PET/CT
in GI Tract cancer

Esophageal Cancer (EC)
Colorectal Cancer (CRC)

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Outline of this talk

Additional value of whole-body FDG-PET and PET/CT in

- Pre-surgical TNM staging of primary disease (EC- CRC)
- Detection of (early) recurrence (CRC - EC)
  - What is still operable?
- Treatment response assessment (EC – CRC)

TNM staging of primary disease

T- staging of primary disease

Pre-surgical staging of primary disease
T-status

- Detection rate for GI carcinoma's is high
  - FDG uptake is related to
    - cellularity/gram tissue
    - GLUT-1 expression (hypoxia and proliferation)
    - Higher uptake in SSC compared to adenocarcinoma (EC°
  - False negatives occur in
    - small volume disease
    - Flat mucosal lesions
    - mucinous carcinoma's (signet cell carcinomas)

- No additional value of PET with current definitions (~ depth of invasion) because of insufficient anatomical resolution

N- staging of primary disease

Pre-surgical staging of primary disease
N-status

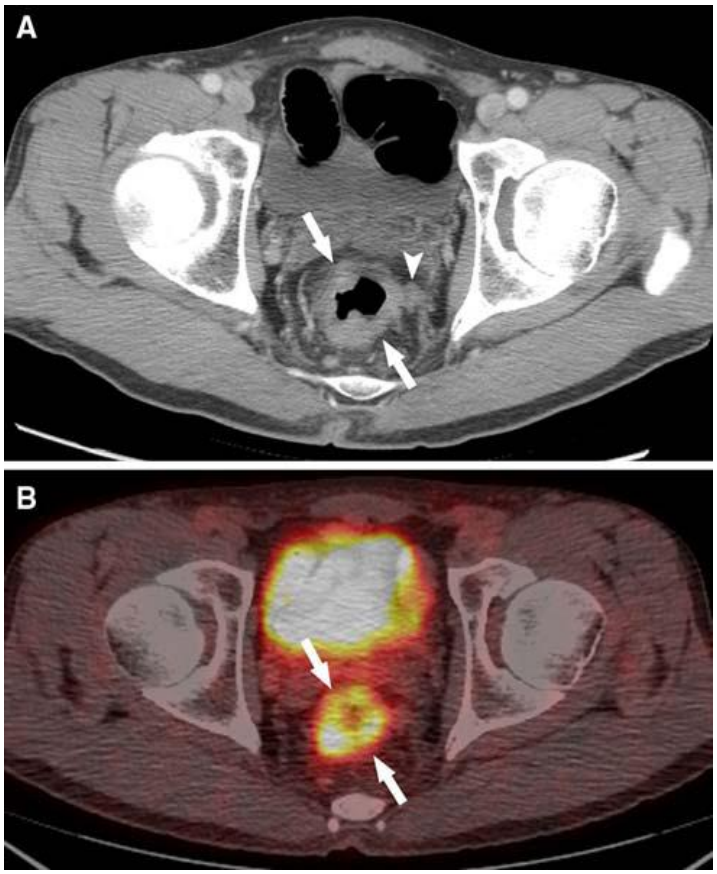
- CT = size-based
  - low sensitivity ~ 45-60%, higher with MDCT
  - micrometastasis in normal sized nodes is frequent

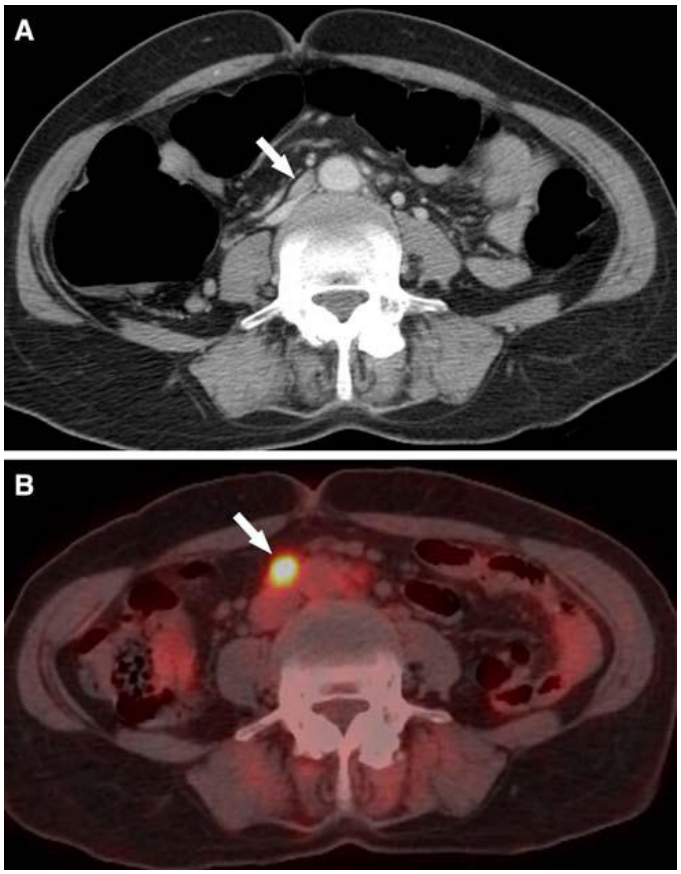
- EUS= size, shape and echogenicity
  - sens 65-95%
  - FNAC

- PET or PET/CT
  - few studies in CRC
  - extensively studied in EC

CRC – LN staging

S. S. Shin et al.: Preoperative staging of colorectal cancer; Abdom Imaging (2008) 33:270–277





Sensitivity 29 – 43%

Specificity 83 – 96%

EC - Nodal staging of primary disease

Flamen et al. JCO 2000 N=74

	CT + EUS	PET	p-value
Sensitivity			
N_{1-2}	15/18 (83%)	4/18 (22%)	p=0.002
M_{+Ly}	6/13 (46%)	10/13 (77%)	NS
Specificity			
N_{1-2}	5/11 (45%)	10/11 (91%)	NS (p=0.07)
M_{+Ly}	20/29 (69%)	26/29 (90%)	p=0.04
Accuracy			
N_{1-2}	20/29 (69%)	14/29 (48%)	NS (p=0.07)
M_{+Ly}	26/42 (62%)	36/42 (86%)	p=0.009

EC - Nodal staging of primary disease

- Meta-analysis van Westreenen JCO 2004
  - 421 patients
  - pooled sensitivity 51% (95% CI 34-69)
  - pooled specificity 84 % (95% CI 76-91)

- PET-CT superior?

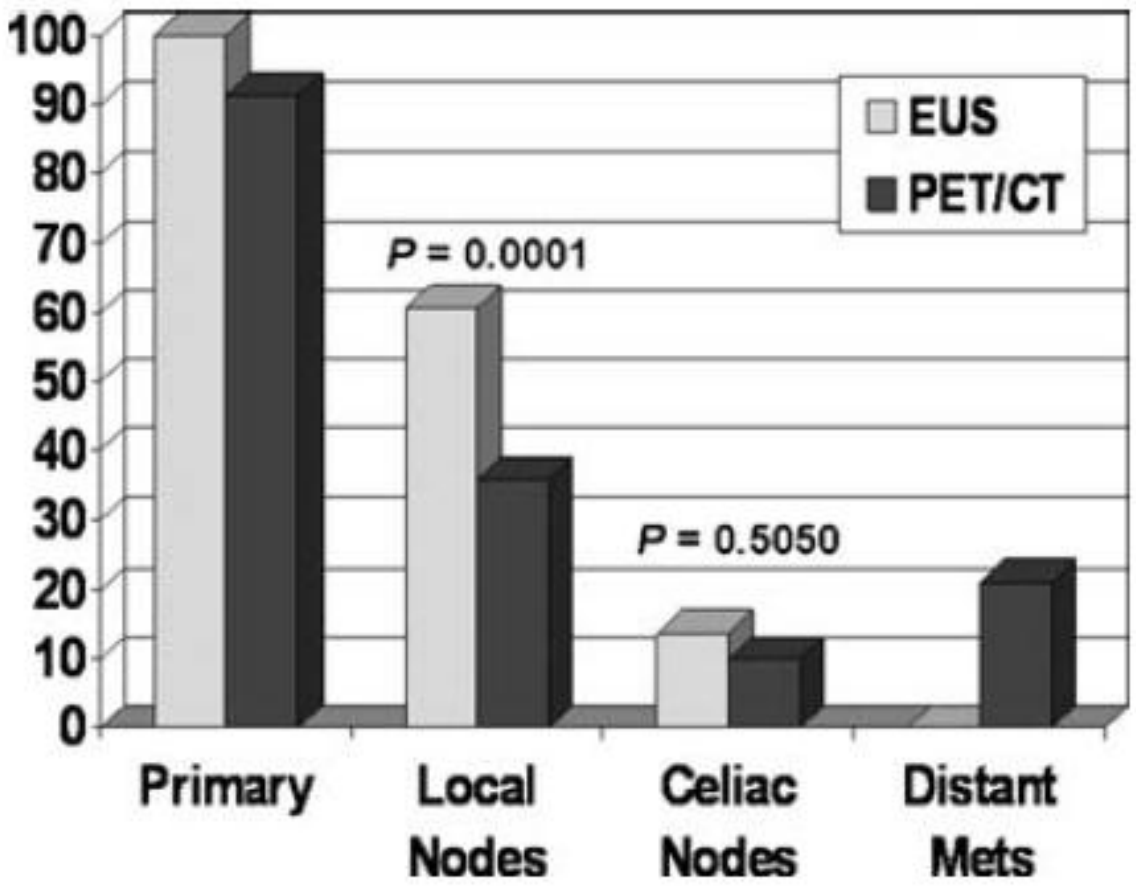
  Walker et al, Mol Imaging Biol 2010

  81 patients, PET/CT and EUS prior to surgery

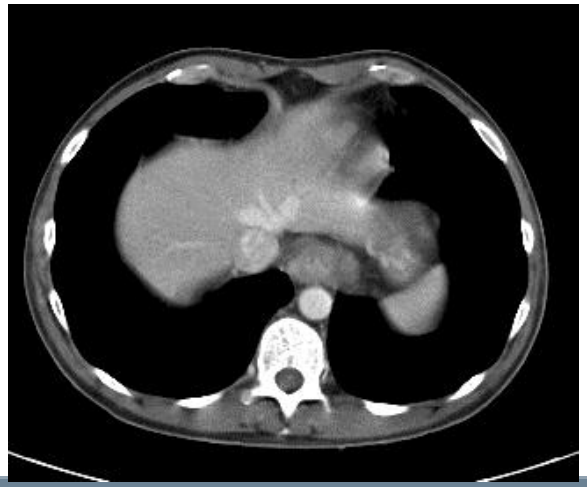
EC - Nodal staging of primary disease

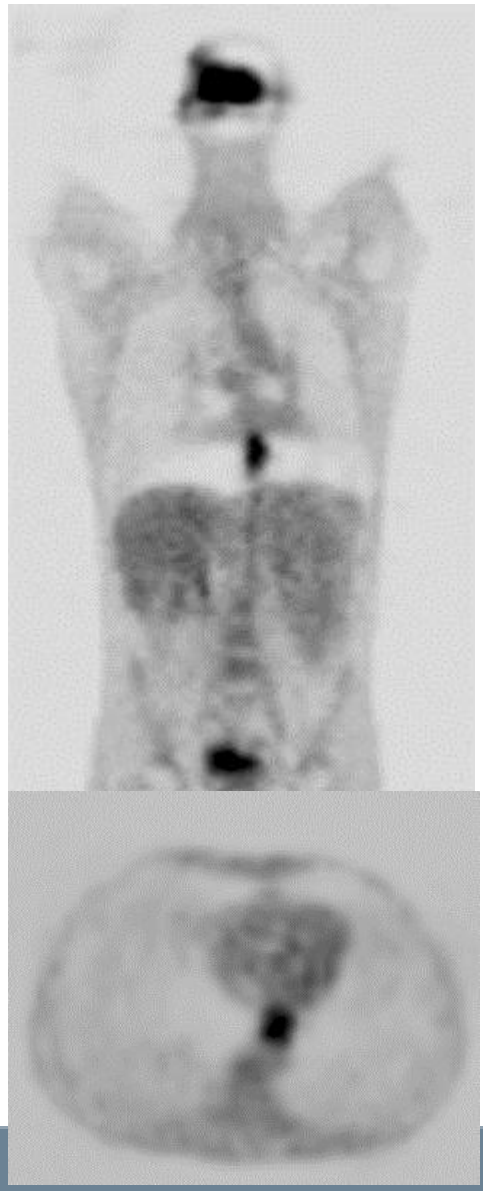
- Walker et al, Mol Imaging Biol 2010

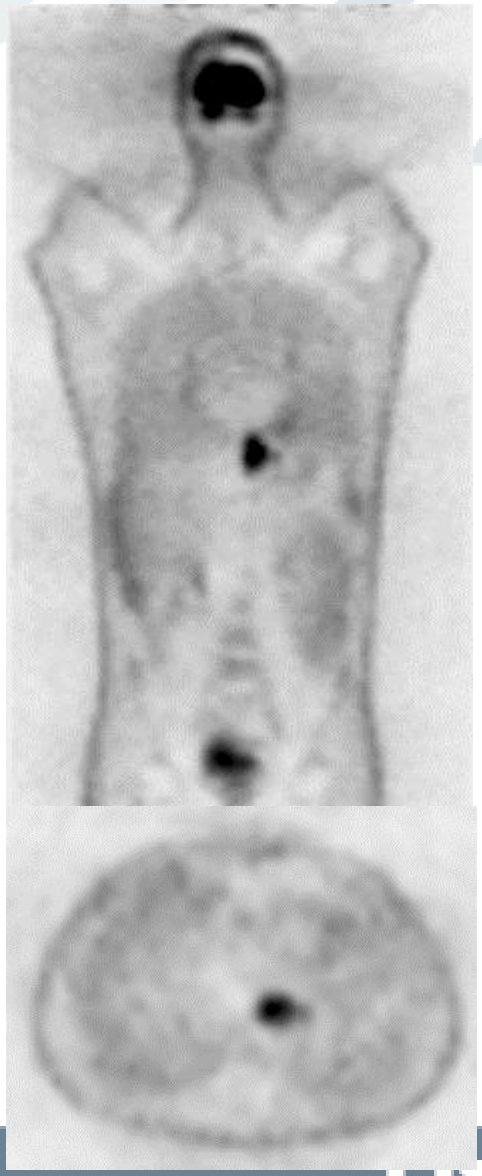
  81 patients, PET/CT and EUS prior to surgery



PET/CT pitfalls







M- staging of primary disease

EC – detection of metastasis (nodes + organs)

Plukker, van Westreenen Best practice and research in clin GE 2006

Table 4. Performance of positron emission tomography (PET) and computed tomography (CT) in the preoperative assessment of distant metastases (stage IV).

Author	PET			CT		
	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Flanagan et al[23]	72	82	76	71	100	94
Kole et al[20]	67	95	88	100	90	92
Luketich et al[65]	69	93	84	46	74	63
Kato et al[63]	32	99	93	23	97	91
Flamen et al[18]	74	90	82	41	94	71
Räsänen et al[62]	47	89	74	33	96	74
Kneist et al[66]	35	87	50	67	13	50

PET Additional metastases in 4-28% of patients (cervical nodes; bones; liver)
CT better for lung and brainM+
Meta-analysis van Weestrenen (2004) pooled sens= 67%, spec 97%

EC – detection of metastasis (nodes + organs)

Is the superiority of PET also true in the PET/CT and MDCT era?

Gilles et al, European Radiology online september 2010

Retrospective analysis on value in 200 consecutive cases

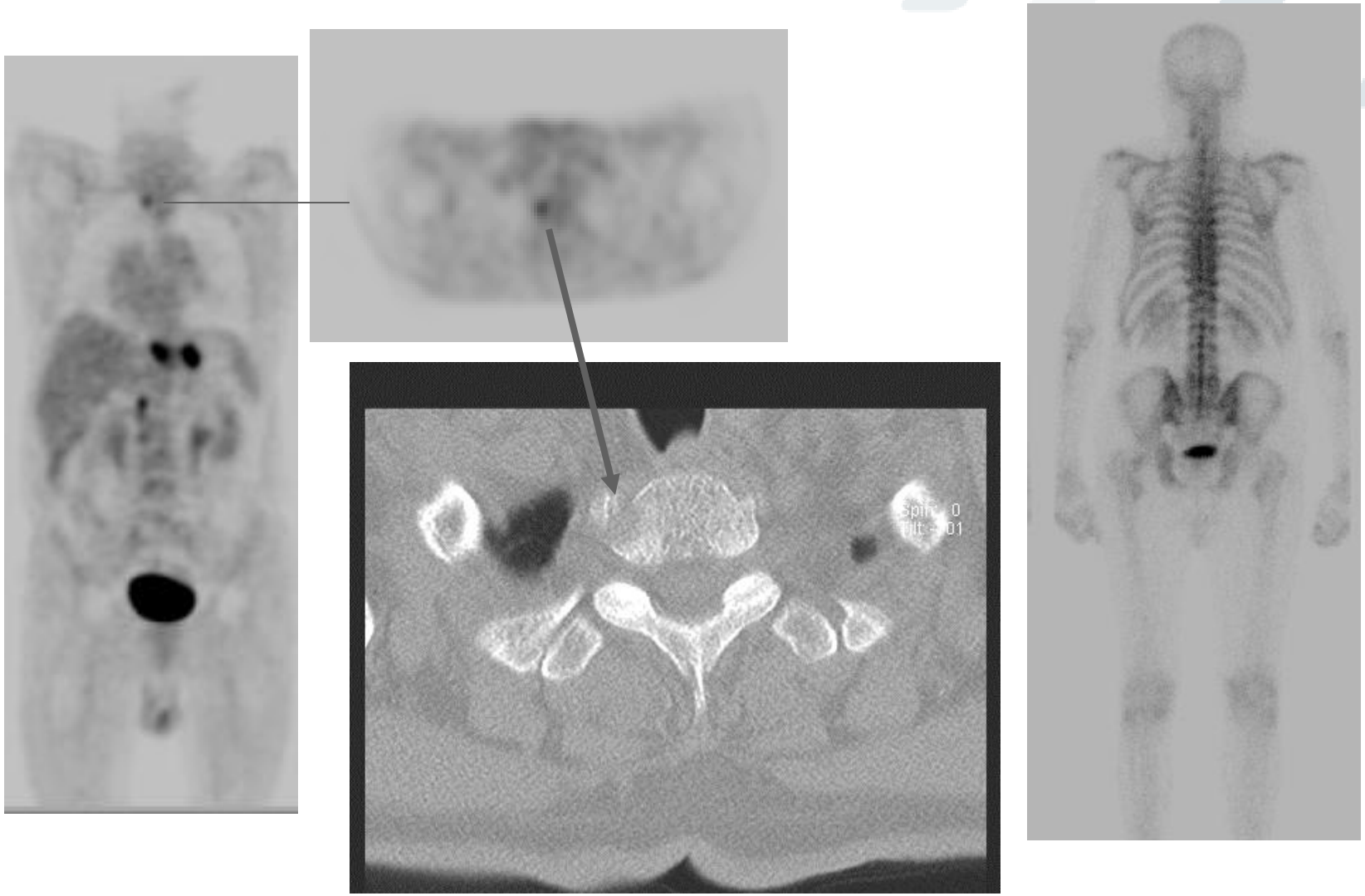
MDCT (16 -128 slice) and PET-CT (16 slice) in preoperative staging

- 50/200 pts had metastatic disease and PET+
  - 22/50 negative on MDCT
  - 28/50 equivocal on MDCT

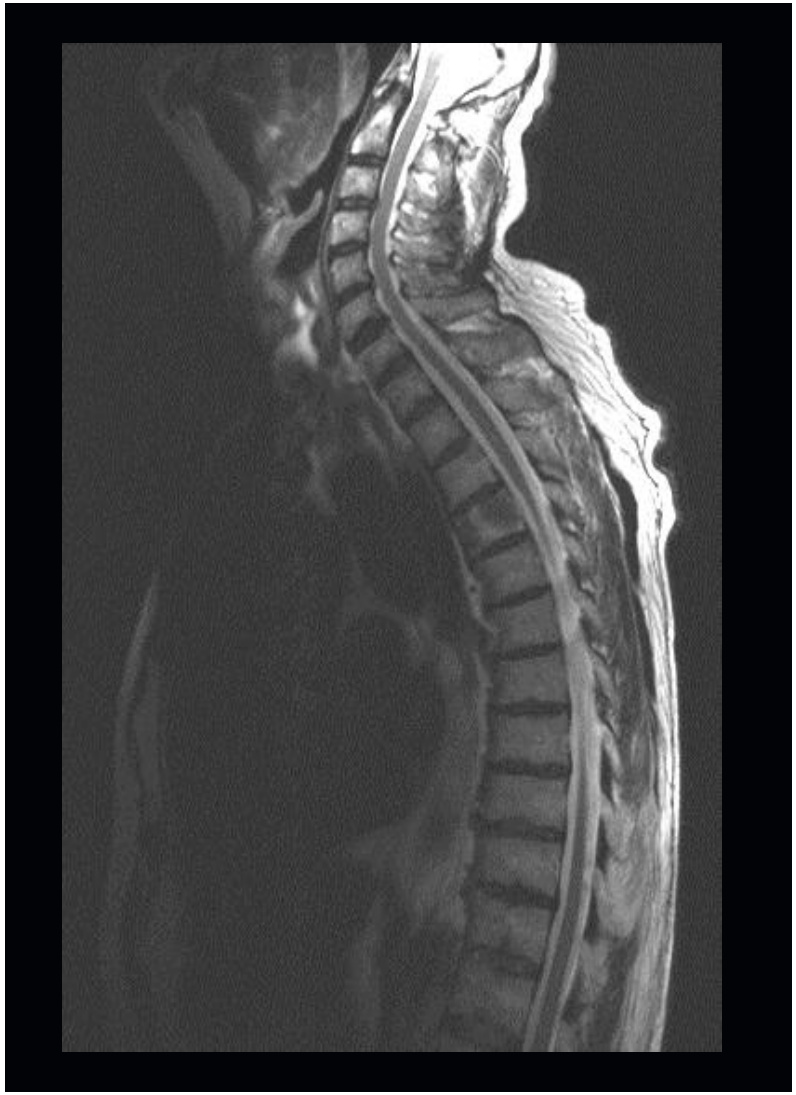
Table 2 Location of metastatic disease detected by PET/CT

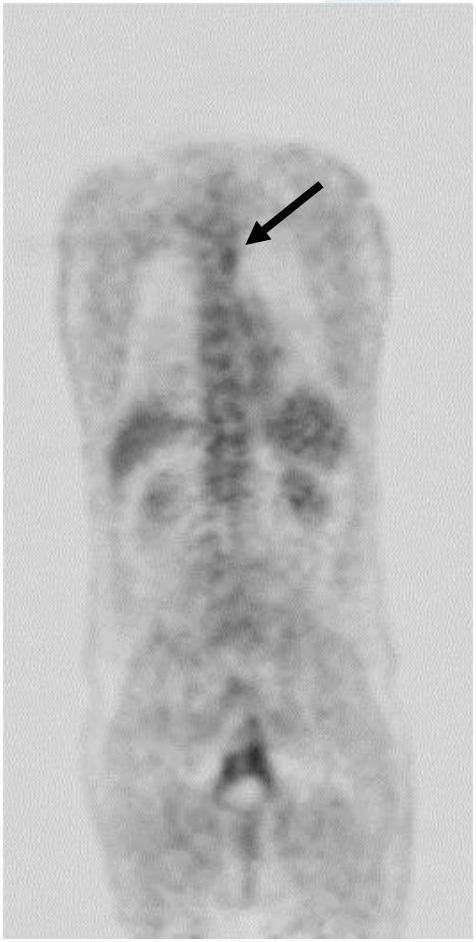
Location of metastatic disease	Number
Distant nodal	36[a]
Neck	27
Retroperitoneum	13
Axilla	4
Systemic	23[b]
Liver	11
Bone	9
Lung/pleura	2
Muscle	1
Parotid	1

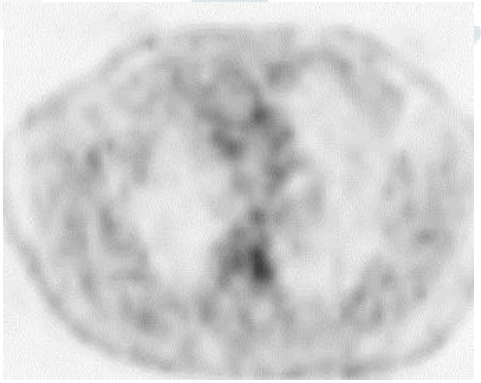
PET/CT in EC- Staging



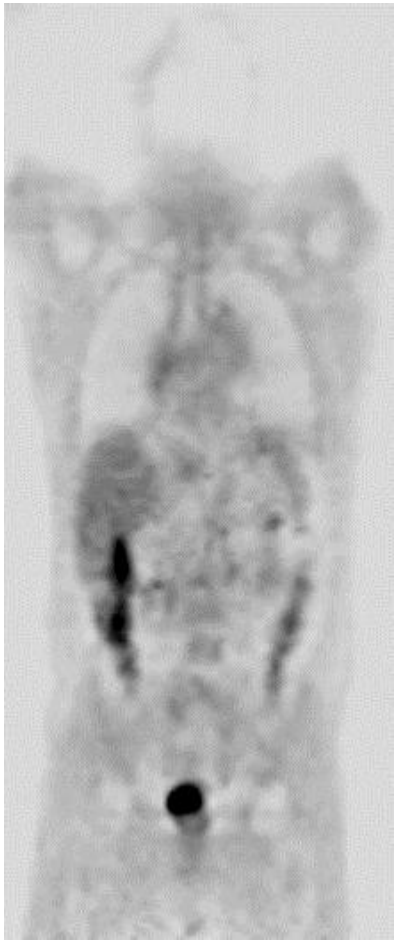
PET/CT in EC - Staging

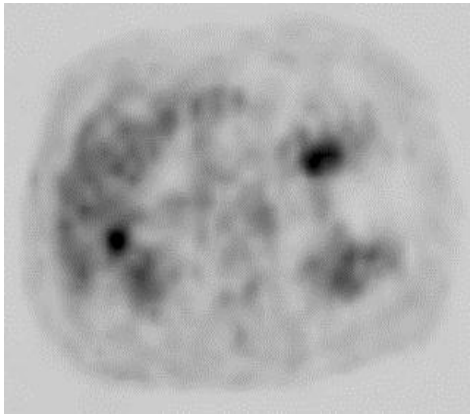


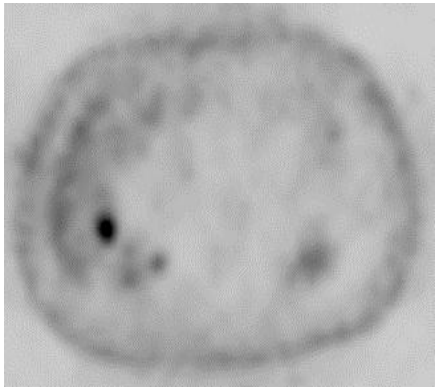


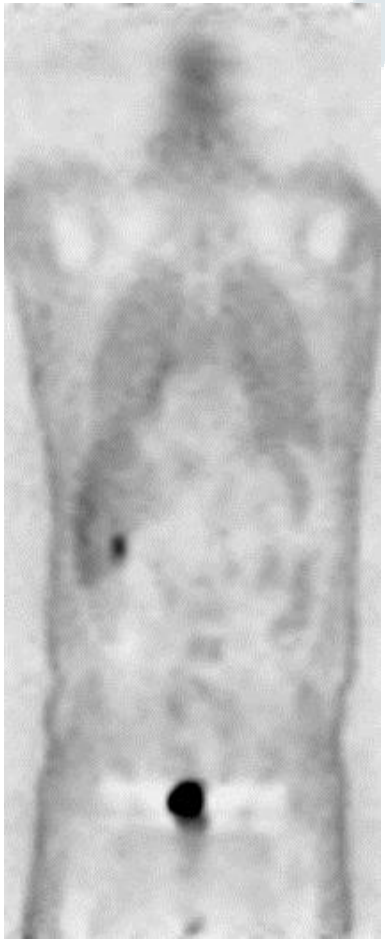


CT attenuation artifacts









EC –Effect of PET on final stage

Table 2 FDG-PET in the pretherapeutic staging of esophageal cancer. Change of stage by FDG-PET after conventional staging by CT scan

Authors	Year	Change UICC stage	% change UICC stage
Flanagan *et al.*	1997	5/36	14
Rankin *et al.*	1998	7/25	28
Luketich *et al.*	1999	21/91	23
Flamen *et al.*	2000	16/74	22
Heeren *et al.*	2004	19/74	26
Kato *et al.*	2005	20/149	13
Stahl *et al.*	2005	6/40	15
		94/489	**19.2%**

Ott el al. Review. Diseases of the Esophagus 2006

PET for M-staging in CRC

- Few studies
- Llamas et al, EJNMM 2007
  - Prospective study in 104 patients with potentially operable CRC
  - PET (Ecat Exact) and CT (single slice, 7 mm, slices)

Table 3 Diagnostic accuracy in M0/M+ staging

	FDG-PET	CT
Sensitivity	89% [64–98%]	44% [22–69%]
Specificity	93% [85–97%]	95% [88–98%]
Overall accuracy	92% [85–96%]	87% [78–92%]
PPV	73% [50–88%]	67% [35–89%]
NPV	98% [91–100%]	89% [80–94%]

Confidence interval [CI]: 95%

  - 14 patients were upstaged to stage IV (liver M+, lung M, RP LN)
  - Change in patient management in 18%

PET for M-staging in CRC

Floriani et al, meta-analysis of imaging modalities for liver M+ for CRC
J . of Magnetic Resonance Imaging 2010 (Studies between 2000-2008)

US		CT		MRI		FDG-PET	
sens	spec	sens	spec	sens	spec	sens	spec
86,3	-	82,6	58,6	86,3	87,2	86	97,2

Spiral CT most sensitive technique for detection of lungM+

→ Use of PET for initial staging CRC is limited
Equivocal cases,
operabel M+ disease prior to neoadjuvant Chemo

PET/CT for staging primary disease

- EC
  - detection of LN distant from the tumor and organ metastasis
  - PET/CT routine use in T1b tumors without obvious M+

- CRC
  - no routine indication
  - characterization of equivocal lesions
  - operable M+ prior to CTx to exclude more extended disease

Detection of recurrence

CRC - recurrences

- More treatment options to salvage local relapse or recurrences limited to the liver
  - early detection of relapse to increase cure rates
    sometimes difficult on CT due to treatment-induced anatomical alterations
  - exclusions of other metastases

CRC –recurrences

Huebner et al, JNM 2000 Meta-analysis (11 studies)

	N	sens	spec
Whole Body	**281**	**97%**	**76%**
Pelvis	**366**	**94%**	**98%**
Liver			
Patients	**393**	**96%**	**99%**
Lesions	**182**	**91%**	**97%**

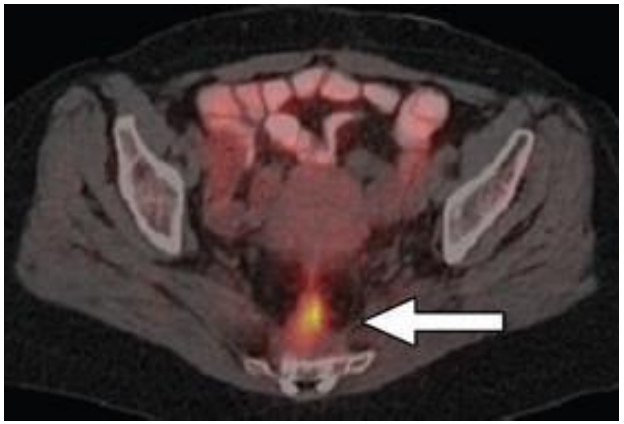
29% change in treatment management

CRC –recurrences

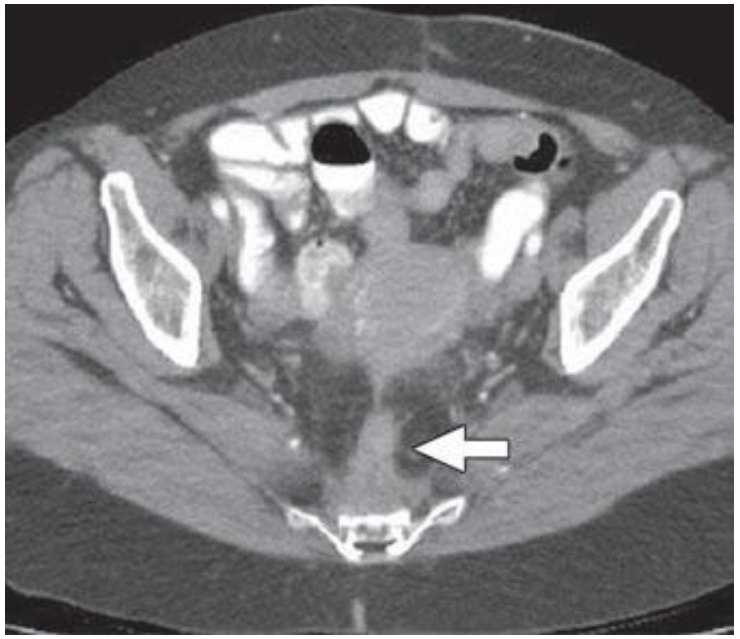
Zhang et al et al, Int. J Cancer, 2009 Meta-analysis (27 studies, 1995-2008))

	sens	spec
Distant M+	91%	83%
LiverM+	97%	98%
Pelvic rec	94%	94%

CRC Local recurrence



1 month later
APO +

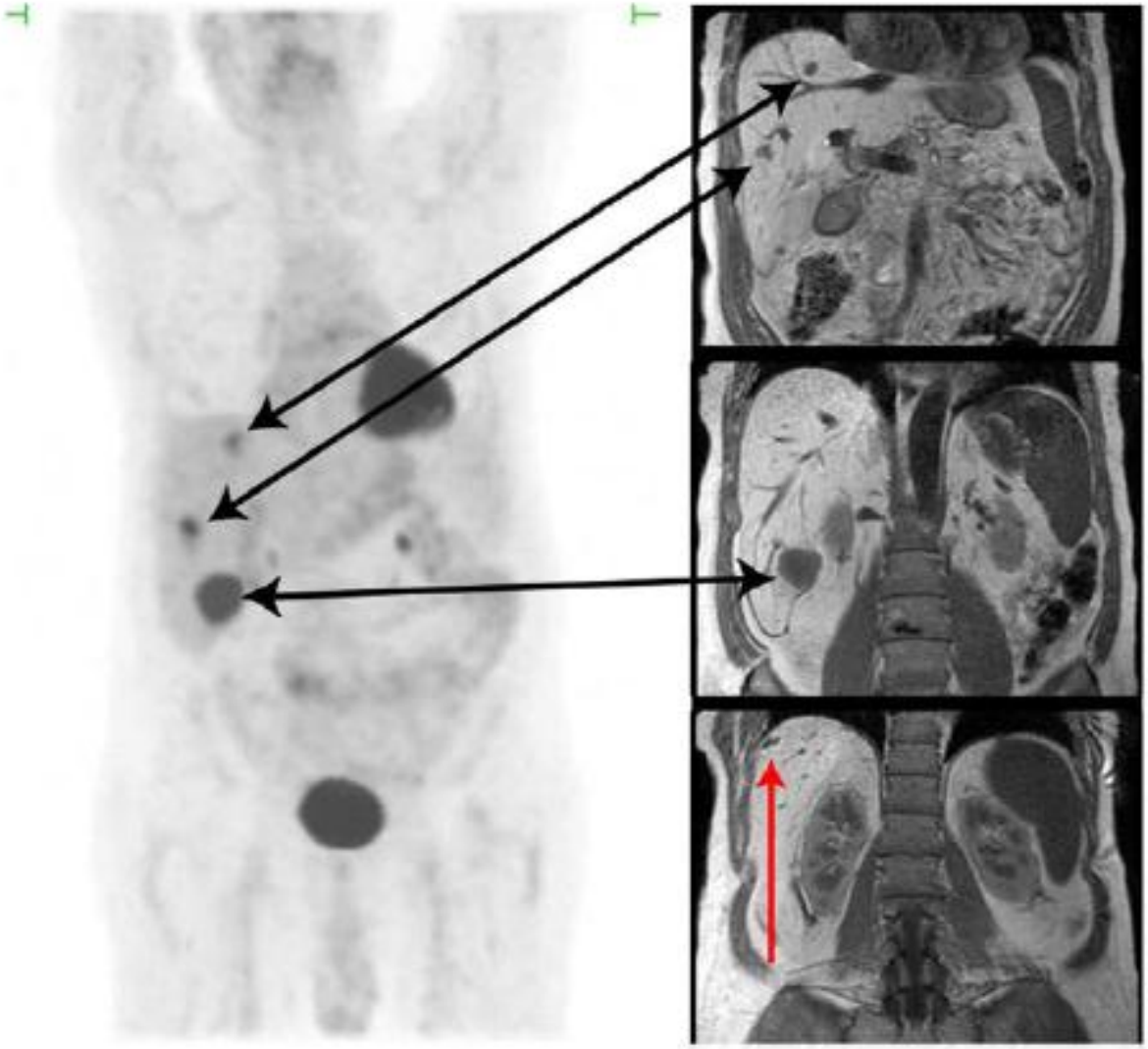


CRC – recurrences

Wiering et al, cancer 2005; meta-analysis focusing on liver recurrences

TABLE 4
Sensitivity and Specificity by Diagnostic Modality for the Six Studies with the Highest Scores

	FDG-PET hepatic lesions		FDG-PET extrahepatic lesions		CT hepatic lesions		CT extrahepatic lesions	
Study	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specifici
Lai et al., 1996[32]	0.93	0.44	0.92	0.95	1.00	0.14	—	—
Fong et al., 1999[26]	0.71	0.93	0.85	0.91	0.88	1.00	0.30	0.81
Valk et al., 1999[44]	0.95	1.00	0.92	0.99	0.84	0.95	0.61	0.96
Imdahl et al., 2000[29]	0.84	0.86	—	—	0.86	0.88	—	—
Ruers et al., 2002[37]	0.65	—	0.95	0.97	0.80	—	0.65	0.94
Langenhoff et al., 2002[33]	1.00	0.98	—	—	—	—	—	—
Combined studies	0.80	0.92	0.91	0.98	0.86	0.88	0.55	0.96
All studies (n=32)	**0.88**	**0.96**	**0.92**	**0.97**	**0.82**	**0.84**	**0.61**	**0.91**

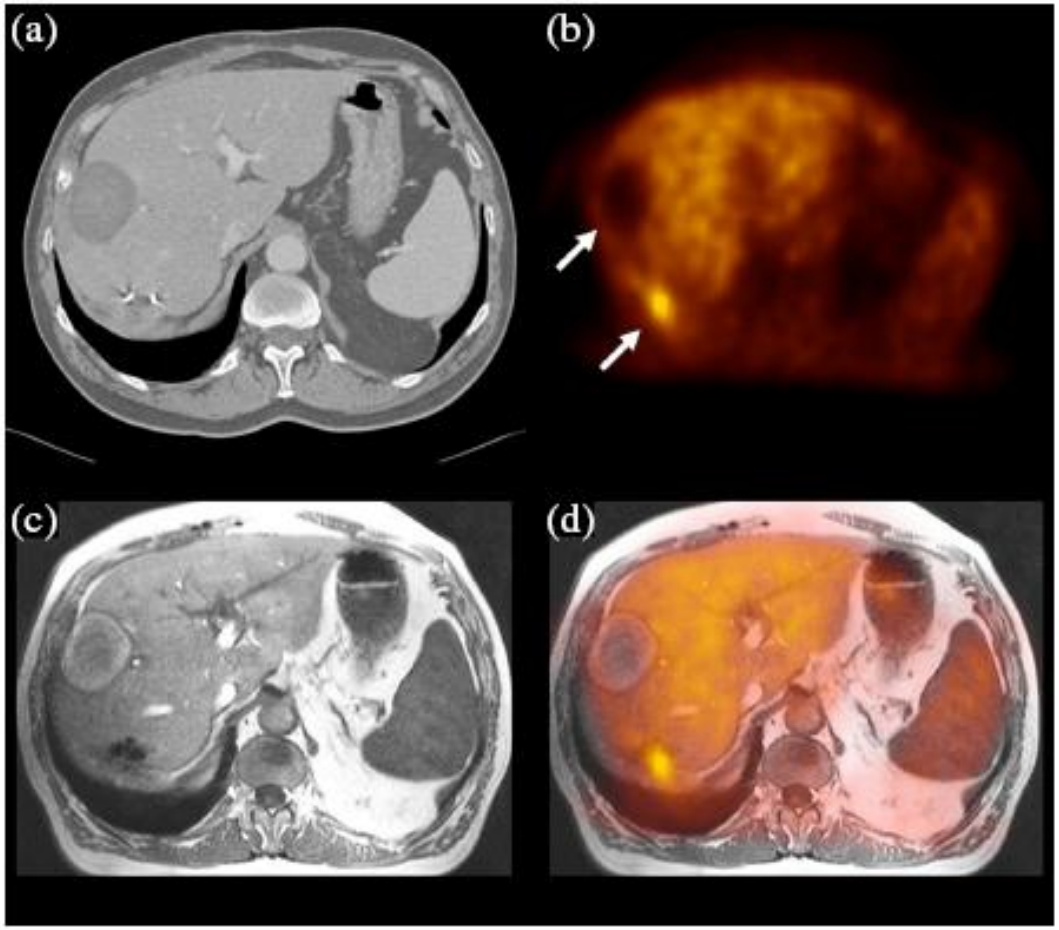


CRC – Liver M

Spatz et al, Int J Colorectal Dis 2010
Retrospective analysis in 34 ptn with liverM+ of CRC scheduled for surgery
Correlation of imaging with hostopatholgy
Imaging: 16 slice MDCT or 1.5 T MR ; 16 slice PET/CT and IUS

	Chemotherapy + (n=17)	Chemotherapy − (n=17)
Number of metastasis found (histopathology)	37	25
Mean diameter	3 cm	3.2 cm
PET		
sensitivity	0.63 (0.45–0.78)	0.92 (0.72–0.99)
PPV	0.96 (0.76–0.99)	1 (0.82–1)
CT/MRI		
Sensitivity	0.65 (0.48–0.80)	0.64 (0.43–0.81)
PPV	0.92 (0.72–0.99)	0.89 (0.64–0.98)
IUS		
Sensitivity	0.94 (0.79–0.99)	1.0 (0.83–1.0)
PPV	0.94 (0.79–0.99)	0.96 (0.78–0.99)

CRC liver recurrences



Vogel et al, Cancer Imaging 2005

Patient with prior RFA (upper arrow) and liver resection for liver metastasis of colon carcinoma. Both CT (a) and MRI (c) are difficult to interpret
The PET image (b) clearly shows a recurrent liver metastasis (lower arrow), which could be localized only after image fusion with MRI (d). This permitted guided locoregional therapy

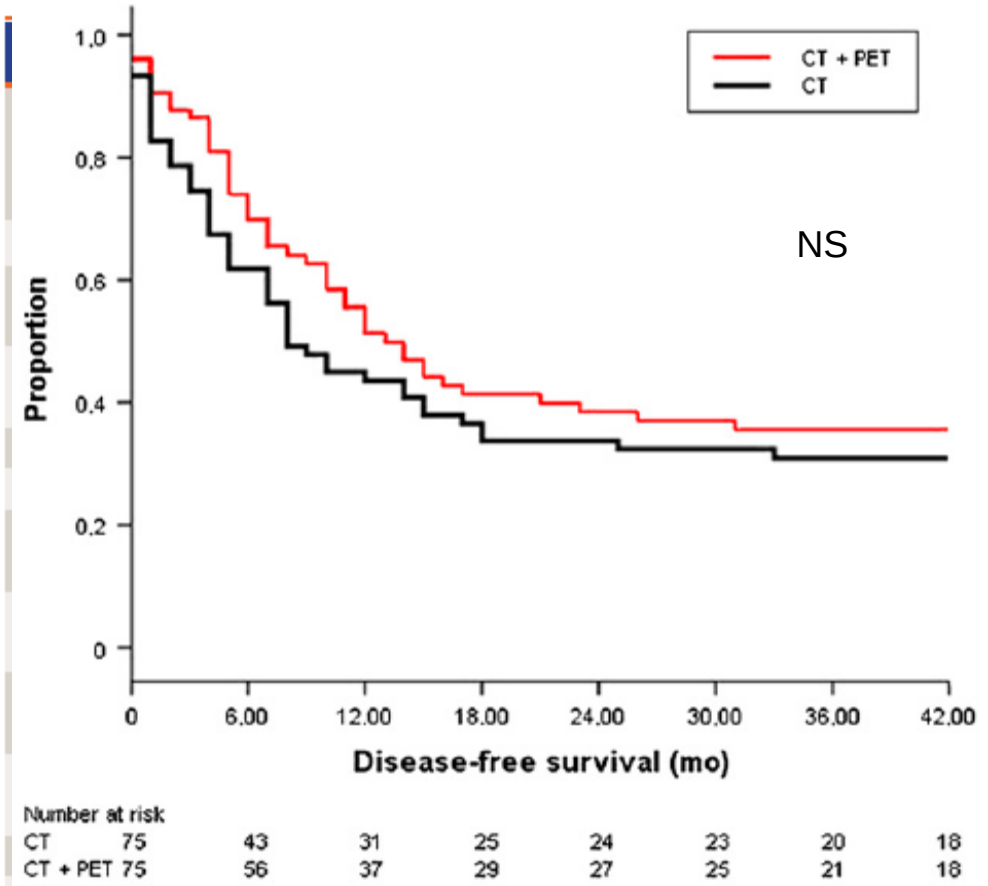
Improved Selection of Patients for Hepatic Surgery of Colorectal Liver Metastases with ^{18}F-FDG PET: A Randomized Study

JNM 2009

van der Sijp[2], Rudi M. Roumen[3], Koert P. de Jong[4],
[7], Paul F.M. Krabbe[8], and Wim J.G. Oyen[9]

TABLE 1. Demographic Data

Variable	Control arm (CT; n = 75)	Experimental arm (CT plus PET; n = 75)	P
Mean age (y)	62.9	62.6	0.94
Age range (y)	37.9–79.9	32.8–78.1	
Sex (female:male)	19:56	27:48	0.21
Primary tumor			0.87
pN0	34	32	
pN ≥ 1	41	43	
DFS			0.40
<12 mo	29	35	
≥12 mo	46	40	
Number of hepatic tumors*			1.0
1	41	42	
>1	34	33	
Size of greatest hepatic tumor*			0.84
<50 mm	60	58	
>50 mm	15	17	
CEA preoperatively			1.0
<200 ng/mL	75	75	
≥200 ng/mL	—	—	
Fong criteria			0.76
0	9	7	
1	17	24	
2	29	24	
3	19	19	
4	1	1	
5	—	—	



NS

CRC – elevated CEA

Metser et al, Nuc Med and Biology 2009
Retrospective analysis in 55 ptn with elevated CEA after surgery for CRC and underwent PET-CT and 64 slice MDCT. In 65% of the patients, malignancy was diagnosed.

TABLE 3: Results of Tumor Site–Based Analysis of Accuracy (*n* = 62)

	MDCT			
PET/CT	True-Positive	True-Negative	False-Positive	False-Negative
True-positive	36		0	17
True-negative		4	2	
False-positive		1	1	
False-negative				1

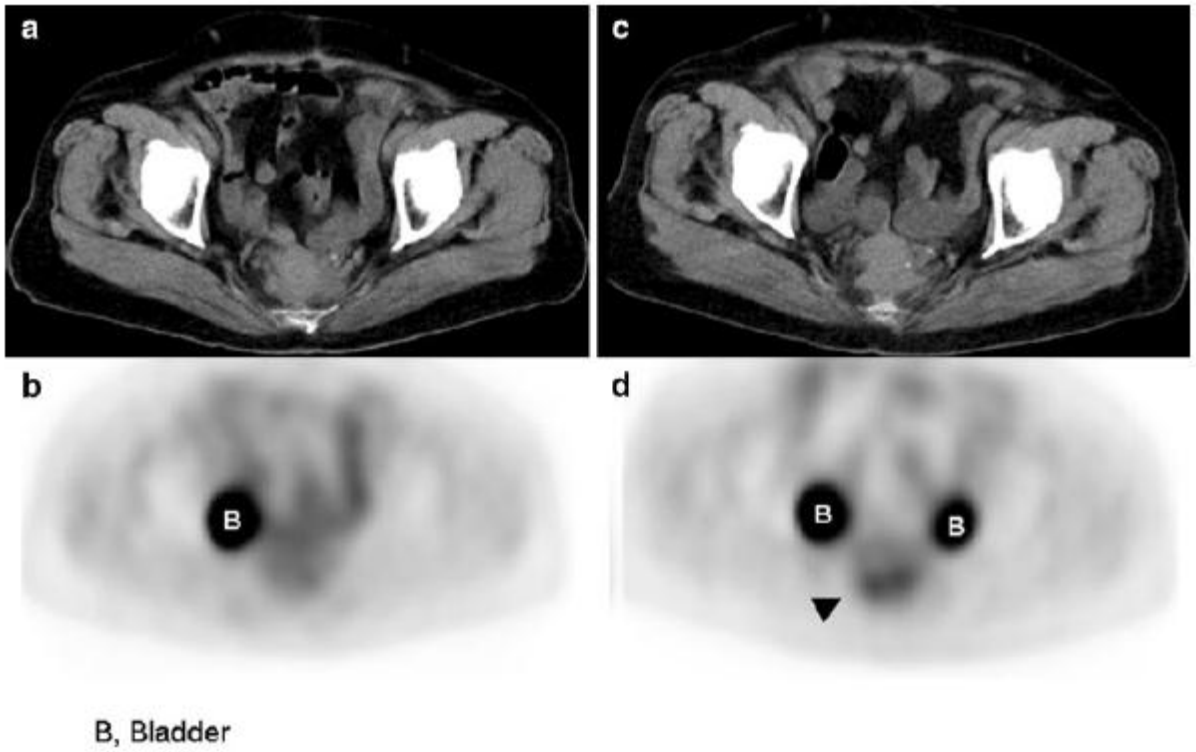
Note—Values are number of tumor sites.

	sens	spec
PET/CT	98%	75%
MDCT	67%	62%

presacral recurrence (*n = 5)*
LN < 1cm (*n = 4)*
peritoneal deposits (n = 3)
recurrences at RFA sites (*n = 3)*
abdominal wall (n = 2)

CRC – elevated CEA

Kyoto et al, Ann Nuc Med 2010
Retrospective analysis in 57 ptn with elevated CEA after surgery for CRC, 13 pts multiple scans



B, Bladder

CEA 7ng/ml

6 months later
CEA 14,2ng/ml

EC - Recurrences

- Few studies
- Guo et al. JNM 2007
  - Retrospective analysis of 56 patients who underwent PET/CT for suspicion of recurrence after curative therapy for Sq EC

TABLE 2
Diagnostic Value of PET/CT for Detecting Recurrent ESCC

Diagnostic value	Confirmed recurrent sites +	Confirmed recurrent sites −	Sensitivity (% [*n*])	Specificity (% [*n*])	Accuracy (% [*n*])
PET/CT locally*	32	12	96.9 (31/32)	50.0 (6/12)	84.1 (37/44)
PET/CT regionally	19	11	89.5 (17/19)	81.8 (9/11)	86.7 (26/30)
PET/CT distantly	21	14	90.5 (19/21)	92.9 (13/14)	91.4 (32/35)
PET/CT overall	72	37	93.1 (67/72)	75.7 (28/37)	87.2 (95/109)
Patient-based analysis	45	11	95.6 (43/45)	54.5 (6/11)	87.5 (49/56)

*Including primary tumor, esophagogastric anastomosis, gastric pull-up, and adjacent tissue to all above sites.

PET for detection of Recurrence

- CRC
  - High accuracy for local relapse
  - Similar accuracy than CT/MR for hepatic M+
  - CT better for lung and brain M+
  - PET/CT= best test to exclude other M+ prior to salvage R/
    - !!! Perform PET BEFORE the start of chemotherapy!!!

- EC
  - Few studies
  - EUS+FNAC for local relapses
  - PET-CT to exclude other M+

Therapy response assessment

EC – neoadjuvant setting

CRC – neoadjuvant setting
Local liver M+ therapy

Definition of PET response

- No guidelines for definition of PET response
- Different definitions/methodology
  - Standard of reference (path response vs survival)
  - Threshold vs Fractional change
  - Which PET parameter
    - SUV of MRglu
    - Mean or max values
    - Definition of overall response
- Optimal Timing
  - Early vs Late
  - Effect of concommittant RT

Esophageal Cancer

Flamen et al, Annals of Oncology 2002

Design

36 patients: cT_4 EC without organ metastases

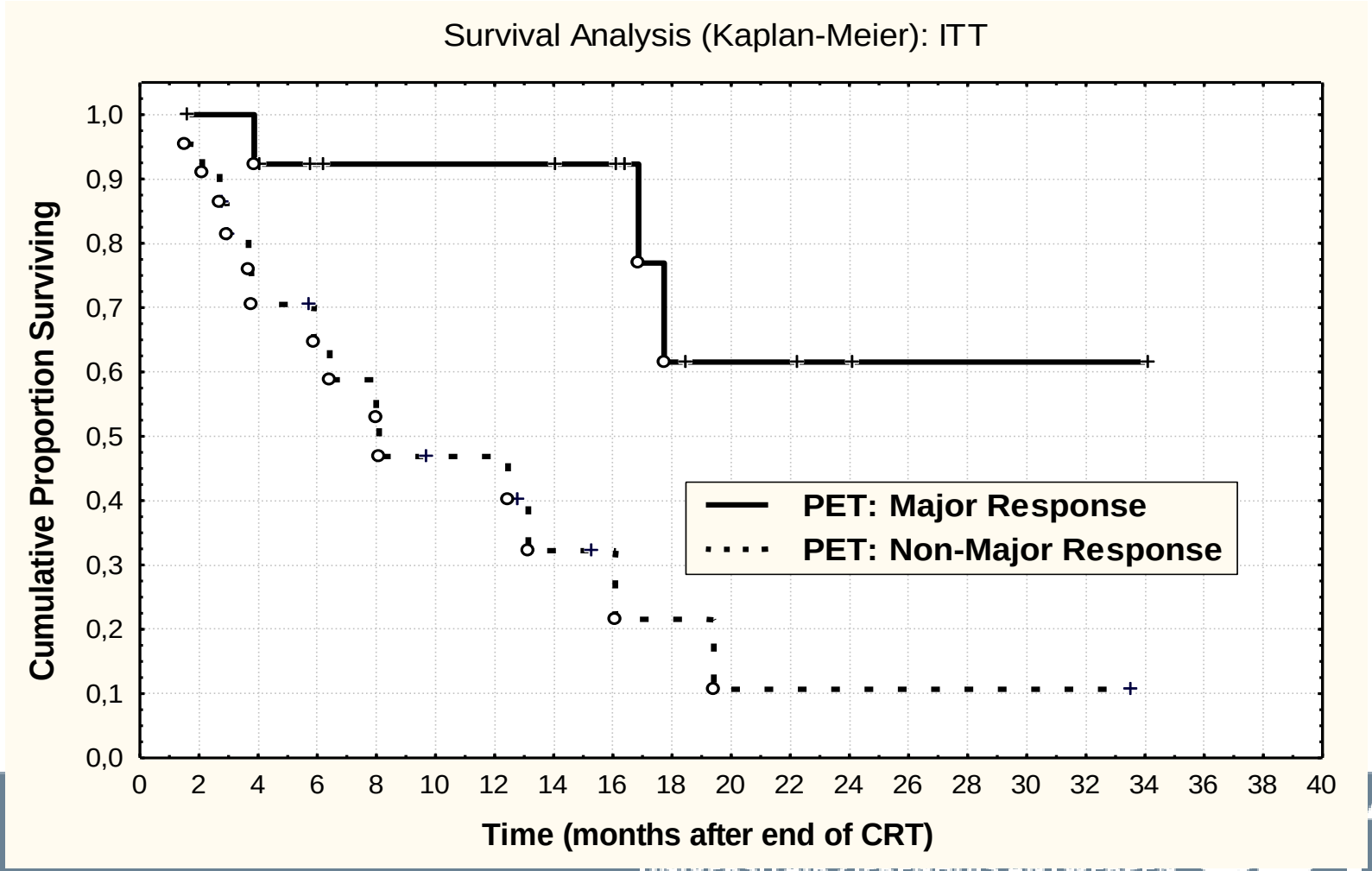
PET before and 4 weeks after chemoradiation

PET response = > 80% reduction of the FDG uptake (Tumor to Liver Ratio) in prim T, no LN, no new lesions

Correlation with patholgical response and survival

PET in Esophageal cancer - Response after induction treatment

Flamen et al, Annals of Oncology 2002



PET in Esophageal cancer - Response assessment after induction treatment

Downey et al, JCO 2003

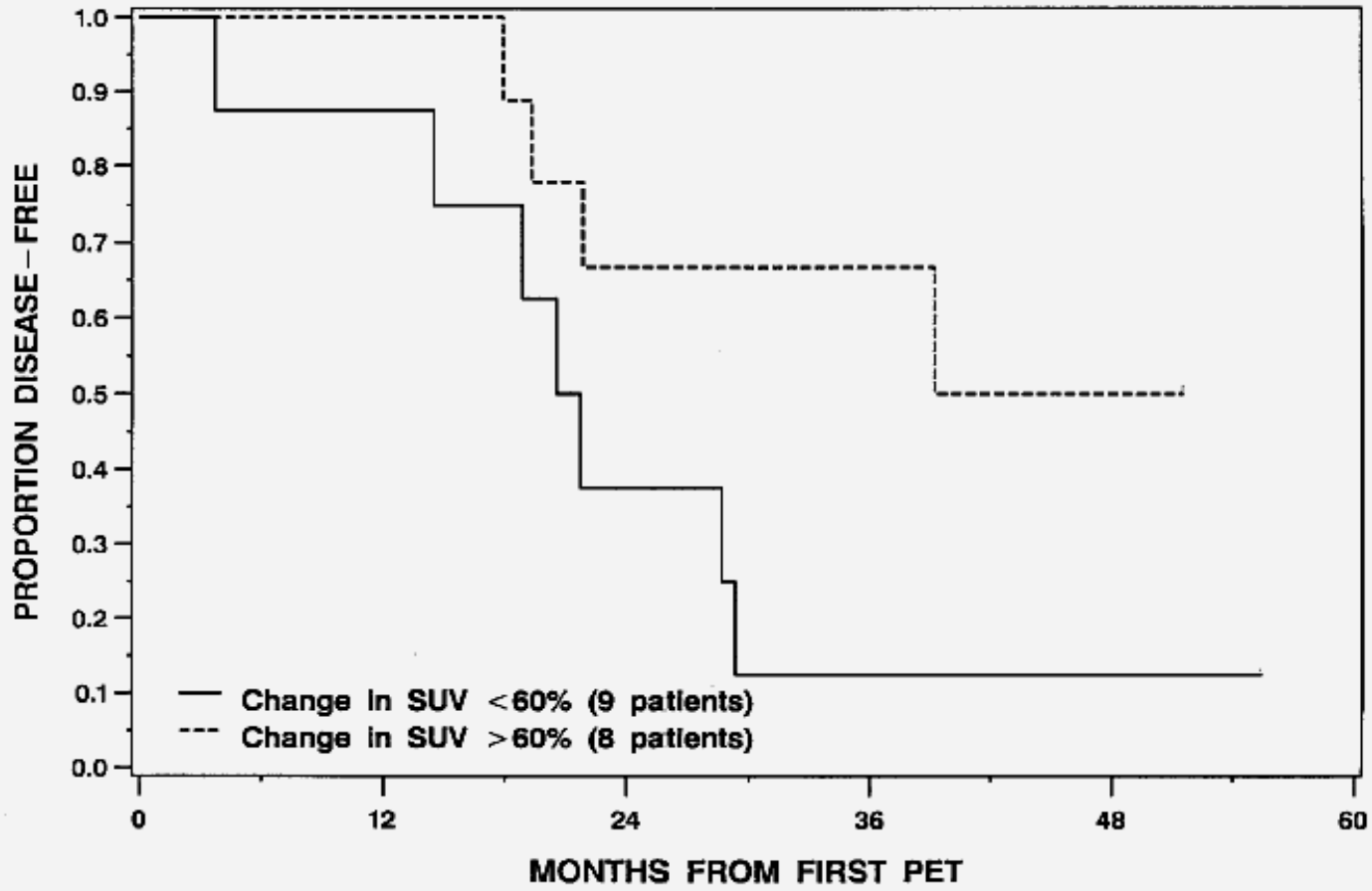
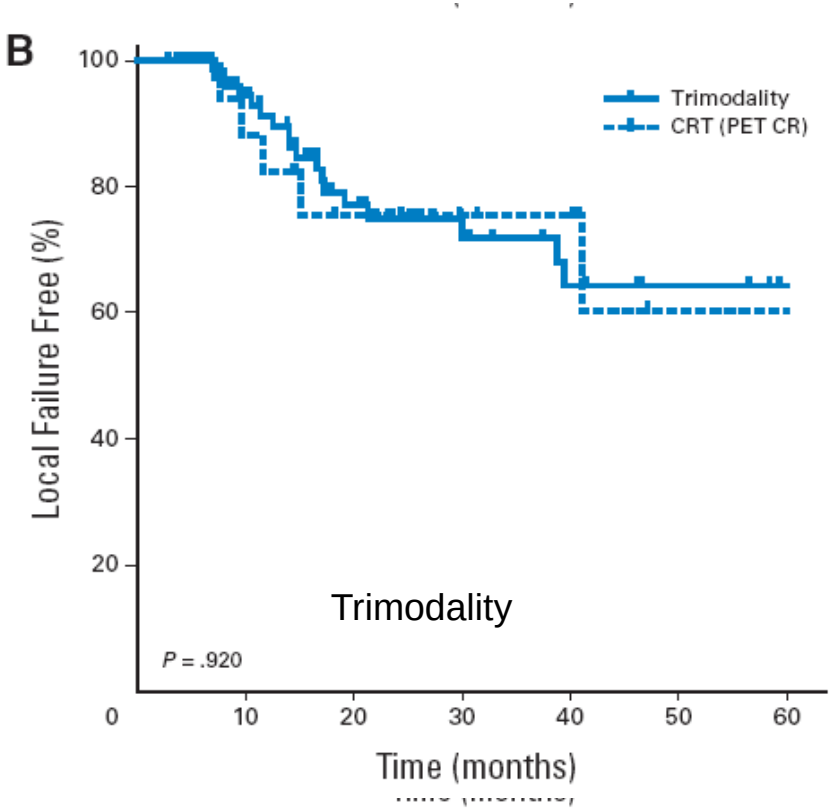
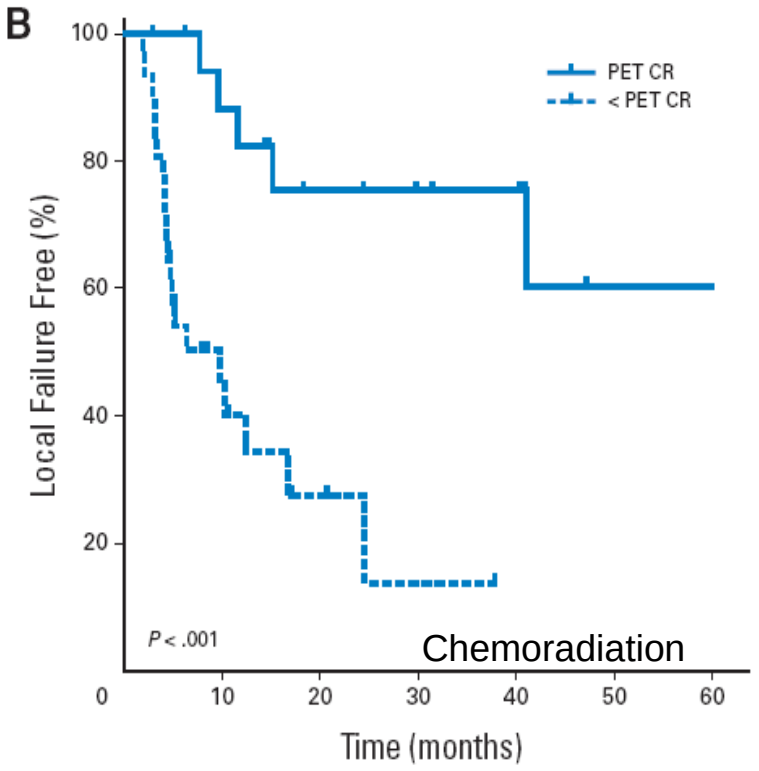


Fig 2. Disease-free survival of 17 patients undergoing PET imaging before and after induction chemoradiation therapy stratified by the median percentage change in the standardized uptake value (SUV). PET, positron emission tomography (P = .055).

PET in EC- Response after induction

Monjazeb et al, J Clin Oncology, nov 2010
Retrospective analysis in 163 ptn EC receiving ichemoradiation with or without surgery
PET at the end of CRT; PET positive if SUV max >3
Effect of PET-CR on outcome (local faiilure and OS)



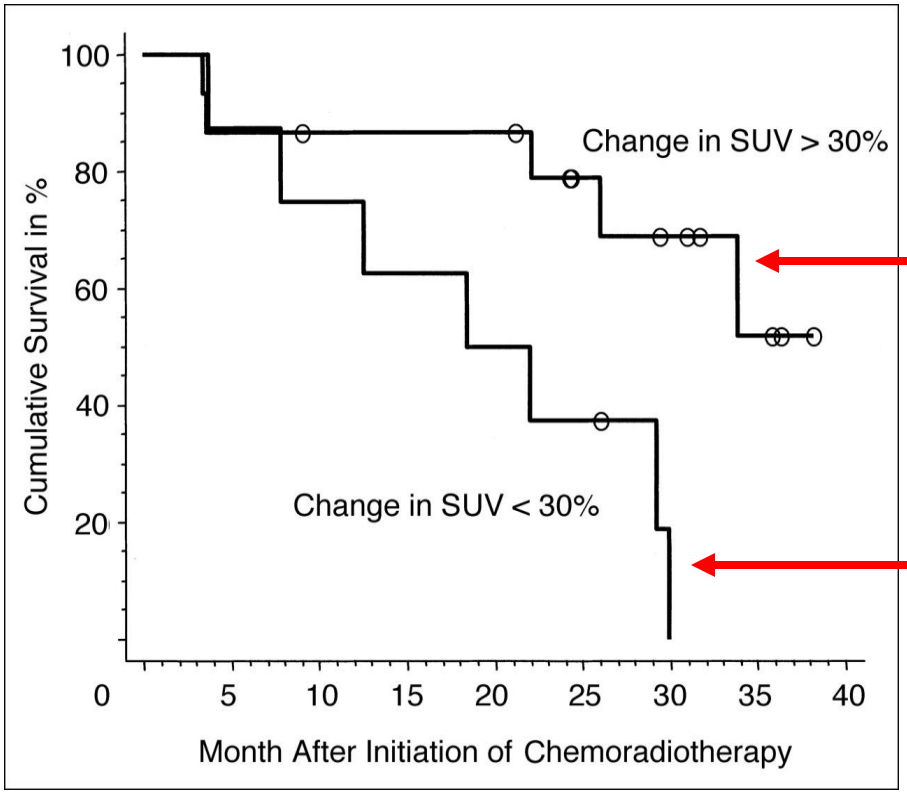


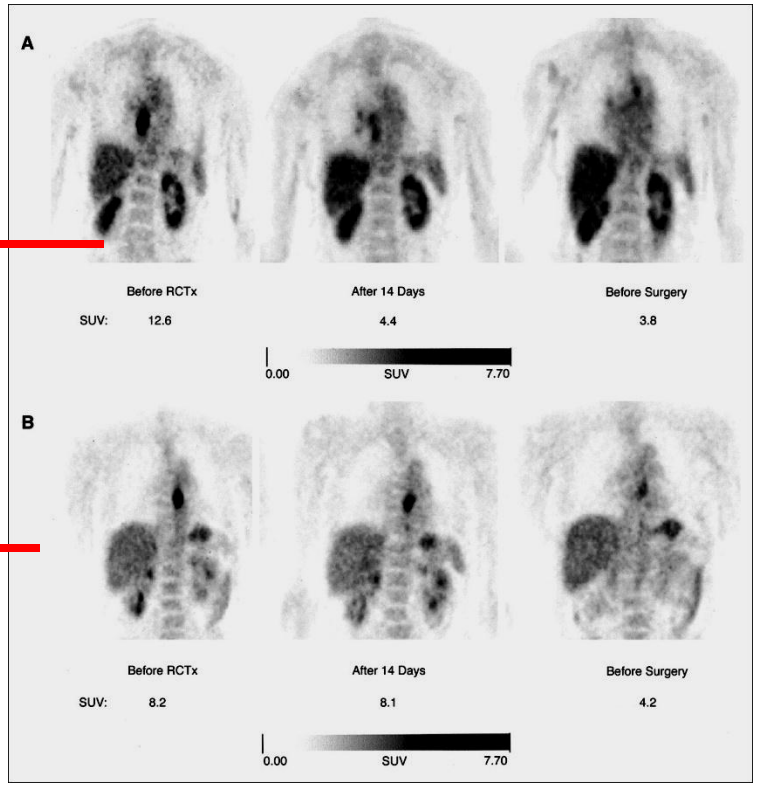
Use PET to decide who need additional surgery?

* No correlation between pathological response and outcome.
PET-CR rate higher in SSC and Adeno but association with outcome=identical

EC- PET early during chemoradiation

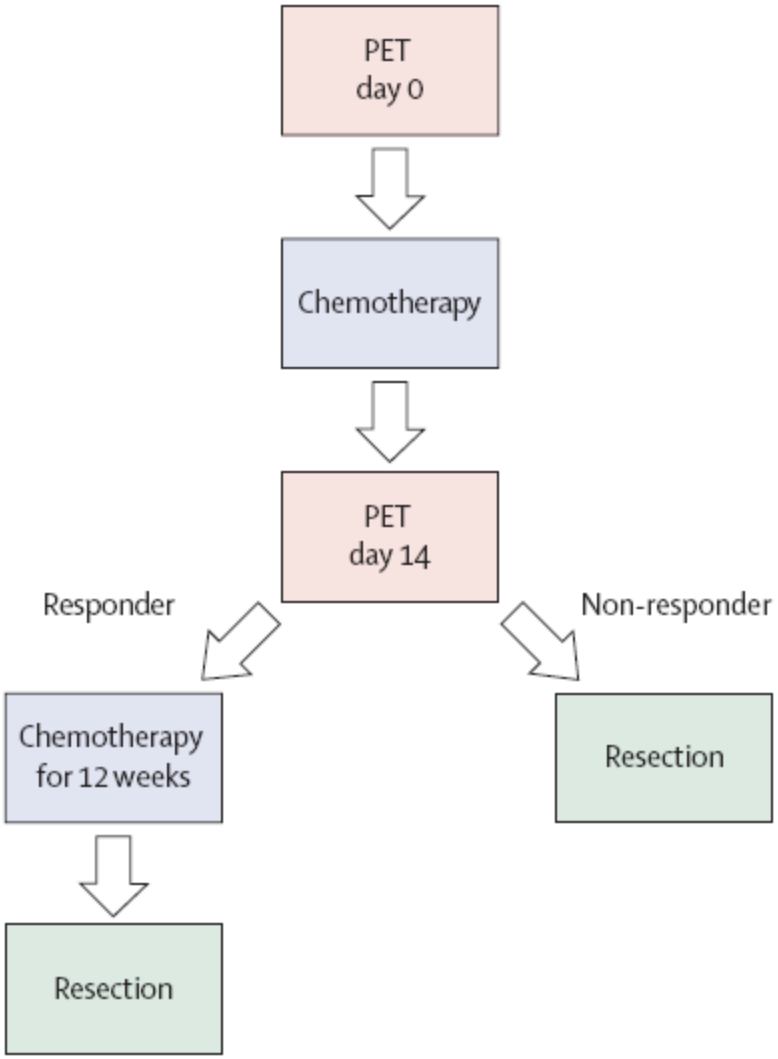
Wieder et al, Journal of Clinical Oncology, 2004

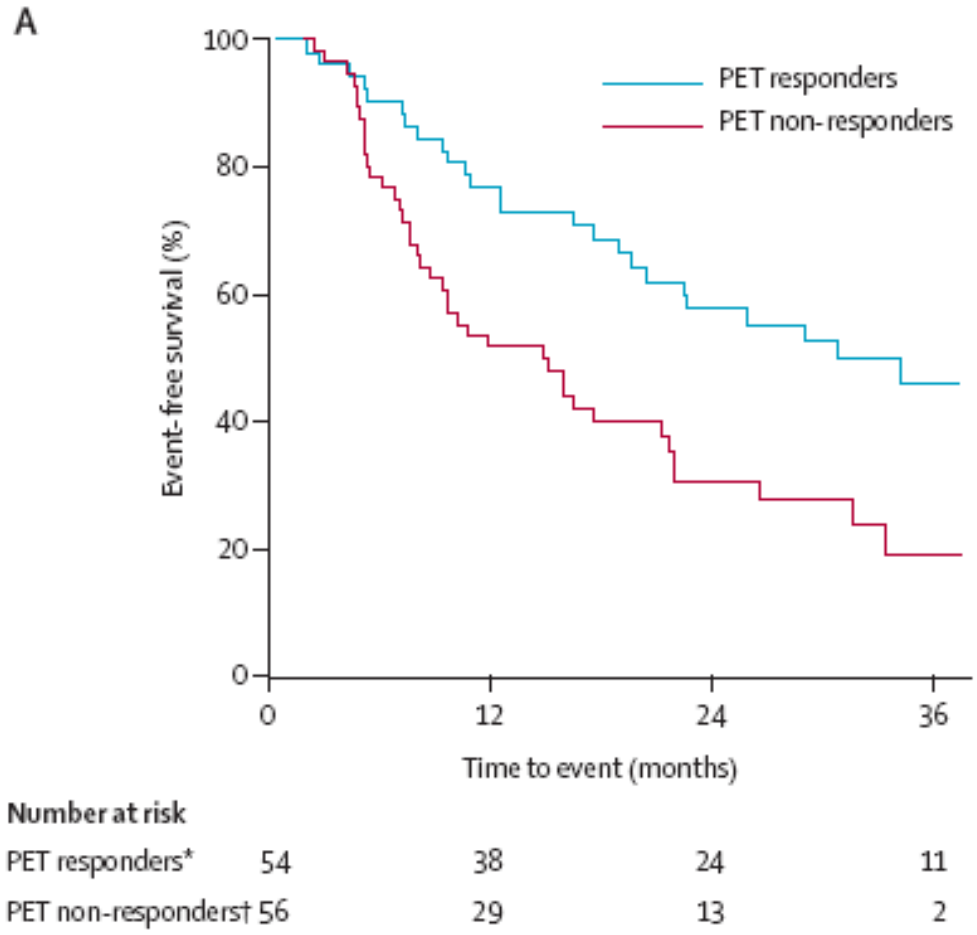




MUNICON Trial

Lordick et al. Lancet Oncology 2007





PET for response evaluation in rectal cancer

Amthauer et al, EJNMI 2004

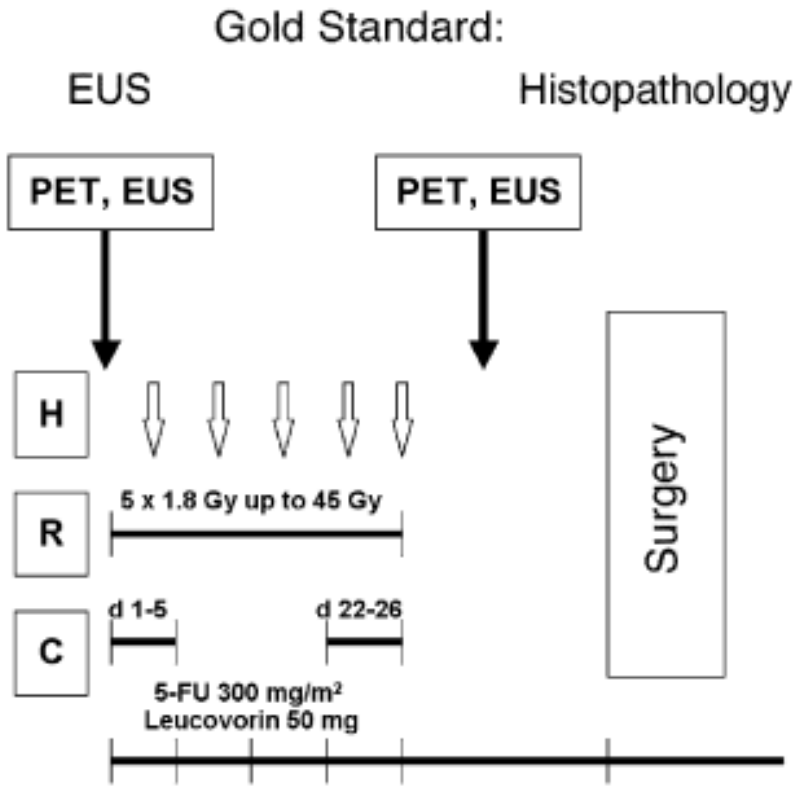


Fig. 1. Study design. *H*, Hyperthermia; *R*, radiotherapy; *C*, chemotherapy. 5-FU is escalated to 350 mg/m² on days 22–26 when not contraindicated by toxicity

N=20 rectal ca

PET response
2-4 w after
SUV max
EORTC PET criteria

Path response
T-status
Downstaging T
or
Size /invasion depth
> 30%↓

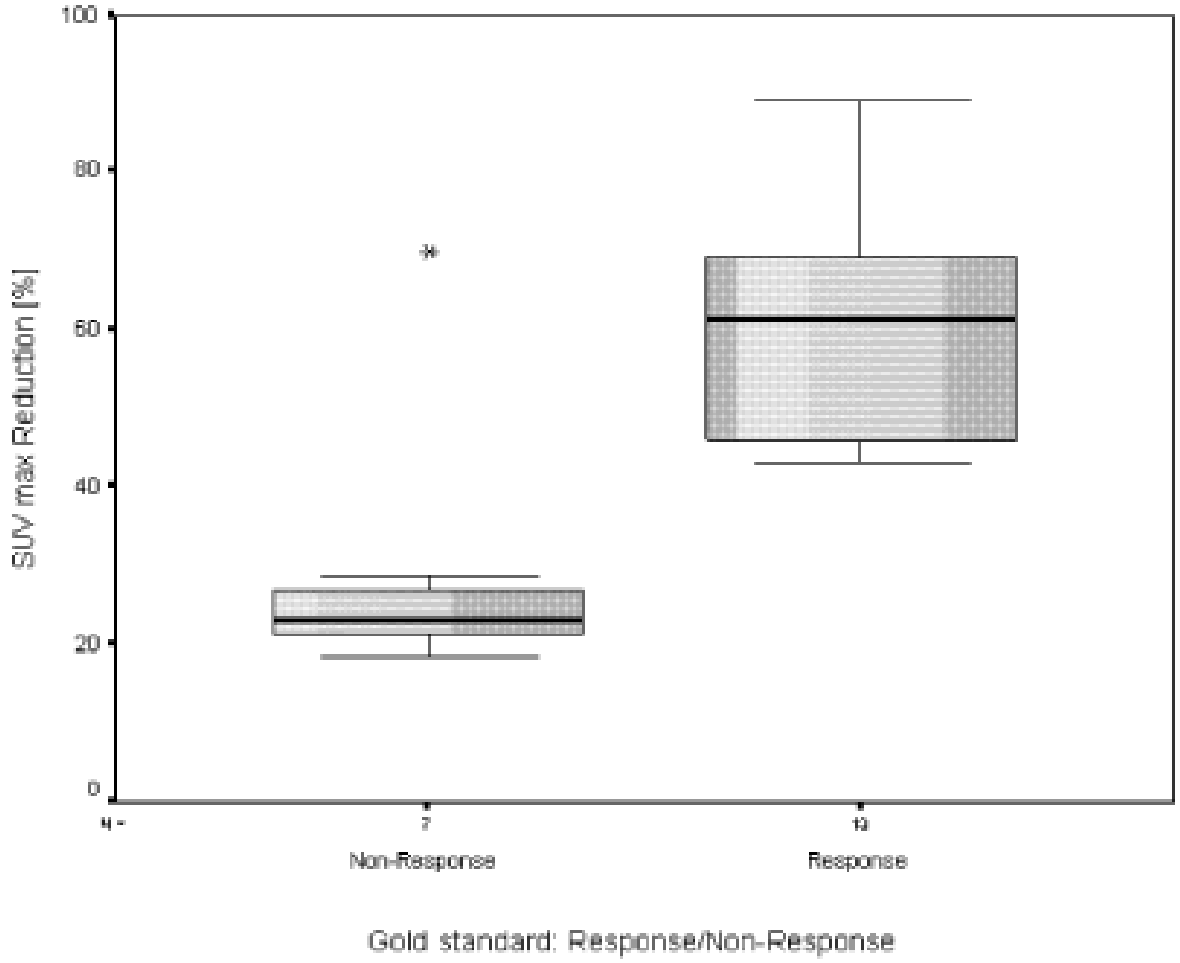
Amthauer et al, EJNMI 2004

Table 3. FDG uptake by the tumour before and after neoadjuvant therapy for responders and non-responders as classified by the gold standard

	SUV_{max} before	SUV_{max} after	Fisher's exact test	SUV_{max} reduction (%)
Responder (n=13)	15.7±7.5	5.9±3.1	P=0.001	59.8±14.6
Non-responder (n=7)	12.5±8.0	7.6±4.2	P=0.018	29.7±18.1
Total (n=20)	14.6±7.6	6.5±2.8	P<0.001	49.3±21.3

In patients with good pathological response, FDG uptake can remain high due to accompaning inflammatory reactions

Amthauer et al, EJNMI 2004

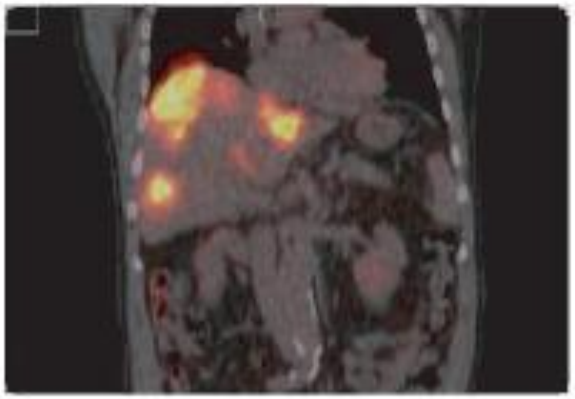


ROC analysis
Best cut-off:
PR> 36%!

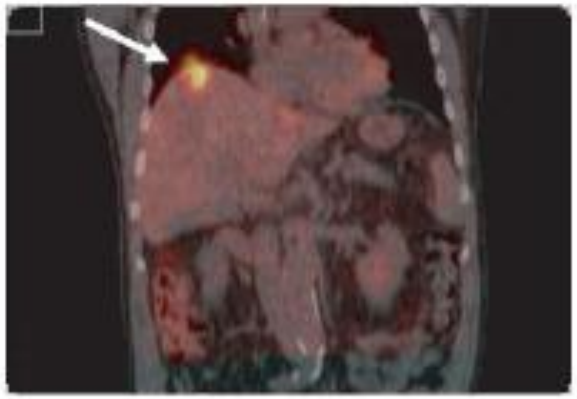
More definition of Non-response?

PET for response after radioactive microspheres

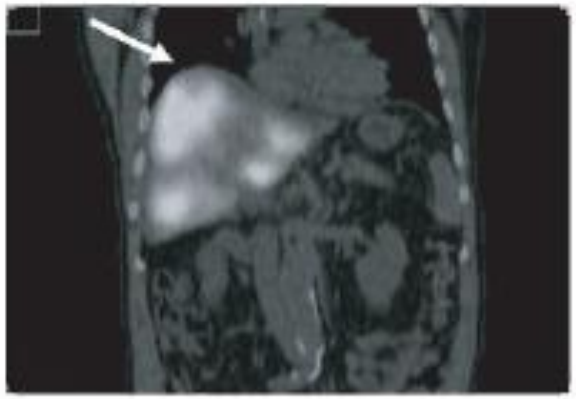
Flamen et al. physics in med and biol 2008



PET pre



PET 6w post



MAA pre

FDG-PET in GI cancer

- Esophageal Cancer
  - Strong indication for primary staging to exclude M1 disease
  - Recurrences
    - locally: high false positive rate
    - Best technique to exclude M+ if salvage surgery is considered
  - Promising results for PET response evaluation of neoadjuvant therapy

FDG-PET in GI cancer

- PET in CRC
  - Limited indications for primary staging
    - Equivocal lesions on CT/MR
    - resectable M+ to exclude more extensive disease
  - Strong indication for recurrence detection/staging
    - Rising tumor marker
    - Patient selection for salvage surgery
      - ! Perform PET prior to chemotherapy
  - Response evaluation
    - For local liver treatments
    - ? After neoadjuvant therapy in rectal cancer (hampered by inflammation)