Associations between patterns of neuroendocrine liver metastatic burden and outcomes after embolization, CapTem and PRRT

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Introduction

Post hoc analysis of NETTER-1 suggested that tumor size but not tumor burden predicted response and PFS after PRRT, whereas a multicenter analysis of LDT found that tumor burden was predictive. We analyzed imaging datasets from two completed multicenter prospective clinical trials, ECOG-ACRIN E2211 and RETNET, and an institutional cohort of patients treated with PRRT to investigate whether morphologic subgroups of NET liver metastatic disease based on lesion size, lesion number or tumor burden might be more optimally treated with embolization, CapTem chemotherapy or PRRT.

Materials & Methods

Data Collection

Images from all patients with liver metastases from the Capecitabine + Temozolomide (CapTem) arm of E2211 (N=67) were reviewed and categorized by liver metastasis number, maximum lesion diameter, and tumor burden as a fraction of liver volume (N=67). Diameters of up to five index metastases were measured before and after therapy to assess response at the lesion level. A similar number of cases from the RETNET trial imaging archive (N=76) and from an institutional cohort of patients treated with PRRT (N=77) were analyzed.

Statistical Analysis

Morphologic categories were correlated with RECIST 1.1 response and PFS. Descriptive and graphical analyses were followed by multivariable modeling to test treatment by stratum interaction. Patient-level random intercepts were used to account for correlation between lesions from the same individual.

1. Sunnybrook Cancer Center
2. Abramson Cancer Center
3. MD Anderson Cancer Center
4. Moffitt Cancer Center
5. Hospital Italiano, BA, AR
6. UCSF
7. Fox Chase Cancer Center
8. Yale Cancer Center

Results

Treated Populations

ECOG-ACRIN 2211

EA2211 was a randomized phase II trial comparing temozolomide versus capecitabine/temozolomide in patients with locally unresectable or metastatic G1-2 pancreatic NETs. Key eligibility criteria included progression within the preceding 12 months. 72 patients were randomized to the CapTem. Among these, 67 patients had liver metastases measurable for response.

RETNET

RETNET was a randomized trial comparing bland and chemoembolization for well-differentiated liver-dominant neuroendocrine tumors of any grade or histologic origin that were symptomatic or progressive on somatostatin analog therapy or that presented with a liver tumor burden exceeding 25% of the liver volume. Embolizations were performed with a doxorubicin-based lipiodol emulsion and/or microspheres ranging between 40-500 microns. The imaging archive is blinded to embolization modality for central review. Images from five of the highest accruing sites were analyzed to provide a sample size similar to the CapTem cohort.

PRRT

Consecutive patients with measurable liver metastases were treated with PRRT at a single institution between August 2018 and September 2020. Patients had progressive, Dotatate-avid tumors of any histologic origin. Prescribed treatment was four 200 mCi administrations of Lutathera, with 78% receiving all four doses, 9% three dose, 8% two doses, and 5% a single dose.

Table 1 compares the baseline data for the three cohorts.

Table 1: Baseline Characteristics

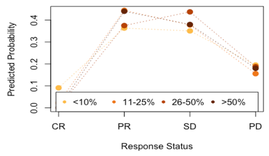
	CapTem	Embolization	PRRT
N	67	77	76
Mean age, years (SD)	61 +/-11	61 +/- 11	64 +/- 10
Gender M/F, %	56%/46%	52%/48%	54%/46%
Primary #/%			
Pancreas	67 (100%)	49 (64%)	21 (28%)
Bowel	-	20 (26)	39 (51%)
Lung	-	1 (1%)	6 (8%)
Other/Unknown	-	7 (9%)	10 (13%)
Grade 1/2/3	51%/49%/0	40%/55%/1%	35%/52%/17%
Race			
White	86%	80%	80%
Black	8%	9%	16%4%
Asian	6%	1%	
ECOG Performance Status 0/1/2	46%/54%/0%	69%/28%/3%	36%/51%/13%
Extrahepatic Disease	-	46 (60%)	72 (95%)
Lymph nodes	47%	34 (44%)	66 (87%)
Osseus	12%	12 (16%)	53 (70%)
Pulmonary	12%	3 (4%)	9 (8%)
Peritoneum	10%	11 (14%)	28 (37%)
Prior Therapy			
SSA	63%	63%	95%
Surgery	54%	33%	63%

KEY RESULT #1: There are no statistically significant differences in ORR or PFS by tumor burden, number, or largest lesion size for any treatment.

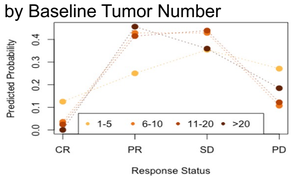
Table 2: ORR and Median PFS by Tumor Burden Categorization for each Modality and for the Entire Population

	CapTem		Embolization		PRRT		ALL	
N	67		77		76		220	
	ORR	PFS	ORR	PFS	ORR	PFS	ORR	PFS
Liver Tumor Burden								
<10%	.27	23.7	.83	21.4	18	16.8	.46	23.0
11-25%	.33	10.5	.56	24.0	16	15.8	.47	15.8
26-50%	.15	17.5	.64	15.0	21	29.0	.38	21.9
>50%	.22	17.7	.55	18.0	21	21.6	.44	18.0
# Liver Metastases								
1-5	.28	23.7	.81	21.2	.17	18.6	.38	22.2
6-10	.20	28.6	.70	19.3	.50	21.9	.46	26.9
11-20	0	20.3	.67	24.0	.33	24.9	.44	24.0
>20	.30	11.2	.59	17.0	.44	21.2	.46	15.8
Diameter of Largest Liver Metastasis								
< 3 cm	.41	28.2	.65	21.0	.45	24.0	.50	22.2
5. cm	.28	12.1	.78	19.3	.38	15.8	.49	18.9
> 5 cm	.16	16.6	.57	17.7	.27	14.0	.35	16.6

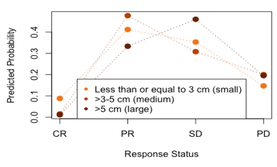
Probability of RECIST Response Category by Baseline Tumor Burden

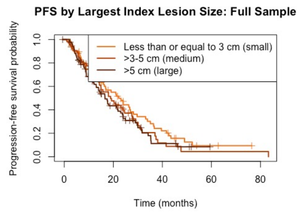


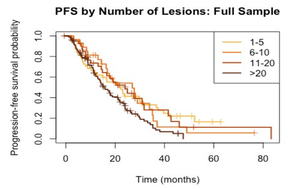
Probability of RECIST Response Category by Baseline Tumor Number

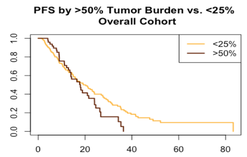


Probability of RECIST Response Category by Baseline Largest Tumor Diameter



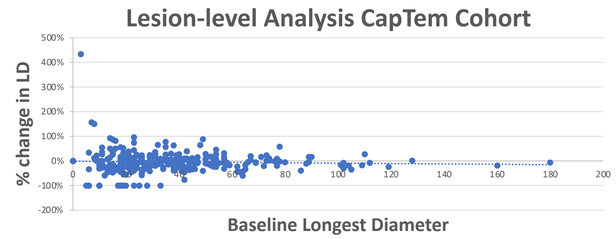


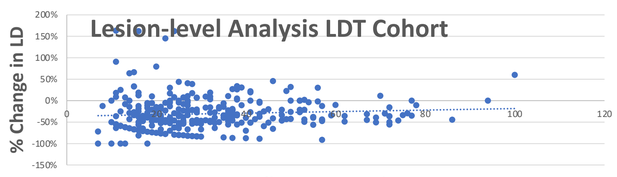


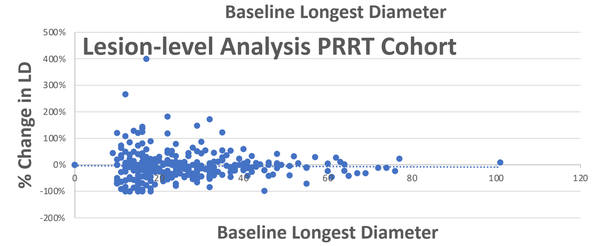


KKEY RESULT #2: There is no correlation between ORR and lesion size for any treatment

Figure 3: Scatterplot of % change in tumor size versus baseline longest diameter of individual metastases for CapTem cohort, LDT cohort, and PRRT cohort







Conclusions

- No morphologic features of liver metastases were identified that predicted treatment outcome within a particular modality nor to favor one over another when triaging patients.
- Diameter of individual metastases did not correlate with response rate for any modality.

References

[1] Fang JM, Shi J. A clinicopathologic and molecular update of pancreatic neuroendocrine neoplasms with a focus on the new World Health Organization classification. Arch Pathol Lab Med. 2019;143:1317-1326.

[2] Wang R, Zheng-Pywell R, Chen HA, Bibb JA, Chen H, Rose JB. Management of Gastrointestinal Neuroendocrine Tumors. Clin Med Insights Endocrinol Diabetes. 2019 Oct 24;12:1179551419884058. doi: 10.1177/1179551419884058. PMID: 31695546; PMCID: PMC6820165.

[3] Botling J, Lamarca A, Bajic D, Norlén O, Lönngren V, Kjaer J, Eriksson B, Welin S, Hellman P, Rindi G, Skogseid B, Crona J. High-Grade Progression Confers Poor Survival in Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2020;110(11-12):891-898. doi: 10.1159/000504392. Epub 2019 Oct 29. PMID: 31658459.