Evolving Role of Upfront and Postoperative Imaging in Ovarian Cancer

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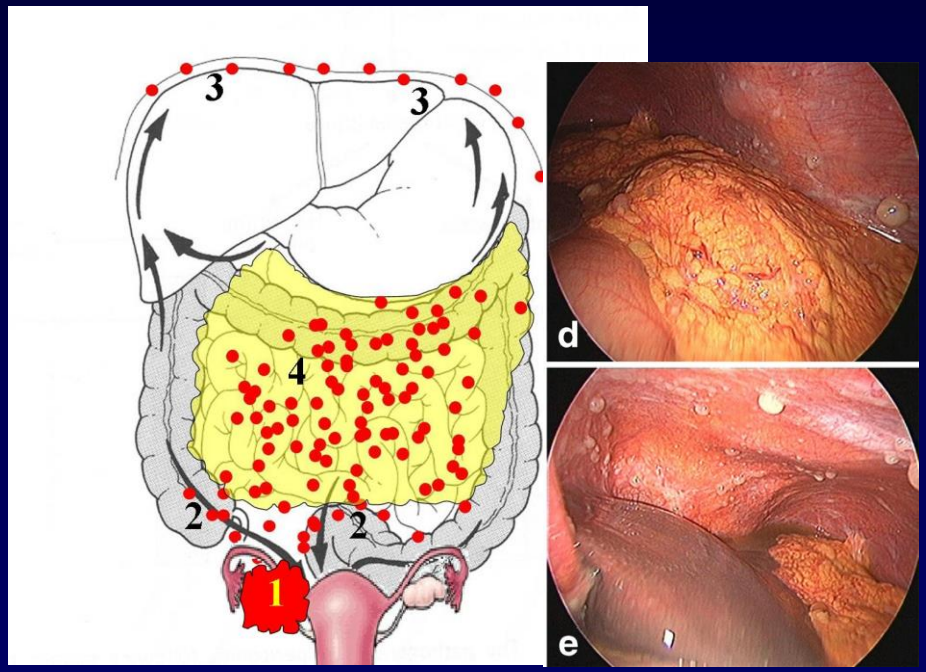
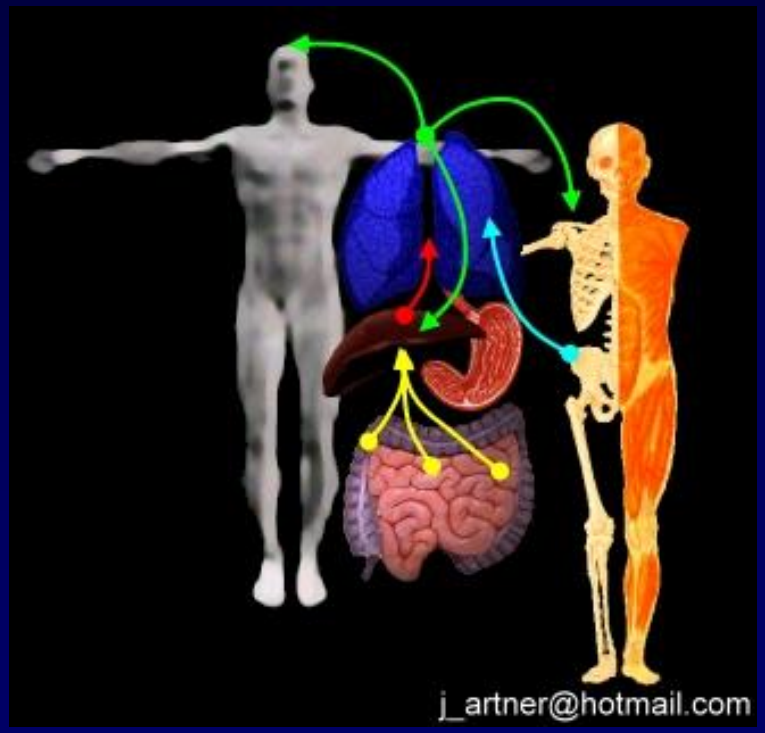
prIME oncology

Ovarian Cancer : Upfront Imaging

The “operable” metastasis
Significant impact on treatment and survival



(Resectable) peritoneal metastases
Direct spread in the abdomen



Nodal/distant metastases:
adverse and often nonresectable
Primary resection not possible

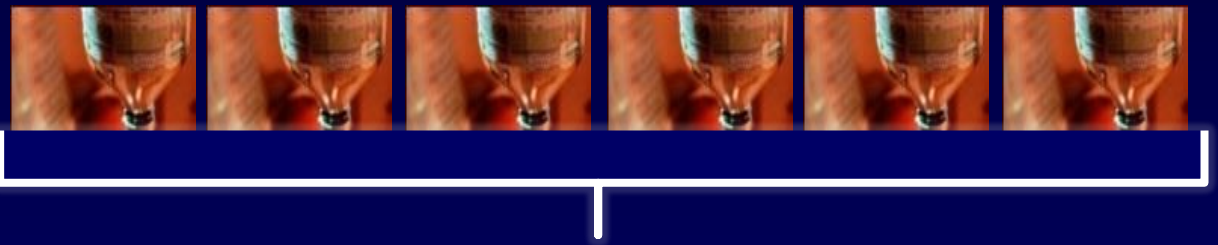
Whole-body evaluation necessary

The objective is to achieve complete macroscopic removal of tumor (R0)

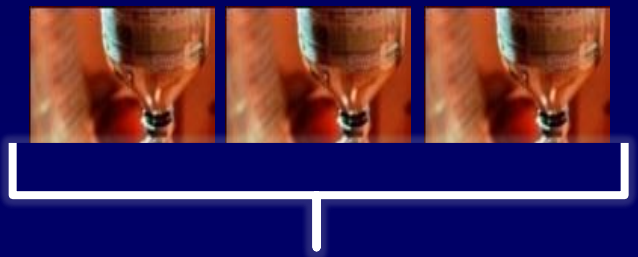
Requires highly accurate tools for treatment selection

Minimize failed surgery (not reaching R0)
Avoid to delay surgery in operable patient

Primary debulking surgery

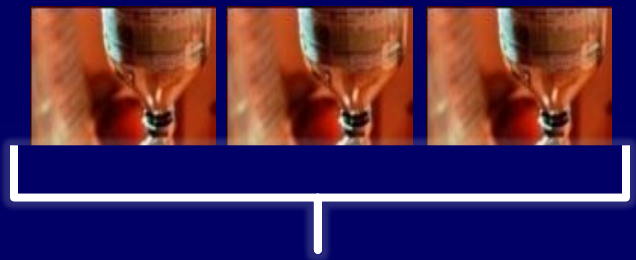


6 cycles of platinum-based chemotherapy



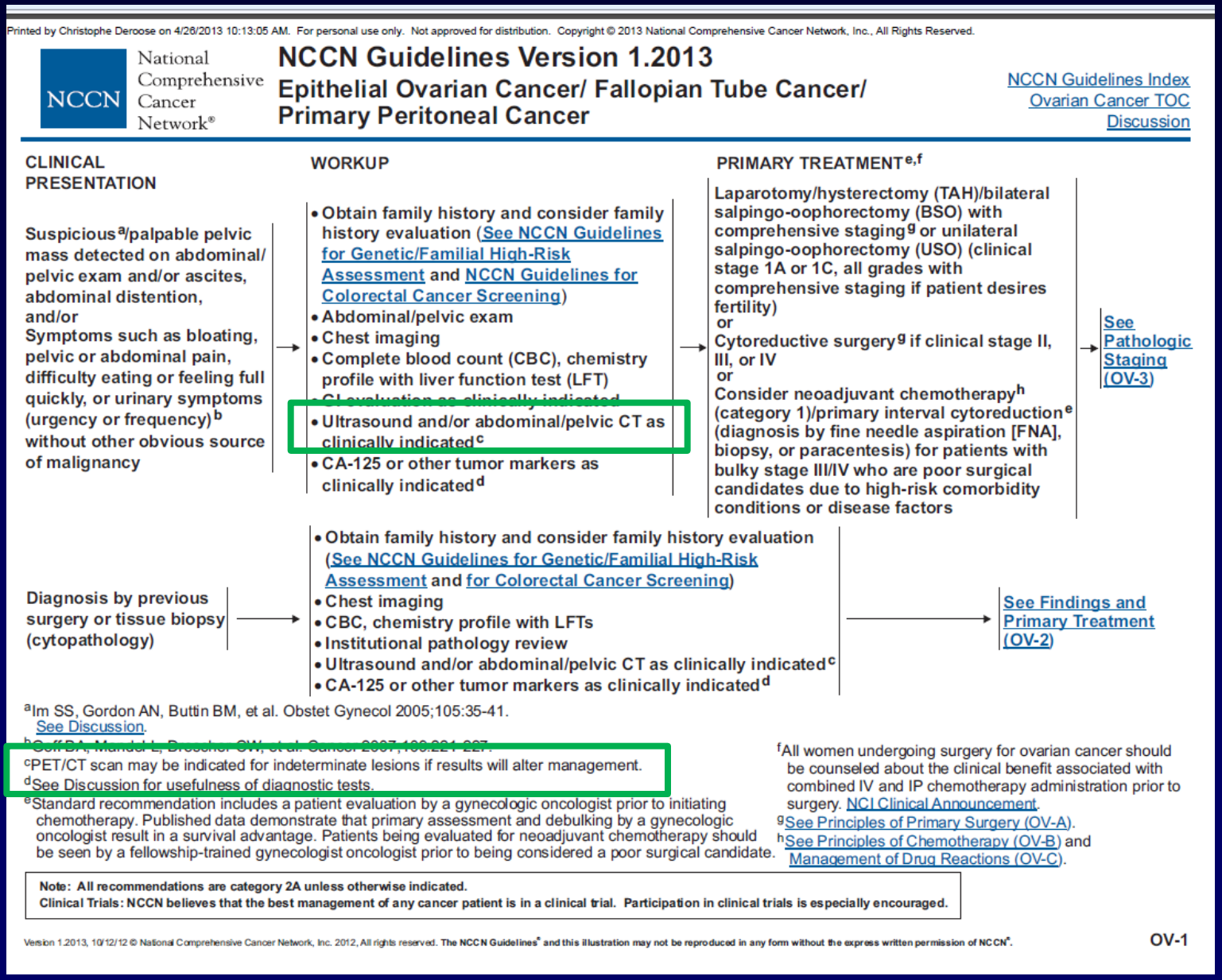
3 cycles of platinum-based chemotherapy

Interval debulking surgery (IDS)



3 cycles of platinum-based chemotherapy

Computed Tomography : The Workhorse



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Ovarian Cancer TOC
Discussion

CLINICAL PRESENTATION

WORKUP

PRIMARY TREATMENT[e,f]

Suspicious[a]/palpable pelvic mass detected on abdominal/pelvic exam and/or ascites, abdominal distention, and/or Symptoms such as bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or urinary symptoms (urgency or frequency)[b] without other obvious source of malignancy

- Obtain family history and consider family history evaluation (See NCCN Guidelines for Genetic/Familial High-Risk Assessment and NCCN Guidelines for Colorectal Cancer Screening)
- Abdominal/pelvic exam
- Chest imaging
- Complete blood count (CBC), chemistry profile with liver function test (LFT)
- GI evaluation as clinically indicated
- Ultrasound and/or abdominal/pelvic CT as clinically indicated[c]
- CA-125 or other tumor markers as clinically indicated[d]

Laparotomy/hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO) with comprehensive staging[g] or unilateral salpingo-oophorectomy (USO) (clinical stage 1A or 1C, all grades with comprehensive staging if patient desires fertility)
or
Cytoreductive surgery[g] if clinical stage II, III, or IV
or
Consider neoadjuvant chemotherapy[h] (category 1)/primary interval cytoreduction[e] (diagnosis by fine needle aspiration [FNA], biopsy, or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors

→ See Pathologic Staging (OV-3)

Diagnosis by previous surgery or tissue biopsy (cytopathology)

- Obtain family history and consider family history evaluation (See NCCN Guidelines for Genetic/Familial High-Risk Assessment and for Colorectal Cancer Screening)
- Chest imaging
- CBC, chemistry profile with LFTs
- Institutional pathology review
- Ultrasound and/or abdominal/pelvic CT as clinically indicated[c]
- CA-125 or other tumor markers as clinically indicated[d]

→ See Findings and Primary Treatment (OV-2)

[a] Im SS, Gordon AN, Buttin BM, et al. Obstet Gynecol 2005;105:35-41. See Discussion.

[b] Goff BA, Mandel L, Drescher CW, et al. Cancer 2007;109:221-227.

[c] PET/CT scan may be indicated for indeterminate lesions if results will alter management.

[d] See Discussion for usefulness of diagnostic tests.

[e] Standard recommendation includes a patient evaluation by a gynecologic oncologist prior to initiating chemotherapy. Published data demonstrate that primary assessment and debulking by a gynecologic oncologist result in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynecologist oncologist prior to being considered a poor surgical candidate.

[f] All women undergoing surgery for ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration prior to surgery. NCI Clinical Announcement.

[g] See Principles of Primary Surgery (OV-A).

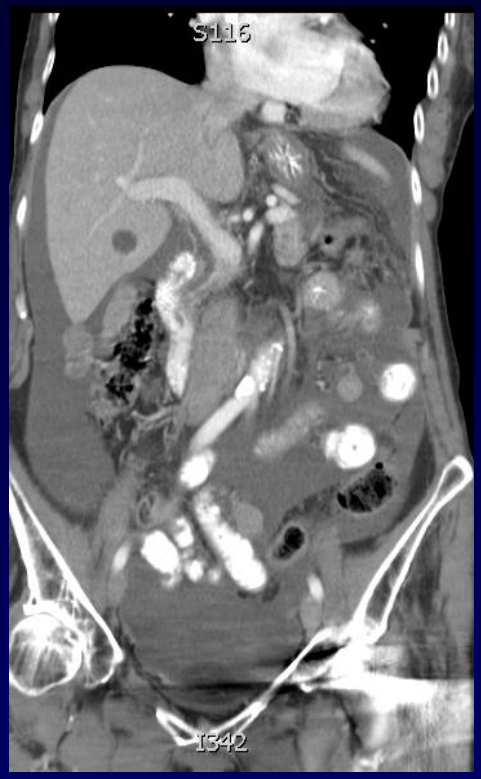
[h] See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Computed Tomography : The Workhorse

Role of radiology in diagnosing ovarian lesions

- Confirmation of a malignant adnexal mass
- Assessment of tumour burden, mapping of the distribution of metastatic disease and diagnosis of possible complications, e.g. bowel obstruction, hydronephrosis or venous thrombosis
- Exclusion of a primary site in the gastrointestinal tract or pancreas whose metastatic spread might mimic primary ovarian cancer



Operable disease?

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ORIGINAL REPORT

Multi-Institutional Reciprocal Validation Study of Computed Tomography Predictors of Suboptimal Primary Cytoreduction in Patients With Advanced Ovarian Cancer

Allison E. Axtell, Margaret H. Lee, Robert E. Bristow, Sean C. Dowdy, William A. Cliby, Steven Raman, John P. Weaver, Mojan Gabbay, Michael Ngo, Scott Lentz, Ilana Cass, Andrew J. Li, Beth Y. Karlan, and Christine H. Holschneider

Conclusion

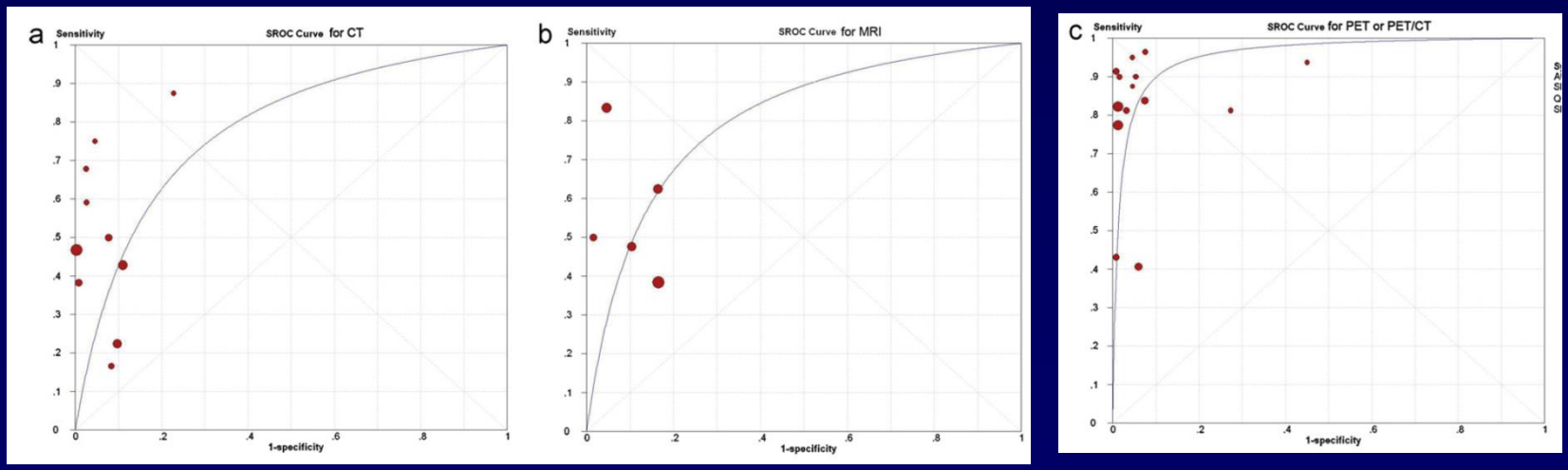
The high accuracy rates of CT predictors of suboptimal cytoreduction in the original cohorts could not be confirmed in the cross validation. Preoperative CT predictors should be used with caution when deciding between surgical cytoreduction and neoadjuvant chemotherapy.

CT scan alone cannot predict optimal debulking surgery

FDG-PET/CT - Potential Strength: Lymph Node Involvement

N = 882	CT	MRI (conventional)	PET or PET/CT
Sensitivity	42%	55%	**73%**
Specificity	95%	88%	97%
Odds ratio	20	12	90

CT **MRI** **PET – PET/CT**



FDG-PET or FDG-PET/CT is more accurate than CT and *conventional* MR imaging in the detection of lymph node metastasis in patients with ovarian cancer.

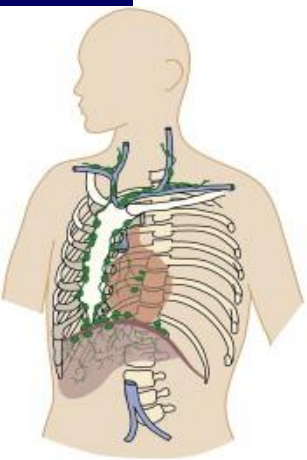
Yuan Y, et al. *Eur J Radiol.* 2012;81(5):1002-1006.

PET/CT Dectects More Supradiafragmatic LN in Advanced Stage (IIC-IV)

Detection of supradiaphragmatic LN:

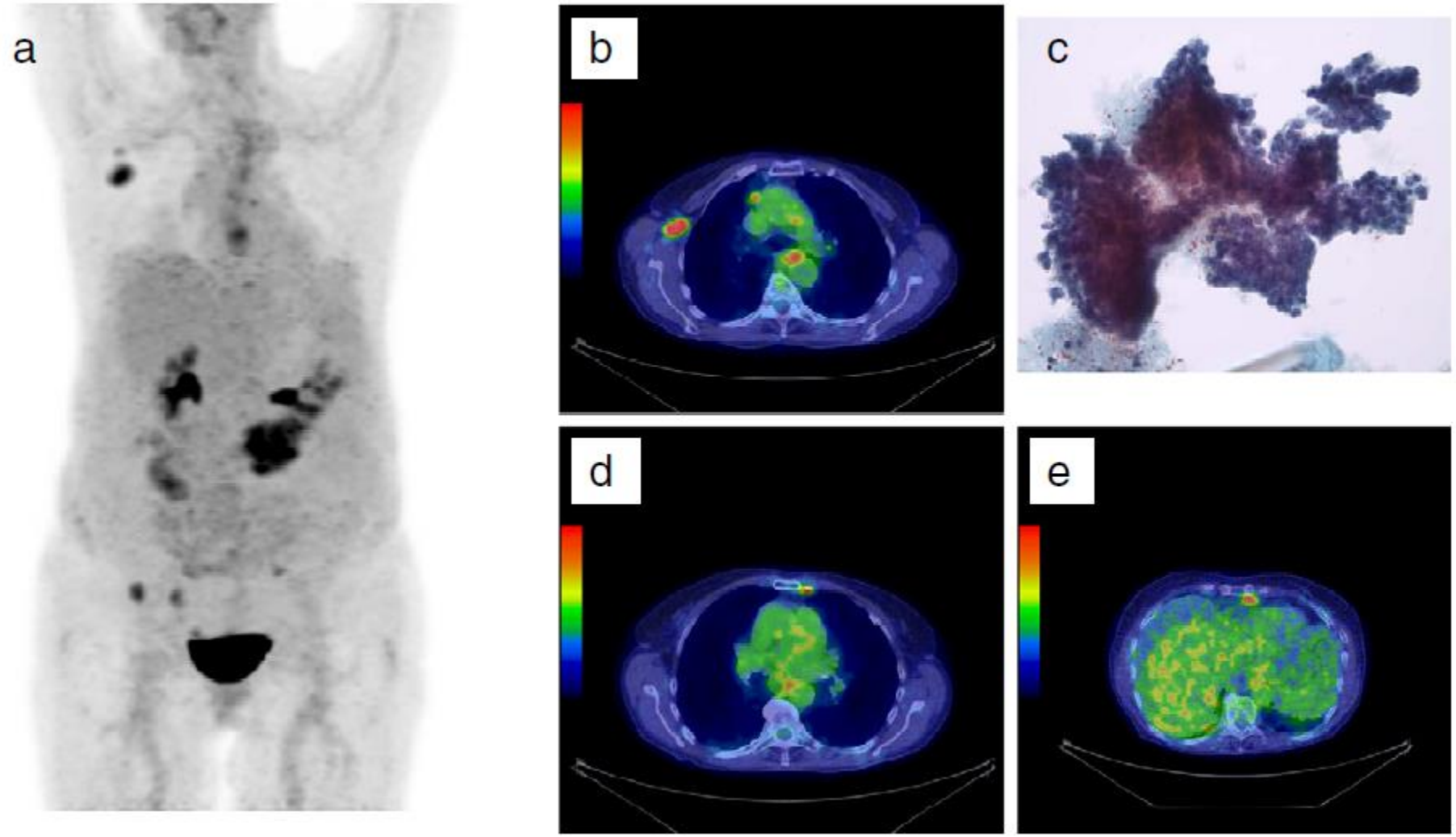
- **In 20/30 patients (67%), FDG PET/CT detected in one or more locations**
- **Conventional CT in 10 patients (33%).**

Lymph node site	Patients with PET-positive LNs	Patients with abnormal LNs in CT
Supradiaphragmatic LNs	20	10
Cardiophrenic	14	6
Parasternal	14	1
Middle/posterior mediastinal	8	4
Axillary	6	1
Subclavian	1	1
More than 1 site	14	3



Hinninen J, et al. *Gynecol Oncol.* 2012;126(1):64-68.

PET/CT Dectects More Supradiafragmatic LN in Advanced Stage (IIC-IV)



Hinninen J, et al. *Gynecol Oncol.* 2012;126(1):64-68.

FDG-PET/CT – Potential Weakness: Peritoneal Staging

N = 40 - PET positive in all patients

Tumour size in quadrant at laparoscopy

no	≤5 mm	>5 mm ≤5 cm	>5 cm	Not Evaluable

Quadrant	Absence of tumour *n.* (%)	≤5 mm *n.* (%)	>5 mm ≤5 cm *n.* (%)	>5 cm *n.* (%)	n.e. *n.* (%)
Q0 (mesogastrium)	3 (7.5)	7 (17.5)	3 (7.5)	27 (67.5)	0
Q1 (right upper)	2 (5.0)	19 (47.5)	6 (15.0)	9 (22.5)	4 (10.0)
Q2 (epigastrium)	11 (27.5)	14 (35.0)	6 (15.0)	6 (15.0)	3 (7.5)
Q3 (left upper)	7 (17.5)	17 (42.5)	5 (12.5)	6 (15.0)	5 (12.5)
Q4 (left flank)	4 (10.0)	24 (60.0)	3 (7.5)	8 (20.0)	1 (2.5)
Q5 (left lower)	4 (10.0)	11 (27.5)	1 (2.5)	24 (60.0)	0
Q6 (pelvis)	0	8 (20.0)	4 (10.0)	28 (70.0)	0
Q7 (right lower)	2 (5.0)	13 (32.5)	4 (10.0)	21 (52.5)	0
Q8 (right flank)	5 (12.5)	22 (55.0)	6 (15.0)	6 (15.0)	1 (2.5)
Total	38 (10.6)	135 (37.5)	38 (10.6)	135 (37.5)	14 (3.8)

	11%	38%	11%	38%	4%

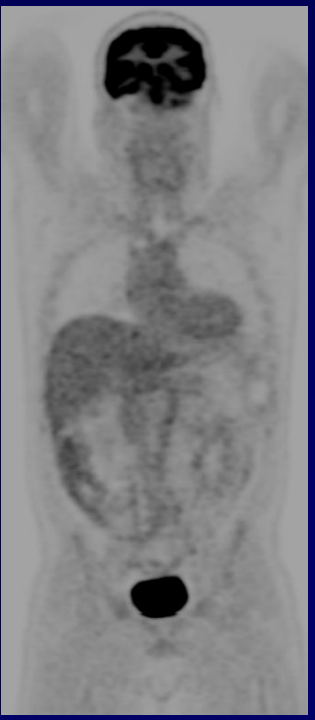
	True Negative	True Positive	False Positive	False Negative
N	26	269	12	65
%	7.5%	77.7%	3.5%	18.8%

Sensitivity: 79% - Specificity: 68% - PPV 95%

De Iaco P, et al. *Eur J Radiol*. 2011;80(2):e98-103.

Reasons for False-Negative PET

- **Diffusely infiltrative serosal deposits, mimicking physiologic bowel activity**
- **Implants <5 mm**
  - **low tracer concentration**
  - **limited spatial resolution of PET**
  - **Breathing motion**
- **Mucinous tumors**



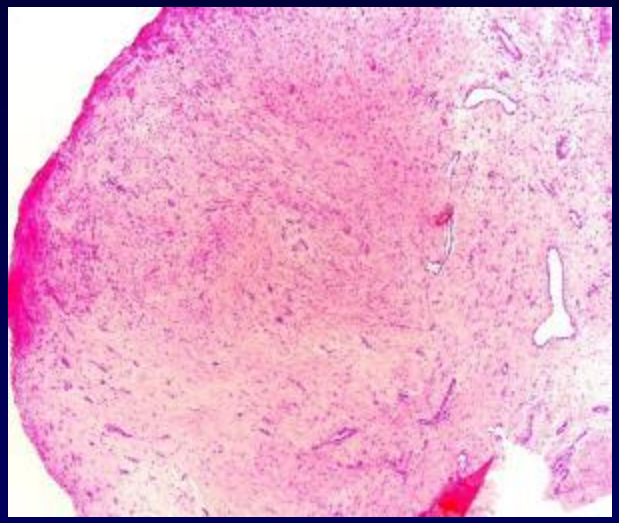
FDG-PET/CT can improve patient selection for treatment

Cannot sufficiently predict optimal debulking surgery

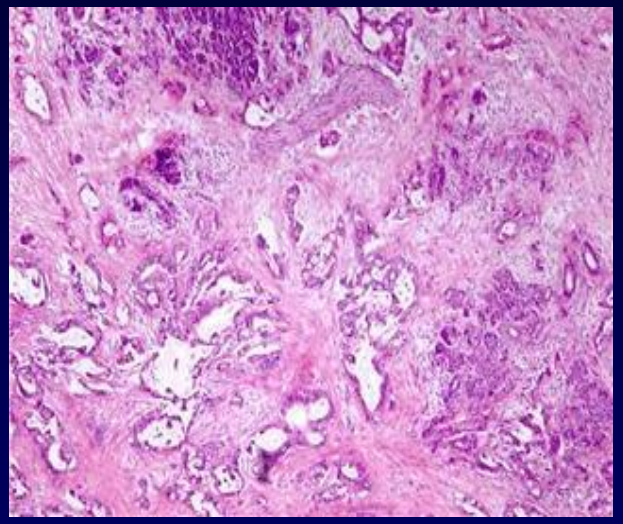
Kyriazi, Nat Rev Oncol, 2012

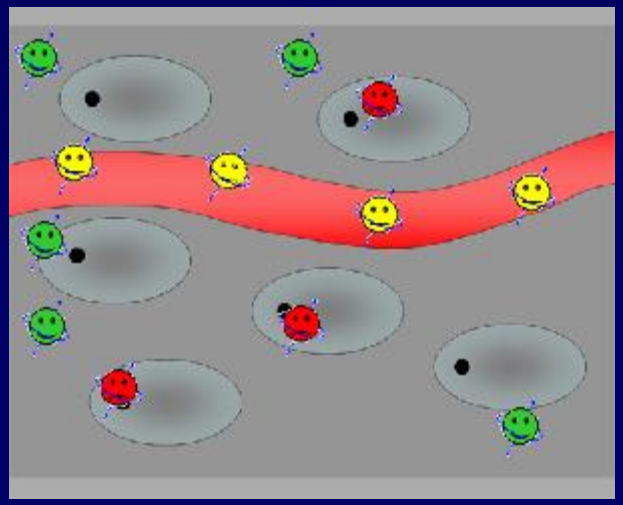
Diffusion MRI: Basic Principle

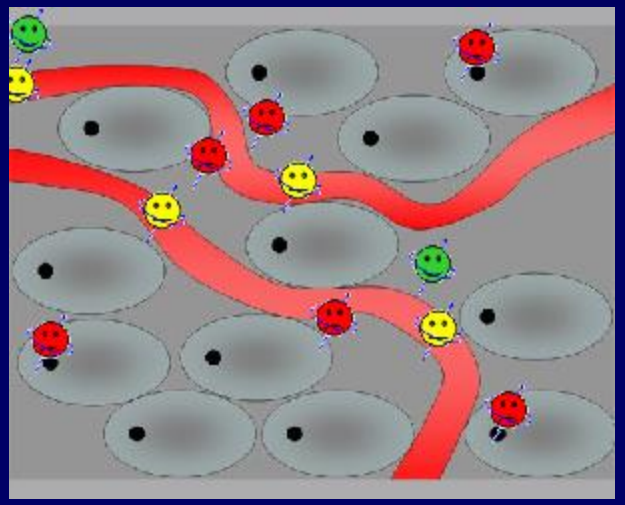
Differences in microstructure



Changes in H_20 mobility

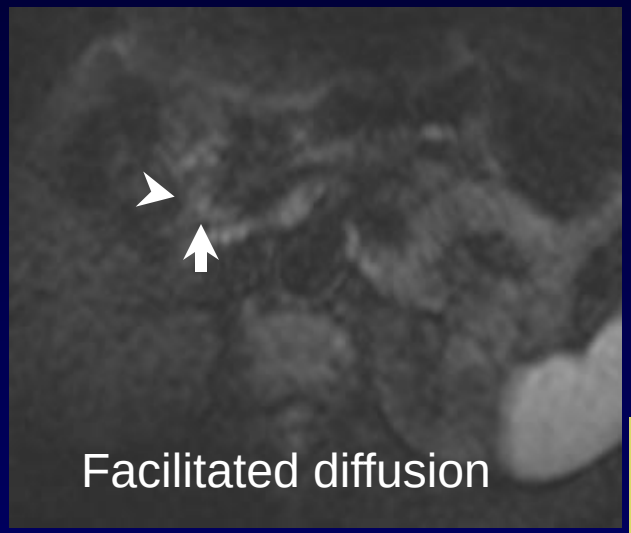






Diffusion MRI: Basic Principle

Differences in microstructure



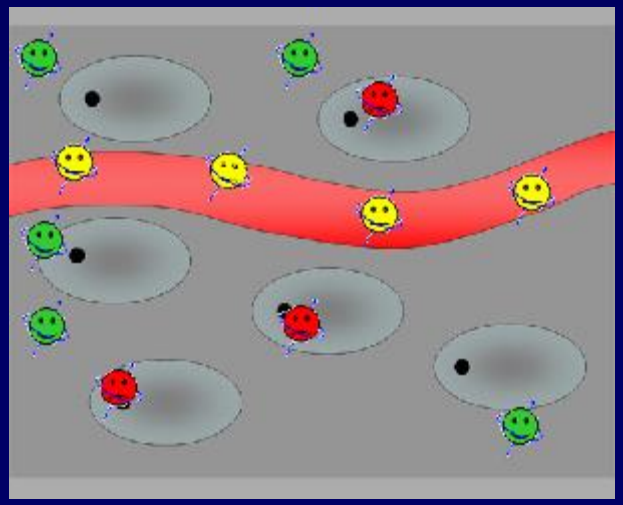
Facilitated diffusion

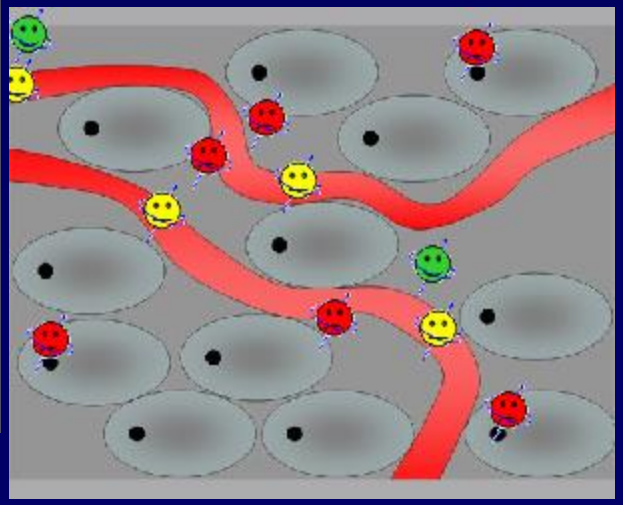
Changes in H_20 mobility

*Diffusion-weighted image contrast
-Mathematical quantification Apparent diffusion coefficient
- No need for exogenic contrast agent
- No irradiation → magnetic

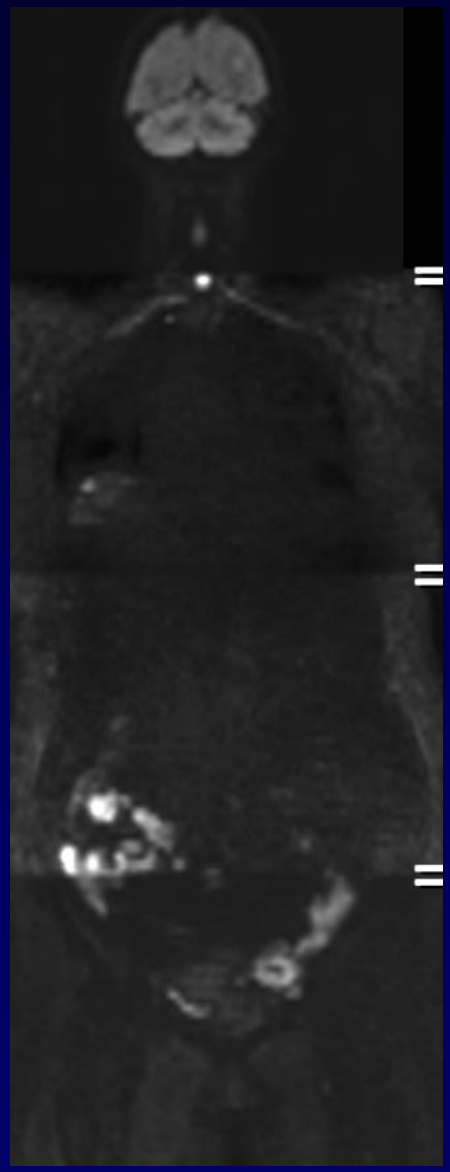
- High expertise per center
  -Research
  - Clinical routine

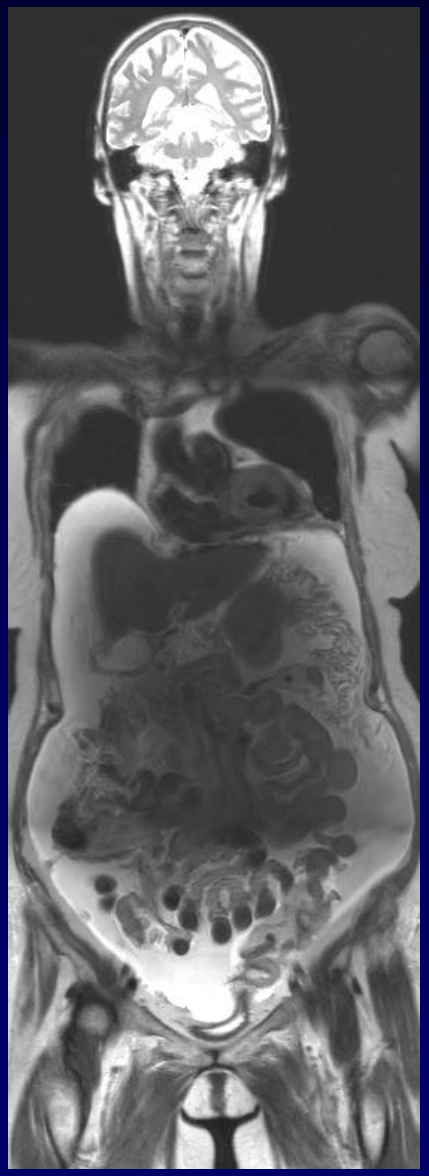
Restricted diffusion

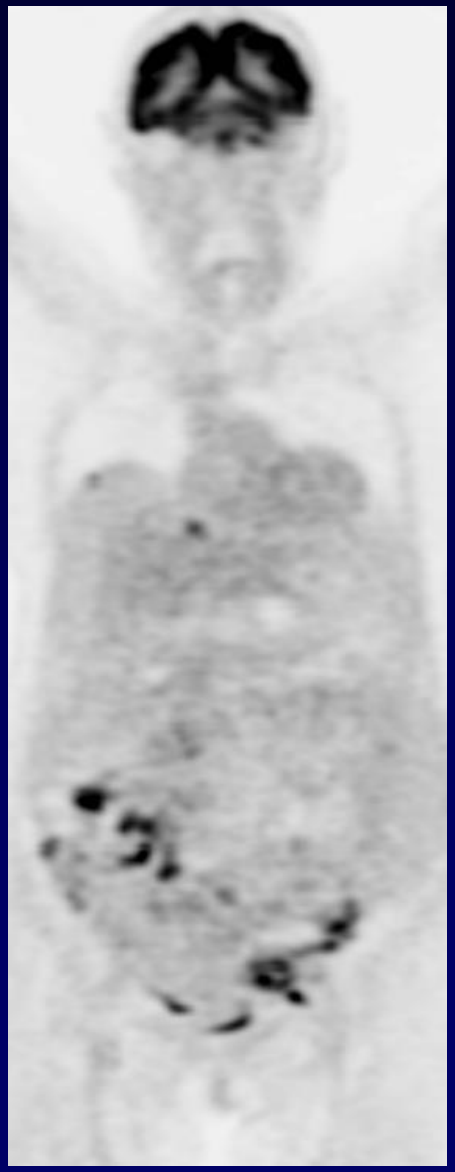




(Whole Body) Diffusion MRI







Microstructure

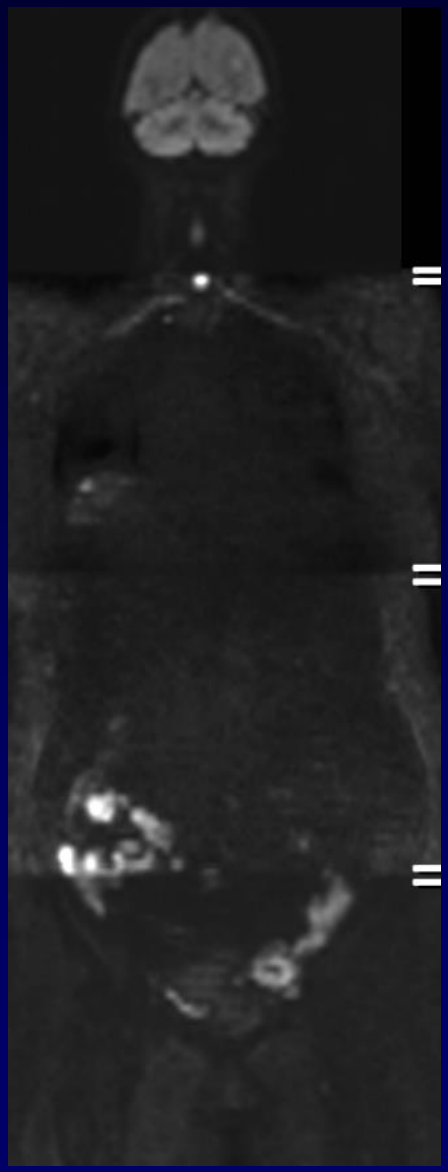
T2/T1 contrast

Glucose metabolism

Ceci n'est pas un PET

(Whole Body) Diffusion MRI

Ceci n'est pas un PET



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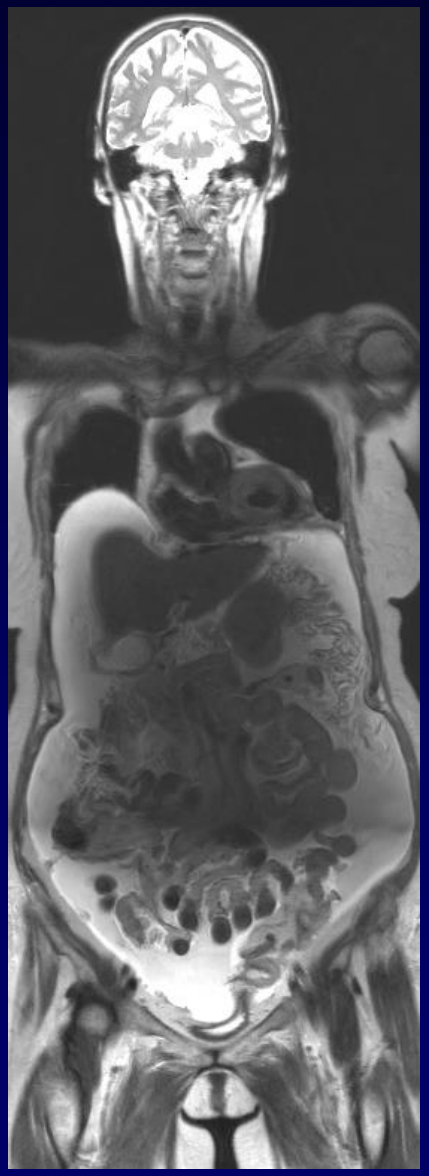

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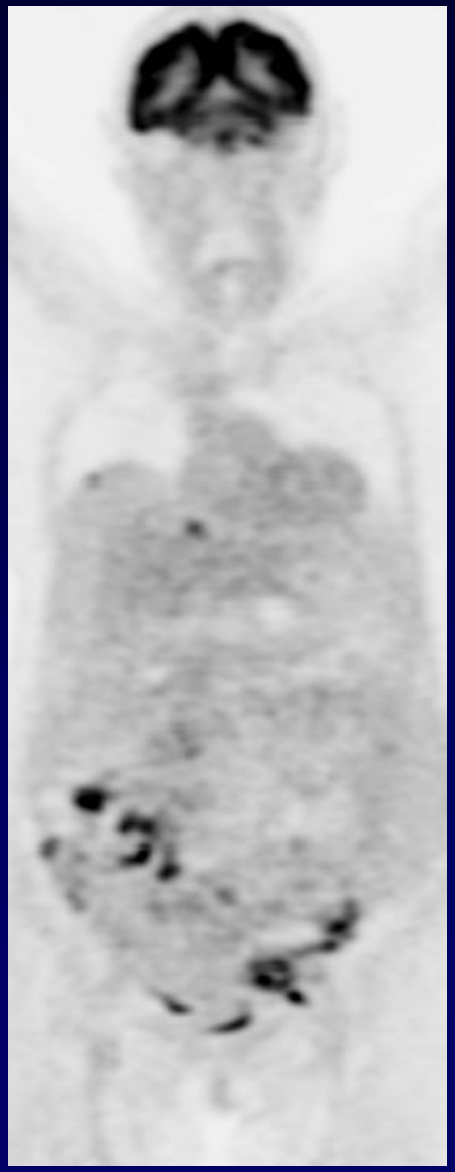

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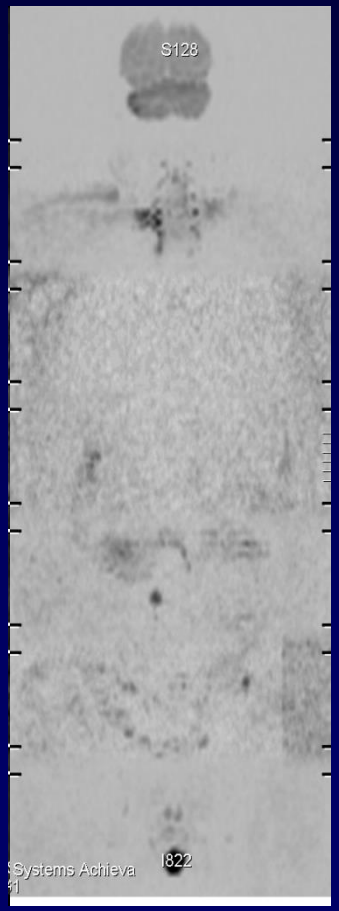

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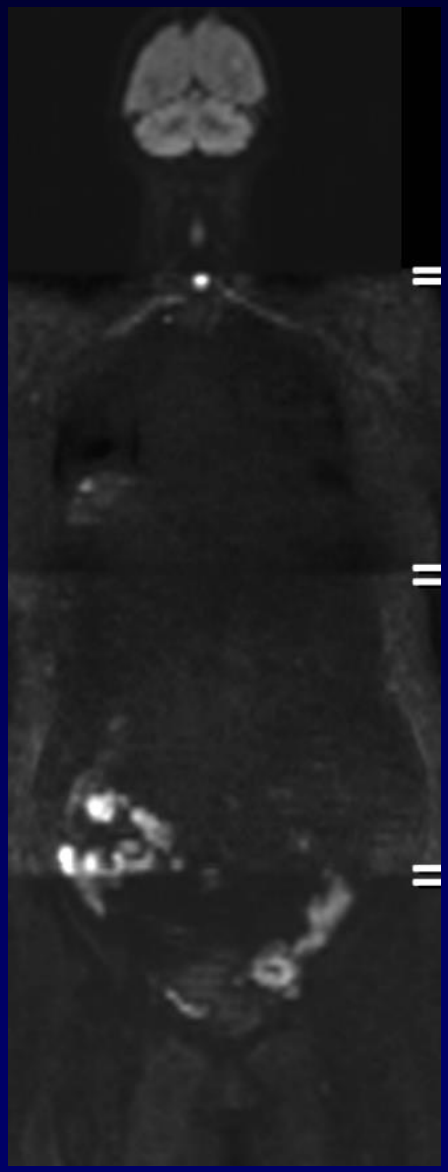

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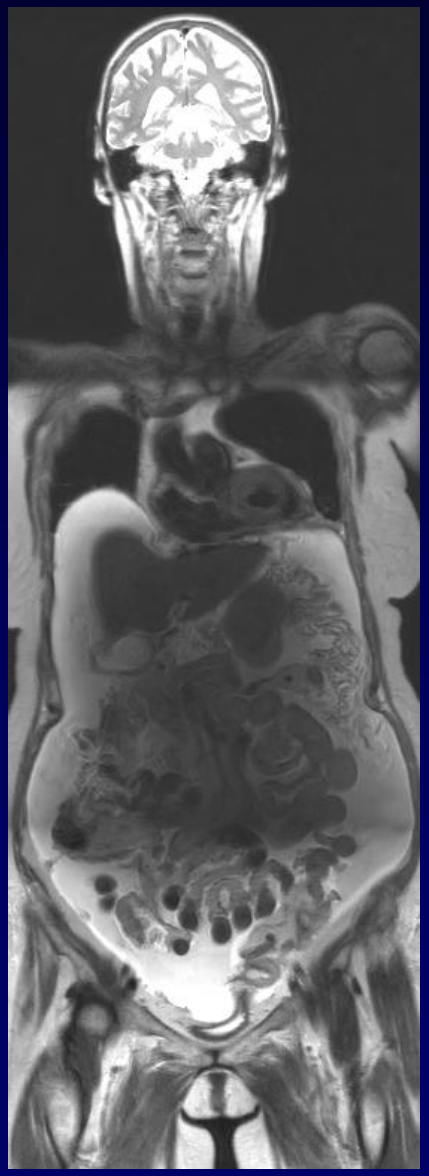

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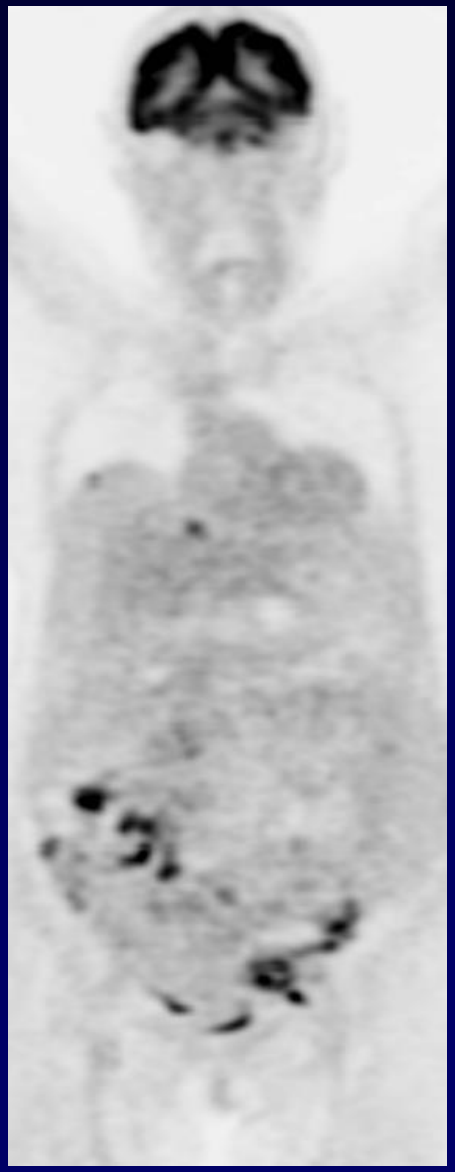

Glucose metabolism

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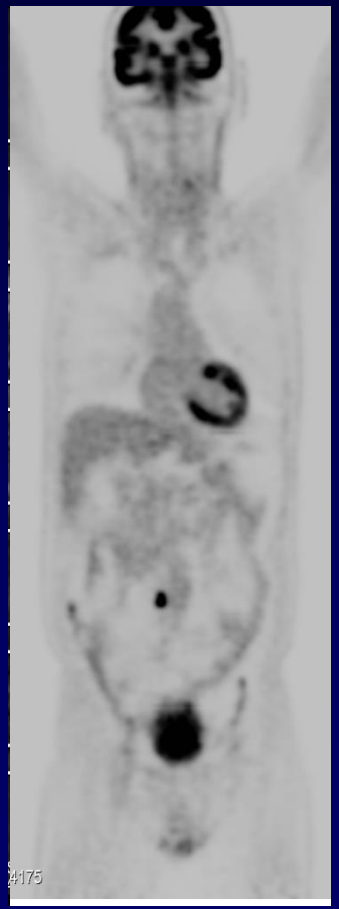

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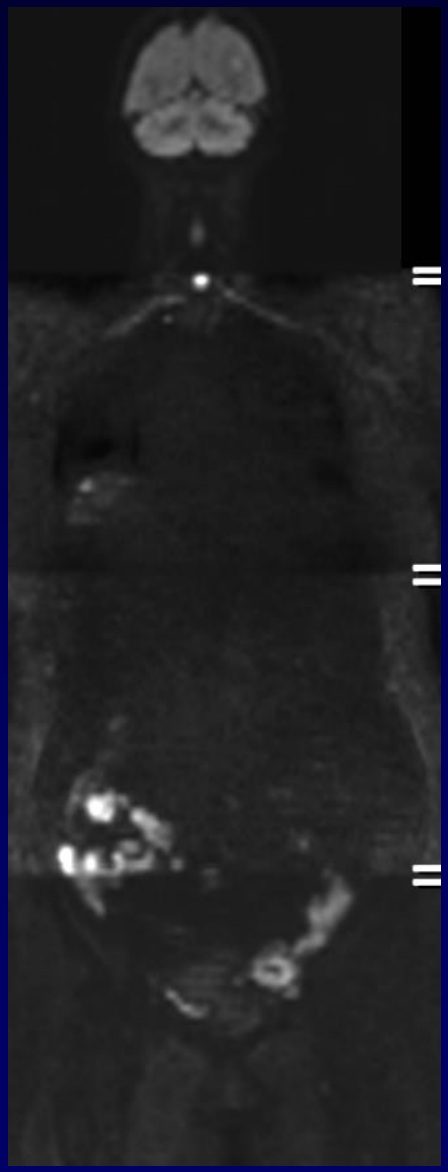
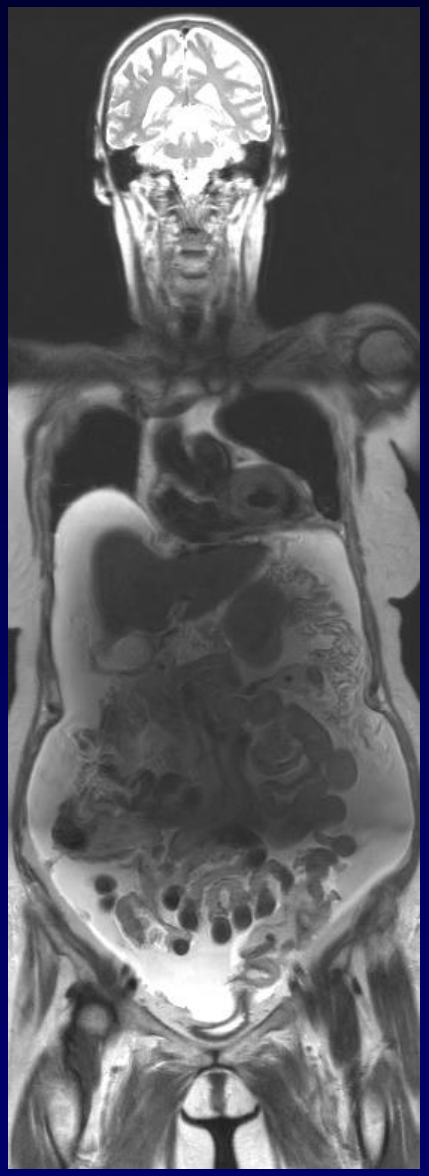


Microstructure



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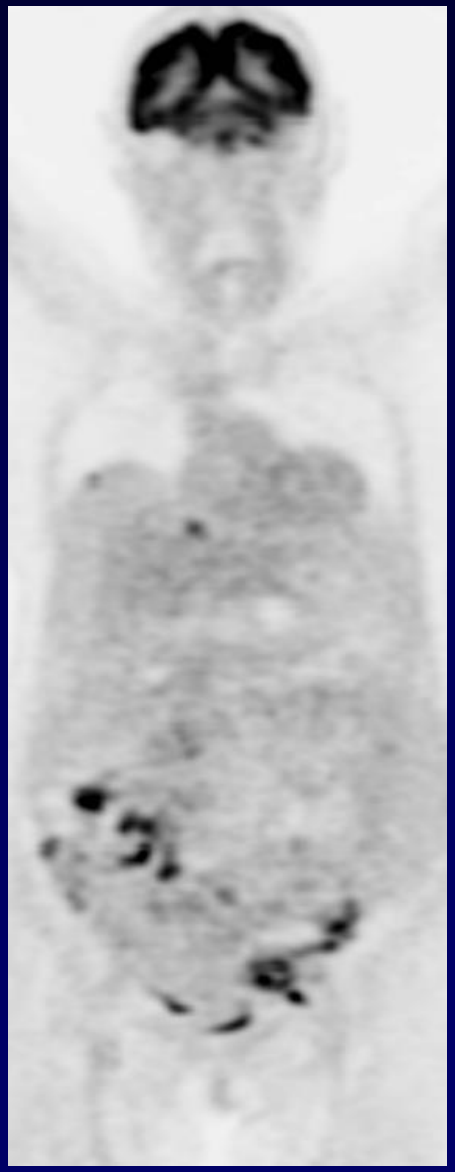

Glucose metabolism

(Whole Body) Diffusion MRI

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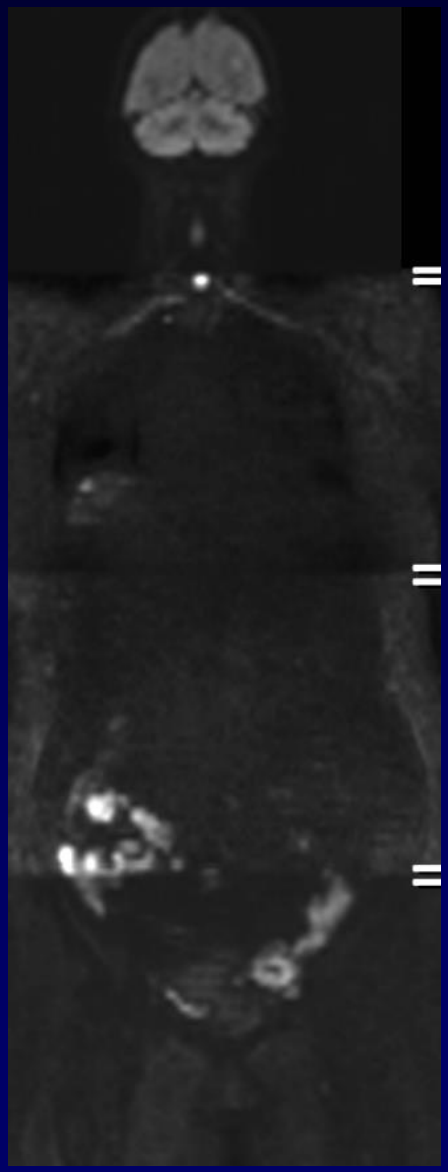

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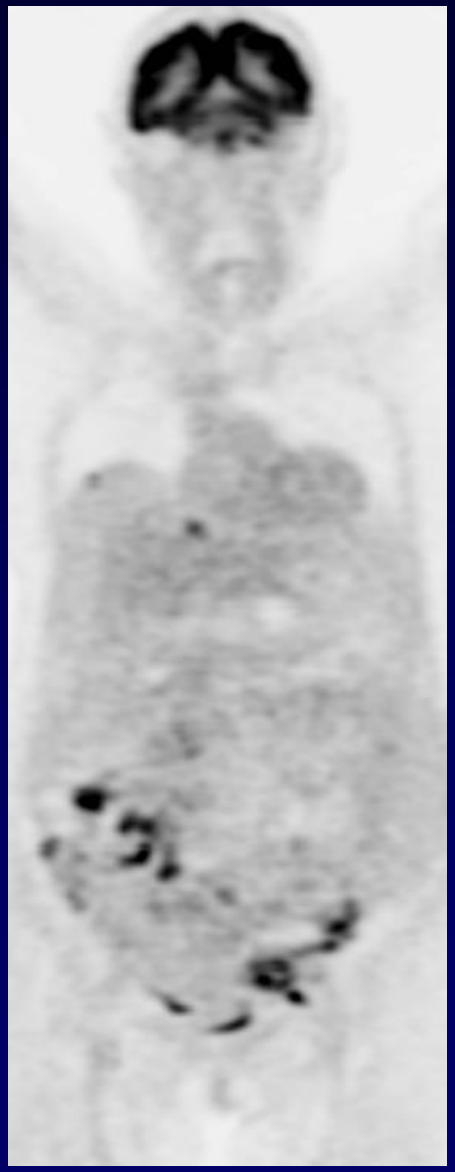


Glucose metabolism

Rationale to Use (WB-)DWI for Peritoneal Staging

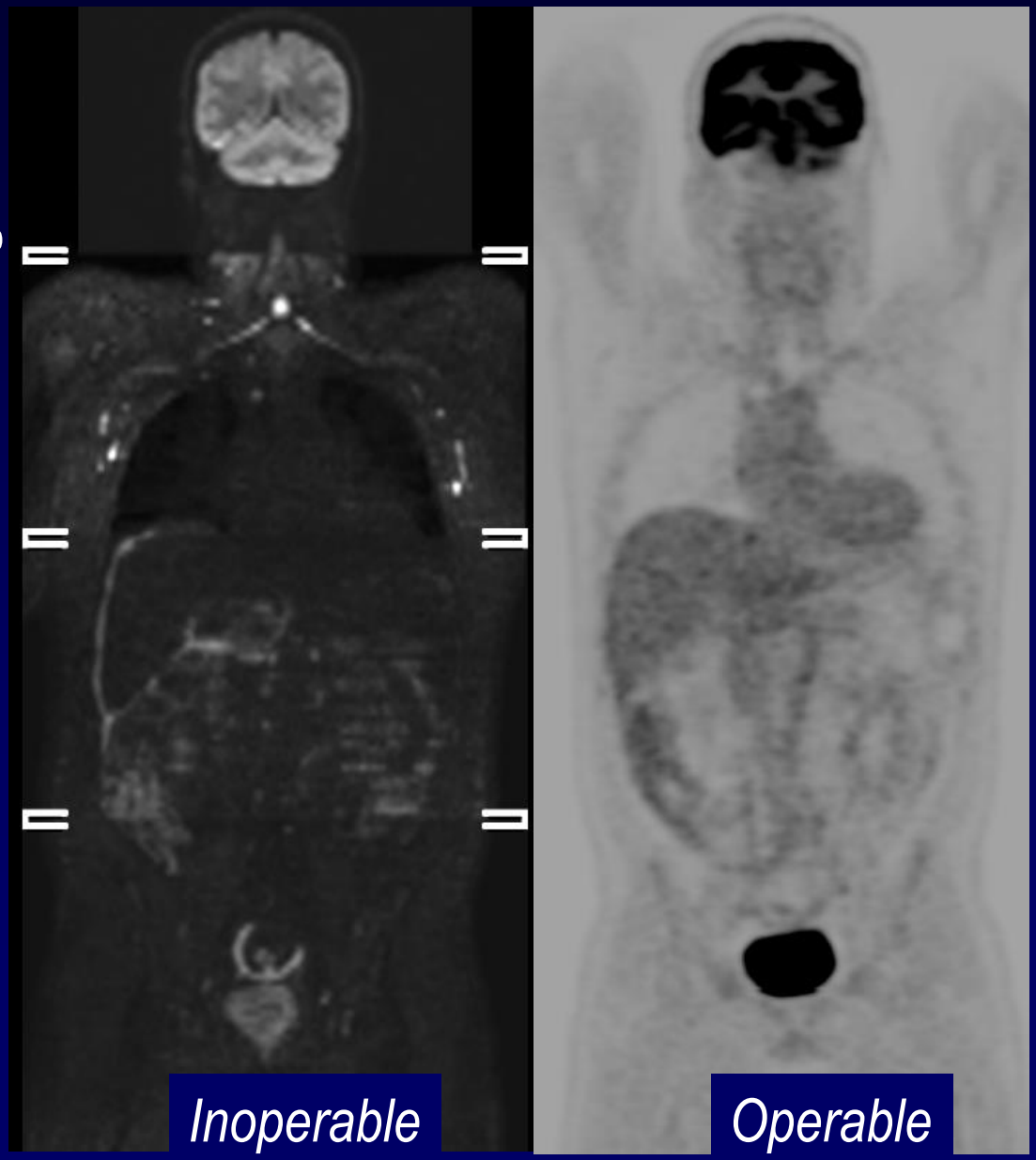
Ultrasound: sens = 69%

CT all lesions: sens = 85%-93%
CT (<1cm): sens = 7%-28 %

PET/CT: sens = 58%-100%

DWI: sens = 92%-95% (<1cm)

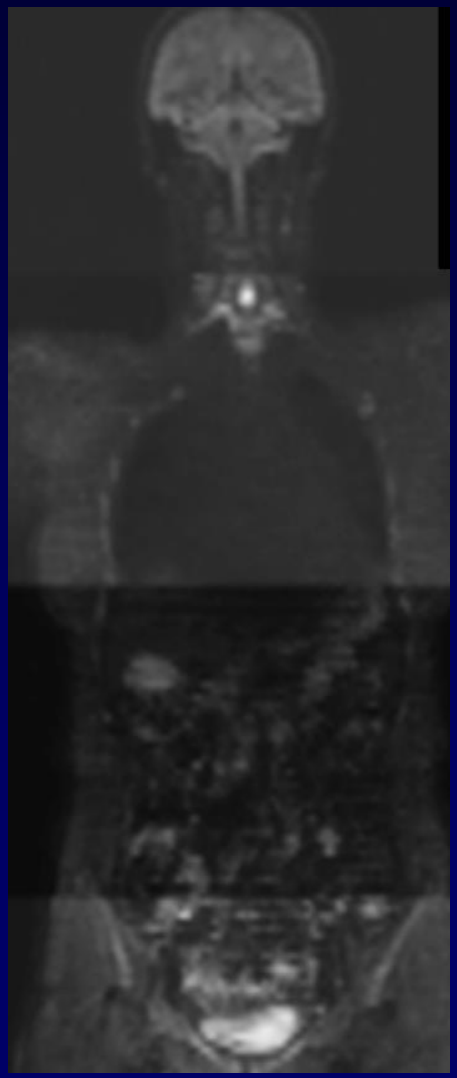
High spatial resolution (3-4 mm)
High contrast resolution
Functional capability
→ Independent of anatomy
→ Independent of metabolism



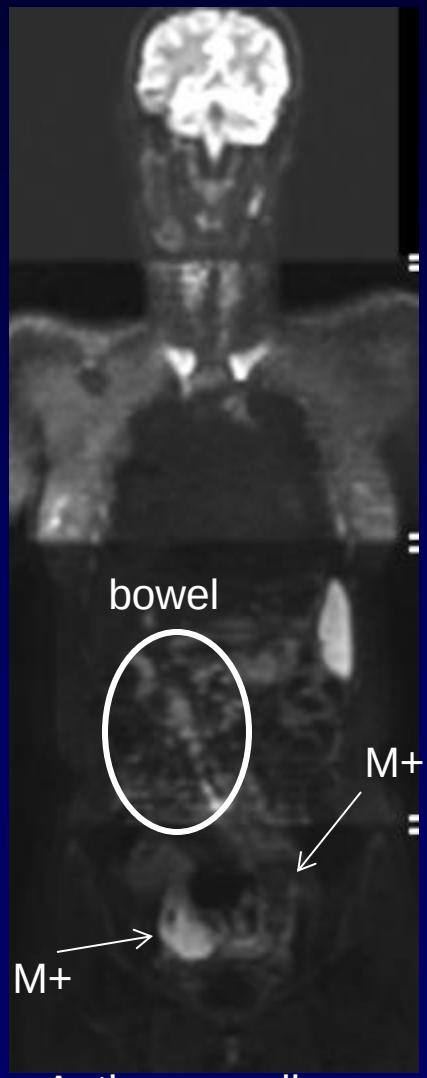
Kyriazi, Nat Rev Oncol, 2012

Patient Preparation:

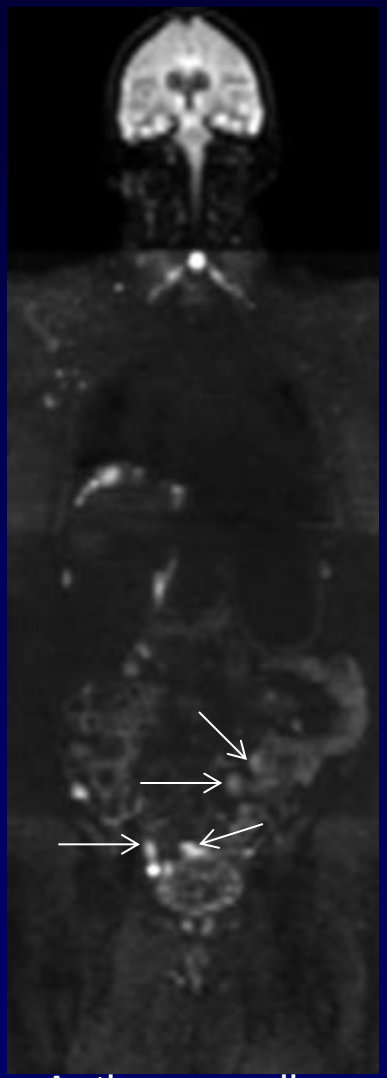
Antispasmodic
Peroral negative contrast



Physiological small bowel signal volunteer



Antispasmodic
Peroral PEG solution



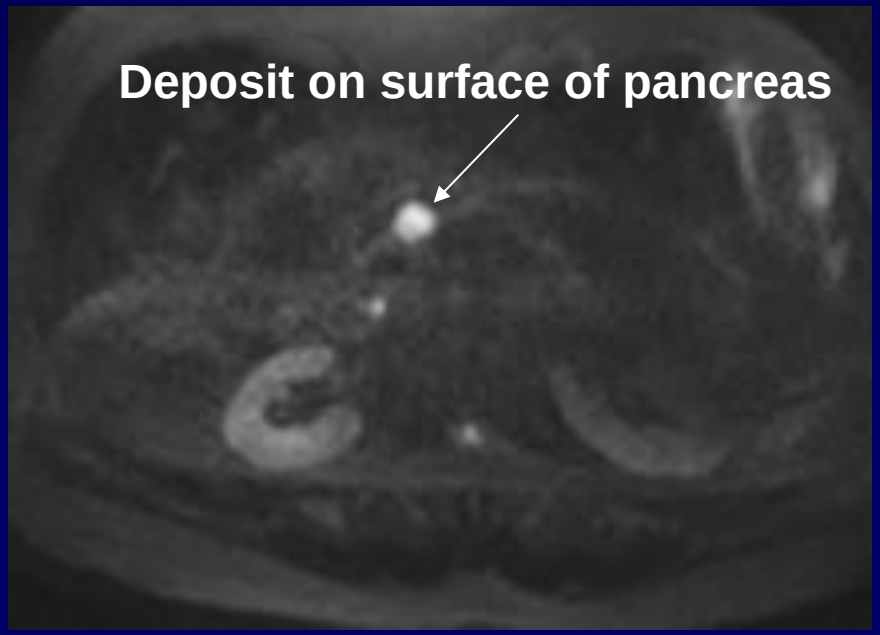
Antispasmodic
Peroral pineapple juice
(Manganese)

Staging of Ovarian Cancer : Problems

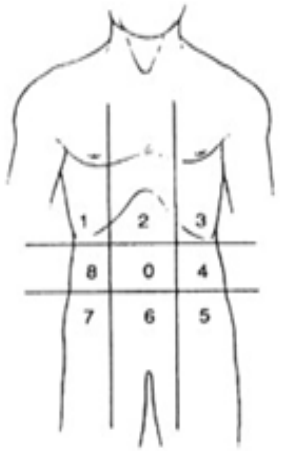
Large variability in definition of optimal debulking

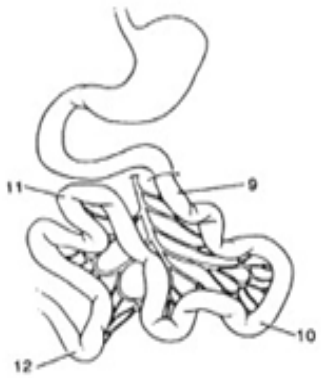
Large variability in operability criteria to achieve R0 resection

- → **DWI = flexible imaging technique and "personalized/adaptive radiology to the clinician**
- → **Oncologic board: Radiologist can provide better platform for decision making**
- → **Collaboration !!!!!!!!**

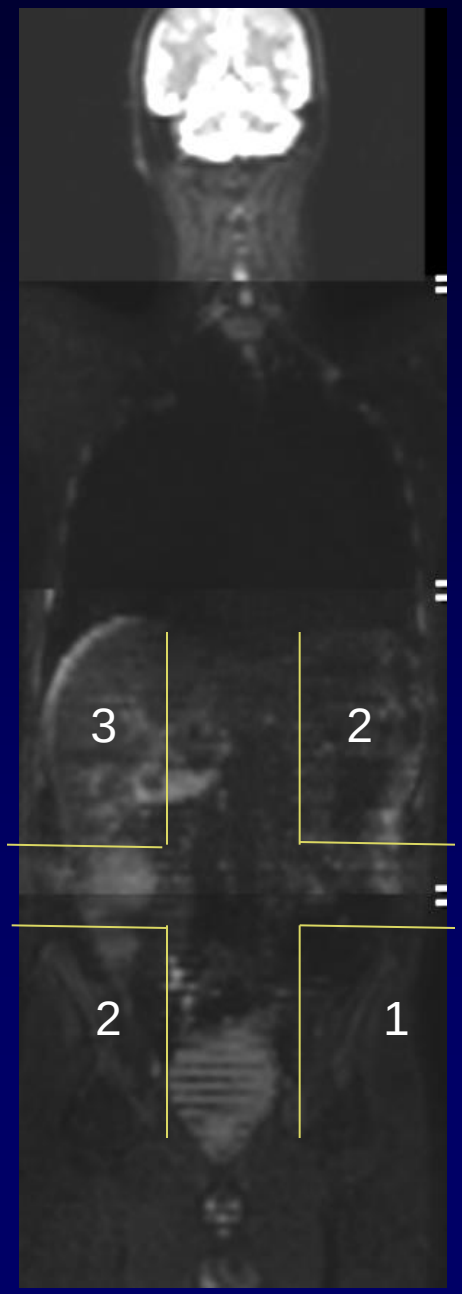


Quantified Scoring of Peritoneal Disease Load

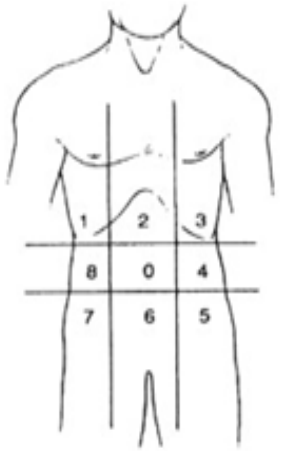


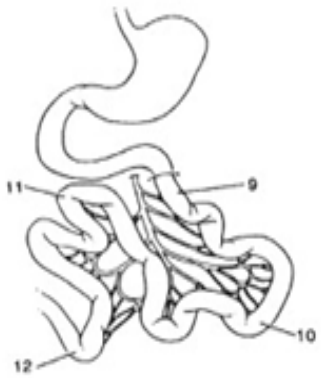


Regions		Lesion Size	Lesion SizeScore (the largest implants scored in each regions)
0	central	_____	LS 0 No tumor seen
1	Right upper	_____	LS 1 ≤ 0.5 cm
2	Epigastrium	_____	LS 2 > 0.5 cm to ≤ 5.0 cm
3	Left upper	_____	LS 3 > 5 cm or confluence
4	Left flank	_____	
5	Left lower	_____	
6	Pelvis	_____	
7	Right lower	_____	
8	Right flank	_____	
9	Upper jejunum	_____	
10	Lower jejunum	_____	
11	Upper ileum	_____	
12	Lower ileum	_____	
	PCI	0-39	



Quantified Scoring of Peritoneal Disease Load





Regions	Lesion Size
0 central	_____
1 Right upper	_____
2 Epigastrium	_____
3 Left upper	_____
4 Left flank	_____
5 Left lower	_____
6 Pelvis	_____
7 Right lower	_____
8 Right flank	_____
9 Upper jejunum	_____
10 Lower jejunum	_____
11 Upper ileum	_____
12 Lower ileum	_____
PCI	0-39

Lesion SizeScore (the largest implants scored in each regions)

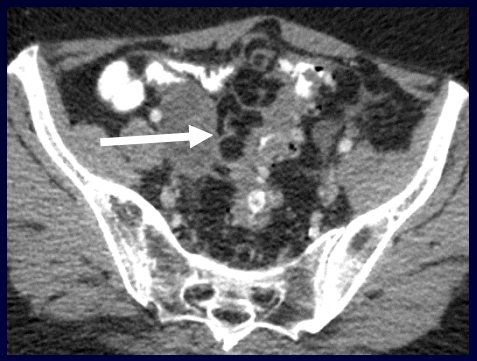
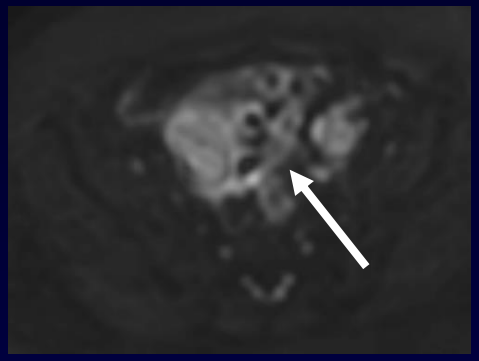
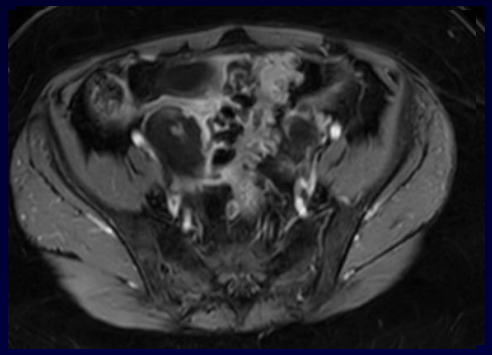
- **LS 0** No tumor seen
- **LS 1** ≤ 0.5 cm
- **LS 2** > 0.5 cm to ≤ 5.0 cm
- **LS 3** > 5 cm or confluence

Site-Based Anatomical Scoring – Leuven / ESSEN

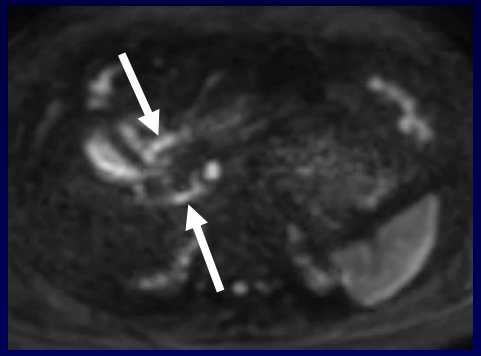
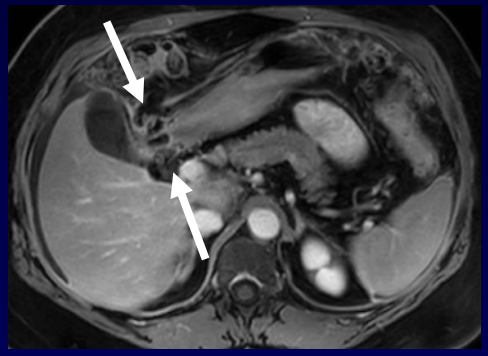
Table 1
Criteria for primary chemotherapy and for interval debulking surgery in FIGO stages IIIC and IV ovarian carcinoma.

Criteria	Essen criteria	Leuven criteria
Diagnosis:	Biopsy with histologically proven epithelial ovarian (or tubal or peritoneal) cancer FIGO stage IIIC-IV	
	-	Or fine needle aspiration proving the presence of carcinoma cells in patients with a suspicious pelvic mass if CA125 (KU/L)/CEA (ng/mL) ratio is > 25. If the serum CA125/CEA ratio is ≤ 25, imaging or endoscopy is obligatory to exclude a primary gastric, colon or breast carcinoma
Abdominal metastases:	Involvement of the superior mesenteric artery	
	Diffuse deep infiltration of the radix mesenterii of the small bowel	
	Diffuse and confluent carcinomatosis of the stomach and/or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy	
	Multiple parenchymatous liver metastases in both lobes	Intrahepatic metastases
	Tumor involving large parts of the pancreas (not only tail) and/or the duodenum	Infiltration of the duodenum and/or pancreas and/or the large vessels of the ligamentum hepatoduodenale, truncus coeliacus or behind the porta hepatis
	Tumor infiltrating the vessels of the lig. Hepatoduodenale or truncus coeliacus	
Extra-abdominal metastases:	Not completely resectable metastases, as eg. - Multiple parenchymal lung metastases (preferably histologically proven) - Non resectable lymphnode metastases - Brain metastases	All excluding: - Resectable inguinal lymph nodes - Solitary resectable retrocrual or paracardial nodes - Pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumors
Patients characteristics/others	Impaired performance status and co-morbidity not allowing a "maximal surgical effort" to achieve a complete resection	
	Patients' non-acceptance of potential supportive measures as blood transfusions or temporary stoma	

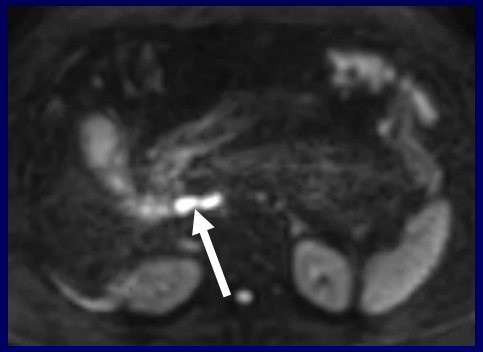
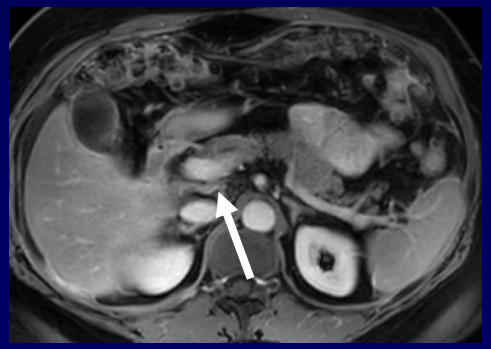
Vergote I, et al. *Gynecol Oncol.* 2013;128(1):6-11.

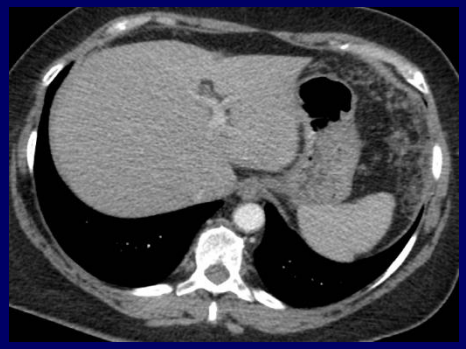
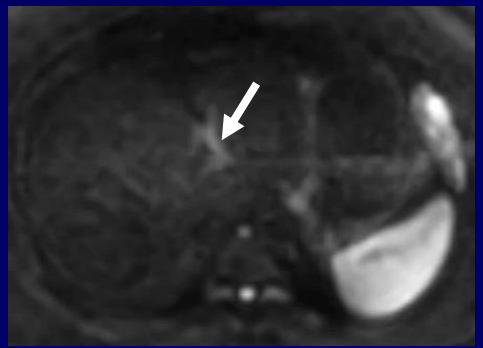
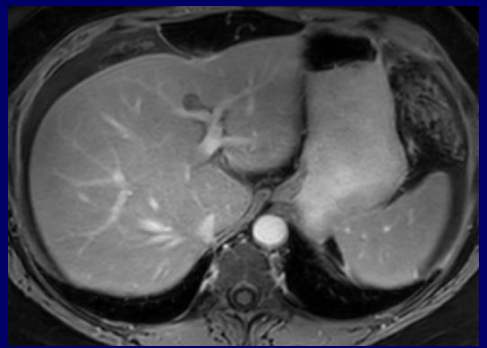
Invasion
(meso)sigmoid

Invasion
- Stomach
- Duodenum

Nodal metastases
Behind porta hepatis

Deep infiltration
Liver hilum
Behind porta hepatis

Recent Studies: (WB) DWI

- **Low RN, 2012 – n = 32 – DWI + DCE-MRI: 88% sensitivity, 74% specificity**
  disease sites
  : Match of PCI with laparoscopy 29 of 33 patients

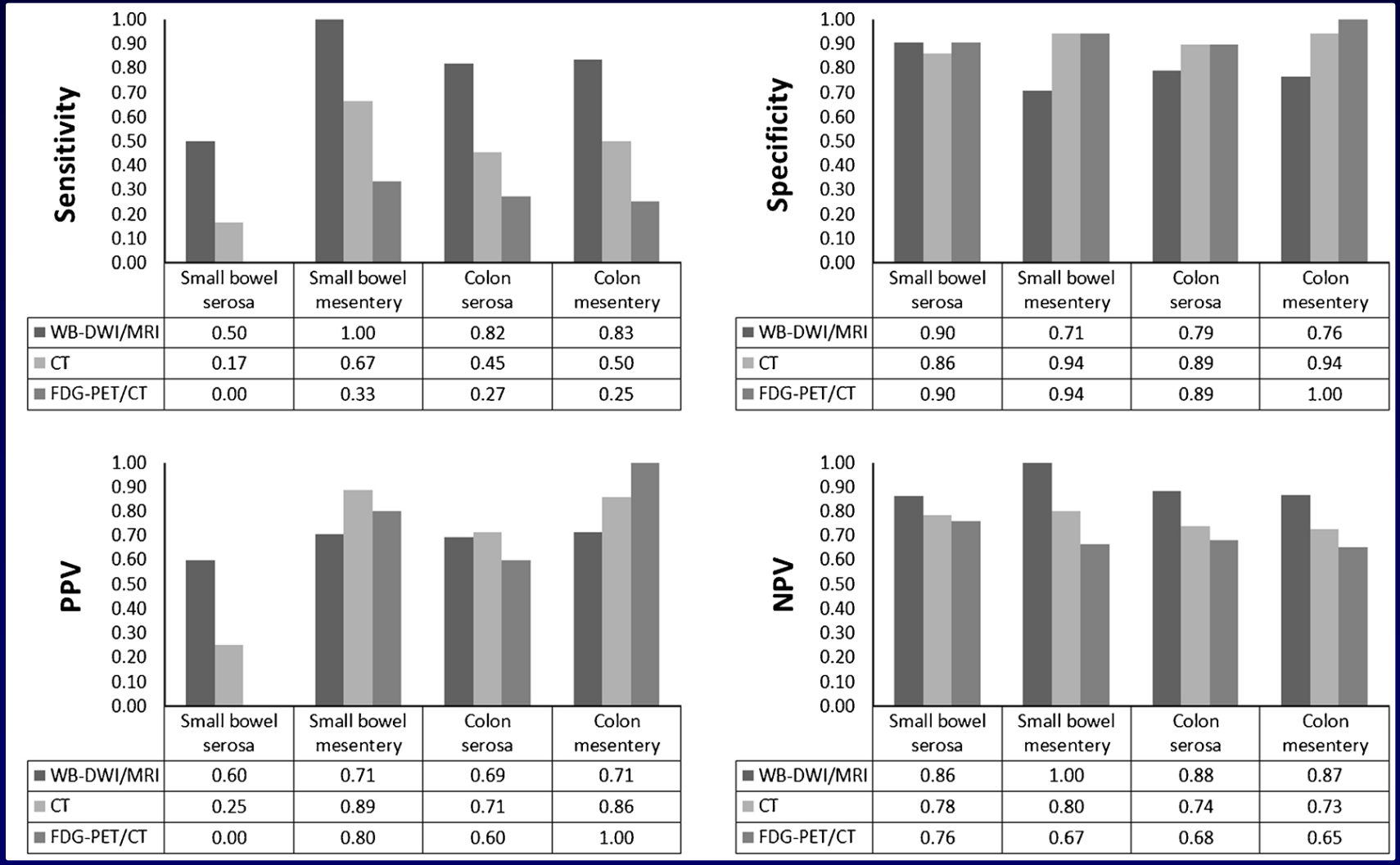
- **Espada et al, 2013 – n = 34 – DWI: 91% accuracy for predicting suboptimal surgery**
  Compared to explorative laparotomy

- **Michielsen et al, 2014 = n = 32 – WB-DWI: 91% accuracy peritoneal staging**
  CT: 75% accuracy peritoneal staging
  FDG-PET/CT: 71% accuracy peritoneal staging

Equal accuracy WB-DWI – FDG-PET/CT > CT for detecting distant metastases.

Rockall AG. *Curr Opin Oncol.* 2014;26(5):529-535.

Where Does DWI Make a Major Difference?



	Small bowel serosa	Small bowel mesentery	Colon serosa	Colon mesentery
WB-DWI/MRI	0.50	1.00	0.82	0.83
CT	0.17	0.67	0.45	0.50
FDG-PET/CT	0.00	0.33	0.27	0.25

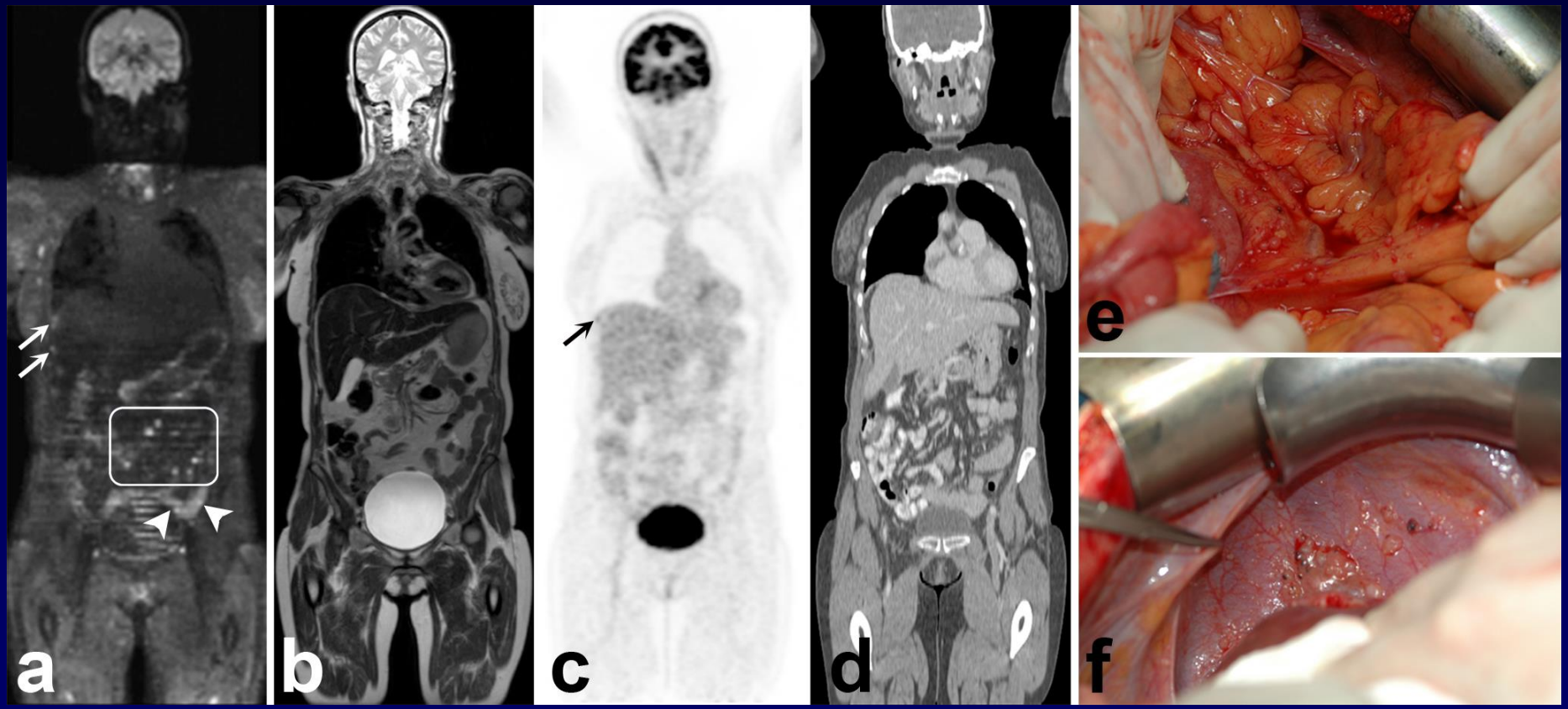
	Small bowel serosa	Small bowel mesentery	Colon serosa	Colon mesentery
WB-DWI/MRI	0.60	0.71	0.69	0.71
CT	0.25	0.89	0.71	0.86
FDG-PET/CT	0.00	0.80	0.60	1.00

	Small bowel serosa	Small bowel mesentery	Colon serosa	Colon mesentery
WB-DWI/MRI	0.90	0.71	0.79	0.76
CT	0.86	0.94	0.89	0.94
FDG-PET/CT	0.90	0.94	0.89	1.00

	Small bowel serosa	Small bowel mesentery	Colon serosa	Colon mesentery
WB-DWI/MRI	0.86	1.00	0.88	0.87
CT	0.78	0.80	0.74	0.73
FDG-PET/CT	0.76	0.67	0.68	0.65

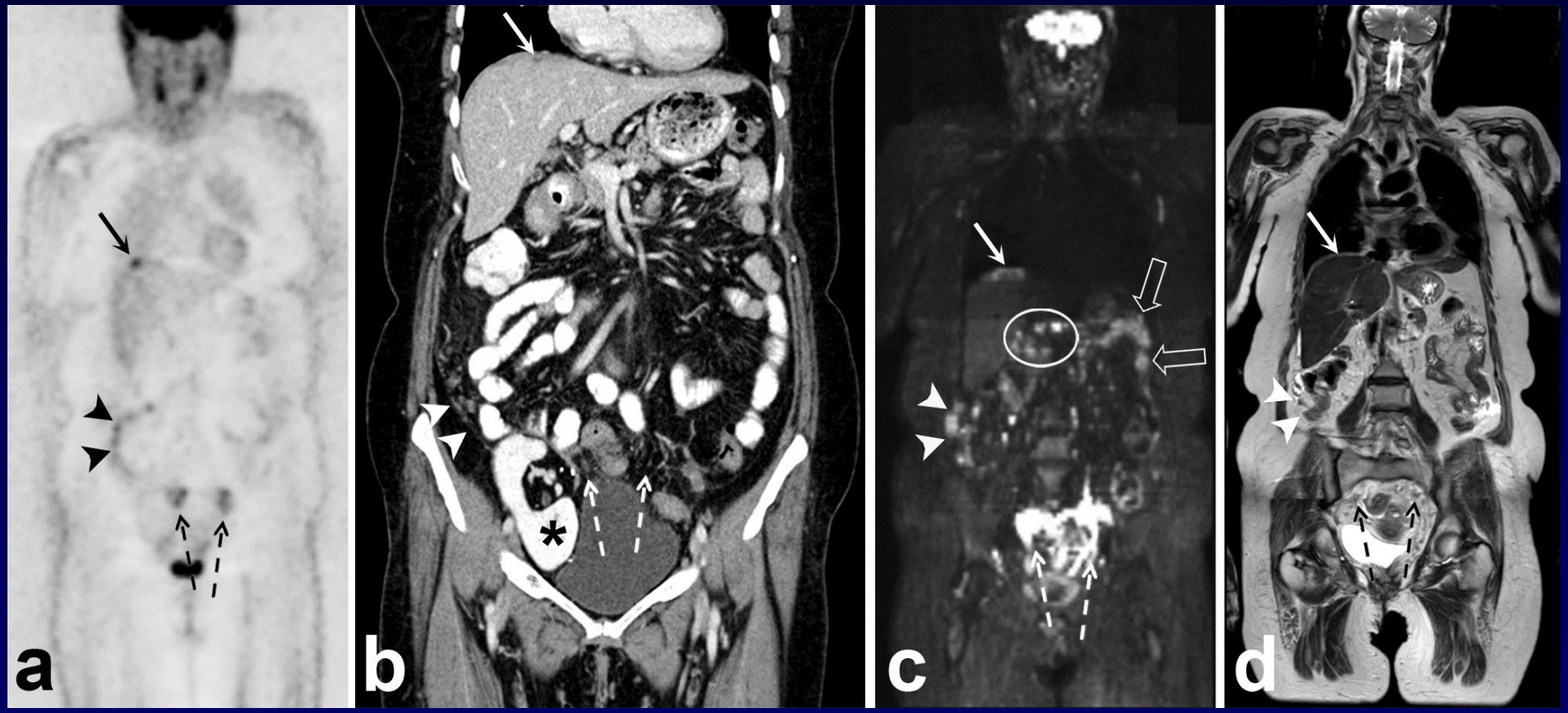
Main gain by assessing disease load at intestinal serosa and mesentery

Staging of Ovarian Cancer: Key Points



Stage IIIB ➔ operable disease

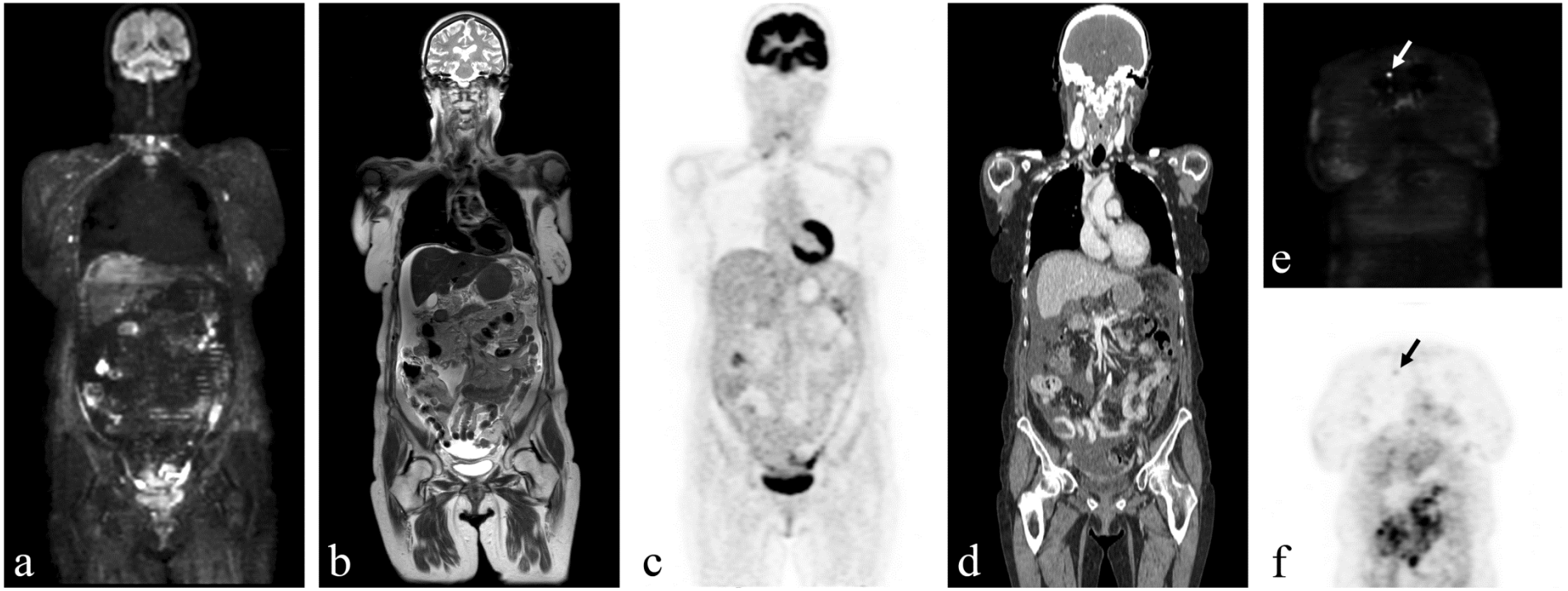
Staging Ovarian Cancer: Key Points



Unlikely to reach R0 resection

Diffuse and confluent carcinomatosis of the stomach and/or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy

Staging of Ovarian Cancer: Key Points

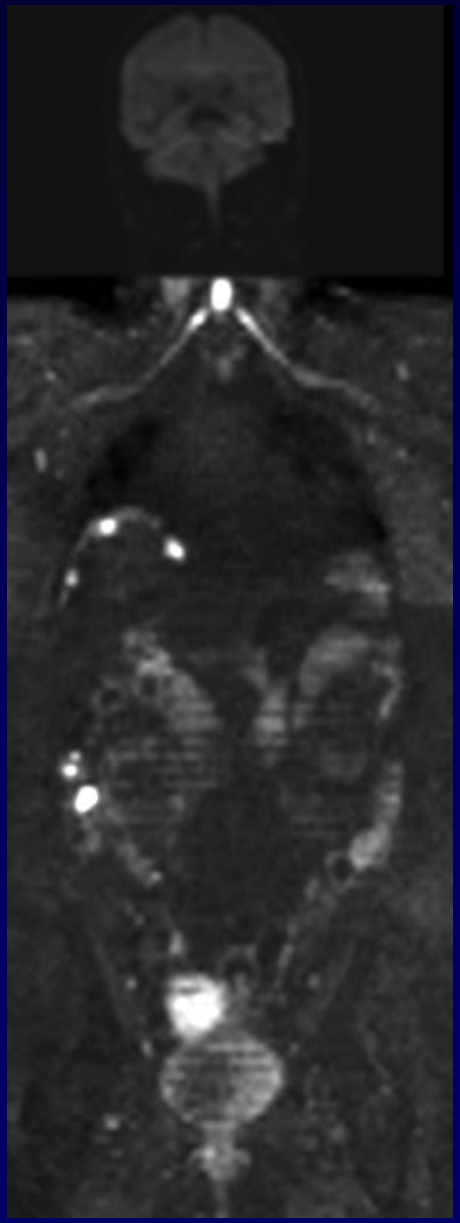


Diffuse and confluent carcinomatosis of the stomach and/or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy

Extra-abdominal metastases:	Not completely resectable metastases, as eg. - Multiple parenchymal lung metastases (preferably histologically proven) - Non resectable lymphnode metastases - Brain metastases	All excluding: - Resectable inguinal lymph nodes - Solitary resectable retrocrual or paracardial nodes - Pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumors

Stage IVb ➔ Unlikely to reach R0 resection

Staging Ovarian Cancer: Key Points



Extensive disease at the diaphragm:

Diaphragmatic resection necessary

↓

Age and general condition of patient

DWI needs clinical correlation
Oncologic board

Ovarian Cancer : Postoperative Imaging

- Current standard for assessment of completeness of resection:
  →Intraoperative macroscopic visual evaluation

- Imaging (computed tomography) not always used in routine clinical situation

- Frequently required in prospective clinical trials

- Possible advantage of “objective” imaging assessment post-operative?:
  - Baseline for chemotherapy
  - Patient referred for systemic treatment, surgery elsewhere
  - Document amount of residual disease

- Postoperative or more importantly, postchemotherapy, CT can serve as baseline examination in case of imaging evaluation of suspected recurrence

Concordance Intraoperative Findings Versus CT?

Table 5. Subset Analysis of Concordant and Discordant Groups

Variable	No Lesions > 1 cm or Masses > 1 cm (QA scale 1 or 2; n = 41)		Residual Lesions > 1 cm (QA scale 4 or 5; n = 30)		*P*
	No. of Patients	%	No. of Patients	%	
BMI, kg/m^2					.17
Median	25		23		
Range	17-39		18-42		
BMI > 30 kg/m^2	7	17	5	17	.88
EBL, mL					.35
Median	700		900		
Range	50 to 7,000		100 to 7,000		
EBL > 1,000 mL	14	34	14	47	.29
Residual disease					
Microscopic/no gross residual	19	46	8	27	.07
0.1-0.5 cm	14	34	9	30	
0.6-1.0 cm	8	20	13	43	
Time between surgery and CT scan, days					.69
Median	14		20		
Range	6-32		4-33		
No. of patients with > 14 days between surgery and CT scan	20	49	17	57	.51
No. of patients with > 21 days between surgery and CT scan	12	29	13	43	.22

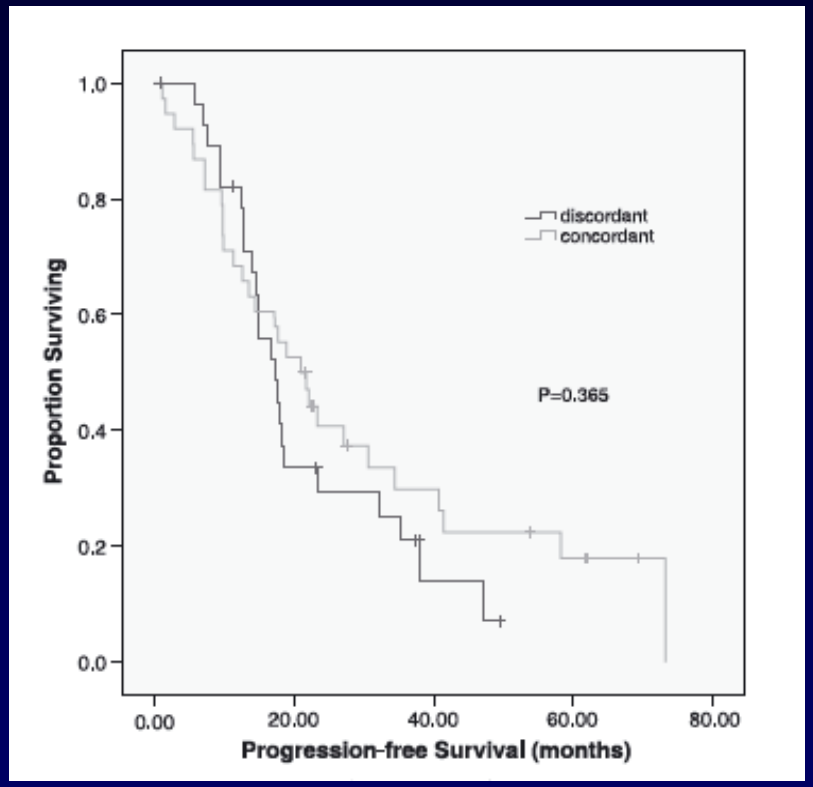
Abbreviations: QA, qualitative analysis; BMI, body mass index; EBL, estimated blood loss; CT, computed tomography.

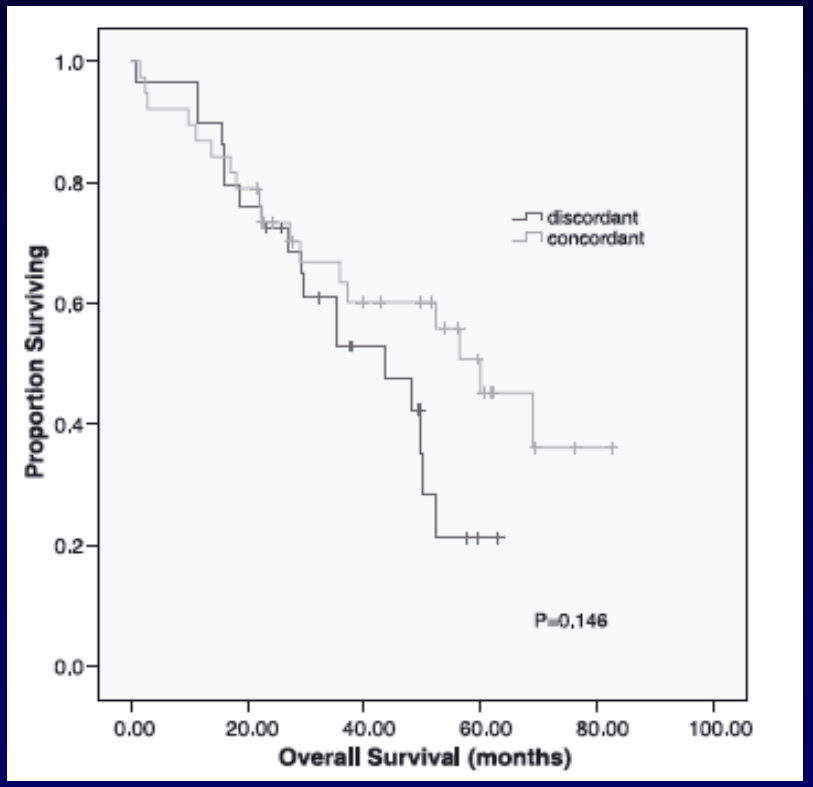
Optimal debulking :
52% concordance between surgical assessment and post-operative CT-scan
Underestimation by surgeon?
Overestimation by radiologist?
Clinical impact?

Routine post-operative CT-scan not recommended

Chi DS, et al. *J Clin Oncol*. 2007;25(31):4946-4951.

Concordance Intraoperative Findings Versus CT? Clinical Impact ?





Residual disease (at surgery), age, and disease stage prognostic for survival

No impact on survival of disconcordant findings
Possibly disease overestimation at CT or early tumor regrowth
Routine postoperative CT not recommended

Chi DS, et al. *Int J Gynecol Cancer.* 2010;20(3):353-357.

Intraoperative Findings Versus CT Clinical Impact ?

TABLE 2. Reported residual lesions status by CT

	Total Patients (n = 51)	PS Group (n = 26)	IDS Group (n = 25)
No masses >1 cm or masses >1 cm (QSS scale 1 or 2), n (%)	30 (59)	20 (77)	10 (40)
Masses >1 cm (QSS scale 3), n (%)	2 (4)	0	2 (8)
Masses >1 cm (QSS scale 4), n (%)	5 (10)	2 (8)	3 (12)
Masses >1 cm (QSS scale 5), n (%)	14 (27)	4 (15)	10 (40)

TABLE 3. Univariate and multivariate Cox regression for overall survival

Variables	HR	95% CI	*P*
Univariate Cox regression			
Age	1.03	0.98–1.07	0.27
Residual disease by CT (QSS = 4–5) compared with no residual disease	1.76	0.74–4.19	0.20
Residual disease by CT (QSS = 4–5) <1 cm compared with no residual disease	0.63	0.08–5.11	0.66
Residual disease by CT (QSS = 4–5) >1 cm compared with no residual disease	2.57	1.02–6.48	0.045
Residual disease assessed by surgeon	3.06	1.29–7.27	0.011
Patient group (PS or IDS)	1.88	0.78–4.54	0.16
FIGO stage 3	2.50	0.83–7.53	0.10
Grade 3	2.06	0.80–5.32	0.14
Multivariate Cox regression			
Residual disease assessed by surgeon FIGO stage 3	3.40	1.42–8.16	0.006

Sala E, et al. *Int J Gynecol Cancer.* 2011;21(2):296-301.

Intraoperative Findings Versus CT Clinical Impact ?

- Only 59% correlation between intraoperative findings and postoperative CT
- Optimal primary or interval debulking
- Upper left quadrant and midabdomen
- No explanation for disconcordance
- Only disease stage and surgical assessment of residual disease significant prognostic factors
- Possible additional value of postoperative CT =
  → Baseline for chemotherapy
  → Only when surgically documentend residual disease <1 cm

Take-Home Messages

- **Upfront or pretreatment imaging :**
  Functional imaging may improve prediction of optimal debulking, aid in patient selection for primary or interval surgery

FDG-PET/CT → nodal staging as major strength
→ insufficient accuracy to predict peritoneal operability alone

WB-DW/MRI → peritoneal staging major strength – roadmap for surgeon
→ Currently early stage of development
→ Need for standardized disease score

- **Postoperative imaging :**
  No routine indication
  Surgical intraoperative prognostic/residual disease
  Postoperative CT may be useful if surgically residual disease <1 cm

2015

Progress and Controversies in Gynecologic Oncology Conference