NEUROENDOCRINE TUMOURS: THE CUTTING EDGE AND A GLIMPSE INTO THE FUTURE

Do minimal access and robotic surgery bring benefit to neuroendocrine tumours?

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U.O.C. Chirurgia del Pancreas

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Ancona (ITALY)

Madrid, September 28, 2014

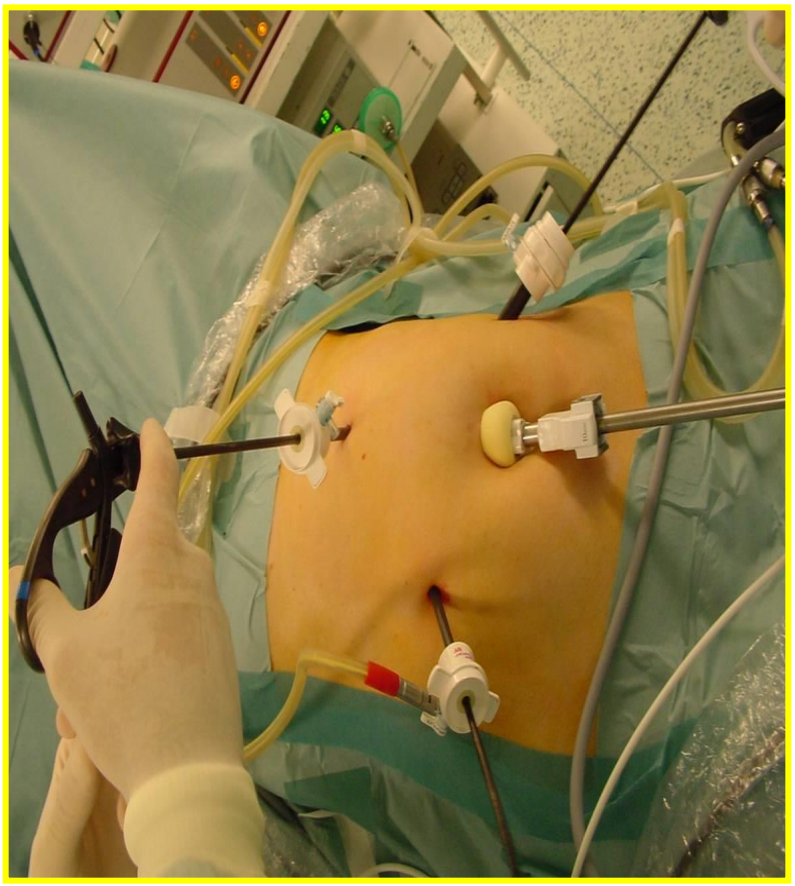
Disclosure

I have no conflicts of interest to declare but that I am a surgeon who ever performed neither a laparoscopic nor a robotic operation by himself

M Falconi

MADRID 2014 ESMO

The cutting edge of surgery

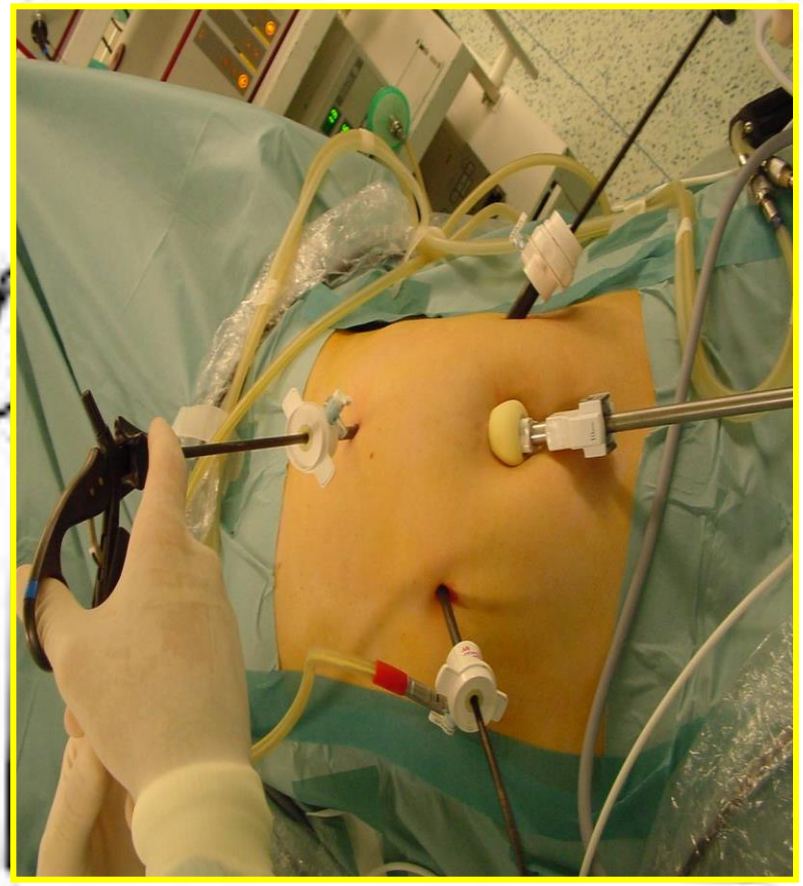


Laparoscopic surgery

Robotic surgery

A glimpse into the future

Robotic surgery



Laparoscopic surgery

Imagine above us a blue sky … (modified from John Lennon)

Diagnosis of appendicitis

Here Houston, no problem at all we have a program of robotic surgery!!!

Here Apollo 2020, we have a problem!!!

What is the actual room for mini-invasive surgery (MIS) in NENs world?

- ✓ Anatomical districts
- ✓ Surgical skill (learning curve)
- ✓ Underlying disease (size and stage)
- ✓ EBM results (RCTs)

NENs are a very large family

- Adrenalectomy
- Appendectomy
- Colon

MIS [and] NENs

- Adrenalectomy √(size and extension)
- Appendectomy √
- Colon √

A first conclusion

There are no reasons for thinking that a MIS approach should follow different rules when a surgeon deals with a NEN located in organs for which such an approach is already established for either a benign or a malignant disease

NENs are a very large family

- Adrenalectomy √
- Appendectomy √
- Colon √
- Small bowel ?

Jejunum & ileum NENs

Well-differentiated endocrine cell carcinoma of ileum treated by laparoscopy-assisted surgery--a case report.

Sasada S, Ojima Y, Nishizaki M, Harano M, Matsukawa H, Aoki H, Shiozaki S, Ohno S, Ninomiya M, Matsuura H, Takakura N.

Hiroshima J Med Sci. 2010 Jun;59(2):35-8.

A recent larger contribution

Surgery for small-bowel neuroendocrine tumors: Is there any benefit of the laparoscopic approach?

Marleny N. Figueiredo · Léon Maggiori · Sébastien Gaujoux · Anne Couvelard · Nathalie Guedj · Philippe Ruszniewski · Yves Panis

Figuereido MN, et al. Surg Endosc 2014, 28:1720-26

A recent larger contribution

Table 1 Comparison of clinical and operative findings between the open surgery group and the laparoscopy group

	Open surgery (n = 61)	Laparoscopy (n = 12)	p value
Age [years; median (range)]	56.5 (27–79)	54 (40–60)	0.08
median (IQR)]			
Length of resected specimen [cm; median (IQR)]	47.5 (27.5–70)	19 (14.5–28)	*0.009*
Postoperative morbidity [n (%)]			0.95
Overall	13 (21.3)	3 (25)	
Severe	4 (6.6)	1 (8.3)	
Length of stay [days; median (range)]	8 (2–34)	6 (4–10)	*0.003*

Conclusion Complete resection of primary SBNE tumors with or without liver metastasis is associated with good long-term survival. In selected patients, laparoscopy for SBNE tumors is feasible and associated with a shorter hospital stay than laparotomy.

Figuereido MN, et al. Surg Endosc 2014, 28:1720-26

A contribution with some tricks

Table 1 Comparison of clinical and operative findings between the open surgery group and the laparoscopy group

	Open surgery (n = 61)	Laparoscopy (n = 12)	p value
Age [years; median (range)]	56.5 (27–79)	54 (40–60)	0.08
Gender [male; n (%)]	34 (55.7)	6 (50)	0.75
BMI [median (IQR)]	24 (21.9–27.4)	26.6 (22.6–28.4)	0.49
Secreting tumor [n (%)]	25 (41)	1 (8.3)	0.07
Presence of nodes at diagnosis [n (%)]	52 (85.2)	3 (25)	*<0.001*
Liver metastases [n (%)]	42 (68.9)	1 (8.3)	*<0.001*
Type of surgery [n (%)]			*0.008*
Small-bowel resection	36 (59)	2 (16.7)	
Ileocolectomy	18 (29.5)	7 (58.3)	
SB + IC	4 (6.6)	3 (25)	
Not known/not described	3 (4.9)	–	
Operative time [min; median (IQR)]	180 (130–300)	145 (120–160)	0.34
Length of resected specimen [cm; median (IQR)]	47.5 (27.5–70)	19 (14.5–28)	*0.009*
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Figuereido MN, et al. Surg Endosc 2014, 28:1720-26

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Figuereido MN, et al. Surg Endosc 2014, 28:1720-26

NENs are a very large family

- Adrenalectomy √
- Appendectomy √
- Colon √
- Small bowel X
- Pancreas ?

Pancreas [and] Surgery [and] NENs

- ✓ Pancreaticoduodenectomy
- ✓ Middle pancreatectomy
- ✓ Distal pancreatectomy (± splenectomy)
- ✓ Enucleation
- ✓ Total Pancreatectomy

I am a lucky man: somebody else did my job!

REVIEW ARTICLE

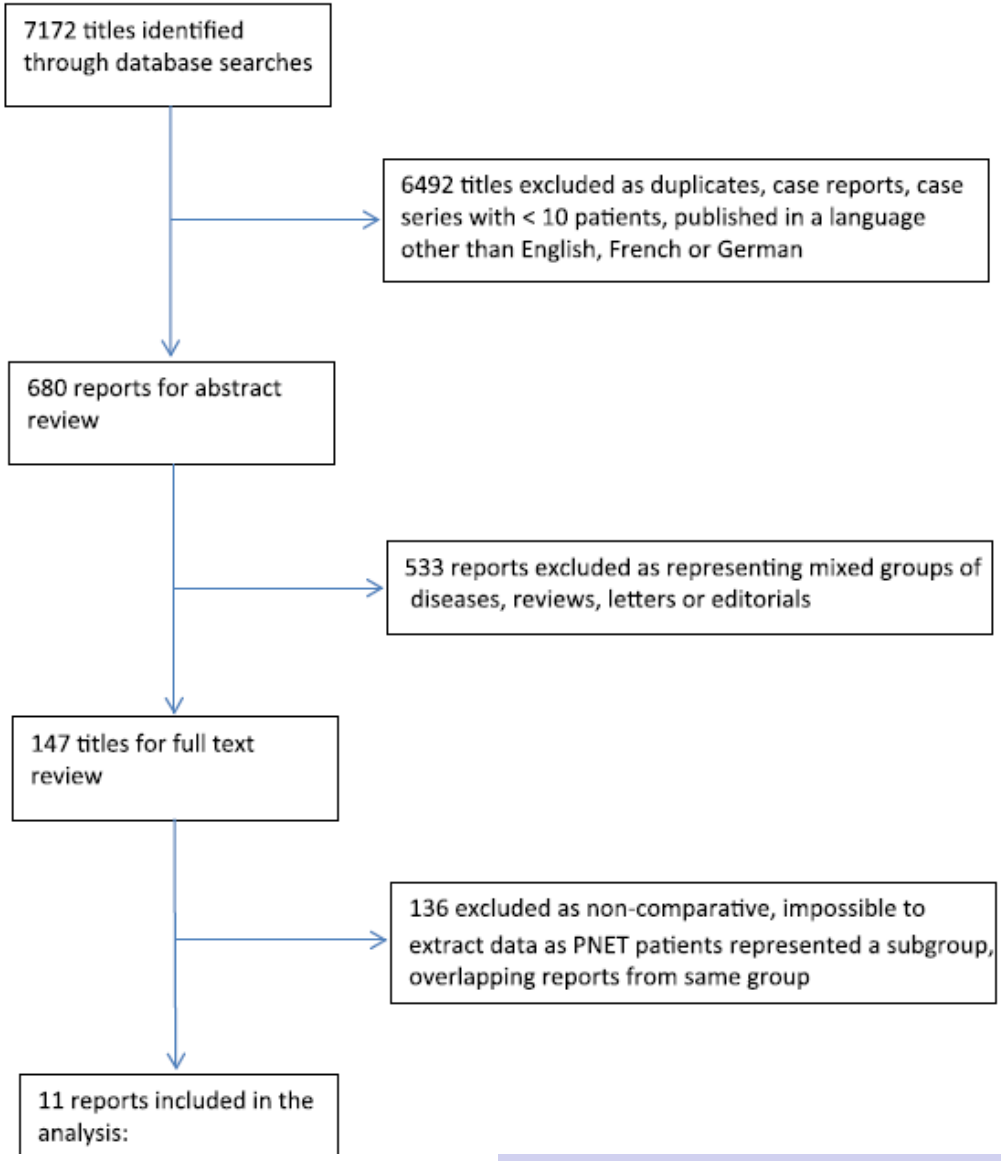
Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis

Panagiotis Drymousis[1], Dimitri A. Raptis[2*], Duncan Spalding[1*], Laureano Fernandez-Cruz[3], Deepak Menon[1], Stefan Breitenstein[4], Brian Davidson[5] & Andrea Frilling[1]

[1]Department of Surgery and Cancer, Hammersmith Hospital Campus, Imperial College London, London, UK, [2]Departmentof Visceral and Transplantation Surgery, University Hospital Zurich, Zurich, Switzerland, [3]Bilio-Pancreatic Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain, [4]Department of Surgery, Kantonsspital Winterthur, Winterthur, Switzerland and [5]Department of Surgery, Royal Free Campus, University College London Medical School, London, UK

Drymousis P, et al. HPB 2014, 16, 397–406

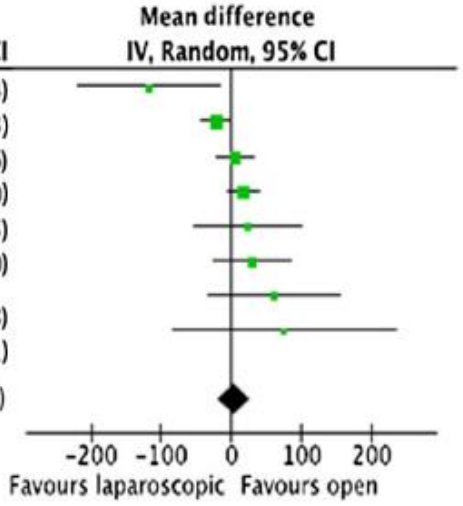
The usual PRISMA flow chart



Drymousis P, et al. HPB 2014, 16, 397–406

… and interesting results on operative time (a)

Study or subgroup in:	Laparoscopic Mean	SD	Total	Open Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Gumbs *et al.*[20] (2008)	188	56	18	305	182	13	4.4%	-117.00 (-219.26, -14.74)
Zhao *et al.*[29] (2011)	179	68	46	201	75	246	24.3%	-22.00 (-43.77, -0.23)
Liu *et al.*[24] (2007)	159	21	7	154	48	21	22.4%	5.00 (-20.76, 30.76)
Hu *et al.*[21] (2011)	211	57	43	195	54	46	23.7%	16.00 (-7.10, 39.10)
Sa Cunha *et al.*[27] (2006)	172	14	12	149	115	9	7.1%	23.00 (-52.55, 98.55)
Karaliotas & Sgourakis[22] (2009)	121	53	5	92	41	7	11.1%	29.00 (-26.50, 84.50)
Roland *et al.*[26] (2008)	318	74	22	258	174	15	5.1%	60.00 (-33.33, 153.33)
Lo *et al.*[25] (2004)	300	92	4	225	164	6	2.0%	75.00 (-84.21, 234.21)
Total (95% CI)			**157**			**363**	**100.0%**	**3.83 (-19.17, 26.83)**



(a)

Drymousis P, et al. HPB 2014, 16, 397–406

… and interesting results on operative time (a) and blood loss (b)

Study or subgroup in:	Laparoscopic Mean	SD	Total	Open Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Gumbs *et al.*[20] (2008)	188	56	18	305	182	13	4.4%	-117.00 (-219.26, -14.74)
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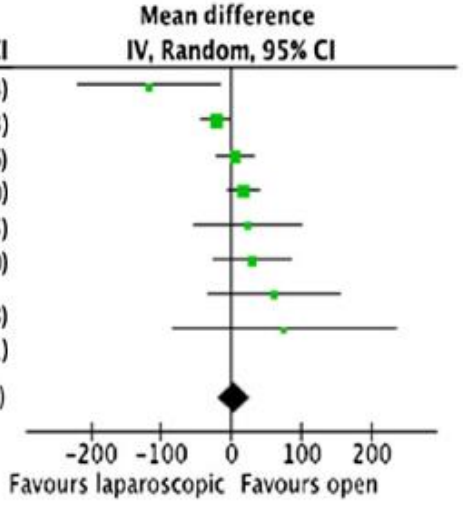
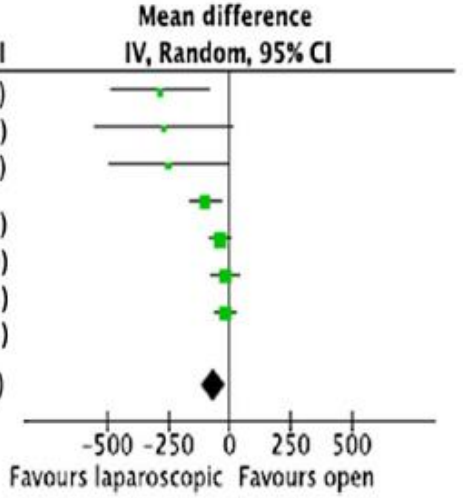


(a)

Study or subgroup in:	Laparoscopic Mean	SD	Total	Open Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Gumbs *et al.*[20] (2008)	217	141	18	500	354	13	4.9%	-283.00 (-486.16, -79.84)
Lo *et al.*[25] (2004)	125	115	4	395	320	6	2.8%	-270.00 (-549.75, 9.75)
Espana-Gomez *et al.*[19] (2009)	211	317	21	462	368	13	3.7%	-251.00 (-492.66, -9.34)
Liu *et al.*[24] (2007)	77	50	7	174	163	41	20.1%	-97.00 (-159.14, -34.86)
Zhao *et al.*[29] (2011)	125	134	46	164	206	246	23.4%	-39.00 (-85.50, 7.50)
Hu *et al.*[21] (2011)	133	156	43	151	115	46	21.1%	-18.00 (-75.26, 39.26)
Sa Cunha *et al.*[27] (2006)	100	56	12	115	67	19	24.0%	-15.00 (-58.72, 28.72)
Total (95% CI)			**151**			**384**	**100.0%**	**-66.84 (-116.31, -17.36)**



(b)

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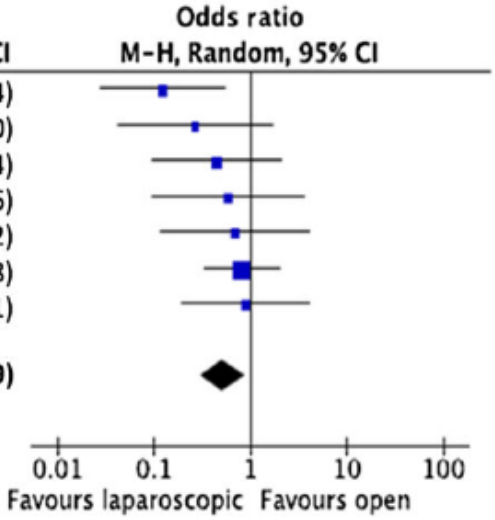
… and interesting results on overall complication (a)

Study or subgroup in:	Laparoscopic Events	Total	Open Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Zerbi *et al.*[28] (2011)	2	21	111	241	13.1%	0.12 (0.03, 0.54)
Sa Cunha *et al.*[27] (2006)	3	12	5	9	8.3%	0.27 (0.04, 1.70)
Roland *et al.*[26] (2008)	4	22	5	15	12.3%	0.44 (0.10, 2.04)
Espana-Gomez *et al.*[19] (2009)	16	21	11	13	8.7%	0.58 (0.10, 3.56)
Liu *et al.*[24] (2007)	2	7	15	41	9.2%	0.69 (0.12, 4.02)
Hu *et al.*[21] (2011)	13	43	16	46	36.1%	0.81 (0.33, 1.98)
Gumbs *et al.*[20] (2008)	12	18	9	13	12.2%	0.89 (0.19, 4.11)
Total (95% CI)		**144**		**378**	**100.0%**	**0.52 (0.30, 0.89)**
Total events	52		172			



(a)

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… and interesting results on overall complication (a) and PF (b)

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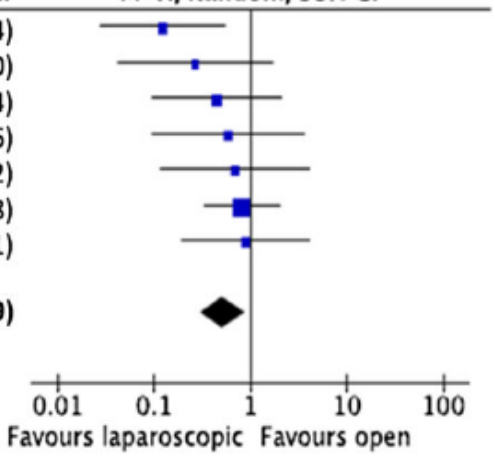

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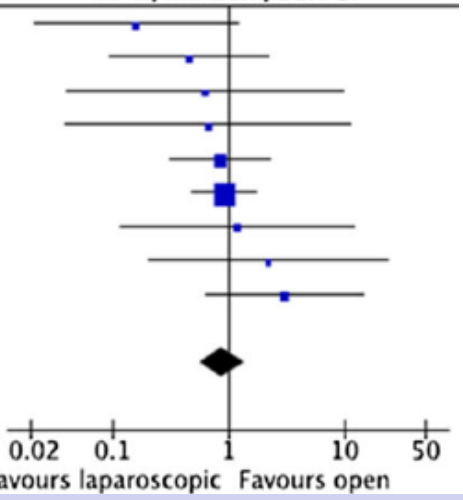
Karaliotas & Sgourakis[22] (2009)	1	5	2	7	2.6%	0.63 (0.04, 9.65)
Lo *et al.*[25] (2004)	1	4	2	6	2.4%	0.67 (0.04, 11.29)
Hu *et al.*[21] (2011)	9	43	11	46	19.3%	0.84 (0.31, 2.29)
Zhao *et al.*[29] (2011)	20	46	112	246	48.0%	0.92 (0.49, 1.74)
Liu *et al.*[24] (2007)	1	7	5	41	3.6%	1.20 (0.12, 12.14)
Roland *et al.*[26] (2008)	3	22	1	15	3.5%	2.21 (0.21, 23.56)
Espana-Gomez *et al.*[19] (2009)	10	21	3	13	8.1%	3.03 (0.64, 14.26)
Total (95% CI)		**178**		**396**	**100.0%**	**0.89 (0.57, 1.38)**
Total events	51		146			



(b)

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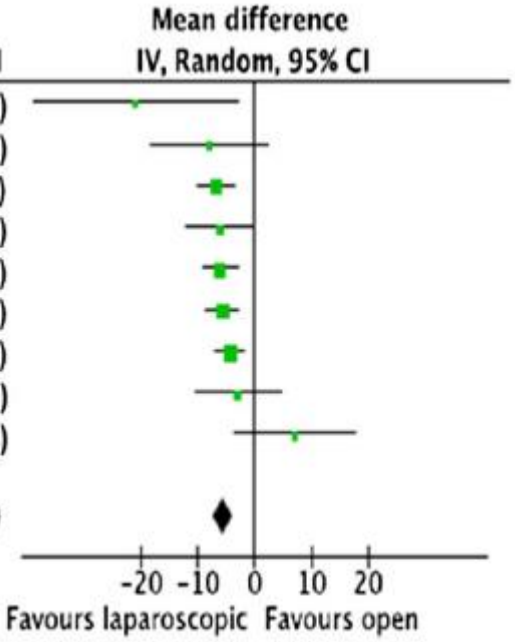
… resulting in a shorter LOS

Study or subgroup in:	Laparoscopic Mean	SD	Total	Open Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Lo *et al.*[25] (2004)	10	5.3	4	31	21.6	6	0.9%	-21.00 (-39.05, -2.95)
Espana-Gomez *et al.*[19] (2009)	9.8	11.6	21	17.8	16.8	13	2.5%	-8.00 (-18.39, 2.39)
Liu *et al.*[24] (2007)	11.8	3.4	7	18.5	6.7	41	18.3%	-6.70 (-9.95, -3.45)
Sa Cunha *et al.*[27] (2006)	11.5	5.8	12	17.6	7.5	9	7.2%	-6.10 (-12.00, -0.20)
Zhao *et al.*[29] (2011)	15.1	7.8	46	21.2	17.3	246	19.3%	-6.10 (-9.22, -2.98)
Roland *et al.*[26] (2008)	13.4	4.6	22	19.1	4.3	15	21.2%	-5.70 (-8.60, -2.80)
Hu *et al.*[21] (2011)	9.1	5.6	43	13.5	7.2	46	23.5%	-4.40 (-7.07, -1.73)
Karaliotas & Sgourakis[22] (2009)	11	6.1	5	14	7.2	7	4.6%	-3.00 (-10.55, 4.55)
Gumbs *et al.*[20] (2008)	27	11	18	20	17.2	13	2.4%	7.00 (-3.64, 17.64)
Total (95% CI)			**178**			**396**	**100.0%**	**-5.44 (-7.14, -3.75)**



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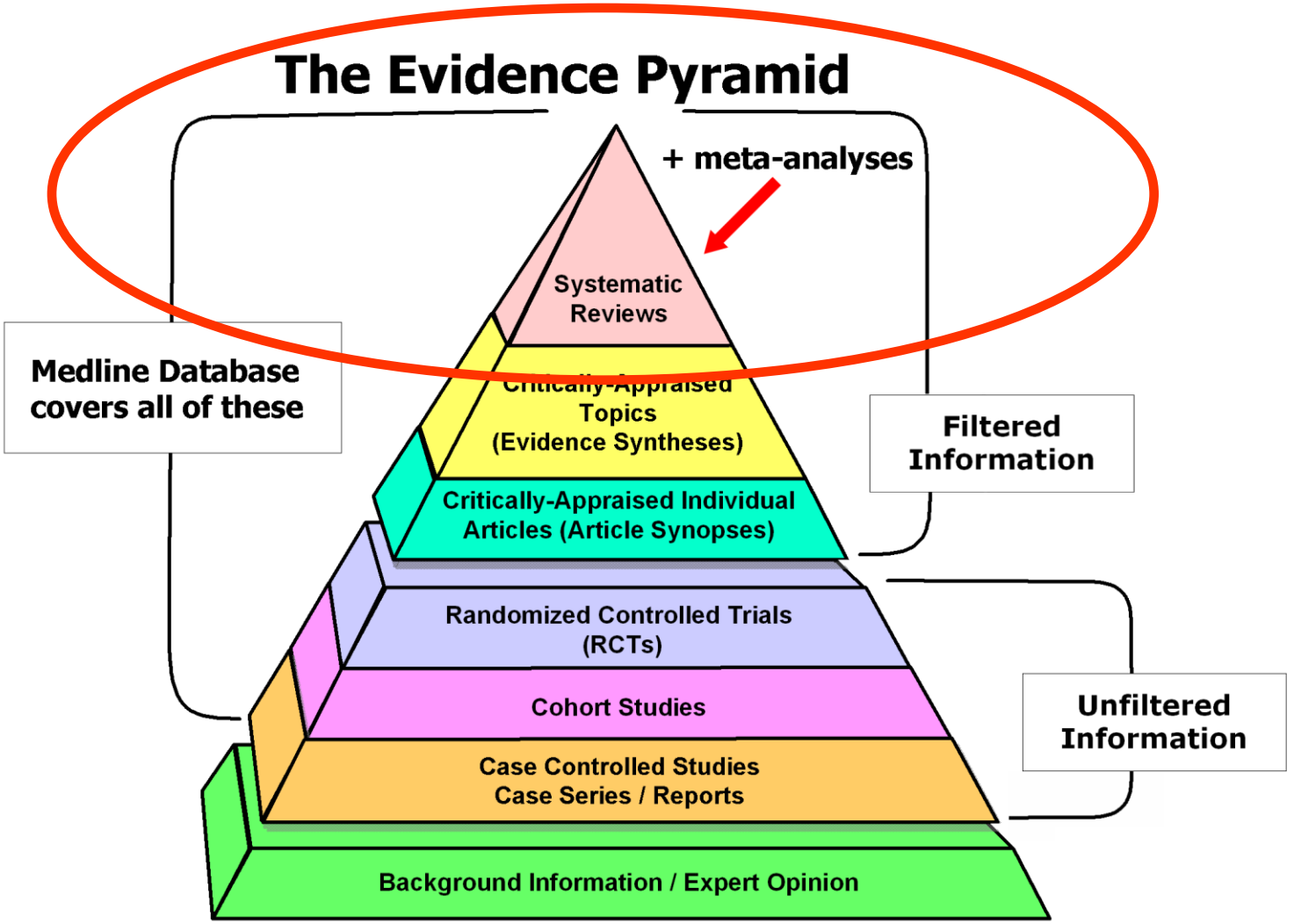
Wonderful: we are at the top of EBM!!!



but again with some tricks (sic!)

Authors	Year	Study type	Type of PNET	Period of patient recruitment	Country	Patients, *n*	UPS, *n*	OPS, *n*	Conversion, *n*
Espana-Gomez *et al.*[19]	2009	Retrospective	Insulinomas	1995–2007	Spain	34	21	13	7
Gumbs[20]	2008	Retrospective	Functioning (23%) Non-functioning (77%)	1992–2006	France	31	18	13	1
Hu *et al.*[21]	2011	Retrospective	Insulinomas	2000–2008	China	89	43	46	2
Karaliotas & Sgourakis[22]	2009	Retrospective	Insulinomas	1994–2008	Greece	12	5	7	1
Kazanjian *et al.*[23]	2006	Retrospective	Functioning (29%) Non-functioning (71	1990–2005	USA	70	4	66	NR
Liu *et al.*[24]	2007	Retrospective	Insulinomas	2000–2006	China	48	7	41	3
Lo *et al.*[25]	2004	Retrospective	Insulinomas	1999–2002	China	10	4	6	0
Roland *et al.*[26]	2008	Retrospective	Insulinomas	1998–2007	USA	37	22	15	2
Sa Cunha *et al.*[27]	2006	Retrospective	Insulinomas	1999–2005	China	21	12	9	3
Zerbi *et al.*[28]	2011	Prospective	Functioning (27%) Non-functioning (73%)	2004–2007	Italy	262	21	241	NR
Zhao *et al.*[29]	2011	Retrospective	Insulinomas	1990–2010	China	292	46	246	19
Total						**906**	**203**	**703**	

10 retrospective, 1 prospective no RCT, 0 RCT

The surgeons and statistic: a new love?

To make the story short

- ✓ More systematic reviews and meta-analyses than patients comparing
  - ✓ open vs lap; lap vs. rob; rob vs. lap for either PD or DP
- ✓ No one RCT either for laparoscopy or robot
- ✓ Usual words in the conclusion “the technique is”
  - ✓ feasible
  - ✓ safe
  - ✓ same pancreas-related complications
  - ✓ some trouble as regard the cost effectiveness
  - ✓ but usually less LOH

Pancreas [and] Surgery [and] NENs

- ✓ Reproducible in any place?
- ✓ Possible biases:
  - ✓ Patients selection
  - ✓ Intention to treat analysis (conversion rate)
  - ✓ Fast-track postoperative protocol also in historical series of open resection?

Needs for well designed RCTs!!!

To be unbiased and rational in a cutting edge era:

pancreas [and] surgery [and] NENs

- ✓ Pancreaticoduodenectomy
- ✓ Middle pancreatectomy

Pancreatic and/or biliary anastomosis

- ✓ **Distal pancreatectomy (± splenectomy)**
- ✓ **Enucleation**
- ✓ Total Pancreatectomy

Biliary anastomosis

The MIS cutting edge for a “human” pancreatic surgeon: size as possible cut-off

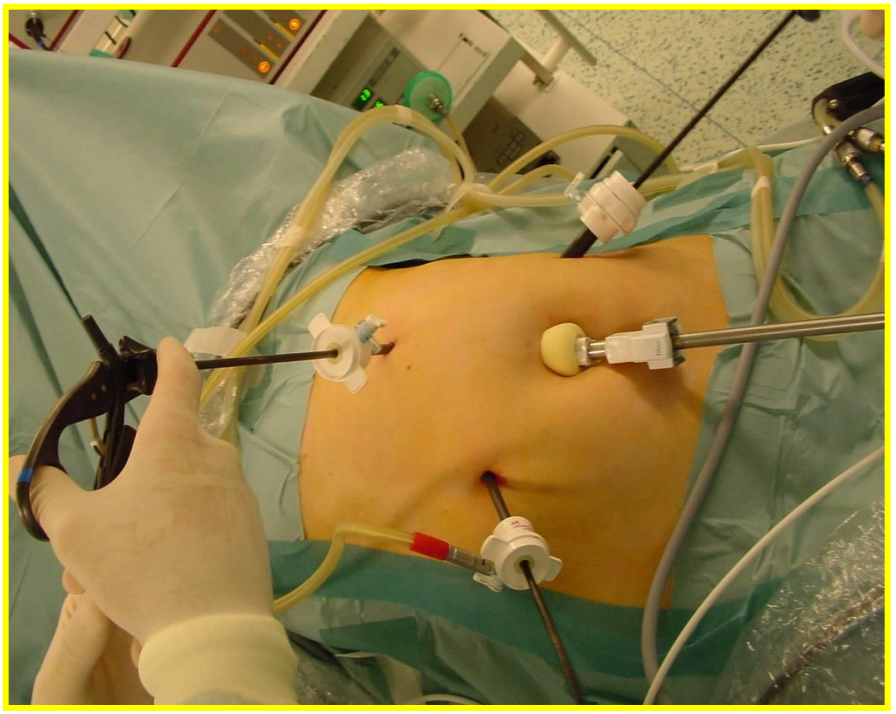
Type of approach	open	laparoscopy[1]	robotic[1]
Distal pancreatectomy	> 4-5 cm	< 4-5 cm but high surgical skill	
Enucleation	deep in the head	superficial providing Lap IOUS	superficial providing Lap IOUS
PD	ever	but high surgical skill	
Middle pancreatectomy	ever	but high surgical skill	

[1] **providing specific programs and minimal expertise**

Why Lap pancreatectomies are not routinely performed?

Not very “natural”:

- ✓ Bi-dimensional vision
- ✓ Minimal tactile perception
- ✓ Arms and head in a forced position



Advantages of the robot

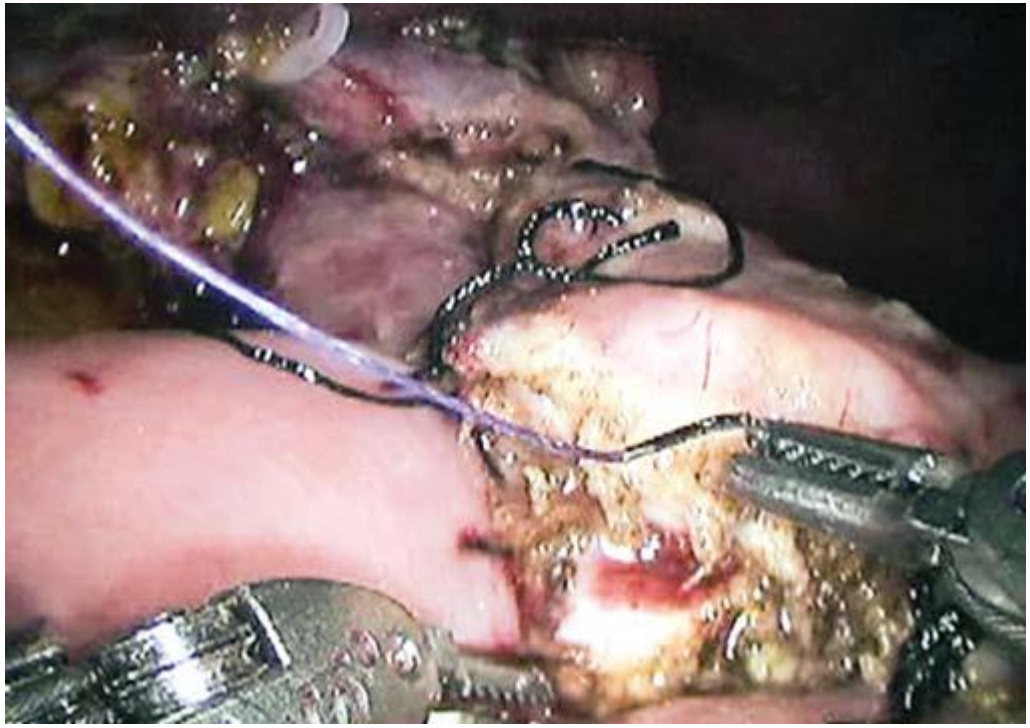
More “natural”:

- ✓ Three-dimensional vision
- ✓ Enhanced dexterity through articulated instruments

Advantages of the robot

More “natural”:

- ✓ Three-dimensional vision
- ✓ Enhanced dexterity through articulated instruments
- ✓ Higher magnification of the surgery site
- ✓ Arms that provide fixed traction and exposure



Do minimal access and robotic surgery bring benefit to neuroendocrine tumours?

- Adrenalectomy √
- Appendectomy √
- Colon √
- Pancreas √
- Small bowel X

Some truths over all the truths

1. MIS approach requires specific experience on different organs and diseases
2. NENs require both single expertise and a MDT before any surgical skill
3. The surgeon must offer the “right” operation whichever the approach