Ente Ospedaliero Cantonale

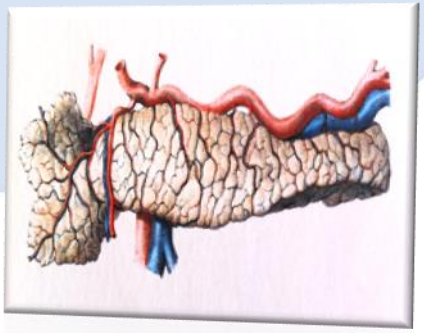
Tumori del pancreas: chirurgia sì o no?

Tumori gastro-intestinali: attualità e aspetti pratici

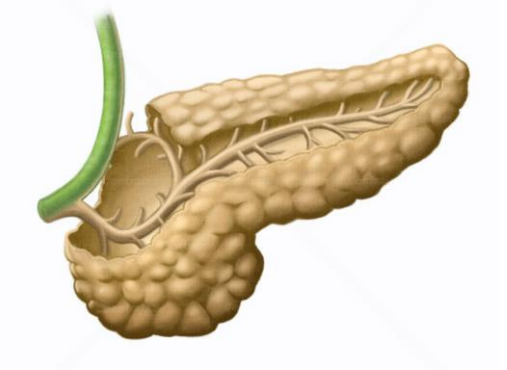
24 ottobre 2019

RC Balzarotti Canger

Chirurgia epato-bilio-pancreatica



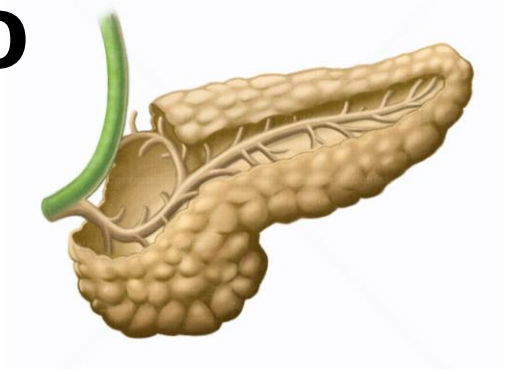
Classificazione



- **Endocrini**

- **Esocrini**
  - ✓ Adenocarcinoma canalare
  - ✓ IPMN
  - ✓ Cistadenoma (sieroso, mucinoso)
  - ✓ Tumore solido e pseudopapillare
  - ✓ Tumori rari
    - Carcinoma a cellule acinari
    - Pancreatoblastoma

Fattori di rischio



Fattori genetici

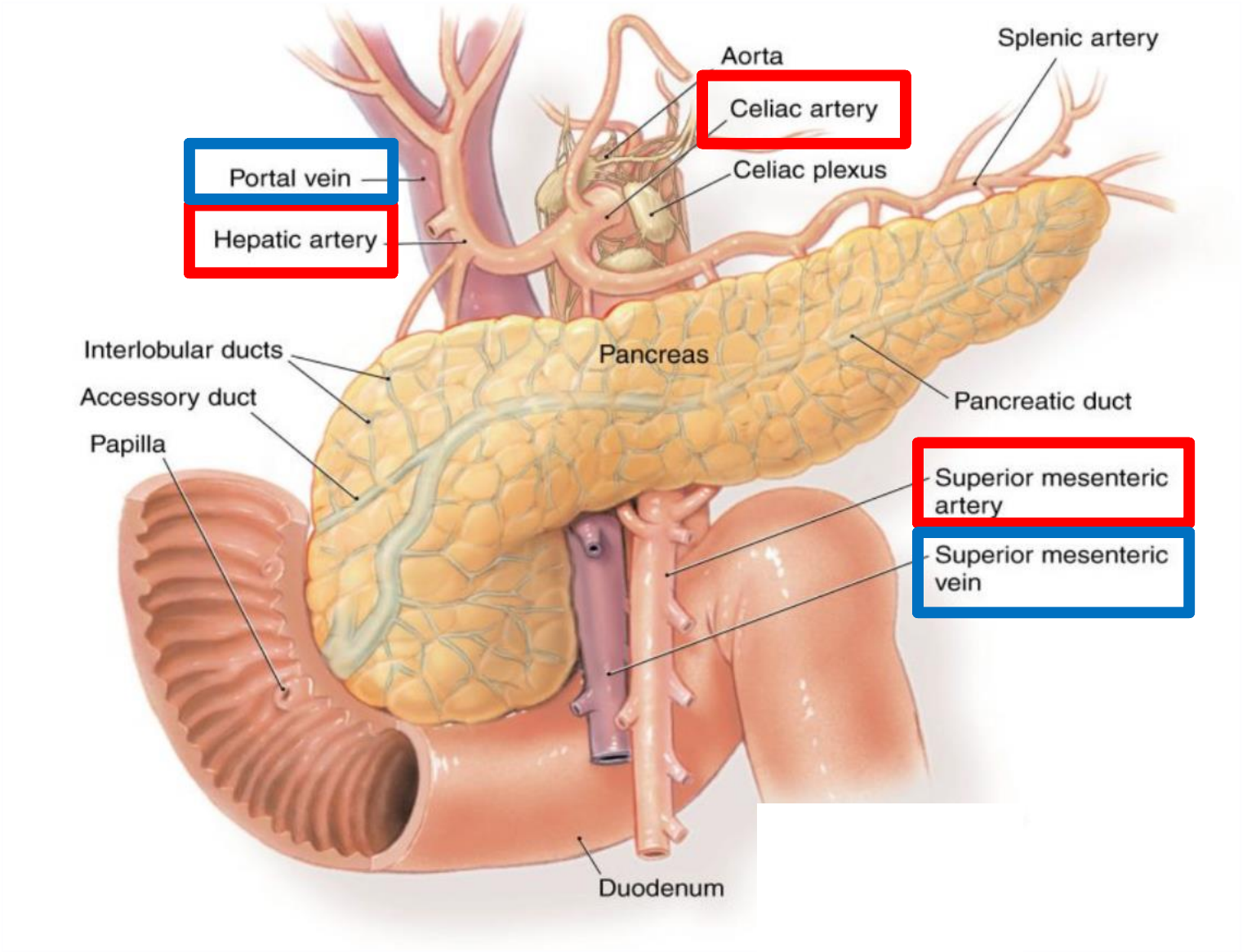
Pancreatite cronica

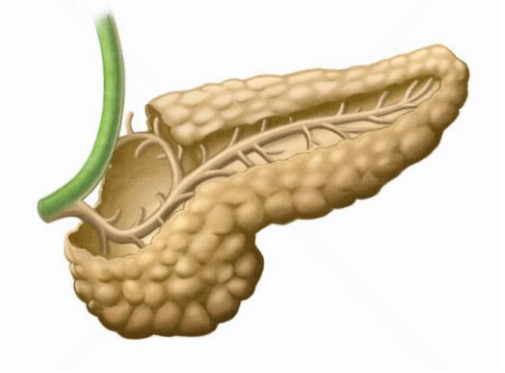
Adenocarcinoma canalare

Obesità

Tabacco

Diabete


Aorta
Splenic artery
Celiac artery
Celiac plexus
Portal vein
Hepatic artery
Interlobular ducts
Pancreas
Accessory duct
Pancreatic duct
Papilla
Superior mesenteric artery
Superior mesenteric vein
Duodenum



PDAC

- 90% delle neoplasie pancreatiche
- 70-80% testa – 20-30% corpo/coda
- 2° causa di mortalità da k in Europa nel 2030
- K digestivo con prognosi peggiore (OS < 10%)
  - ✓ in 30 anni: 3% → 8.9%
  - ✓ pz resecati: < 30%

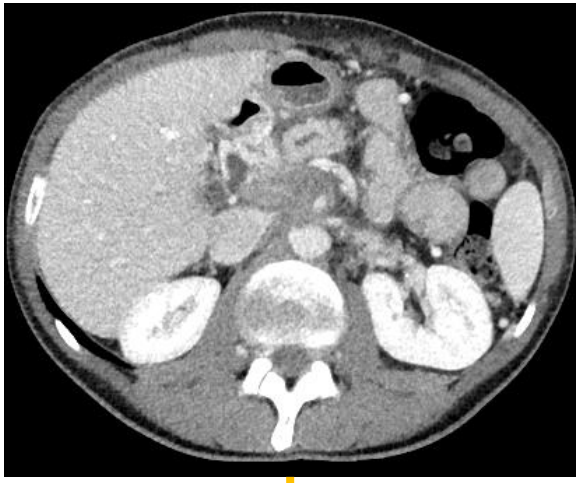
Hishinuma et al 2006
Ferlay et al 2016
Rahib et al 2014
Roth et al 2018

Resecabile

15-20%

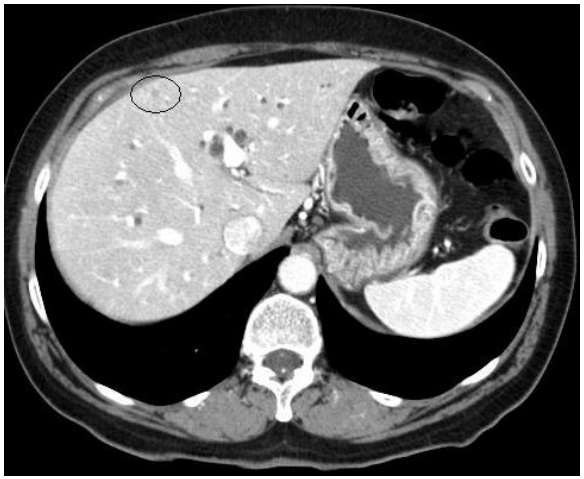
Localmente avanzato

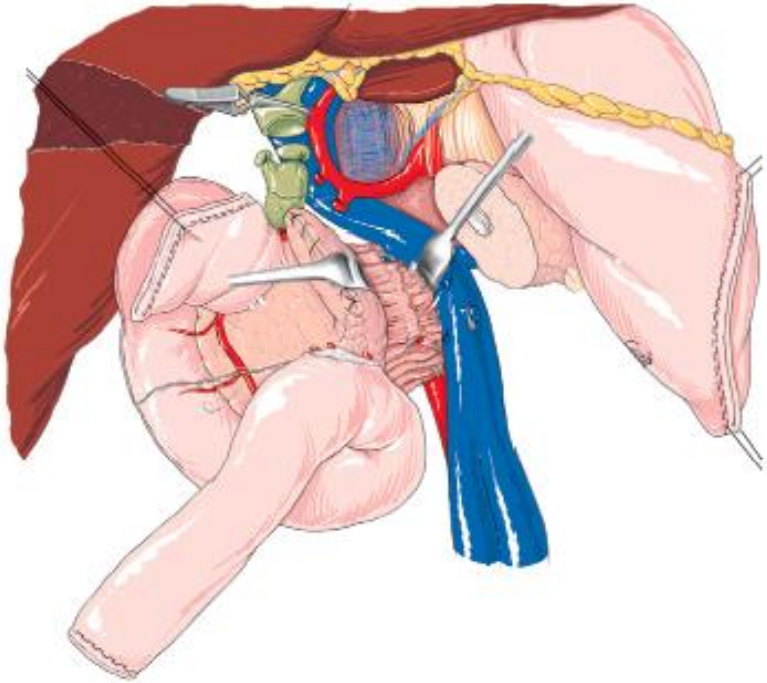
25%

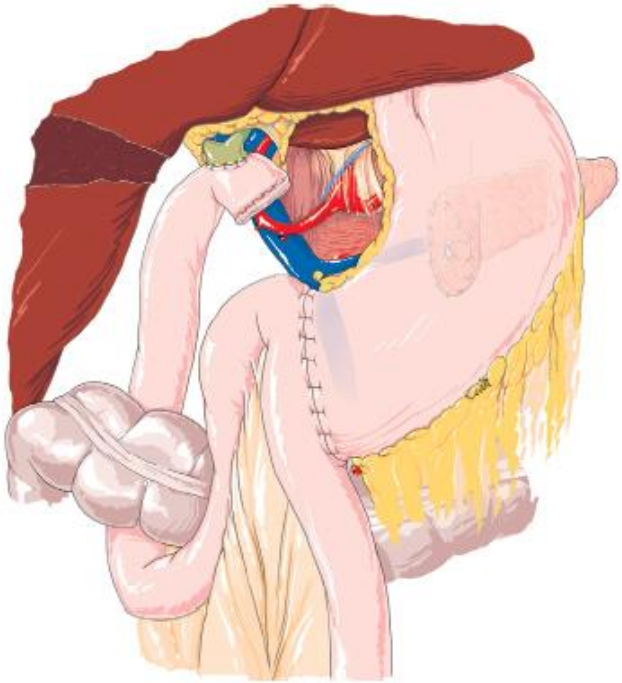


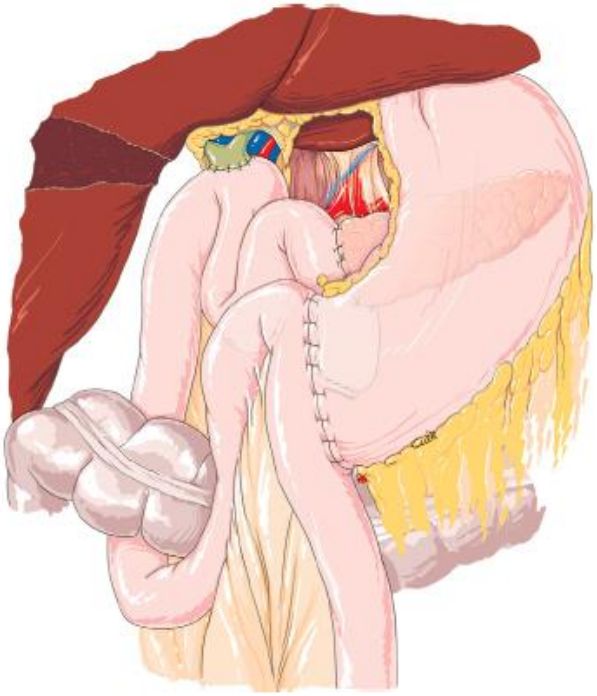
Metastatico

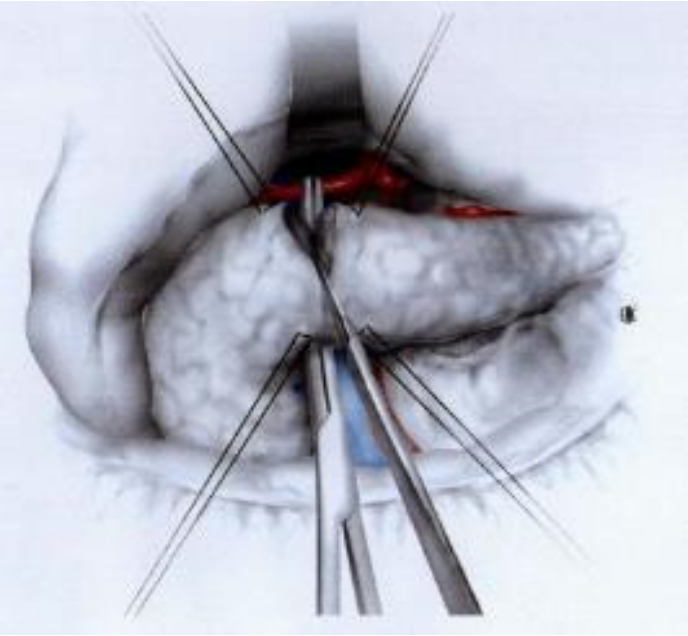
> 50%

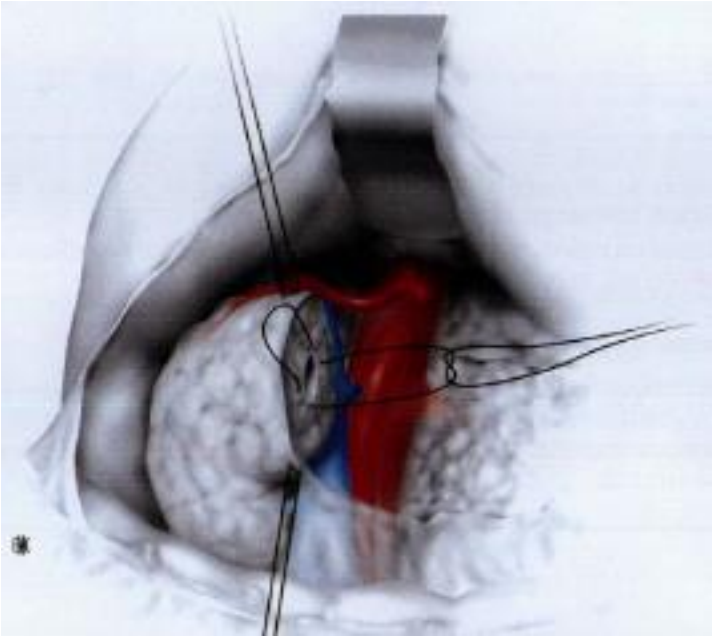












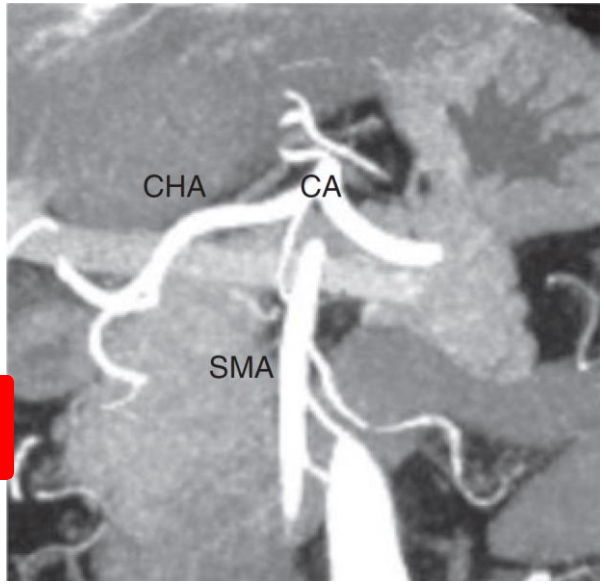
Tumori localizzati

Resecabili

Borderline

Avanzati

- Resezione R1
- Resezione vascolare



Storia

- **1940**: 1° PD
- **1963**: 1° PD con resezione portale
- **1973**: resezione *en bloc* vena porta e/o arteria
  - Caveat ➢ <u>morbilità/mortalità proibitive</u>
- **Anni '90** ➢ *outcome* comparabile alle resezioni standard

  superiore ai pz non resecati

➡ Borderline resectable

5-10%

Asada et al 1963
Fortner et al 1973
Allema et al 1994
Leach et al 1998

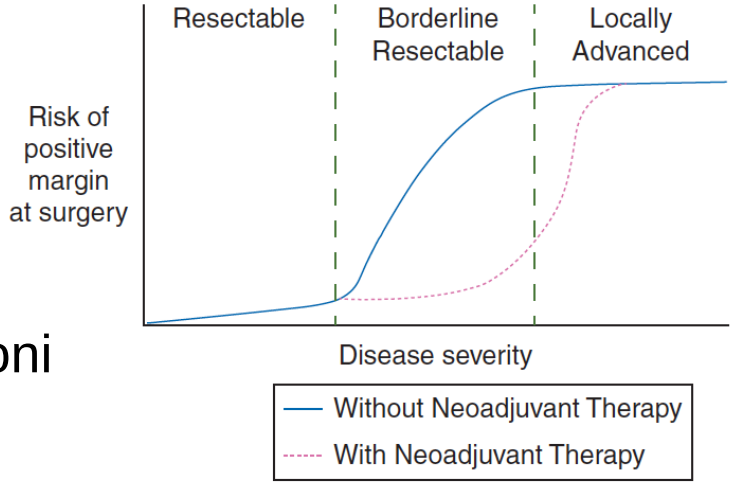
Storia

- **2001**: concetto di *marginal resectable* ➢ 5-FU/RT + chir

- **2006**: termine *borderline resectable* (MDACC ➢ NCCN)

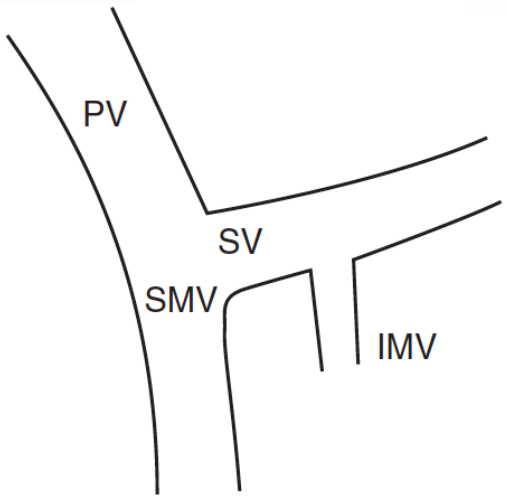
  - Rischio R1 +++

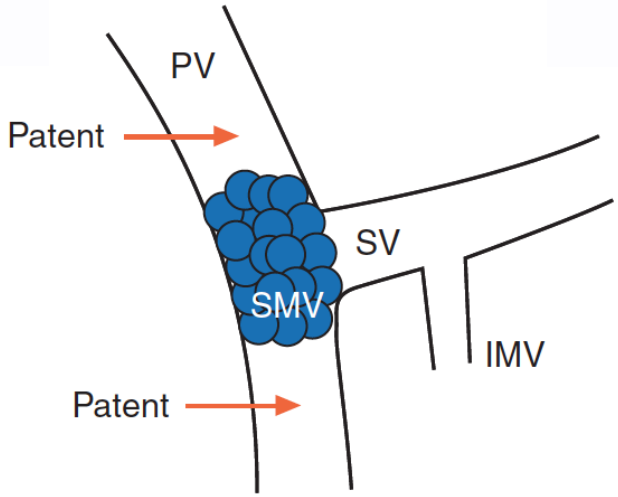
  - Terapia neoadiuvante

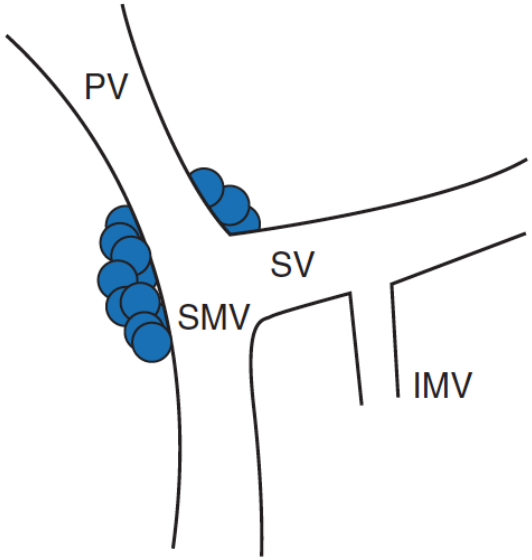


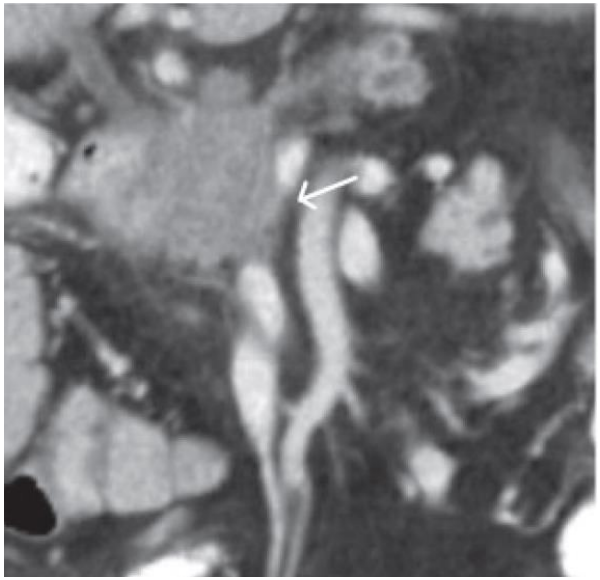
- Diversi gruppi ➢ diverse definizioni

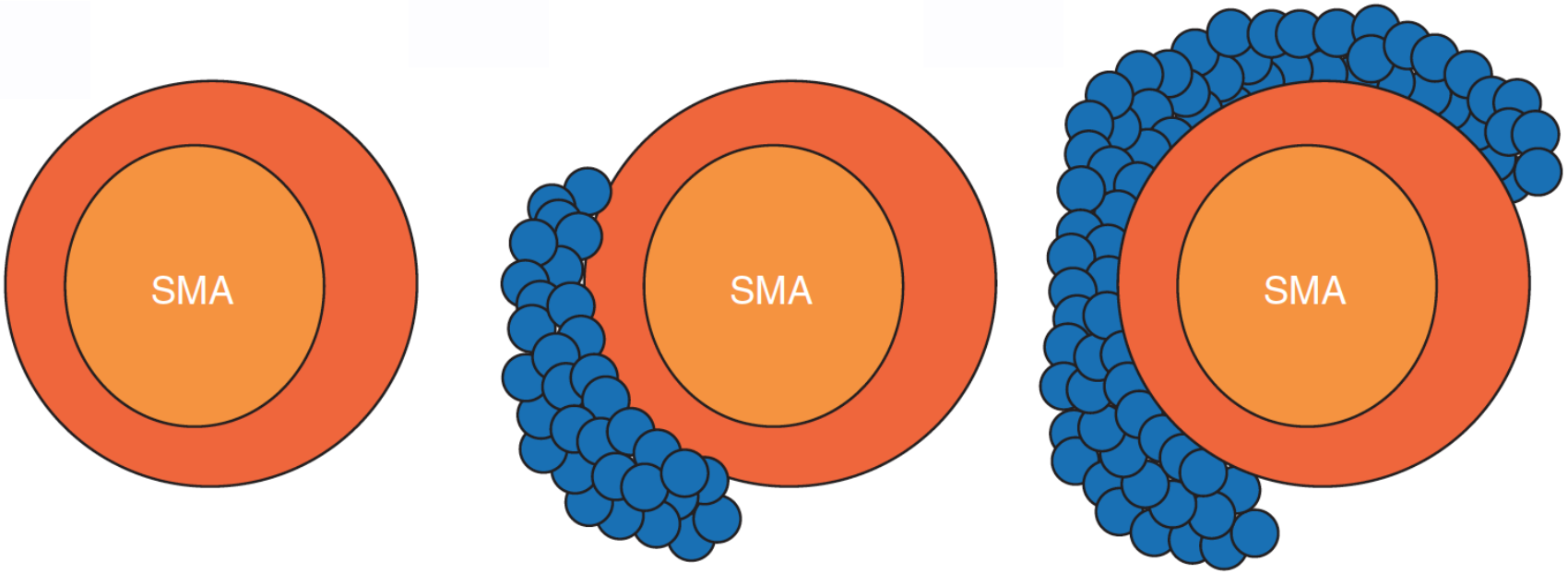
Metha et al 2001
Varadhachary et al 2006

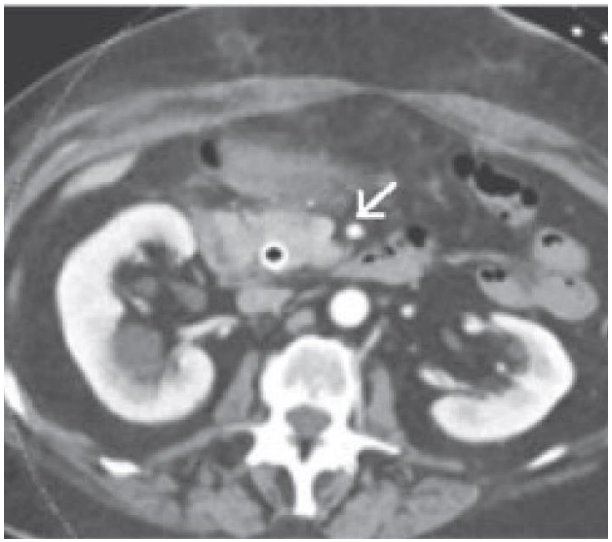

PV
SV
SMV
IMV

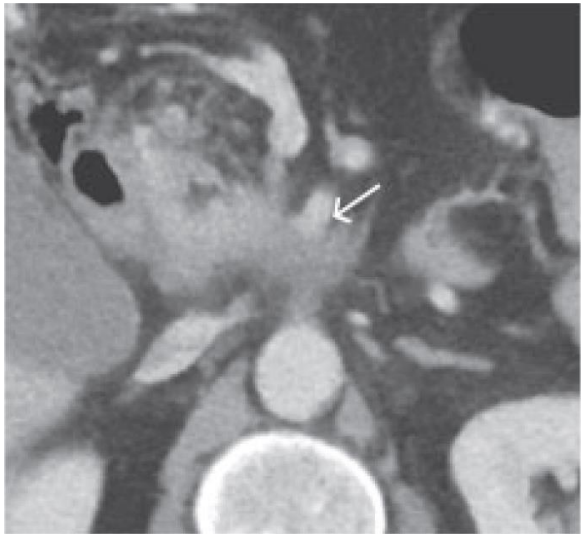

PV
Patent
SV
SMV
IMV
Patent

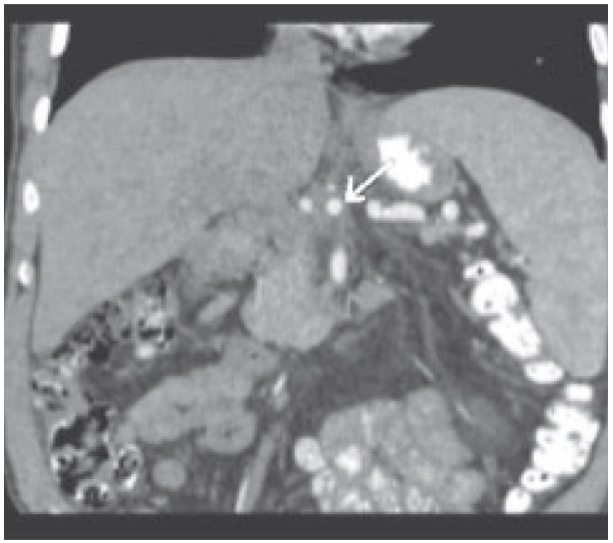

PV
SV
SMV
IMV




SMA
SMA
SMA







Definizione

		MD Anderson	AHPBA/SSAT/SSO	Alliance
Celiac	Resectable	No involvement	No involvement	No involvement
	Borderline	No involvement	No involvement	Tumor-vessel interface $<180°$
	Locally Advanced	Any involvement	Any involvement	Tumor-vessel interface $\geq 180°$
SMA	Resectable	No involvement	No involvement	No involvement
	Borderline	Abutment $\leq 180°$	Abutment $\leq 180°$	Tumor-vessel interface $<180°$
	Locally Advanced	$>180°$ involvement	$>180°$ involvement	Tumor-vessel interface $\geq 180°$

Katz et al 2008
Callery et al 2009
Katz et al 2013

Consensus

Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS)

Maximilian Bockhorn, MD,[a] Faik G. Uzunoglu, MD,[a] Mustapha Adham, MD,[b] Clem Imrie, MD,[c] Miroslav Milicevic, MD,[d] Aken A. Sandberg, MD,[e] Horacio J. Asbun, MD,[f] Claudio Bassi, MD,[g] Markus Büchler, MD,[h] Richard M. Charnley, MD,[i] Kevin Conlon, MD,[j] Laureano Fernandez Cruz, MD,[k] Christos Dervenis, MD,[l] Abe Fingerhutt, MD,[m] Helmut Friess, MD,[n] Dirk J. Gouma, MD,[o] Werner Hartwig, MD,[h] Keith D. Lillemoe, MD,[p] Marco Montorsi, MD,[q] John P. Neoptolemos, MD,[r] Shailesh V. Shrikhande, MD,[s] Kyoichi Takaori, MD,[t] William Traverso, MD,[u] Yogesh K. Vashist, MD,[a] Charles Vollmer, MD,[v] Charles J. Yeo, MD,[w] *and* **Jakob R. Izbicki, MD,[a] for the International Study Group of Pancreatic Surgery,** *Hamburg, Heidelberg, and Munich, Germany, Lyon and Poissy, France, Glasgow, Newcastle upon Tyne, and Liverpool, UK, Belgrade, Serbia, Huddinge, Stockholm, Sweden, Jacksonville, FL, Verona and Milan, Italy, Dublin, Ireland, Barcelona, Spain, Athens, Greece, Amsterdam, The Netherlands, Boston, MA, Mumbai, India, Kyoto, Japan, Boise, ID, and Philadelphia, PA*

- TC <u>protocollo pancreas</u> nelle precedenti 4 settimane
- Board multidisciplinare
- Centro ad alto volume
- *NCCN criteria*

Surgery
June 2014

Consensus

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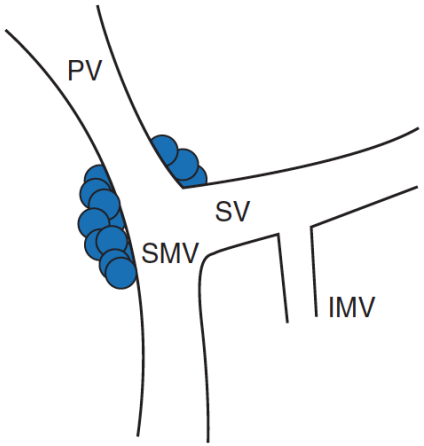

- Sopravvivenza simile alle resezioni standard
- Neoadiuvante non sistematica
- Resezione venosa se R0
- Centro ad alto volume

Surgery
June 2014

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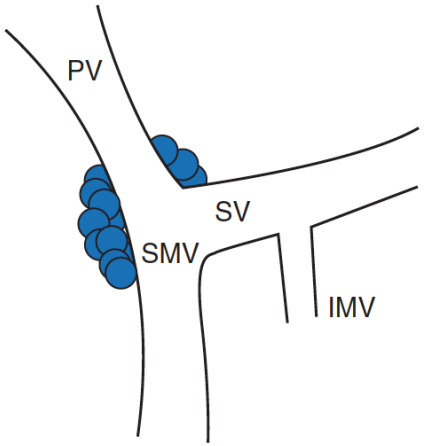

Resezione venosa

1. **Tangenziale** con sutura diretta (venorrafia)
2. **Tangenziale** con *patch* (vena, peritoneo, pericardio bovino)
3. **Segmentaria** con ricostruzione diretta
4. **Segmentaria** con *graft* (vena, PTFE armato)

Surgery
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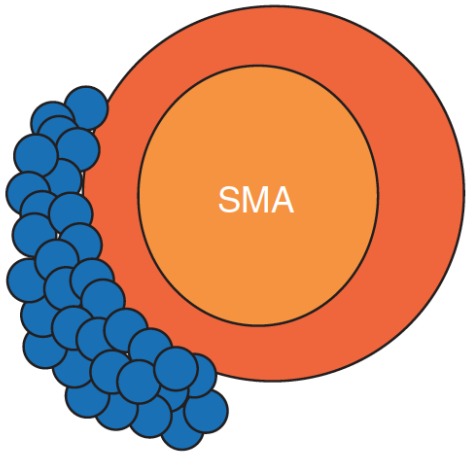

- Beneficio non dimostrato della resezione arteriosa
  - Caveat ➢ <u>morbilità/mortalità</u>
- Esplorazione chirurgica necessaria
  - Fibrosi, aderenza pseudotumorale, infiltrazione tumorale (Sp 67-91%)
- Infiltrazione arteriosa ➢ trattamento palliativo

Surgery
June 2014

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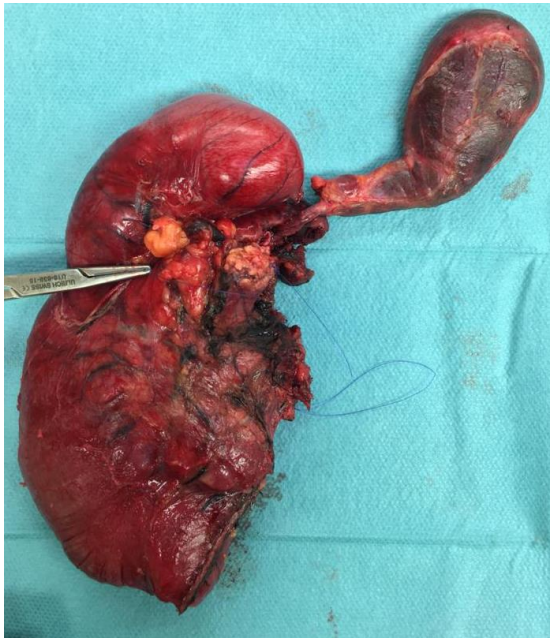


British Royal College of Pathologists (RCPath)

- **R1 ≤ 1 mm**
- Esame patologico protocollato
- 7 margini
  - anteriore, posteriore (*mobilization margin*)
  - **mediale (SMV), <u>SMA</u>**
  - pancreas, VBP, intestino
- Grado di infiltrazione venosa ➢ avventizia, media, intima/lume

Surgery
June 2014

Borderline resectable

Tecnico

Biologico

Trattamento sistemico

Petralli et al 2016

Borderline resectable

Tecnico

- ↑ tasso di risposta
- ↑ tasso di resezione
- ↑ tasso di resezione R0
- Sopravvivenza mediana ➢ *resectable*

Petralli et al 2016
Tang et al 2016

Borderline resectable

Biologico

- Selezione dei pz
- Escludere i pz con potenziale rapida progressione
- Trattare precocemente le micrometastasi

Petralli et al 2016
Barugola et al 2009

Borderline resectable

Fattori prognostici di recidiva precoce

- Diametro > 3 cm
- Parametri infiammatori (mGPS)
- *Grading*
- *Imaging* dubbio per metastasi
- CA 19-9 > 1000
- Linfonodi regionali + alla biopsia

Biologico

	mGPS 0	*mGPS 1*	*mGPS 2*
CRP	<10 mg/L	CRP <10 mg/L or	≥10 mg/L
Albumin	≤35 g/L	albumin >35 g/L	<35 g/L

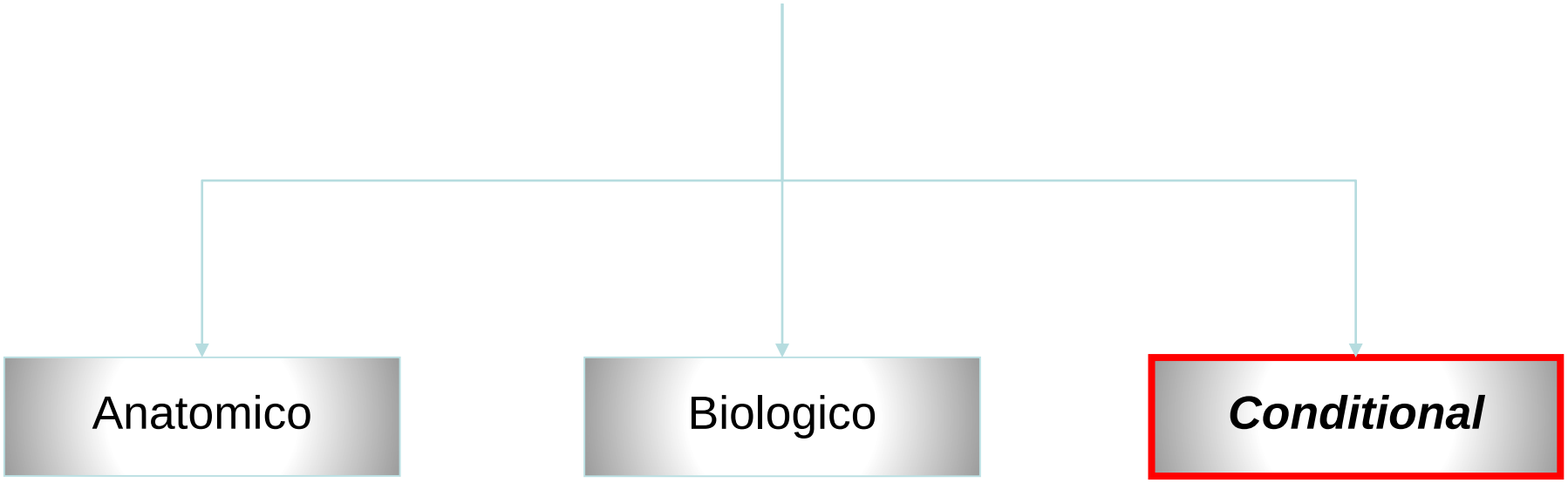
46.3% meta dopo neoadiuvante

McMillan et al 2013
Matsumoto et al 2015
Crippaet al 2012
Tzeng et al 2012

International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017

Shuji Isaji [a,*], Shugo Mizuno [a], John A. Windsor [b], Claudio Bassi [c], Carlos Fernandez-del Castillo [d], Thilo Hackert [e], Aoi Hayasaki [a], Matthew H.G. Katz [f], Sun-Whe Kim [g], Masashi Kishiwada [a], Hirohisa Kitagawa [h], Christoph W. Michalski [e], Christopher L. Wolfgang [i]

Borderline resectable



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Shuji Isaji [a,*], Shugo Mizuno [a], John A. Windsor [b], Claudio Bassi [c], Carlos Fernandez-del Castillo [d], Thilo Hackert [e], Aoi Hayasaki [a], Matthew H.G. Katz [f], Sun-Whe Kim [g], Masashi Kishiwada [a], Hirohisa Kitagawa [h], Christoph W. Michalski [e], Christopher L. Wolfgang [i]

Definizione ***conditional***

- *Performance status* - ECOG ≥ 2
- Risposta infiammatoria sistemica - mGPS

	MST (months) in all patients	MST in patients with PS 0 or 1	MST in patients with PS = />2	p-value(PS 0,1 v.s. PS = />2)
Local diseaseStage I/II	22.1 (n = 59)	23.5 (n = 52)	12.4 (n = 7)	0.015
Locally advancedStage III	10.3 (n = 122)	10.7 (n = 100)	4.6 (n = 22)	0.01
MetastaticStage IV	6.0 (n = 154)	7.4 (n = 102)	3.1 (n = 52)	<0.001

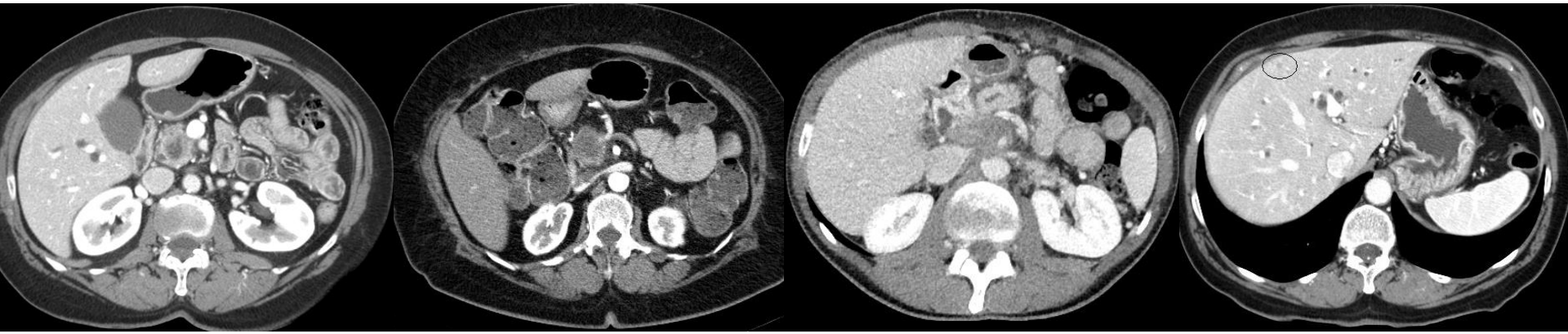
MST: median survival time, PS: Eastern Cooperative Oncology Group (ECOG) performance status.
Stage: the International Union Against Cancer TNM classification 5th edition.

Pancreatology 18 (2018) 2–11

Tas et al 2013
Tseng et al 2014
Imrie et al 2015

Stadiazione

15-20%	25%		> 50%
Resecabile	Borderline	Localmente avanzato	Metastatico



- ⌀ meta	- ⌀ meta	- ⌀ meta	- Fegato 70-80%
- contatto venoso ≤ 180°	- asse venoso ricostruibile	- asse venoso non ricostruibile	
- ⌀ contatto arterioso	- contatto arterioso ≤ 180°	- contatto arterioso > 180°	
	- **Biologia** (meta?, CA 19.9)		
	- **Generale**		

Chirurgia

Resezione vascolare

- Morbilità/mortalità proibitive
- Coinvolgimento vascolare ➢ controindicazione alla resezione
- ↑ gestione perioperatoria, tecnica chirurgica
    - **resezione venosa** sicura e accettabile
    - standard di cura in centri ad alto volume
- **Resezione arteriosa**, non universalmente accettata

Mollberg et al 2011
Zhou et al 2012

Resezione arteriosa

- **Indicazioni**
  - lesione/trauma intraoperatorio
  - varianti congenite
  - condizioni acquisite
  - infiltrazione tumorale

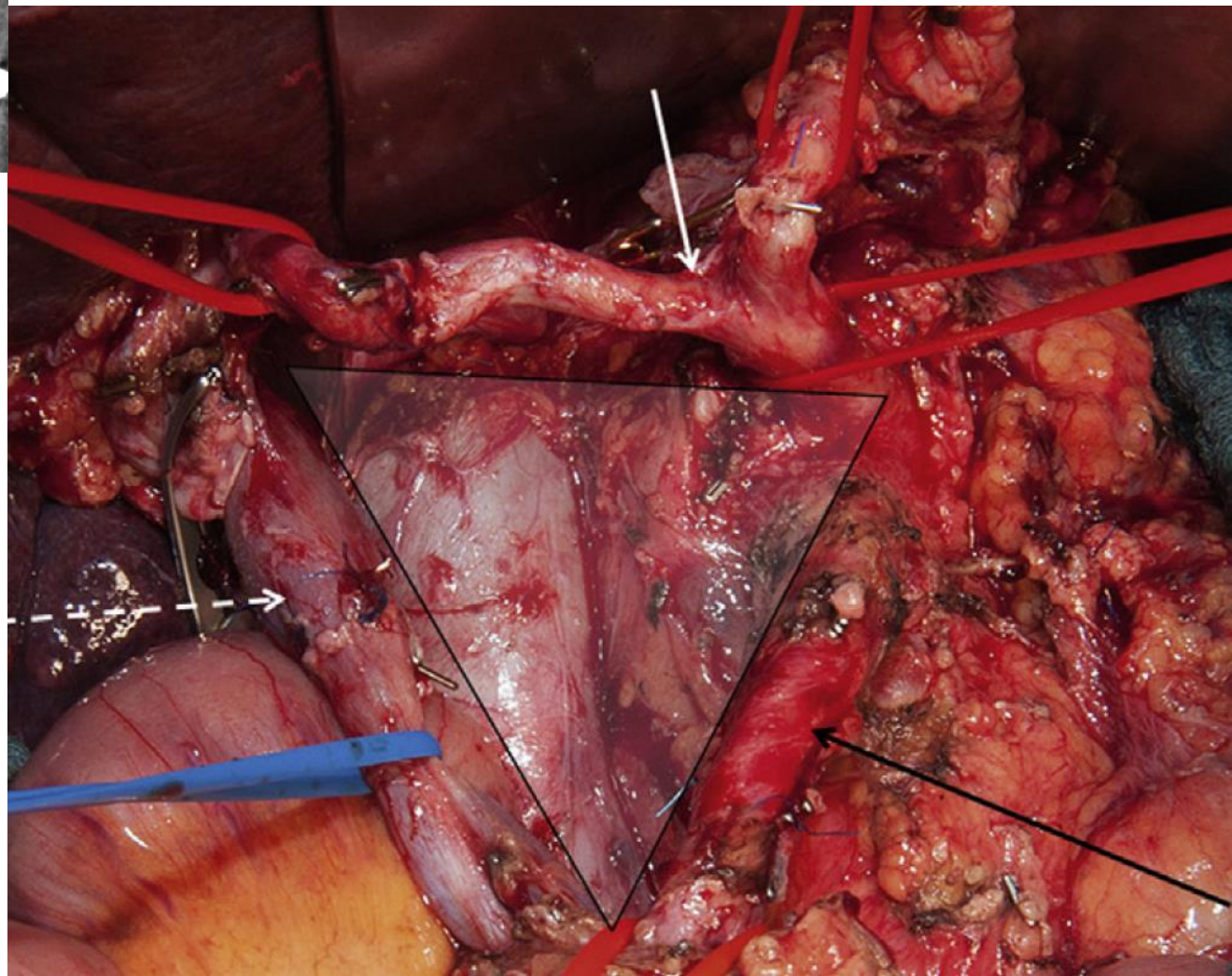
- **Rischio operatorio**
  - emorragia
  - trombosi
  - ischemia viscerale/epatobiliare

- **Alternativa terapeutica**
  - moderne CT di induzione +/- CT/RT
  - sopravvivenza mediana > 18 mesi (LA non M)

Amano et al 2009
Bokhorn et al 2011
Mian et al 2014
Faisal et al 2016

TRIANGLE OPERATION

Artery-sparing



Hackert et al 2017

Arterial Resection During Pancreatectomy for Pancreatic Cancer

A Systematic Review and Meta-Analysis

Nathan Mollberg, MD,† Nuh N. Rahbari, MD,* Moritz Koch, MD,* Werner Hartwig, MD,* Yumiko Hoeger, MD,† Markus W. Büchler, MD,* and Jürgen Weitz, MD**

- **26 studi, 7 paesi, dal 1977 al 2010**

- **Pancreatectomie elettive con AR per PDAC**
  - studi retrospettivi
  - *outcome* chirurgico e oncologico

Reference	Year	Inclusion Period	Sample Size (Total/AR)	Country	Study Type	Follow-up Period (mo)	Risk of Bias
Allendorf[13]	2008	2000–2006	198/11	United States	Retrospec.	—	High
Amano[14]	2009	2005–2009	23/23	Japan	Retrospec.	—	High
Bockhorn[15]	2010	1994–2007	478/29	Germany	Retrospec.	—	Low
Boggi[16]	2009	1987–2004	307/26	Italy	Retrospec.	22	Low
Denecke[17]	2010	2007–2009	6/6	Germany	Retrospec.	—	High
Fortner[18]	1977	1974–1976	18/6	United States	Retrospec.	—	High
Hartwig[19]	2009	2001–2007	216/14	Germany	Retrospec.	15	High
Hirano[20]	2007	1998–2005	23/23	Japan	Retrospec.	27.4	High
Hishinuma[21]	2007	1984–2003	25/7	Japan	Retrospec.	—	High
Kato[22]	2009	1981–2007	176/17	Japan	Retrospec.	20.6	Low
Kinoshita[23]	2001	1965–2001	139/6	Japan	Retrospec.	—	High
Klempnauer[24]	1996	1971–1993	189/16	Germany	Retrospec.	—	High
Martin[25]	2009	1997–2007	36/5	United States	Retrospec.	24	High
Miyakawa[26]	2002	1987–1998	8/8	Japan	Retrospec.	9.5*	High
Miyazaki[27]	2003	1990–2003	80/13	Japan	Retrospec.	—	High
Ogata[28]	1997	1974–1997	192/21	Japan	Retrospec.	—	High
Ouaissi[29]	2010	1977–2008	149/8	Belgium	Retrospec.	17	High
Park[30]	2001	1996–1999	40/15	Korea	Retrospec.	—	High
Settmacher[31]	2004	1989–2003	18/18	Germany	Retrospec.	8*	High
Shimada[32]	2006	1990–2004	88/12	Japan	Retrospec.	20	Low
Sperti[33]	2010	1989–2007	54/5	Italy	Retrospec.	—	High
Stitzenberg[34]	2008	1996–2000	252/12	United States	Retrospec.	17	High
Sugiura[35]	2009	1978–2007	107/25†	Japan	Retrospec.	—	High
Tamura[36]	1992	1980–1991	15/7	Japan	Retrospec.	—	High
Wang[37]	2008	1996–2005	80/19	China	Retrospec.	—	High
Wu[38]	2010	2003–2008	36/9	China	Retrospec.	—	High

Annals of Surgery • Volume 254, Number 6, December 2011

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- **Risultati perioperaotori**
  - ↑ tempo operatorio
  - ↑ perdite ematiche
  - ↑ morbilità maggiore
  - ↑ reintervento
  - ↑ mortalità ➢ **OR 5** (→ 46%)

- **Risultati oncologici**
  - tasso mediano di R0 60% vs 74.8% (non significativo)
  - nessuna differenza per incidenza di metastasi linfonodali
  - sopravvivenza a 1, 3, 5 anni significativamente ridotta per AR
  - tasso mediano di sopravvivenza a 1, 3, 5 anni per AR
    - ✓ 49.1%, 8.3%, 0%

Annals of Surgery • Volume 254, Number 6, December 2011

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Markus W. Büchler, MD, and Jürgen Weitz, MD**

- **Pancreasetomia con AR**
  - AR ➢ <u>controindicazione alla resezione</u>
  - AR ➢ rischio di mortalità postoperatoria
  - rischio non controbilanciato dal beneficio oncologico
  - vantaggio oncologico sui non resecati ➢ bias (stadio, CT)
  - discutibile per pazienti iper selezionati?

Annals of Surgery • Volume 254, Number 6, December 2011

Indications and Perioperative Outcomes for Pancreatectomy with Arterial Resection

May C Tee, MD, MPH, Adam C Krajewski, MD, Ryan T Groeschl, MD, Michael B Farnell, MD, FACS, David M Nagorney, MD, FACS, Michael L Kendrick, MD, FACS, Sean P Cleary, MD, FACS, Rory L Smoot, MD, FACS, Kristopher P Croome, MD, MS, Mark J Truty, MD, MS, FACS

- **Analisi retrospettiva 1990 – 2017, 111 pz**
- **Pancreatectomie elettive con AR**
  - qualsiasi indicazione
  - AR pianificata o meno
- **Analisi pre e post <u>2010</u>**
  - ↑ interventi annui
  - moderne poli-CT in neoadiuvante
  - ↑ aggressività chirurgica

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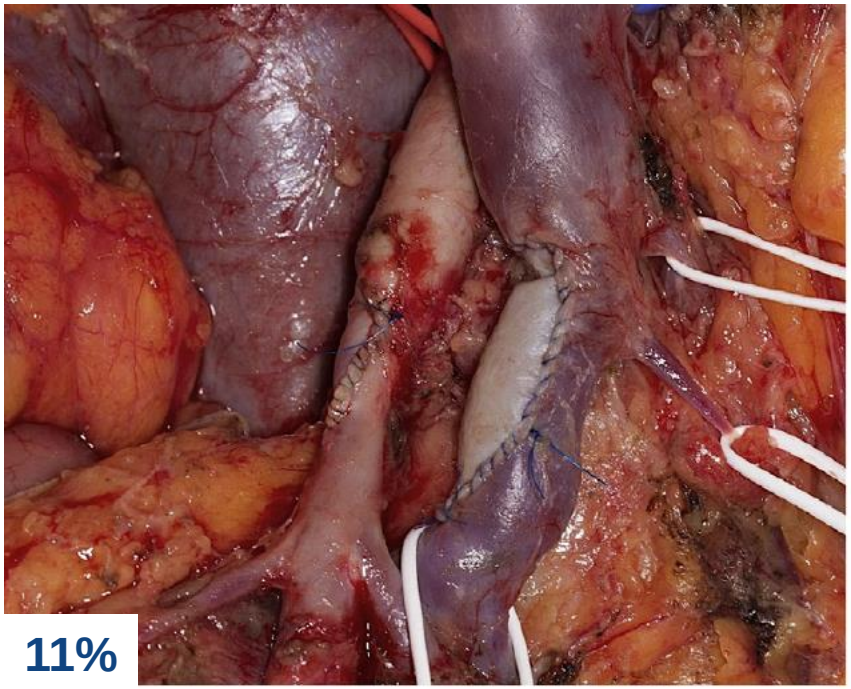
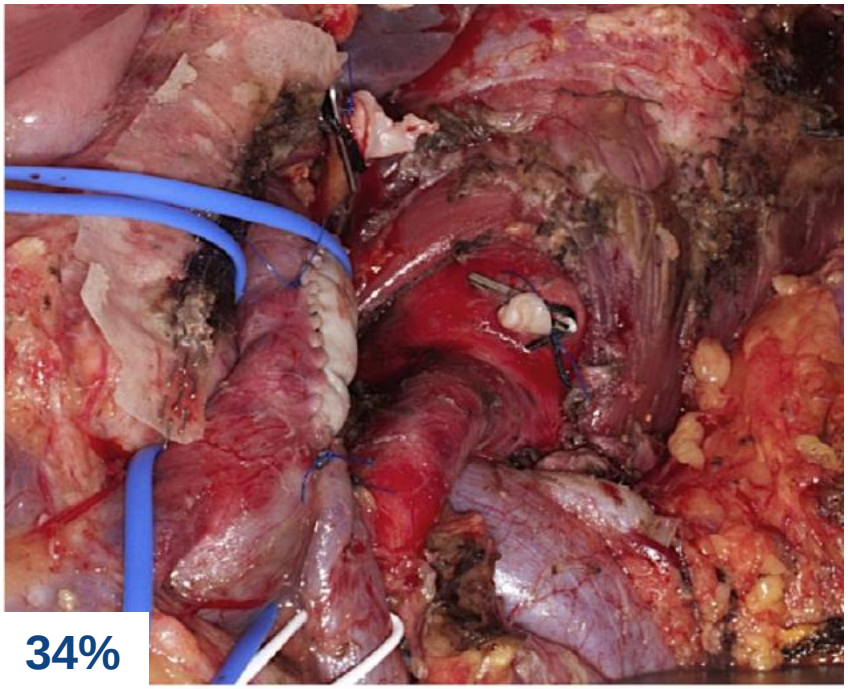
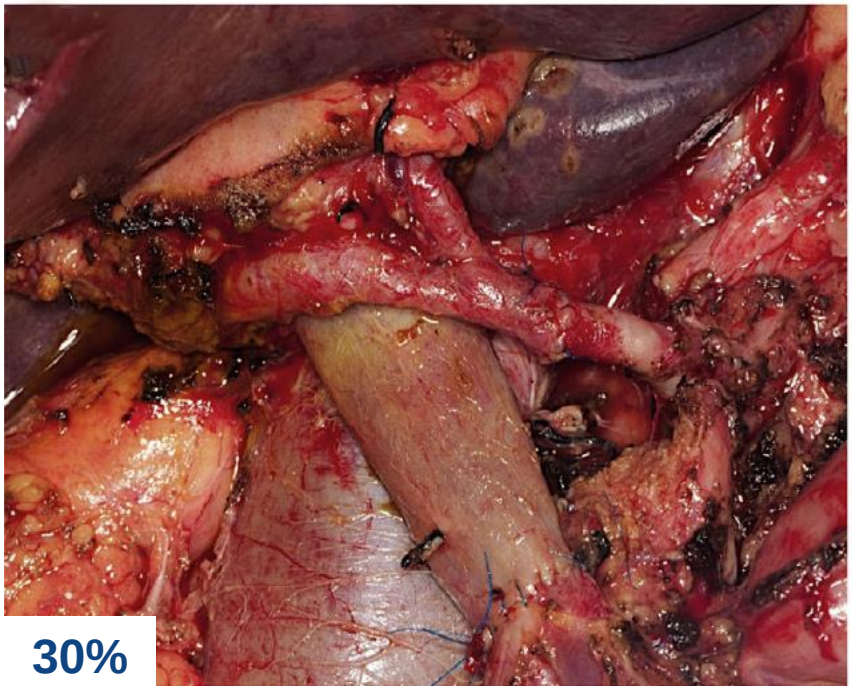
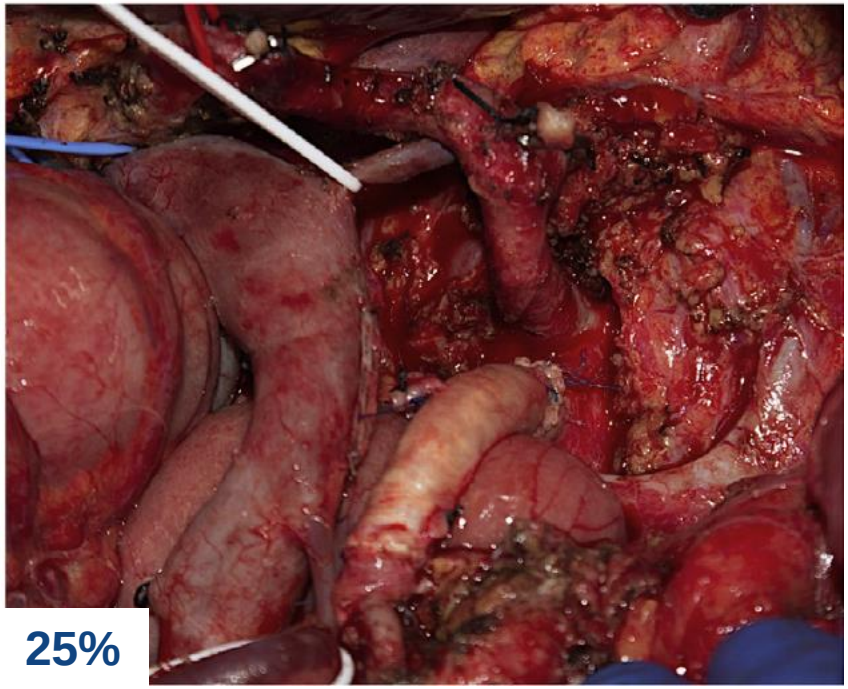

11%


34%


30%


25%

Indications and Perioperative Outcomes for Pancreatectomy with Arterial Resection

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- **Risultati perioperatori**
  - tempo operatorio medio 8 ore
  - perdite ematiche medie 1.2 l
  - morbilità maggiore 54%
  - **PPH** 15%, **POPF** 23%, DGE 23%
  - reintervento 16%, riammissione 36%
  - mortalità 90 gg/intraospedaliera 13% (29% ➢ 9%)

- **Risultati oncologici** ➢ sottogruppo PDAC
  - solo sopravvivenza a breve termine
  - sopravvivenza mediana, 1 anno, 2 anni
    - ✓ *upfront resection* 16.6 M, 72%, 25.8%
    - ✓ neoadiuvante 53.6 M, 81%, 62.3%

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Indications and Perioperative Outcomes for Pancreatectomy with Arterial Resection

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- **Pancreasetomia con AR**
  - ↑ rischio postoperatorio
  - rischio non proibitivo per il beneficio oncologico
  - <u>moderne poli-CT in neoadiuvante</u>
  - procedure epatobiliari di analogo rischio comunemente accettate
  - qualità di vita???

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Pancreatectomy With Arterial Resection for Pancreatic Adenocarcinoma: How Can It Be Done Safely and With Which Outcomes?

A Single Institution's Experience With 118 Patients

Philippe Bachellier, MD, Pietro Addeo, MD,* François Faitot, MD,* Gennaro Nappo, MD,* and Patrick Dufour, MD†*

- **Analisi retrospettiva 1990 – 2017, 118 pz**
- **Pancreatectomie elettive con AR per PDAC**
- **Analisi pre e post <u>2008</u>**
  - tumori BR o LA <u>potenzialmente chirurgici</u> dopo CT neoadiuvante
  - 26 resezioni pre *versus* 92 post (10% delle resezioni dopo il 2008)
- **Folfirinox neoadiuvante per BR - LA**
  - tasso di resezione 63.5% - 22.5%
  - tasso di resezione R0 86% (risposta patologica completa 15%)

Annals of Surgery • Volume XX, Number XX, Month 2018

Petrelli et al 2015
Ferrone et al 2015

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- **Risultati perioperaotori**
  - tempo operatorio medio 10 ore
  - trasfusione 70%
  - morbilità maggiore 24%
  - POPF 7% (0% Whipple)
  - reintervento 10%
  - mortalità 90 gg/intraospedaliera 5.1%

Annals of Surgery • Volume XX, Number XX, Month 2018

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- **Risultati istologici**
  - N+ 80.5%
  - infiltrazione venosa 74.2%, arteriosa 58.4%
  - tasso di R0 52.5%, R1 47.4%
  - risposta patologica completa ➢ 4 pazienti (3.3%)

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A Single Institution's Experience With 118 Patients

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- **Risultati oncologici**
  - sopravvivenza mediana 13.67 M
  - sopravvvivenza mediana DF 7.4 M
  - CT neo + chir 22.85 M
  - sopravvivenza a 1, 3, 5 anni ➢ 59%, 13%, 11.8%
  - <u>R0N0</u> (n = 12)
    - ✓ sopravvivenza mediana 67 M
    - ✓ sopravvivenza a 1, 3, 5 anni ➢ 90%, 54%, 54%

Annals of Surgery • Volume XX, Number XX, Month 2018

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- **Pancreasetomia con AR**
  - rischio chirurgico e beneficio oncologico accettabili
  - moderne poli-CT in neoadiuvante
  - qualità di vita???

Annals of Surgery • Volume XX, Number XX, Month 2018

Schema terapeutico

Resecabile

Borderline

Localmente avanzato

Metastatico

Chirurgia

±

CT adiuvante

mFOLFIRINOX
Gemcitabina + Capecitabina
Gemcitabina o 5FU/FA

CT neoadiuvante

±

Chirurgia

CT palliativa

CT neoadiuvante sistematica

15-20%

Resecabile

Chirurgia

±

CT adiuvante

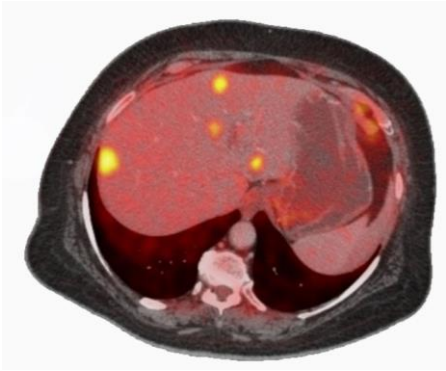
80%

resezioni «curative»

CT neoadiuvante

±

Chirurgia



70% metastasi

30% recidiva locale

Ferlay et al 2016
Rahib et al 2014

CT neoadiuvante sistematica

- **K retto e stomaco**
- **Malattia sistemica *ad initio***
- **Vantaggi potenziali**
  - ↑ R0
  - micrometastasi
  - CT aggressiva
  - selezione pz
- **Svantaggi potenziali**
  - perdita di *chance*
  - morbilità CT

CT neoadiuvante sistematica

Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer

E. Versteijne[1], J. A. Vogel[2], M. G. Besselink[2], O. R. C. Busch[2], J. W. Wilmink[3], J. G. Daams[4], C. H. J. van Eijck[5], B. Groot Koerkamp[5], C. R. N. Rasch[1] and G. van Tienhoven[1], on behalf of the Dutch Pancreatic Cancer Group

Potentially Curable Pancreatic Adenocarcinoma: ASCO Clinical Practice Guideline Update

Alok A. Khorana, MD[1]; Shannon E. McKernin[2]; Jordan Berlin, MD[3]; Theodore S. Hong, MD[4]; Anirban Maitra, MBBS[5]; Cassadie Moravek[6]; Matthew Mumber, MD[7]; Richard Schulick, MD, MBA[8]; Herbert J. Zeh, MD[9]; and Matthew H.G. Katz, MD[5]

Systemic neoadjuvant chemotherapy in modern pancreatic cancer treatment: a systematic review and meta-analysis

K Rangarajan[1], PH Pucher[1,2], T Armstrong[1], A Bateman[3], ZZR Hamady[1]

- **Linee guida ASCO**
- **Meta-analisi**
  - ↑ R0
  - ↑ risultato oncologico
  - ↑ risultato chirurgico

Versteijne et al 2018
Khorana 2019
Rangarajan et al 2019

Conclusione

- **Il vero problema sta a monte** ➢ diagnosi tardiva, biologia
- **Definizione in evoluzione**
- ***Continuum* patologico** ➢ R1/N+ costante
- **Resecabilità**: termine improprio
- **Ragionevole terapia/palliazione**

➢ anatomia, biologia, condizioni

➢ rischio/beneficio

Conclusione

- **CT neoadiuvante**

  - ➢ in tutti i *resectable*?
  - ➢ nei *resectable* sospetti/certi N+?
  - ➢ spazio della chirurgia nei BR/LA?