Y-90 in Liver Metastatic Disease

Nima Kokabi, MD FRCPC

Assistant Professor of Interventional Radiology and Image Guided Medicine

Associate Program Director of Interventional Radiology Residency

CIOctober 2020 ONLINE

Symposium on Clinical Interventional Oncology

Disclosures

Consultant – Sirtex Medical Ltd

Grant Support – Sirtex Medical Ltd

Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

Agenda

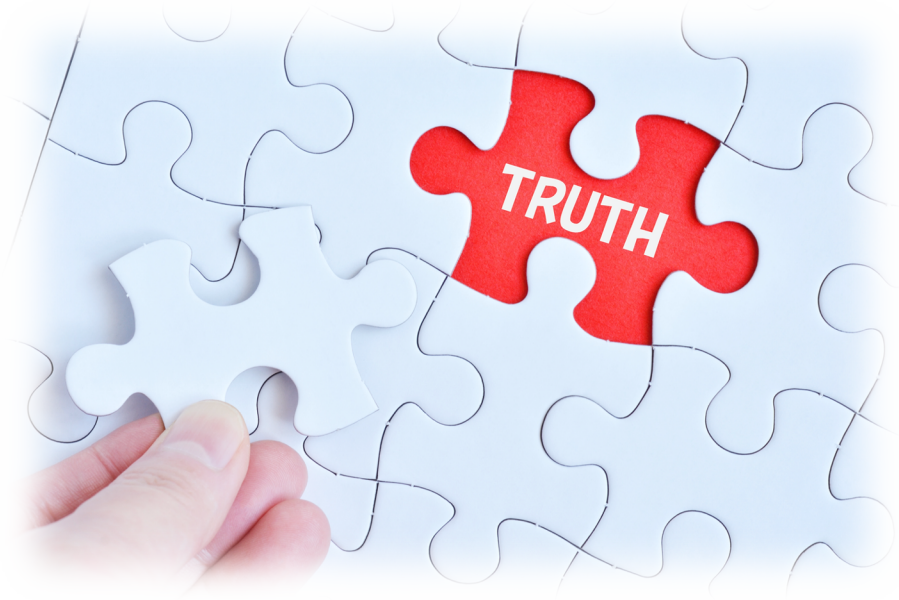
- Role of Y90 in metastatic liver disease
- Personalization of Y90 Therapy
- Timing of Y90 (i.e. number of chemotherapy lines used)
- Genomics
- Synergistic effect of Y90 to systemic therapies
- Long term toxicity of Y90
- Future directions

Ideal World of Y90 RE of Metastatic Dz

- Early Referral (? First line vs. 2nd line)
- Appropriate liver function
- Limited tumor bulk
- Favorable Tumor Biology
- Personalized Treatment Planning

Real World of Y90 RE of Metastatic Dz

- Referral: PD after multiple lines of chemotherapy
  - Hepatotoxic
- "Normal" LFT's
- Extensive tumor bulk
- Aggressive Disease
- BSA or MIRD Model of Y90 Dosimetry→ Not personalized



Role of Y90 in Metastatic Disease to the Liver

- **CRLM: Only FDA approved indication (SIR-Spheres®)**
- **All other metastatic diseases are off label**
- **Most referral in community: salvage**

Commonly Treated Diseases

- Colorectal Ca
- Breast Ca
- Neuroendocrine tumors
- Uveal/Cutaneous Melanoma

Current State of Breast Ca

› World J Gastrointest Oncol. 2020 Feb 15;12(2):228-236. doi: 10.4251/wjgo.v12.i2.228.

Yttrium-90 radioembolization for unresectable hepatic metastases of breast cancer: A systematic review

Michael Feretis [1], Andriy Solodkyy [2]

- 12 studies (452 pts)
- 2007-2018
- Resin & glass
- 52% of extra-hepatic Mets
- Tumor control in 81% (CR, PR, SD)
- Mean OS post Y90: 11.3 months (Range: 3.6 to 20.9 months)

Gaps in Knowledge: Liver mBRCA treated with Y90

- Optimal timing of Y90 w/ respect chemotherapies
  - After how many lines
  - How long to hold current systemic therapy when undergoing Y90
- Receptor status of patients
- Synergistic effect of systemic therapy + Y90

J Vasc Interv Radiol. 2020 Jun;31(6):925-933. doi: 10.1016/j.jvir.2019.12.013. Epub 2020 Apr 16.

Predictors of Survival after Yttrium-90 Radioembolization of Chemotherapy-Refractory Hepatic Metastases from Breast Cancer

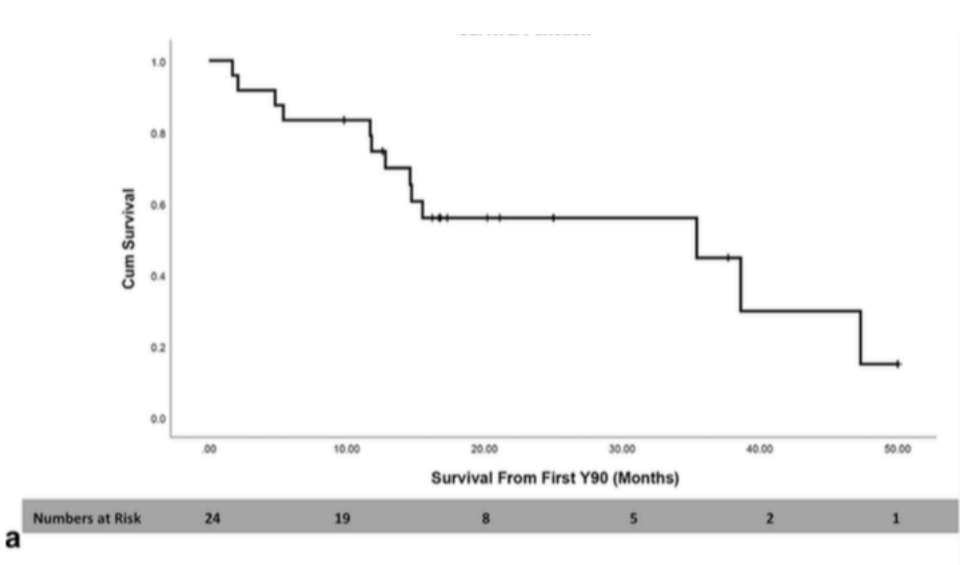
Neena A Davisson [1], Zachary L Bercu [1], Sarah C Friend [2], Elisavet Paplomata [2], Robert M Ermentrout [1], Janice Newsome [1], Bill S Majdalany [1], Nima Kokabi [3]

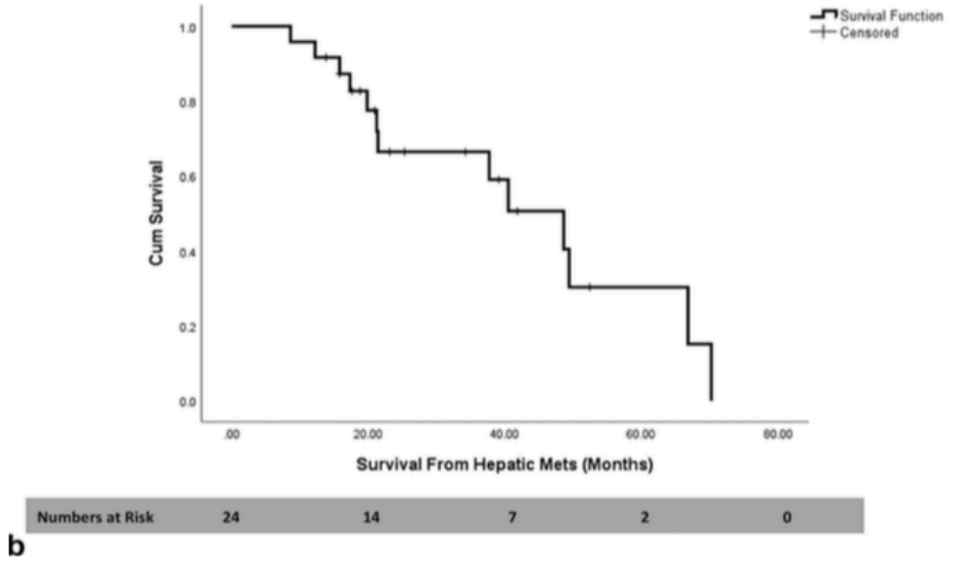
- 24 pts (2013-2018)
- Resin
- 10 (42%) pts undergoing Y90 within 6 mo of diagnosis of hepatic mets
- 20 (83%) ER+
- 18 (75%) w/ extrahepatic disease
  - Bone (70%) >> lung (20%), brain (20%), LN (25%)

J Vasc Interv Radiol. 2020 Jun;31(6):925-933. doi: 10.1016/j.jvir.2019.12.013. Epub 2020 Apr 16.

Predictors of Survival after Yttrium-90 Radioembolization of Chemotherapy-Refractory Hepatic Metastases from Breast Cancer

Neena A Davisson [1], Zachary L Bercu [1], Sarah C Friend [2], Elisavet Paplomata [2], Robert M Ermentrout [1], Janice Newsome [1], Bill S Majdalany [1], Nima Kokabi [3]

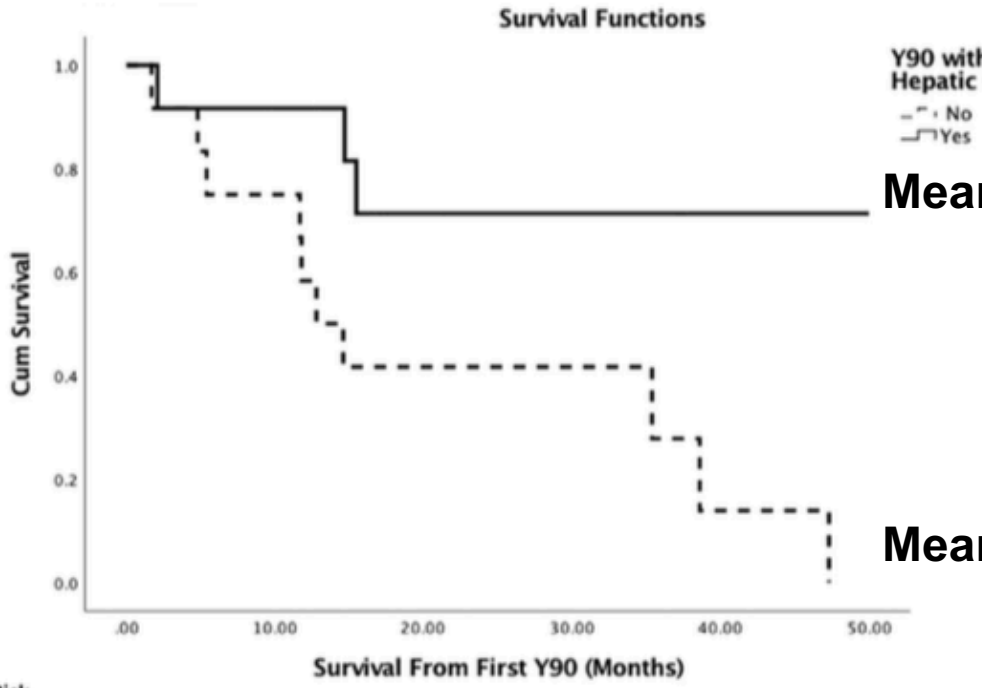




Median OS from 1st Y90: 35.4 mo

Median OS from Dx of Hepatic Mets: 48.6 mo

Timing of Y90



Numbers at Risk

Y90 within 6 mo	10	9	3	2	1	1
Y90 after 6 mo	14	10	5	3	1	0

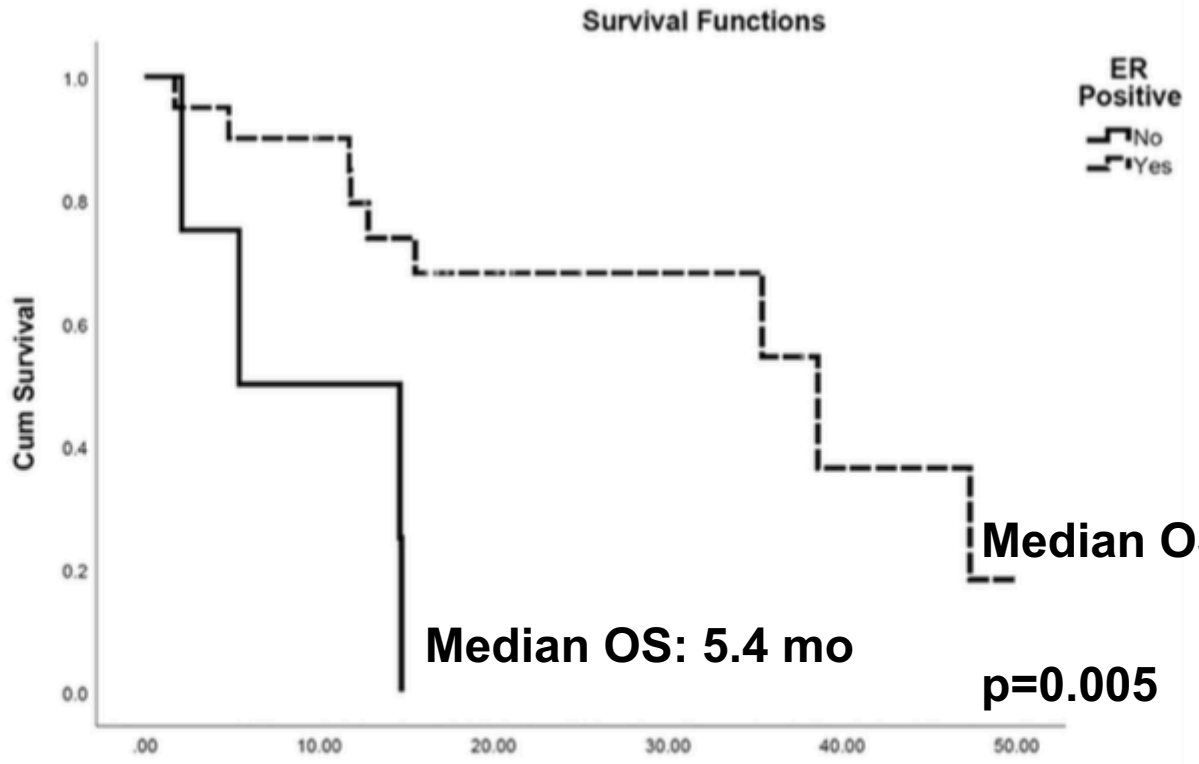
a

Mean OS: 38.9 mo

Mean OS: 22.1 mo

p=0.033

Receptor Status



Numbers at Risk

ER +	20	17	8	5	2	1
ER -	4	2	0	0	0	0

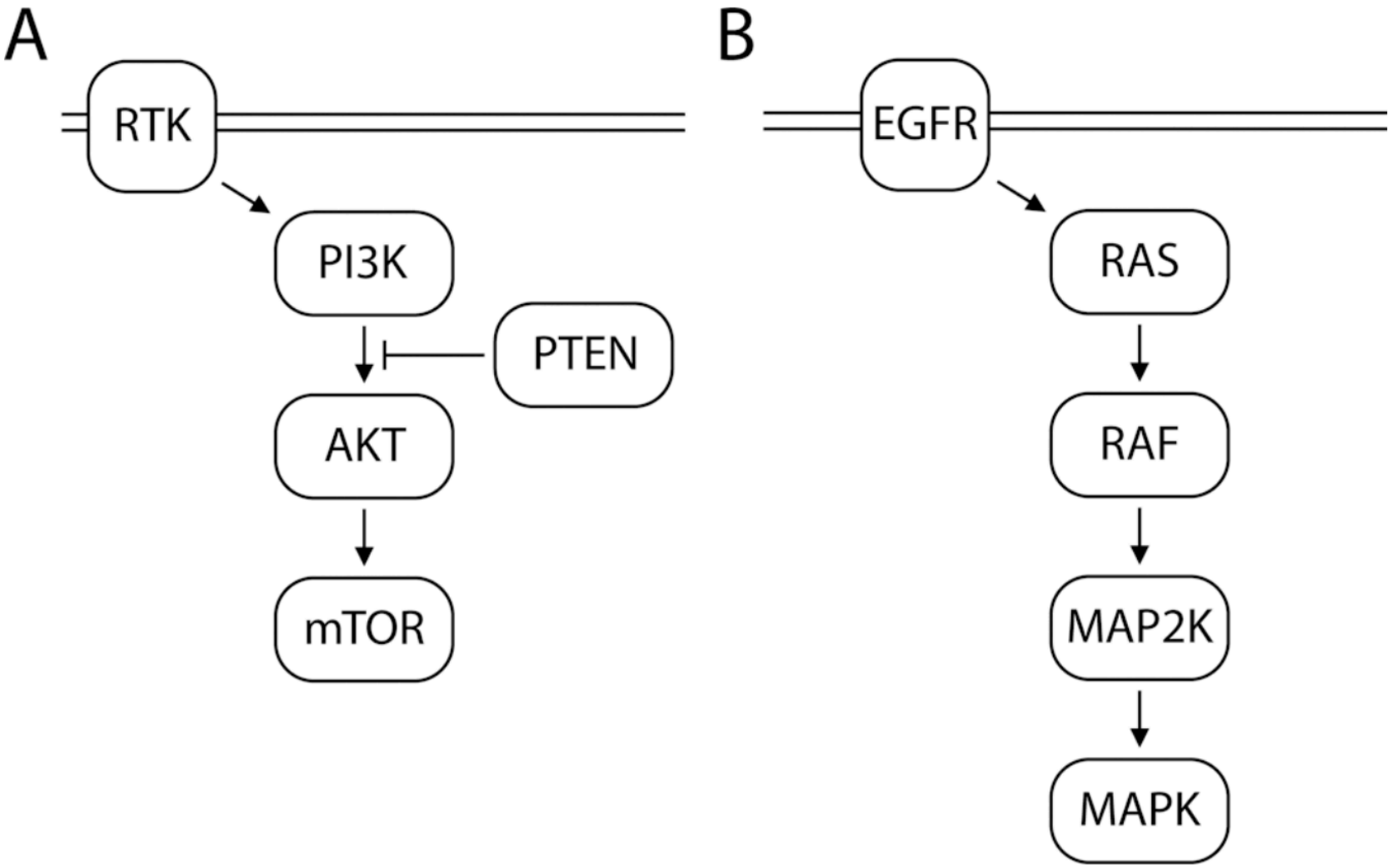
b

J Vasc Interv Radiol. 2018 Sep;29(9):1226-1235. doi: 10.1016/j.jvir.2018.04.018. Epub 2018 Aug 3.

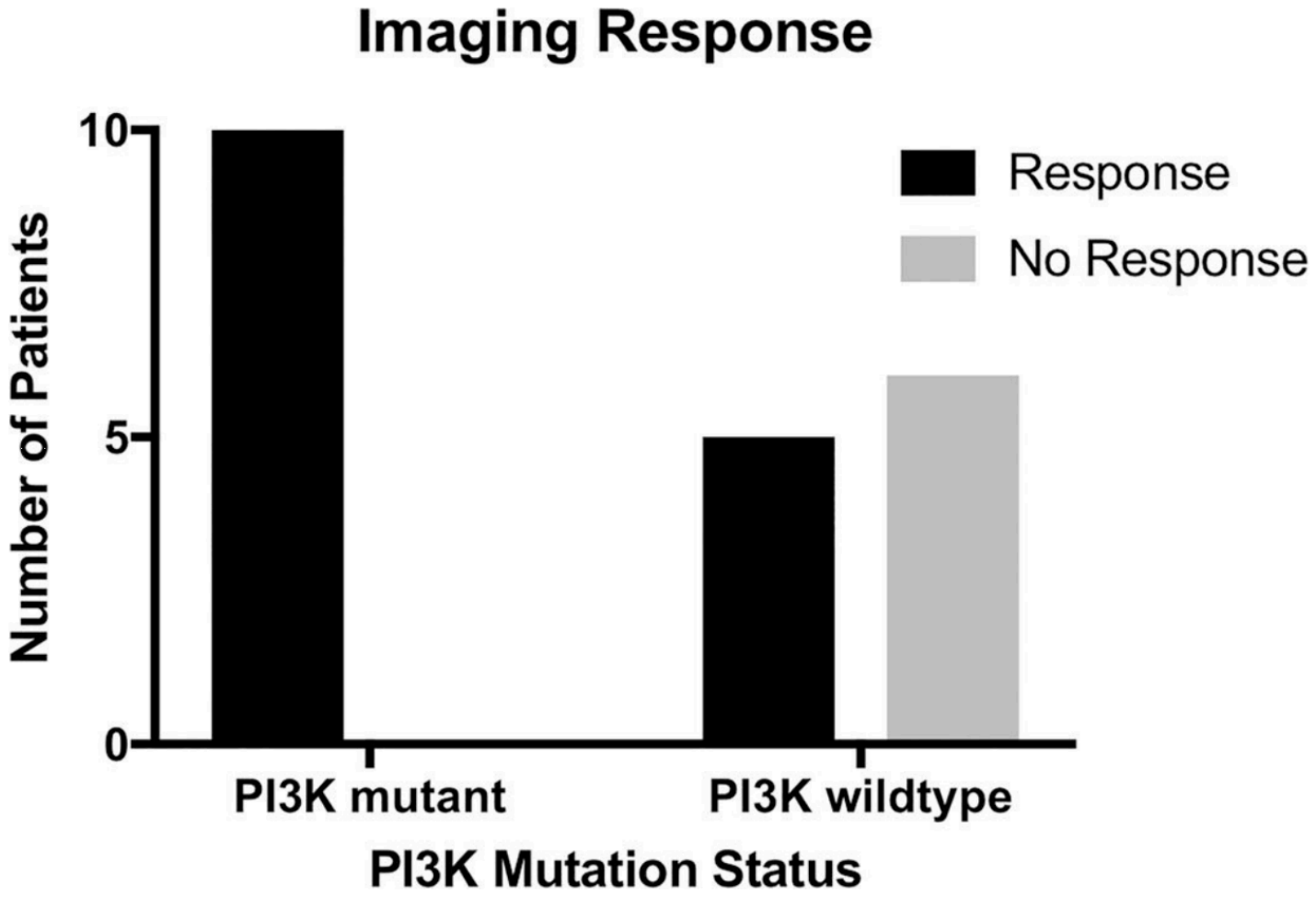
Association of PI3K Pathway Mutations with Early Positron-Emission Tomography/CT Imaging Response after Radioembolization for Breast Cancer Liver Metastases: Results of a Single-Center Retrospective Pilot Study

Amy R Deipolyi [1], Christopher C Riedl [2], Jacqueline Bromberg [3], Sarat Chandarlapaty [3], Christopher A Klebanoff [4], Constantinos T Sofocleous [5], Hooman Yarmohammadi [5], Lynn A Brody [5], F Edward Boas [5], Etay Ziv [5]

- 31 pts (2011-2017)
- 3+ lines of chemo
- PI3K & MAPK Pathways


A
RTK
PI3K
PTEN
AKT
mTOR
B
EGFR
RAS
RAF
MAP2K
MAPK

PI3K Mutation and Tumor Response



Tumor Response: Mutation & Receptor Status

Pathway Mutations	Mutant	Wildtype	
PI3K pathway	10/10 (100%)	5/11 (45%)	0.01
MAPK/ERK pathway	3/4 (75%)	12/17 (71%)	>0.99
TP53	7/10 (70%)	8/11 (73%)	>0.99
Hormone Receptor	Positive	Negative	
ER	15/21 (71%)	3/5 (60%)	0.63
PR			
HER2	4/5 (80%)	12/17 (71%)	>0.99
Total mutation count	> 6 Mutations	≤ 6 Mutations	
	9/10 (90%)	6/11 (55%)	0.15

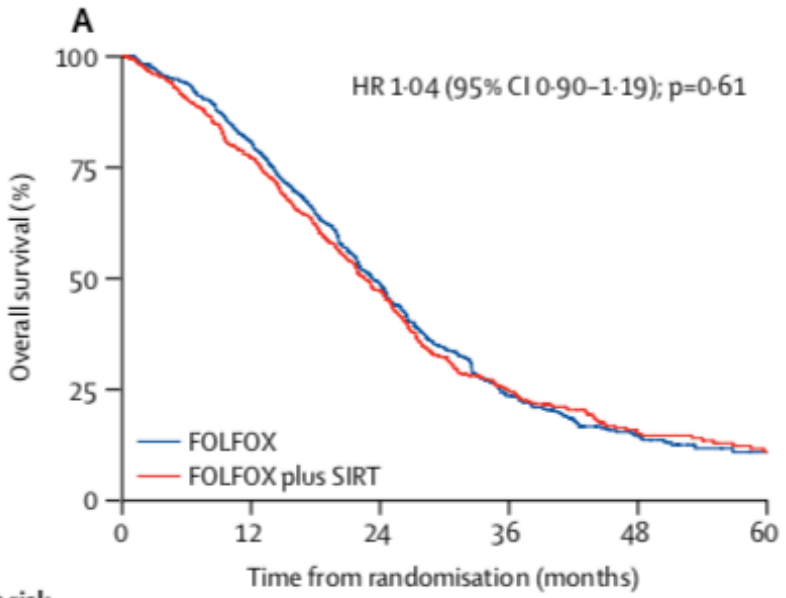
What about Colorectal Ca?

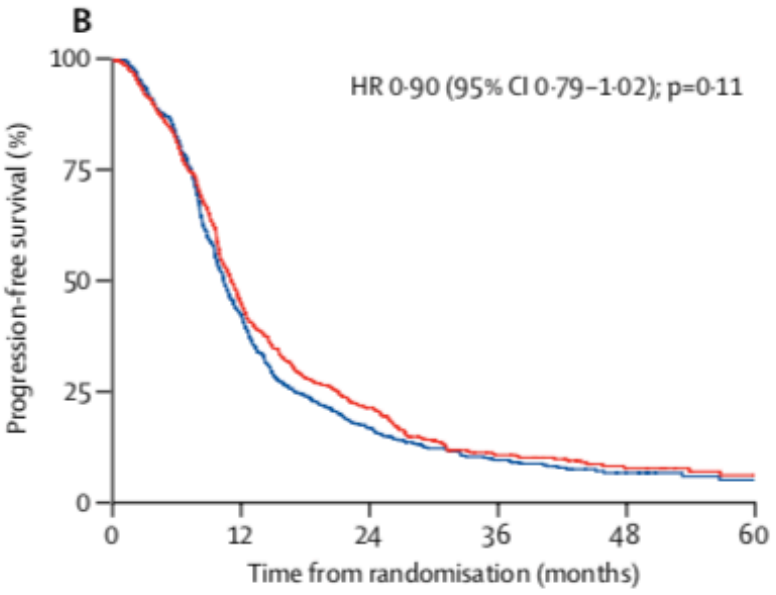
FOXFIRE, SIRFLOX & FOXFIRE-Global

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, Peter Gibbs*, Navesh K Sharma, Julien Taieb, Volker Heinemann, Jens Ricke, Marc Peeters, Michael Findlay, Andrew Weaver, Jamie Mills, Charles Wilson, Richard Adams, Anne Francis, Joanna Moschandreas, Pradeep S Virdee, Peter Dutton, Sharon Love, Val Gebski, Alastair Gray, FOXFIRE trial investigators†, SIRFLOX trial investigators†, FOXFIRE-Global trial investigators†, Guy van Hazel*, Ricky A Sharma**

OS & PFS



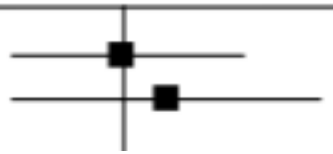


Number at risk (number censored)						
FOLFOX	549 (0)	419 (29)	242 (43)	88 (87)	33 (115)	12 (130)
FOLFOX plus SIRT	554 (0)	417 (13)	247 (23)	91 (74)	35 (101)	17 (112)

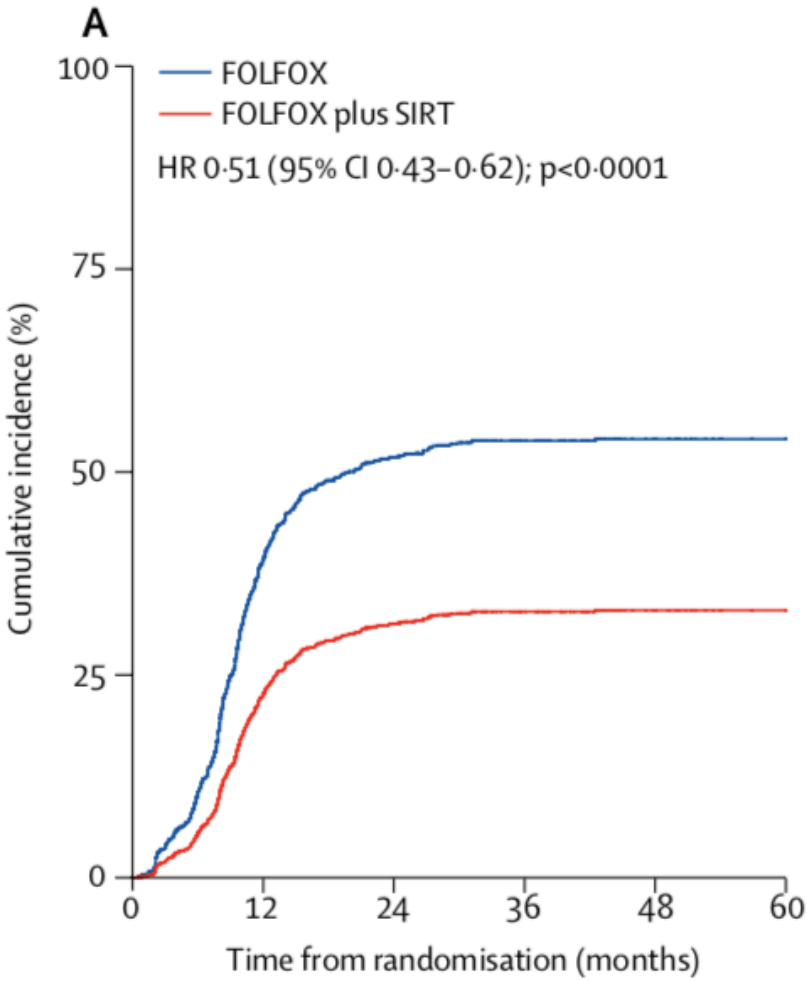
549 (0)	209 (40)	78 (47)	37 (56)	14 (70)	6 (76)
554 (0)	229 (29)	104 (36)	37 (55)	15 (69)	7 (75)

Liver-only Mets OS?

	FOLFOX		FOLFOX plus SIRT		HR (95% CI)
	Events	N	Events	N	
Liver-only metastases	261	358	264	355	1·00 (0·85–1·19)
Liver-dominant metastases	150	191	169	199	1·07 (0·85–1·33)



Progression of Disease in the Liver

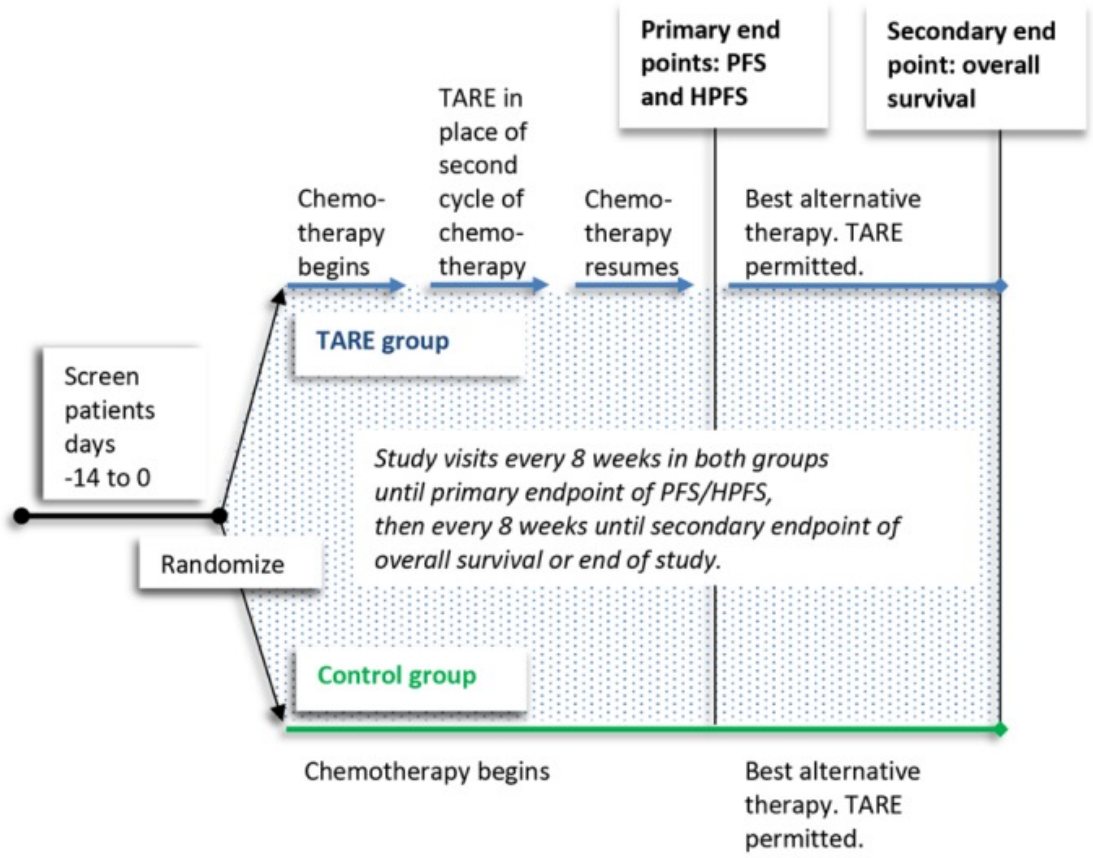


Y90 as a 1st line?

- Resin Y90 radioembolization as 1st line
  - No improved OS or overall PFS
  - **Did** improve local disease control

- **NOT Recommended as a 1st line**

What about Y90 as a 2nd line? EPOCH Trial



> Cardiovasc Intervent Radiol. 2020 Jul;43(7):1006-1014. doi: 10.1007/s00270-020-02463-z. Epub 2020 May 4.

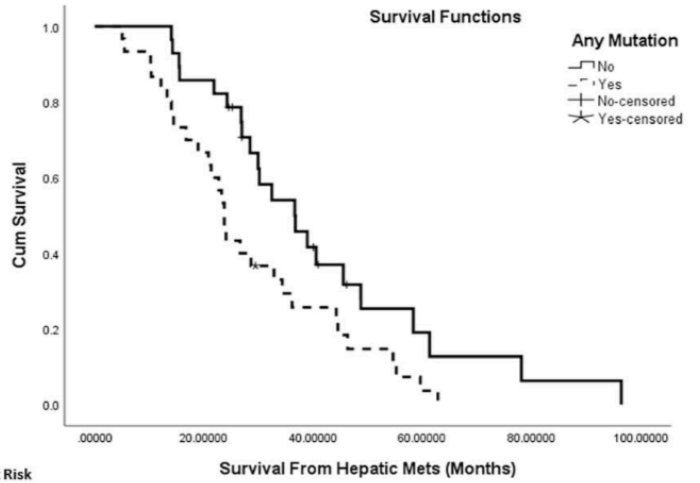
Impact of Genomic Mutation and Timing of Y90 Radioembolization in Colorectal Liver Metastases

Alexander Dabrowiecki [1], Tina Sankhla [2], Kaitlin Shinn [2], Zachary L Bercu [2], Mitchell Ermentrout [2], Walid Shaib [3], Kenneth Cardona [4], Janice Newsome [2], Nima Kokabi [2]

- 58 pts (2013-2018)
- Resin
- No 1st line Y90
- 16 (27%) after failing 1st line
- MAPK WT (incl. KRAS): 32 (55%)

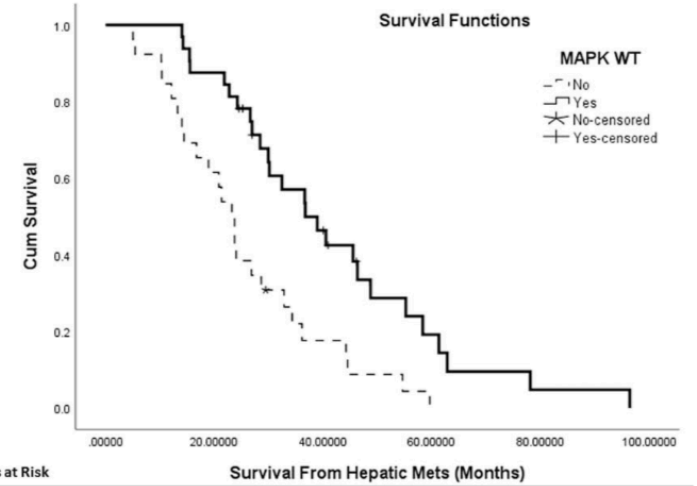
Predictors of Prolonged Survival

A



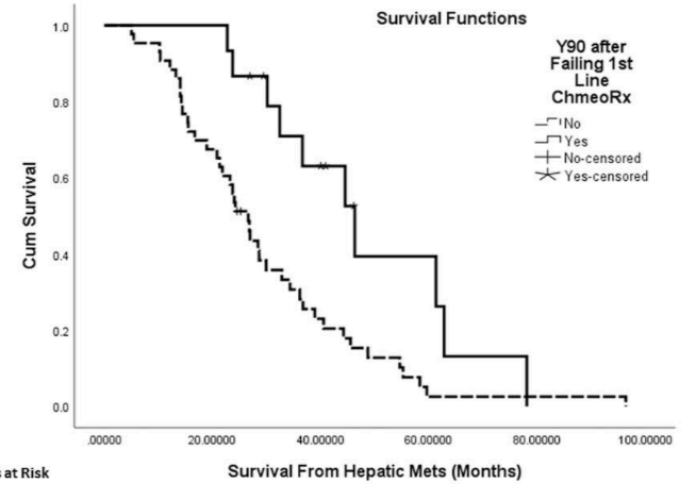
Numbers at Risk						
No Mutation	28	24	10	3	1	0
Any Mutation	30	19	7	1	0	0

B



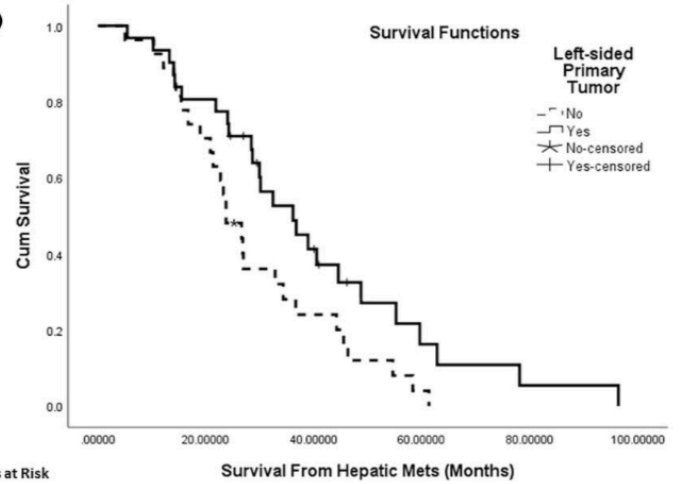
Numbers at Risk						
MAPK WT	32	28	13	4	1	0
MAPK Mutation	26	16	4	0	0	0

C



Numbers at Risk						
After 1st line Chemo	16	16	8	3	0	0
≥2 lines of Chemo	42	19	9	1	0	0

D



Numbers at Risk						
Left Sided	31	25	11	3	1	0
Right Sided	27	19	6	1	0	0

Predictors of Survival-MVA

Factor	Hazard ratio (HR)	95% Confidence interval	*P* value
MAPK WT	1.503	0.361–6.251	0.576
Any mutation	2.904	0.710–11.871	0.138
Left-sided primary	0.416	0.171–1.031	0.054
Y90 after failure of the first-line chemotherapy	0.084	0.021–0.335	**< 0.001**
MELD score ≤ 7	0.261	0.095–0.716	**0.009**
Bilobar disease	2.205	0.577–8.431	0.248
Diffuse disease	2.861	0.911–8.982	0.072
ECOG = 0	0.397	0.163–0.972	**0.043**
Serum CEA level decreased post-Y90	0.521	0.233–1.164	0.112

Bold values indicate $P < 0.05$

Mutation Status Stratified by Timing

- Mutation status
  - Not a predictor of prolonged survival if patient treated after failing 1st line of chemotherapy
  - Predictor of prolonged survival otherwise

KRAS WT in CRLM post Y90

- Predictor of prolonged OS[1,2]
- Predictor of objective tumor response[1,3,4]
- No prospective study
- ?May be related to Y90 timing

1. Dendy et al. *Oncotarget.* 2018.
2. Lathi et al. *JVIR.* 2015.
3. Janowski et al. *Oncol Rep.* 2017.
4. Magnetta et al. *Abdom Raiol.* 2016.

Dosimetry

- **HCC data**: there is a tumor Y90 dose response threshold with implication on prolonged survival

- **No data for metastatic disease**
  - **Prospective personalized dosimetry:** more difficult in the setting of multifocal disease
  - Easier now w/ several options for semi-automated dosimetry software available

Synergistic Effect of Y90 with Systemic Therapy

- Grade 2 NET: Y90 + Capecitabine-Temozolomide[1]
  - PFS @ 3 years: 67% overall, 74% in the liver
- Uveal Melanoma: Y90 + peri-TARE immunotherapy
  - Improved OS and PFS[2,3,4]

1. Soulen et al. *Pancreas.* 2020.
2. Levey et al. *CVIR.* 2020.
3. Zheng et al. *JVIR.* 2018.
4. Itchins et al. *Melanoma Res.* 2017.

Long-term Toxicity of Y90

J Vasc Interv Radiol. 2017 Nov;28(11):1520-1526. doi: 10.1016/j.jvir.2017.05.011. Epub 2017 Jun 30.

Long-Term Hepatotoxicity of Yttrium-90 Radioembolization as Treatment of Metastatic Neuroendocrine Tumor to the Liver

Yu-Kai Su [1], Rosewell V Mackey [1], Ahsun Riaz [1], Vanessa L Gates [1], Al B Benson 3rd [1], Frank H Miller [1], Vahid Yaghmai [1], Ahmed Gabr [1], Riad Salem [1], Robert J Lewandowski [2]

J Vasc Interv Radiol. 2017 Nov;28(11):1520-1526. doi: 10.1016/j.jvir.2017.05.011. Epub 2017 Jun 30.

Long-Term Hepatotoxicity of Yttrium-90 Radioembolization as Treatment of Metastatic Neuroendocrine Tumor to the Liver

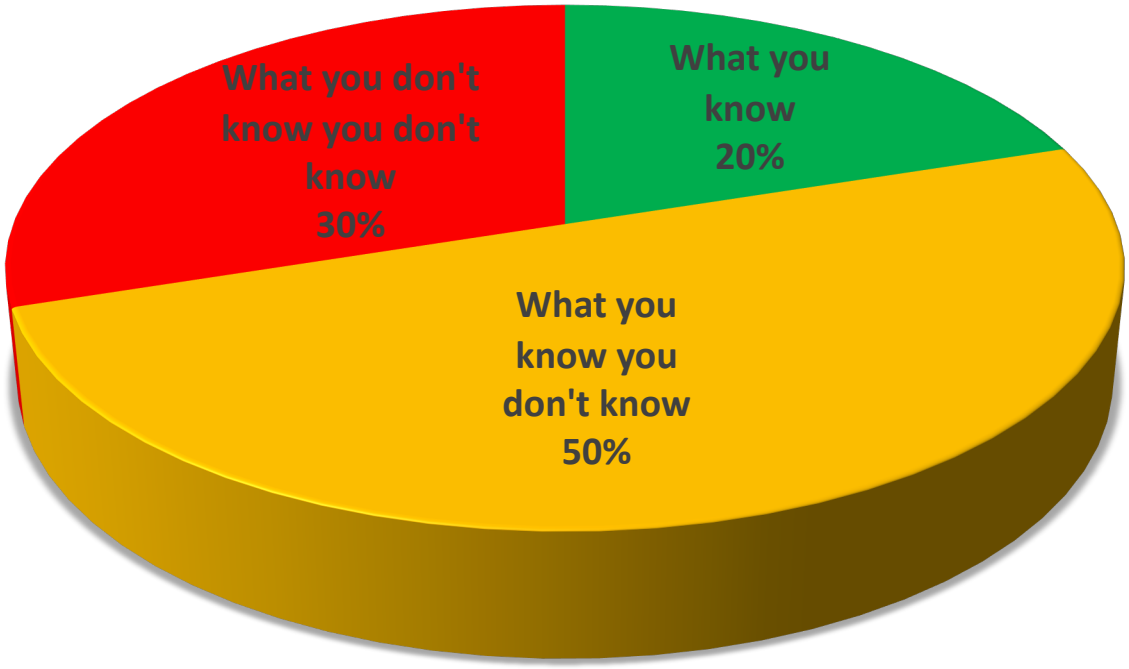
Yu-Kai Su [1], Rosewell V Mackey [1], Ahsun Riaz [1], Vanessa L Gates [1], Al B Benson 3rd [1], Frank H Miller [1], Vahid Yaghmai [1], Ahmed Gabr [1], Riad Salem [1], Robert J Lewandowski [2]

- Predictors of long-term liver toxicity → Whole liver treatment
- 50% of patients w/ stigmata of portal hypertension and cirrhotic changes on imaging
- 21% w/ clinical signs of hepatic decompensation
- Only 2 of 39 patients (5.1%) had no other causes of hepatotoxicity

Current State of Play for Metastatic Disease

?

1. ECOG
2. Liver Fx
3. Dz Burden



1. Y90 as 1st, 2nd line etc
2. Timing w/ respect current systemic Rx
3. Tumor Genetics
4. Receptor Status
5. Tumor Dose Response Threshold
6. Resin vs. Glass
7. Synergistic Chemo Rx
8. Synergistic Immuno Rx
9. Optimal Imaging and timing (PET vs. MRI vs. CT)
10. Rx Related Toxicity
11. etc

Thank You

nkokabi@emory.edu