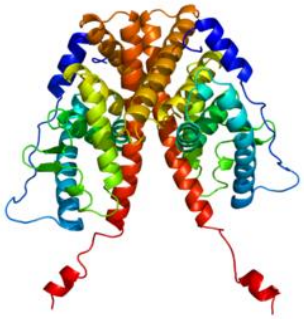
Jusqu'où est il licite d'envisager une désescalade des indications d'hormonothérapie adjuvante pour une tumeur luminale ?

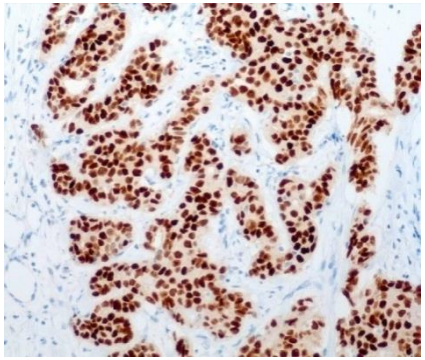
Sylvain LADOIRE



Département d'Oncologie Médicale
Centre Georges François Leclerc

Plateforme UB de Transfert en Biologie Cancérologique

Centre de Recherche INSERM 866
Equipe « Chimiothérapie & réponse immunitaire »
Faculté de Médecine-Université de Bourgogne



DIJON

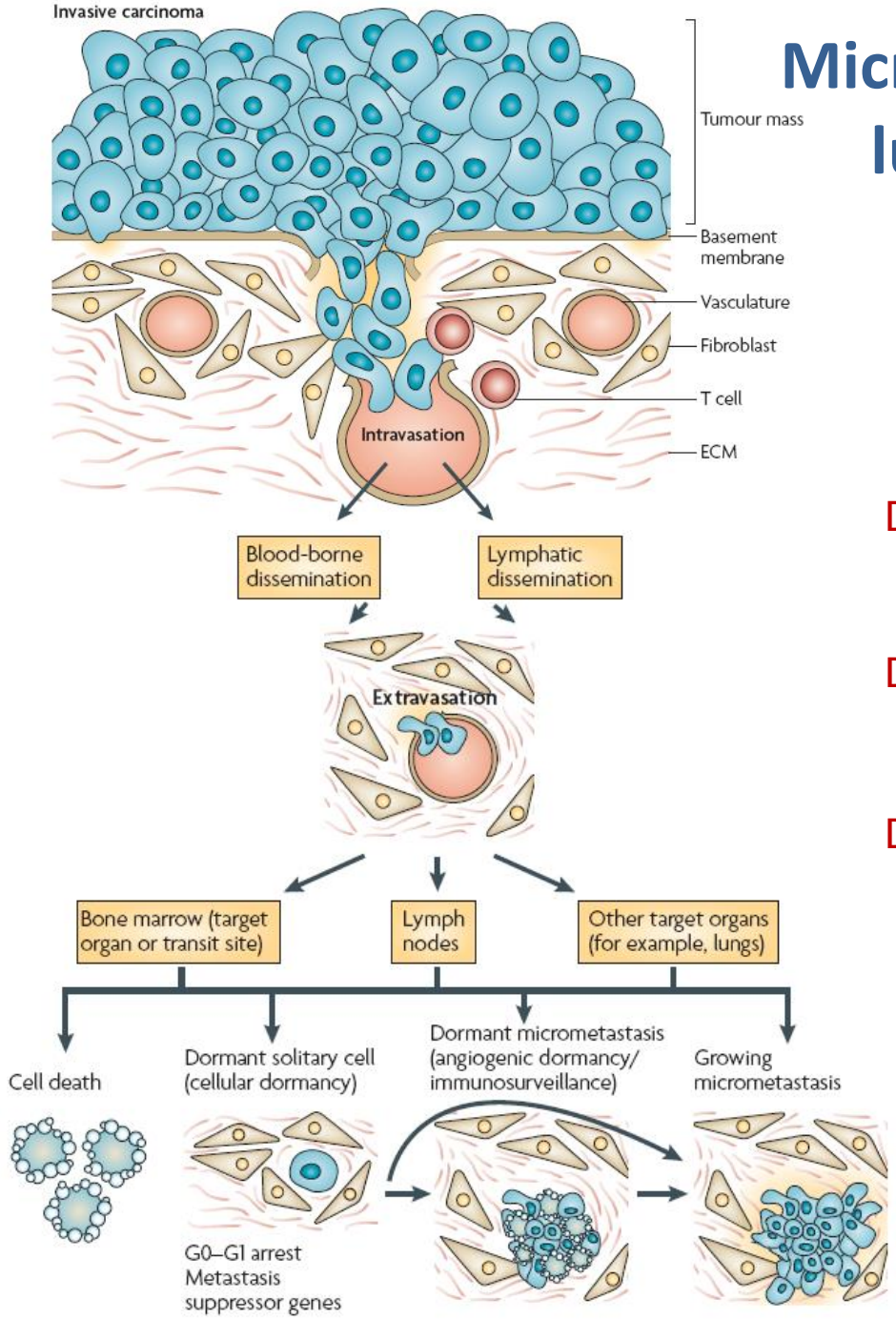
38ES JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE SÉNOLOGIE ET DE PATHOLOGIE MAMMAIRE

CGFL CENTRE GEORGES FRANÇOIS LECLERC
Ensemble, dépassons le cancer

Conflits d'intérêt

	Consulting	Formations	Research grants	Stock-option/patents
Novartis®	X	X		
Pfizer®	X	X	X	
Amgen ®		X		
Esaï ®	X			
Janssen ®		X		
Chugaï ®			X	
Sanofi ®	X	X		
Astellas ®		X		

Micro-métastases des tumeurs luminales: un modèle de DORMANCE



Dormance cellulaire: (G0-G1: quiescence)

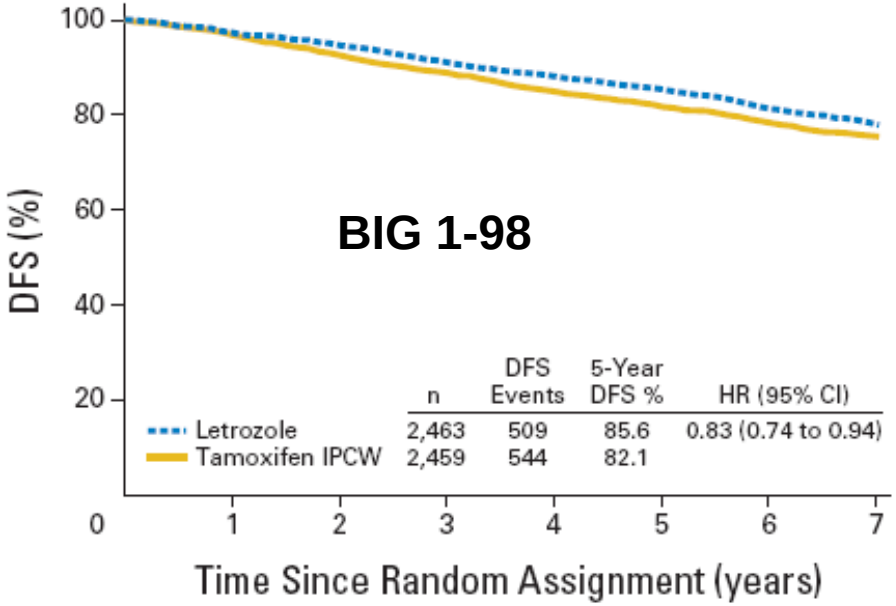
Dormance immunologique: phase d'équilibre

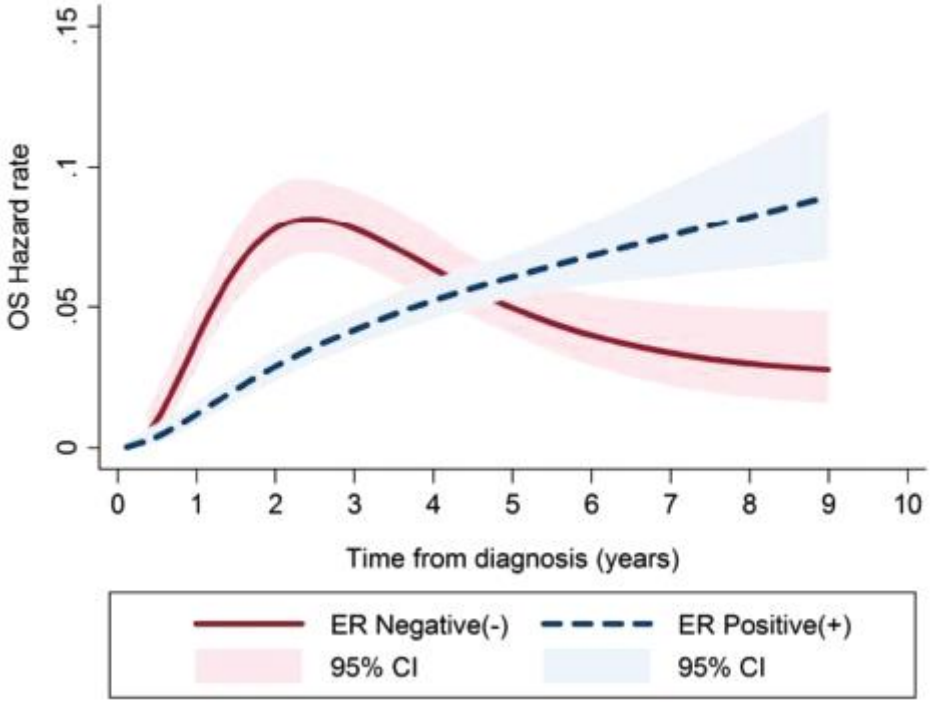
Dormance angiogénique: prolifération/nécrose

Aguirre-Ghiso *Nat Rev Cancer* 2007

Tumeurs luminales localisées: un modèle à part en cancérologie

Hormonothérapie prolongée dans les tumeurs RH+ ?





Colleoni et al, *J Clin Oncol* 2011

Copson et al, *J Natl Cancer Inst* 2013

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

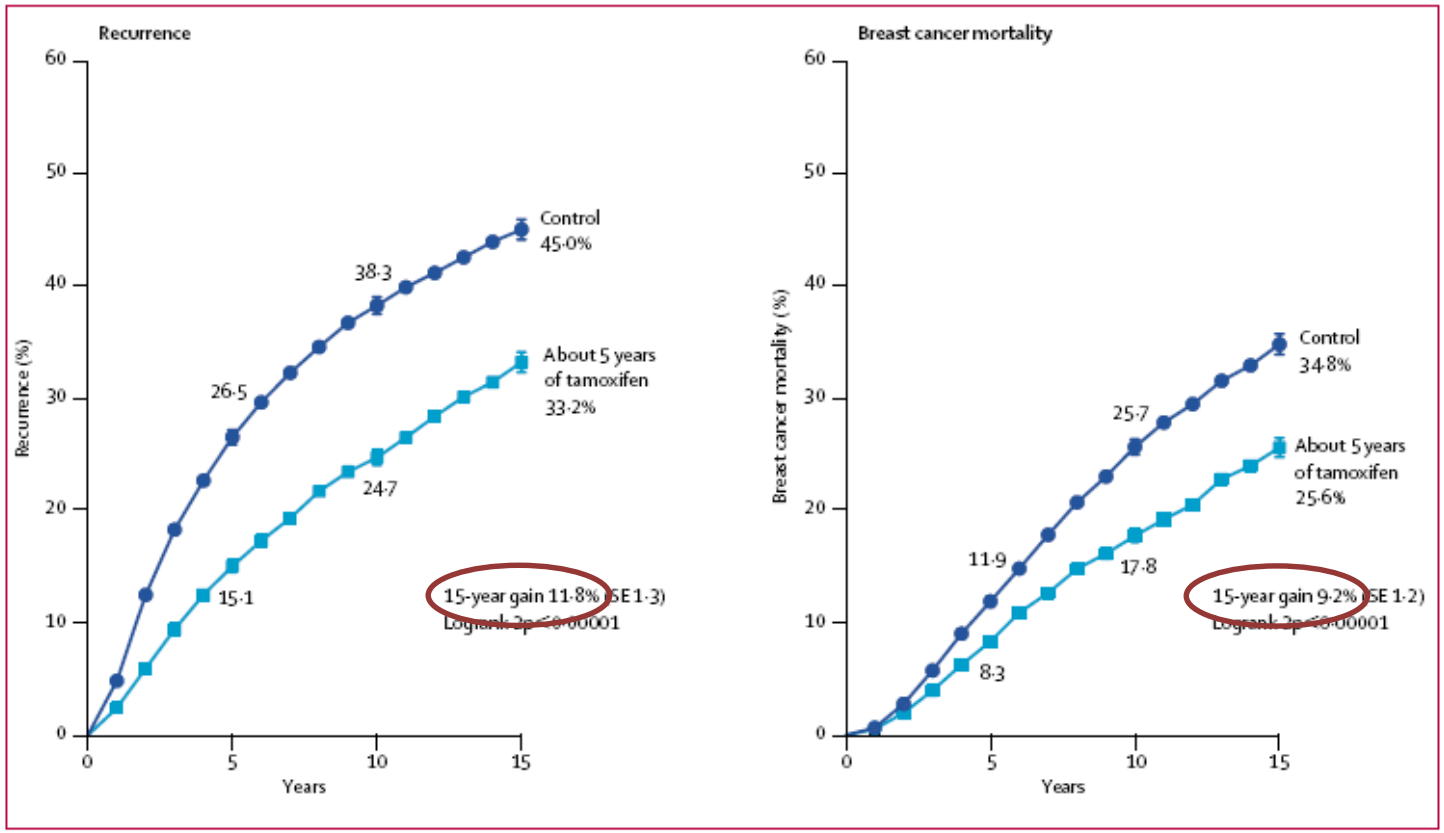
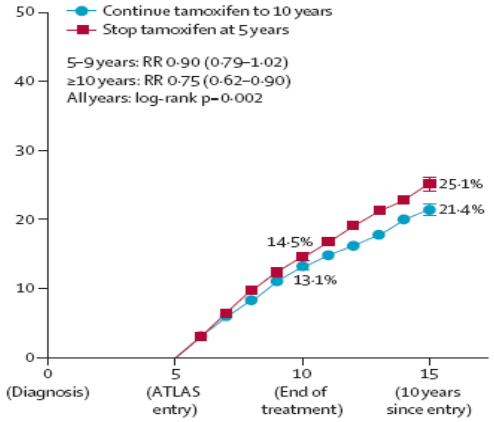


Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

Lancet 2005; 365: 1687–1717

Escalade en durée de traitement adjuvant

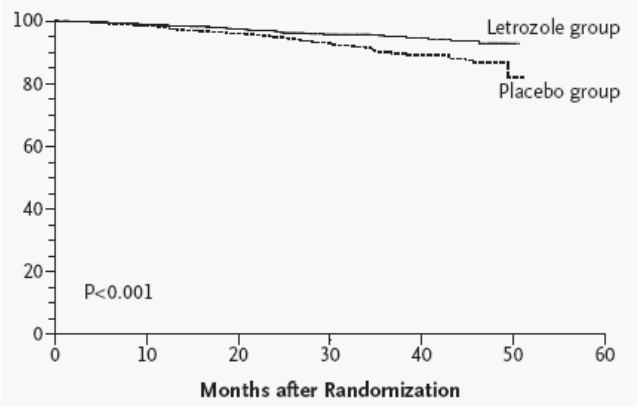


Tamoxifene 10 ans > Tamoxifene 5 ans

ATLAS

Davies et al, *Lancet* 2013

DFS, OS

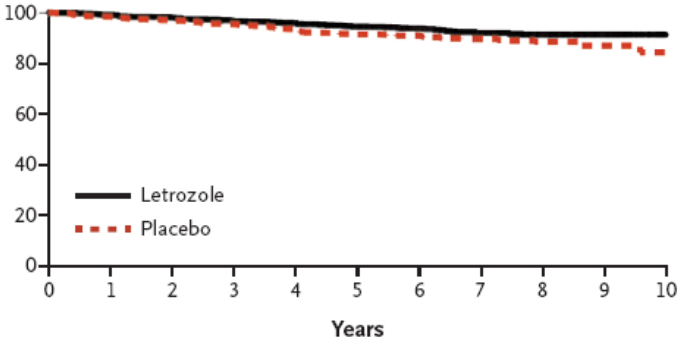


Tamoxifene 5 ans + Antiaromatase 5 ans > Tamoxifene 5 ans

MA.17

Goss et al, *N Engl JMed* 2013

DFS



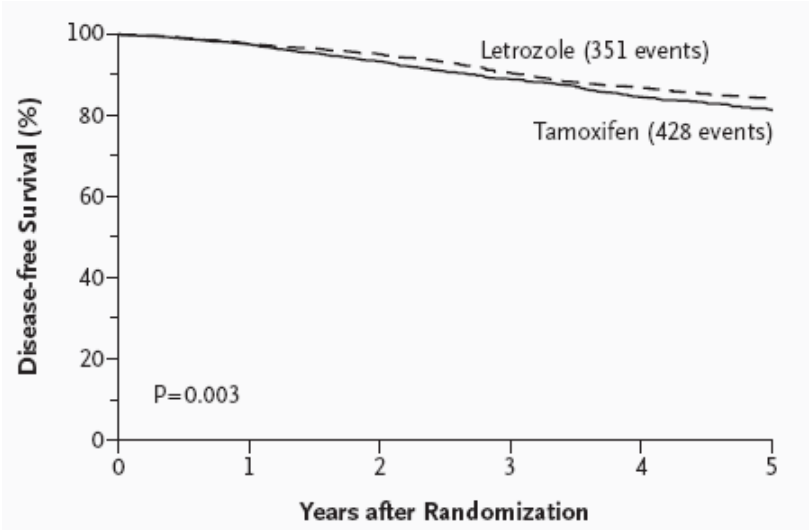
Anti -aromatase 10 ans > Anti -aromatase 5 ans
(après tamoxifene 5 ans)

MA.17R

Goss et al, *N Engl JMed* 2016

DFS

Escalade en qualité de traitement adjuvant



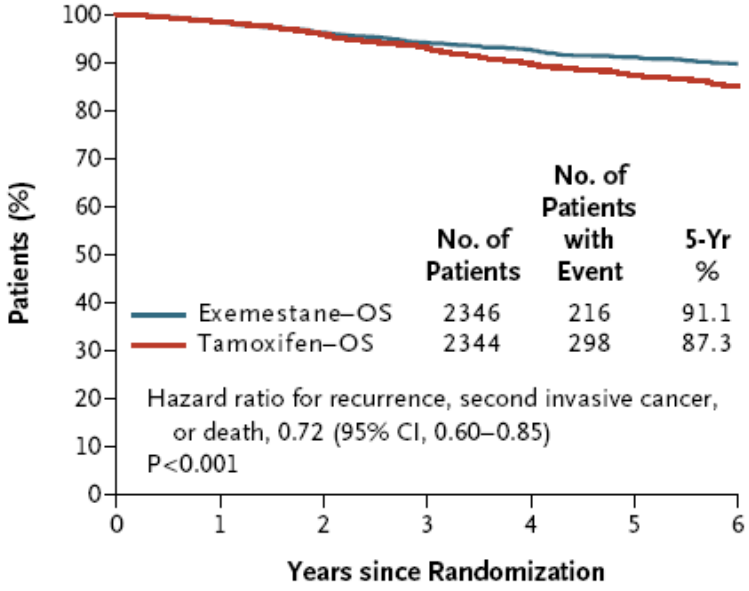
POST-MENOPAUSE:

Anti aromatase 5 ans > Tamoxifene 5 ans

BIG 1-98, ATAC

DFS, OS

BIG collaborative group, *N Engl J Med* 2005
Howell et al, *Lancet* 2005



PRE-MENOPAUSE:

Castration + Anti aromatase 5 ans > Castration + Tamoxifene 5 ans

SOFT & TEXT

DFS

Pagani et al, *N Engl J Med* 2014

Peut on se passer d'Hormonothérapie adjuvante ?

Les petites tumeurs RH+ HER2-
pT1a-b pN0

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Category	Events/woman–years: Allocated tamoxifen	Events/woman–years: Allocated control	Tamoxifen events: Logrank O–E	Tamoxifen events: Variance of O–E	Ratio of annual event rates Tamoxifen : Control
(f) Tumour size (N– only) (trend χ^2_1 = 0·5; 2p > 0·1; NS)					
< 2 cm	323/18863 (1·7%/y)	513/17300 (3·0%/y)	−110·2	201·7	0·58 (SE 0·05)
2 – 5 cm	281/9776 (2·9%/y)	381/8388 (4·5%/y)	−74·6	154·8	0·62 (SE 0·06)
> 5 cm	12/410 (2·9%/y)	18/429 (4·2%/y)	−2·3	6·5	
Unknown	137/5808 (2·4%/y)	205/5400 (3·8%/y)	−38·9	78·6	0·61 (SE 0·09)

Lancet 2005; 365: 1687–1717

Annals of Oncology 26 (Supplement 5): v8–v30, 2015
doi:10.1093/annonc/mdv298

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

clinical practice guidelines

The most recent publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview states the relative benefit of chemotherapy is similar in all the subgroups independent of age, stage, histopathological grade and ER status [89]. This seems to be in contradiction with the results from individual trials, both in the adjuvant and neoadjuvant settings, as well as knowledge of breast cancer biology. One also needs to take into account that many trials included in the EBCTCG overview have incomplete data on ER expression, in particular quantitative immunohistochemistry. Furthermore, these trials have included patients with generally higher risk of recurrence than those seen today and often used suboptimal ETs (by current standards). However, these views can be conciliated when acknowledging that, even if the relative benefit would be similar, the absolute benefit derived from adjuvant chemotherapy varies substantially. The risk to the individual patient is determined by the biology and the burden of the disease, for example the absolute benefit of adjuvant chemotherapy for a low burden luminal-A-like breast cancer, is extremely small and needs to be balanced against the known short- and long-term side-effects.

The authors of this manuscript agree with the 2013 and 2015 St Gallen guidelines, which recommend, for luminal cases with unclear chemotherapy indications, that the decision on systemic adjuvant therapies should be based on the surrogate intrinsic phenotype (Figure 2), that is determined by ER/PgR, HER2 and Ki67 assessment (Tables 2 and 5), with the selective help of genomic tests when available (particularly MammaPrint, Oncotype DX, Prosigna ROR and Endopredict) [23, 33].

It must be stressed that IHC/fluorescence *in situ* hybridisation determination of intrinsic phenotype, is not fully accurate. The prerequisite for using such a surrogate assessment is the use of standardised assays and a meticulous quality control.

All luminal cancers should be treated with ET. Most luminal A tumours, except those with the highest risk of relapse (extensive nodal involvement), require no chemotherapy [I, A] whereas luminal B HER2-negative cancers constitute a population of the highest uncertainty regarding chemotherapy indications [I, C]. Indications for chemotherapy within this subtype depend on the individual's risk of relapse, taking into account

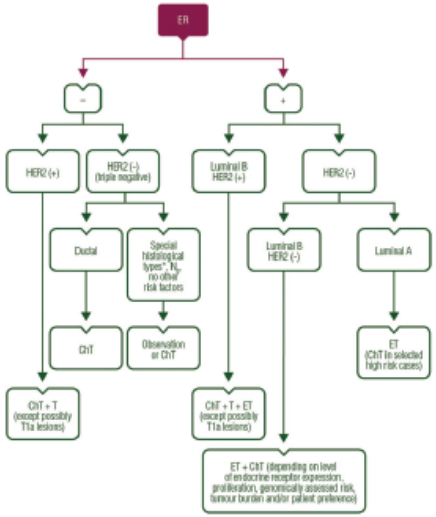


Figure 2. (Neo)adjuvant systemic treatment choice by biomarker expression and intrinsic phenotype. ER, oestrogen receptor; HER2, human epidermal growth factor 2 receptor; ChT, chemotherapy; ET, endocrine therapy; T, trastuzumab.

prerequisite for using such a surrogate assessment is the use of standardised assays and a meticulous quality control.

All luminal cancers should be treated with ET. Most luminal A tumours, except those with the highest risk of relapse (extensive nodal involvement), require no chemotherapy [I, A]

Synthèse des recommandations

Table 3. Comparison of Consensus Guidelines for the Use of Adjuvant Systemic Therapy in the Management of Stage T1a,b N0 M0 Breast Cancer

	T1a N0 M0						T1b N0 M0					
	NCCN 2005		St Gallen 2005*		NIH 2000†		NCCN 2005		St Gallen 2005*		NIH 2000†	
	HR+‡	HR−	HR+	HR−	HR+	HR−	HR+	HR−	HR+	HR−	HR+	HR−
Grade 1	No	No	HT	CT	HT	N/S	No‡	Consider CT	HT	CT	HT	N/S
Grade 2-3	No	No	HT ± CT§	CT	HT	N/S	HT ± CT§	Consider CT	HT ± CT§	CT	HT	N/S
HER-2 positive	No	No	CT + HT‖	CT	HT	N/S	HT ± CT§	Consider CT	CT + HT‖	CT	HT	N/S
LVI positive	No	No	HT ± CT§	CT	HT	N/S	HT ± CT§	Consider CT	HT ± CT§	CT	HT	N/S
Age < 35 years	N/S	N/S	HT ± CT§	CT	HT	N/S	N/S	N/S	HT ± CT§	CT	HT	N/S

NCCN:
option pour pT1a pN0

Préménopause: 10 ans pour toutes les patientes

Tam-Tam ou Tam-AA (fonction de l'évolution hormonale)
Castration 5 ans si FDR

Postménopause: 5 ans AA (éventuellement après Tam)

St Gallen:
Bénéfice pour toutes les tumeurs

Durée > 5 ans à discuter en fonction des FDR

Préménopause: Castration + AA si FDR

Postménopause: 5 ans AA (ou Tam selon FDR et tolérance)

ASCO:
Bénéfice pour toutes les tumeurs

Considérer 10 ans pour toutes les patientes

Préménopause: Castration 5 ans si FDR

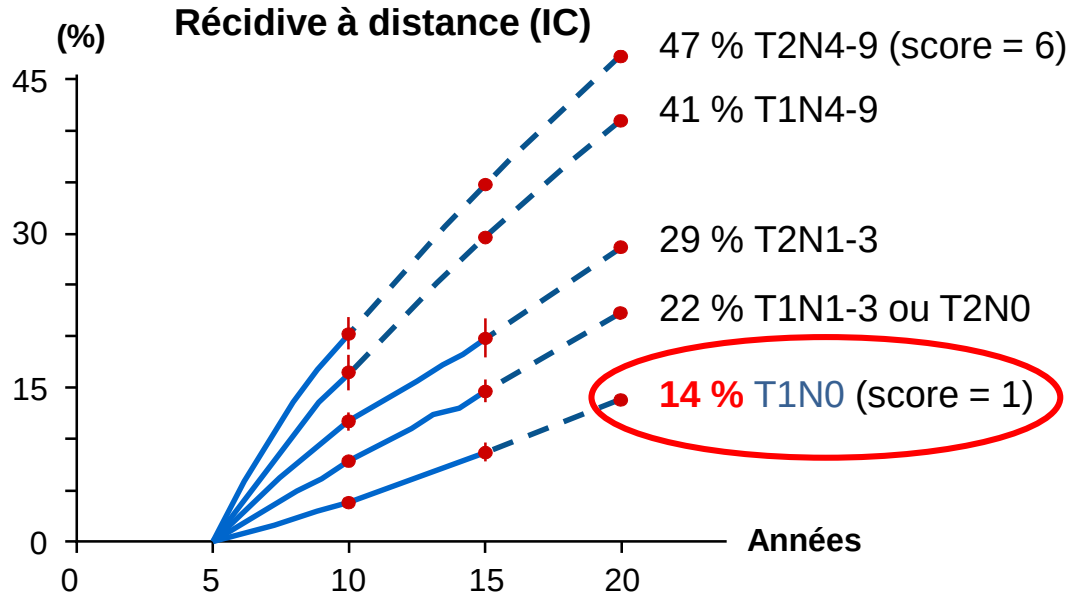
Postménopause: 5 ans AA (ou Tam selon FDR et tolérance)

Risques de récidive après 5 ans d'hormonothérapie adjuvante

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

- Effet du « score additif T+N » (extrêmes : 1-6)
- Score : 1/2 pour T1/T2, plus 0/1/4 pour N0/N1-3/N4-9

- Analyse sur les données individuelles de 46 000 patientes
- 91 essais
- K = 1 000 patientes



Risque annuel de récidive à distance (et nombre d'événements)							
T1N4-9 (n = 2K)	3,6 % (293)	2,9 % (54)	2,5 % (5)	**T2N4-9 (n = 3K)**	4,6 % (544)	3,3 % (79)	2,2 % (6)
T1N1-3 (n = 9K)	1,6 % (504)	1,7 % (123)	1,8 % (16)	**T2N1-3 (n = 8K)**	2,5 % (680)	1,9 % (108)	1,9 % (14)
T1N0 (n = 16K)	0,8 % (465)	1,0 % (191)	1,2 % (40)	**T2N0 (n = 8K)**	1,7 % (451)	1,4 % (131)	1,7 % (29)

ASCO 2016 - D'après Pan H et al., abstr. 505, actualisé

Escalade

Qualitative & Quantitative

De quelles données objectives disposons nous dans la littérature ?

Pas d'essai prospectif randomisé dédié

Niveau de preuve faible

Littérature dédiée aux petites tumeurs: Etudes rétrospectives : Petites tumeurs (pT1 pN0):

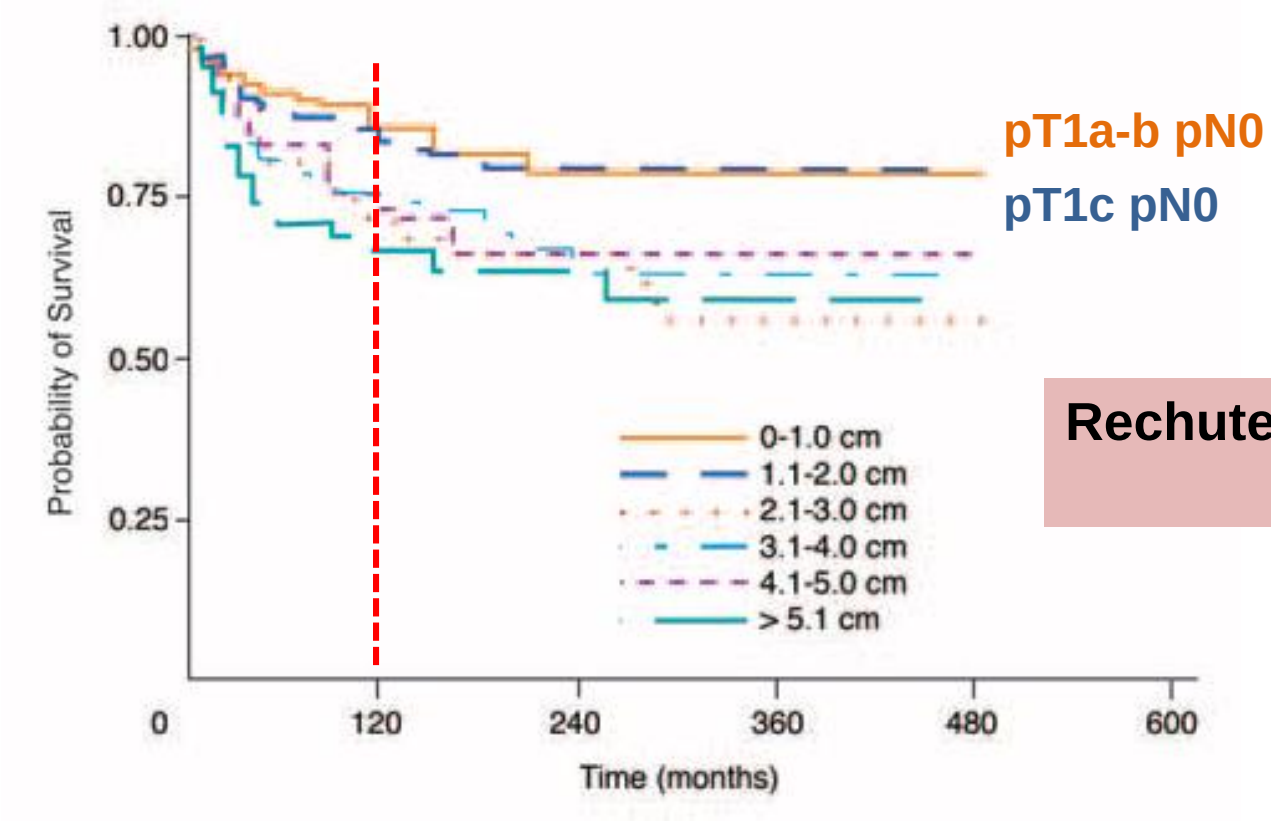
Études rétrospectives GLOBALES sur les petites tumeurs:

- Peu de littérature séparant les T1 (T1a, T1b, T1c N0)
- Peu de littérature sur les petites tumeurs spécifiquement luminales
- Pour les tumeurs RH+: peu de données sur les traitements adjuvants reçus

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Prognosis and Management of Patients With Node-Negative Invasive Breast Carcinoma That Is 1 cm or Smaller in Size (stage 1; T1a,bN0M0): A Review of the Literature

Emer O. Hanrahan, Vicente Valero, Ana M. Gonzalez-Angulo, and Gabriel N. Hortobagyi



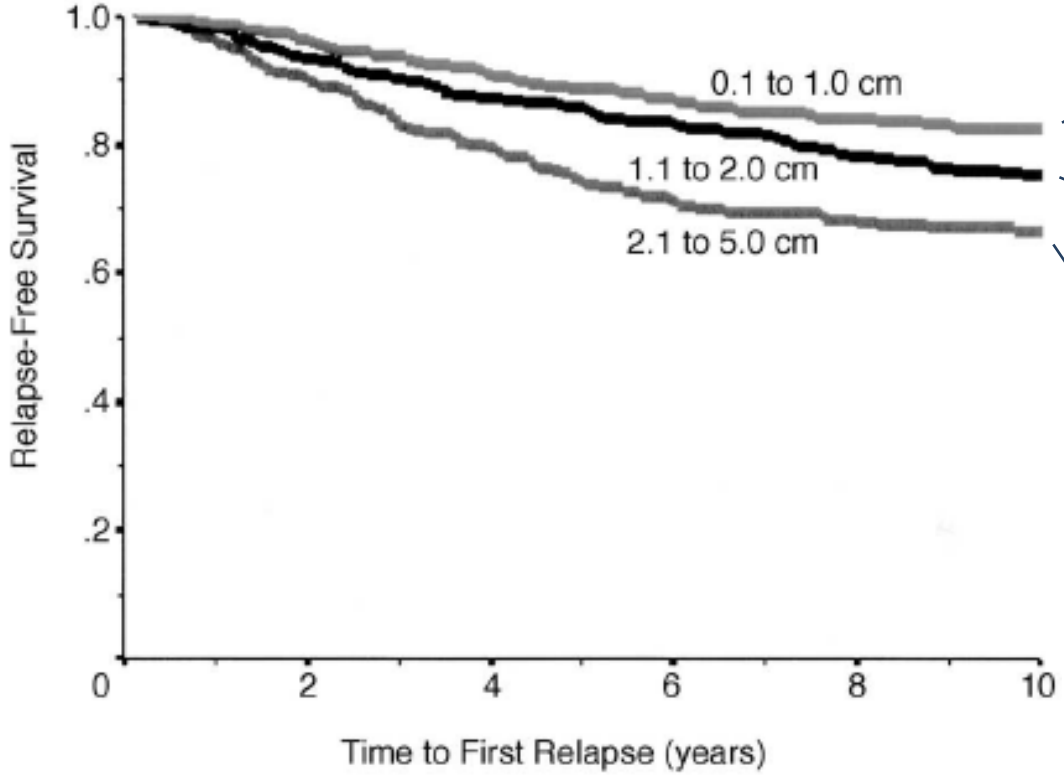
Rechutes au-delà de 10 ans (env 25%)

Hanrahan et al, *J Clin Oncol* 2006

Résultats sans traitement systémique adjuvant

N= 430 pT1a-b pN0 ELV - **SANS TRAITEMENT SYSTEMIQUE ADJUVANT**
Age médian 62 ans

Influence majeure **du grade**: grade 3:
Risque de récidive: +25%
Risque de décès: + 10%



À 10 ans:

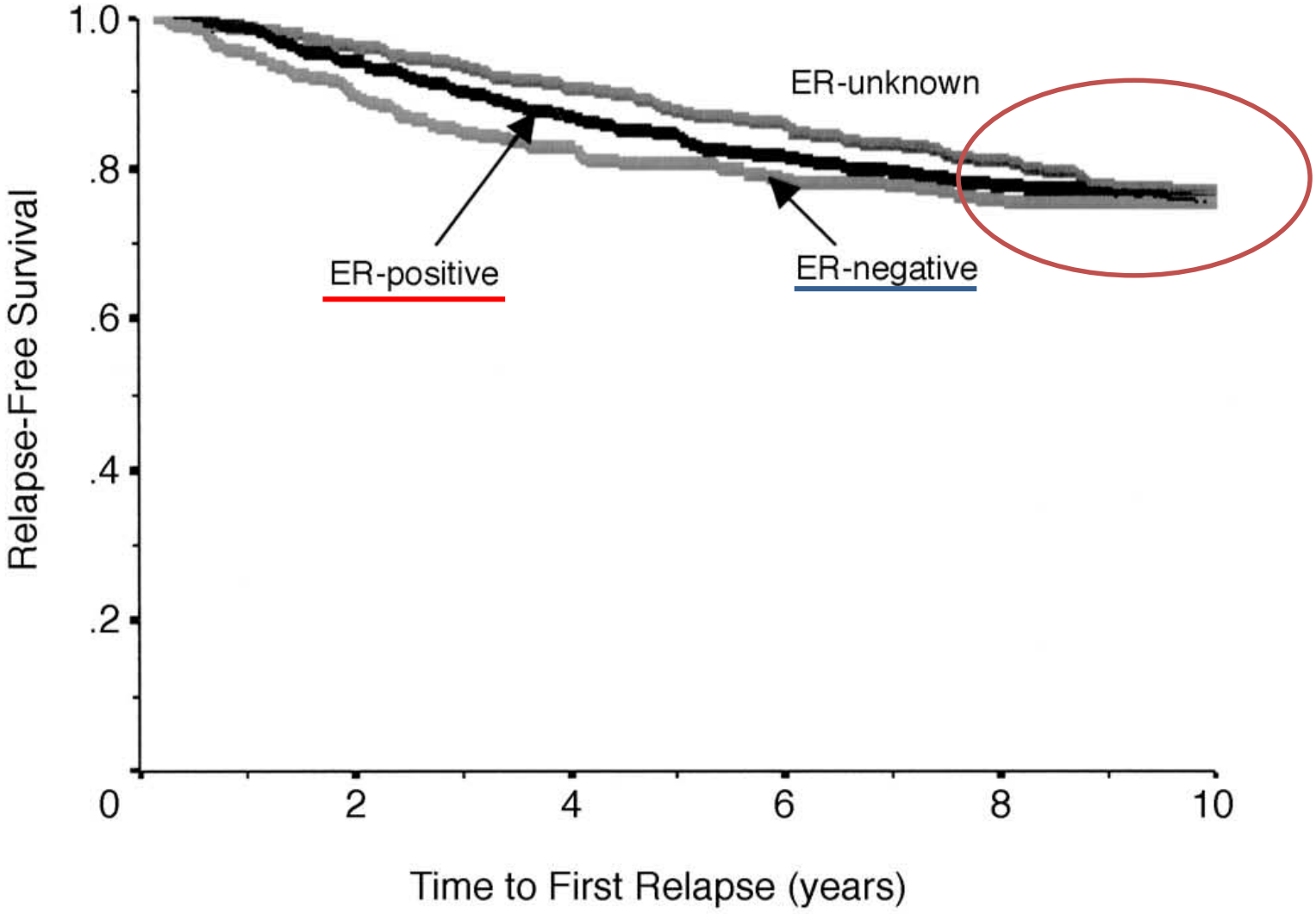
pT1a-b:
RFS: 82%
BCSS: 92%
OS: 79%

pT1c:
RFS: 75%
BCSS: 90%
OS: 78%

pT2:
RFS: 66%
BCSS: 77%
OS: 66%

Chia et al, *J Clin Oncol* 2004

Résultats sans traitement systémique adjuvant



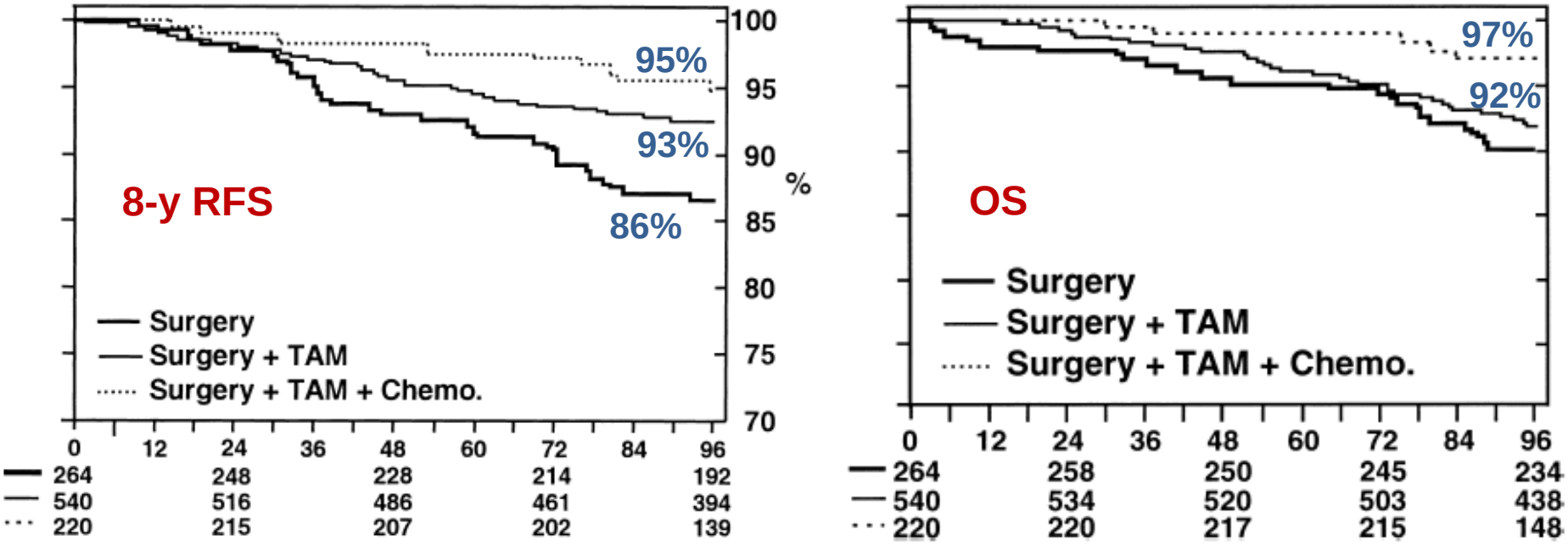
Chia et al, *J Clin Oncol* 2004

Prognosis and Treatment of Patients With Breast Tumors of One Centimeter or Less and Negative Axillary Lymph Nodes

Bernard Fisher, James Dignam, Elizabeth Tan-Chiu, Stewart Anderson, Edwin R. Fisher, James L. Wittliff, Norman Wolmark

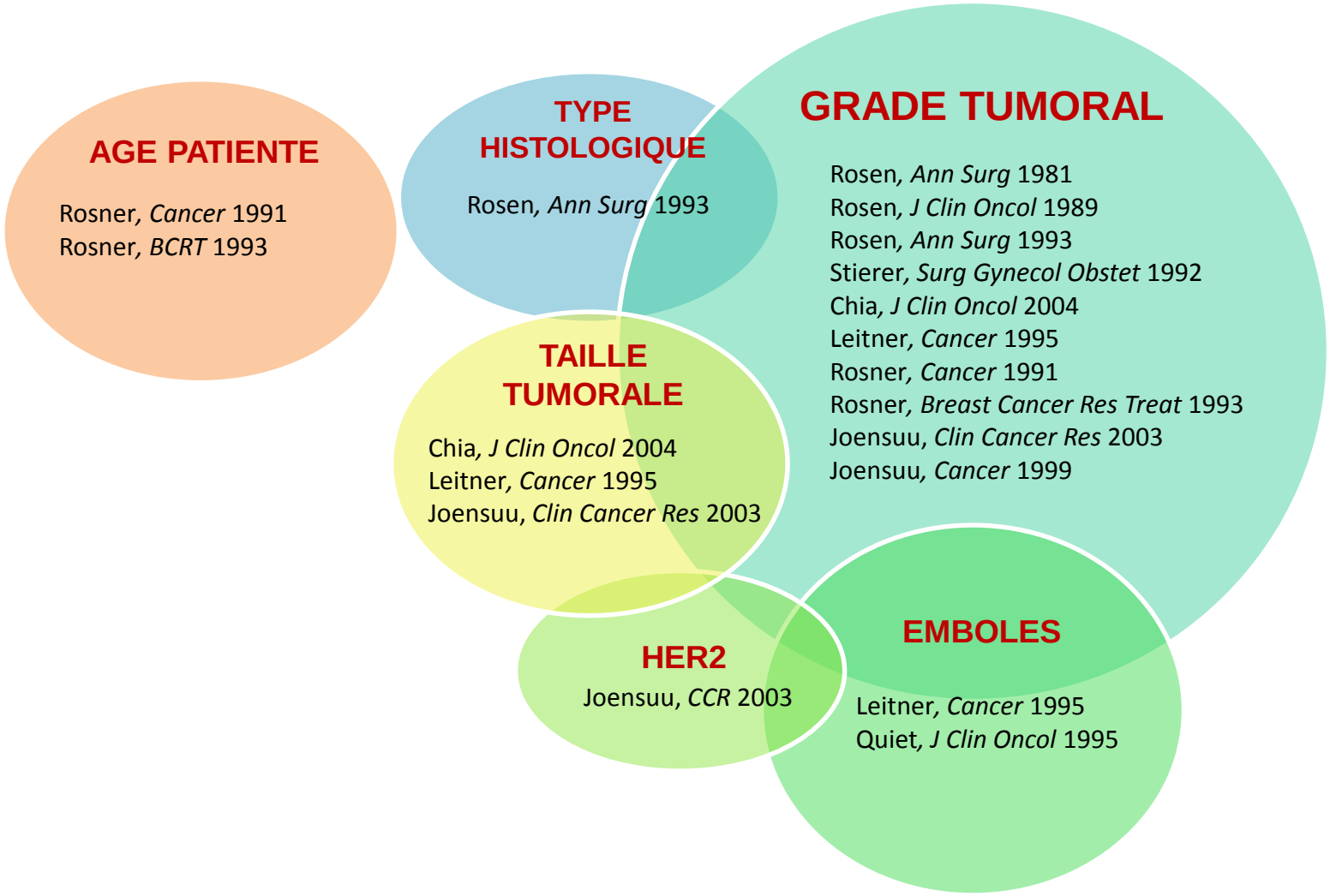
N= 1,259 pT1a-b pN0 dans 5 essais du NSABP

ER+ tumors

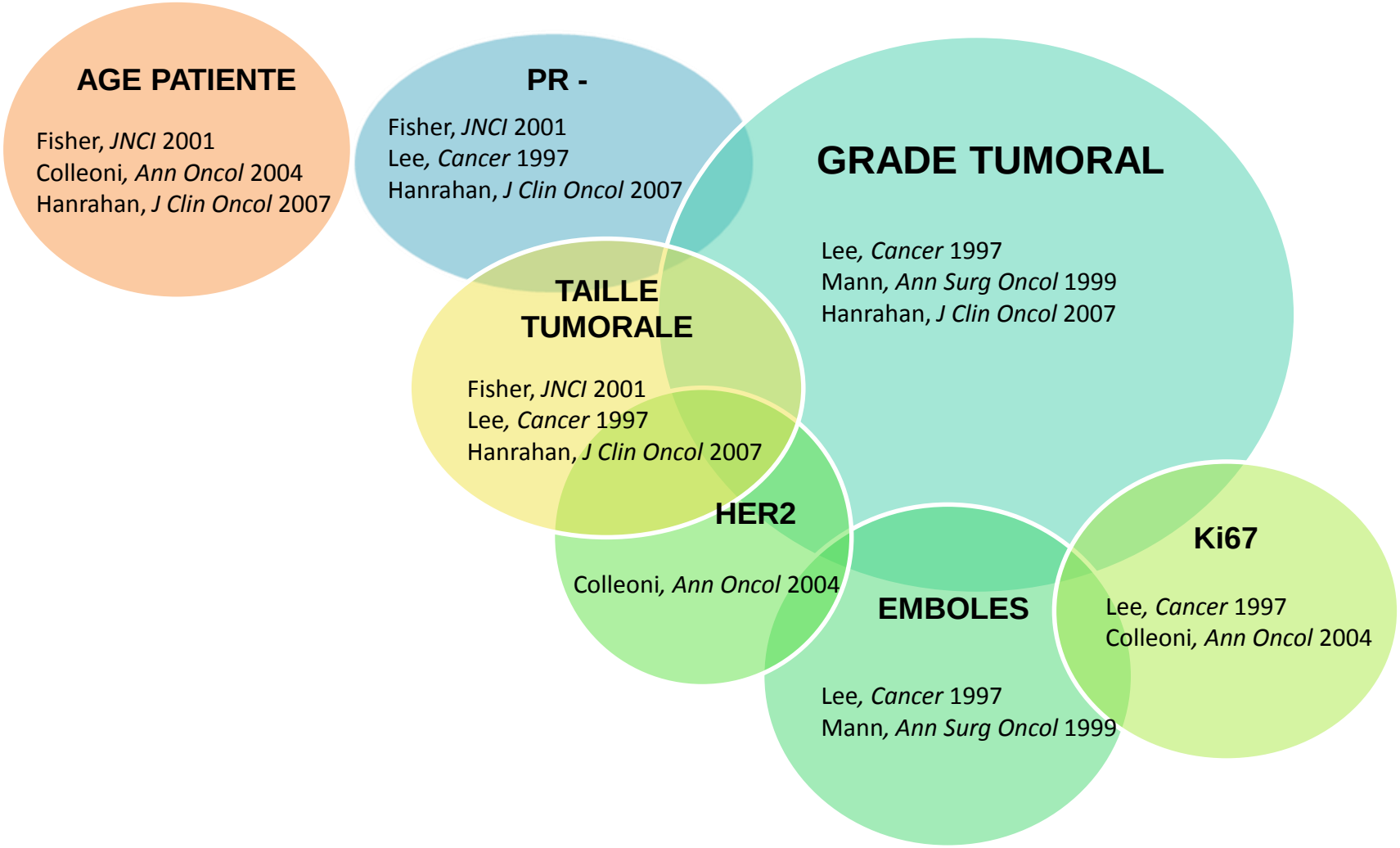


Fisher et al, *J Natl Cancer Inst* 2001

Facteurs pronostics des pT1 pN0 sans traitement systémique adjuvant



Facteurs pronostics des pT1 pN0 avec traitement systémique adjuvant



VOLUME 25 · NUMBER 31 · NOVEMBER 1 2007

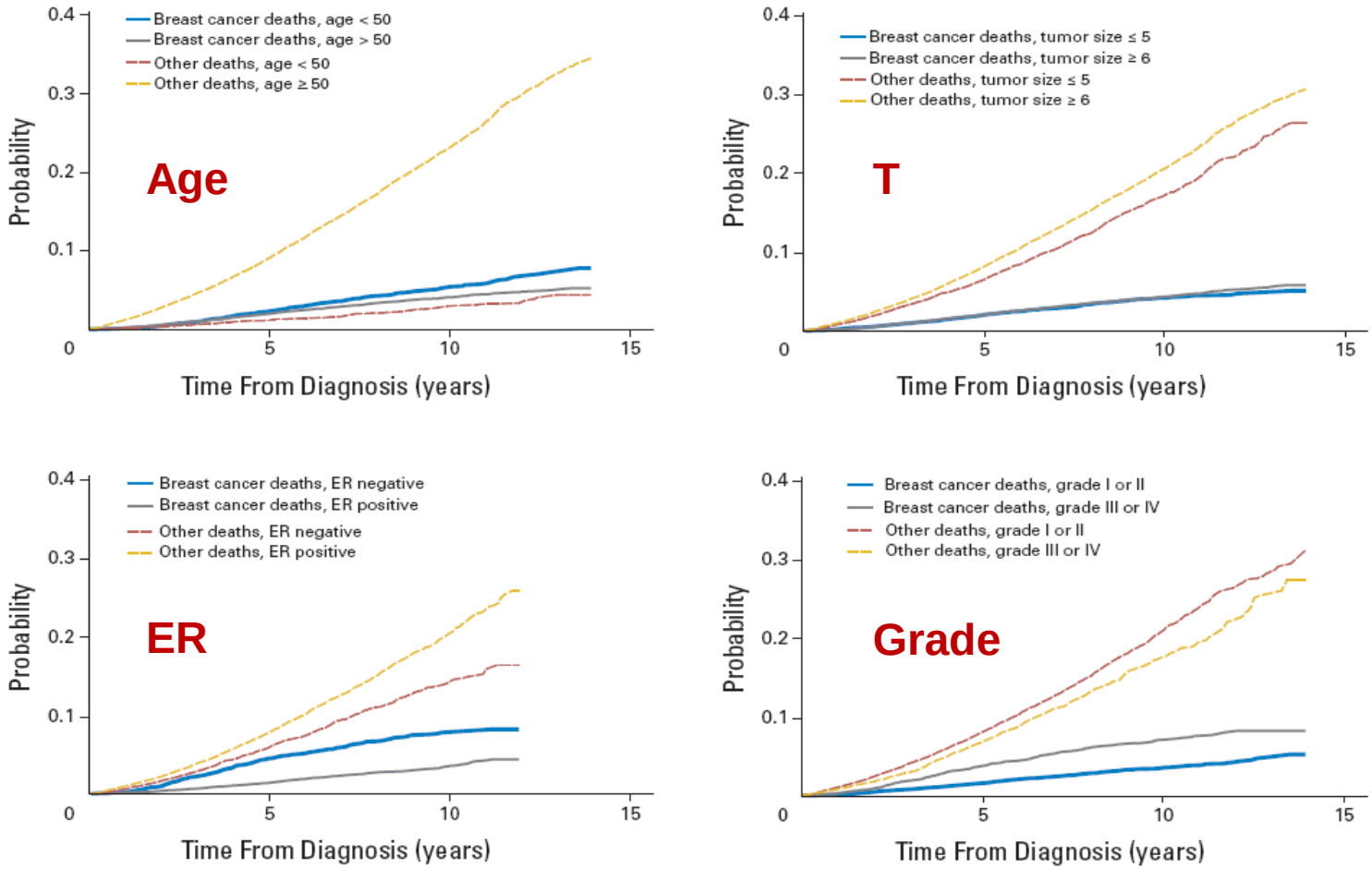
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

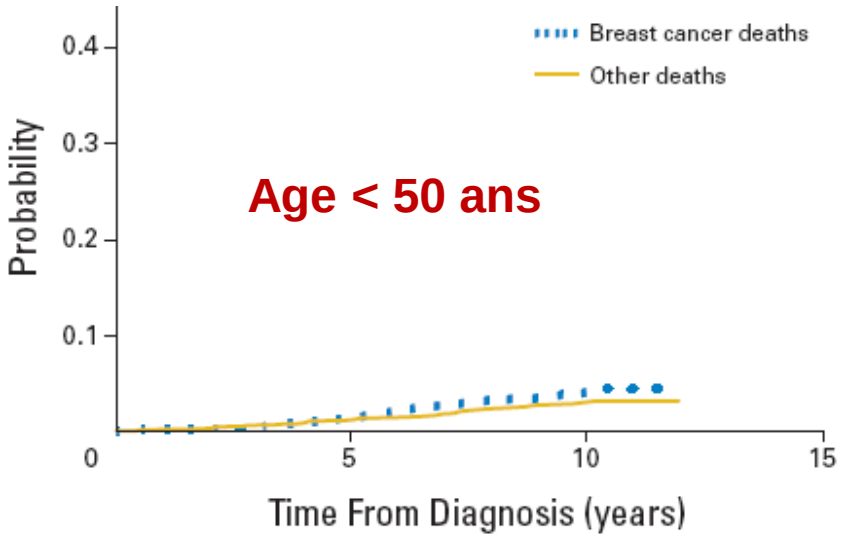
Overall Survival and Cause-Specific Mortality of Patients With Stage T1a,bN0M0 Breast Carcinoma

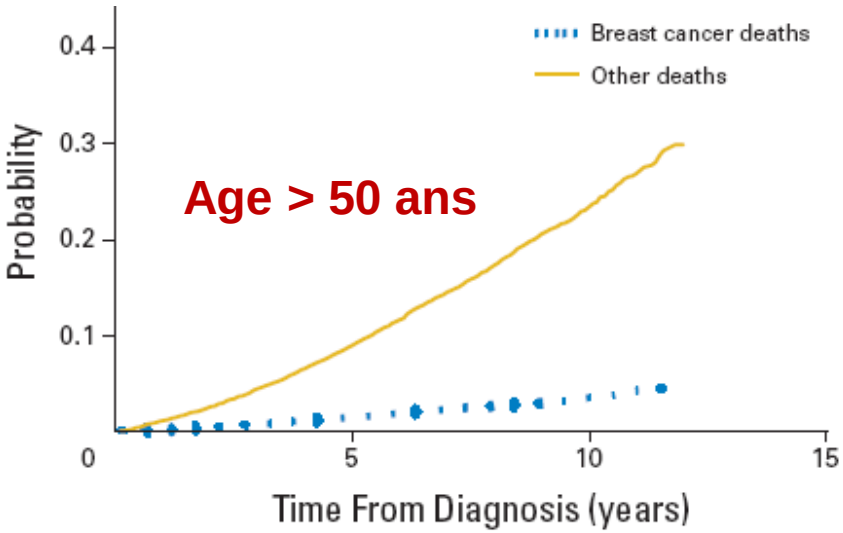
Emer O. Hanrahan, Ana M. Gonzalez-Angulo, Sharon H. Giordano, Roman Rouzier, Kristine R. Broglio, Gabriel N. Hortobagyi, and Vicente Valero

N= 51,246 T1a-b pN0 **SEER DATABASE: probabilité de décès**



Influence majeure de la mortalité compétitive: T1a-b N0 RH+





Cardiovasculaire
Cérébrovasculaire
Cancer bronchique
BPCO
Pneumonies
Autres cancers
Diabète

Causes de mortalité compétitive

Hanrahan al, *J Clin Oncol* 2007

Mortality Rates Among Early-Stage Hormone Receptor–Positive Breast Cancer Patients: A Population-Based Cohort Study in Denmark

ARTICLE

Peer Christiansen, Karsten Bjerre, Bent Ejlertsen, Maj-Britt Jensen, Birgitte B. Rasmussen, Anne-Vibeke Lænkholm, Niels Kroman, Marianne Ewertz, Birgitte Offersen, Dorte B. Toftdahl, Susanne Møller, Henning T. Mouridsen; on behalf of the Danish Breast Cancer Cooperative Group

J Natl Cancer Inst 2011;103:1363–1372

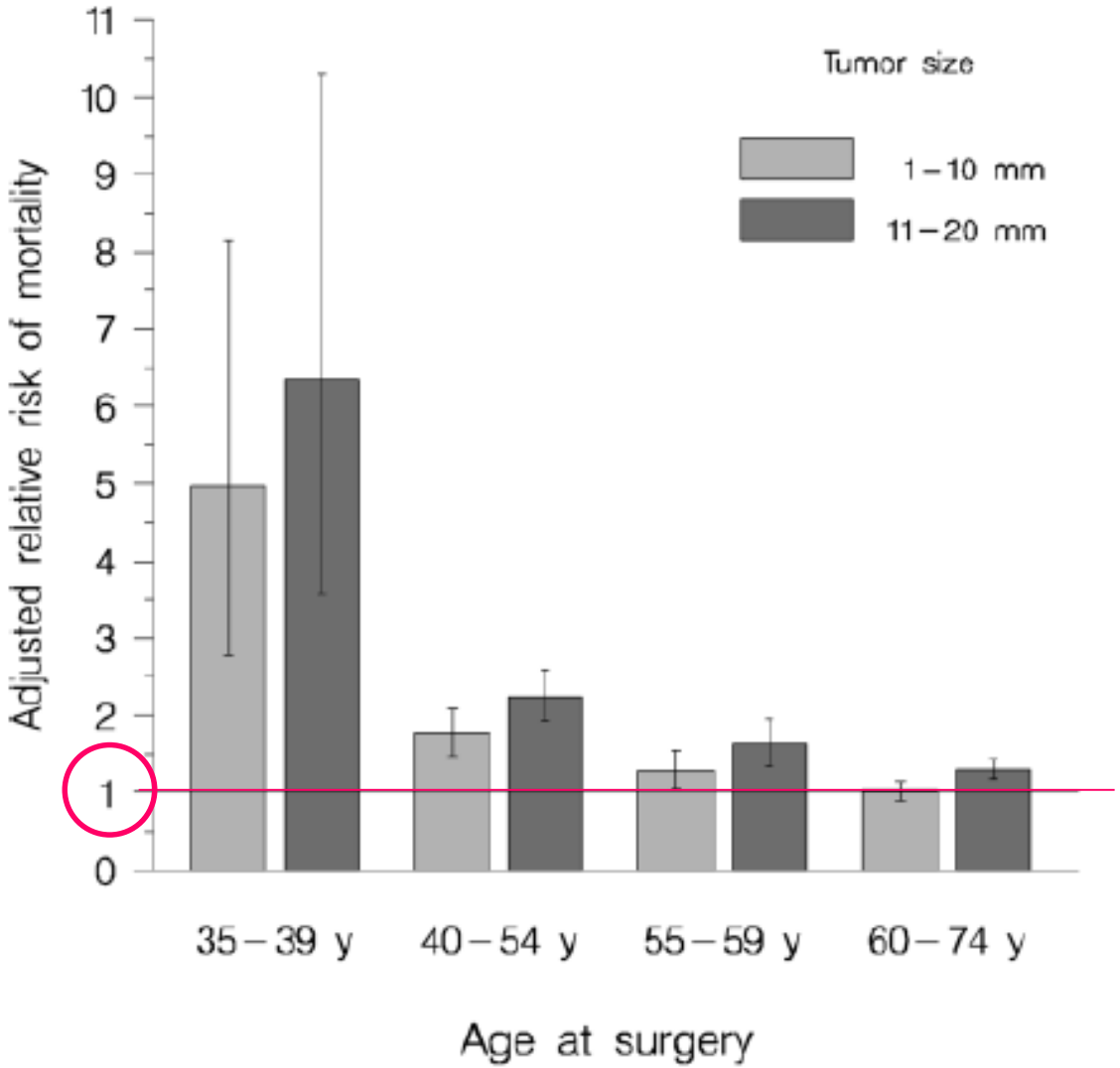
Registre des cancers du sein danois
N= 3197 tumeurs luminales pT1 pN0 **sans traitement adjuvant systémique**
Suivi médian 15 après chirurgie initiale
Comparaison avec la mortalité attendue des femmes de la population générale

Table 2. Mortality in the study cohort compared with mortality in the general population of women*

Risk factor	Person-years at risk	Mortality rate per 100 000 person-years			Relative mortality	Adjusted RR of mortality	
		Observed	Expected	Excess	SMR (95% CI)	RR (95% CI)	P†
Total	41 167	2356	1790	566	1.32 (1.24 to 1.40)		
Age at surgery, y							<.001
35–39	1088	1287	233	1054	5.53 (3.11 to 8.95)	4.88 (2.72 to 8.01)	
40–44	3258	952	356	595	2.67 (1.84 to 3.72)	2.34 (1.59 to 3.31)	
45–49	6425	1043	522	521	2.00 (1.56 to 2.52)	1.72 (1.31 to 2.21)	
50–54	7060	1445	787	658	1.84 (1.50 to 2.22)	1.60 (1.28 to 1.98)	
55–59	6709	1833	1291	542	1.42 (1.18 to 1.69)	1.26 (1.02 to 1.53)	
60–64	7088	2469	2167	301	1.14 (0.98 to 1.32)	0.98 (0.82 to 1.18)	
65–69	5593	4219	3386	833	1.25 (1.09 to 1.41)	1.08 (0.91 to 1.27)	
70–74	3946	5626	5170	456	1.09 (0.95 to 1.24)	0.92 (0.77 to 1.10)	
Tumor size, mm							<.001
1–10	15 147	1888	1679	209	1.12 (1.00 to1.26)	1 (referent)	
11–20	26021	2629	1854	774	1.42 (1.31 to 1.53)	1.28 (1.12 to 1.48)	
Histopathology‡							.0049
Grade 1 ductal carcinoma	27491	2357	1743	614	1.35 (1.25 to 1.46)	1 (referent)	
Grade 1 or 2 lobular carcinoma	6759	2796	1913	883	1.46 (1.26 to 1.68)	1.09 (0.93 to 1.28)	
Other or unknown	6918	1923	1855	67	1.04 (0.87 to 1.22)	0.77 (0.64 to 0.93)	

CCI grade 1

CLI grade 1 ou 2



J Natl Cancer Inst 2011;103:1363–1372

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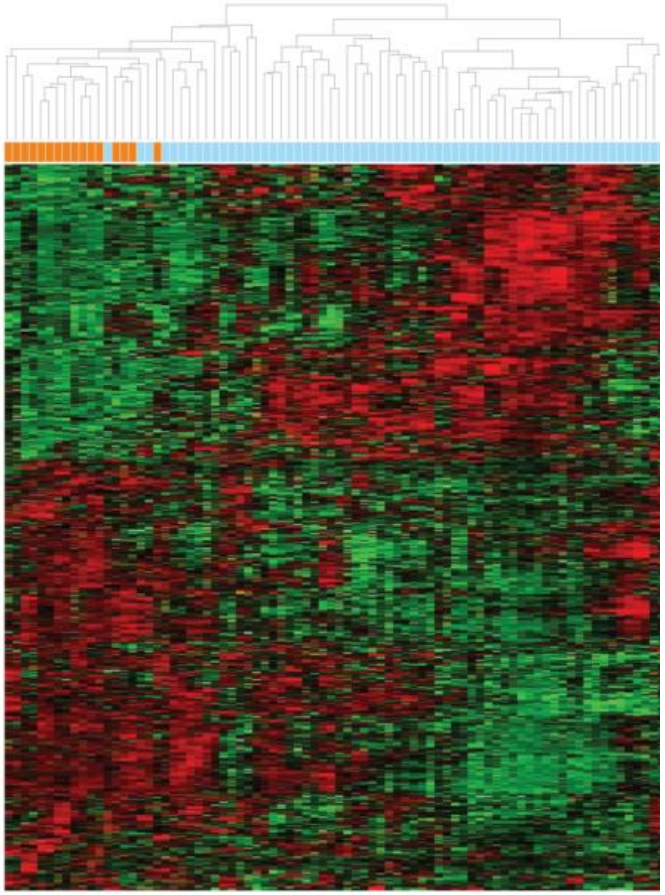
Breast Cancer Recurrence Signature

MAPQUANT DX

prosigna™

La génomique peut elle aider ?

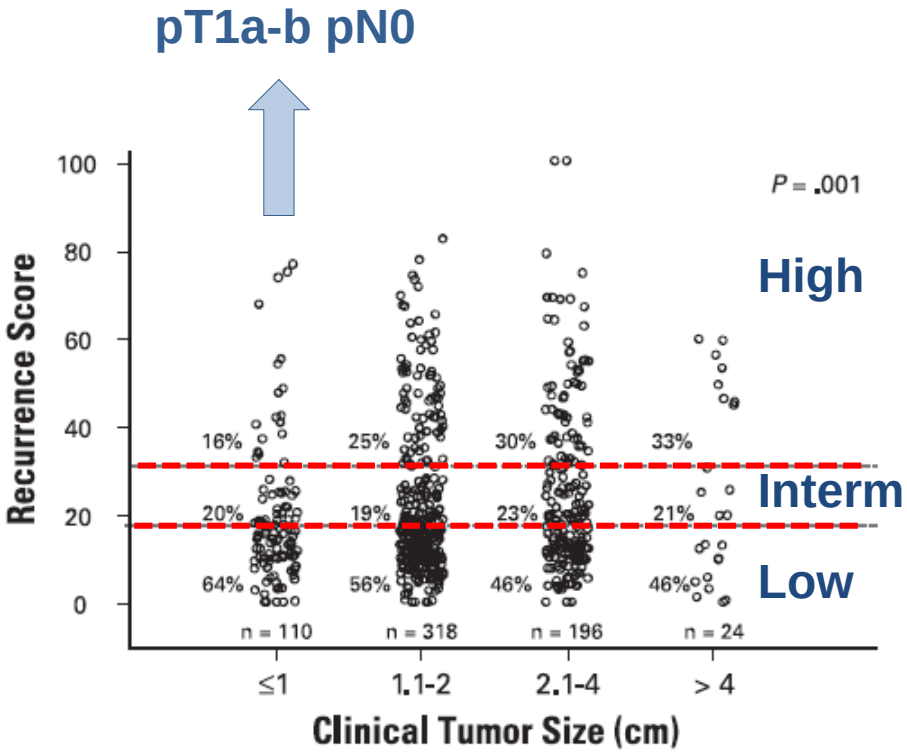


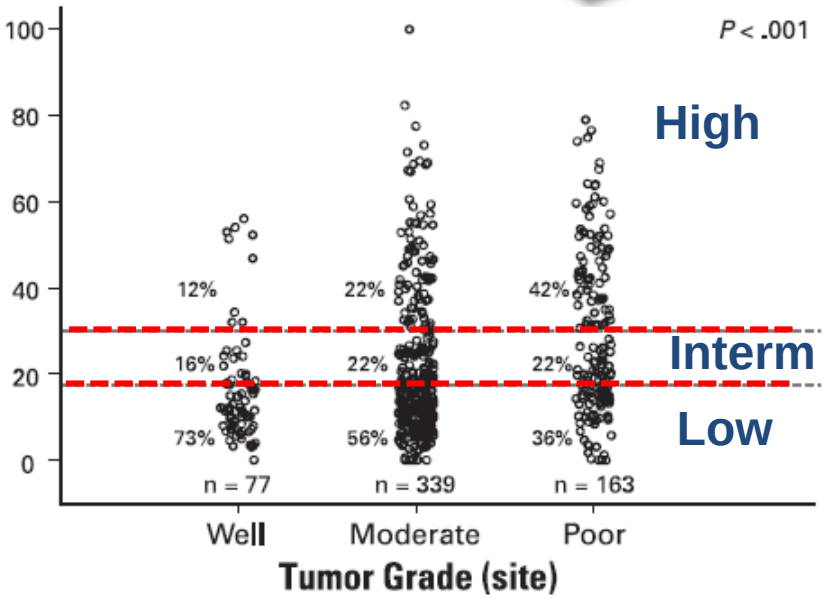
Breast Cancer INDEX™

EndoPredict®

oncotype DX®
Breast Cancer Assay

Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer





JOURNAL OF CLINICAL ONCOLOGY

Paik et al, *J Clin Oncol* 2006

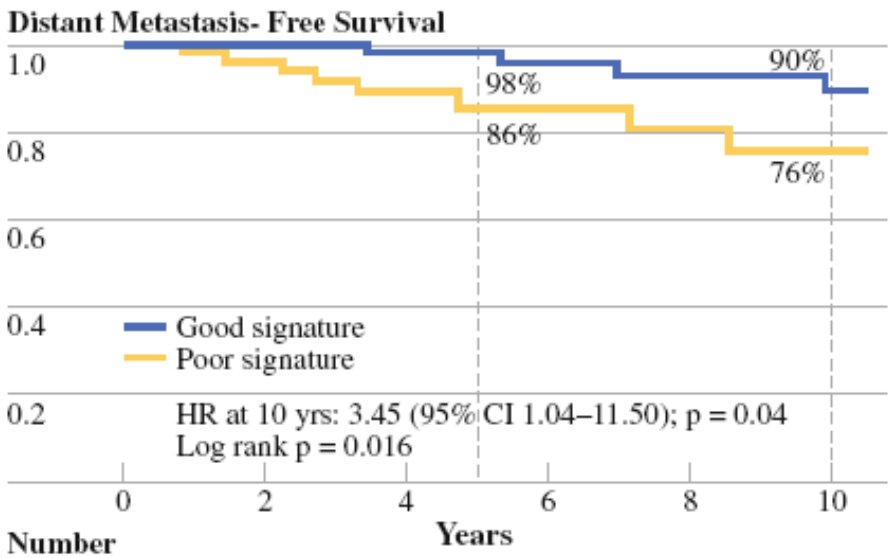
964 pT1 : 57% aucun traitement adjuvant

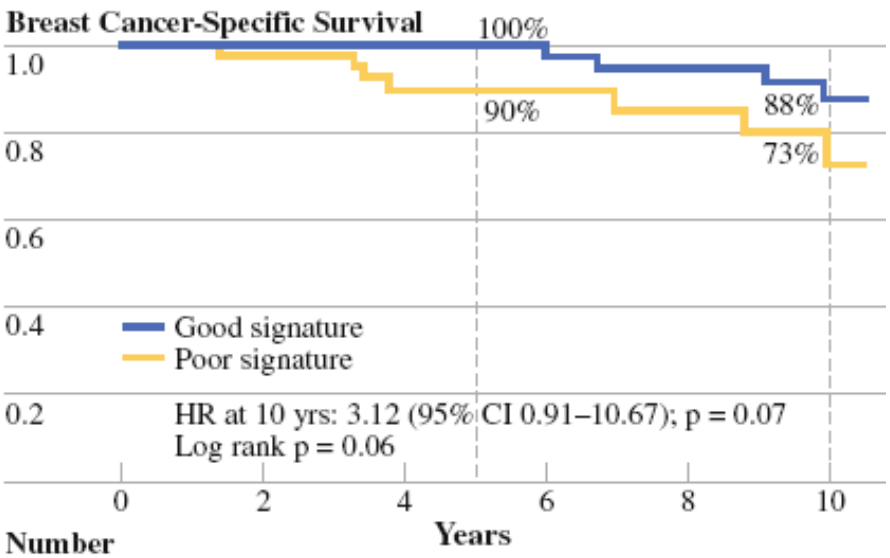
N= 139 pT1a-b pN0 RH+

mammaprint®
Breast Cancer Recurrence Signature

	Good prognosis profile		Poor prognosis profile		*P* value*
Tumor size					.13
pT1a/b	84	16.0%	55	12.5%	
pT1c	441	84.0%	384	87.5%	

55/139 = 40% !!!





Mook et al, *Ann Surg Oncol* 2010

Research article

Open Access

A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients

Cas témoin (décès par cancer du sein / survivantes)

N= 990 pts pN0 RH+ tamoxifène adjuvant ou non

Distributions of tumor size and tumor grade in Recurrence Score categories for all 220 cases and 570 controls

Variable (number of patients)	Recurrence Score						
	<18 (*n* = 379)		18–30 (*n* = 162)		≥30 (*n* = 249)		Correlation[1] (*P* value)
Tumor size and grade							0.42 (<0.0001)
≤2 cm and well or ≤1 cm and moderate (*n* = 285)	204	(72%)	60	(21%)	21	(7%)	
>2 cm and well, or 1.1–2 cm and moderate, or ≤2 cm and poor (*n* = 330)	143	(41%)	63	(19%)	133	(40%)	
>2 cm and moderate/poor (*n* = 175)	41	(23%)	39	(22%)	95	(54%)	

Habel et al, *Breast Cancer Res* 2006

Ten-year risk of death in relation to Recurrence Score and tumor size and grade among ER-positive patients, stratified by treatment with tamoxifen

Risk classifier	Cases	Controls	10-Year risk		
			%		95% CI
Tamoxifen untreated				**Tamoxifen treated**	
Recurrence Score, tumor size and grade					
Recurrence Score low <18 (40 cases and 160 controls)					
≤2 cm and well or ≤1 cm and moderate	35%	63%	3.0	0.4	(1.7–4.3)
>2 cm and well, or 1.1–2 cm and moderate, or ≤2 cm and poor	48%	31%	11.0	4.1	(7.0–14.8)
>2 cm and moderate/poor	17%	6%	20.2	6.9	(6.1–32.2)
Recurrence Score intermediate 18–30 (32 cases and 47 controls)					
≤2 cm and well or ≤1 cm and moderate	34%	38%	17.0	6.8	(8.2–24.9)
>2 cm and well, or 1.1–2 cm and moderate, or ≤2 cm and poor	38%	34%	20.9	21.9	(10.2–30.4)
>2 cm and moderate/poor	28%	28%	22.0	13.5	(9.3–32.9)
Recurrence Score high ≥31 (38 cases and 44 controls)					
≤2 cm and well or ≤1 cm and moderate	13%	14%	25.0	12.2	(7.9–39.0)
>2 cm and well, or 1.1–2 cm and moderate, or ≤2 cm and poor	50%	59%	21.0	10.9	(13.8–27.5)
>2 cm and moderate/poor	37%	27%	25.3	28.9	(15.1–34.3)

Habel et al, *Breast Cancer Res* 2006

Conclusions

Pas de population dans laquelle se passer systématiquement d'HT adjuvante pour une tumeur RH+

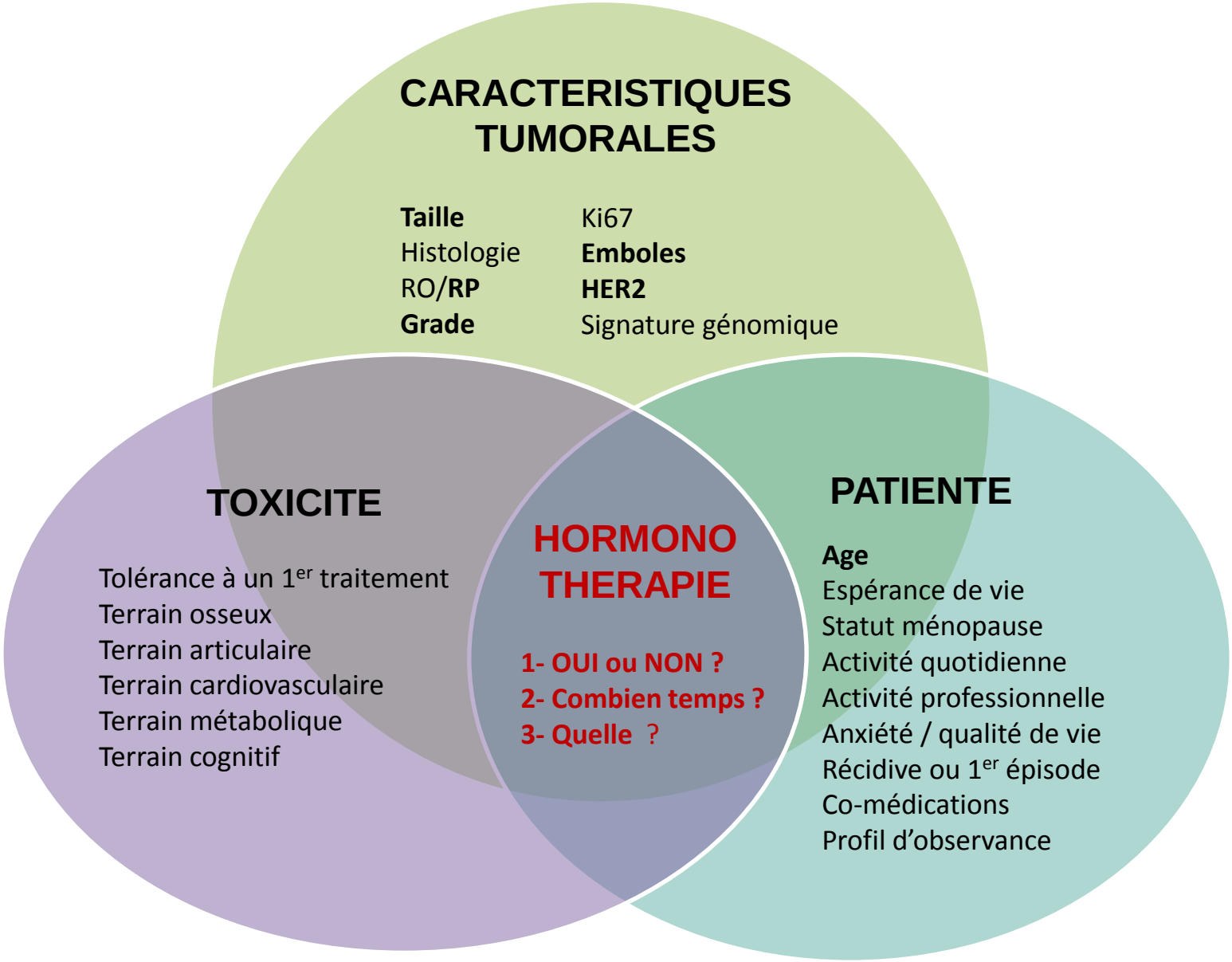
> 60 ans, T1a-b N0, CCI grade 1 ou CLI grade 1-2 ?

Age/espérance de vie, comorbidités

Faible niveau de preuve….

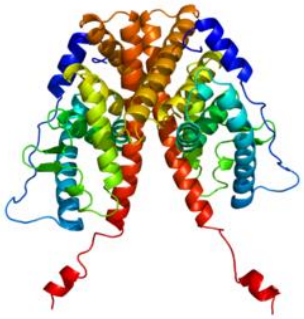
Désescalade = parfois non-escalade

Conclusion: une décision pragmatique !!!



Jusqu'où est il licite d'envisager une désescalade des indications d'hormonothérapie adjuvante pour une tumeur luminale ?

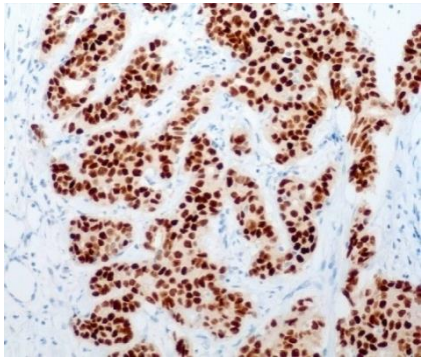
Sylvain LADOIRE



Département d'Oncologie Médicale
Centre Georges François Leclerc

Plateforme UB de Transfert en Biologie Cancérologique

Centre de Recherche INSERM 866
Equipe « Chimiothérapie & réponse immunitaire »
Faculté de Médecine-Université de Bourgogne



DIJON

38ES JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE SÉNOLOGIE ET DE PATHOLOGIE MAMMAIRE

CGFL CENTRE GEORGES FRANÇOIS LECLERC
Ensemble, dépassons le cancer