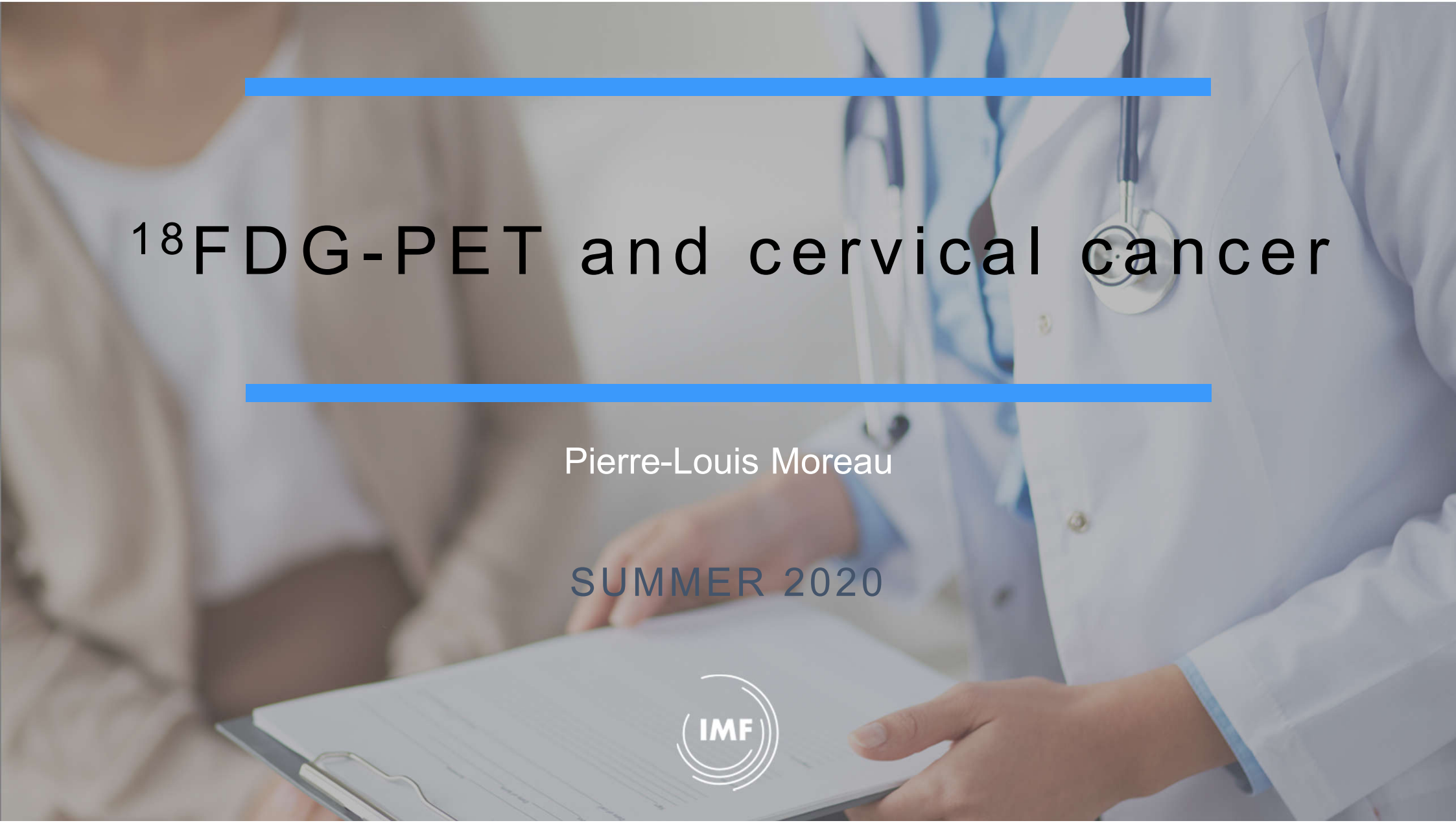


^{18}FDG-PET and cervical cancer

Pierre-Louis Moreau

SUMMER 2020

IMF

Reminders

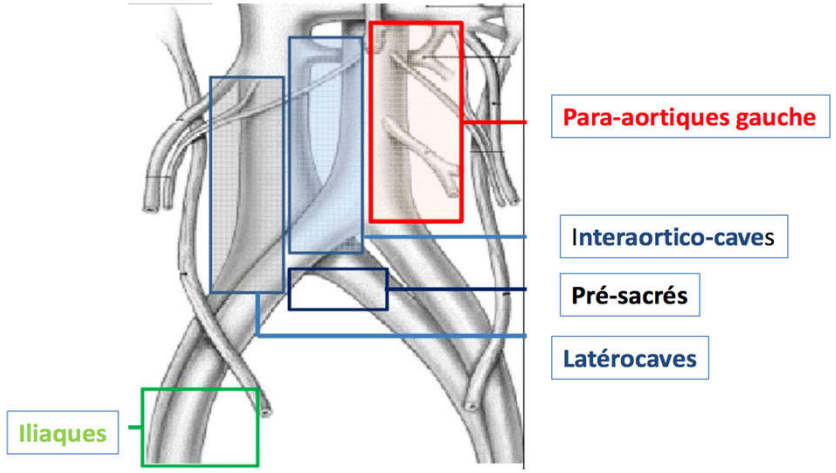
- 4th most common cancer in women, most common cause of death in less than 35 yo
- Most common cause of cancer death in Sub-Saharan Africa and South-Eastern Asia
- Mostly attributable to HPV infection
- Primary prevention by HPV vaccines, secondary prevention by cervical smear
- Mostly asymptomatic, or vaginal bleeding, intermenstrual or postcoital ; renal failure due to ureteric obstruction when advanced.

Reminders

- Initial assessment: clinical T-staging and pelvic MRI with diffusion-weighted sequences.
- Therapeutic strategy: localized excision when microinvasive disease ; radical surgery (exentération) when locally non advanced ; chemoradiotherapy followed by intrauterine brachytherapy when locally advanced.
- Radiation fields extended to pelvic nodes and para-aortic nodes when N+.

Drainage

- High rate of lymphatic extension. Drainage is mostly bilateral.
- First in extern iliac nodes, then primitives iliacs nodes, and para-aortics.
- Extension to para-aortic nodes is exceptional if no external iliac extension.



M. Wartski, place de la TEP au FDG dans le cancer du col

New FIGO staging in 2018

- I : Carcinoma strictly confined to the cervix
- II : Carcinoma invades beyond the uterus but not onto the lower third of the vagina or to the pelvic wall
- III : Extension to the lower third of the vagina/ pelvic wall/ hydronephrosis / pelvic or para-aortic lymph nodes
- Extension beyond the pelvis/bladder/rectum

Table 1 FIGO Staging of Cancer of the Cervix Uteri 2018[5]

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA, lesion limited to cervix uteri)
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or paraaortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumour size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous oedema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Changes in 2018 FIGO

- Validated in an American retrospective involving about 20,000 patients Ib to III
- Appearance of a stage Ib3, because of a high difference in mortality between stage Ib1 and Ib2
- Appearance of stage IIIc1 and IIIc2 because of a high difference in mortality between IIIc with only pelvic nodes and IIIc with para-aortic pelvic nodes.

Table 2 Changes in Cervical Cancer Staging System[6]

Characteristics	2014 FIGO System	2018 FIGO System
Stage IB1	Tumour size <4 cm	Tumour size <2 cm
Stage IB2	Tumour size >4 cm	Tumour size 2-3.9 cm
Stage IB3	n/a	Tumour size >4 cm
Stage IIIC1	n/a	Pelvic lymph node metastasis only
Stage IIIC2	n/a	Para-aortic lymph node metastasis

^{18}F-FDG PET and cervical cancer

I. Staging

II. Prognostic Assessment

III. Response Assessment

IV. Relapse

Staging T and N

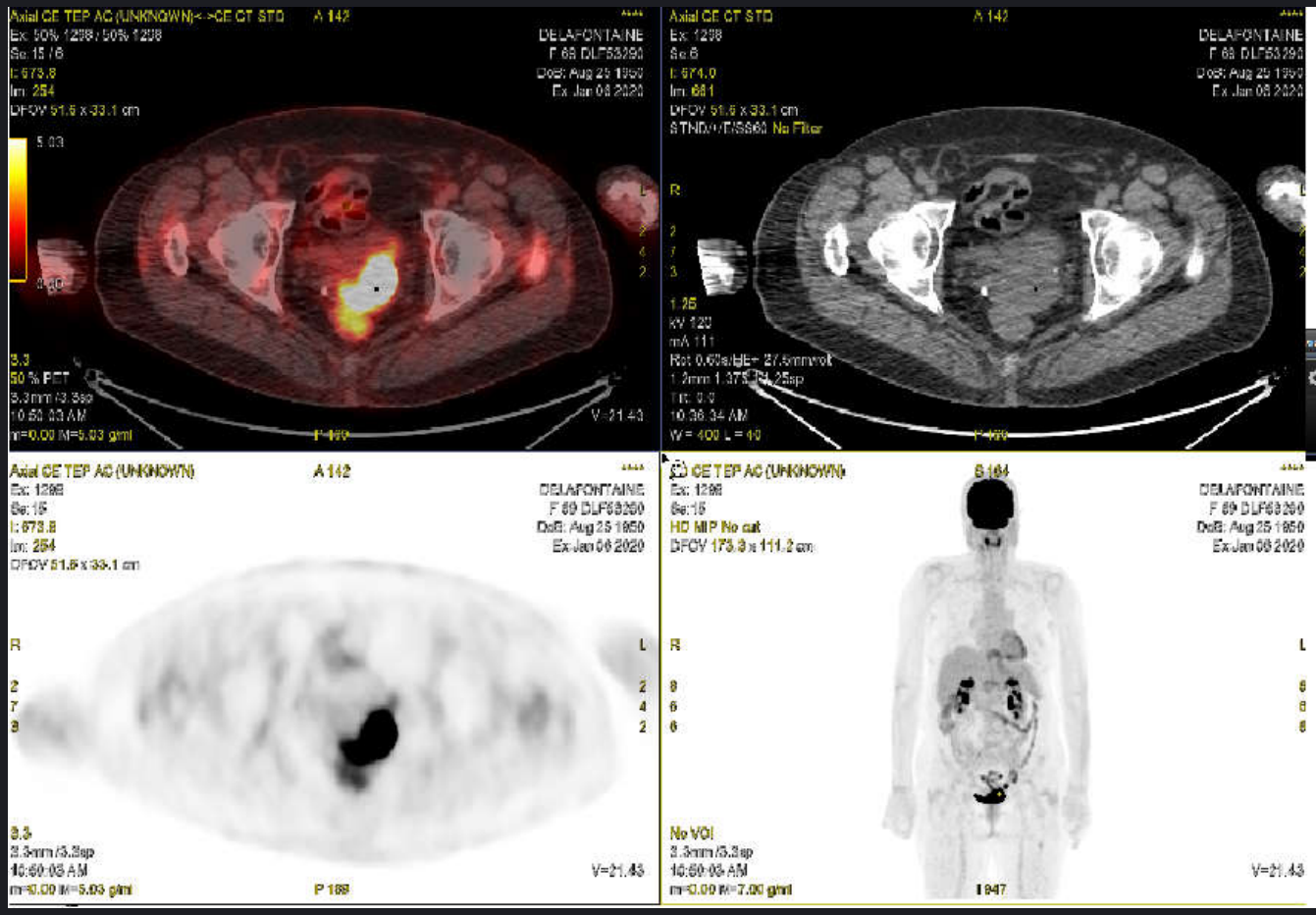
- No indication of PET for T-staging because of limited spatial resolution.
- N : no indication of PET when locally non advanced because of a low prevalence of nodal disease, and even if N+ : micrometastases are mostly not detected by PET (sensitivity of 32% in a prospective study involving 159 patients Ib1 – IIa < 4 cm).
- When locally advanced disease : PET is superior to contrast-enhanced CT and MRI for nodal disease (meta-analysis of 41 studies involving 4121 patients : Se 82% et Sp 95% for PET versus Se 56% et Sp 91% for MRI ; 2nd meta-analysis of 27 studies involving 8507 patients, standard = surgical pathology : Se 72% et Sp 96%)

Stadification N

- Detection of para-aortic nodal disease : Sp 97% but Se 34% in a meta-analysis.
- Sensitivity could be better with contrast-enhanced CT (Se 50% vs 42% and Sp identic in a multicenter prospective trial involving 153 patients).
- Staging lymphadenectomy still indicated even when PET is negative, even if a mlulticenter trial involving 237 patients showed that a lymphadenectomy was positive only in 12% of patients with a negative PET, with a rate of 12% false negative.

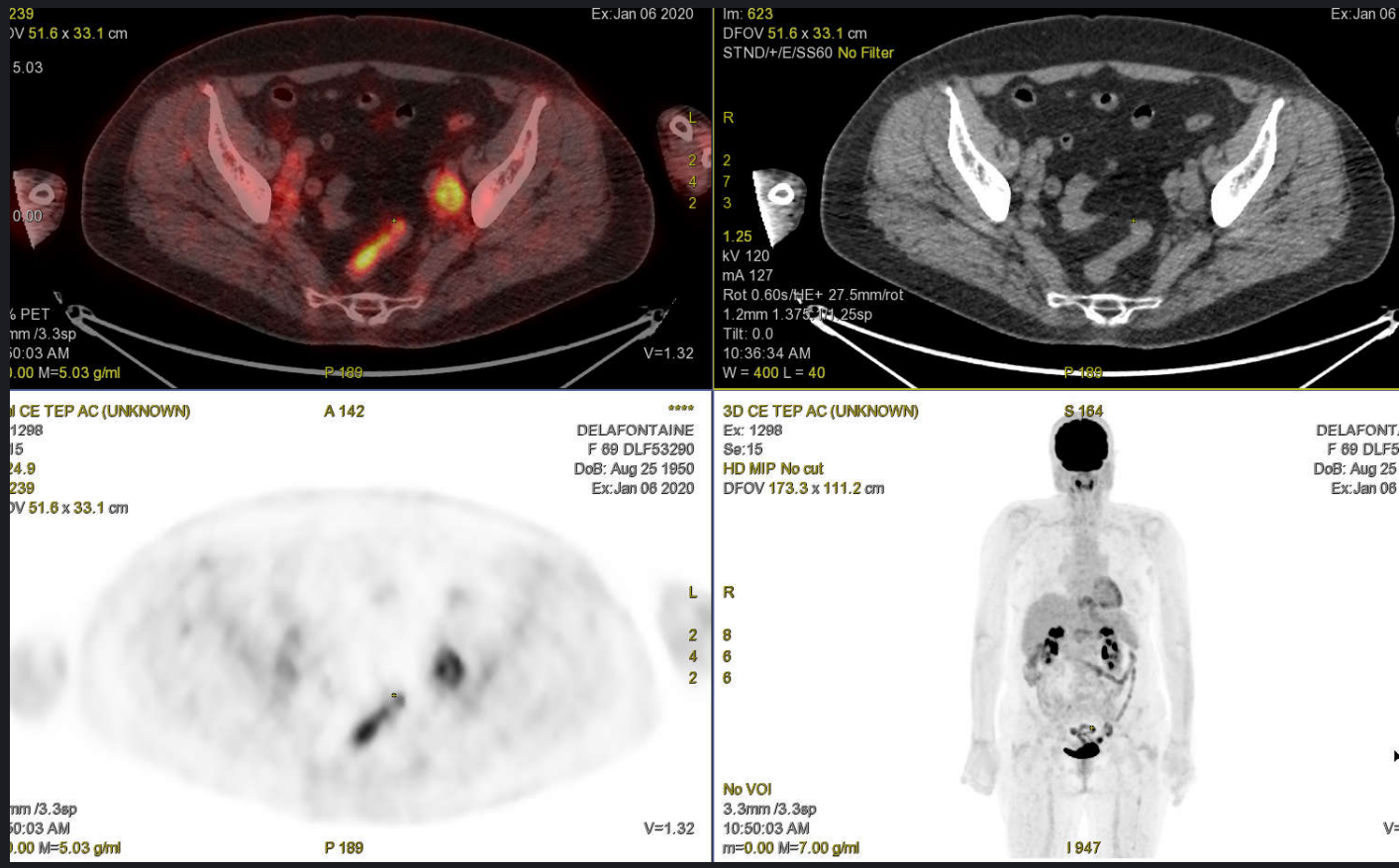
Mrs G, 68 yo

- Initial staging of a 4 cm cervical cancer
- Pelvic lesion in left uterine strongly hypermetabolic, 47 mm and SUVmax 26,5



Mrs G, 68 yo

External iliac nodes strongly hypermetabolic



Stadification M

- 6,2% of metastasis in PET (retrospective single center study involving 1158 patients).
- Main sites : lungs (35%), omentum, bone and liver.
- Major impact of TEP for staging of locally advanced cancer, by altering treatment in one-third of patients. In a meta-analysis of 10 studies : 11 - 19% of patients were upstaged with resulktatn modification radiotherapy treatment field.

Staging : synthesis

- American National Comprehensive Cancer Network : TEP when Ib2
- Royal College of Radiologists UK : if exenteration surgery
- European societies : when locally advanced (Ib2)
- False positive : ovulation, menstruations, uterine fibroids, endometriotic cysts, bladder and bowel activity.
- False negative : some mucinous or necrotic tumours, masking of serosal, peritoneal or nodal disease by bowel or bladder activity, small lymph nodes.

Prognostic impact of TEP: SUVmax

- Main prognostic factors in literature : SUVmax, MLV et TLG.
- In the largest retrospective involving 287 patients [Ia2 - IVb] : SUVmax was the only significant independent predictor for overall survival in multivariate analysis of histology, nodal status, tumor volume (ex : OS 95% if SUVmax < 5,2 ; 44% if SUVmax > 13,3.
- However, SUVmax has a poor prognostic impact pronostique for PFS or relapse, in a retrospective involving 53 patients.
- Limiting factors of SUVmax : does not represent the metabolic activity of the entire tumour, variates with type of scanner, reconstruction algorithm, weight and blood glucose level.

Prognostic impact of PET : other factors

- Méta-analysis of 12 studies involving 660 patients : MLV et TLG are highly predictive of adverse events or death.

- Prospective cohort study involving 560 patients : PET-positive lymph nodes are highly predictive of relapse and disease-specific survival, above all when PET-positive lymph nodes are distant.

- SUVmax of nodes could also be predictive of relapse and OS (SUVmax > 7,5).

- Multiple textural analysis have also been assessed…

Response Assessment

- Several studies recommend the use of PET 3 months post-treatment when locally advanced cancer.
- First, 2 retrospectives involving 238 patients with locally advanced cancer proposed 3 categories of response : complete metabolic response, partial metabolic response and progressive disease. This categorization was significantly correlated with OS, PFS and relapse.
- But risk of false positive when partial response : 65% of patients with partial response had negative biopsy.
- Excellent NPV of post-treatment PET but low PPV.

Response Assessment

- A study proposed a score of therapeutic assessment :
  - Complete response with no residual FDG uptake
  - Focal uptake less than mediastinal blood pool activity
  - Focal uptake greater than mediastinal blood pool but less than liver activity : indeterminate response
  - Partial response whenfocal uptake greater than liver activity
  - Progression disease when focal intense uptake greater than twice background hepatic activity or new foci

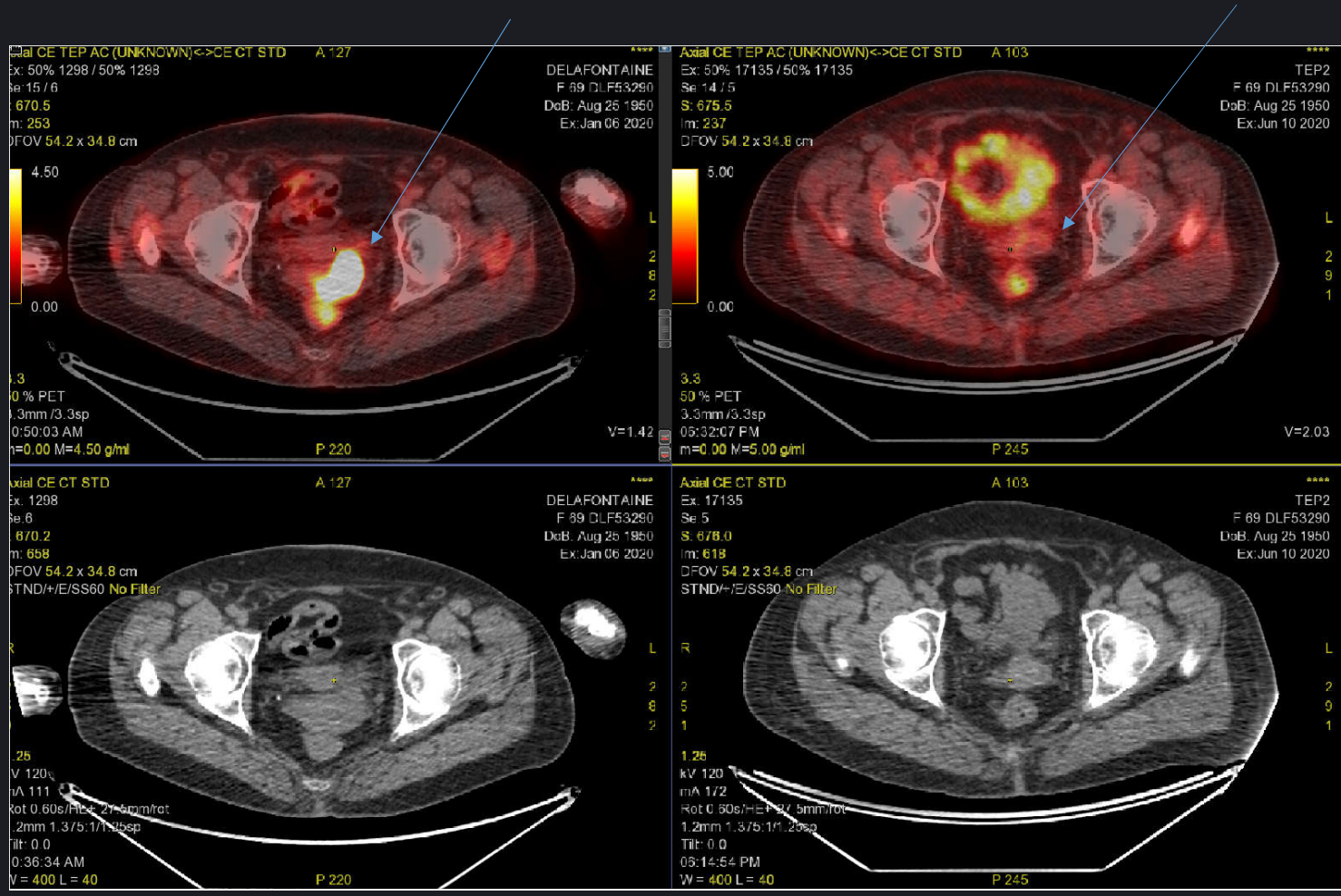
- This score significantly correlated with OS and PFS

Réponse thérapeutique : recommandations

- ANCCN : TEP 3 - 6 mois post-treatment when Ib2
- TEP is superior to MRI when stages II to IV, because RMI can have false positive when post-therapy inflammation or scarring, although the addition of diffusion-weighted imaging.

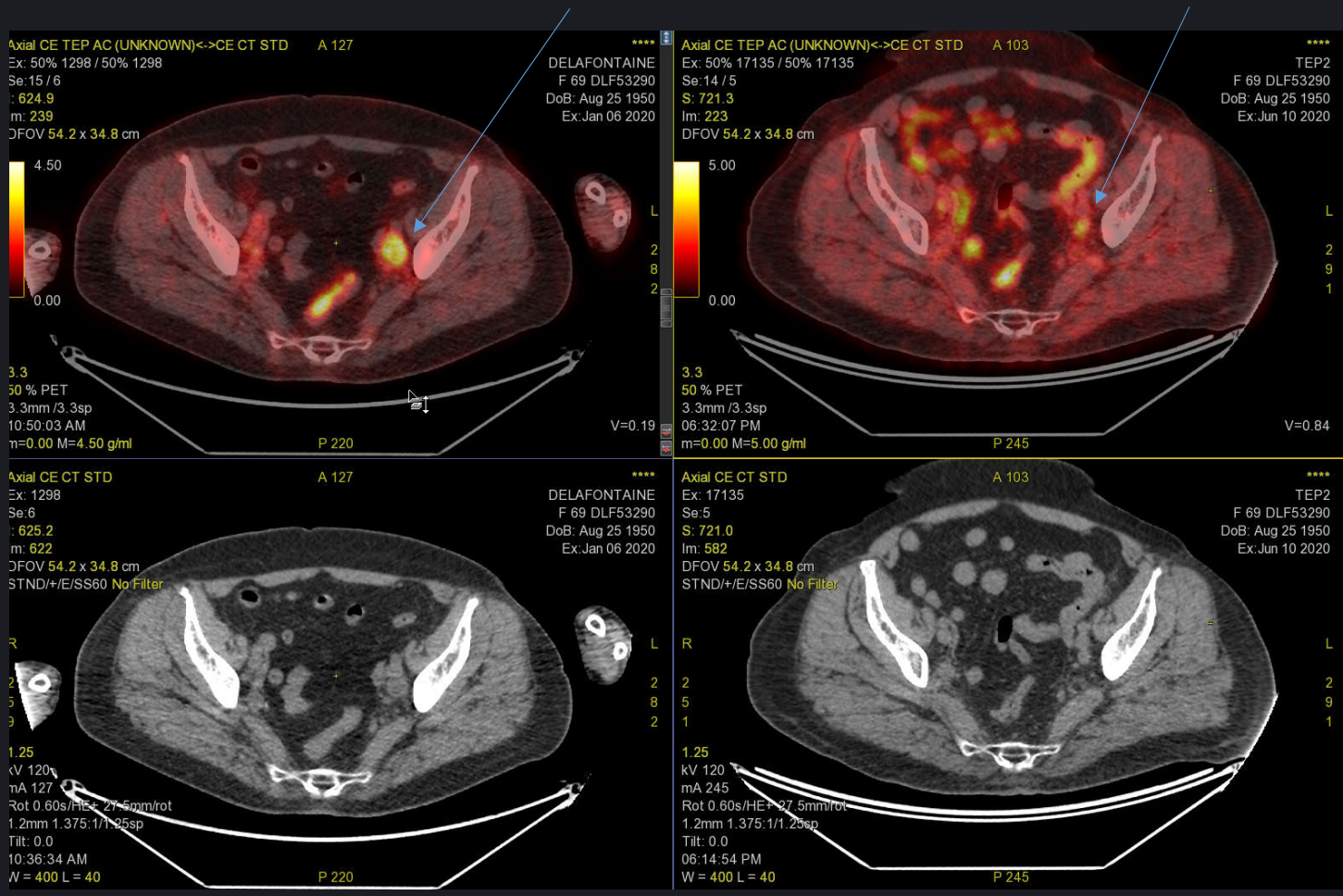
Mrs G, 3 months post-treatment

Disappearance of the primitive lesion



Mrs G

But persistence of a pelvic node, moderatly hypermetabolic (SUVmax 3,5) : doubtful ?



And radiotherapy planning ?

- PET not validated in routine but more and more used.
- MRI is the standard for planning but PET could be prognostic and delineate disease (tumour and nodes) for improved target dose.
- A studie assessed the use of PET immediately post-nodal radiotherapy in 48 patients with FDG avid nodal disease : PFS was significantly better for patients with nodal complete response than those with non-complete response (71% vs 18%).
- But low PPV of early PET when partial response or progression….

Relapse

- Disease recurrence within 2 years is high with one-third of patients with locally advanced cancer, at least 6 months after. Survival rates is low and secondary cure is less efficace when relapse.

- CT and RMI have limited performance for the detection of local, lymph node or metastates when relapse.
- PET is not indicated for the systematic following.
- PET is superior to CT or RMI for detection of recurrence or metastases (prospective study involving 40 patients with relapse), confirmed by a meta-analysis.
- PET recommended when CT/RMI is equivocal (Royal College of Radiologists)
- ANCNN : TEP recommended when suspicion of relapse of metastases.

Future Directions

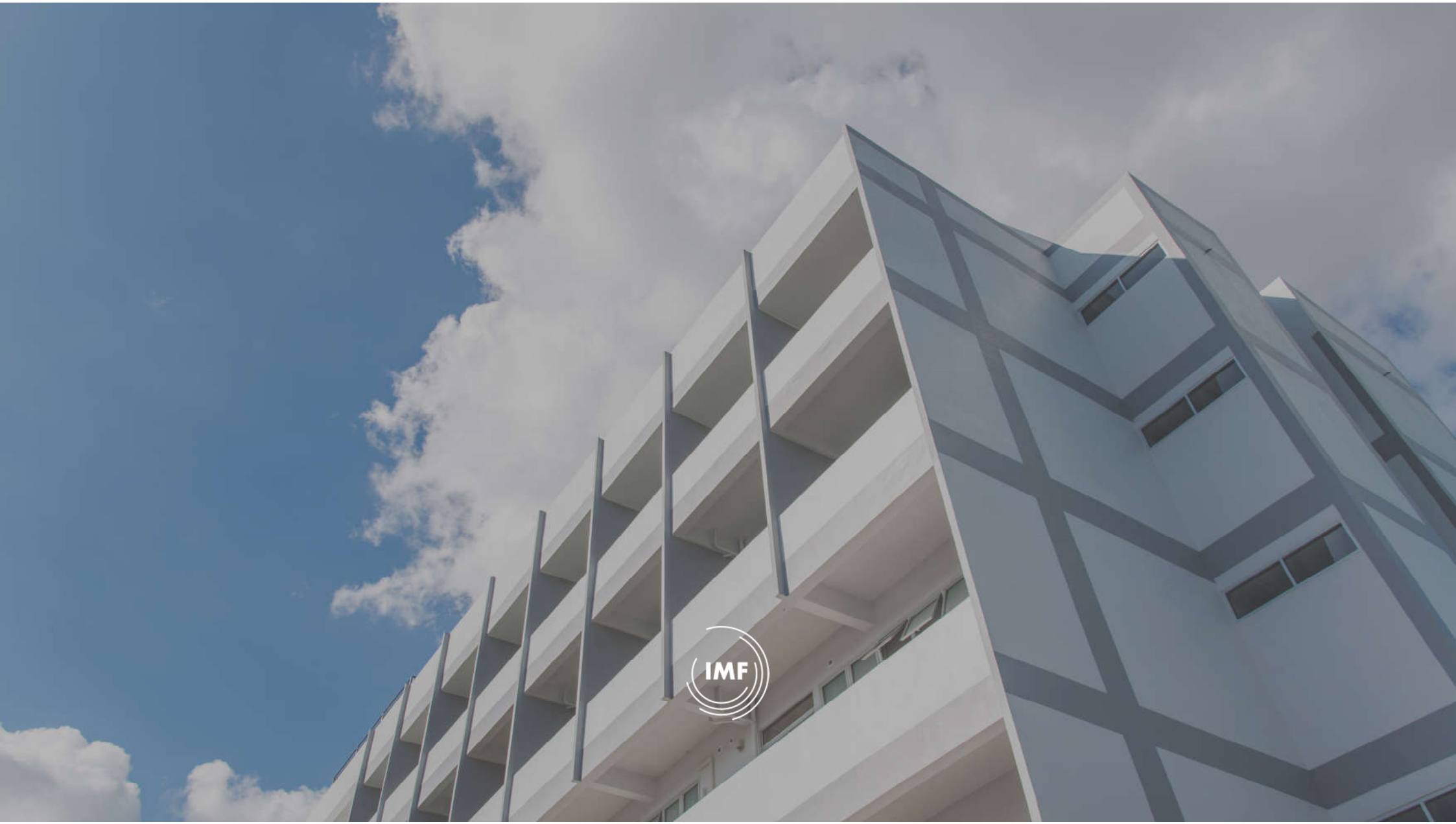
- Texture : in a pilot study, 20 patients with locally advanced cancer benefited pre-treatment, 2 and 4 week treatment and 12 weeks post-treatment PET : the reduction in regional features of heterogeneity during treatment was predictive of complete response, rather than baseline features.
- A study assessed combination intratumoral metabbolic heterogeneity with TLG in 44 patients with tumours less than 4 cm : high prediction of OS.

- A recent study involved PET and MRI in 102 patients with locally advanced cancer : the combination of texture analysis in PET and diffusion-weighted MRI had a, high prediction in efficacy of chemoradiotherapy.

- Role of PET/MRI is still discussed.

Take-home messages

- Established role of PET in the staging and therapy planning when locally advanced cancer, particularly for the assessment of nodal disease and distant metastases.
- PET recommended when stage Ib2 (now > 2 cm).
- Increasing use of PET for treatment assessment, prognosis and before extenteration.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