Proposta di un percorso diagnostico e terapeutico e GIC virtuale di Rete per i NET

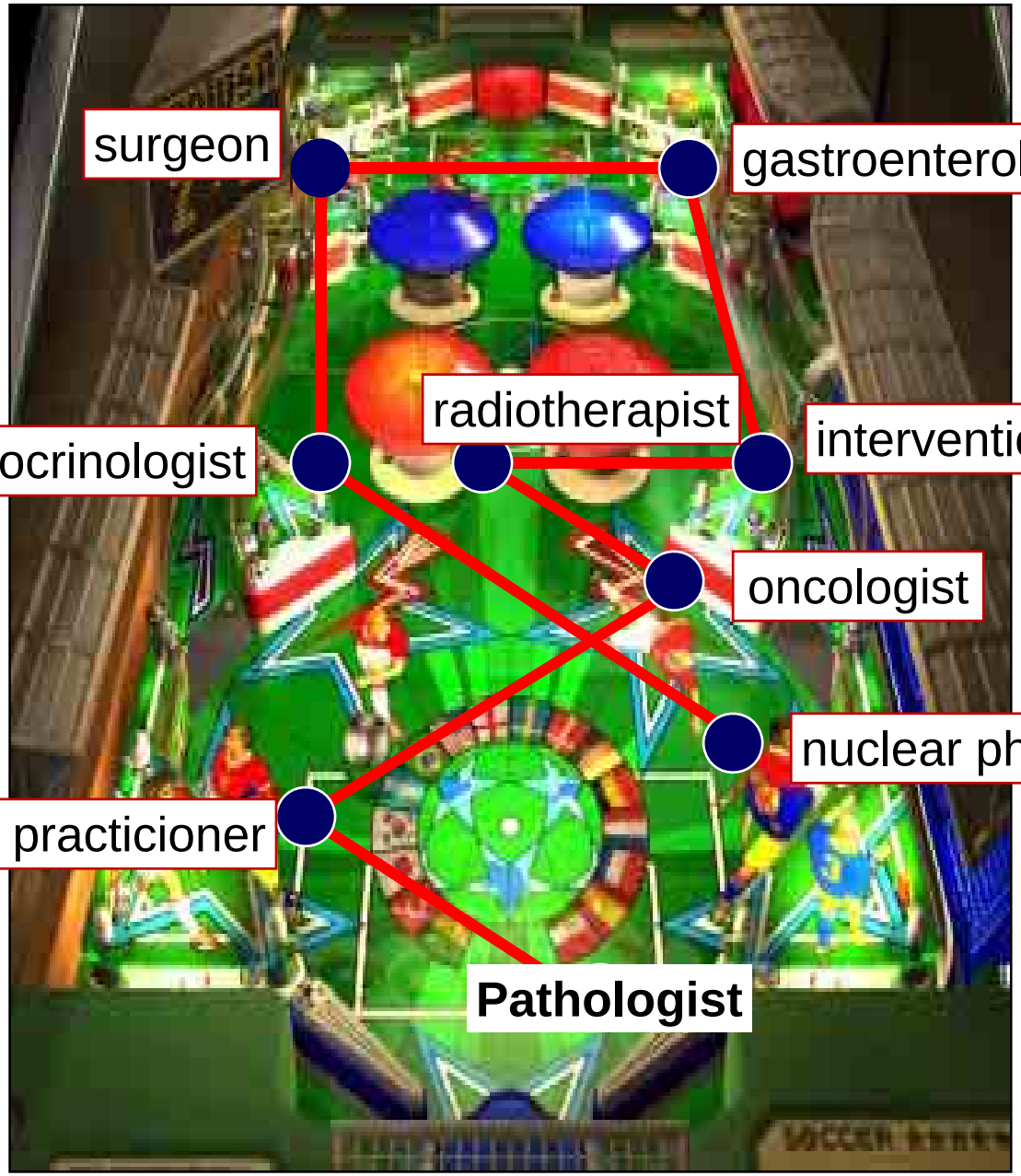
Alfredo Berruti

Dipartimento di Scienze Cliniche e Biologiche
Università di Torino
Oncologia Medica
Azienda Ospedaliera San Luigi
Orbassano

NET: multi-disciplinarity is crucial

N. Fazio IEO MI

“flipper (pinball machine) little ball” effect



N Fazio IEO

Perché un GIC virtuale sui NET

Difficoltà diagnostiche

Condivisione di scelte terapeutiche

Ricerca

42 ANNI

Da Ottobre 2001 episodi ricorrenti di tremore diffuso associato a sudorazione profusa. La paziente riferisce di dover mangiare ripetutamente.

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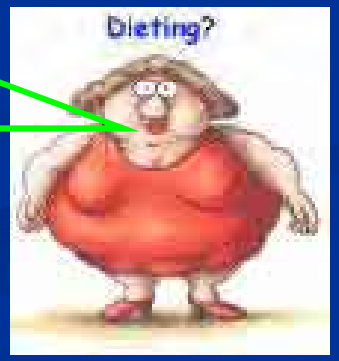
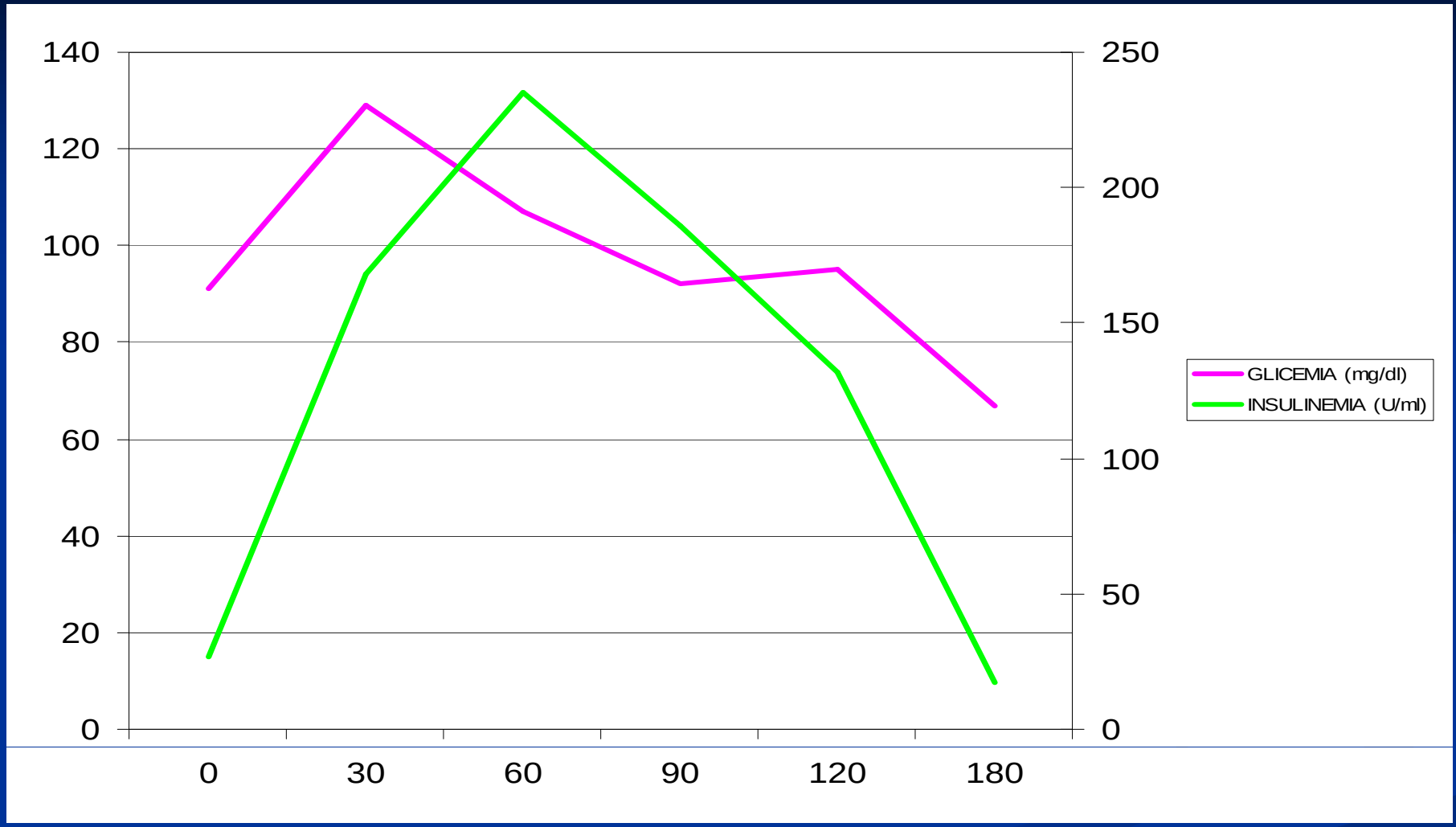
42 ANNI

2002

Negli ultimi mesi rapido incremento ponderale (30 Kg in 1 anno). Se non mangio spesso mi sento male con sensazione di mancamento!



TEST DA CARICO DI GLUCOSIO



Bassi livelli glicemici con iperinsulinemia

Campana D, Sant'Orsola , Bologna

2003

… per la comparsa di un episodio di forte dolore epigastrico con irradiazione al dorso la paziente viene sottoposta a:

RMN: nodulo a livello della coda del pancreas

NSE = 7.1
CgA = nd

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CRISI IPOGLICEMICHE

OBESA

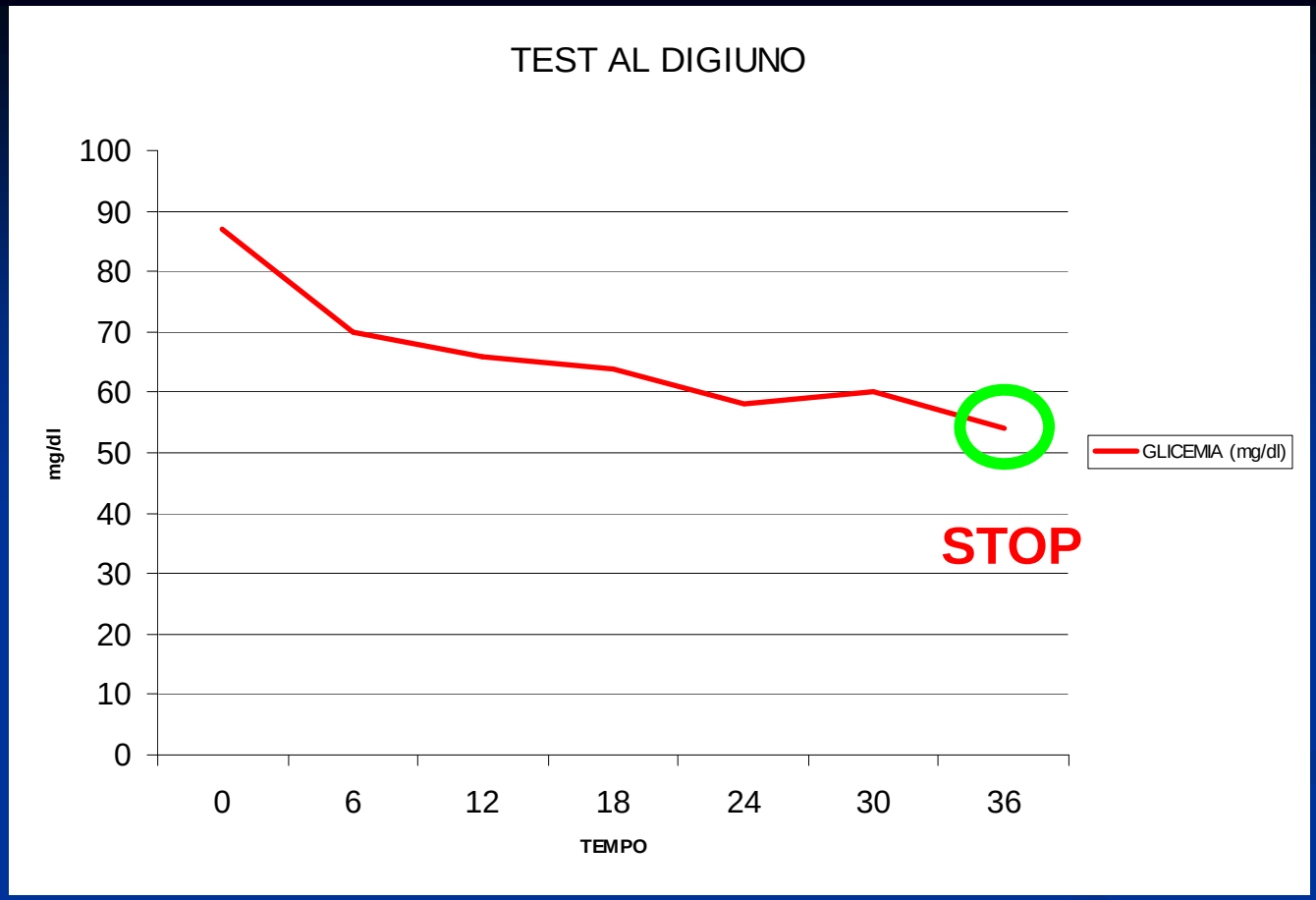
NODULO PANCREATICO

IPOGLICEMIA CON IPERINSULINISMO

ECOENDOSCOPIA

AREA IPERECOGENA DI 5.5 X 6.2 MM A LIVELLO DEL MARGINE ANTERIORE DELLA CODA CON CARATTERISTICHE ECOGENE E (MENO) DI VASCOLARIZZAZIONE COMPATIBILI CON PICCOLO TUMORE ENDOCRINO

Campana D, Sant'Orsola , Bologna



Glicemia: 56 mg/dl

La paziente lamenta malessere generale e sensazione di mancamento

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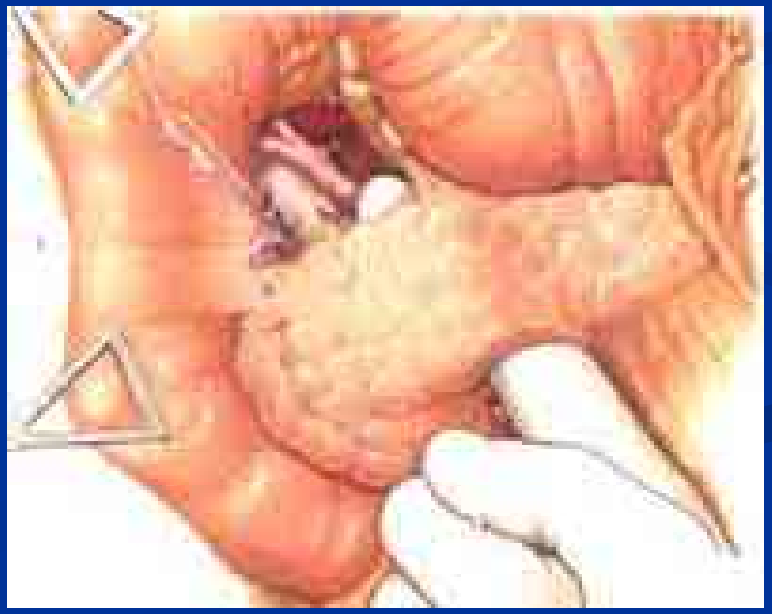
TEST POSITIVO!!!!!!!!

ABBIAMO L'INSULINOMA!!!

2004



PANCREASECTOMIA DISTALE

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Tessuto pancreatico senza evidenza di lesioni.

Il medico mi ha detto che ero affetta da NESIDIOBLASTOSI

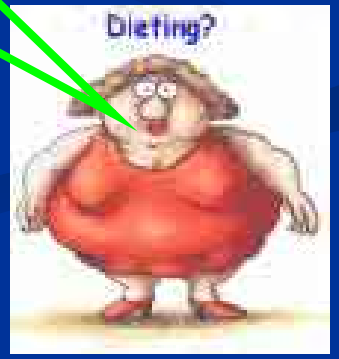

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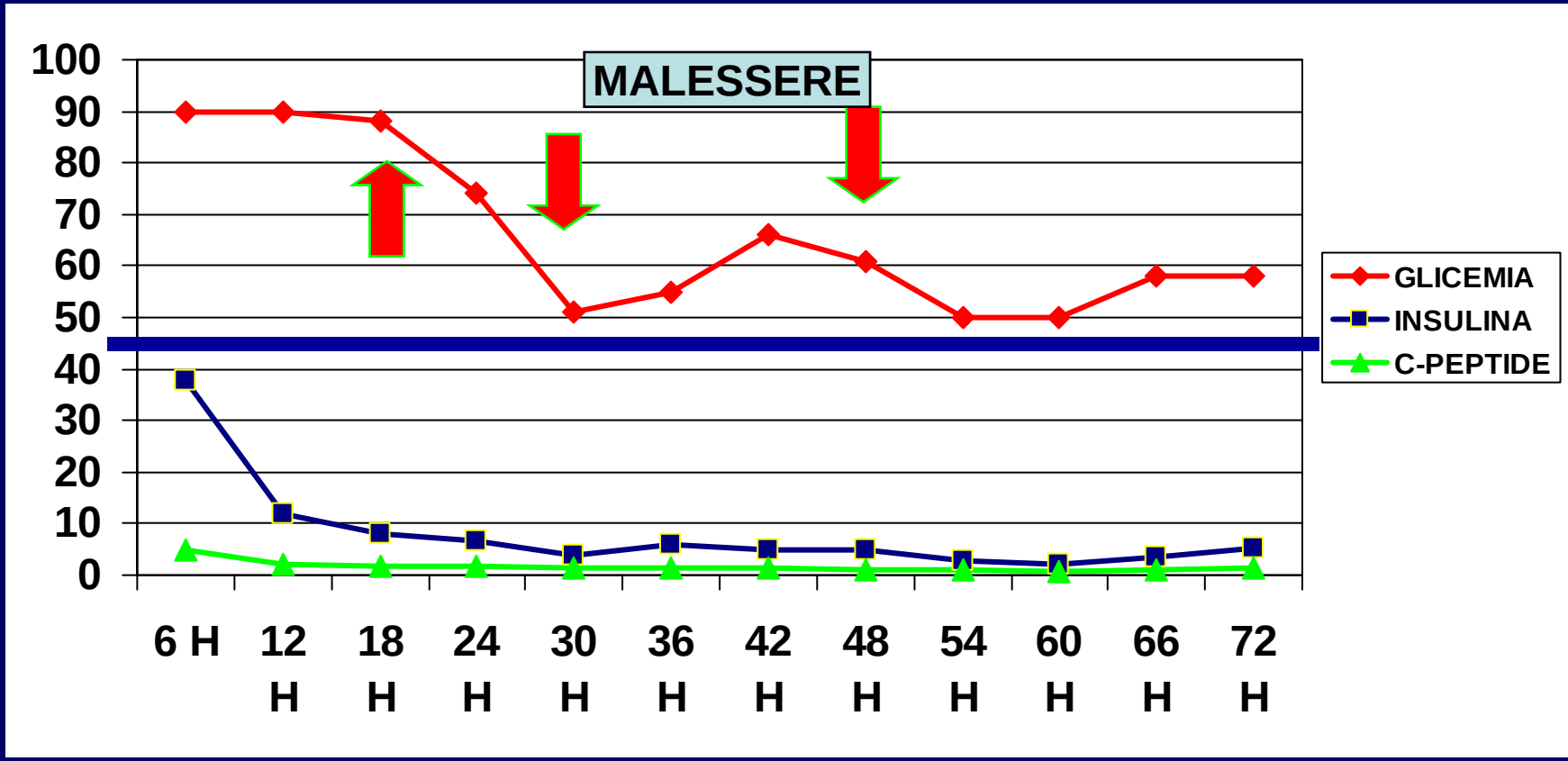
Table 2. Protocol for 72-Hour Fast.

1. Date the onset of the fast as of the last ingestion of calories. Discontinue all nonessential medications.
2. Allow the patient to drink calorie-free and caffeine-free beverages.
3. Ensure that the patient is active during waking hours.
4. Measure the levels of plasma glucose, insulin, C peptide, and proinsulin in the same specimen; repeat measurements every six hours until the plasma glucose level is ≤60 mg per deciliter, when the interval should be reduced to every one to two hours.
5. End the fast when the plasma glucose level is ≤45 mg per deciliter (2.5 mmol per liter) and the patient has symptoms or signs of hypoglycemia.
6. At the end of the fast, measure the plasma levels of glucose, insulin, C peptide, proinsulin, β-hydroxybutyrate, and sulfonylurea in the same specimen; then inject 1 mg of glucagon intravenously and measure the plasma glucose level after 10, 20, and 30 minutes. Then feed the patient.
7. When a deficiency is suspected, measure plasma cortisol, growth hormone, or glucagon at the beginning and end of the fast.

Service F.J., N Engl J Med. 1995

TEST AL DIGIUNO



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ANAMNESI PATOLOGICA RECENTE

- Da settembre 2007 comparsa di alvo diarroico (3/5 scariche di feci liquide al dì).
  PCS: n.n.
- Da qualche mese comparsa di flushing al volto ed arrossamento al collo in caso di forti emozione.

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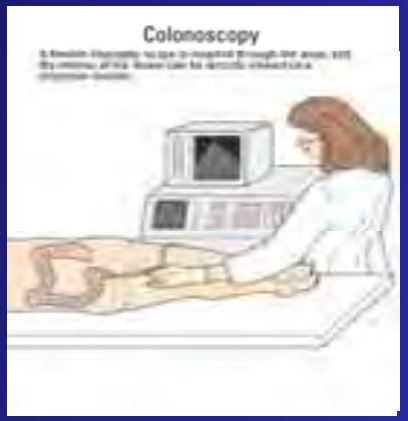
PANCOLONSCOPIA



Diverticolosi del colon ed emorroidi di II grado

ECOGRAFIA ADDOME

Non lesioni focali a livello epatico.
Angiomiolipoma renale

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TC ADDOME CON MDC

NEGATIVA

NON HO TROVATO NULLA….FORSE E’ UN TUMORE ENDOCRINO!!

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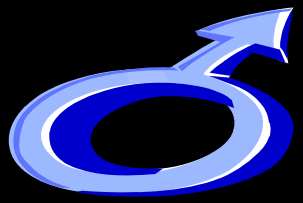
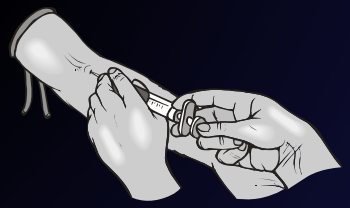
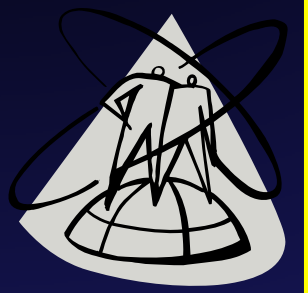


ESAMI BIOUMORALI



5-HIAA: 11 mg/24h
CgA: 395.5 ng/ml (v.n. 19-98)

OCTREOSCAN



Area di focale iperaccumulo del tracciante in regione paramediana destra, anteromedialmente al terzo superiore del rene destro.

ECOENDOSCOPIA

NEGATIVA

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OCTREOSCAN POS.
CgA ELEVATA

HO TROVATO IL TUMORE ENDOCRINO DEL PANCREAS

Marzo 2008

RESEZIONE DI VEROSIMILE NODULO DELLA TESTA DEL PANCREAS.

ISTOLOGICO
TESSUTO NON PATOLOGICO

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TAKE HOME MESSAGE

✓ LE DIARREE ENDOCRINE RAPPRESENTANO MENO DELL'1% DI TUTTE LE DIARREE CRONICHE.

✓ IL SOSPETTO DI DIARREA DI ORIGINE ENDOCRINA SI BASA SULL'ESCLUSIONE DELLE PIU' FREQUENTI CAUSE DI DIARREE CRONICA E SU UNA CORRETTA VALUTAZIONE DEI SINTOMI.

✓ I MARCATORI BIOUMORALI SPECIFICI RIVESTONO GENERALMENTE UN RUOLO DI SECONDARIA IMPORTANZA E LIMITATO A PAZIENTI ATTENTAMENTE SELEZIONATI.

GIC di RETE

Linee guida comuni

Condivisione di casi clinici “difficili”

Neuroendocrine Neoplasms

WHO Classification 2010 of the Digestive System

WHO 2000	WHO 2010
Well-differentiated endocrine tumour (WDET)	Neuroendocrine tumour
Well-differentiated endocrine carcinoma (WDEC)	
Poorly differentiated endocrine carinoma/small-cell carcinoma (PDEC)	Neuroendocrine carcinoma

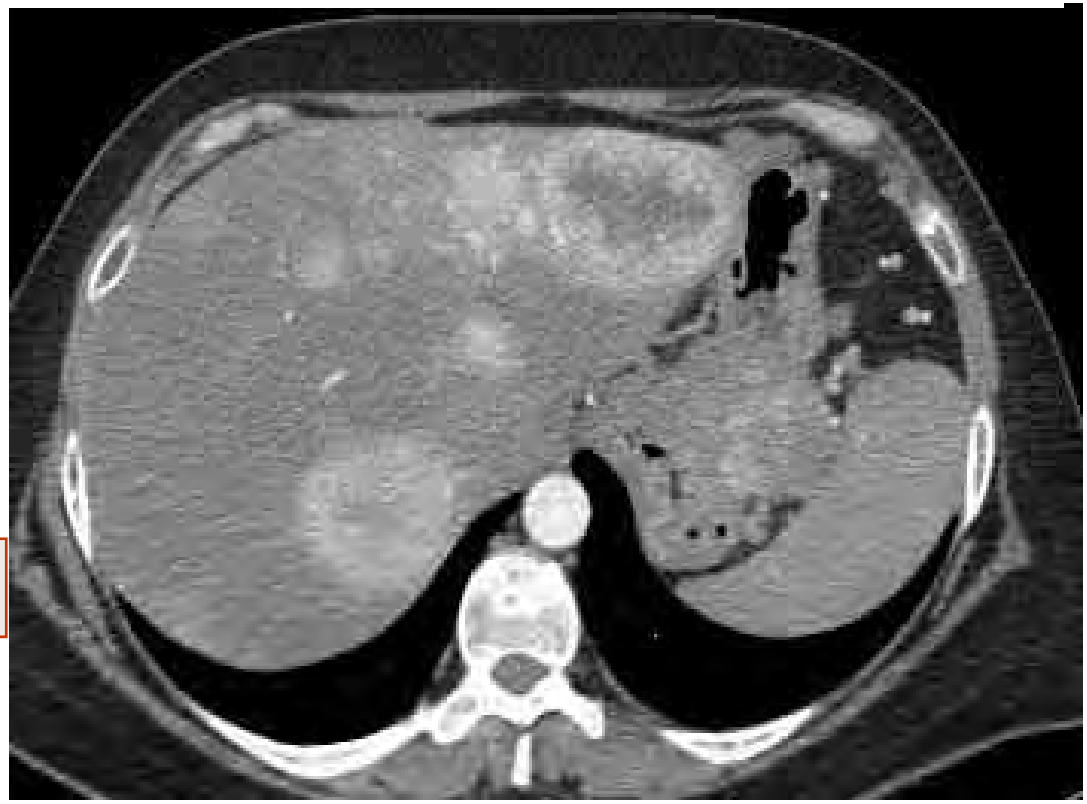
Grading of GEP-NENs According to ENETS/WHO/AJCC

Grade	G1	G2	G3
Ki67 index	≤2	3–20	>20
MI	<2	2-20	>20

1. Rindi G, et al. *Virchows Archiv.* 2006;449:395-401. 2. Rindi G, et al. *Virchows Archiv.* 2007;451:757-762.

Algorhythm

Pancreatic endocrine carcinoma with liver Mets



Well diff
Ki67 ≤ 2 %

Well diff
Ki67 2-20 %

Poorly diff
Ki67 > 20%

Sstr-2 pos.

Sstr-2 neg.

Slow growth

Fast growth

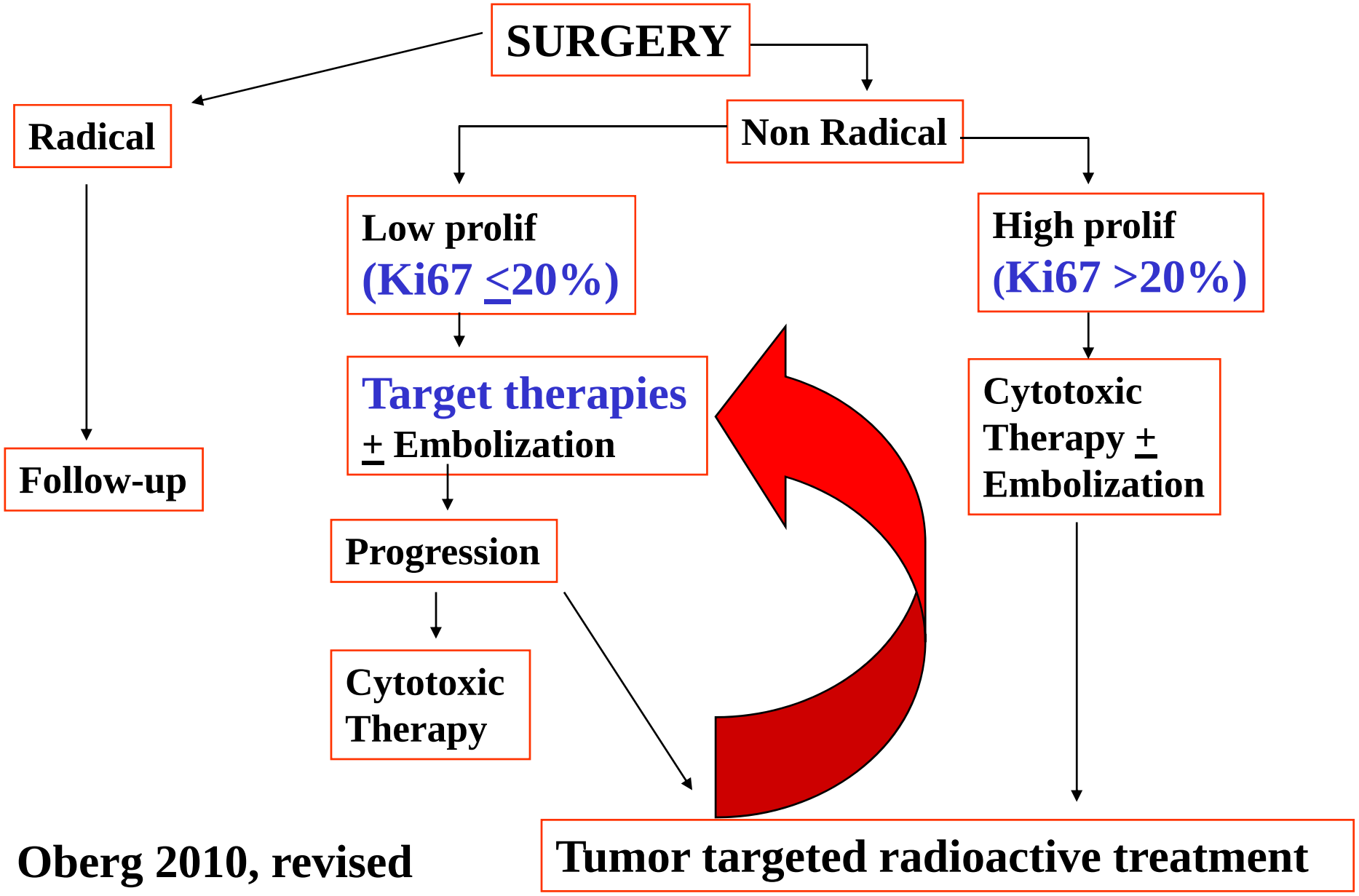
Familial

Sporadic

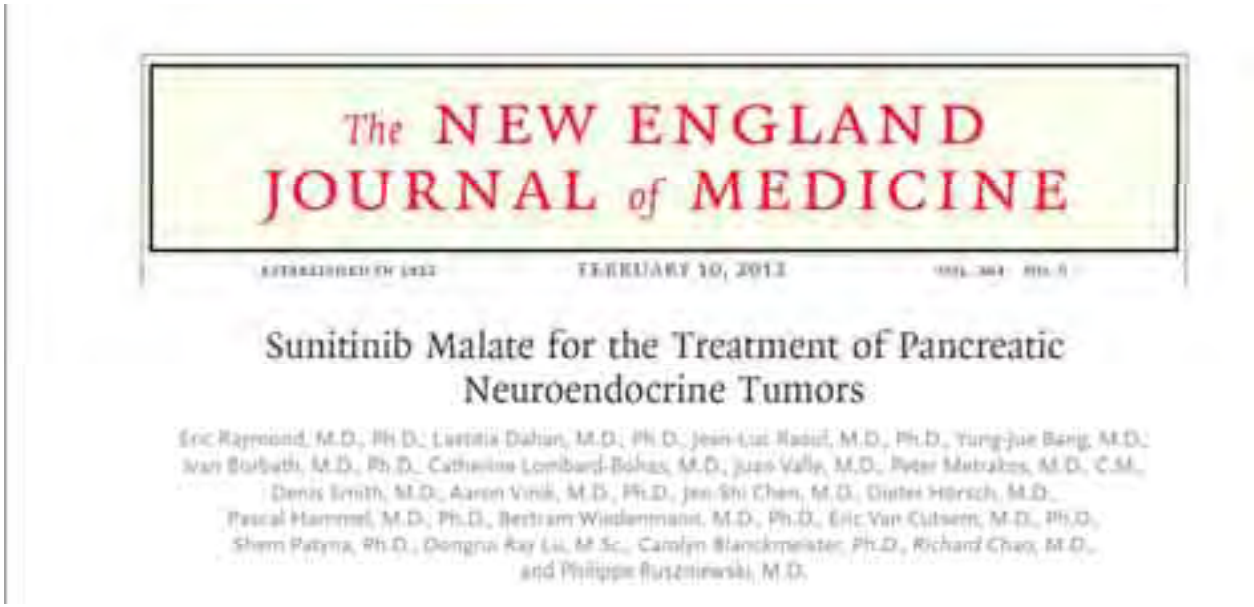
Functioning ↔ Non-functioning

Nicola Fazio IEO MI

Management of neuroendocrine tumors



Oberg 2010, revised



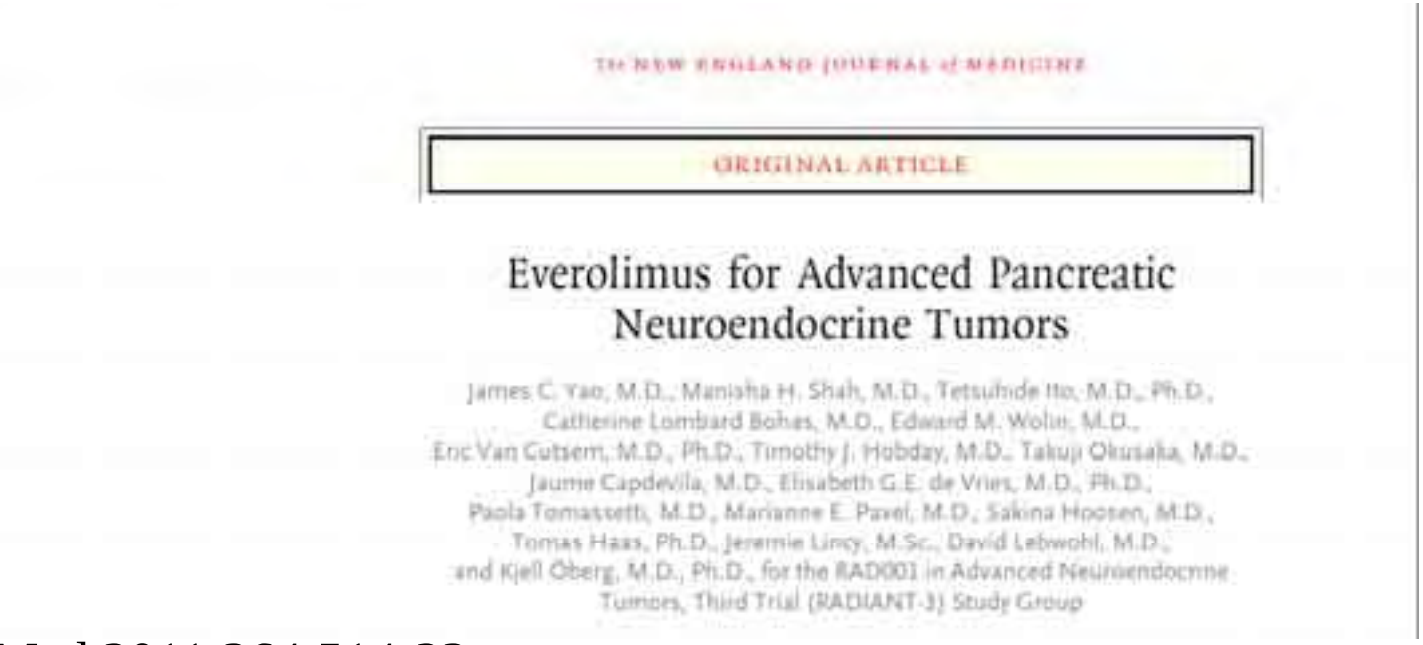
The NEW ENGLAND JOURNAL of MEDICINE

FEBRUARY 10, 2011

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

N Engl J Med 2011;364:501-13.



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

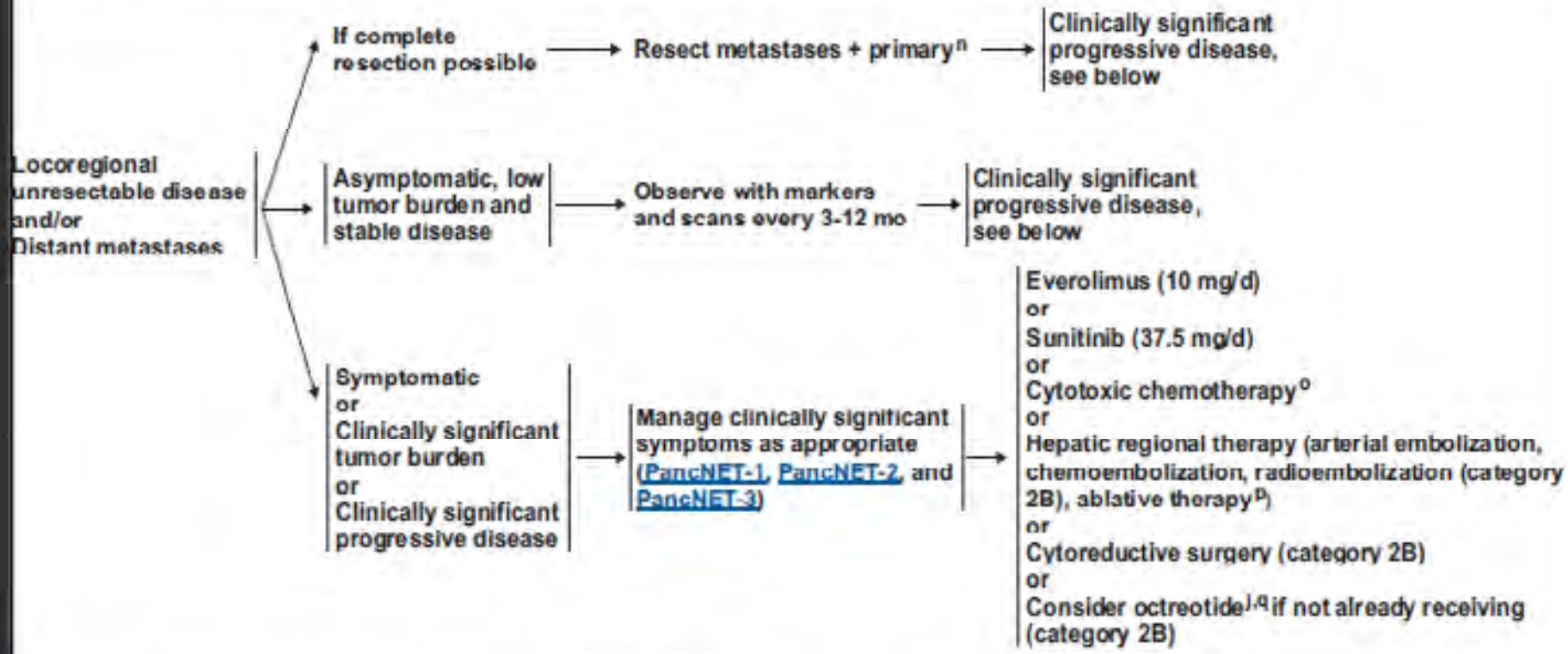
Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

N Engl J Med 2011;364:514-23.

NCCN Guidelines™ Version 1.2011
Pancreatic Endocrine Tumors (Islet Cell Tumors)

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[e]



[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).

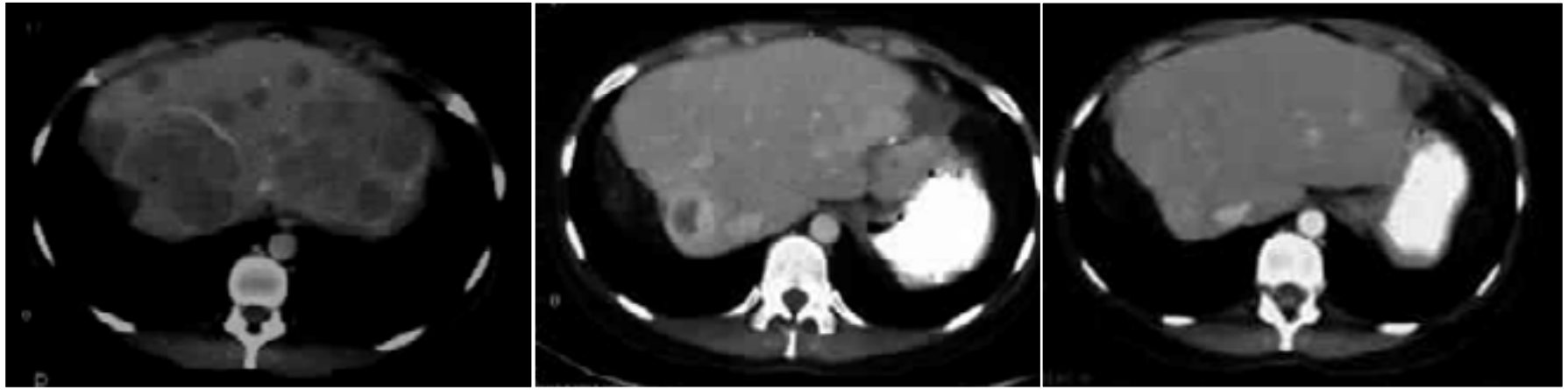
Octreotide should be used with caution in patients with insulinoma as it may transiently worsen hypoglycemia (see discussion).

[n] Staged or synchronous resection when possible. When performing staged pancreaticoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, Farnell MB, Sclabas G, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: A dual-center analysis. Ann Surg 2010;252:142-148.

[o] The following agents have been used: capecitabine, dacarbazine, doxorubicin, 5-FU, streptozocin, and temozolomide.

^{90}Y- DOTATOC Therapy

February 1999 | December 1999 | March 2001



Pre-therapy | Post-therapy (2 cycles) | Last follow-up

R.R. - 37 yrs

Liver metastases from pancreatic insulinoma

N. Fazio IEO MI

Caso clinico

Anni 38 operato di appendicectomia
EI: carcinoide appendicolare
diam 1.7 cm, Ki67 5%

?

BMC Cancer

BioMed Central

Research article

Open Access

Continuous 5-fluorouracil infusion plus long acting octreotide in advanced well-differentiated neuroendocrine carcinomas. A phase II trial of the Piemonte Oncology Network

Maria P Brizzi[1], Alfredo Berruti[1], Anna Ferrero[1], Enrica Milanesi[3], Marco Volante[2], Federico Castiglione[4], Nadia Birocco[3], Sebastiano Bombaci[5], Davide Perroni[6], Benedetta Ferretti[7], Oscar Alabiso[8], Libero Ciuffreda[3], Oscar Bertetto[3], Mauro Papotti[2] and Luigi Dogliotti*[1]

BMC Cancer 2009, ***9:388***

Bevacizumab plus octreotide and metronomic capecitabine as first-line therapy in patients with metastatic well to moderately differentiated neuroendocrine tumors.
The XELBEVOCT multicenter phase II study.

Alfredo Berruti, Nicola Fazio, Anna Ferrero, Maria Pia Brizzi, Marco Volante, Elisabetta Nobili, Lucia Tozzi, Lisa Bodei, Mirella Torta, Antonio D'Avolio, Adriano Massimiliano Priola, Nadia Birocco, Guido Biasco, Mauro Papotti, Luigi Dogliotti.

Ready for submission

GIC di RETE e Ricerca

Forte gruppo multidisciplinare unito e organizzato

Per promuovere nuovi studi

Per accedere a nuovi farmaci

Per fare ricerca traslazionale

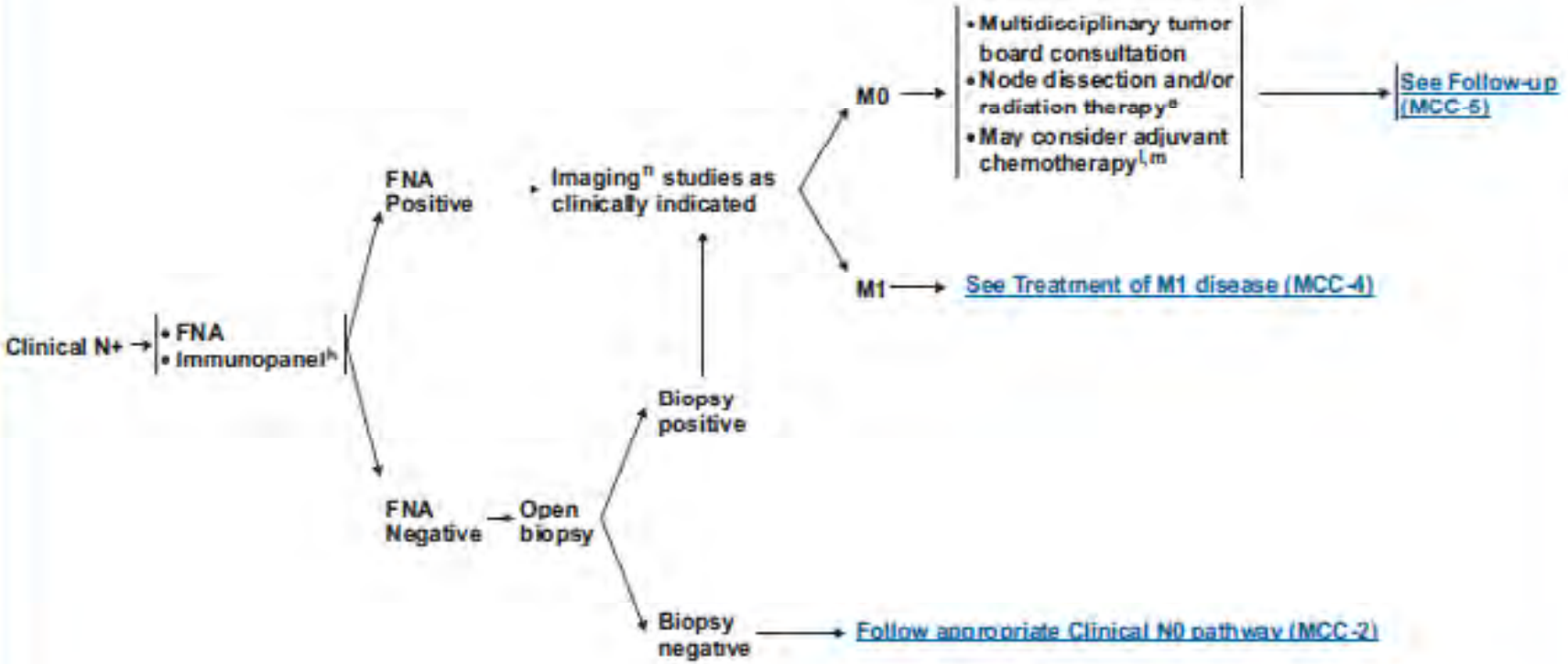
Tumori rari Piemonte

Rete Nazionale
Tumori rari

Gruppi cooperativi
NET internazionali

Gruppi cooperativi
NET nazionali

PRIMARY AND ADJUVANT TREATMENT: CLINICAL N+ DISEASE



[e] See Principles of Radiation Therapy (MCC-A).
[h] An appropriate immunopanel for LN examination should preferably include CK 20 and pancytokeratins (AE1/AE3).
[l] See Chemotherapy Agents (MCC-C).
[m] Available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.
[n] Imaging (CT, MR, or PET-CT) may be indicated to evaluate extent of lymph node and/or visceral organ involvement.

TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system

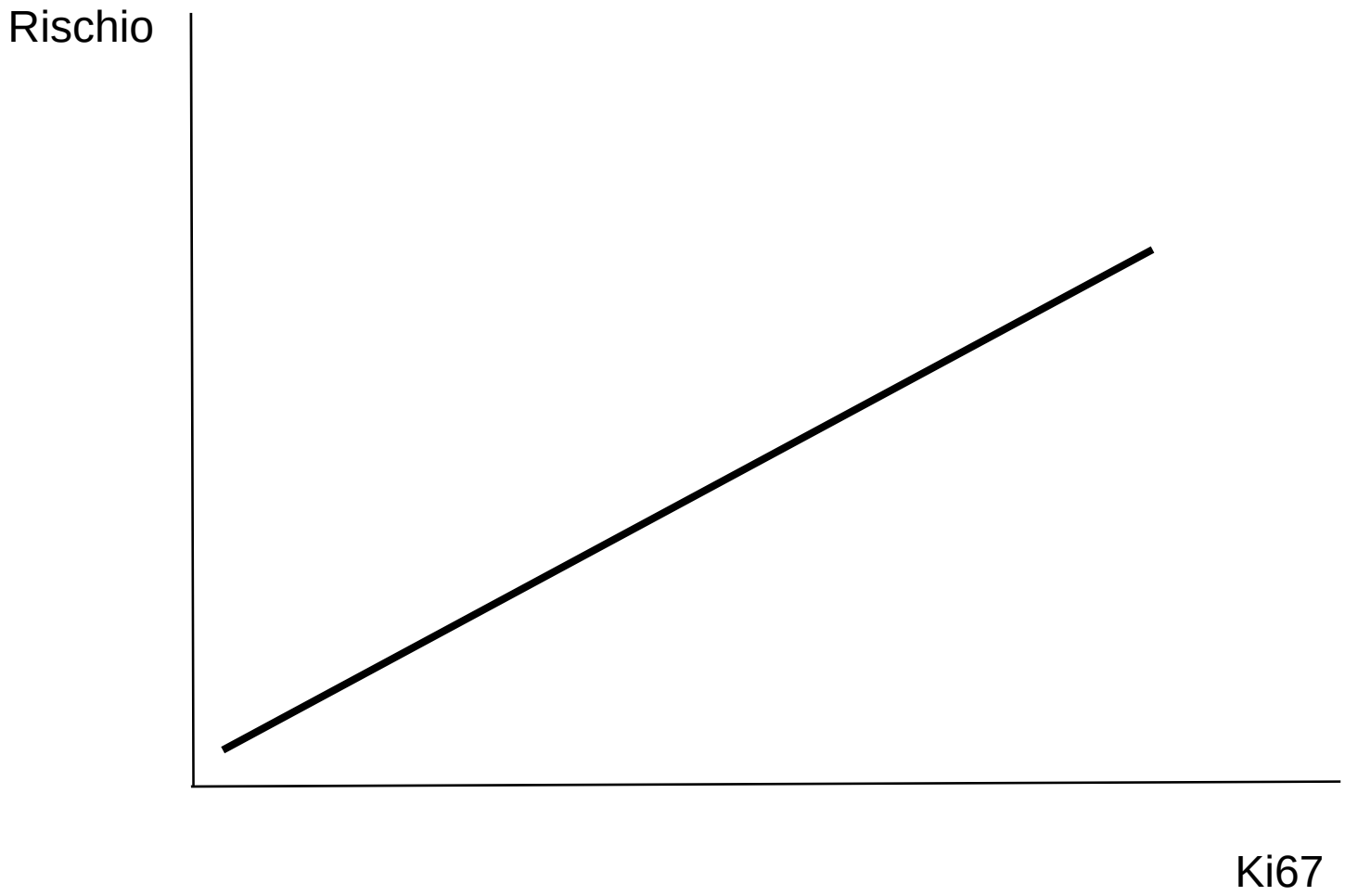
Virchows Arch (2006) 449:395–401

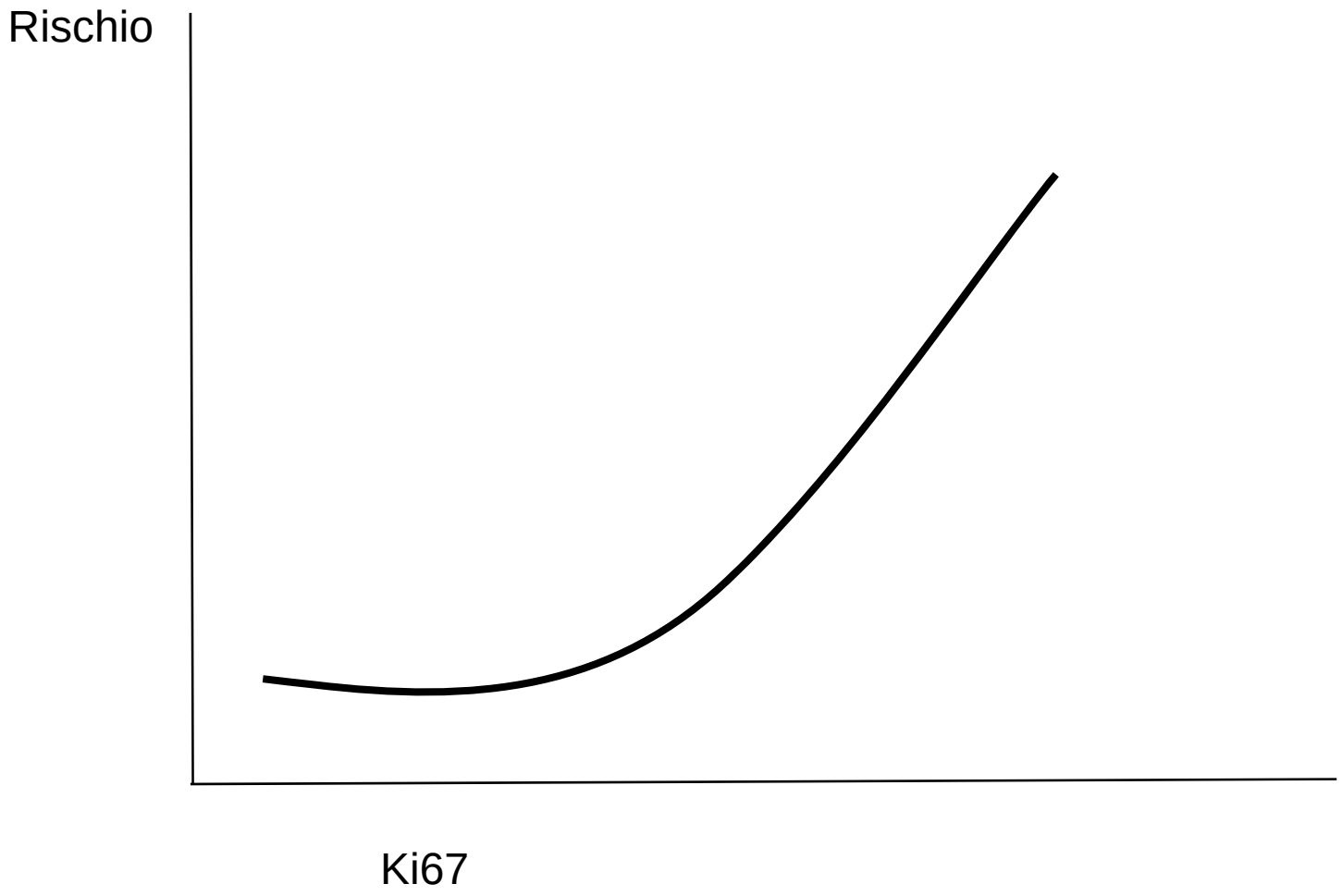
G. Rindi · G. Klöppel · H. Alhman · M. Caplin · A. Couvelard · W. W. de Herder · B. Erikssson · A. Falchetti · M. Falconi · P. Komminoth · M. Körner · J. M. Lopes · A-M. McNicol · O. Nilsson · A. Perren · A. Scarpa · J-Y. Scoazec · B. Wiedenmann · and all other Frascati Consensus Conference participants

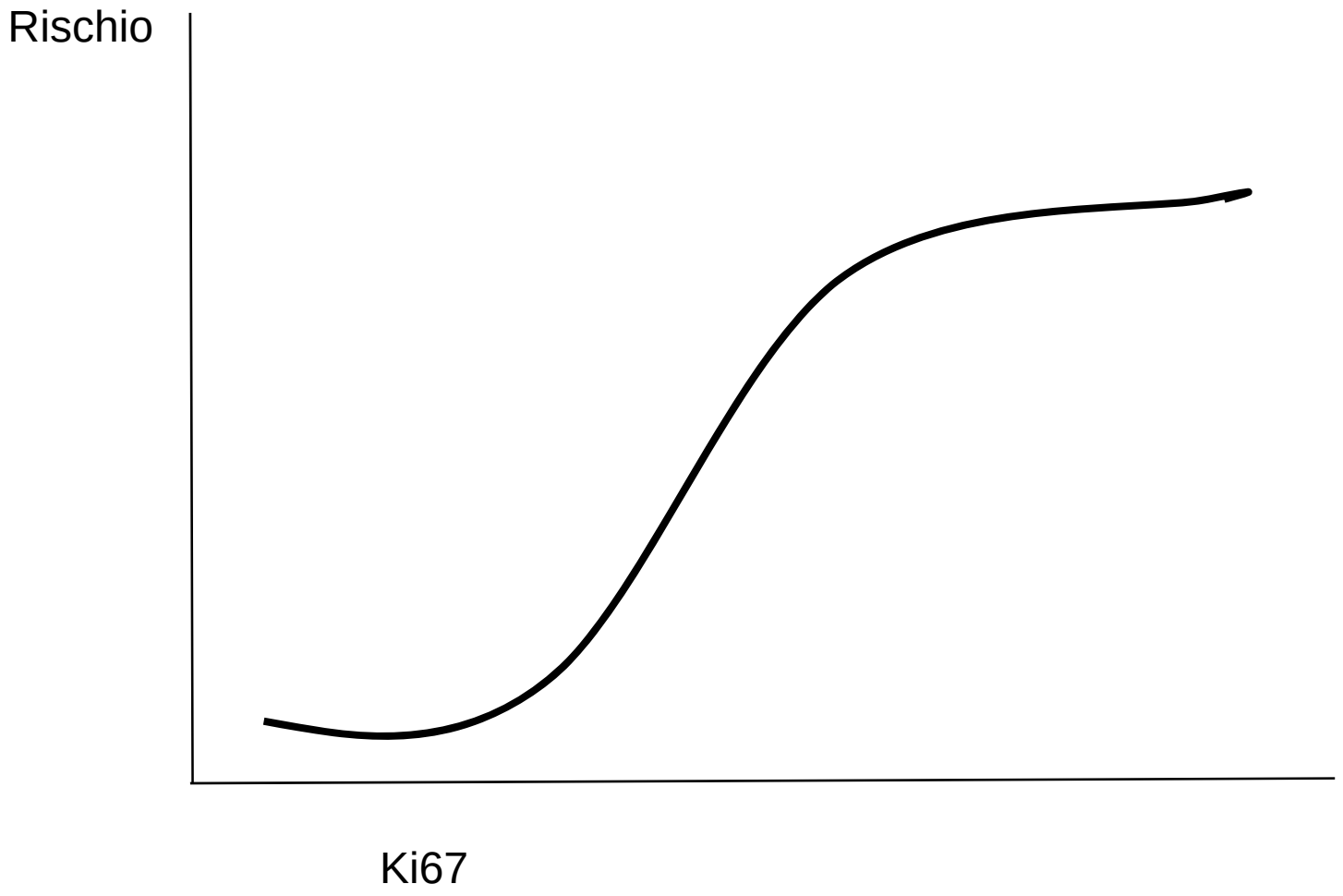
Table 4 Grading proposal for foregut (neuro)endocrine tumors

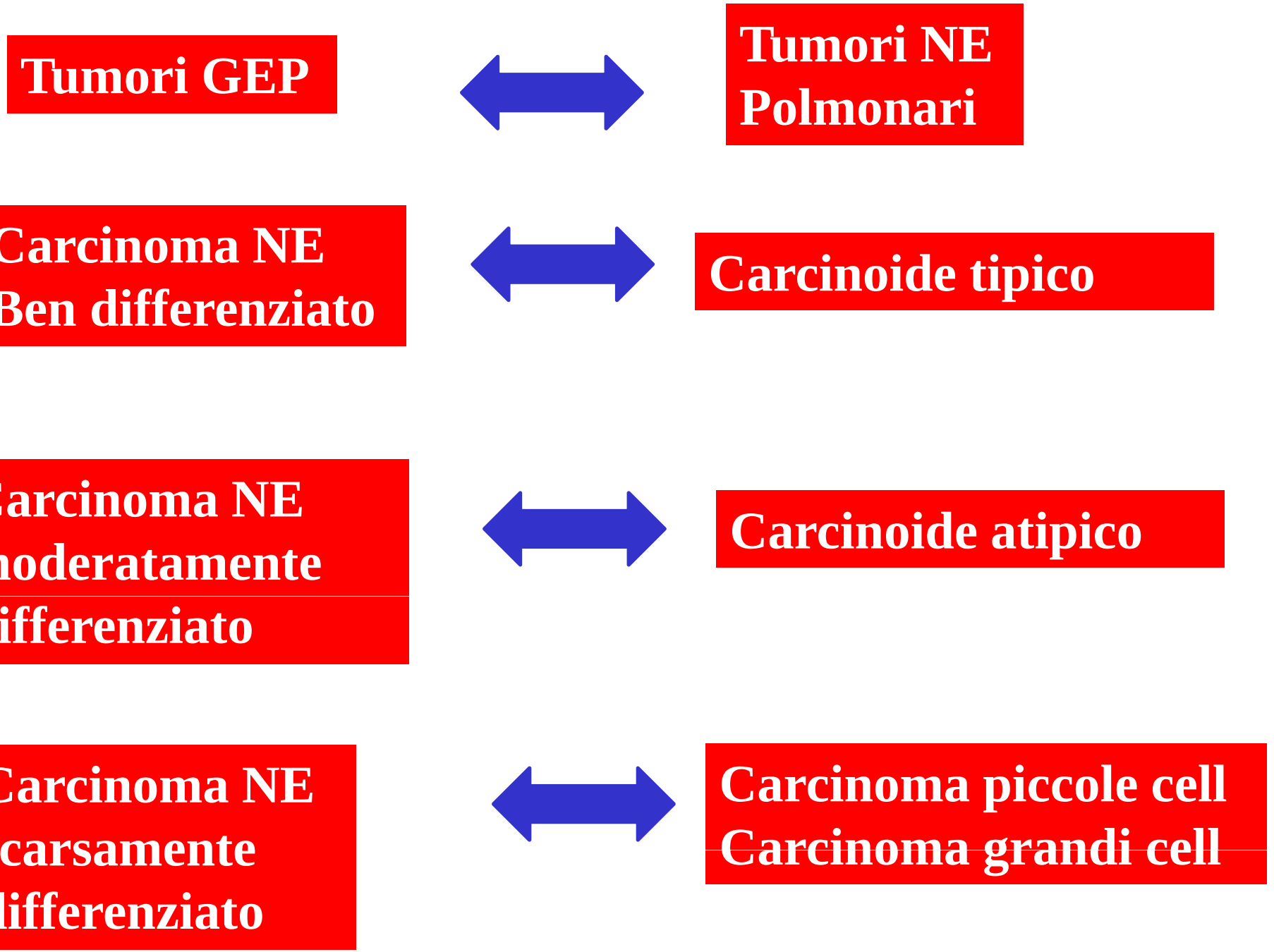
Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20


Rischio
Ki67


Rischio
Ki67


Rischio
Ki67

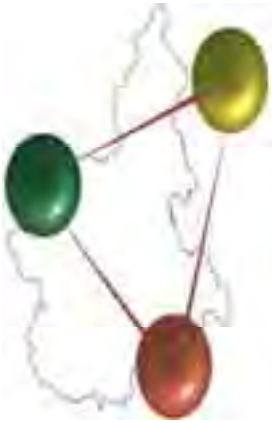

Rischio
Ki67


Tumori GEP
Tumori NE Polmonari
Carcinoma NE Ben differenziato
Carcinoide tipico
Carcinoma NE moderatamente differenziato
Carcinoide atipico
Carcinoma NE scarsamente differenziato
Carcinoma piccole cell
Carcinoma grandi cell

REGIONE PIEMONTE

rete oncologica

www.tumoriraripiemonte.it



Tumori Rari Piemonte

Criticità

Mancano in Regione
-PET Ga Dotanoc
-Servizi di terapia radiorecettoriale

Migrazione di pazienti in altre Regioni