Neuroendocrine Tumor

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Case Presentation

68 year-old female presented to the hospital in August 2018 due to sharp, cramping epigastric pain radiating to the back.

Underwent CT abdomen/pelvis that showed bulky retroperitoneal lymph nodes and hepatic dome lesions concerning for metastatic disease.

She underwent a CT guided biopsy of the retroperitoneum that showed a neuroendocrine tumor, most likely from GI tract (CK8/18, pan-keratin [AE1/AE3/PCK26], synaptophysin, chromogranin, CDX2, and villin with a Ki-67 of approximately 1-2%. Ki-67 positive 1-2%.

October 2018, she underwent a exploratory laparotomy, small bowel and ileocolic resection and wedge liver biopsy. Pathology showed a well differentiated neuroendocrine tumor, KI-67 5%. NM octreoscan Feb 2019 showed positive uptake.

Medical History

- **Past Medical History:** Gastritis, H. pylori
- **Past Surgical History:** cholecystectomy, exploratory laparaotomy, small bowel and ileocolic resection and liver biopsy.
- **Family History:** No familial cancer history
- **Social History:** No tobacco, ethanol or drug usage

Review of Systems

- Constitutional: negative
- HENT: negative
- Cardiovascular: negative
- Respiratory: negative
- Endocrine: negative
- Hematologic/lymphatic: negative
- Skin: negative
- Musculoskeletal: negative
- Gastrointestinal: + abdominal pain, nausea and vomiting
- Genitourinary: negative
- Neurological: negative
- Psychiatric: negative

Physical Exam

- Vitals: T 36.4*C, BP: 146/69, P: 885, R: 14, SpO2 98% RA

Constitutional: Obese, well-developed female patient

HEENT: NC/AT, PERRLA, EOMI, nares patent without erythema, oropharynx without erythema or lesions. Good dentition.

Neck: Supple

Cardiac: RRR, normal S1 and S2, no M/R/G

Pulmonary: No accessory muscle usage, lungs resonant to percussion and clear to auscultation, no wheezes/rales or rhonchi.

Abdomen: BS+, soft, non-distended and tender to palpation in the epigastric area.

Laboratory Studies

CBC with differential

Status: **Final result** Visible to patient: **Yes (not seen)**

0 Result Notes

Component	Ref Range & Units	5 yr ago
WBC	3.5 - 10.0 1000/uL	7.5
ANC (automated diff)	2.00 - 7.15 1000/uL	5.20
Red blood cell count	4.00 - 5.50 Million/uL	4.65
Hemoglobin	11.4 - 15.4 g/dL	12.9
Hematocrit	32.8 - 45.6 %	39.7
MCV	80.0 - 95.0 fL	85.4
MCH	26.0 - 34.0 pg	27.7
MCHC	32.0 - 35.0 g/dL	32.5
Red cell distribution width	11.5 - 14.5 %	13.8
Platelets	150 - 450 1000/uL	319
MPV	9.4 - 12.4 fL	10.7
Neutrophils	42.5 - 73.2 %	68.7
Immature granulocytes %	0.0 - 0.6 %	0.3
Lymphocytes	18.2 - 47.4 %	21.5
Monocytes	4.3 - 11.0 %	6.8
Eosinophils	0.0 - 3.0 %	2.0
Basophils	0.0 - 0.7 %	0.7
Neutrophils Abs	2.00 - 7.15 10*3/uL	5.16
Lymphocytes Abs	1.16 - 3.18 10*3/uL	1.61
Monocytes Abs	0.29 - 0.71 10*3/uL	0.51
Eosinophils Abs	0.03 - 0.27 1000/uL	0.15
Basophils Abs	0.01 - 0.05 10*3/uL	0.05

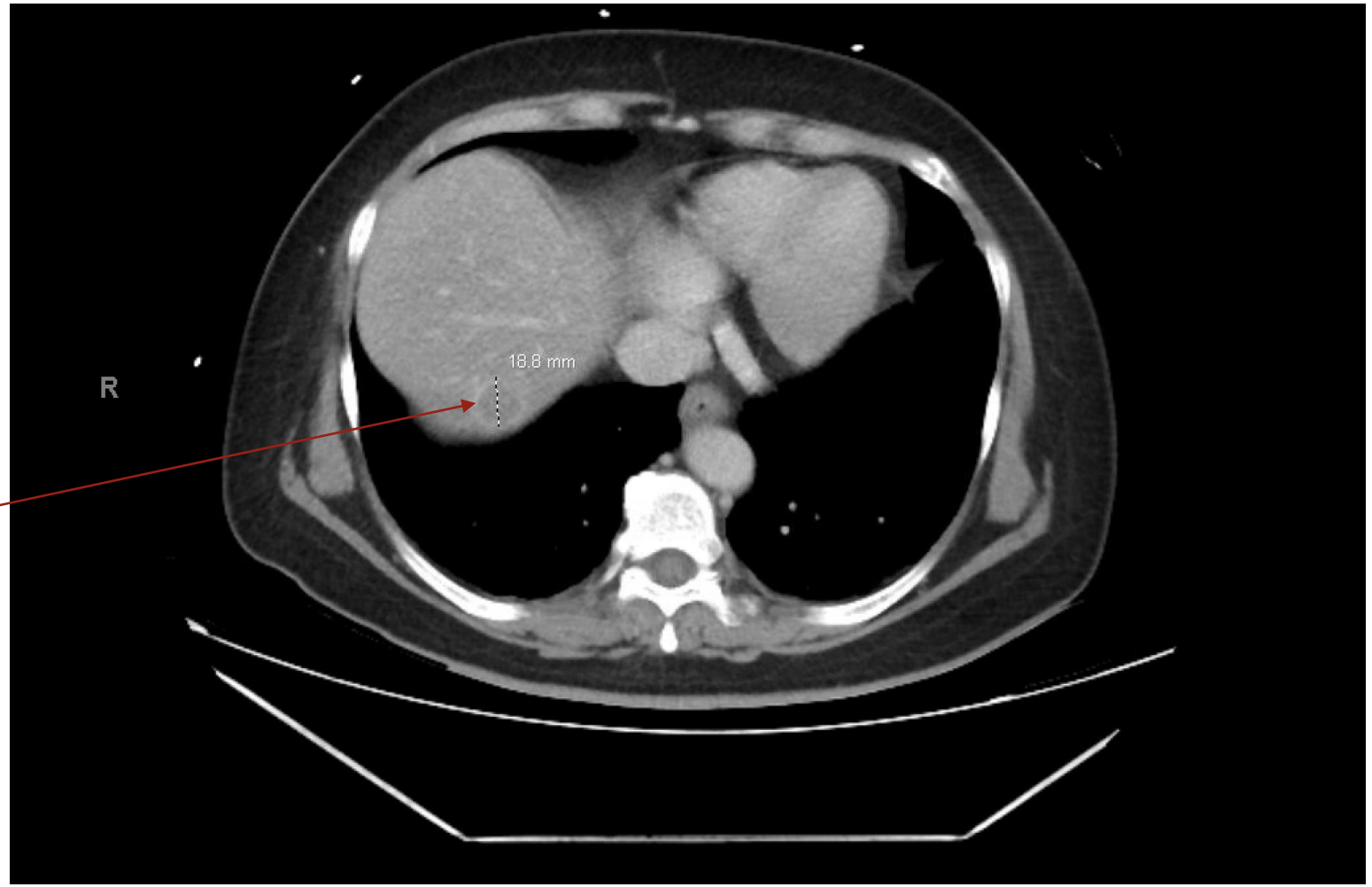
Lipase 135

Component	Ref Range & Units	5 yr ago
Glucose	70 - 99 mg/dL	94
Comment: Note: The reference range for glucose is for fasting subjects. Fasting is defined as no caloric intake for at least 8 hours. The reference range for a random glucose is less than or equal to 140 mg/dL.		
BUN	7 - 18 mg/dL	15
Sodium	136 - 145 mmol/L	139
Potassium	3.5 - 5.1 mmol/L	3.7
Chloride	98 - 107 mmol/L	107
CO2	21 - 32 mmol/L	26
Anion gap	5 - 15 mmol/L	6
Creatinine	0.51 - 0.95 mg/dL	0.67
Calcium	8.5 - 10.1 mg/dL	8.7
Alkaline phosphatase	45 - 117 Units/L	149 ^
Total protein	6.4 - 8.2 g/dL	7.8
Albumin	3.4 - 5.0 g/dL	3.7
ALT (SGPT)	13 - 56 Units/L	28
AST (SGOT)	13 - 37 Units/L	23
Bilirubin total	0.2 - 1.3 mg/dL	0.3
ESTIMATED GFR	mL/min/1.73 m2	94
Comment:		

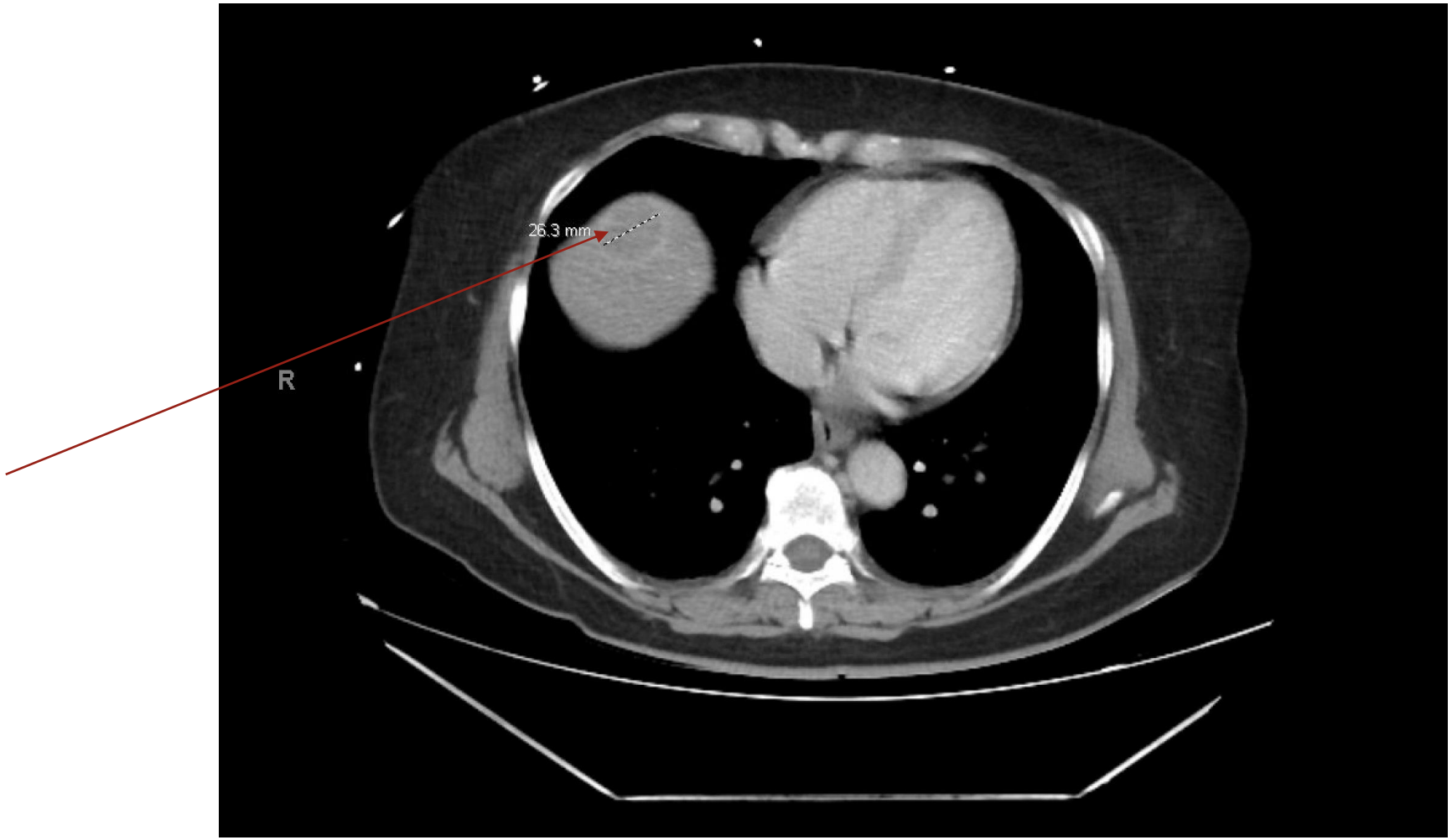
Imaging: CT abdomen/pelvis 08/2018

- CT abd/pelvis 08/2018: enlargement of bulky retroperitoneal lymph nodes and hepatic dome lesions concerning for metastatic lesions.
- The patient was initially started on octreotide weekly.
- CT abdomen/pelvis images on the following slides

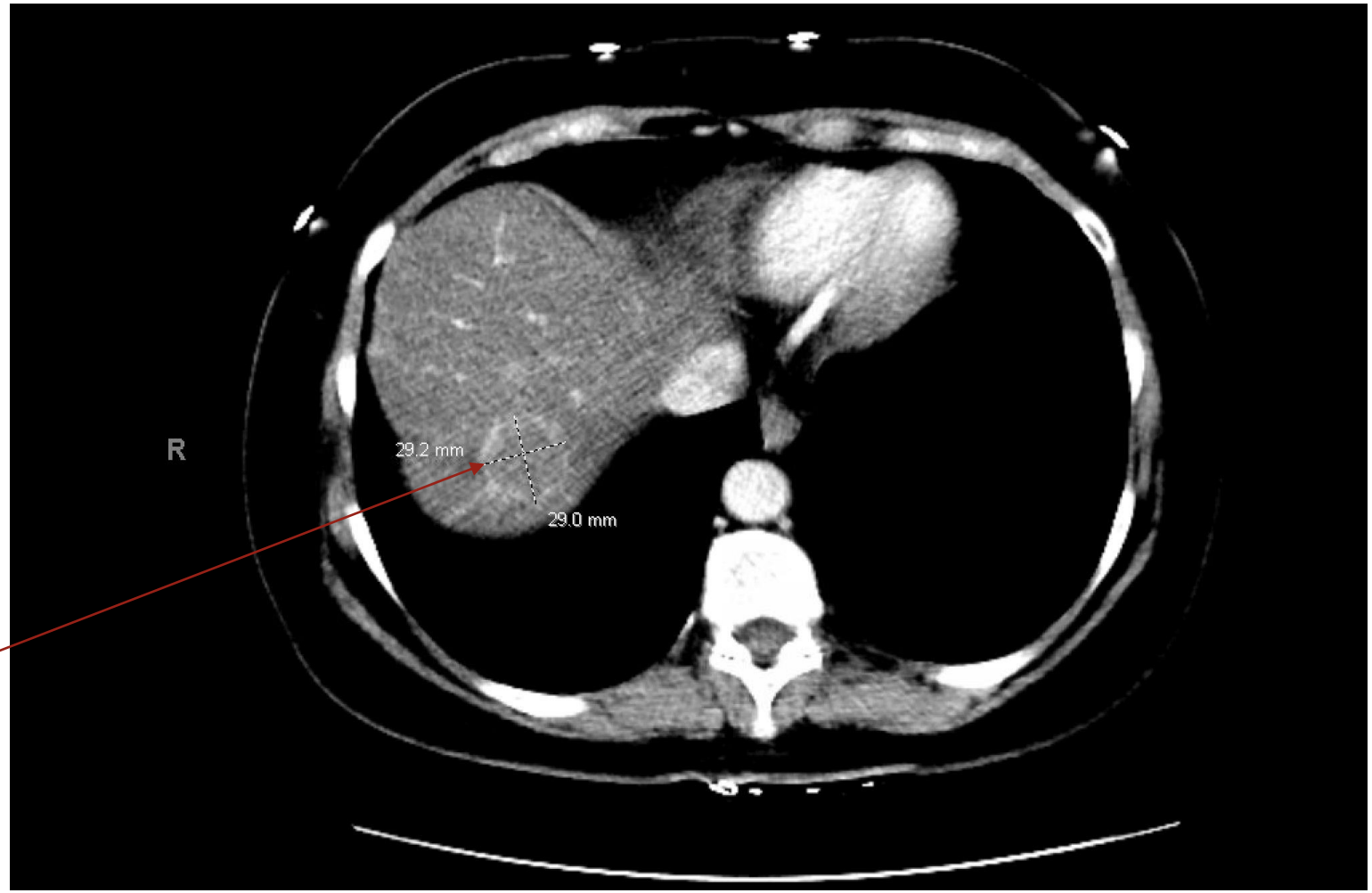
Imaging: CT abdomen/pelvis 08/2018



Imaging: CT abdomen/pelvis 08/2018



Recurrence of Disease – May 2019



Recurrence of Disease – May 2019 and September 2021

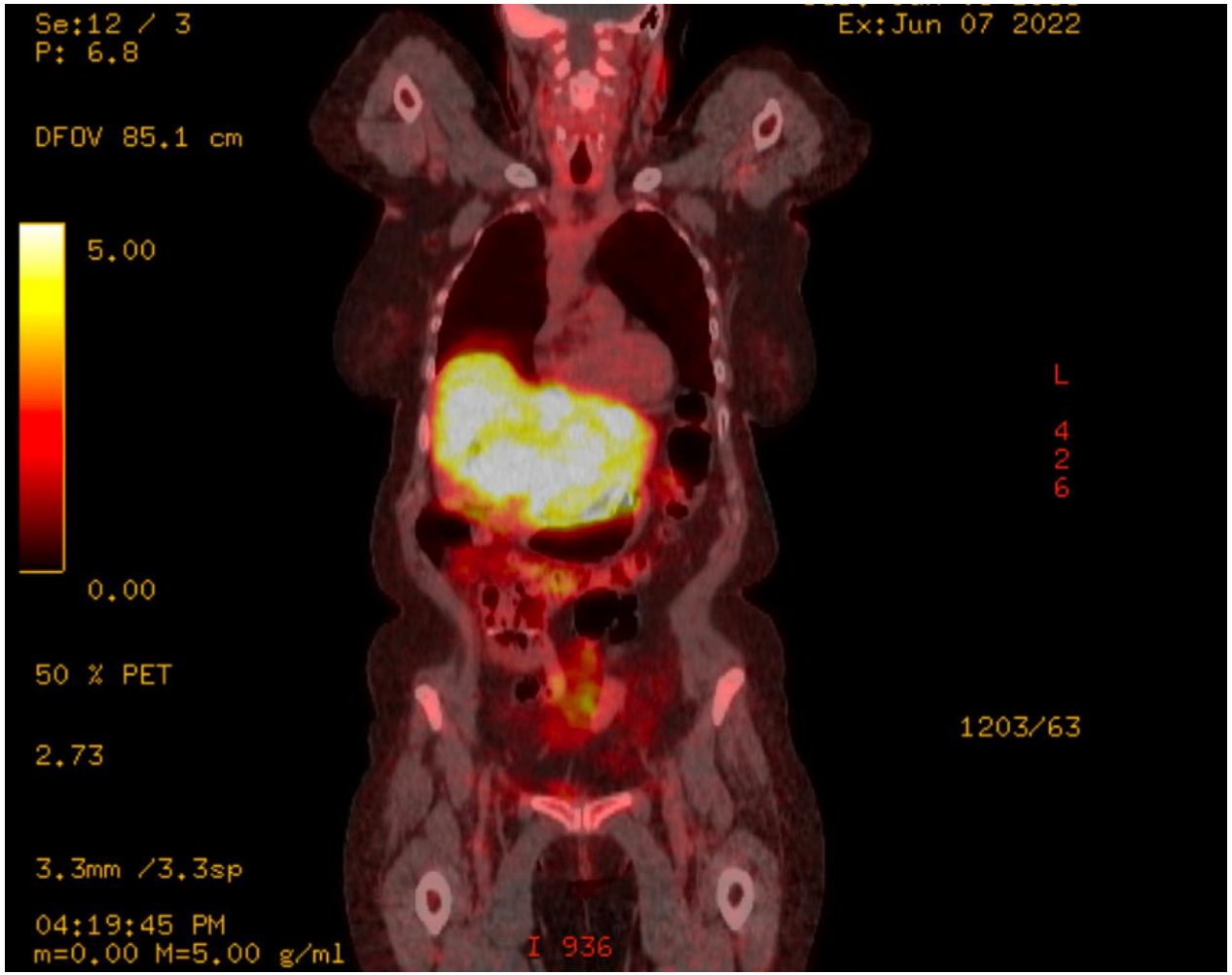
- She underwent Y-90 of the liver 06/2019 and cryoablation of the liver 08/2019.

- Subsequently, In September 2021, she was found to have progression of disease in the left lobe of the liver and was given Y-90 in December 2021.

Progression of Disease – PET Gallium Dotatate scan

- In June 2022, she underwent a restaging PET scan that showed somatostatin receptor avid disease and multiple liver lesions with multiple abdominal and retroperitoneal lymph nodes consistent with progression of disease.

Progression of Disease – PET Gallium Dotatate scan



Plan of Therapy

- Patient unfortunately had developed multifocal metastatic progression of disease that is unresectable. Patient met all eligible criteria to proceed with PRRT-^{177}Lu-Dotatate treatment.

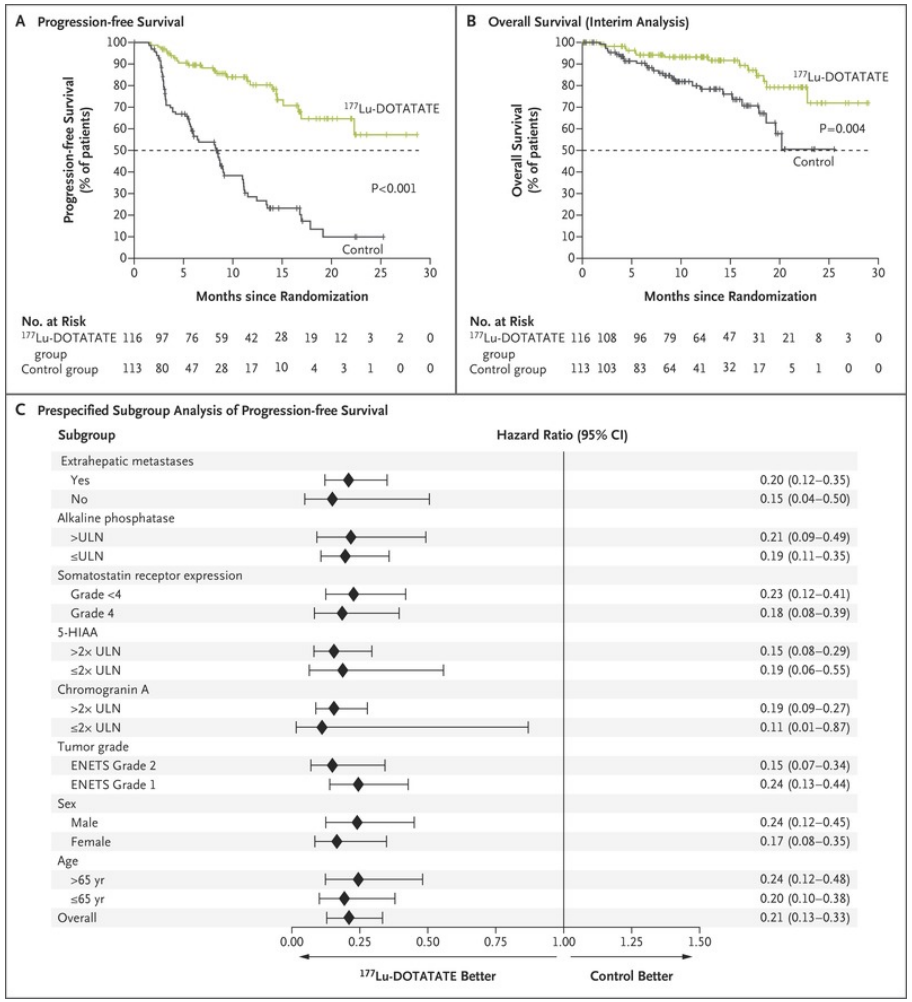
- Restaging scans CT chest/abdomen/pelvis 02/2016 had been re-ordered – progressive retroperitoneal adenopathy. Two dominant liver lesions decreased in size. Multiple small lesions scattered throughout the liver mostly on the left lobe of liver. Pulmonary nodules present.

- Patient had been lost to follow-up and has not received her lu-dotatate treatment.

Lutetium Lu 177 dotatate

- NETTER-1 Study
  - 229 patients received either Lu 177 dotatate 7.4 GBq every 8 weeks and octreotide long-acting repeatable (LAR) or octreotide LAR alone.
  - Primary endpoint was progressive-free survival (PFS)
  - Secondary endpoint was overall response rate (ORR), duration of response (DOR), overall survival (OS) and safety.
  - Patients in both arms could receive short acting octreotide but withheld within 24 hours of treatment.
  - Median duration of follow-up was 76.3 months.
  - Progression-free survival was not reached (95% CI, 18.4-NE), Hazard Ratio 0.21 (79% reduction in risk of progression or death) and Overall response rate 13%.

NEJM. Strosberg et al. 2017



NEJM. Strosberg et al. 2017

Table 4. Adverse Events (Safety Population).*

Event	^{177}Lu-Dotatate Group (N=111)		Control Group (N=110)		P Value†
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade
	number of patients (percent)				
Any adverse event	105 (95)	46 (41)	92 (84)	36 (33)	0.01
Gastrointestinal disorders					
Nausea	65 (59)	4 (4)	13 (12)	2 (2)	<0.001
Vomiting	52 (47)	8 (7)	11 (10)	1 (1)	<0.001
Abdominal pain	29 (26)	3 (3)	29 (26)	6 (5)	1.00
Diarrhea	32 (29)	3 (3)	21 (19)	2 (2)	0.11
Distension	14 (13)	0	15 (14)	0	0.84
General disorders					
Fatigue or asthenia	44 (40)	2 (2)	28 (25)	2 (2)	0.03
Edema peripheral	16 (14)	0	8 (7)	0	0.13
Blood disorders					
Thrombocytopenia	28 (25)	2 (2)	1 (1)	0	<0.001
Anemia	16 (14)	0	6 (5)	0	0.04
Lymphopenia	20 (18)	10 (9)	2 (2)	0	<0.001
Leukopenia	11 (10)	1 (1)	1 (1)	0	0.005
Neutropenia	6 (5)	1 (1)	1 (1)	0	0.12
Musculoskeletal disorders					
Musculoskeletal pain	32 (29)	2 (2)	22 (20)	1 (1)	0.16
Nutrition disorders					
Decreased appetite	20 (18)	0	9 (8)	3 (3)	0.04
Nervous system disorders					
Headache	18 (16)	0	5 (5)	0	0.007
Dizziness	12 (11)	0	6 (5)	0	0.22
Vascular disorders					
Flushing	14 (13)	1 (1)	10 (9)	0	0.52
Skin disorders					
Alopecia	12 (11)	0	2 (2)	0	0.01
Respiratory disorders					
Cough	12 (11)	0	6 (5)	0	0.22

* Shown are all adverse events that were reported in at least 10% of the patients in the ^{177}Lu-Dotatate group, with the exception of neutropenia, which was reported in less than 10% of the patients in the ^{177}Lu-Dotatate group. For the individual events, the system organ classes in the *Medical Dictionary for Regulatory Activities* (MedDRA) hierarchy are shown in bold and are followed by the MedDRA preferred terms (not bold). The safety population included all patients who underwent randomization and received at least one dose of trial treatment.

† P values were calculated with the use of Fisher's exact text.

NEJM. Strosberg et al. 2017

UPDATE: *Final overall survival in the phase 3 NETTER-1 study of lutetium-177-DOTATATE in patients with midgut neuroendocrine tumors.*

- Median OS 48 months in the Lu-DOTATATE arm vs. 36.3 months in the control arm.
- Clinically and statistically significant improvement in PFS as primary end-point (HR 0.18, $p<0.0001$).
- Median OS 11.7 months

ASCO Pubs. Strosberg et al. 2021