SPC

報告者: 宋明璋
指導醫師: 蘇正熙 主任
日期: 2016-08-27

General Data

- Name: OOO
- Age: 66 y/o
- Gender: female
- Chart No.: xxxxxxx
- Admission: 2016/07/31
- Underlying disease: HCVD under regular check-up

Chief Complaint

- Chest tightness and LUQ tenderness off and on for years

Present Illness

- Due to the chief complaints, she called on our CV OPD for help.
  - Treadmill test, EKG, and cardio echo showed normal.
- Becuase of persisted symtoms, she called on OO長庚 H. a month ago.
  - Upper GI panendoscopy told GERD and gastric ulcers.
  - CT scan showed **a lesion over RUL of lung** and **intraabdominal tumors**.
- Then she called on our CS and GS OPD.
  - She denied tarrry stool, poor appetite, diarrhea, loss of body weight, and hematuria. Constipation (+)

Personal History

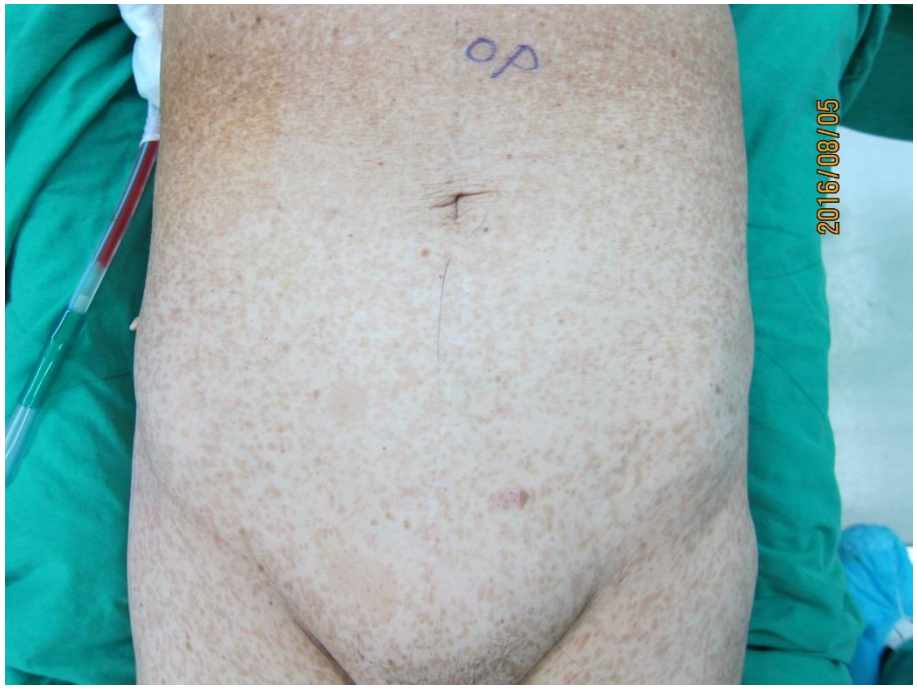
- Smoking: nil
- Alcohol: nil
- Allergy: NKA
- Travel history: nil

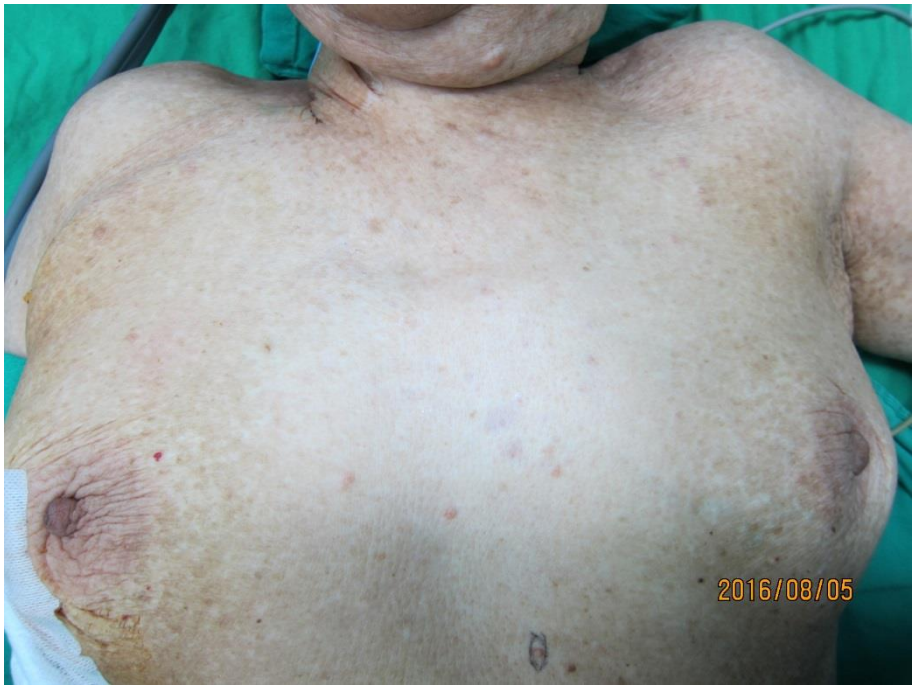
Family History

- Hypertension

Physical Exams

- General appearance:
  - Fair-looking, alert consciousness
- HEENT:
  - Sclera: not icteric, Conjunctiva: not anemic
- Chest:
  - Smooth breath pattern, clear breath sound
- Abdomen:
  - Shape: soft and flat, no op scar
  - Palpation: no palpable mass, mild tenderness over epigastric region and LUQ of abodmen. no muscle guarding, no Murphy sign, no rebounding pain
  - Normoactive bowel sound
  - Liver and spleen: not palpable, shifting dullness(-)
- Extremities:
  - Free movement, no cyanosis, no pitting edema
- Skin:
  - Multiple brownish spots and small nodules over the trunk





Two daughters also have abdominal brownish pigmented spots

Lab Data

項目名稱	判斷	結果值	單位	參考值範圍
CBC				
WBC		6.6	10^3/uL	4.0 - 10.0
RBC	H	5.64	10^6/uL	3.70 - 5.50
HGB	L	11.1	g/dL	11.3 - 15.3
HCT		37.3	%	33.0 - 47.0
MCV	L	66.1	fL	80.0 - 100.0
MCH	L	19.7	pg	25.0 - 34.0
MCHC	L	29.8	g/dL	30.0 - 36.0
PLT		268	10^3/uL	130 - 400
DIFF				
NEUT%		59.7	%	40.0 - 75.0
LYMPH%		30.3	%	20.0 - 45.0
MONO%		8.1	%	2.0 - 10.0
EO%		1.4	%	1.0 - 6.0
BASO%		0.5	%	0 - 1

Lab Data

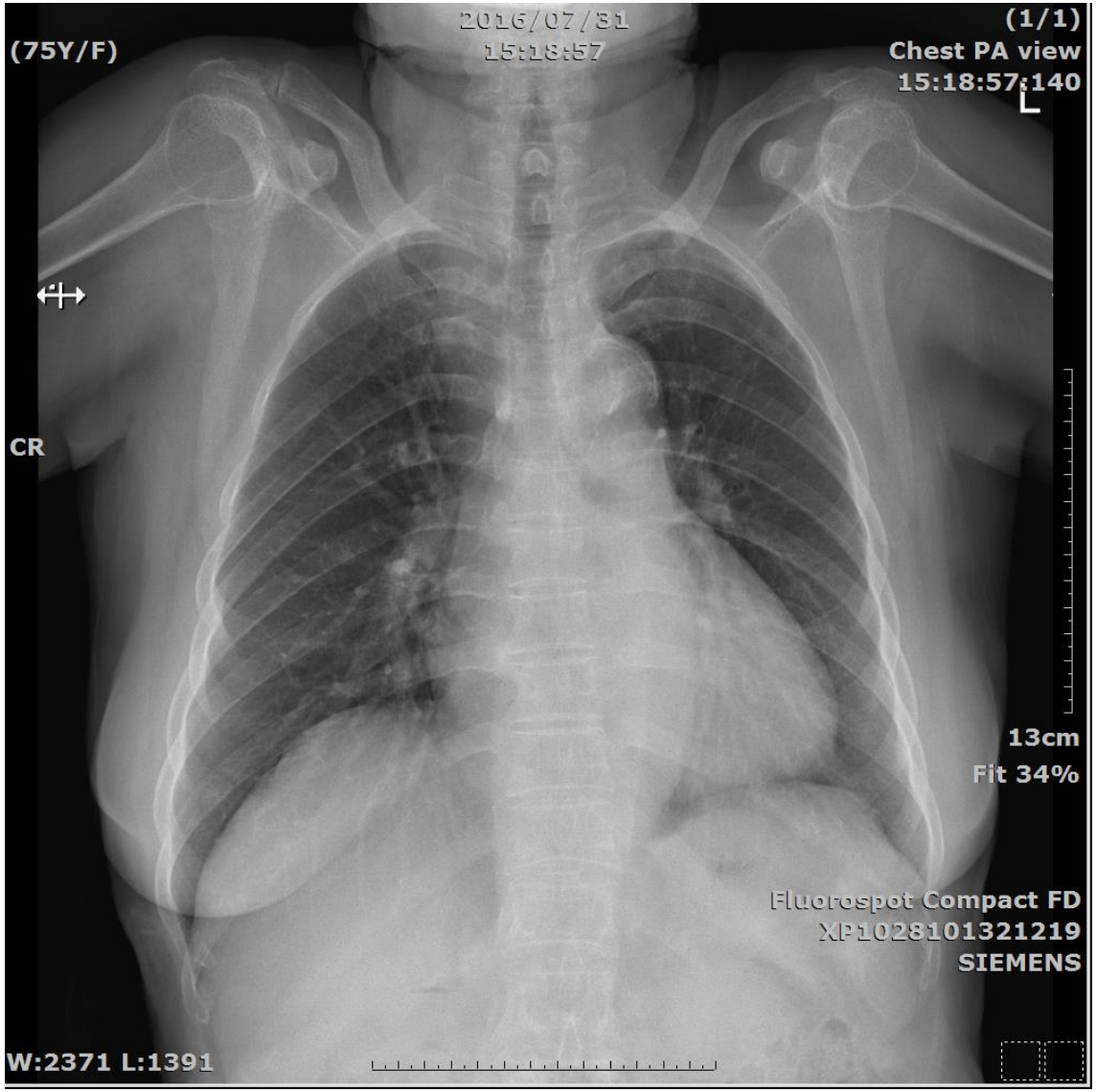
項目名稱	判斷	結果值	單位	參考值範圍
Glucose AC	H	145	mg/dL	70 - 110
BUN		12.2	mg/dL	8.0 - 20.0
Creatinine		0.76	mg/dL	0.44 - 1.27
eGFR		79		> 60
AST		14	IU/L	5 - 50
ALT		9	IU/L	5-50
Ca		8.7	mg/dL	8.5 - 10.1
Na		139	mmol/L	136 - 144
K	L	3.4	mmol/L	3.6 - 5.1
Cl		110	mmol/L	101 - 111

Tumor Markers

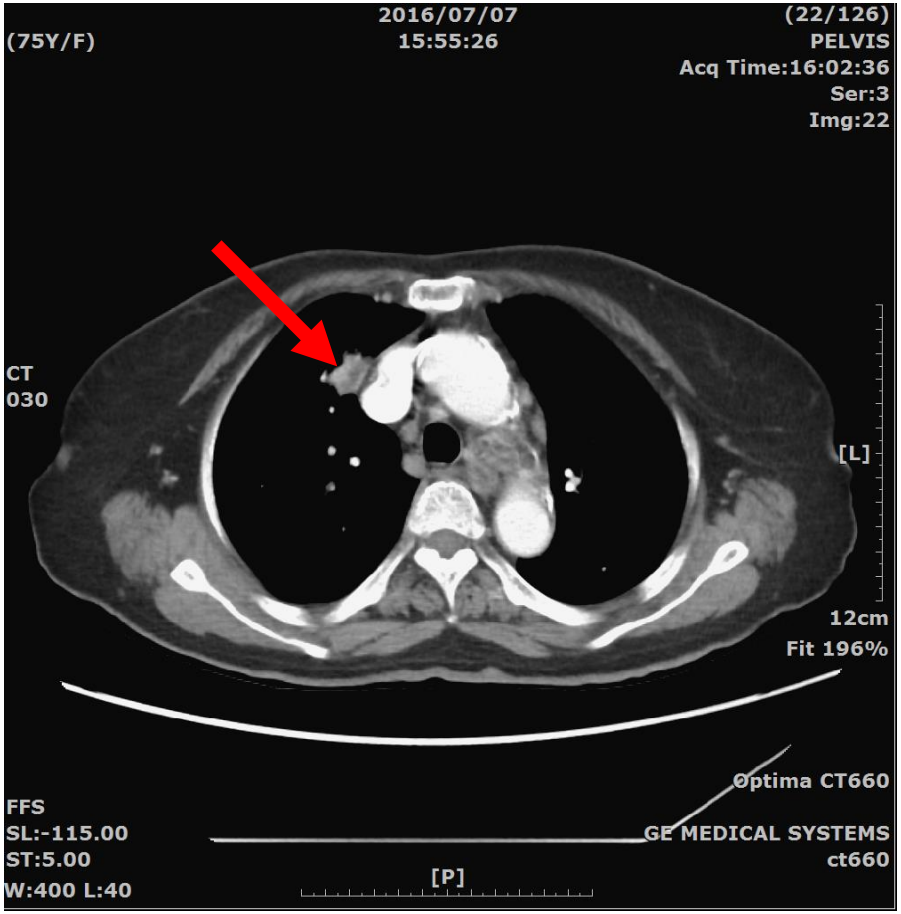
項目名稱	判斷	結果值	單位	參考值範圍
CEA		3.9	ng/mL	MRR
CA125		9.5	U/mL	≦ 35
CA153		7.6	U/mL	≦ 25
CA199		17.7	U/mL	≦ 39
SCC		0.5	ng/mL	≦ 2.5

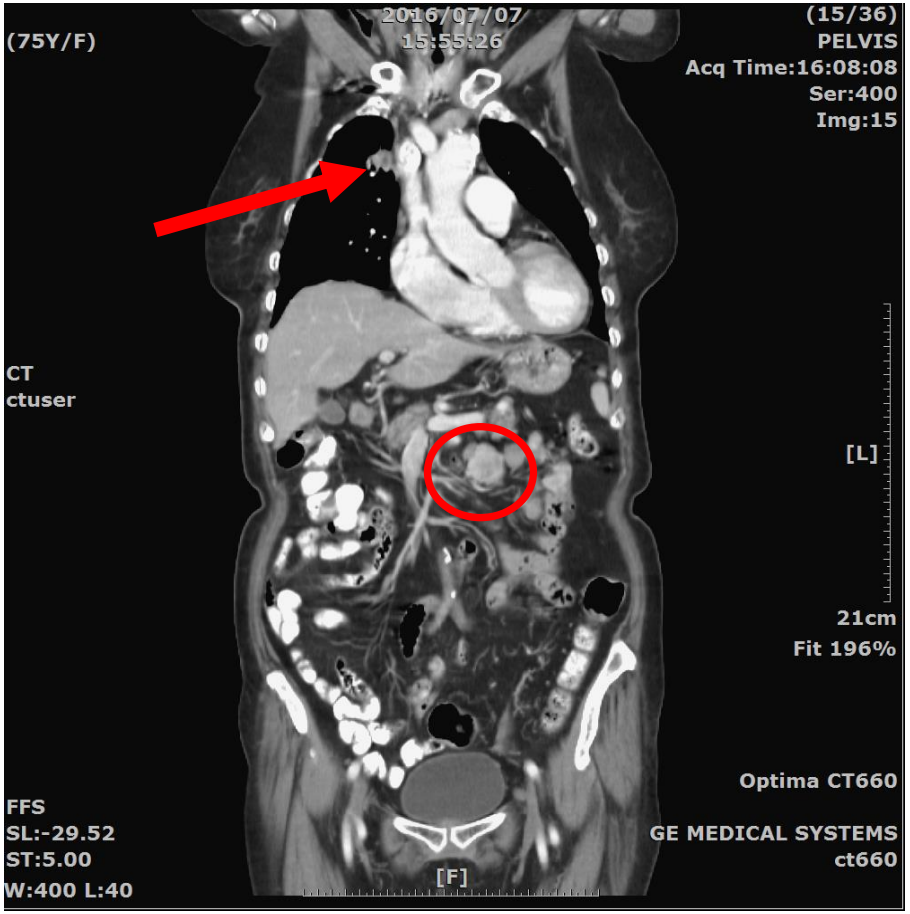
Radiology

CXR


2016/07/31
15:18:57
(75Y/F)
(1/1)
Chest PA view
15:18:57:140
L
CR
13cm
Fit 34%
Fluorospot Compact FD
XP1028101321219
SIEMENS
W:2371 L:1391

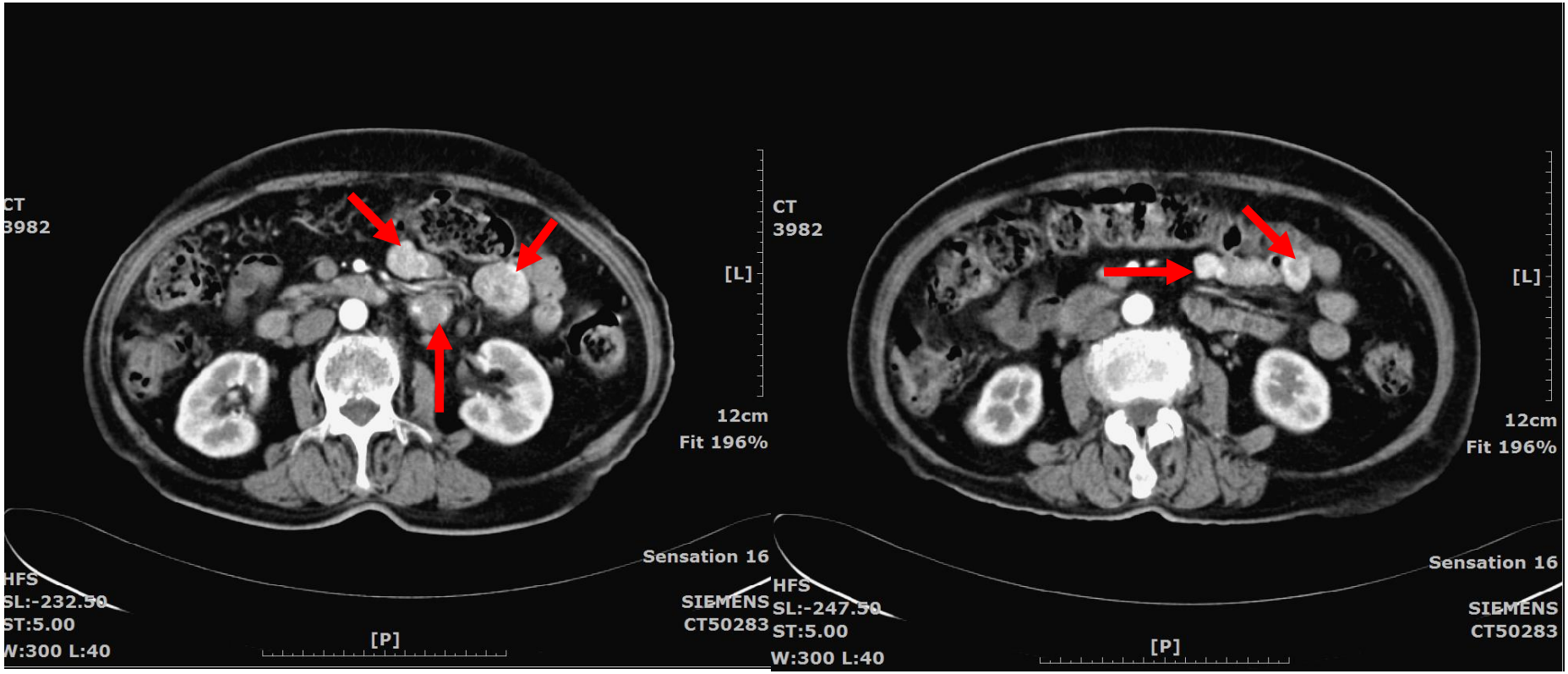
CT of chest


2016/07/07
15:55:26
(75Y/F)
(22/126)
PELVIS
Acq Time:16:02:36
Ser:3
Img:22
CT
030
[L]
12cm
Fit 196%
Optima CT660
FFS
SL:-115.00
ST:5.00
W:400 L:40
GE MEDICAL SYSTEMS
ct660
[P]

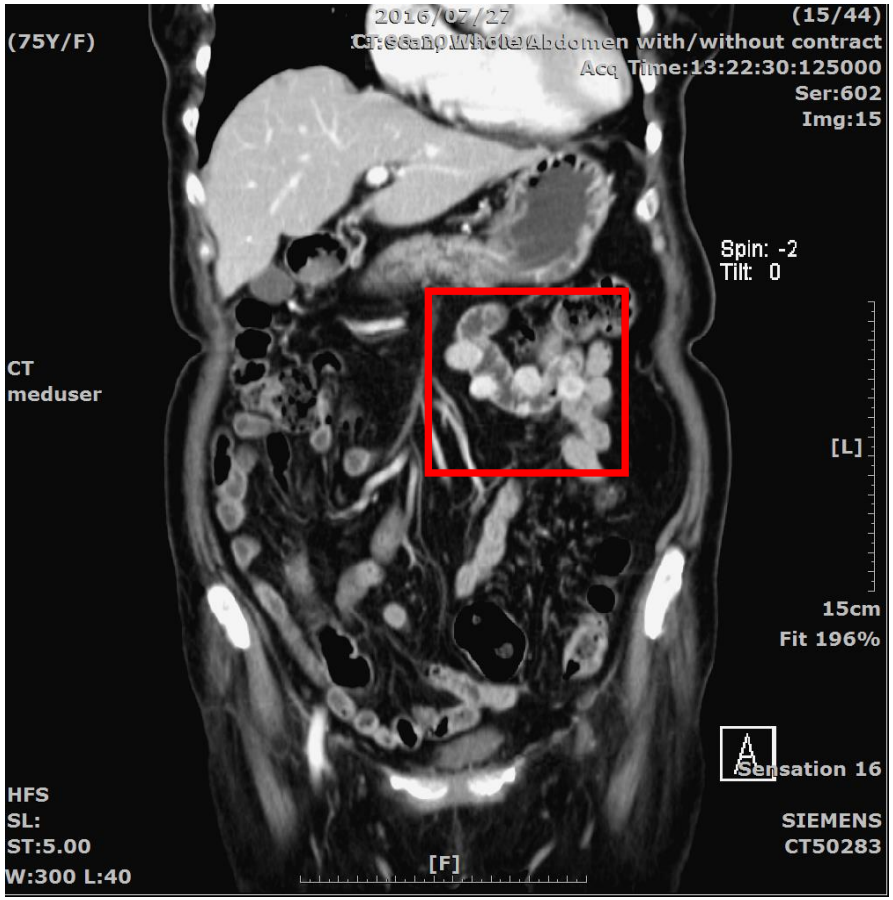

2016/07/07
15:55:26
(75Y/F)
(15/36)
PELVIS
Acq Time:16:08:08
Ser:400
Img:15
CT
ctuser
[L]
21cm
Fit 196%
Optima CT660
FFS
SL:-29.52
ST:5.00
W:400 L:40
GE MEDICAL SYSTEMS
ct660
[F]

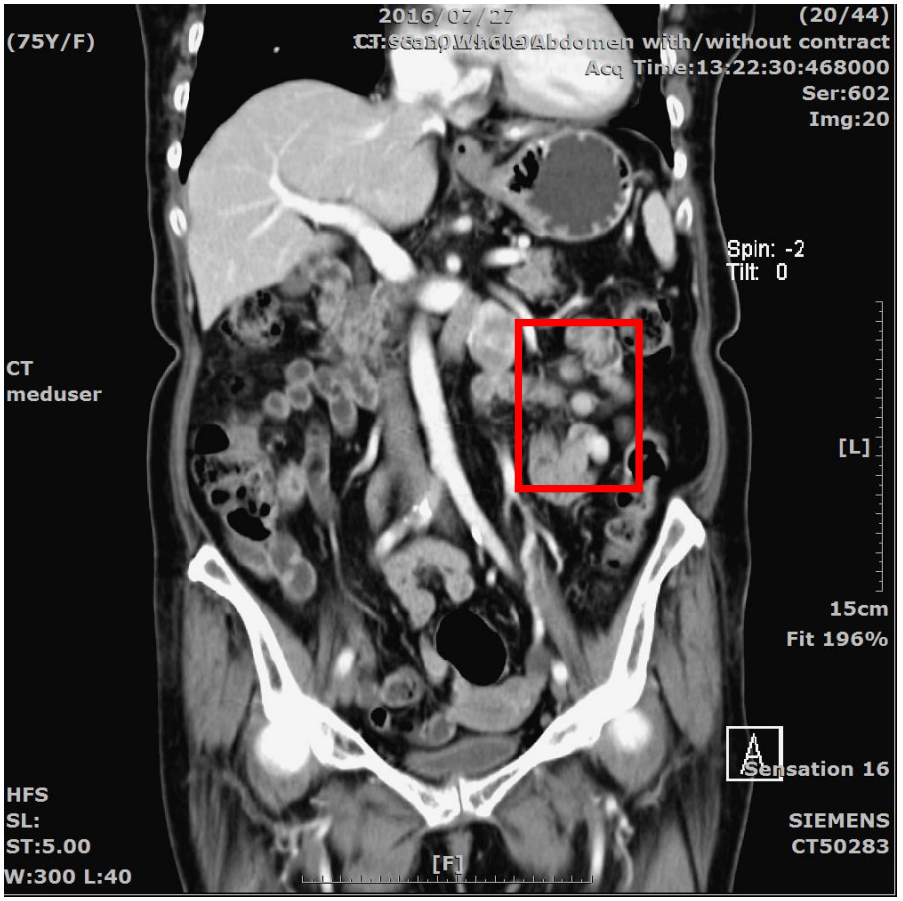
Repeated dynamic CT-scan of abdomen on 2016/07/27

- **Multiple variable sites contrast enhanced on the LUQ of abdomen protruded from bowel wall.**



Repeated dynamic CT-scan of abdomen on 2016/07/27





Impression

- Multiple small bowel tumors
  - Metastasis, origin?
  - GIST
  - Adenocarcinoma
  - Lymphoma
  - Sarcomatoid carcinoma and carconoid
- Tumor of lung, RUL
  - Carcinoma
  - Metastasis
  - Inflammatory nodule

- 2016/08/02 UGI endoscopy:
  - Esophagus: mucosal break < 5 mm at EC junction
  - Stomach: normal.
  - Duodenum: negative to 3rd portion.
- 2016/08/02 Colonoscopy:
  - Mixed hemorrhoids, 位置:Anus
  - Colonic diverticulum, 位置:Ascending colon

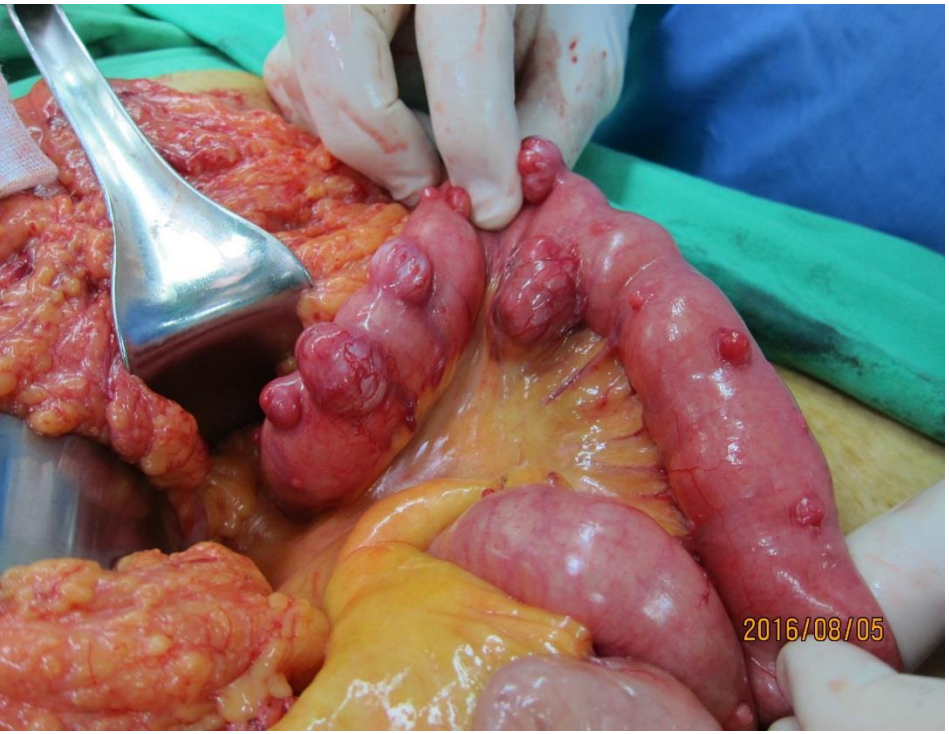
2016/08/05 Operation

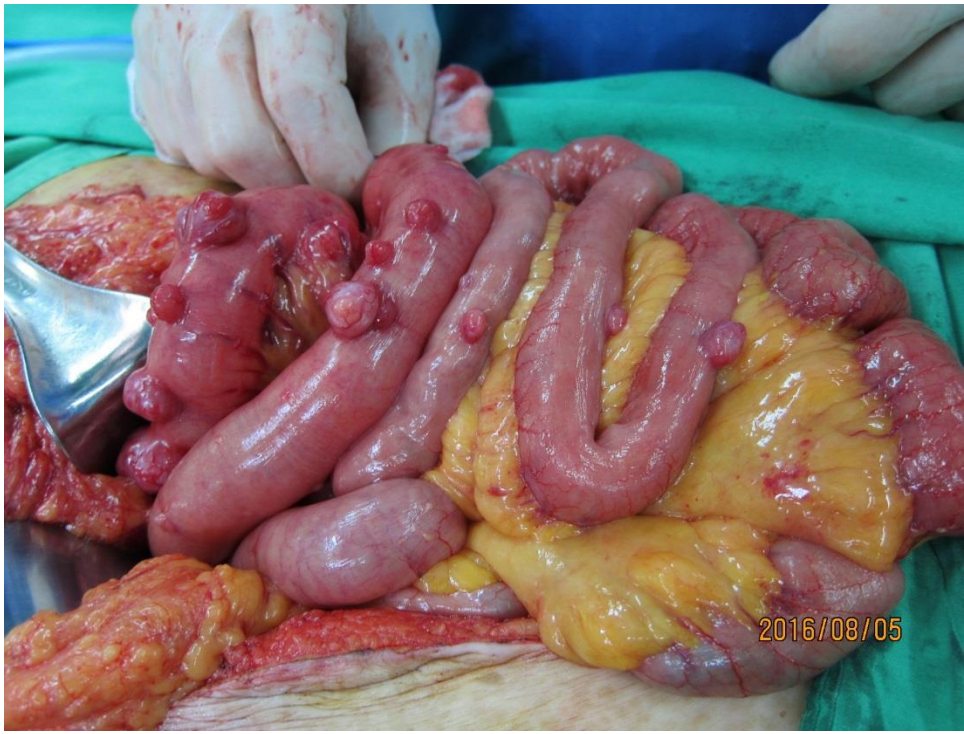
- Combine CS:
  - VATS op with wedge resection of RUL lung tumor

- Exploratory laparotomy

OP findings

- Multiple variable size tumors (the maximum was about 4 cm in size) were noticed over the walls of small bowel and stomach, and omentum, especially the proximal jejunum.
- These tumors grew over serosa layer without submucosal invasion.





Pathological Diagnosis

Pathological Diagnosis:

- Lung, right upper lobe, VATS
  ---Pneumonia
  ---Atypical adenomatous hyperplasia

- Jejunum, proximal, segmental resection
  ---Gastrointestinal stromal tumor (GIST)

- Small bowel nodules, excisional biopsy
  ---Gastrointestinal stromal tumor (GIST)

- Skin, epigastric region, biopsy
  ---Neurofibroma

Micrology

- Mitotic rate: 1/50 HPF
- Histologic grade: low grade
- Risk assessment: low risk

AJCC stage

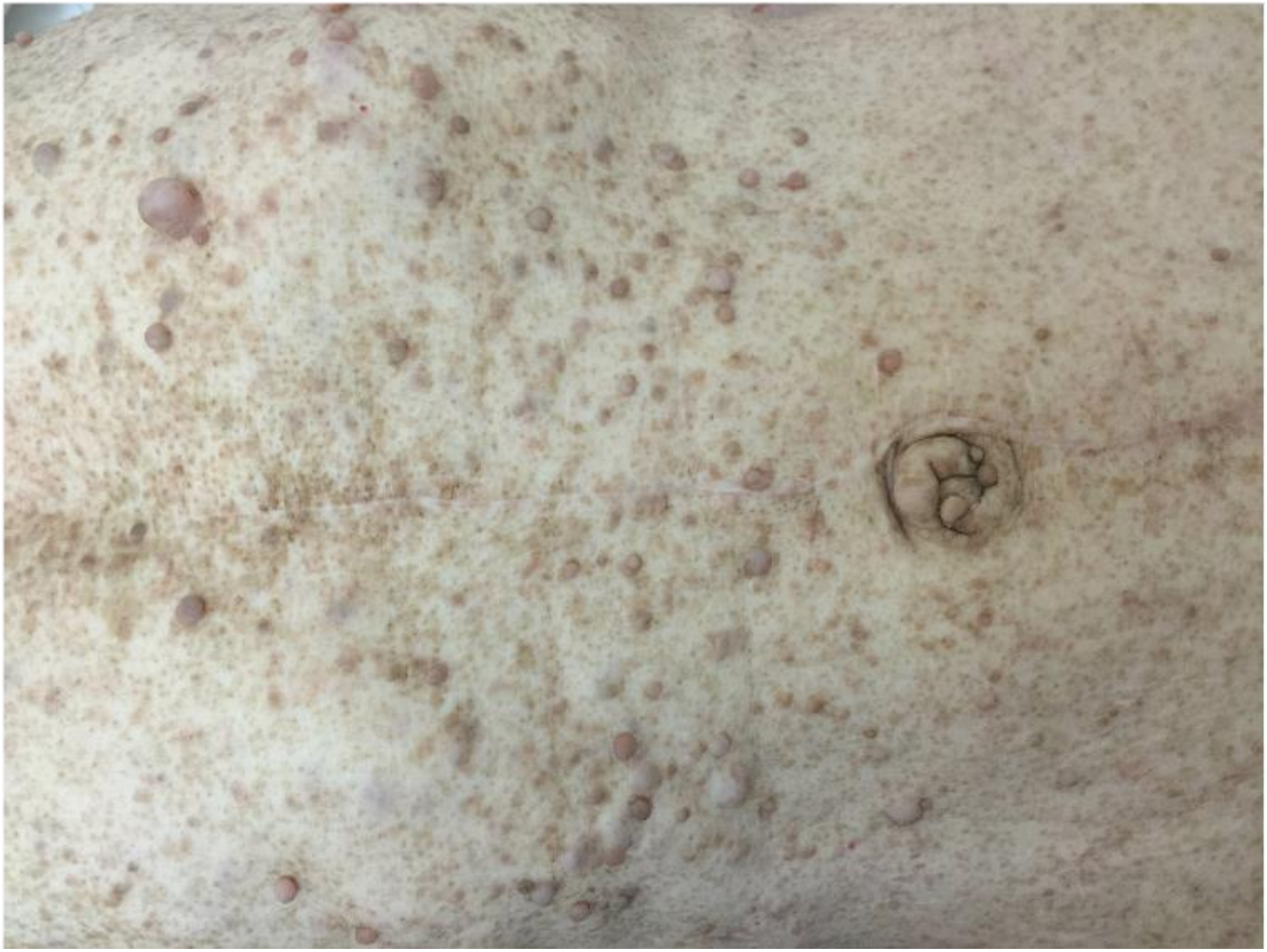
Primary Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence for primary tumor.
T1	Tumor ≤2 cm.
T2	Tumor >2 cm but not >5 cm.
T3	Tumor >5 cm but not >10 cm.
T4	Tumor >10 cm in greatest dimension.

The largest size? Total tumors size?

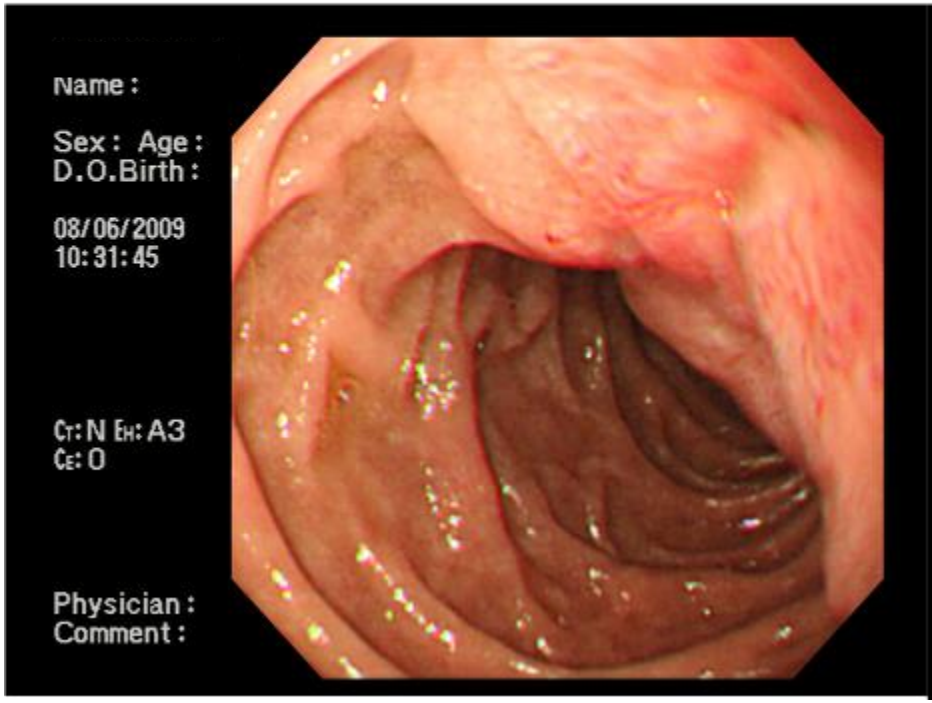
Neurofibromatosis type 1 with multiple GIST

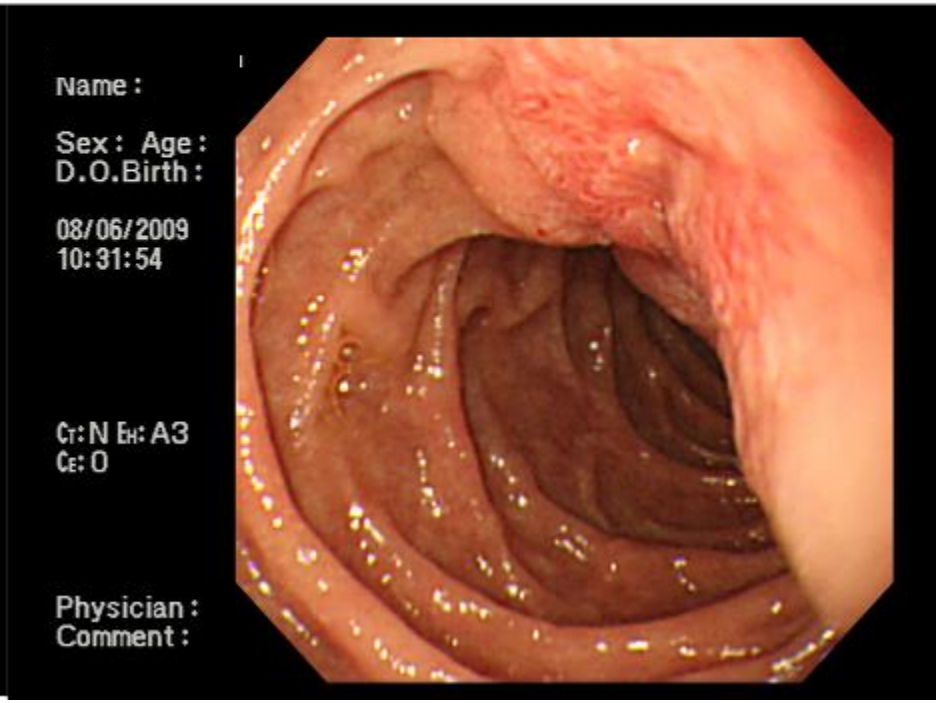
Case 2

- Name: [redacted]
- Age: 60 y/o
- Gender: male
- Neurofibromatosis with intestinal GIST and pancreatic neuroendocrine tumor

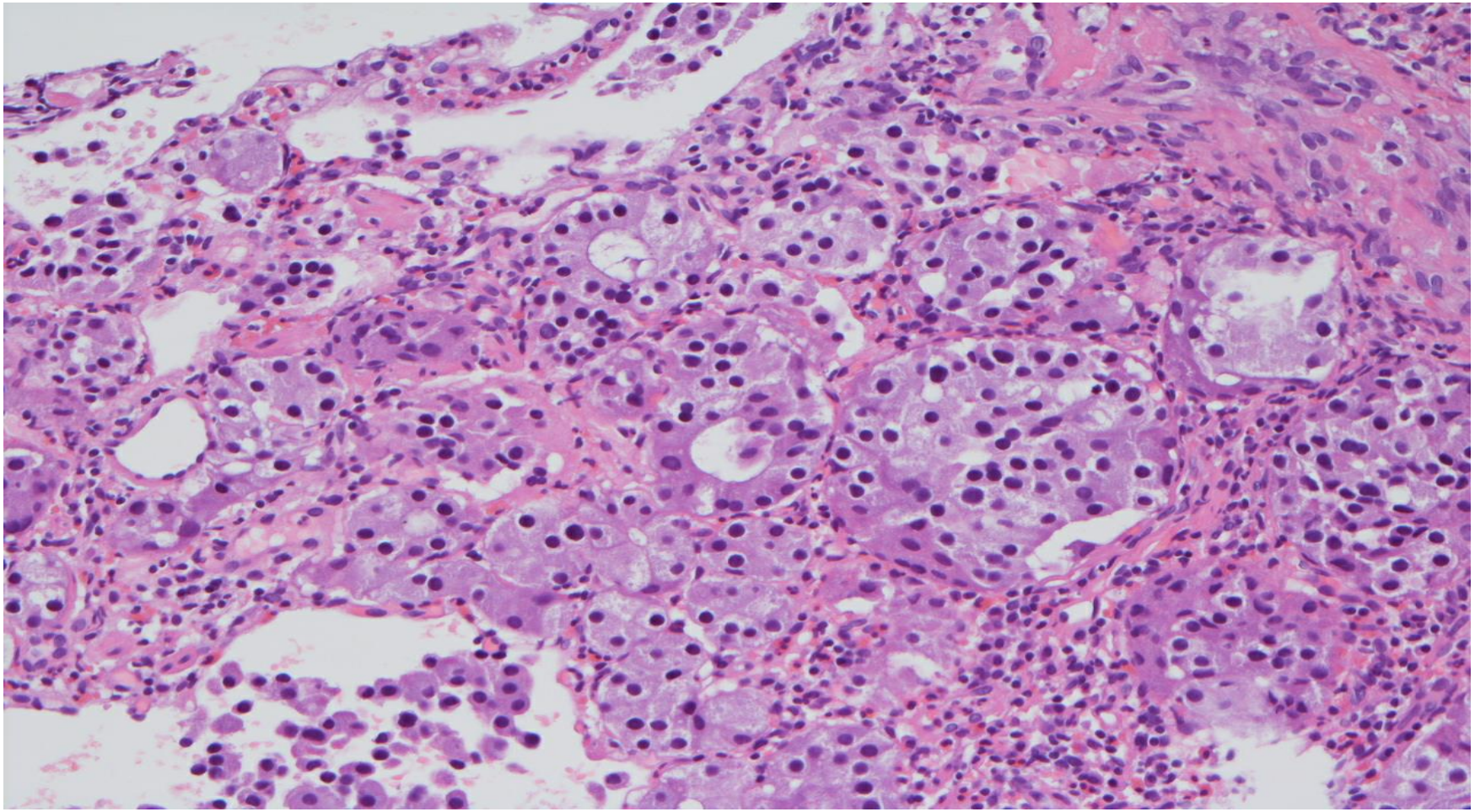


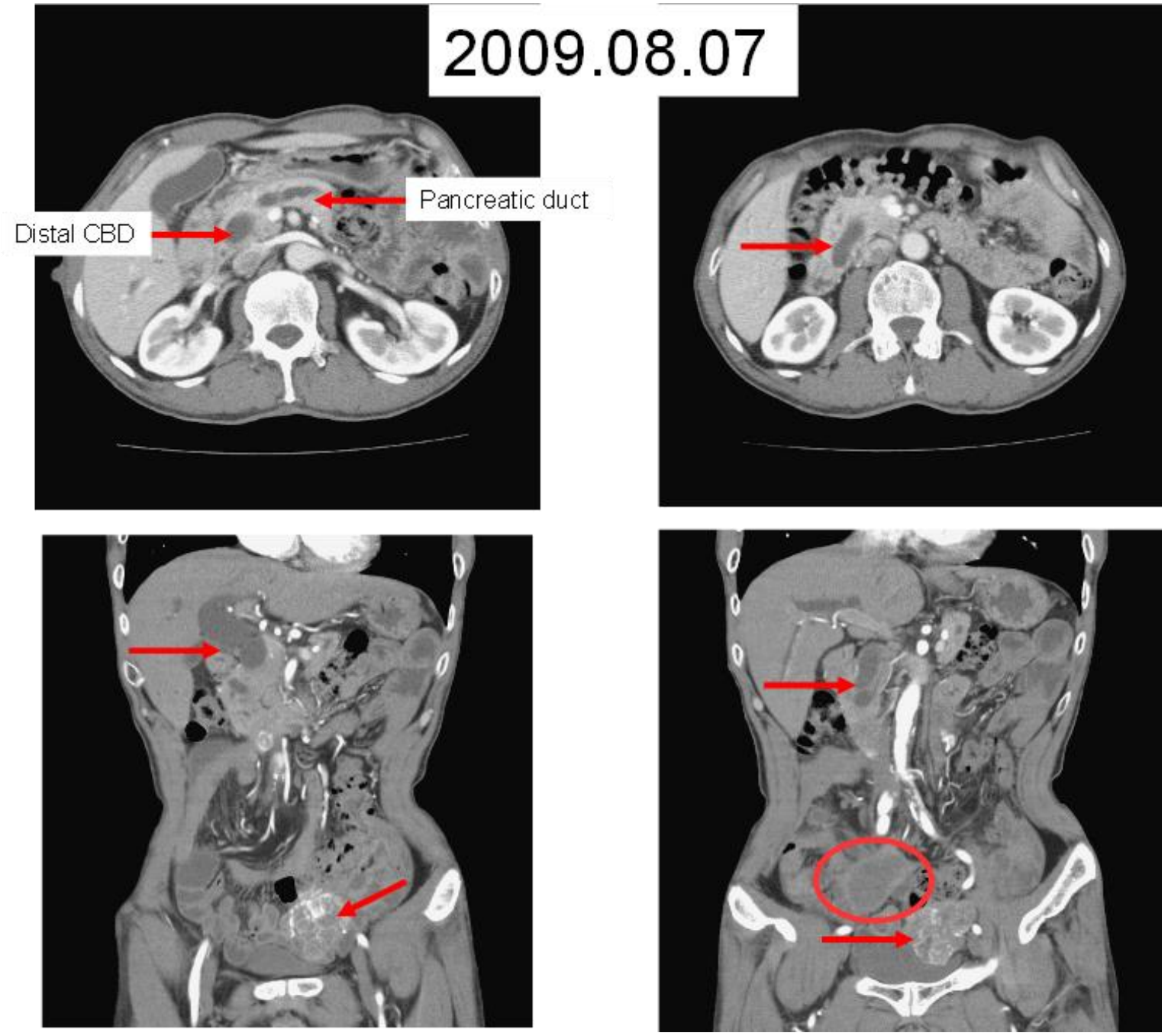
2009.08.06

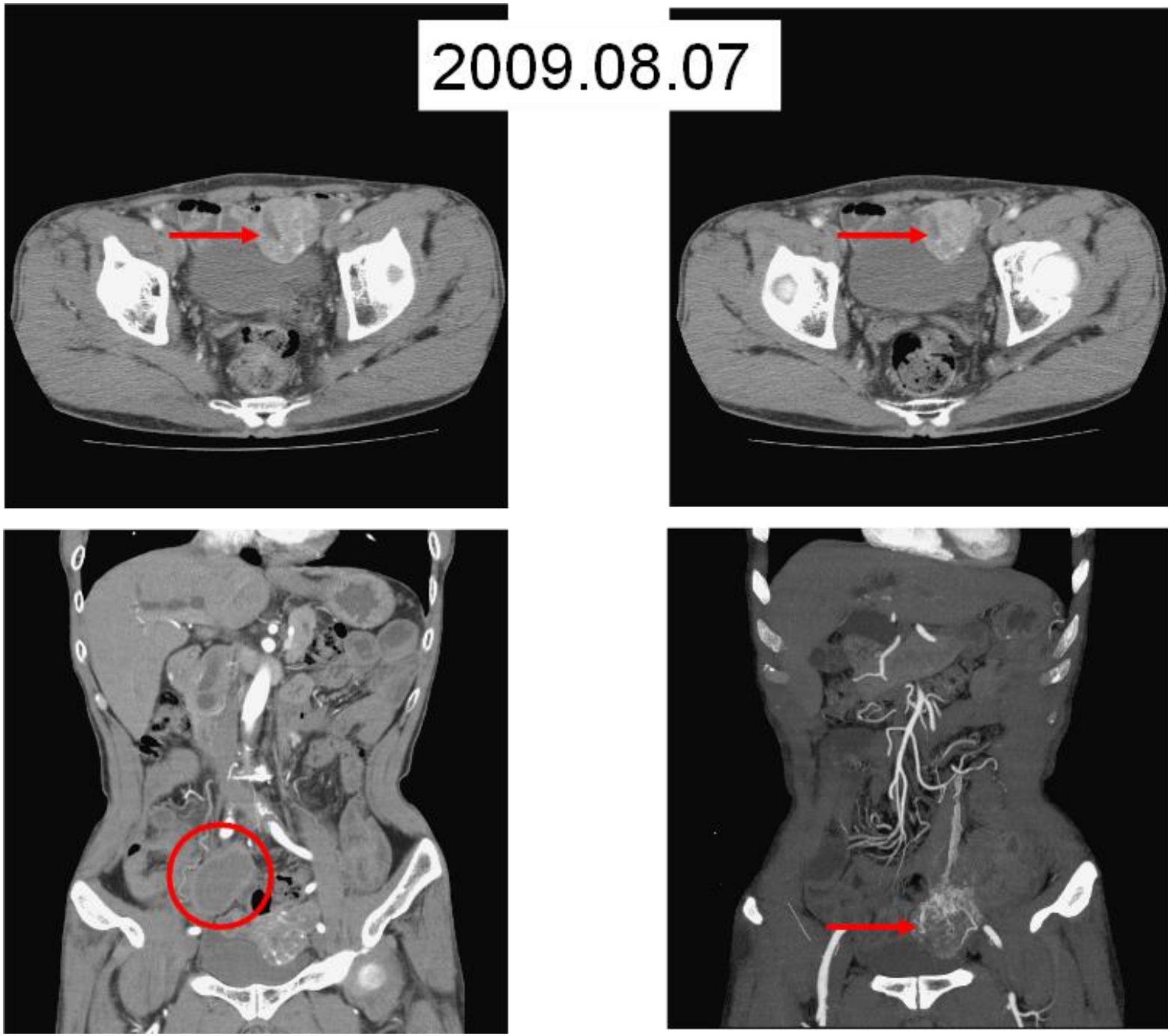

Name :
Sex : Age :
D.O.Birth :
08/06/2009
10:31:45
CT: N EH: A3
CE: 0
Physician :
Comment :


Name :
Sex : Age :
D.O.Birth :
08/06/2009
10:31:54
CT: N EH: A3
CE: 0
Physician :
Comment :

Ampulla of Vater biopsy




2009.08.07
Pancreatic duct
Distal CBD


2009.08.07

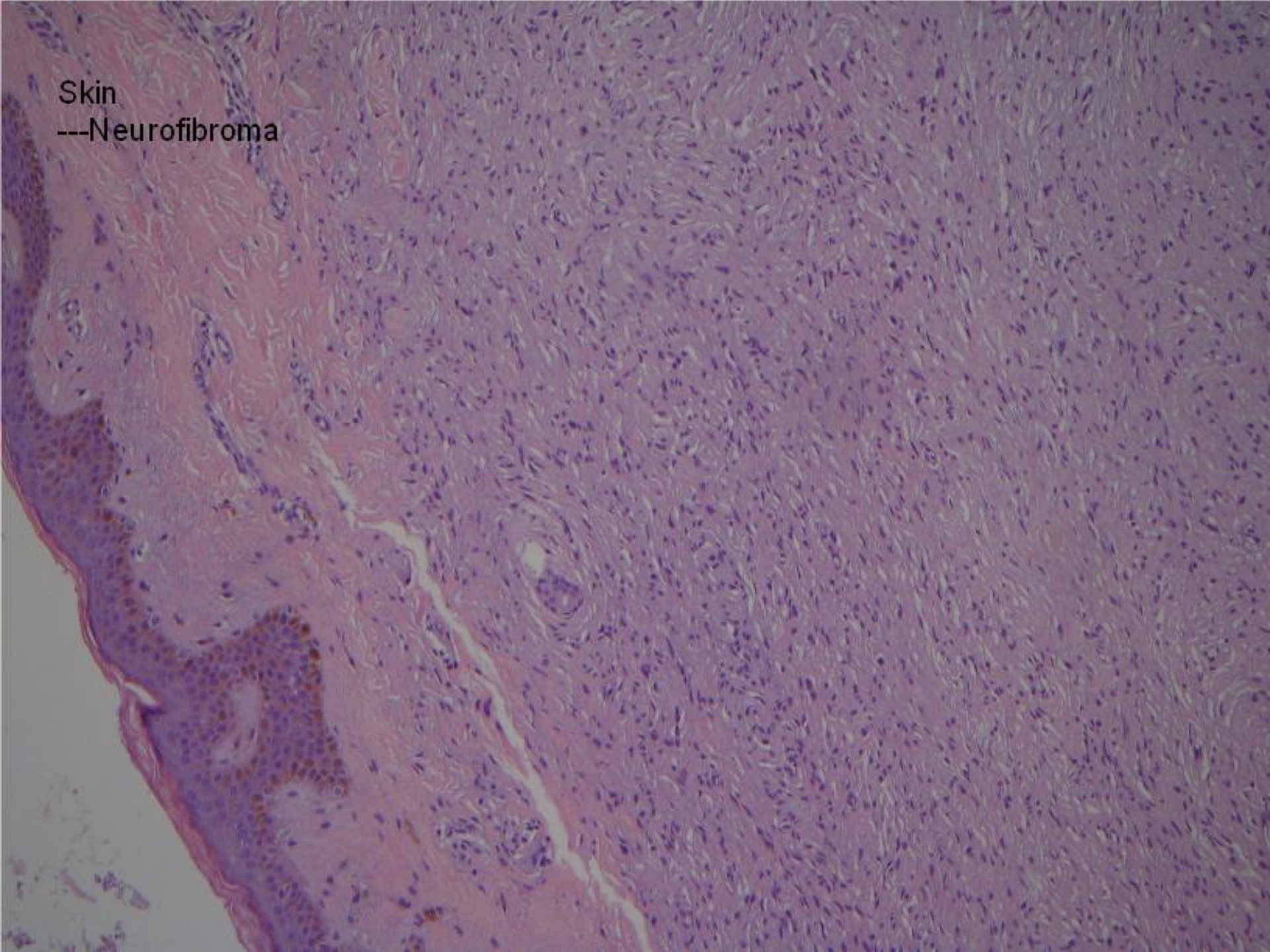
- Operation on [redacted]
- **Pancreaticoduodenectomy**

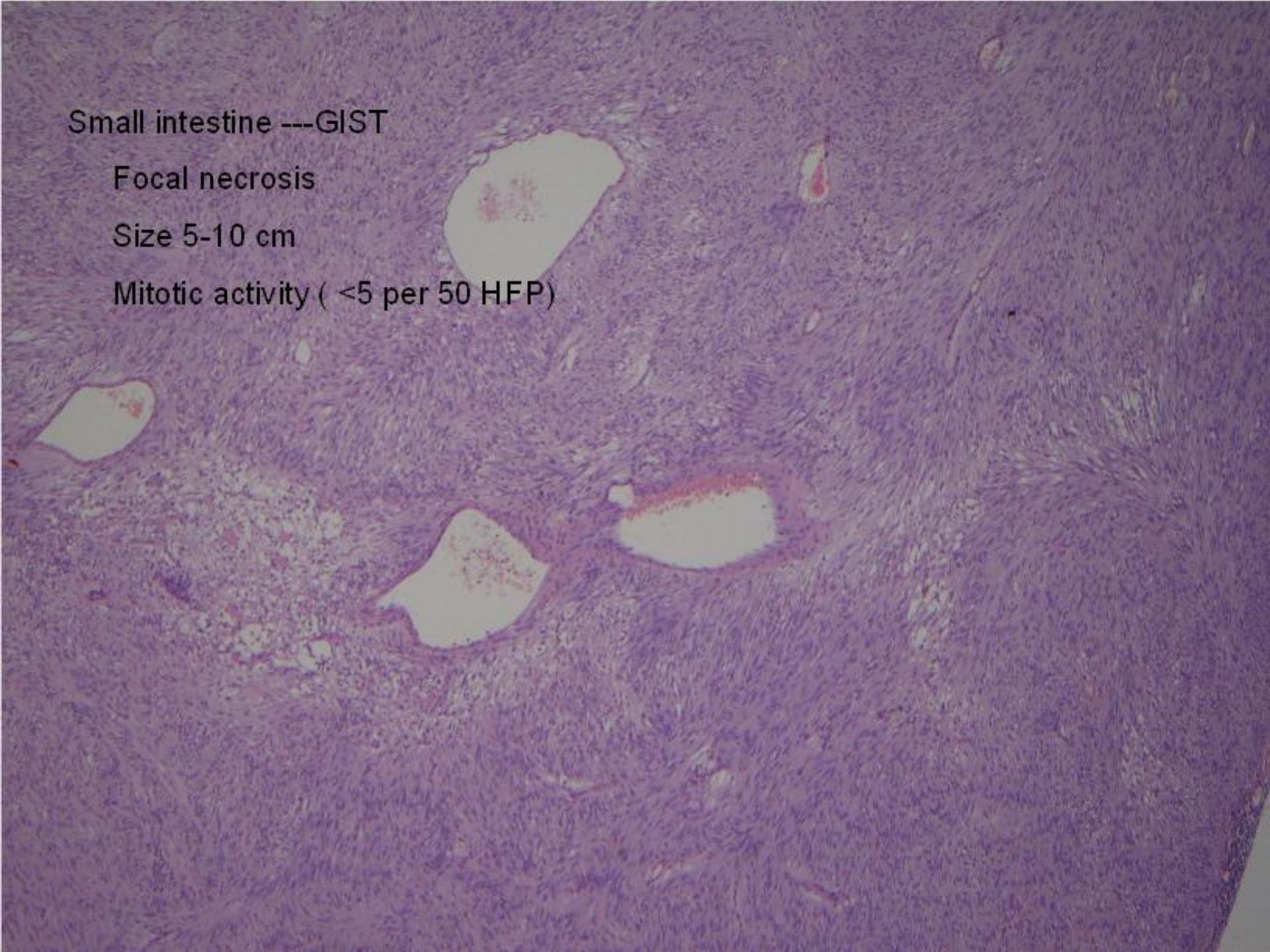
Periampullar vater ---Well differentiated endocrine carcinoma

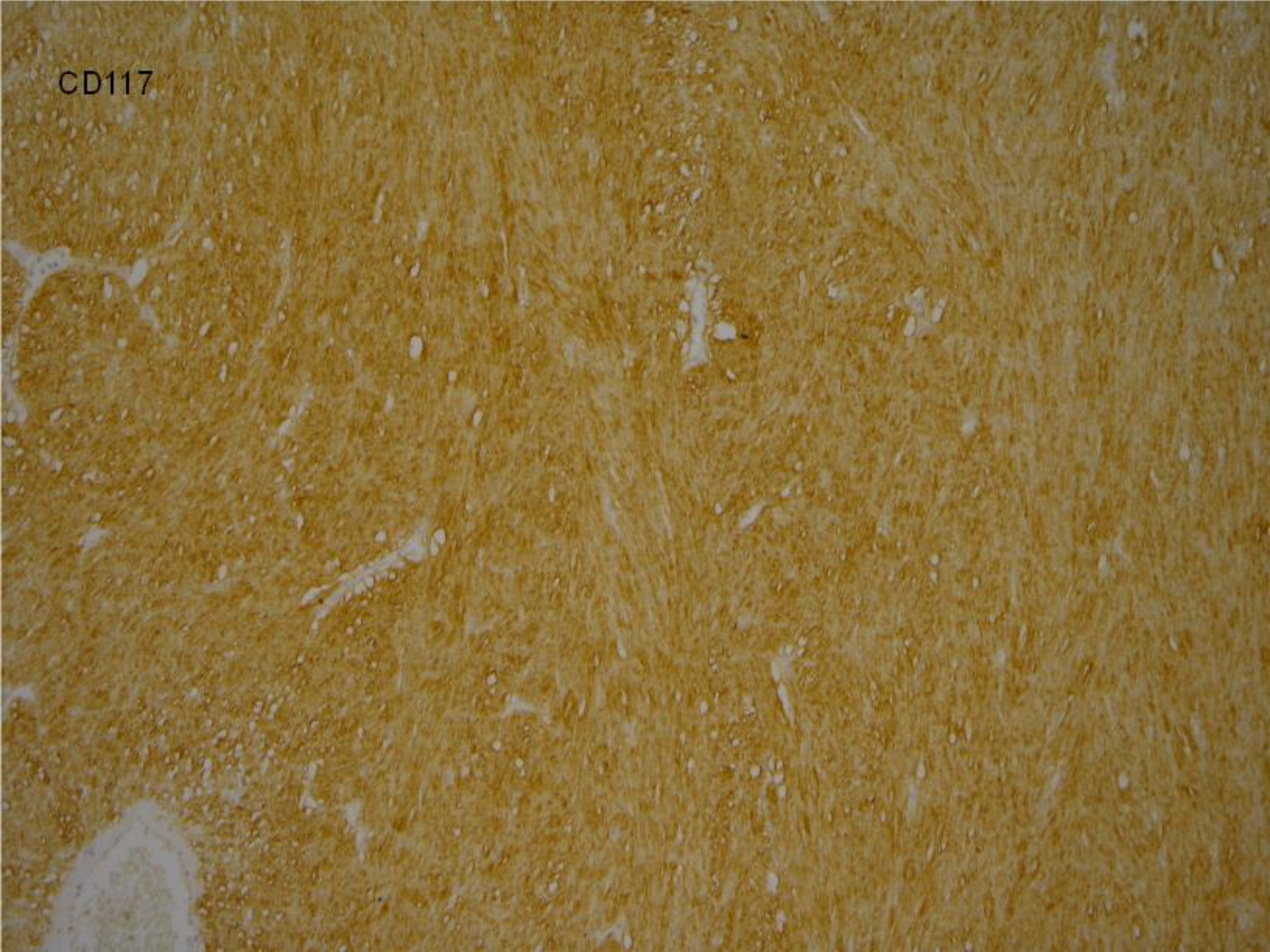
Lymph node, peri-pancreatic (3/11) ---Metastatic endocrine carcinoma

- **Segmental resection of ileum**

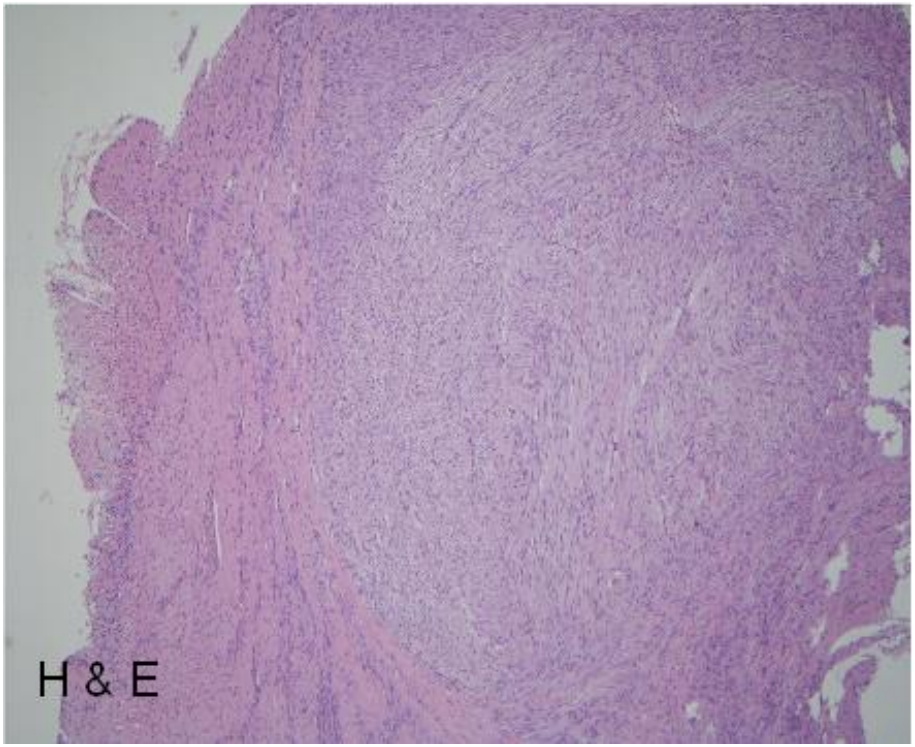
Ileum --- GIST

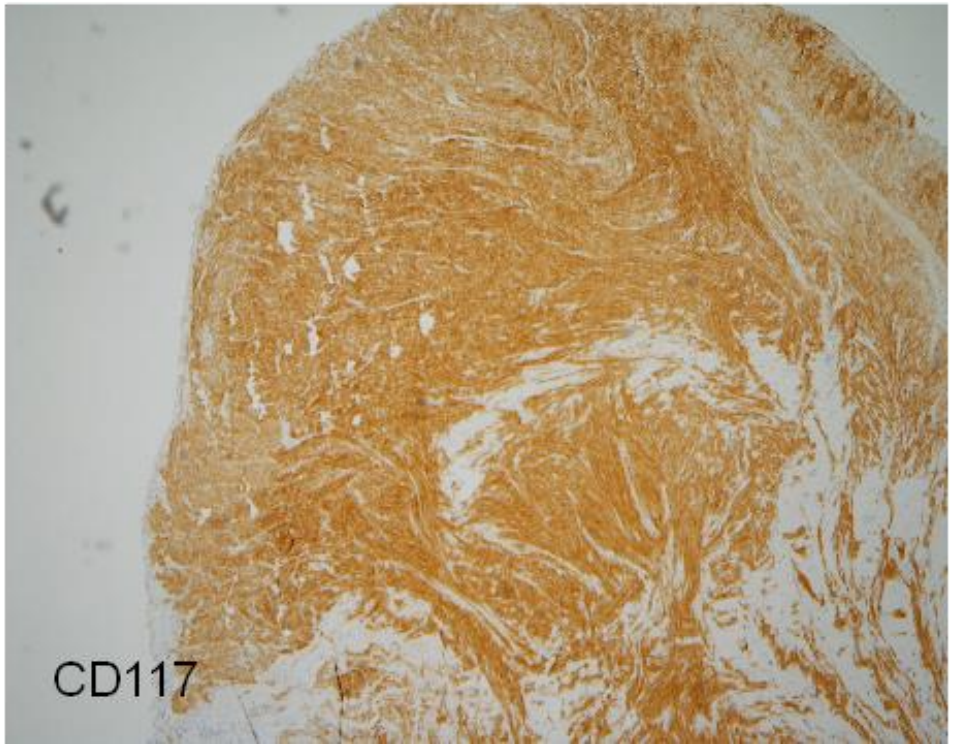

Skin
---Neurofibroma


Small intestine ---GIST
Focal necrosis
Size 5-10 cm
Mitotic activity (<5 per 50 HFP)


CD117

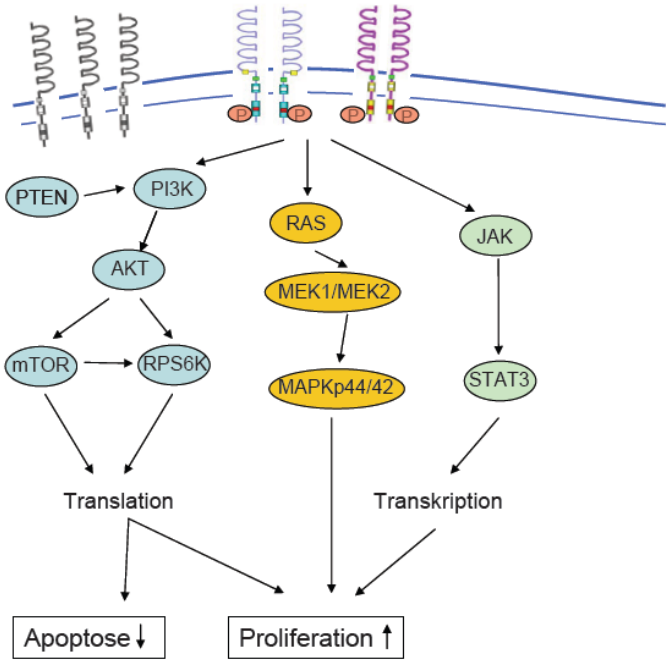
Duodenal GIST





Neuroibromatosis type 1

- Recklinghausen disease
- Autosomal dominant hereditary tumor syndromes with an incidence of **1:3000** births
- NF-1 gene (**tumor suppressor gene**) located on chromosome 17q11.2
  - NF-1 encodes **neurofibromin**, a cytoplasmic protein which **controls cellular proliferation** by inactivating the p21 RAS and the MAP kinase pathway



Neuroibromatosis type 1

- The NF-1 gene has one of the **highest/new mutation rates in humans.**
  - 50% of NF-1 patients have no family history of the disorder
- The **large size** of the NF-1 gene and **lack of mutation hot spots**
  - **Mutation analysis** is usually not practicable as an initial tool for identifying NF-1.
  - Clinical criteria established by the National Institutes of Health (NIH) Consensus Development Conference in 1988

Diagnostic criteria of neuroibromatosis type 1

Six or more café au lait macules (>0.5 cm in children or > 1.5 cm in adults).
Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma.
Axillary or inguinal freckling.
Optic pathway glioma
Two or more Lisch nodules (iris hamartomas seen on slit lamp examination)
One first-degree relative with NF-1
Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/– pseudoarthrosis)

*two or more criteria are needed for diagnosis (from ref. 1).

Reported gastrointestinal manifestations in NF-1

1. True neurogenic neoplasms
   - Solitary neurofibroma
   - Diffuse or plexiform neurofibroma
   - Gastric schwannoma (single case reported)
   - Diffuse mucosal/submucosal neurofibromatosis
   - Ganglioneuromatosis
   - Gangliocytic paraganglioma
   - Malignant peripheral nerve sheath tumor (very rare)

2. Interstitial cell of Cajal lesions
   - Multifocal clinical gastrointestinal stromal tumors (GISTs)
   - Minute incidental GIST tumorlets (usually non-gastric)
   - Microscopic diffuse or multifocal interstitial cell of Cajal hyperplasia
   - Motility disorders related to Cajal cell lesions

3. Neuroendocrine tumors
   - Carcinoid tumors at any gastrointestinal location
   - Periampullary somatostatinoma
   - Rarely, insulinoma and gastrinoma

4. Miscellaneous neoplasms and lesions
   - Adenocarcinoma at different gastrointestinal sites
   - Vasculopathy

Coexistence of GIST and neuroendocrine neoplasms

Disease	Associated gastrointestinal and abdominal tumors	Gene/s affected	Mode of inheritance
NF-1	Multiple GIST, NET (adrenal, ampulla, pancreas and other sites)	*NF-1*	Autosomal dominant
Multiple endocrine neoplasia type 1 & 2	Multifocal NETs, very rare cases of GISTs were reported in MEN-1 &MEN-2 patients	*MEN-1 or RET*	Autosomal dominant
Carney triad	Multiple gastric GIST and extra-adrenal paraganglioma	Unknown	Non-heritable
Carney-Stratakis syndrome	Familial GIST and multiple paragangliomas	*SDH A,B,C,D*	Autosomal dominant
Von Hippel Lindau disease	Renal cell carcinoma, endocrine pancreas tumors, one case of GIST reported	*vHL*	Autosomal dominant
Miscellaneous	GIST at different sites and various NET types (carefully exclude underlying syndromes)	Unknown	Sporadic, non-hereditary, etiology unknown

NF-1 associated GISTs

- GISTs were detected in **25%** of NF-1 patients at autopsy.
  - **The most common** gastrointestinal manifestation of NF-1
- Most NF-1 associated GISTs present as small asymptomatic lesions with low mitotic activity and they generally follow a benign clinical course.
- GISTs in the setting of NF-1 **do not harbor mutations in KIT or PDGFRA** (**wild type**)

Wild-type tumors

- No detectable *KIT* or *PDGFRA* mutations
- **12% ~ 15%** of all GIST
- **< 5%** of GIST occur in the setting of syndromic diseases
  - Neurofibromatosis type 1 (NF1)
  - Carney triad syndrome
  - Other familial diseases

CTOS-Seattle, November 2007

TERAPEUTIC CONSEQUENCES FROM MOLECOLAR BIOLOGY FOR GIST PATIENTS AFFECTED BY NEUROFIBROMATOSIS TYPE 1

Mussi C, Schildhaus HU, Gronchi A, Wardelmann E, Hohenberger P

Mannheim University Hospital, Germany

Bonn University Hospital, Germany

Istituto Nazionale Tumori, Italy

supported by Conticanet

PATIENTS

28 PATIENTS OPERATED

- **13 MALES**
- **15 FEMALES**
- **M:F=0,87:1**
- **Median age 57 (range 28-72)**

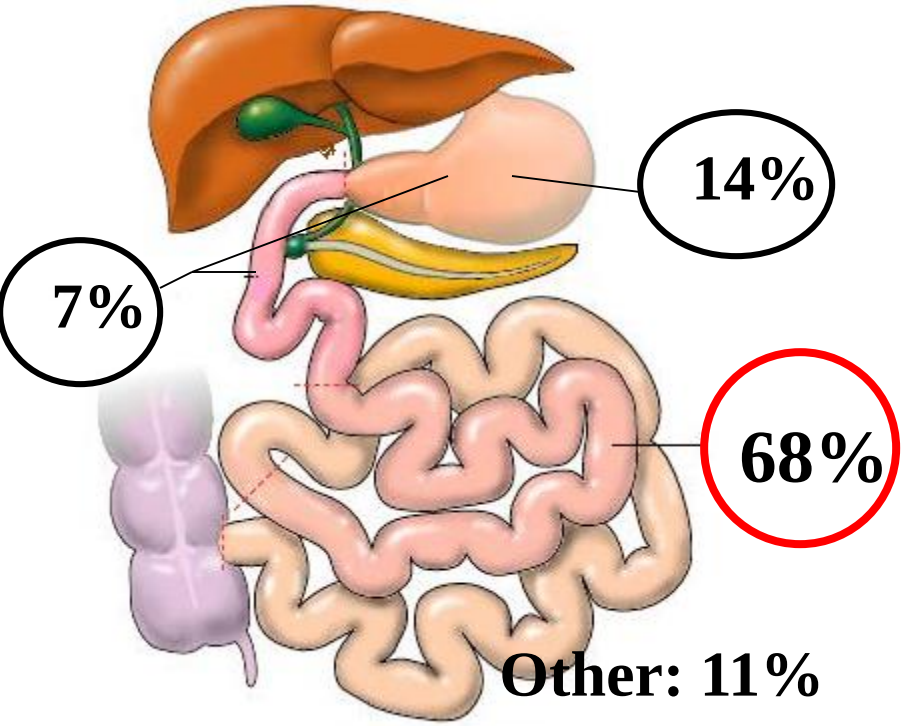
universitäts klinikum bonn

KLINIKUM MANNHEIM gGmbH
Universitätsklinikum
Fakultät für Klinische Medizin Mannheim der Universität Heidelberg

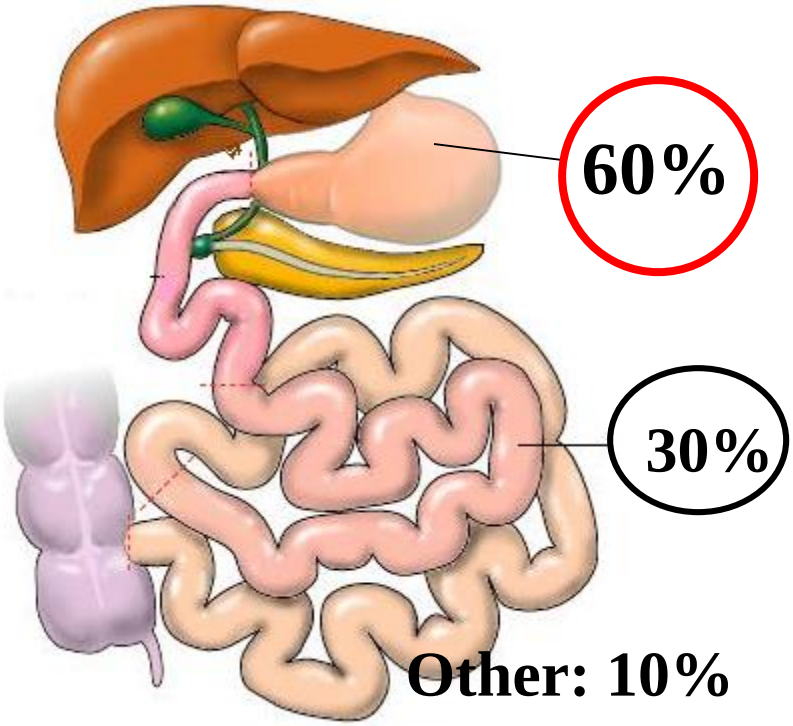
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

SITE

PRESENT SERIES



SPORADIC GIST



NUMBERS OF TUMORS

MULTIPLE TUMORS

PRESENT SERIES

43 %

SPORADIC GIST

Occasional

Exceptions for c-kit or PDGFRA gene mutations

- Yantiss et al (2004) described a patient with an exon 11 mutation.
- Cheng (2004) also reported one mutant case.
- Takazawa et al (2005) reported mutations in at least one tumor from 3 of 9 NF1 patients.
  - Different tumors from a single patient could show different mutations, and the same patient could have both GISTs with mutations and other tumors that were wild-type.
- Mussi et al (2008) found c-kit mutations in primary tumors of 3 of 28 NF1 GIST patients (both exon 11 and exon 9) and PDGFRA mutation in one patient.
  - A secondary mutation in exon 17 of c-kit was found after imatinib (Gleevec) treatment in one patient whose primay tumor had been wild-type.

MOLECULAR ANALYSIS

NF-1 ASSOCIATED GIST

- KIT Mutations **7,8%**
  - Exon 11 5,6%
  - Exon 9 1,1%
  - Exon 13 1,1%
  - Exon 17 0%
- PDGFRA Mutations **3,3%**
  - Exon 12 1,1%
  - Exon 14 0%
  - Exon 18 2,2%

SPORADIC GIST

- KIT Mutations **80%**
  - Exon 11 67,5%
  - Exon 9 11%
  - Exon 13 0,9%
  - Exon 17 0,5%
- PDGFRA Mutations **7,5%**
  - Exon 12 0,9%
  - Exon 14 0,3%
  - Exon 18 6,3%

[redacted]醫院

分子醫學檢查報告

病理號碼	[redacted]	病歷號碼	[redacted]			類　別	N
姓　名	[redacted]	性　別	—	年齡	—	編　號	G16168
醫　院	振興醫院			科　別		一般外科	
主治醫師	蘇正熙	收件日期	[redacted]			報告日期	[redacted]

Diagnosis:

Presence of nonsynonymous single-nucleotide polymorphism in exon 10 of PDGFRA.

Response of NF1 GIST to Imatinib and Sunitinib

- Lee et al (2006) reported a case of NF1 GIST that did respond to imatinib (Gleevec).
- Kalender et al (2007) reported a patient with initial response to imatinib (Gleevec) who subsequently became resistant and experienced progression. However, the metastatic lesions in liver and omentum did decrease in size during the first four cycles of sunitinib (Sutent).
- Mussi et al (2008) described imatinib treatment results for 8 NF1 patients.
  - 4 patients who received adjuvant imatinib after **complete resection** did not experience recurrence.
  - 4 additional patients with **metastases** received imatinib, and
    - 3 of them demonstrated primary resistance (rapid progression)
    - 1 patient with a PDGFRA mutation had stable disease temporarily.

IMATINIB THERAPY: resectable GIST

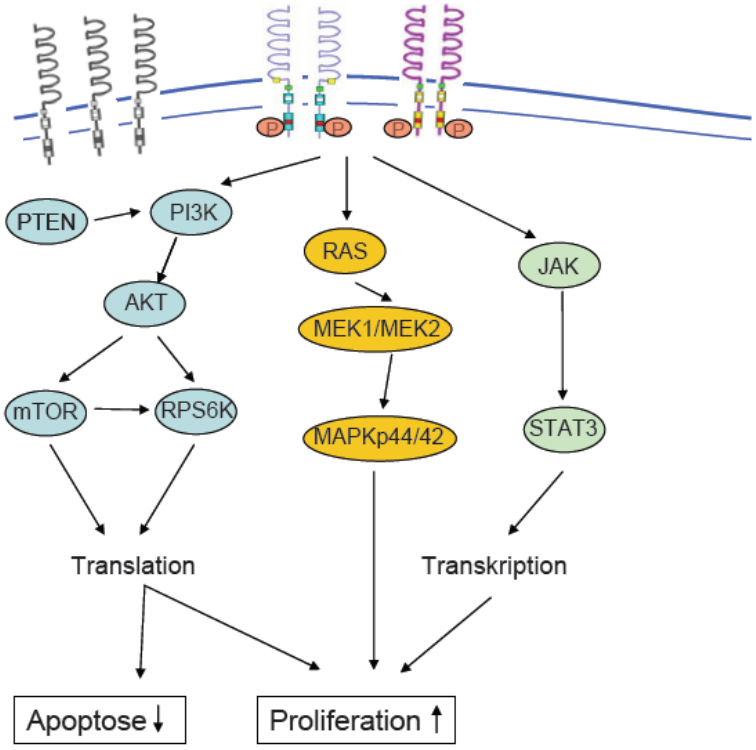
Pts	Primary	Setting	Trial	Imatinib	EFS	Status
1	**Localized**	**postop.**	**EORTC 62024**	**400mg/d**	**11**	**NED**
2	**Localized**	**postop.**	**SSGVIII/ AIO**	**400mg/d**	**8**	**NED**
3	**Syncronous resectable metastasis**	**postop.**	**/**	**400mg/d**	**22**	**NED**
4	**Multiple recurrent tumors**	**postop.**	**/**	**400mg/d**	**45**	**NED**
5	**Localized**	**postop.**	**EORTC 62024**	**Control Arm**	**14**	**NED**

IMATINIB THERAPY: advanced GIST

Pts	Site (prim.)	Risk	Metastasis	Molecular analysis	Resp.	Post IM Surv (EORTC 62005 trial)	Status
1	**ExGI**	**H**	**liver, peritoneal**	**WT**	**PD**	**22**	**DOD**
2	**Small Bowel**	**H**	**liver, peritoneal**	**WT**	**PD**	**19**	**DOD**
3	**Stomach**	**I**	**liver, peritoneal**	**EX 18**	**SD**	**22**	**DOD**
4	**Small Bowel**	**H**	**peritoneal**	**WT prim; Secondary ex 17**	**PD**	**10**	**DOD**

Median survival after imatinib onset 21 months

- The future treatent of this subset of GIST is likely dependent from further investigations of the molecular pathways activated by neurofibrin as new molecular targets.



The End

Thanks for your attention!