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TITRE

Le cancer du sein métastatique de l'homme : Etude rétrospective multicentrique de 149 cas à partir de la base de données ESME.

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

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les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

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l'instruction que j'ai reçue de leurs pères.

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Résumé

Management et résultats dans le cancer du sein métastatique de l'homme: analyse complète à partir du programme national observationnel multicentrique ESME (EpidemioStrategy and Medical Economics).

Introduction : Dans 1% des cas, le cancer du sein concerne un homme. Partageant certaines caractéristiques avec celui de la femme, il présente néanmoins quelques particularités. Actuellement, les stratégies de traitement sont fondées sur celles de la femme, mais certains auteurs suggèrent que ces recommandations ne sont pas toujours suivies, notamment au stade localisé. Les données sont plus réduites au stade métastatique. Nous souhaitons donc, à partir d'une base de données nationale, fournir une analyse complète de la prise en charge du cancer du sein de l'homme au stade IV.

Matériel et méthodes : La plateforme ESME est une base de données rétrospective de "vie réelle" réalisée au sein de 18 CLCC. Elle comprend les données de tous les cancers du sein ayant débuté leur prise en charge métastatique entre janvier 2008 et décembre 2014. Tous les cas d'hommes ont été retrouvés et comparés à la population totale de femmes, et à une cohorte de femmes appariées (1/1) sur l'âge, les caractéristiques immuno-histochimiques, le grade, la présence d'une hormonothérapie adjuvante, le caractère viscéral ou non des métastases, ainsi que leur découverte *de novo* ou non. L'objectif premier était la description complète des caractéristiques et du management du cancer du sein métastatique de l'homme. Les objectifs secondaires étaient la description des traitements et de leurs résultats en termes de survie globale (SG) et de survie sans progression (SSP), ainsi que la comparaison avec la cohorte appariée.

Résultats : Sur 16 701 patients évaluables, 149 (0.89%) hommes ont été identifiés. Leurs principales caractéristiques sont décrites dans le tableau ci-dessous.

Caractéristiques	**hommes** *n=149*	**Femmes** *n=16 552*	**p**
Âge moyen Âge médian	68,1 ans 69 ans	60,6 ans 61 ans	<0,0001
Statut immuno-histochimique			
- *RH+/HER2-*	105 (78,4%)	9 815 (65,6%)	0,0019
- *HER2 +++*	23 (17,1%)	2 840 (19%)	0,62
- *Triple négatif*	6 (4,5%)	2 315 (15,4%)	0,0005
- *Manquant*	15	1582	
Histologie du primitif			<0,0001
- *carcinome canalaire infiltrant (CCI)*	133 (95,7%)	12 404 (80,3%)	
- *carcinome lobulaire infiltrant (CLI)*	2 (1,4%)	2 185 (14,1%)	
- *CCI + CLI*	1 (0,7%)	258 (1,7%)	
- *autre*	3 (2,2%)	598 (3,9%)	
Métastatique de novo	49 (32,9%)	4 754 (28,7%)	0,26
Localisation métastatique			
- *encéphalique*	4 (2,7%)	1 196 (7,2%)	0,03
- *hépatique*	21 (14,1%)	4 470 (27%)	0,0004
- *pulmonaire*	68 (45,6%)	4 035 (24,4%)	<0,0001

Dans la population appariée, la SG était statistiquement similaire entre les hommes et les femmes: 41,8 mois et 34,9 mois (p=0,74), respectivement.
Dans la population RH+/HER2-, 45/105 (42.9%) hommes ont reçu une première ligne de traitement par hormonothérapie (HT) exclusive: anti-oestrogène (19/45), anti-aromatase (18/45) dont 3 avec co-administration d'agoniste de la LHRH, et une autre HT pour 8/45. La SSP médiane était de 9,8 mois (m) sans difference significative entre anti-oestrogène et anti-aromatase. Comparée aux femmes, la SSP était similaire: 9,8m versus 13m (p=0,8). Pour ceux ayant reçu une chimiothérapie en première ligne (éventuellement suivie d'une hormonothérapie de maintenance), soit 59/105 (56.1%), la SSP médiane était de 9,5 mois et n'était pas différente de celle des patients ayant eu une hormonothérapie seule (p=0,22). Globalement, la SG des patients RH+/HER2- était de 41,8 mois et la SSP de 9,5 mois. Pour les HER2+, la SSP médiane en première ligne était de 11,6 mois et la SG de 42,5 mois sans différence significative avec les femmes. Enfin, la SSP et la SG atteintes par les patients triples négatifs étaient respectivement de 11,4 mois (bornes; 4,7 – 34,3) et 43,7 mois (bornes; 8,9 – 64,8).

Conclusion : Nous rapportons les résultats de l'une des plus importantes séries de cancers du sein métastatique chez l'homme. Comparativement aux femmes, il semble que le pronostic et l'effet des traitements soient comparables. Il apparait également que, comme en adjuvant, les hommes ne soient pas toujours traités selon les recommandations, notamment en ce qui concerne le choix de l'hormonothérapie de première intention, ou la co-administration d'un agoniste de la LHRH quand une anti-aromatase est prescrite. D'autres études sont nécessaires afin de mieux personnaliser la prise en charge des cancers mammaires métastatiques masculins.

Mots clés : cancer sein de l'homme, métastatique, hormonothérapie, cohorte appariée de femmes.

ABSTRACT

Management and outcome of metastatic breast cancer in men: a comprehensive analysis based on the multi-center national observational ESME (EpidemioStrategy and Medical Economics) program.

Introduction: Breast Cancer (BC) in men accounts for about 1% of all BC. Although male and female BC share several similarities, they also have many differences. Current management is still largely following female BC treatment algorithms. But some data suggest that men do not receive treatment as frequently as women notably in adjuvant settings. Data regarding metastatic male breast cancer and its management are even more scaled down. Based on a national database, we aimed at providing a large comprehensive analysis of metastatic BC in men.

Patients and methods: ESME platform is a French multi-center retrospective real life database using a clinical trial-like methodology to collect data from 18 French Comprehensive Cancer Centers. It includes data from each newly diagnosed metastatic BC patients having initiated at least one treatment between 01/2008 and 12/2014. Cases occurring in men were retrieved and compared to the overall female population (characteristics, Student T-test), and to a population of women matched (1/1) on age, histological subtype, grade, adjuvant treatment and metastasis localization and *de novo* or not disease, regarding treatment effects and survival. The primary objective was a comprehensive description of the characteristics and management of metastatic male breast cancer. Our secondary objectives were the description of the outcome as overall survival (OS) and progression-free survival (PFS) according to the different type of treatment and the comparison with a matched population of women extracted from the database.

Results: Of 16 701 evaluable patients, 149 (0.89%) men were identified. Main comparative characteristics are listed in table below.

Characteristics	**Men (*n=149)***	**Women (*n=16 552)***	**p-value**
Mean age Median age	68.1 years 69 years	60.6 years 61 years	<0.0001
Histological subtype			
- *HR+/HER2-*	105 (78.4%)	9 815 (65.6%)	0.0019
- *HER2 +*	23 (17.1%)	2 840 (19%)	0.62
- *Triple negative*	6 (4.5%)	2 315 (15.4%)	0.0005
- *Missing*	15	1582	
Histology			<0.0001
- *invasive ductal carcinoma*	133 (95.7%)	12 404 (80.3%)	
- *invasive lobular carcinoma*	2 (1.4%)	2 185 (14.1%)	
- *mix*	1 (0.7%)	258 (1.7%)	
- *other*	3 (2.2%)	598 (3.9%)	
De novo metastatic	49 (32.9%)	4 754 (28.7%)	0.26
Metastase localization			
- *encephal*	4 (2.7%)	1 196 (7.2%)	0.03
- *liver*	21 (14.1%)	4 470 (27%)	0.0004
- *lung*	68 (45.6%)	4 035 (24.4%)	<0.0001

In the matched cohort, OS was statistically similar in men and women: 41.8 months and 34.9 months (p=0.74) respectively.
In HR+/HER2- men, 45/105 (42.9%) received frontline hormonal therapy (HT): anti-estrogens (19/45), aromatase inhibitor (AI) (18/45) including 3 with LHRH analogues co-administration, others (8/45). Median PFS was 9.8 months without evidence of statistically difference between HT types. Compared to women, median PFS was similar: 9.8m versus 13.0m (p=0.8). For HR+/HER2- men receiving front line CT (59/105 (56.1%)) eventually associated with maintenance HT, median PFS was 9.5m and was not different from patient receiving HT frontline (p=0.22). Globally, the median OS of HR+/HER2- men was 41.8 months and median PFS was 9.5 months. For HER2+ men, median PFS for first line therapy was 11.6 months and median OS was 42.5 months without significant difference from women. PFS and OS achieved in triple negative men was respectively 11.4 months (range, 4.7 – 34.3) and 43.7 months (range, 8.9 – 64.8).

Conclusion: We report on one of the largest series of MBC in men. Compared with women, prognosis and treatment effects look the same. Interestingly, it appears that men are not always treated following recommendations notably as regards of the first choice of HT in metastatic setting, and the co-administration of LHRH analogues when AI is prescribed. More biological information is needed to improve the customized management of MBC in men.

Key words : male breast cancer, metastatic, hormonotherapy, matched women cohort.

TABLES DES MATIERES

ABBREVIATIONS

AA : anti-androgen
ABC : Advanced Breast cancer
AE : Anti-Estrogens
AI : Aromatase inhibitor
BC : Breast Cancer
BRCA1 : BReast CAncer 1
BRCA2 : BReast CAncer 2
CI : Confidence Interval
CT : Chemotherapy
EORTC : European Organisation for Research and Treatment of Cancer.
ER : Estrogens Receptor
PR : Progesterone Receptor
ESME program : EpidemioStrategy and Medical Economics program
FSH : Follicle-stimulating hormone
GCP : Good Clinical Practices
GnRH : Gonadotropin-releasing Hormone
GnRHa : Gonadotropin-releasing Hormone analogue
HER2 : Human Epidermal Growth Factor Receptor 2
HR : Hormone receptor
HT : Hormonotherapy / Hormonal Therapy
LH : Luteinizing Hormone
NCCN : National Comprehensive Cancer Network (USA)
NE : Not Estimable
ORR : Overall Response Rate
OS : Overall survival
PFS : Progression Free Survival
RT : Radiotherapy
SBR : Scarff-Bloom-Richarson
SD : Standard Deviation
SEER : Surveillance Epidemiology ans End Results
TNBC : Triple Negative Breast Cancer
UICC : Union for International Cancer Control

TABLES AND FIGURES

Introduction.

Breast cancer (BC) is culturally associated with female gender but it affects men in about 1% of cases.[1,2] With an incidence of BC of 58 968 in France in 2017, we estimate that around 500 new men are diagnosed with BC each year.[3] Because of this low prevalence, characterizing men's disease has been tremendously challenging.

Although male and female BC share several similarities, they also have many differences. Like in women, the data from the Surveillance, Epidemiology, and End Results (SEER) program show a growing incidence from 0.85 cases per 100 000 men in the general population in 1975 to 1.43 cases per 100 000 in 2011.[4] These data are conflicting with an international report, which shows a stable incidence over the time unlike to women.[2] Controversial data also exist about the influence of sex on prognosis and the improvement in the treatment of breast cancer does not seem to benefit to men compared to women.[5,6]

Some risk factors are shared by the two genders like family history and genetic factors. A family history of breast cancer is associated with a two or threefold risk and *BRCA2* is the most common associated genetic mutation with a lifetime risk of 8.3% for men with *BRCA2* mutation.[7-10] Other shared risk factors include an abnormal oestrogen to androgen ratio (obesity) and environmental factors like the lack of exercise, liver cirrhosis and irradiation. Some risk factors are specific like Klinefelter's syndrome, orchitis/epididymitis and exogenous testosterone use (Appendix). Men appear to be significantly older at diagnosis compared to women, with a more advanced stage and histological subtype is less likely lobular. [1,2,6,11-13] Interestingly, histological grade is often lower than in women, hormone receptor positivity (HR) is more frequent (99% according to Vermeulen) and HER2 receptor overexpression is really rare.[12,14]

Despite these similarities and differences, current management is largely following female BC treatment algorithms.[15,16] The frequent exclusion of men from prospective breast cancer trials and the difficulty to conduct specific trial in this rare disease explains this situation. However, little is known about the validity of such approach in men and some data indicate that men do not receive adjuvant therapy as frequently as women without any specific rationale. [2,17-19]

Data regarding metastatic male breast cancer and its management are even more scaled down. The reports are mainly based on small retrospective series with incomplete data regarding clinical management, histology, follow-up and BRCA status. The biggest reported series examined prognostic factors that affected survival outcomes in 394 men with metastatic BC selected between 1988 and 2012. This publication is based on the Surveillance, Epidemiology, and End Results database.[19] Besides the number of patients, strong limitations have to be underlined, as HR status and HER2 positivity are unknown for 25% and 80% of the patients respectively. Furthermore, no details on the type of treatment in the metastatic setting are reported. More recently, a retrospective-joint-analysis of cases diagnosed during a 20-year-period has been reported by EORTC.[20] This study has included 1483 patients, with only 57 patients with de novo metastatic disease.

In summary, with only a few, mainly small single center studies available in metastatic BC in men, a number of unsolved questions influence daily practices. Further researches are needed in order to improve risk stratification and patient's management. By interrogating the ESME database, we identified 149 patients with metastatic BC. Our goal is to provide a comprehensive analysis of these patients and their management.

Patients and Methods.

ESME database.

ESME Platform is a unique national real-life database including individual data from all consecutive women and men ≥18 years treated for a metastatic breast cancer between January 2008 and December 2014 in one of the 18 French Cancer Centres participating in the ESME program. Patients' data were retrospectively collected. Metastatic features as well as primitive tumour characteristics were retrieved: age at diagnosis, estrogen, progesterone and HER2 receptors expression, TNM stage and metastatic localization, grade, and histology. Besides, type of treatment such as chemotherapy, endocrine treatment in the adjuvant and metastatic setting were also collected and outcome. In accordance with French regulation, the French data protection authority authorized the database. R&D Unicancer in compliance with the Good Clinical Practices (GCP) managed it and an independent ethic committee approved the study. Considering the retrospective character of the study, no informed consent was deemed necessary. Nevertheless, all patients had approved the re-use of their electronically recorded data.

Study population.

In the present study, all men with metastatic breast cancer in the ESME database were included. To allow specific comparison with women, we designed a matched population of women according to the following criteria: age, SBR grade, adjuvant hormonotherapy, HR and HER2 status, *de novo* metastatic disease or not, and metastases localization (visceral / no visceral). Data were collected until the cut-off date (January 15th, 2017), death, or date of last contact if lost to follow-up.

Objectives and Endpoints.

The primary objective was a comprehensive description of the characteristics of men and the management of their metastatic disease. Our secondary objectives were the description of the outcome according to the different type of treatment and the comparison with a matched population of women extracted from the database.

The primary endpoint of the study was the prevalence of metastatic breast cancer in men in the ESME database. Secondary endpoints included overall survival (OS) defined as the time between date of metastases diagnosis and date of death of any cause, and progression free survival (PFS) as the time between date of metastases diagnosis and date of first disease progression or death. Disease progression was defined as the occurrence of a new metastatic site, progression of existing metastasis, local or loco-regional recurrence of the primary tumour, discontinuation of chemotherapy and/or targeted therapy due to metastatic progression, or death from any cause.

Statistical analysis.

Patients' characteristics were summarized using descriptive statistics (means and standard deviations [SD]) and compared using the Pearson's χ^2 test or Student t-test, when appropriate; a *p*-value <0.05 was considered statistically significant. Both OS and PFS were estimated using the Kaplan-Meier method, and median follow-up durations using the reverse Kaplan–Meier method. Survival curves with their log-rank tests were generated. Censored data were descriptively summarized for the two groups.

Variables, including prognostic factors, were selected for univariate analysis. The multivariate analysis was performed using a Cox model adjusted and stratified for prognostic factors of survival and potential cofounders. The Breslow Estimator was used to generate adjusted survival curves. HRs are presented on a descriptive basis with 95% confidence intervals (CI). Statistical analyses were performed using the SAS® software (version 9.4).

Results.

Characteristics of men in the ESME cohort and comparison to women.

16 703 patients were retrieved in database, 1 died before diagnosis of metastatic disease, 1 other was deleted from database.

Out of the 16 701 evaluable patients in the database, 149 (0.89%) men were identified with a mean age of 68 years (median 69 years, range 44-90). The disease was hormone receptor positive HR+/HER2- in 105 (78.3%) patients, HER2+ in 23 (17.2%) patients and triple negative in 6 (4.5%) patients. HER2 status was missing for 15 cases. Invasive ductal carcinoma was the most frequent histology (95.7% of cases). The main characteristics of patients are presented in the Table 2.

Metastatic disease occurred *de novo* in 49 patients (32.9%) and after a primary disease in 100 (67.1%) patients. For these latter patients, 25% had a biopsy of a metastatic site to determine the last characteristics of the disease and the median time between the primary diagnosis of and the relapse was 52.5 months (range, 8.9 - 331.4). The characteristics of their primary disease are presented in the Table 3. Briefly, adjuvant chemotherapy was delivered for 62/100 patients with 54/100 patients receiving anthracyclines and 36/100 receiving taxanes. Adjuvant radiotherapy was delivered to 84/100 patients and 86/100 had received adjuvant HT.

The number of metastatic sites at diagnosis was ≥ 3 in one quarter of patients (n= 38; 25.5%). The main sites of metastatic disease were bone n=94 (63.1%), lung n=68 (45.6%), and lymph node n=44 (29.5%) while brain and liver metastases were relatively rare with n=4 (2.7%) and n=21 (14.1%) respectively.

Regarding the treatment of first line, 86 (58.1%) received CT, 107 (72.3%) received HT (among which 62 HT alone and 45 as maintenance therapy) and 14 (9.5%) received anti HER2 therapy. Data were missing for one patient. With a median follow-up of 41.9 months, median OS of men was 41.8 months (CI 95% ; [26.9-49.7]) and median PFS for the first line of treatment was 9.3 months (CI 95% ; [7.4-11.5]).

Some striking differences were observed between men and the whole population of women of the ESME database (Table 4 and 5, Appendix).

Men were significantly older at the diagnosis of metastatic disease: mean age 68 vs 60.6 years ($p<0.0001$). The disease was more frequently HR+ (93.9% of men versus 78.6% in women; ($p<0.0001$)) while HER2+ disease was similar with 23 cases in men (17.2%) and 2840 women (18.9%) ($p=0.061$). Infiltrating ductal carcinoma was more predominant in men (95.7% versus 80.3%, $p<0.0001$) whereas lobular subtype was tenfold less frequent than in women (1.4% vs 14.1%, $p<0.0001$).

Metastatic disease occurred *de novo* in the same proportion for men and women (32.9% versus 28.7% respectively, $p=0.26$). For relapsing patients, the delivery of adjuvant treatment was similar in men compared to women for chemotherapy (62% vs 70%, $p=0.08$) and radiotherapy (84% vs 87.5%, $p=0.29$) but more men received adjuvant endocrine therapy (86% vs 66.3%, $p<0.0001$) reflecting the higher proportion of HR+ disease in men compared to women. The localization of metastatic sites was slightly different with less brain metastases for men versus women (2.7% versus 7.2%, $p=0.03$), more lung metastases (45.6% versus 24.4%, $p<0.0001$) and less liver lesions (14.1% versus 27%, $p=0.0004$).

Based on the above-mentioned matching procedure using six criteria (age, SBR grade, HR and HER2 status, *de novo* metastatic disease, visceral metastases or not, and adjuvant endocrine therapy) the 149 men were paired with 149 women to compare survival in men and women. The Table 6 and 7 display the characteristics of that cohort. With a median follow-up of 41.9 months for men (range, 33.5 - 59 months) and 46.2 months for women (range, 38.4 – 53.4 months), OS was statistically similar in men and women: 41.8 months (CI 95%, [26.9-49.7]) and 34.9 months (CI 95%, [28.4-48.4]) ($p=0.74$) respectively. (Figure 1).

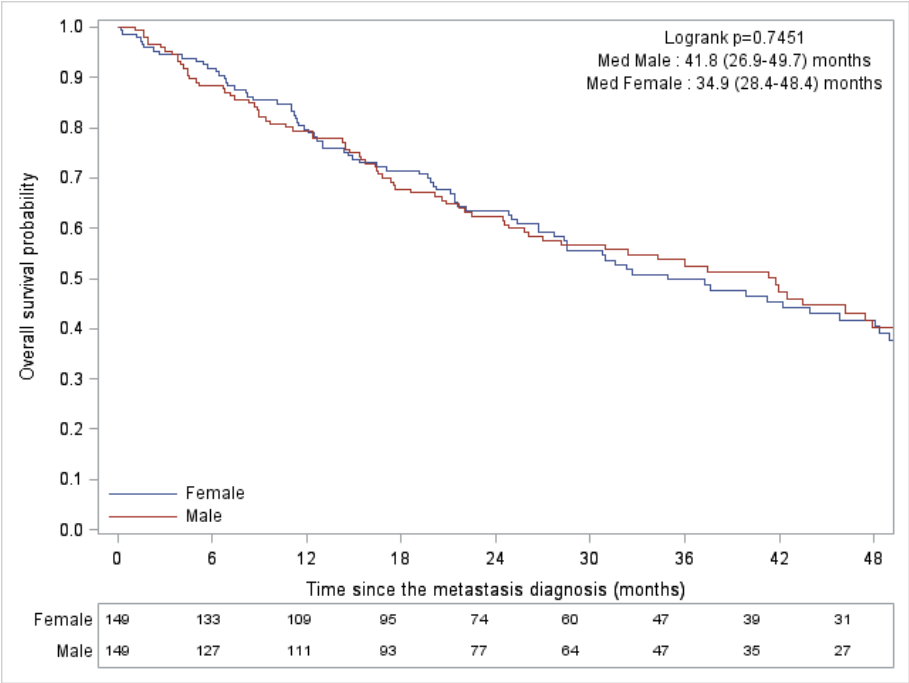

Figure 1. Overall survival in men and in a matched cohort women

HR+/HER2- population: characteristics, management and outcome.

Out of the 149 men, 105 (78.4%) had a HR+/HER2- disease. Mean age was 66.6 months. Disease was ER+/PR+, ER+/PR-, and ER-/PR+ in 71.2%, 26%, 2.9% of cases respectively. Visceral metastatic disease was present in 60.9% of men, 26.7% had bone only disease at initial presentation and the number of metastatic sites was ≥ 3 in 28 of patients (26.7%). The metastatic sites were distributed as follows: bone (62.9%), lung (43.8%), lymph node (30.5%) liver (13.3%) and brain (2.9%).

Metastatic disease was *de novo* in 31 (29.5%) patients. For the 74 relapsing patients, TNM stage at initial diagnosis was distributed as follows: T1 n=10 (33.3 %), T2 n=14 (46.7 %), T4 n=6 (20 %) and 14 patients (46.7 %) were node positive. Of note, data were missing for 44 patients. Adjuvant CT, RT and HT had been administrated in 68.9%, 82.4%, and 91.9% of patients respectively. Details on the type and length of adjuvant HT were not available.

In the metastatic setting, 45 (43.3%) patients received HT alone as frontline therapy. HT was anti-estrogens (AE) in 19 (42.2%) cases including Tamoxifen (n=16), Fulvestrant (n=2) and Tamoxifen+Fulvestrant (n=1). Fifteen patients (33.3%) received an aromatase inhibitor (AI) alone or in combination with an LHRH analogs (n=3) (6.7%). The remaining 8 (17.7%) patients received various combinations including AE+AI; AE+AI+LHRH analogs, AE+LHRH analogs and LHRH analogs alone, which correspond to sequential treatments administered as first line. The details of frontline HT are shown on Table 8.
Median PFS achieved by HT alone as frontline was 9.8 months (CI 95% ; [6.9-17.4]) and median OS was 43.5 months (CI 95% ; [34.3-NE]) for that subgroup of patients. Despite the low number of patients, PFS and OS seemed similar for patients receiving AE versus AI as frontline: 8.5 (CI 95% ; [4.9-20.2]) vs 6.9 months (CI 95% ; [3.2-27.9]) (p=0.37) and 41.9 (CI 95% ; [27.1-NE]) vs 43.5 (CI 95% ; [34.3-74.9]) months (p=0.80) respectively (Figure 2 and 3).

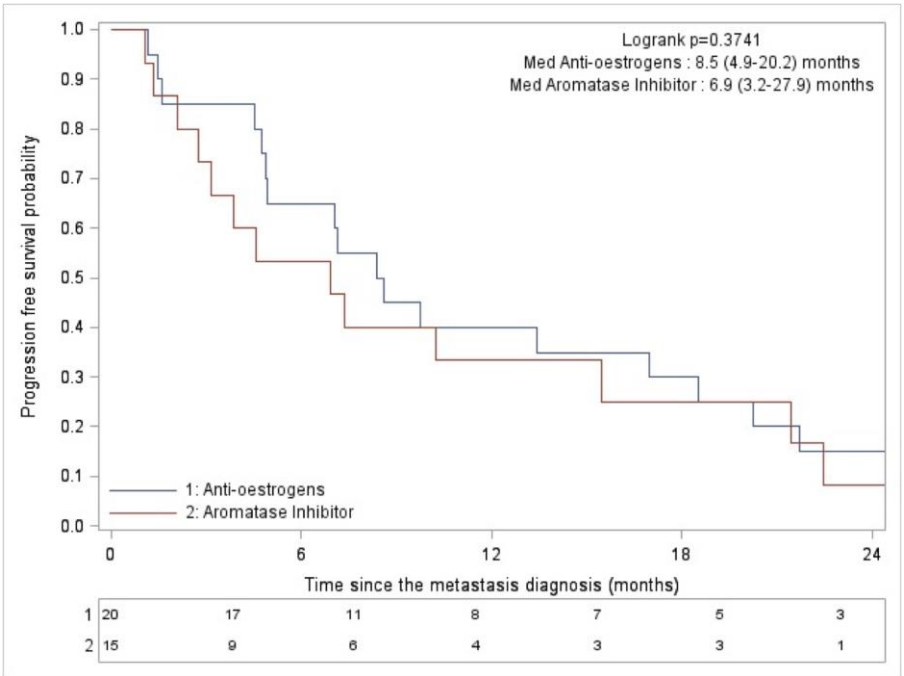

Figure 2. PFS in HR+ men according to the type of frontline hormonal therapy

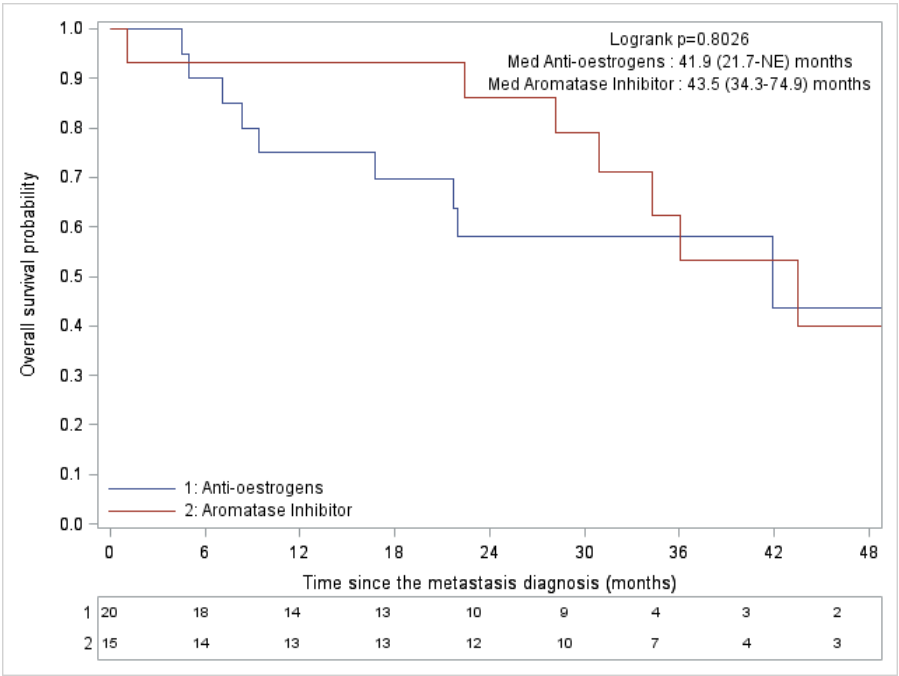

Figure 3. OS in HR+ men according to the type of frontline hormonal therapy

The remaining 59 patients (56.7%) received frontline CT +/- HT as maintenance therapy. The different regimens of chemotherapy are described Table 9. Out of the 59 men treated by frontline CT, 30 received HT as maintenance therapy. This HT was Tamoxifen or AI alone in 56.7% and 30% of cases respectively. The remaining patients received various schemes of treatment due to a switch of drugs without progression to lower side effects. Details are shown on Table 10. For those patients, median PFS was 9.5 months (CI 95% ; [7.4-11.7]) and OS was 37.5 months (CI 95% ; [24.5-50.6]). Of note, OS and PFS were statistically similar for HR+ patients receiving HT or CT (+/- HT) as frontline: 43.5 (CI 95% ; [34.3-NE]) vs 37.5 (CI 95% ; [24.5-50.6]) months (p=0.13) and 9.8 (CI 95% ; [6.9-17.4]) vs 9.5 (CI 95% ; [7.4-11.7]) months (p=0.22) respectively.

Globally, the median OS of HR+/HER2- men was 41.8 months (CI 95% ; [30.9-54.6]) and median PFS was 9.5 months (CI 95% ; [7.4-12.7]). In univariate analysis, grade SBR (III versus I or II) was the only prognostic factor with a median OS of 25.8 months versus 50.6 months (HR= 2.12 [1.23-3.68]; p=0.0061) respectively. This prognostic factor was confirmed in multivariate analysis. As described above, we designed a matched cohort of 105 HR+/HER2- women. OS was similar for women and men with respectively median of 39.9 (CI 95% ; [28.5-49]) and 41.8 (CI 95% ; [30.9-54.6]) months (Figure 4). In that cohort, the proportion of men and women receiving HT as initial treatment was similar 45 (43.3%) vs 47 (45.2%) (p=0.78), as also was proportion receiving CT +/- HT with 59 (56.7%) vs 57 (54.8%). Interestingly, the median PFS achieved by HT as front was statistically similar in men and women: 9.8 (CI 95% ; [6.9-17.4]) months versus 13 (CI 95% ; [8.4-30.8]) months (p=0.81) respectively. The median PFS achieved by CT +/- HT as front line was 9.3 (CI 95% ; [6.5-16.5]) months in women versus 9.5 (CI 95% ; [7.4-11.7]) months in men without statistical difference either (p=0.48). Similarly, OS was not different between women and men for HT (39.9 vs 43.5 months, p=0.56) neither for CT (37.3 vs 37.5 months, p=0.95) as frontline therapy in the metastatic setting.

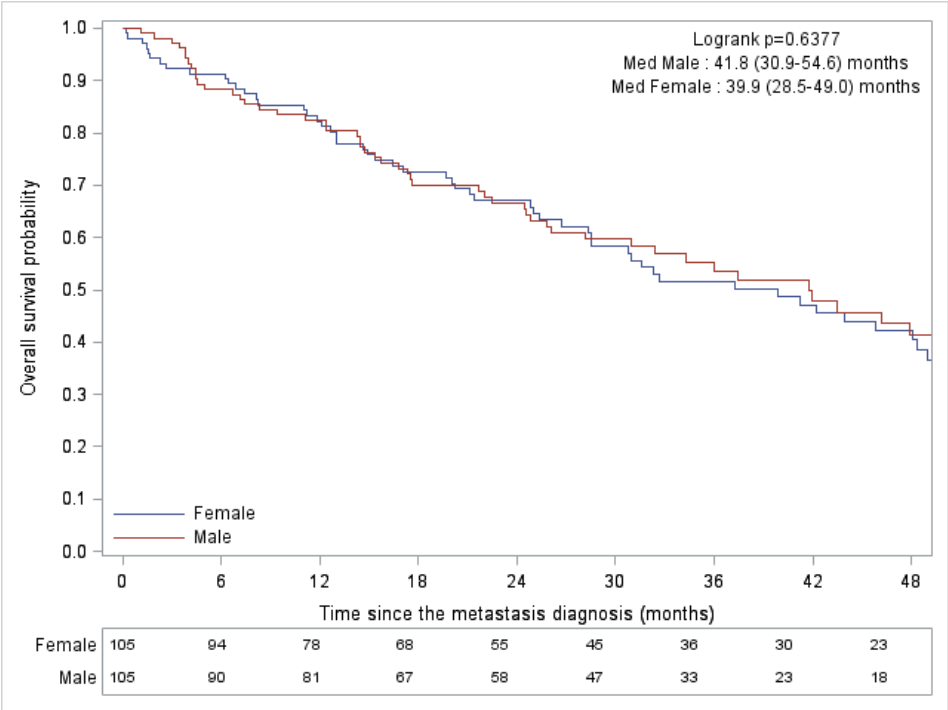

Figure 4. OS in HR+/HER2- men compared to a matched cohort of HR+/HER2- women

HER2+ population: characteristics, management and outcome.

Twenty-three men were identified with HER2+ metastatic disease, with a mean age of 70.3 years. Among them, 20 were triple positive (RH+/HER2+). Metastatic sites were: bone n=14 (60.9%), lymph node n=9 (39.1%), lung n=14 (60.9%), liver n=5 (21.7%). Visceral metastases concerned 17 patients (73.9%) and 3 patients (13%) had bone only disease. *De novo* metastatic disease occurred in 12 patients (52.2%) while relapsing disease occurred in 11 patients (47.8%). Among these latter, 3 (27.3%) had received adjuvant Trastuzumab and 6 (54%) had received adjuvant chemotherapy

The initial treatment of these patients included anti HER2 therapy in 14/23 patients (60.9%). This treatment was chemotherapy with trastuzumab (n=10 ; 71.4%), chemotherapy with trastuzumab and pertuzumab (n=1 ; 7.1%), lapatinib (n=2 ; 14.3%) alone or in combination with trastuzumab (n=1 ; 7.1%). For the remaining 9 patients, 7 patients with HR+ disease received initial HT alone and data were missing for 2 patients.

In that population, the median PFS for first line therapy was 11.6 months (CI 95% ; [8.4-21.6]) and median OS was 42.5 months (CI 95% ; [18.6-NE]). In the matched population, OS were similar (42.5 (CI 95% ; [18.6-NE]) months versus 34.9 (CI 95% ; [14.4-NE]) months, p=0.83) for men and women respectively. PFS was 11.6 (CI 95% ; [8.4-21.6])months for men and 14.4 (CI 95% ; [7.8-26.9]) for women without statistical difference either (p=0.24). (Figure 5 and 6).

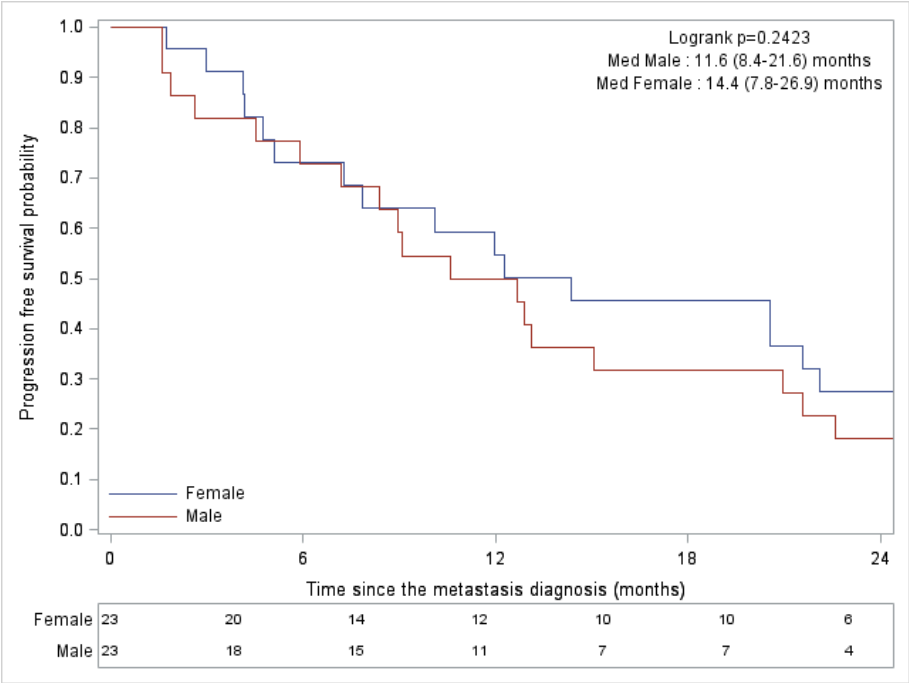

Figure 5. PFS in HER2+ men and in a matched cohort of HER2+ women

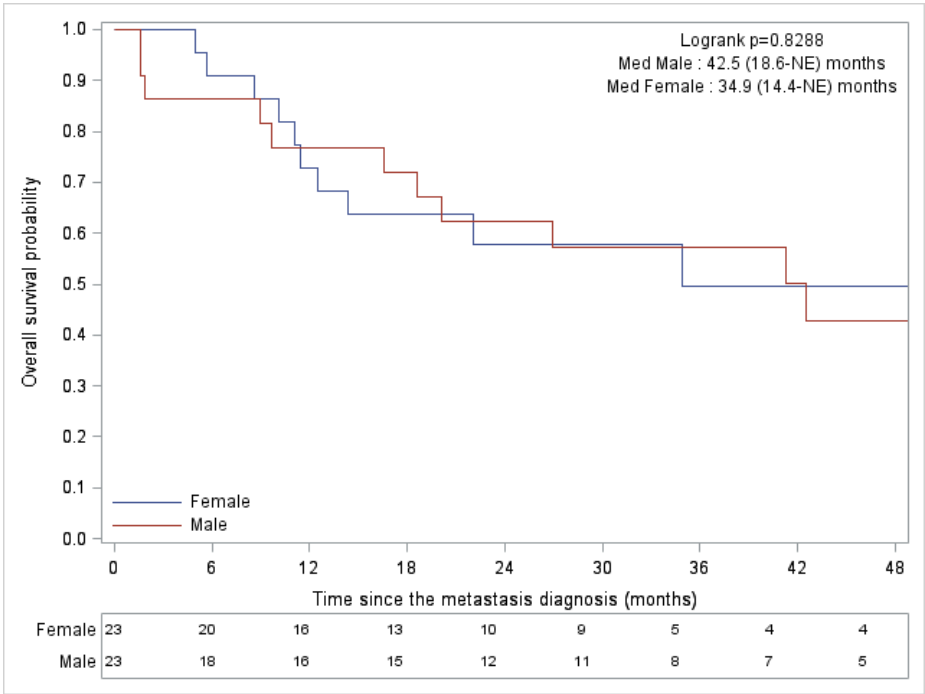

Figure 6. OS in HER2+ men and in a matched cohort of HER2+ women

Management and outcome in the triple negative population:

Only 6 men were identified with a triple negative disease. All of them received chemotherapy and median OS was 43.7 (CI 95% ; [10.7-71.9]) months (range, 8.9 – 64.8) and PFS was 11.4 (CI 95% ; [6-34.3])months (range, 4.7 – 34.3).

Discussion.

We report on one of the largest and comprehensive series of men with metastatic breast cancer. We show that men and women share globally the same prognosis despite some clinic-pathological differences. We believe that these are important information.

The biggest reported population of metastatic male breast cancer is based on the SEER database.[20] In 394 men with a median age of 43 years (range, 30 – 93), ER and PR were respectively positive in 66.8% and 52%. Of note, HER2 status was unknown in 82.2% of cases. Median OS was 21 months with a median follow-up of 21 months. OS was not described according to histological subtype. The study highlights a favorable impact of primary tumor surgery, PR positive status and younger age. Unfortunately, despite impressive data collection information on systemic therapy are lacking. Chen and colleagues recognized these limitations in this study.[20] Moreover, HER2 status is only recorded in this database since 2010, and it seems difficult to compare patient without knowing such an important prognostic factor.
Recently, an International Program directed by the Pr. Fatima Cardoso has been undertaken in order to improve Male Breast Cancer characterization.[12,21] This Program consists of three parts: i) a retrospective collection of Male BC treated in participating centres, over 20 years, for whom centralized clinical information and tumour samples were collected (part I); ii) a prospective registry of newly diagnosed cases during a period of approximately 30 months, with clinical data and tumour samples (part II); iii) prospective clinical studies to optimize the management of these patients (part III). To date, the published data concerned only Part I. This retrospective study enrolled male patients with histologically proven BC with all stages diagnosed between 1990 and 2010, in all participating institutions. The objective was to describe patient's characteristics, the disease and its management (including histological and pathological markers), and the clinical outcomes. The last publication has reported 1483 male breast cancer eligible for analysis including only 57 with metastatic disease, and this latter population is poorly described. Only median OS was published for metastatic patients: 31.2 months (CI 95% ; [24 – 44.4]).

Ultimately, Foerster and colleagues in Germany have published the most comprehensive study dedicated to metastatic breast cancer in men.[41] This study evaluated clinical features,

treatment and outcomes, of all male breast cancer consecutively registered between 1995 and 2011 in Saxony. Information was collected for items such as age, histology, TNM and UICC status, grading, date and site of metastasis, and accomplished treatments, as well as date of primary and secondary diagnosis and death. Detailed information was gathered regarding receptor status (estrogen, progesterone, HER2) as well as chemotherapy, endocrine therapy, and radiotherapy in both the adjuvant and the palliative setting. Forty one men were enrolled. Study population was really comparable to ours: *de novo* metastatic disease representing 39% of patients, median age was 65.5 years (range, 43 – 81), 30 were HR+ (90.2%) with 10 missing data, HER2 was positive for 5 men (12.2%) and 4 had triple negative disease (9.8%). Moreover, metastatic sites were available with concordant predominance of bone (n=23 ; 56.1%) and lung disease (n=21 ; 51.2%) whereas liver and brain were infrequent. Chemotherapy was administered for 17 (41.5%) as first line. Hormonotherapy was Tamoxifen for 12 (29.2%), AI for 15 (36%), AI with gonadotrophin-releasing hormone for 4 (9,8%) and Fulvestrant for 2 patients (4.9%). Median OS was 32 months in this cohort and survival analysis were not presented according to histological subtype.

Our data corroborate some results of these previous studies. Firstly, the prevalence of male breast cancer in ESME database (0.89%) was comparable to previous published data and notably those extracted from the SEER database with about 0.66% of all BC.[1,2,6] Secondly, the older age at diagnosis compared to women is also reported with a median age varying of 65 and 70 years compared to 68 years in our population.[2,6,11,21] In addition, *de novo* metastatic disease accounted for one third of our population, as in the study of Foerster et al.,(39% of patients).[41]

Pathological differences between men and women are also reported in the literature. For example, Vermeulen et al. found the predominance of invasive ductal carcinoma in men (86.6%) and the low prevalence of lobular subtype (1.4%) as in our study 95.7% and 1.4% respectively.[12] Similar data were found by other authors in the last decade, with as well significant difference with female breast cancer.[11,13,42-46] The large predominance of HR+/HER2- disease in men compared to women has been also shown in past studies (92% vs 78%).[6,13] For Vermeulen et al. Luminal A or Luminal B with HER2 negative profile was found in 91,2% of Male Breast Cancer. In our study, we found 78.4% HR+/HER2- but data regarding HER2 were missing for 15 patients (10%) leading probably to underestimate rate of HR+/HER2-

The localization of metastases seemed to differ between sexes. Our data showed a lower frequency of brain metastases (2.7%) and liver localization (14.1%) in men while lung metastases were more frequent (45.6%). These results confirm data from the SEER database (Wu et al., 2017), except the difference for brain metastases.[46] As detailed above, the same findings were described in Germany with Foerster and colleagues with about 51% Male Breast Cancer with lung localizations and only 17.1% with liver ones.[41] These discrepancies in terms of localization could be impacted by the predominance of HR+/HER2- in men compared to women.

Regarding survival, Cardoso et al. found median OS was 31.2 months (CI 95% ; [24.0-44.4]) what is lower than in our cohort with 41.8 months (CI 95% ; [26.9-49.7]). The improvement in effectiveness of treatment over the last decade could plays a role in that difference. Of note, 73.6% of patients in that cohort were treated before 2005 while our patients were enrolled from 2008 to 2014. Similarly, in the SEER database[20] median OS was 21 months with patients treated between 1988 and 2012, and Wu et al.[46] using the same database from 2010 to 2013 showed a median OS of 40 months. Thus, we suppose that older and larger collection period than ours might have an impact on outcomes.

As we have shown, HR+ disease accounts for the majority of men with metastatic breast cancer. Some specific recommendations exist in guidelines regard HT management. The *NCCN* guidelines state that men should be treated similarly to postmenopausal women except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.[15] The ABC 3 recommendations *3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)* state that for HR+ male metastatic breast cancer, hormone therapy is the preferred option, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response. In that case, Tamoxifen is the preferred option. However, if AI is necessary, a concomitant LHRH agonist or orchiectomy is the preferred option. AI monotherapy may also be considered, with close monitoring of response.[47]

Our results show that only 43% of the population received HT alone as initial treatment. This low rate may be due to the assumption that HT is less effective in men than in women.

However, median PFS was 9.8 months and median OS was 43.5 months in HR+/HER2- men receiving HT alone as frontline and this outcome was similar for women with respectively 13 and 39.9 months. In addition, in HR+/HER2- men, PFS was similar with HT or CT administered in as first-line. Therefore, the use of HT in men with HR+ metastatic breast cancer should be encouraged even in the presence of visceral metastases and in the absence of a visceral crisis.

Surprisingly, only few patients received LHRH analogues. The question of whether LHRH are worth being administered in combination with AIs is unsolved even it is stated in guidelines. Physiologically in males, peripheral aromatization of androgens products 80% of circulating estrogens and also 20% are directly secreted by the testicles.[48] In males, AIs lead to increased levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T).[49] Implications of increased T levels are twofold: i) the counteraction of the block imposed by AIs through an excess of substrate and ii) a direct stimulation of cancer cells equipped with the androgen receptor. Thereby it is supposed that in the absence of (chemical or surgical) castration with AI, this phenomenon interferes with marked estrogen suppression by aromatase inhibitors in men. Data on the efficacy of AIs +/- GnRH or LHRH analogues in metastatic male BC are very few with retrospective series including a maximum of 60 patients and the level of proof is not more than expert opinion, but actually no prospective trial has been realized successfully until today. For example, SWOG-S0511 trial (ID: NCT00217659), a phase II trial design to show effect of Anastrozole plus Goserelin in men with recurrent or de novo metastatic breast cancer, closed prematurely owing to poor accrual, illustrating difficulties to study such rare population correctly.

In our cohort, 19 patients received anti-estrogen (42.2 %) as first line of treatment, AI for 15 patients (33.3 %), AI + LHRH analogues in three (6.6%). PFS and OS was similar for AE or AI, and we did not perform any comparison between AI +/- LHRH analogues due to small number of patient. This pattern of treatment is similar to the one reported in the study of Foerster: tamoxifen (29.2%), AI (36.6%), and only 4 (9.8%) patients receiving AI in combination with AI. The best HT in the metastatic setting is so far not known. In a retrospective German Cancer Registry Cohort, OS was improved with the use of adjuvant tamoxifen but not with adjuvant aromatase inhibitors in 257 men.[50]

In the metastatic context, data regarding the efficacy and the type of HT are mostly based on small monocentric series. Tamoxifen remains the cornerstone (ABC3) of treatment in first line rather than AI, notably because of their differential outcomes in adjuvant settings. Table 11 summarizes main reported data in literature evaluating hormone therapy and their outcomes. Of note the final results of a prospective, randomized multi-center phase II study evaluating endocrine treatment with either tamoxifen +/- gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients will be reported at ESMO meeting 2018.

Our study show that the recommendations are not always followed notably Tamoxifen is not always the first choice of practitioners, and furthermore the co-administration of LHRH analogues is not systematic when AI is prescribed. It could be assumed that comorbidities, patient desire, adverse events or toxicity, might play a role but unfortunately, this data were not gathered.

type	author	year of publicatio	number of cases	HR status	HER2 status	molecule	Best response	ORR	median PFS (months)	median OS (months)
Tamoxifen	Ribeiro et al.(51)	1983	24	NA	NA	Tamoxifen	5 CR (20.8%), 4 PR (16.6%), 2 SD (8.3%), 13 PD (54.1%)	37.5%	NA	NA
Multiple	Lopez et al.(52)	1985	14	NA	NA	11 Cyproterone, 7 Tamoxifen, 5 Estrogen, 5 Aminoglutethimide, 3 Medroxyprogesterone, 1 Androgens, 3 Orchidectomy.	NA	44%	NA	OS 23.5 if CR or PR
AI + aLHRH	Lopez et al.(53)	1993	7	NA	NA	Cyproterone acetate + buserelin	7 PR (63.6%), 3 SD (27.2%)	63.6%	NA	18.5
AI	Giordano et	2002	5	positive	NA	Anastrozole	3/5 SD, 2/5 PD	0%	NA	NA
Fulvestrant	Agrawal et al.(55)	2006	1	positive	NA	fulvestrant	SD	0%	14	NA
AI	Doyen et al.(56)	2009	15	NA	NA	Anastrozole, Letrozole, or Exemestane	2 CR (13%), 4 PR (27%), 2 SD (13%), 7 PD (47%)	40%	4.4	33
Fulvestrant	De La Haba Rodriguez et al.(57)	2009	1	positive	negative	fulvestrant	PR	100%	NA	NA
Fulvestrant	Masci et al.(58)	2011	5	NA	NA	NA	1/5 PR, 2/5 SD, 2/5 PD	20%	6, 12 and 22	NA
AI +/- aLHRH	Zagouri et al.(59)	2013	23	positive	negative	exemestane (17,4%), letrozole or anastrozole (82,6%) +/- aLHRH	6 PR (26.1%), 13 SD (56.5%), and 4 PD (17.4%)	26,10%	13	39
AI + aLHRH	Vici et al.(60)	2013	19	positive	negative (5 unknown)	Letrozole + aLHRH	2 CR (10.5 %), 7 PR (36.8 %), 7 SD (36.8%), and 3 PD (15.8%)	47.4%	12.5	35.8
Everolimus and Tamoxifen	Kattan et al.(61)	2014	1	positive	negative	everolimus + tamoxifen	PR	100%	NA	NA
Tamoxifen and AI	Bradley et al.(62)	2014	35	NA	NA	Tamoxifen and aromatase inhibitors	Tamoxifen: CR 2/11, PR 5/11, SD 1/11, PD 3/11, ORR = 64% ; Aromatase inhibitors 0/24 CR, 2/24 PR, 9/24 SD, 13/24 PD	NA	NA	NA
AA +/- aLHRH	Di Lauro et al.(63)	2014	36	positive (64%)	NA	CPA +/- aLHRH	4 CR (11.1%), 15 PR (41.7%), 11 SD (30.5%), 6 PR (16.5%)	52.8%	8.9	24.3
AI or AA +/- LHRH analogs	Di Lauro et al.(64)	2015	60	positive	NA	AI or CPA +/- aLHRH	NA	51.3% aLHRH vs 43.5% (p=0.6)	11 aLHRH vs 6 (p=0,05)	29.7 aLHRH vs 22 (p=0.05)
Fulvestrant	Zagouri et al.(65)	2015	23	positive	negative (82.6%)	Fulvestrant	CR 0%, PR 26%, SD 48%, PD 22%	26%	5	NA
Everolimus and Exemestane	Ballatore et al.(66)	2016	1	positive	negative	everolimus + exemestane	PR	100%	NA	NA

Table 11. Published literature of palliative hormonal therapy in metastatic male breast cancer.

Keys: AI = aromatase inhibitor, AA = anti-androgen, aLHRH = LHRH analogues, OS = overall survival, PFS = progression free survival, ORR = overall response rate, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NA = not available.

We report on a population of 23 men with HER2+ disease. This population is really rare and few specific data are reported. We show that these patients have a similar PFS and OS than women (respectively, 11.6 vs 14.4 months (p=0.84) and 42.5 vs 34.9 (p=0.83)). This is an important information as only few men have been included in clinical trials, 2 (0.2%) in CLEOPATRA Trial, 5 in EMILIA (0.5%) and TH3RESA, 0.6%.[67-69]

We have to admit some limits that hinder our conclusions. First of all, we are aware of the retrospective nature of data collection for these patients. Moreover, as most of analyses were realised in subgroup with small number of patients, confidence intervals (CI) are sometimes very wide and upper limit cannot be estimated (notably when this upper limit exceeds the follow-up time). Thus, our results must be considered with caution.

However, as previously explained with SWOG-S0511 trial, such a rare disease makes it difficult to include a significant number of patients prospectively. Then previous published cohorts are either small or incomplete, preventing from drawing conclusions.

Compared to these studies, we present a very comprehensive description of characteristics of the disease and management. And with 149 cases, our study reports one of the largest cohort of metastatic male breast cancer.

Although the risk of bias is not zero, the comprehensive collection of patient in the ESME database prevents some biases of selection, and using a matched-cohort design we tried to control some confounding factors. Finally, led on a recent restricted period (6 years from January 1st, 2008 to December 31st, 2014), our results were probably less impacted by the evolution of treatment strategies than in other studies.

Conclusion.

Our study shows that despite the existence of characteristics discrepancies, the management of metastatic breast cancer in men leads to similar outcomes than women, especially in HR+/HER2- patients that represents almost 80% of cases. To our knowledge, this is one of the largest reported cohort of metastatic male breast cancer describing management and comparing its results. It appears that men are not always treated following recommendations notably as regards of the first choice of HT in metastatic setting, and the co-administration of LHRH analogues when AI is prescribed. Larger studies are needed in order to fully elucidate the role of GnRHa in male breast cancer.

Male breast cancer is actually a challenging research subject. Some prospective trials are ongoing and their results would probably lead to better comprehension of this disease:

1. *The EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program* will probably bring some answers to improve our knowledge of this particular disease.

2. *CLARITY-01 (ID NCT02580448), CYP17 lyase and androgen receptor inhibitor treatment:* This is an open-label, Phase 2 study of seviteronel (an oral selective CYP17 lyase inhibitor and androgen-receptor blocker) in subjects with TNBC or ER+/HER2- unresectable locally advanced male and women breast cancer. Primary objective is to estimate clinical benefit rate at 16 and 24 weeks, and secondary objectives will measure efficacy in terms of overall response rate (ORR) and PFS, and safety profile.

3. *MALE (ID NCT01638247):* A prospective, randomised multi-centre phase II study evaluating the adjuvant, neoadjuvant or palliative treatment with tamoxifen +/- GnRH analogue versus aromatase inhibitor + GnRH analogue in male breast cancer patients. Primary objective is to determine estradiol suppression between the three arms. Secondary objectives regard efficacy as overall response, compliance and safety profile. For the time being, 56 patients have been enrolled in this study. Final results would be presented at ESMO meeting 2018.

APPENDIX

Table 1. Main risk factors for breast cancer in men

Age[22]	
Genetic factors	
Well established	Family history[7]
	BRCA2 (BRCA1) [8-10,23]
Possible	PALB2[24,25]
	CHEK2[26-29]
	CYP17[30]
	PTEN[31]
	RAD51B[32]
	Other nucleotidic polymorphisms[33]
	Ethnic group[22]
Abnormal estrogen-to-androgen ratio	Klinefelter's syndrome[34,35]
	Obesity[7,35]
	Orchitis/Epididymitis[36]
	Exogenous testosterone use[37]
Environmental factors	Lack of exercise[7]
	Liver cirrhosis[38]
	Radiation[39,40]

Table 2. Characteristics of metastatic disease in men

Characteristics	Category	Men N=149 (%)
Age at diagnosis	< 50 years	7 (4.7%)
	[50 – 70 years]	78 (52.3%)
	> 70 years	64 (43%)
Mean age at diagnosis ; SD		68.05 ; SD = 11.23
Median age at diagnosis ; range		69 ; 44 – 90
Performans Status	PS 0	29 (37.7%)
	PS 1	32 (41.6%)
	PS 2	10 (13%)
	PS 3	6 (7.8%)
	PS 4	0 (0%)
	Missing	72
Histological subtypes	Triple Negative	6 (4.5%)
	HER2+	23 (17.2%)
	HR+/HER2-	105 (78.3%)
	Missing	15
HR status	Negative	9 (6.1%)
	Positive	138 (93.9%)
	Unknown	2
HER2 status	Negative	111 (82.8%)
	Positive	23 (17.2%)
	Unknown	15
Localization of metastases		
	Bone	94 (63.1%)
	Liver	21 (14.1%)
	Lung	68 (45.6%)
	Brain	4 (2.7%)
	Lymph node	44 (29.5%)
	Skin	11 (7.4%)
	Other	16 (10.7%)
	Visceral	92 (61.7%)
	Non Visceral	57 (38.3%)
Number of metastatic sites	< 3	111 (74.5%)
	≥ 3	38 (25.5%)
Number of metastatic sites (Mean)		1.85
Settings	De novo	49 (32.9%)
	Relapsing disease	100 (67.1%)
Delay between primitive and relapse	[6 - 24[	26 (26%)
	≥ 24	74 (74%)
Median delay between primitive and relapse		52.5 months

Table 3. Characteristics of primitive tumor for relapsing men

Characteristics	Category	Men n=100 (%)
Age at diagnosis (years)	< 50	14 (14%)
	[50 - 70]	56 (56%)
	> 70	30 (30%)
Mean age at diagnosis - SD		62.89 ; SD = 11.67
Median (range)		62 (40 – 86)
Classification TNM : T	Tx/T0/Tis	0 (0%)
	T1	14 (33%)
	T2	20 (47.6%)
	T3	0 (0%)
	T4	8 (19.1%)
	Missing	58
Classification TNM : N	Nx	0 (0%)
	N0	22 (52.4%)
	N1	15 (35.7%)
	N2	3 (7.1%)
	N3	2 (4.8%)
	Missing	58
Primitive tumor grade	Grade I	9 (9.7%)
	Grade II	36 (38.7%)
	Grade III	48 (51.6%)
	Missing	7
Primitive tumor ER status	Negative	6 (6.1%)
	Positive	92 (93.9%)
	Missing	2
Primitive tumor PR status	Negative	27 (27.8%)
	Positive	70 (72.2%)
	Missing	3
Primitive tumor HR status	Negative	5 (5.1%)
	Positive	93 (94.9%)
	Unknown	2
Primitive tumor HER2 status	Negative	69 (88.5%)
	Positive	9 (11.5%)
	Unknown	22
Histology	Invasive ductal carcinoma	91 (97.8%)
	Invasive lobular carcinoma	0 (0%)
	Mix	0 (0%)
	Other	2 (2.2%)
	Missing	7
Adjuvant treatment	Chemotherapy therapy	62 (62%)
	Anthracyclines	54 (54%)
	Taxanes	36 (36%)
	Trastuzumab	3 (3%)
	Radiotherapy	84 (84%)
	Hormonotherapy	86 (86%)

Table 4. Characteristics of metastatic disease in men compared to women in ESME database

Characteristics	Category	Men n=149 (%)	Women n=16 552 (%)	p-value (2-sided)
Age at diagnosis	< 50 years	7 (4.7%)	3784 (22.9%)	**<0.0001**
	[50 – 70 years]	78 (52.3%)	8544 (51.6%)	
	> 70 years	64 (43%)	4224 (25.5%)	
Mean age at diagnosis ; SD		68.05 ; SD = 11.23	60.57 ; SD = 13.77	**<0.0001**
Median age at diagnosis ; range		69 ; 44 – 90	61 ; 19 – 99	
Histological subtypes				**0.0009**
	Triple Negative	6 (4.5%)	2315 (15.5%)	**0.0005**
	HER2+	23 (17.2%)	2840 (19%)	0.62
	HR+/HER2-	105 (78.3%)	9815 (65.6%)	**0.0019**
	Missing	15	1582	
ER status	Negative	13 (8.8%)	3731 (23.3%)	<0.0001
	Positive	134 (91.2%)	12303 (76.7%)	
	Unknown	2	518	
PR status	Negative	45 (30.8%)	6674 (43.1%)	0.0029
	Positive	101 (69.2%)	8822 (56.9%)	
	Unknown	3	1056	
HR status	Negative	9 (6.1%)	3442 (21.4%)	**<0.0001**
	Positive	138 (93.9%)	12609 (78.6%)	
	Unknown	2	501	
HER2 status	Negative	111 (82.8%)	12194 (81.1%)	0.6112
	Positive	23 (17.2%)	2840 (18.9%)	
	Unknown	15	1518	
Localization of metastases				
	Bone	94 (63.1%)	9418 (56.9%)	0.1289
	Liver	21 (14.1%)	4470 (27%)	**0.0004**
	Lung	68 (45.6%)	4035 (24.4%)	**<0.0001**
	Brain	4 (2.7%)	1196 (7.2%)	0.0326
	Lymph node	44 (29.5%)	4434 (26.8%)	0.4520
	Skin	11 (7.4%)	1823 (11%)	0.1581
	Other	16 (10.7%)	1711 (10.3%)	0.8728
	Visceral	92 (61.7%)	9579 (57.9%)	0.3405
	Non Visceral	57 (38.3%)	6973 (42.1%)	0.3405
Number of metastatic sites	< 3	111 (74.5%)	13230 (79.9%)	0.0996
	≥ 3	38 (25.5%)	3322 (20.1%)	
Mean number of metastatic sites (Mean)		1.85	1.75	0.2184
Settings	De novo	49 (32.9%)	4754 (28.7%)	0.2636
	Relapsing disease	100 (67.1%)	11798 (71.3%)	
Delay between primitive and relapse	[6 - 24[	26 (26%)	2159 (13.1%)	0.081
	≥ 24	74 (74%)	9634 (58.4%)	

Table 5. Characteristics of primary disease in men compared to women for in ESME database (*de novo* and relapsing)

Characteristics	Category	Men n=149 (%)	Women n=16 552 (%)	p-value (2-sided)
Age at diagnosis	< 50 years	17 (11.4%)	6241 (37.8%)	**<0.0001**
	[50 – 70 years]	81 (54.4%)	7801 (47.3%)	
	> 70 years	51 (34.2%)	2465 (14.9%)	
Mean age at diagnosis		64.31	55.02	**<0.0001**
Classification TNM : T	Tx/T0/Tis	0 (0%)	363 (4.8%)	0.1212
	T1/T2	44 (62.9%)	4185 (55.2%)	
	T3/T4	26 (37.1%)	3028 (40%)	
	Missing	79	8976	
Classification TNM : N	Nx	2 (2.9%)	316 (4.4%)	0.5393
	N0	27 (38.6%)	3142 (43.3%)	
	N1/N2/N3	41 (58.6%)	3796 (52.3%)	
	Missing	79	9298	
Primitive tumor grade	Grade I	10 (7.3%)	1153 (7.9%)	0.7836
	Grade II	63 (46%)	7082 (48.4%)	
	Grade III	64 (46.7%)	6407 (43.8%)	
	Missing	12	1910	
Primitive tumor ER status	Negative	12 (8.2%)	3822 (24.9%)	**<0.0001**
	Positive	134 (91.8%)	11526 (75.1%)	
	Missing	3	1204	
Primitive tumor PR status	Negative	44 (30.3%)	6331 (42.6%)	0.0029
	Positive	101 (69.7%)	8514 (57.4%)	
	Missing	4	1707	
Primitive tumor HR status	Negative	9 (6.2%)	3547 (23.1%)	**<0.0001**
	Positive	137 (93.8%)	11822 (76.9%)	
	Unknown	3	1183	
Primitive tumor HER2 status	Negative	103 (83.7%)	10987 (81.4%)	**0.5061**
	Positive	20 (16.3%)	2511 (18.6%)	
	Unknown	26	3054	
Histology	Invasive ductal	133 (95.7%)	12404 (80.3%)	**<0.0001**
	Invasive lobular	2 (1.4%)	2185 (14.1%)	
	Mix	1 (0.7%)	258 (1.7%)	
	Other	3 (2.2%)	598 (3.9%)	
	Missing	10	1107	
Adjuvant treatment				
	Chemotherapy or	62 (62%)	8223 (70%)	0.0830
	Anthracyclines	54 (54%)	7472 (63.5%)	0.0497
	Taxanes	36 (36%)	5242 (44.5%)	0.0867
	Trastuzumab	3 (3%)	1048 (8.9%)	0.0379
	Radiotherapy	84 (84%)	10311 (87.5%)	0.2936
	Hormonotherapy	86 (86%)	7809 (66.3%)	<0.0001

Table 6. Characteristics of metastatic disease in men and in a matched cohort of women

Characteristics	Category	Men n=149 (%)	Women n=149 (%)	p-value (2-sided)
Age at diagnosis	< 50 years	7 (4.7%)	7 (4.7%)	1
	[50 – 70 years]	78 (52.3%)	78 (52.3%)	
	> 70 years	64 (43%)	64 (43%)	
Mean age at diagnosis ; SD		68.05 ; SD = 11.23	68.07 ; SD = 11.28	0.9877
Performans Status	PS 0	29 (37.7%)	30 (36.6%)	0.40
	PS 1	32 (41.6%)	29 (34.5%)	
	PS 2	10 (13%)	10 (12.2%)	
	PS 3	6 (7.8%)	10 (12.2%)	
	PS 4	0 (0%)	3 (3.7%)	
	Missing	72	67	
Histological subtypes	Triple Negative	6 (4.5%)	6 (4.5%)	1
	HER2+	23 (17.2%)	23 (17.2%)	
	HR+/HER2-	105 (78.3%)	105 (78.4%)	
	Missing	15	15	
Localization of metastases	Bone	94 (63.1%)	87 (58.4%)	0.4063
	Liver	21 (14.1%)	38 (25.5%)	**0.0135**
	Lung	68 (45.6%)	37 (24.8%)	**0.0002**
	Brain	4 (2.7%)	4 (2.7%)	1
	Lymph node	44 (29.5%)	41 (27.5%)	0.7003
	Skin	11 (7.4%)	14 (9.4%)	0.5307
	Other	16 (10.7%)	21 (14.1%)	0.3798
	Visceral	92 (61.7%)	92 (61.7%)	1
	Non Visceral	57 (38.3%)	57 (38.3%)	
Number of metastatic sites	< 3	111 (74.5%)	117 (78.5%)	0.4123
	≥ 3	38 (25.5%)	32 (21.5%)	
Mean number of metastatic sites		1.85 ; SD=1.05	1.75 ; SD=1.05	0.4073
Settings	De novo	49 (32.9%)	49 (32.9%)	1
	Relapsing disease	100 (67.1%)	100 (67.1%)	
Delay between primitive and relapse	[6 - 24[	26 (26%)	10 (10%)	**0.0131**
	≥ 24	74 (74%)	90 (90%)	
Median delay between primitive and relapse		52.5 months	81 months	**0.0002**

Table 7. Characteristics of the primitive tumor in men compared to matched women for relapsing patients

Characteristics	Category	Men n=100 (%)	Women n=100 (%)	p-value (2-sided)
Age at diagnosis (years)	< 50	14 (14%)	21 (21%)	0.1757
	[50 - 70]	56 (56%)	59 (59%)	
	> 70	30 (30%)	20 (20%)	
Mean age at diagnosis - SD		62.89 ; SD = 11.67	59.85 ; SD=12.37	0.0764
Median (range)		62 (40 – 86)	60 (35 – 91)	
Classification TNM : T	Tx/T0/Tis	0 (0%)	3 (5.8%)	**0.0157**
	T1	14 (33%)	9 (17.3%)	
	T2	20 (47.6%)	26 (50%)	
	T3	0 (0%)	8 (15.4%)	
	T4	8 (19.1%)	6 (11.5%)	
	Missing	58	48	
Classification TNM : N	Nx	0 (0%)	4 (7.8%)	0.4118
	N0	22 (52.4%)	26 (51%)	
	N1	15 (35.7%)	17 (33%)	
	N2	3 (7.1%)	3 (5.9%)	
	N3	2 (4.8%)	1 (2%)	
	Missing	58	48	
Primitive tumor grade	Grade I	9 (9.7%)	9 (9.7%)	1
	Grade II	36 (38.7%)	36 (38.7%)	
	Grade III	48 (51.6%)	48 (51.6%)	
	Missing	7	7	
Primitive tumor ER status	Negative	6 (6.1%)	9 (9.4%)	0.3964
	Positive	92 (93.9%)	87 (90.6%)	
	Missing	2	4	
Primitive tumor PR status	Negative	27 (27.8%)	31 (35.2%)	0.2791
	Positive	70 (72.2%)	57 (64.8%)	
	Missing	3	12	
Primitive tumor HR status	Negative	5 (5.1%)	7 (7.3%)	0.5267
	Positive	93 (94.9%)	89 (92.7%)	
	Unknown	2	4	
Primitive tumor HER2 status	Negative	69 (88.5%)	70 (86.4%)	0.6979
	Positive	9 (11.5%)	11 (13.6%)	
	Unknown	22	19	
Histology	Invasive ductal	91 (97.8%)	76 (80.9%)	**0.0009**
	Invasive lobular	0 (0%)	12 (12.8%)	
	Mix	0 (0%)	3 (3.2%)	
	Other	2 (2.2%)	3 (3.2%)	
	Missing	7	6	
Adjuvant treatment	Chemotherapy	62 (62%)	66 (66%)	0.5557
	Anthracyclines	54 (54%)	62 (62%)	0.2517
	Taxanes	36 (36%)	40 (40%)	0.5601
	Trastuzumab	3 (3%)	3 (3%)	1
	Radiotherapy	84 (84%)	84 (84%)	1
	Hormonotherapy	86 (86%)	86 (86%)	1

Table 8. Details of frontline HT alone administered in HR+/HER2- metastatic male breast population

Hormonotherapy	Frequence	%
Tamoxifen	16	35.56
Anastrozole	6	13.33
Letrozole	5	11.11
Exemestane	3	6.67
Fulvestrant	2	4.44
Letrozole+Tamoxifen	2	4.44
Anastrozole+Exemestane	1	2.22
Anastrozole+Exemestane+Triptoreline	1	2.22
Anastrozole+Letrozole+Tamoxifen+Triptoreline	1	2.22
Anastrozole+Tamoxifen	1	2.22
Anastrozole+Triptoreline	1	2.22
Fulvestrant+Tamoxifen	1	2.22
Letrozole+Leuproreline+Tamoxifen	1	2.22
Letrozole+Tamoxifen+Triptoreline	1	2.22
Letrozole+Triptoreline	1	2.22
Tamoxifen+Triptoreline	1	2.22
Triptoreline	1	2.22
Total	45	100

Table 9. Details of frontline CT administered in HR+/HER2- metastatic male breast population

Chemotherapy	Frequence	%
Bevacizumab	9	15.25
Paclitaxel	8	13.56
Cyclophosphamide	7	11.86
Capecitabine	6	10.17
Cyclophosphamide+Docetaxel	4	6.78
Bevacizumab+Paclitaxel	3	5.08
Capecitabine+Paclitaxel	3	5.08
Capecitabine+Bevacizumab	2	3.39
Capecitabine+Vinorelbine	2	3.39
Docetaxel	2	3.39
Gemcitabine	2	3.39
Bevacizumab+Eribuline	1	1.69
Capecitabine+Bevacizumab+Cyclophosphamide+Fuorouracile	1	1.69
Capecitabine+Cyclophosphamide	1	1.69
Capecitabine+Cyclophophamide+Paclitaxel+Cyclophosphamide	1	1.69
Capecitabine+Vinorelbine+Bevacizumab	1	1.69
Carboplatine	1	1.69
Cyclophosphamide+Cyclophosphamide	1	1.69
Cyclophosphamide+Paclitaxel	1	1.69
Everolimus	1	1.69
Paclitaxel+Trastuzumab	1	1.69
Vinorelbine	1	1.69
Total	59	100

Table 10. Details of frontline HT administered as maintenance in HR+/HER2- metastatic male breast population

Hormonotherapy	Frequence	%
Tamoxifen	17	56.67
Letrozole	4	13.33
Anastrozole	3	10.00
Anastrozole+Tamoxifen	1	3.33
Exemestane	1	3.33
Exemestane+Letrozole	1	3.33
Exemestane+Letrozole+Leuproreline+Tamoxifen+Triptoreline	1	3.33
Fulvestrant+Letrozole	1	3.33
Gosereline+Letrozole+Tamoxifen	1	3.33
Total	30	100

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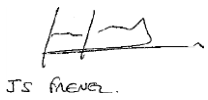

Vu, le Doyen de la Faculté
de Médecine de Tours
à Tours, le

Junien SIRIEIX

54 pages – 11 tableaux – 6 figures

Résumé

Introduction : Dans 1% des cas, le cancer du sein concerne un homme. Partageant certaines caractéristiques avec celui de la femme, il présente néanmoins quelques particularités. Actuellement, les stratégies de traitement sont fondées sur celles de la femme, mais certains auteurs suggèrent que ces recommandations ne sont pas toujours suivies, notamment au stade localisé. Les données sont plus réduites au stade métastatique. Nous souhaitons donc, à partir d'une base de données nationale, fournir une analyse complète de la prise en charge du cancer du sein de l'homme au stade IV.

Matériel et méthodes : La plateforme ESME est une base de données rétrospective de "vie réelle" réalisée au sein de 18 CLCC. Elle comprend les données de tous les cancers du sein ayant débuté leur prise en charge métastatique entre janvier 2008 et décembre 2014. Tous les cas d'hommes ont été retrouvés et comparés à la population totale de femmes, et à une cohorte de femmes appariées (1/1) sur l'âge, les caractéristiques immuno-histochimiques, le grade, la présence d'une hormonothérapie adjuvante, le caractère viscéral ou non des métastases, ainsi que leur découverte *de novo* ou non. L'objectif premier était la description complète des caractéristiques et du management du cancer du sein métastatique de l'homme. Les objectifs secondaires étaient la description des traitements et de leurs résultats en termes de survie globale (SG) et de survie sans progression (SSP), ainsi que la comparaison avec la cohorte appariée.

Résultats : Sur 16 701 patients évaluables, 149 (0.89%) hommes ont été identifiés. La médiane d'âge était de 69 ans pour les hommes. La proportion de profil RH+/HER2- était de 78,4%, les HER2+ représentaient 17,1% et les triples négatifs 4,5%. Le carcinome canalaire infiltrant était l'histologie la plus fréquente (95,7%).
Dans la population appariée, la SG était statistiquement similaire entre les hommes et les femmes: 41,8 mois et 34,9 mois (p=0,74), respectivement.
Dans la population RH+/HER2-, 45/105 (42.9%) hommes ont reçu une première ligne de traitement par hormonothérapie (HT) exclusive: anti-oestrogène (19/45), anti-aromatase (18/45) dont 3 avec co-administration d'agoniste de la LHRH, et une autre HT pour 8/45. La SSP médiane était de 9,8 mois (m) sans différence significative entre anti-oestrogène et anti-aromatase. Comparée aux femmes, la SSP était similaire: 9,8m versus 13m (p=0,8). Pour ceux ayant reçu une chimiothérapie en première ligne (éventuellement suivie d'une hormonothérapie de maintenance), soit 59/105 (56.1%), la SSP médiane était de 9,5 mois et n'était pas différente de celle des patients ayant eu une hormonothérapie seule (p=0,22). Globalement, la SG des patients RH+/HER2- était de 41,8 mois et la SSP de 9,5 mois. Pour les HER2+, la SSP médiane en première ligne était de 11,6 mois et la SG de 42,5 mois sans différence significative avec les femmes. Enfin, la SSP et la SG atteintes par les patients triples négatifs étaient respectivement de 11,4 mois (bornes; 4,7 – 34,3) et 43,7 mois (bornes; 8,9 – 64,8).

Conclusion : Nous rapportons les résultats de l'une des plus importantes séries de cancers du sein métastatique chez l'homme. Comparativement aux femmes, il semble que le pronostic et l'effet des traitements soient comparables. Il apparait également que, comme en adjuvant, les hommes ne soient pas toujours traités selon les recommandations, notamment en ce qui concerne le choix de l'hormonothérapie de première intention, ou la co-administration d'un agoniste de la LHRH quand une anti-aromatase est prescrite. D'autres études sont nécessaires afin de mieux personnaliser la prise en charge des cancers mammaires métastatiques masculins.

Mots clés : cancer sein de l'homme, métastatique, hormonothérapie, cohorte appariée de femmes.

Jury :

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