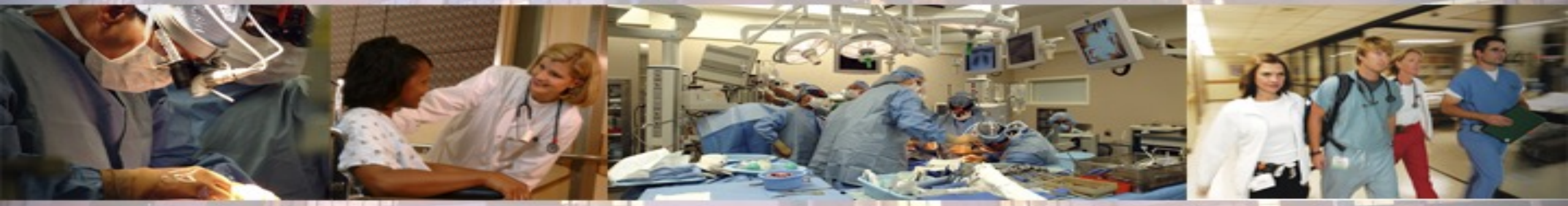
Where Does IO Stand in the NCCN Guidelines: Metastatic Colorectal Cancer

Ahmed Kamel MD, PhD, FSIR
Chief of Interventional Radiology
Vice Chair of Faculty Affairs



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Disclosures

Consultant: Abbott Vascular, Baxter Healthcare Corporation, Bard Peripheral Vascular, Boston Scientific, W.L. Gore, Sirtex Medical, Guerbet, Eisai Medical, Trisalus, Astra Zeneca.

Grants: BTG, Medtronic, Bard Peripheral Vascular, Boston Scientific, Sirtex Medical.

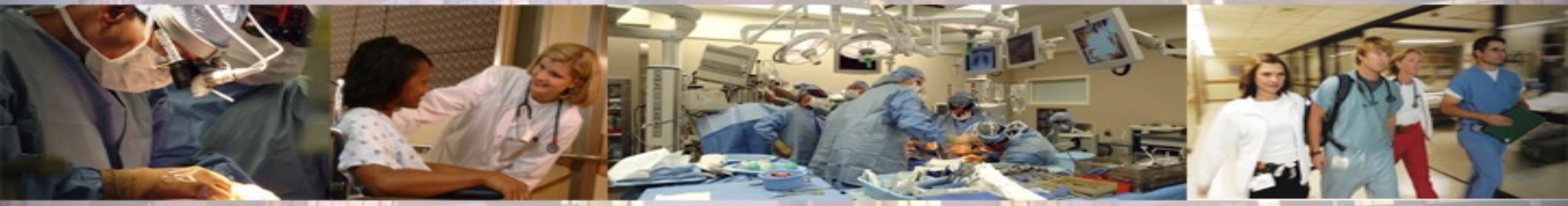
Objectives

- The NCCN guidelines for Y90 Radioembolization of CRLM
  - Second line chemotherapy
  - Salvage therapy

- The NCCN guidelines for Ablation of CRLM

Y90 Radioembolization

With Second line chemotherapy



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

Aim:

- To investigate the impact of transarterial Yttrium-90 radioembolization in combination with second line systemic chemotherapy for colorectal liver metastases.

Mulcahy et al, J clin Oncol 2021

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

Study Design:

- Multicenter, open-label phase III trial
- 428 patients
- 95 centers in North America, Europe, and Asia

Mulcahy et al, J clin Oncol 2021

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

Country	Active Sites	Screened Patients	Randomized Patients
UK	24	159	127
United States	22	122	104
Poland	8	91	56
Spain	12	47	39
France	9	41	33
Korea	4	25	22
Canada	7	17	15
Germany	3	17	15
Singapore	1	7	7
Belgium	2	4	4
Hong Kong	2	6	4
Austria	1	3	2
Totals	**95**	**539**	**428**

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

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

Study Design:

- CLM who progressed on oxaliplatin or irinotecan-based first-line therapy were randomly assigned 1:1 to receive:
  - Second-line chemotherapy and TARE (n=215).
  - Second-line chemotherapy (n=213).
- Random assignment was performed by:
  - Unilobar or bilobar disease
  - oxaliplatin- or irinotecan-based first-line chemotherapy
  - KRAS mutation status

Mulcahy et al, J clin Oncol 2021

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Mulcahy et al, J clin Oncol 2021

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

Inclusion criteria:

- Age >18 years,
- Unresectable unilobar or bilobar CLM
- Ability to receive second-line irinotecan- or oxaliplatin-based chemotherapy
- Measurable disease by RECIST 1.1
- ECOG Performance status 0 or 1
- Bilirubin < 1.2 upper limit normal
- Albumin > 3.0 g/dL.

Mulcahy et al, J clin Oncol 2021

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

Exclusion criteria:

- Prior arterial or radiotherapy to the liver
- Clinically evident ascites
- Unresolved toxicities from first-line therapy
- Confirmed extrahepatic metastases
- Contraindication to angiography.

Mulcahy et al, J clin Oncol 2021

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

Treatments and procedures:

- Treatment was planned for 120 Gy +/- 10% using single-compartment dosimetry to either:
  - One lobe
  - Both lobes in a single setting
- Glass-based TARE (Therasphere) was performed.

Mulcahy et al, J clin Oncol 2021

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

End Points:

- **Primary end points:**
  - Progression-free survival (PFS)
  - Hepatic progression-free survival (hPFS)
- **Secondary endpoints:**
  - Overall survival (OS)
  - Objective response rate (ORR)
  - Disease control rate (DCR)

Study success: either PFS or hPFS must statistically significant

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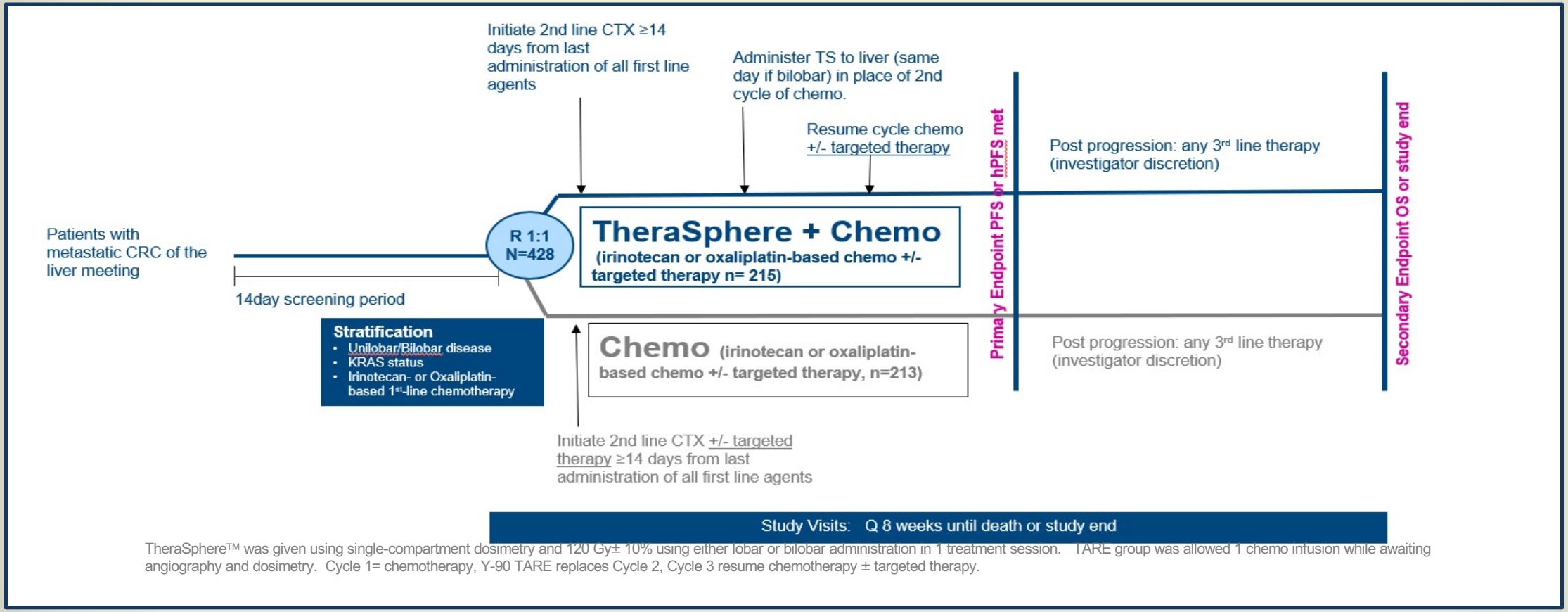
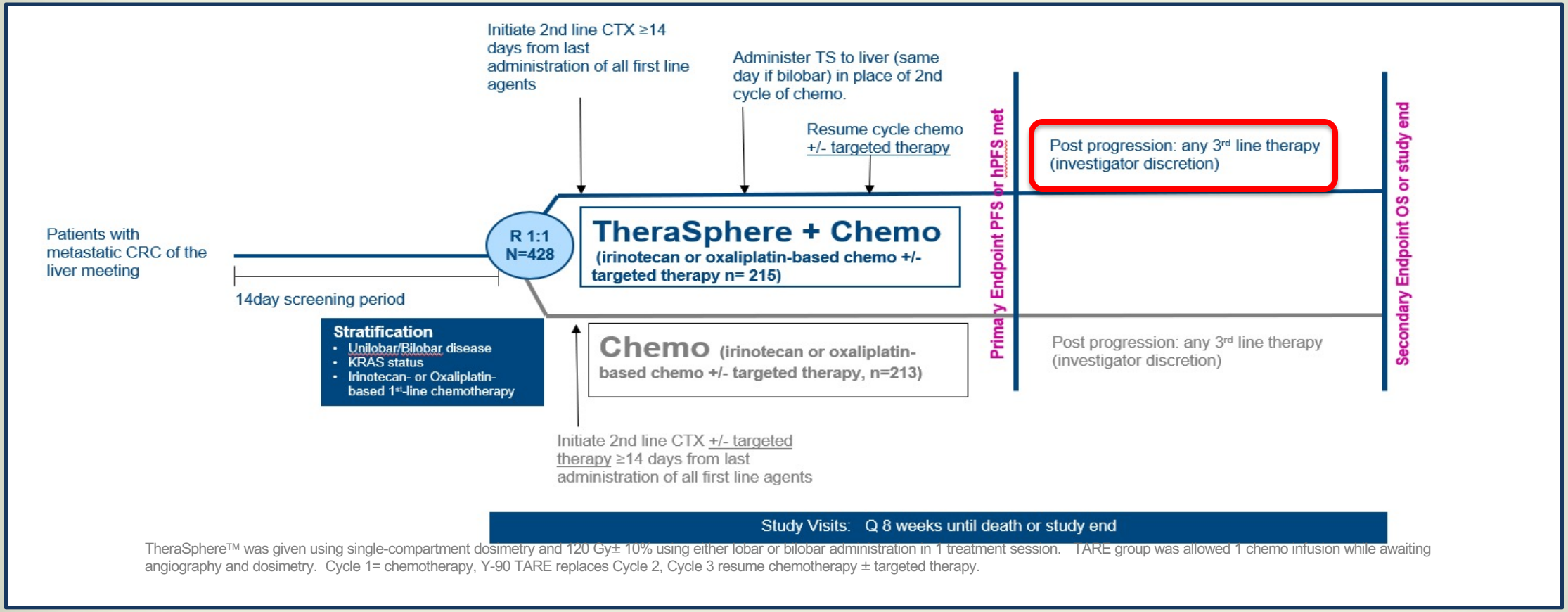
Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial



TheraSphere™ was given using single-compartment dosimetry and 120 Gy± 10% using either lobar or bilobar administration in 1 treatment session. TARE group was allowed 1 chemo infusion while awaiting angiography and dosimetry. Cycle 1= chemotherapy, Y-90 TARE replaces Cycle 2, Cycle 3 resume chemotherapy ± targeted therapy.

Mulcahy et al, J clin Oncol 2021

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



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

The groups were well balanced

	Y-90 + Chemo (N=215)	Chemo (N=213)
Median Age	63.0 years	60.0 years
Male	135 (62.8%)	138(64.8%)
Region		
North America	63 (29.3%)	56 (26.3%)
Europe	131 (60.9%)	145 (68.1%)
Asia	21 (9.8%)	12 (5.6%)
ECOG 0	119 (55.3%)	133 (62.4%)
Albumin ≥site LLN	182 (84.7%)	177 (83.1%)
CEA ≥35 ng/mL	116 (54.0%)	105 (49.3%)
KRAS Status (stratification parameter)		
Mutant	100 (46.5%)	101 (47.4%)
Wild type	115 (53.5%)	112 (52.6%)

	Y-90 + Chemo (N=215)	Chemo (N=213)
Bilobar disease (stratification parameter)	176 (81.9%)	173 (81.2%)
Liver Tumor Burden[a]		
<10%	124 (57.7%)	121 (56.8%)
≥10% to <25%	54 (25.1%)	47 (22.1%)
≥25%	29 (13.5%)	28 (13.1%)
Maximum Liver Lesion Size ≥40 mm[a]	162 (75.3%)	142 (66.7%)
Primary tumor in situ	83 (38.6%)	69 (32.4%)
Left side primary tumor location	150 (69.8%)	136 (63.8%)
Extrahepatic Lesions at Baseline	113 (52.6%)	95 (44.6%)
Number of Lesions		
<3	25 (11.6%)	21 (9.9%)
3-5	40 (18.6%)	38 (17.8%)
6-10	54 (25.1%)	60 (28.2%)
>10	88 (40.9%)	77 (36.2%)
Missing	8 (3.7%)	17 (8.0%)

Well-balanced patient and disease characteristics between treatment and control arms in this advanced disease patients

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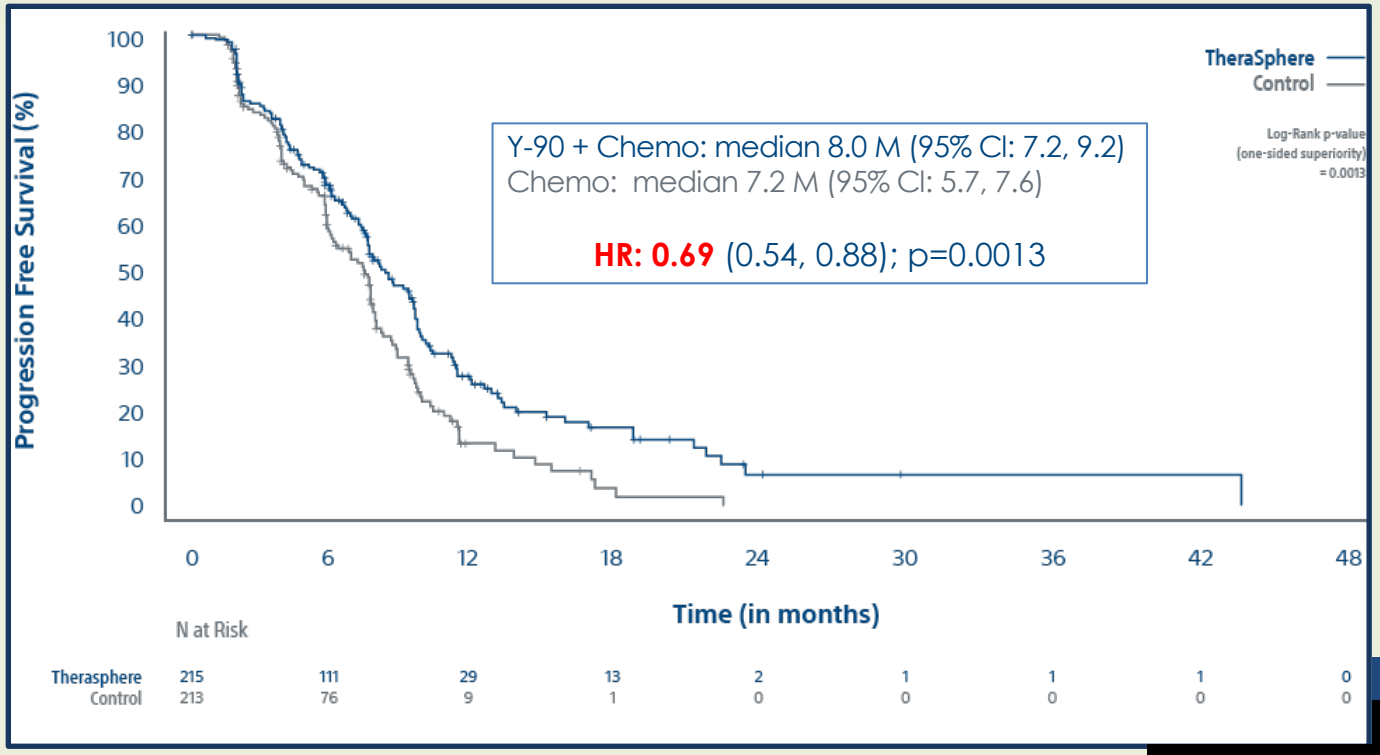
Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

	Y-90 + Chemo (N=215)	Chemo (N=213)
Received Assigned Therapy	187 (87.0%)*	191 (89.7%)
2nd Line Chemo Administered (stratification parameter)	203 (94.4%)	191 (89.7%)
Irinotecan-based	130 (60.5%)	123 (57.7%)
Irinotecan Mean Number of Cycles / Median of Average Dose per Cycle (mg/m^2)	9.0 / 180	9.3 / 180
Oxaliplatin-based	73 (34.0%)	68 (31.9%)
Oxaliplatin Mean Number of Cycles / Median of Average Dose per Cycle (mg/m^2)	8.5 / 85	8.8 / 85
Biological Agent	88 (40.9%)	93 (43.7%)
Aflibercept	9 (4.2%)	11 (5.2%)
Bevacizumab	74 (34.4%)	65 (30.5%)
Cetuximab	5 (2.3%)	10 (4.7%)
Panitumumab / Ramucirumab	2 (0.9%) / 0	6 (2.8%) / 1 (0.5%)
Y-90 Treatment		
Median absorbed dose to perfused volume prior to progression by investigator determination, Gy (range)	117 (61.7, 156)	NA
Median time to Y-90, days (range)	25 (12-90)	NA

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



Positive Outcome

	% Progression-Free Survival (95% CI)		
	6 M	12 M	18 M
Y-90 + Chemo (N=215)	65.2 (58.0, 71.5)	25.8 (18.9, 33.1)	16.7 (10.6, 23.9)
Chemo (N=213)	55.4 (47.2, 62.8)	13.2 (7.5, 20.5)	1.8 (0.2, 8.1)

Patients receiving Y90 + chemo were **31%** less likely to show disease progression or death vs. chemo alone

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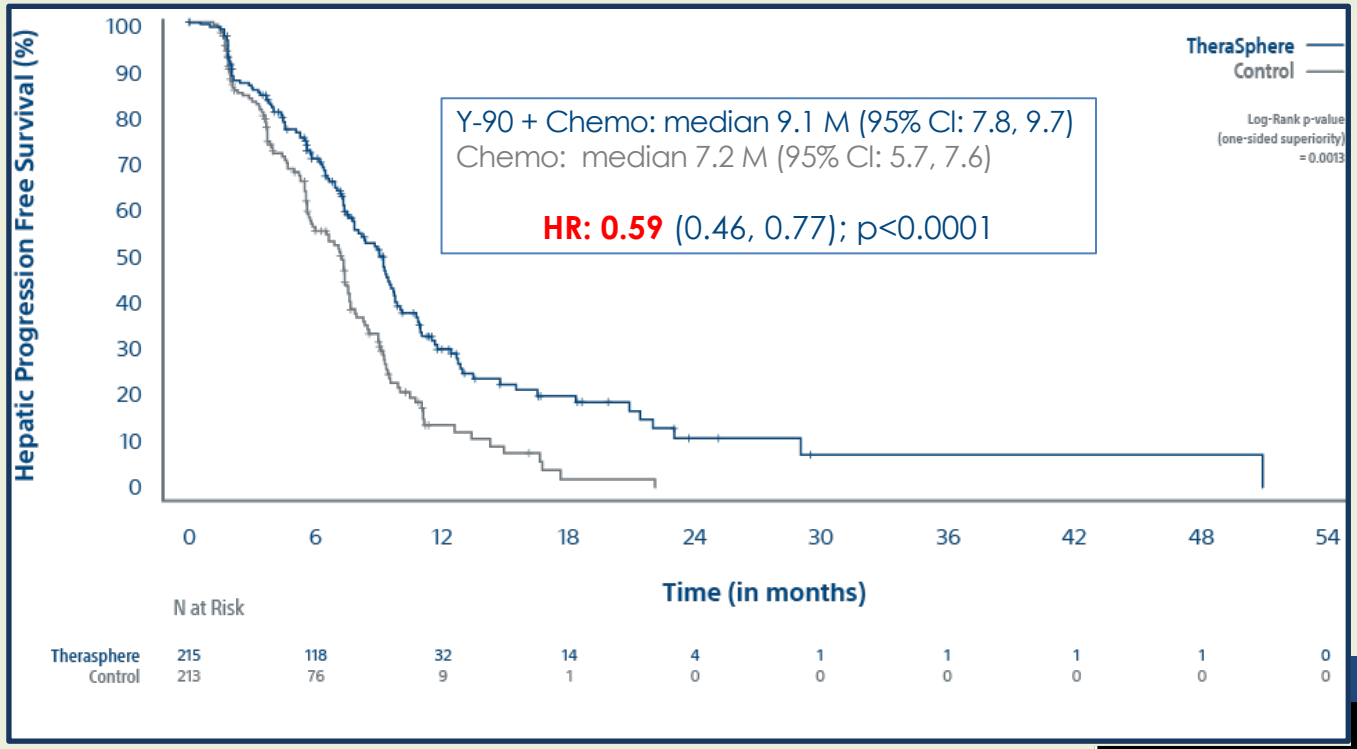
Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial



Positive Outcome

	% Hepatic Progression-Free Survival (95% CI)		
	6 M	12 M	18 M
Y-90 + Chemo (N=215)	70.7 (63.6, 76.6)	29.8 (22.4, 37.6)	19.8 (13.0, 27.6)
	55.2 (47.1, 62.7)	13.5 (7.7, 20.9)	1.9 (0.2, 8.3)

Patients receiving Y90 + chemo were **41%** less likely to show hepatic disease progression or death vs. chemo alone

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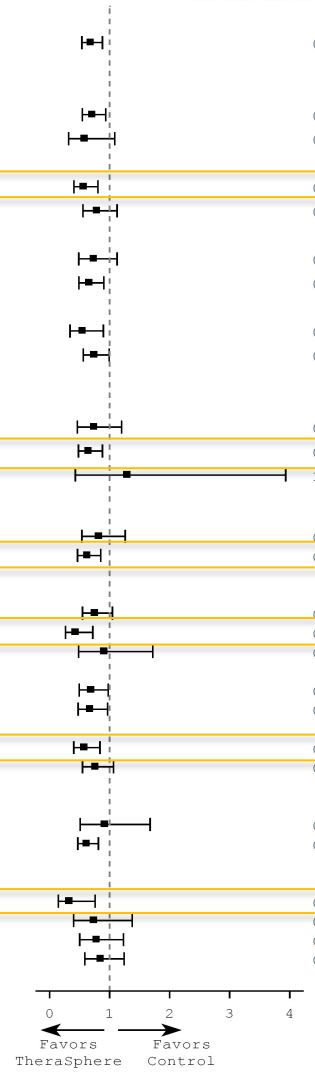
Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

PFS benefit with Y-90+chemo include:

- Tumors with KRAS mutation
- Hepatic tumor burden 10 - 25%
- < 3 lesions
- Left sided primary tumor
- Addition of a biologic agent
- Resected Primary

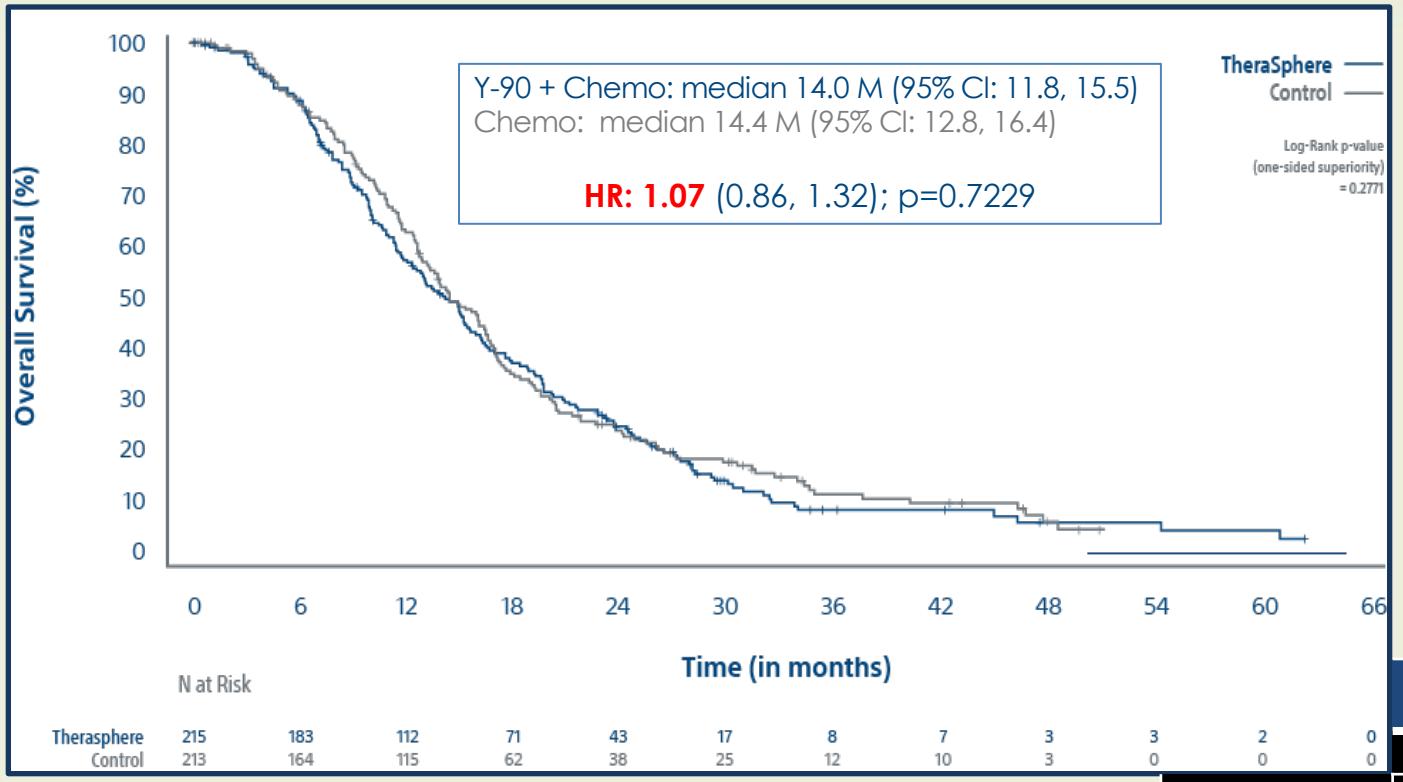
Subgroup	No. of Patients (No. of Events) TheraSphere	Control	Hazard Ratio for PFS (95% CI)
Overall	215(140)	213(127)	0.69 (0.54, 0.88)
Unilobar or Bilobar Disease at baseline (stratification factor corrected)			
Bilobar	176(115)	173(107)	0.71 (0.54, 0.93)
Unilobar	39(25)	40(20)	0.59 (0.32, 1.09)
KRAS at baseline (stratification factor corrected)			
Mutant	100(67)	101(67)	0.57 (0.40, 0.80)
Wild type	115(73)	112(60)	0.79 (0.55, 1.12)
Gender			
Female	80(56)	75(43)	0.74 (0.48, 1.12)
Male	135(84)	138(84)	0.66 (0.49, 0.90)
US and non-US region			
US Region	54(37)	50(34)	0.55 (0.34, 0.89)
Non-US Region	161(103)	163(93)	0.74 (0.56, 0.99)
Location of primary tumors at time of first diagnosis of primary CRC			
Right Side	49(33)	61(37)	0.74 (0.46, 1.20)
Left Side	150(99)	136(81)	0.65 (0.48, 0.88)
Both	10(6)	14(8)	1.30 (0.43, 3.93)
Not Available	6(2)	2(1)	
Primary tumor in situ at baseline			
Yes	83(51)	69(39)	0.82 (0.54, 1.26)
No	132(89)	144(88)	0.63 (0.46, 0.85)
Tumor replacement at baseline by Blinded Independent Central Review			
<10%	124(83)	121(70)	0.76 (0.55, 1.05)
>=10 to <25%	54(34)	47(37)	0.43 (0.26, 0.72)
>=25%	29(21)	28(19)	0.91 (0.48, 1.72)
Extrahepatic lesions at baseline			
Yes	113(77)	95(62)	0.69 (0.49, 0.98)
No	102(63)	118(65)	0.68 (0.47, 0.96)
Biological agent received as part of second-line treatment			
Yes	88(59)	93(61)	0.58 (0.40, 0.84)
No	127(81)	120(66)	0.76 (0.55, 1.06)
Maximum Liver lesion size at baseline by Blinded Independent Central Review			
<40 mm	40(28)	41(20)	0.92 (0.51, 1.67)
>=40 mm	162(109)	142(105)	0.62 (0.47, 0.81)
Number of lesions at baseline by Blinded Independent Central Review			
<3 lesions	25(13)	21(15)	0.33 (0.14, 0.76)
3-5 lesions	40(25)	38(19)	0.74 (0.40, 1.37)
6-10 lesions	54(38)	60(41)	0.78 (0.50, 1.23)
>10 lesions	88(62)	77(51)	0.85 (0.59, 1.24)

Progression Free Survival



Forest plot

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



Did not meet secondary endpoint

	% Overall Survival (95% CI)		
	6 M	12 M	18 M
Y-90 + Chemo (N=215)	88.5 (83.3, 92.1)	56.3 (49.2, 62.8)	36.4 (29.7, 43.1)
	87.8 (82.3, 91.7)	62.4 (55.0, 68.9)	34.3 (27.5, 41.2)

PER PROTOCOL OS: TARE+Chemo 15.2 M (95% CI: 12.7-17.7) versus Chemo 14.3 M (95% CI: 12.6, 16.4)
HR: 0.96 (0.74, 1.24); p=0.3841

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Outcome	TARE (n = 215)		Control (n = 213)
Best overall response,[a] No. (%)			
CR	2 (0.9)		3 (1.4)
PR	71 (33.0)		42 (19.7)
SD	98 (45.6)		110 (51.6)
PD	27 (12.6)		27 (12.7)
Not evaluable or missing	0/17 (7.9)		1 (0.5)/30 (14.1)
ORR			
CR plus PR, No. (%) (95% CI)	73 (34.0) (28.0 to 40.5)		45 (21.1) (16.2 to 27.1)
Difference (95% CI)		12.8% (4.0 to 21.4)	
Superiority 1-sided *P*		.0019	
DCR			
CR plus PR plus SD, No. (%) (95% CI)	171 (79.5) (73.6 to 84.4)		155 (72.8) (66.4 to 78.3)
Difference (95% CI)		6.8% (–1.6 to 15.1)	
Superiority 1-sided *P*		.0626	

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

	Y-90 + Chemo (N=187)	Chemo (N=207)
Any TEAEs (n, %)	181 (96.8%)	194 (93.7%)
Chemotherapy-Related TEAEs	172 (92.0%)	189 (91.3%)
Adverse Device Events (ADEs)	103 (55.1%)	0
Angiographic Procedure-Related TEAEs	55 (29.4%)	2 (1.0%)
TEAEs with CTCAE ≥ Grade 3	128 (68.4%)	102 (49.3%)
Serious TEAEs	70 (37.4%)	43 (20.8%)
Serious Treatment Emergent ADEs	20 (4.3%)	0
TEAEs Leading to Fatal Outcome	8 (4.3%)	4 (1.9%)
TEAEs Requiring Discontinuation of Chemotherapy	24 (12.8%)	25 (12.1%)

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Serious Treatment Emergent ADEs		
TEAEs Leading to Fatal Outcome		
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- Exposure to chemotherapy was similar for both groups
- No reduction in dose intensity or ability to receive planned chemotherapy

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

Conclusion:

- The addition of TARE to second line chemotherapy for CLM led to longer PFS and hPFS.

Mulcahy et al, J clin Oncol 2021

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

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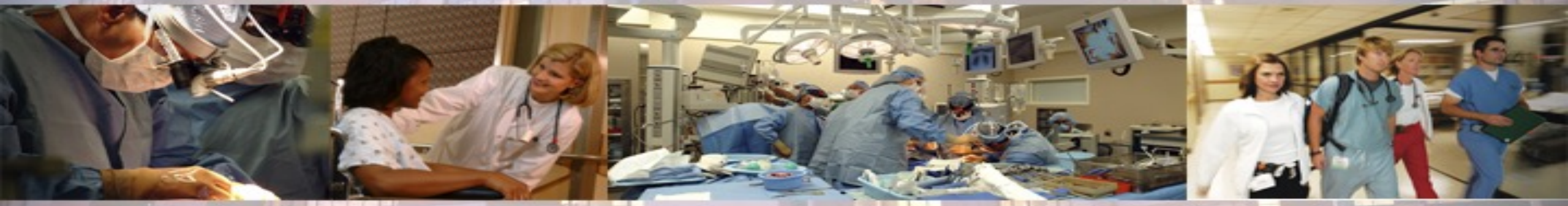
This can be addressed with the NCCN CRC panel

Mulcahy et al, J clin Oncol 2021

Y90 Radioembolization

Salvage Therapy



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Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study

Aim:

- Assess the survival benefit of adding transarterial radioembolization to systemic therapy in the salvage setting.

Haber et al, Acad Radiol, 2021

Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study

Study Design

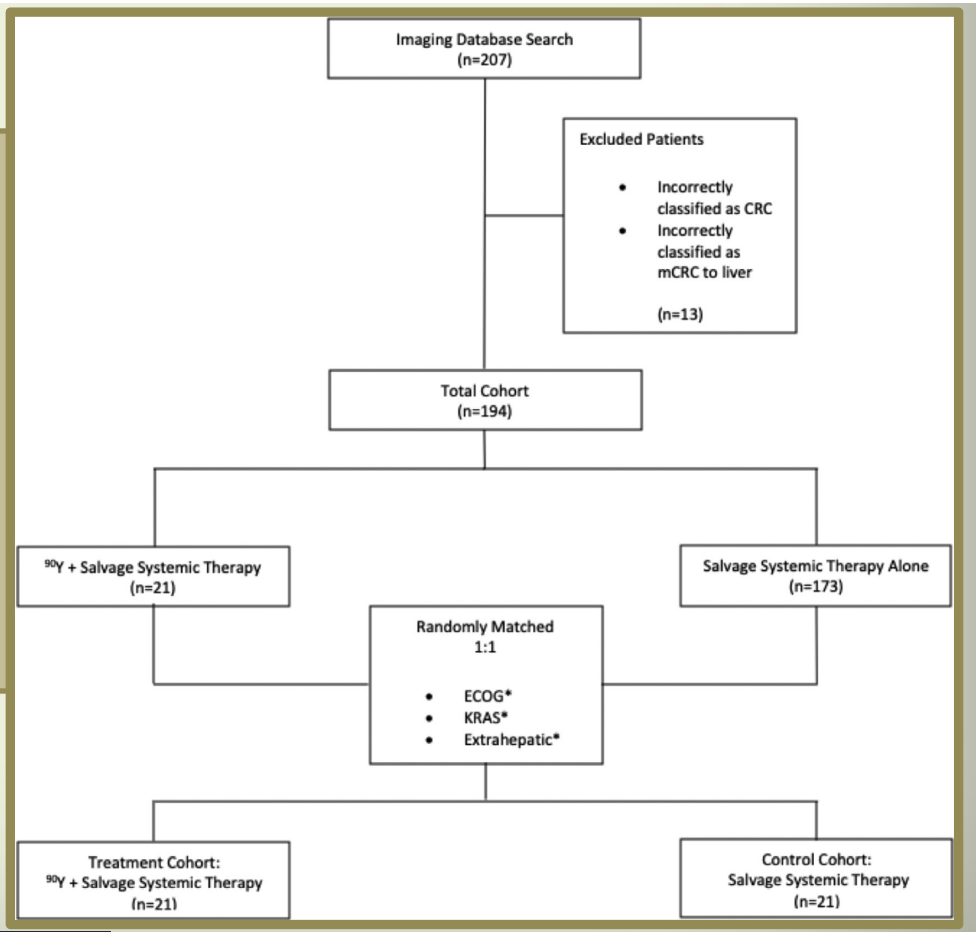
- Retrospective, matched-pair study
- Radioembolization plus systemic therapy (n=21)
- Matched cohort received systemic chemotherapy (n=73)
- Salvage setting: progression on at least two regimens of systemic chemotherapy.

Haber et al, Acad Radiol, 2021

Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study

Study Design

- Patients were matched 1:1 based on:
  - ECOG Performance Status
  - Extrahepatic disease
  - KRAS mutation



Haber et al, Acad Radiol, 2021

Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study

	TARE + Salvage systemic therapy	Salvage systemic therapy
Sex		
Male	14	14
Female	7	7
Age±	62	59
ECOG*±		
0	10	10
1	9	9
2	2	2
KRAS mutation present*	9	9
Extrahepatic disease present*	9	9
^{90}Y Microsphere Particle		
Glass	3	
Resin	17	
Combination	1	
Treatment approach		
Unilobar	4	
Sequential bilobar	17	

	TARE + Salvage systemic therapy	Salvage systemic therapy
FOLFOX±	17	12
FOLFIRI±	13	10
XELOX±	13	12
Bevacizumab	21	21
Regorafenib	4	4
Trifluridine/tipiracil	0	3
Rituximab	1	1
Nivolumab	1	1
Durvalumab	0	1
Monalizumab	0	1
Dabrafenib	0	1
Vemurafenib	0	1
Trametinib	0	1
Aflibercept	0	1

Haber et al, Acad Radiol, 2021

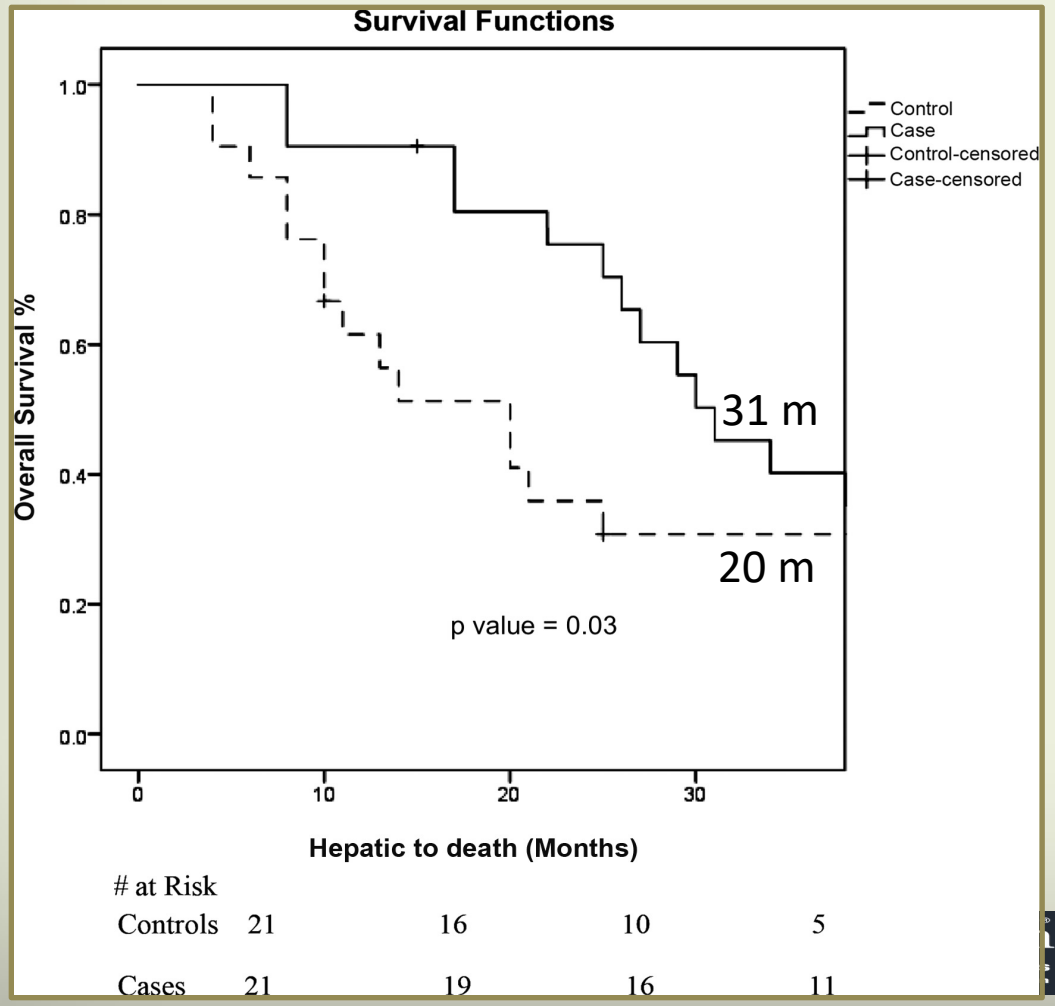
Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study

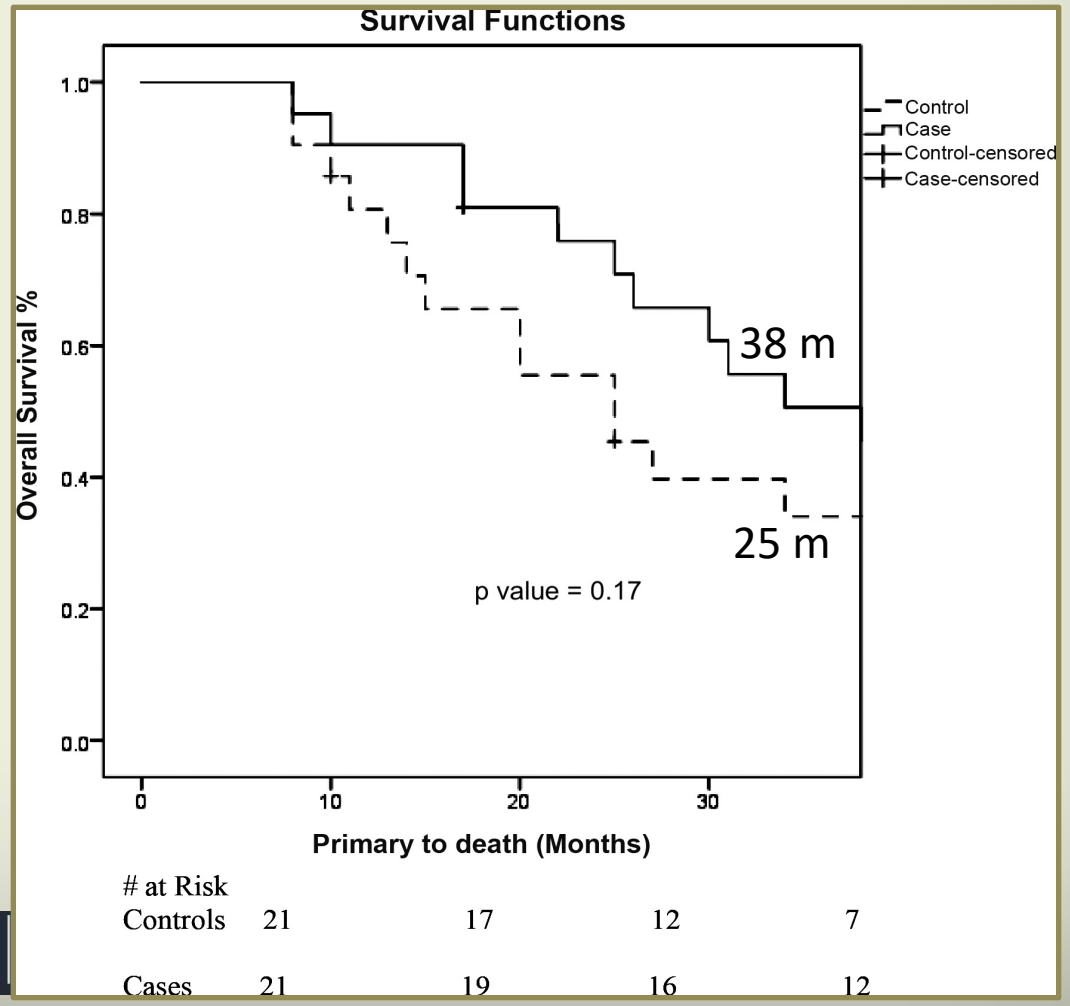
	TARE + Salvage systemic therapy	Salvage systemic therapy
Sex		
Male	14	14
Female	7	7
Age±	62	59
ECOG*±		
0	10	10
1	9	9
2	2	2
KRAS mutation present*	9	9
Extrahepatic disease present*	9	9
^{90}Y Microsphere Particle		
Glass	3	
Resin	17	
Combination	1	
Treatment approach		
Unilobar	4	
Sequential bilobar	17	

	TARE + Salvage systemic therapy	Salvage systemic therapy
FOLFOX±	17	12
FOLFIRI±	13	10
XELOX±	13	12
Bevacizumab	21	21
Regorafenib	4	4
Trifluridine/tipiracil	0	3
Rituximab	1	1
Nivolumab	1	1
Durvalumab	0	1
Monalizumab	0	1
Dabrafenib	0	1
Vemurafenib	0	1
Trametinib	0	1
Aflibercept	0	1

Haber et al, Acad Radiol, 2021

Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study





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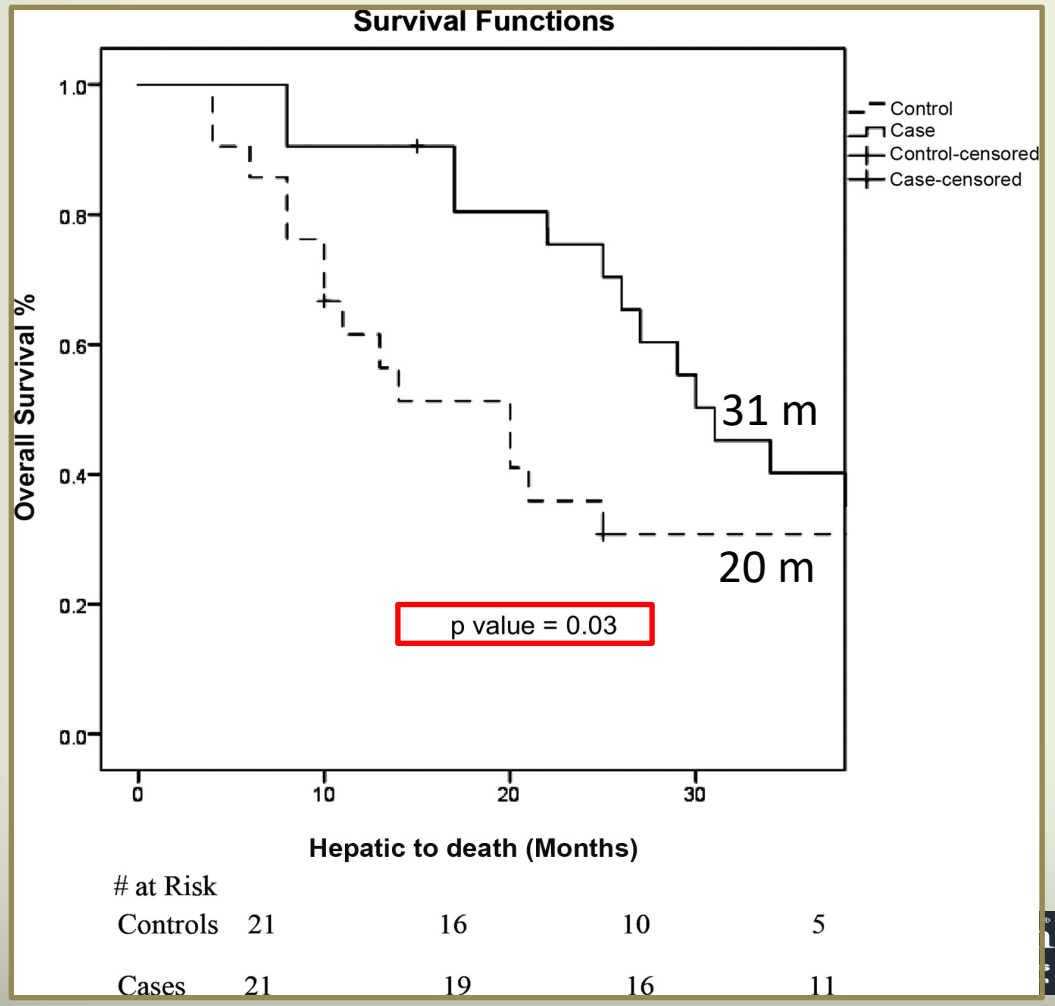
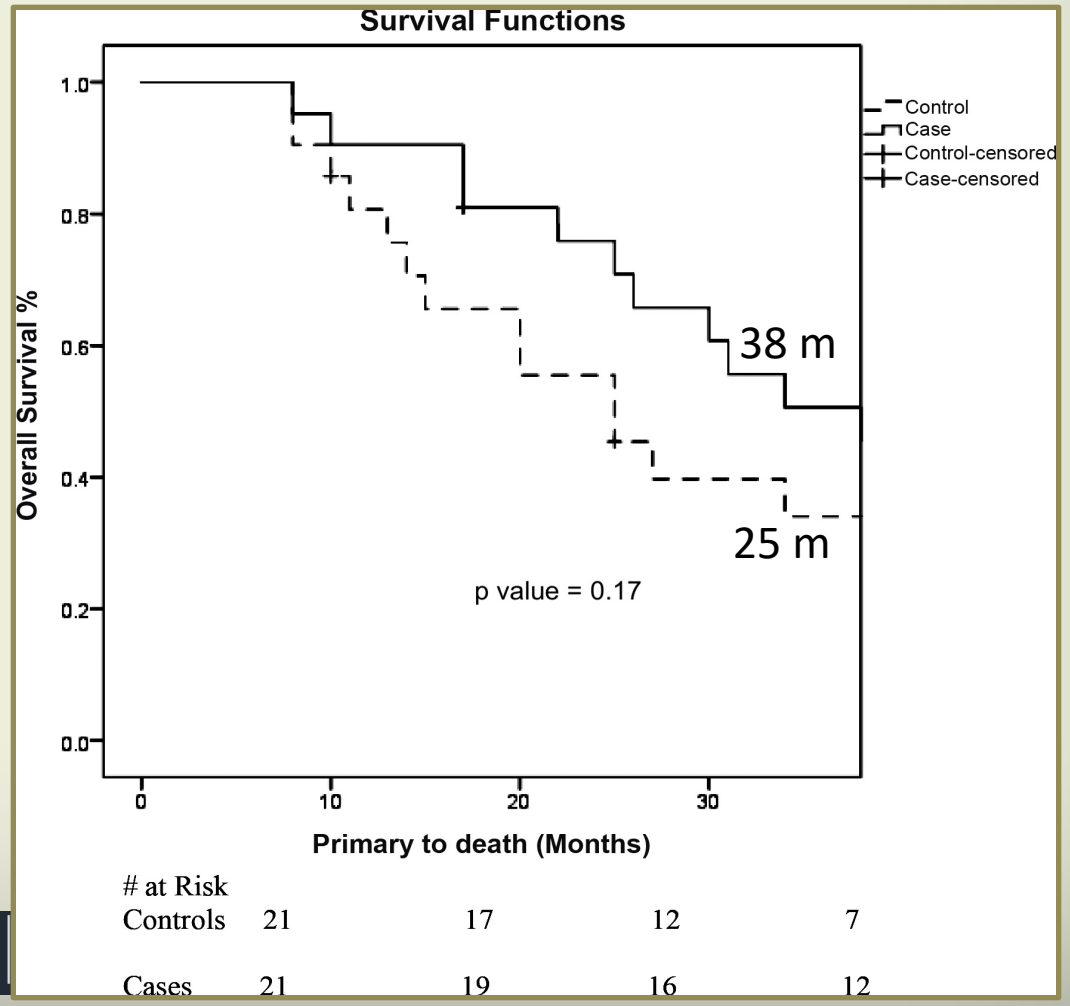




Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study

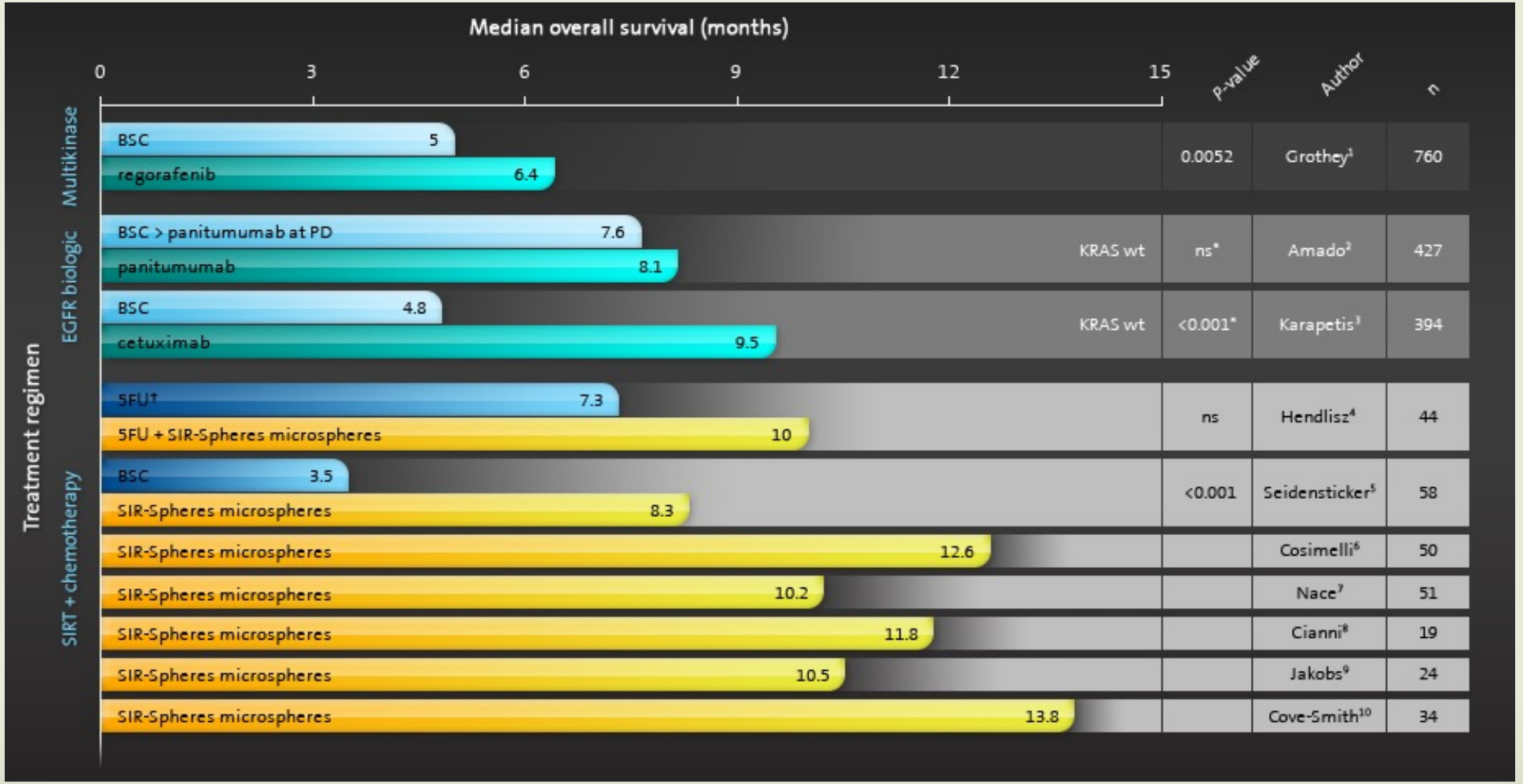
Conclusion:

- The addition of radioembolization to systemic therapy in patients with colorectal cancer metastatic to the liver may improve survival in the salvage setting.

Haber et al, Acad Radiol, 2021

Salvage therapy of CRC Liver Metastases

Salvage therapy of CRC Liver Metastases



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Salvage therapy of CRC Liver Metastases: Comparative or Prospective Studies

Author	N	Treatment	ORR, %	SD, %	‡TTP or †PFS, mo	Survival, mo
Hendlisz[1]	**44**	**SIR-Spheres* + 5-FU**	**10**	**76**	**5.5‡/4.5**	**10.0**
Level 1		**5-FU** (SIR-Spheres* at PD)	**0** (*P*=.22)	**35** (*P*=.001)	**2.1** (HR: 0.38‡/0.51, *P*=.003‡/.03)	**7.3**
Seidensticker[2]	**29**	**SIR-Spheres***	**41**	**17**	**5.5†**	**8.3**
Level 3	**29**	**BSC (matched-pairs)**	NR	NR	**2.1†**	**3.5** (HR: 0.26, *P*<.001)
Cosimelli[3] Level 2	**50**	**SIR-Spheres***	**24**	**24**	**3.7†**	**12.6**
Systemic chemotherapy Salvage Options						
Grothey[4]	**505**	**Regorafenib**	**1**	**41**	**1.9**	**6.4**
Level 1	**255**	**BSC**	**0.4**	**15**	**1.7** (HR:0.49, *P*<0.001)	**5** (HR: 0.77, *P*.0052)
Mayer[5]	**534**	**TAS-102 (Lonsurf)**	**1.6**	**44**	**2.0**	**7.1**
Level 1	**266**	**BSC**	**0.4**	**16**	**1.7** (HR: 0.48, *P*<0.001)	**5.3** (HR: 0.77, *P*.0052)

*SIR-Spheres Y-90 resin microspheres cross-over was allowed upon progression; †PFS; ‡TTP liver; §retrospective data. PD, progressive disease; SD, stable disease; BSC, Best supportive care

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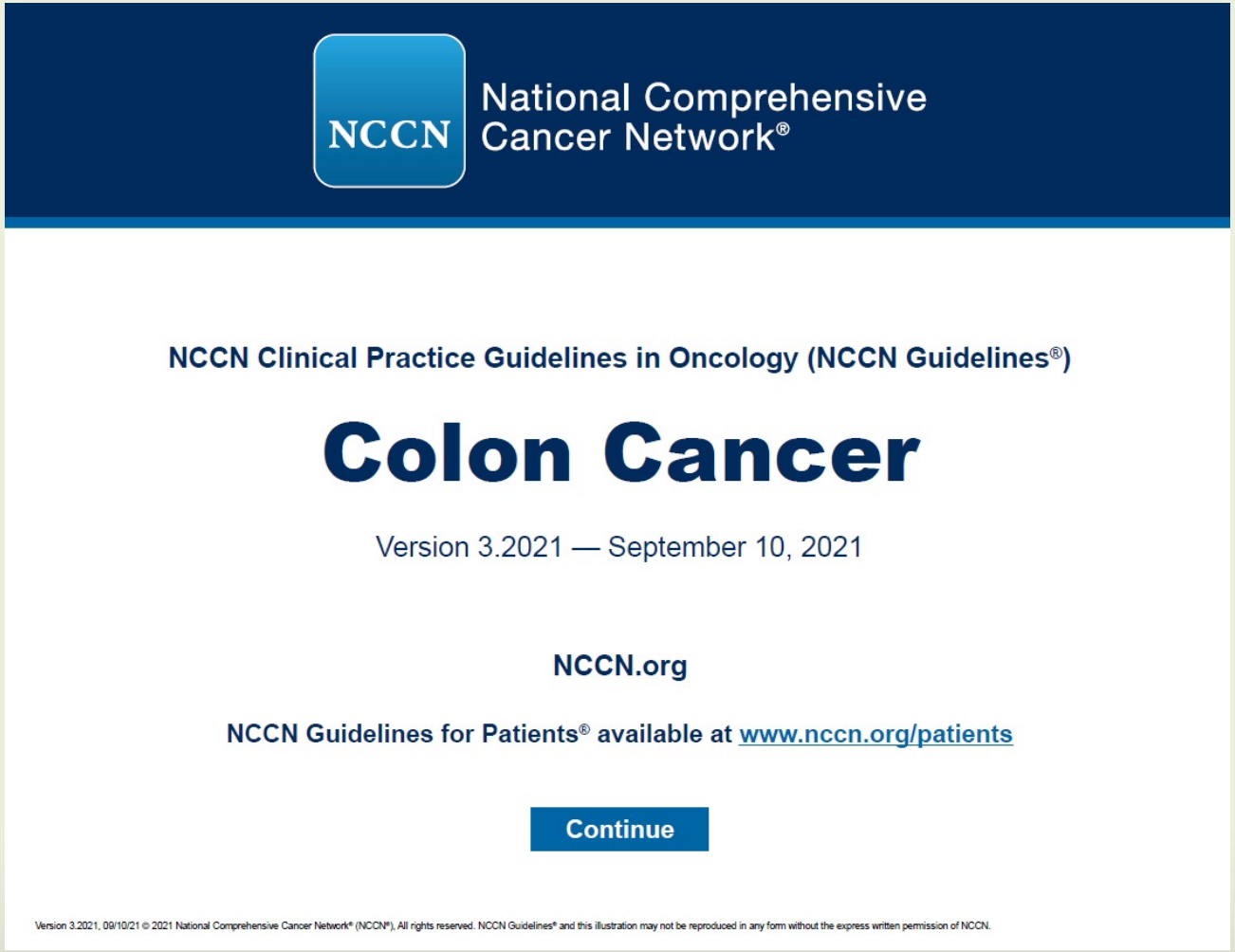
Background



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PRINCIPLES OF SURGERY
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[6]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[7]
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.[8-11] Having a plan for a debulking resection (less than an R0 resection) is not recommended.[7]
- Patients with resectable metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.[12]
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization,[13] staged liver resection,[14] or yttrium-90 radioembolization[15] can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.[16]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[17-20]
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Evaluation for Conversion to Resectable or Ablatable Disease

- Re-evaluation for resection and ablation should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[26-29]
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.[30]
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[31]

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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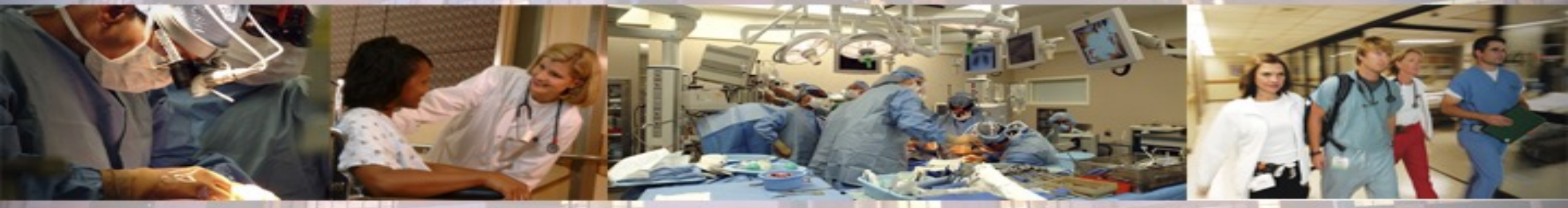
Ablation



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McGovern Medical School

Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

- CLOCC Trial
- Randomized phase II trial
- 119 patients with unresectable colorectal liver metastases (n<10 and no extrahepatic disease)
- Systemic treatment alone (n=59).
- Systemic treatment plus aggressive local treatment by radiofrequency ablation +/- resection (n=60).
- Median follow up was 9.7 years

Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

CLOCC trial

Level 1 evidence

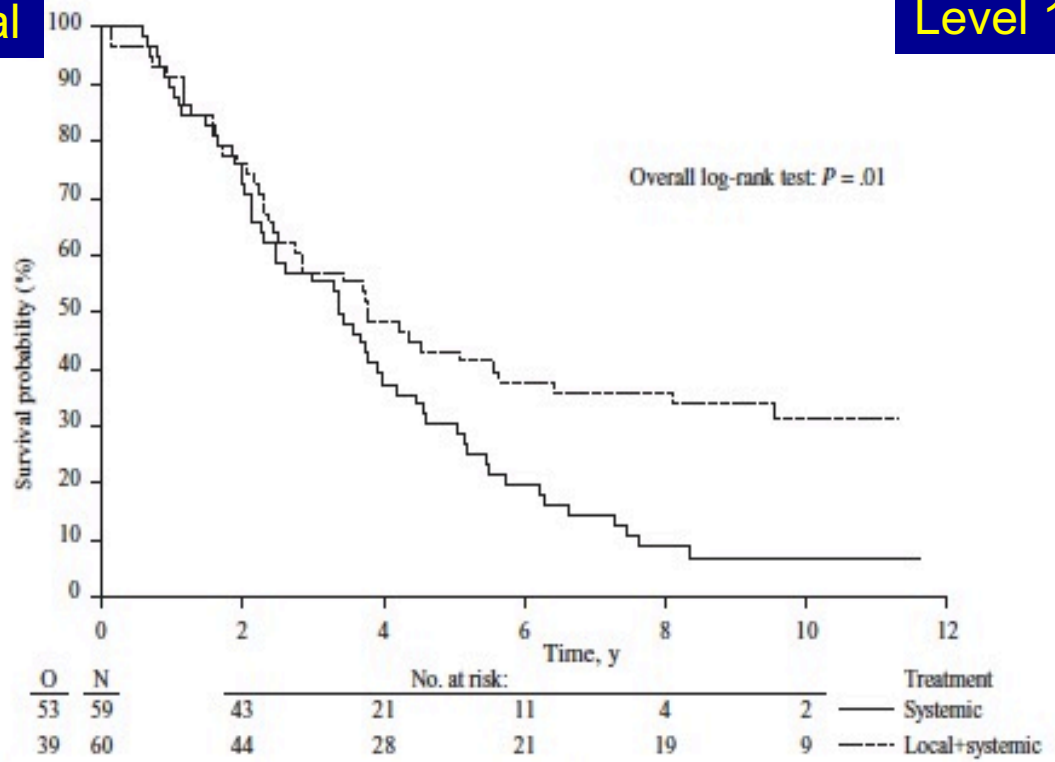

Figure 2. Kaplan-Meier curves for overall survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .01). P value was calculated using a two-sided log-rank test.

Courtesy of Professor Costantinos Sofocleous

SURVIVAL	Median Months	3	5	8 years	P value
Folfox	40.5	55.2	30.3%	8.9%	0.01
Folfox+RFA	45.6	56.9	43.1.%	35.9%	

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- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[7]
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- Patients with resectable metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.[12]
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- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.[16]

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- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[17-20]
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Evaluation for Conversion to Resectable or Ablatable Disease

- Re-evaluation for resection and ablation should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[26-29]
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.[30]
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[31]

Note: All recommendations are category 2A unless otherwise indicated.
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References

NCCN Guidelines

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

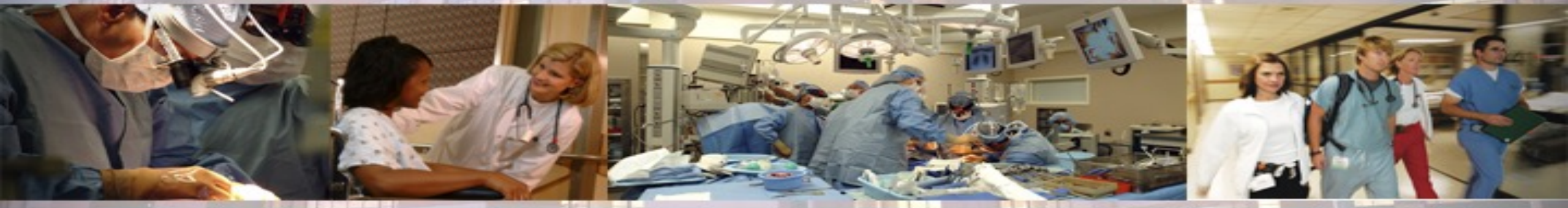
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Thank you

Twitter: @ahmed_kamel_ir
Email: ahmed.k.abdelaal@uth.tmc.edu



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