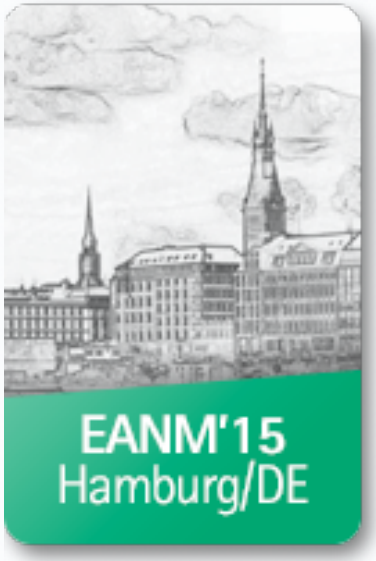

Long term survival analysis after i.a. ^{90}Y-DOTATATE PRRT, in patients with non-resectable, advance progressive liver dominant neuroendocrine neoplasms

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Introduction

- In GEP-NET patients with advanced, non-resectable extensive liver involvement standard PRRT could be not optimal approach;
- The hepatic artery embolisation or chemoembolisation (TAE/TACE) is rather historical and it is not used in current clinical practice;
- Aggressive approach to treat patients with extensive liver involvement increases OS;
- Local treatment strategies in those cases, including targeted radionuclide therapy (PRRT) could be potentially more effective, due to potential reduction of general side effect of systemic therapy.

Touzious JG et al. *Ann Surg* 2005;241776-785

Inclusion and exclusion criteria

- Inclusion criteria:
  - biopsy proven GEP-NET, not eligible for other type of standard therapy, or relapse after standard therapy approaches;
  - Hb > 8g/dl, PLT>80x10^3/ml, WBC > 2x10^6/ml; ACN > 1,5x10^6/ml;
  - GFR >30ml/min/1.73m^2;
  - Bilirubin <2mg/dl, ALAT i ASPAT, AP<5 ULN;
  - positive SRS, base on ^{99m}Tc Tektrotyd;
  - PS WHO/ECOG 0-2;
- Exclusion criteria:
  - pregnancy, lactation, poor bone marrow function and severe kidney impairment.

McStay M et al. *Radiology* 2005;237:718-726
Steward MJ et al. *Radiographics* 2008;28:1131-1145
Baum R et al. *Eur J Nucl Med Mol Imaging.* 2004;31:Supl.S238

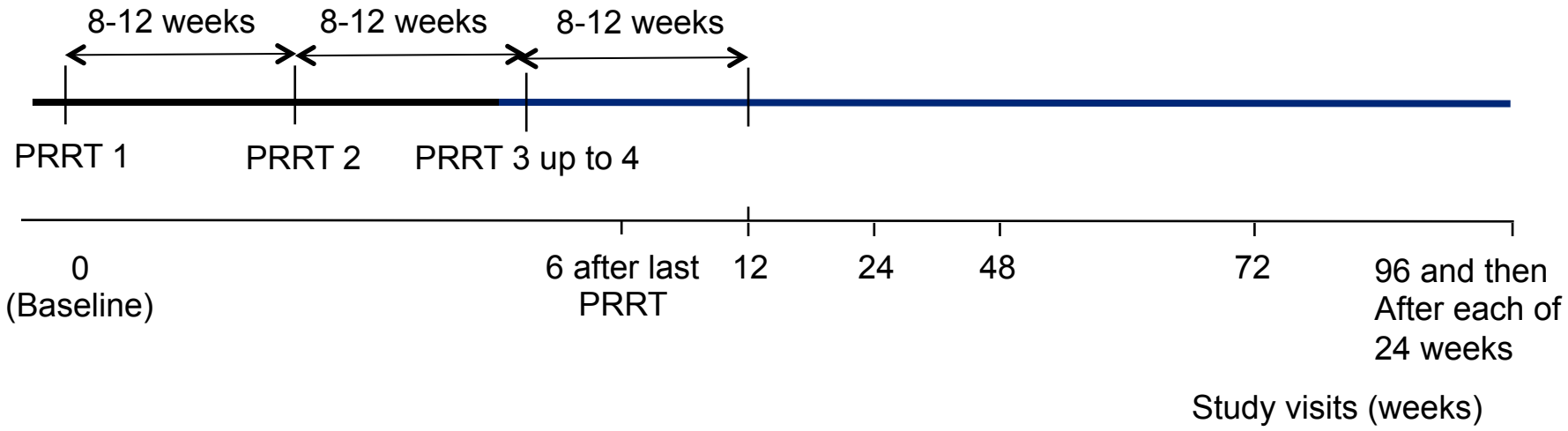
Study aim and design

Aim

- To evaluate long tem survival in group of patients with non-resectable, progressive, liver dominant gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NEN) after i.a. ^{90}Y DOTATATE (PRRT) in somatostatin receptor–positive tumours.

Design

- Prospective, open label, single center, interventional, phase 2 study.



Patients population

- Sporadic non-functioning and functioning GEP-NET;
- NETG1 and NETG2, except 2 pts with NECG3 Ki-67<50% and very high expression of SST in SRS;
- Non-resectable, progresive, metastatic with dominant liver involvement;
- Tumour measurable according to RECIST 1.0 criteria (local assessment), base on CT or MRI;
- Grade ≥2 on somatostatin receptor scintigraphy ^{99m}Tc HYNICTOC (Tektrotyd, Polatom, PL) using Krenning scale of tumour uptake;
- Previously use of SSA analogues, chemotherapy, or i.v. ^{90}Y DOTATATE.

	All n=38	Previous i.v. PRRT n=16 (%)	Only i.a. n=22 (%)
Men n (%)	21 (55)	12 (75)	10 (45)
Age in years (mean, SD)	56.4 (9,2)	55.4 (8.2)	57.5 (9.9)
NET origin			
Foregut	14 (37)	7 (44)	7 (32)
Midgut	13 (34)	5 (31)	8 (36)
Hindgut	4 (11)	1 (6)	3 (14)
UNO (FPI)	7 (18)	3 (19)	4 (18)
Secretor tumours	**19 (50)**	**9 (56)**	**10 (46)**
Tumour Grade n (%)			
NETG1	8 (21)	4 (25)	4 (18)
NETG2	**28 (74)**	**11 (69)**	**17 (77)**
NECG3	2 (5)	1 (6)	1 (5)
Hepatic load (mean %)	**38**	**44**	**34**
< 25% - n (%)	18 (47)	7 (44)	11 (50)
< 50 % - n (%)	9 (24)	3 (19)	6 (27)
>50 % - n (%)	11 (29)	6 (38)	5 (23)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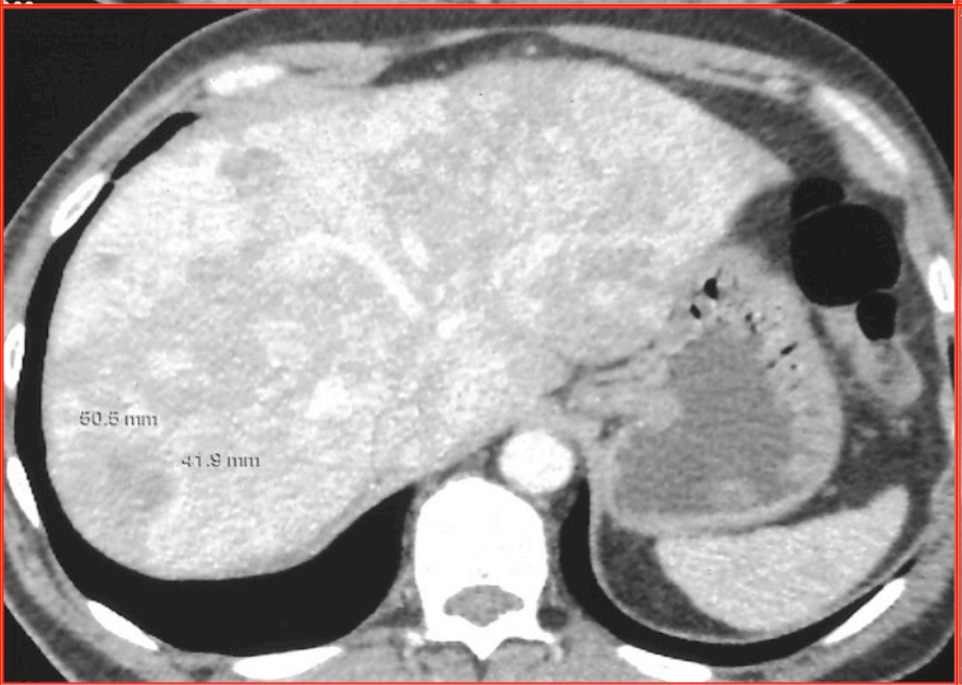
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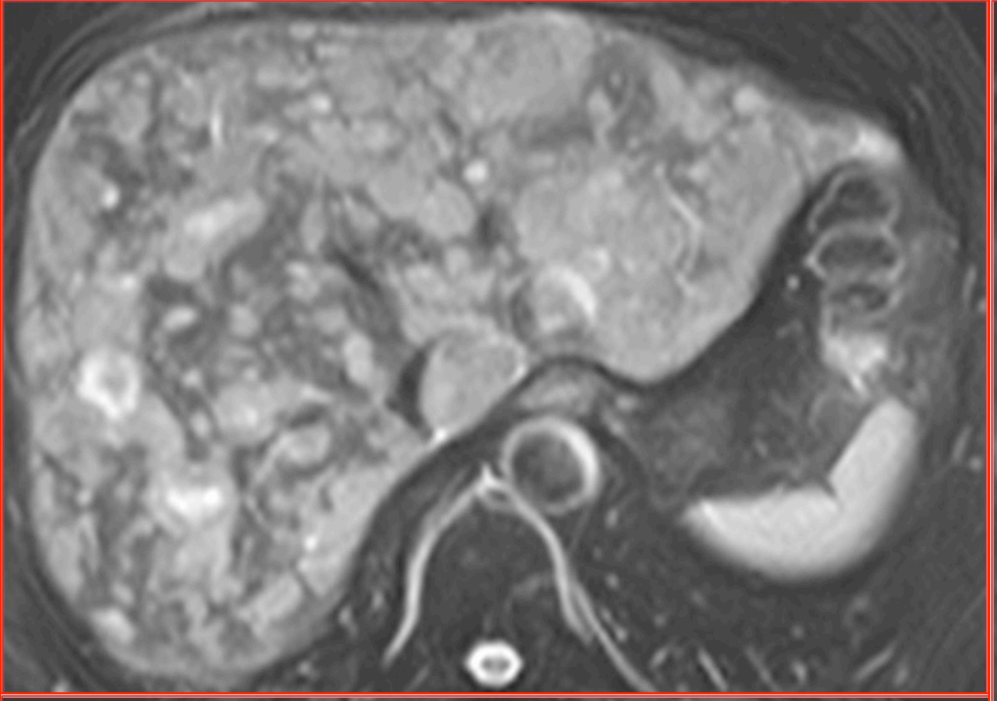
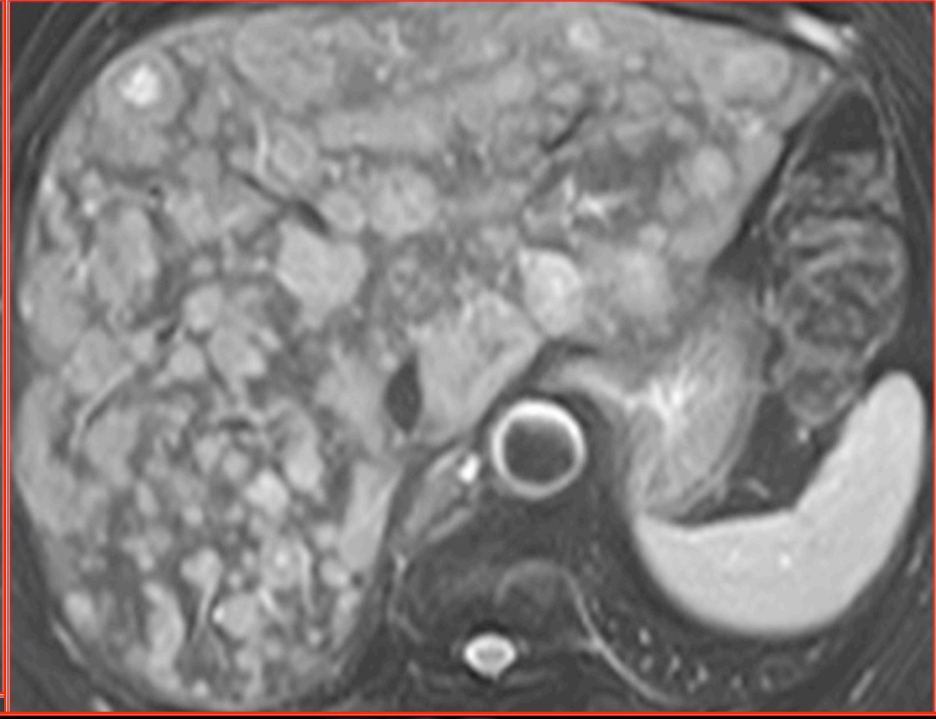
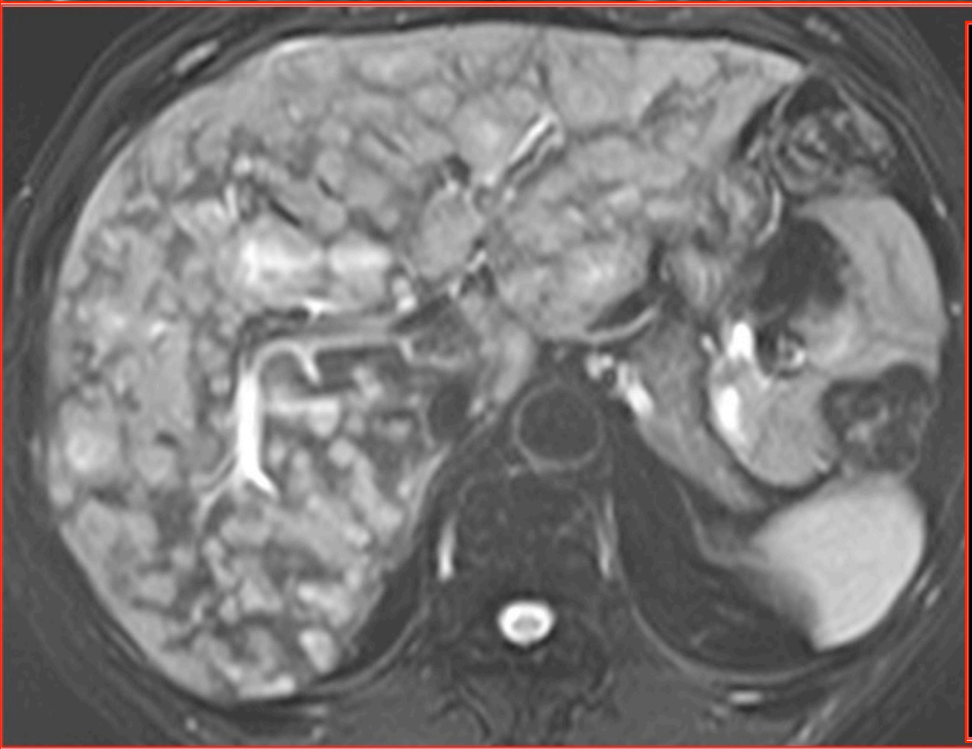
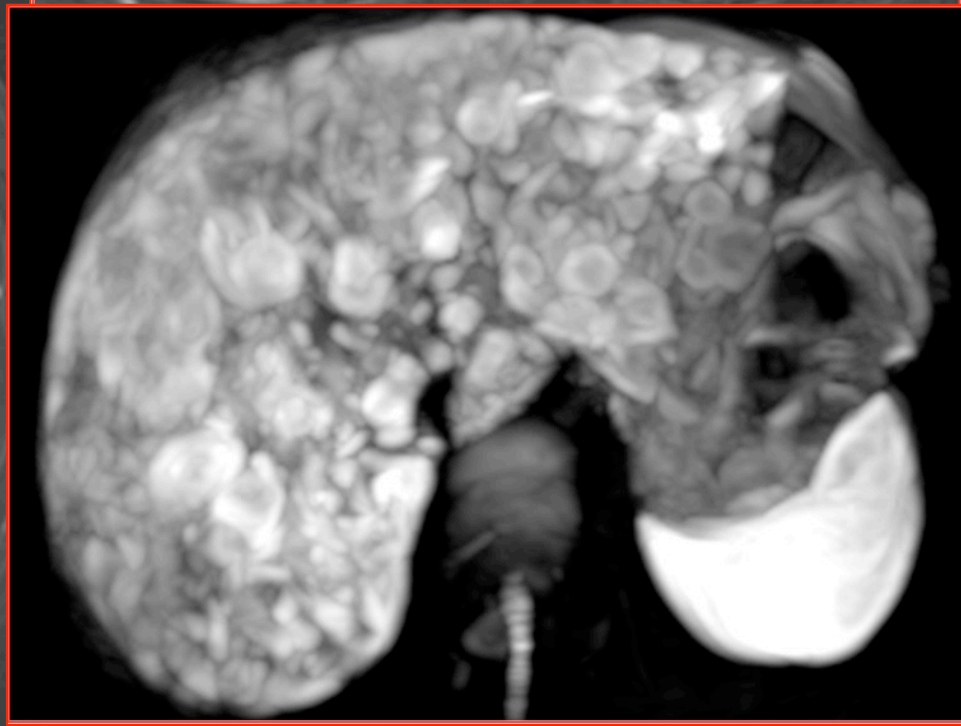


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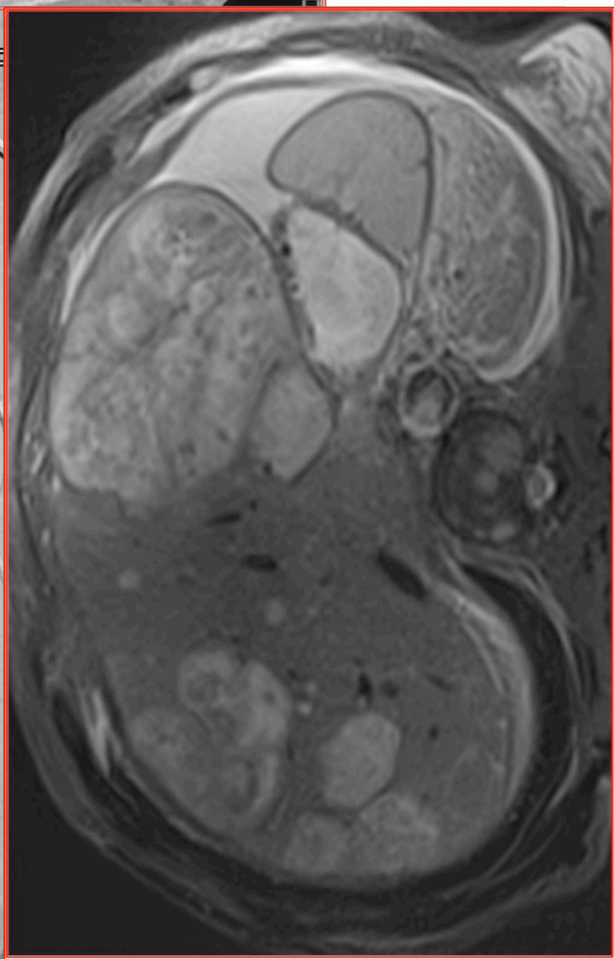


i.a. PRRT ^{90}Y DOTATATE

	All (n=38)	Previous i.v. PRRT	Only i.a. PRRT
Mean therapy sessions	**2.74**	2.5	3.0
Mean Activity (GBq) per therapy session	**1.15**	1.12	1.16
Mean Cumulative activity (GBq)	**3.13**	2.8	3.4
Mean time between i.a. PRRT (weeks)	**9.2**	10	8.4

Previous therapies

	All (n=38)	Previous i.v. PRRT	Only i.a. PRRT
Surgery (ITT)	**23 (60 %)**	9 (56 %)	23 (61 %)
Analogues SST	**31 (82 %)**	13 (81 %)	18 (82 %)
Chemotherapy	**12 (32 %)**	**9 (56 %)**	**3 (14 %)**
Previous i.v. PRRT	**16 (42 %)**	16 (100 %)	

Initial parameters before i.a. PRRT after previous tx.

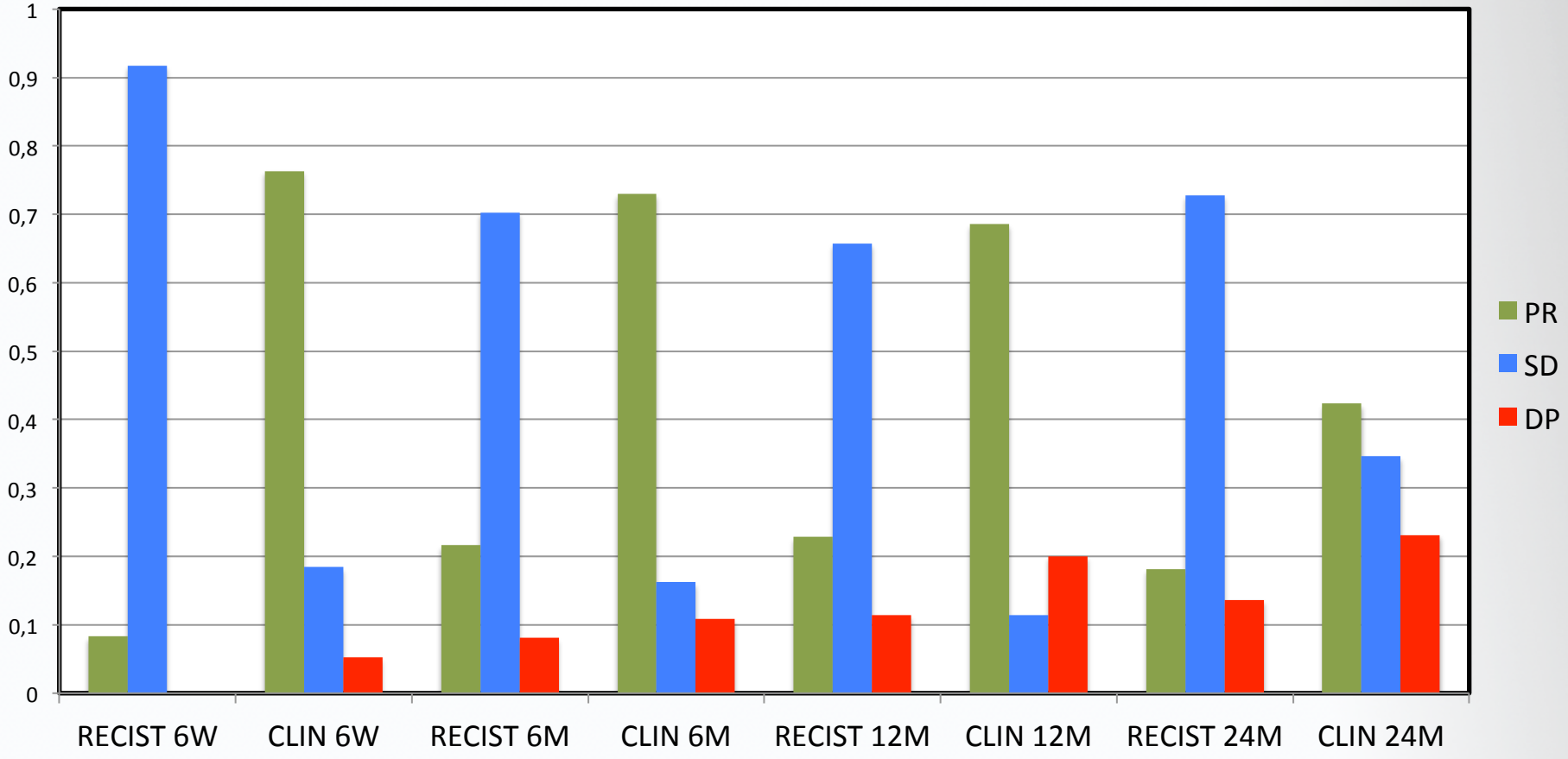
	All (n=38)	Previous i.v. PRRT	Only i.a. PRRT
WBC (x10^6/ml)	6.78	7.34	6.37
Hb (g/dl)	12.8	12.0	13.4
PLT (x10^3/ml)	288	297	282
Creatinine (mg/dl)	**0.97**	**1.24**	**0.78**

Hormonal Response

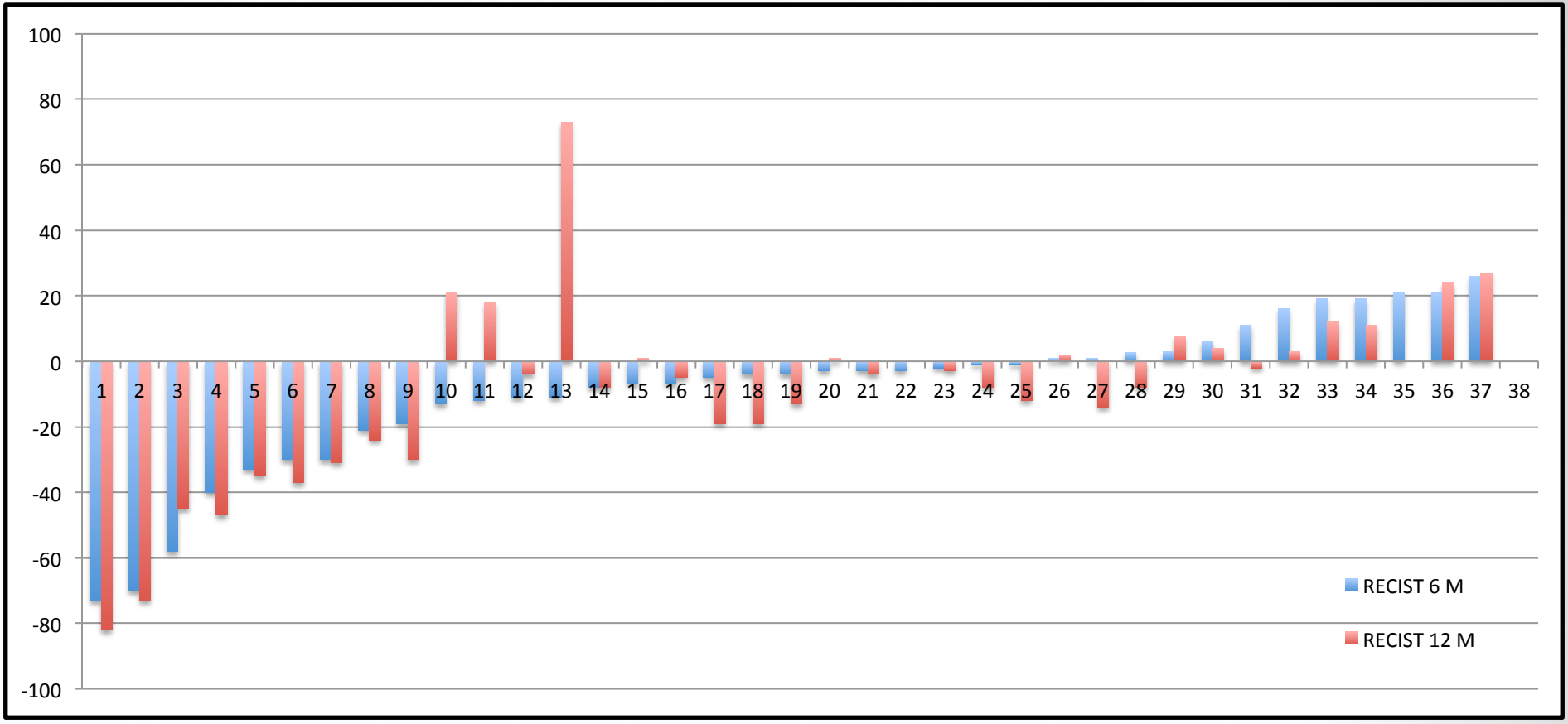
- Clinical (hormonal) response:
  - Hypoglycemia – significant reduction in 2 cases;
  - diarrhoea (18 pts before therapy) in 15 cases reduction, in 3 cases bowel movements back to normal;
  - flushing (17 subjects pre-therapy) reduction after therapy in 12 pts;
  - abdominal pain (18 pts before) - 6 reduction of pain during therapy and most of them 10 pts 4-8 weeks after completed therapy.

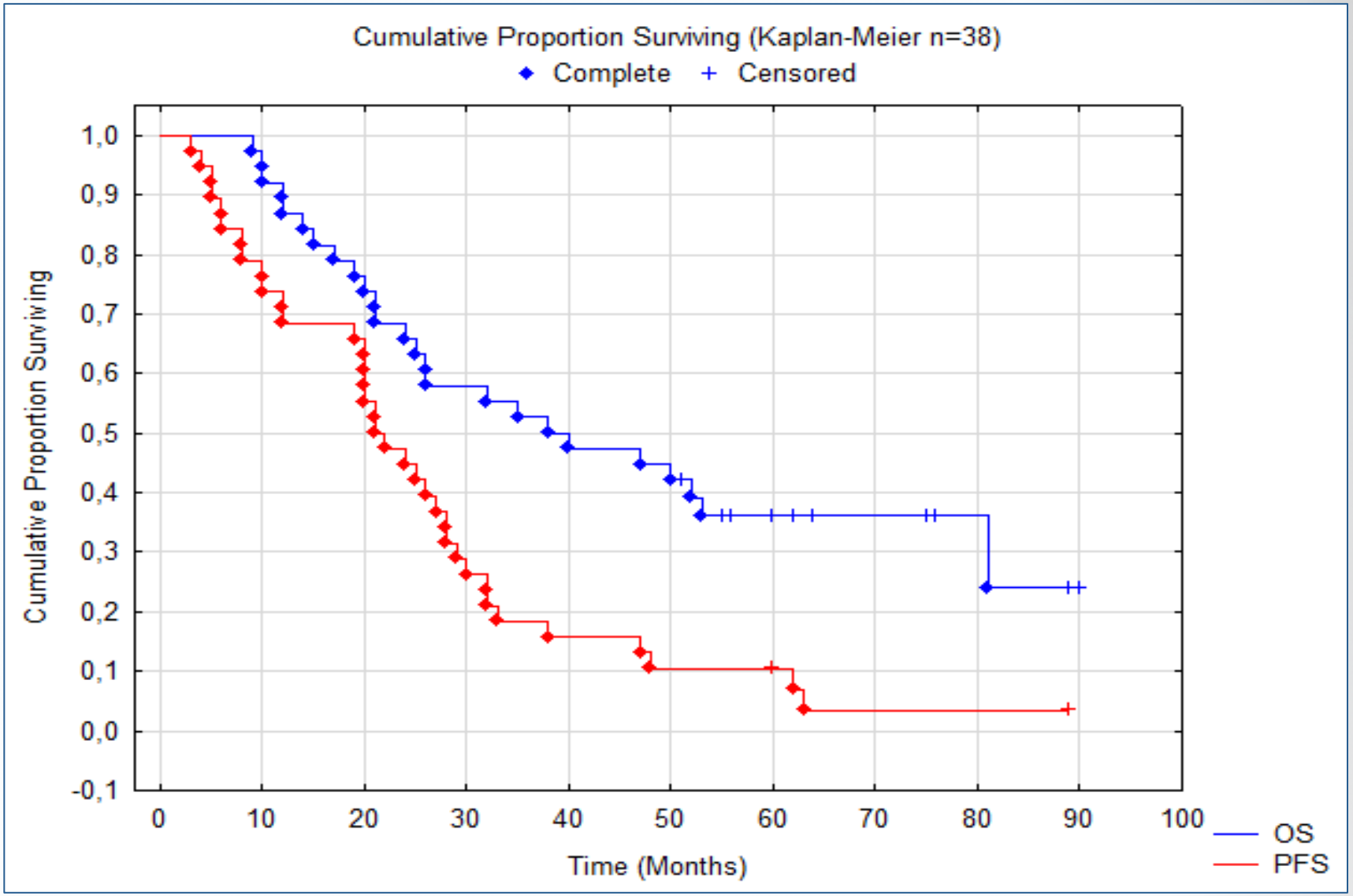
PS WHO	Before Therapy	6 W After Therapy
WHO 0	0	18 (47%)
WHO 1	30 (79%)	18 (47%)
WHO 2	8 (21%)	2 (6%)

RECIST and Clinical Response



ORR base on RECIST 1.0 after 6 M and 12 M (n=37)

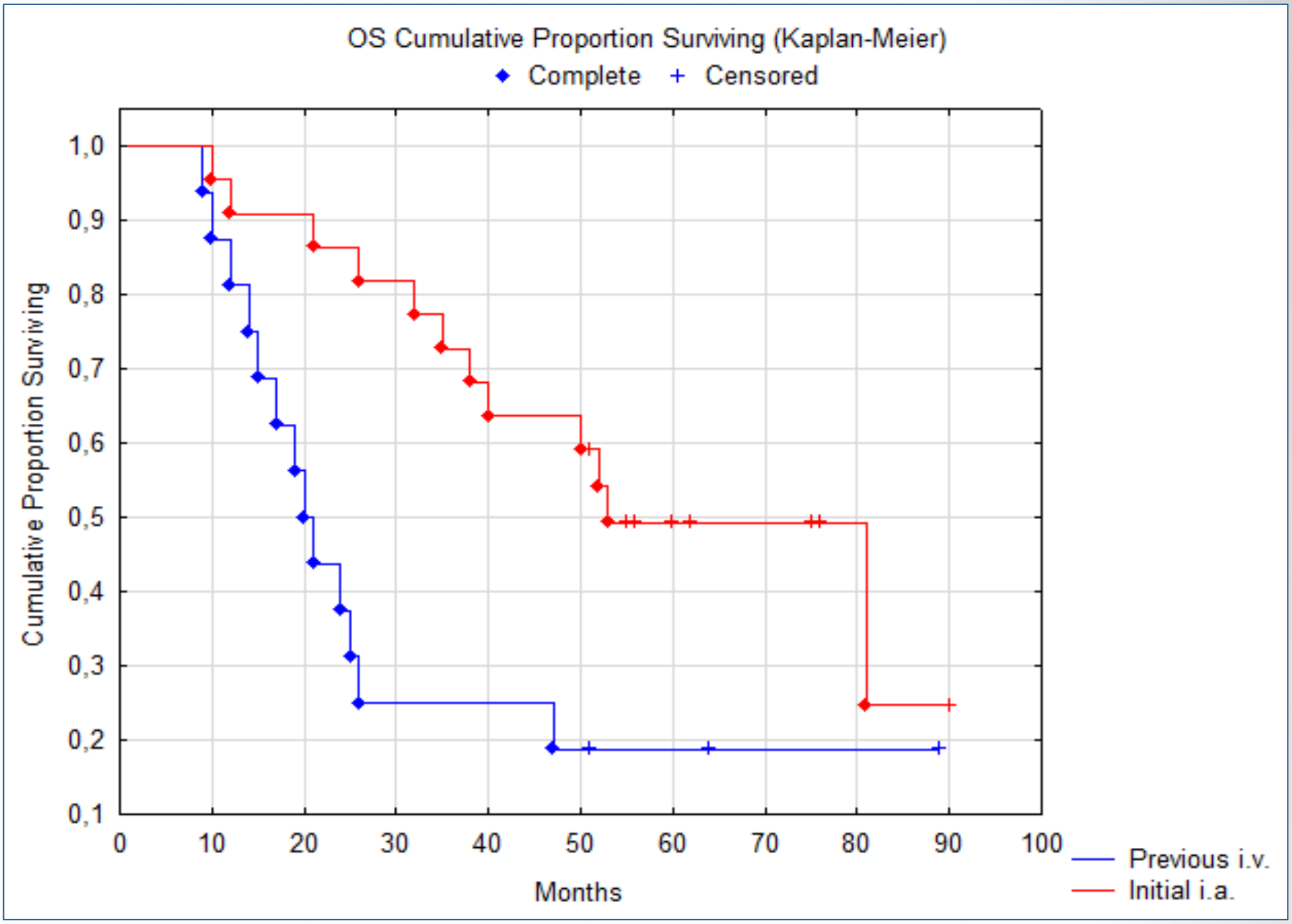




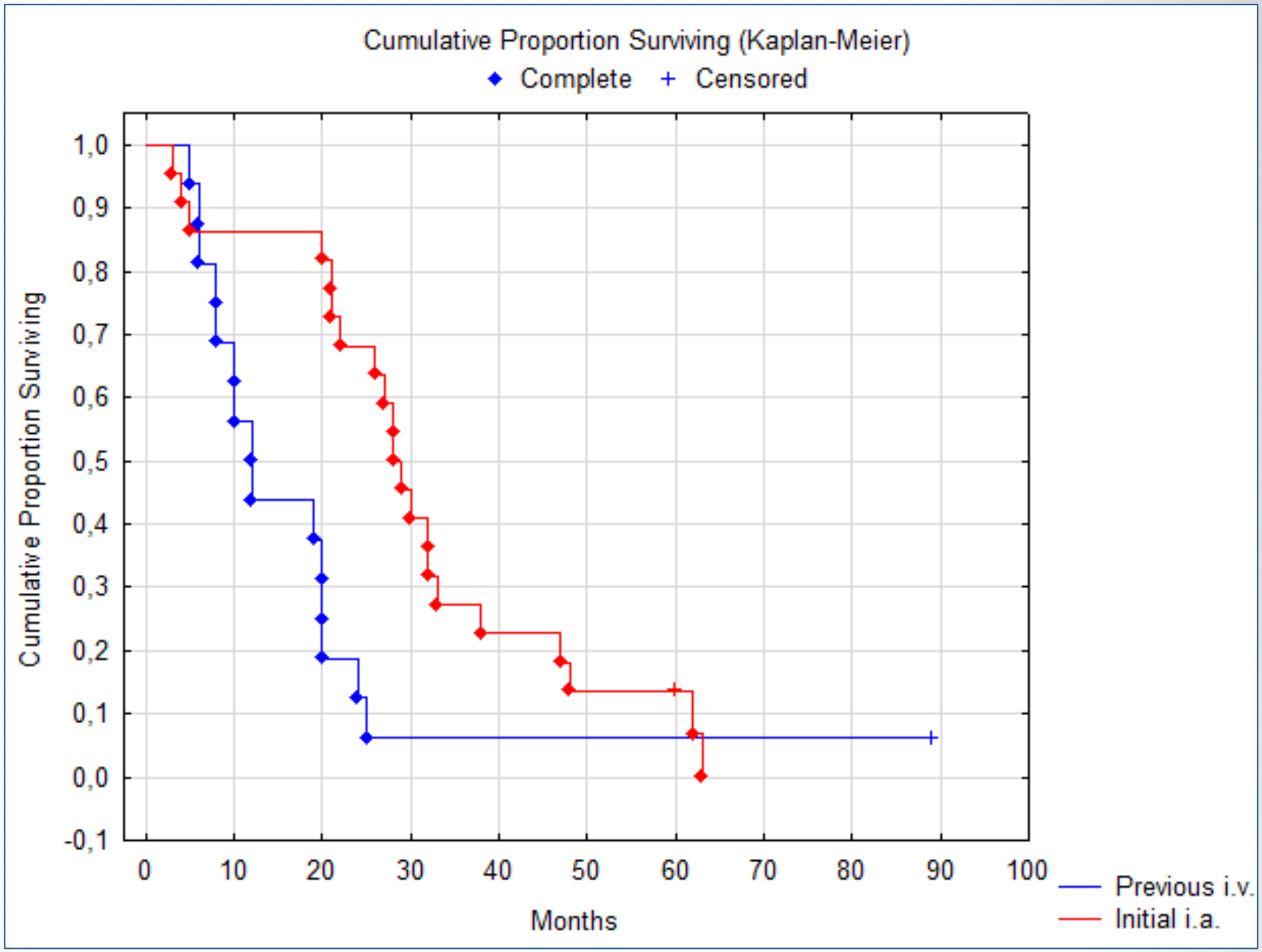
No. at Risk

OS	38	33	26	22	18	14	7	1	1	0
PFS	38	26	18	10	6	4	3	1	1	0

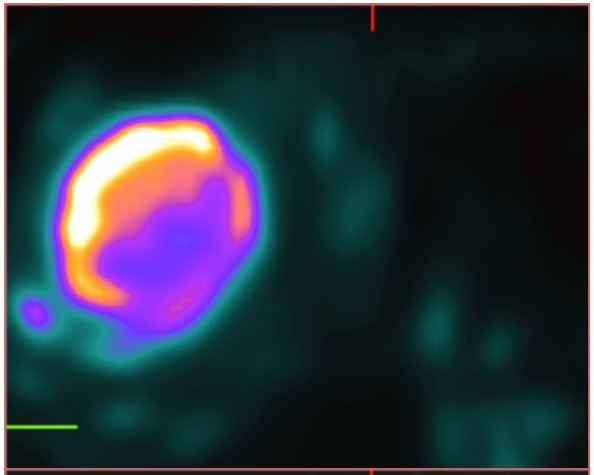
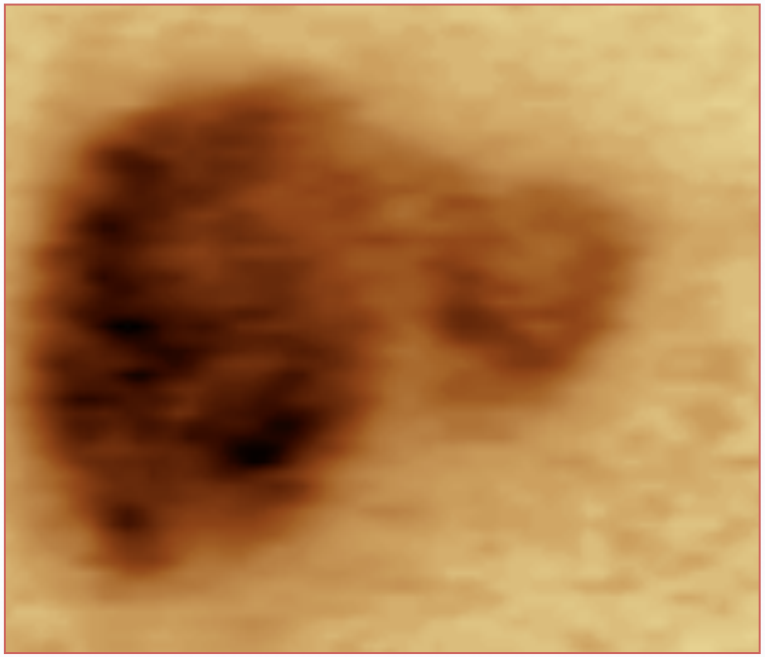
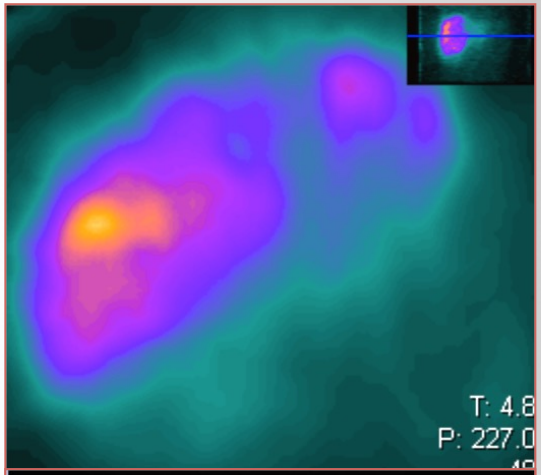
OS (N=38) = **39.5 M** (CI -/+ 33.0 – 48.6); **PFS** (N=38) = **21.5 M** (CI -/+ 19.32 – 31.9).



OS initial i.a. (N=22) **52.5 M** (CI -/+ 40 – 59); **OS previous i.v.** (N=16) = **20.5 M** (CI -/+ 17 - 41)



PFS initial i.a. (N=22) **28.5 M** (CI -/+ 23 – 38); **OS previous i.v.** (N=16) = **12.0 M** (CI -/+ 8 - 29)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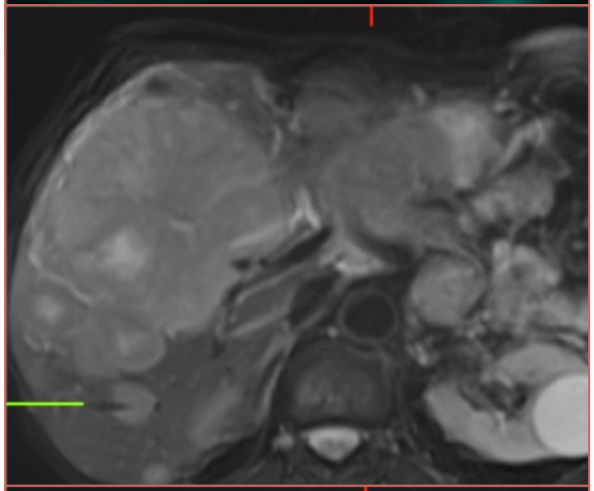
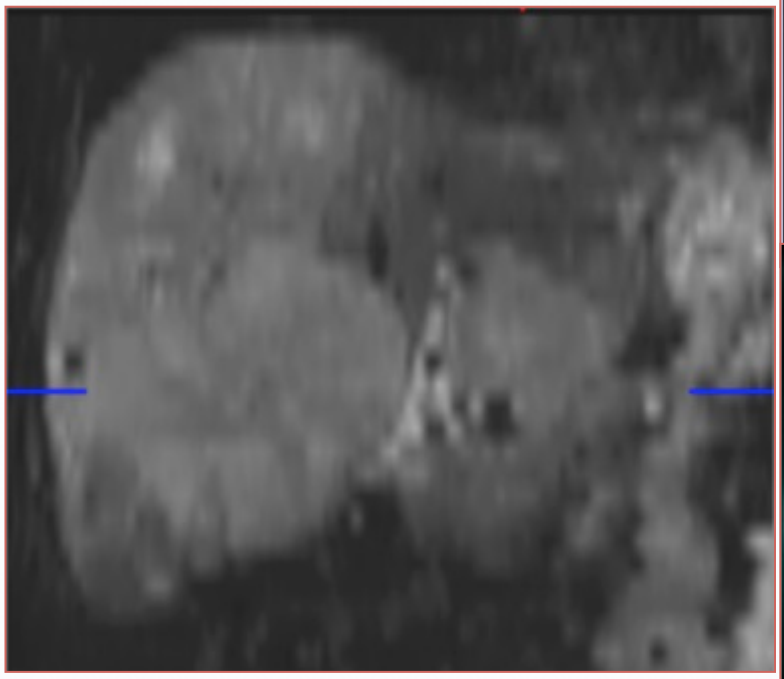
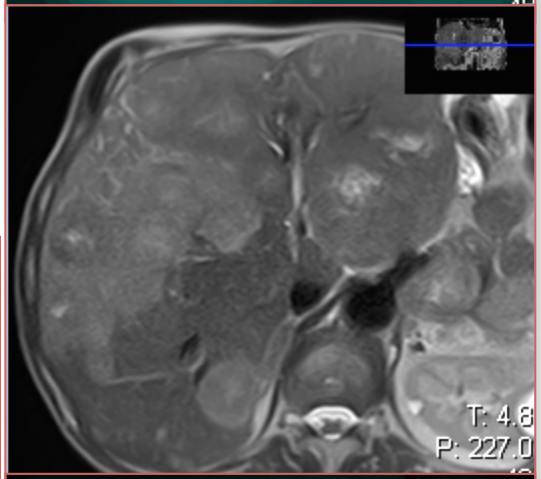
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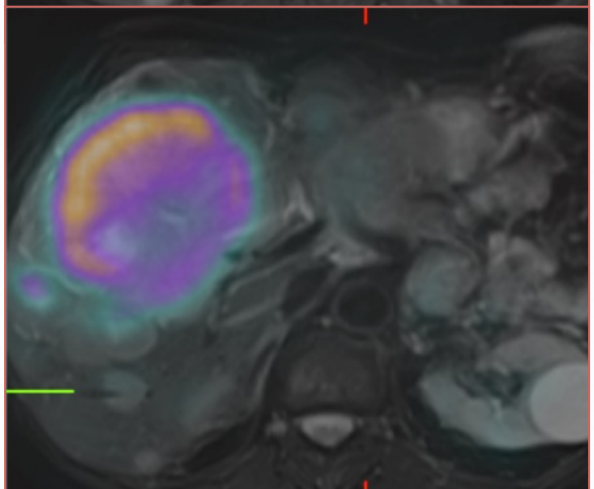
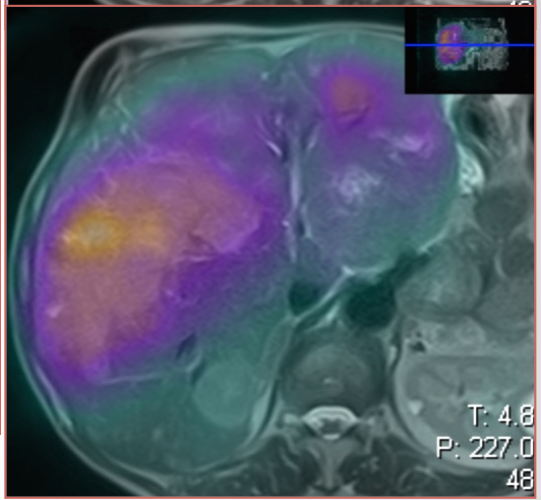
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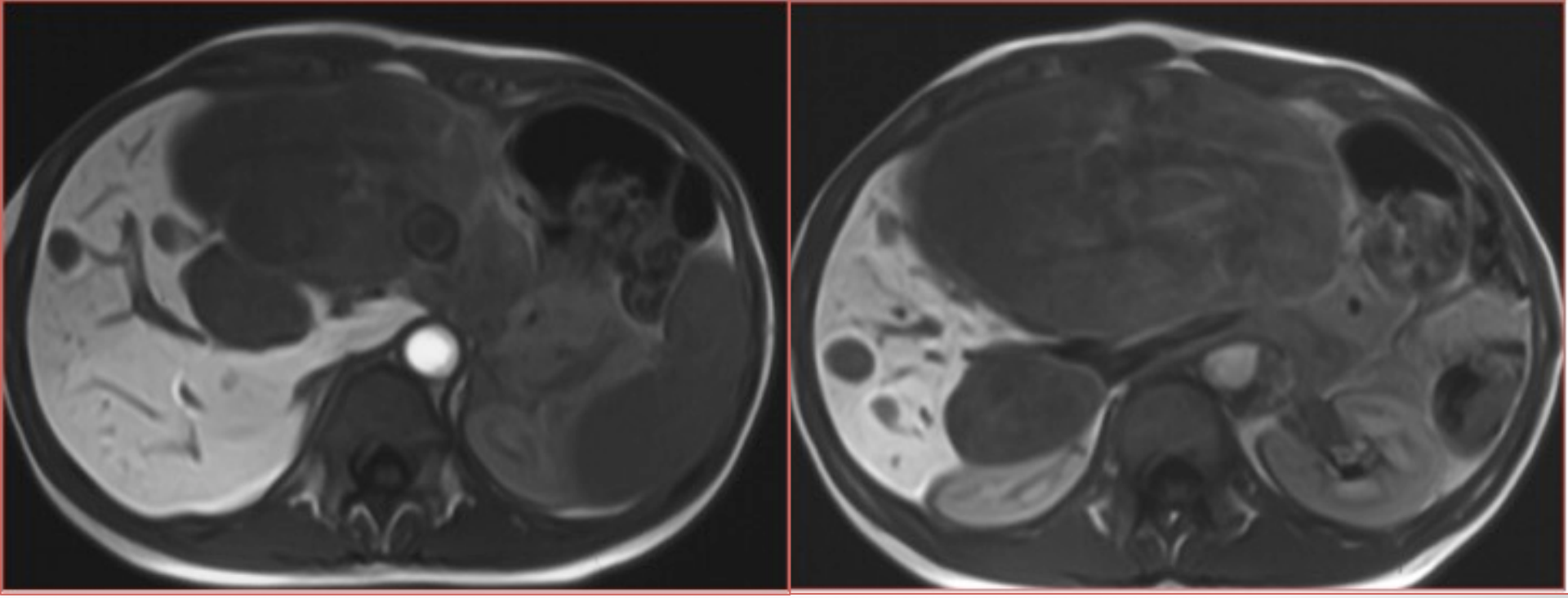

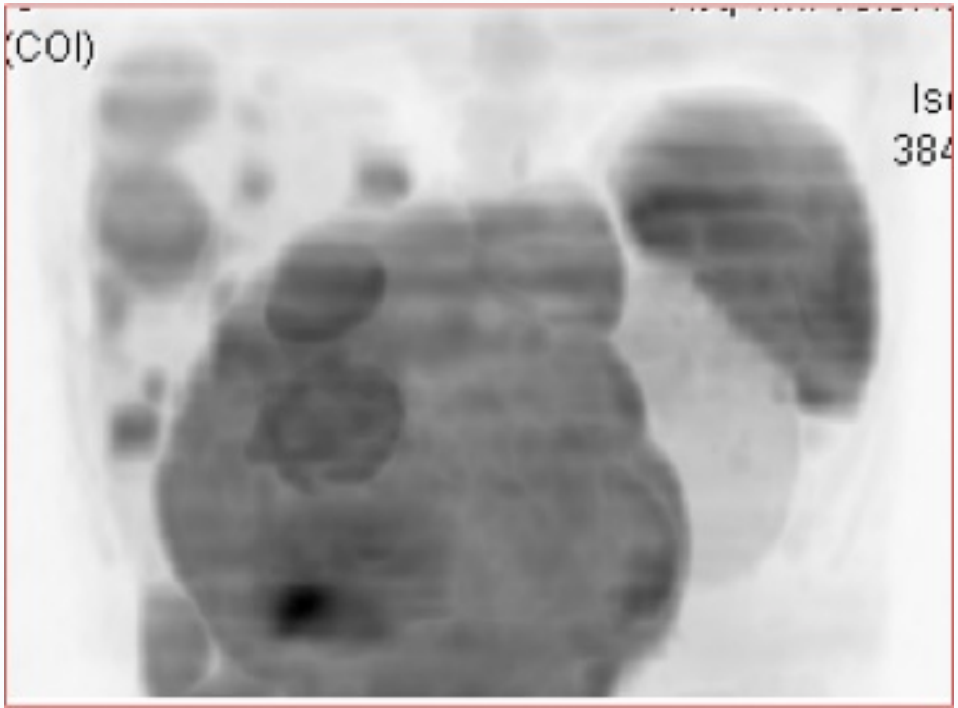
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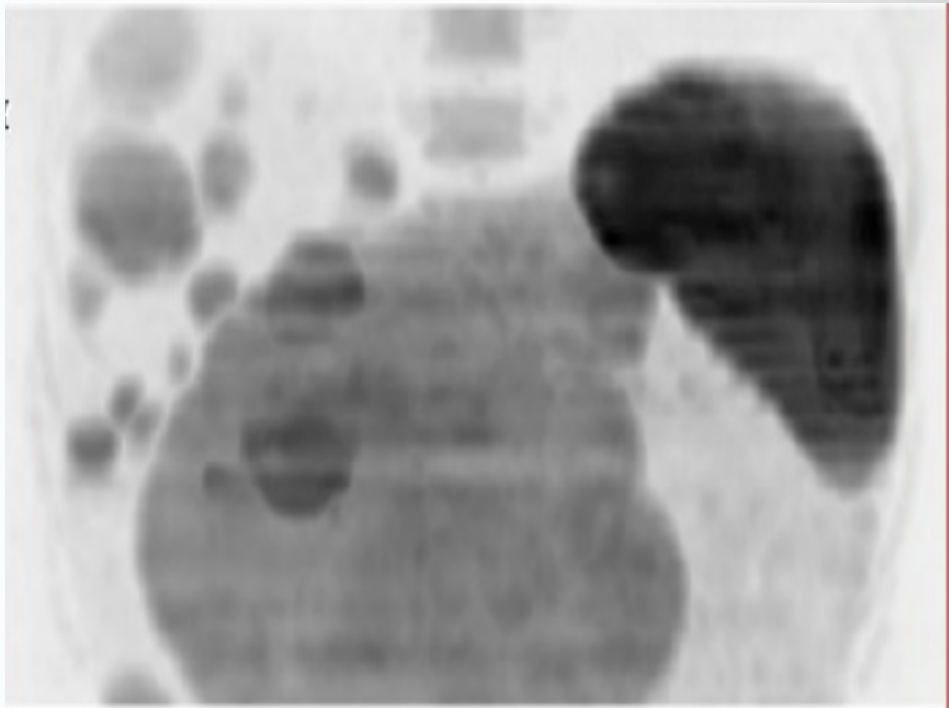

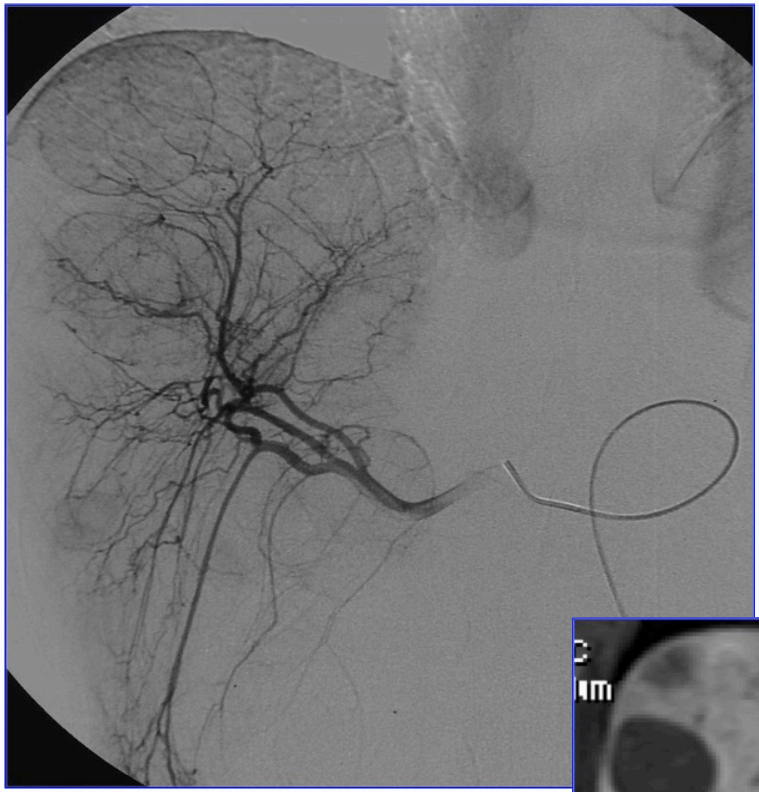

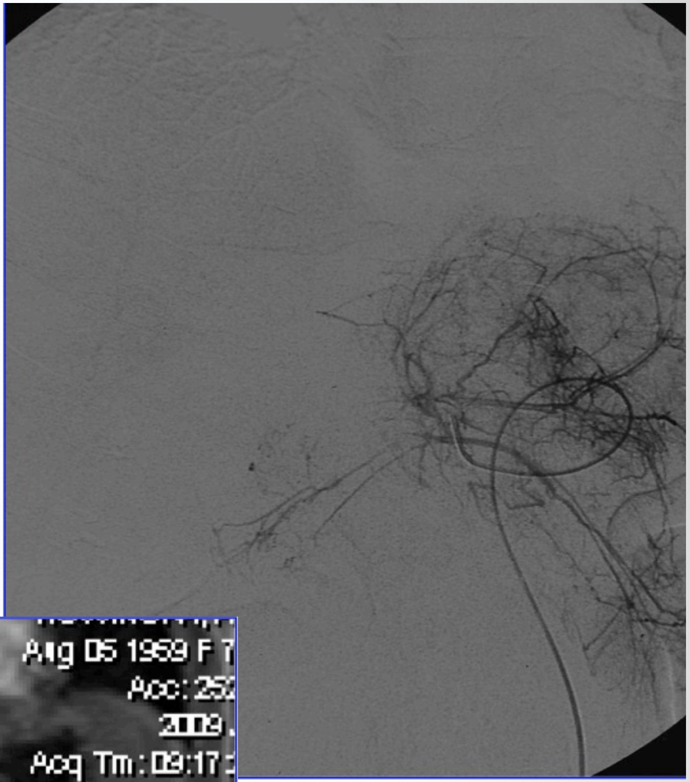

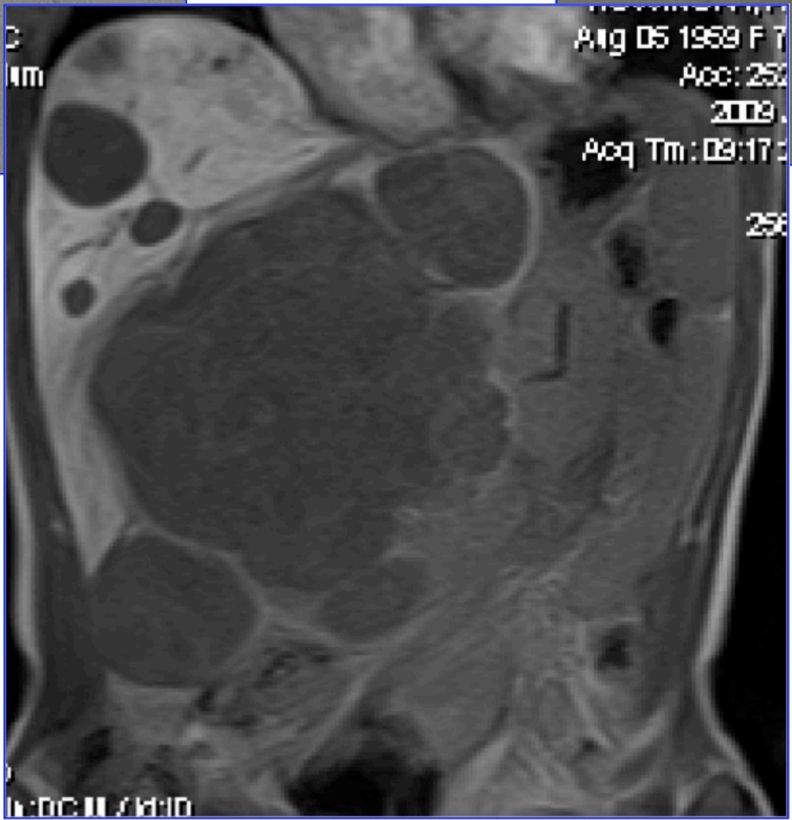
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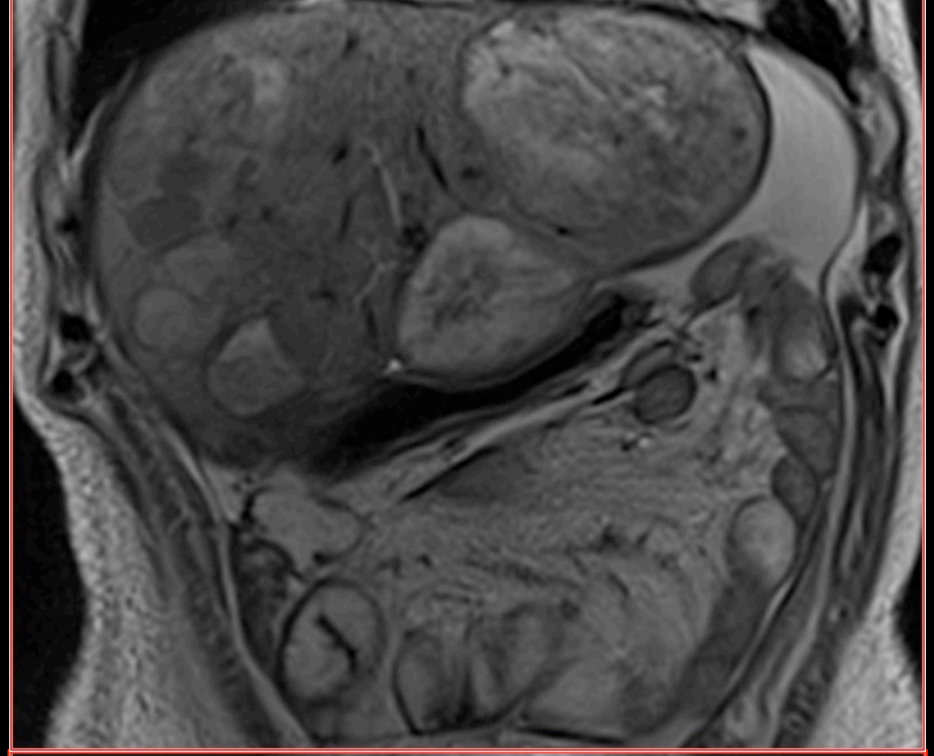
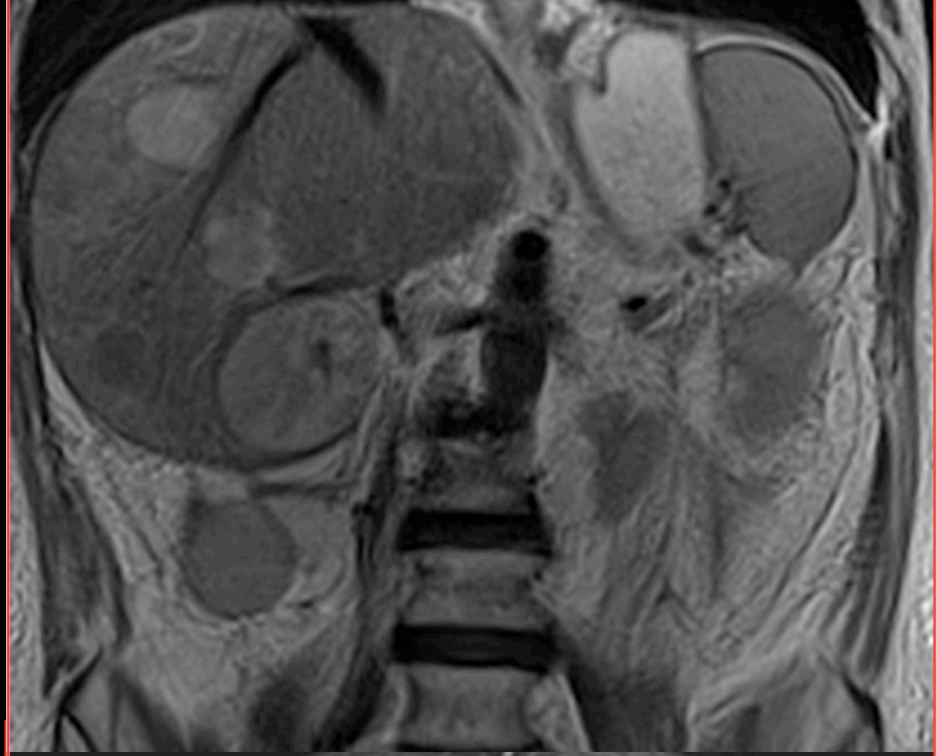
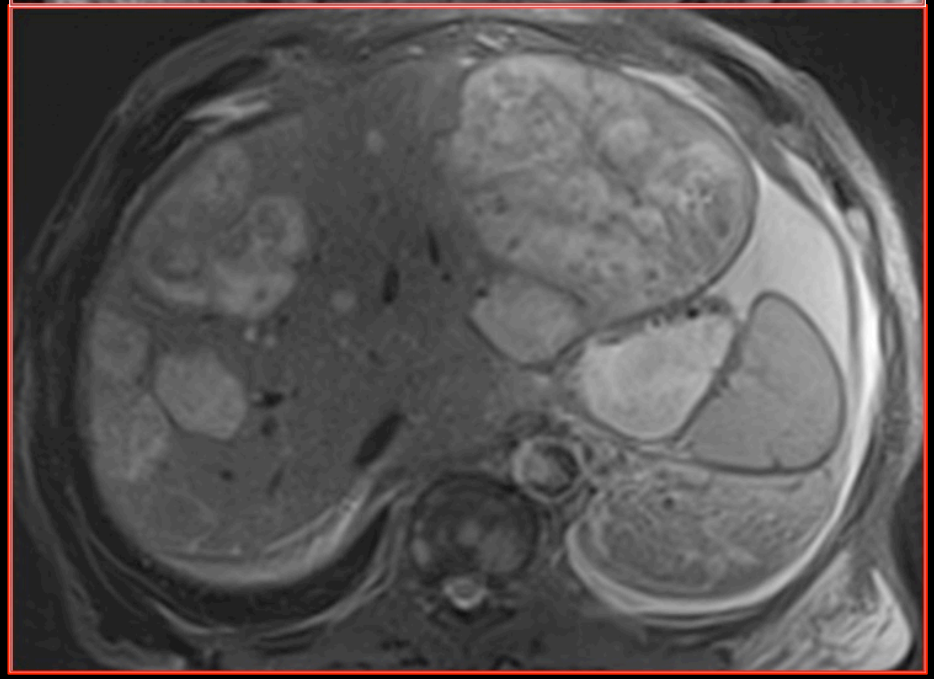
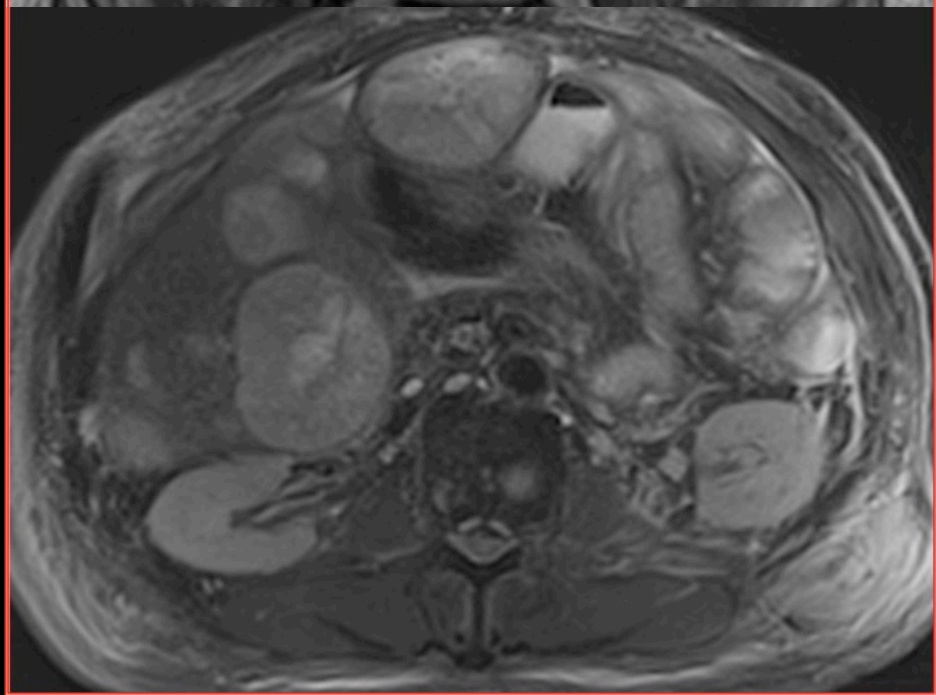
Conclusion

- Intra-arterial PRRT using ^{90}Y DOTATATE seems to be effective palliative method of therapy, in patients with extensive nonresectable and progressive liver dominant metastatic GEP NET/NEN;
- Could be used as initial therapy and also in those who had previous i.v. PRRT and who developed further progression;
- Most of patients have clinical response after i.a. PRRT;
- Objective response of i.a. ^{90}Y DOTATATE, base on RECIST, similar like i.v. PRRT underestimate clinical benefits of this type of therapy.



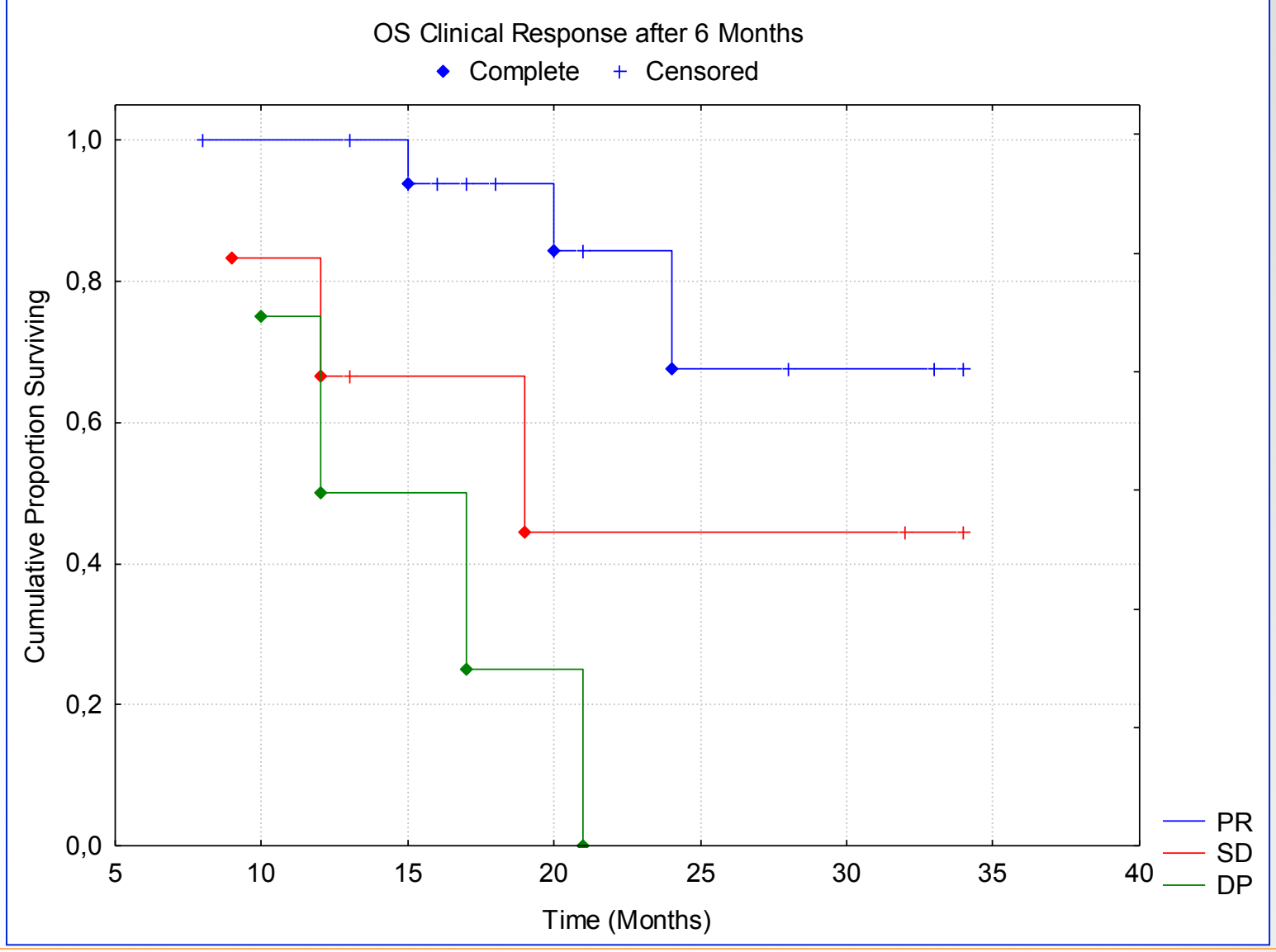






AEs of i.a. PRRT

	WBC	Hemoglobin	Creatinine
Initial (N=28)		**2xG2** (7%)	**2xG1 & 2xG2** (14%)
6 Weeks (N=28)		**2xG2 & 1xG3** (11%)	**1xG1 & 2xG2** (11%)
6 Months (N=28)	**1xG2** (4%)	**1xG2 & 1xG3** (7%)	**1xG1 & 3xG2** (14%)
12 Months (N=26)	**2xG2** (8%)	**2xG2 & 1xG3** (12%)	**2xG1 & 2xG2** (15%)
24 Months (N=7)	**1xG3** (14%)		



Clinical 6M - PR Median OS (N = 18) = **20 M** (CI -/+ 17.1 - 24.5) ***P*=0.09**

Clinical 6M - SD Median OS (N=6) = **16 M** (CI -/+ 8.7 – 31.2) ***P*=0.25**

Clinical 6M - DP Median OS (N = 12) **14 M** (CI -/+ 7.2 – 22.9); ***P*=0.0001**

Toxicity NCI CTC v. 4.0(G2-4)

	WBC	Hemoglobin	Creatinine
Initial (N=28)		**2xG2** (7%)	**2xG1 & 2xG2** (14%)
6 Weeks (N=28)		**2xG2 & 1xG3** (11%)	**1xG1 & 2xG2** (11%)
6 Months (N=28)	**1xG2** (4%)	**1xG2 & 1xG3** (7%)	**1xG1 & 3xG2** (14%)
12 Months (N=26)	**2xG2** (8%)	**2xG2 & 1xG3** (12%)	**2xG1 & 2xG2** (15%)
24 Months (N=7)	**1xG3** (14%)		