2èJFMN Journées Francophones de Médecine Nucléaire

Le 18-FLuoroestradiol (FES): indications, perspectives

19-22 mai 2016
WTC-Grenoble

Pr F. Courbon
Dpt Imagerie Institut Universitaire du Cancer de Toulouse France

CRCT équipe 15 Cholesterol metabolism & therapeutic innovation

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

CRCT Cancer Research Center of Toulouse

Liens d’intérêts

Financements de travaux scientifiques

Ovidien /Mallinkrodt /

IBA

Roche

GEHC

ISPSystem

Expertises

Covidien /Mallinkrodt

Ipsen

Novartis

Norgine

Bayer

GEHC

Cyclopharma

AAA

ISP System

Pas de conflit d’intérêt

Cancer du sein: épidémiologie

- le plus fréquent chez la femme **50000 nouveaux cas** (33,5 % de l'ensemble des cas de cancers chez la femme) devant le cancer colorectal et le cancer du poumon).
- Première cause de mortalité **11 400** décès en 2011.
- Effet combiné des progrès diagnostiques et thérapeutiques
  - : **le taux d'incidence standardisé a presque doublé**, passant de 56,8 en 1980 à 101,5 en 2005.
  - : **La mortalité baisse** le taux d'évolution annuel de la mortalité

    -0,4 % sur la période 1980-2005

    -1,3 % sur la période 2000–2005.

Hospices civils de Lyon/Institut de veille sanitaire/Institut National du Cancer/Francim/Institut national de la santé et de la recherche médicale. Projections de l'incidence et de la mortalité par cancer en France pour l'année 2008. Rapport technique. Mars 2009. http://www.invs.sante.fr/surveillance/ cancers

- La survie moyenne à 5 ans est estimée à près de 85 %.
- Moins de 10% métastatique d'emblée
- Environ 30% métastatique secondairement
  - Médiane de survie : 36 mois
  - Localisation des métastases :
    - Os (40%)
    - Viscères (poumon 15 à 25%; foie 5 à 15%; cerveau 5 à 10%)
    - Autres (ganglions, peau etc..) : environ 20%

Survie des patients atteints de cancer en France, étude des registres du réseau Francim.

Classification des cancers du sein

Classification OMS des cancers du sein 2003
21 types différents de carcinomes infiltrants !

Cancers in situ pas de risque théorique d'envahissement ganglionnaire.

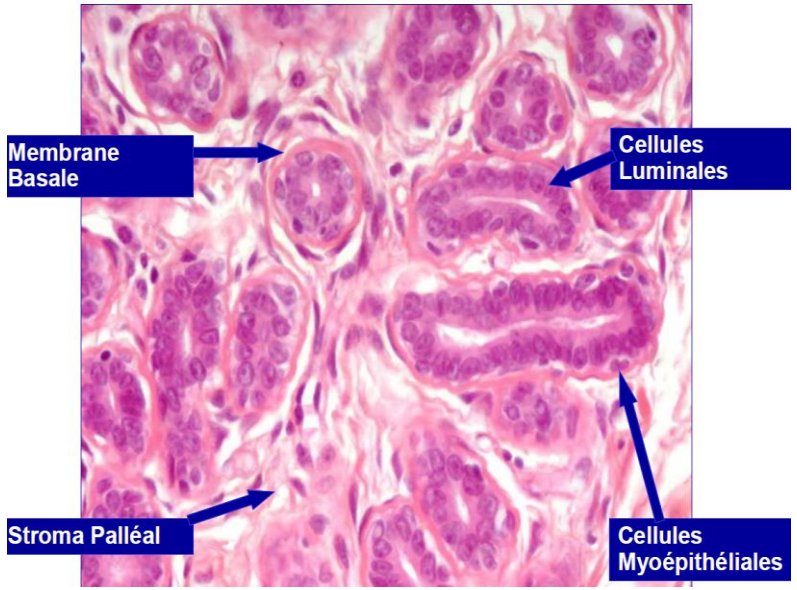
- **Carcinomes canalaires in situ**
- **Carcinomes lobulaires in situ**

Carcinomes infiltrants

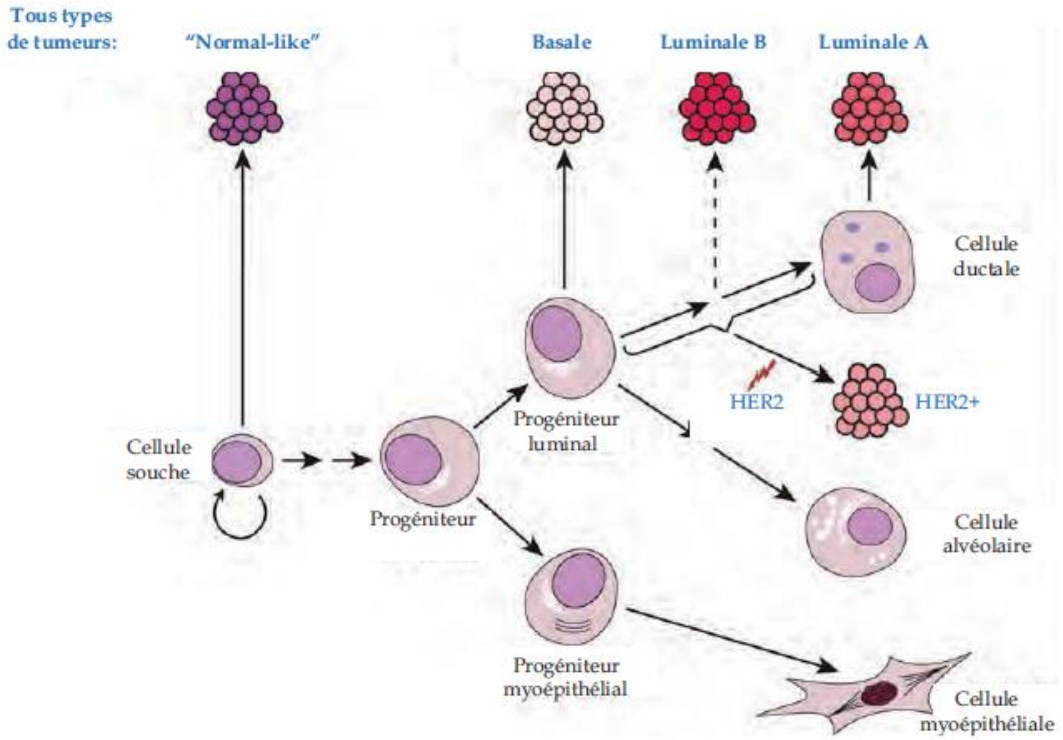
- **Le carcinome canalaire infiltrant** represente plus de 70 % des carcinomes infiltrants.
- **Le carcinome lobulaire infiltrant** est plus rare, representant de 5 a 15 %
- **Le carcinome médullaire** qui represente environ 1 a 5 % des cancers du sein

Etc etc !!!

L'Unité Terminale Ductulo-Lobulaire (UTDL)

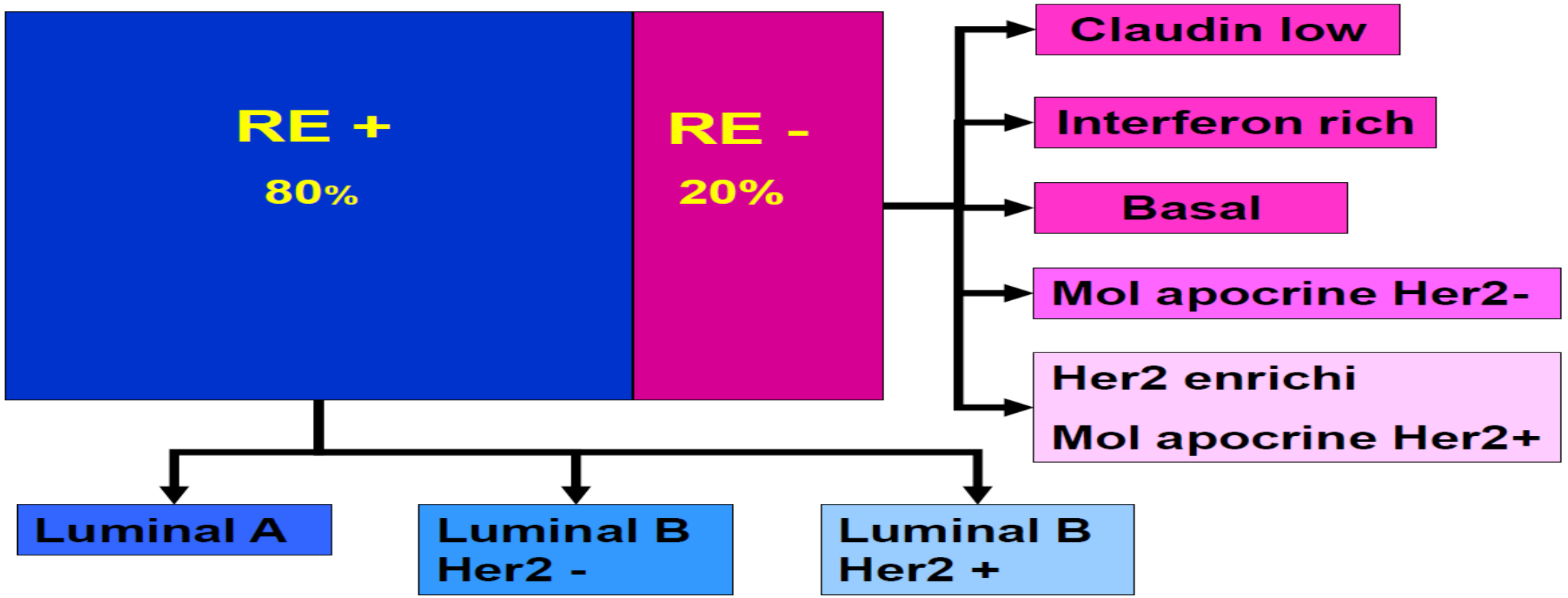


récepteurs des œstrogènes et de la progestérone



de Visvader J.E., 2010

Classification Intrinsèque des cancers du sein 2010



Luminal A

- ≈ 60% cancers du sein
- Expression élevée de RE
- Faible expression des gènes liés à la proliferation
- P53 mutée : 13%

Luminal B

- ≈ 20% cancers du sein
- Expression plus faible de RE
- Expression élevée des gènes liés à la proliferation
- P53 mutée : 66%

Bilan d’extension initial des cancers du sein

- Recommandation de l ‘INCA* :
- pour les tumeurs cT3-T4 (>5 cm)
- macrométastatique.
- le bilan d'extension peut reposer sur l'une des trois options suivantes :
  - la radiographie de thorax + l'échographie abdominale + la scintigraphie osseuse ;
  - TDM thoracoabdominal + la scintigraphie osseuse ;
  - la TEP-TDM au FDG seule.

T3 : tumeur > 5 cm dans sa plus grande dimension

T4 : tumeur, quelle que soit sa taille, avec une extension directe soit à la paroi thoracique (a), soit à la peau (b)

- T4a : extension à la paroi thoracique en excluant le muscle pectoral
- T4b : œdème (y compris peau d’orange) ou ulcération de la peau du sein, ou nodules de perméation situés sur la peau du même sein
- T4c : T4a + T4b
- T4d : cancer inflammatoire

Classification TNM du cancer du sein, 6e édition, 2002, et stade UICC

PET/PET–CT should not be used routinely as part of the initial work-up but can be useful for identifying the site of relapse when traditional imaging methods are equivocal or conflicting. It may also be helpful to identify or confirm isolated locoregional relapse or isolated metastatic lesions, a situation where patients may benefit from a more aggressive multidisciplinary approach

*Cancer du sein infiltrant non métastatique, Synthèse. ref Institut National du Cancer ; 2012. www.e-cancer.fr.

PRINCIPES DU TRAITEMENT

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii11–vii19, 2012
doi:10.1093/annonc/mds232

Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1,2], N. Harbeck[3], L. Fallowfield[4], S. Kyriakides[5] & E. Senkus[6], on behalf of the ESMO Guidelines Working Group*

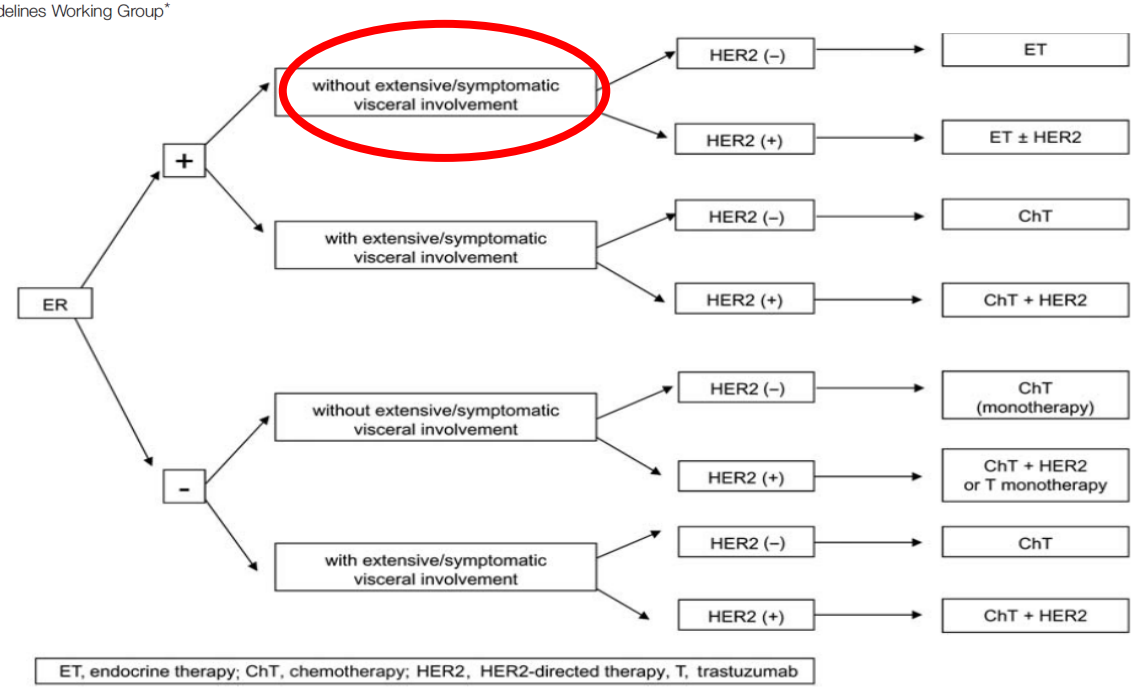
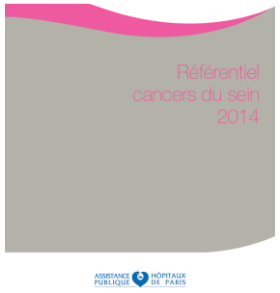


Figure 2 First-line systemic therapy for advanced breast cancer.

Voir aussi



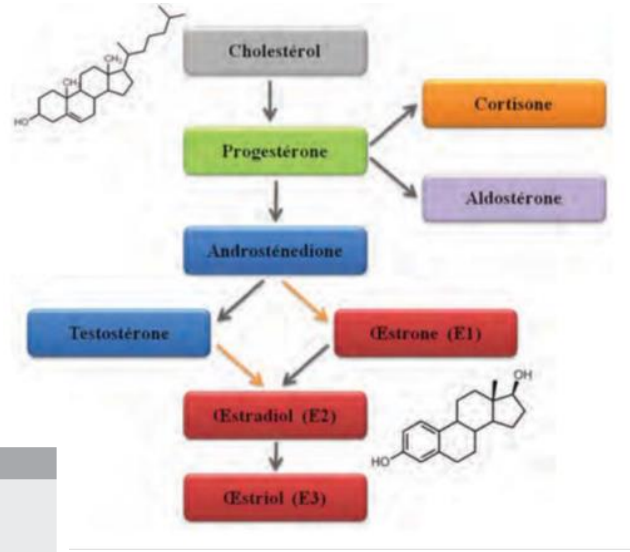
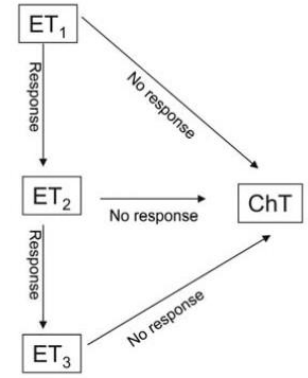


Table 3. Available endocrine therapies for MBC

Class of agent	
Selective estrogen receptor modulators	Tamoxifen; toremifene
Estrogen receptor down-regulator	Fulvestrant
Luteinizing hormone-releasing hormone analogues	Goserelin, leuprorelin, triptorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Anabolic steroids	Nandrolone decanoat
Estrogens	Estrogens



ET, endocrine therapy; ChT, chemotherapy

Figure 3 Management of endocrine-responsive advanced breast cancer.

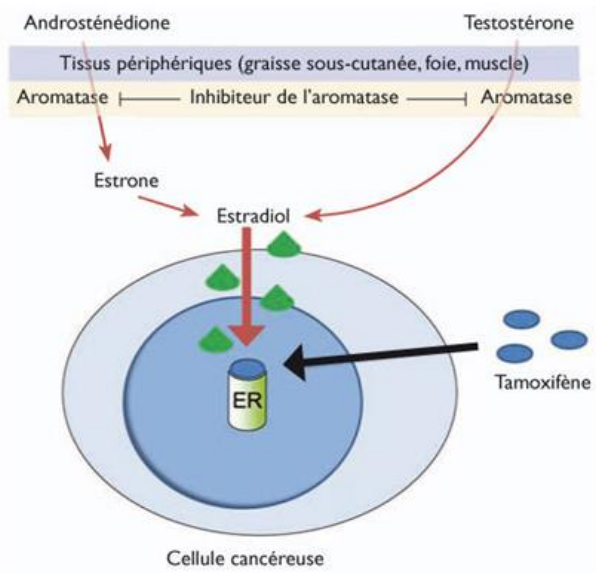


Figure 1
Mécanisme d'action du tamoxifène et des inhibiteurs de l'aromatase
ER : Récepteur des œstrogènes.

En situation métastatique : bases de la discussion

- Facteurs liés à la patiente
  - Etat général de la patiente
  - Statut hormonal
- Facteurs liés à la maladie
  - Antécédent de traitements adjuvants

    Doses d'anthracyclines
  - Intervalle libre

    < 6 mois, 6 – 12 mois - > 1 an
  - Phénotype
    - Statut RH (ER , PR)
    - HER2

Tumeur Primitive

clinical practice guidelines

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Estrogen, progesterone and HER-2 receptors of the metastatic lesion should be obtained at least once in the evolution of the disease, if technically possible, and particularly if not available from the primary tumor

Prediction de réponse 50%– 60% of the patients
Harvey et al . J Clin Oncol. 1999;
DeSombre et al Cancer Res. 1986;.

Faut -il RE biopsier ?

- Nombre et taille des localisations métastatiques
  - 1 à 10% des patientes oligométastatiques
  - Rapidité de la progression - Symptomatologie
  - localisation des sites métastatiques (os vs viscères)

Métastases

FAUT-IL-RE BIOPSIER ?

ESMO 2012 Estrogen, progesterone and HER-2 receptors of the metastatic lesion should be obtained at least once in the evolution of the disease, if technically possible, and particularly if not available from the primary tumor

- Thompson et al, Breast Cancer Res 2010

- 137 échantillons analysables
- RE – 10.2% pour; RP – 24.8%
- Changement de stratégie thérapeutique : 17.8%

Simmons et al, Annals of Oncology 2009

- 29 échantillons analysables
- 3/29 (10%) étaient des lésions bénignes
- 40% de discordance pour RH, 8% pour HER2
- Changement de stratégie thérapeutique : **20%**

RE-BIOPSIE

VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

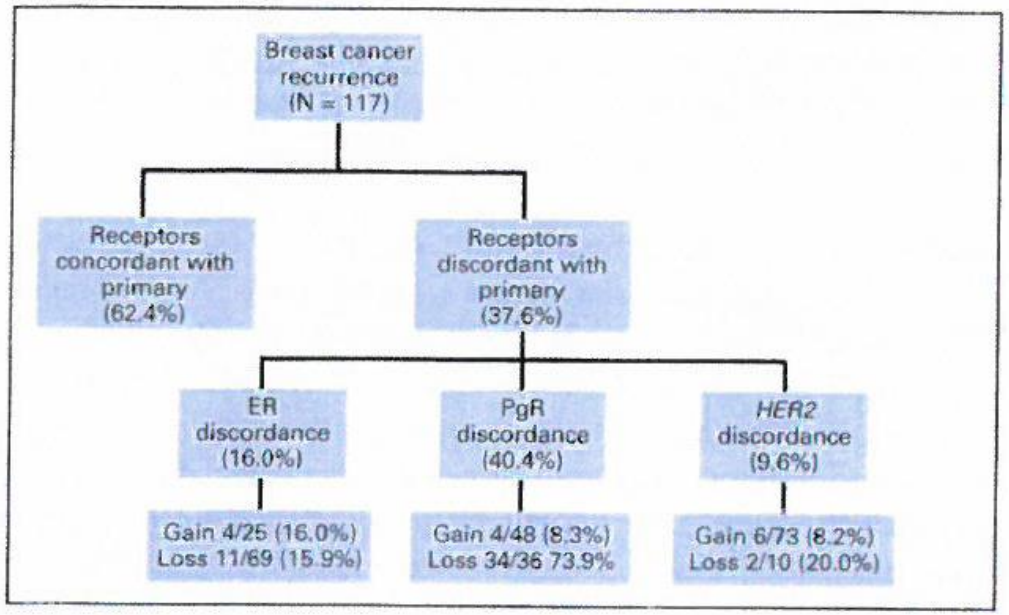
Prospective Study Evaluating the Impact of Tissue Confirmation of Metastatic Disease in Patients With Breast Cancer

36% d'échec !

Modification du traitement 14%

151 pts

- 16 (10,5%) refus par peur des biopsies
- 11 (7.0%) refus par peur du retard dans la prise en charge
- 6 (3,0%) lésions inaccessibles ou non retrouvées
- 22 (14.0%) sous échantillonnage



Impact sur la survie ????

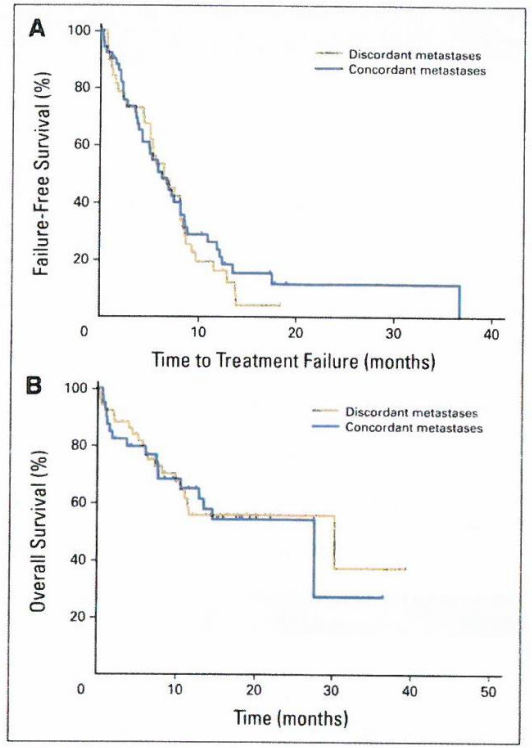


Fig 4. Survival by discordance. (A) Time to treatment failure. (B) Overall survival

^{18} FES TEP et Cancer du sein

JNM The Journal of NUCLEAR MEDICINE

Preparation of Four Fluorine-18-Labeled Estrogens and Their Selective Uptakes in Target Tissues of Immature Rats

Dale O. Kiesewetter, Michael R. Kilbourn, Scott W. Landvatter, Daniel F. Heiman, John A. Katzenellenbogen and Michael J. Welch

J Nucl Med. 1984;25:1212-1221

1984

The lancet oncol 2011

Review

PET imaging of oestrogen receptors in patients with breast cancer

Michel van Kruchten, Elisabeth G E de Vries, Myles Brown, Erik F J de Vries, Andor W J M Glaudemans, Rudi A J O Dierckx, Carolien P Schröder, Geke A P Hospers

Oestrogen receptors are overexpressed in around 70% of all breast cancers, and are a target for endocrine therapy. *Lancet Oncol* 2013; 14: e465–75

- Deux sous types, α and β, CHS 6q25.1 and 14q23.4
- 94 % d homologies mais des répartitions et des fonctions différentes
- La cible ER α
- De très nombreux vecteurs candidats

- 16α-[^{18}F]-fl uoro-17β-oestradiol (^{18}F-FES)
- 18 F-FES affinité pour ERα 6 x > ER β

Typiquement

200 MBq 18F-FES

- Activité spécifique 25 000 GBq/mmol, < 8 n mol 18 F-FES.
- Métabolisation rapide

@60 minutes activité circulante = 5%

80 % suflo/ glucuronoconjugaison , élimination biliaire recirculation entéro hépatique et élimination rénale

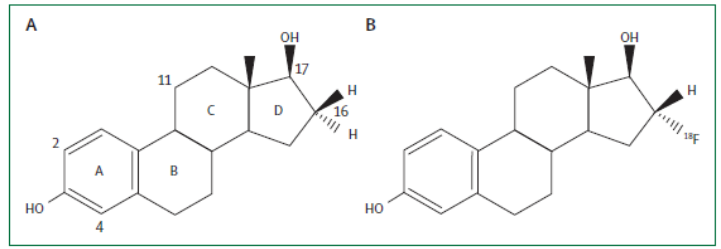


Figure 2: **Structures of 17β-oestradiol and 16α-[^{18}F]-17β-oestradiol**
(A) 17β-oestradiol consists of four cycloalkane rings and two hydroxyl groups. The numbers indicate commonly used positions for substituents. (B) 16α-[^{18}F]-17β-oestradiol.

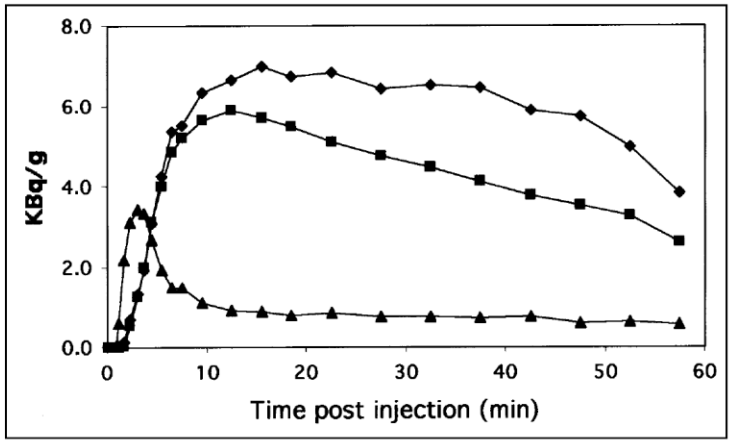


FIGURE 1. Example of TACs for FES in gallbladder (◆), liver (■), and blood (▲). Data are normalized to 37 MBq injected per 56 kg body weight.

[^{18}F]Fluoroestradiol Radiation Dosimetry in Human PET Studies

David A. Mankoff, Lanell M. Peterson, Timothy J. Tewson, Jeanne M. Link, Julie R. Gralow, Michael M. Graham, and Kenneth A. Krohn

Departments of Radiology and Medical Oncology, University of Washington School of Medicine, Seattle, Washington

4mSv pour 60Kg @ 3MBq/kg

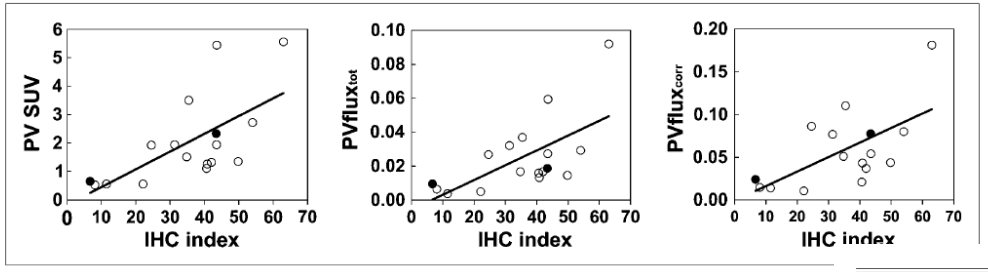


FIGURE 5. Comparison of ^{18}F-FES uptake measures with IHC index (Photoshop analysis). Treated patients are identified by closed circles.

Quantitative Imaging of Estrogen Receptor Expression in Breast Cancer with PET and ^{18}F-Fluoroestradiol

Lanell M. Peterson[1], David A. Mankoff[1], Thomas Lawton[2], Kevin Yagle[1], Erin K. Schubert[1], Svetlana Stekhova[1], Allen Gown[3], Jeanne M. Link[1], Timothy Tewson[4], and Kenneth A. Krohn[1]

Un traceur SPECIFIQUE

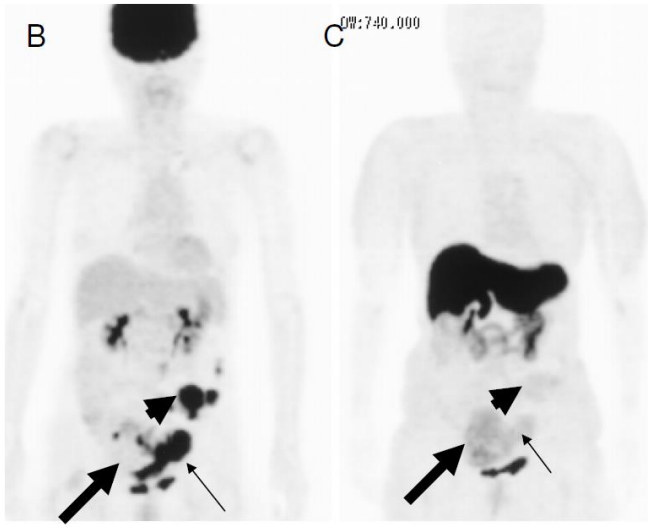
	Biopsy results	Sensitivity or specificity (95% CI)	Number of lesions
Sensitivity			
Dehdashti et al[61]	ER-positive tumour	69% (44–86)	16
Mintun et al[3]	ER-positive tumour	100% (77–100)	13
Mortimer et al[60]	ER-positive tumour	76% (55–89)	21
Peterson et al[47]	ER-positive tumour	100% (76–100)	12
Overall	..	84% (73–91)	62
Specificity			
Dehdashti et al[61]	Benign	100% (68–100)	10
Dehdashti et al[61]	ER-negative tumour	100% (82–100)	17
Mortimer et al[60]	ER-negative tumour	100% (84–100)	20
Peterson et al[47]	ER-negative tumour	80% (38–96)	5
Overall	..	98% (90–100)	52

ER=oestrogen receptor.

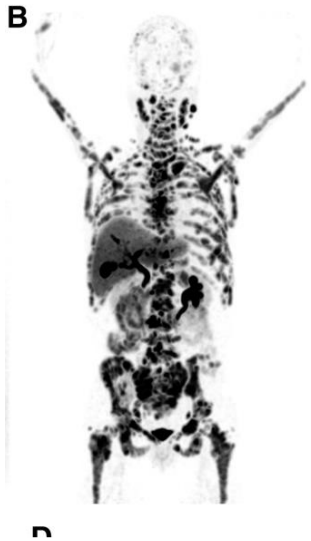
Table 2: Sensitivity and specificity of 16α[^{18}F]-fluoro-17β-oestradiol PET

Considérations méthodologiques

Qu'est ce qu'un TEP FES + ?



FDG



FES 200MBq @ 60min

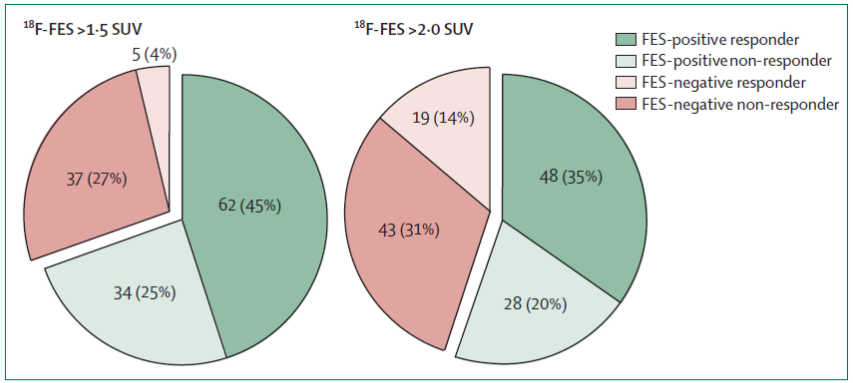
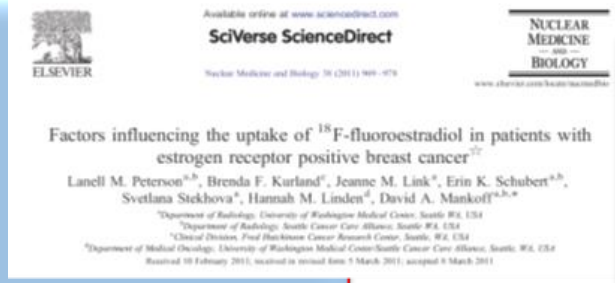


Figure 4: Predictive value of ^{18}F-FES-PET (n=138 patients)
In 138 patients, use of an SUV higher than 2·0 compared with a value of 1·5 did not increase the positive predictive value of ^{18}F-FES-PET, [46,53,54,57] whereas the negative value dropped. ^{18}F-FES=16α-[^{18}F]-fluoro-17β-oestradiol. SUV=standardised uptake value.

SUV seuil 1.5

Facteurs interférents ?

- Statut Hormonal
- BMI
- Traitements hormonaux
- Sex hormone-binding globulin (SHBG)


ELSEVIER
SciVerse ScienceDirect
NUCLEAR MEDICINE AND BIOLOGY

Factors influencing the uptake of ^{18}F-fluoroestradiol in patients with estrogen receptor positive breast cancer

Lanell M. Peterson, Brenda F. Kurland, Jeanne M. Link, Erin K. Schubert, Svetlana Stekhova, Hannah M. Linden, David A. Mankoff

↗SHBG ↘SUV

↗ BMI ↗ SUV : correction selon LBM et non BMI

Pas d'influence de l'âge/du taux d'oestradiol

Quelles applications cliniques ?

UN BON POTENTIEL

- Cartographie des lésions FES +
- Prédiction de la réponse
- Biomarqueur d'efficacité

Dilemme clinique

MAIS….

BENFICE CLINIQUE NON CLAIREMENT DEMONTRE A CE JOUR

CARTOGRAPHIE DE L'HETEROGENEITE TUMORALE

ARTICLE IN PRESS

Original Study

Can Fluorine-18 Fluoroestradiol Positron Emission Tomography—Computed Tomography Demonstrate the Heterogeneity of Breast Cancer In Vivo?

Zhongyi Yang, Yifei Sun, Yongping Zl
Beiling Zhu, Silong Hu, Zhifeng

- Variation **inter**patient du SUV x 33
- Variation **intra** patient du SUV x 8
- F-FES faible correlation avec FDG .

Figure 1 A 52-Year-Old Female Breast Cancer Patient (Primary Tumor: Estrogen Receptor [ER] Positive) Underwent Both Fluorine-18 (^{18}F) Fluoroestradiol (FES) and ^{18}F-Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography (PET-CT). We Detected Multiple Bone Metastasis (C, F; CT Images). Both Thoracic Vertebra (Arrows in Left Column) and Right Ilium (Arrows in Right Column) Demonstrated Abnormal ^{18}F-FDG Uptake (A, D; PET Images); Maximum Standardized Uptake Value (SUVmax) was 5.5 and 4.7, Respectively. However, They Showed Different ^{18}F-FES Uptake: Thoracic Vertebra was a Low ER Expression With a SUVmax = 1.3; Whereas, Right Ilium was High, SUVmax = 2.7 (B, E PET Images), Which Suggested That she had Heterogeneity Metastatic Lesions

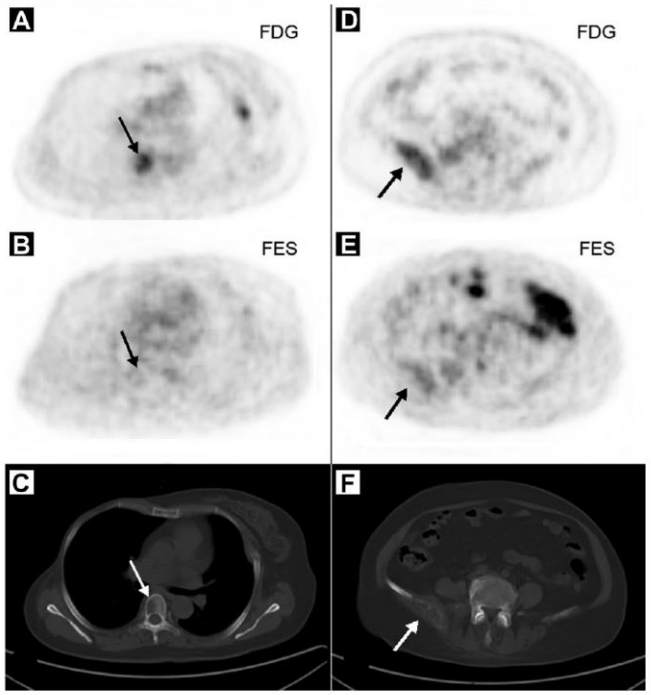


Table 1 Patient Characteristics

Characteristic	
Mean (range) age, years	53 (27 to approximately 77)
Purpose of FES PET, no. (%)	
Predict of response	10 (31.3)
Correlation with in vitro assay of ER	14 (43.7)
Assisting in clinical dilemma	8 (25.0)
Menopausal status, no. (%)	
Premenopausal	8 (25.0)
Postmenopausal	24 (75.0)
Primary tumor histology, no. (%)	
Ductal	27 (84.3)
Lobular	3 (9.4)
Others	2 (6.3)
Immunology, no. (%)	
ER^+	28 (87.5)
PR^-	21 (65.6)
HER2/*neu*$^+$	13 (40.6)
Prior adjuvant treatment, no. (%)	
Chemotherapy	22 (68.8)
Radiotherapy	10 (31.3)
Endocrine treatment	20 (62.5)

Abbreviations: ER = estrogen receptor; FES = fluoroestradiol; HER2 = human epidermal growth factor receptor 2; PET = positron emission tomography; PR = progesterone receptor.

Table 2 Lesion Characteristics of ^{18}F-FES PET-CTs

Tumor Site	n	^{18}F-FES$^+$	^{18}F-FES$^-$
Bone	152	121	31
Lymph node	54	33	21
Lung	12	2	10
Breast	10	7	3
Soft tissue	5	1	4
Pleura	3	3	0
Adrenal gland	1	1	0
Total	237	168	69

Abbreviations: ^{18}F = fluorine 18; CT = computed tomography; FES = fluoroestradiol; PET = positron emission tomography.

QUEL BENEFICE CLINIQUE ?

^{18}F-FES PET pour “dilemmes Cliniques “ 33 pts ER +

- 21 pts lésions équivoques (bénin – malin)
- 10 pts évaluation du statut ER
- 2 pts Meta avec deux primitifs possibles

JNM 2012

STOP TAMOXIFEN pdt 5 SEMAINES

Whole-body 18F-FES PET @ 60 min,

- 398 lésions ^{18}F-FES +
- 319 lésions selon le bilan conventionnel dont 24% FES neg
- ^{18} FES PAS BON POUR LE FOIE
- GRANDE DISPERSION DES VALEURS

- **45% des pts avec des lésions ^{18}F-FES + et ^{18}F-FES -**
- **Avis cliniciens : gains “cognitif” pour 88%**
- **Modification du traitement 48%**

Patient Characteristics

Characteristic	Category I (n = 21)	Category II (n = 10)	Category III (n = 2)	All patients (n = 33)
Age (y)				
Mean	57	61	55	58
Range	43–78	48–77	54–56	43–78
Sex (n)				
Male	0	0	0	0
Female	21	10	2	33
Menopausal status (n)				
Premenopausal	1	0	0	1
Postmenopausal	16	10	2	28
Unknown	4	0	0	4
Breast cancer stage (n)				
Suspected distant recurrence	12	0	2	14
Metastatic	9	10	0	19
Prior lines of endocrine therapy (n)*				
0	13	0	2	15
1	5	4	0	9
>1	3	6	0	9
Time between primary diagnosis and ^{18}F-FES PET (y)				
Mean	8	10	3	8
Range	0–18	3–22	2–4	0–22

Does not include
^{18}F-FES PET exam
(category II), or origin

ER status

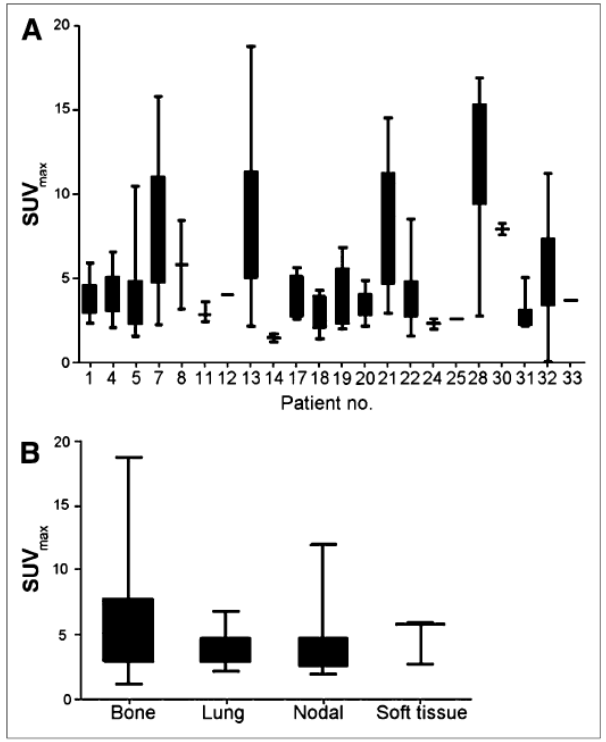


FIGURE 1. Differences in tracer uptake in all 22 patients with positive lesions on ^{18}F-FES PET (A) and tracer uptake at different sites of metastases (n = 398 lesions) (B). No significant differences in average SUV_{max} were observed; however, bone metastases did show significantly higher coefficient of variance. Bars represent 25–75 percentiles, and whiskers represent minimal to maximum values.

PREDICTION DE LA REPONSE ?

VOLUME 24 · NUMBER 18 · JUNE 20 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Quantitative Fluoroestradiol Positron Emission Tomography Imaging Predicts Response to Endocrine Treatment in Breast Cancer

Hannah M. Linden, Svetlana A. Stekhova, Jeanne M. Link, Julie R. Gralow, Robert B. Livingston, Georgiana K. Ellis, Philip H. Petra, Lanell M. Peterson, Erin K. Schubert, Lisa K. Dunnwald, Kenneth A. Krohn, and David A. Mankoff

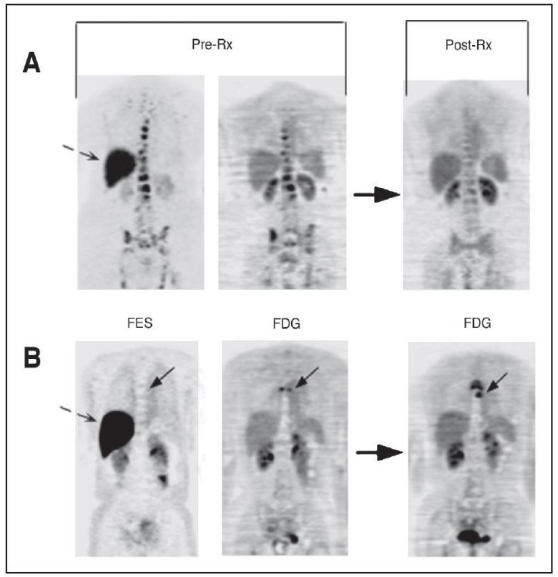


Fig 1. Imaging examples: Pretreatment [^{18}F]fluoroestradial (FES; left) and fluorodeoxyglucose (FDG; middle) scans and follow-up FDG post-therapy (right) are shown. Dashed arrows show normal liver FES uptake. (A; top) bone metastasis with robust FES and FDG uptake, response at 3 months. (B; bottom) bone metastasis (solid arrow) without FES but with FDG uptake; progressive disease at 6 months. Rx, treatment.

PAS de relation significative entre statut TEP FES et réponse

Cependant

si SUV <1.5 = 0 répondeurs

46% avec SUV > 1.5 répondent

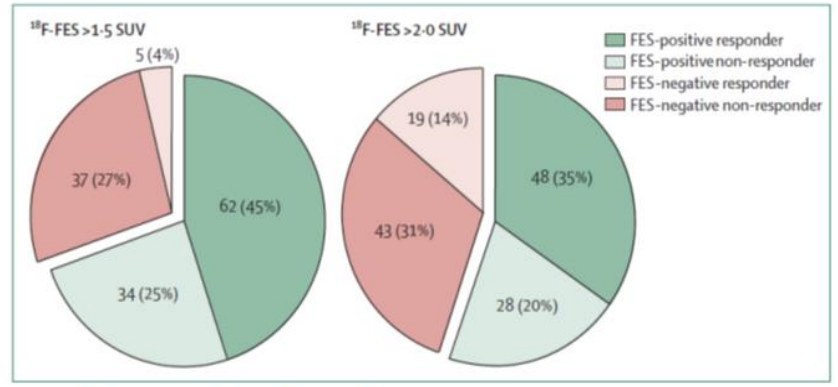
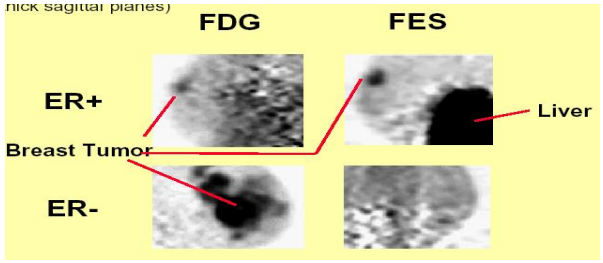
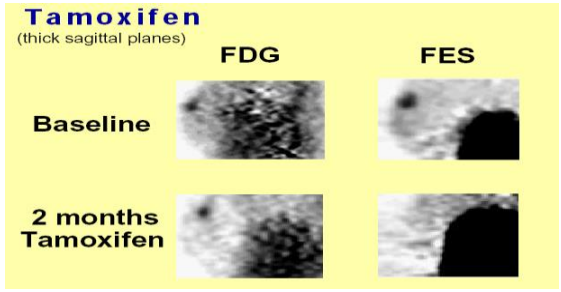


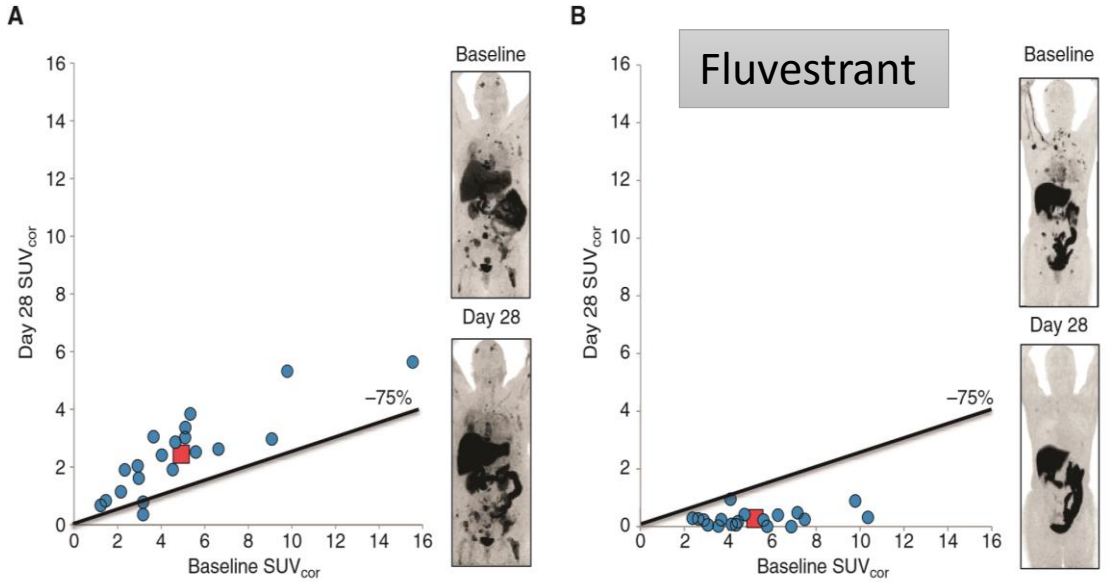
Figure 4: Predictive value of ^{18}F-FES-PET (n=138 patients)
In 138 patients, use of an SUV higher than 2·0 compared with a value of 1·5 did not increase the positive predictive value of ^{18}F-FES-PET, [46,53,54,57] whereas the negative value dropped. ^{18}F-FES=16α-[^{18}F]-fluoro-17β-oestradiol. SUV=standardised uptake value.

- Voir un récepteur ne signifie pas qu'il est fonctionnel
- Actions pharmacologiques non médiées par la voie ER

La logique !







Measuring Residual Estrogen Receptor Availability during Fulvestrant Therapy in Patients with Metastatic Breast Cancer Michel van Kruchten et al Cancerdiscovery 2015

Différence entre structure et fonction

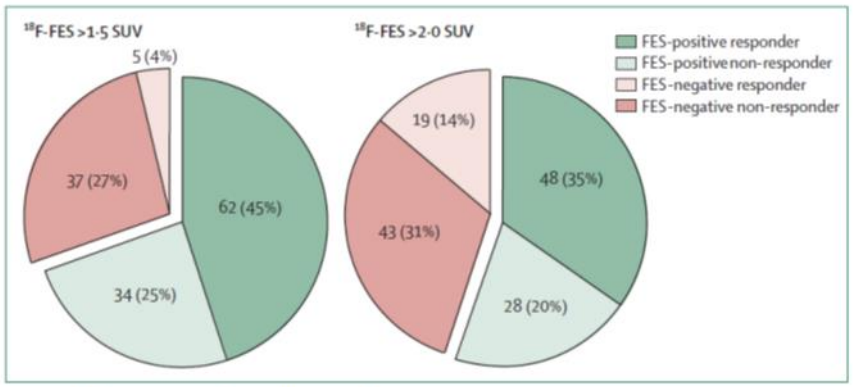
Breast Cancer Res Treat (2009) 113:509–517
DOI 10.1007/s10549-008-9953-0

CLINICAL TRIAL

PET-based estradiol challenge as a predictive biomarker of response to endocrine therapy in women with estrogen-receptor-positive breast cancer

↘ FES

FDG Flair up



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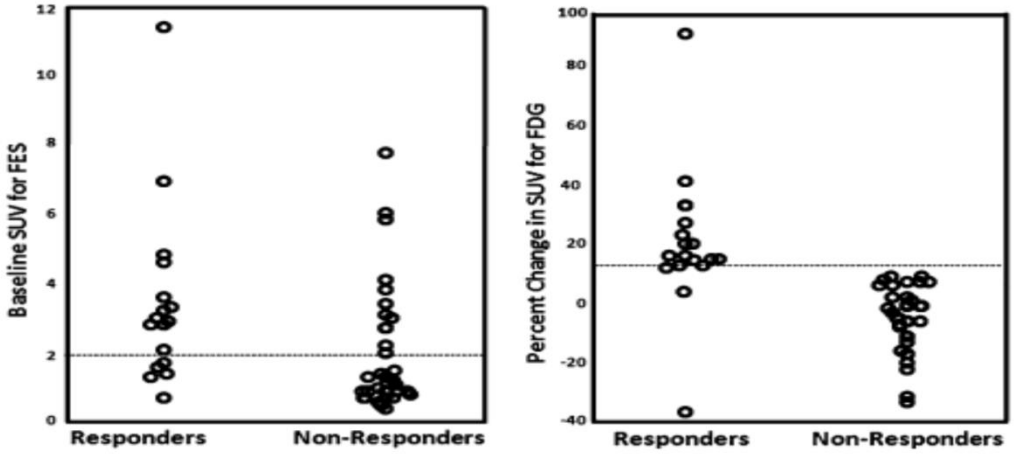
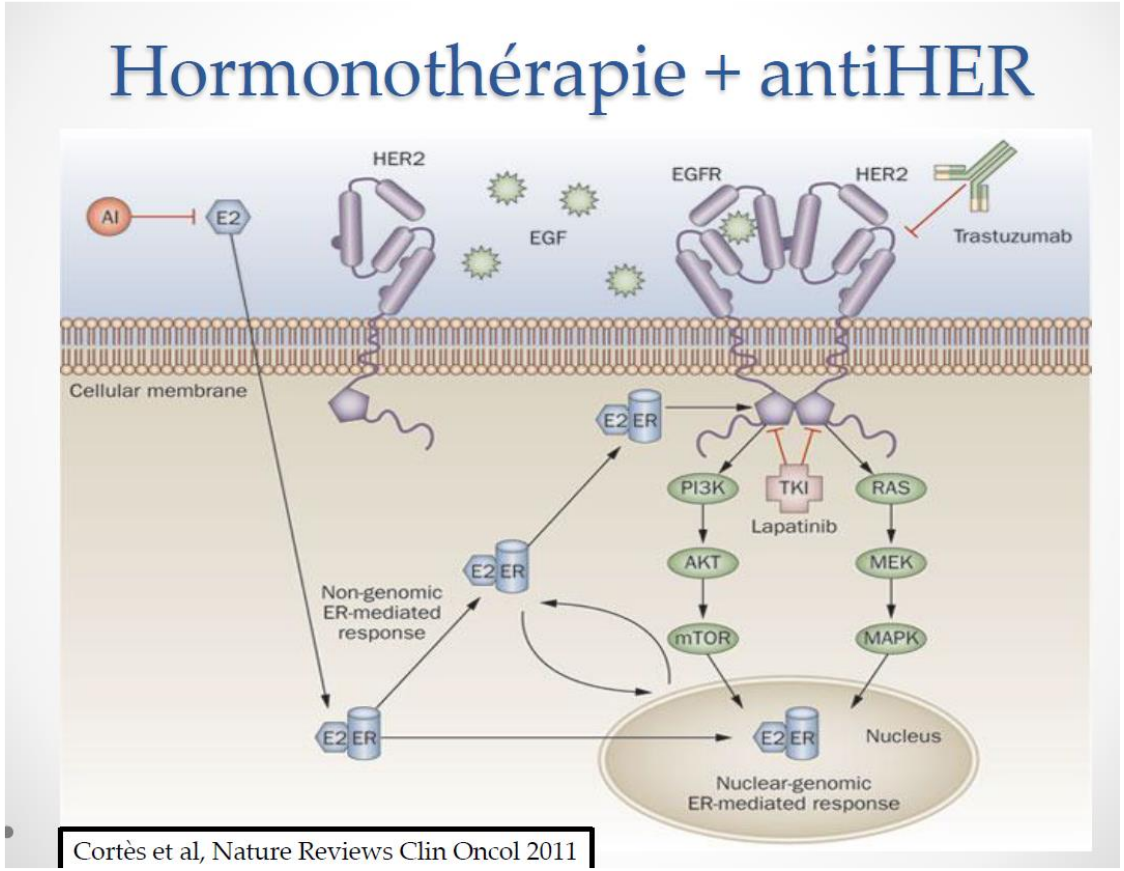
ine tumor FES
change in
) uptake after
e in patients
id who did not
rine therapy

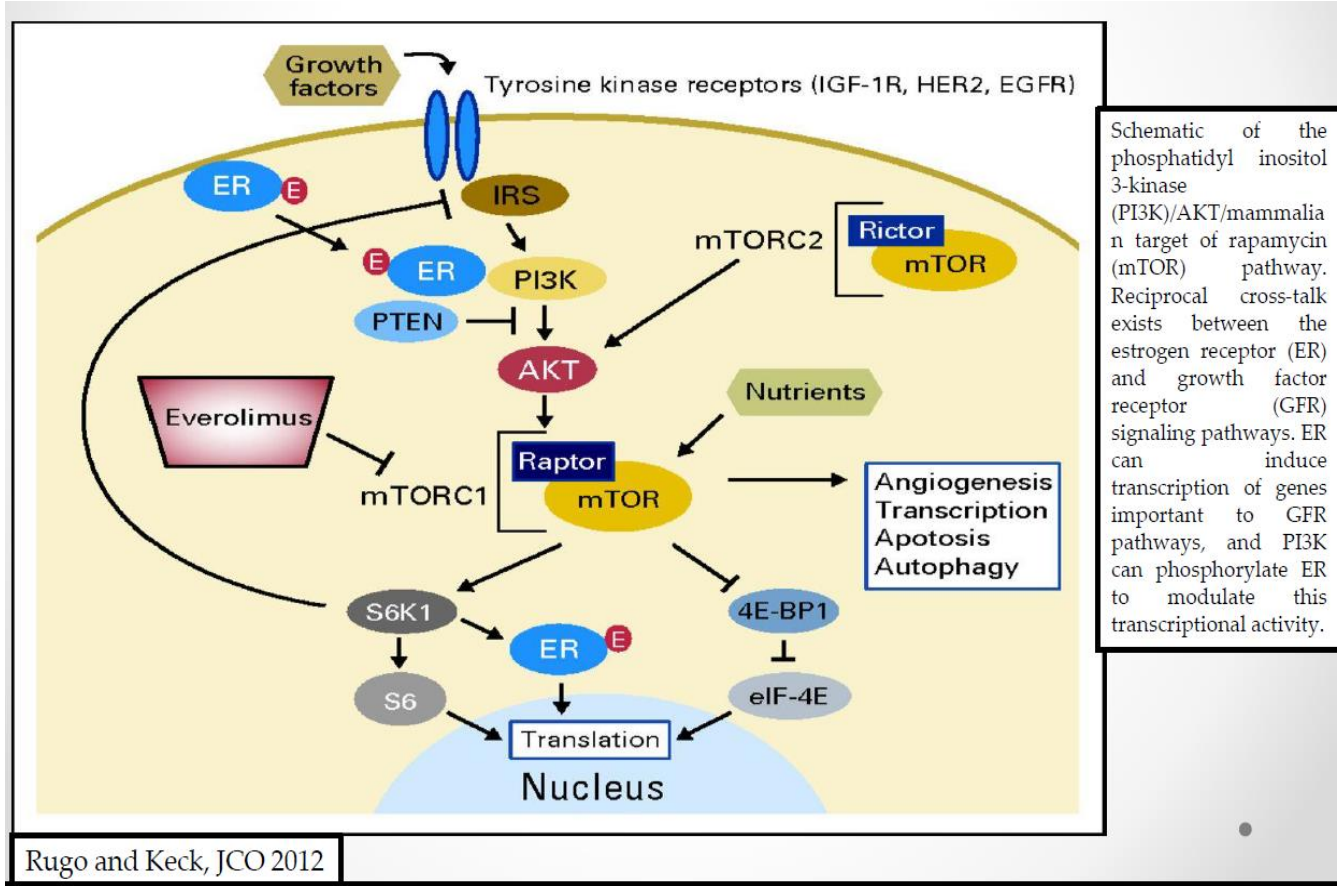


CROSS TALKS /

hormonorésistance : Activation de la voie ER indépendamment du ligand

Idem mTOR i





Schematic of the phosphatidyl inositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway. Reciprocal cross-talk exists between the estrogen receptor (ER) and growth factor receptor (GFR) signaling pathways. ER can induce transcription of genes important to GFR pathways, and PI3K can phosphorylate ER to modulate this transcriptional activity.

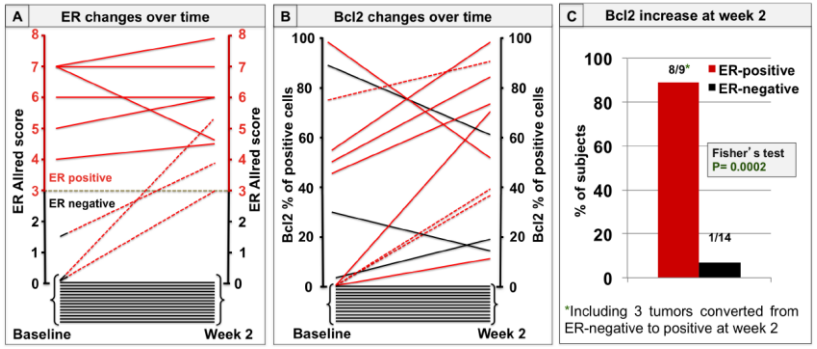
RESTAURATION DU PHENOTYPE RE + ?

Upregulation of ER signaling as an adaptive mechanism of cell survival in HER2-positive breast tumors treated with anti-HER2 therapy

Mario Giuliano[1,2], Huizhong Hu[1], Yen-Chao Wang[1], Xiaoyong Fu[1], Agostina Nardone[1], Sabrina

Clin Cancer Res , 2015.

Figure 2. ER and Bcl2 changes upon neoadjuvant treatment with lapatinib.

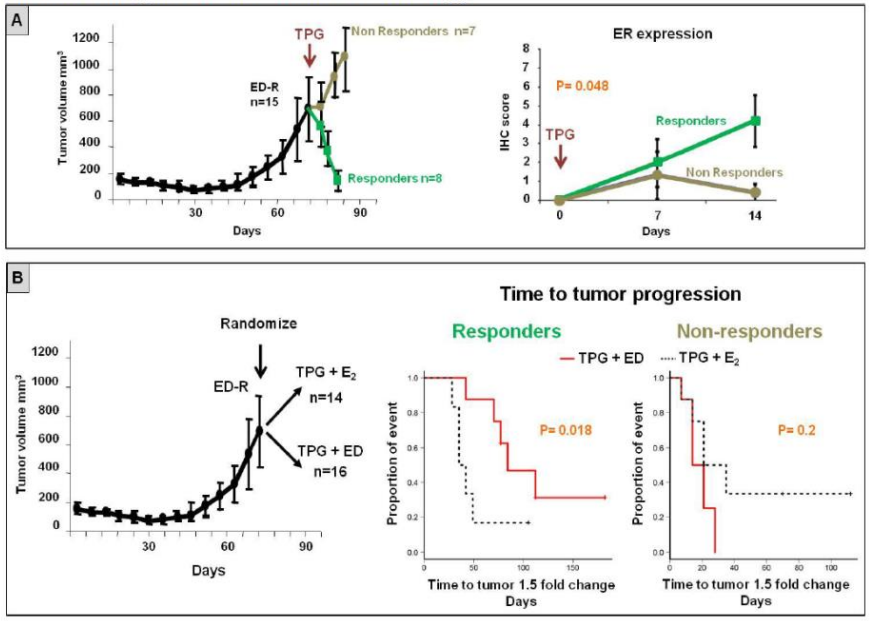


tumors with ER-positive status at baseline(Allred score ≥ 3);

that were ER-negative at baseline(Allred score < 3) and became positive at week 2

ER negative status at baseline that remained negative at week 2 (14 tumors).

Figure 4. Endocrine therapy delays tumor progression in presence of restored ER expression in tumor xenografts treated with anti-HER therapy.



Restauration de l'efficacité du TT hormonal

Coktail d'anti HER

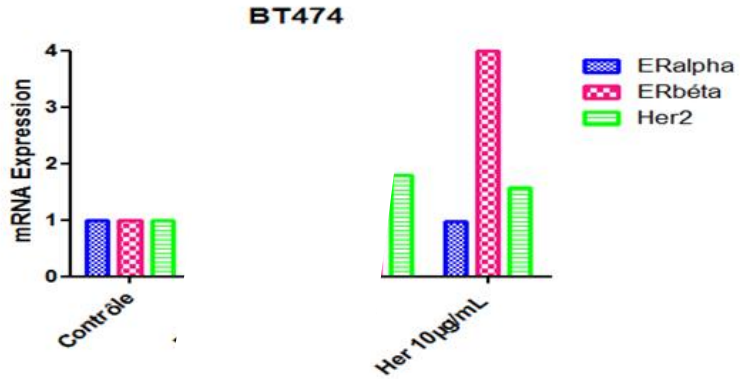
A. Mice bearing MCF7 HER2-18 HER therapy induced tumor regression in 53% of mice (responders),

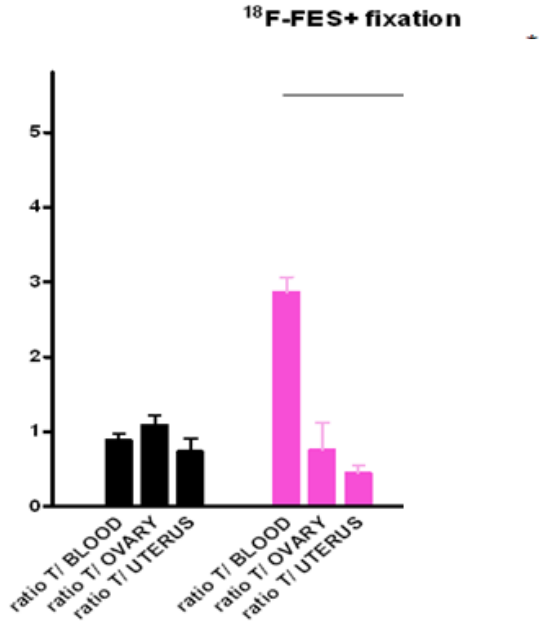
B. Mice bearing MCF7 HER2-18 tumor xenografts were randomized at the time of ED-resistance to receive TPG with or without continuing endocrine therapy (ED).

La TEP au 18 FES pour mesurer la restauration du phénotype

Caractérisation de la re-expressison des RE par le trastuzumab (Herceptine)

- BT474 : REα+, REβ+, HER2++





équipe 15 M POIROT S Brillouet

CRCT
Cancer Research Center of Toulouse

PERSPECTIVE NATIONALE

- AMM XXX 2016
  - Déploiement national progressif
  - Première phase Mise en production de la chaine logistique
  - Objectifs du GT oncologie
    - Harmonisation des pratiques / Formation / Evaluation
    - Aide à la maturation de projets x centriques REUNION WORK SHOP XX SEPTEMBRE

Indication Statut de la maladie métastatique (pas de méta hépatique isolée)

Patient Selection

femme et homme

Kc du sein (RH +) Métastatique (en rechute) après 1 ligne de tt

Ayant eu un TEP FDG

Pas de restriction sur l 'Age et le statut hormonal de la patiente

wash out 4- 6 semaines après CT , Tamoxifène (5 S)

Exclusion ?

grossesse

Réunion GT oncologie,

« workshop » imagerie des récepteurs aux oestrogènes pour les cancers du sein

- Paris sept 2016
- Le point de vue de l'anatomopathologiste
- Le point de vue clinicien
- Retour d'experience
  - Canada
  - France
- Place de la FES par rapport au FDG
- Lancement de la phase opérationnelle ; objectifs 60-80 patients
- Table ronde : au-delà de l AMM ! vers un projet de recherche clinique multicentrique ?

Déploiement : standardisation du protocole

- **Préparation**
  - Sevrage thérapeutique
  - Hydratation (standard cf fdg)
- **Posologie**
  - 1- 4 MBq/ Kg
- **Acquisition TEP**
  - A « l'équilibre »
  - Zone explorée
    - Corps entier
- **Acquisition TDM (optionnel)**
  - Low-dose CT-scan
  - high dose was
  - contrast-enhanced diagnostic CT scan
  - FOV
  - Taille de la matrice

- **Analyse d'image TEP**
  - Visuelle
  - Semi Q (5 lesions cf RECIST en mélangeant les sites M)
  - SUV max mean BSA LBM
  - SUV moyen
  - SUV cut-off max 1,5 ou 2 (à clarifier)
  - (rapport de fixation à évaluer)
  - Combien de lésions/patient ? maximum of 20 BoellaardEANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010*
- **Analyse des images TDM ? Optionnel**

Description mesure densité

TABLE 1
Patient and Disease Characteristics (n = 91) as Recorded at Time of ^{18}F-Fluoroestradiol PET Scan

Characteristic	n
Patient population	
Female	89 (98)
Premenopausal (women only, n = 89)	15 (17)
Weight	
Normal (body mass index ≤ 25)	30 (33)
Overweight	32 (35)
Obese (body mass index > 30)	29 (32)
Primary tumor immunohistochemistry and histology	
ER+	90 (99)
Progesterone receptor–positive (n = 88)	74 (84)
HER2/neu–positive	12 (13)
Histology	
Ductal	67 (73)
Lobular	18 (20)
Ductal and lobular	6 (7)
Breast cancer and treatment history	
Advanced disease	86 (95)
Chemotherapy for metastatic breast cancer (n = 82)*	21 (26)
Endocrine therapy for metastatic breast cancer (n = 82)*	38 (46)
Radiation therapy for metastatic breast cancer (n = 82)*	28 (34)
Aromatase inhibitor therapy at time of scan (n = 90)	55 (61)
Tumor characteristics†	
Bone lesions present	67 (74)
Soft-tissue lesions present	54 (59)
Both bone and soft-tissue lesions present	31 (34)
Endocrine therapy after ^{18}F-fluoroestradiol PET	
Tamoxifen	6 (7)
Aromatase inhibitor	60 (66)
Aromatase inhibitor and fulvestrant	18 (20)
Other or unknown‡	7 (7)

Les facteurs pronostiques de survie

- Etude rétrospective, monocentrique. 4958 patientes traitées pour un cancer du sein non métastatique
- 1038 patientes ont développé une maladie métastatique (21 %)

Facteurs	HR	IC95%
Âge ≥ 50 ans	1.45	1.16-1.80
Taille tumeur primitive > 20mm	1.240	1.02-1.50
Récepteurs hormonaux positifs	0.65	0.50-0.85
Site métastatique		
os	1.62	1.16-1.24
poumon	2.01	1.41-2.88
foie	4.30	2.92-6.34
multiple	4.87	3.35-7.06
cerveau	15.00	8.17-27.50

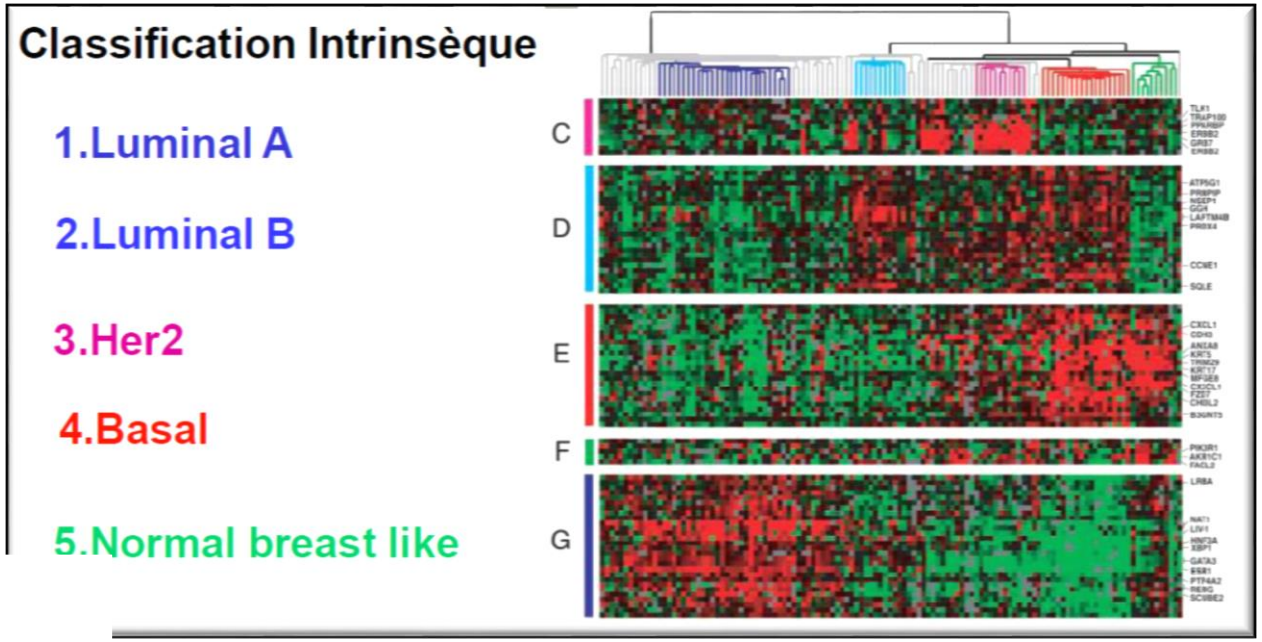
Largillier et al, Ann Oncol 2008

Classification moléculaire des cancers du sein 2000 puis 2010

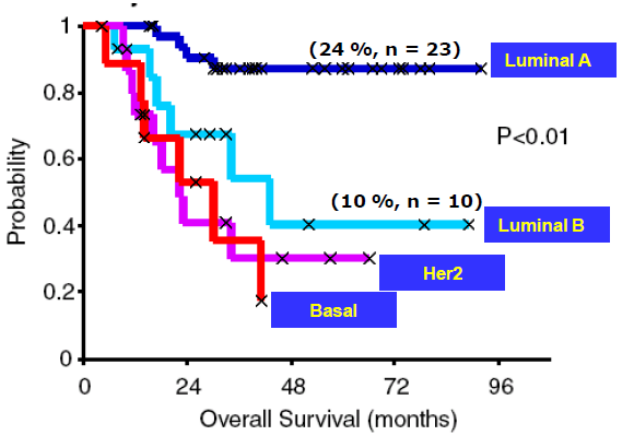
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[f], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[f], John C. Matese[c], Patrick O. Brown[a,h], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]

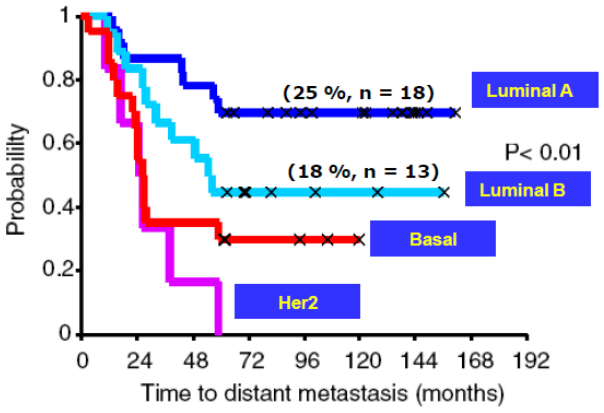
PNAS | September 11, 2001 | vol. 98 | no. 19 | 10869–10874



Norway/Stanford data–set



van't Veer data–set



Between-Patient and Within-Patient (Site-to-Site) Variability in Estrogen Receptor Binding, Measured In Vivo by ^{18}F-Fluoroestradiol PET

Brenda F. Kurland[1], Lanell M. Peterson[2], Jean H. Lee[2], Hannah M. Linden[3], Erin K. Schubert[2], Lisa K. Dunnwald[2], Jeanne M. Link[2], Kenneth A. Krohn[2], and David A. Mankoff[2]

[1]Department of Clinical Statistics, Fred Hutchinson Cancer Research Center, Seattle Washington; [2]Department of Radiology, University of Washington, Seattle, Washington; and [3]Division of Medical Oncology, University of Washington, Seattl

ELSEVIER

Seminars in NUCLEAR MEDICINE

Imaging Breast Cancer Bone Metastases: Current Status and Future Directions

Jennifer Glendenning, MBBS, FRCR,* and Gary Cook, MBBS, MSc, MD, FRCR, FRCP†

The skeleton is commonly affected in the context of metastatic breast cancer and is a cause of significant morbidity in these individuals. Therapeutic options include systemic therapy, radiotherapy, and surgery given with the intent of preserving function and quality of life. As the spectrum of available therapies increases, key challenges comprise reliable diagnosis of bony metastatic disease and accurate evaluation of response that permits rapid therapeutic transition in those responding inadequately prior to development of significant skeletal morbidity. The ^{99m}Tc-diphosphonate bone scan remains one of the most commonly requested investigations for skeletal evaluation in patients with breast cancer. However a time lag of 3-6 months for accurate response evaluation from the start of treatment limits its utility for response evaluation in routine clinical practice or as a progression end point in the research setting. Functional imaging strategies using more tumor-specific radiopharmaceuticals show promise as an effective means of imaging response at a clinically relevant time point and are the subject of this review.

Semin Nucl Med 43:317-323

A-t-on besoin de la FES ?

Clinical Cancer Research

Positron emission tomography with 2-[18F]Fluoro-2-deoxy-D-glucose and 16alpha-[18F]fluoro-17beta-estradiol in breast cancer: correlation with estrogen receptor status and response to systemic therapy.

J E Mortimer, F Dehdashti, B A Siegel, et al.

Clin Cancer Res 1996;2:933-939.

Breast Cancer Res Treat (2009) 113:509–517
DOI 10.1007/s10549-008-9953-0

CLINICAL TRIAL

PET-based estradiol challenge as a predictive biomarker of response to endocrine therapy in women with estrogen-receptor-positive breast cancer

Farrokh Dehdashti · Joanne E. Mortimer · Kathryn Trinkaus · Michael J. Naughton · Matthew Ellis · John A. Katzenellenbogen · Michael J. Welch · Barry A. Siegel

VARIATIONS

X 34 du SUV FES inter Patients

X 8 Intra Patient

28.1% of the patients (9/32FES + et FES –

After treatments, 37.5% (9/24) patient with recurrent or metastatic breast cancer showed heterogeneity, whereas no untreated patient was detected to exist discordant ER expression.
There was statistical difference of heterogeneity between these 2 groups

Qu'est ce que TEP FES - ?

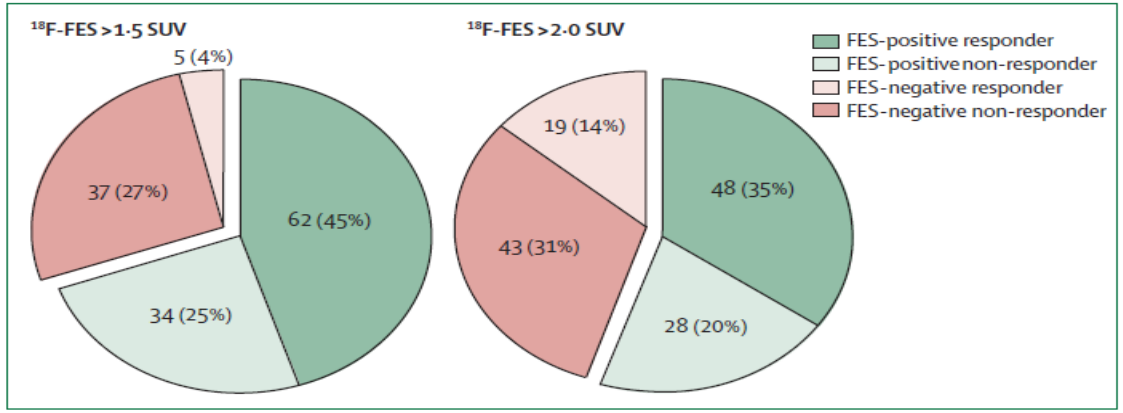


Figure 4: **Predictive value of ^{18}F-FES-PET (n=138 patients)**
In 138 patients, use of an SUV higher than 2·0 compared with a value of 1·5 did not increase the positive predictive value of ^{18}F-FES-PET, [46,53,54,57] whereas the negative value dropped. ^{18}F-FES=16α-[^{18}F]-fluoro-17β-oestradiol. SUV=standardised uptake value.

PET imaging of oestrogen receptors in patients with breast cancer

Michel van Kruchten, Elisabeth G E de Vries, Myles Brown, Erik F J de Vries, Andor W J M Glaudemans, Rudi A J O Dierckx, Carolien P Schröder, Geke A P Hospers

Oestrogen receptors are overexpressed in around 70% of all breast cancers, and are a target for endocrine therapy. These receptors can be visualised on PET with use of 16α-[^{18}F]-fluoro-17β-oestradiol (^{18}F-FES) as a tracer. Compared with biopsy, which enables assessment of individual sites, whole-body ^{18}F-FES-PET enables quantification of oestrogen-receptor expression in all metastases. In several studies, measurement of tumour protein expression in oestrogen receptors by ^{18}F-FES-PET, concurrent with biopsy, detected oestrogen-receptor-positive tumour lesions with a sensitivity of 84% and specificity of 98%. Roughly 45% of patients with metastatic breast cancer have discordant oestrogen-receptor expression across lesions (ie, ^{18}F-FES-positive and ^{18}F-FES-negative metastases). Low tumour ^{18}F-FES uptake in metastases can predict failure of hormonal therapy in patients with oestrogen-receptor-positive primary tumours. Finally, ^{18}F-FES-PET has shown that oestrogen-receptor binding capacity changes after intervention with hormonal drugs, but findings need to be confirmed. Factors other than oestrogen-receptor expression, including menopausal status and concomitant therapies, that can affect tumour ^{18}F-FES uptake must be taken into account.

	Disorder	Number of patients	Study aim	Conclusions
Zhao et al, 2013[37]	Uterine tumours	47	Assess relation between tumour ^{18}F-FDG and ^{18}F-FES uptake with ER, GLUT-1, and Ki-67	^{18}F-FES uptake correlated with ERα and PR expression, and ^{18}F-FDG-uptake with GLUT-1 and Ki-67
Van Kruchten et al, 2012[38]	Breast cancer	33	Assess clinical value of ^{18}F-FES-PET in patients with unresolved diagnosis after conventional workup	^{18}F-FES-PET aided diagnosis and therapy decision making
Peterson et al, 2011[39]	Breast cancer	239	Assess correlations between ^{18}F-FES uptake and clinical and laboratory data, effects of previous treatments and ^{18}F-FES metabolism	^{18}F-FES uptake correlated positively with BMI and inversely with plasma SHBG levels and binding capacity
Yoshida et al, 2011[40]	Suspected uterine sarcoma	24	Assess usefulness of ^{18}F-FES-PET and ^{18}FDG-PET to differentiate uterine sarcoma from leiomyoma	^{18}F-FDG-to-^{18}F-FES ratios >2·0 differentiated with 90·9% sensitivity and 92·3% specificity
Kurland et al, 2011[41]	Metastatic breast cancer	91	Measure variability in ^{18}F-FES uptake between and within patients	Substantial variation seen between patients (37% had low or absent uptake; roughly 40% had mixed uptake)
Linden et al, 2011[42]	Metastatic breast cancer	30	Measure changes in ^{18}F-FES uptake during treatment with aromatase inhibitors, tamoxifen, or fulvestrant	No effect with aromatase inhibitors, decreases of around 55% with tamoxifen and fulvestrant
Tsujikawa et al, 2009[43]	Endometrial cancer	19	Assess correlation between ^{18}F-FES-PET, ^{18}F-FDG-PET, and ER-status on immunohistochemistry	Correlations for tumour ERα status good
Tsujikawa et al, 2009[44]	Endometrial cancer	31	Assess correlation between ^{18}F-FES-PET, ^{18}F-FDG-PET, and clinicopathological features	^{18}F-FES-to-^{18}F-FDG ratios correlated with tumour aggressiveness
Yoshida et al, 2009[45]	Ovarian cancer	3	Review role of PET in ovarian cancer (plus preliminary results of ^{18}F-FES-PET in three patients)	^{18}F-FES uptake was seen in ER-positive tumours
Dehdashti et al, 2009[46]	Metastatic breast cancer	59	Investigate whether ^{18}F-FES-PET and serial ^{18}F-FDG-PET (plus oestradiol challenge) predicts response to endocrine therapy	Baseline tumour ^{18}F-FES uptake and metabolic flare after oestradiol challenge both predictive of treatment response
Peterson et al, 2008[47]	Primary and metastatic breast cancer	17	Assess correlation between ^{18}F-FES uptake and immunohistochemistry	Good correlation for ERα
Tsujikawa et al, 2008[48]	Endometrial hyperplasia	2	Assess effect of tamoxifen on ^{18}F-FES uptake	Take endocrine therapy into account when using ^{18}F-FES-PET to assess ER status
Tsujikawa et al, 2008[49]	Benign and malignant uterine tumours	38	Assess relation between ^{18}F-FES and ^{18}F-FDG uptake in benign and malignant uterine tumours	^{18}F-FES-to-^{18}F-FDG ratios aided differentiation of diagnosis of uterine tumours
Tsuchida et al, 2007[50]	Healthy volunteers	16	Assess relation between ^{18}F-FES uptake, menstrual cycle, and endogenous oestrogen concentrations	Changes in ^{18}F-FES uptake were consistent with changes in ER concentrations on immunohistochemistry
Yoshida et al, 2007[51]	Endometrial cancer	1	Use ^{18}F-FES-PET to assess response to medoxyprogesterone in endometrial cancer	Focal uptake, confirmed by histology
Kanne et al, 2007[52]	Metastatic breast cancer	1	Investigate use of ^{18}F-FES-PET and ^{18}F-FDG-PET in a patient with gastric linitis plastica from metastasis of ER-positive lobular breast cancer	^{18}F-FES-PET confirmed regional ER binding in metastases

Linden et al, 2006[53]	Metastatic breast cancer	47	Quantify tumour ^{18}F-FES uptake as predictor of response to endocrine therapy	Absence of uptake predicts failure of endocrine therapy
Mortimer et al, 2001[54]	Breast cancer	40	Assess serial ^{18}F-FES-PET and ^{18}F-FDG-PET to predict response to tamoxifen	Increase in ^{18}F-FDG uptake and decrease in ^{18}F-FES uptake after the start of tamoxifen predicted response
Mankoff et al, 2001[55]	Breast cancer	49	Radiation dosimetry of ^{18}F-FES-PET	Radiation dose is similar to commonly used nuclear medicine tests
Tewson et al, 1999[56]	Breast cancer	18	Assess interaction between SHBG and ^{18}F-FES	Around 45% of ^{18}F-FES was bound to SHBG and could affect tracer uptake
Dehdashti et al, 1999[57]	Metastatic breast cancer	11	Asses serial ^{18}F-FES-PET and ^{18}F-FDG-PET to predict response to tamoxifen	Increase in ^{18}F-FDG uptake and decrease in ^{18}F-FES uptake after the start of tamoxifen predicted response
Moresco et al, 1997[58]	Meningioma	6	Assess ER-status of meningiomas by means of ^{18}F-FES-PET	Four of six patients showed focal ^{18}F-FES uptake, and uptake correlated with immunohistochemistry status in five of six patients
Mankoff et al, 1997[59]	Primary or metastatic breast cancer	15	Assess clearance of labelled ^{18}F-FES metabolites	Rapid clearance
Mortimer et al, 1996[60]	Primary or metastatic breast cancer	43	Assess correlation between ^{18}F-FES-PET and ^{18}F-FDG and in-vitro assays for response to therapy	^{18}F-FES-PET had a sensitivity of 76% and specificity of 100% compared with immunohistochemistry
Dehdashti et al, 1995[61]	Primary or metastatic breast cancer	53	Compare ^{18}F-FES-PET with ^{18}F-FDG-PET and immunohistochemistry	^{18}F-FES-PET 88% agreement with immunohistochemistry and provided information not obtained by ^{18}F-FDG-PET
McGuire et al, 1991[62]	Metastatic breast cancer	16	Assess use of ^{18}F-FES-PET in ER-positive metastatic postmenopausal breast cancer	^{18}F-FES-PET sensitivity 93%
Mintun et al, 1989[3]	Primary breast cancer	13	Assess feasibility of ^{18}F-FES-PET to detect primary ER-positive breast-tumour lesions and correlation with in-vitro ER status	Focal uptake seen in all patients with ^{18}F-FES and uptake correlated well with in-vitro assays (r=0·96)

^{18}F-FES=16α-[^{18}F]-fluoro-17β-oestradiol. ^{18}F-FDG=2-deoxy-[^{18}F]fluoro-D-deoxyglucose. ER=oestrogen receptor. PR=progesterone receptor. BMI=body-mass index. SHBG=sex-hormone-binding globulin.

***Table 1*: Overview of clinical ^{18}F-FES-PET studies**

PET Imaging of Estrogen Receptors as a Diagnostic Tool for Breast Cancer Patients Presenting with a Clinical Dilemma

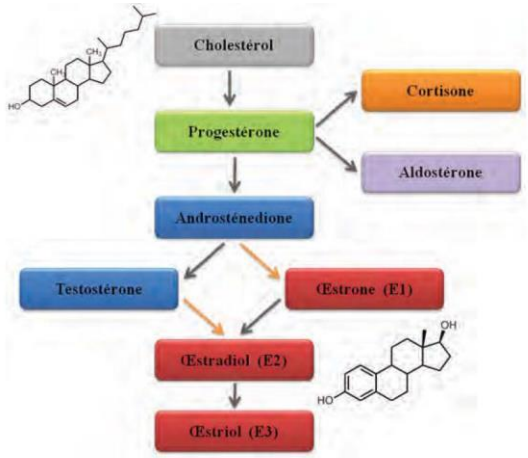
Michel van Kruchten[1], Andor W.J.M. Glaudemans[2], Erik F.J. de Vries[2], Regina G.H. Beets-Tan[3], Carolien P. Schröder[1], Rudi A. Dierckx[2], Elisabeth G.E. de Vries[1], and Geke A.P. Hospers[1]

[1]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; and [3]Department of Radiology, Maastricht University Medical Center, M

Discordant oestrogen-receptor expression

In retrospective studies discordant oestrogen-receptor expression between the primary tumour and distant metastases was found in 14·5–40·0% of patients.[11] Prospective data have shown loss of oestrogen-receptor expression in distant metastases in three (12%) of 25 patients with oestrogen-receptor-positive primary tumours[12] and in 11 (16%) of 69 patients in another study.[1] Gain of oestrogen-receptor expression was seen in the distant metastases of four (16%) of 25 patients with oestrogen-receptor-negative primary tumours.[1] The clinical relevance of change in oestrogen-receptor status is supported by a retrospective study in 459 patients, in which oestrogen-receptor expression in metastases predicted overall survival independent of the status of the primary tumour.[13] The researchers concluded that patients in whom a status switches from negative to positive might benefit from endocrine therapy.

Br J Cancer. 2015 May 12;112(10):1617-25. doi: 10.1038/bjc.2015.138. Epub 2015 Apr 16.
The value of PET/CT with FES or FDG tracers in metastatic breast cancer: a computer simulation study in ER-positive patients.
Koleva-Kolarova RG1, Greuter MJ2, van Kruchten M3, Vermeulen KM1, Feenstra T4, Buskens E1, Glaudemans AW5, de Vries EF5, de Vries EG3, Hospers GA3, de Bock GH1.
Author information
Abstract
BACKGROUND:
The aim of this study was to evaluate the effect on the number of performed biopsies and costs associated with implementing positron emission tomography (PET) and computed tomography (PET/CT) with 16α-[(18)F]fluoro-17β-oestradiol (FES) or 2-[(18)F]fluoro-2-deoxy-D-glucose (FDG) as an upfront imaging test for diagnosing metastatic breast cancer (MBC) in comparison with the standard work-up in oestrogen receptor-positive women with symptoms.
METHODS:
A published computer simulation model was adapted and validated. Three follow-up strategies were evaluated in a simulated cohort of women with primary breast cancer over a 5-year-time horizon: (1) the standard work-up, (2) upfront FES-PET/CT and (3) upfront FDG-PET/CT. The main outcome was the number of avoided biopsies to assess MBC. The costs for all three strategies were calculated based on the number of imaging tests and biopsies. The incremental cost-effectiveness ratio (ICER) to avoid a biopsy was calculated only based on the costs of initial imaging and staging tests.
RESULTS:
The FES-PET/CT strategy decreased the number of biopsies by 39±9%, while upfront FDG-PET/CT increased the number of biopsies by 38±15% when compared with the standard work-up. Both PET/CT strategies reduced the number of imaging tests and false positives when compared with the standard work-up. The number of false negatives decreased only in the FES-PET/CT strategy. The ICER in the FES-PET/CT strategy per avoided biopsy was 12.1±3.4 thousand Euro. In the FDG-PET/CT strategy, the costs were higher and there were no avoided biopsies as compared with the standard work-up, hence this was an inferior strategy in terms of cost effectiveness.
CONCLUSIONS:



Les traitements hormonaux :

- Diminuer le taux d'oestrogène circulant
  - La castration chirurgicale (ovariectomie) ou ≪ medicale ≫ (par des agonistes de la GnRH)
  - anti-aromatases l'Anastrozole®, le Letrozole ®ou l'Exemestane®,

- Bloquer l'activité du récepteur ; anti-oestrogenes (AEs) sont des **antagonistes** partiels (aussi appeles SERM, selective estrogen receptor modulator) ER. Tamoxifen

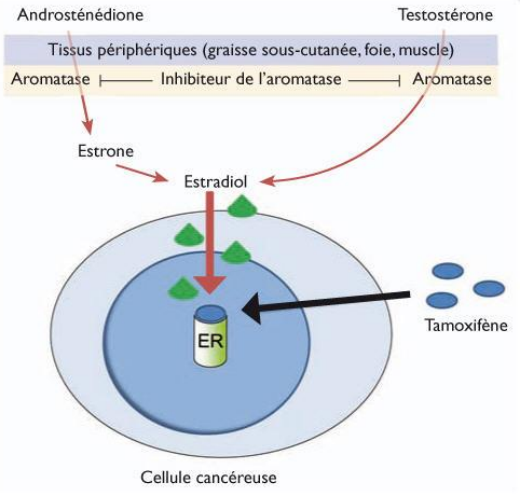


Figure 1
Mécanisme d'action du tamoxifène et des inhibiteurs de l'aromatase
ER : Récepteur des œstrogènes.

Types	Substances	Doses	Préménopause	Postménopause
Inhibiteur du récepteur des œstrogènes	Tamoxifène	20 mg/jour	+	+
Inhibiteurs de l'aromatase	Anastrozole (Arimidex)	1 mg/jour	–	+
	Létrozole (Fémara)	2,5 mg/jour	–	+
	Exémestane (Aromasin)	25 mg/jour	–	+
Suppression médicamenteuse de la fonction ovarienne	Goséréline (Zoladex)	3,6 mg 1 x/28 jours	+	–
	Leuproréline (Lucrin) Leuproréline (Lucrin Dépôt)	3,75 mg 1 x/mois 11,25 mg 1 x/3 mois	+	–

Tableau 1
Substances et doses dans l'hormonothérapie adjuvante du cancer du sein
Types Substances Doses Préménopause Postménopause Inhibiteur du récepteur des œstrogènes Tamoxifène 20 mg/jour + + Inhibiteurs de l'aromatase Anastrozole (Arimidex) 1 mg/jour – + Létrozole (Fémara) 2,5 mg/jour – + Exémestane (Aromasin) 25 mg/jour – + Suppression médicamenteuse de la fonction ovarienne Goséréline (Zoladex) 3,6 mg 1 x/28 jours + – Leuproréline (Lucrin) 3,75 mg 1 x/mois + – Leuproréline (Lucrin Dépôt) 11,25 mg 1 x/3 mois

RESISTANCE HORMONAL AVEC ER +

- Activation de la voie ER independante du ligand
- Crosse talk EFGR et mTOR
- ^{18}F-FES Pos : effet neg
- In these instances, oestrogen receptor degradation by fulvestrant might remain effective.
- Endocrine therapy combined with other targeted therapies might also bypass ligand-independent
  - activation of oestrogen receptors: mTOR inhibition
- combined with aromatase inhibition has shown
- promising results in patients with endocrine-resistant

- RECEPTEUR INTANUCLEAIRE
- DE CLASSE 1