10º congresso nacional cancro digestivo


# Objetivos e o das terapêuticas dos NET G1 e G2

# es e sequências terapêuticas

centro hospitalar do Porto

Serviço de Oncologia Médica Centro Hospitalar do Porto

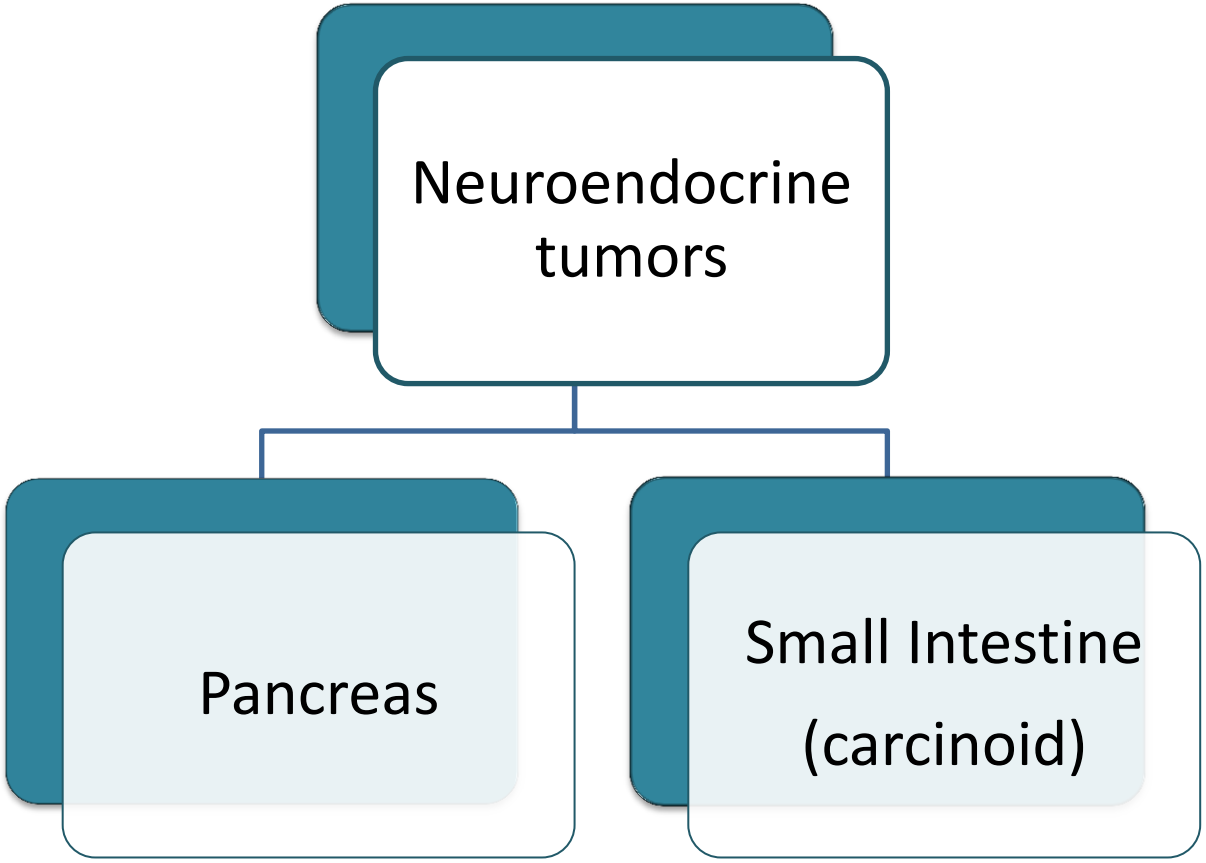
U.PORTO

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

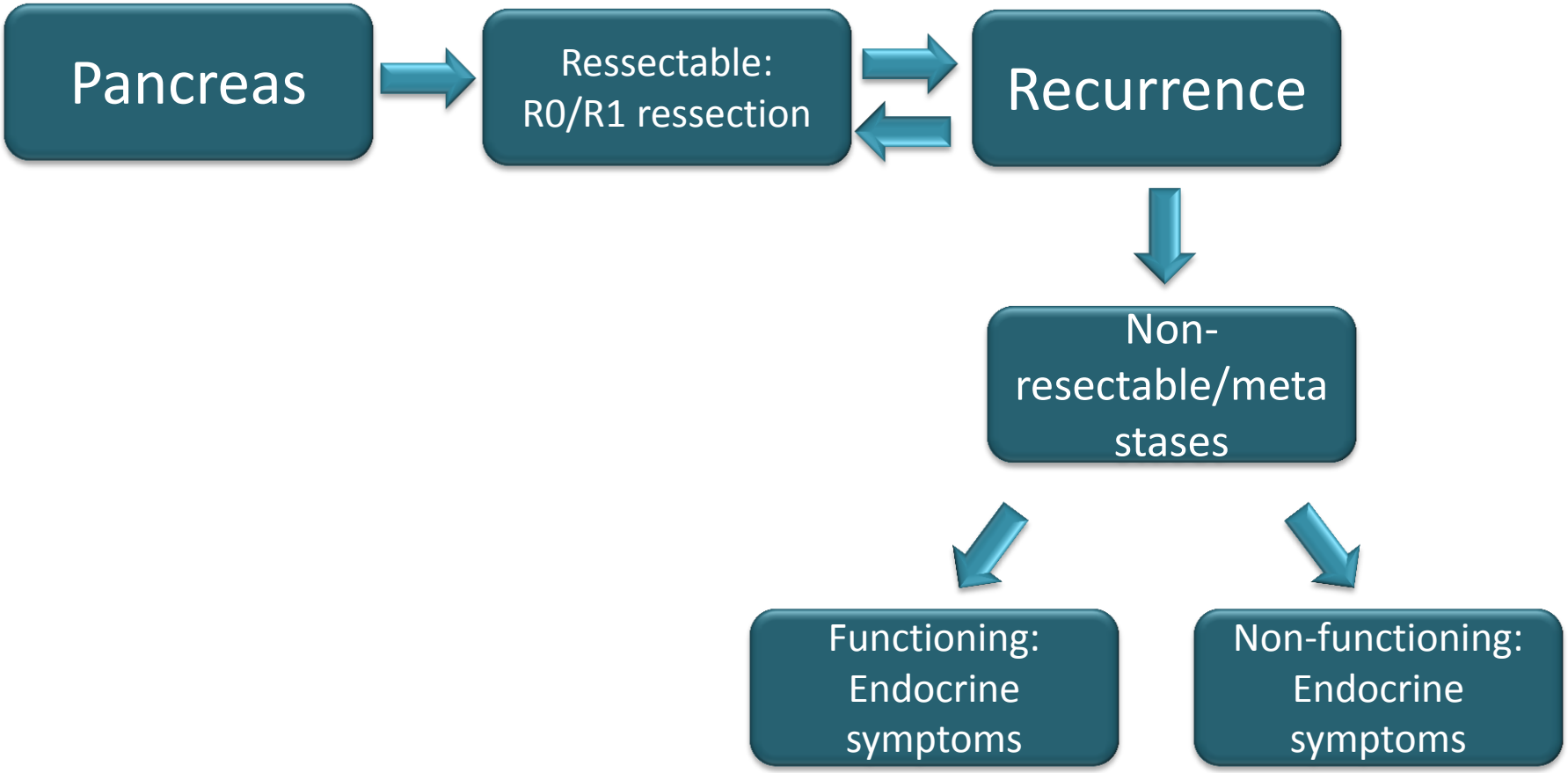
*Ana Ferreira Castro, MD*
Oncologia Médica
Centro Hospitalar do Porto

Instituto de Ciências Biomédicas de Abel Salazar

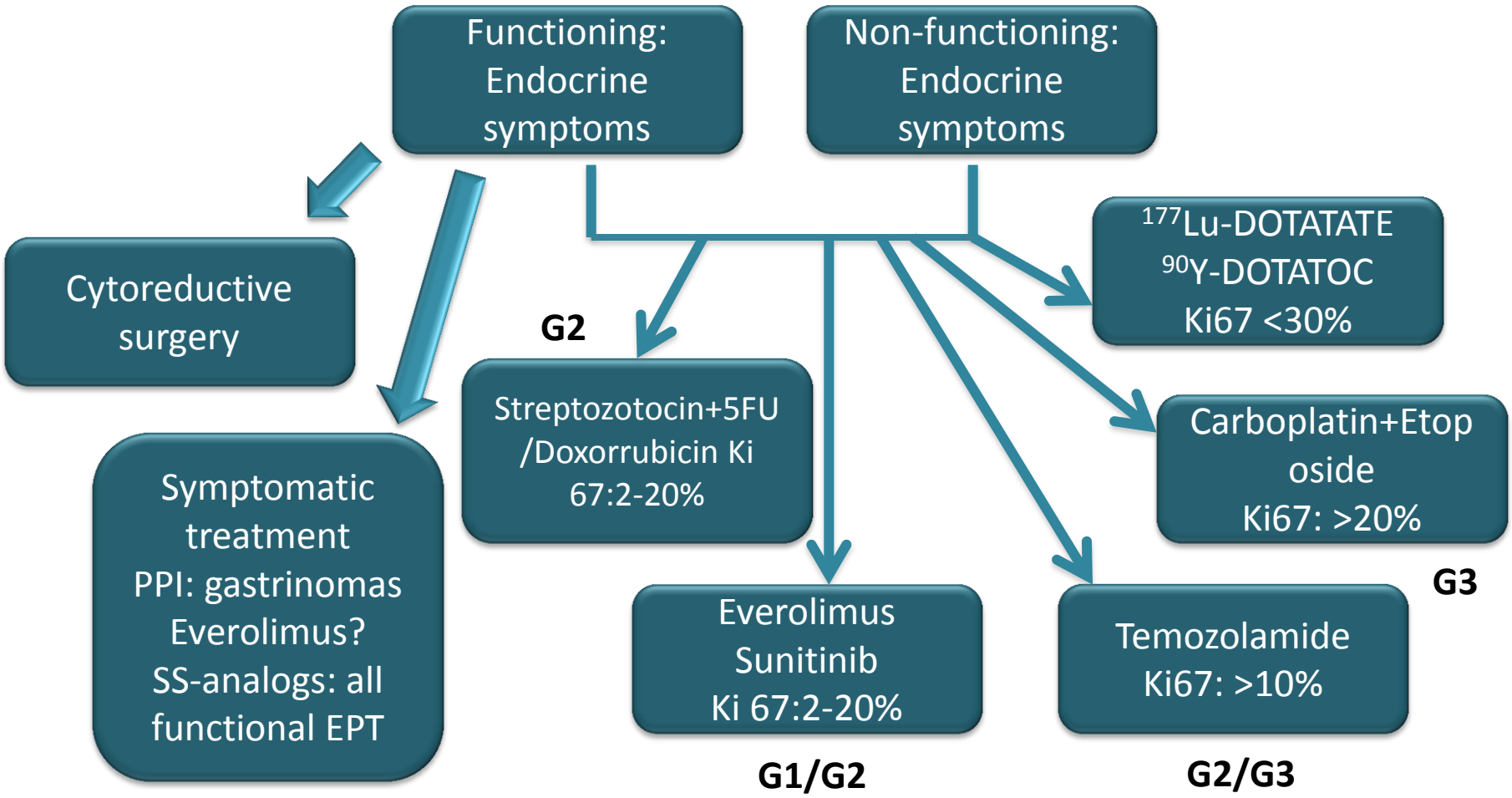
# Classification of neuroendocrine tumors



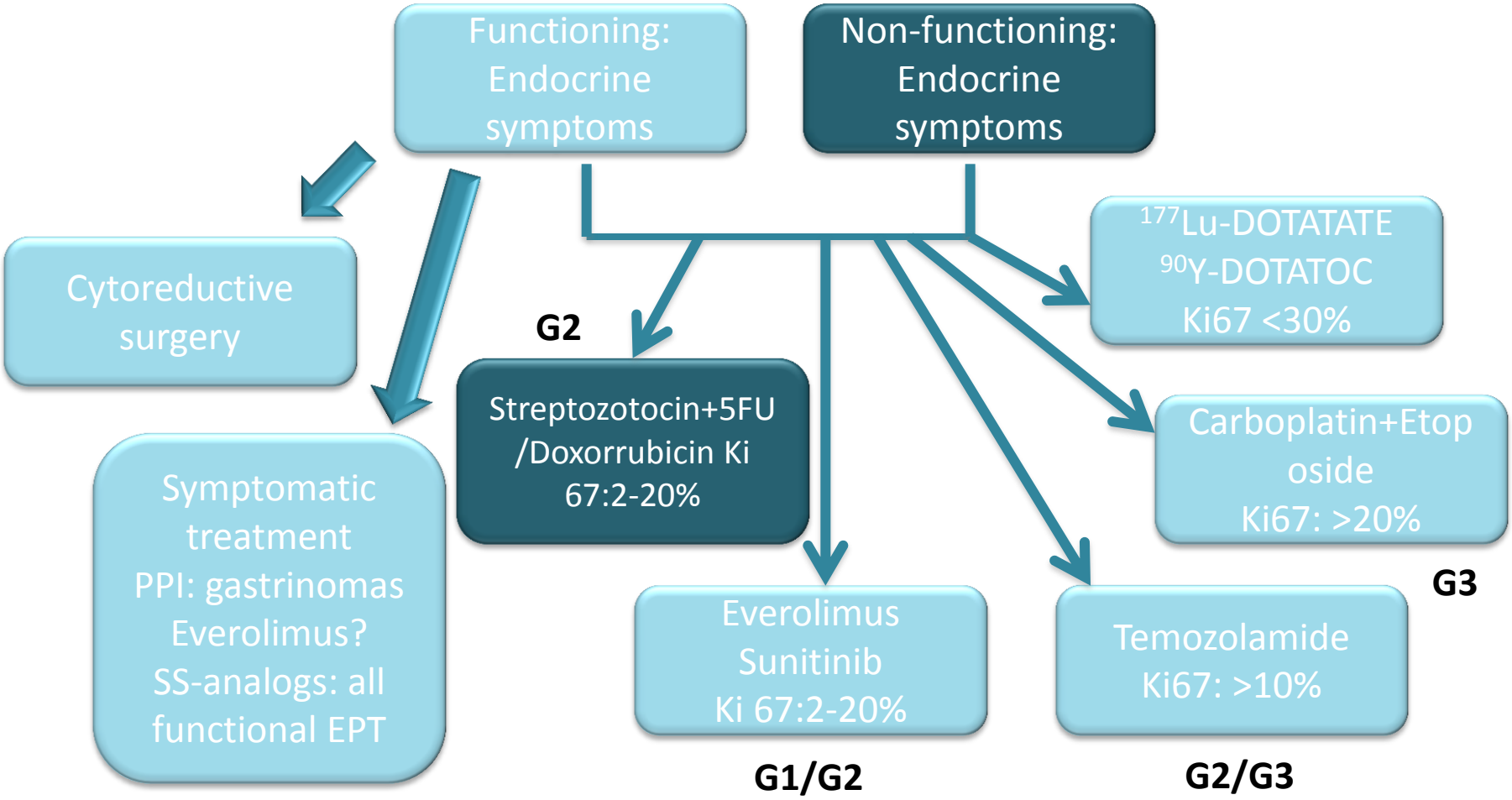
# Pancreas Neuroendocrine tumors



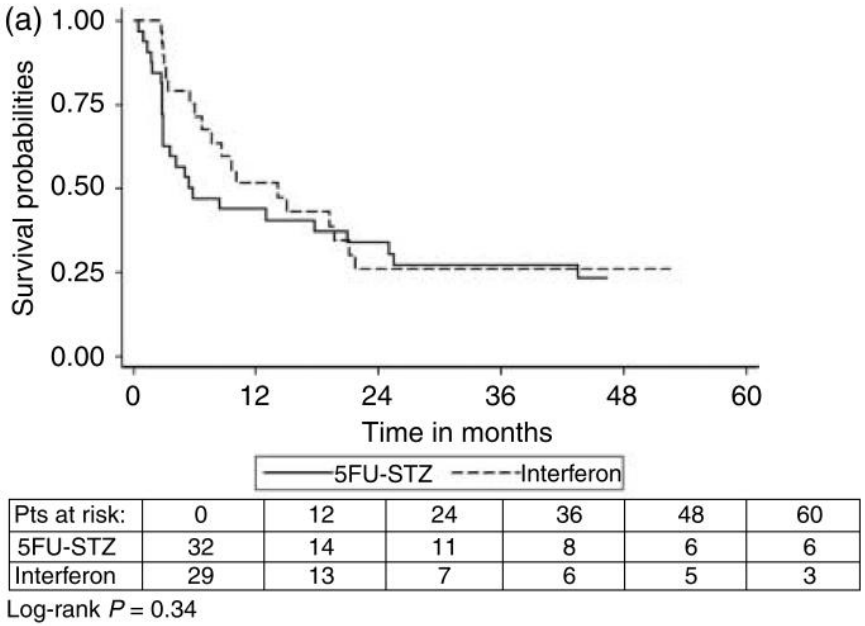
# Pancreas Neuroendocrine tumors



# Pancreas Neuroendocrine tumors

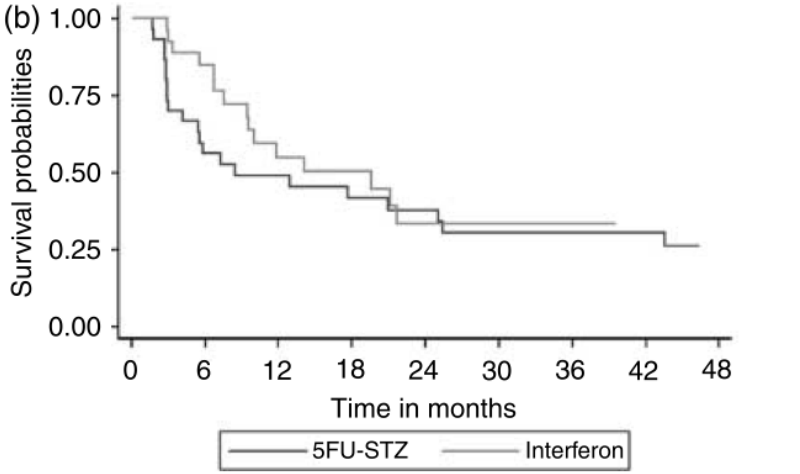


# 5FU+STZ vs Interferon




| Pts at risk: | 0 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|
| 5FU-STZ | 32 | 14 | 11 | 8 | 6 | 6 |
| Interferon | 29 | 13 | 7 | 6 | 5 | 3 |

Log-rank $P = 0.34$




Number at risk

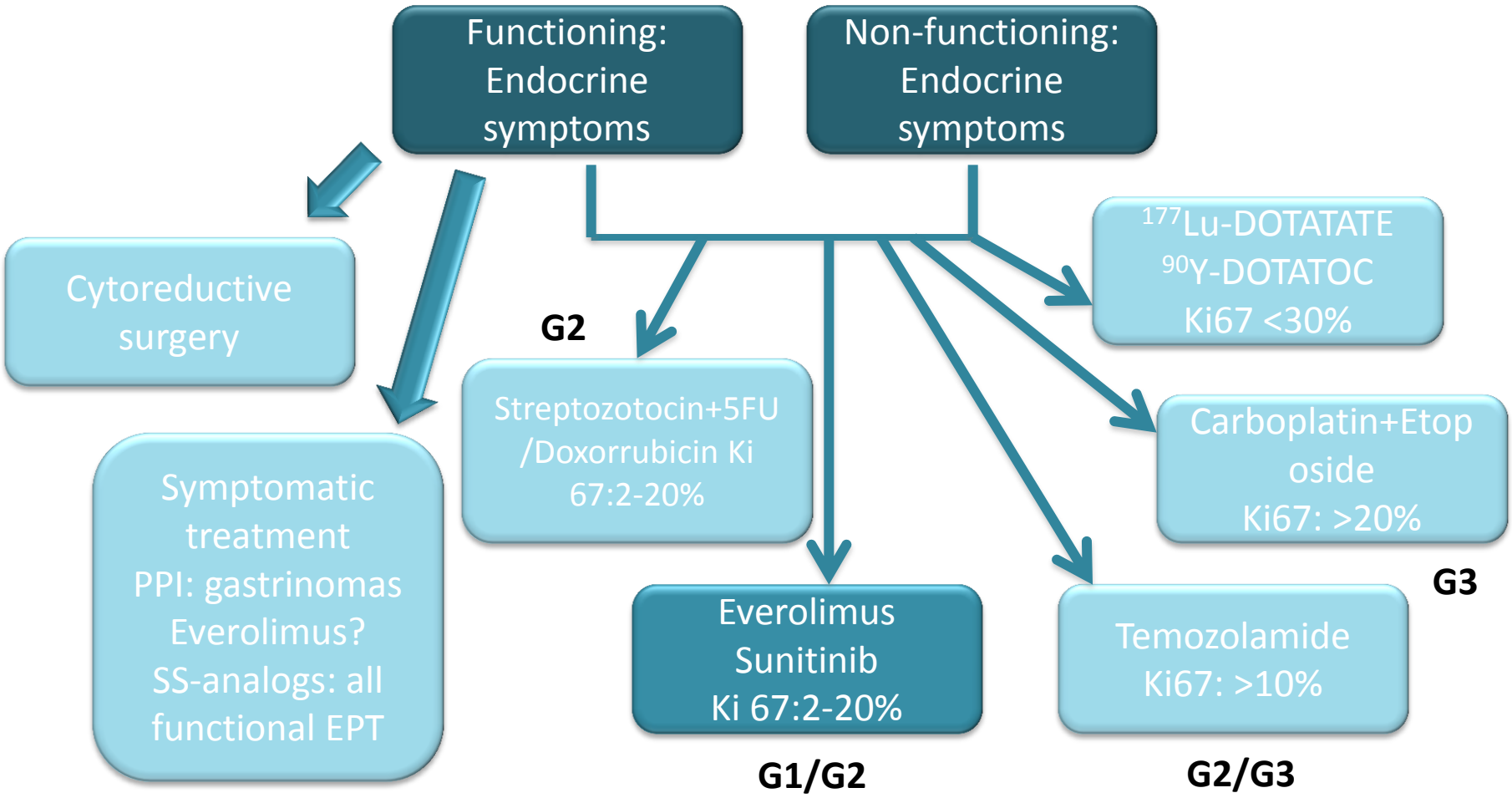
| 5FU-STZ | 30 | 16 | 13 | 11 | 10 | 7 | 7 | 7 | 0 |
|---|---|---|---|---|---|---|---|---|---|
| Interferon | 27 | 21 | 12 | 10 | 6 | 5 | 5 | 0 | 0 |

Log-rank $P = 0.32$

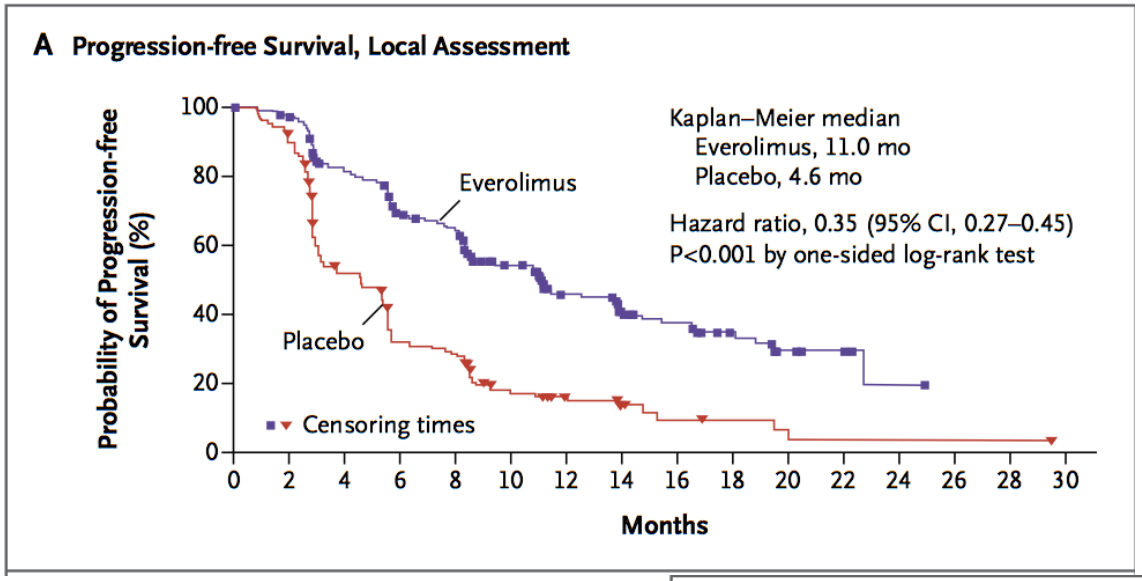
| Date | Regimen | Number of patients | Response (%) | Survival (months) | P value |
|---|---|---|---|---|---|
| 1984 | 5FU/STZ | 80 | 22 | 15 | 0.25 |
| | DOX | 81 | 21 | 11 | |
| 2005 | 5FU/Dox | 85 | 16 | 16 | 0.027 |
| | 5FU/STZ | 78 | 16 | 24 | |

L. Dahan, et al. Chemotherapy in advanced carcinoid tumors

# Pancreas Neuroendocrine tumors

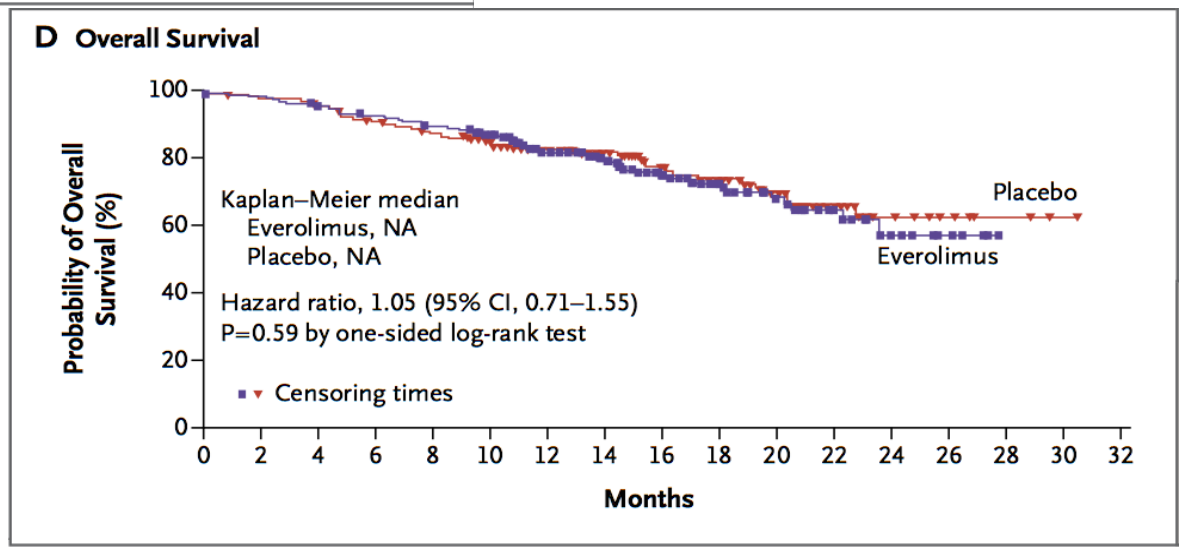


# Everolimus



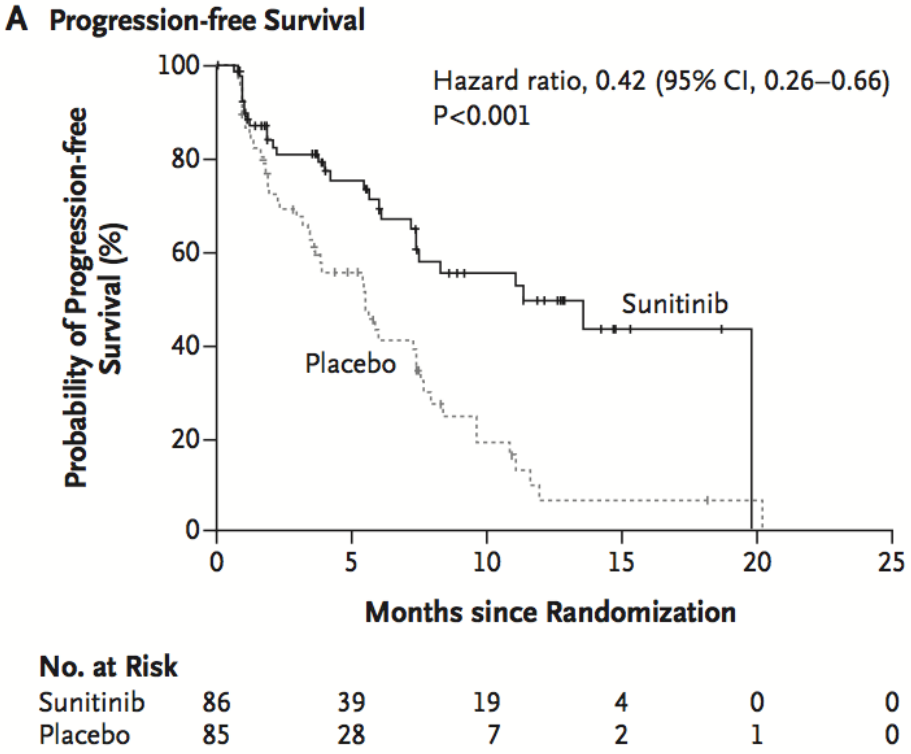

**Everolimus vs Placebo**

**Metastatic or unressectable disease with or without prior chemotherapy**

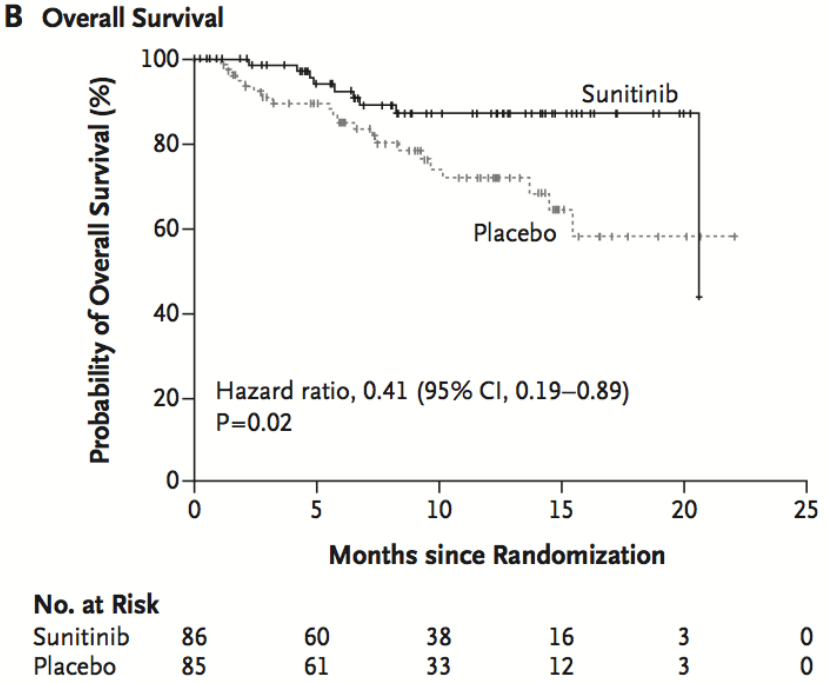



James C Yao, et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumors . N Engl J Med 2011;364:514-23.

# Sunitinib

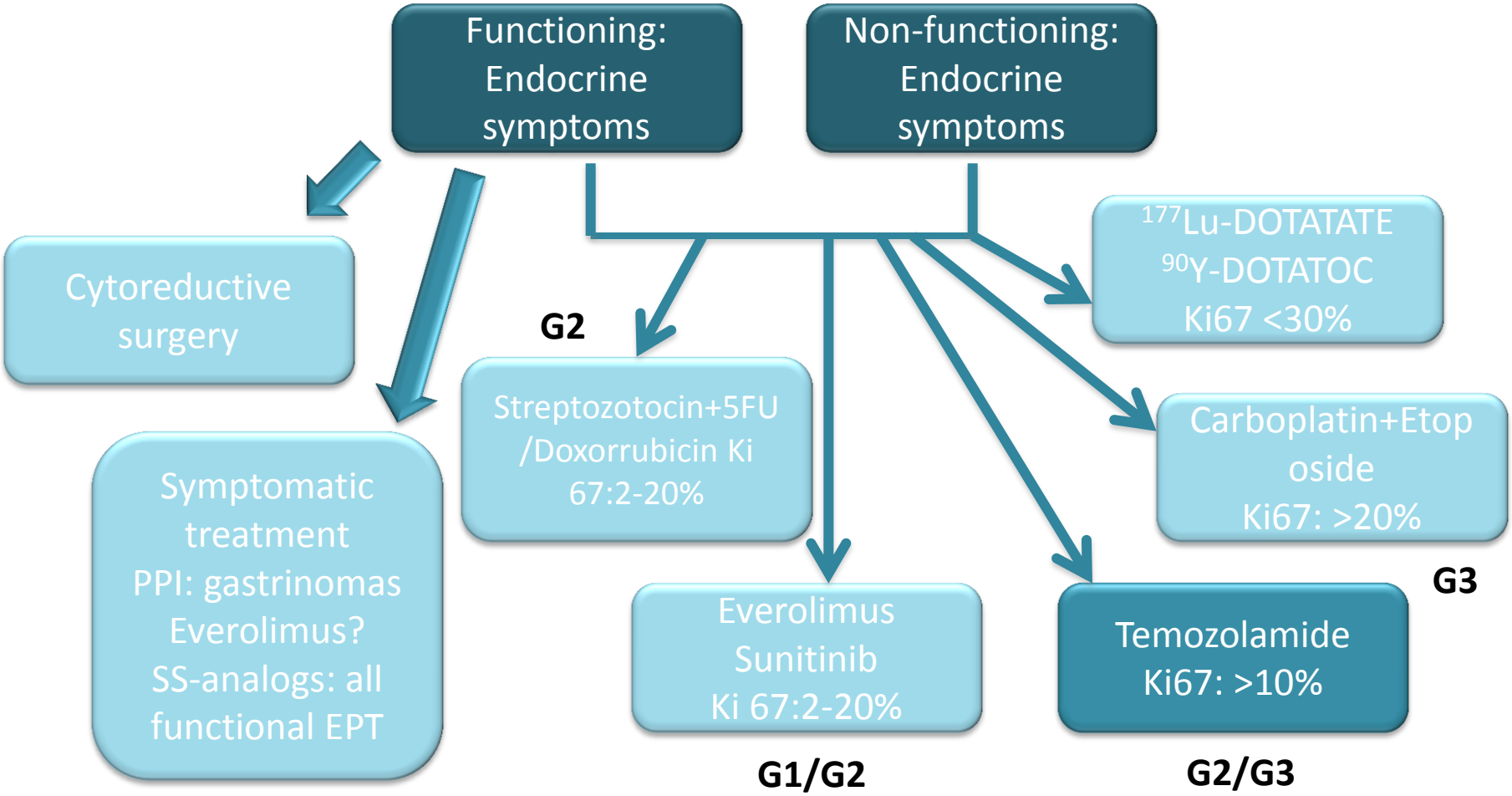



**Sunitinib vs Placebo**
**Metastatic disease with or without prior chemotherapy**




Eric Raymond, et al; Sunitinib Malate for the treatment of Pancreatic Neuroendocrine Tumors, N Engl J Med 2011;364:501-13.

# Pancreas Neuroendocrine tumors



# Temozolamide

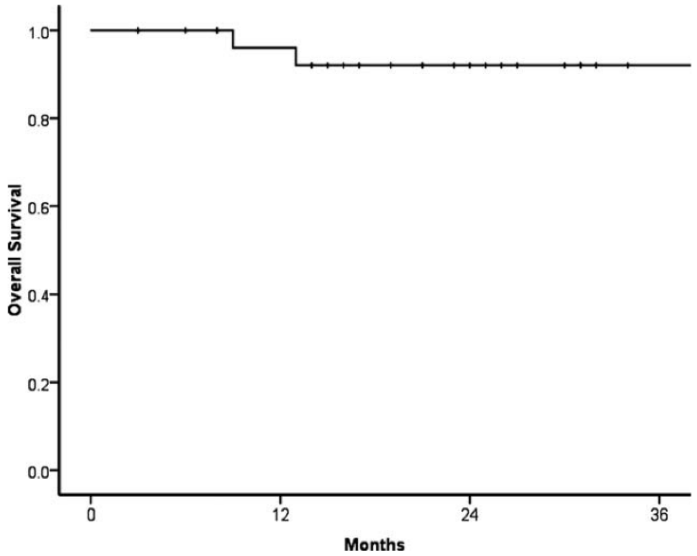



**Figure 3.** Overall survival from onset of treatment.

**Temozolamide+Capecitabine**

**First-line Chemotherapy in metastatic pancreatic neuroendocrine tumors**

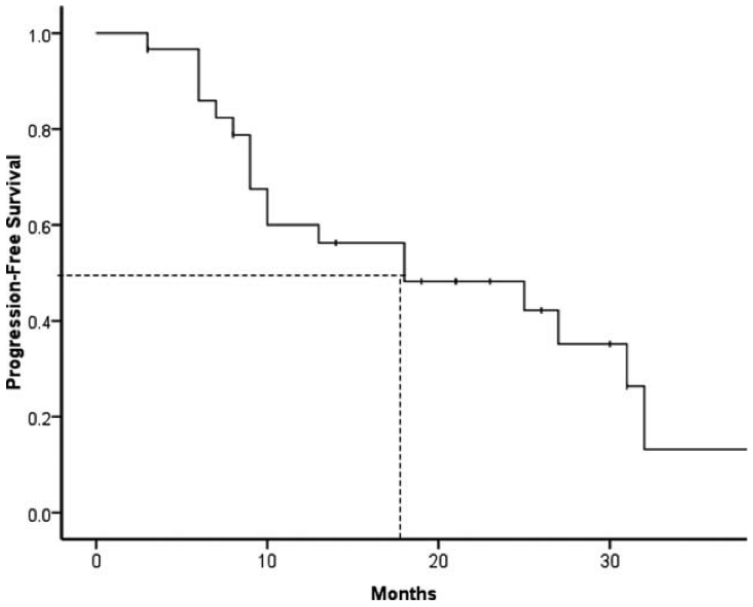
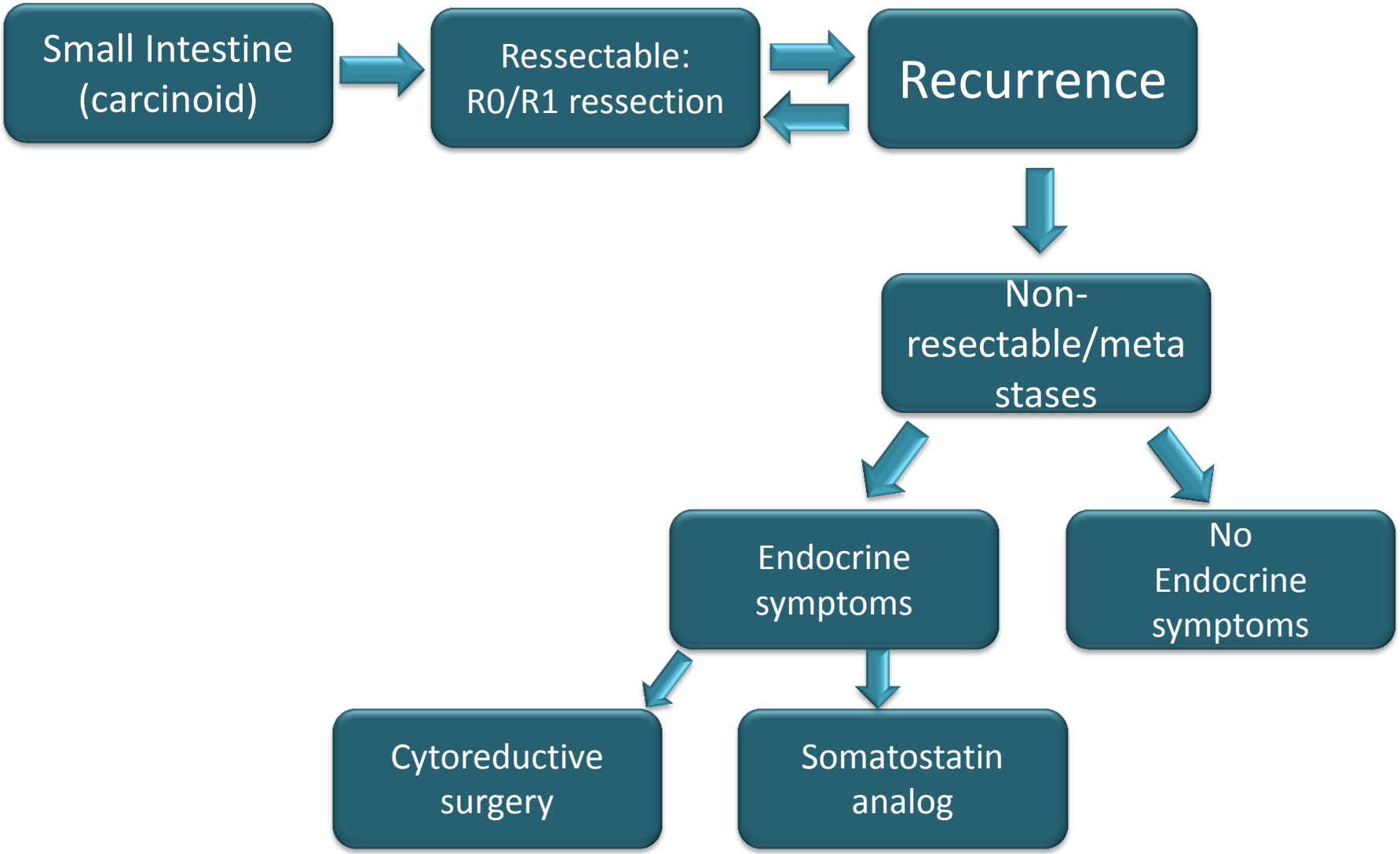


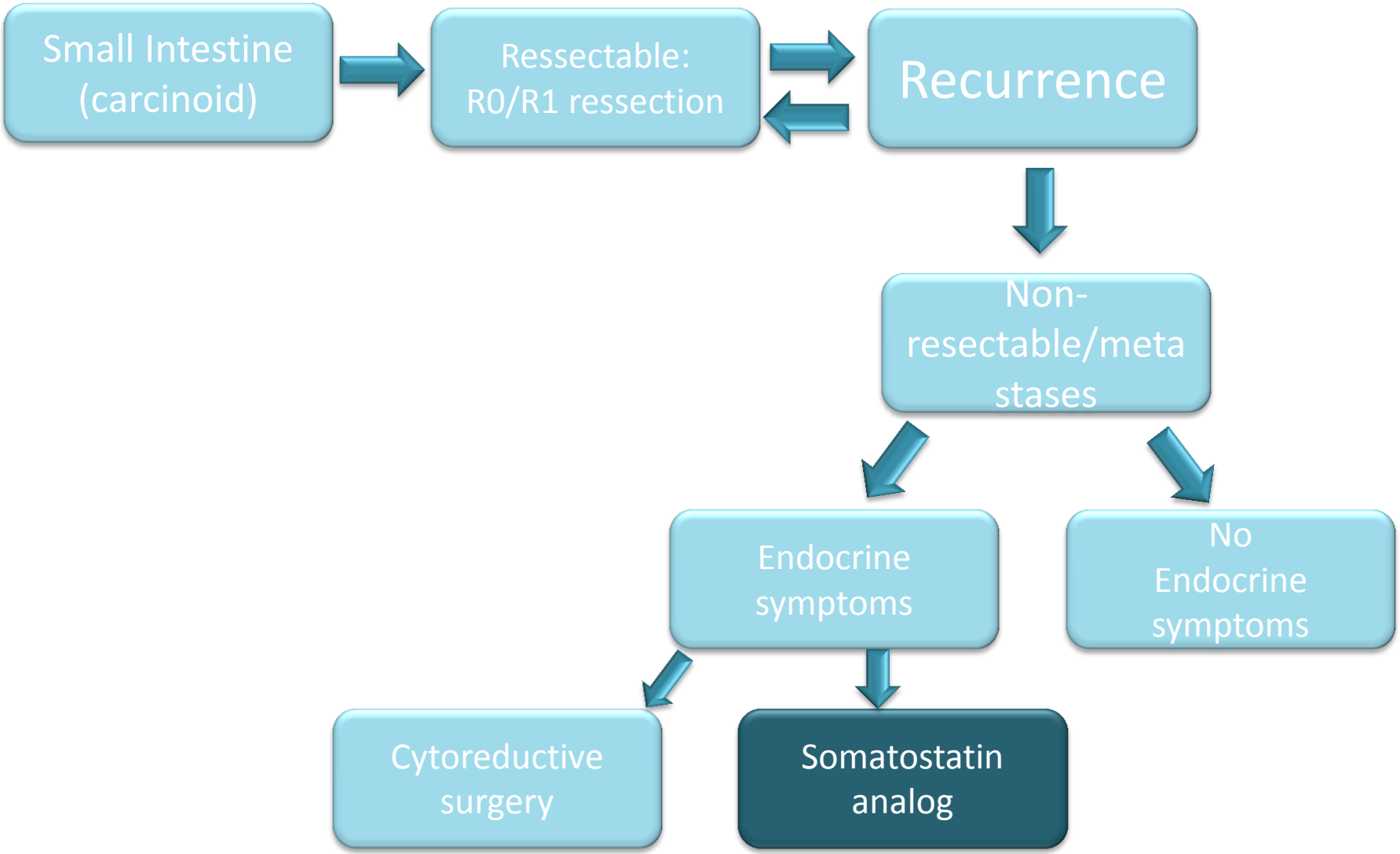

**Figure 4.** Progression-free survival.

Pancreatic Endocrine Carcinoma Treatment/Strosberg et al - Cancer January 15, 2011

# Small intestine endocrine tumors

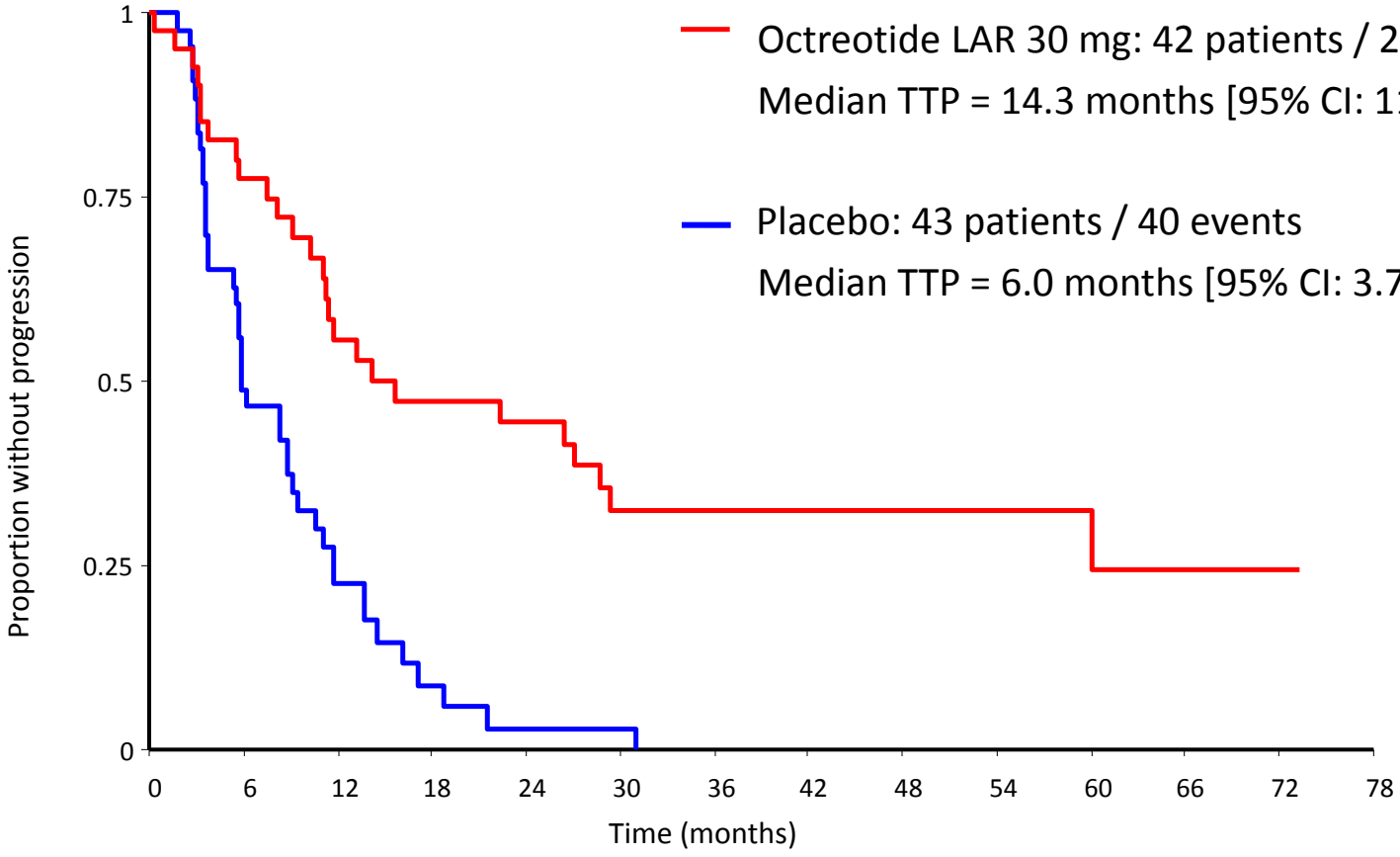


# Small intestine endocrine tumors



# Octreotide LAR 30 mg significantly prolongs time to tumour progression compared with placebo

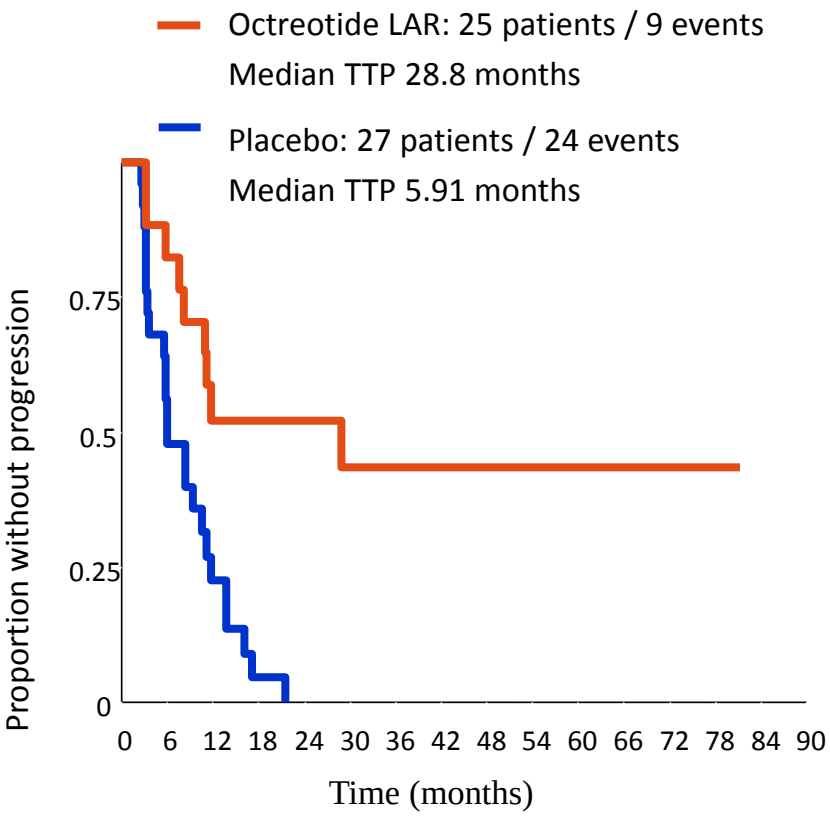
66% reduction in the risk of tumour progression
HR=0.34; 95% CI: 0.20–0.59; *P*=0.000072




Based on the conservative ITT analysis

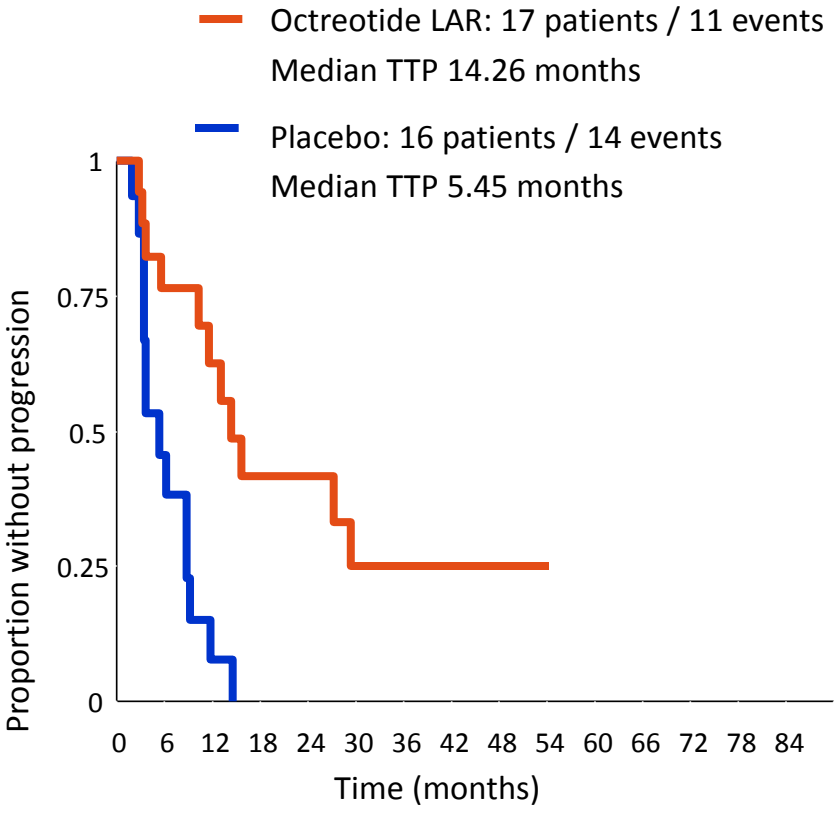
# Octreotide LAR 30 mg extends TTP in patients with functioning or non-functioning tumours

## Patients with non-functioning tumours




*P*=0.0008; HR=0.25 [95% CI: 0.10–0.59]

## Patients with functioning tumours




*P*=0.0007; HR=0.23 [95% CI: 0.09–0.57]

Based on the per protocol analysis


Arnold R. Abst # 4508 presented at ASCO 2009, Orlando FL

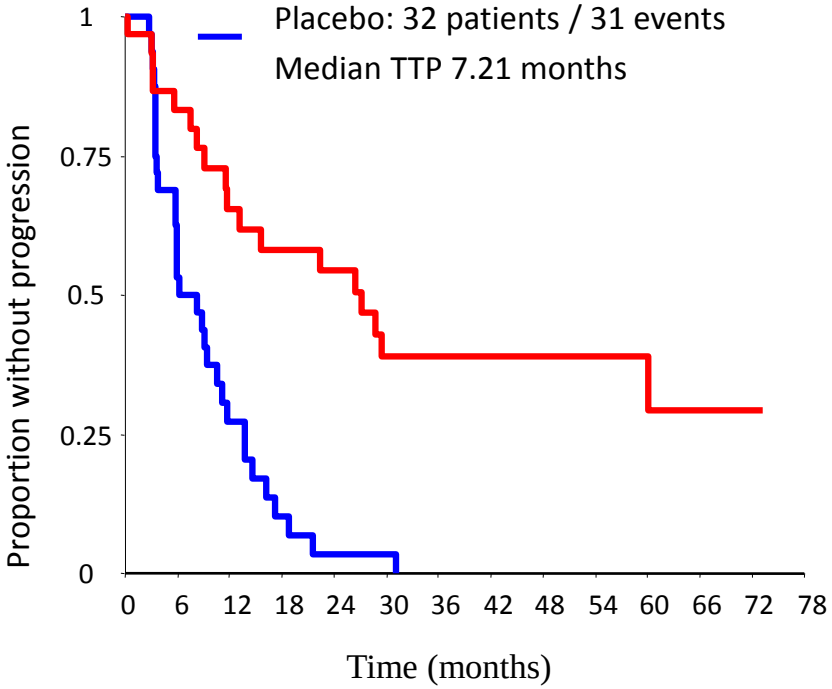
Rinke A *et al. J Clin Oncol* 2009

# Octreotid LAR 30 mg vs placebo: hepatic tumour load

## Patients with tumour load ≤10%

Octreotide LAR: 32 patients / 18 events
Median TTP 27.14 months

Placebo: 32 patients / 31 events
Median TTP 7.21 months

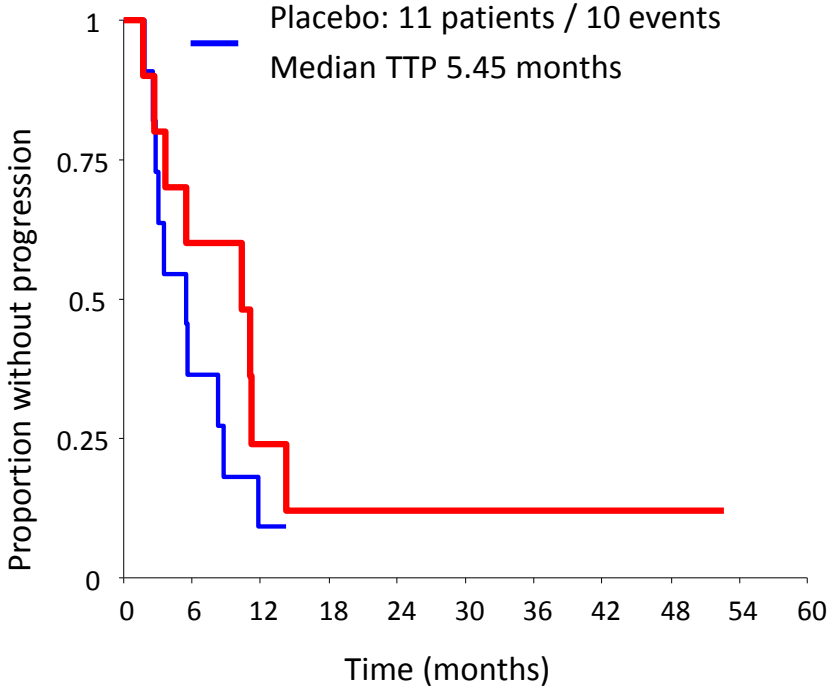



Stratified log-rank test
*P*<0.0001; HR=0.26 [95% CI: 0.14–0.50]

## Patients with tumour load >10%

Octreotide LAR: 10 patients / 8 events
Median TTP 10.35 months

Placebo: 11 patients / 10 events
Median TTP 5.45 months

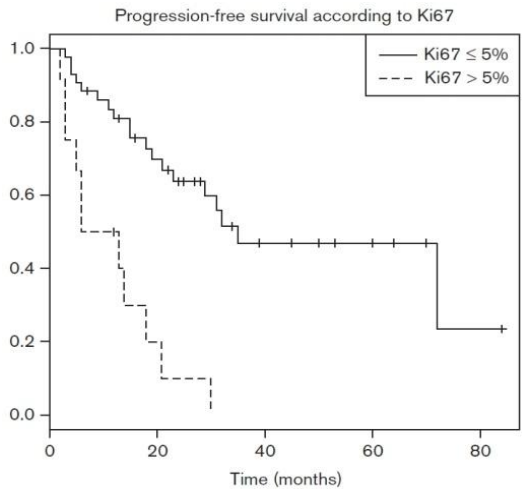



Stratified log-rank test
*P*=0.345; HR=0.64 [95% CI: 0.25–1.63]

Based on the ITT analysis

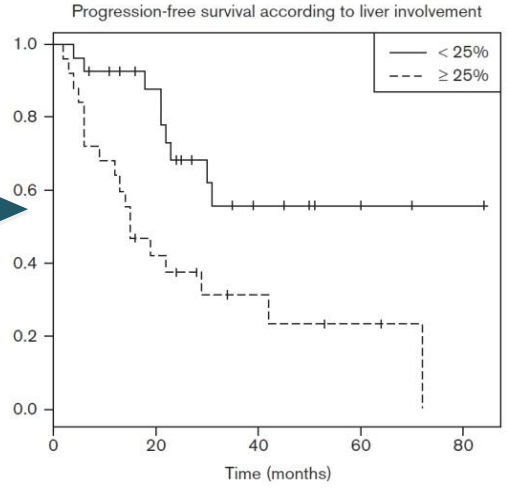
Arnold R. Presented at ASCO-GI 2009

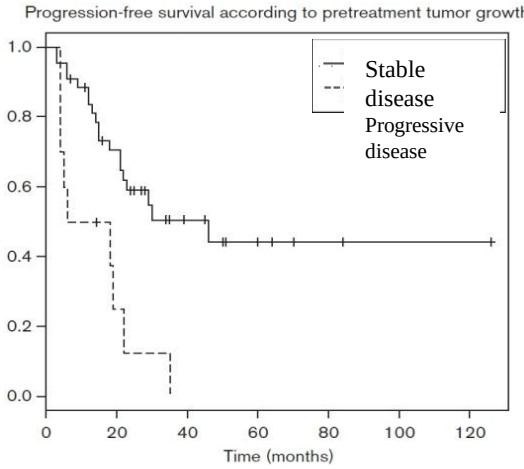
# Lanreotide




**Ki-67**

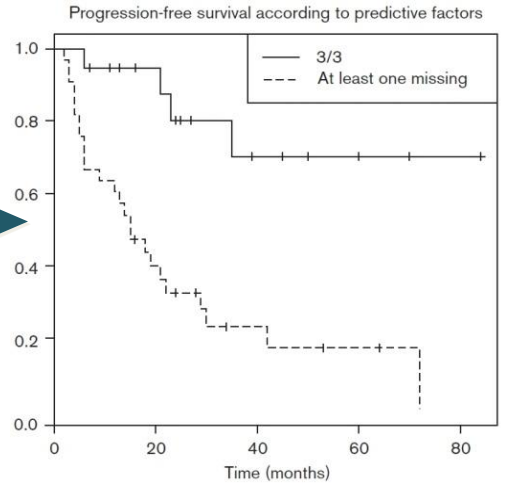
**Liver involvement**



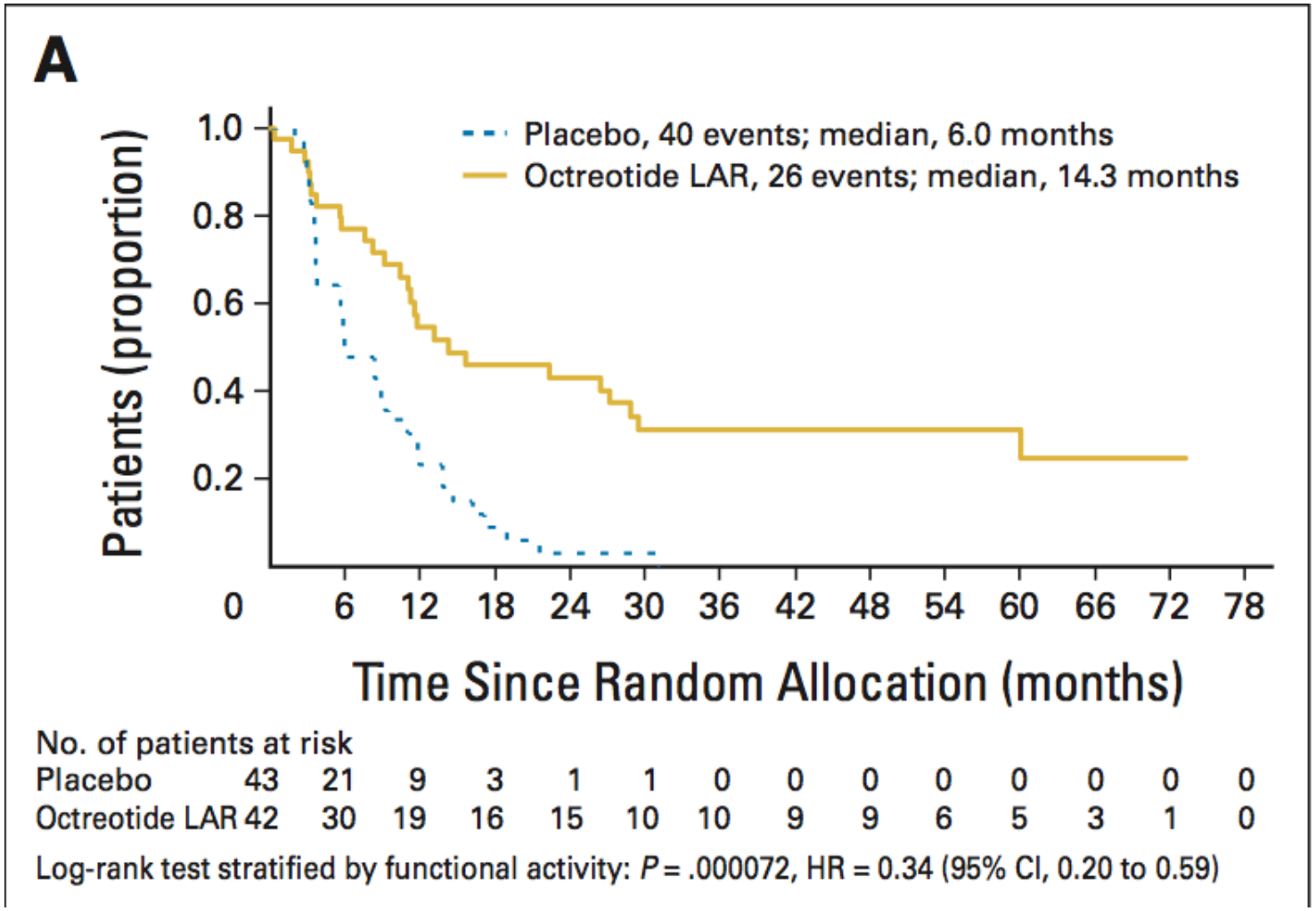

**Disease stability**

**All 3 factors**



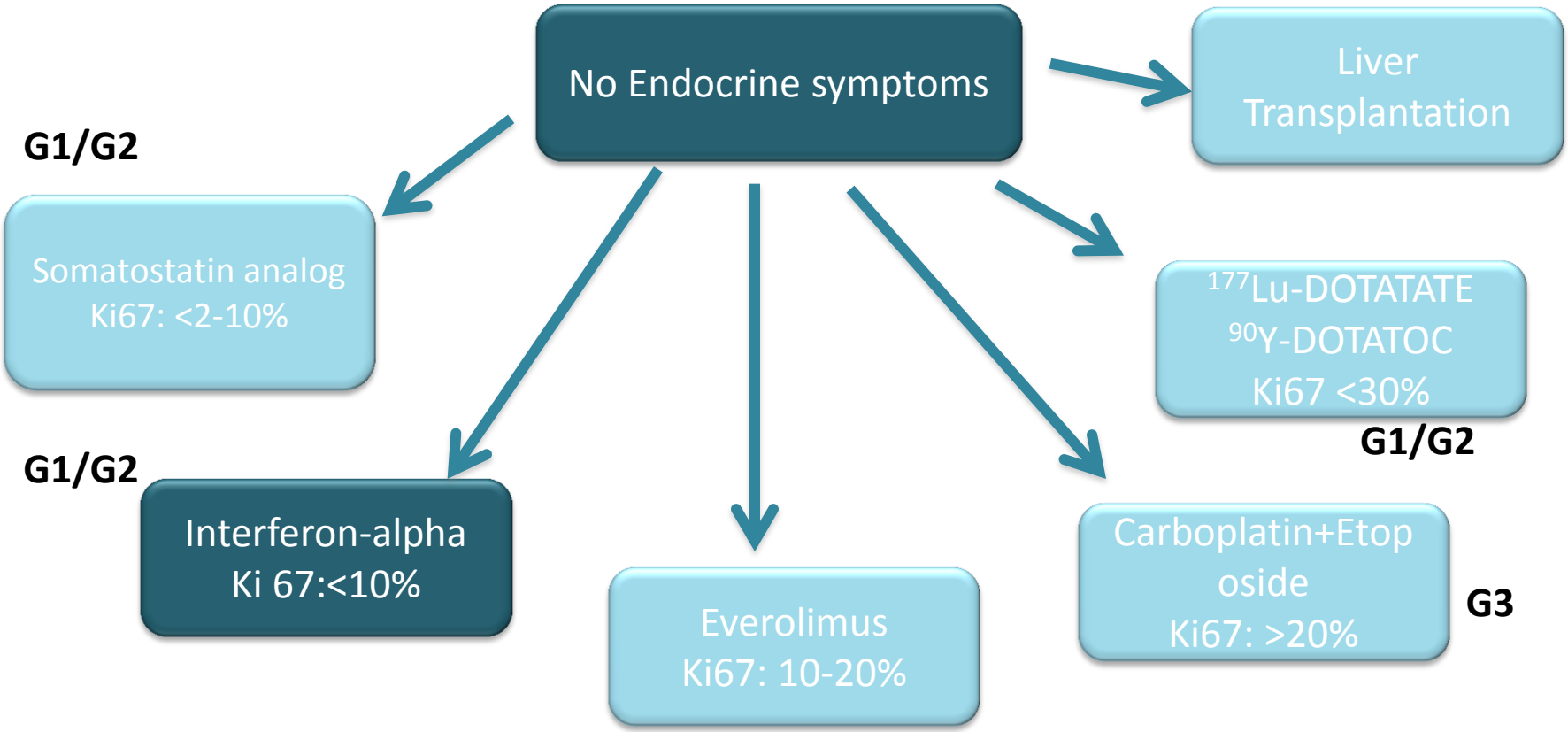

**Palazzo et al. Eur J Gastroenterol Hepatol 2013;25(2):232-238**

# PROMID




Octreotide Controls Growth in Neuroendocrine Midgut Tumors - *J Clin Oncol 27:4656-4663*

# Small Intestine (Carcinoid) Neuroendocrine tumors



# Interferon-alpha

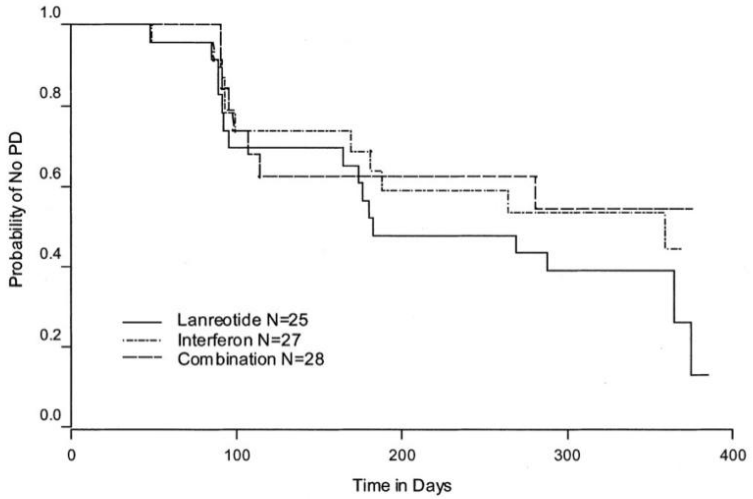



**Fig 2. Time to tumor progression according to treatment groups (Kaplan-Meier estimates, log-rank *P* = .312).**

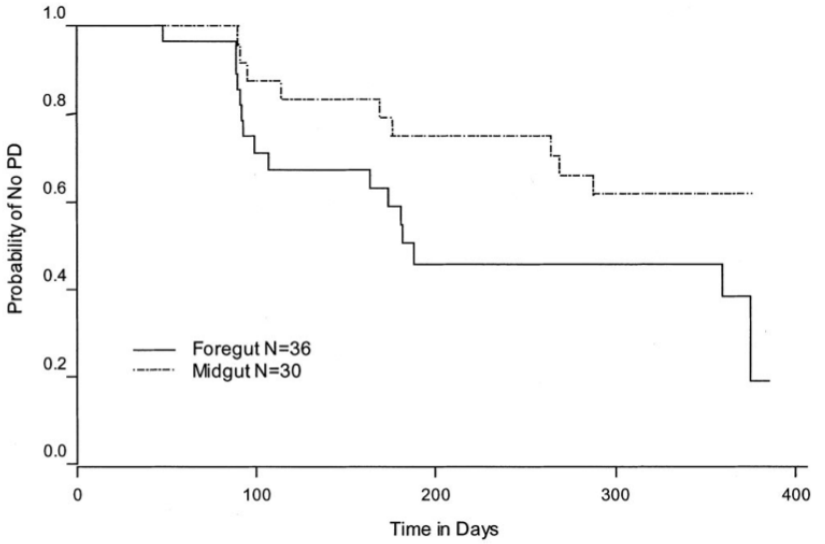
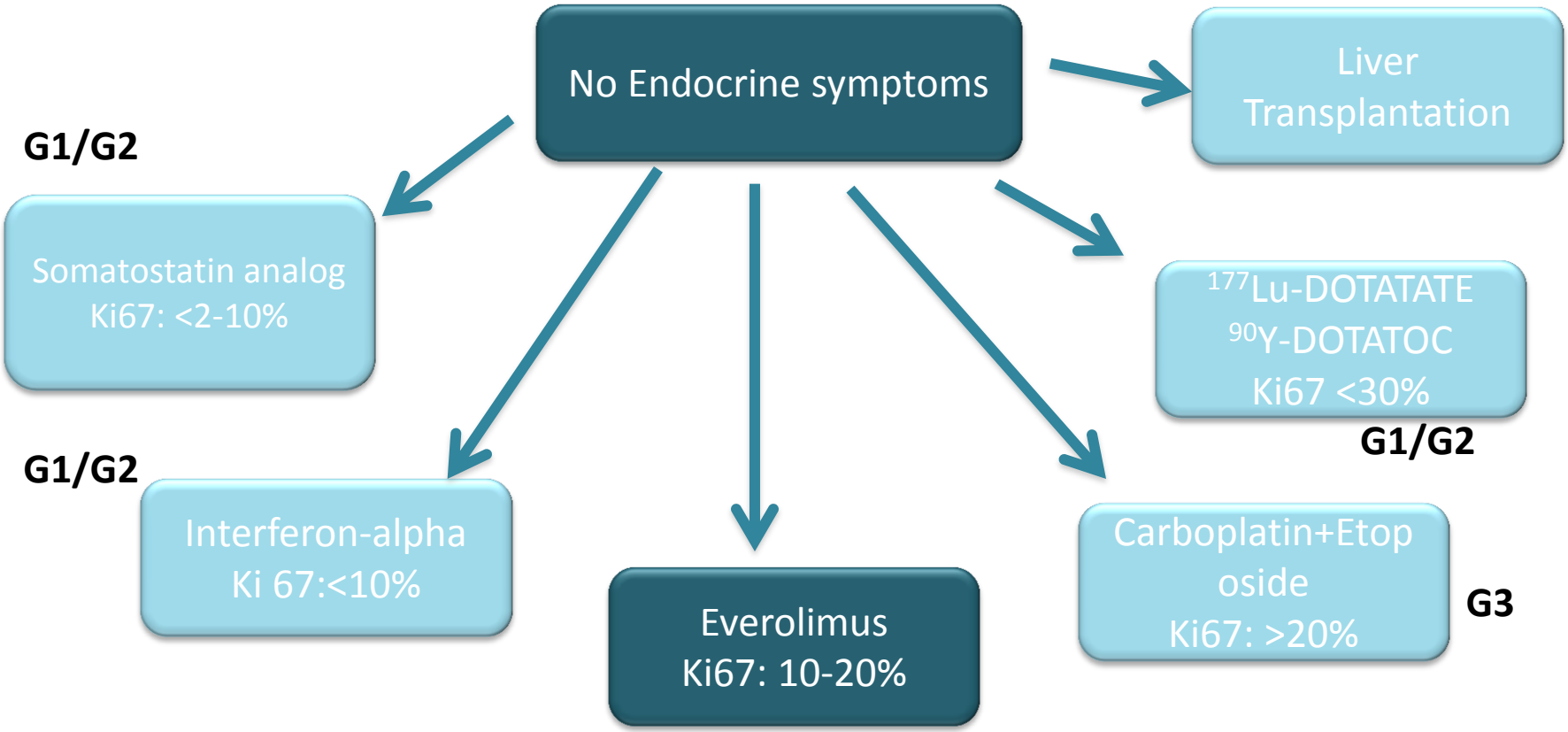



**Fig 3. Time to tumor progression according to primary tumor localization (Kaplan-Meier estimates, log-rank *P* = .039).**

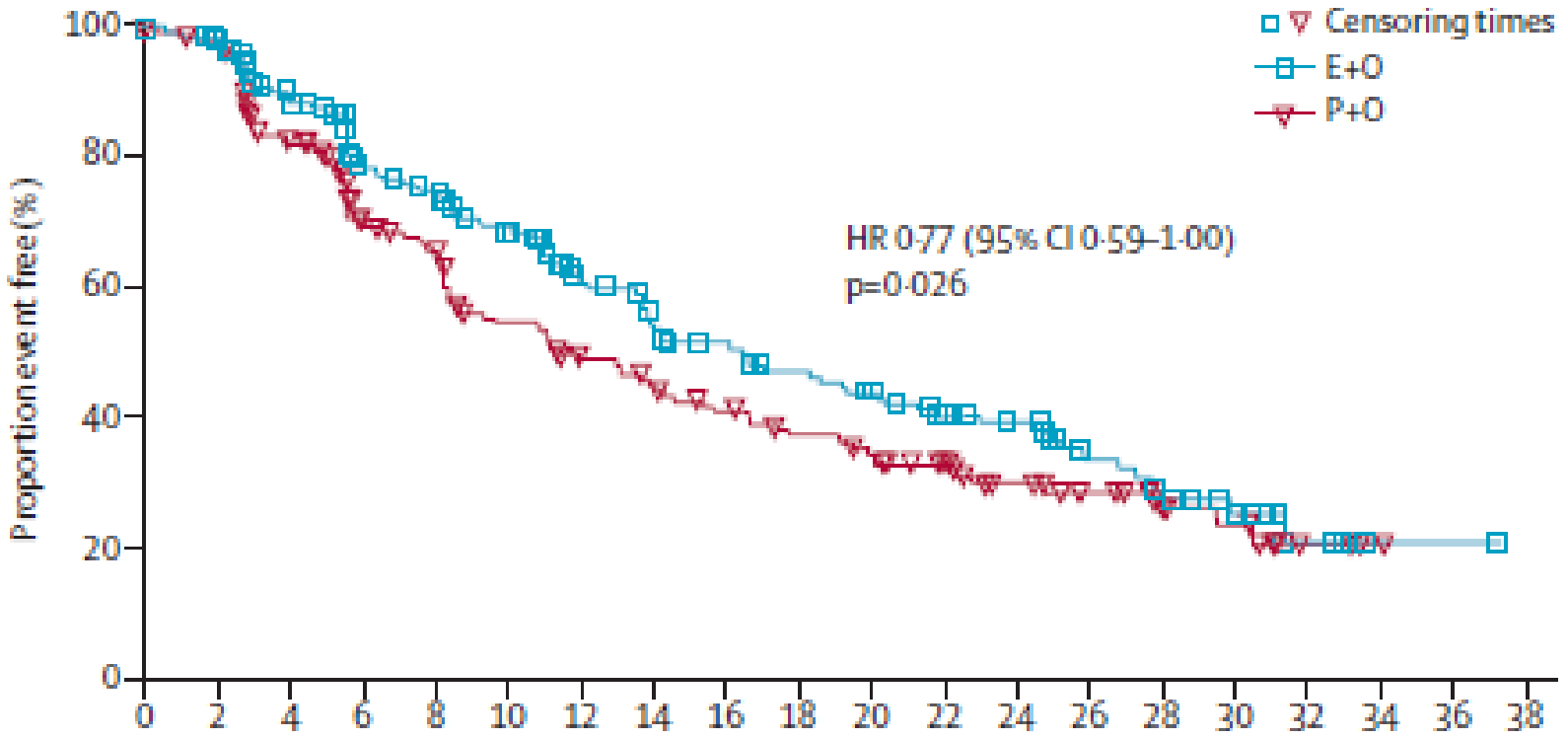
*Journal of Clinical Oncology*, Vol 21, No 14 (July 15), 2003: pp 2689-2696

# Small Intestine (Carcinoid) Neuroendocrine tumors



# Combined therapy with Everolimus+Octreotide RADIANT 2

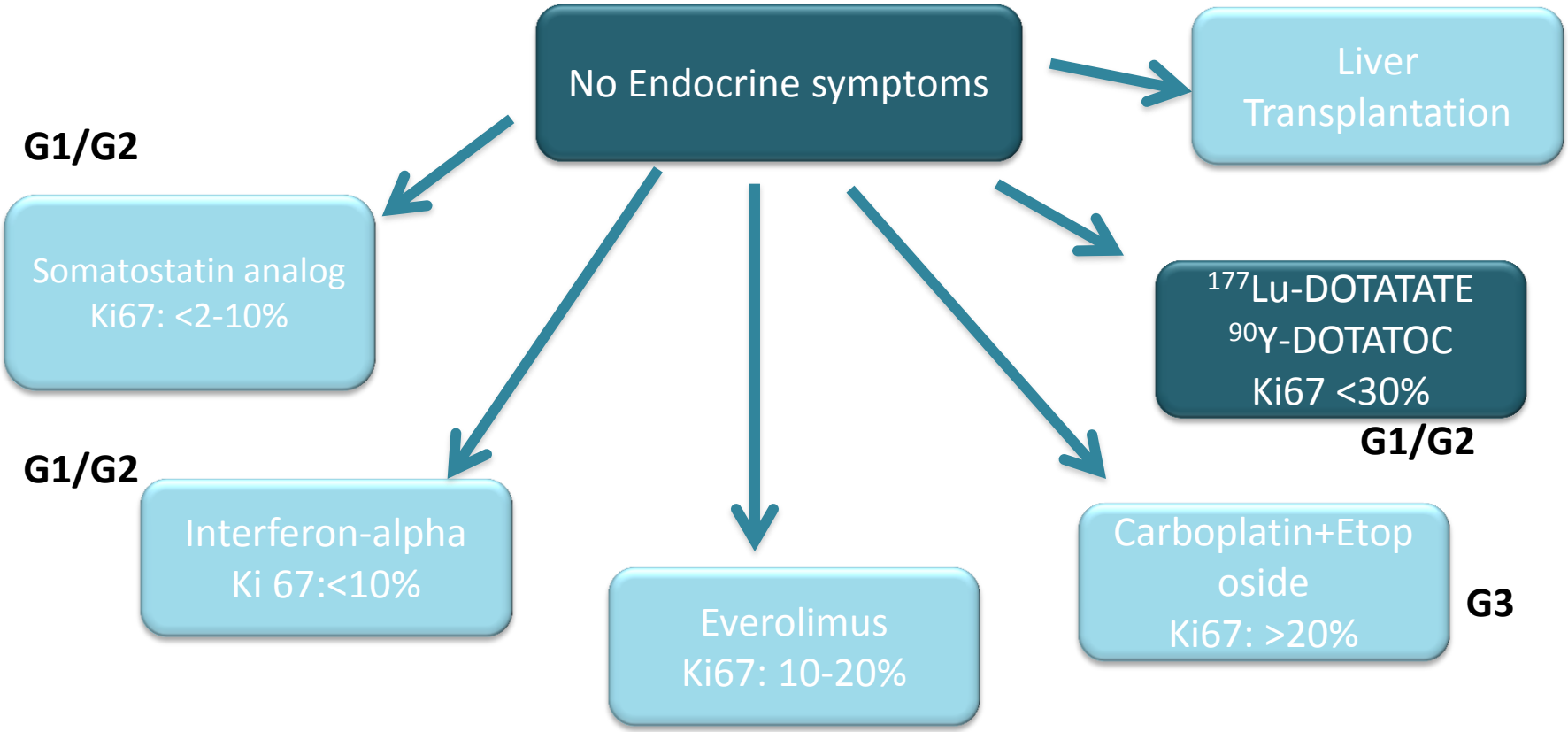
**PFS (Central review)**




Median PFS: 16.4 vs 11.3 months
ORR = 2% in both arms

Pavel et al. Lancet 2011

# Small Intestine (Carcinoid) Neuroendocrine tumors



# PRRT

**TABLE 1**
Tumor Responses in Patients with GEP Tumors and Treated with Various Radiolabeled Somatostatin Analogs

| Center (reference) | Ligand | No. of patients | Tumor response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | CR* | PR* | MR* | SD* | PD* | CR + PR† |
| Rotterdam (*2*) | [$^{111}$In-DTPA$^{0}$]octreotide | 26 | 0 | 0 | 5 (19) | 11 (42) | 10 (38) | 0 |
| New Orleans (*3*) | [$^{111}$In-DTPA$^{0}$]octreotide | 26 | 0 | 2 (8) | NA | 21 (81) | 3 (12) | 8 |
| Milan (*10*) | [$^{90}$Y-DOTA$^{0}$, Tyr$^{3}$]octreotide | 21 | 0 | 6 (29) | NA | 11 (52) | 4 (19) | 29 |
| Basel (*5,6*) | [$^{90}$Y-DOTA$^{0}$, Tyr$^{3}$]octreotide | 74 | 3 (4) | 15 (20) | NA | 48 (65) | 8 (11) | 24 |
| Basel (*7*) | [$^{90}$Y-DOTA$^{0}$, Tyr$^{3}$]octreotide | 33 | 2 (6) | 9 (27) | NA | 19 (57) | 3 (9) | 33 |
| Rotterdam (*11*) | [$^{90}$Y-DOTA$^{0}$, Tyr$^{3}$]octreotide | 54 | 0 | 4 (7) | 7 (13) | 33 (61) | 10 (19) | 7 |
| Rotterdam (*18*) | [$^{177}$Lu-DOTA$^{0}$, Tyr$^{3}$]octreotate | 76 | 1 (1) | 22 (29) | 9 (12) | 30 (39) | 14 (18) | 30 |

*Reported as number (percentage) of patients. SD = stable disease; NA = not available.
†Reported as percentage of patients.

Overview of Results of Peptide Receptor Radionuclide Therapy with 3 Radiolabeled Somatostatin Analogs - ***J Nucl Med.* 2005;46:62S-66S.**

# PRRT

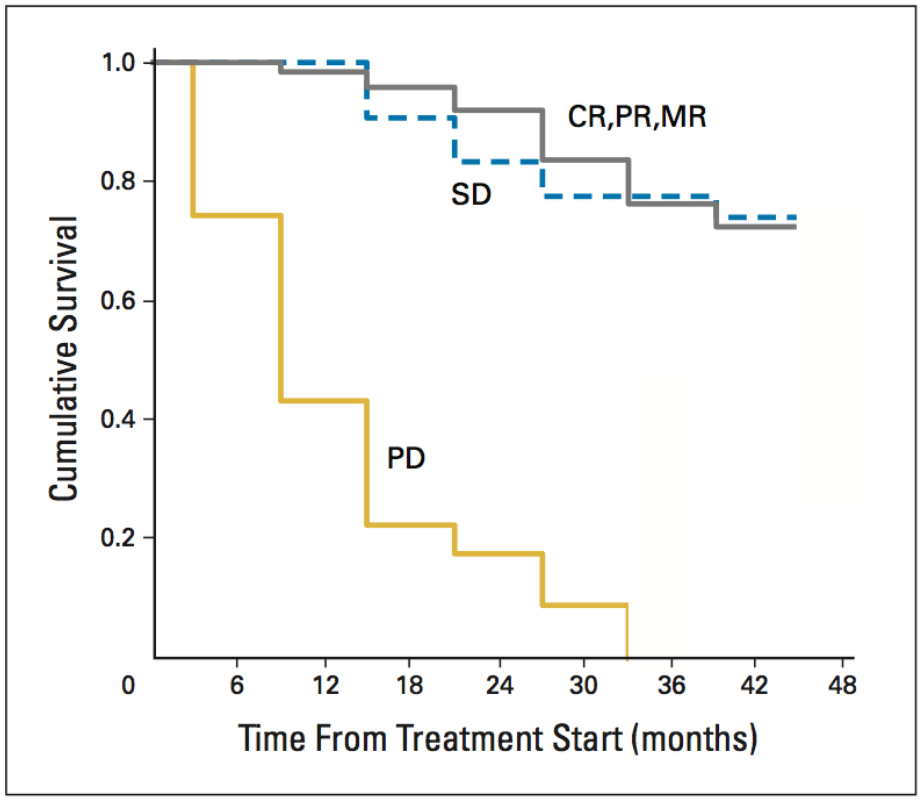
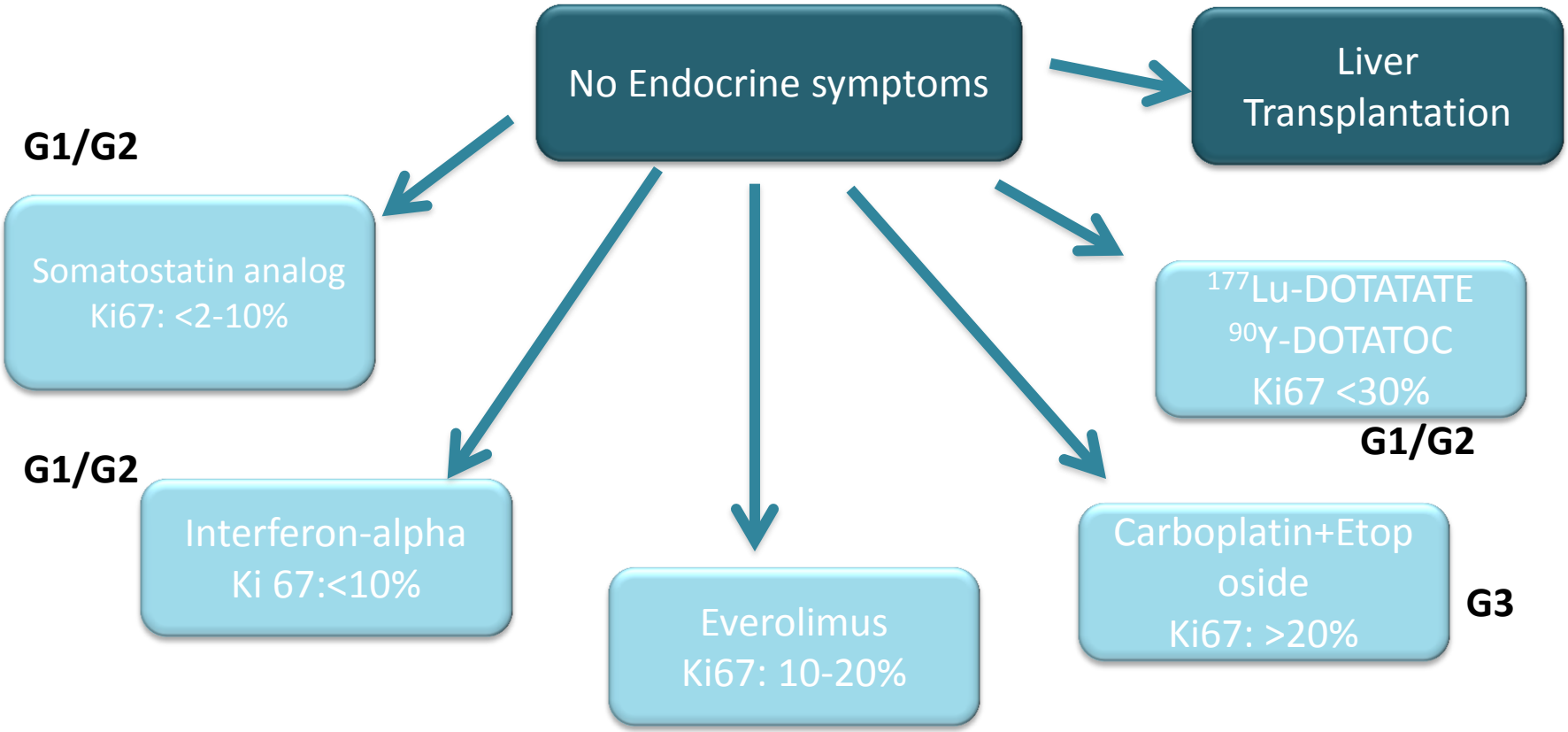



**Fig 1.** Disease-related survival in 310 patients according to treatment outcome. Patients with progressive disease (PD) have significantly shorter survival. Survival between other treatment outcomes did not differ significantly. CR, complete response; PR, partial response; MR, minimal response; SD, stable disease.

177Lu-octreotate treatment for GEP tumors - *J Clin Oncol 26:2124-2130.*

# Small Intestine (Carcinoid) Neuroendocrine tumors



# Liver transplantation

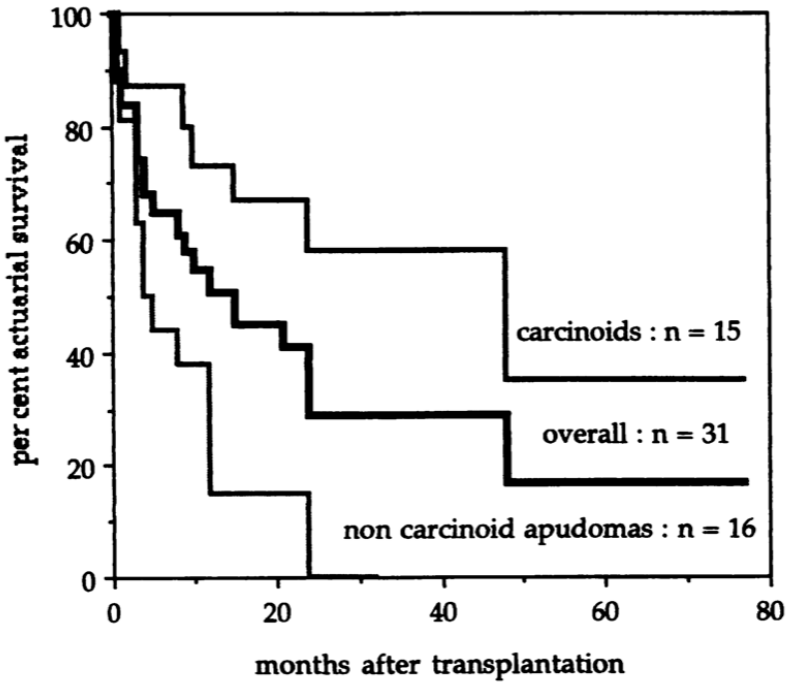



**Figure 2.** Disease-free survival after OLT for metastatic neuroendocrine tumors. Carcinoids *vs.* noncarcinoid apudomas; $p < 0.001$.

LeTreut et al. – Ann. Surg.*April1997

# Liver transplantation

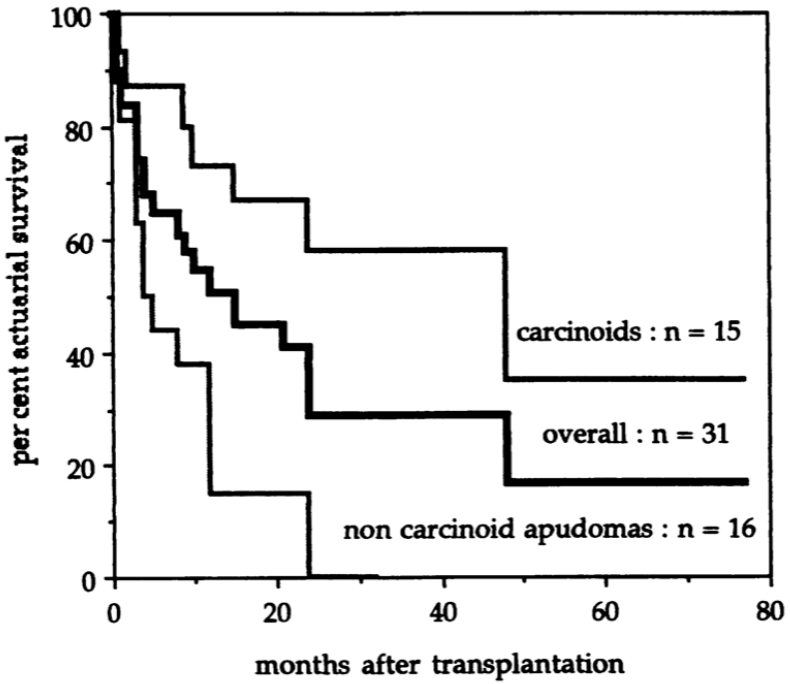
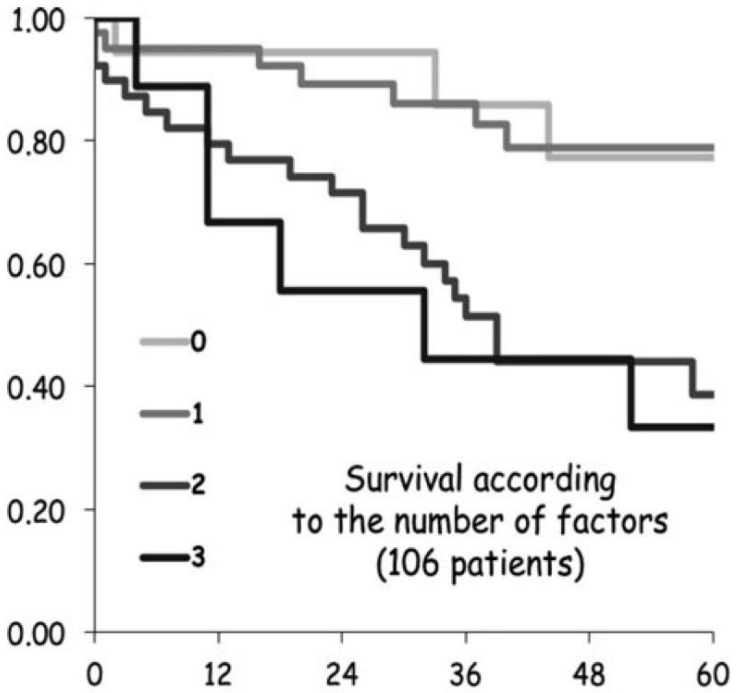
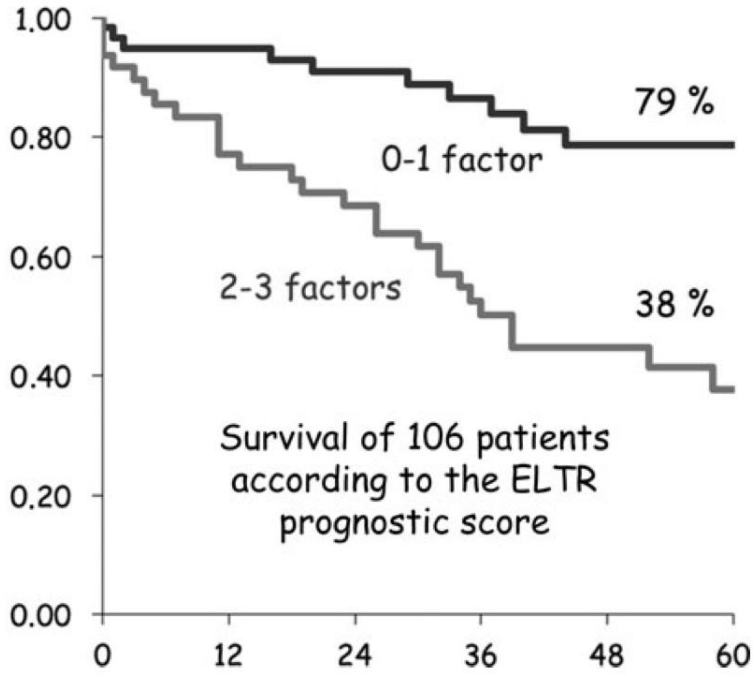



**Figure 2.** Disease-free survival after OLT for metastatic neuroendocrine tumors. Carcinoids *vs.* noncarcinoid apudomas; $p < 0.001$.

LeTreut et al. – Ann. Surg.*April1997

# Liver transplantation




Overall survival of 106 patients according to the number of adverse prognostic factors: hepatomegaly, resec- tion in addition to LT, and age more than 45 years. Top: 5- year survival rates: 77%, 79%, 39%, and 33% for 0, 1, 2, or 3 factors, respectively. Bottom: after gathering in 2 groups. 0–1 factors (n = 58) and 2–3 factors (n = 48). $P < 0.0001$.

LeTreut et al. – ***Annals of Surgery*** **r Volume 257, Number 5, May 2013**