ has this quality -> allows for various embolization techniques

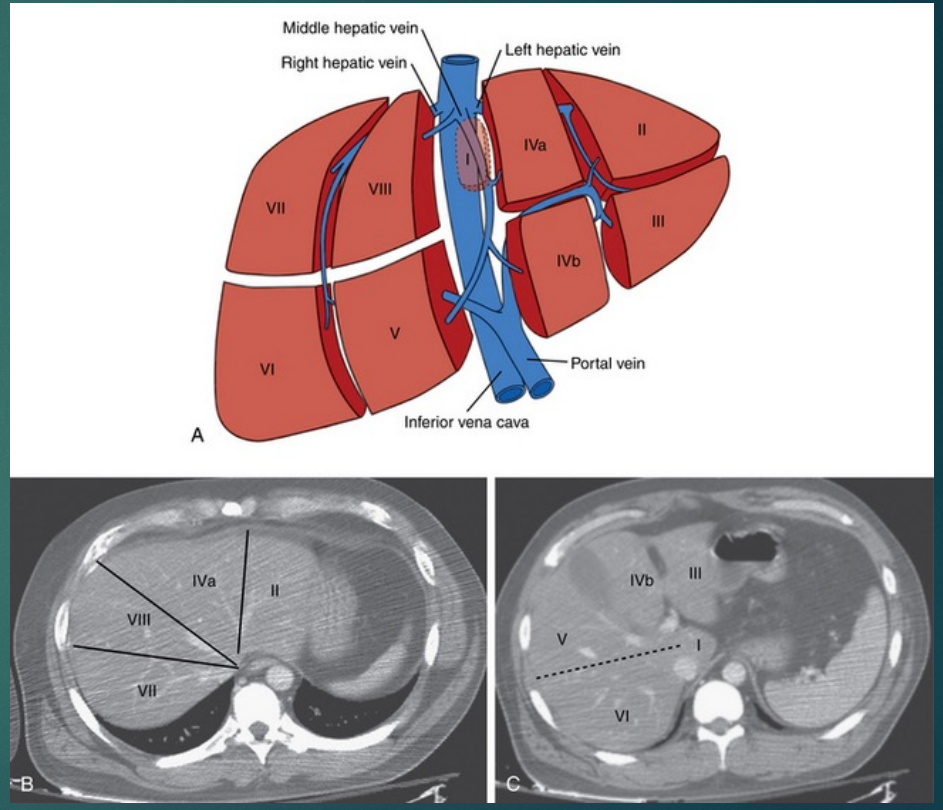


1. https://ib.bioninja.com.au/options/option-d-human-physiology/d3-functions-of-the-liver/liver-blood-flow.html
2. https://labpedia.net/liver-anatomy/
3. www.sirtex.com

Standard Interventional Oncology Treatment Strategies

Historical background for IO management of Hepatic Metastases

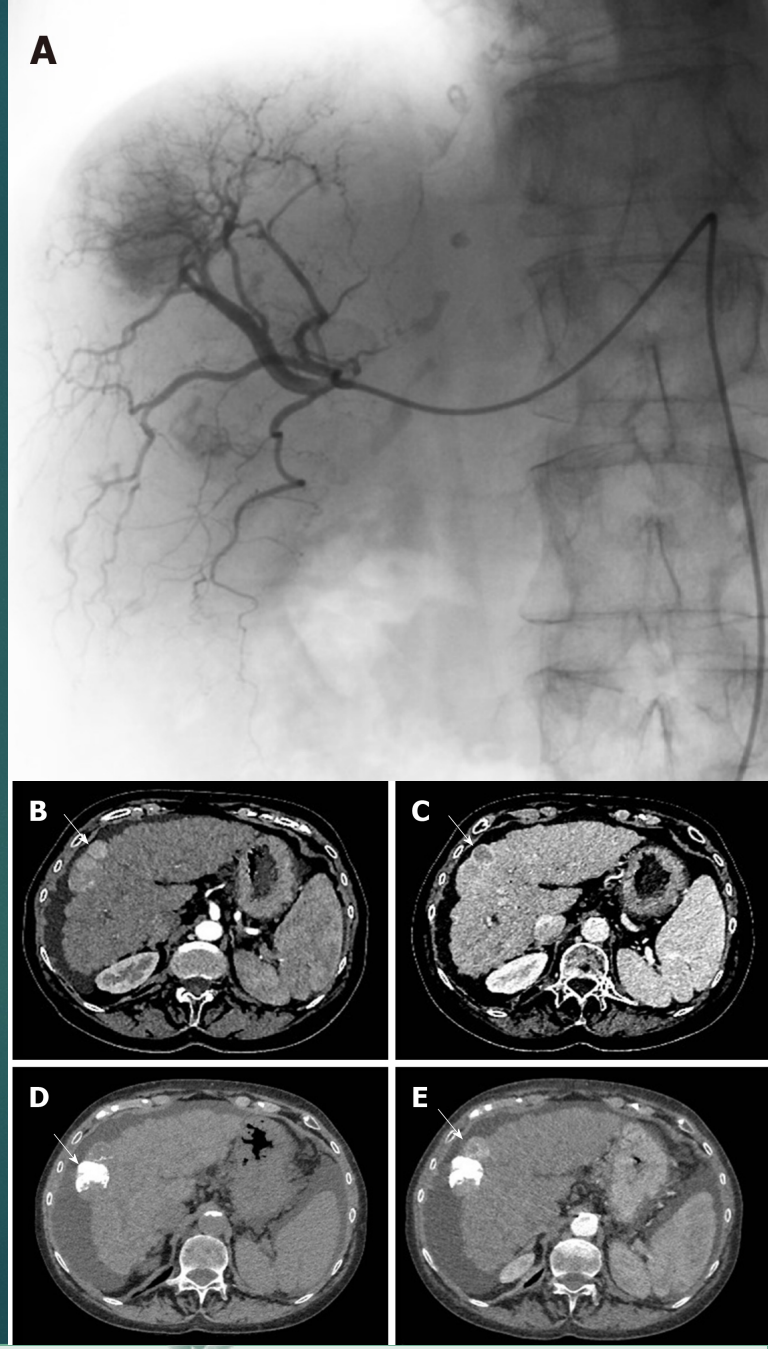
- Patients are typically non-operative
  - Palliative, local disease progression reduction
- Oligometastatic -> "segmentectomy"
  - Bridge to lobectomy or liver transplant (low complication rate)[32]
- Rarely focal tumor can be cured
- Liver-directed tx may allow chemo holiday for dose-limiting adverse events



https://radiologykey.com/hepatic-splenic-and-portal-vascular-systems/

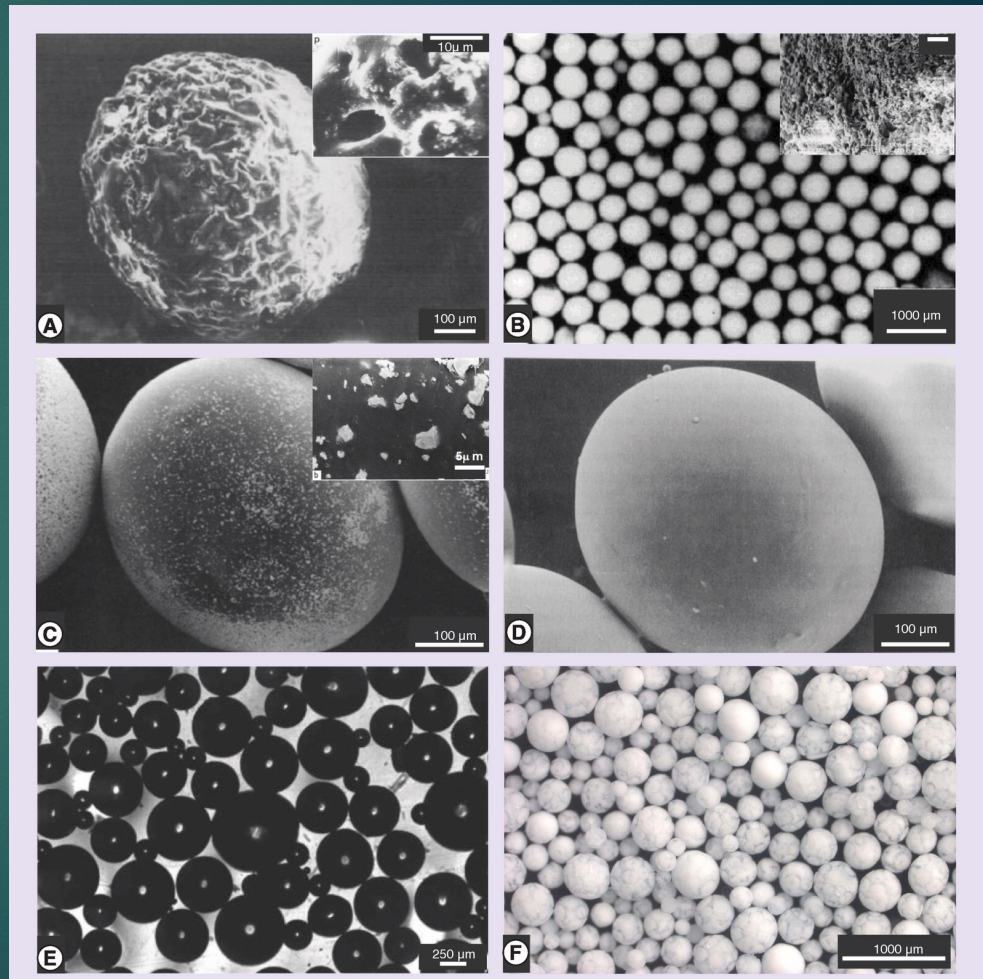
Chemoembolization[5] (TACE)

- Specifically-sized particles coated with chemotherapeutics
- Most data
  - HCC (tx of choice for intermediate stage disease)[33]
  - Metastatic disease
- TACE-> in high-dose chemo to liver w/ selective ischemia
- Effective for HCC and cholangiocarcinoma, but also liver metastases from mCRC, mNET, and mBrCA
- Drugs include irinotecan (mCRC), doxorubicin (HCC), lipiodol, some immunotherapies
- May result in greater intrahepatic progression compared to radioembolization, but less chronic hepatotoxicity



Bland embolization (TAE)

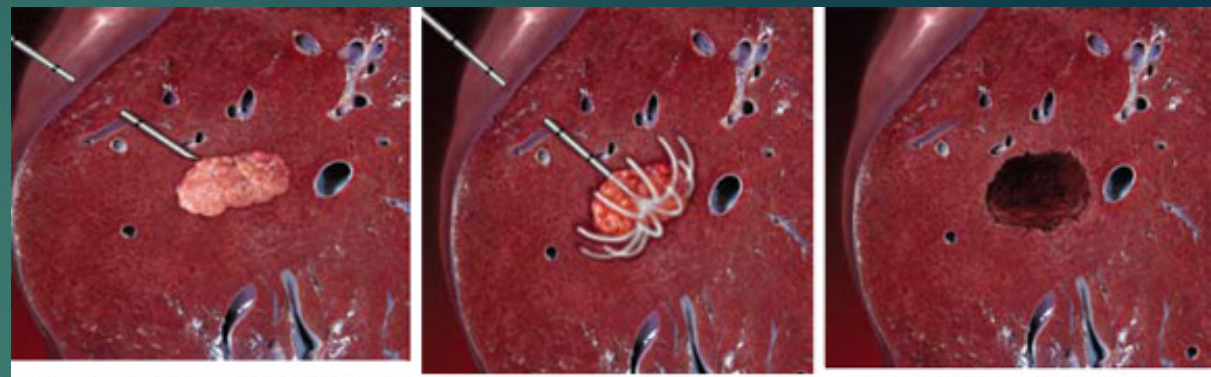
- Specifically-sized particles -> tumoral ischemia
  - 100-500 µm particles typical
- Requires no specific medication
- Repeatable and generally well-tolerated
- Very effective in mNET



https://www.futuremedicine.com/doi/10.2217/fon-2018-0182

Ablation

- Thermal ablation[5]
  - Radiofrequency, Microwave, Cryo
  - Goal similar to R0 resection, with >/=10 mm around outer margin of lesion
  - Compared to RFA, MWA allows larger volume cell necrosis in shorter time with higher temperatures
  - MWA is less dependent on change in morphology of treated area due to heat sink effects from adjacent vasculature
- Ethanol -> direct injection
- Irreversible electroporation (IRE)



The radiofrequency probe is inserted into the liver tumor.

The surgeon deploys electrodes from the probe which deliver radiofrequency energy. This high heat causes death of tumor cells.

Following the procedure, the tumor cells are destroyed and will eventually be replaced by scar tissue.

Multimodality therapy[5]

- Combo embo and ablation efficacious, oligometastatic dz, lesions >3 cm
- Devascularize and inflame tumor to increase multimodality effect
  - Decrease "heat sink" effect
- Faiella et al review[5] (2022)
  - > 3 cm, non-op candidates
- Two reviewers -> indep lit search (8 articles)
  - Studies published between 2009-2020, sample size < 100 patients for all studies

Review > J Clin Med. 2022 Sep 22;11(19):5576. doi: 10.3390/jcm11195576.

Combined Trans-Arterial Embolization and Ablation for the Treatment of Large (>3 cm) Liver Metastases: Review of the Literature

Eliodoro Faiella [1], Alessandro Calabrese [2], Domiziana Santucci [1 3], Carlo de Felice [2], Claudio Pusceddu [4], Davide Fior [1], Federico Fontana [5], Filippo Piacentino [6 7], Lorenzo Paolo Moramarco [1], Rosa Maria Muraca [1], Massimo Venturini [5]

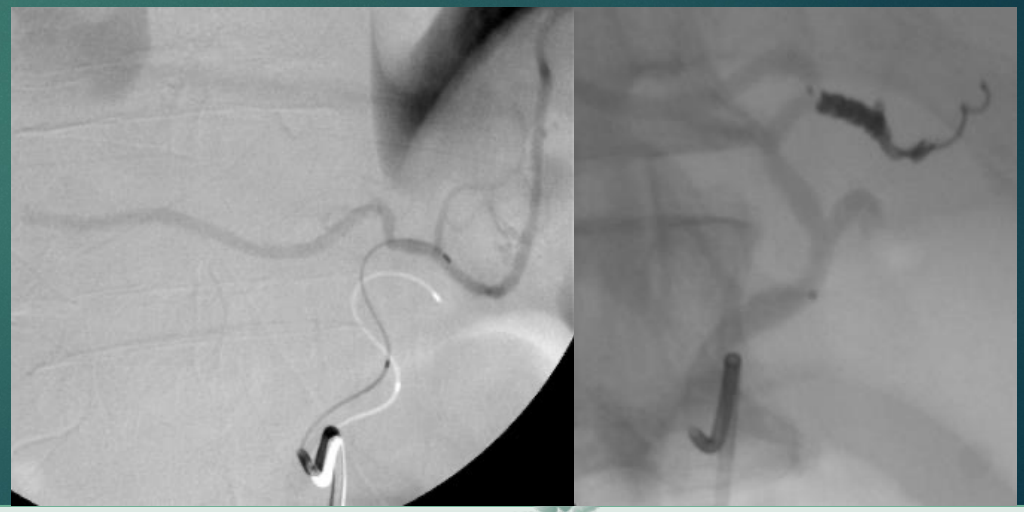
- Safety of combined approach
  - Low complication rate
- Issues
  - Non-uniform systemic chemotherapy
  - Variability in sequence of embolization and ablation
  - Improved survival

Radioembolization (TARE, SIRT, Y90)

- Radioactive particles injected to produce tumoral DNA damage, generally non-ischemic
  - Small particles, not enough to occlude (in terms of volume)
- Two devices
  - Resin Y-90 microspheres
  - Glass Y-90 microspheres
- Therapy that is usually best tolerated
- Requires more complex preparation

Radioembolization (TARE, SIRT, Y90)

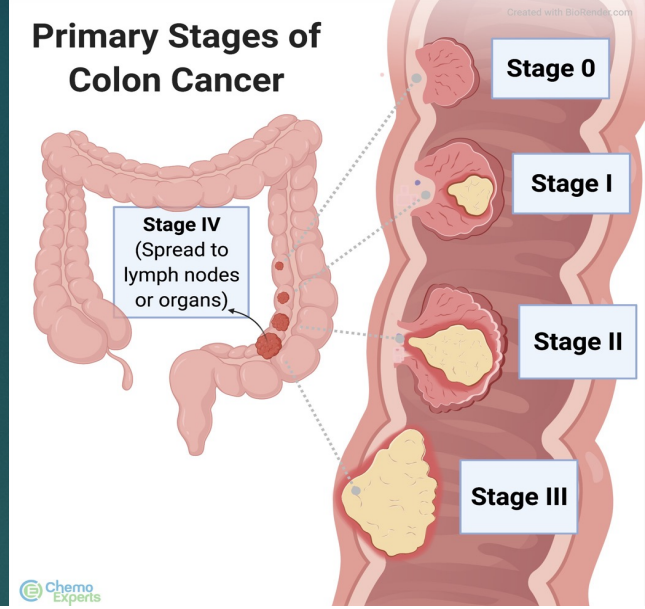
- Mapping
- Evaluation of perihepatic plexus
  - Anastomoses -> beneficial and damaging
- Complications[12]
  - Non-target embolization -> ulceration
  - Radioembolization-induced Liver Disease (REILD)
- Dosimetry based on lung-shunt fraction and nuclear imaging
  - Cumulative dose important
  - Work with Radiation Oncologist
  - Optimal dosimetry methodology requires further investigation
- Treatment
  - Lobar
  - Radiation Segmentectomy[8] ≤ 3 segments
    - Safely provide 2-year local tumor control rate of 83%
    - Pts with limited mets and limited options

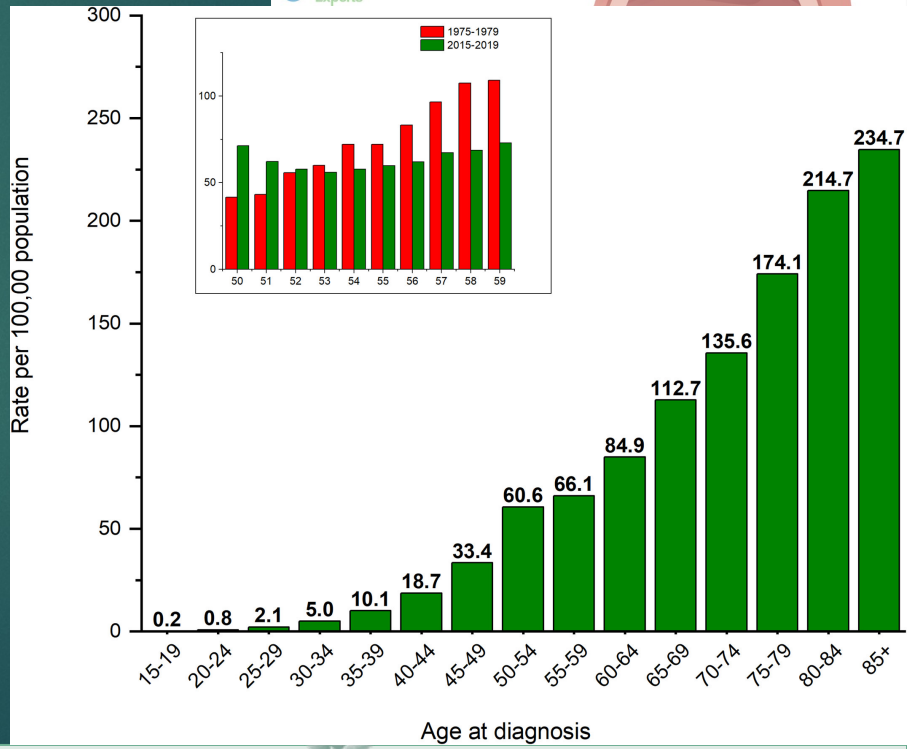


Y90 Management of Metastatic Colorectal (mCRC) and Neuroendocrine Tumor (mNET)

Management of mCRC

- 2023 estimated ~153,020 new dx with CRC, 52,550 deaths[41]
- Metastases at least 50% CRC cases[11]
- Liver metastases in ~60–70% metastatic colorectal cancer (mCRC)
- Liver-centric mets in ~35–55% of mCRC[13-21]
- Opportunities to improve OS in 1st/2nd-Line treatment
- Limited options in chemorefractory/salvage





Radioembolization in First Line

- FOXFIRE, SIRFLOX, and FOXFIRE-Global – (Resin y-90)
- Randomized, phase 3 trials in 14 countries; 2017
- Inclusion:
  - Chemo-naive mCRC pts (WHO performance status 0 or 1) with liver mets not suitable for resection or ablation
- Random 1:1 (n_1=549 FOLFOX alone; n_2=554 FOLFOX + SIRT)
  - Oxaliplatin based regimen -> FOLFOX (leucovorin, fluorouracil, and oxaliplatin)
  - FOLFOX plus single SIRT concurrent with chemo cycle 1 or 2
    - In FOXFIRE, FOLFOX chemotherapy was oxaliplatin modified de Gramont chemotherapy
    - In SIRFLOX and FOXFIRE-Global, FOLFOX chemotherapy was modified FOLFOX6

THE LANCET
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Volume 18, Issue 9, September 2017, Pages 1159-1171

Articles

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 MRCP [a] *, Peter Gibbs MD [b] *, Navesh K Sharma FACRO [c], Prof Julien Taieb MD [d], Prof Volker Heinemann MD [e], Prof Jens Ricke MD [f], Prof Marc Peeters MD [g], Prof Michael Findlay MD [h], Andrew Weaver MD [i], Jamie Mills FRCR [j], Charles Wilson FRCR [k], Prof Richard Adams MD [l], Anne Francis DPhil [m], Joanna Moschandreas PhD [n], Pradeep S Virdee MSc [n], Peter Dutton MSc [n], Sharon Love BSc [n], Prof Val Gebski MStat [q], Prof Alastair Gray PhD [o]
FOXFIRE trial investigators†
...Prof Ricky A Sharma PhD [p s] *

Radioembolization in First Line

- Primary endpoint
  - Overall Survival
- Secondary endpoints
  - Progression-free survival
  - Liver-specific progression-free survival
  - Health-Related QoL
  - Tumor response
  - Liver resection rate
  - Adverse events

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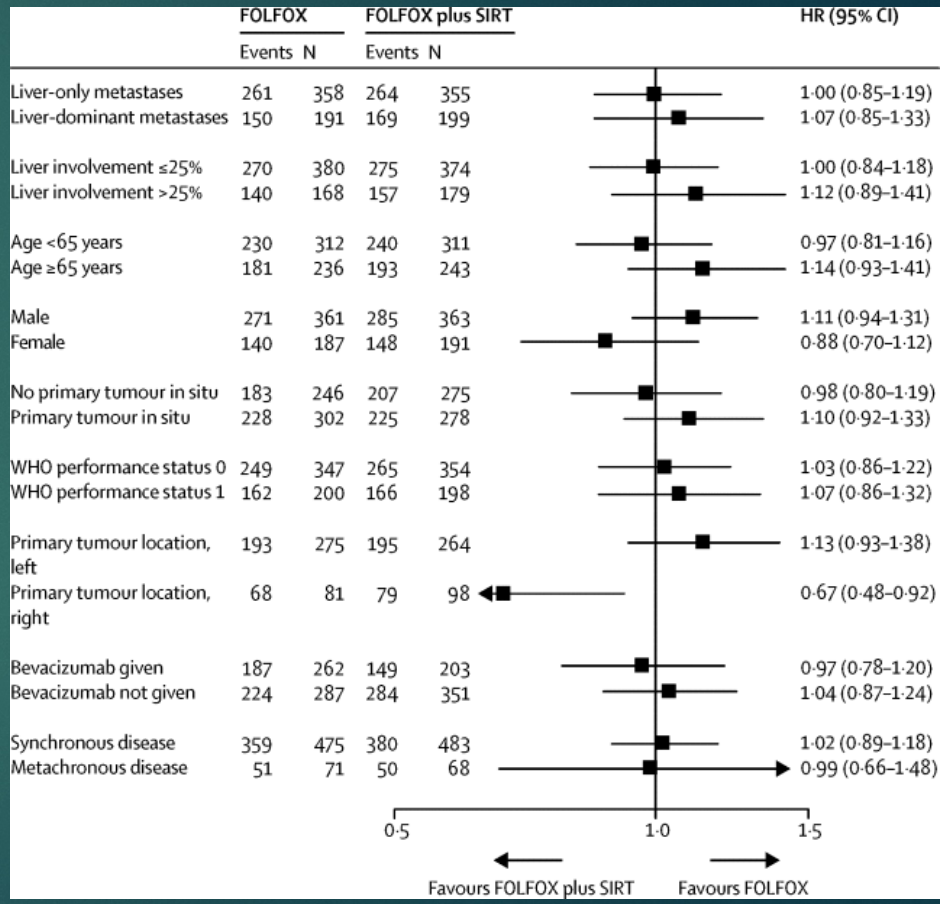
Radioembolization in First Line

- Failure of 1° endpoint in first-line therapy[10]
  - Did not improve overall survival
  - PFS - 11.0 mo (95% CI 10.2–11.8) vs 10.3 mo (9.7–10.9)
  - Positive impact on hPFS (20.5 vs 12.6 mo; p = 0.02)
  - Combo SIRT/chemo > effective for liver-limited mCRC
  - Additional significant benefit for *right hepatic-dominant* disease

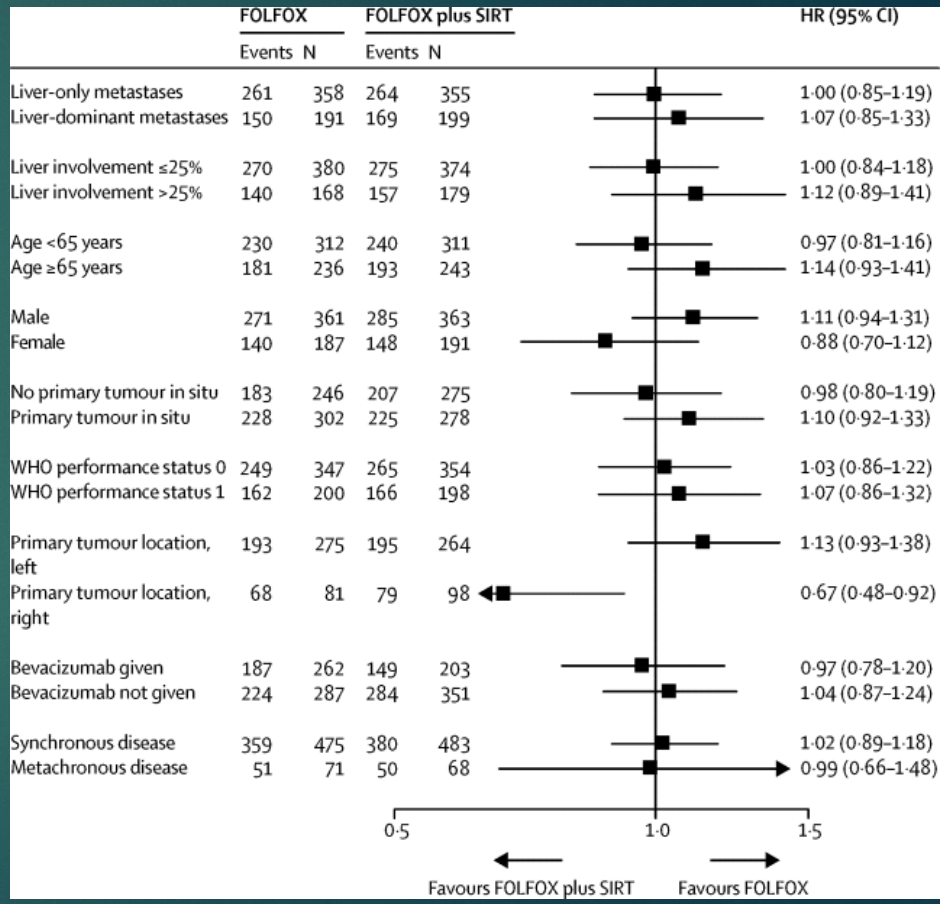


Treatment effect on overall survival by subgroup

HR=hazard ratio. SIRT=selective internal radiotherapy.

Radioembolization in First Line

- Critiques
  - 40% SIRFLOX pts had extra-hepatic dz
  - No measures of improvement nor delays to deterioration of QoL
  - Abandon OS for PFS[28]?
    - Generates larger number of events
    - Not influenced by post-progression treatment
    - Less vulnerability to competing causes of death



Treatment effect on overall survival by subgroup

HR=hazard ratio. SIRT=selective internal radiotherapy.

Radioembolization in Second Line

- EPOCH study (Glass Y-90)
- n=428 (random 1:1)
  - 215 pts to TARE + chemo
  - 213 pts to chemo alone
- Open-label, prospective, multicenter, randomized, phase 3 trial (US, Canada, Europe, and Asia)
- Inclusion:
  - mCRC to liver and disease progression after first-line chemotherapy (oxaliplatin or irinotecan-based tx)
  - Eligible for second-line chemo with alternate regimen
- Chemo alone vs TARE + chemo
- Primary endpoints PFS and hepatic PFS
- Secondary endpoints are overall survival, time to symptomatic progression, objective response rate, disease control rate, QoL, adverse events

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JMIR Res Protoc. 2019 Jan; 8(1): e11545. PMCID: PMC6354199
Published online 2019 Jan 17. doi: 10.2196/11545 PMID: 30664496

Yttrium-90 Glass Microspheres Combined With Chemotherapy Versus Chemotherapy Alone in Second-Line Treatment of Patients With Metastatic Colorectal Carcinoma of the Liver: Protocol for the EPOCH Phase 3 Randomized Clinical Trial

Monitoring Editor: Gunther Eysenbach

Reviewed by Sharlene Gill, Wouter Leclercq, and Andrew Kennedy

Nikhil Chauhan, PhD,[✉1], on behalf of the TheraSphere EPOCH Protocol Study Group Mary F Mulcahy, MD,[2] Riad Salem, MD, MBA,[2,3,4] Al B Benson III, MD, FACP, FASCO,[2,5] Eveline Boucher, MD,[1] Janet Bukovcan, BSc (Hons),[1] David Cosgrove, MD,[6] Chantal Laframboise, BScN,[1] Robert J Lewandowski, MD, FSIR,[2,3,4] Fayaz Master, BSc,[1] Bassel El-Rayes, MD,[7,8] Jonathan R Strosberg, MD,[9] Daniel Y Sze, MD, PhD,[10] and Ricky A Sharma, MA, PhD, MB BChir, FRCP, FRCR[11]

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ORIGINAL REPORTS | Gastrointestinal Cancer

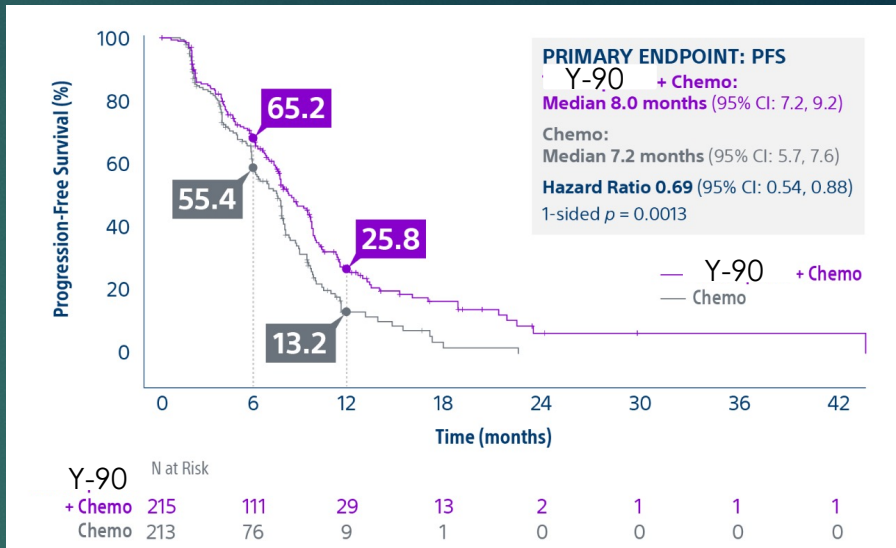
Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

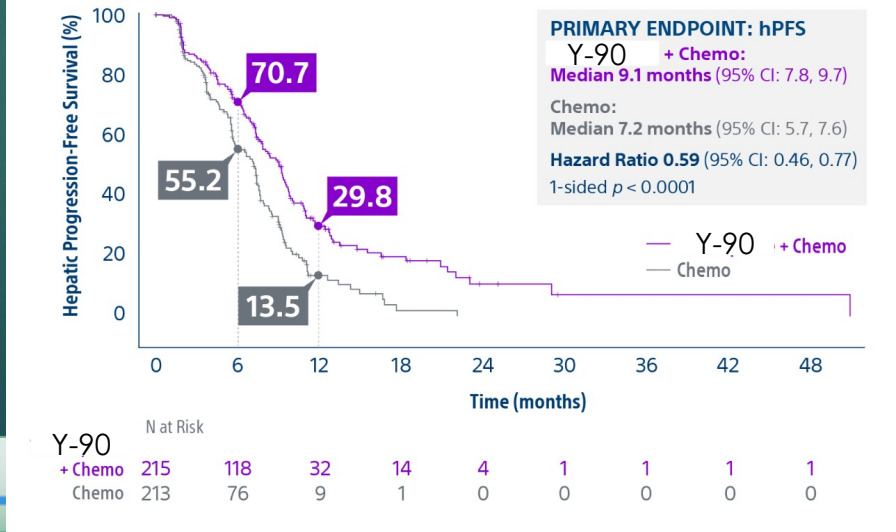
Check for updates

Mary F. Mulcahy, MD[1]; Armeen Mahvash, MD[2]; Marc Pracht, MD[3]; Amir H. Montazeri, MD[4]; Steve Bandula, MD, PhD[5]; Robert C. G. Martin II, MD[6]; ...

Radioembolization in Second Line

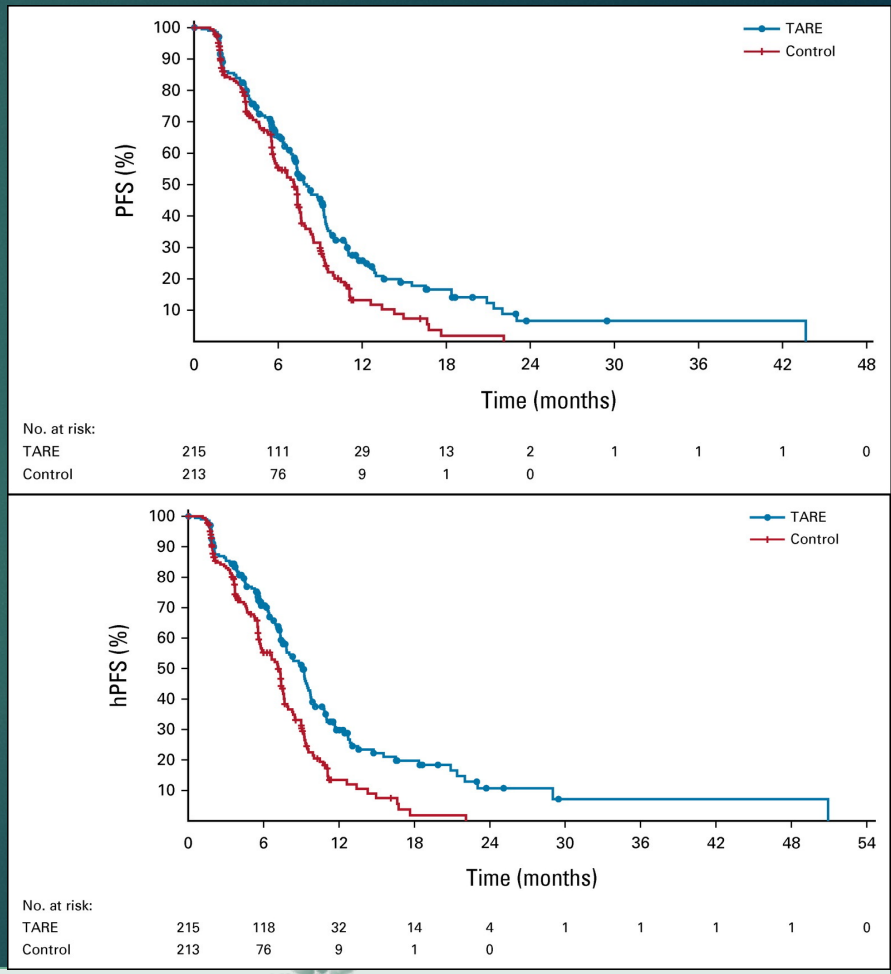
- Median PFS of 8.0 (CI, 7.2-9.2) and 7.2 (CI, 5.7-7.6) months, respectively (p = 0.0013)
- Median hPFS of 9.1 (CI, 7.8-9.7) and 7.2 (CI, 5.7-7.6) months, respectively (p< 0.0001)
- PFS benefit of TARE
  - Tumors with KRAS mutation (HR 0.57, CI: 0.40-0.80)
  - Left-side primary tumor (HR 0.65, CI: 0.48-0.88)
  - Hepatic tumor burden 10-25% (HR 0.43, CI: 0.26-0.72), ≤3 lesions (HR 0.33, CI: 0.14-0.76)
  - Addition of biologic agent (HR 0.58, CI: 0.40-0.84)
  - Resected primary (HR 0.63, CI: 0.46-0.85)
- TARE + systemic therapy for second-line colorectal liver metastases significant > PFS and hPFS[9]





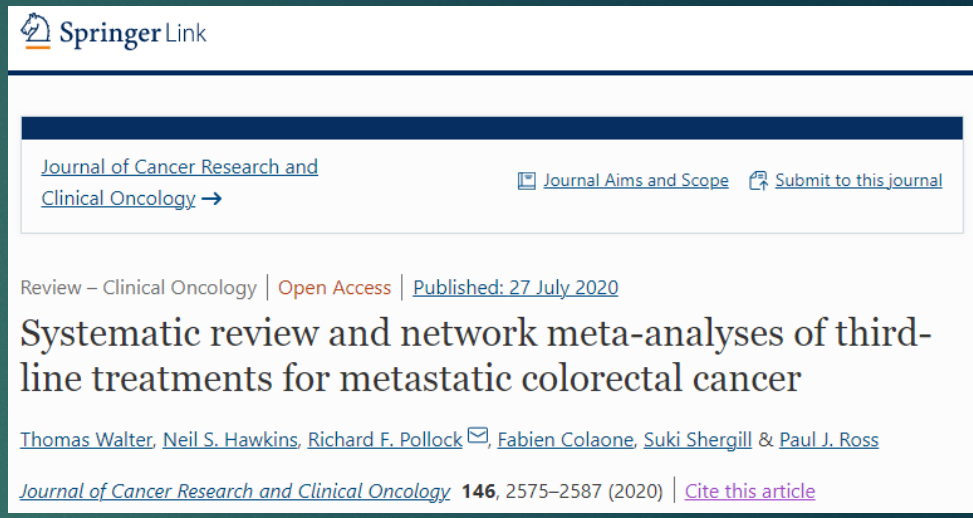
Radioembolization in Second Line

- TARE not compromise subsequent full-dose chemo
- *****Patients in TARE arm with biologic agent during second-line therapy fared better*****
- Glass Y-90 performed poorly in right-sided tumor vs left (opposite of Resin Y-90 at SIRFLOX trial)
  - Suggests different optimal timepoints for TARE for mets based on left- versus right-side tumors



Radioembolization in Third Line

- Third-line (chemo-refractory)
  - Regorafenib vs trifluridine/tipiracil vs SIRT vs best supportive care (BSC)
  - SIRT using Y-90 resin microspheres more effective than BSC in 3° tx of mCRC
  - Favorable AE profile should be considered in the therapeutic decision-making process[11]



Radioembolization in Salvage

- Salvage RE well-tolerated and permits additional therapies and led to a median OS of 12.7 months
- Evaluation using PERCIST more likely than RECIST to document response or progression compared with baseline assessment before RE

ELSEVIER

Clinical Colorectal Cancer

Volume 14, Issue 4, December 2015, Pages 296-305

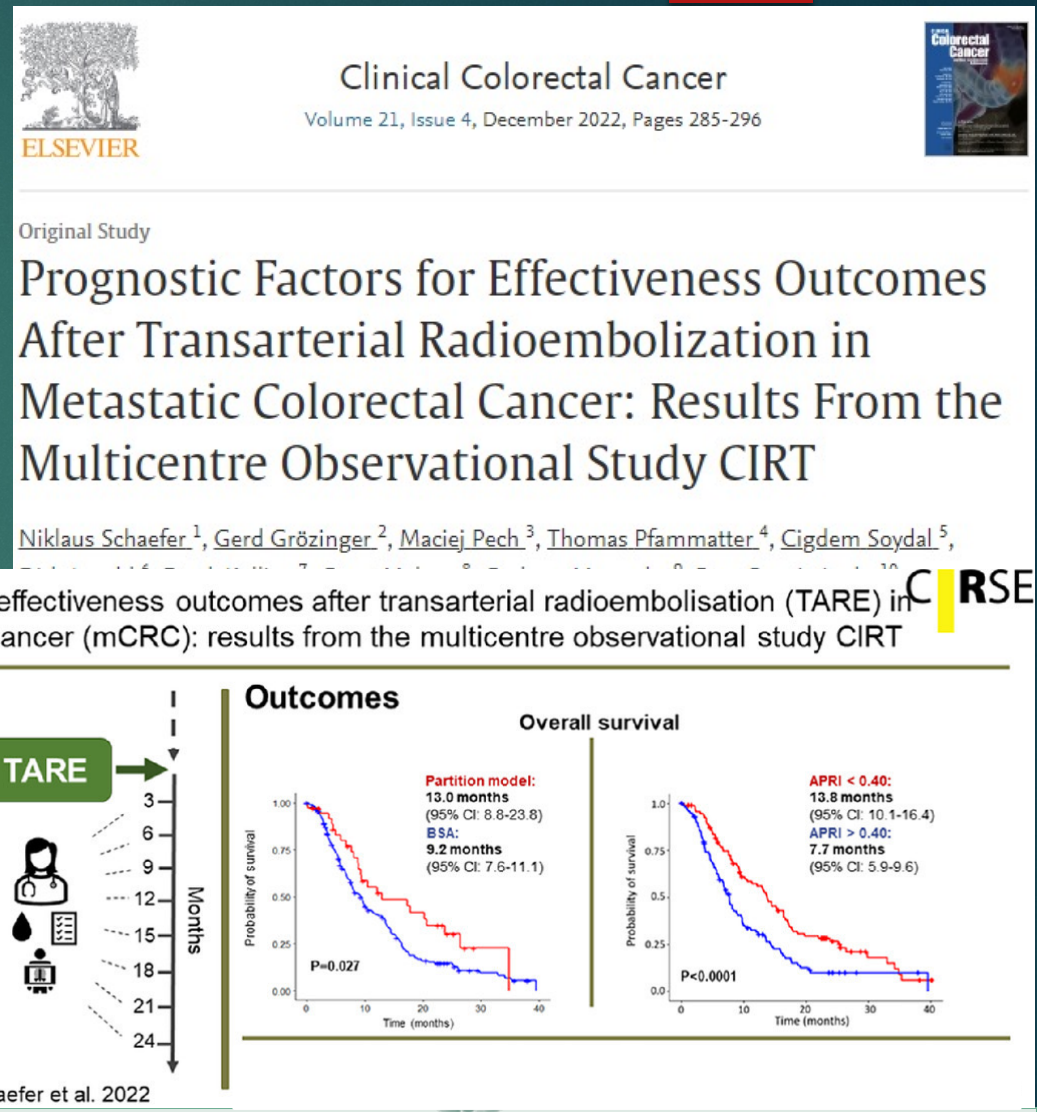
Original Study

Radioembolization as a Salvage Therapy for Heavily Pretreated Patients With Colorectal Cancer Liver Metastases: Factors That Affect Outcomes

Constantinos T. Sofocleous [1], Elena G. Violari [1], Vlasios S. Sotirchos [1], Waleed Shady [1], Mithat Gonen [2], Neeta Pandit-Taskar [1], Elena N. Petre [1], Lynn A. Brody [1], William Alago [1], Richard K. Do [1], Michael I. D'Angelica [3], Joseph R. Osborne [1], Neil H. Segal [4], Jorge A. Carrasquillo [1], Nancy E. Kemeny [4]

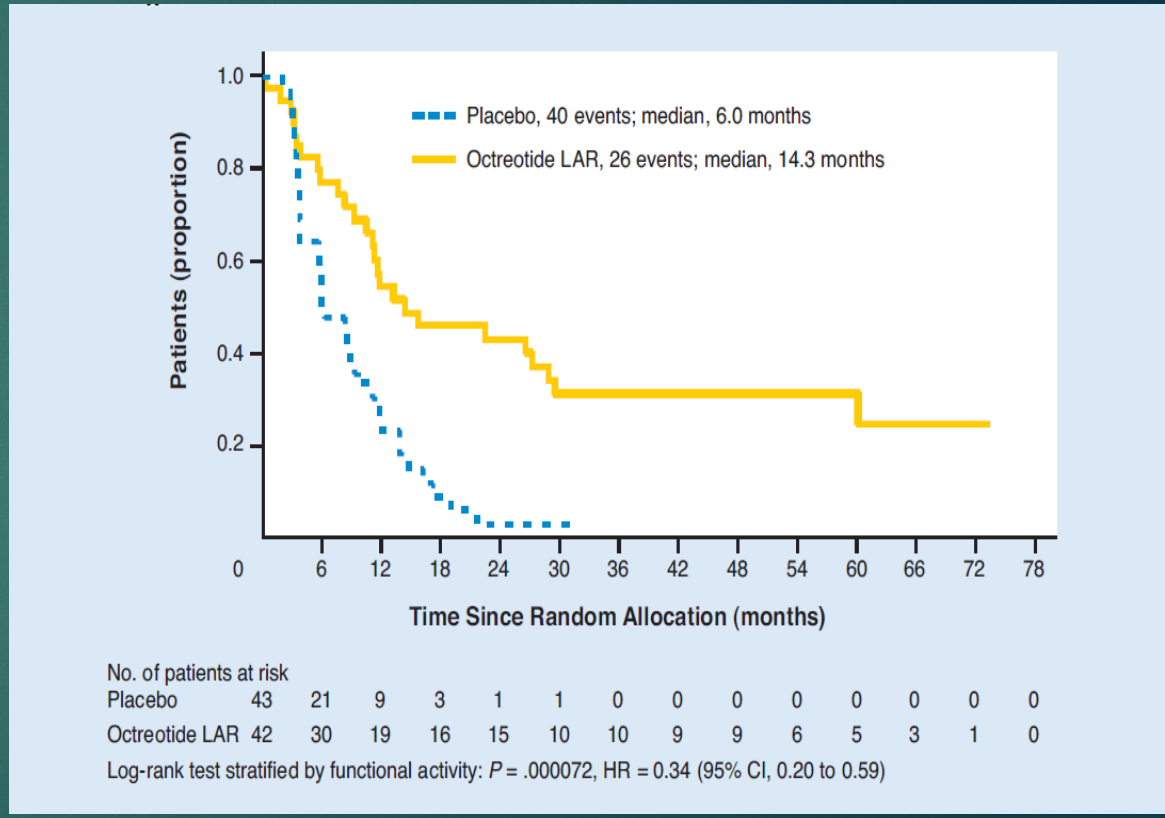
Radioembolization Prognostic Factors in mCRC

- CIRSE Registry for Resin Y-90 Therapy (CIRT)
- n=237
  - Prospective observational study
  - OS, PFS, hPFS
- Prognostic factors OS:
  - absence of extra-hepatic disease (P= .0391)
  - prior locoregional procedures (P= .0037)
  - AST Platelet Ratio Index (APRI) ≤0.40 (P< .0001)
  - INR ≤1 (P= .0078)
- Prognostic factors PFS:
  - APRI >0.40 (P = .0416)
  - Prior ablation (P = .0323)
- Prognostic factors hPFS
  - 2 to 5 tumor nodules (P = .0148)
  - Albumin-bilirubin (ALBI) grade 3 (P = .0075)
  - APRI >0.40 (P = .0207)



Management of mNET

- Carcinoid, GI NET, & pancreatic NET
- Incidence 1.09->6.98/100,000 from 1973-2012
- Hormonal sx, pain, anorexia, wt loss
- 40–90% present w/ liver mets -> inferior survival
  - Median OS 5–57 mo
- Management[2,34-36]
  - Resection
    - Most not candidates for ablation or surgical resection -> mNET usually diffuse
  - Systemic
    - Somatostatin analogs, INF-a, angiogenesis inhibitors, mTOR inhibitors, cytotoxic hemotherapy



Management of mNET

- Non-operative, not responding to systemic tx, w/o extrahepatic progression
- TAE preferred to TACE in extrapancreatic mNET
  - Similar efficacy and better tolerated
- TACE ~ more effective in pancreatic mNET
- SIRT has shown promising, good tolerance
  - Preferred over other CDT in pts with colonized biliary systems[39]
- Kennedy et al retrospective multicenter study[37]
  - n=148 patients (Resin Y-90)
  - Objective radiographic response rate was 63%; median survival 70 mo
- Rhee et al retrospective study[38]
  - n=42 patients (Resin or Glass Y-90)
  - Objective response rate of 51%

Review > J Clin Med. 2020 Jul 20;9(7):2302. doi: 10.3390/jcm9072302.

The Role of Interventional Radiology for the Treatment of Hepatic Metastases from Neuroendocrine Tumor: An Updated Review

Maxime Barat [1 2], Anne-Ségolène Cottereau [2 3], Alice Kedra [1], Solène Dermine [2 4], Lola-Jade Palmieri [2 4], Romain Coriat [2 4], Raphael Dautry [1], Lambros Tselikas [5], Philippe Soyer [1 2], Anthony Dohan [1 2]

Affiliations + expand

PMID: 32698459 PMCID: PMC7408651 DOI: 10.3390/jcm9072302

- Large randomized controlled trials lacking
  - Small sample size, retrospective studies, heterogeneity
- Lit review
  - CDTs are safe and effective
  - Dx control w/ biological and symptom improvement
- Experienced IO's should have a central role in care

Y90 for mNET

- Devcic[40] et al 2014 - Meta-analysis
- 156 studies -> 12 selected -> 435 procedures
- Panc mNET poorer responses (P = 0.030)
- % CR vs PR correlated with median survival (R = 0.85; P = 0.008)
- Radioembolization effective treatment option for patients with hepatic mNET
- High response rate and improved survival for patients responding to therapy

Preferences – Hepatic Metastatic Disease

- Y90 and TAE are tolerated best, repeatable within acceptable limits
- Who to send?
  - mCRC not as first-line, but patients in second-line chemotherapy to salvage
    - Increased PFS and hPFS
    - Addition of biologic has additional benefit in 2nd line
  - mNET
    - Diffuse disease, poor response to systemic therapy

Conclusions

- Interventional Oncologist is an important ally to Hem-Onc/Rad-Onc/Surg-Onc practices
- Hepatic disease accounts for significant morbidity and mortality associated with metastatic cancers
- IO treatment strategies can significantly improve progression-free survival and symptom control
- Low side-effect procedures like radioembolization (y90) may be complimentary to standard therapies for mCRC and mNET

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