5th Milan NET Conference

A live and web multimodal meeting among active Italian NET Centers

Wednesday June 12th, 2019
Fondazione IRCCS Istituto Nazionale dei Tumori
Milano

Session 3: Web Multimodal Tumor Board

Tumor Board 2

Case1

PRRT and loco-regional therapies

female 64 yo

PS (ECOG) 0

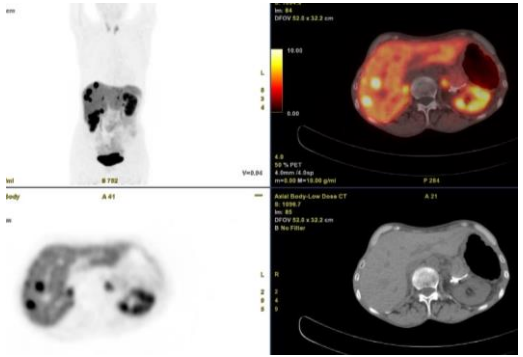
Medical history

JUN 2016
Total colectomy for intestinal adenocarcinoma and multiple polyps pT3 pN0 M0 (Dukes B2 stage) +
Concomitant distal splenopancreasectomy Well Differentiated pNET(tail), pT4 pN1(IIIb) Mib-1/ki67: 1,2%

OCT 2016

abdominal **CT scan** and **68Ga PET DOTA**: multiple liver metastasis

Negative FDG PET



OCT 2016

start **Octreotide LAR 30 mg** q28 days

MAR 2017

Radiological numerical **PD** of liver metastasis

Multidisciplinary board:

switch to Lanreotide 120 mg q28 days and

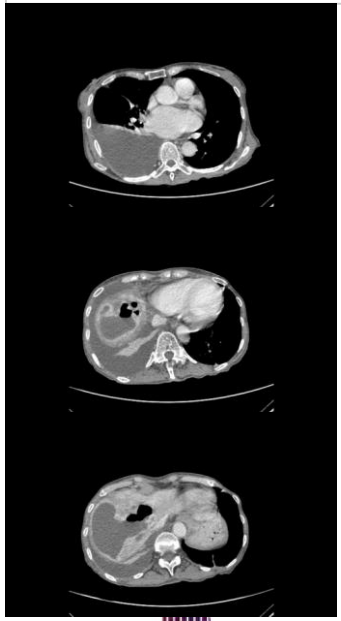
Feasibility evaluation for loco-regional therapy

JUL 2017

Multidisciplinary board decision

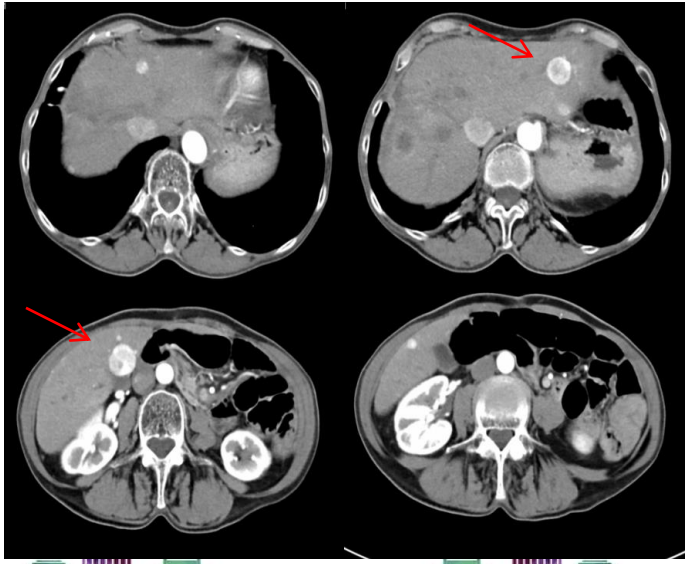
in consideration of PD

TACE (right lobe)



TACE SIDE EFFECTS : ABSCESS

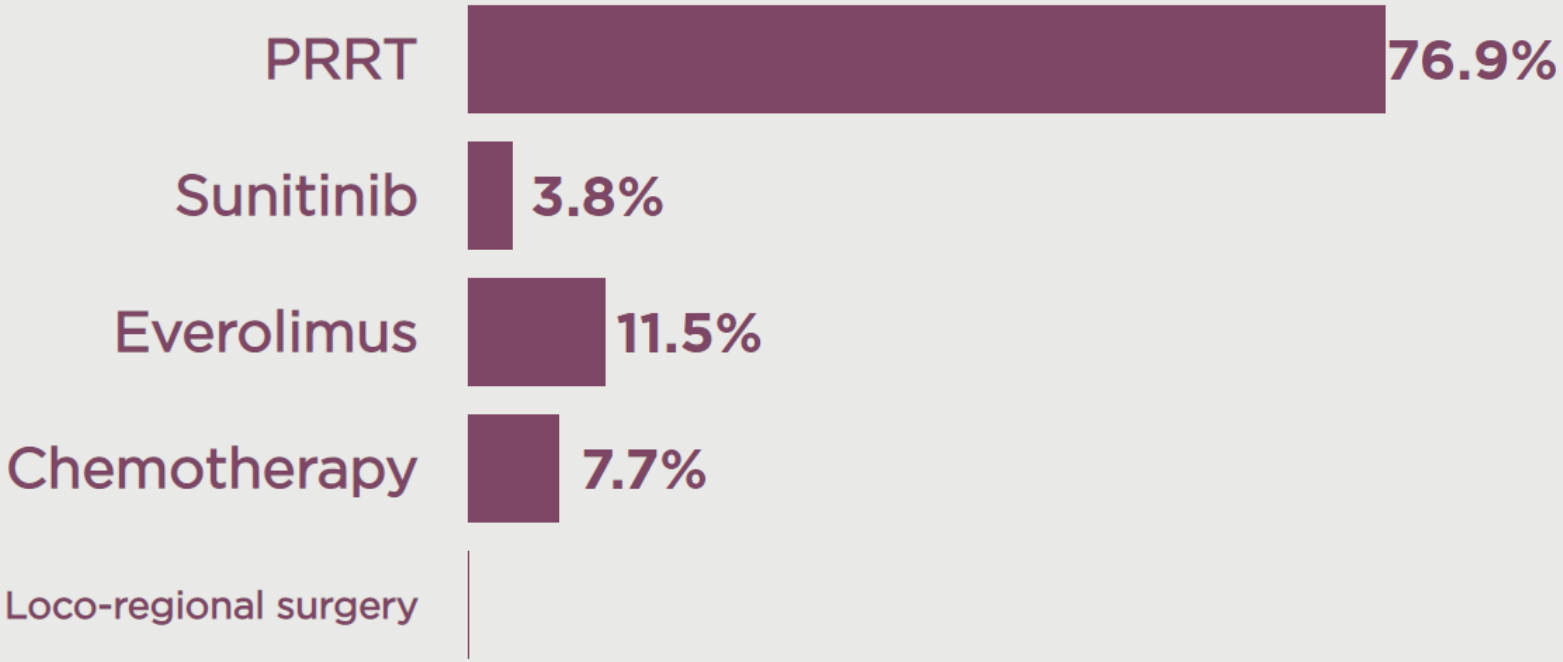
NOV 2017
(after TACE), ongoing SSA therapy:
Radiological **PD of non treated liver mts** (left lobe).



In your opinion which is the best therapeutical choice?

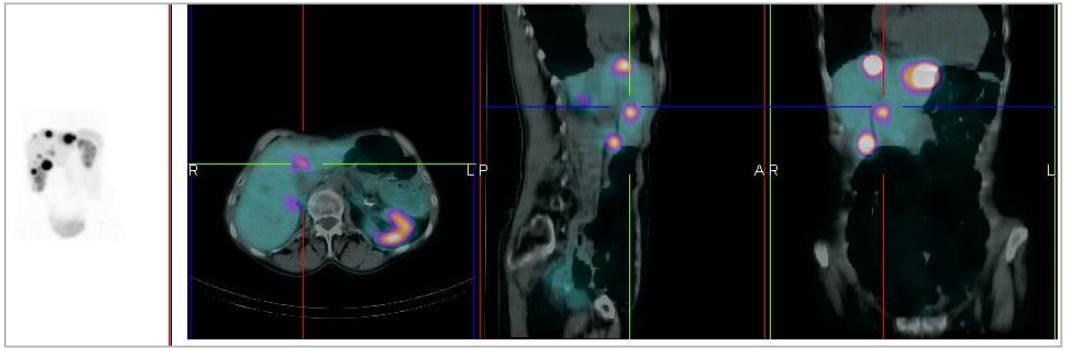
1. PRRT
2. Sunitinib
3. Everolimus
4. Chemotherapy
5. Loco-regional surgery

In your opinion which is the best therapeutical choice?



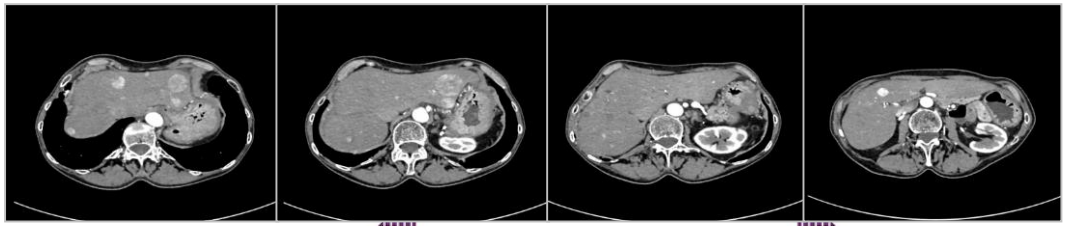
TUMOR BOARD EVALUATION: PRRT + SSA

[177- Lu-DOTATOC 7.4 GBq per cycle, 4 cycles, **AUG 2018 - FEB 2019**]



➢ **99TcTektrotyd Scintigraphy:**

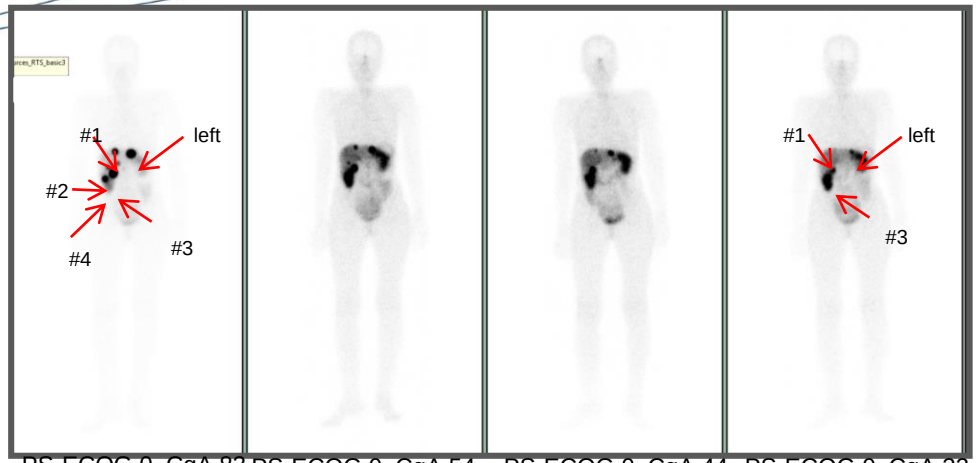
significant uptake of liver metastasis



➢**CT before PPRT:** liver PD

➢**CgA before PRRT**: 83

➢ **BMI before PRRT**: **13,76**



PS-ECOG 0, CgA 83 PS-ECOG 0, CgA 54 PS-ECOG 0, CgA 44 PS-ECOG 0, CgA 32

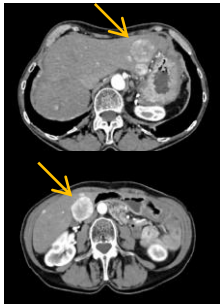
1st cycle PRRT ----------→ 4th cycle PRRT

Organs	Organ Doses (Gy)
NORMAL LIVER	0,2
Left Hepatic Lesion	41
Right Hepatic Lesion #1	246
Right Lesion #2	1136
Right Lesion #3	96
Right Lesion #4	902
Kidneys	3

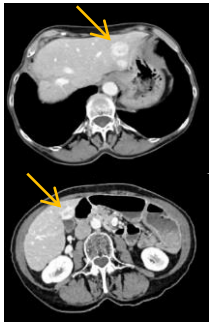
1st cycle PRRT

Organs	Organ Doses (Gy)
NORMAL LIVER	0,1
Left Hepatic Lesion	55
Right Hepatic Lesion #1	Too small
Right Lesion #2	Too small
Right Lesion #3	941
Right Lesion #4	Too small
Kidneys	3

4th cycle PRRT



Before 1st cycle



After 2nd cycle

FOLLOW-UP

APR 2017

CT scan: further response to treatment

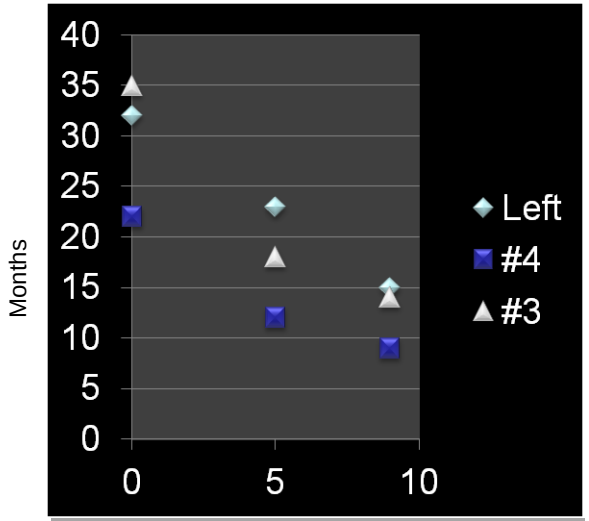
PS-ECOG 0,

BMI 17.7 (before PRRT: 13,76)

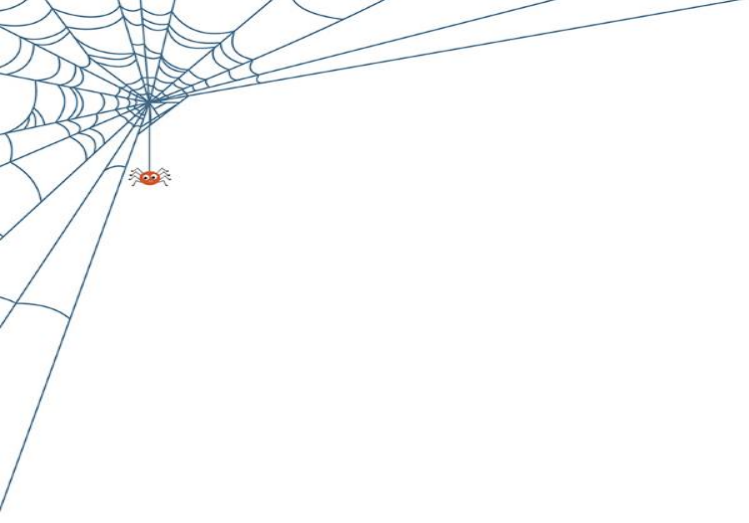
CgA 0.9 (before PPRT 83)

Normal blood count, potassium 5.5mEq/L, GGT 125 U/L,

Normal creatinine clearance



Thank you for your attention



Session 3: Web Multimodal Tumor Board

Tumor Board 2

Case 2

Cardias NEC G3

Male, 67 y.o.
PS (ECOG): 0

Past medical history

Arterial hypertension
2007 right colectomy for CRC pT2N0

Medications

Pantoprazole 20 mg 1 cp/die, losartan/HCT 50/12.5 mg

Background

SEP 2016

onset of epigastric pain (VAS 6/10), no dysphagia, no weight loss.

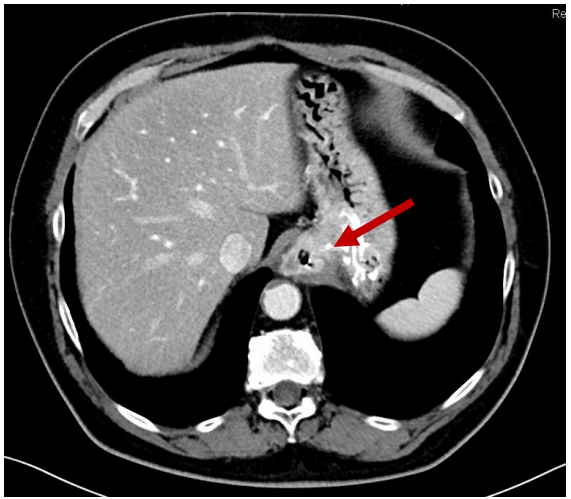
Upper endoscopy: vegetative distal oesophageal lesion.

At Pathology: large cell, poorly differentiated neuroendocrine carcinoma **(NEC) G3 Ki67: 70%.**

CT scan: diffuse thickening of distal oesophageal, conditioning stenosis; diaphragmatic and crural pathological lymph node

OCT 2016

FDG PET: uptake on distal oesophagus, lymph nodes on gastric lesser curvature and hepato-gastric recess



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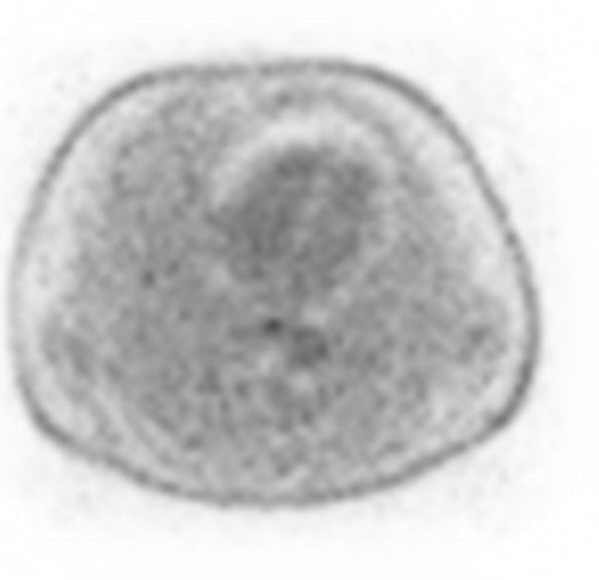

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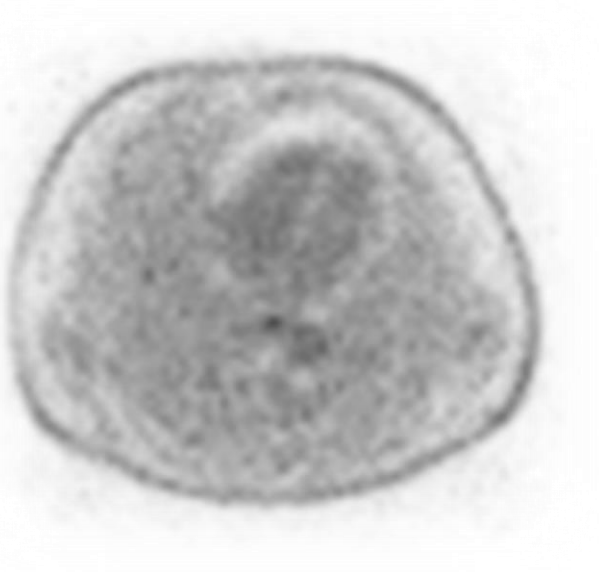


→ **OCT 2016 Starts chemotherapy with Cisplatin + VP16 (total of 6 cycles)**

PS=0; adverse effects: G2 peripheral neuropathy

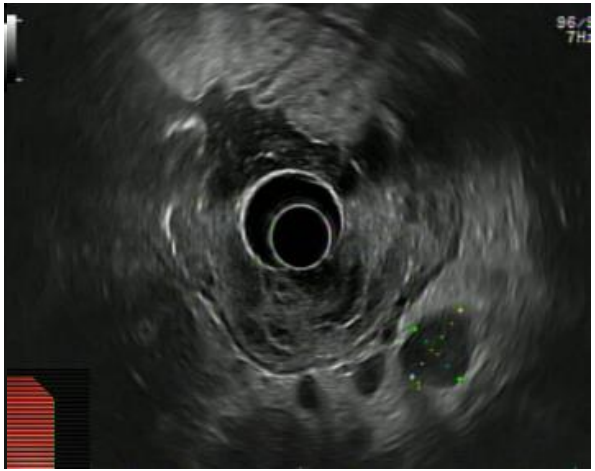
Treatment

JAN 2017

PR at PET/TC: T= SUV 42 →25 N: SUV 15 → 4 and 24 →15

FEB 2017

EUS: hypoechoic, depressed, oesophageal-gastric junction lesion, involving extensively the mucosal layer reaching the serosa. Pathological subcarinal/hepato-gastric lymph nodes (max 14 mm).

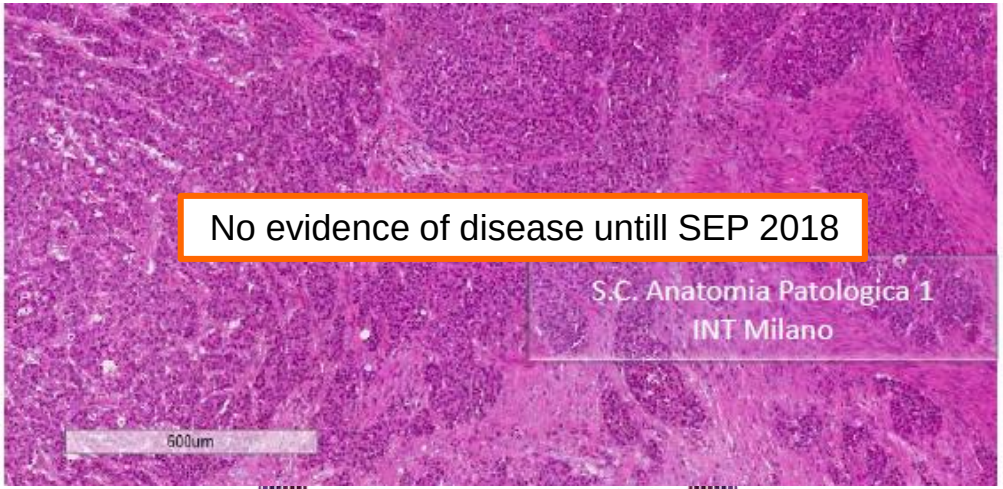


Treatment

MAY 2017

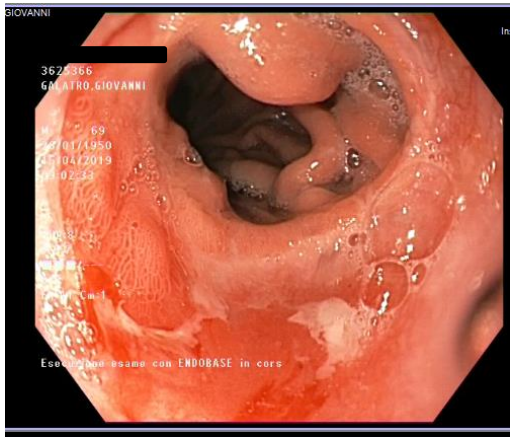
Esophago-gastric resection with gastric tubulation.

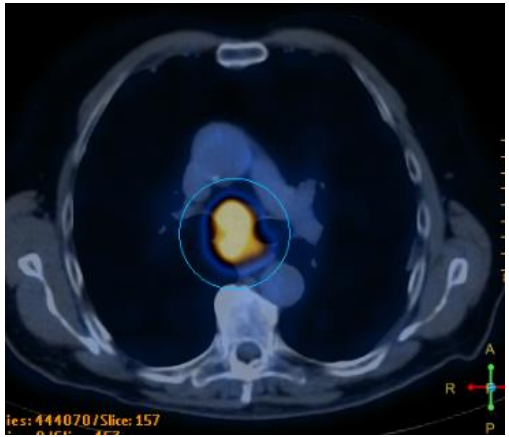
At Pathology: **MANEC (**WHO 2010) composed by PD large cell NEC G3 (60%) and adenocarcinoma (40%), invading the subserosal tissue. Neuro/angioinvasion, positive lymph nodes 4/13 Ki-67: 70%.



Follow-up

SEP 2018





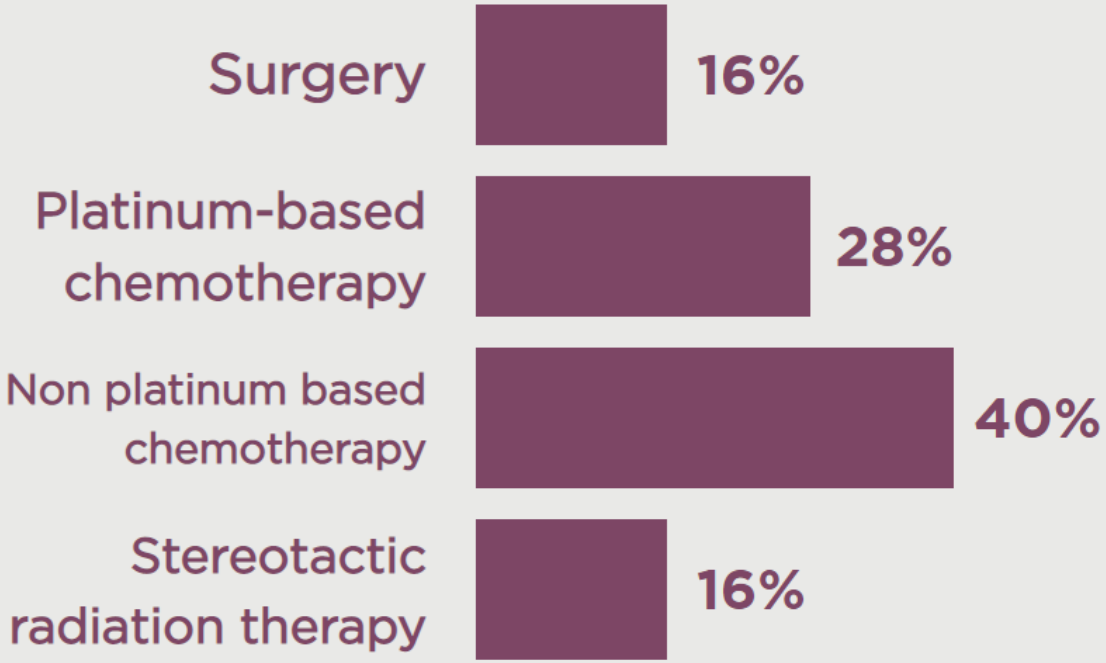
Upper endoscopy: suspicion of a 10 mm recurrence at the oesophageal-gastric anastomosis.
At Pathology: **NEC, Ki-67: 70%**

FDG-PET: subcarinal adenopathy with intense uptake (SUV 28)

Which treatment would you propose next?

1. Surgery
2. Platinum-based chemotherapy
3. Non platinum based chemotherapy
4. Stereotactic radiation therapy

Which treatment would you propose next?

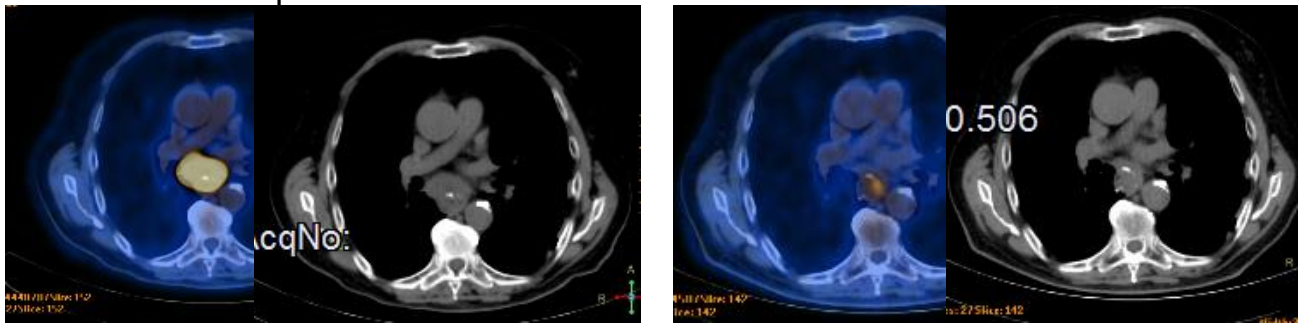


Follow-up

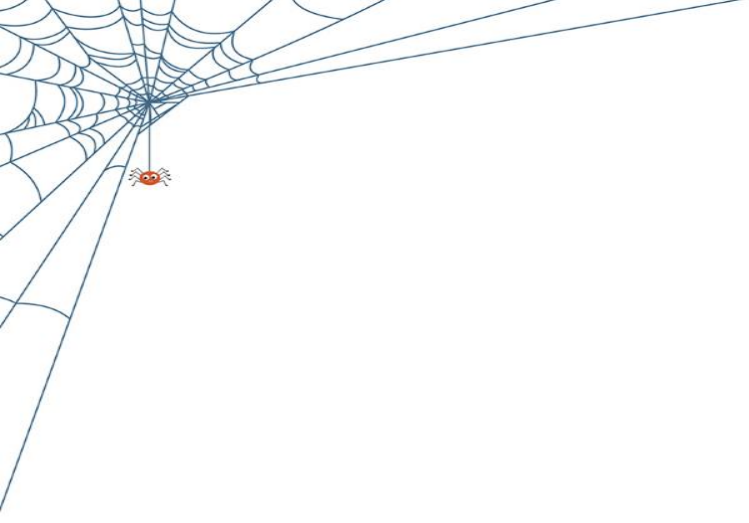
→OCT 2018 START II line CHT with CAPTEM (6 cycles)

APR 2019

PET- TC: no longer up-take in the subcarinal, tracheal lymph nodal RC, hesitates colliquative 20 mm area.



EGDS: no evidence of pathological tissue with biopsy negative



Session 3: Web Multimodal Tumor Board

Tumor Board 2

Case 3

“extremely sustained” response to SSA

Female, 64 y.o.
PS (ECOG): 0

JUL 2005
sudden onset of nausea, vomiting and diarrhea
Colonoscopy: solid lesion-mass at the ileo-cecal valve (3,2 cm).
At Pathology: well differentiated neuroendocrine tumor.
Abdominal-US: multiple solid lesions within liver (Ø17 mm in S2, Ø18 mm in S3, Ø15 and 19 mm in S8, Ø9 mm in S7).

SEP 2005
right colectomy + locoregional lymphoadenectomy + liver biopsy.
At Pathology: ileal NET, neuroinvasive and angioinvasive, infiltrating sottosierosa, Mib1/Ki67 <2%. Hepatic biopsy positive for NET localization. pT1 N1 (3/24)M1 (liver).

OCT 2005

CT-scan: confirmed bilateral nodular lesions within the liver (Ø7x8mm in S1, Ø21x16mm in S4, Ø24x20 mm in S5, Ø23x20mm and Ø11x9mm in S6, Ø32x29 mm in right-left lobe, Ø8x9mm in the central portion of left lob , Ø11x9mm and Ø11x14 mm in S8).

Octreoscan: significant uptake in all hepatic lesions.

CgA and 5HIIA within the limits.

DEC 2005

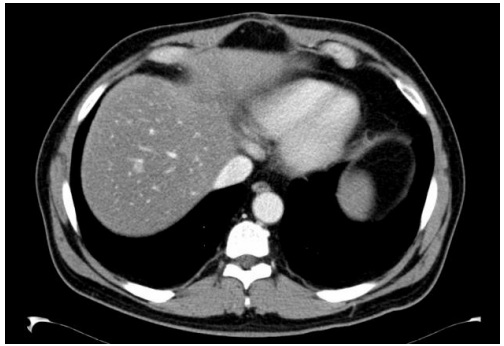
Octreotide LAR 20 mg every 28 days.

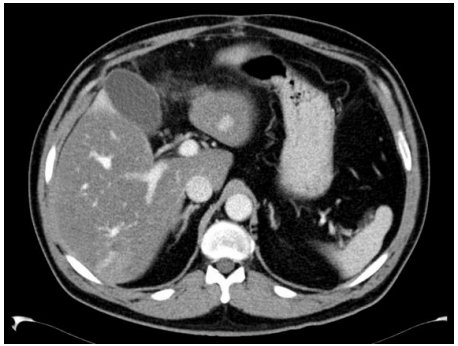
MAR 2006

Multidisciplinar Tumor Board discussion: TACE and subsequent evaluation for liver transplantation + SSA analogue

April 2006:

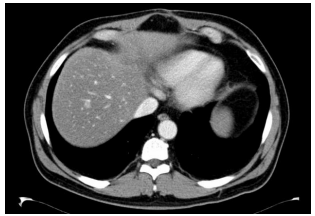
-TACE (right lobe lesions, S6 and S7)
- Octreotide LAR 20 mg every 28 days

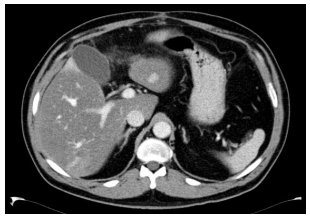




APR 2006
TACE (right lobe lesions, S6 and S7)

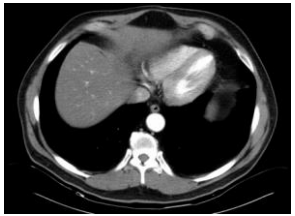
APR 2006

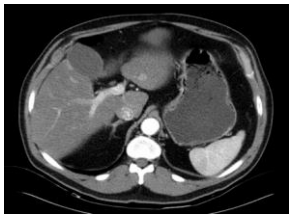




SD

FEB 2019





Octreotide LAR 20 mg every 28 days

How would you consider SSA analogues having an impact on history of disease?

1. SSA analogues guarantee stable disease and should be continued (favorable to continuation)
2. SSA analogues have had a secondary role compared to a previous successfull surgery on primitive tumor together with loco-regional treatment (favorable to treatment discontinuation).
3. Considering that pt has received an undertreatment (lower doses of SSA analogue), it could be hypothized that evolution of NET is indipendent of continuation of SSA analogues (favorable to treatment discontinuation).

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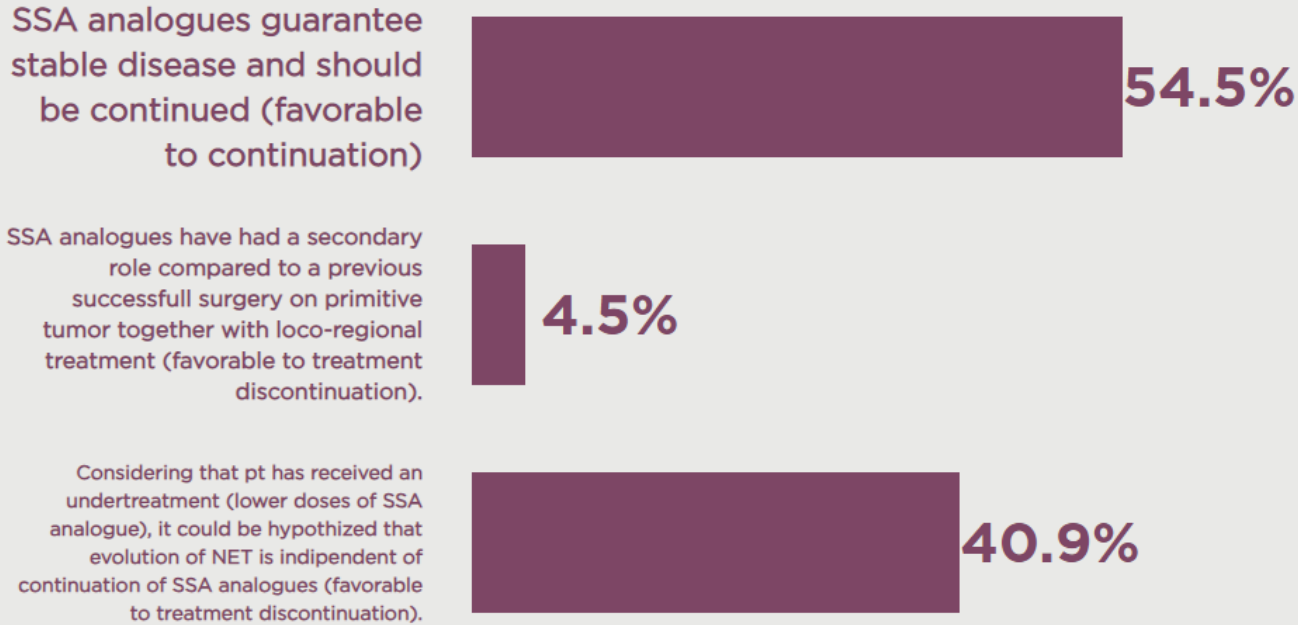

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ENETS GUIDELINES: continuation of SSA analogue until disease progression

Institutional best long-responders

LG

male, NET G1, unknown p.o., M + liver, 1997

22 years, Octreotide 30 mg every 28

CG

female, ileal NET G1, M + liver, 2005 right emicolectomy + TACE

14 years, Octreotide 20 mg every 28

BP

male, NET G1, unknown p. o., M + liver, TACE + RF in 2006

13 years , Octreotide 30 mg every 28

CS

male, NET G1, unknown p.o., M + liver, 2010

9 years, Lanreotide 120 mg every 28

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

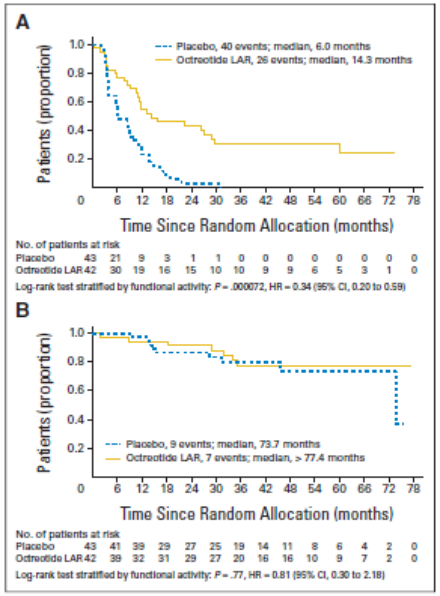


Fig 2. (A) Conservative intent-to-treat analysis of time to progression or tumor-related death. (B) Intent-to-treat analysis of overall survival. HR, hazard ratio.

BJC

British Journal of Cancer (2016) 115, 1321–1327 | doi: 10.1038/bjc.2016.349

Keywords: octreotide LAR; neuroendocrine tumours; antiproliferative activity

Predictive factors of antiproliferative activity of octreotide LAR as first-line therapy for advanced neuroendocrine tumours

Faidon-Marios Laskaratos[*,1], Martin Walker[2], Keval Naik[1], Emmanouil Maragkoudakis[1], Nikolaos Oikonomopoulos[1], Lee Grant[3], Tim Meyer[1,4], Martyn Caplin[1] and Christos Toumpanakis[1]

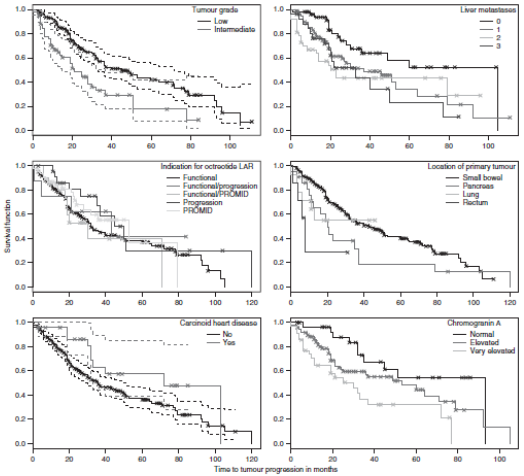


Figure 2. Kaplan-Meier estimates of the survival function for time to tumour progression in patients with advanced neuroendocrine tumours, stratified by different variables.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

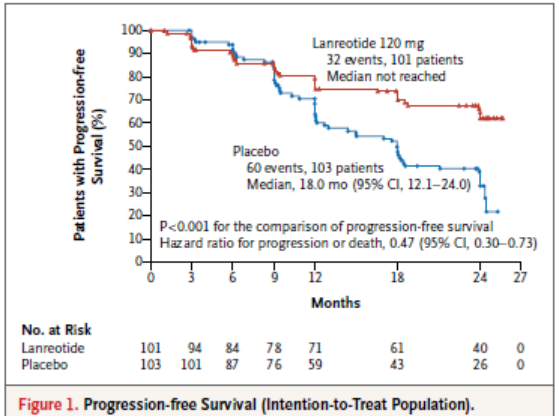
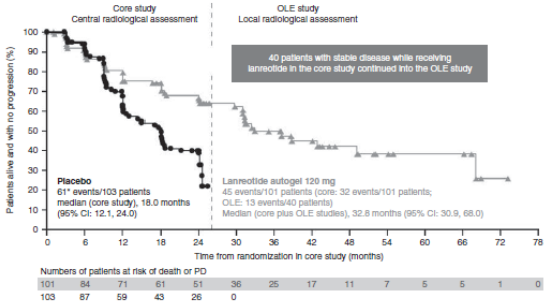


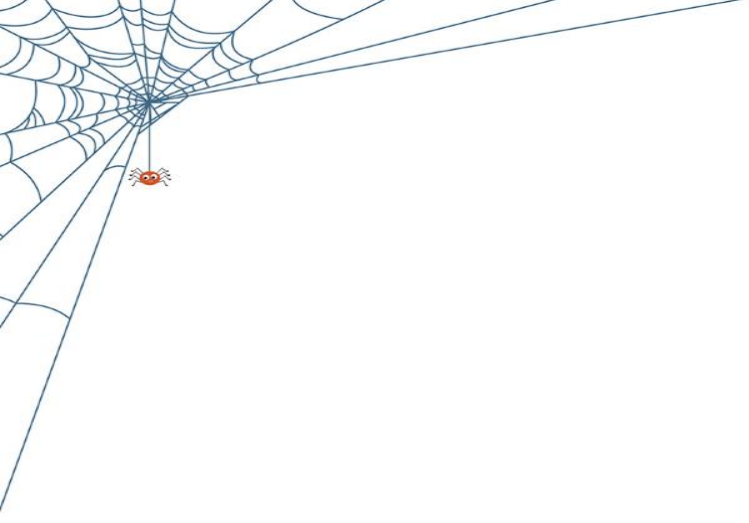
Figure 1. Progression-free Survival (Intention-to-Treat Population).

Research
Open Access
M E Caplin et al. | Anti-tumour effects of lanreotide | 23:3 | 191–199

Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study

Martyn E Caplin[1], Marianne Pavel[2], Jarosław B Ćwikła[3], Alexandria T Phan[4], Markus Raderer[5], Eva Sedláčková[6], Guillaume Cadiot[7], Edward M Wolin[8], Jaume Capdevila[9], Lucy Wall[10], Guido Rindi[11], Alison Langley[12], Séverine Martinez[12], Edda Gomez-Panzani[13,*], Philippe Ruszniewski[14,15] and on behalf of the CLARINET Investigators





Session 3: Web Multimodal Tumor Board

Tumor Board 2

Case 4

Urogenital NEC G3

Female 74 yo

PS (ECOG) 0

Medical history

Silent medical history till September 2017

Diagnostic Work-up

SEP 2017

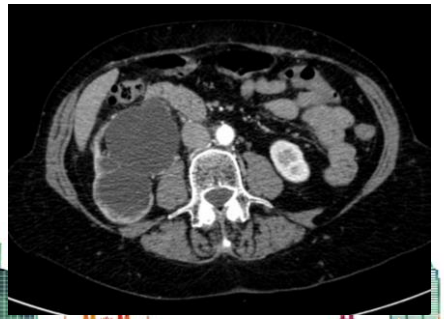
pain on the right side of abdomen and in the iliac fossa

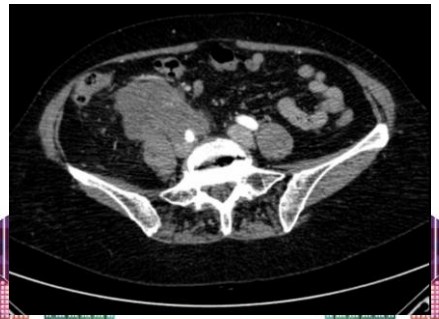
OCT 2017 – NOV 2017:

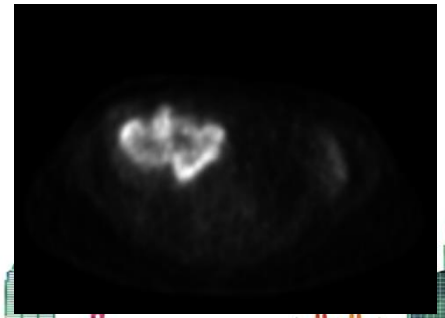
CT Scan: huge lesion close to the IVC, the duodenum and the right kidney showing marked hydronephrosis; the lesion comes into contact with the right psoas muscle and the right common and external iliac arteries

18FDG-PET: intense uptake in the right pararenal region

US-guided biopsy, citology: **Neuroendocrine carcinoma, G3; Ki-67 70%**







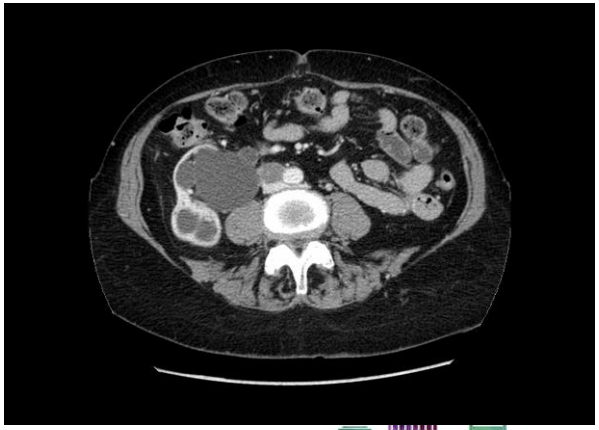
Therapy

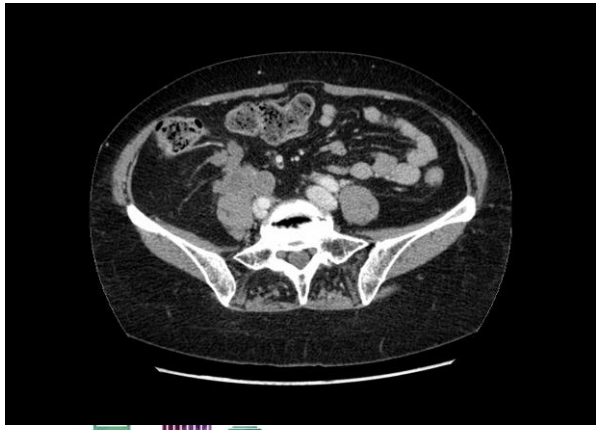
DEC 2017 – SEP 2018

chemotherapy with carboplatin and etoposide (6 cycles) following etoposide alone

AUG 2018

CT scan: dimensional response but still close connection to vessels (PD)





Which treatment would you propose next?

1. Surgery
2. Radiotherapy
3. PRRT
4. Chemotherapy

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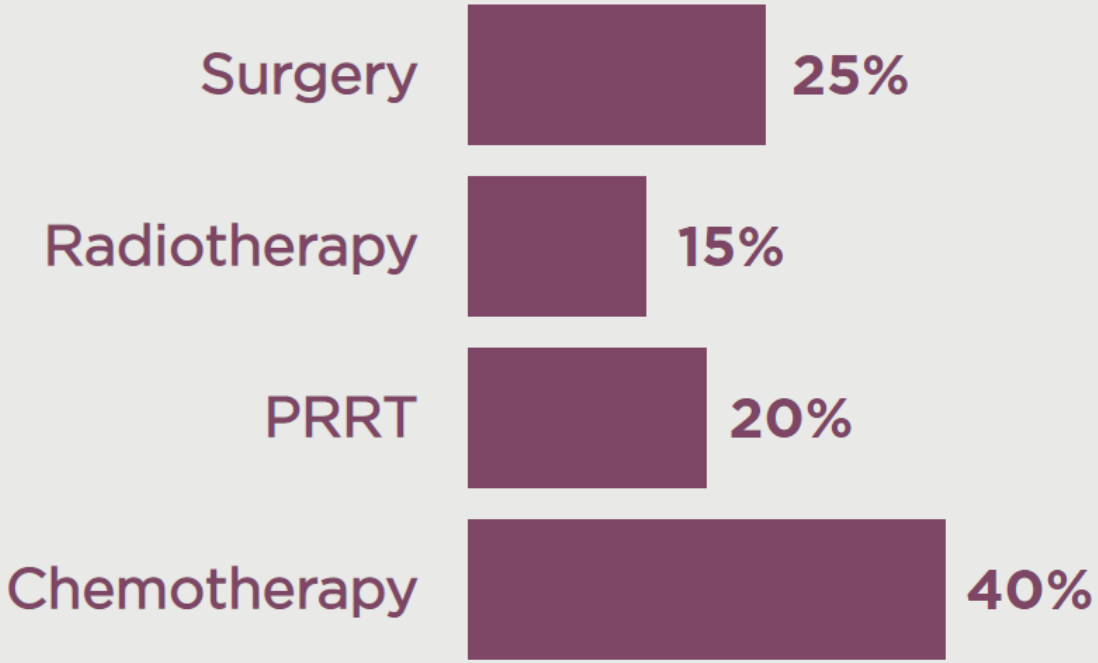


Preoperative Exams

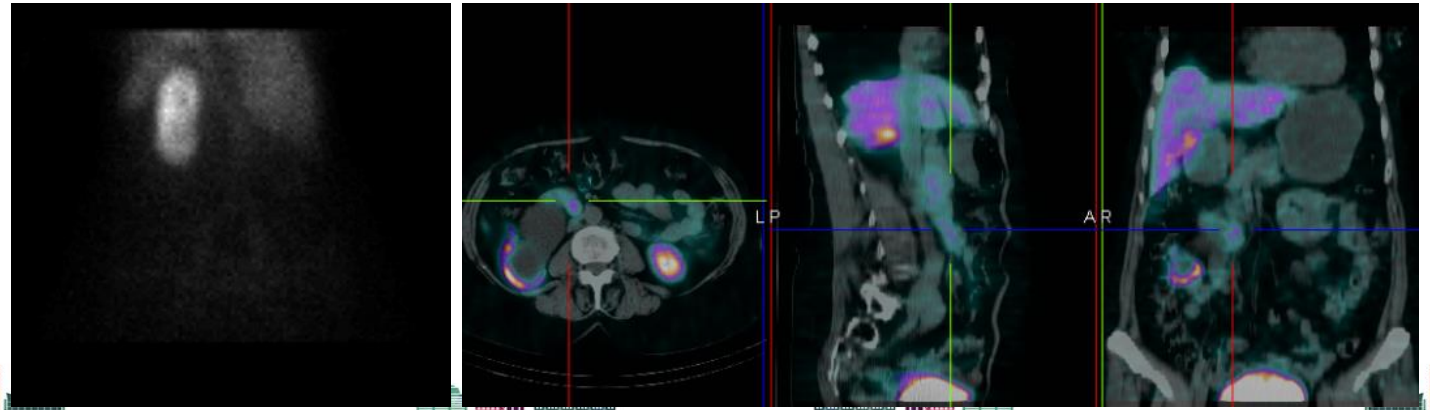
AUG 2018

Tumor Board Discussion: indication to surgery after exclusion of any other possible site of primary tumor (pancreas or small gut)

SEP 2018

Renal Scintigraphy: left kidney uptake 99,96%; right kidney uptake 0,04%

SPECT CT with 99mTc-Tektrotyd: intense uptake in the right retroperitonal space



Surgery

SEP 2018

Surgical Intervention: removal of the right retroperitoneal lesion together with right kidney, right adrenal gland and the right colon + pelvic locoregional lymphadenectomy

At pathology: **NEC of the urinary tract, Ki-67>90%;** the tumor invades the right psoas muscle and two lymph nodes in the pelvic region. Positive right ureteral margin: microfoci of cancer

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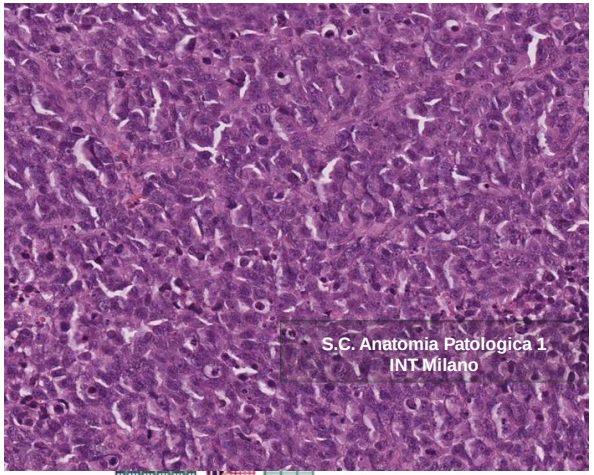
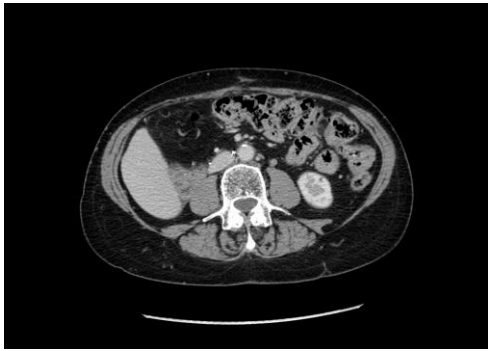
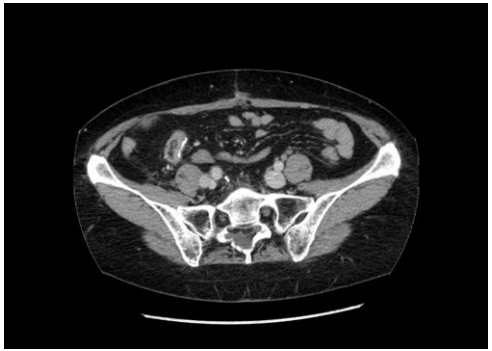


Adjuvant Therapy

JAN 2019

CT scan: no evidence of disease; adjuvant radiotherapy





Literature Review

Upper Urinary Tract Neuroendocrine Carcinoma 1985-2017

(*Systematic review and two new cases of primary upper urinary tract neuroendocrine carcinoma, T. Nakasato 2018*): **70 cases**

Renal Pelvis	22 (31,4)
Ureter	41 (58,6)
Renal Pelvis + Ureter	6 (8,6)
Ureter + Bladder	1 (1,4)