How to optimize the sequence of multidisciplinary treatment in patients with non resectable liver metastases and pancreatic neuroendocrine primary

Surgical options and timing in advanced disease

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Disclosure

I have no conflicts of interest to declare

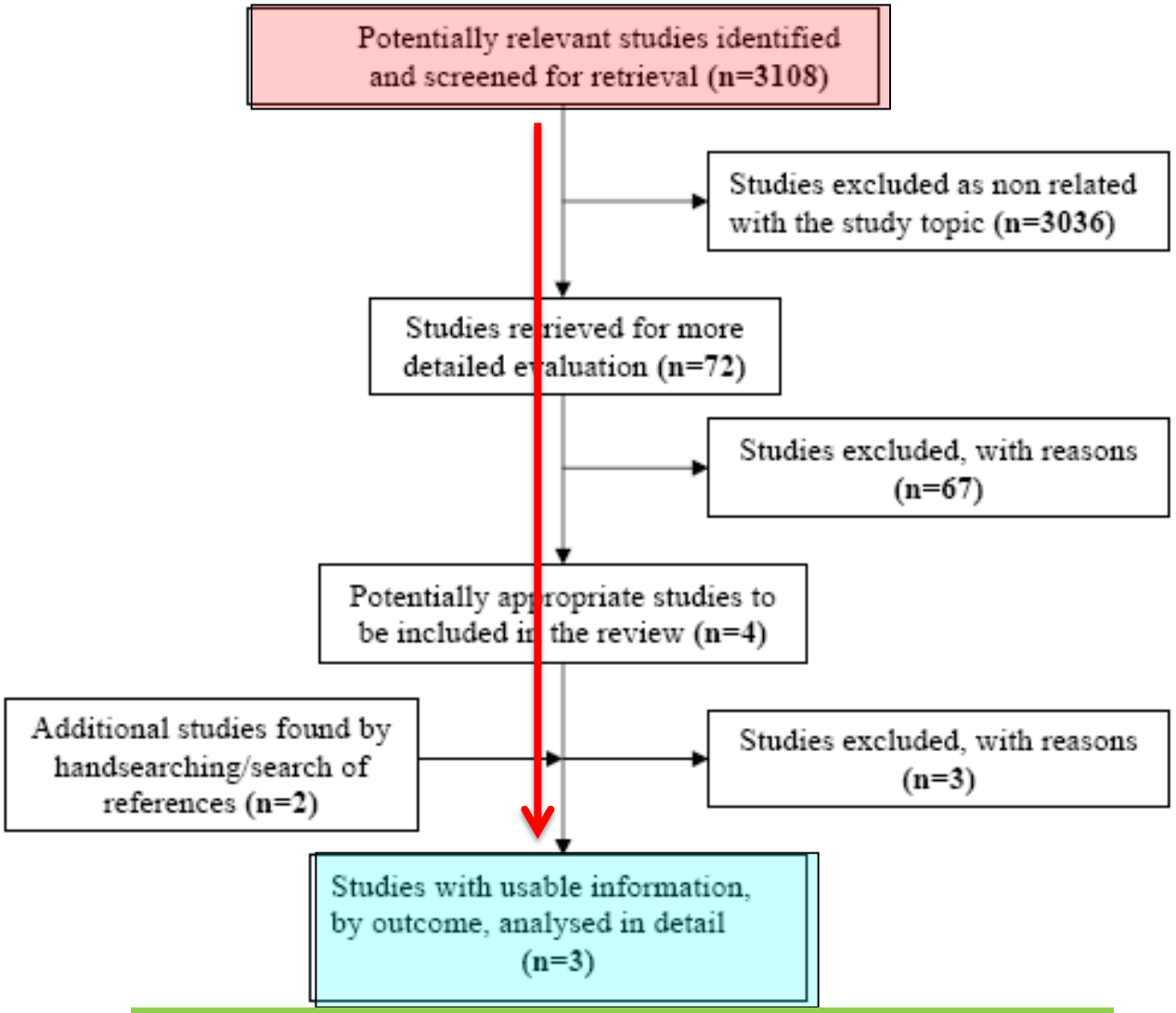
M Falconi

The figures of panNETS at diagnosis

- ✓ 100 patients with panNETs
- ✓ 40 patients with liver mets
  - ✓ 4 (10%)patients will be radically resected on both sites
  - ✓ 36 patients with unresectable liver mets
    - ✓ **12 with resectable primary**

Falconi M. Data on file

Systematic review



Capurso G, et al. Neuroendocrinology 2011;93(4):223-9

Overall survival

	Overall Survival median; months	***P***
Bettini		
Resected	**54.3 (95%CI 25-86)**	**0.74**
Unresected	**39.5 (95%CI 5.4-73.6)**	
Nguyen		
Resected (5 yrs surv)	**60%**	**0.025**
Unresected (5 yrs surv)	**30%**	
Solorzano		
Resected	**36 (95%CI 26.4-96)**	**0.06**
Unresected	**21.6 (95%CI 16.8-32.4)**	

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PFS

	PFS median; months	*P*
Bettini		
Resected	7.6 (95%CI 0.5-14.7)	0.9
Unresected	12 (95%CI 3.7-20.3)	

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An inconclusive conclusion!

Available data suggest a possible benefit of resection of the primary lesion only in this setting. However, a bias towards a more aggressive surgical approach in patients with a better performance status or less advanced disease seems likely, and **no conclusion can be drawn except for the need of randomised trials**.

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From EBM point of view …

However in the daily practice …

Does it make any sense to resect the primary despite unresectable liver mets?

Rational theoretical advantages

- ✓ “Regionalize” the disease
- ✓ “Open” to ablative therapies (i.e. TAE; RFTA)
- ✓ Increase the response to further therapies
- ✓ Increase PFS and OS

I have to confess that …

From **now** we are moving throughout

- ✓ low evidences
- ✓ many hypotheses
- ✓ personal experiences

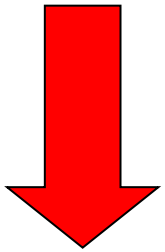
looking at

No resection | resection

To “regionalize” the disease: nice word

Stage the disease

(MDCT/MRI and Octreoscan/68Ga PET)



If extra abdominal disease

stop your hands!

10-15% of the patients have extrabdominal disease

In the oncological world biology is the king

Resection vs. biology

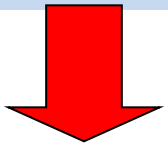
	Overall survival median; months	p
Bettini		
PDEC and Ki67 ≥ 10%	**11.8** (95%CI 0.0-24.5)	**0.0005**
WDEC and Ki67 < 10%	**57.8** (95%CI 36.1-79.5)	

Bettini R, et al. Dig Liver Dis 2009 Jan;41(1):49-55

A second practical advice

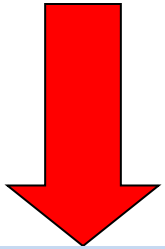
Stage the disease

(MDCT/MRI and Octreoscan/68Ga PET)



If only liver mets and primary is resectable

TAKE A BIOPSY!



If Ki67% >20% (> 10%?)

stop your hands!

The story is not finished yet

Stage the disease

(MDCT/MRI and Octreoscan/68Ga PET)

If only liver mets and the primary is resectable take a biopsy

?

If Ki67% >20% (> 10%?)

stop your hands!

If Ki67% < 20% (> 10%?)

A further step toward the decision

Stage the disease

(MDCT/MRI and Octreoscan/68Ga PET)

If only liver mets and the primary is resectable take a biopsy

If Ki67% >20% (> 10%?)

stop your hands!

If Ki67% < 20% (> 10%?)

Consider the site of the lesion!

It is not by chance that …

More LPs than PDs

	Bettini		Solorzano	
	Resected n=19	**Unresected n=32**	**Resected n=16**	**Unresected n=80**
Age (median)	51	Median 57	-	-
Sex (M%)	52%	43%	-	-
Site= Head	**5 (26%)**	14 (43%)	**4 (25%)**	-
Site= Body-tail	**14 (74%)**	18 (56%)	**12 (75%)**	-

Capurso G, et al. Neuroendocrinology 2011;93(4):223-9

One reason: surgery can differently hurt!

Palliative resection		
	Morbidity	Mortality
Solorzano, et al	n.a.	n.a.
Nguyen, et al	27%	2 pts (?)
Bettini, et al	42.1%	0%

Complication rate > after PD than LP

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A possible additional warning

Bilio-digestive anastomosis as after PD contraindicates:

- ✓ TACE or HAE*
- ✓ RFTA*

Risk of fatal septic complications

Abcess – cholangitis (vascular)

***De Baer, Radiology 1996; Curley, Ann Surg 2004; Kianmanesh, Ann Surg 2008**

This opens to an additional question

Which is the right timing?

? → **Palliative resection** → **?**

? means SST, PRRT, Chemo; everolimus, sunitinib, etc.

Palliative resection & timing (I)

PRRT: the lesser the burden the better the response

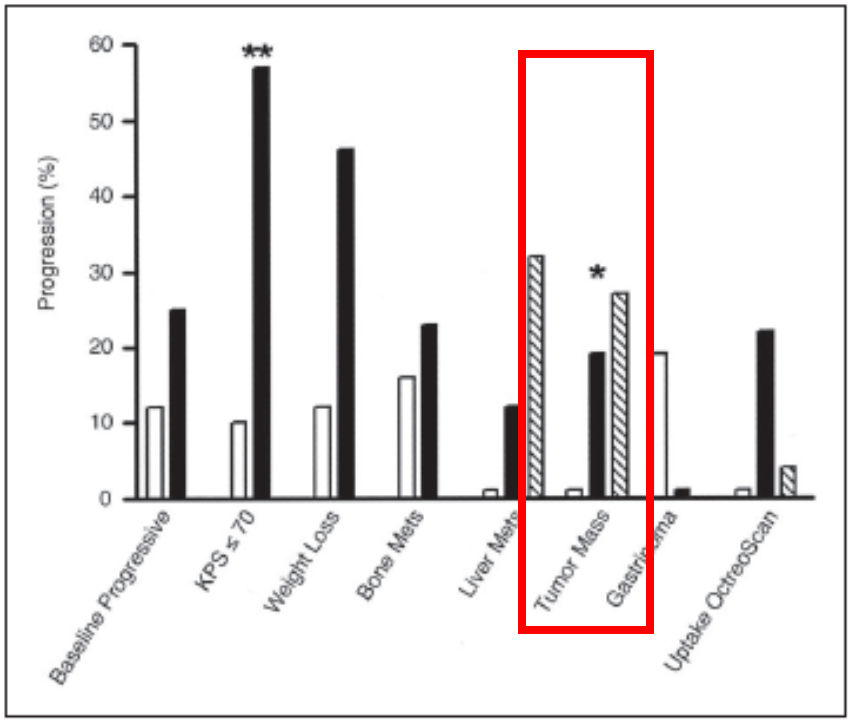

Fig 6. Analysis of factors that may predict tumor progression (progressive disease). (*) $P < .05$; (**) $P < .01$, logistic regression. KPS, Karnofsky performance score.

Kwekkeboom DJ, et al. J Clin Oncol 2005; 23:2754-62.

Favoring such a sequence

Palliative resection

+

HAE ± RFTA

PRRT

Palliative resection & sequence (II)

Risk factors for disease progression after PRRT during follow-up at multivariate analysis (n= 69 pts)

Variable	Hazard Ratio	95% CI	P
WHO 2010 (NET G2 vs NET G1)	3.48	1.51-7.83	0.003
Previous TACE	3.53	1.51-8.18	0.003
PR 6 months after PRRT (no vs yes)	6.63	2.18-20.16	0.001

After TACE radionucleotides do not get the target!

Campana D, et al. to be submitted

How putting together all these informations?

Stage the disease

(MDCT/MRI and Octreoscan/68Ga PET)

If extra abdominal disease

stop your hands!

If only liver mets and the primary is resectable take a biopsy

If Ki 67% >20% (> 10%?)

stop your hands!

If Ki 67% <20% (> 10%?)

If head location

Reconsider resection after PRRT

This opens to an additional question

Which is the right timing in body-tail locations?

Palliative resection* → **PRRT** → **TACE**

* Providing a low morbidity and nil mortality rates

Conclusions (I)

- ✓ EBM does not unequivocally support palliative resection of the primary tumor in case of unresectable liver mets for panNETs
- ✓ The contraindications are quite clear

Contraindications

- ✓ Extraepatic disease
- ✓ Ki67 > 20% (> 10%?)
- ✓ PD if ablative therapies are planned

Conclusions (II)

- ✓ EBM does not unequivocally support palliative resection of the primary tumor in case of unresectable liver mets for panNETs
- ✓ The contraindications are quite clear
- ✓ If feasible an upfront LP might favor further therapeutic options

Even if the better response should be a RCT

	5-yrs survival	Δ%	Patients for arm	α -error	B-error
Hypothesis 1					
No resected	20%	30	50	0.10	0.05
Resected	50%				
Hypothesis 1					
No resected	25%	20	118	0.10	0.05
Resected	45%				

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