Liver-directed therapy for metastatic neuroendocrine carcinoma and grade 3 well-differentiated neuroendocrine tumors

A. Zhou[1], A. Paciorek[2], E. Bergsland[3], S. Piawah[3], W. Kidder[3], N. Joseph[3], N. Fidelman[1]

[1]Department of Radiology and Biomedical Imaging, University of California, San Francisco; [2]Department of Epidemiology and Biostatistics, University of California, San Francisco; [3]UCSF Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco.

Introduction

Neuroendocrine carcinoma (NEC) and grade 3 neuroendocrine tumors (NET) are aggressive, often unresectable malignancies with poor prognosis despite systemic therapies. Liver-directed therapy (LDT) has been shown to provide effective disease control in studies including primarily patients with low-grade well-differentiated NET. Outcomes **of LDT** for high-grade NET and NEC are not well-studied.

Methods

- Single center retrospective cohort study of patients with Grade 3 NET or NEC who underwent LDT from 2015 to 2024
- Radiologic response evaluated using mRECIST criteria
- Progression and survival analyses performed using Andersen-Gill and Cox proportional hazards regression, respectively
  - Local progression-free survival (PFS) ended with radiologic progression of the treated tumor or death
  - Hepatic PFS ended with radiologic progression of any hepatic tumor or death
  - Overall PFS ended with radiologic progression of any disease or death
  - Overall survival ended with death

Table 1. Patient Characteristics

	Grade 3 NET	NEC
No. of patients	20	6
Median age (years)	59.3	60.5
Female	60%	33.3%
No. of procedures:	30	13
Y90 Radioembolization	9	8
Chemoembolization	12	4
Bland embolization	9	1
Median Ki-67 index (range)	28.5 (21-65)	55 (32-90)
Mean largest tumor diameter (mm)	66	68
Primary tumor site:		
Pancreas	35%	17%
Gastrointestinal	20%	33%
Other (renal, unknown)	45%	50%
Bilobar hepatic metastases	93%	92%
Extrahepatic metastases at time of LDT	90%	46%

Results

Table 2. Radiologic response of treated tumors following LDT (%).

	Grade 3 NET	NEC
Complete Response	6.7	0.0
Partial Response	53.3	30.8
Stable Disease	26.7	38.4
Progressive Disease	13.3	30.8

Table 3. Progression-free and overall survival after LDT (months).

	Grade 3 NET	NEC	P-value
Local PFS	5.1 (2.11-7.70)	2.7 (1.94-7.27)	0.199
Hepatic PFS	4.8 (2.24-7.07)	1.9 (1.22-2.73)	0.062
Overall PFS	3.8 (0.99-6.09)	1.9 (1.22-2.73)	0.188
Overall Survival	14.6 (NC)	5.9 (NC)	0.384

Figure 1. Univariate analysis of local progression-free survival after LDT.

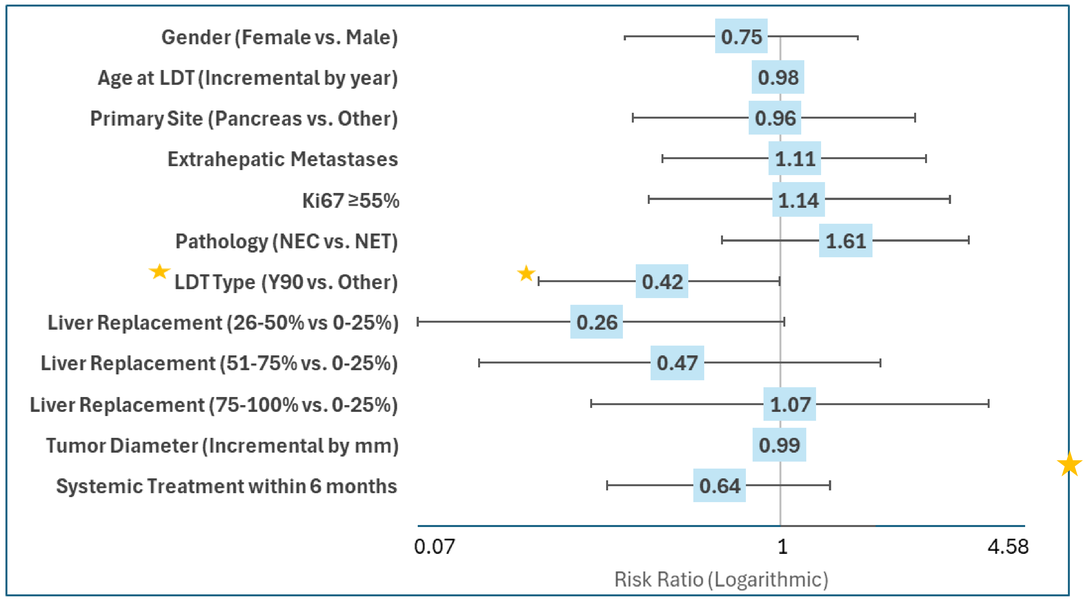

Table 4. Short and long-term complication rates following LDT for grade 3 NET and NEC (%).

	All	Y90	Bland/Chemo-embolization
Short-term (within 30 days)	*n = 43 procedures*	*n = 17 procedures*	*n = 26 procedures*
Post-embolization syndrome	27.9	11.8	38.5
Grade 3 Hyponatremia	4.6	0	7.7
Hepatic infarct	18.6	11.8	23.1
Hepatic abscess	0	0	0
Biloma	4.7	0	7.7
Carcinoid crisis	2.3	0	3.9
Clavien-Dindo grade ≥2	2.3	0	3.8
ICU admission	0	0	0
Total	32.6	11.8	46.2
	All	**NEC**	**Grade 3 NET**
Long-term (after 30 days)	*n = 26 patients*	*n= 6 patients*	*n = 20 patients*
Heart failure	0	0	0
Chronic hepato-toxicity	11.5	0	15.0
Portal hypertension	7.7	0	10.0
Total	15.4	0	20.0

★ **Y90 radioembolization was associated with reduced risk of local progression or death** after LDT on univariate (HR 0.42, p=0.048) and multivariate (HR 0.32, p=0.001) analyses when compared to bland or chemoembolization. However, it did not show reduced risk of death alone (HR 0.76, p=0.584).

Conclusion

- Liver-directed therapies induce local response in approximately 60% of grade 3 NET patients with treated tumor median PFS of 5.1 months.
- While not reaching significance in this small cohort study, outcomes in NEC patients appear worse, with approximately 31% local response rate and treated tumor median PFS of 2.7 months.
- As a modality, Y90 radioembolization is associated with significantly reduced risk of progression or death combined, when compared to bland and chemoembolization.

Future Directions

- Continued patient accrual, multicenter collaboration for larger sample sizes
- Subgroup and multivariate analyses further examining Y90 characteristics, distribution of disease, Ki-67 index gradation, genetics, combination or sequencing of therapy, etc.

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