Evaluation of response to treatment of cancer with PET-CT

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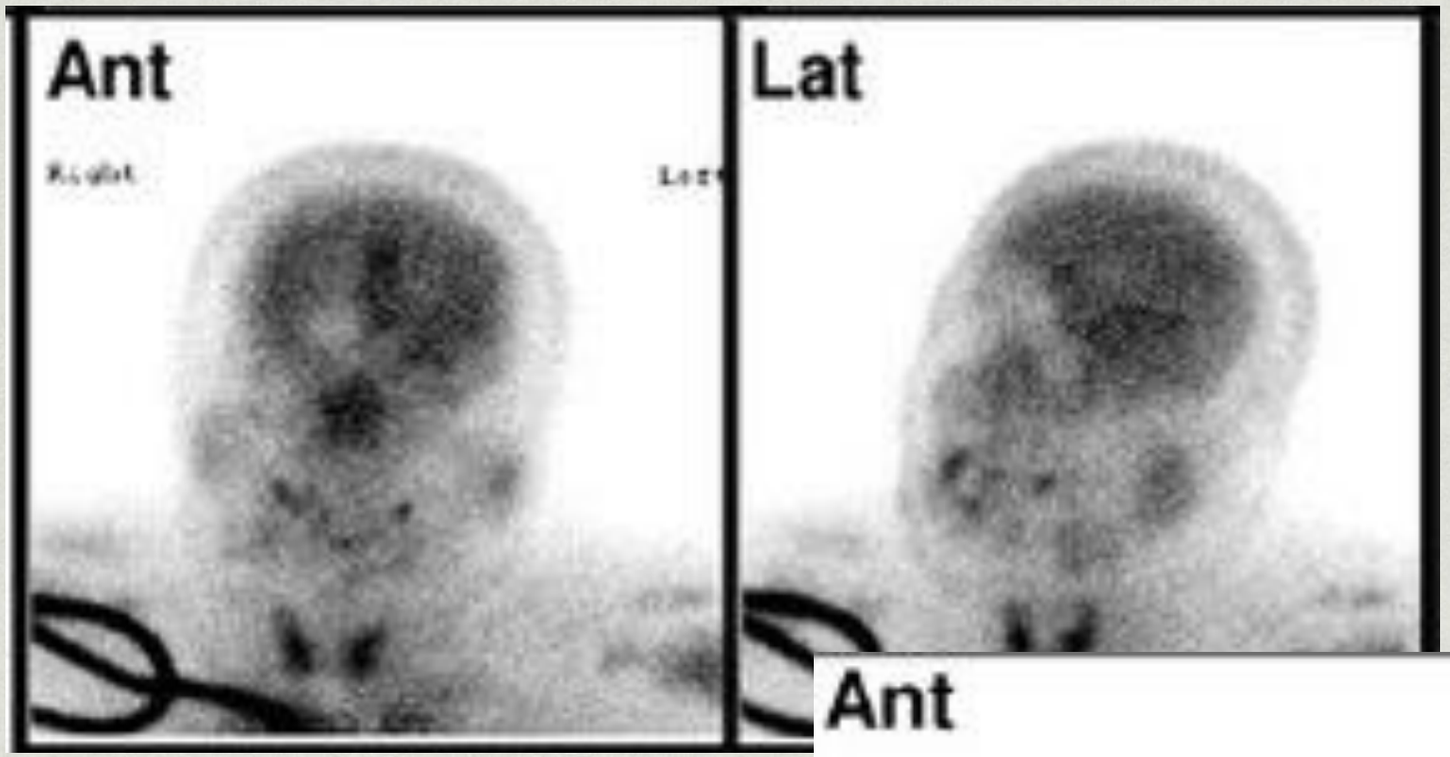
CHIREC Cancer Institute
Medical Imaging - Nuclear Medicine
March 6th, 2020

Clinical Workshop

Global medical imaging approach in oncology: which way to go?

PET-CT in oncology
The Basics

- An image in nuclear medicine is a picture of a particular cellular function
- One radiotracer = one function
- If the function stops, the image disappears


Ant
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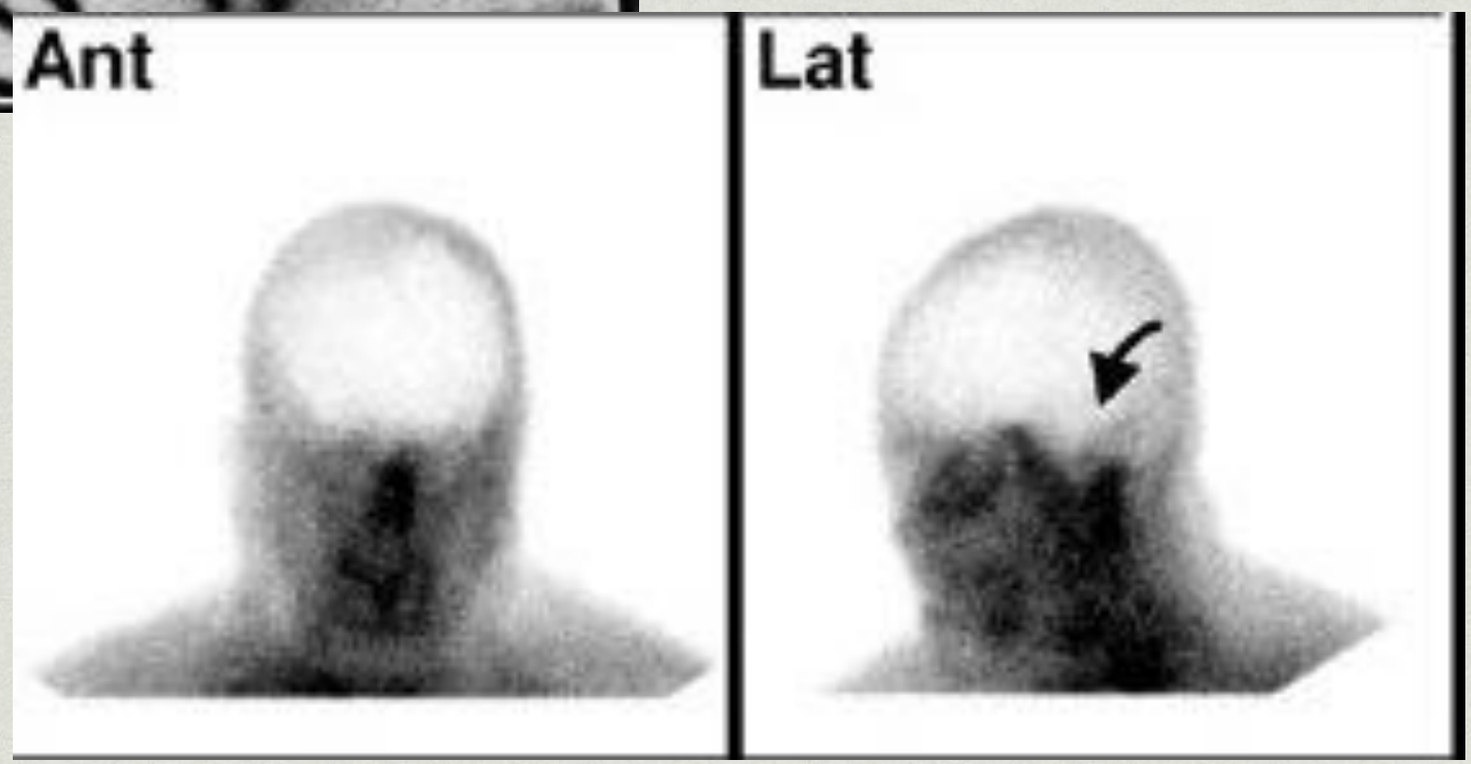
Ant
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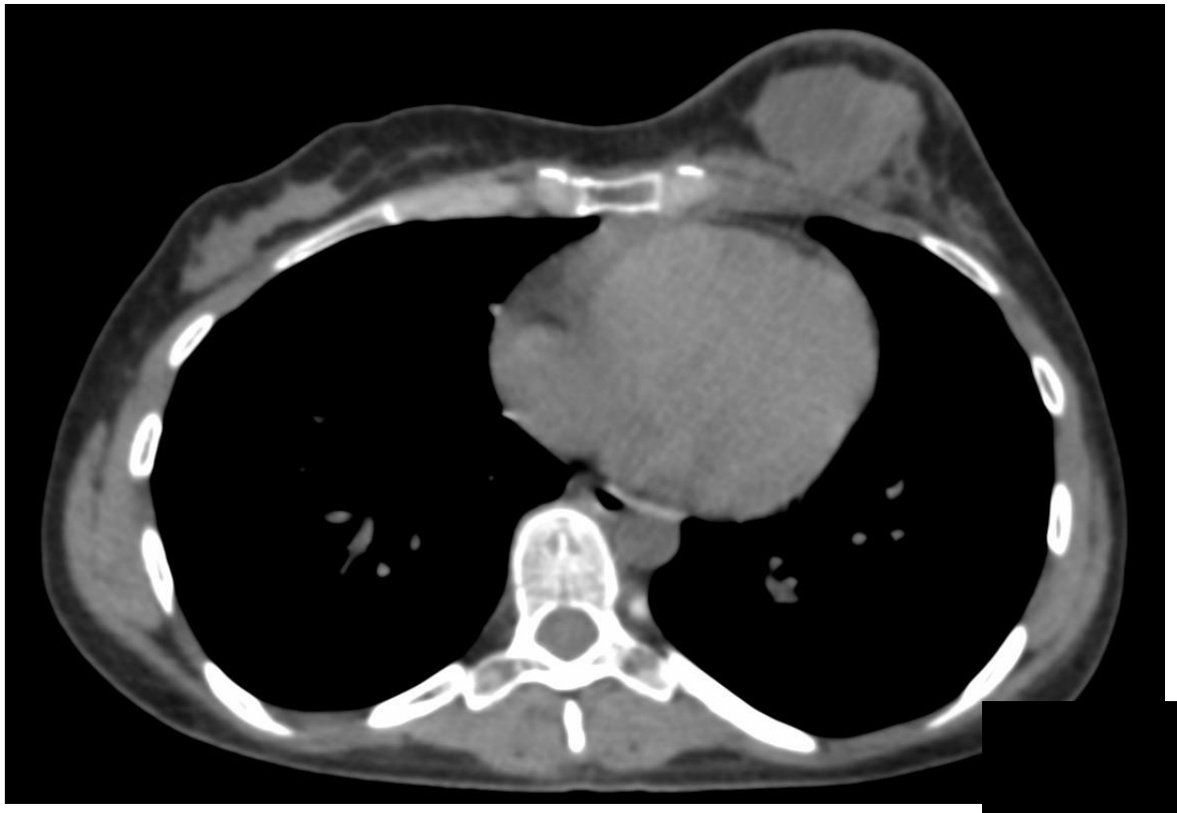
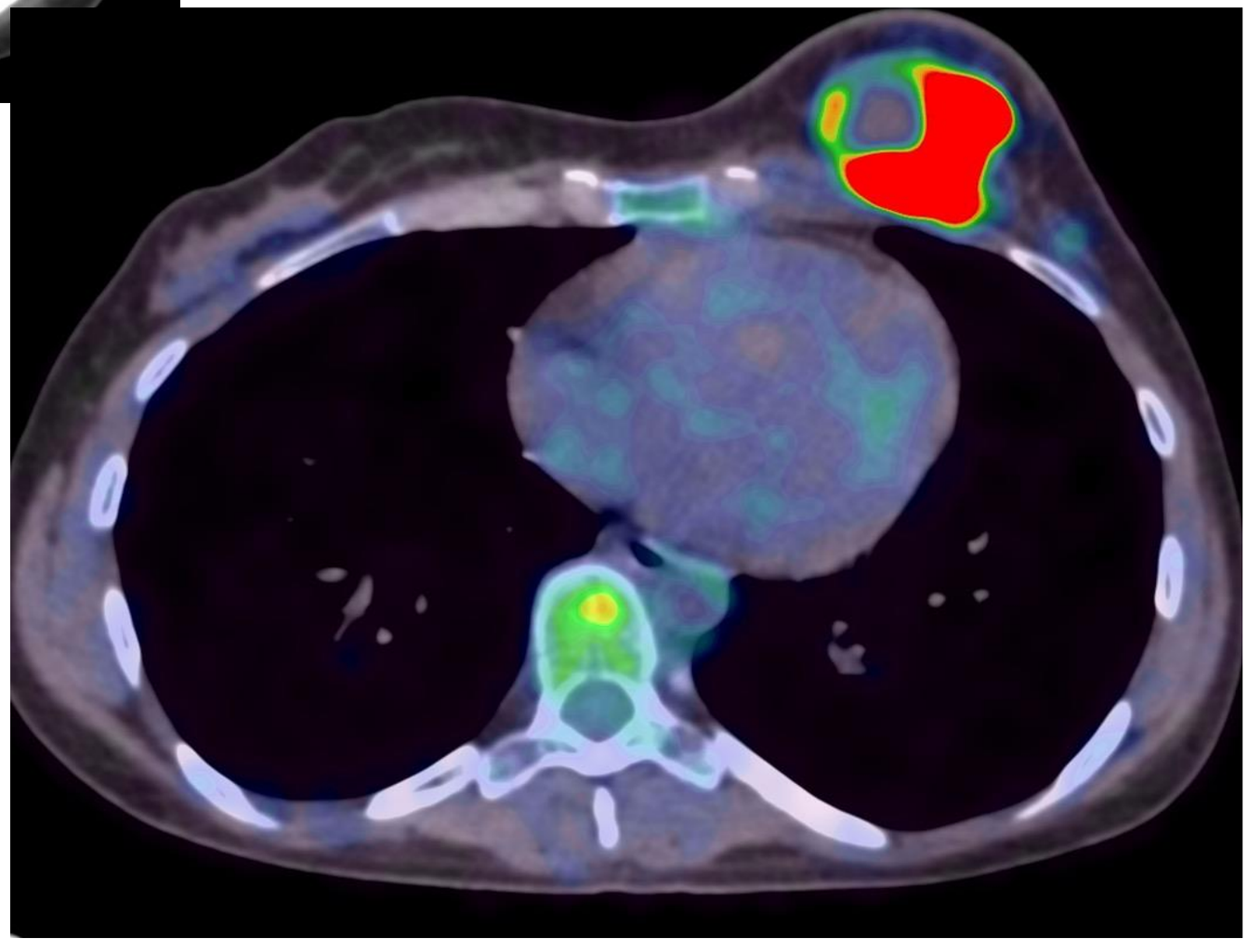




Tissular architecture
Tumor
Necrosis

PET-CT in oncology
FDG

- FDG = GLUT + HK activity
  - both increased in the majority of cancers
- FDG is also taken up by inflammatory cells (lymphocytes, macrophages)
- FDG // cellular proliferation
- FDG // hypoxia

Response assessment

- Functional response is an early phenomenon
- Tumor response can be assessed early in the course of therapy
- However, evaluation of response must be evaluated only « when it makes sense »
  - is this the right time for imaging ?
  - are they alternatives ?
  - cost - side effects

PET-CT FDG
Response assessment : when ?

- Chemo : 15 days after last cycle. Day -1 from the next cycle

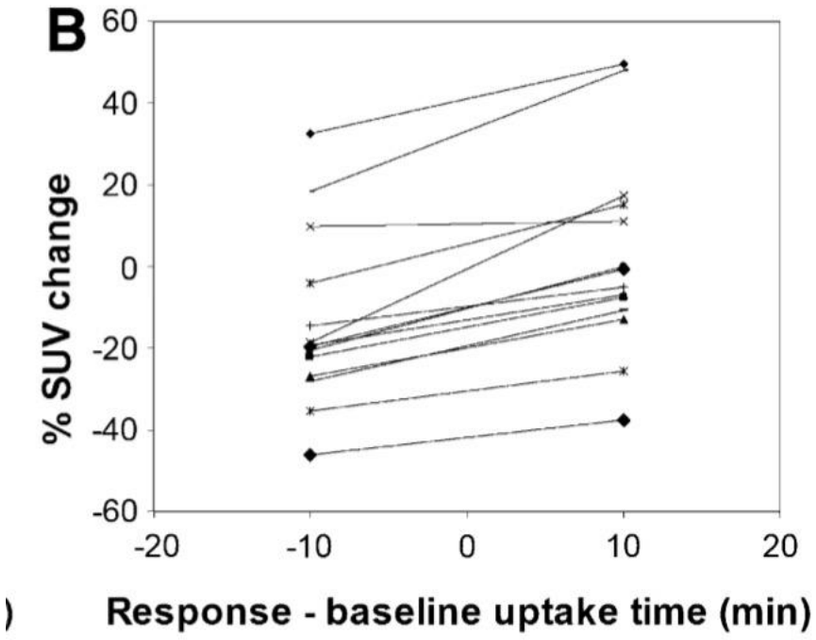
- Radiotherapy : 12 weeks EOT, if you want to get rid of the radiation-induced inflammation

- Hormonotherapy : ?

- Immunotherapy : ??

PET-CT FDG
Response assessment : how ?

- The key question is the reproducibility
- Same machine, same reconstruction algorithm, same interval between injection and scanning, same glycemia = ideal situation
- Interpretation : visual ? quantitative ?
- It’s PET-CT, so you need to use both informations (and there might be some discrepancies)

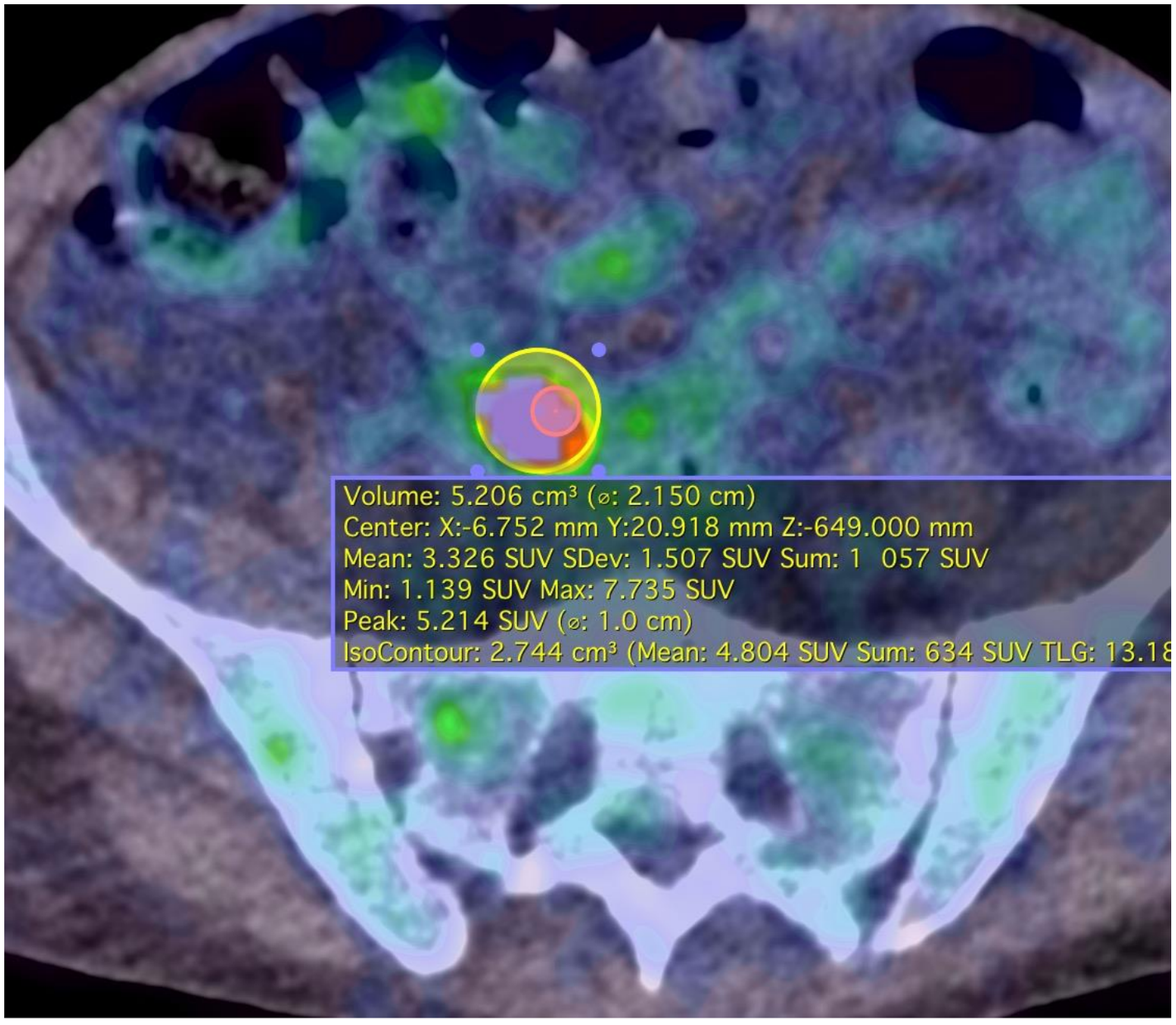


- Methodological considerations
  - interval between injection and imaging must be as stable as possible
  - importance of acquisition/reconstruction technologies : PSF increases SUV (QClear, etc…), TOF increases the signal-to-noise ratio (which could upstage a visual scale)
  - difference in SUV values between machines : EANM harmonization, core lab for multi-centric studies
  - SUV-TLG, etc… : beware of the methods used ! large variations based on thresholds used, etc…

Image interpretation

- Visual
- « Quantitative »
  - SUVbw, SUVbsa, SUVbw, TLG, MTV, etc…

- SUVmax = hottest pixel in the ROI
- SUVmean = average in the ROI
- SUVpeak = average within a VOI containing the hottest pixel (less sensitive to noise than SUVmax)



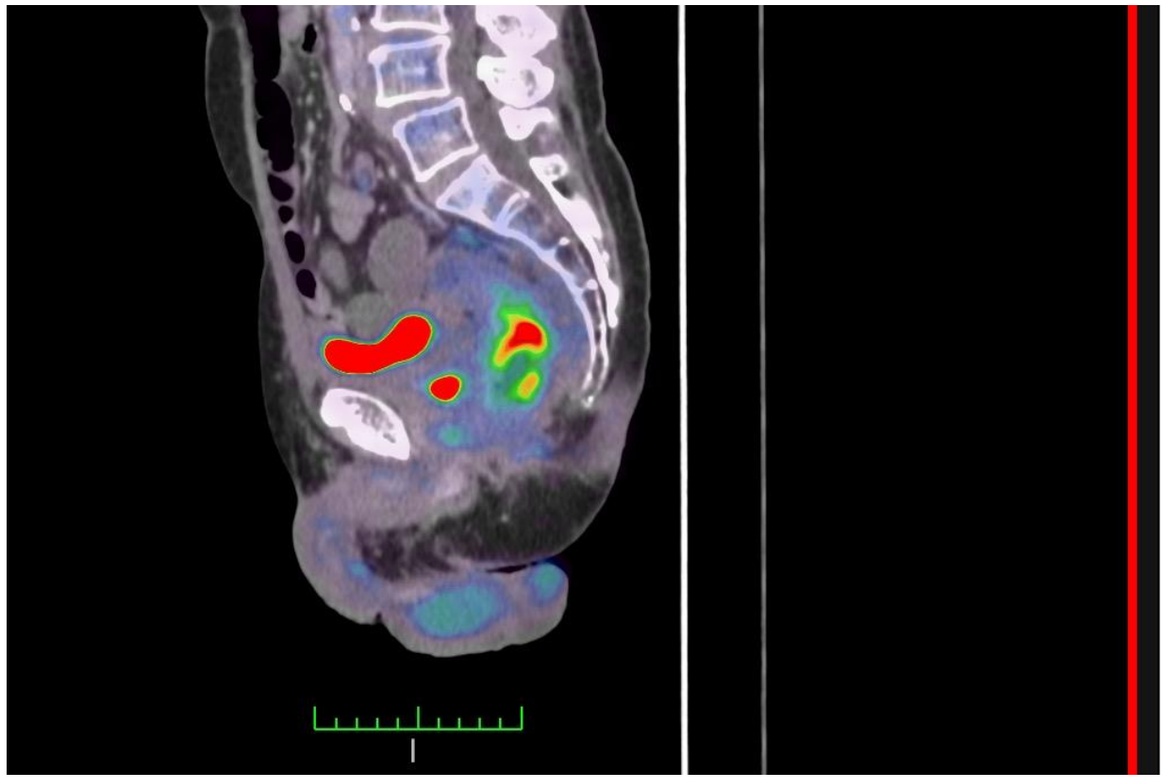
- How do we report the results ?
  - lymphoma : the Deauville scoring system
  - solid tumors : visual scores (e.g. Ann Arbor for H&N) - EANM or PERCIST criteria

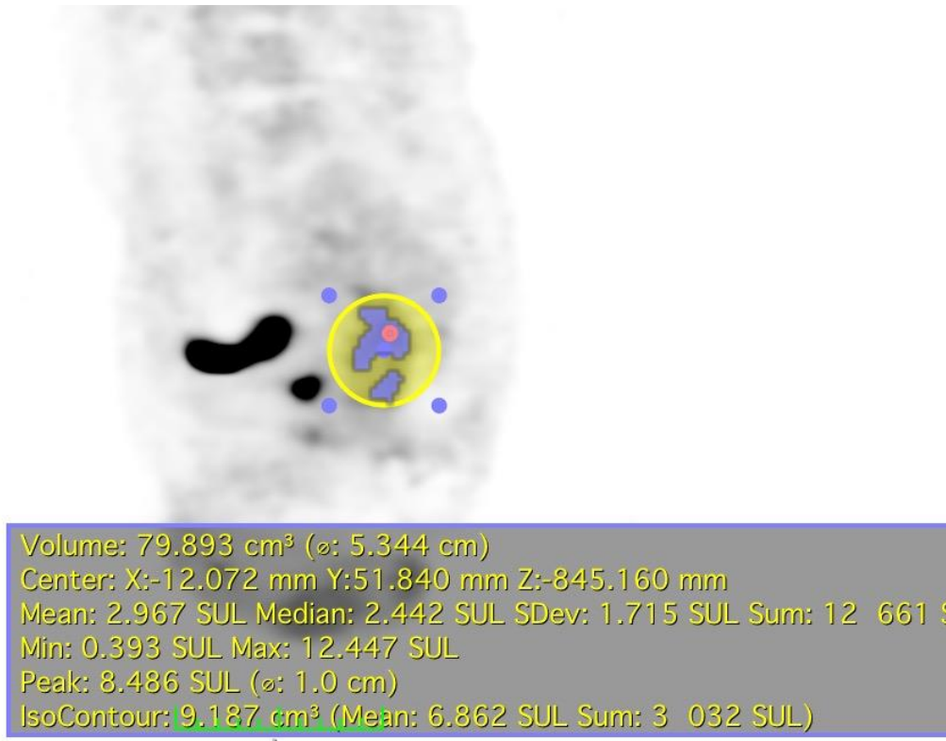
Table 1

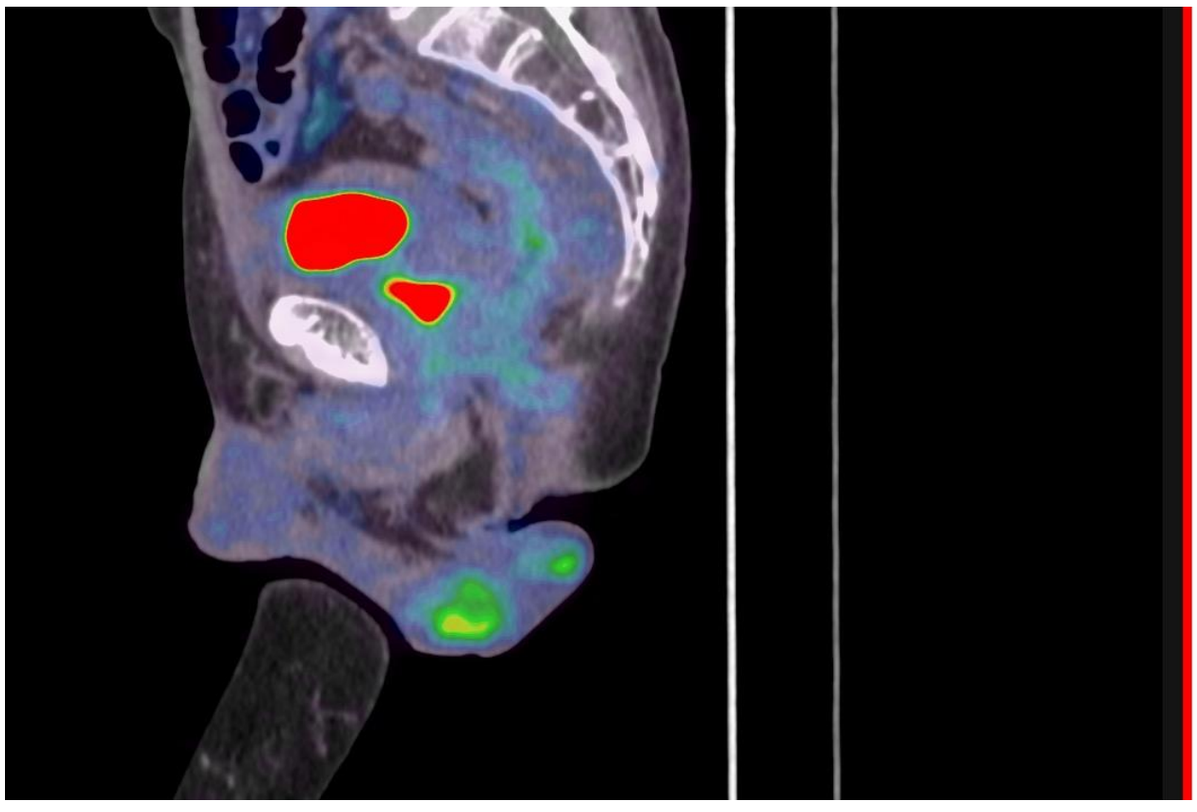
Overview of response classification by EORTC criteria and PERCIST

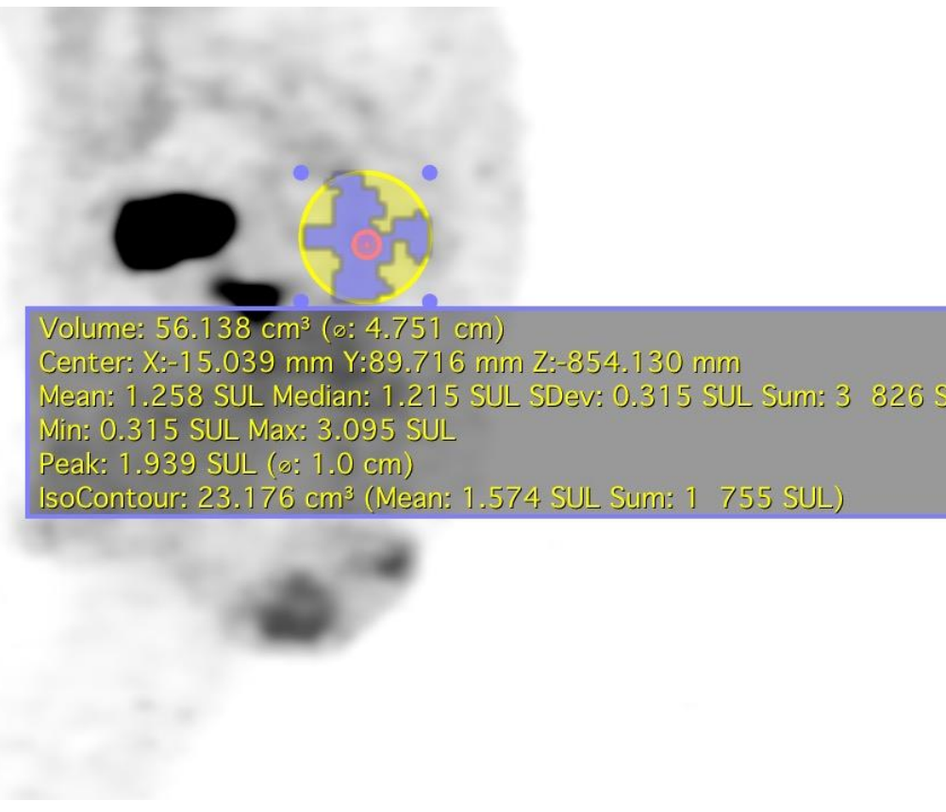
	EORTC 1999	PERCIST 2009
Quantitative parameter (SUV)	SUVmean, normalized body surface area	SUVpeak, normalized to lean body mass (SUL)
Response Classification		
PMD	Increase in SUV of greater than 25% - Or- Increase of the longest diameter by 20% - Or - new FDG avid lesion(s)	SUL increase by at least 30% and increase in by at least 0.8 SUL units of the target lesion - Or Development of at least one new lesion - Or - Increase in target lesion size by 30% - Or - Unequivocal progression of nontarget lesions
SMD	Increase of SUV by < 25% or decrease less than 15% - And - no increase in longest diameter > 20%	Increase or decrease of SUL by less than 30%
PMR	Decrease of SUV by 15–25% after one cycle of chemotherapy and > 25% after more than one treatment cycle	Decrease of SUL by >= 30% and at least 0.8 SUL units difference - And- No new FDG-avid lesions,(br4/)- And - No increase in size > 30% of the target lesion - And - No increase in SUL or size of non-target lesion
CMR	Resolution of FDG uptake (indistinguishable from surrounding normal tissue)	FDG uptake indistinguishable from surrounding background - And - SUL less than liver.

- SUVbw and max : EORTC
- SUVlean and peak : PERCIST

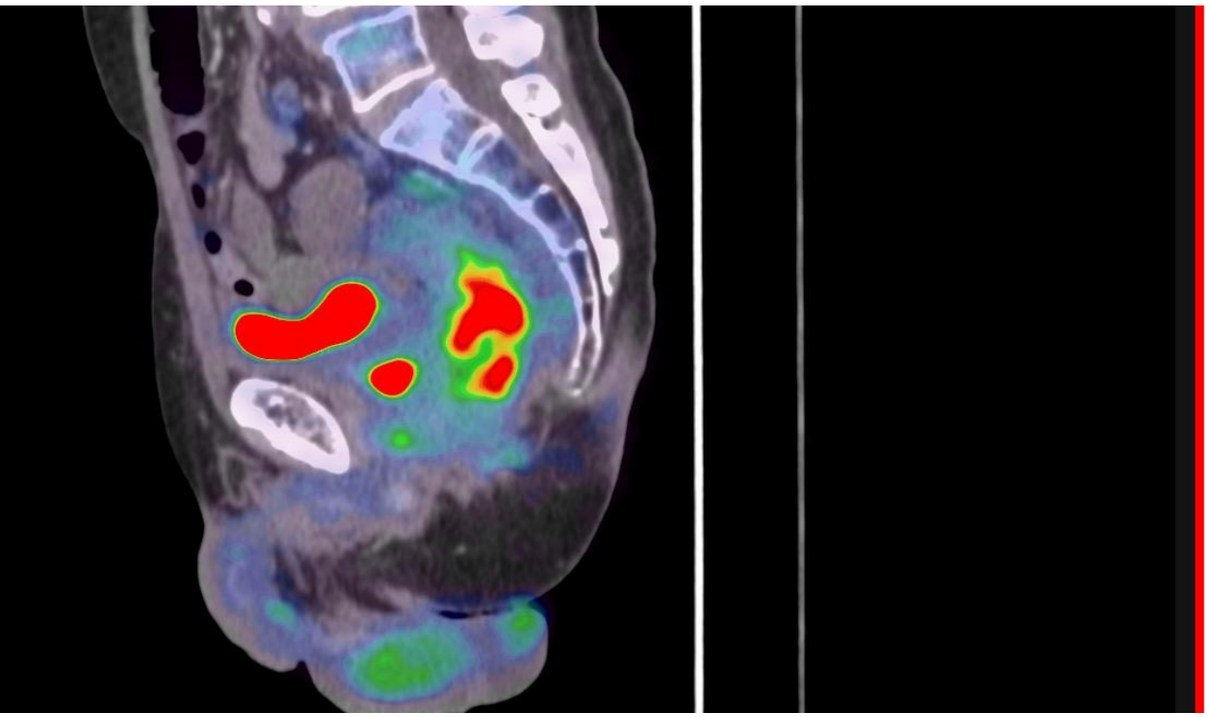


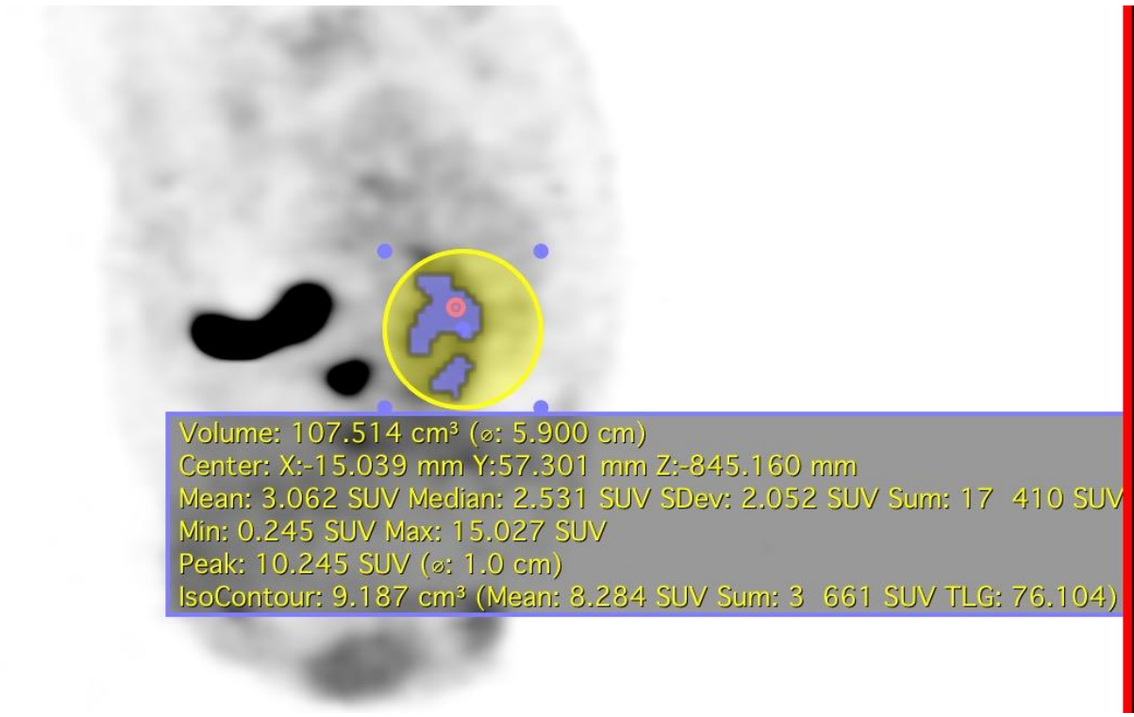

Volume: 79.893 cm³ (⌀: 5.344 cm)
Center: X:-12.072 mm Y:51.840 mm Z:-845.160 mm
Mean: 2.967 SUL Median: 2.442 SUL SDev: 1.715 SUL Sum: 12 661
Min: 0.393 SUL Max: 12.447 SUL
Peak: 8.486 SUL (⌀: 1.0 cm)
IsoContour: 9.187 cm³ (Mean: 6.862 SUL Sum: 3 032 SUL)

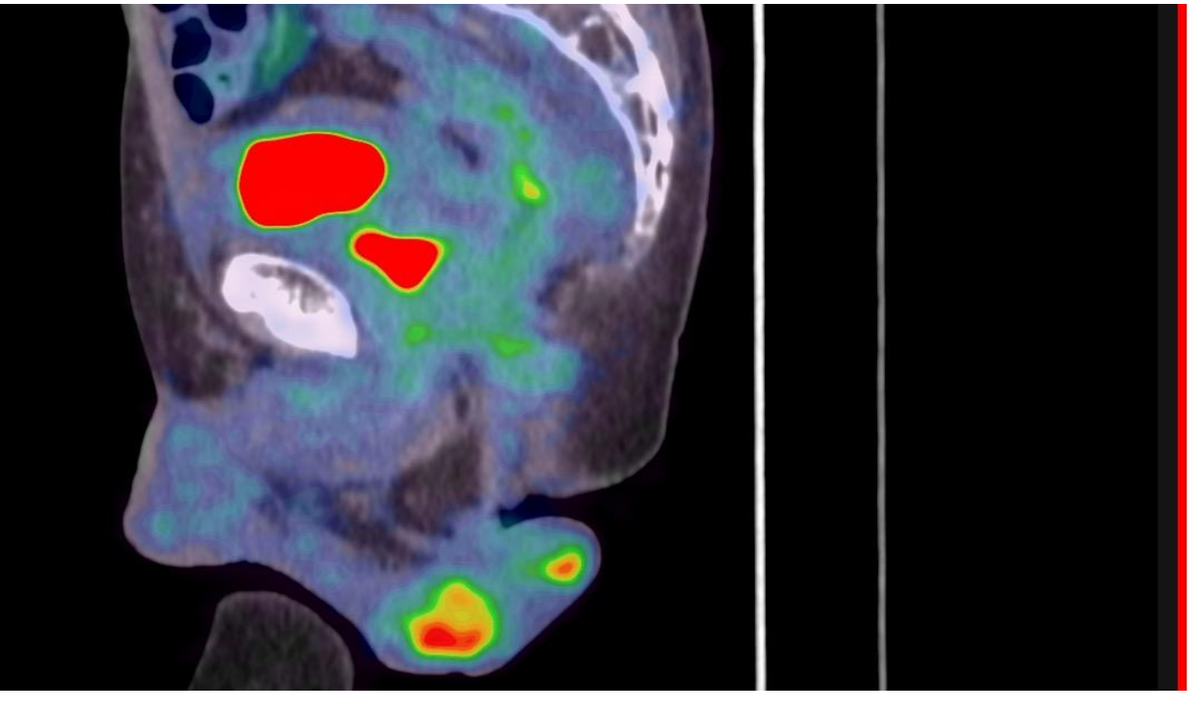


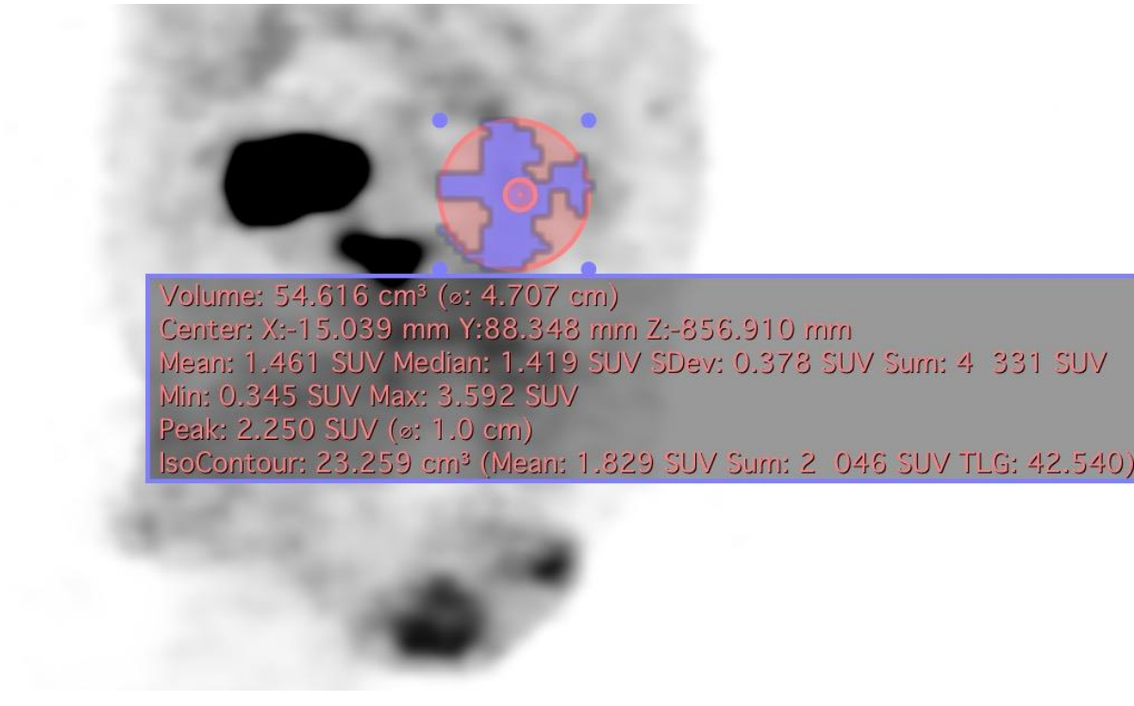

Volume: 56.138 cm³ (⌀: 4.751 cm)
Center: X:-15.039 mm Y:89.716 mm Z:-854.130 mm
Mean: 1.258 SUL Median: 1.215 SUL SDev: 0.315 SUL Sum: 3 826
Min: 0.315 SUL Max: 3.095 SUL
Peak: 1.939 SUL (⌀: 1.0 cm)
IsoContour: 23.176 cm³ (Mean: 1.574 SUL Sum: 1 755 SUL)

PERCIST : - 77 %




Volume: 107.514 cm³ (⌀: 5.900 cm)
Center: X:-15.039 mm Y:57.301 mm Z:-845.160 mm
Mean: 3.062 SUV Median: 2.531 SUV SDev: 2.052 SUV Sum: 17 410 SUV
Min: 0.245 SUV Max: 15.027 SUV
Peak: 10.245 SUV (⌀: 1.0 cm)
IsoContour: 9.187 cm³ (Mean: 8.284 SUV Sum: 3 661 SUV TLG: 76.104)




Volume: 54.616 cm³ (⌀: 4.707 cm)
Center: X:-15.039 mm Y:88.348 mm Z:-856.910 mm
Mean: 1.461 SUV Median: 1.419 SUV SDev: 0.378 SUV Sum: 4 331 SUV
Min: 0.345 SUV Max: 3.592 SUV
Peak: 2.250 SUV (⌀: 1.0 cm)
IsoContour: 23.259 cm³ (Mean: 1.829 SUV Sum: 2 046 SUV TLG: 42.540)

EORTC : - 76 %

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PMCID: PMC5541084
PMID: 28623376

EANM/EARL harmonization strategies in PET quantification: from daily practice to multicentre oncological studies

Nicolas Aide,[1,2] Charline Lasnon,[2,3] Patrick Veit-Haibach,[4,5] Terez Sera,[6] Bernhard Sattler,[7] and Ronald Boellaard[8,9]

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541084/

Lymphoma

DEAUVILLE score	REPONSE
1 : pas de fixation supérieure au bruit de fond environnant.	iTEP* ou fTEP* score 1, 2 ou 3[†]: REPONSE métabolique COMPLETE[‡] (RmC)
2 : fixation ≤ médiastin	
3 : médiastin < fixation ≤ foie	
4 : fixation > foie (supérieure à la SUVmax dans une large région d'intérêt de foie normal)	iTEP* ou fTEP* score 4 ou 5 : Baisse de l'intensité de fixation : REPONSE métabolique PARTIELLE (RmP) Sans baisse de l'intensité de fixation/nouveau(x) foyer(s) : MALADIE STABLE (MS) Augmentation de l'intensité de captation et/ou nouvelle(s) lésion(s) : MALADIE en PROGRESSION métabolique (MPm)
5 : fixation très nettement > foie (définition différente selon les groupes de travail**) et/ou progression/ nouveau(x) foyer(s)	

**iTEP : TEP intermédiaire à 2 ou 4 cures; fTEP ou TEP final (fin de traitement)*

*** Le LYSA (Lymphoma Studies Association) utilise une SUVmax de la lésion résiduelle ≥ 2 fois la SUVmax mesurée dans une large région d'intérêt de foie normal. Le UK-MCRI (United Kingdom National Cancer Research Institute) utilise une SUVmax de la lésion résiduelle ≥ 3 fois la SUVmax mesurée dans une large région d'intérêt de foie normal.*

[†]En cas de protocole de désescalade thérapeutique, iTEP score 3 est à considérer comme une réponse insuffisante (pour éviter le sous-traitement).

[‡]Pour les sites extra-ganglionnaires (tube digestif, foie, os) et l'anneau de Waldeyer, la fixation en cas de réponse métabolique complète peut être supérieure au médiastin mais doit rester inférieure à la fixation physiologique avoisinante.

- Diffuse B-Cell lymphoma

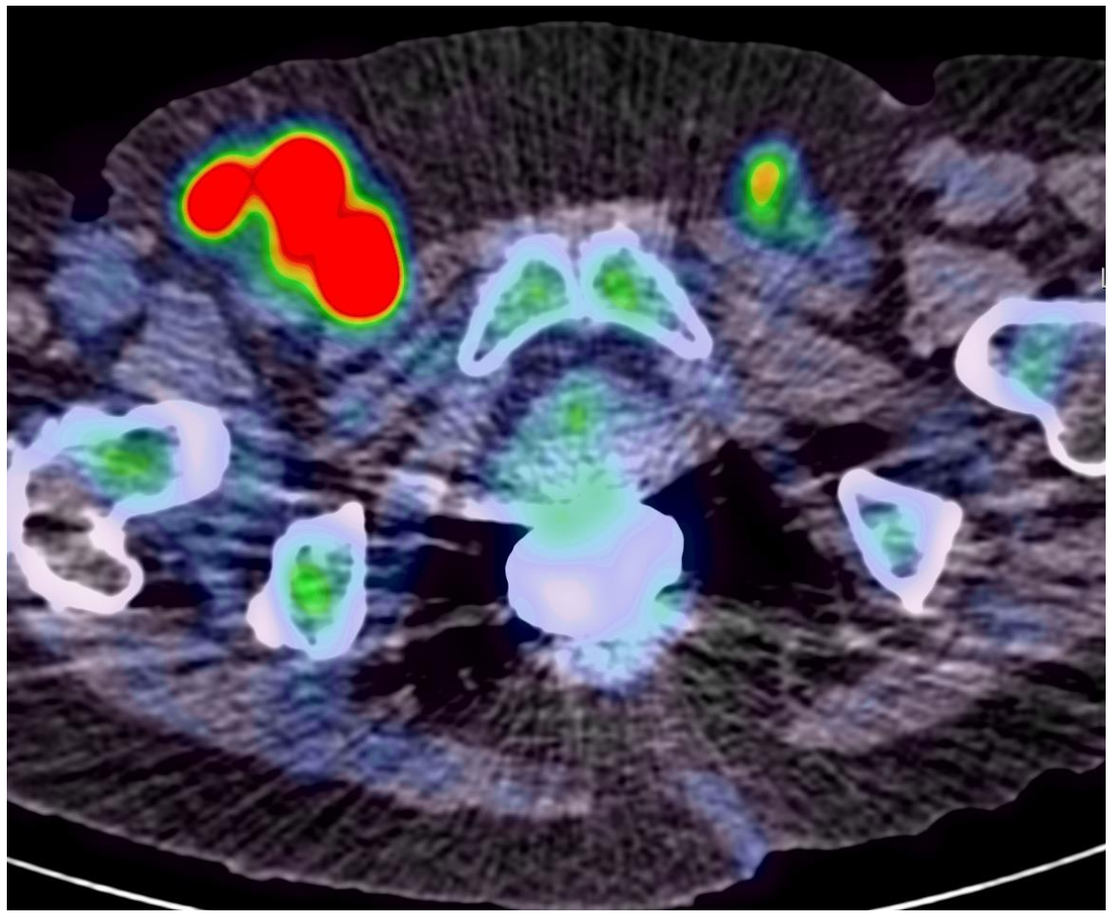
- Baseline

- After 3 courses of chemotherapy

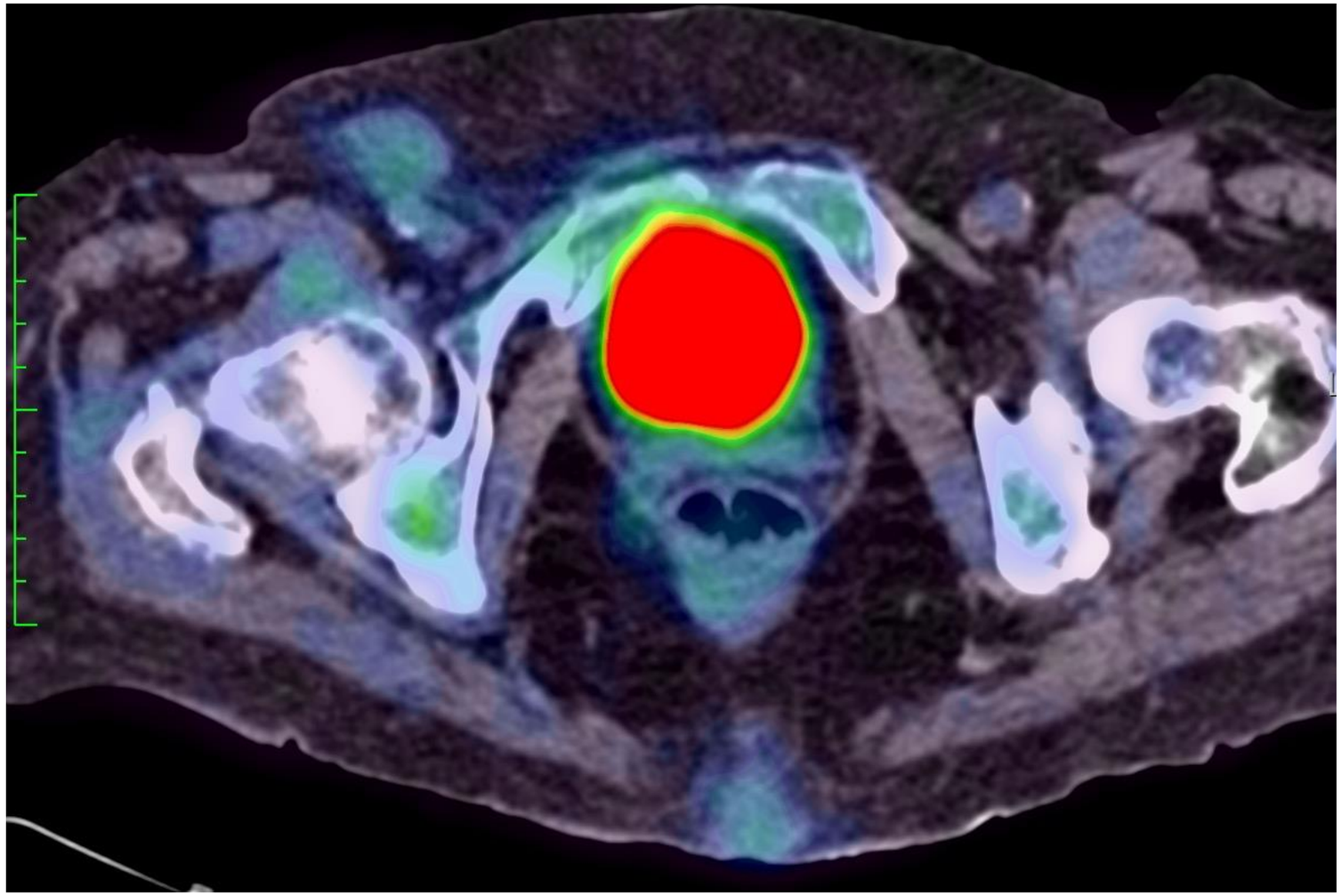
10/2015

01/2016

HM 030537

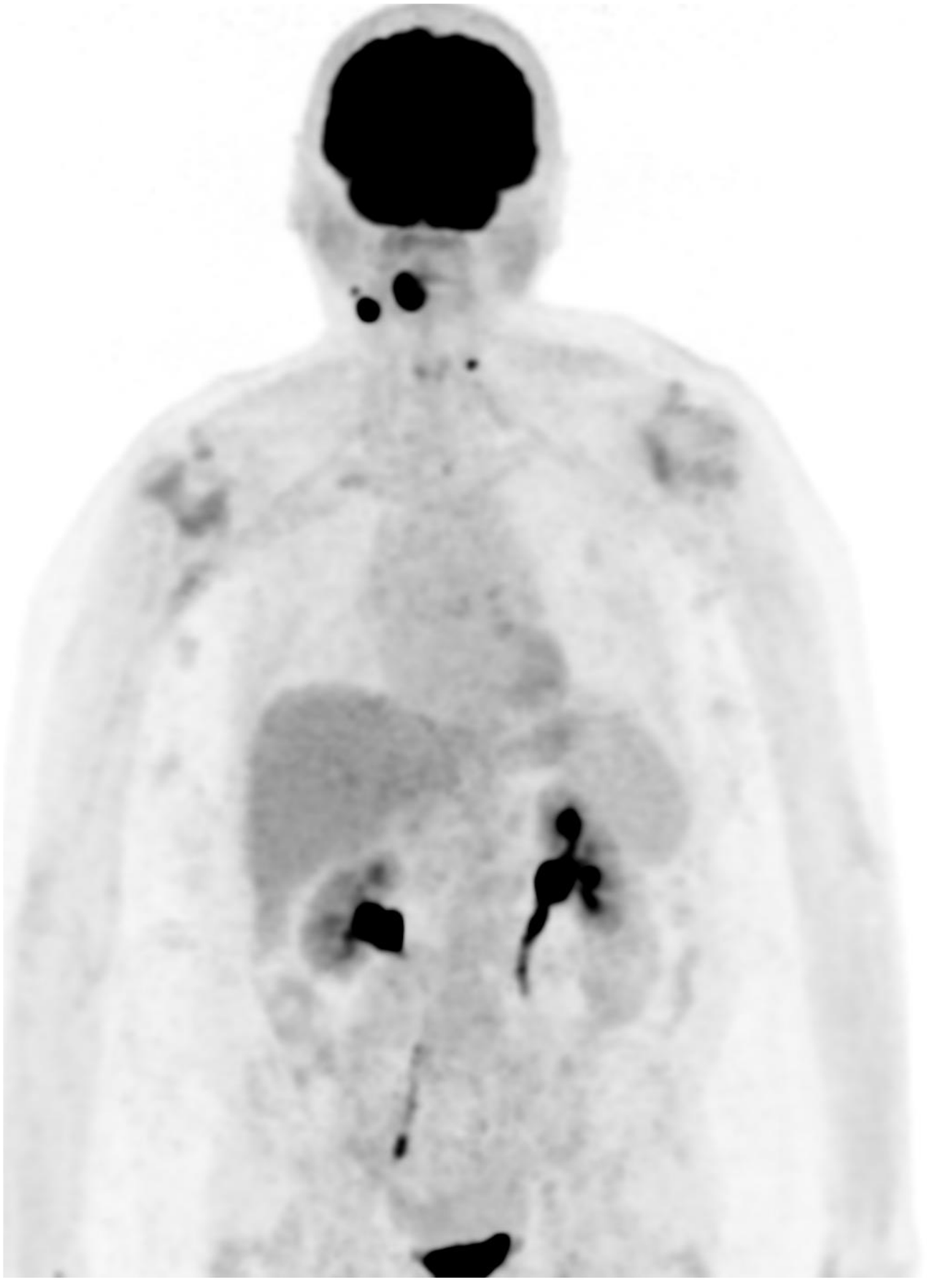


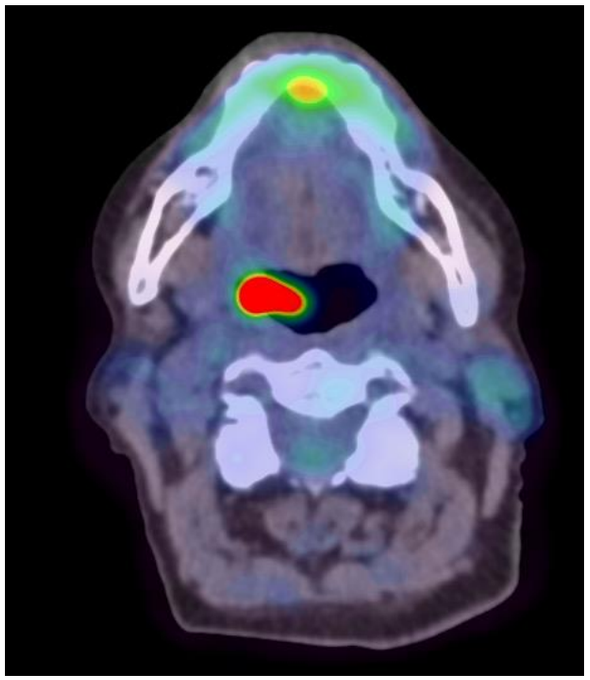
SUVmax 14,7

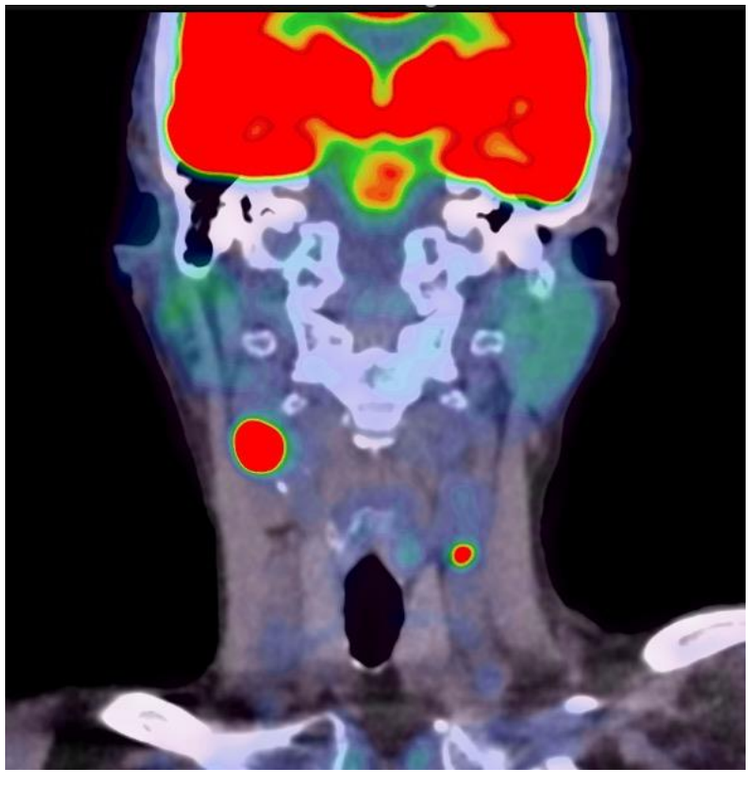


SUVmax 2,4

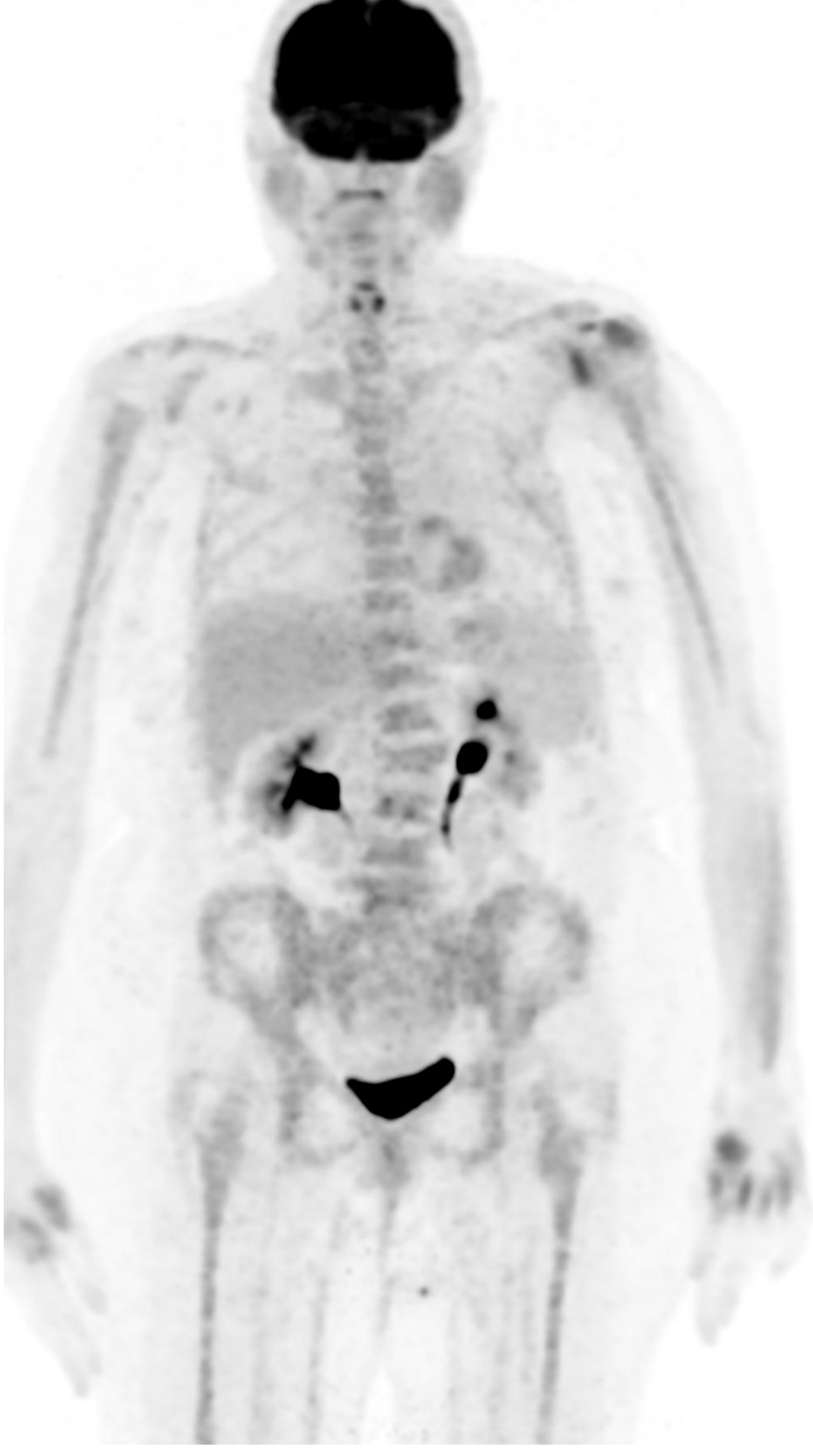
- SUVmax mediastinum : 2,2
- SUVmax liver : 2,7
- SUVmax residual mass : 2,4
- Deauville score : 3 - complete metabolic response

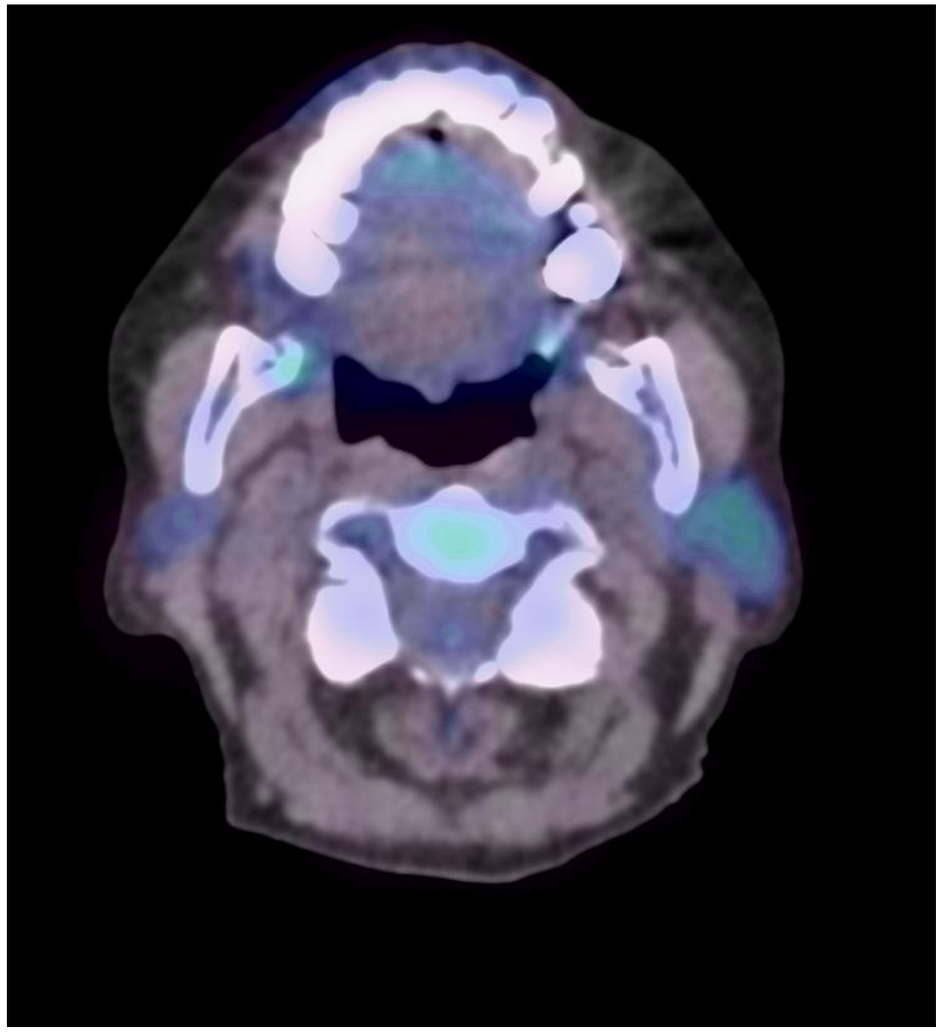






05/2018





R-CHOEP 6 courses
01/2019 : CMR

DLBCL

07/2018

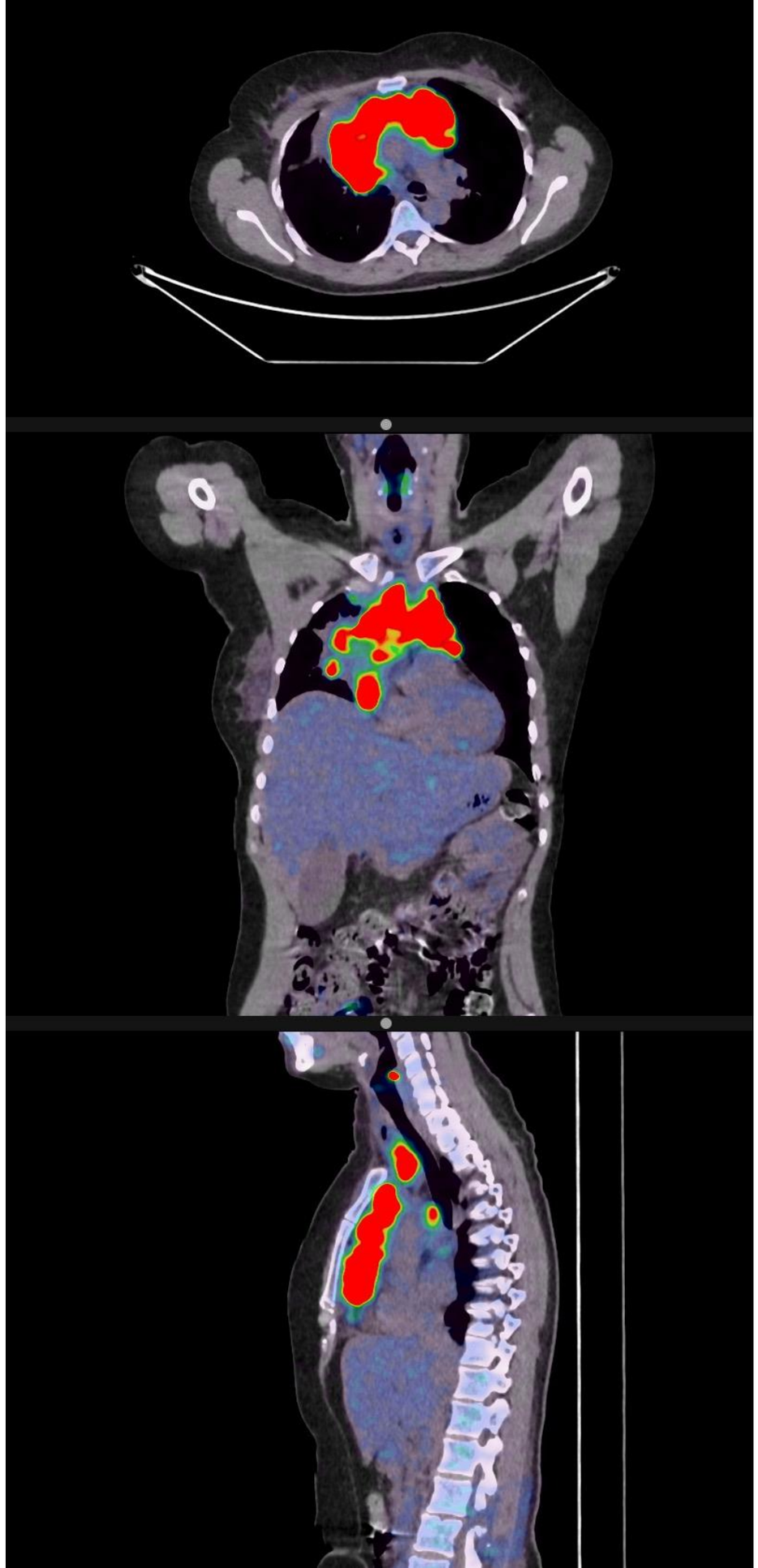
R-CHOP
3 cycles

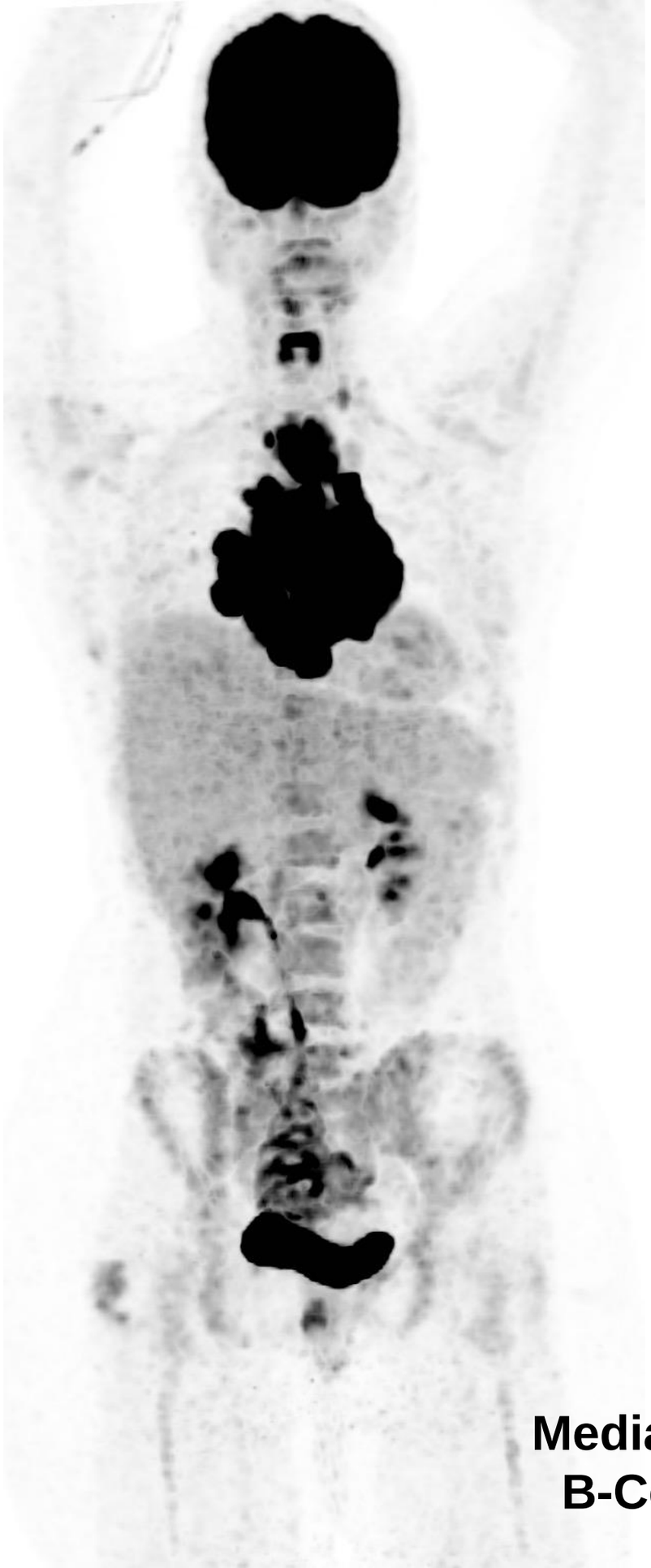
10/2018

R-ESHAP
3 cycles

01/2019

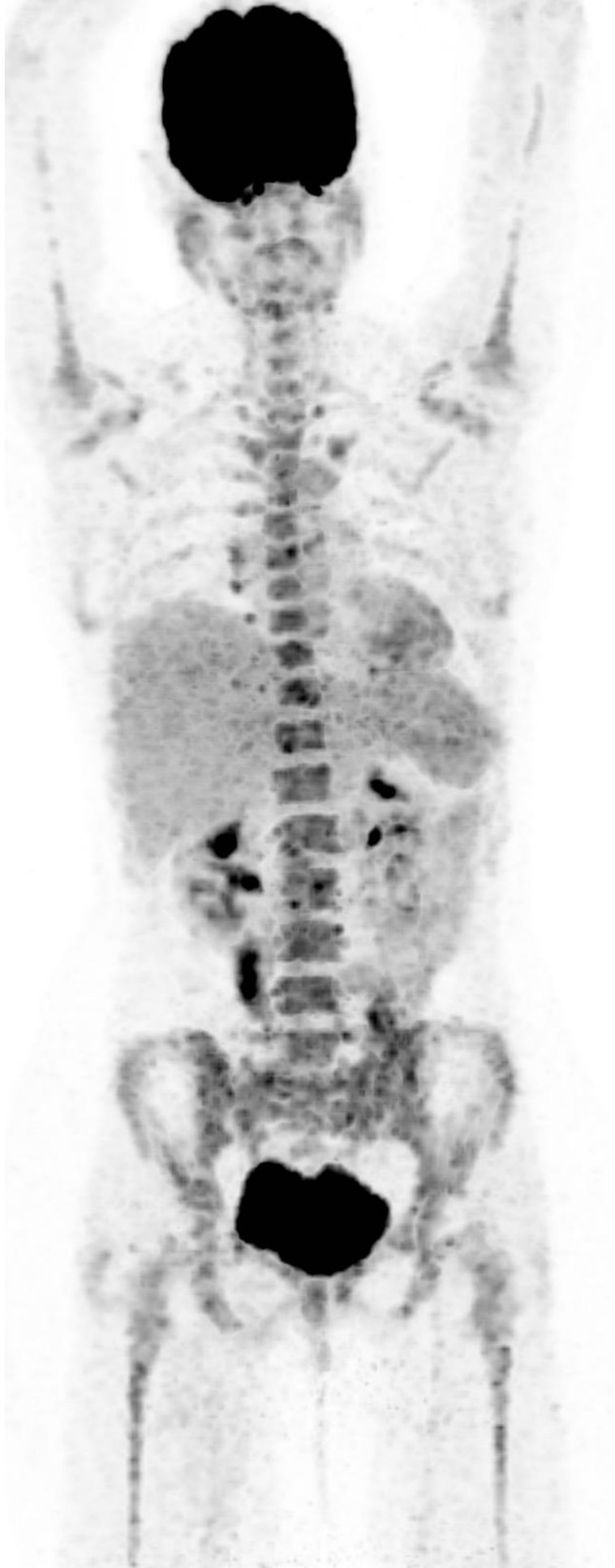
PP2411965

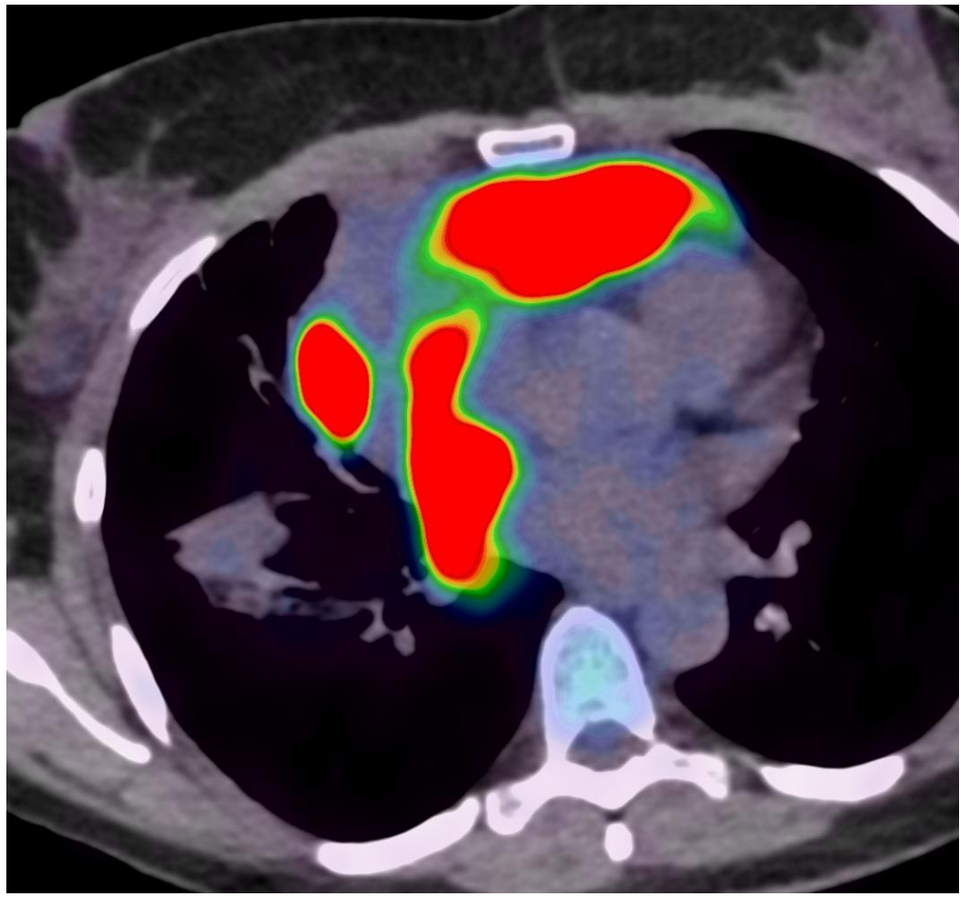


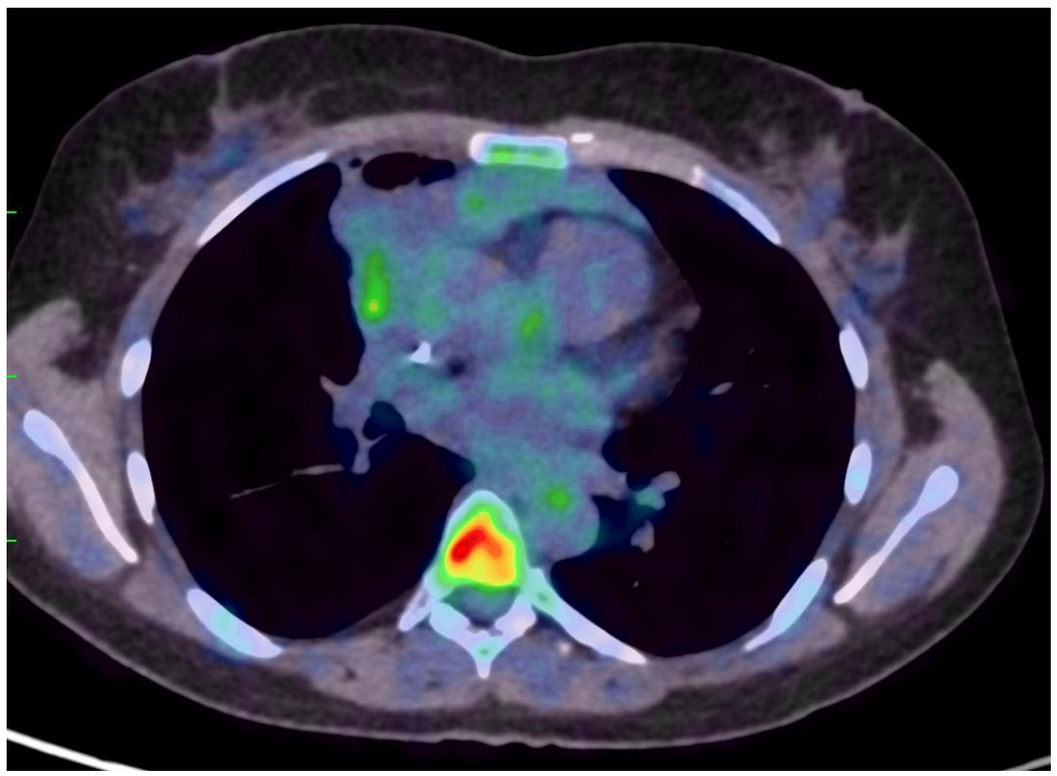


10/2019
Mediastinal primary
B-Cell lymphoma

DT 070775







11/2019
2 cycles

Deauville 4

- (early, after 2 cycles) metabolic response is a prognostic indicator

- Metabolic response can be used to adapt treatment
  - early switch in non responders
  - influence on the total number of cycles

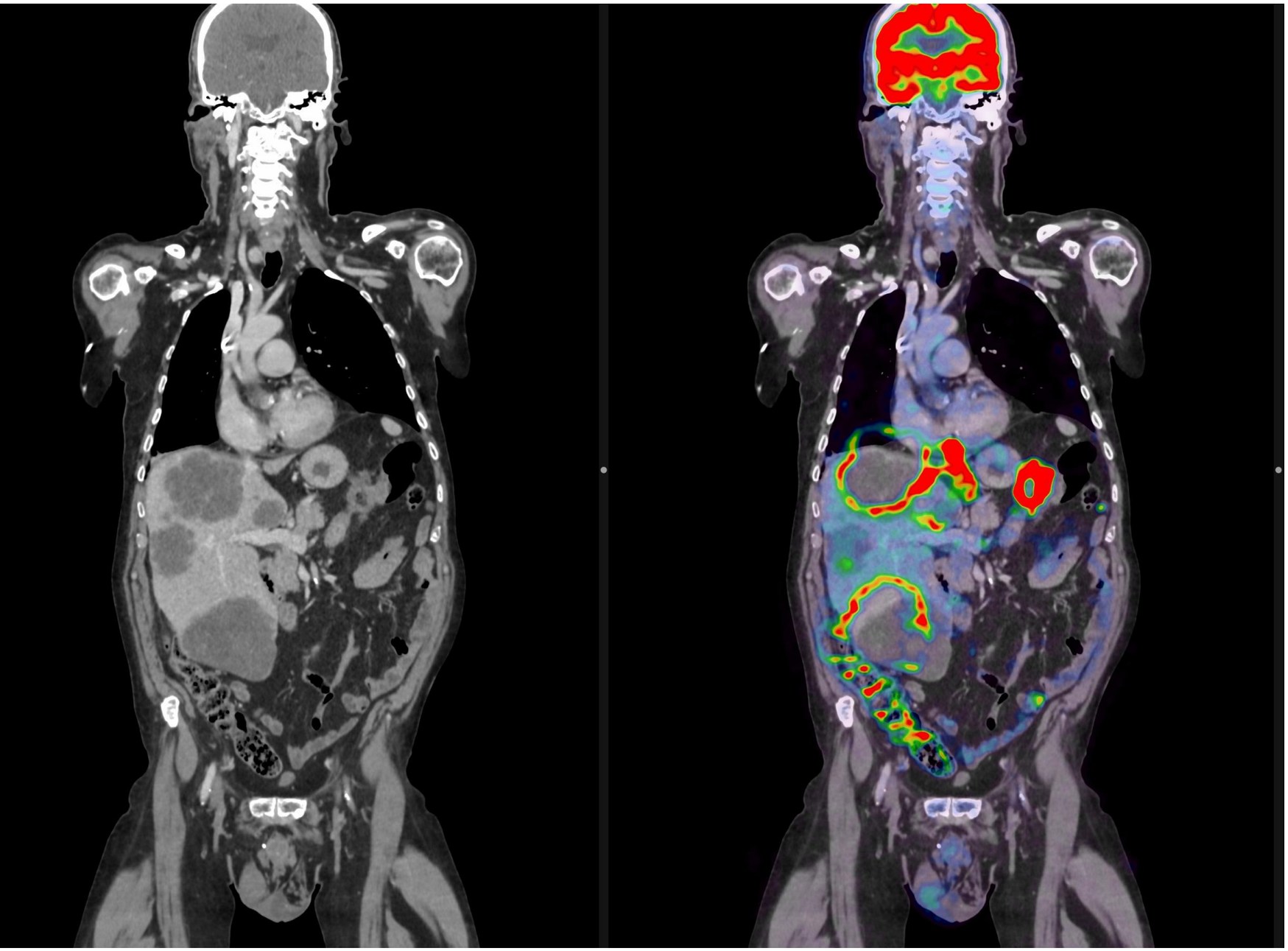
US Intergroup Trial of Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose–Positron Emission Tomography Imaging: Southwest Oncology Group S0816

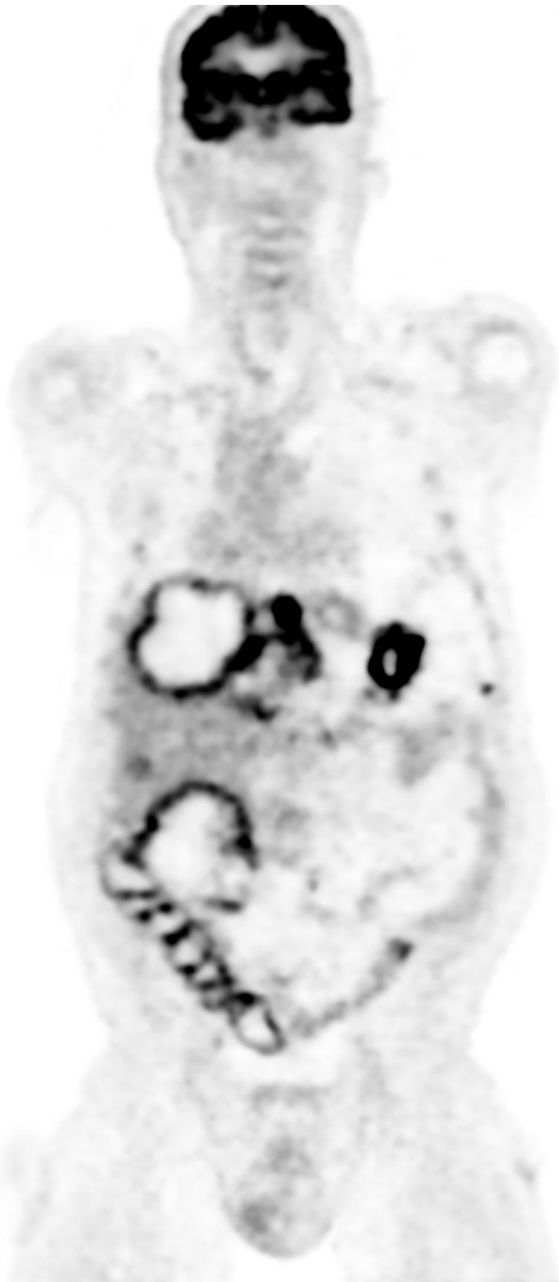
Oliver W. Press⇑, **Hongli Li**, **Heiko Schöder**, **David J. Straus**, **Craig H. Moskowitz**, **Michael LeBlanc**, **Lisa M. Rimsza**, **Nancy L. Bartlett**, **Andrew M. Evens**, **Erik S. Mittra**, **Ann S. LaCasce**, **John W. Sweetenham**, **Paul M. Barr**, **Michelle A. Fanale**, **Michael V. Knopp**, **Ariela Noy**, **Eric D. Hsi**, **James R. Cook**, **Mary Jo Lechowicz**, **Randy D. Gascoyne**, **John P. Leonard**, **Brad S. Kahl**, **Bruce D. Cheson**, **Richard I. Fisher** and **Jonathan W. Friedberg**

Patients and Methods The Southwest Oncology Group S0816 (Fludeoxyglucose F 18-PET/CT Imaging and Combination Chemotherapy With or Without Additional Chemotherapy and G-CSF in Treating Patients With Stage III or Stage IV Hodgkin Lymphoma) trial enrolled 358 HIV-negative patients between July 1, 2009, and December 2, 2012. A PET scan was performed after two initial cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and was labeled PET2. PET2-negative patients (Deauville score 1 to 3) received an additional four cycles of ABVD, whereas PET2-positive patients (Deauville score 4 to 5) were switched to escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) for six cycles. Among 336 eligible and evaluable patients, the median age was 32 years (range, 18 to 60 years), with 52% stage III, 48% stage IV, 49% International Prognostic Score 0 to 2, and 51% score 3 to 7.

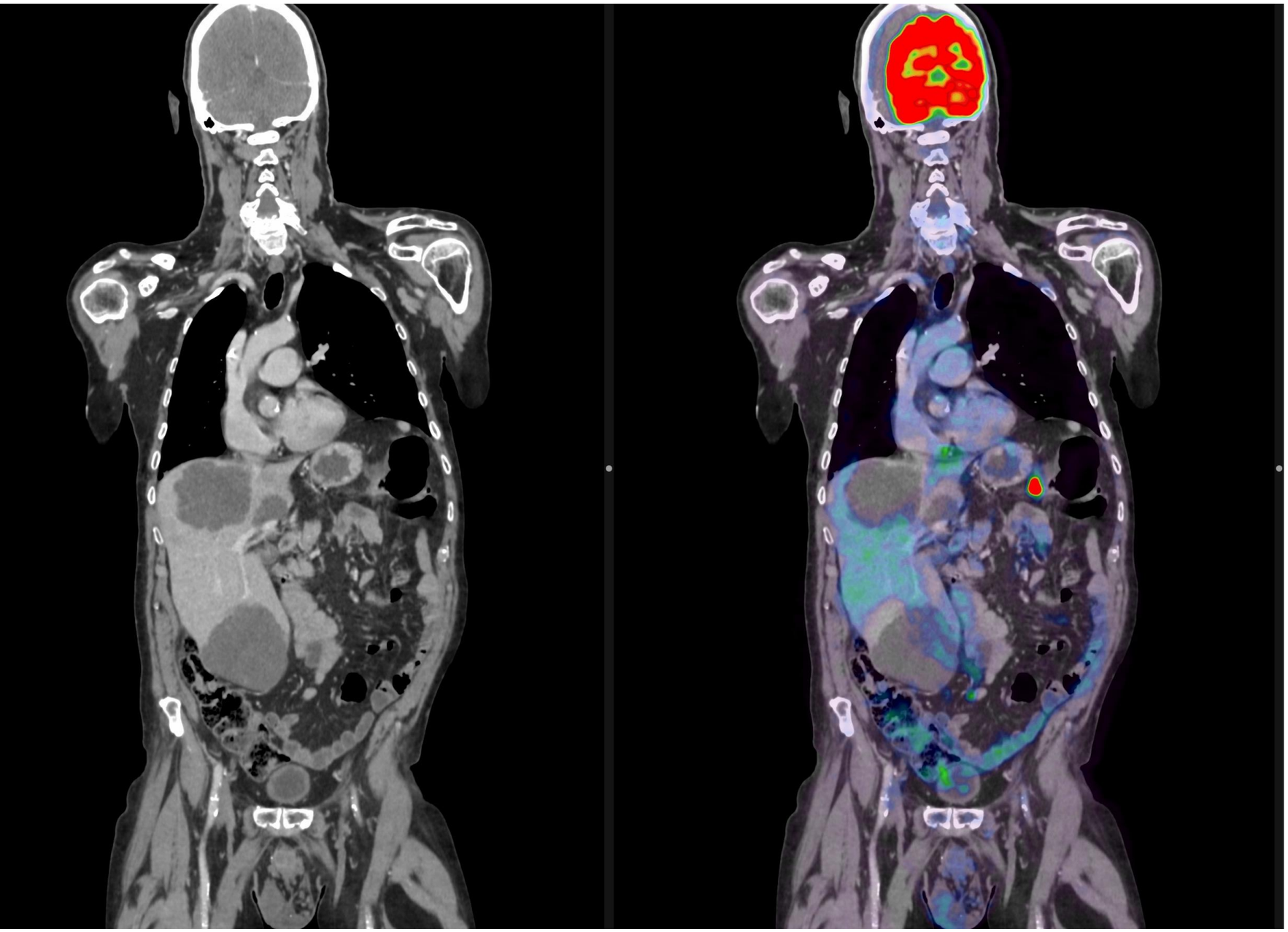
Conclusion Response-adapted therapy based on interim PET imaging after two cycles of ABVD seems promising with a 2-year PFS of 64% for PET2-positive patients, which is much higher than the expected 2-year PFS of 15% to 30%.

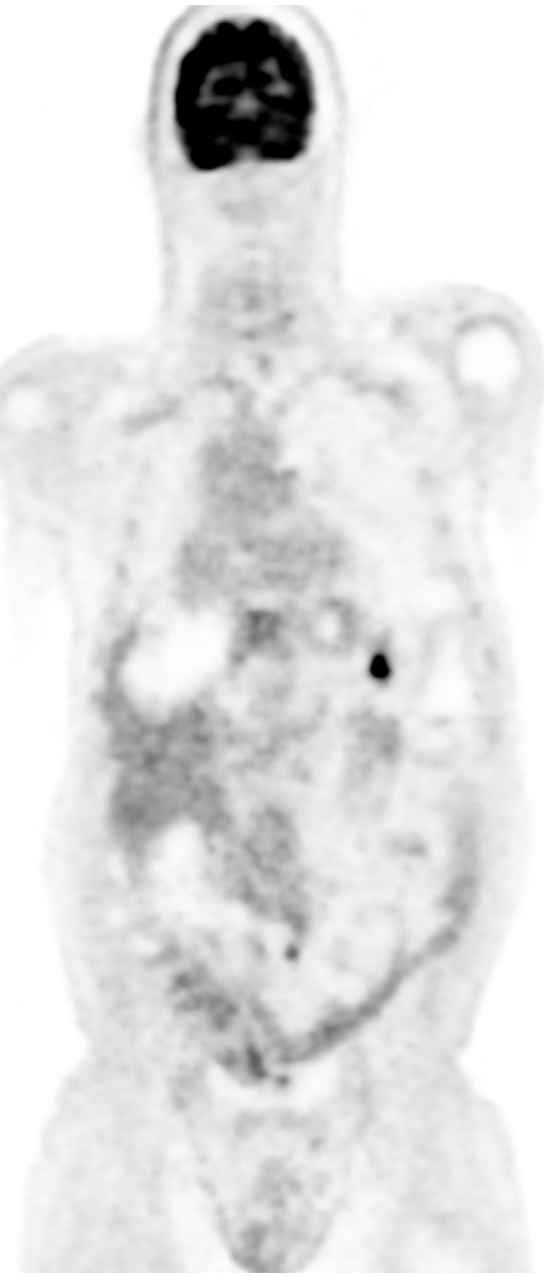
Colo-rectal cancer





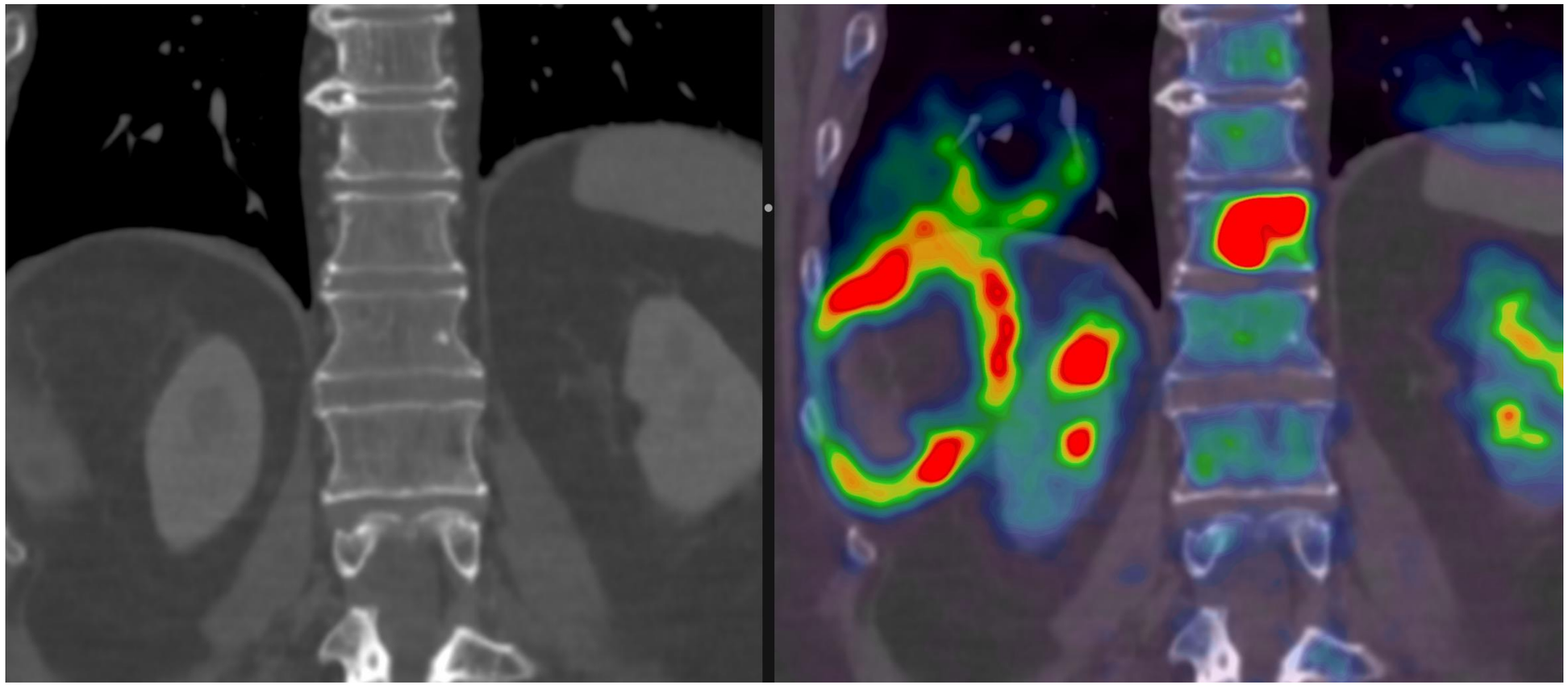
10/2018
VM - 140346

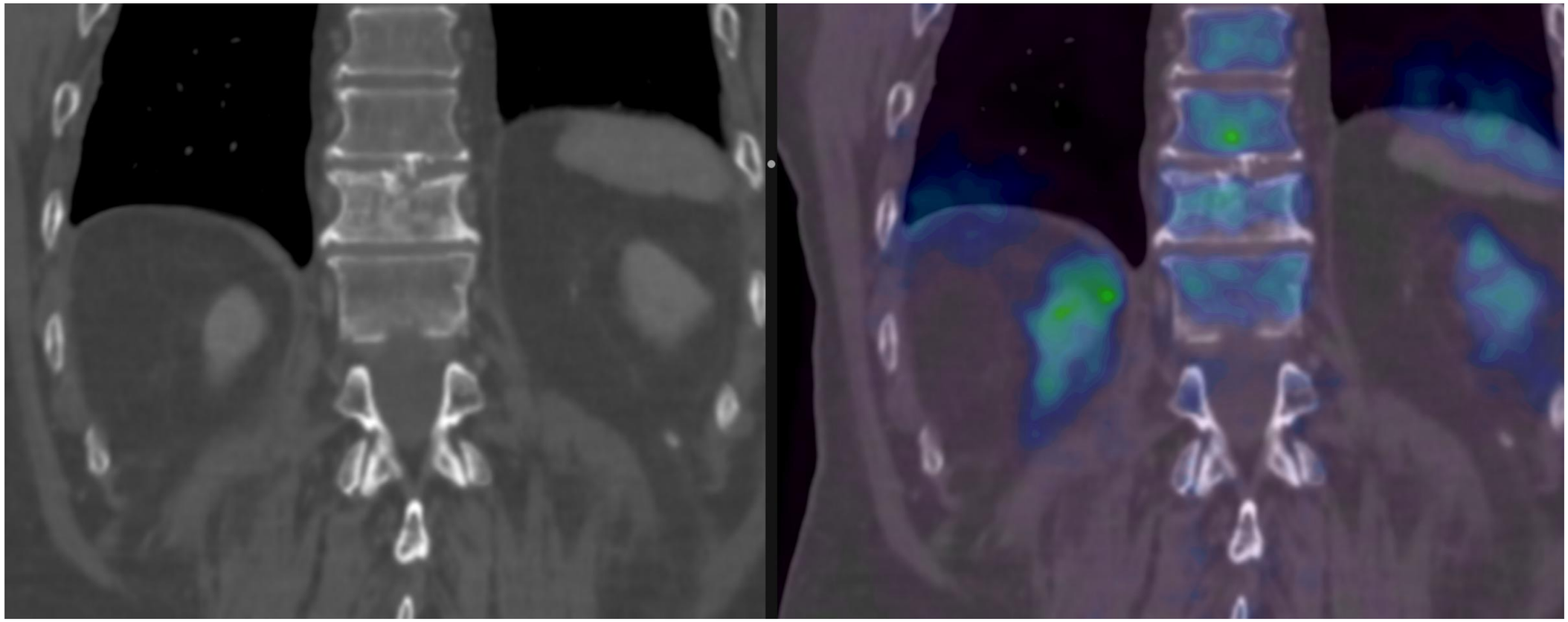


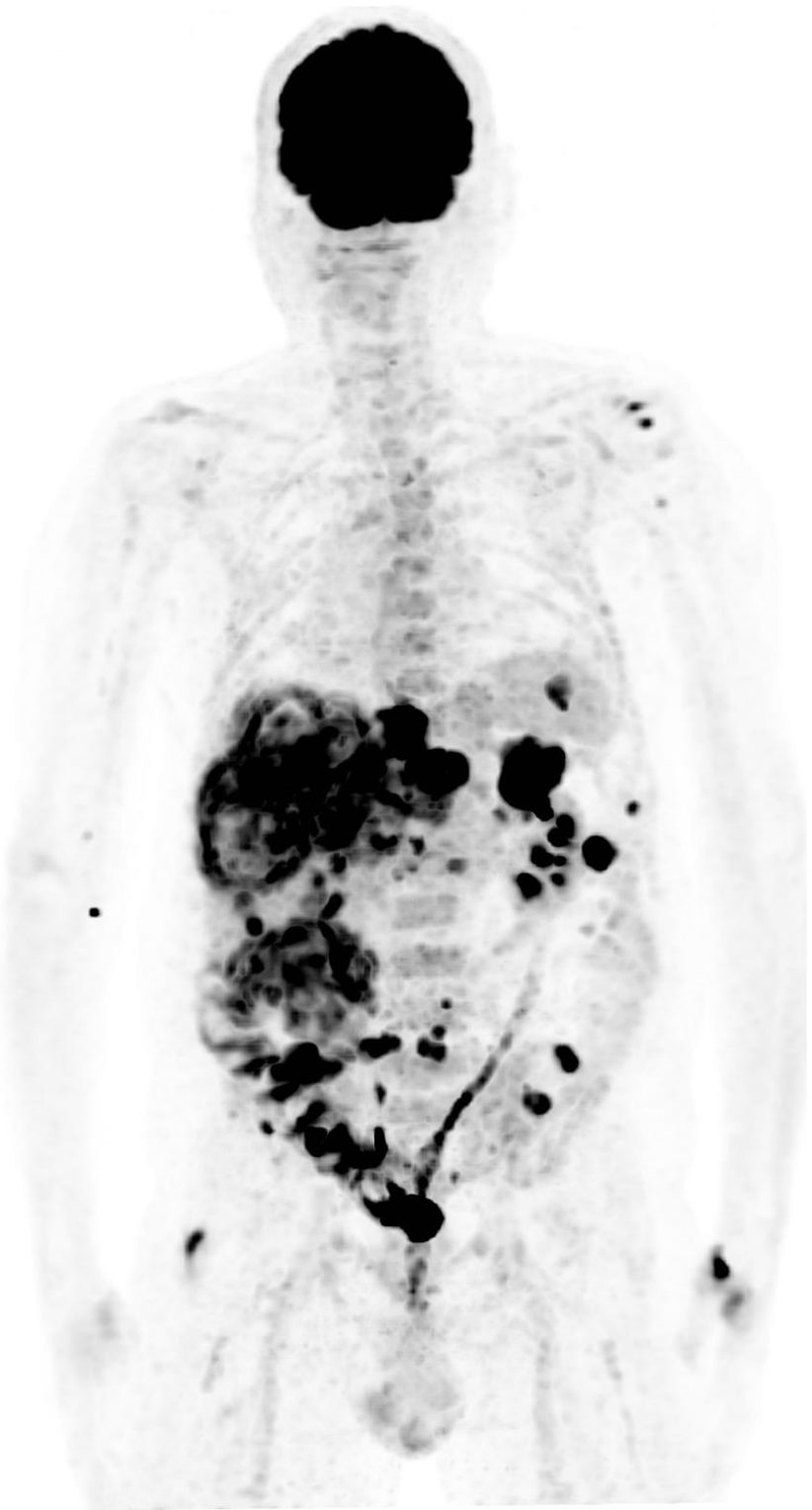


01/2019

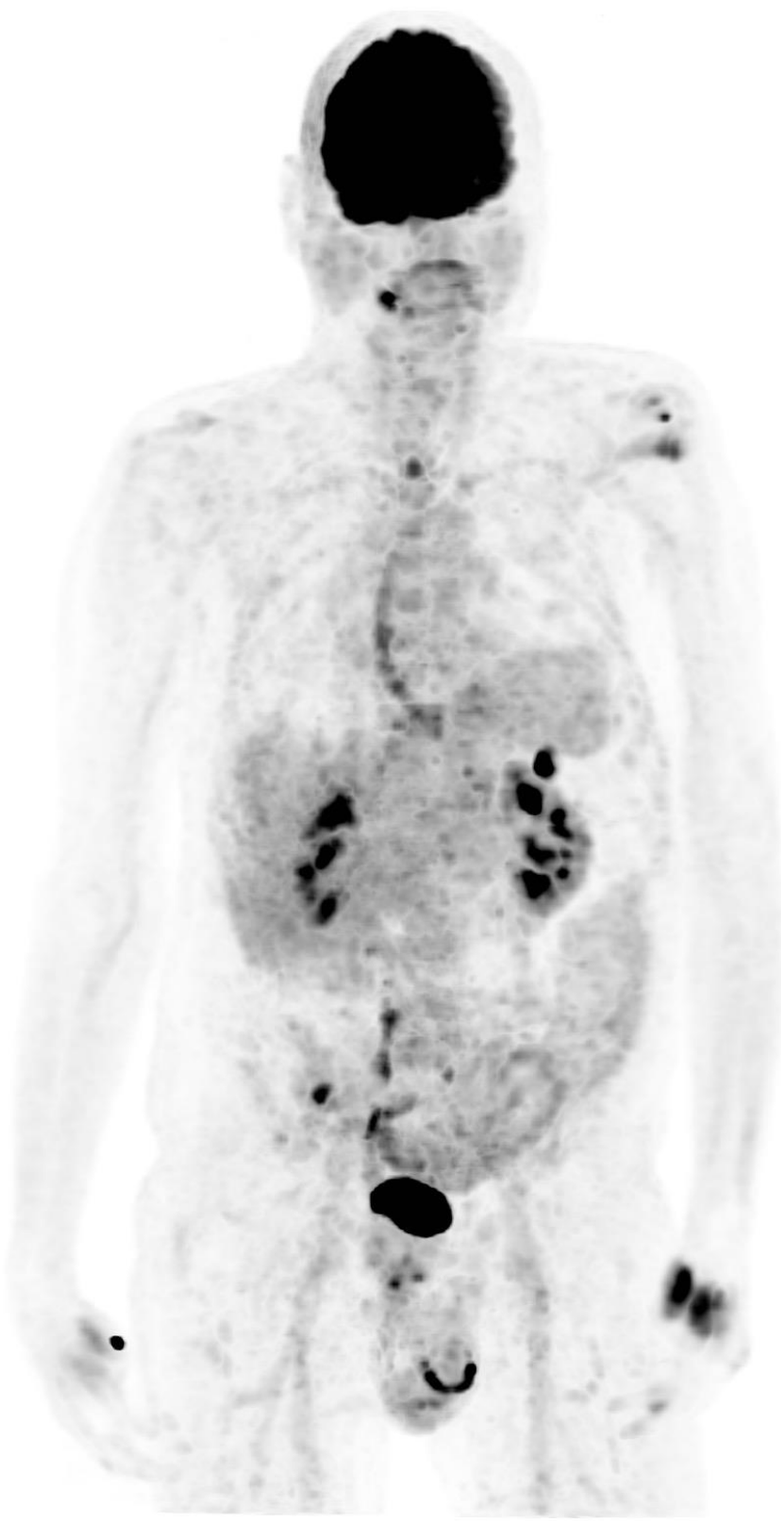
FOLFOX-Bevacizumab



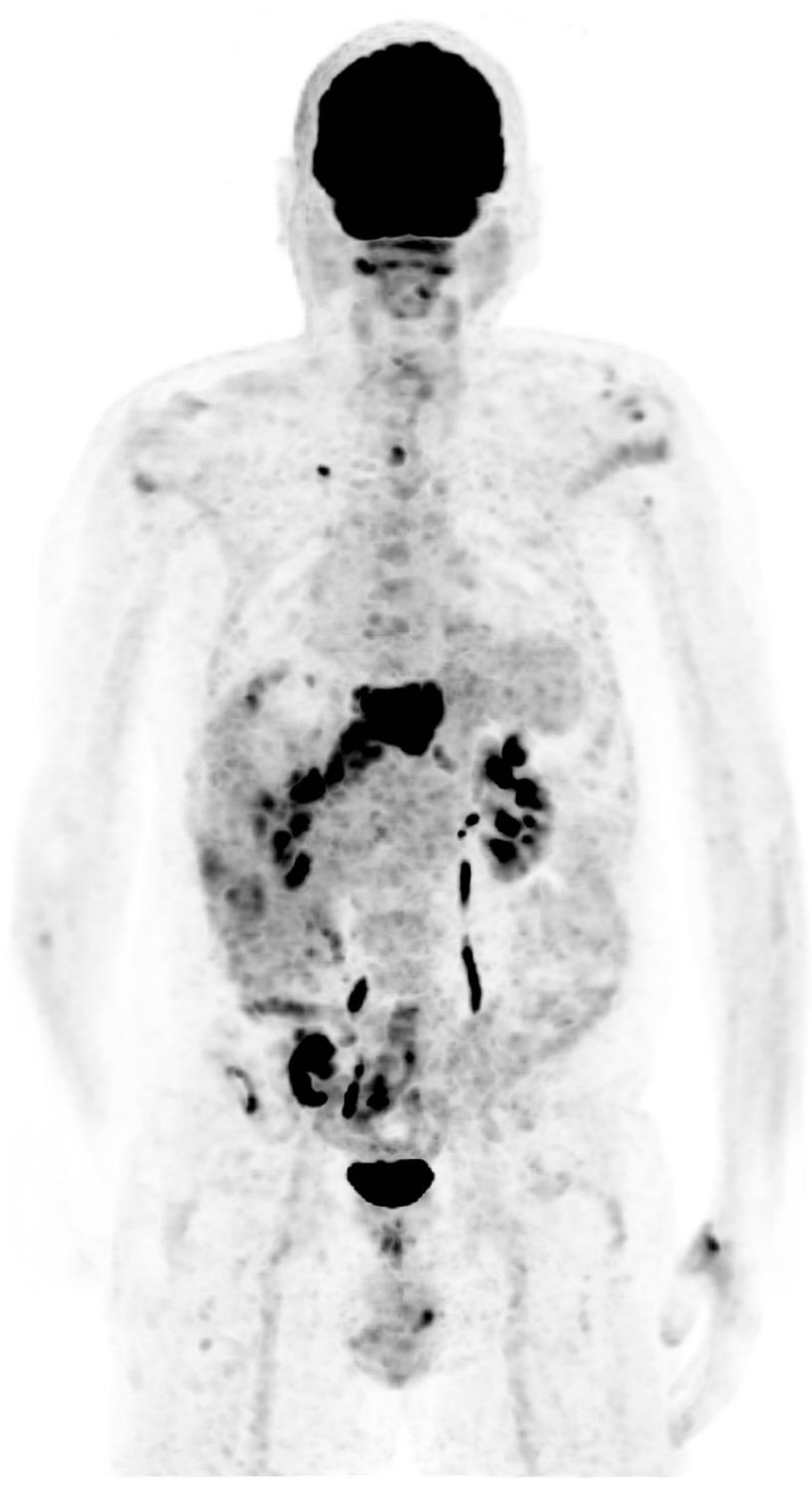


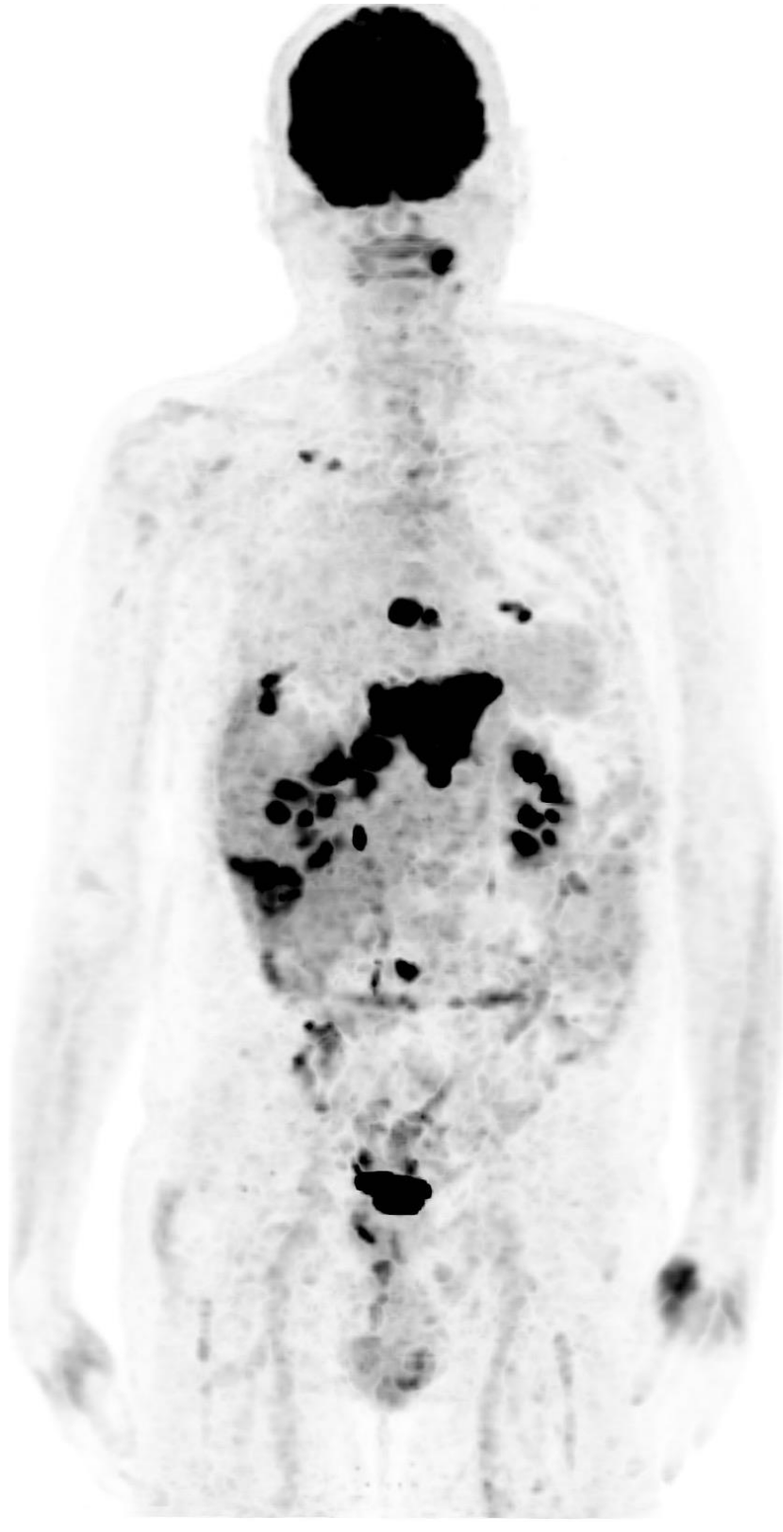


10/2018

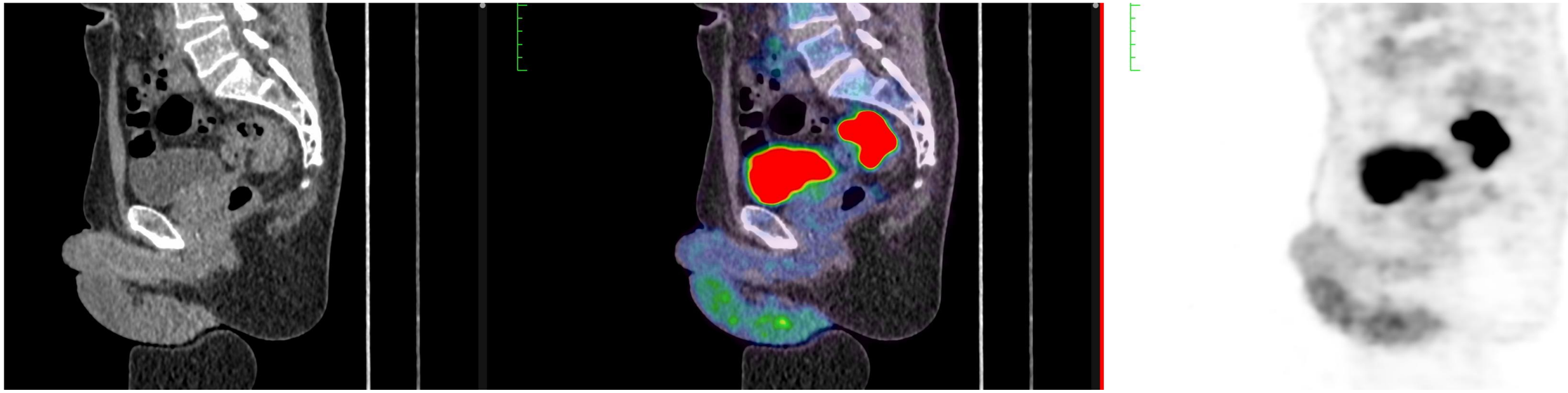


01/2019





06/2019 **Folfiri+Avastin** **01/2020**



11/2019 - SUVmax 35 - TLG 208

02/2020 - SUVmax 7,9 - TLG 9,5

CG 130761

Indications of PET-FDG in HNSCC

- Pretherapeutic Staging : M detection TNM CHANGE : 20 %
- Restaging the neck after organ-preservation protocols (neck dissection or not) NPV 95 %
- Diagnosis of relapse in symptomatic patient SENS 94 % - SPEC 80 %
- Systematic follow-up in high-risk (stages III-IV, HPV -) patients NPV 100 % - PPV 77 %
- Radiation treatment planning

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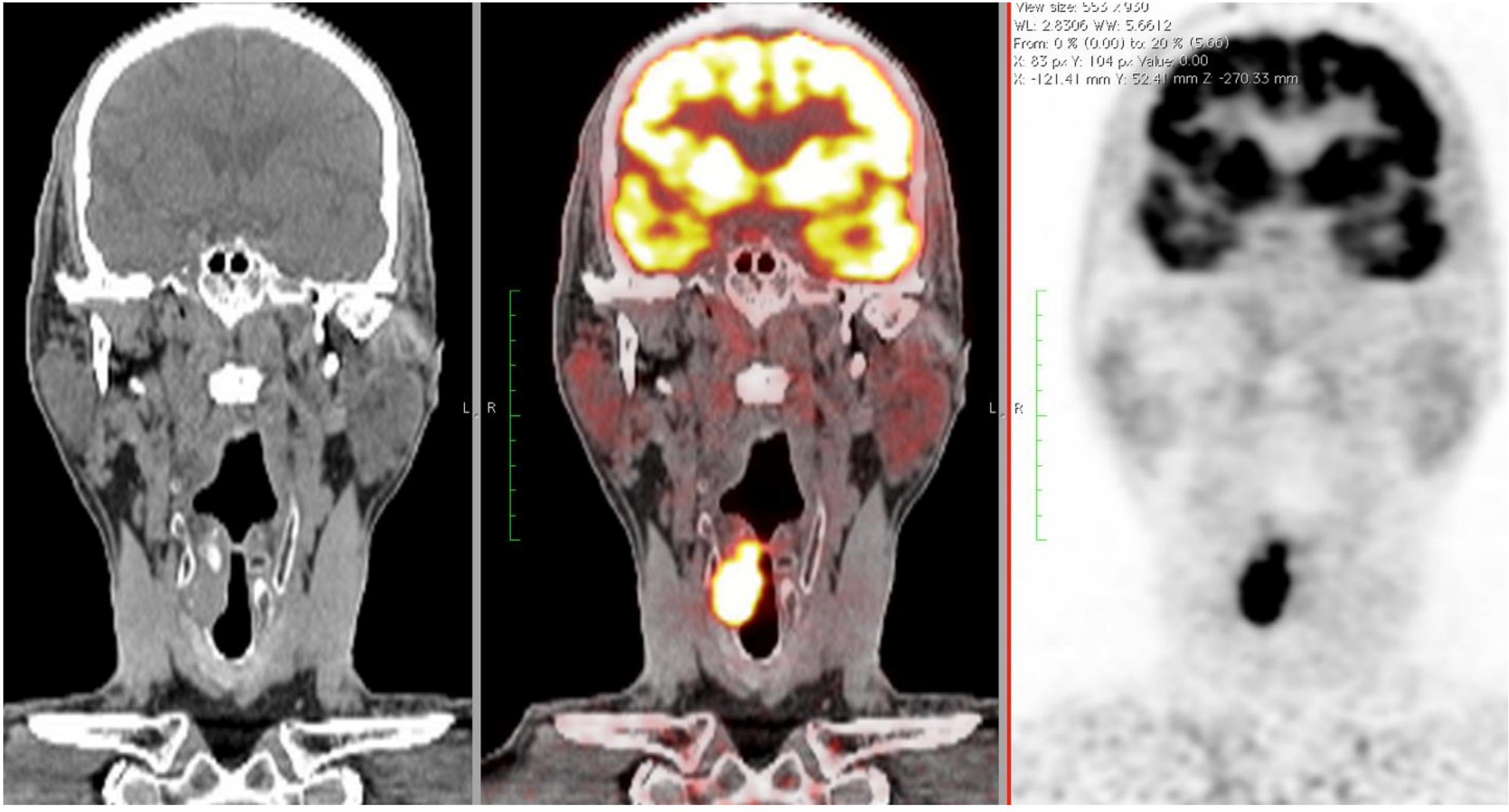

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Restaging the neck

- The clinical problem:
  - After organ-preservation protocols (chemo-radiotherapy), many patients are clinically « N0 ».
    - However, many patients with pre-therapeutic cN+ status would undergo neck dissection (uni- or bilateral)
    - More than 50 % of removed lymph nodes do not harbour tumor cells
- There is (was ?) a controversy about the place of systematic lymph node dissection....

Restaging the neck

- What the clinician needs is an imaging modality with a **near 100 % negative predictive value**

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REVIEW

A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy

Isles, M.G.*, McConkey, C. [‡] & Mehanna, H.M.*[†]

*Institute of Head and Neck Studies and Education, Department of Otorhinolaryngology Head Neck Surgery, University Hospital, Coventry , [†] Department of Otorhinolaryngology Head Neck Surgery, Heart of England Foundation Trust, Birmingham , and [‡] Warwick Medical School Clinical Trials Unit, University of Warwick, Coventry, UK

- Meta-analysis

Sens	94 %
Spec	82 %
PPV	75 %
NPV	**95 %**

- Better accuracy if PET performed more than 10 weeks after the end of therapy

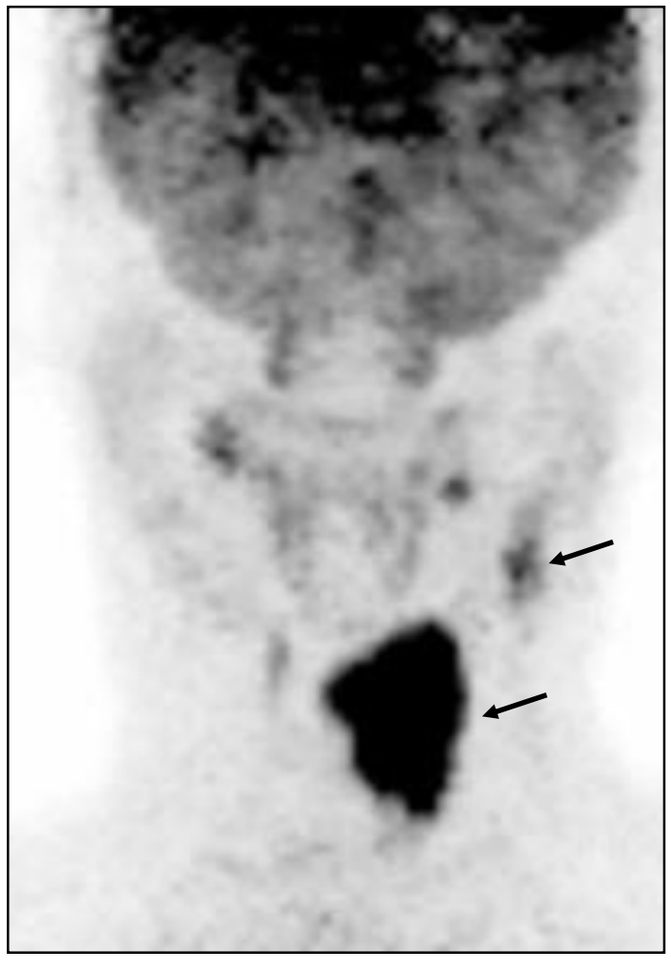
Cost-effectiveness of CT and PET-CT for determining the need for adjuvant neck dissection in locally advanced head and neck cancer

D. J. Sher[1,2]*, R. B. Tishler[1], D. Annino[3] & R. S. Punglia[1,2]

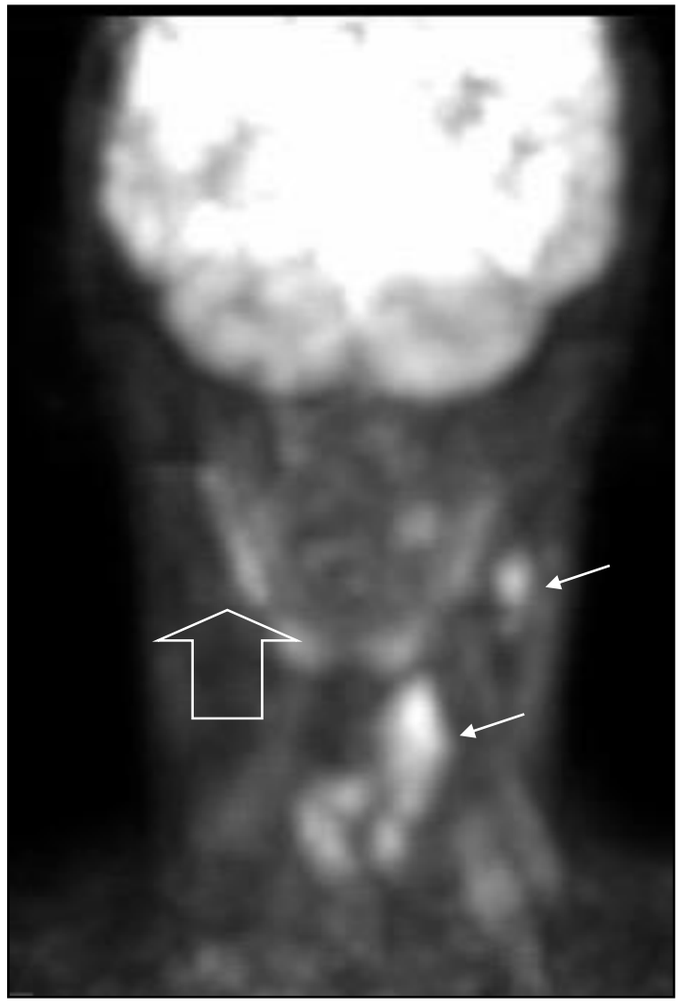
[1]Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston; [2]Center for Outcomes and Policy Research, Dana-Farber Cancer Institute, Boston, MA, USA and [3]Division of Otolaryngology, Brigham and Women's Hospital, Boston, MA, USA

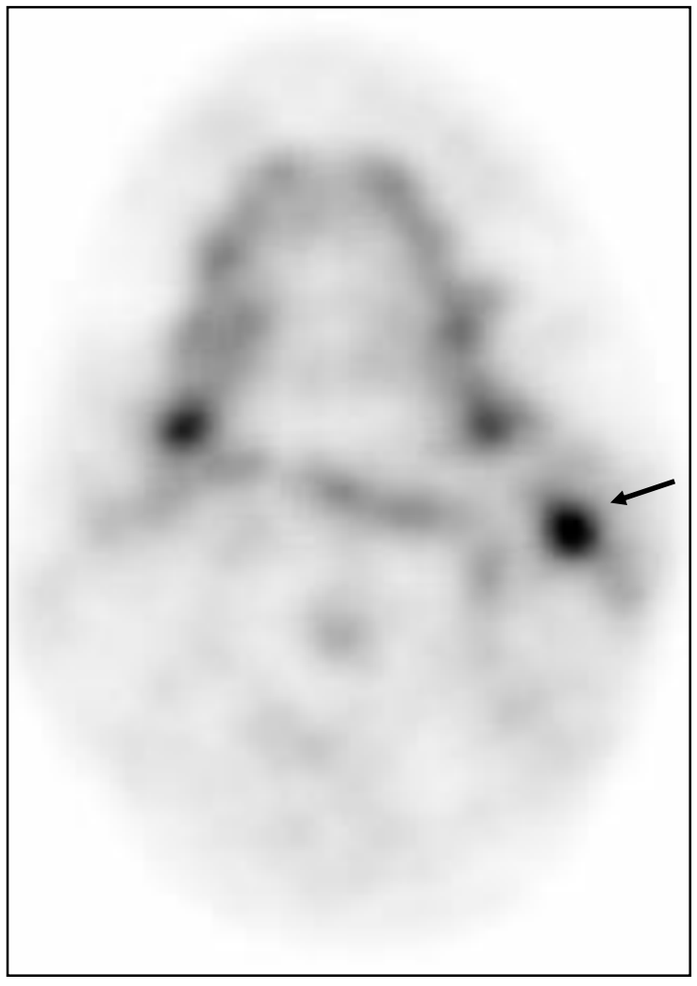
- *«Adjuvant neck dissection reserved for patient with residual disease on PET-CT is the dominant and cost-effective strategy.»*

SHER, ANN. ONCOL. 2009



PRE-R/





AFTER R/
RESIDUAL PRIMARY AND NODAL DISEASE

NOTE THE MUCOSAL UPTAKE DUE TO INFLAMMATION (OPEN ARROW)

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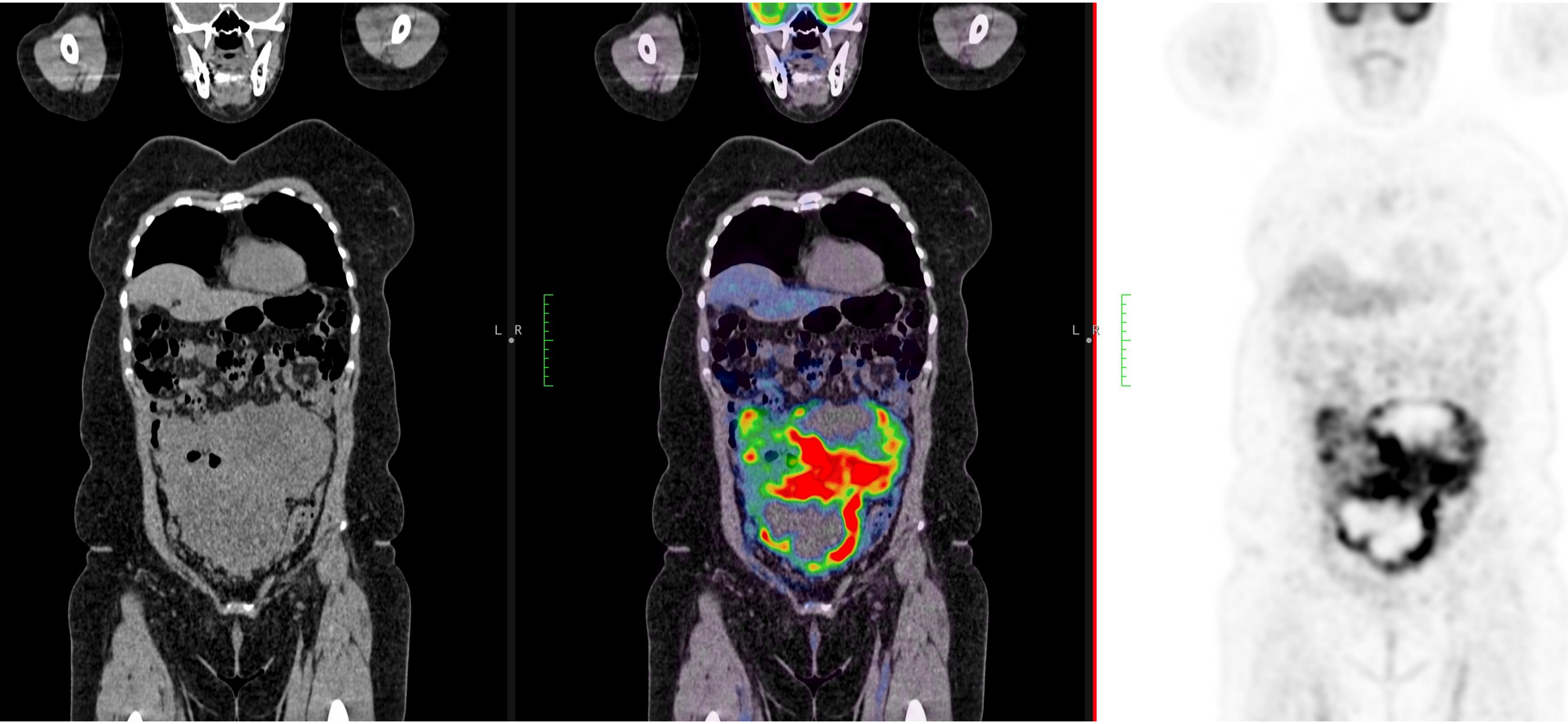
Criteria

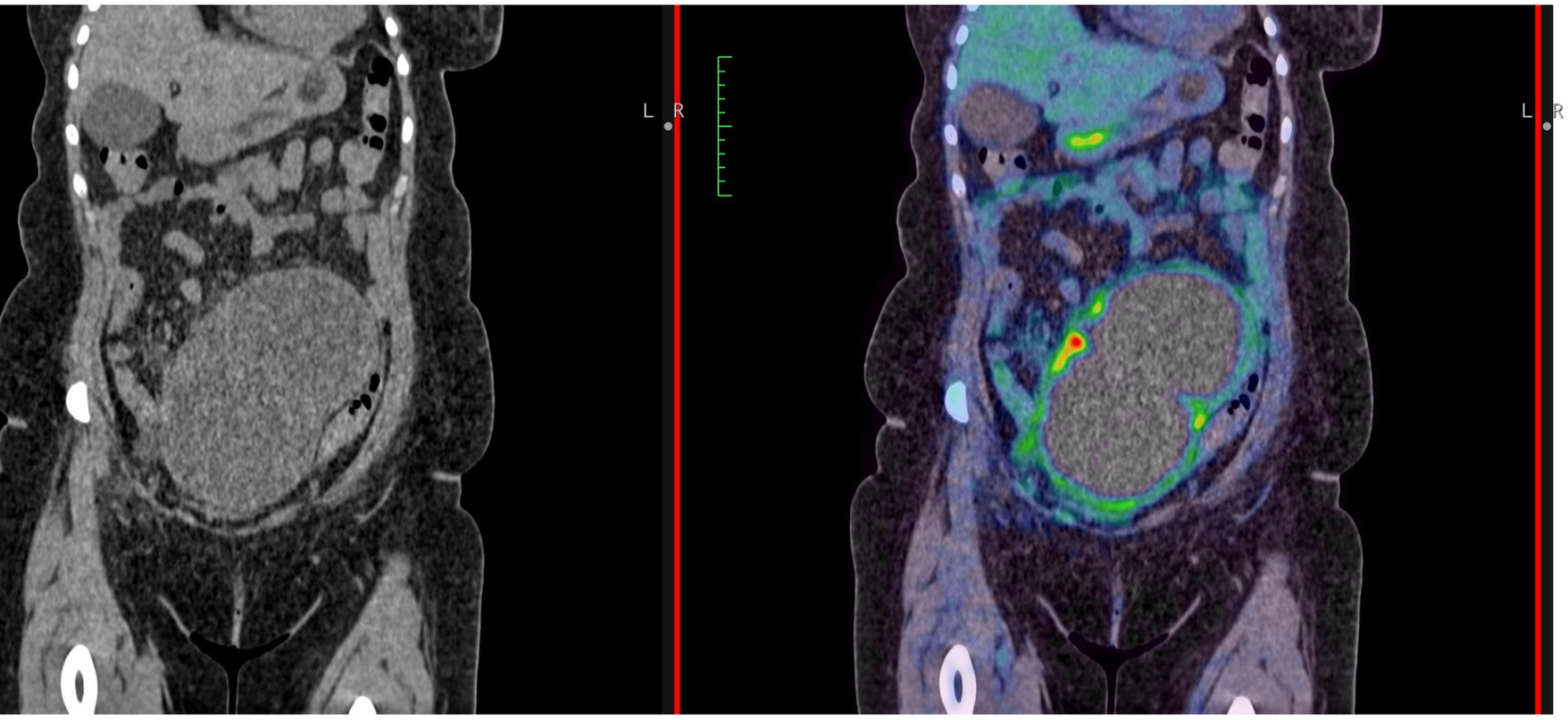
Five-point qualitative post-therapy assessment scoring system (Hopkins criteria) for head and neck PET-CT:

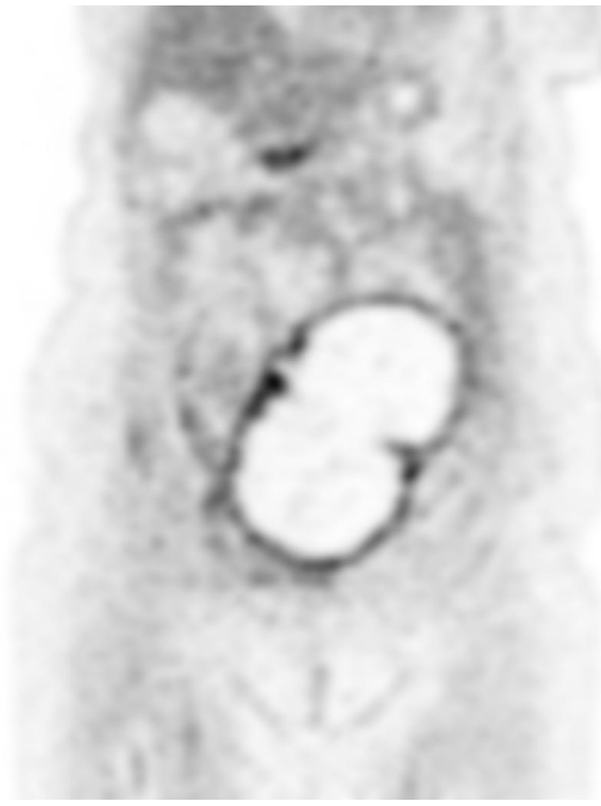
1. Response category F-18-FDG uptake at the primary site and nodes less than internal jugular vein (IJV). Complete metabolic response.
2. Focal F-18-FDG uptake at the primary site and nodes greater than IJV but less than liver. Likely complete metabolic response.
3. Diffuse F-18-FDG uptake at the primary site or nodes is greater than IJV or liver. Likely postradiation inflammation.
4. Focal F-18-FDG uptake at the primary site or nodes greater than liver. Likely residual tumor.
5. Focal and intense F-18-FDG uptake at the primary site or nodes. Residual tumor.

GIST



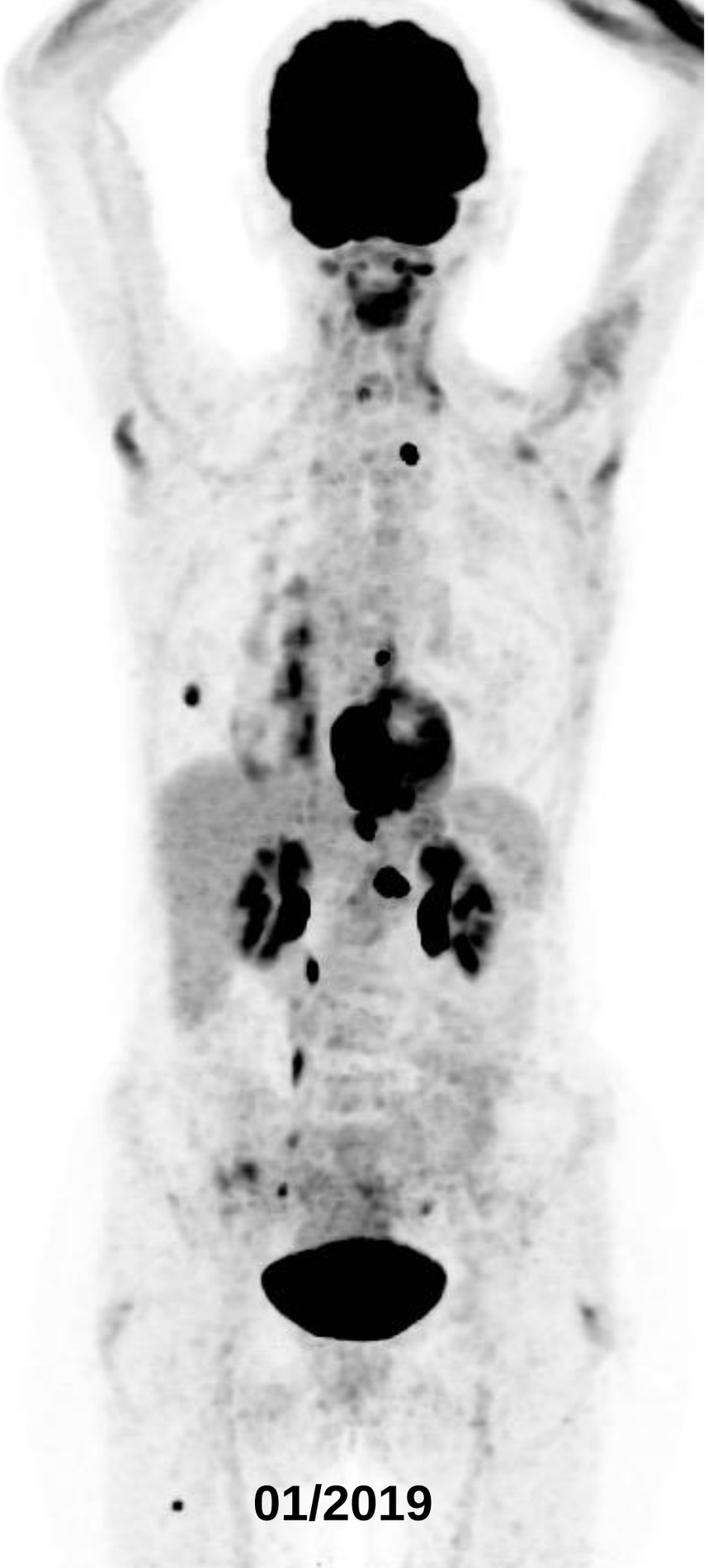
6/2014





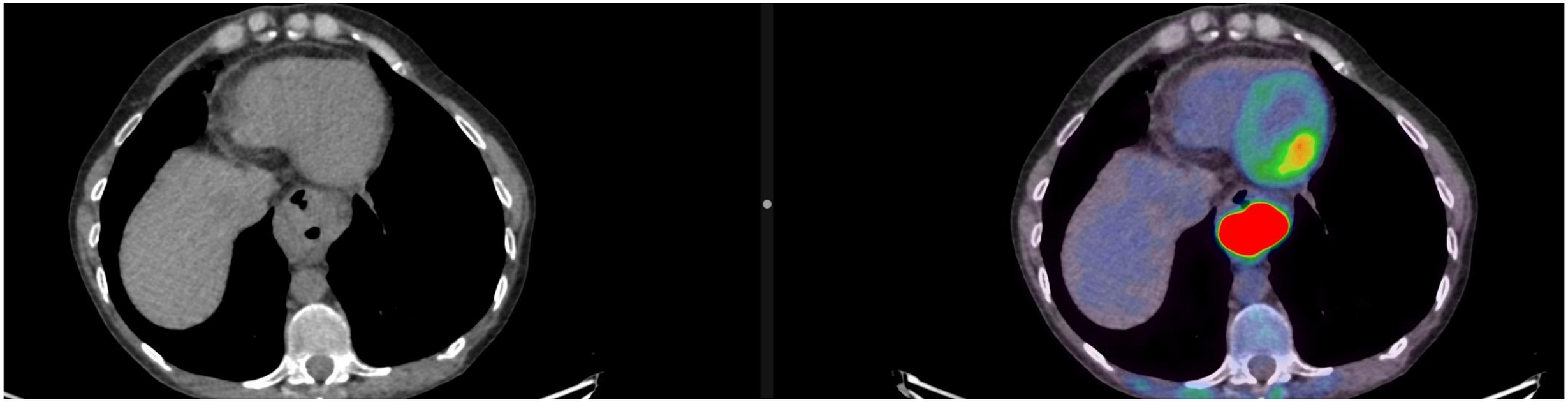
8/2014
2 months Glivec

Oesophagus



01/2019

VM 2/5/1962



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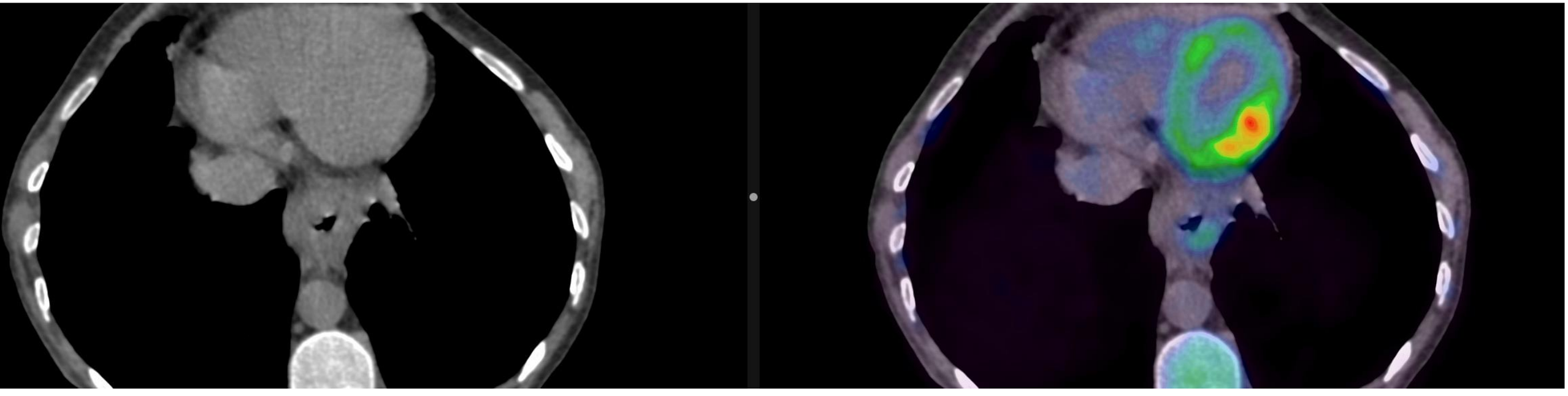
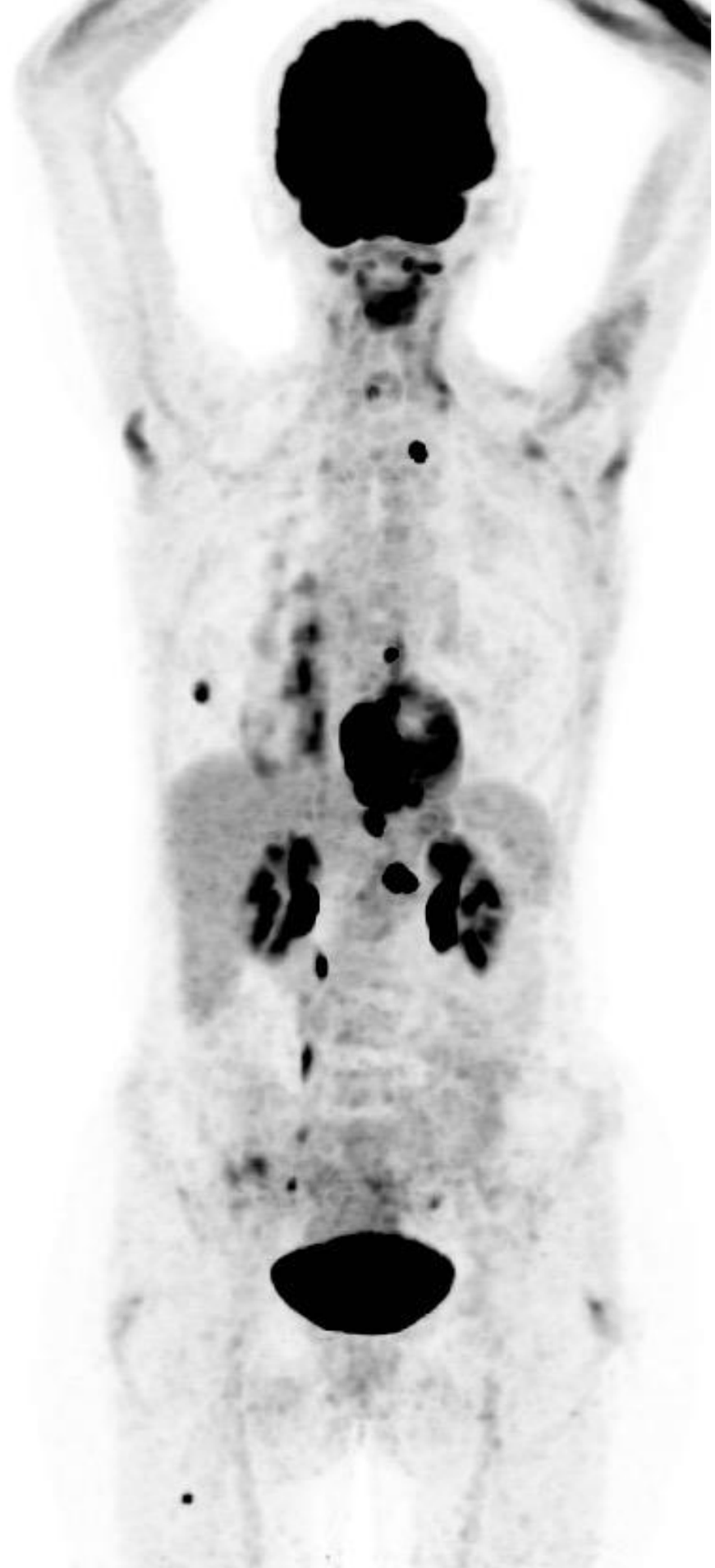
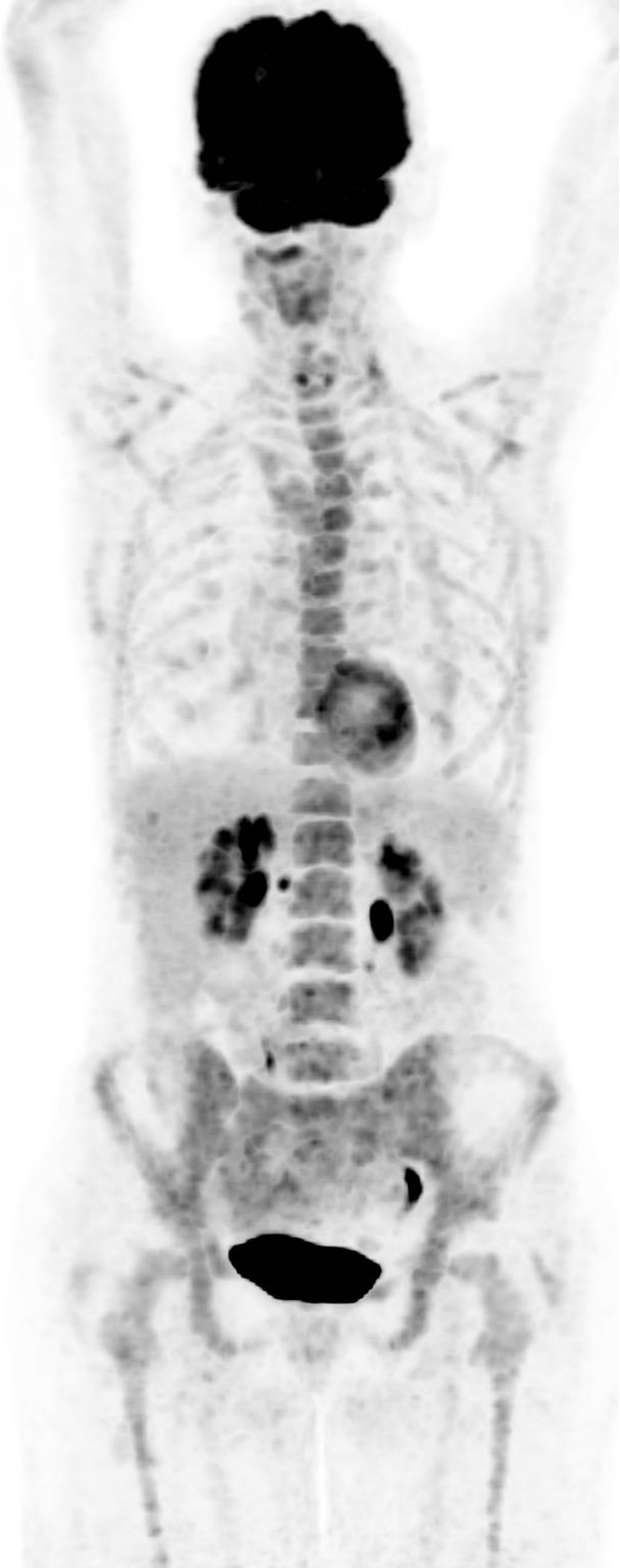
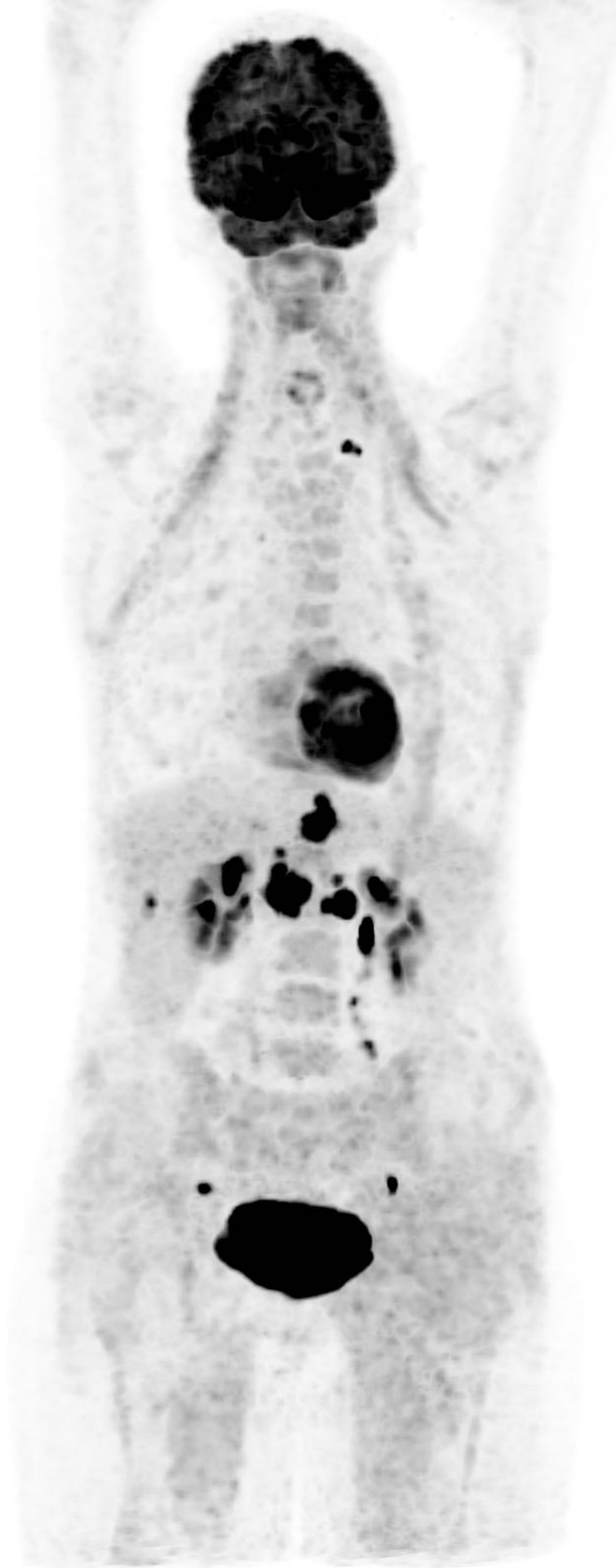


04/2019

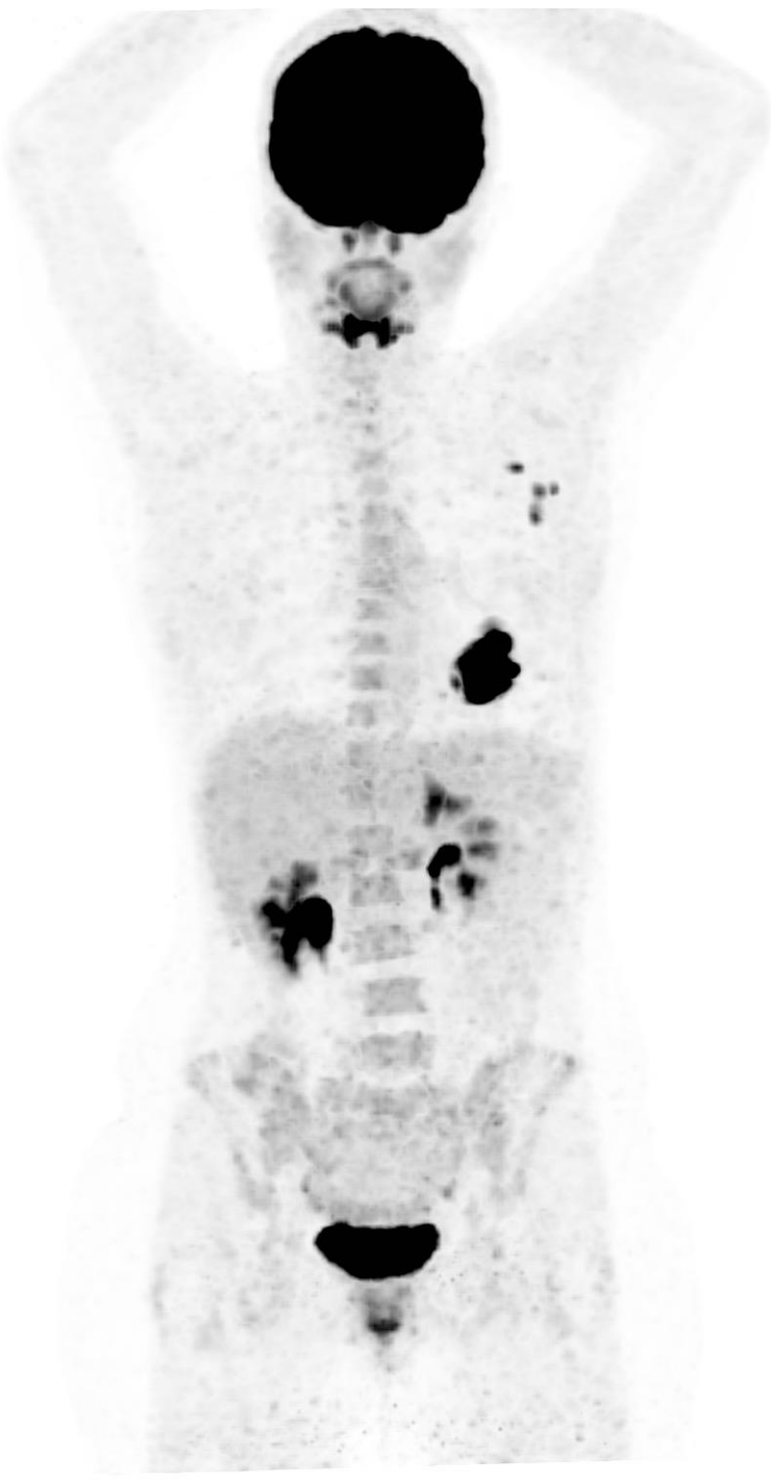




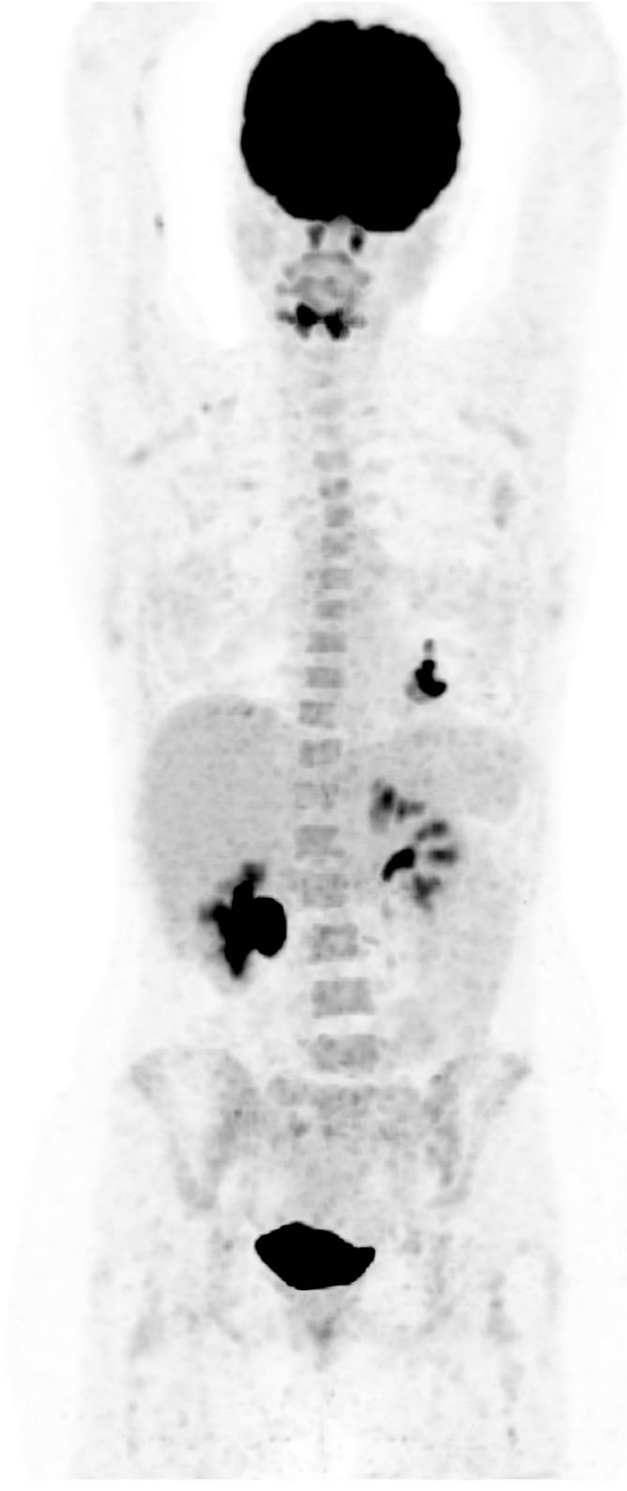


08/2019

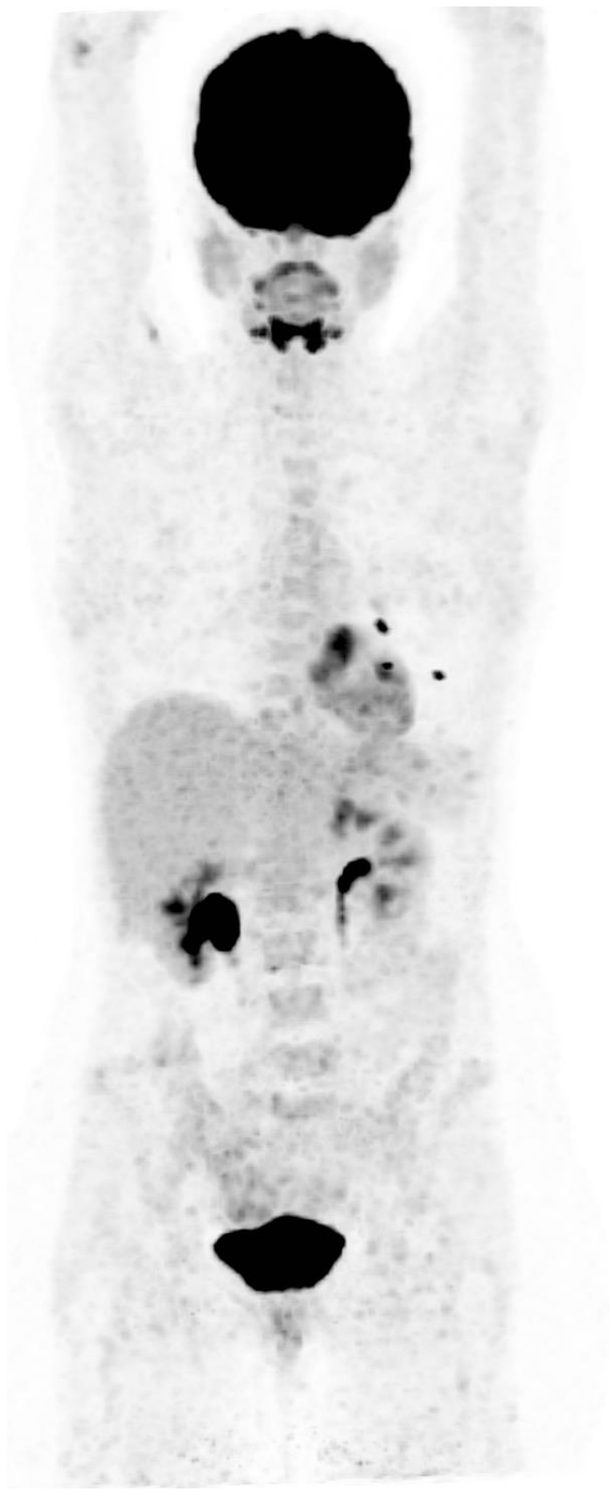
Breast



Baseline
SUVmax 28,3
TLG 115



1 cycle chemo
SUVmax 11,3 : -60 %
TLG 14 : -87 %



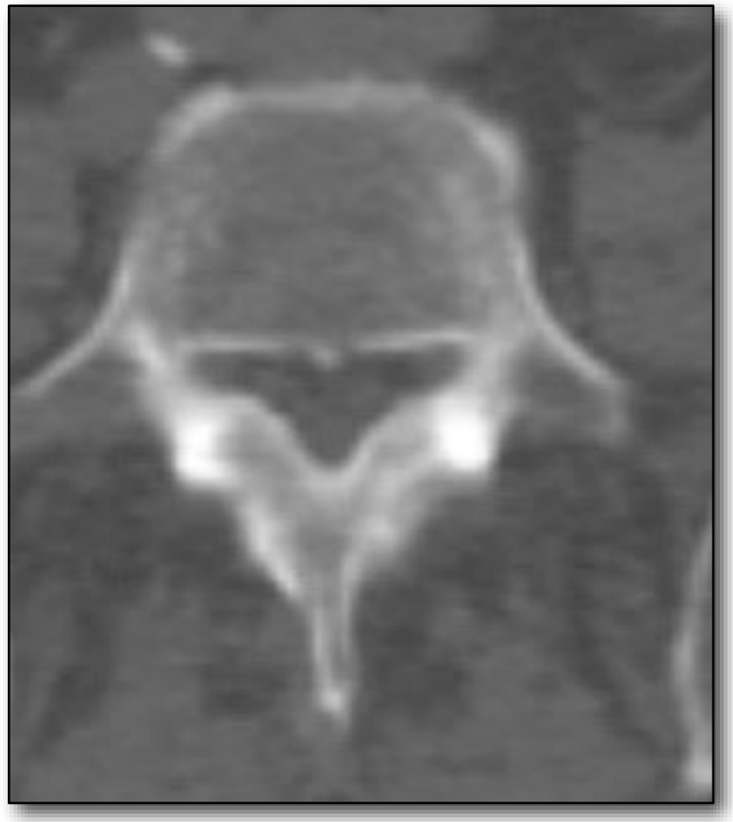
End of chemo
SUVmax 10 : -11 %
TLG 3,1: -77 %

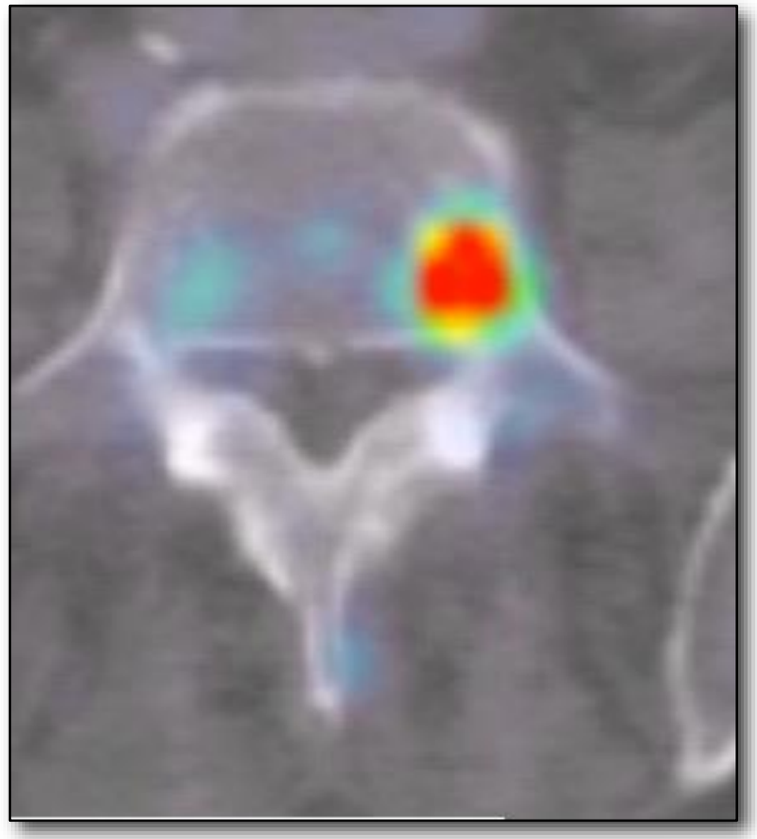
LV 030276

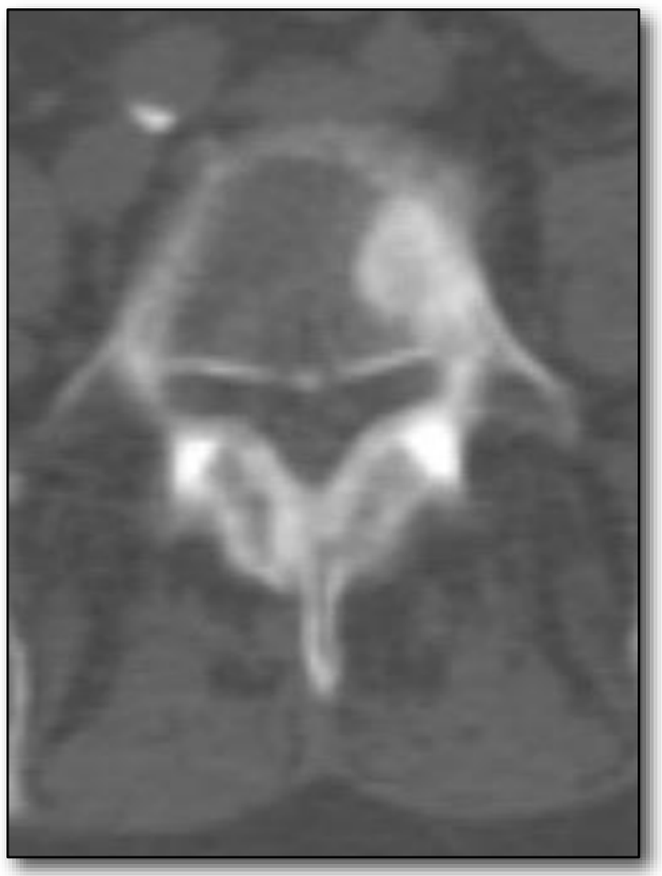
18/09/2007

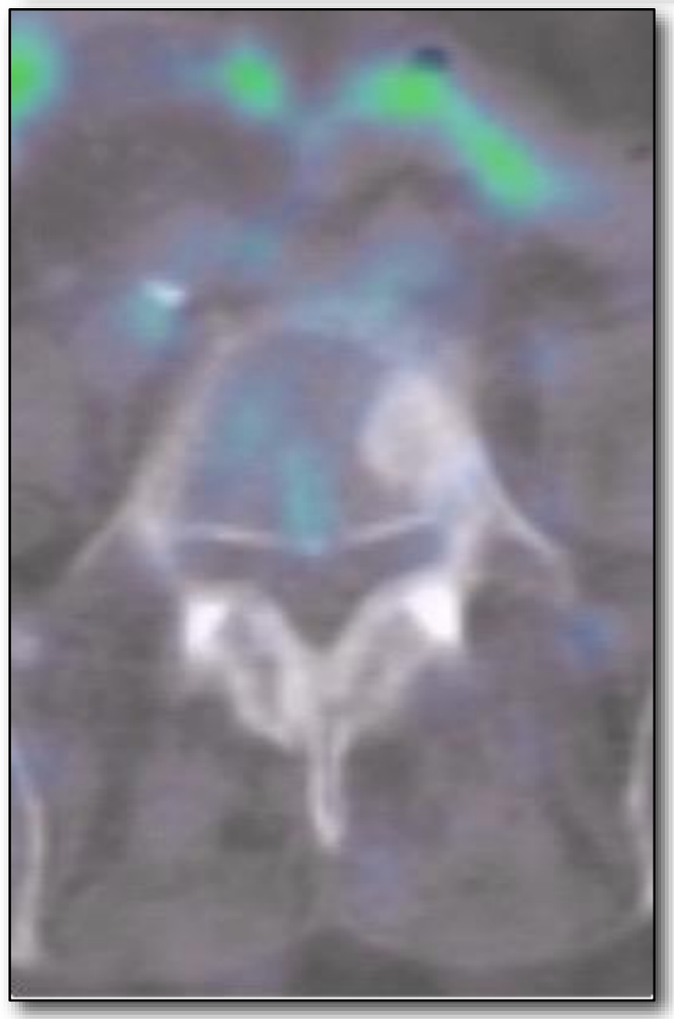
6 CYCLES OF CHEMO

20/01/2008









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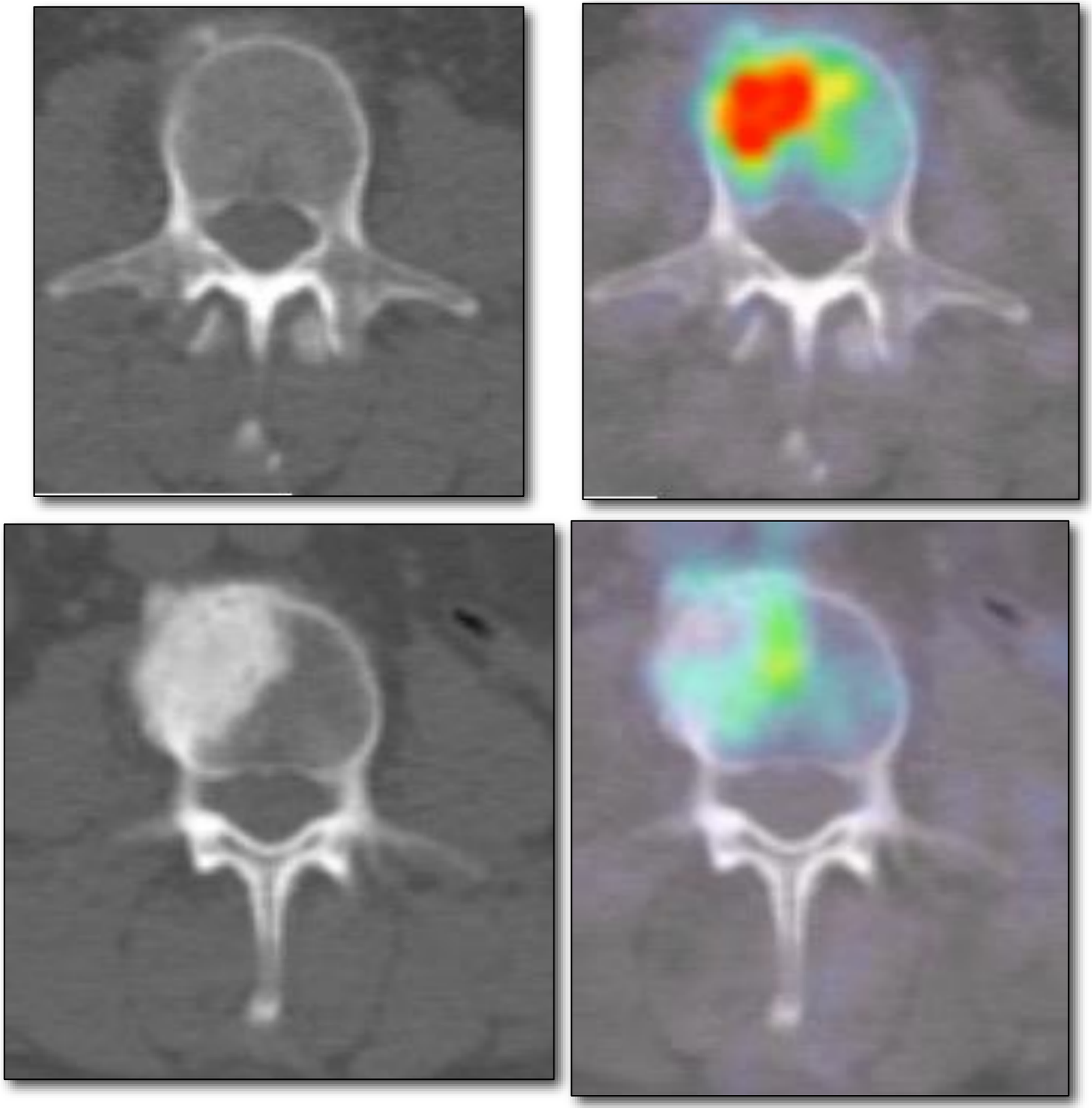
L67223C

18/09/2007

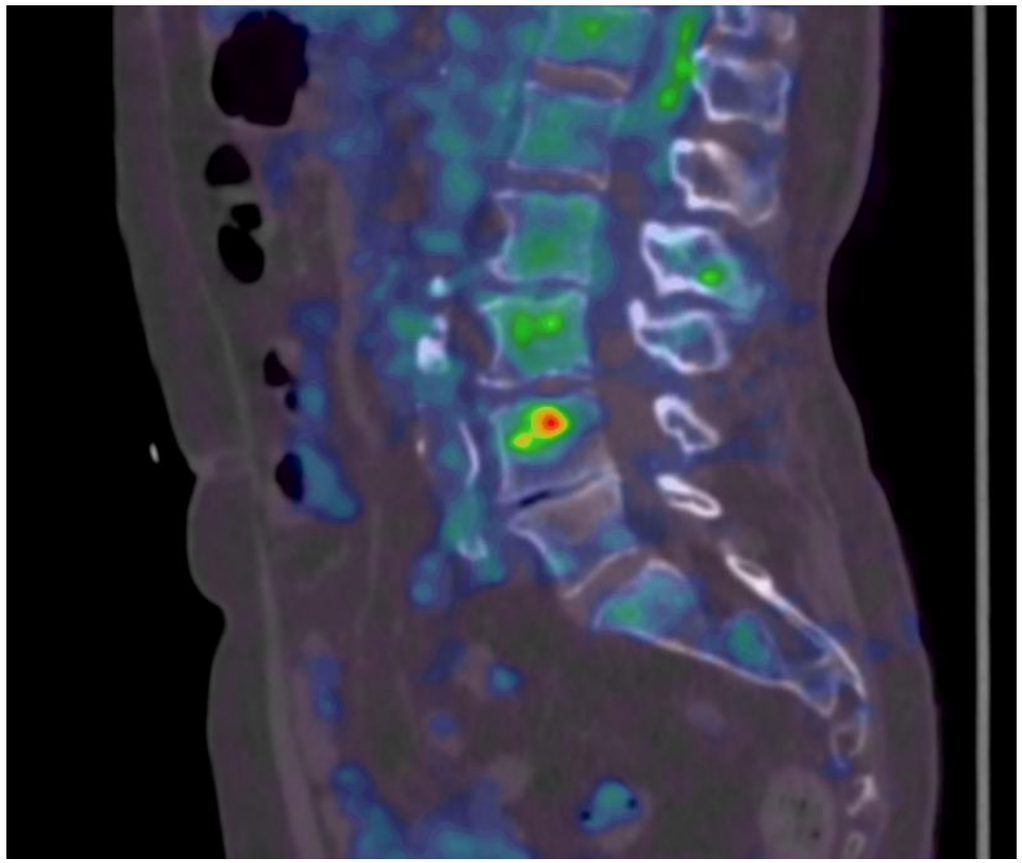
6 CYCLES OF CHEMO

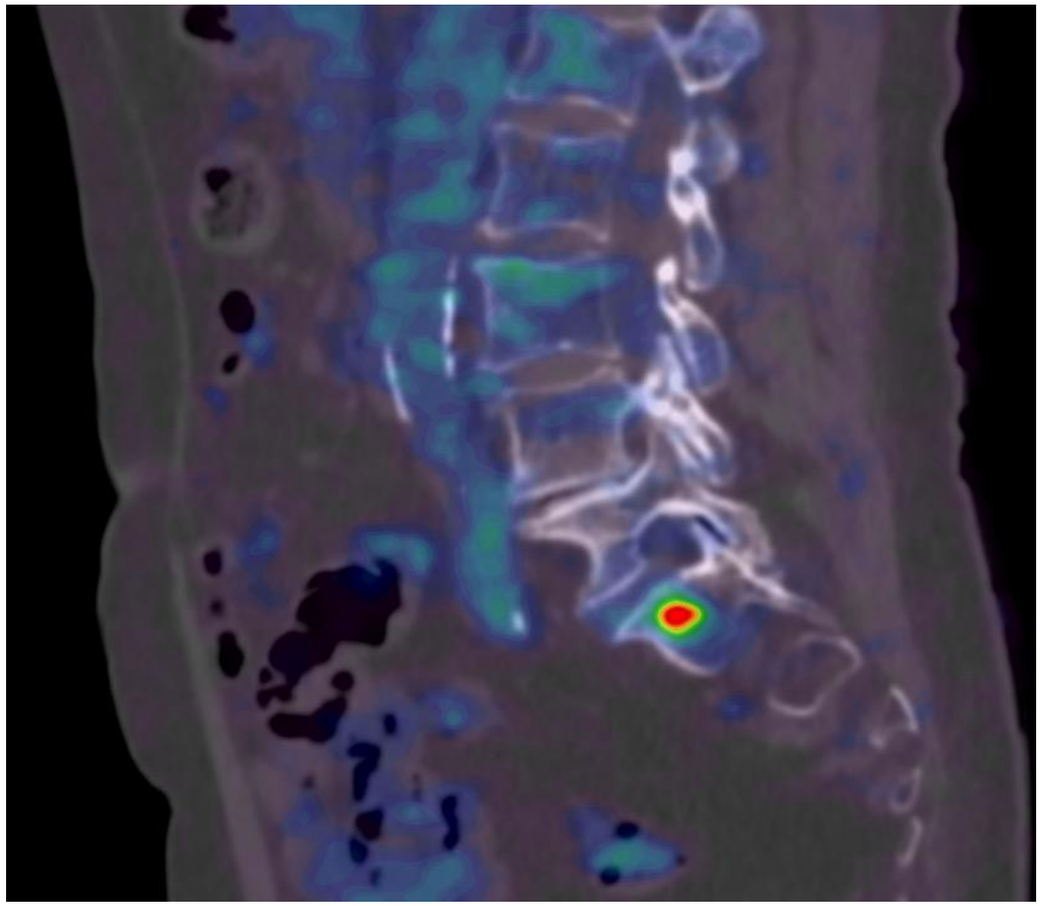


20/01/2008

Chirec Cancer Institute

L67223C



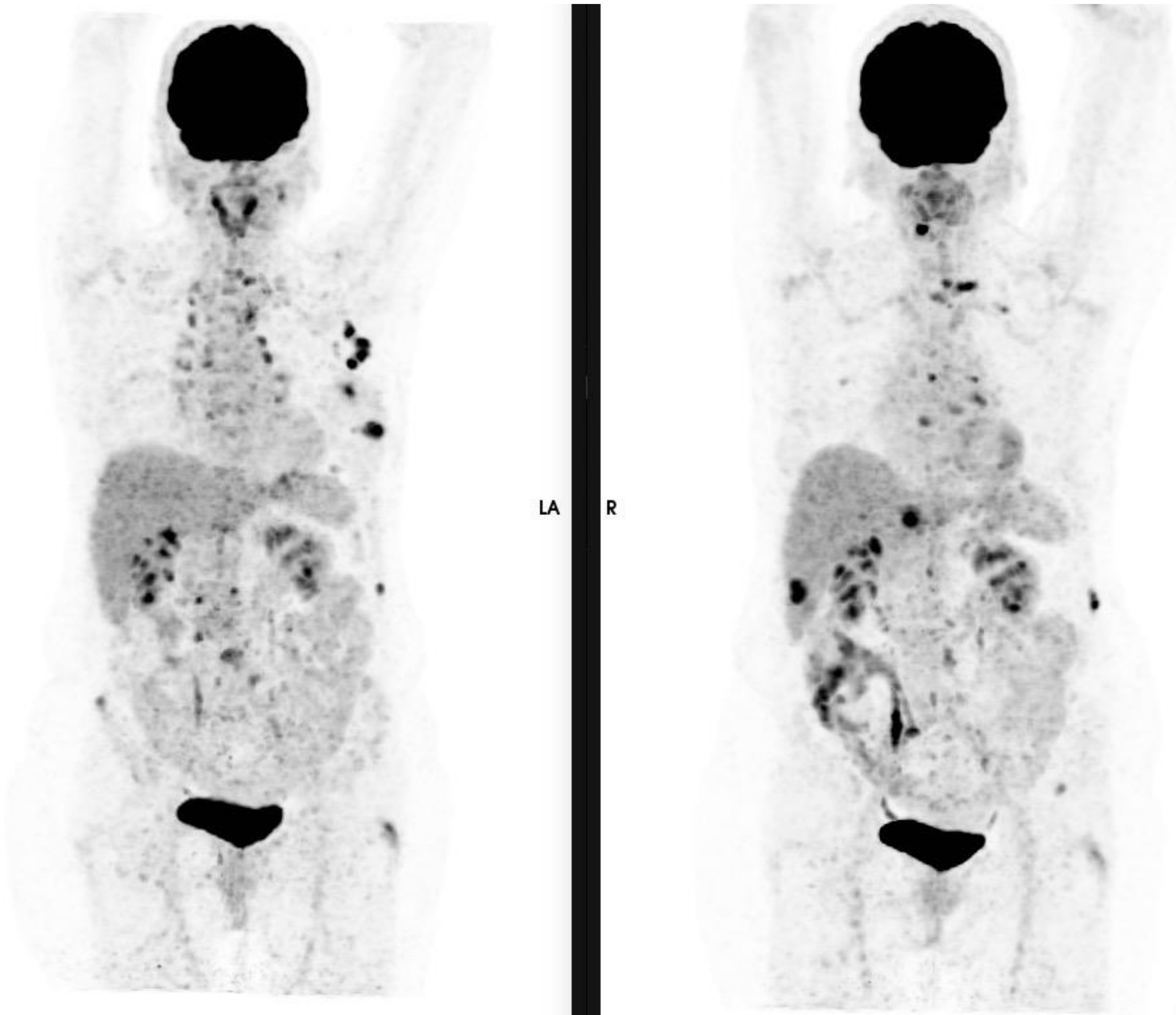


7/2019 **2/2020**

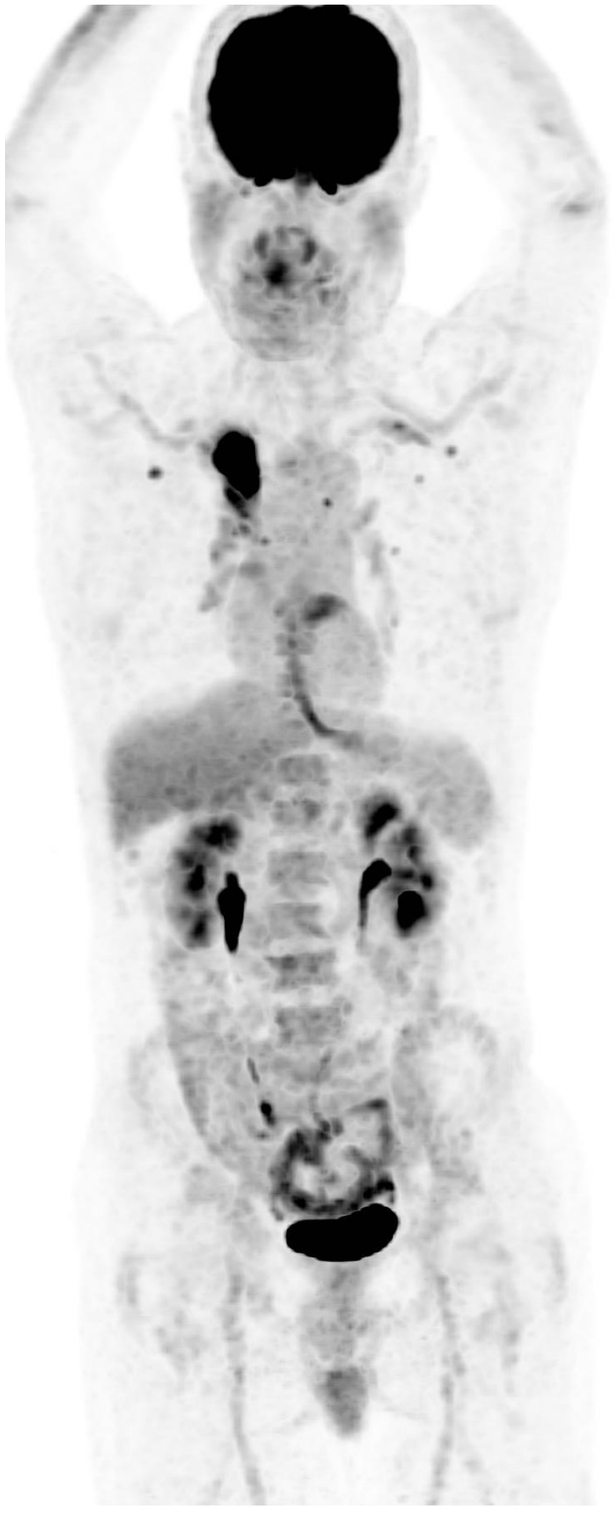
example of mixed response and progression

Femara-Ibrance-XGeva

MD 05081945


LA
R

Immunotherapy



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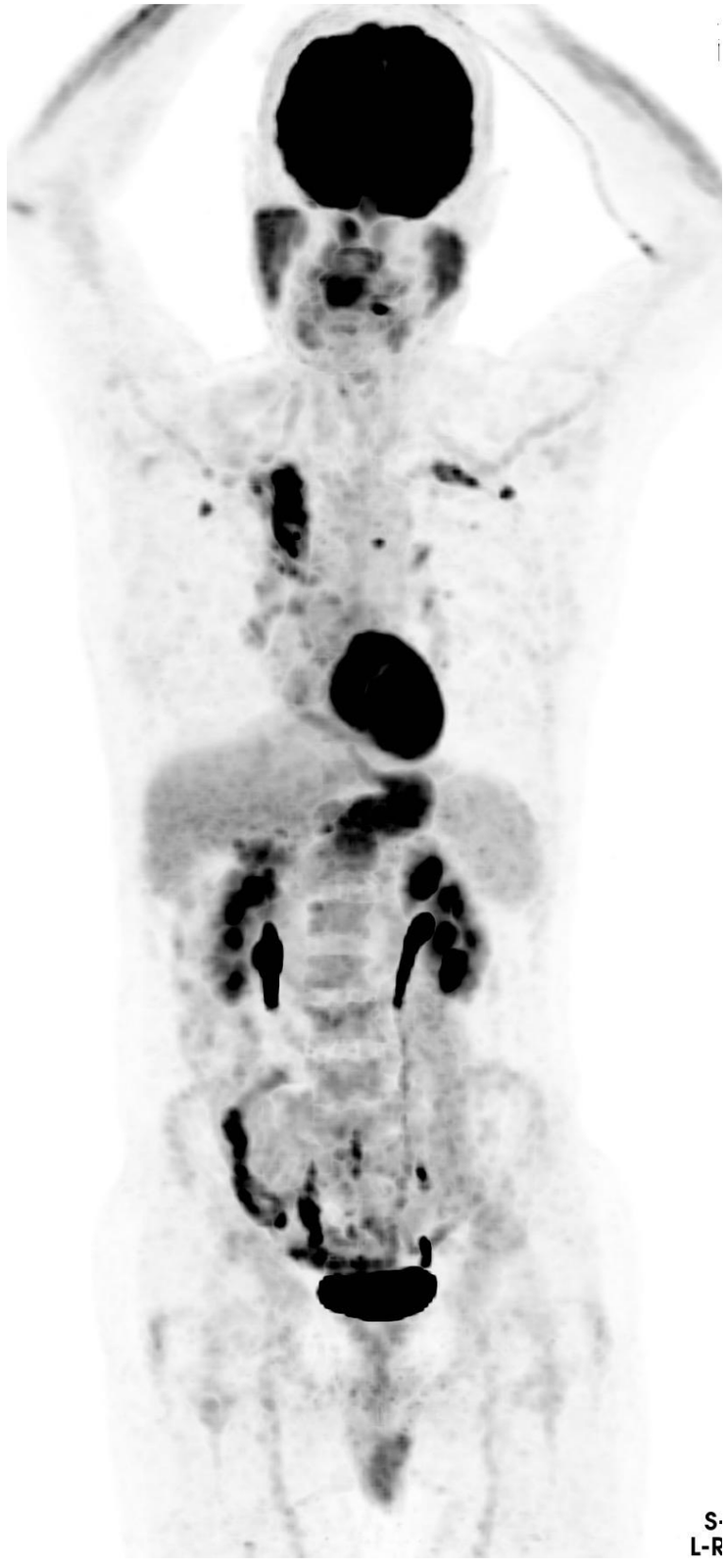

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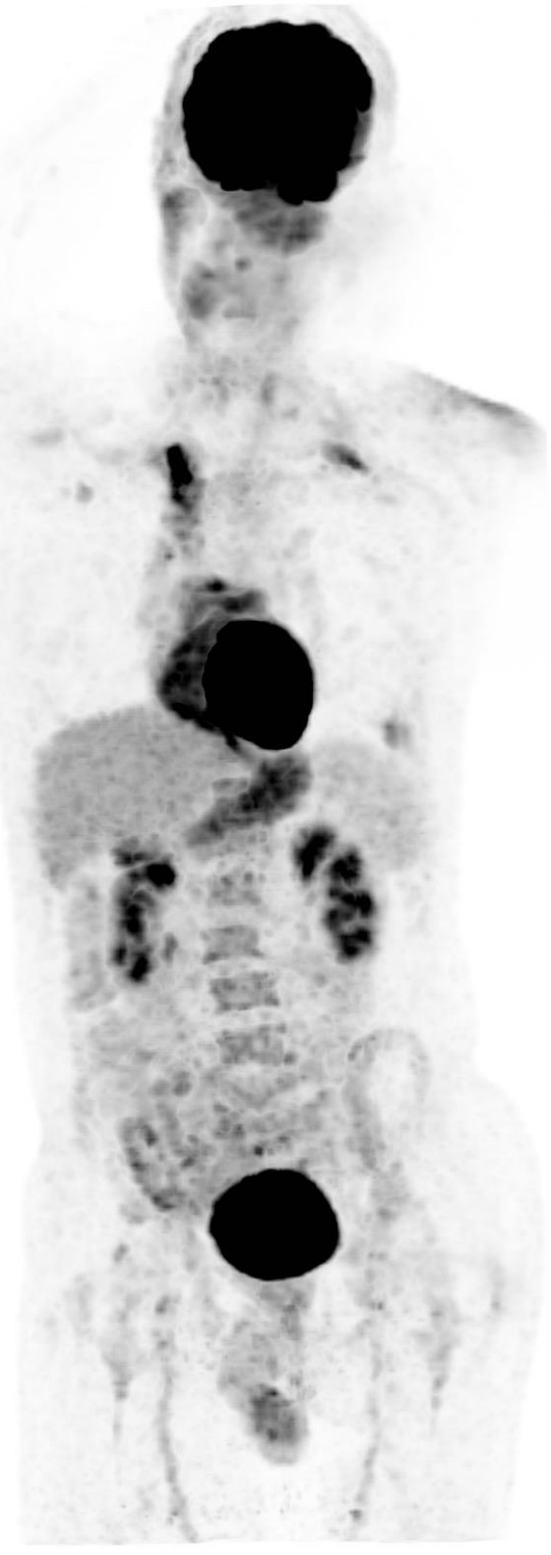
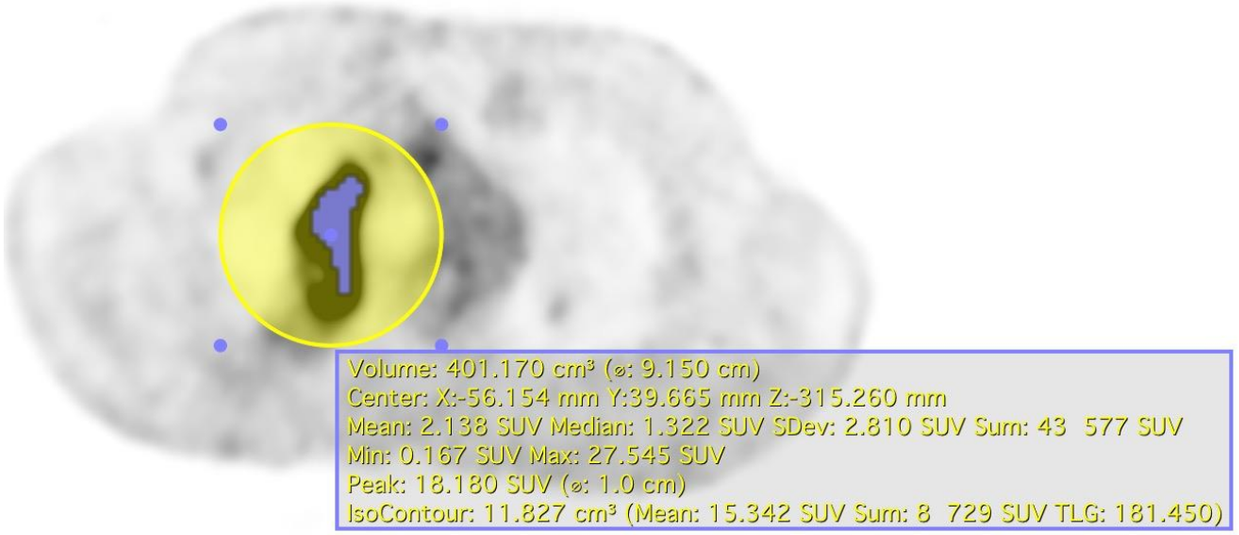
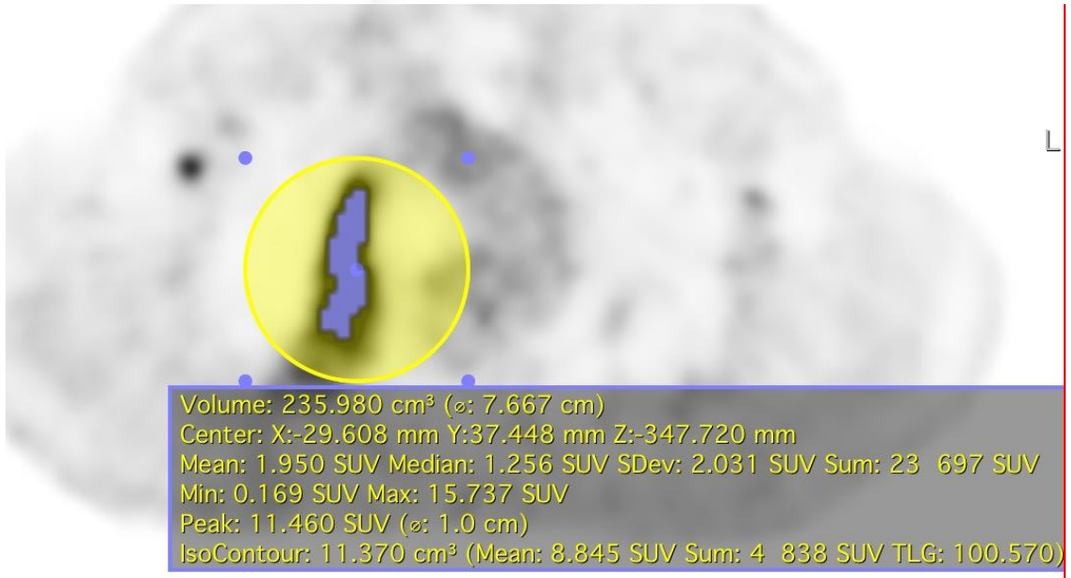
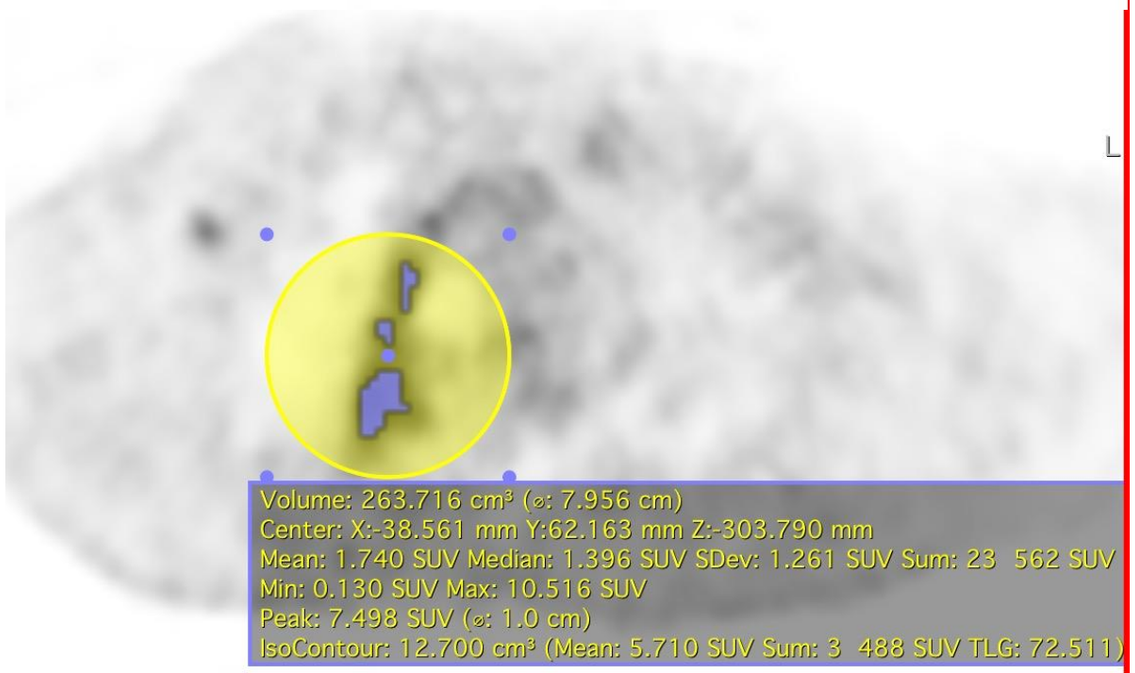


03/2020

CM 010145


Volume: 401.170 cm³ (⌀: 9.150 cm)
Center: X:-56.154 mm Y:39.665 mm Z:-315.260 mm
Mean: 2.138 SUV Median: 1.322 SUV SDev: 2.810 SUV Sum: 43 577 SUV
Min: 0.167 SUV Max: 27.545 SUV
Peak: 18.180 SUV (⌀: 1.0 cm)
IsoContour: 11.827 cm³ (Mean: 15.342 SUV Sum: 8 729 SUV TLG: 181.450)


L
Volume: 235.980 cm³ (⌀: 7.667 cm)
Center: X:-29.608 mm Y:37.448 mm Z:-347.720 mm
Mean: 1.950 SUV Median: 1.256 SUV SDev: 2.031 SUV Sum: 23 697 SUV
Min: 0.169 SUV Max: 15.737 SUV
Peak: 11.460 SUV (⌀: 1.0 cm)
IsoContour: 11.370 cm³ (Mean: 8.845 SUV Sum: 4 838 SUV TLG: 100.570)


L
Volume: 263.716 cm³ (⌀: 7.956 cm)
Center: X:-38.561 mm Y:62.163 mm Z:-303.790 mm
Mean: 1.740 SUV Median: 1.396 SUV SDev: 1.261 SUV Sum: 23 562 SUV
Min: 0.130 SUV Max: 10.516 SUV
Peak: 7.498 SUV (⌀: 1.0 cm)
IsoContour: 12.700 cm³ (Mean: 5.710 SUV Sum: 3 488 SUV TLG: 72.511)

- Immunotherapy increases the « non specific » FDG uptake in and around tumors

- Flare-up phenomenon possible : don’t panic !

- Multiple side effects, often infra-clinical : hypophysitis, pneumonitis, lymph node activation, pancreatitis, etc… all are possible « false positive » hot spots

PET for assessment of therapeutic response in oncology

- Image wisely : when it makes sense
- Always use a baseline set of images for comparison
- Be consistent : standardize your imaging protocol as much as possible (incubation period, technical parameters)
- Caution when comparing with other PET centers (even if they use the same PET system, parameters could be different)
- Visual interpretation remains the standard, and is more robust (i.e. less variable) than quantification