First-line Capecitabine and Temozolomide Chemotherapy in Combination with Somatostatin Analogs in Poorly Differentiated Metastatic Pancreatic Neuroendocrine Carcinoma Patient

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56세 여환이 2달간의 설사, 1달간의 복통, 오심, 구토를 주소로 내원하였다. 알려진 특별한 과거력 없던 분으로 상기 주소 및 5달간 5 kg의 체중감소가 있어 2011년 8월 외부병원 내원하여 시행한 검사상 pancreatic neuroendocrine carcinoma with superior mesenteric vein invasion and hepatic metastasis 의심되고, 폐쇄성 황달 동반되어 2012년 8월 12일 총담관 스텐트 삽입 시행 후 본원으로 전원 되었다. 초기 화학검사상 obstructive hyperbilirubinemia 소견 보였고, 혈청 chromogranin A는 777.0 ng/mL 이상이었다. 외부 병원에서 시행한 초음파 유도 하 간 조직 검사와 본원에서 시행한 초음파 내시경 유도 하 췌장 세침 흡인 검사상 poorly differentiated pancreatic neuroendocrine carcinoma 진단되었다. 일차 치료로 2011년 9월부터 capecitabine/temozolomide 항암화학요법 시작하였으며, 2012년 11월까지 총 14번째 주기까지 투약 진행 중으로 항암화학요법 기간 중 3개월마다 시행한 복부 CT상 stable disease로 유지되었다. 환자 초기 내원 시부터 호소하던 오심, 구토, 전신쇠약 증상이 항암 치료 중 악화되어 수 차례 입원하여 보존적 치료 받았으며, functioning neuroendocrine carcinoma의 hormone secretion에 따른 증상 악화로 판단하여 2012년 8월부터 somatostatin 유사체인 octreotide 투약 시작하였고, 투약 이후 환자의 증상은 호전 되었다. 혈청 chromogranin level은 항암화학요법을 시작한 후에도 변화없이 지속적으로 높게 유지되었으나, 2012년 8월 octreotide 투여 시작한 이후 3개월 뒤 2012년 11월 시행한 검사상에서는 107.42 ng/mL로 현저히 감소하였다.

56 years-old, Female

■ Chief complaint
- Diarrhea (for 2 month)
- Abdominal pain, Nausea, Vomitting (for 1 month)

■ Past history
- DM/HTN/TBc/Hepatitis (-/-/-/-), Nothing considerable

■ Familiy history
- Mother (DM), Brother (Stroke, HTN, DM)

■ Review of system
- General weakness, Nausea, Vomiting, Diarrhea, Abdominal pain
- Poor oral intake
- Weight loss (-5 kg/5 months)

■ Physical examination
- Soft and flat abdomen
- Abdominen direct tenderness/rebound tenderness (-/-)

Laboratory study

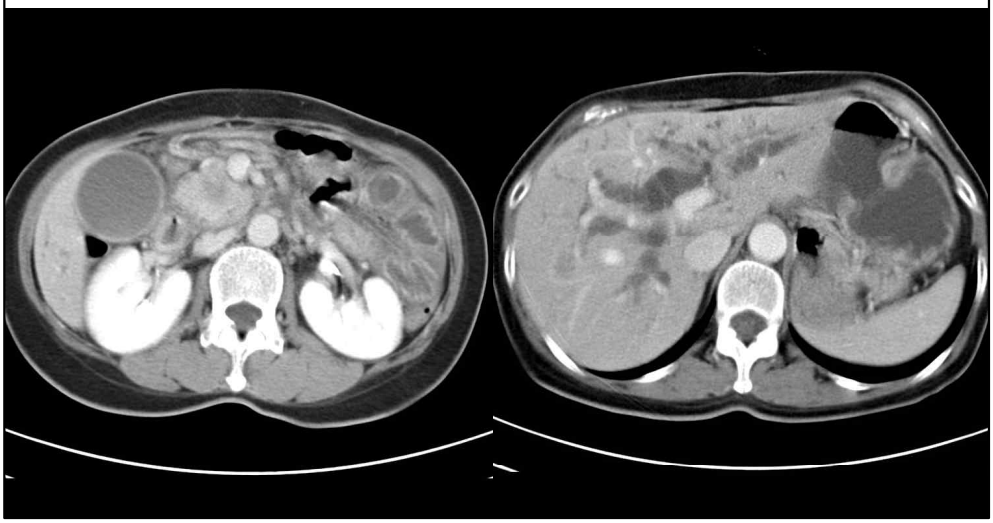
■ **SMA**

AST (GOT)	150 IU/L
ALT (GPT)	219 IU/L
Total Bilirubin	2.1 mg/dL
Direct Bilirubin	1.5 mg/dL
Gamma-GT	63 IU/L
Alk. Phos	115 IU/L
24hr urine 5-HIAA	6.0 mg/day (2.0~8.0 mg/day)

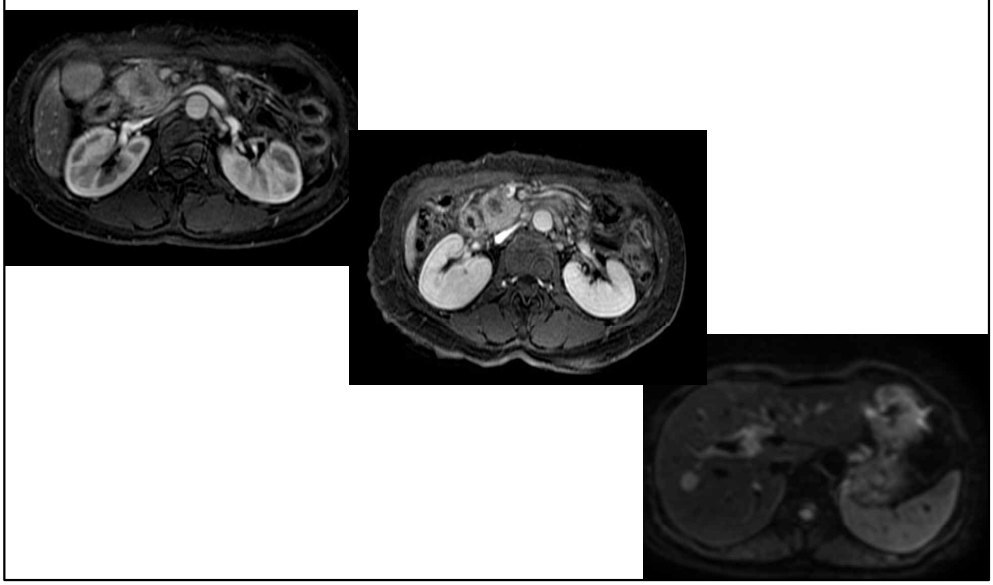
■ **Tumor marker**

Chromogranin A	>770.00 ng/mL
CEA	2.15 ng/mL
CA 19-9	13.3 U/mL

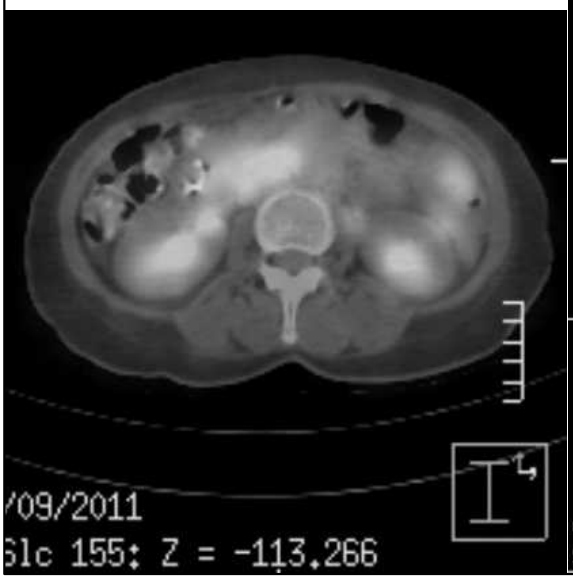
Imaging study – Abdomen-Pelvic CT 2011.08.09

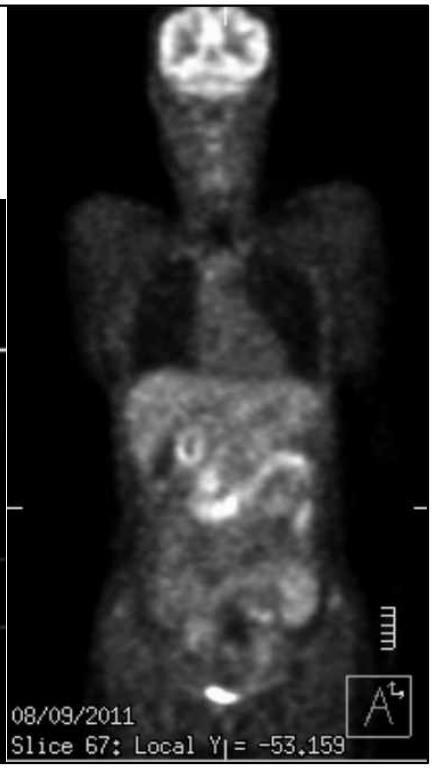


Imaging study – MRI Pancrease (2011.08.09)

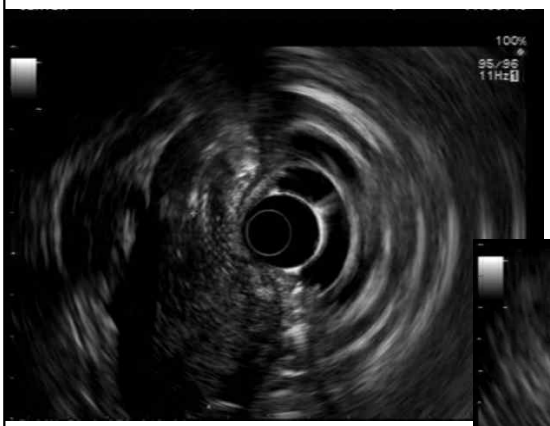


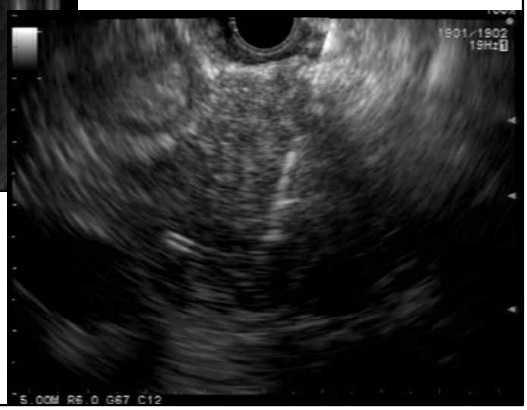
Imaging study – PET-CT (2011.08.09)





Imaging study–EUS-FNA of pancrease (2011.09.01)

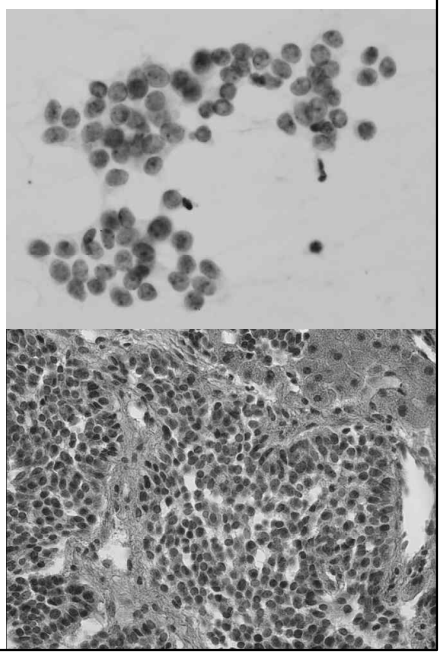




Pathologic Diagnosis

■ EUS-FNA (2011.09.01)
Cellular smear showing many clusters of epithelial cells with minimal nuclear atypia, suspicious for neuroendocrine neoplasm

■ U/S-guided liver biopsy (2011.08.11)
High-grade (G3), poorly differentiated neuroendocrine carcinoma, composed of small round cells
30 mitoses/10hpf, Ki-67 index 45%
Result of immunohistochemistry stain
-Positive: Cytokeratin7, Synaptophysin
-Negative: Cytokeratin 20, Chromogranin, Hepatocyte antibody



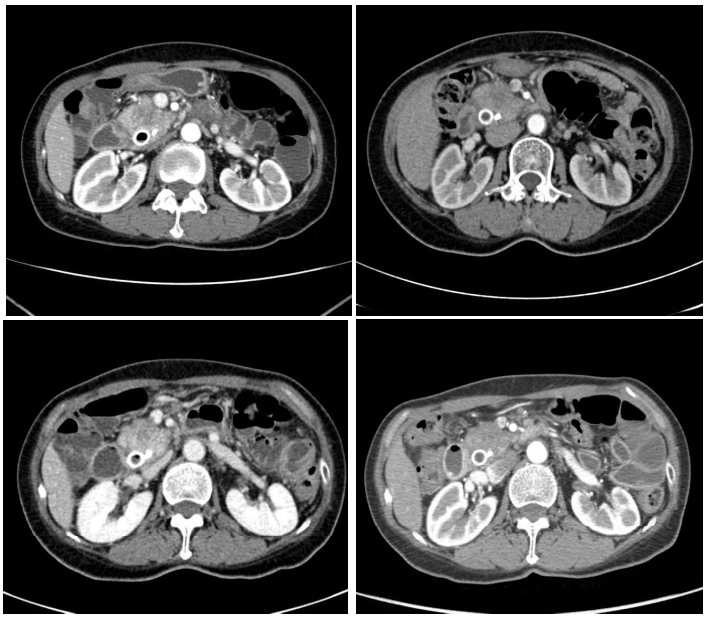
Progress

■ **1st line Capecitabine/Temozolomide ChemoTx, Q4wks**

Capecitabine (Xeloda®) 750 mg/m2 BID, D1-14

Temozolomide (Temodal®) 200 mg/m^2 QD at bedtime, D10-14

Progress – follow up



Stable Disease

Progress

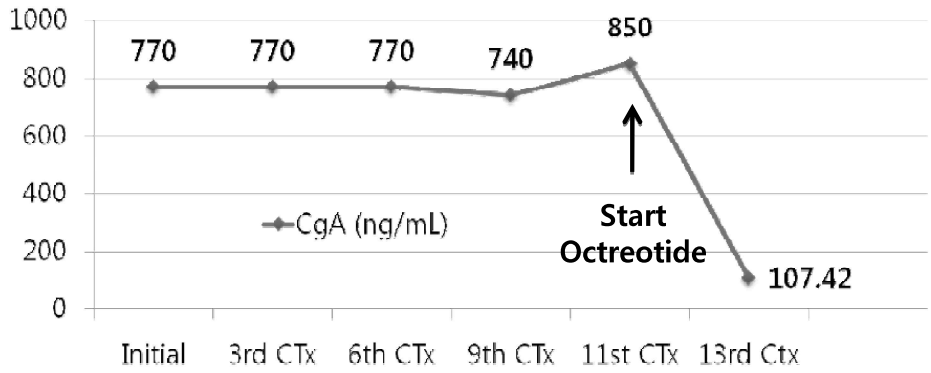
- Patient admitted several times

  (during the 3rd, 8th, 9th, 11st cycle of chemoTx)

  - C.C; **Nausea, Vomiting, General weakness**
  - which may be related to the NET itself and chemoTx (Grade 3)

- Somatostatin analog Tx was started
  - To control NET-related Sx. (on 11th chemo cycle)
  - Octreotide (Sandostatin LAR®) 20 mg IM Q4wks
  - **NET-related Sx was subsided**
  - **Also, serum chromogranin A level was decreased**

Serum Chromogranin A (CgA) Level



Cytotoxic chemotherapy of Pancreatic NET

- Streptozocin (STZ) / STZ + 5-FU / STZ + Doxorubicin
- Dacarbazine (DTIC)
- Temozolomide

- **Temozolomide + Capecitabine**
  - Synergistic for apoptosis in vitro
  - Hypothesis; Depletion of the DNA repair enzyme O^6 methylguanine DNA methyltransferase (MGMT) by capecitabine may potentiate the effect of temozolomide

Strosberg et al. Cancer 2011;117:268-75
Fine et al. ASCO Abstract No. 4216. 2005
Murakami et al. Oncol Rep. 2007;17:1461-1467

Cytotoxic chemotherapy of Pancreatic NET

Regimen	Number of patients*	Tumor response rate, percent
Prospective studies		
Chlorozotocin	33	30•
Fluorouracil + streptozocin	33	45•
Doxorubicin + streptozocin	36	69•
Dacarbazine (DTIC)	50	34
Temozolomide + thalidomide	11	45
Temozolomide + bevacizumab	15	33
Temozolomide + everolimus	24	35
Retrospective series		
Steptozocin + doxorubicin + fluorouracil	84Δ	39
Temozolomide (diverse regimens)	53	34
Temozolomide (single agent)	12	8
Temozolomide + capecitabine	30	70

First-Line chemotherapy with capecitabine + temozolomide in patients with pancreatic NET

- 30 metastatic well or moderately differentiated(G1 or G2) pancreatic NET
- Radiographic response; 21 (70%) patients
- Median PFS; 18 months
- The rate of survival at two years; 92%
- Superior to streptozocin-based CTx

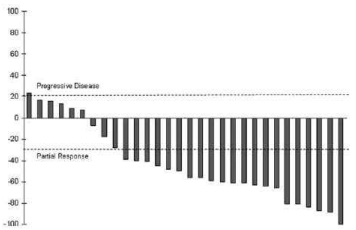


Figure 1. Waterfall plot illustrating best radiographic response (percent change) in each patient.

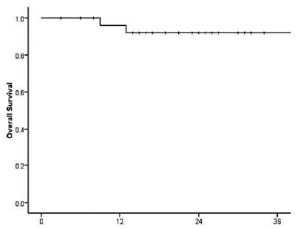


Figure 3. Overall survival from onset of treatment.

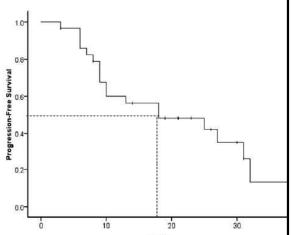


Figure 4. Progression-free survival.

Strosberg et al. Cancer 2011;117:268-75

Temozolomide-Based CTx in Poorly Differentiated Endocrine Carcinoma (PDEC) After Progression on First-Line CTx

- Most common 1st line regimen of PDEC; cisplatin + etoposide

- 25 **PDEC (including 10 pNET)** patients who failed 1st line CTx
- Temozolomide alone or in combination with capecitabine or bevacizumab
- Overall response rate; 33%
- One patient achieved a CR
- Objective response or stabilization rate; 71%

Table 2. Median Progression-Free Survival and Overall Survival in Months

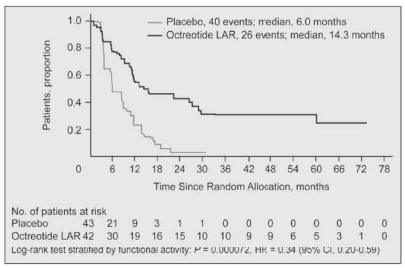
Category	No.	PFS (95% CI)	OS (95% CI)	OS From Diagnosis (95% CI)
All patients	25	6 (4-14)	22 (8-27)	32 (22-42)
CR+PR	8	15 (8-22)	22 (7.5-36)	31 (10-52)
SD	10	7 (4-10)	18[a]	21 (19-60)
PD	7	2 (2)	8 (0-8)	16 (0-40)

Welin et al. Cancer 2011;15;117:4617-22

Somatostatin Analogs (SSAs) in the Management of NETs

- Octreotide (Sandostatin®, Sandostatin LAR®)
- Lanreotide (Somatuline®, Somatuline PR®, Somatuline AG®)
- Reduces Sx of excessive hormone secretion by NETs
- Effective both before and after surgery and inoperable disease
- Antiproliferation effect
  - Direct; tumor cell somatostatin receptors
  - Indirect; inhibition of growth factor secretion and angiogenesis
    immunomodulatory effects on peripheral target organs

Susini et al. Ann Oncol 17:1733–1742, 2006
Eriksson at al. Ann Oncol 10(suppl 2): S31–S38, 1999



PROMID Study

- Randomized, placebo-controlled, double-blind, phase IIIb
- 85 Treatment-naïve, locally inoperable or metastatic well-differentiated midgut NETs patients
- Octreotide LAR 30 mg/month IM
- Primary endpoint; Median PFS

Rinke et al. J Clin Oncol 27:4656–4663, 2009

Antitumor effect of SSAs in patients with pancreatic NETs is controversial

Conclusion

- **Capecitabine + temozolomide** is associated with a high and durable response rate in low or intermediate-grade metastatic pNET
- **Temozolomide based chemoTx** resulted in objective response or stabilization in 71% of high-grade endocrine carcinoma (including pNET) patients who failed on 1st-line chemoTx
- **Somatostatin analogs** reduce Sx by NETs, and **octreotide LAR** lengthens time to tumor progression compared with placebo in patients with low-grade (G1) metastatic midgut NETs

Conclusion

- Most of the reported cytotoxic chemotherapy trials for pNET
  - Non-randomized, small patient cohorts
  - Interpretation is still controversial
- We experienced a case of
  - **High grade (G3) metastatic pNET**
  - Which shows favorable disease control with
  - Temozolomide and capecitabine chemoTx in combination with octreotide LAR
- More studies about this combination of therapy for High grade (G3) pNET should be conducted in the future