Patient with Insulinoma & Falling BG Levels

Isabel Casimiro, MD PhD
Endorama Jan 12, 2017

Pt with Hx of insulinoma & dropping BGs. Please call.

HPI

- 62F at home with daughter & other family members for the holidays
- Was at the “cookie exchange” when she began to feel funny
- Developed lip numbness & diaphoresis; had cookies & juice then checked BG, 75
- Drank 2 more cups of juice with sugar and BG rose to 97; Ate food and it rose to 120
- Has not taken insulin in months
- Recently been off her chemo (Everolimus) due to ear infection (held 10d in consultation with Primary Oncologist), but has recently resumed it for a week now

Chart Review

- 61F with recurrent metastatic insulinoma with hypoglycemia

- Hx of insulin pump for BG management (Hx T2DM) now off pump; requiring “small amounts of insulin”; Not on insulin anymore per Pt

- Follows in Hem/Onc and has been on Everolimus for her insulinoma since 1/2013

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Advice to Pt

- Glucagon prescribed to pharmacy, Pt advised to go to ER if BG continues to drop; Primary Endocrinologist emailed

- 20 mins later: Pt called again to state that her BG had dropped again to 105 (1hr pp)

- Advised Pt to go ER in case she would need a D5 drip

Insulinoma

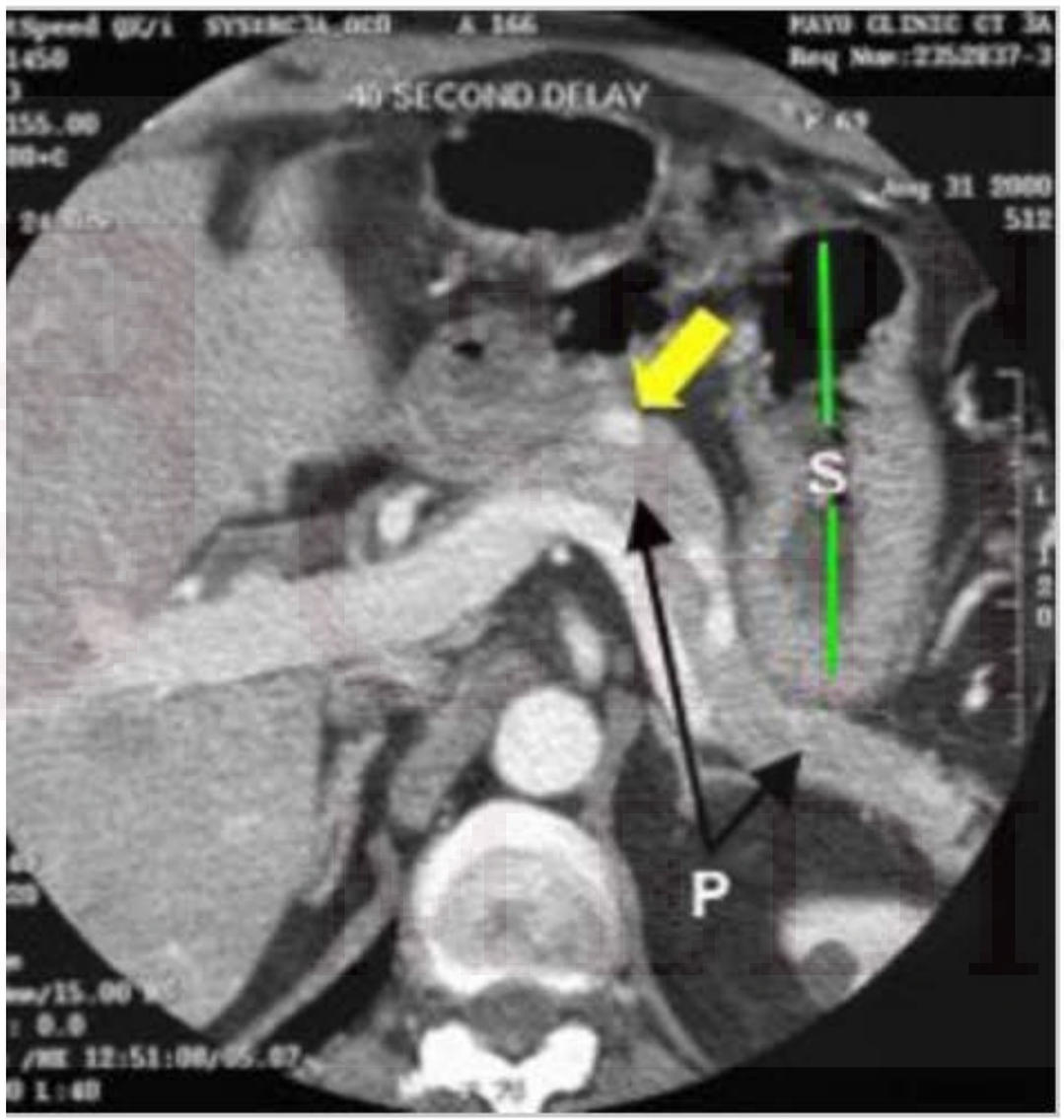


Figure 2:

A. CT scan showing an insulinoma (white dot pointed to by yellow arrow) in the body of the pancreas (P with arrows pointing to the body and tail of the pancreas). The stomach (S with green lines up and down) has air (black) and fluid (darker gray) with it (stomach wall at end of lower green line).

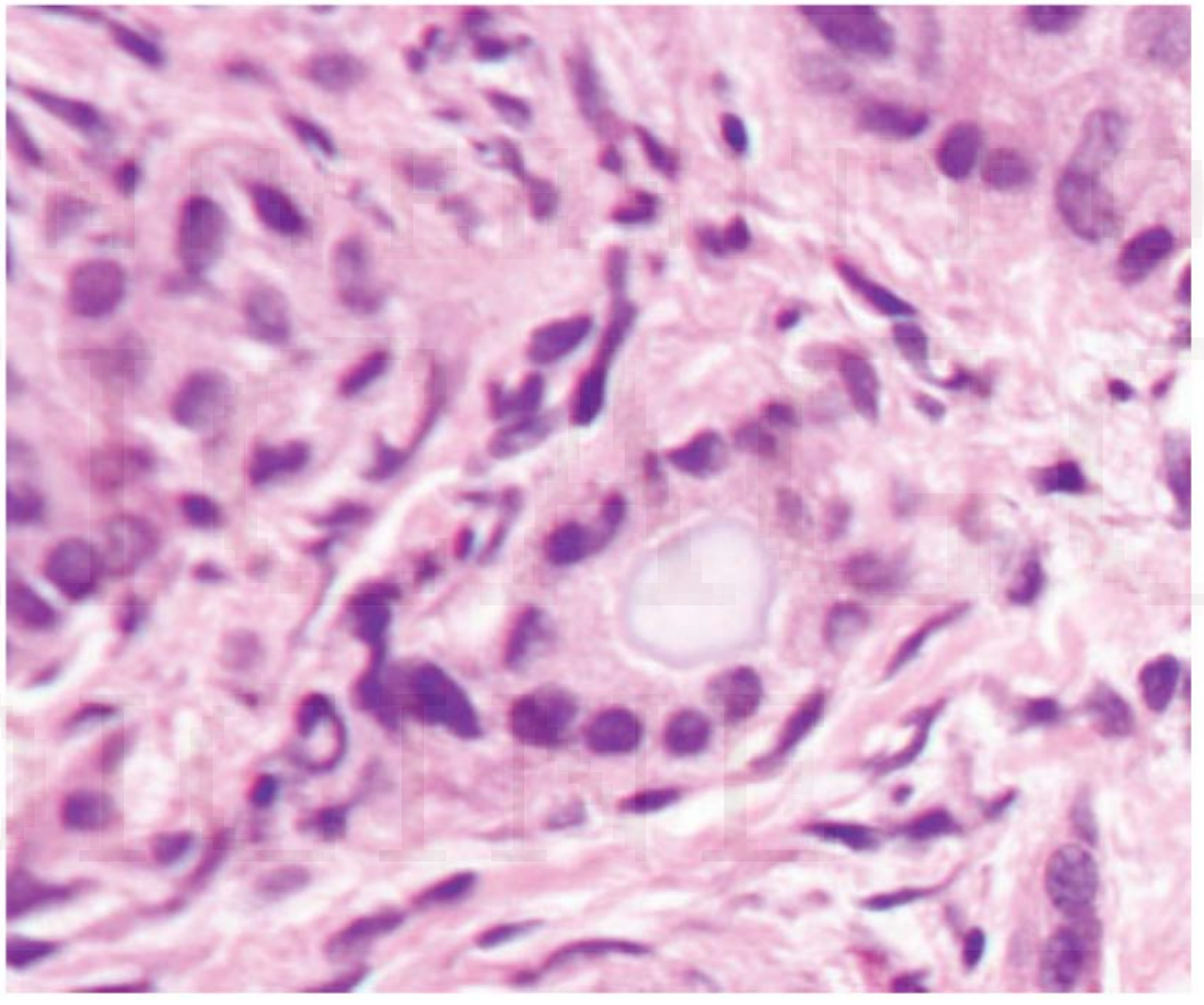
The American Association of Endocrine Surgeons (http://endocrinediseases.org/neuroendocrine/insulinoma_tests.shtml)

Insulinoma

- Tumor of the pancreas (islet cell) that produces excessive amounts of insulin
- Incidence is low: 0.4 per 100,000 person-years (4 cases per million per year)
- Symptoms: Fasting hypoglycemia; neuroglycopenic symptoms like confusion, visual change, and unusual behavior; sympathoadrenal symptoms may include palpitations, diaphoresis & tremulousness, amnesia
- Most are benign >90%, small percent associated with MEN1
- Diagnosed by demonstrated inappropriately high serum insulin during hypoglycemia (insulin >>>3 when glucose <55)
- Malignant insulinomas are rare & therefore there are few data regarding their clinical presentation & long term prognosis, usually seen on abdominal CT

Malignant Insulinoma

The distinction between benign from malignant tumors is the presence of metastasis



Metastatic insulinoma. This hepatic met of insulinoma shows trabecular & pseudoacinar architecture typical of neuroendocrine tumor. The nuclei are small & oval with minimal pleomorphism. Mitotic figures not observed. IH positive for insulin & synaptophysin.

Cancer. July 15, 2005. Vol 104 No2

Patient Hx

PMH

- Malignant insulinoma
- Hx breast cancer
- Atrial fibrillation
- DM, s/p partial pancreatectomy
- CAD
- Obesity

PSH

- Hysterectomy 2016
- Pancreatectomy, distal subtotal , & splenectomy 2005
- Mastectomy 2000

SH

- Ethnicity: Hispanic
- Lives with husband has adult children & several grandchildren
- Never smoker, occasional EtOH on social occasions

FH

- Father: prostate ca, T2DM, CAD, HTN, heart dz, stroke
- Mother: HTN
- Sister DM
- Sister Uterine cancer
- No FH of insulinoma or MEN syndromes

Initial Pt Presentation

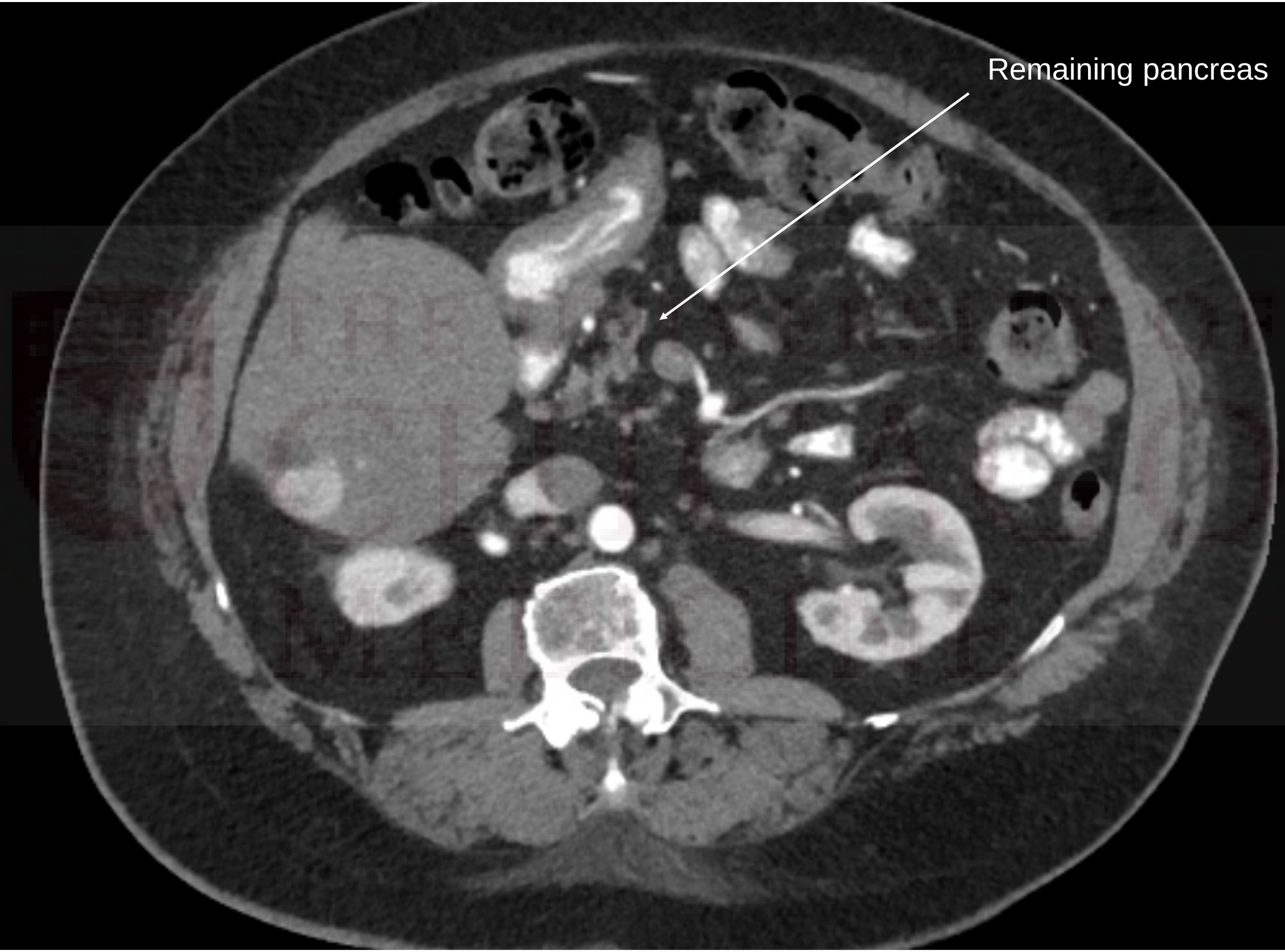
- “Potential tumor” of the pancreas noted in 2005 with potential metastatic lesions to the liver
- Underwent partial pancreatectomy in 2005 & developed DM, started on insulin pump
- 2009: Pt begins to have hypoglycemia; insulin pump turned off; prescribed novolog as needed with meals
- Gained >60 pounds in 3 years
- Continued to wake up with BGs in the 30s with sweating and mental status changes
- Off all insulin since early 2016

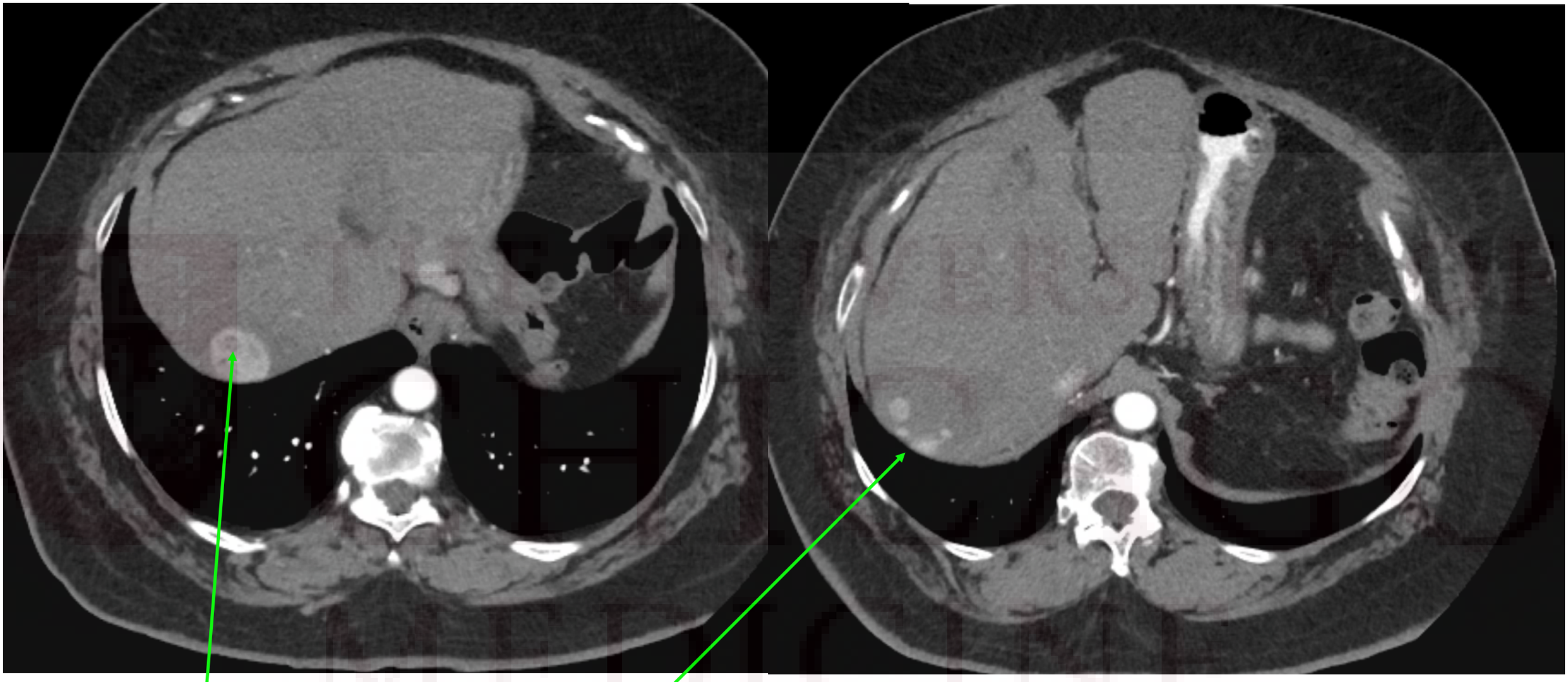
Path Reports

- 2004: Pancreatic mass FNA: Findings consistent with islet cell tumor. Note: no reading on immunochemistry
- 2005: Distal pancreas & spleen
  - Pancreatic endocrine neoplasm (2.1 cm)
  - Margins of resection, negative for neoplasia
  - 13 reactive LNs with no evidence of tumor
  - Spleen with passive congestion
  - Accessory spleen (0.6cm) without diagnostic abnormality
  - IH stains for insulin, glucagon, and somatostatin are negative in the neoplastic cells
  - **Neuroendocrine tumor with no evidence of insulin type granules**

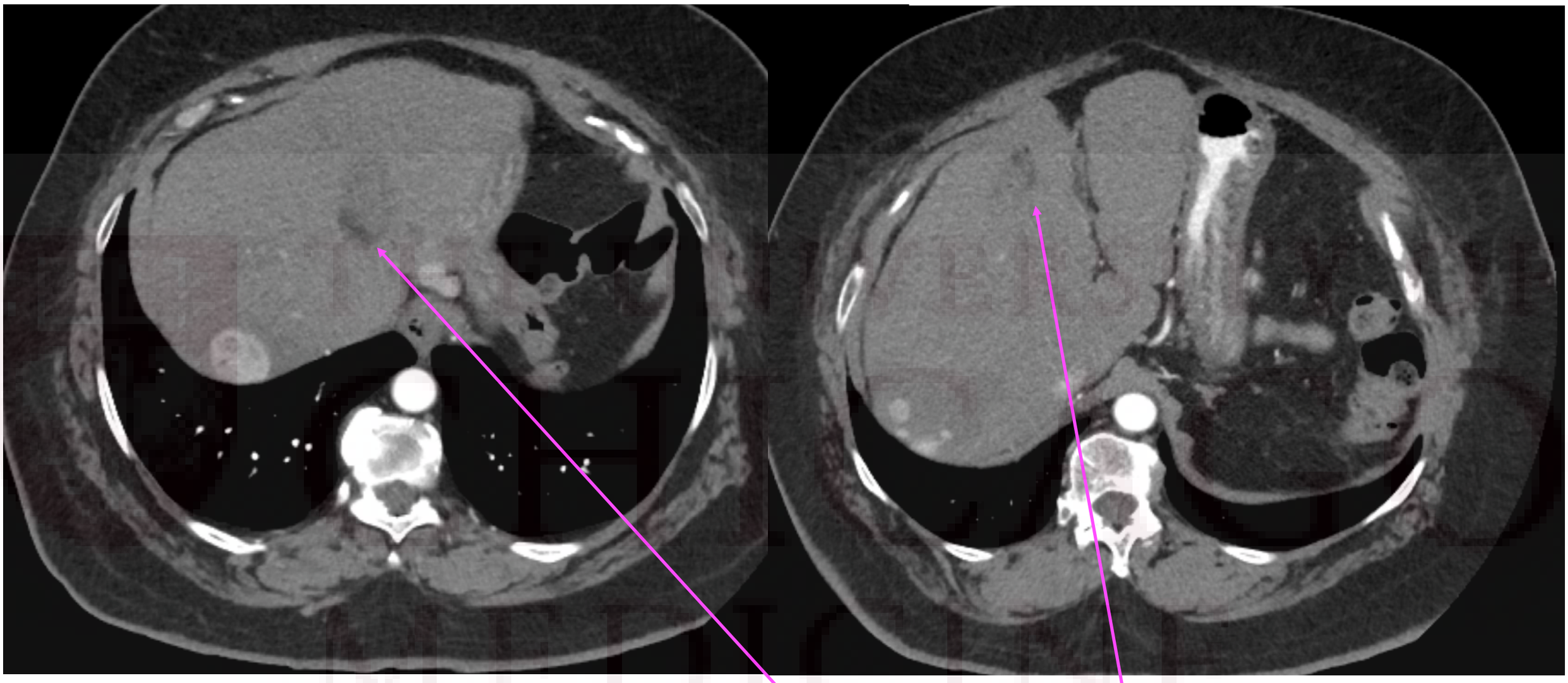
Early Labs

- Earliest labs in our system 4/8/2011:
  - glucose 64
  - C peptide 6.76
  - Proinsulin 4300
  - Glucagon 53 (<80)
  - Insulin 578

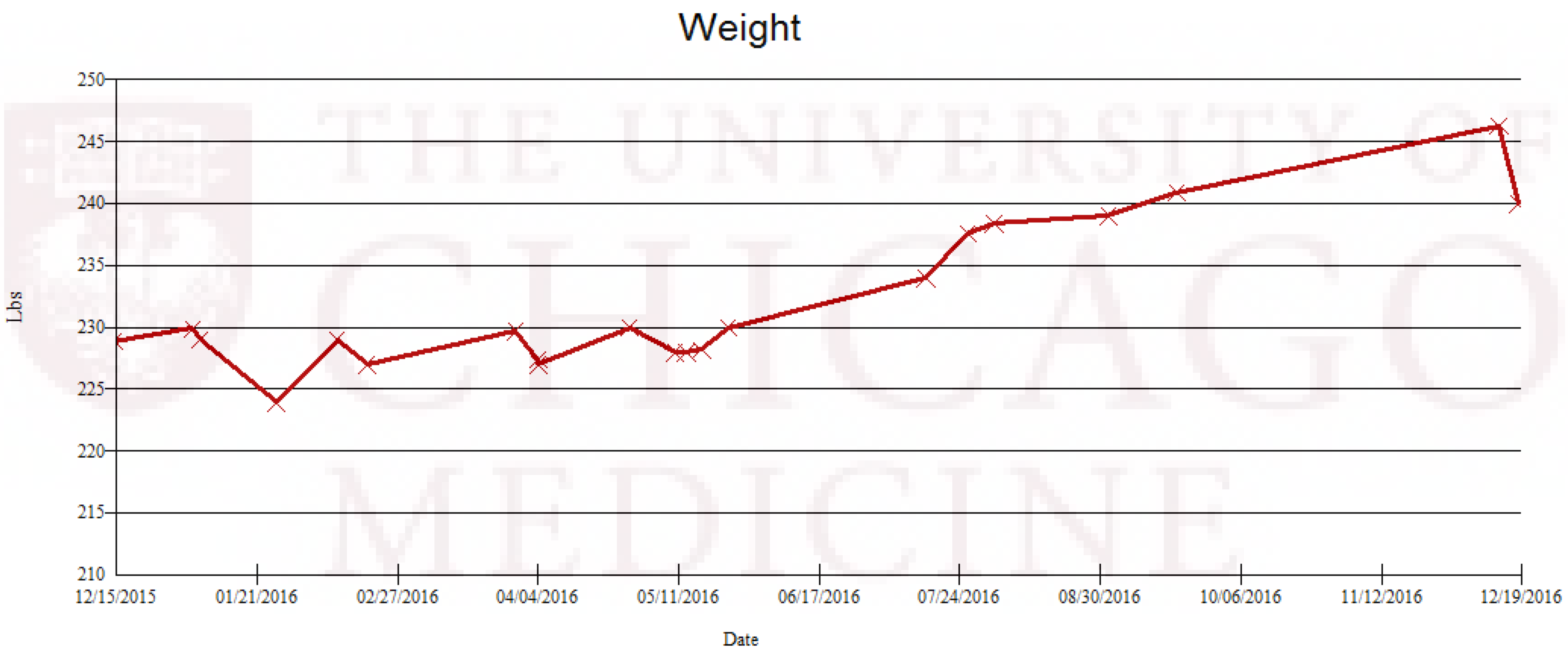

Remaining pancreas



Metastatic lesions



TACE/RFA treated areas



Weight
Lbs
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245
240
235
230
225
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210
12/15/2015
01/21/2016
02/27/2016
04/04/2016
05/11/2016
06/17/2016
07/24/2016
08/30/2016
10/06/2016
11/12/2016
12/19/2016
Date

Insulinoma Treatment

- Surgical removal is the treatment of choice
  - Enucleation of insulinoma (preserves healthy pancreatic parenchyma, low risk of pancreatic insufficiency)
  - Partial distal pancreatectomy
    - Enucleation of the insulinoma & partial pancreatectomy
    - Whipple procedure
    - Total pancreatectomy
    - Resections (partial or total) are done when lesion is embedded deep in the pancreatic tissue or is close to the main pancreatic duct
- Radio frequency ablation (RFA), high intensity focused US ablation (HIFU), US-assisted alcoholizaition or transarterial chemoembolization (TACE)

Surgical Outcomes

- In a series from 1927-1986:
- 196 (87.5%) patents were cured
- 19 (8.5%) had persistent hypoglycemia
- 5 (2.2%) developed DM
- 4 (1.8%) died peri-operatively (before 1941)

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Multicenter retrospective analysis (1983-2014)

Table 1 Basal blood glucose, insulin, and C-peptide levels at diagnosis, at the end of the prolonged fasting test (72 h), and on the last visit.

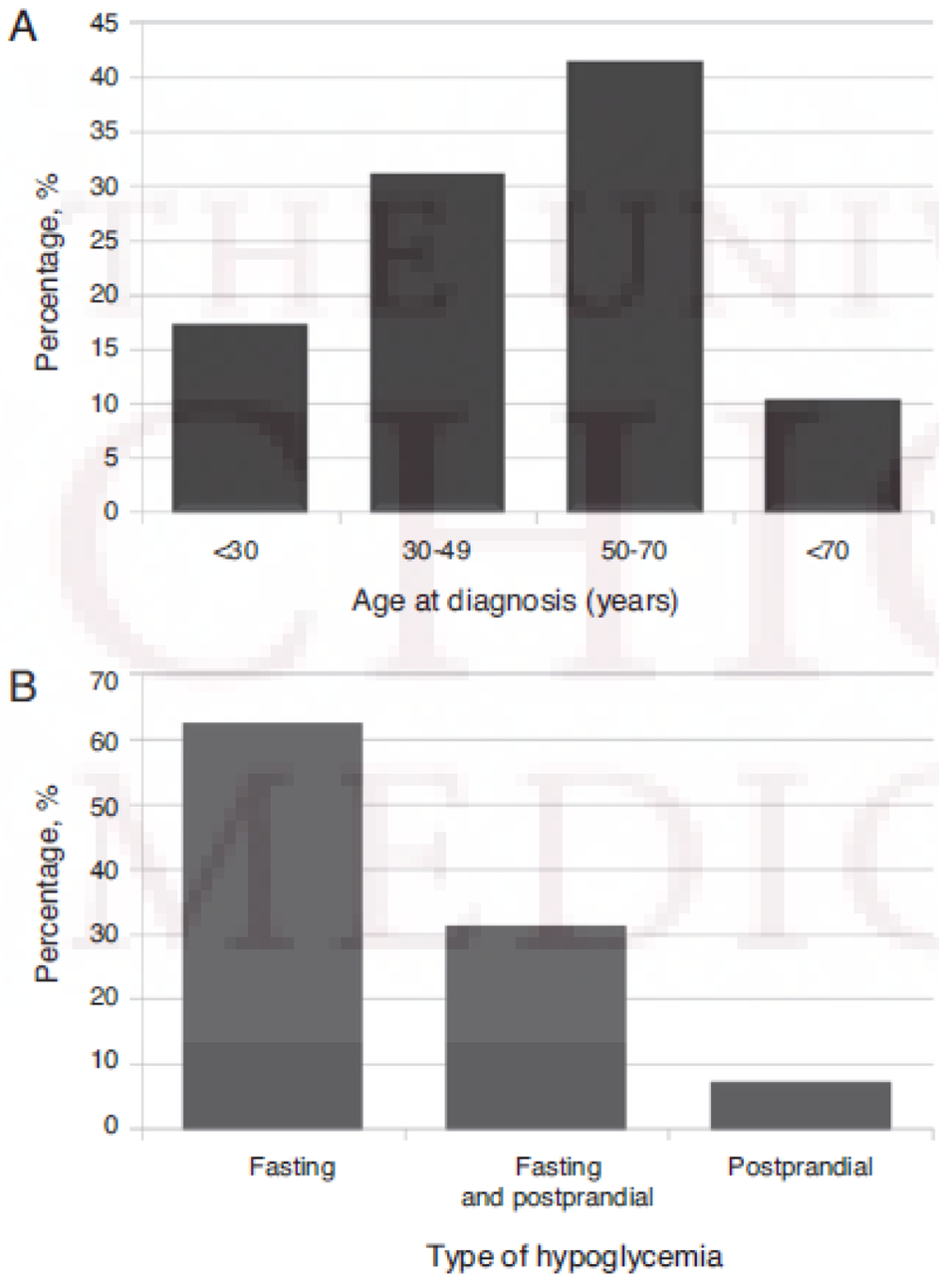
	Basal levels at diagnosis	Fasting (72 h)	Basal levels, last visit[a]
Glucose (mg/dl)	64.1 ± 22.3	37.3 ± 6.5*	102.8 ± 26.0*
Insulin (μU/ml)	24.4 ± 24.5	25 ± 20.3	10.2 ± 15.3**
C-peptide (ng/ml)	3.17 ± 1.86	3.17 ± 1.54	1.74 ± 1.30***
Time to nadir (h)		9.0 ± 4.4	

[a] Time to the last visit: median, 53 months; range, 1–378. Normal levels: blood glucose 80–120 mg/dl; insulin 5–25 μU/ml; and C-peptide 0.5–2.0 ng/ml.
* $p < 0.001$ versus basal level at diagnosis.
** $p < 0.01$.
*** $p < 0.05$.

Endocrinol Nutr. 2015 Aug-Sep;62(7):306-13.

- Four hospitals in Spain (Madrid, Zamora, Avila, Segovia)
- Inclusion criteria: Histological evidence of the tumor or presence of biochemical & morphological criteria consistent with insulinoma; Biochemical criteria: Whipple's triad (fasting hypoglycemia (BG<50), symptoms of hypoglycemia & immediate relief of symptoms after the administration of IV glucose)
- 29 patients with insulinoma (26/89.7% sporadic, 3/10.3% in context of MEN1, 2/6.9% malignant)
- Insulinoma detected in 75% of patients on abdominal CT

Multicenter retrospective analysis (1983-2014)



Insulinoma was mostly seen in women aged 45-50 years

Endocrinol Nutr. 2015 Aug-Sep;62(7):306-13.

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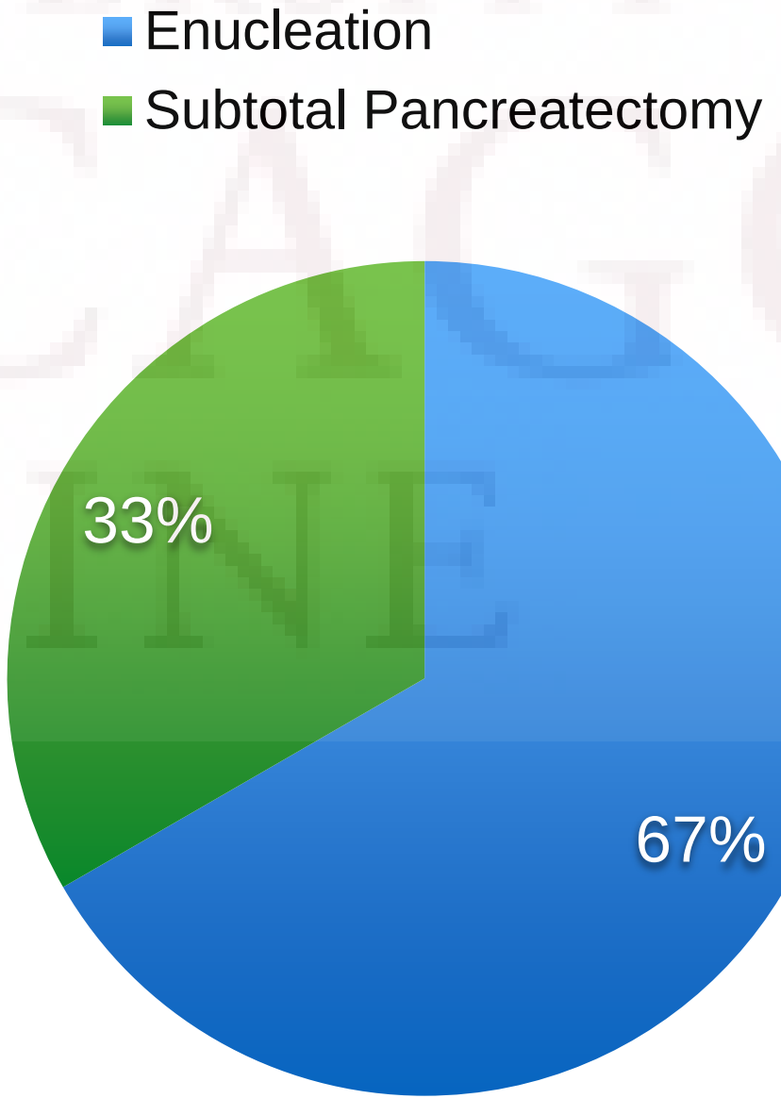
- Surgery was performed in 27/93.1% of patents

- Surgery achieved cure in majority 24/88.9%



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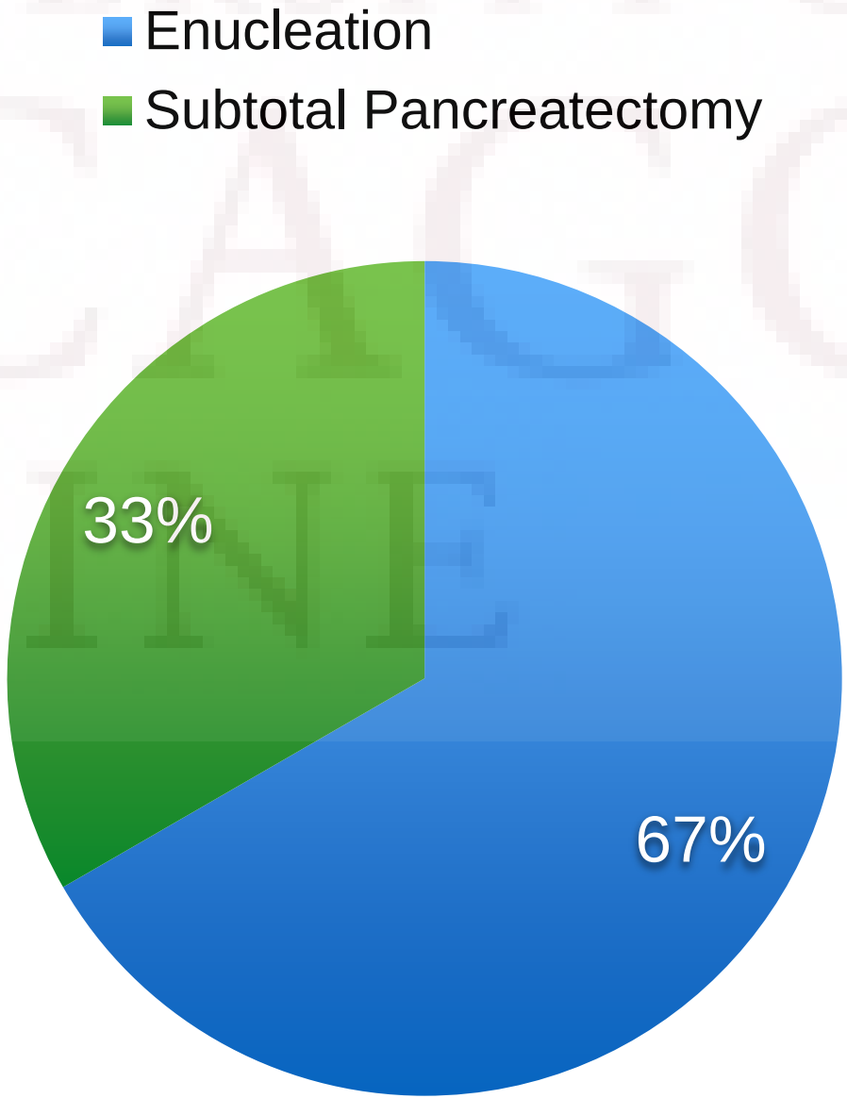

Endocrinol Nutr. 2015 Aug-Sep;62(7):306-13.

Medical Therapy to Control Symptomatic Hypoglycemia

- Diazoxide: Diminishes insulin secretion
  - Opens ATP dependent K channels on pancreatic beta cells resulting in insulin inhibition
  - Given in divided doses up to 1500mg/day
  - Can cause edema (usually given with diuretic), n/v & hirsutism
- Octreotide: Somatostatin analog; inhibits GH & in large doses also insulin, TSH & glucagon
  - More effective in glucagonomas, VIPopmas, carcinoid tumors, less predictable efficacy in insulinomas
  - SSTR only expressed in subgroup of insulinomas

Medical Therapy to Control Symptomatic Hypoglycemia

- Diazoxide: Diminishes insulin secretion
  - Opens ATP dependent K channels on pancreatic beta cells resulting in insulin inhibition
  - Given in divided doses up to 1200mg/day
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- Octreotide: Somatostatin analog; inhibits GH & in large doses also insulin, TSH & glucagon
  - More effective in glucagonomas, VIPopmas, carcinoid tumors, less predictable efficacy in insulinomas
  - SSTR only expressed in subgroup of insulinomas

- Diazoxide modestly improved Pt's BGs but the "taste & feeling" in her mouth was so awful she discontinued it
- Octreotide caused atrial fibrillation in Pt

NIH study of 10 patients with metastatic insulinoma

Patient no.	Age of presentation to NIH/gender	Age of diagnosis (yrs)	Time from diagnosis to indication of metastatic disease	Duration of symptoms till first diagnosis	Initial tumor location	Initial treatment	Metastatic location	Treatment of metastatic disease	Follow-up
1	59/male	47	12 yrs	17 yrs	1st surgery: head 15-mm 2nd surgery: head 3.5-cm	Enucleation, whipple	Liver, pancreas	Chemotherapy, embolization, radiofrequency, diazoxide	Alive 20 yrs after initial diagnosis
2	26/male	26	4 mos	6 yrs	Tail 0.2 ×-3-cm	Distal pancreatectomy	Liver	Diazoxide	Disease recurrence in liver at 4 mos; lived 30 yrs with disease; diazoxide
3	43/female	37	6 yrs	1 yr	Tail 1.5-cm; enucleation; distal nothing found	Enucleation, blind 2/3 distal pancreatectomy	Liver	Chemotherapy	Disease recurrence in liver at 6 yrs; 30 yrs after diagnosis; diazoxide
4	33/female	25	8 yrs	4 yrs	Head 2.6-cm	Enucleation	Liver	Diazoxide	Stable 3 yrs postmetastasis
5	29/female	29	4 yrs	6 mos	Head	Enucleation	1.5-cm lymph node and lesion near tail		Stable for 3 yrs with no treatment
6	82/female	82	At diagnosis	3 mos	Liver	Radiofrequency ablation	Liver	Radiofrequency ablation	Died 4 mos post-ablation
7	47/female	47	At diagnosis	5 yrs	Tail 3–4 cm from tail	Distal pancreatectomy	Lymph nodes		Alive 24 yrs after diagnosis
8	68/female	68	At diagnosis	3 yrs	Body-right of confluence of splenic and IMV 8 ×-6.5 ×-5-cm	Distal pancreatectomy	Lymph nodes		No disease recurrence; alive 25 yrs after diagnosis
9	30/male	30	At diagnosis	4 mos	Body-firmly attached to stomach 8 × 9 × 5.5 cm, 130 g	Distal pancreatectomy	Lymph nodes, vessels		No disease recurrence; alive 23 yrs after diagnosis
10	33/female	33	At diagnosis	1 mo	Body-superior border	Distal pancreatectomy	Lymph nodes		No disease recurrence, alive 10 yrs after

Cancer 2005;104:264-272

Everolimus

- Oral inhibitor of mTOR; A Ser/Thr kinase that stimulates cell growth, proliferation & angiogenesis

- Autocrine activation of mTOR mediated through insulin-like growth factor 1, has been implicated in the proliferation of pancreatic neuroendocrine tumor cells

- Inhibition of mTOR has anti proliferative effect on pancreatic neuroendocrine tumor cell lines

RADIANT-3

- Randomized phase 3 study to determine if everolimus vs placebo would prolong progression free survival among Pts with advanced pancreatic neuroendocrine tumors

- Inclusion criteria: Age >18, low grade or intermediate grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumors & radiologic documentation of disease progression

- 410 patients (from 82 centers in 18 countries) randomly assigned to receive everolimus or placebo both in conjunction with best supportive care

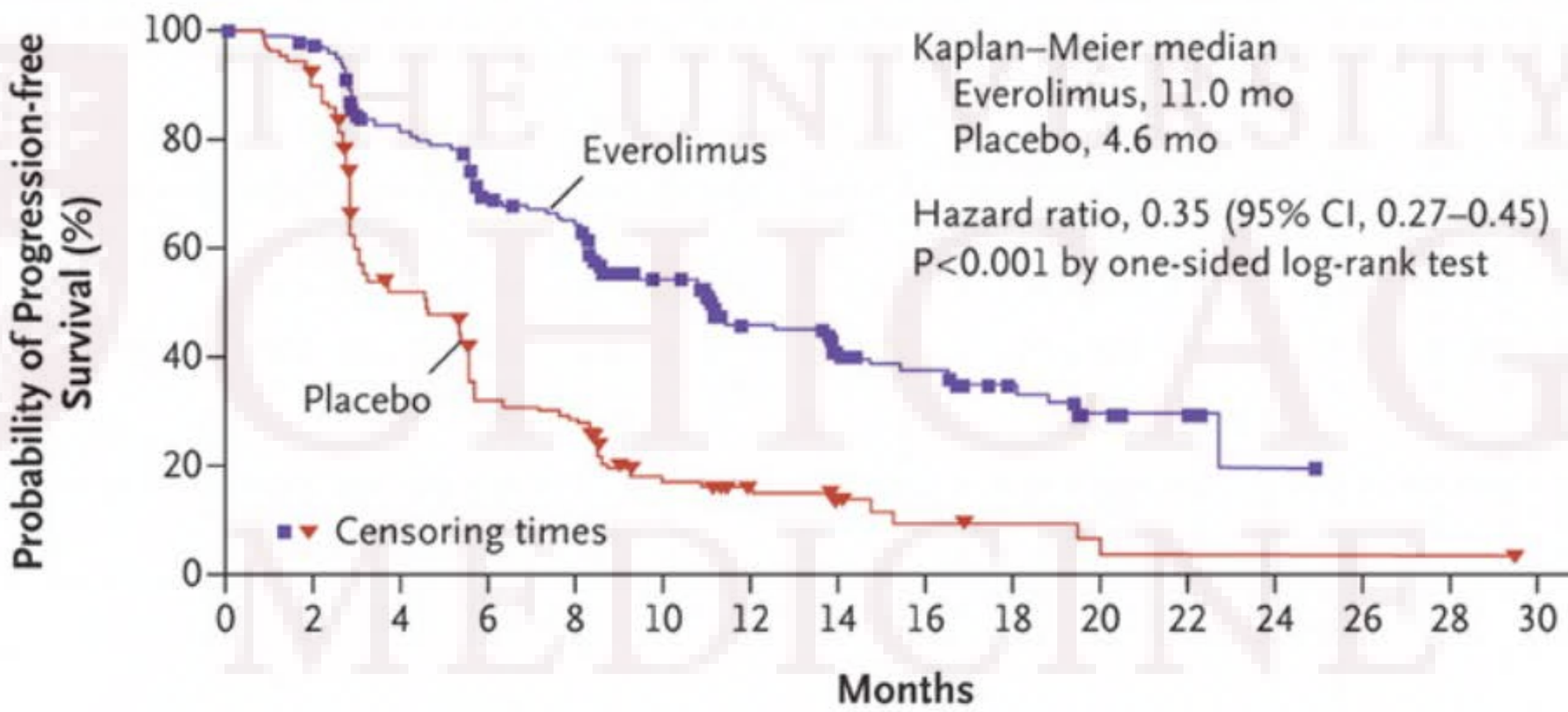
- Patients assigned to placebo could switch to everolimus if there was evidence of disease progression during study

Table 2. Progression-free Survival.

Variable	Everolimus (N=207)	Placebo (N=203)	Difference	Hazard Ratio for Disease Progression or Death with Everolimus (95% CI)	P Value
Assessment by local investigator					
Progression-free survival events — no. (%)*	109 (53)	165 (81)			
Censored data — no. (%)	98 (47)	38 (19)			
Median progression-free survival — mo	11.0	4.6	6.4	0.35 (0.27–0.45)	<0.001
Review by central adjudication committee					
Progression-free survival events — no. (%)*	95 (46)	142 (70)			
Censored data — no. (%)	112 (54)	61 (30)			
Median progression-free survival — mo	11.4	5.4	6.0	0.34 (0.26–0.44)	<0.001

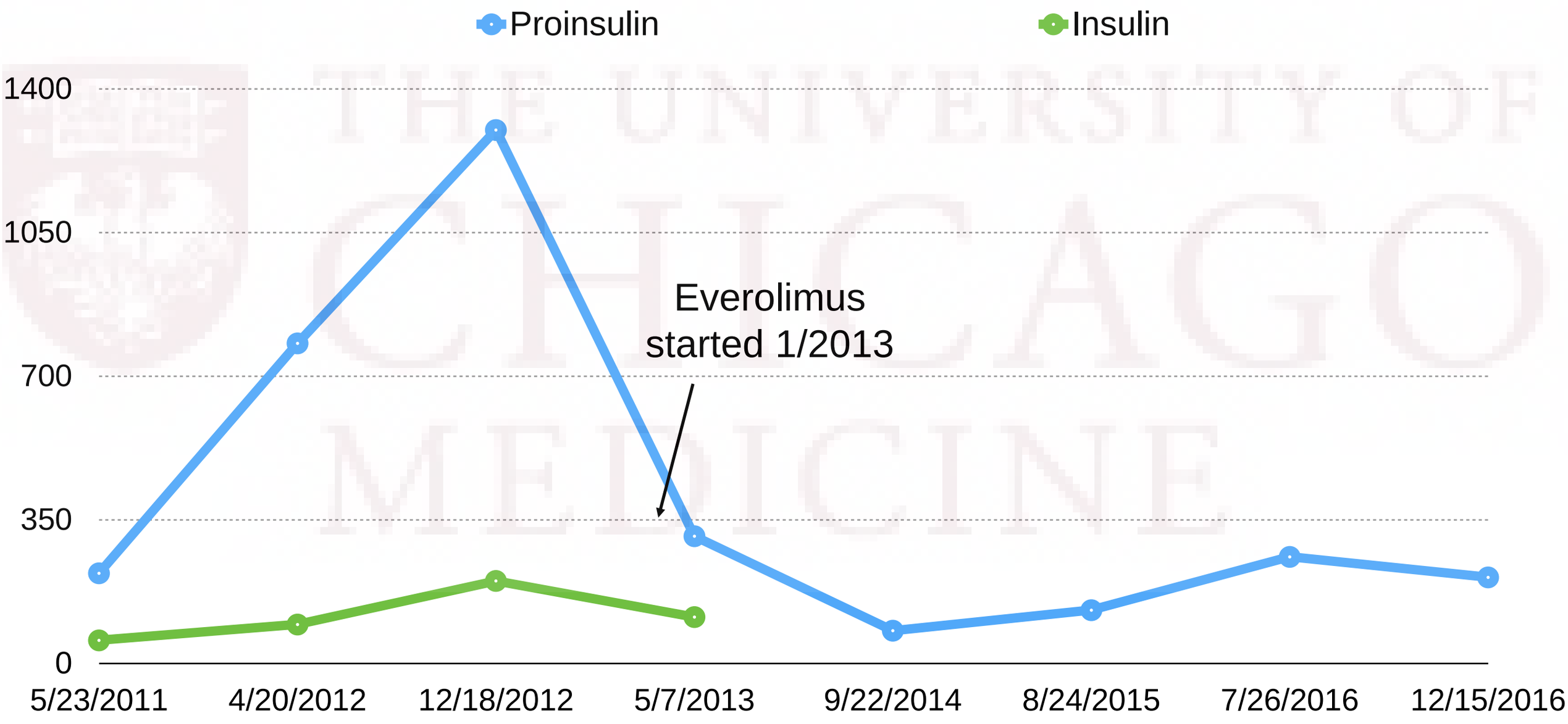
* Progression-free survival events include disease progression and death.

Median progression free survival was 11 months vs 4.6 months; 65% reduction in the estimated risk of progression

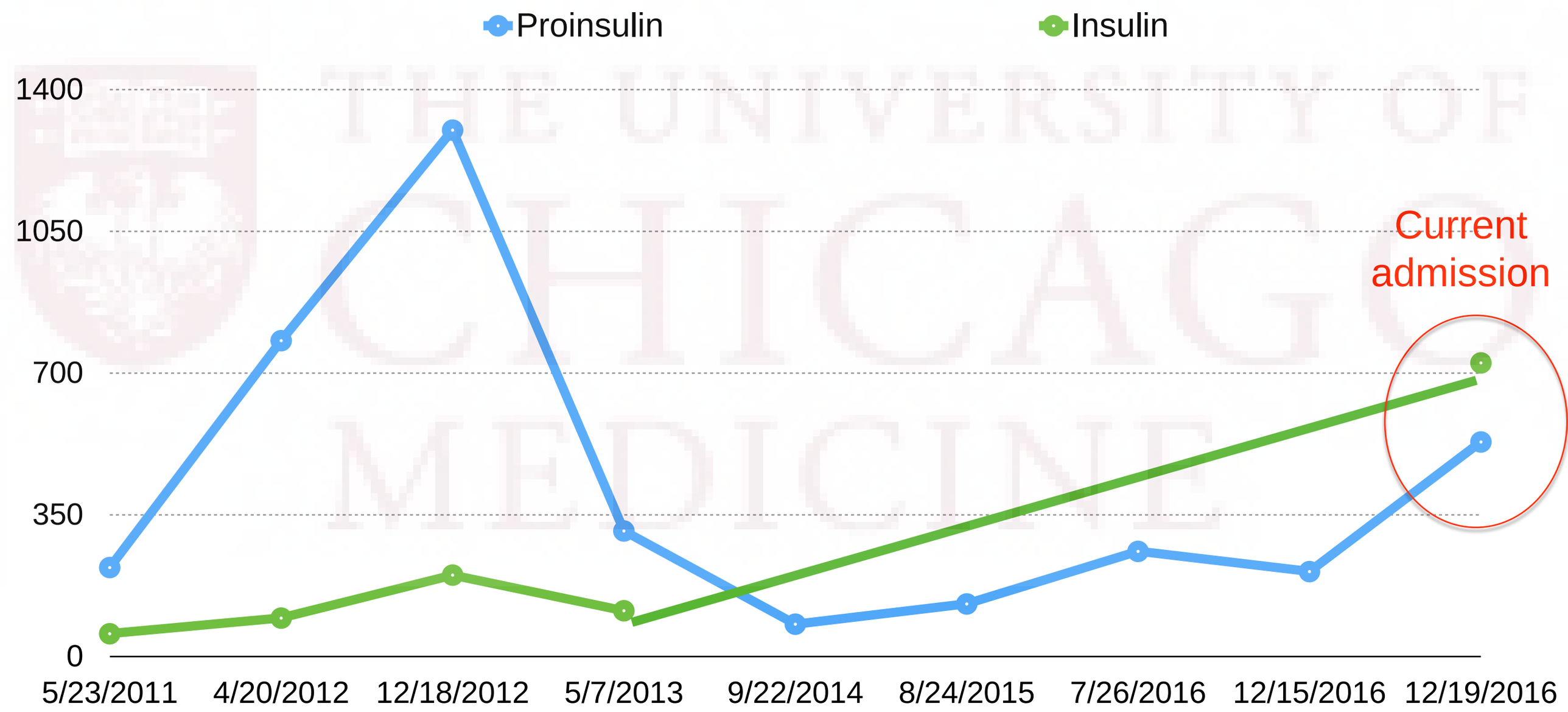


Proportion of Pts who were alive and progression free at 18 months were 34% with Everolimus as compared to 9% with placebo

Continued Course



Continued Course



Unclear prognosis

“This is the six year mark since I started seeing her for metastatic insulinoma.

Now has 7 grandchildren, 3 since I started being involved.

She wants at least to see two more babies.”

Conclusions

- Therapy for insulinoma is surgical and is curative in most cases (>90% benign)
- Malignant insulinomas are rare conditions presenting with 2 major challenges: tumor is metastatic & there is unregulated secretion of insulin/proinsulin products leading to hypoglycemia
- Treatment for malignant insulinomas is aimed at symptom & tumor control; It includes surgery, RFA, embolization, and chemotherapy
- Prognosis for malignant insulinomas is poor (median survival period <2 yrs)
- Everolimus can be used to treat refractory hypoglycemia in malignant insulinomas

References

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Objectives

Patient with Insulinoma & Falling BG Levels

1. To learn about the clinical presentation and diagnosis of insulinomas
2. To learn about medical management of insulinomas
3. To discuss data regarding Everolimus use in the treatment of insulinomas