Données clinico-biologiques pronostiques des carcinomes métaplasiques de haut grade

Olivier TREDAN, MD PhD

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Liens d’intérêt :

Roche, Pfizer, Novartis-Sandoz, Lilly, MSD, Astra-Zeneca, Pierre Fabre, Seagen, Daiichi-Sankyo, Gilead, Eisai, Menarini-Stemline, Veracyte

Introduction :

Bas grade	Haut grade

Adénosquameux
Fibromatosis-like

	purs	mixtes
Fusiforme	100%	%
Epidermoïde	100%	%
Mésenchymateux	100%	%
		%
		%
		+/- CI-NS

Composant métaplasique

métaplasique = entité hétérogène

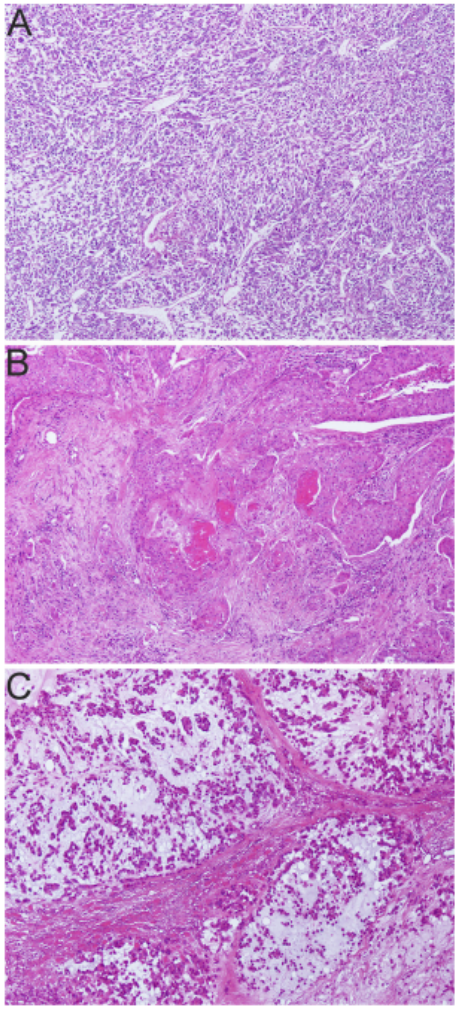
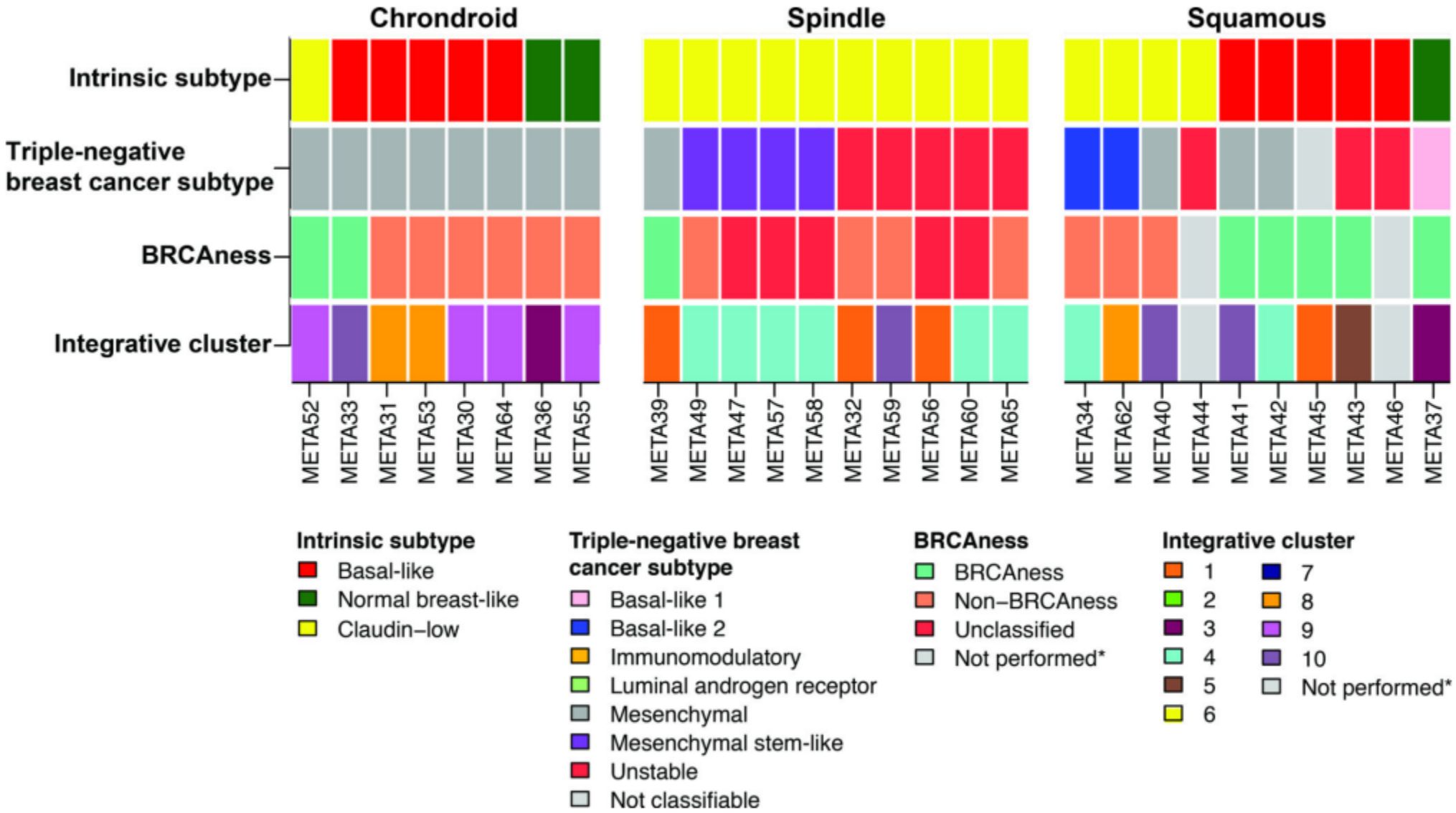


Figure 1. Representative micrographs of histologic subtypes of metaplastic breast cancers included in this study
(a) Metaplastic breast carcinoma with spindle cell metaplasia, (b) with squamous metaplasia, and (c) with mesenchymal elements (chondroid metaplasia). Original magnification ×40.

Weigelt B, et al. Mod Pathol 2015;28(3):340-51

Introduction :



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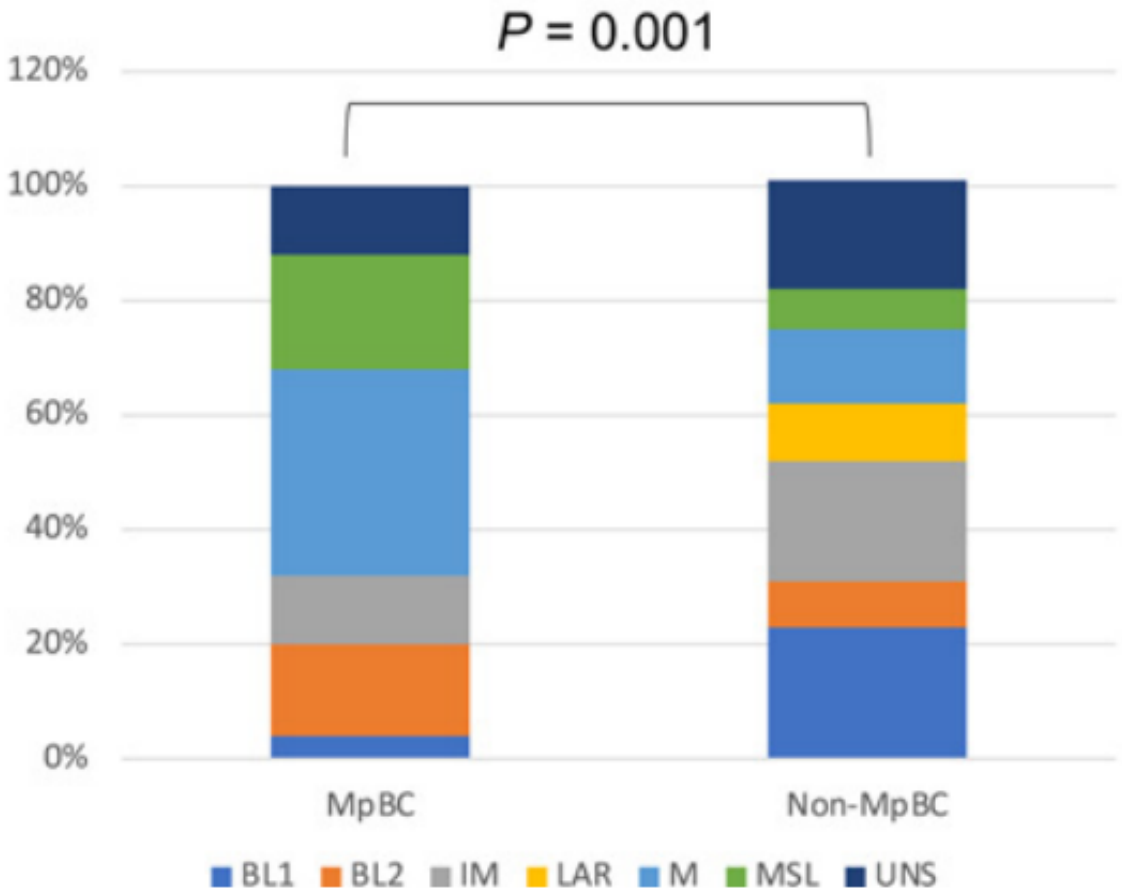
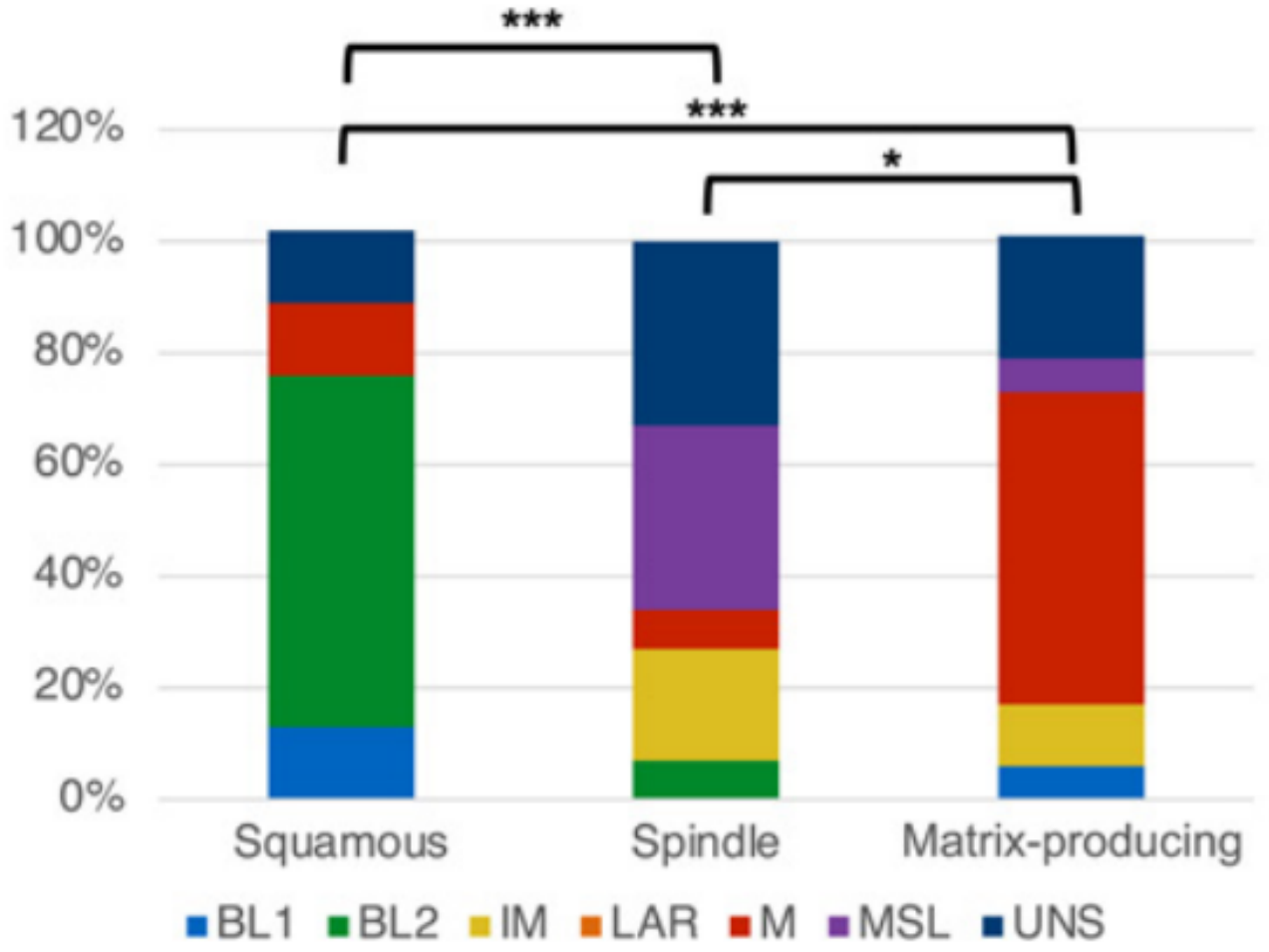




Yam C, et al. Clin Cancer Res 2022;28(13):2878-2889

Introduction :

- quid des facteurs histo-pronostiques habituels et moléculaires :
  - **grade III** (70% des cas) ?
  - **triple-négative** (> 80% des cas) *vs* RH+/HER2+++ ?
  - marqueurs de différenciation basale CK5/6, CK14, EGFR ??
  - activation des voies PI3K ou MAPK / Wnt ??
- reste la taille et l'envahissement ganglionnaire !

Introduction :

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 23 June 2022
doi: 10.3389/fonc.2022.924342

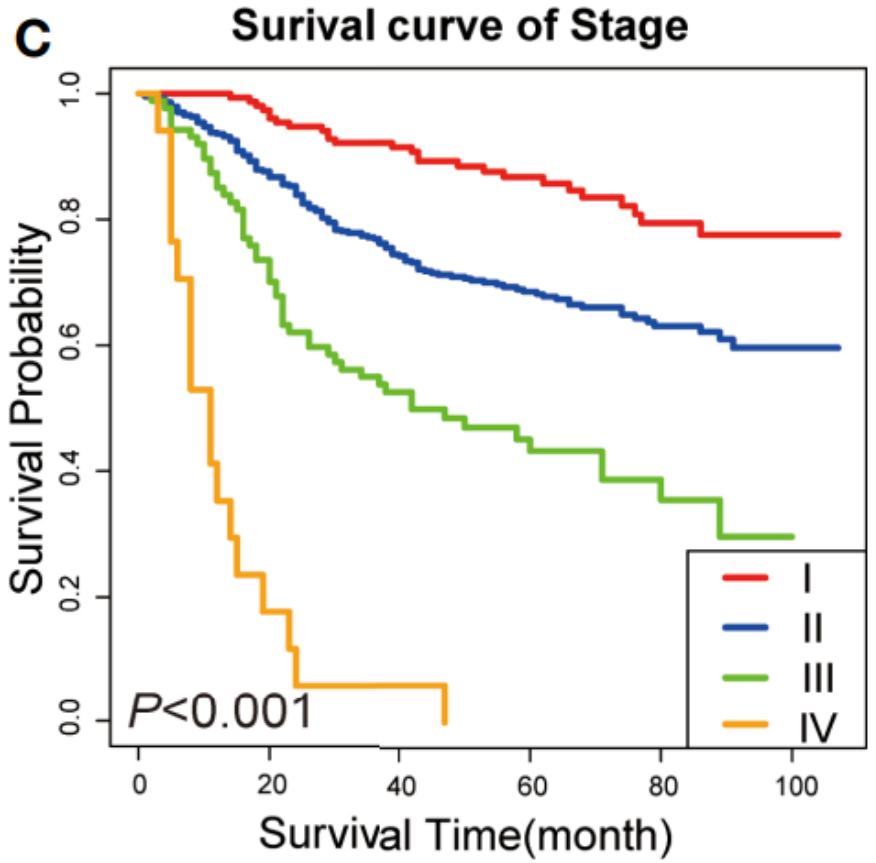
Prognostic Factor Analysis and Model Construction of Triple-Negative Metaplastic Breast Carcinoma After Surgery

Keying Zhu†, Yuyuan Chen†, Rong Guo†, Lanyi Dai, Jiankui Wang, Yiyin Tang, Shaoqiang Zhou, Dedian Chen and Sheng Huang**

près de 1.000 ptes SEER

TABLE 2 | Univariate and multifactorial Cox analysis of risk factors in TN MpBC patients after surgery.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (yrs.)				
<63	Reference		Reference	
≥63	1.644 (1.268–2.131)	<0.001*	1.283 (0.959–1.717)	0.094
Clinical stage				
I	Reference		Reference	
II	2.336 (1.538–3.548)	<0.001*	2.968 (1.285–6.858)	0.011*
III	5.256 (3.273–8.441)	<0.001*	4.497 (1.597–12.663)	0.004*
IV	29.673 (15.809–55.694)	<0.001*	40.977 (11.044–152.045)	<0.001*



1. pur *vs* mixte ?

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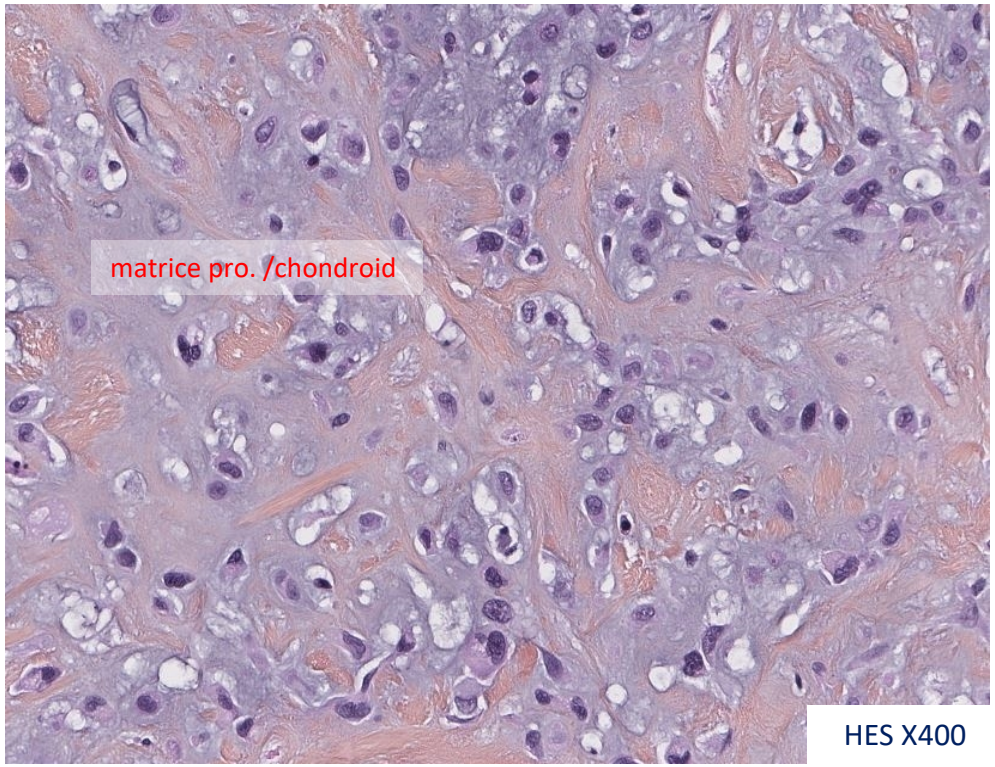


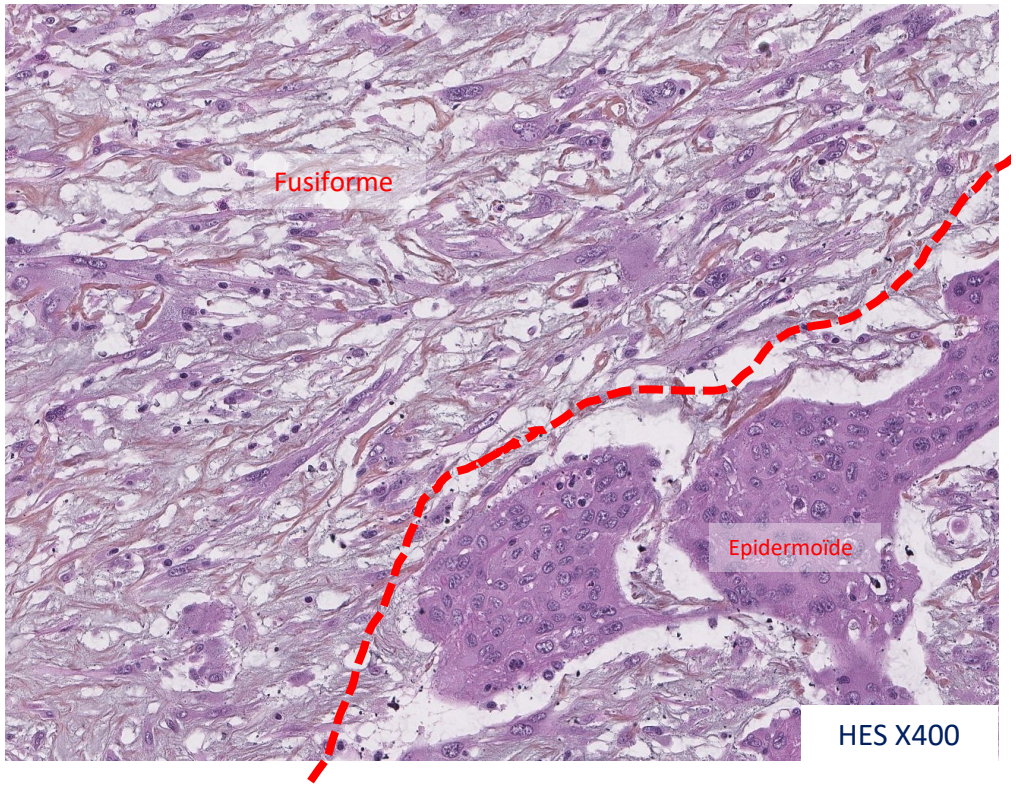
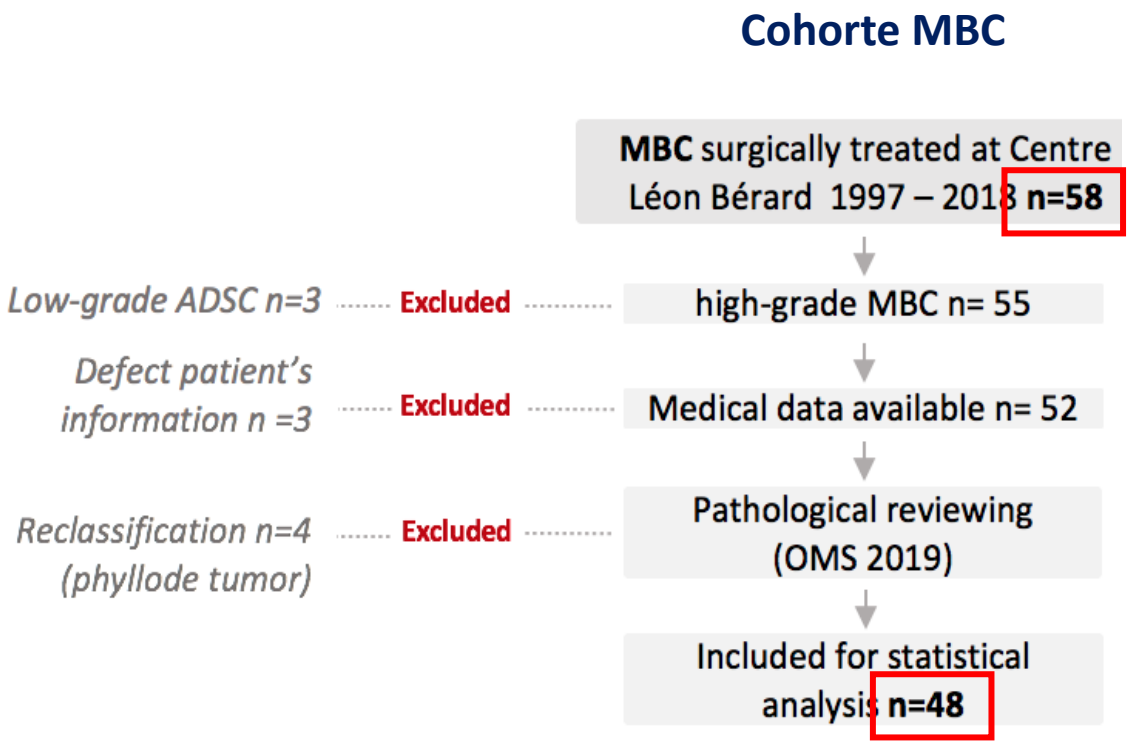


Photo : laboratoire de biopathologie CLB
V. Cockenpot / I. Treilleux

1. pur *vs* mixte : thèse de M. Laurent



Etude **rétrospective**

CJP : **survie globale**

MBCs Metaplastic Breast Cancer; HG-TN-MBCs High Grade Triple Negative MBCs; TN-IDCs Triple Negative Invasive Ductal Carcinoma; Low-grade ADSC : Low-grade adenosquamous carcinoma.

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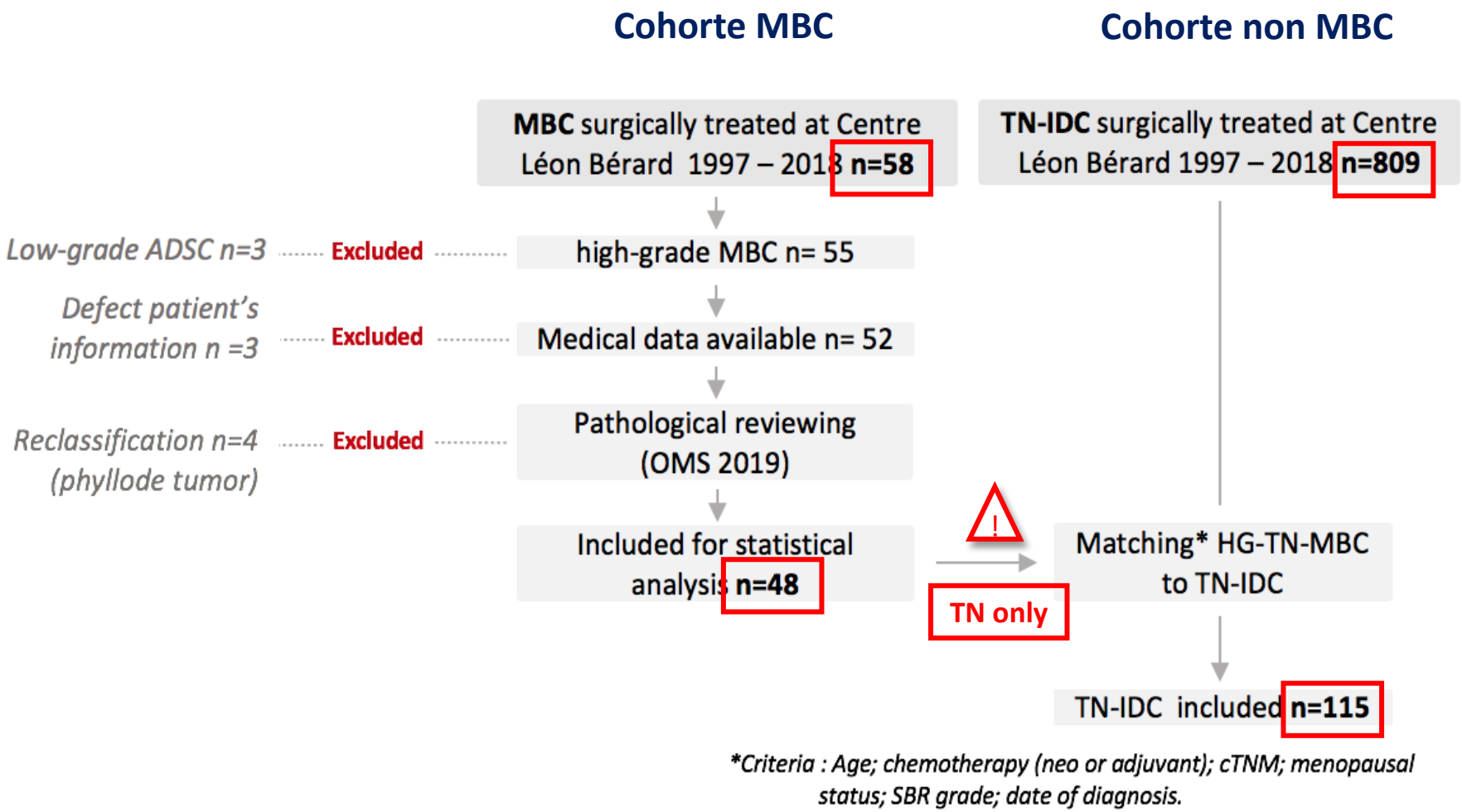

Etude **rétrospective**

CJP : **survie globale**

Design : **appariement** 3:1

Analyse statistique : Modèle de Cox stratifié sur strates d' appariement

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1. pur *vs* mixte : thèse de M. Laurent

Histologic features	n (%)
Pure metaplastic	
Squamous	8 (20%)
Spindle	2 (5%)
Mesenchymal	5 (13%)
Mixed metaplastic	
Mixed metaplastic with NST	
Spindle – NST	5 (13%)
Squamous – NST	2 (5%)
Mesenchymal – NST	6 (15%)
Mesenchymal – squamous –NST	1 (3%)
Mixed metaplastic whithout NST	
Squamous – spindle	4 (10%)
Squamous – mesenchymal	2 (5%)
Reclassified	
Phyllode tumor (low grade)	1 (3%)
Phyllode tumor (high grade)	3 (8%)

Détails - histologie

(n=39)

- Reclassés : 11%
- Sous-types
  - Purs : 38%
  - Mixtes : 51%

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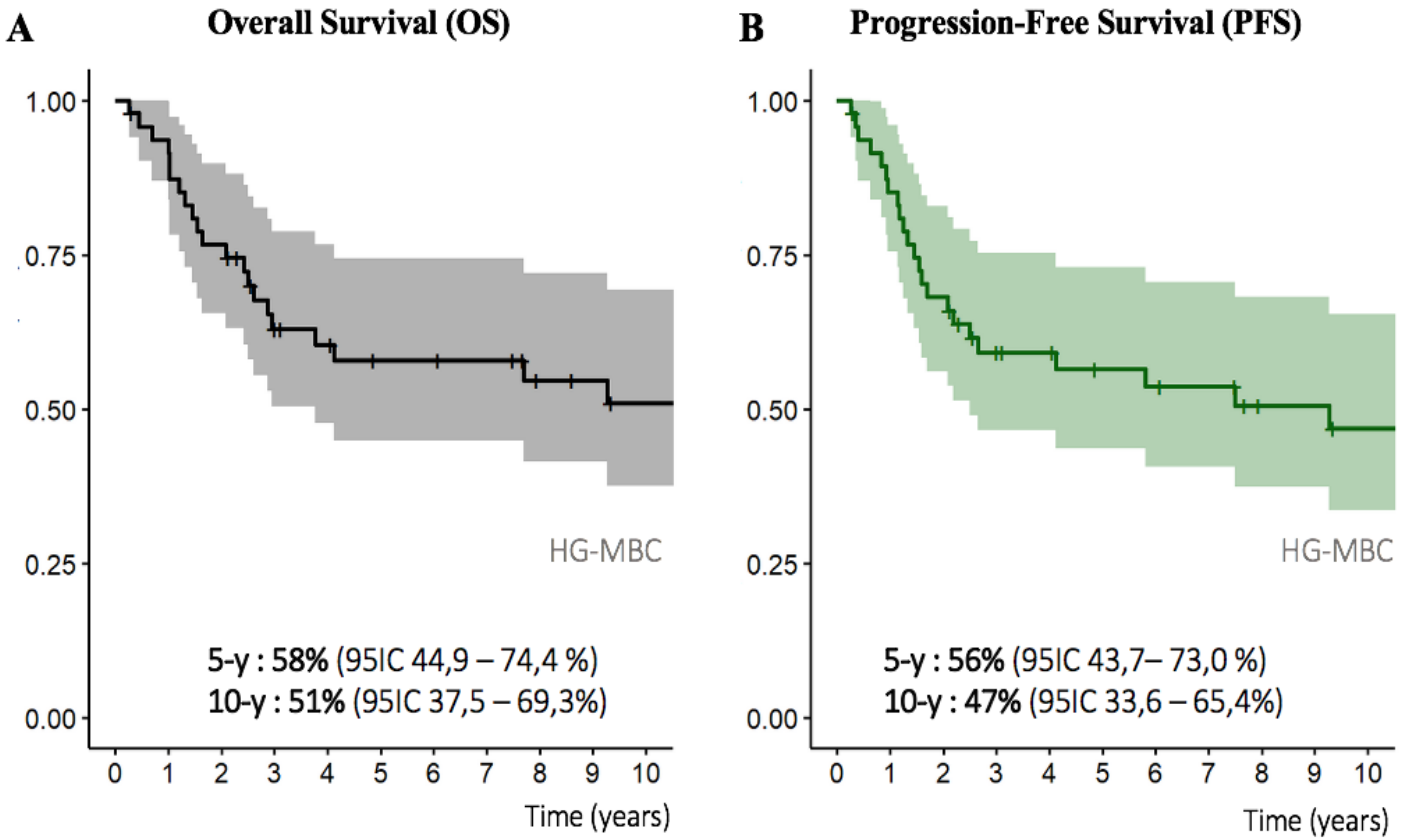

Données de survie à 10 ans

- Médiane suivi **11 ans** (8 – 16)
- SG 51% (IC95% 37,5 – 69,3%)
- SSP 47% (IC 95% 33,6 – 65,4%)

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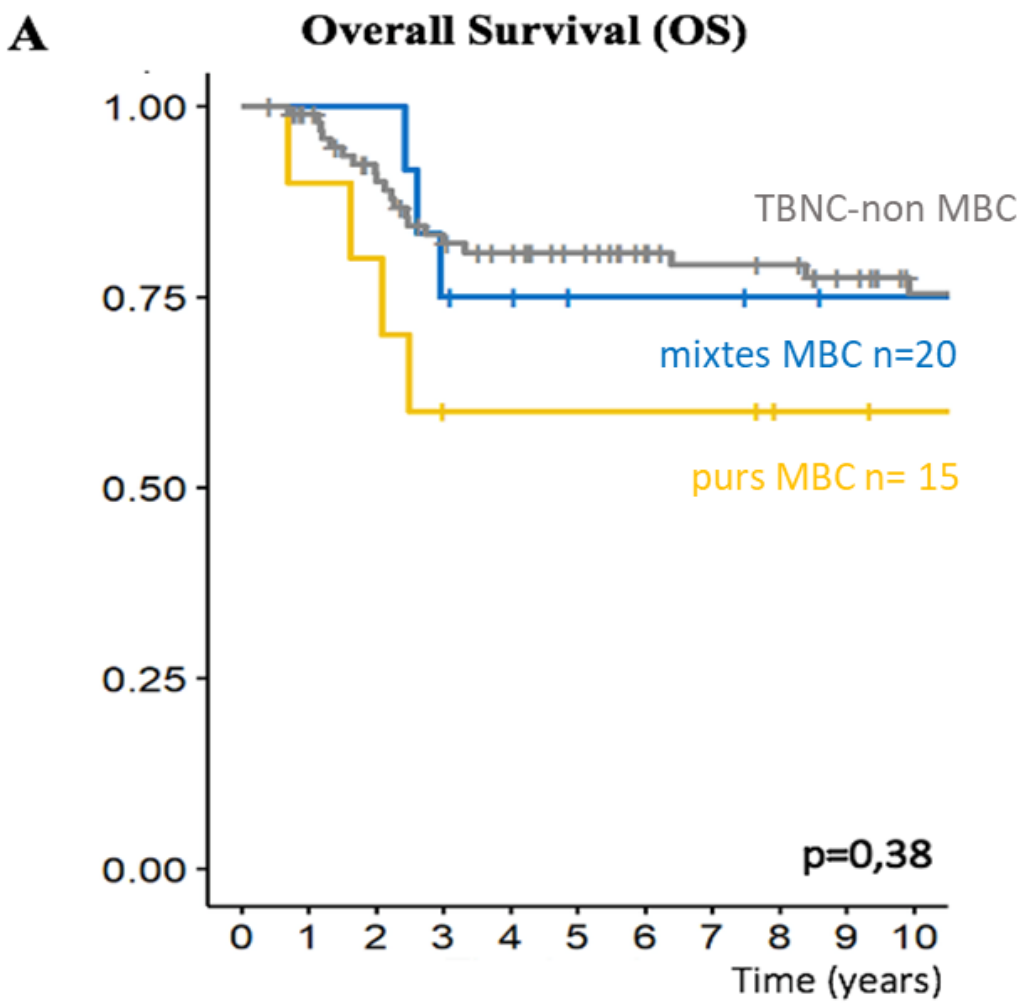
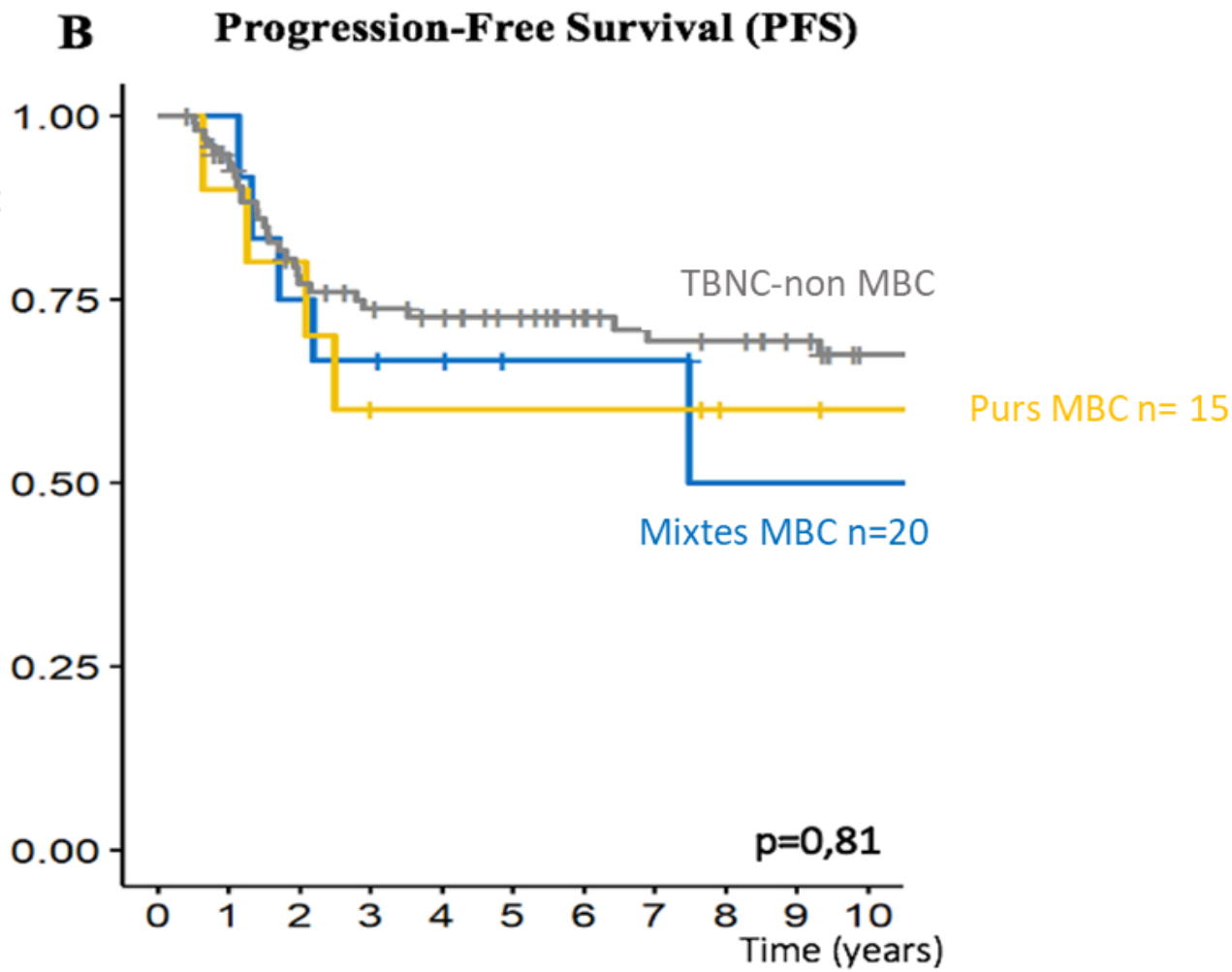




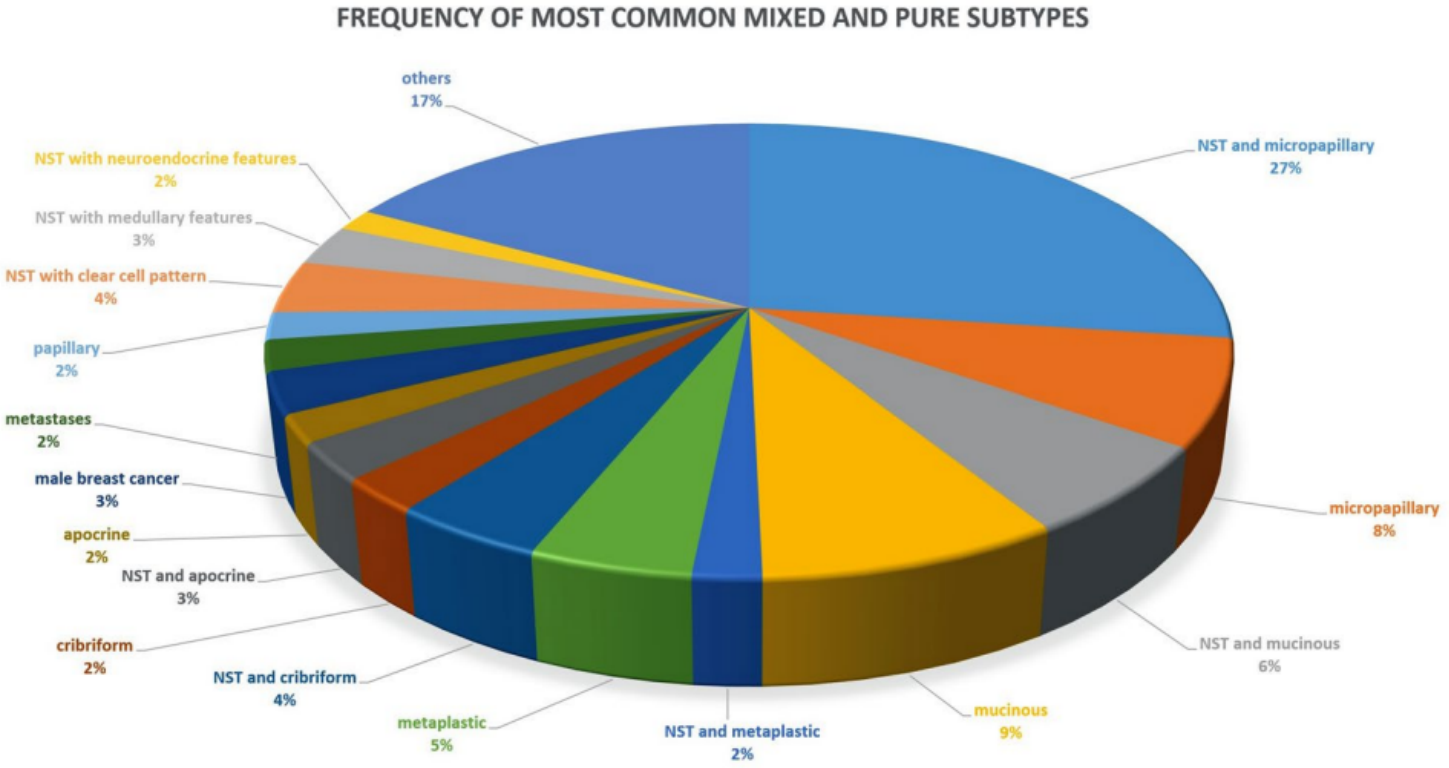
1. pur *vs* mixte :

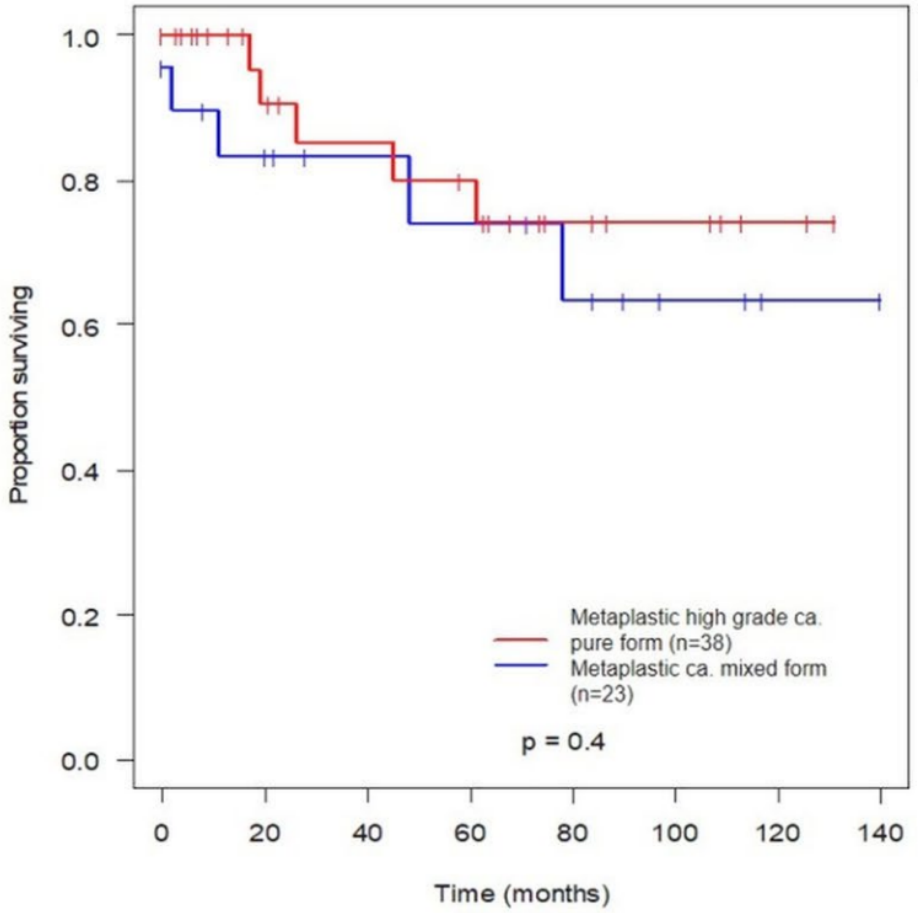
Journal of Cancer Research and Clinical Oncology (2023) 149:4967–4978
https://doi.org/10.1007/s00432-022-04443-x

RESEARCH

Prognostic relevance of mixed histological subtypes in invasive breast carcinoma: a retrospective analysis

Anna Rechsteiner[1] · Daniel Dietrich[2] · Zsuzsanna Varga[1]





1. pur *vs* mixte :

Breast Cancer Research and Treatment (2023) 200:23–36
https://doi.org/10.1007/s10549-023-06945-9

PRECLINICAL STUDY

The mixed subtype has a worse prognosis than other histological subtypes: a retrospective analysis of 217 patients with metaplastic breast cancer

Jiayue Hu[1] · Ronggang Lang[2] · Weipeng Zhao[1] · Yongsheng Jia[1] · Zhongsheng Tong[1] · Yehui Shi[1]

Table 1 Clinicopathological characteristics of MpBC and IDC-NST in a 1:1 ratio matching

		MpBC ($N=217$) (%)	IDC-NST ($N=217$) (%)	P value
Age at diagnosis				0.998
< 40 years		25(11.5)	24(11.1)	
40 ~ 65 years		168(77.4)	169(77.9)	
> 65 years		24(11.1)	24(11.1)	
Histological type				
Pure	Pure Squamous	33(15.2)	NA	
	Pure Spindle	27(12.4)	NA	
With mesenchymal differentiation		59(27.2)	NA	
Mixed	Mixed squamous	53(24.4)	NA	
	Mixed spindle	45(20.7)	NA	
Molecular type				0.997
HR-HER2-		151(69.6)	153(70.5)	
HR + HER2-		52(24.0)	50(23.0)	
HR-HER2 +		11(5.1)	11(5.1)	
HR + HER2 +		3(1.4)	3(1.4)	
HR status				0.912
Negative		162 (74.7)	164(75.6)	
Positive		55(25.3)	53(24.4)	

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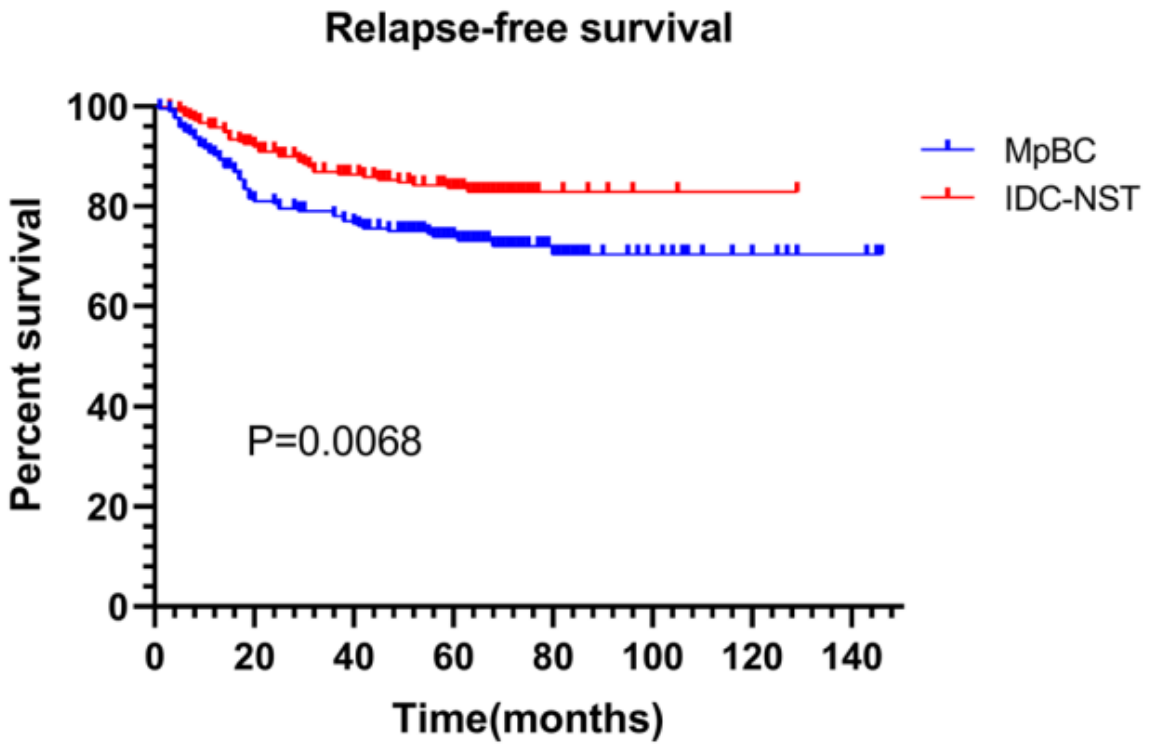

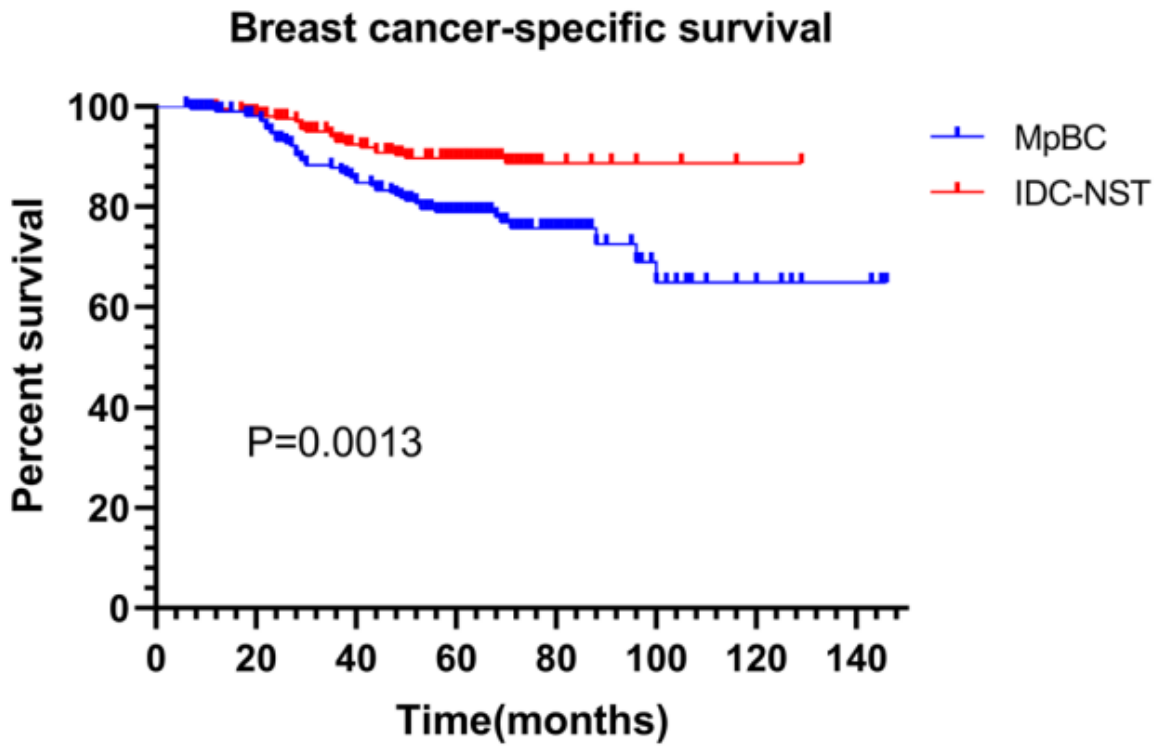

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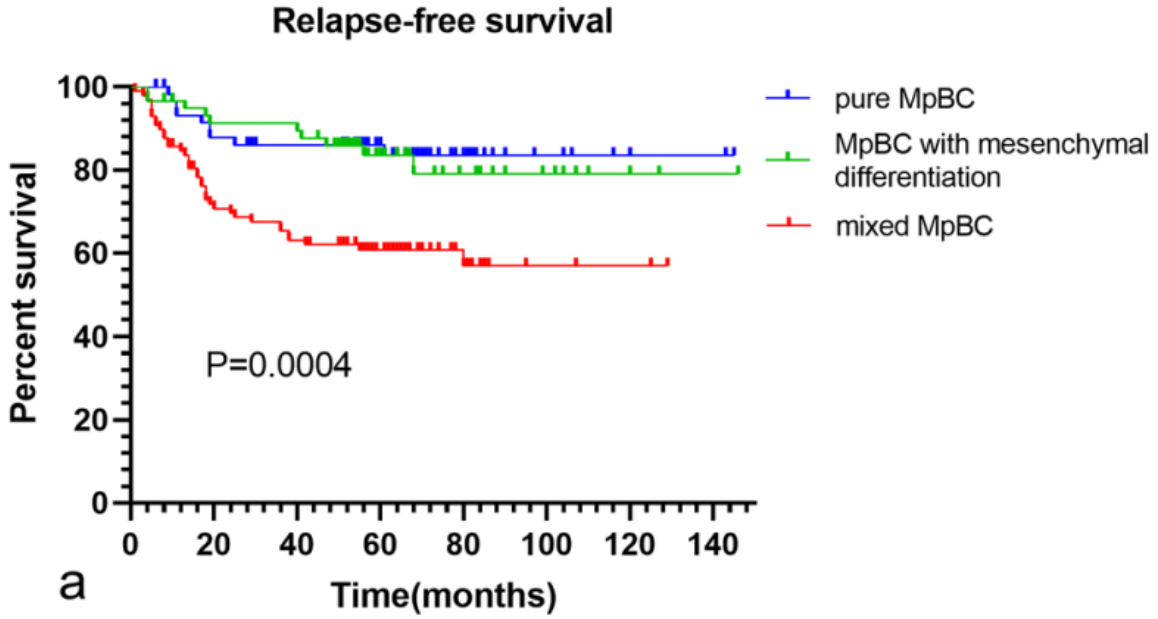

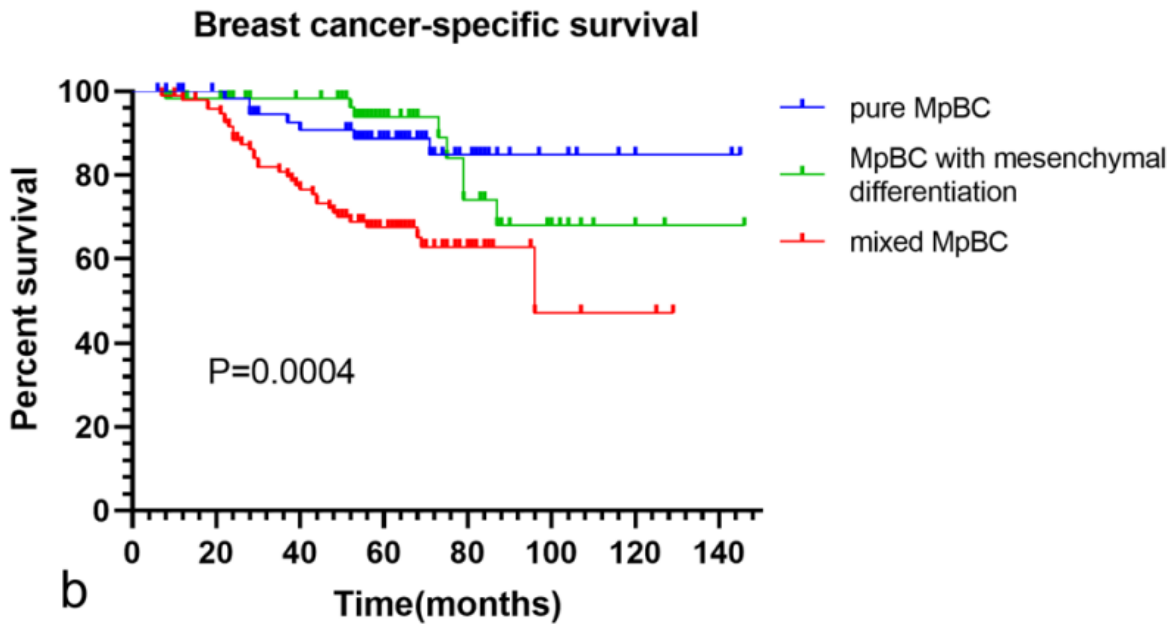

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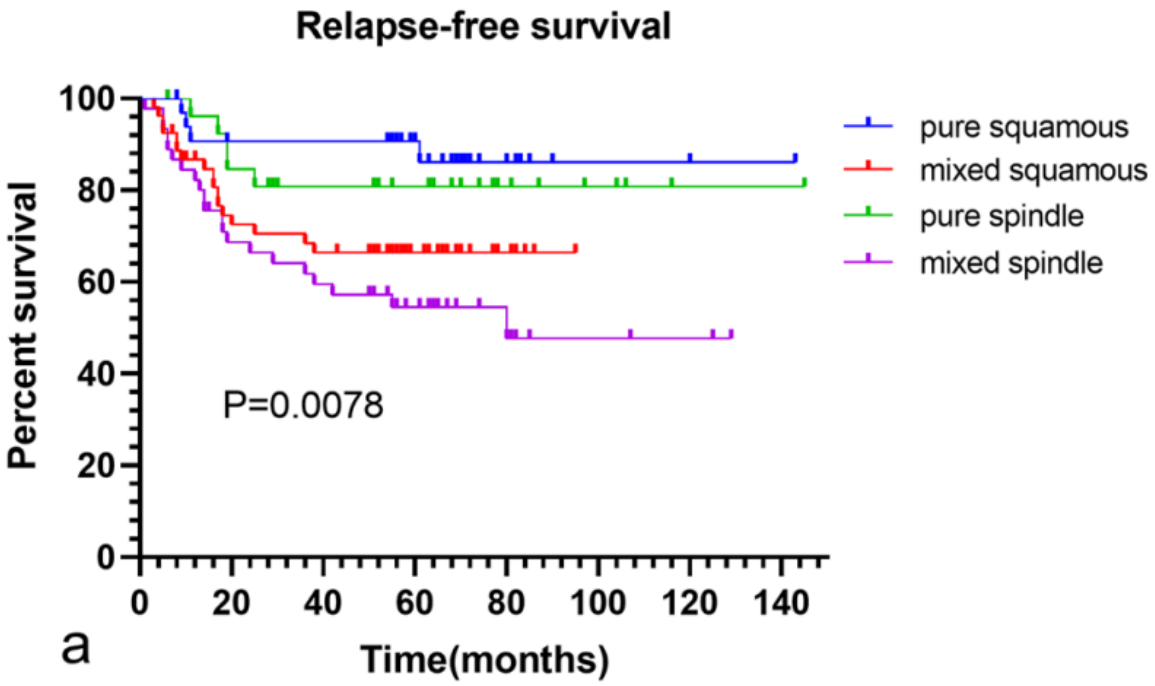

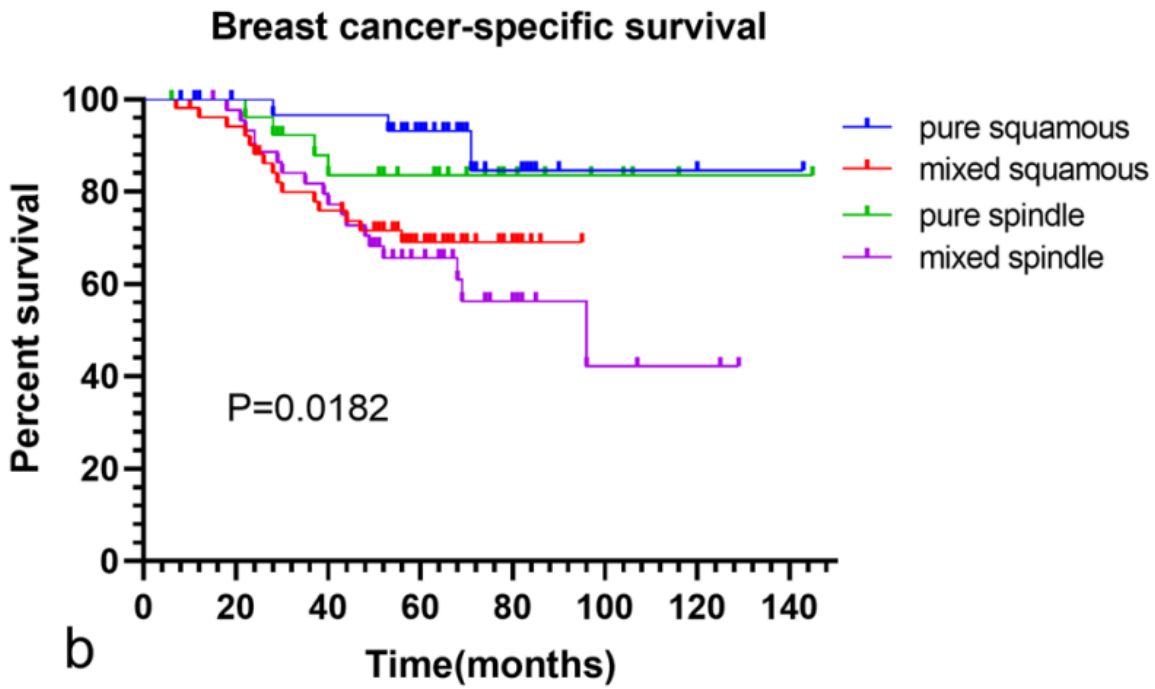

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Table 3 Multivariate Cox regression analysis of prognostic factors for MpBC patients

	RFS Hazard ratio (95%CI)	*P* value	BCSS Hazard ratio (95%CI)	*P* value
AJCC stage		0.029*		0.011*
0-I	Ref		Ref	
II	2.698(1.046–6.956)	0.040*	5.439 (1.286–22.999)	0.021*
III	4.294(1.463–12.600)	0.008*	10.080(2.153–47.199)	0.003*
Histological type		0.012*		0.027*
Pure vs. with mesenchymal differentiation	1.229(0.498–3.037)	0.654	1.321(0.476–3.666)	0.593
Pure vs. mixed	2.626(1.253–5.502)	0.011*	2.731(1.183–6.305)	0.019*
With mesenchymal differentiation vs. mixed	2.136(1.043–4.371)	0.038*	2.067(0.931–4.591)	0.075
Chemotherapy				
No	Ref		Ref	
Yes	0.271(0.126–0.584)	0.001*	0.260(0.117–0.576)	0.001*

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Table 4 Clinicopathological characteristics of MpBC between histological subtypes

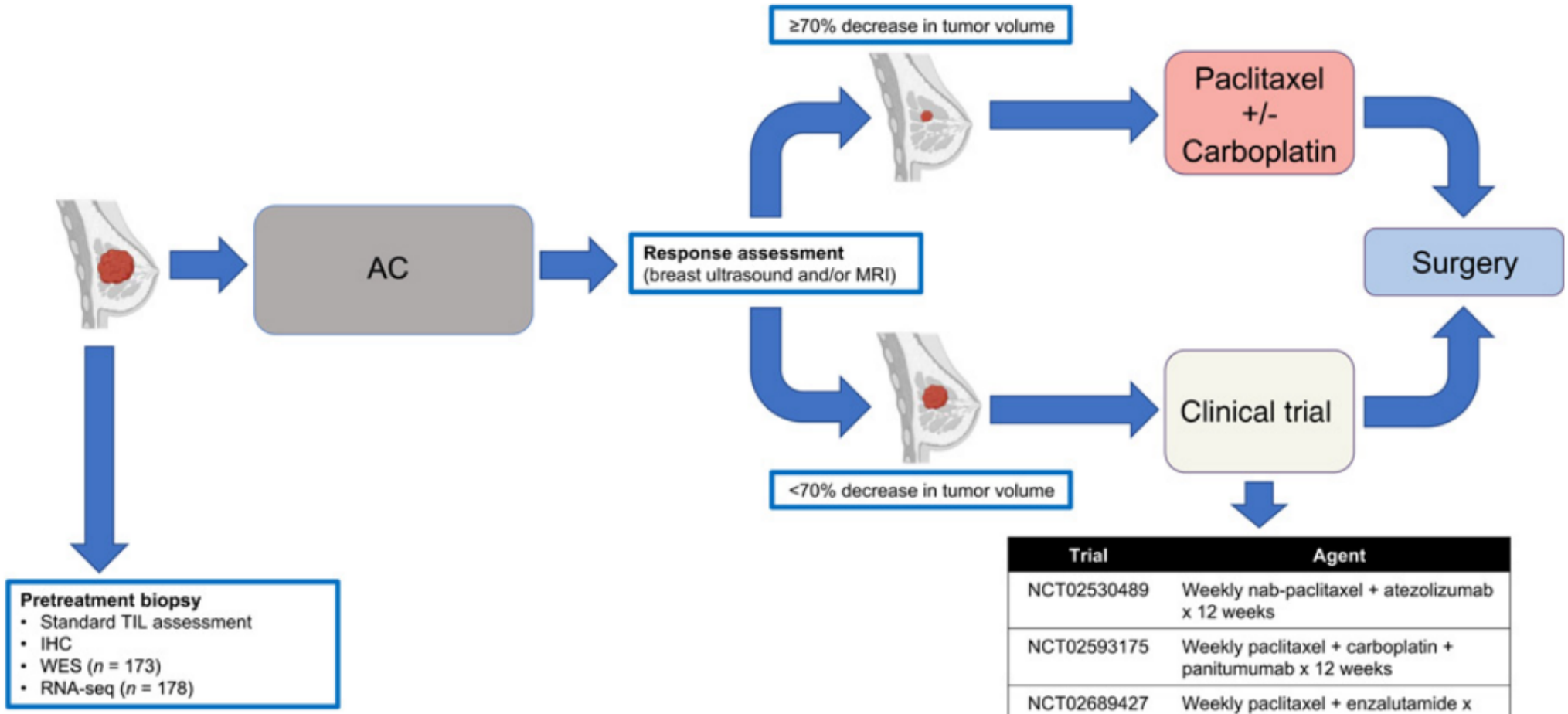
	Pure ($N=60$) (%)	With mesenchymal differentiation ($N=59$) (%)	Mixed ($N=98$) (%)	P value
Age at diagnosis				0.545
<40 years	5(8.3)	9(15.3)	11(11.2)	
40~65 years	46(76.7)	46(78.0)	76(77.6)	
>65 years	9(15.0)	4(6.8)	11(11.2)	
Lymph node metastases				0.024*
N0	50(83.3)	46(78.0)	60(61.2)	
N1	7(11.7)	9(15.3)	21(20.4)	
N2–3	3(5.0)	4(6.8)	17(17.3)	
HER2 status				0.032*
Negative	58(96.7)	58(98.3)	87(88.8)	
Positive	2(3.3)	1(1.7)	11(11.2)	
KI-67 index				P<0.001*
<30%	17(28.3)	5(8.5)	6(6.1)	
≥30%	41(68.3)	50(84.7)	91(92.9)	
Unknown	2(3.3)	4(6.8)	1(1.0)	

trastu ?

2. place de la chimiothérapie ?

2. place de la chimiothérapie :

Etude prospective (NCT02276443) du MD Anderson Cancer Center néoadj. TNBC pour transfert



Trial	Agent
NCT02530489	Weekly nab-paclitaxel + atezolizumab x 12 weeks
NCT02593175	Weekly paclitaxel + carboplatin + panitumumab x 12 weeks
NCT02689427	Weekly paclitaxel + enzalutamide x 12 weeks
NCT02456857	Liposomal doxorubicin, bevacizumab, everolimus x 12 weeks

Yam C, et al. Clin Cancer Res 2022;28(13):2878-2889

2. place de la chimiothérapie :

Etude prospective (NCT02276443) du MD Anderson Cancer Center néoadj. TNBC pour transfert

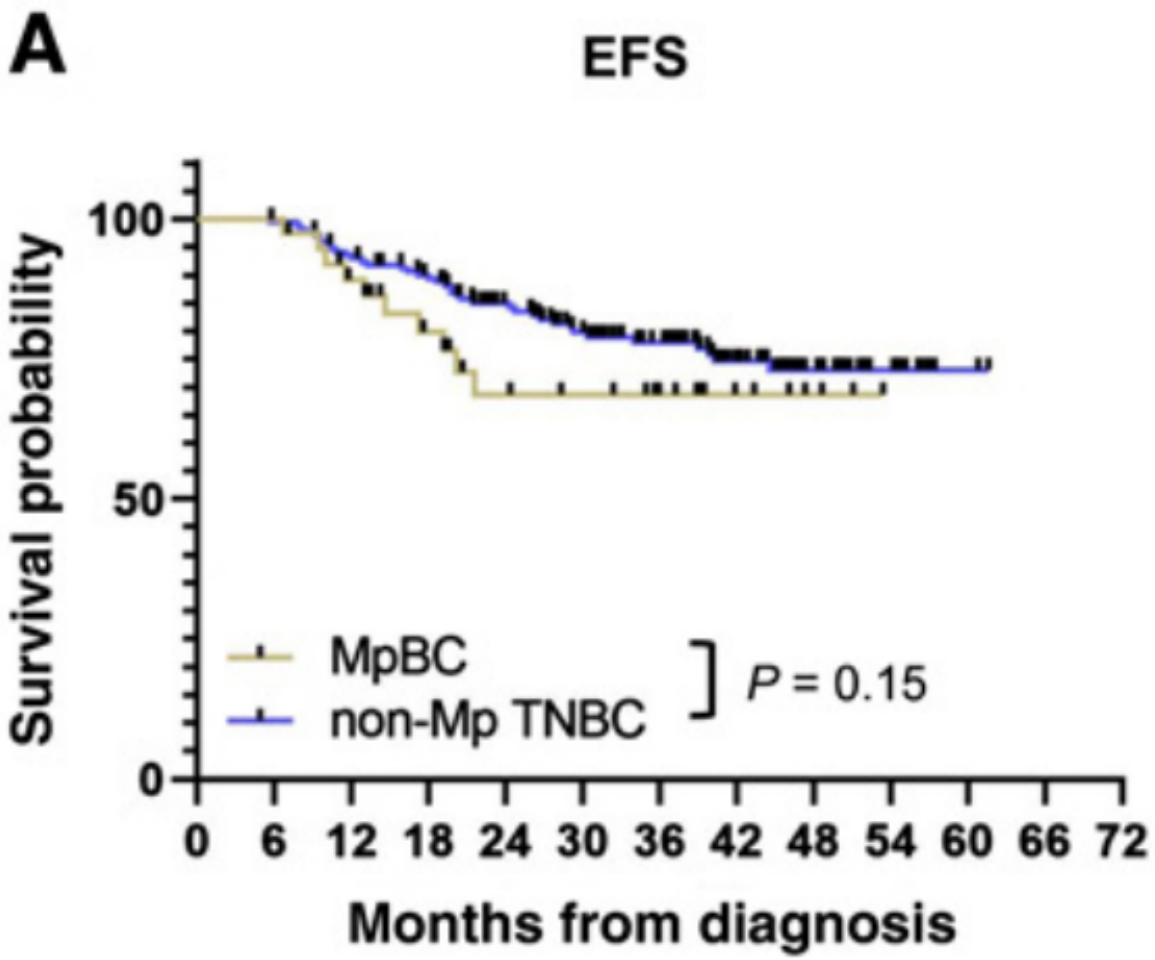
Table 1. Clinicopathologic characteristics and neoadjuvant therapy received.

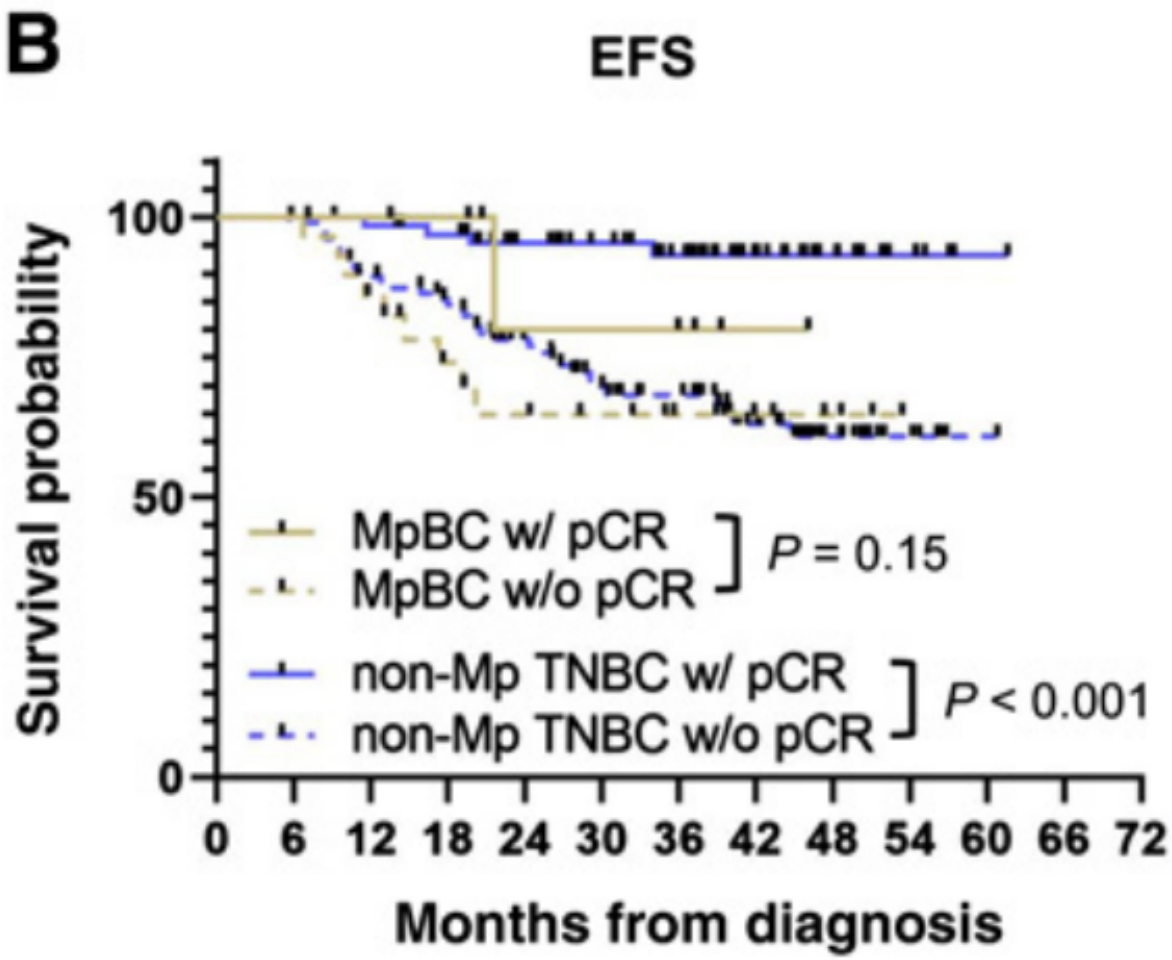
Characteristic		Metaplastic *n* = 39	Non-Mp *n* = 172	Total *n* = 211	*P*
Median age at diagnosis-years (interquartile range)		56.2 (45.6–63.5)	54.9 (45.1–61.1)	55.1 (45.4–61.6)	0.47
Nodal status - *n* (%)	Negative	33 (84.6)	90 (52.3)	123 (58.3)	<**0.001**
	Positive	6 (15.4)	82 (47.7)	88 (41.7)	
TNM stage - *n* (%)	I	5 (12.8)	15 (8.7)	20 (9.5)	0.35
	II	28 (71.8)	114 (66.3)	142 (67.3)	
	III	6 (15.4)	43 (25.0)	49 (23.2)	
Histologic grade - *n* (%)	1	1 (2.6)	0	1 (0.5)	**0.04**
	2	9 (23.1)	22 (12.8)	31 (14.7)	
	3	29 (74.4)	150 (87.2)	179 (84.8)	
Ki-67 - *n* (%)	Low	3 (7.7)	8 (4.7)	11 (5.2)	**0.03**
	Moderate	12 (30.8)	28 (16.3)	40 (19.0)	
	High	21 (53.9)	133 (77.3)	154 (73.0)	
	Missing	3 (7.7)	3 (1.7)	6 (2.8)	
Metaplastic subtype - *n* (%)	Matrix producing	18 (46.2)[a]			
	Spindle	14 (35.9)			
	Squamous	5 (12.8)			
	Mixed spindle/matrix producing	2 (5.1)			

Yam C, et al. Clin Cancer Res 2022;28(13):2878-2889

2. place de la chimiothérapie :

Etude prospective (NCT02276443) du MD Anderson : 23 % de pCR !!





Yam C, et al. Clin Cancer Res 2022;28(13):2878-2889

2. place de la chimiothérapie néoadjuvante :

Études (nb de patientes en néoasjuvant)	Schéma de traitement	Nb de patientes avec pCR
Cimino-Mathews A, et al. 2016 (6)	AC > T	1 (16 %)
Han M, et al. 2019 (29)	AC > T	5 (17 %) dont 1 avec HER2+++
Al-Hilli Z, et al. 2019 (18)	AC +/- T +/- carbo	2 (11 %) dont 1 avec mutation *BRCA2*
Wong W, et al. 2021 (44)	AC > T	1 (2 %) avec une mutation *BRCA1*
Abada E, et al. 2022 (29)	?	4 (14 %)
Yam C, et al. 2022 (39)	AC > T +/- carbo	9 (23 %) dont 3 des 5 carcinomes épidermoïdes
Hu J, et al. 2023 (16)	AC > T +/- carbo	1 (6 %)
Laurent M, et al. 2022 (17)	AC > T	0

2. place de la chimiothérapie néoadjuvante :

Memorial Sloan Kettering Cancer Center

Prospective Evaluation of Pathologic Response with Neoadjuvant Chemo-Immunotherapy in Metaplastic Triple-Negative Breast Cancer

Nour Abuhadra, Yuan Chen, George Plitas, Pedram Razavi, Fresia Pareja, Jorge Reis-Filho, Hannah Wen, Atif Khan, Tiffany Traina, Stephanie Downs-Canner, Mark Robson, Larry Norton, Giacomo Montagna

Background

- Metaplastic breast cancer (MpBC) is a rare aggressive histologic type of breast cancer that is often resistant to standard chemotherapy with reported rates of pathologic complete response (pCR) rates ranging between 2-23%.
- PDL1 expression has been reported in up to 95% of primary MpBCs suggesting that these tumors may respond to immune checkpoint blockade (ICB).
- We sought to prospectively evaluate pCR rates (ypT0/is ypN0) in stage I-III MpBCs treated with neoadjuvant chemo-immunotherapy (NAT).

Methods

- MSKCC Rare Breast Cancer Program (CARE-4-RARE) is a new clinical and translational program dedicated to the study of rare breast cancers (Figure 2.)
- At the time of this abstract 20 patients (pts) with early-stage MpBC have completed treatment with the neoadjuvant KEYNOTE-522 regimen.

CARE-4-RARE. Evaluating Clinical Outcomes And MolecularR Features of RARE Breast Cancer Subtypes; A Prospective Biospecimen Repository.

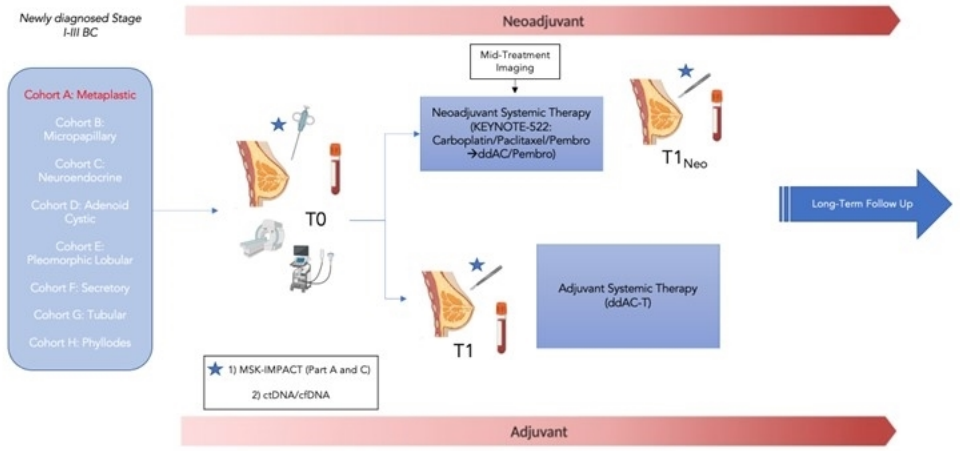


Table 1. Patient Clinicopathological Characteristics

Characteristic		Total Patients N (%)
Overall Clinical Stage – n (%)	I	1 (5)
	II	17 (85)
	III	2 (10)
Metaplastic Subtype – n (%)	Matrix producing	7 (35)
	Spindle	3 (15)
	Squamous	5 (25)
	Mixed	5 (25)
Tumor Mutation Burden (mt/Mb)	Low (<10)	9 (45)
	High (≥10)	0
	Unknown	11 (55)
Tumor Infiltrating Lymphocytes (%)	≥ 10%	2 (10)
	<10%	10 (50)
	Unknown	8 (40)
Pathologic Response	pCR	4 (20)
	Residual Disease	16 (80)
Residual Cancer Burden	RCB-0	4 (20)
	RCB-I	0
	RCB-II	9 (45)
	RCB-III	1 (5)
	Unknown	6 (30)

Conclusions :

➢ <u>pour les carcinomes triple-négatifs métaplasiques de haut grade :</u>

- le stade est encore le facteur pronostique essentiel
- l'hétérogénéité biomoléculaire ne permet pas (encore) une classification pronostique fiable
- les carcinomes mixtes semblent être de moins bon pronostic
- la place de la chimiothérapie néoadjuvante doit-être interrogée !
- l'immunothérapie n'est pas (encore) la solution…
- les thérapies ciblées (voie PI3K, EMT, …)

et les Ac-conjugués restent à évaluer.