Les récidives locorégionales

Quand et comment proposer un traitement systémique ?

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Liens d'intérêt

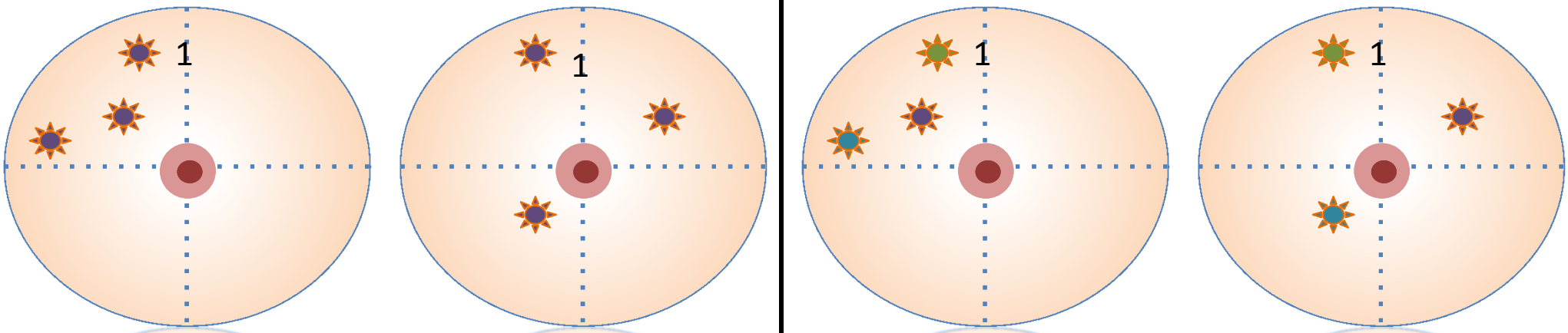
- Amgen® (orateur)
- Eisai® (soutien recherche, conseil, invitations congrès, orateur)
- Genomic Health Inc ® (soutien recherche, orateur)
- Glaxosmithkline (invitations congrès, orateur)
- Roche-Genentech® (soutien recherche, conseil, invitations congrès, orateur)
- Novartis ® (conseil, orateur)

Les quatre points exposés

- Le diagnostic de récidive locorégionale
- Les enjeux de la prise en charge locorégionale
- Les niveaux de preuve de l'intérêt des traitements systémiques
- Les recommandations actuelles

LE DIAGNOSTIC DE RÉCIDIVE LOCOREGIONALE

Caractéristiques tumorales des cancers métachrones



Cancers Multifocaux	Cancers Multicentriques	Cancers Multifocaux	Cancers Multicentriques
Caractéristiques similaires	Caractéristiques similaires	Caractéristiques différentes	Caractéristiques différentes

Qu'est-ce qu'un nouveau (second) cancer
et qu'est-ce qu'une rechute locorégionale d'un premier cancer ?

Est-on sur qu'il s'agit d'un second cancer ?

Table 2. Tumor Classification According to Mean Tumor Size Estimates in Multifocal and Unifocal Tumors

Tumor Dimension and Classification (mm)	Multifocal Tumors (n = 94)			Unifocal Tumors (n = 754)	
	Aggregate Size and Distribution (%)	Dominant Focus Size and Distribution (%)	*P*	Tumor Size and Distribution (%)	*P*
Mean tumor size	31.3	21.1	< .0001*	20.3	< .0001*
Tumor dimensions					
T1a,b, 1-10	4.3	17.0	.009†	20.4	.0003†
T1c, 11-20	28.7	44.7	.03†	42.6	.01†
T2, 21-30	20.2	25.5	.487†	24.7	.410†
T2, 31-40	26.6	7.4	.001†	6.4	< .0001†
T2, 41-50	11.7	3.2	.05†	3.7	.001†
T3, > 50	8.5	2.1	NS†	2.3	.002†

Abbreviation: NS, not significant.
*Two-tailed *t* test used for comparison with multifocal tumors measured using aggregate dimensions.
†A χ^2 test was used for comparison with multifocal tumors measured using aggregate dimensions.

94 des 848 patientes (11.1%) avaient un cancer multifocal parmi lesquels 49 (52.1%) avaient un envahissement ganglionnaire contre 37.5% dans le cas de cancers unifocaux (*p* .007).

Coombs NJ et al. JCO 2005

Comparaison des facteurs prédictifs et pronostiques

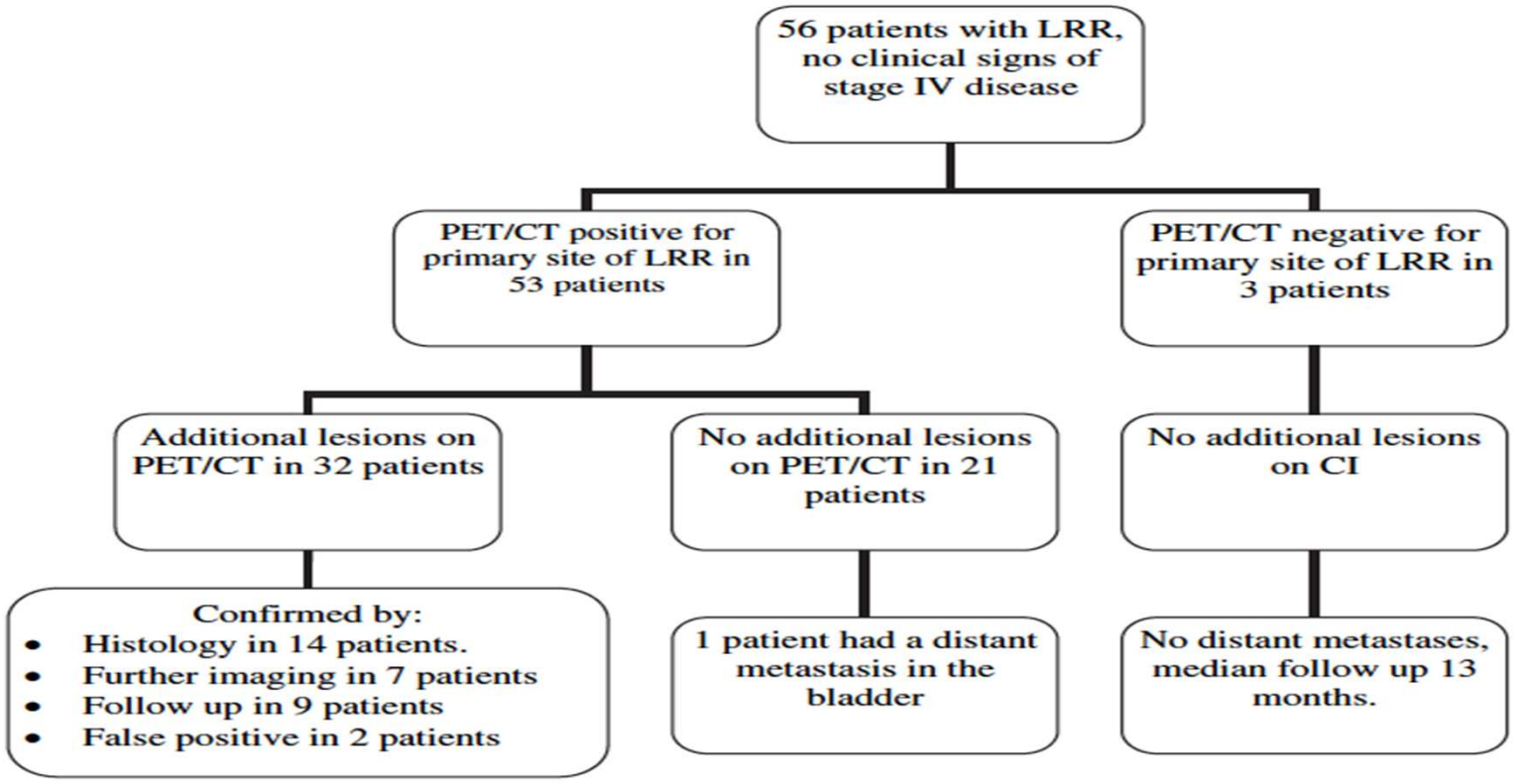
Table 4. Comparison of the expression of ER and PgR in the primary and matching recurrent lesion

Recurrence	Primary		*p*-Value (RR; 95% CI) (Fisher's exact test)
	Positive	Negative	
ER			
Positive	12	3	
Negative	22	32	<0.01 (RR 2.96; 95% CI: 1.05–8.35)
n.a.	0	1	
PgR			
Positive	11	8	
Negative	11	39	<0.01 (RR 1.85; 95% CI: 1.07–3.2)
n.a.	0	1	

n.a., not available.

Rom J et al. Path Res Treat 2006

Est-on sur qu'il s'agit d'une récidive locorégionale ?



Abbreviations: LRR, locoregional recurrence; CI, conventional imaging

Figure. 1. Flowchart of the results of FDG PET/CT.

Aukema TS et al. EJSO 2010

LOCALLY ADVANCED INOPERABLE BC (LABC)

Since LABC patients have a significant risk of metastatic disease, a full staging workup, including imaging of chest, abdomen and bone, prior to initiation of systemic therapy is strongly recommended (LoE: I B), as well as a complete history, physical examination and lab tests.

PET-CT, if available, may be used. (LoE: II B).

NOT YET PUBLISHED

Total number of votes:

1. **YES: 100 (37)**
2. **NO:**
3. **ABSTAIN:**

ABC2 Consensus Conf 2013

Conclusions 1

- La rechute locorégionale est-elle:
  - Un second cancer
  - Le premier cancer
    - Non pris en charge de façon optimale
    - Pris en charge de façon optimale

- La rechute locorégionale est-elle vraiment une rechute locorégionale ?
  - Importance du bilan d'extension

LES ENJEUX DE LA PRISE EN CHARGE DE LA RECIDIVE LOCOREGIONALE

Facteurs de risque “classiques” de récidive locorégionale

- Age jeune
- Marges de résection positives
- Cancer *in situ* étendu
- Embols vasculaires
- Taille tumorale (>pT1)
- Atteinte ganglionnaire (pN1)
- Grade

RPC St Paul de Vence 2011; AGO 2012

Le pronostic des femmes jeunes présentant une rechute locorégionale

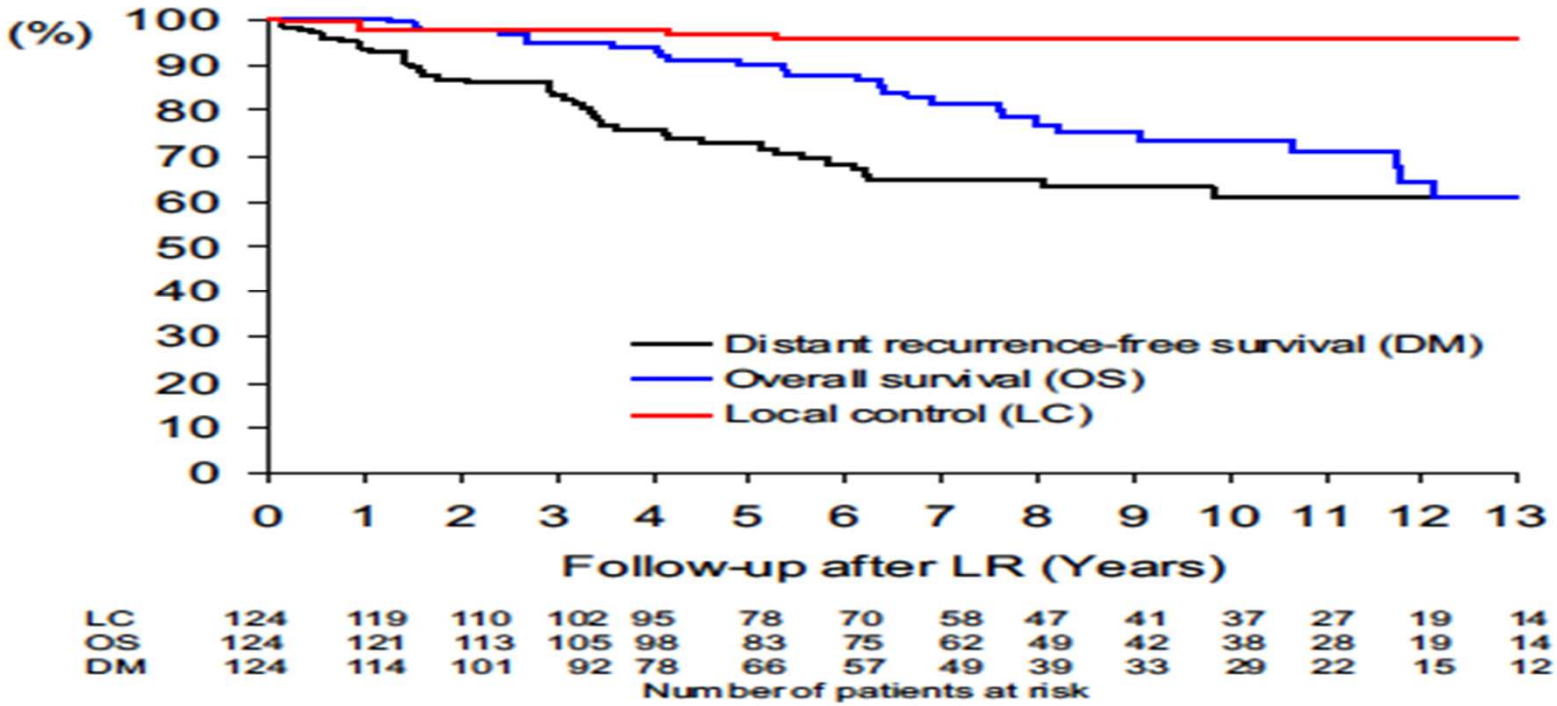


Figure 1. Overall survival, distant recurrence-free survival and local control following diagnosis of local recurrence after breast-conserving treatment ($n = 124$).

Van der Sangen MJC et al. EJSO 2013

Y a t'il un impact du sous-type moléculaire sur le risque de récidive locorégionale ?

- **15 essais (n= 12,592)**

<u>En cas de chirurgie conservatrice (n=7,174):</u>

- **Les cancers luminaux (RH+) ont un risque plus faible de rechute locorégionale**
  - **que les cancers "triples négatifs" (RR 0.38; 95% CI 0.23–0.61)**
  - **que les cancers HER2 "positifs" (RR 0.34; 95% CI 0.26–0.45)**

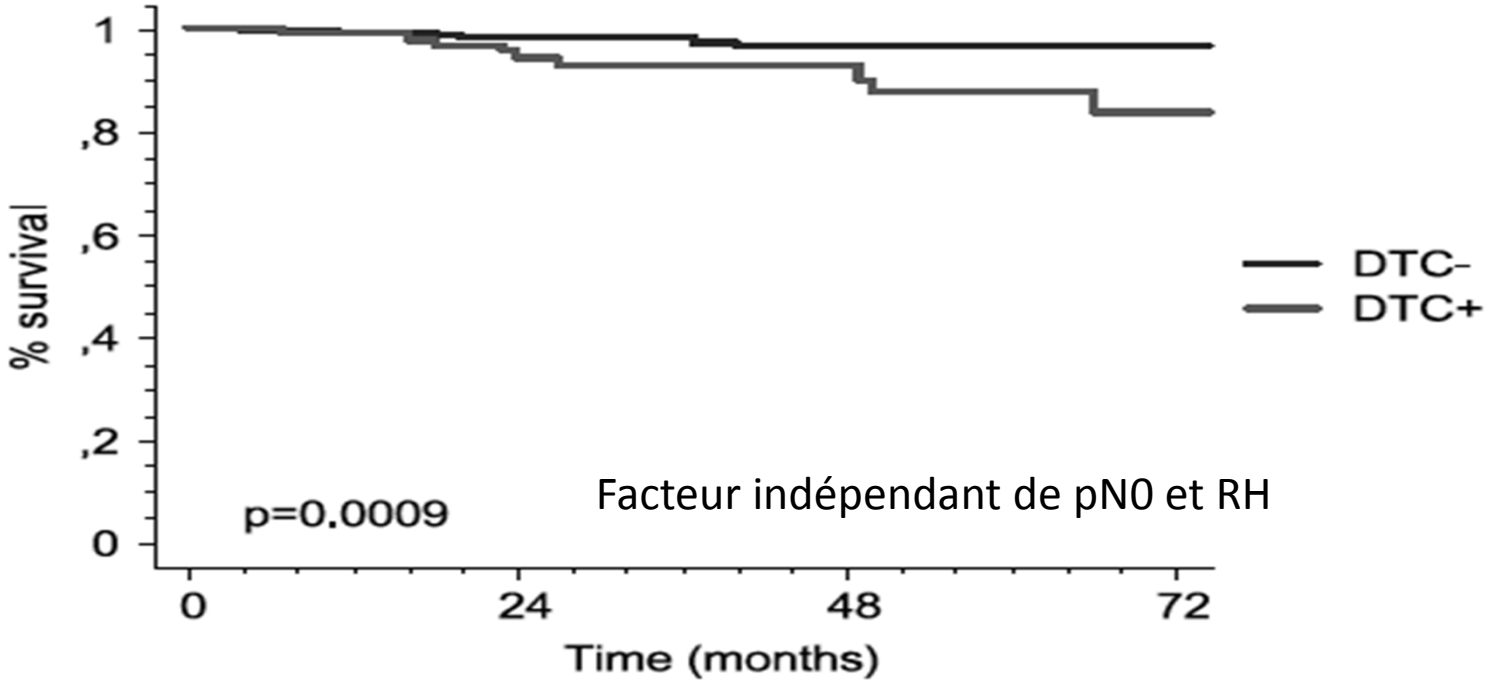
- **Les cancers du sein HER2 "positifs" ont un risque plus élevé de rechute locorégionale que les cancers "triples négatifs" (RR 1.44; 95% CI 1.06–1.95)**

<u>En cas de mastectomie (n=12,592):</u>

- **Les cancers luminaux (RH+) ont un risque plus faible de récidive locorégionale**
  - **que les cancers "triples négatifs" tumors (RR 0.61; 95% CI 0.46–0.79)**
  - **que les cancers HER2 "positifs (RR 0.69; 95% CI 0.54–0.89)**

Lowery A et al. BCRT 2012

Y’a t’il une autre évaluation du risque de récidive locorégionale: les micrométastases



Facteur indépendant de pN0 et RH

DTC-	527	476	282	97
DTC+	94	76	33	20

Bidard FC et al. Clin Cancer Res 2008

Impact des traitements systémiques sur la récidive locorégionale

Le taux de rechute locorégionale est passé de 30 à 15 % en près de 20 ans (ρ = -0.40, p<0.001)

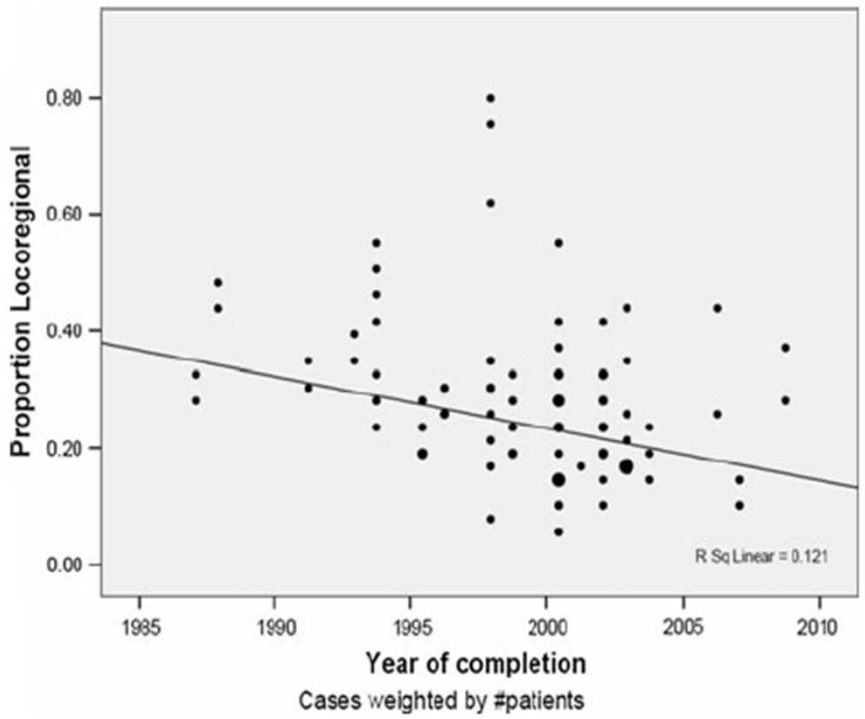


Fig. 1 Proportion of locoregional recurrences over time

L'impact de la chimiothérapie sur la réduction de la rechute locorégionale est moins importante que celle des traitements antihormonaux. (ρ = 0.49 vs. ρ = 0.24)

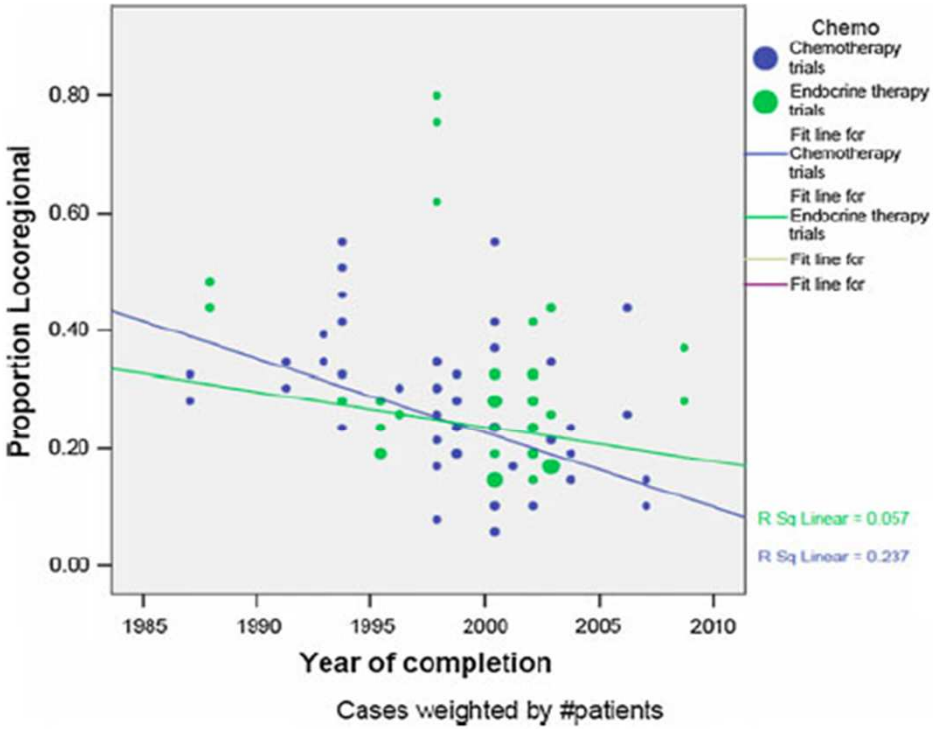
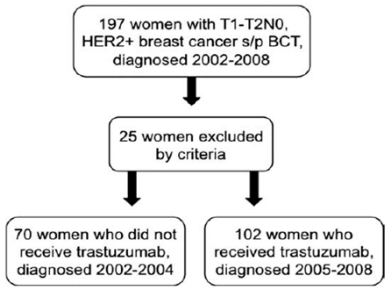


Fig. 2 Proportion of locoregional recurrences for endocrine and chemotherapy over time

Bouganim N et al. BCRT 2013

Impact du traitement antiHER2 sur la récidive locorégionale



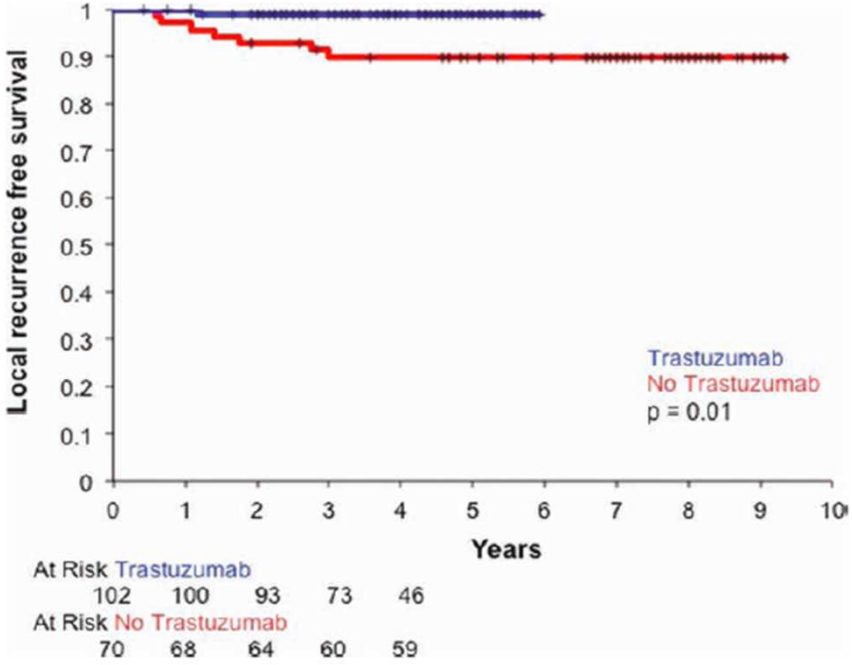


Figure 2. Locoregional recurrence-free survival (LRRFS) is illustrated. At 3 years, the no-trastuzumab cohort (n = 70) had a 90% LRRFS rate (95% confidence interval, 83%-97%), and the trastuzumab cohort (n = 102) had a 99% LRRFS rate (95% confidence interval, 97%-100%). These groups were statistically different (*P* = .01; log-rank test).

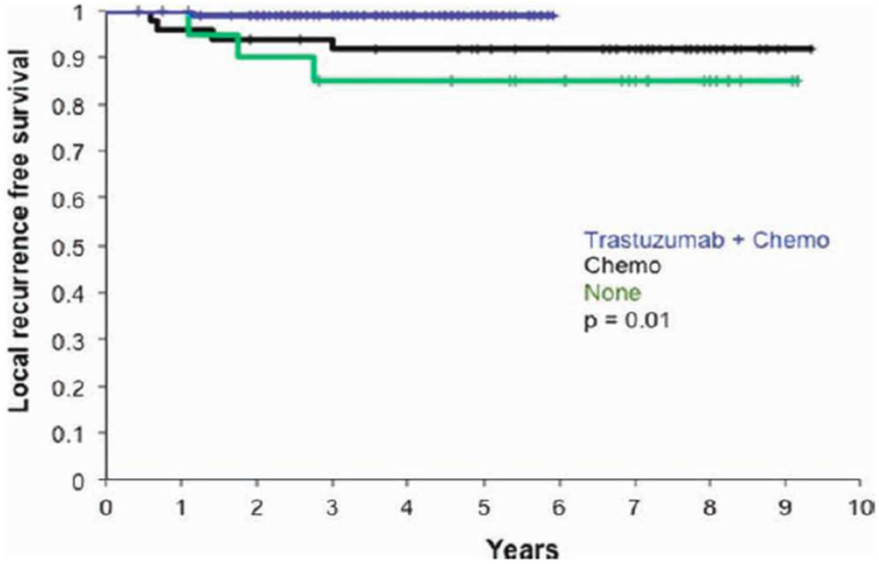


Figure 3. Locoregional recurrence-free survival (LRRFS) is illustrated by chemotherapy (chemo) subgroup. At 3 years, the trastuzumab plus chemotherapy subgroup (n = 102) had a 99% LRRFS rate (95% confidence interval, 97%-100%), the chemotherapy subgroup (n = 51) had a 92% LRRFS rate (95% confidence interval, 85%-100%), and the no-chemotherapy subgroup (n = 19) had an 84% LRRFS rate (95% confidence interval, 68%-100%). These groups were statistically different (*P* = .01; log-rank test).

Kiess AP et al. Cancer 2012

Y a t'il un impact économique de la rechute locorégionale ?

199/1015

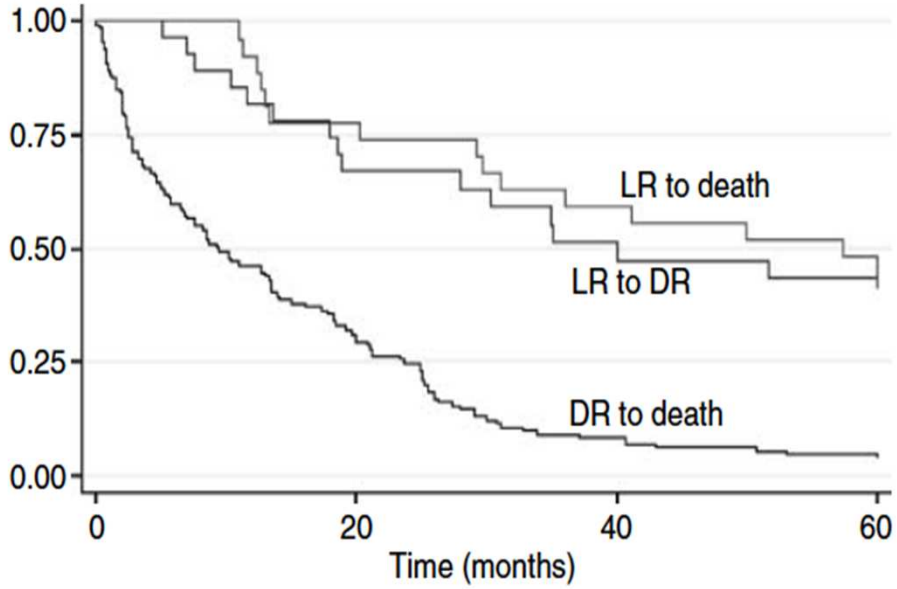


Figure 1 Kaplan–Meier curves for survival and time to metastases.

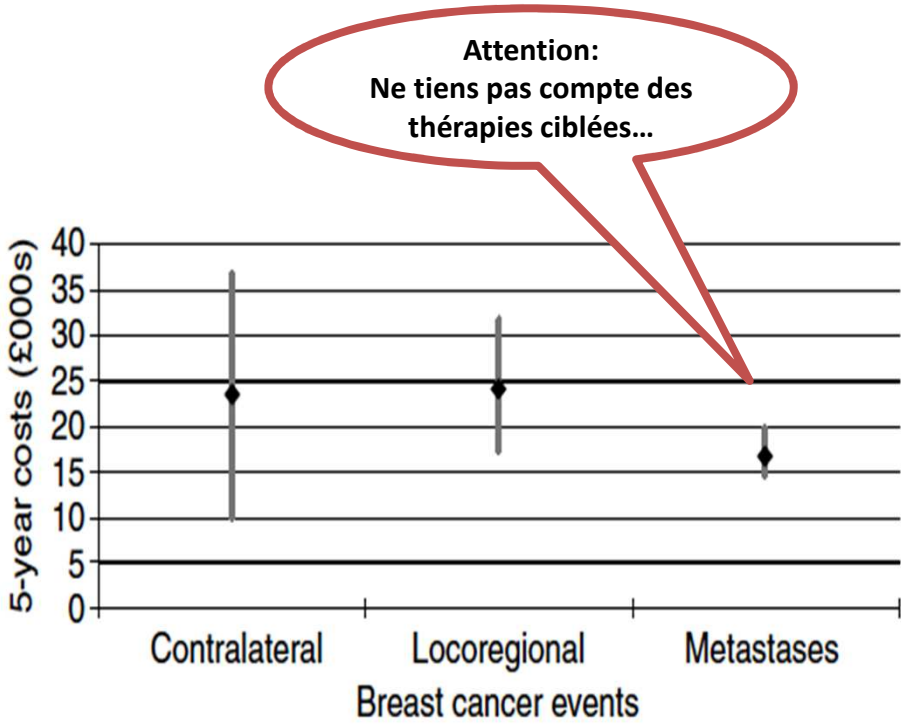


Figure 2 Five-year costs (with 95% confidence intervals) from diagnosis by first recurrent event.

Karnon J et al. BJC 2007

Quel est le pronostic d'une récidive locorégionale ?

Localisation		Fréquence	Survie à 5 ans
Sein ou paroi	Rechute homolatérale (Chir cons. + RT)	10 (2-20)	65 (45-79)
	Rechute pariétale (Mastectomie)	4 (2-20)	50 (24-78)
Axillaire	Après curage axillaire	1 (0.1-8)	55 (31-77)
	Après GS	0.25 (0-2)	ND
Multiple	Multisite **(sein +/- paroi +/- axillaire)**	16 (8-19)	21 (18-23)
	Atteinte sus/sous-claviculaire associée	ND (peu de données)	49% (à 3 ans)

RPC St Paul de Vence 2011; AGO 2012

Conclusions 2

- **La récidive locorégionale est un événement :**
  - non rare
  - grave pouvant engager le pronostic vital
  - plus fréquent dans les formes agressives de cancers du sein
    - Selon l'âge
    - selon les caractéristiques biologiques des cancers
  - entrainant un impact économique non négligeable

- **Les récidives locorégionales semblent diminuer ces 20 dernières années du fait peut-être:**
  - d'une meilleure approche diagnostique des cancers multifocaux et multicentriques
  - D'une meilleure à une prise en charge thérapeutique

LES NIVEAUX DE PREUVE DE L'INTÉRÊT DES TRAITEMENTS SYSTÉMIQUES

Original article

Annals of Oncology 14: 1215–1221, 2003
DOI: 10.1093/annonc/mdg347

Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: definitive results of a phase III randomized trial (SAKK 23/82) comparing tamoxifen with observation

M. Waeber[1], M. Castiglione-Gertsch[2], D. Dietrich[2], B. Thürlimann[3], A. Goldhirsch[2], K. W. Brunner[1] & M. M. Borner[1]*
On behalf of the Swiss Group for Clinical Cancer Research (SAKK)

[1]*Institute of Medical Oncology, Inselspital, University of Bern, Bern;* [2]*SAKK Koordinationszentrum, Bern;* [3]*Kantonsspital, St. Gallen, Switzerland*

Received 28 December 2002; revised 12 April 2003; accepted 23 April 2003

Characteristics	Observation ($n = 40$)		TAM ($n = 39$)	
	No.	%	No.	%
Age (years)				
Median	52		57	
Range	35–75		35–70	
Disease-free interval (months)				
Median	45		39	
Range	2–175		3–149	

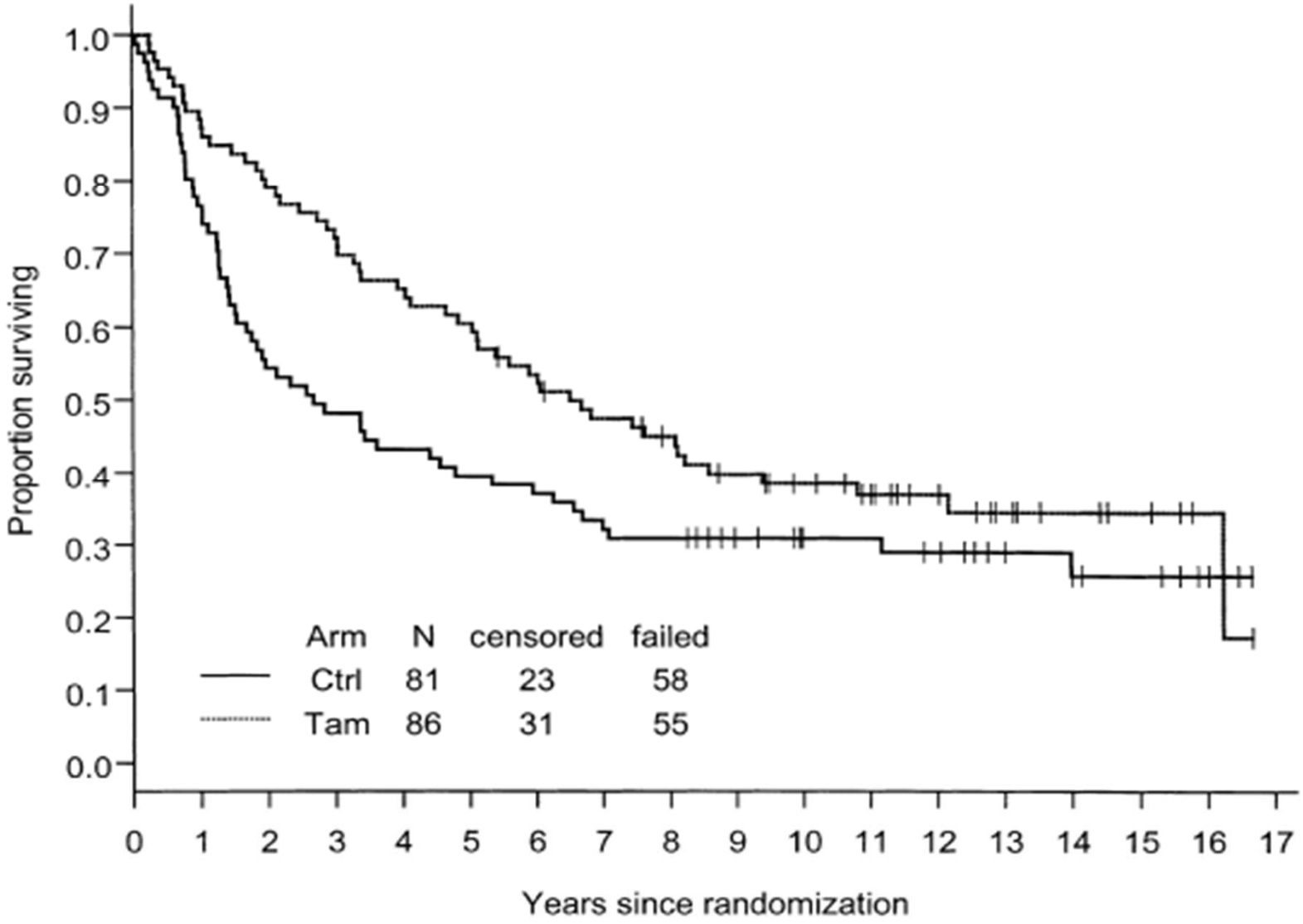


Figure 1. Disease-free survival by treatment. Ctrl, control; Tam, tamoxifen.

Critères impactnat la DFS

Table 2. Multivariate analysis of disease-free survival

Variable	Hazard ratio	95% confidence interval	*P* value
Treatment			
Surgery + radiotherapy	1.00[a]		
Surgery + radiotherapy + tamoxifen	0.57	0.39–0.84	0.004
Disease-free interval			
≤12 months	1.00[a]		
>12 months	0.48	0.26–0.88	0.017
Primary tumor size			
<2 cm	1.00[a]		
≥2 cm	1.25	0.81–1.92	0.325
Pretreatment adjuvant chemotherapy			
Yes	1.00[a]		
No	1.44	0.81–2.56	0.210
Nodal involvement (primary tumor)			
Negative	1.00[a]		
Positive	1.55	0.88–2.71	0.128
Menopausal status (first relapse)			
Premenopausal	1.00[a]		
Postmenopausal	1.71	1.00–2.92	0.051
Skin lesion (first relapse)			
No	1.00[a]		
Yes	1.04	0.57–1.90	0.889
Nodal involvement (first relapse)			
No	1.00[a]		
Yes	1.79	0.95–3.38	0.071
Hormonal receptors			
Unknown	1.00[a]		
Positive	0.96	0.65–1.43	0.851
Age			
≤65 years	1.00[a]		
>65 years	1.34	0.83–2.16	0.234

[a]Reference values.

- TAM
- Interval sans maladie
- Statut ménopausique
- Atteinte ganglionnaire

Table 3. Cumulative incidence rates of first failure events

	First failure incidence (%)						
	3 year		5 year		10 year		
	Ctrl	TAM	Ctrl	TAM	Ctrl	TAM	*P* value
Local relapse alone	21	5	25	8	31	16	0.011
Distant relapse alone	22	15	25	22	25	32	0.387
Distant + local relapse	2	5	4	5	4	7	0.348
Death/second cancer	6	3	7	5	10	7	0.541

Ctrl, control; TAM, tamoxifen.

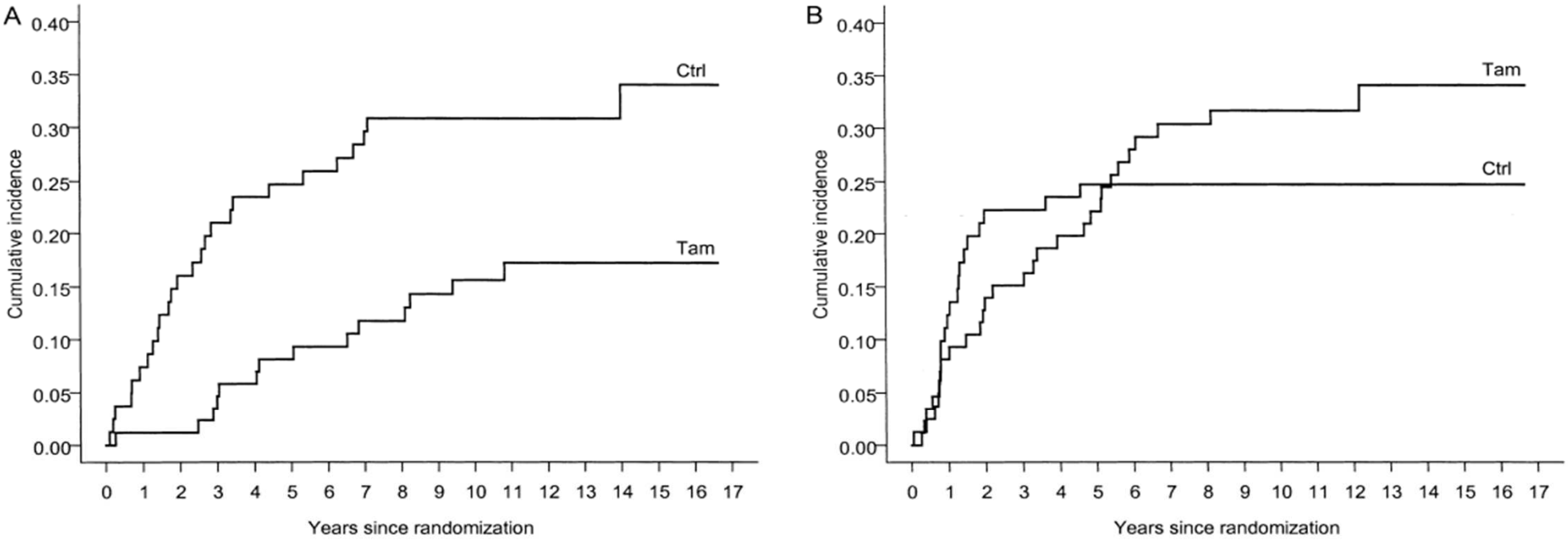


Figure 2. Cumulative incidence analysis of site of first relapse. (**A**) Local failure; (**B**) distant failure. Ctrl, control; Tam, tamoxifen.

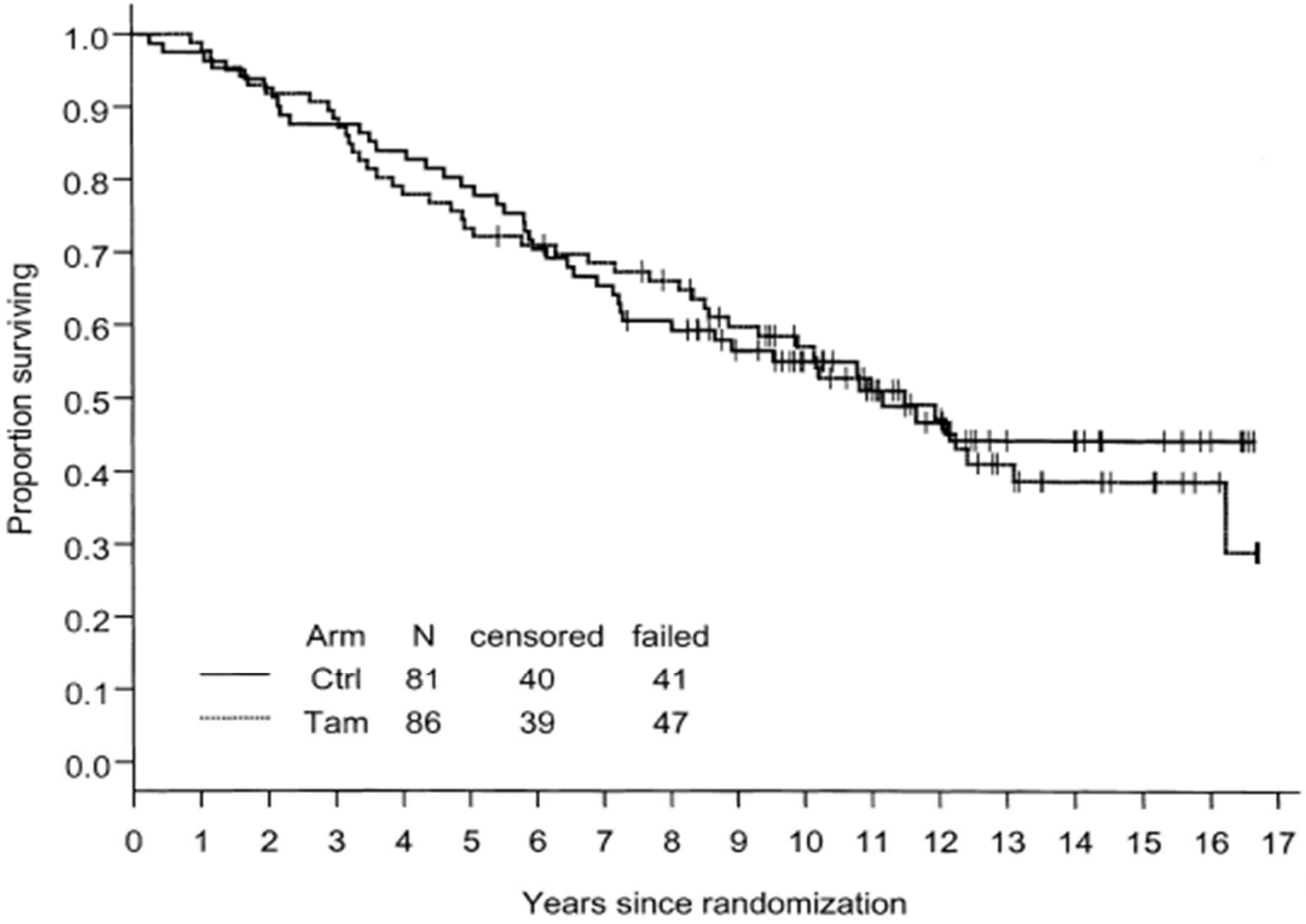


Figure 3. Overall-survival by treatment. Ctrl, control; Tam, tamoxifen.

First Isolated Locoregional Recurrence Following Mastectomy for Breast Cancer: Results of a Phase III Multicenter Study Comparing Systemic Treatment With Observation After Excision and Radiation

By M. Borner, M. Bacchi, A. Goldhirsch, R. Greiner, F. Harder, M. Castiglione, W.F. Jungi, B. Thürlimann, F. Cavalli, J.P. Obrecht, S. Leyvraz, P. Alberto, H. Adam, M. Varini, T. Loehnert, H.J. Senn, U. Metzger, and K. Brunner for the Swiss Group for Clinical Cancer Research

J Clin Oncol 12:2071-2077. © 1994

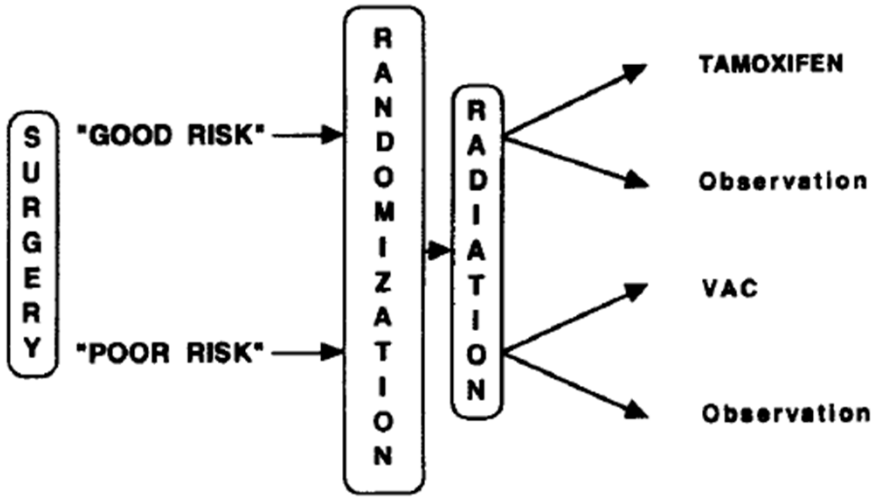


Fig 1. Study design.

Table 1. Characteristics of Eligible Patients

Characteristic	Observation (n = 81) No.	%	TAM (n = 86) No.	%
Age (years)				
Median	55		58	
Range	27-79		31-78	
DFI (months)				
Median	35		33	
Range	2-252		3-149	
Primary tumor				
Size (cm)				
< 2	29	36	20	23
2-5	48	59	62	72
> 5	3	4	3	3
Unknown	1	1	1	1
Axillary node involvement				
Negative	45	56	42	49
Positive	36	44	41	48
Unknown	0	0	3	3
Postmastectomy radiation	3	4	2	2
Adjuvant chemotherapy				
Yes	32	40	38	44
No	48	59	47	55
Unknown	1	1	1	1
Locoregional recurrence				
Localization				
Chest wall and locoregional skin	76	94	71	83
Regional nodes (± skin)	7	9	19	22
Receptor status				
ER+	52	64	59	69
PR+	35	43	34	40
Menopausal status				
Pre-	20	25	15	17
Post-	61	75	71	83

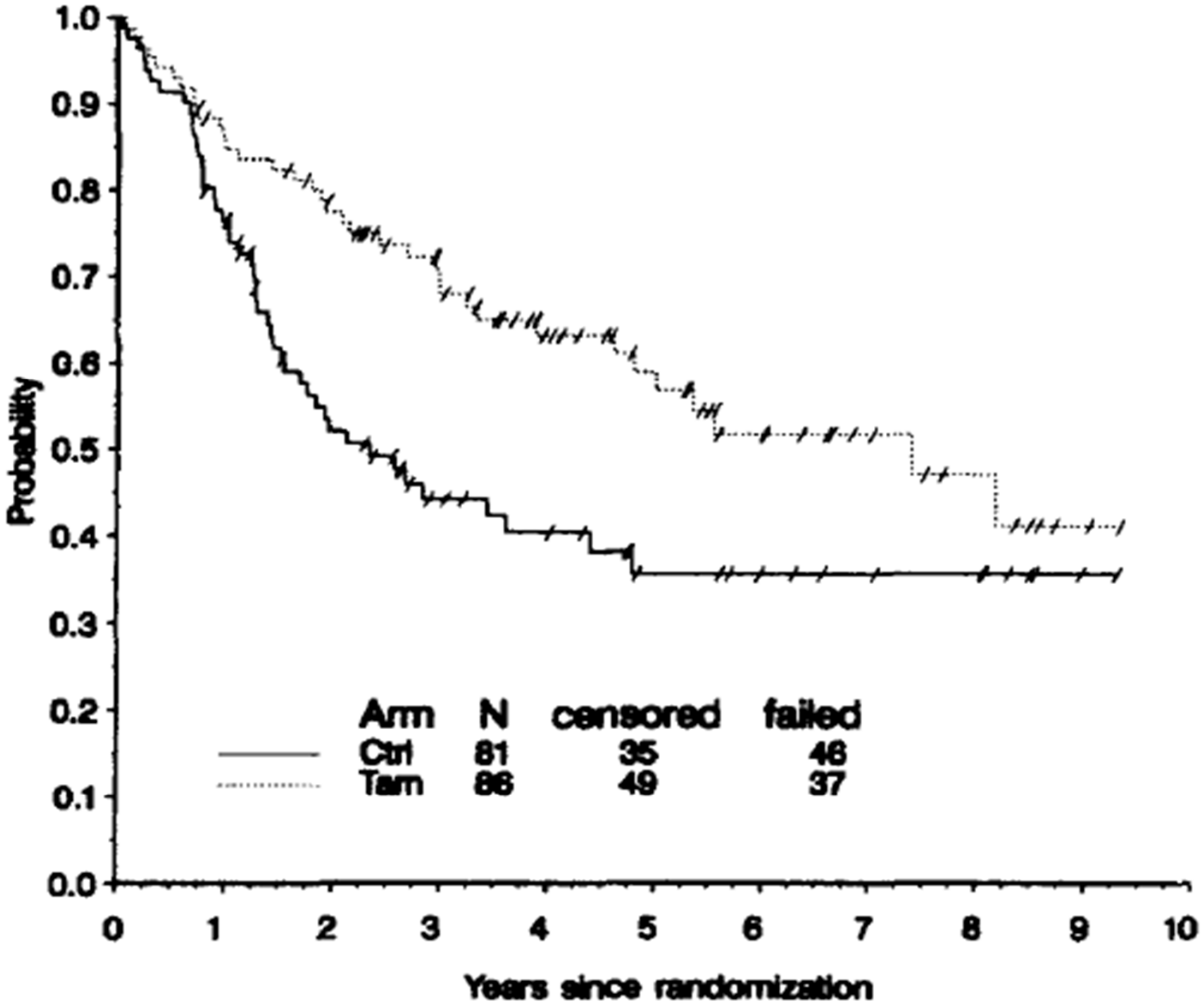


Fig 2. DFS by treatment.

Critères impactnat la DFS

Table 2. Cox Regression Analysis (DFS)

Variable	Hazards Ratio	95% Confidence Interval (reference)	P
Primary tumor size (cm)			
≤ 2			
> 2	0.99	.61-1.61	.97
Nodal involvement primary			
Negative			
Positive	1.24	.64-2.44	.55
Adjuvant chemotherapy			
Yes			
No	1.34	.69-2.61	.39
Disease-free interval (months)			
≤ 12			
> 12	.45	.23-.89	.02
Menopausal status (relapse)			
Pre-			
Post-	1.70	.95-3.05	.08
Nodal involvement (relapse)			
No			
Yes	2.25	.96-5.25	.06
Treatment arm			
Local treatment alone			
Local treatment + TAM	.49	.30-.78	.003

- Interval sans maladie

- Statut ménopausique

- Atteinte ganglionnaire

- TAM

Table 3. Cumulative Incidence Rates of First Failure Events

Type of Event	First Failure Incidence (%)				
	3-Year		5-Year		
	Observation	TAM	Observation	TAM	*P*
Local relapse alone	23	9	28	10	<.001
Distant relapse alone	23	14	25	25	NS
Distant + local relapse	2	2	5	2	NS
Death/second cancer	6	4	6	4	NS
Total	54	29	64	41	

Abbreviation: NS, not significant.

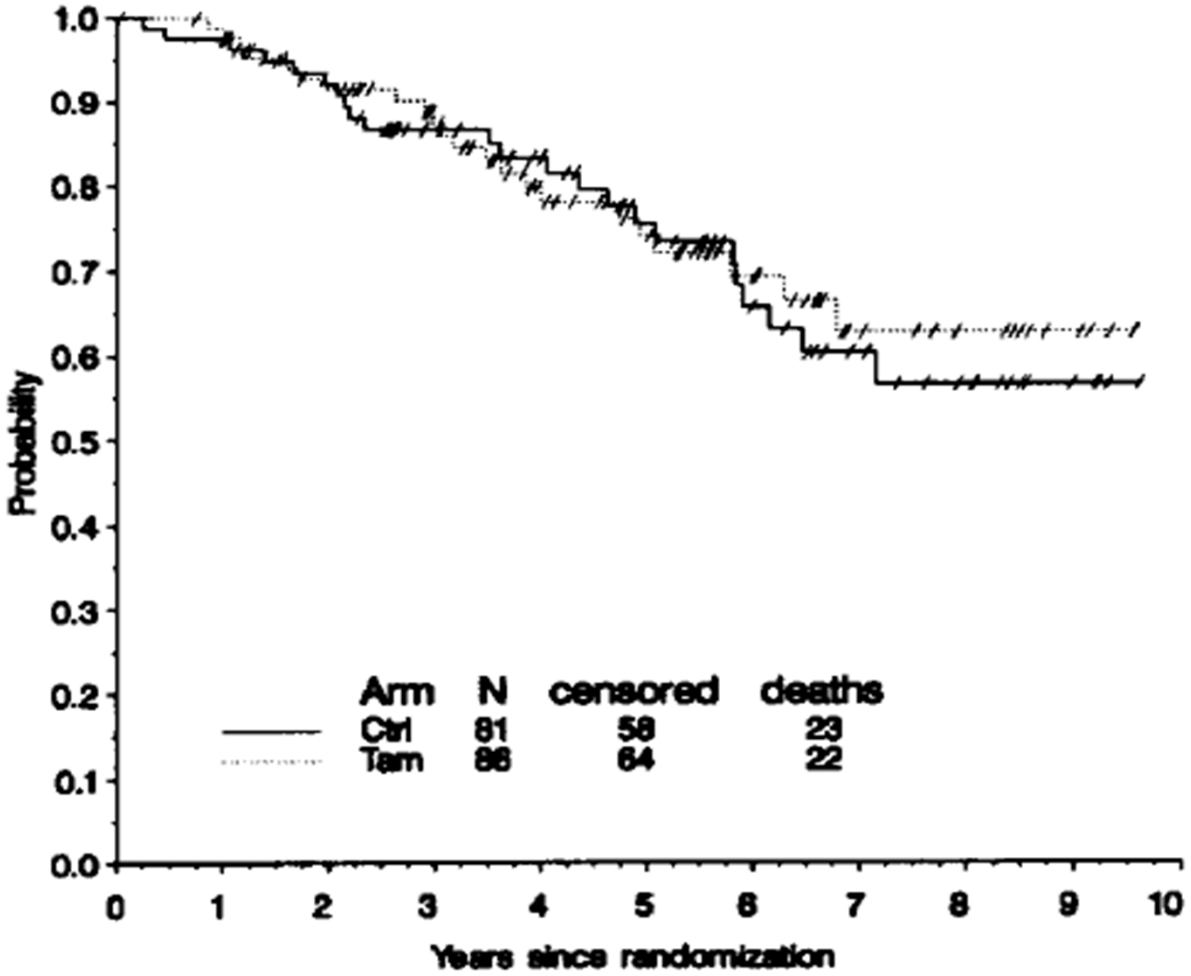


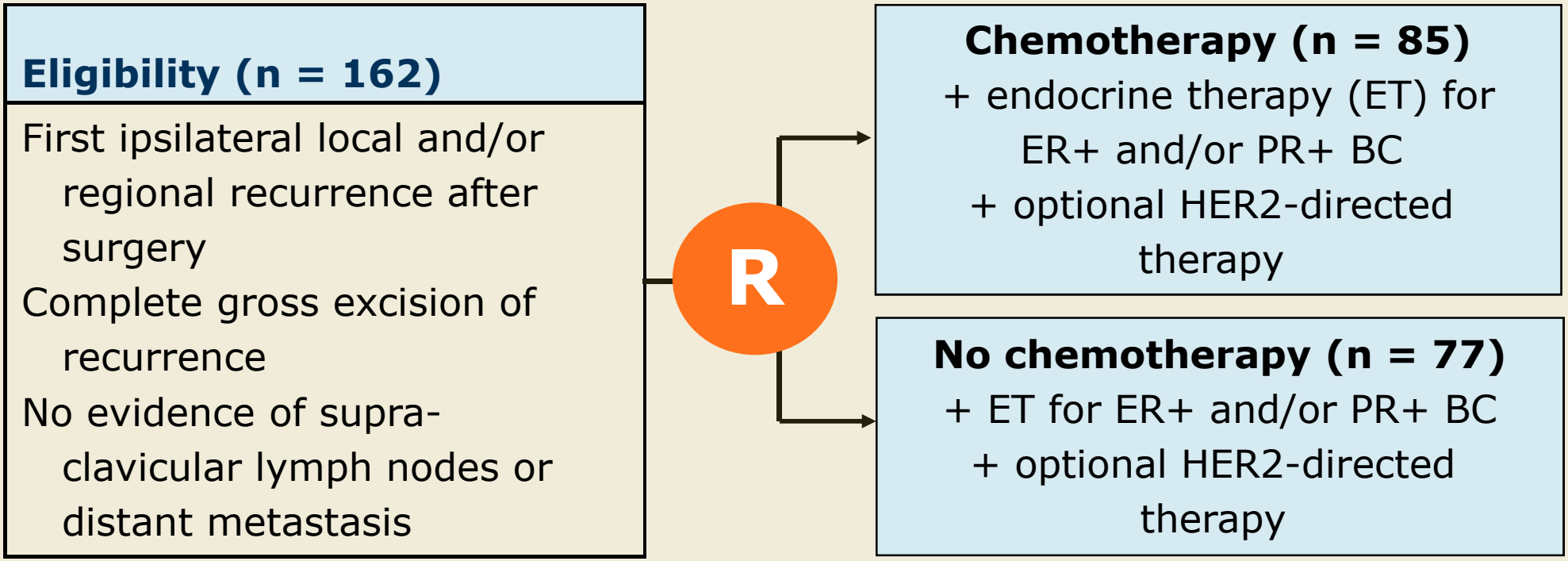
Fig 4. OS by treatment.

Chemotherapy Prolongs Survival for Isolated Local or Regional Recurrence of Breast Cancer: The CALOR Trial (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer; IBCSG 27-02, NSABP B-37, BIG 1-02)

Aebi S et al.

Proc SABCS 2012;Abstract S3-2.

Phase III CALOR Trial Design



- Patients with resected ILRR were stratified according to prior chemotherapy, ER and/or PR status of the recurrent tumor and location of recurrence prior to randomization.
- Chemotherapy chosen by investigators: ≥2 drugs, 3-6 mo of therapy
- Radiation therapy mandatory for patients with microscopically involved margins

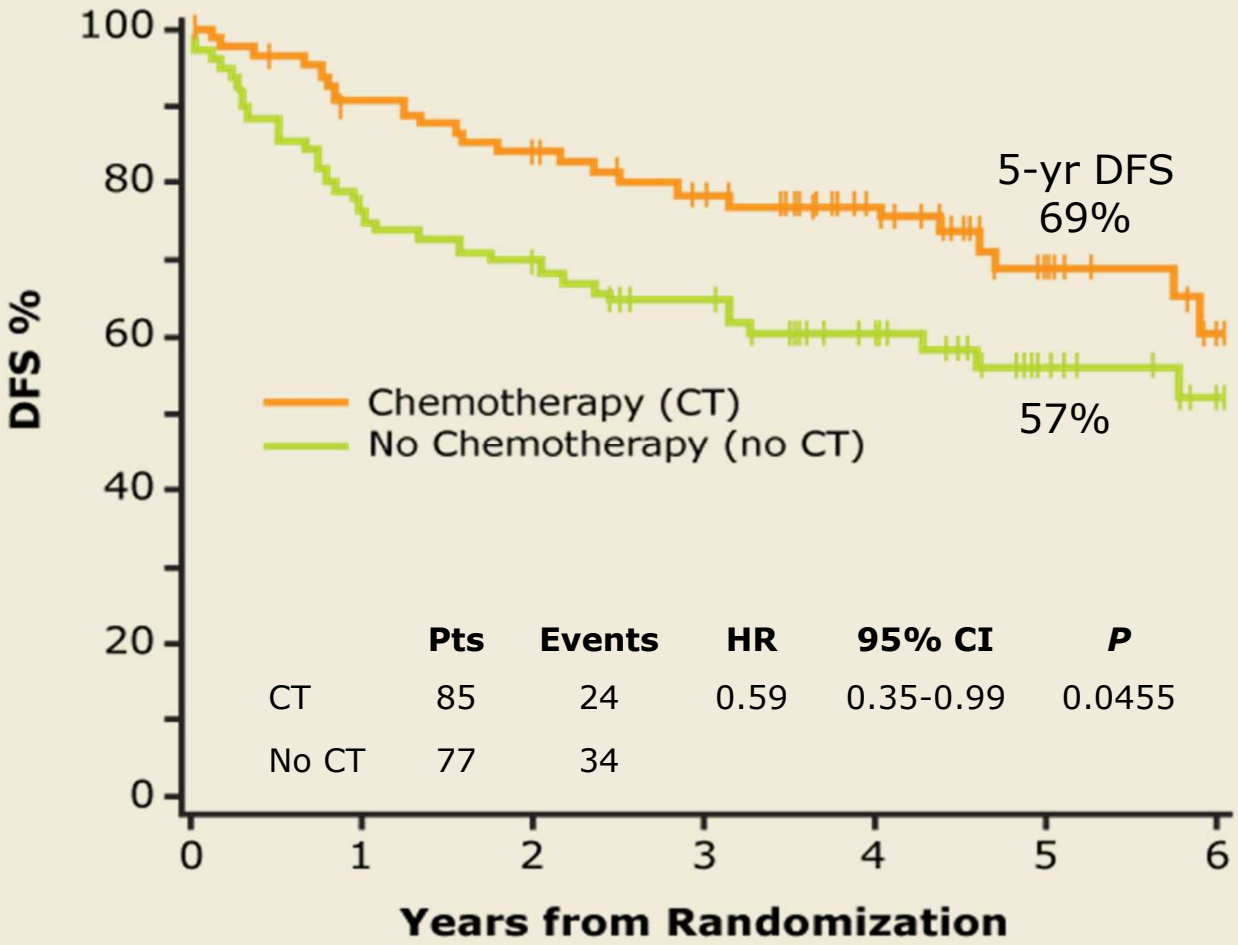
Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Statistical Considerations

- Original sample size for hazard ratio (HR) of 0.74:
  - 977 patients, 347 DFS events
- Due to low accrual rate and newer, more effective chemotherapies, amendment 3 in 2008 resulted in a revised sample size for HR of 0.6:
  - 265 patients, 124 events
  - 5-year DFS for the observation group = 50%
  - $1-\beta = 0.8$, log-rank $\alpha = 0.05$, 1 interim analysis
- On January 31, 2010, the trial was closed with 162 patients (no interim analysis).
- Analysis was conducted when the median follow-up reached 4 years, with a minimum follow-up of 2.5 years.

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

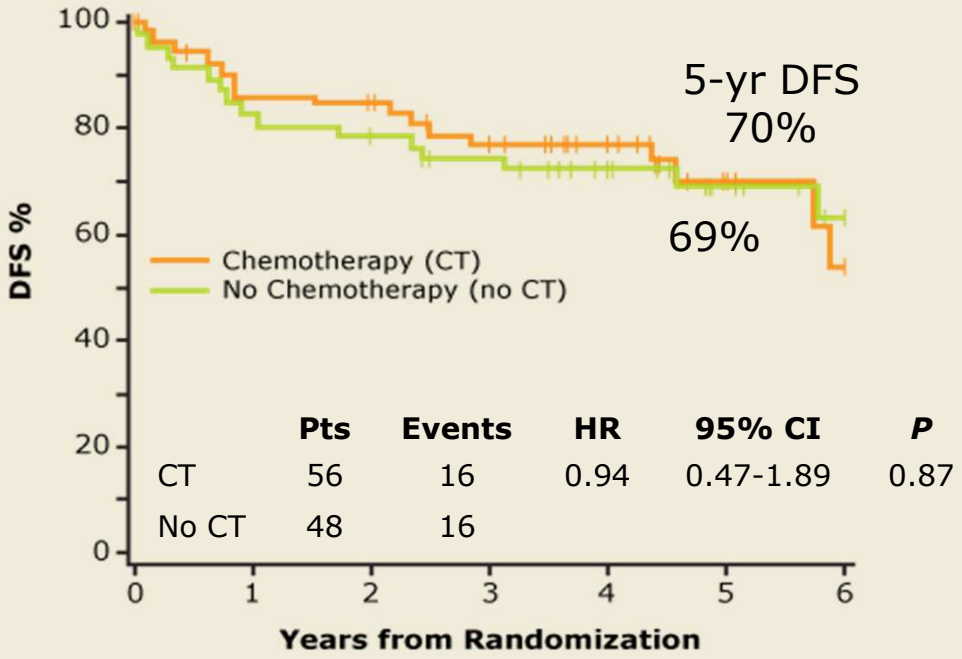
DFS: Overall Population



With permission from Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

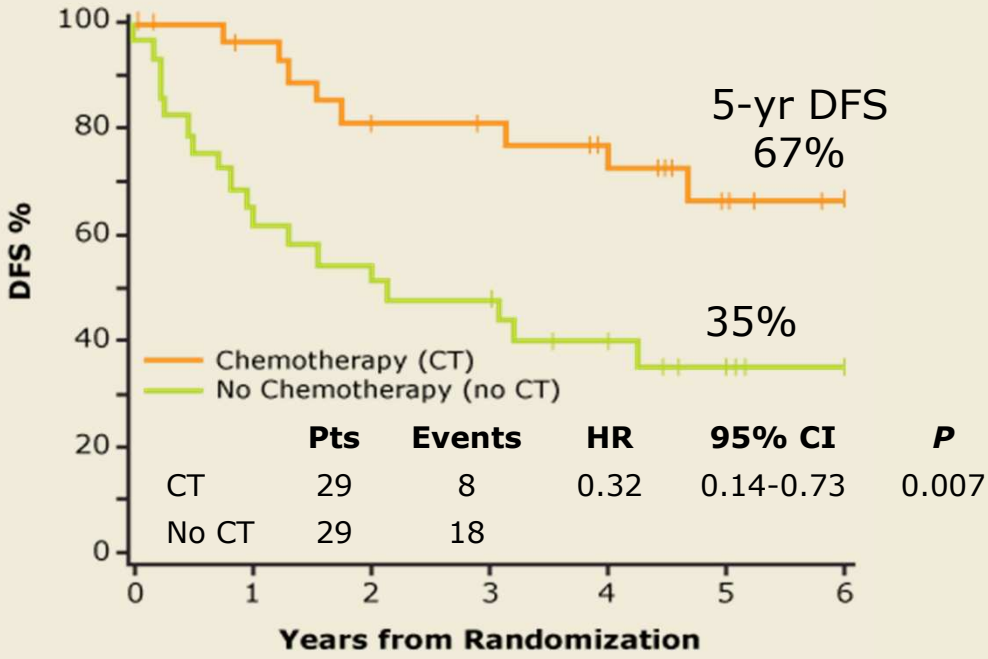
DFS by ER Status

ER+



	Pts	Events	HR	95% CI	*P*
CT	56	16	0.94	0.47-1.89	0.87
No CT	48	16			

ER-



	Pts	Events	HR	95% CI	*P*
CT	29	8	0.32	0.14-0.73	0.007
No CT	29	18			

Univariate interaction term: Treatment x ER: $p = 0.044$

With permission from Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

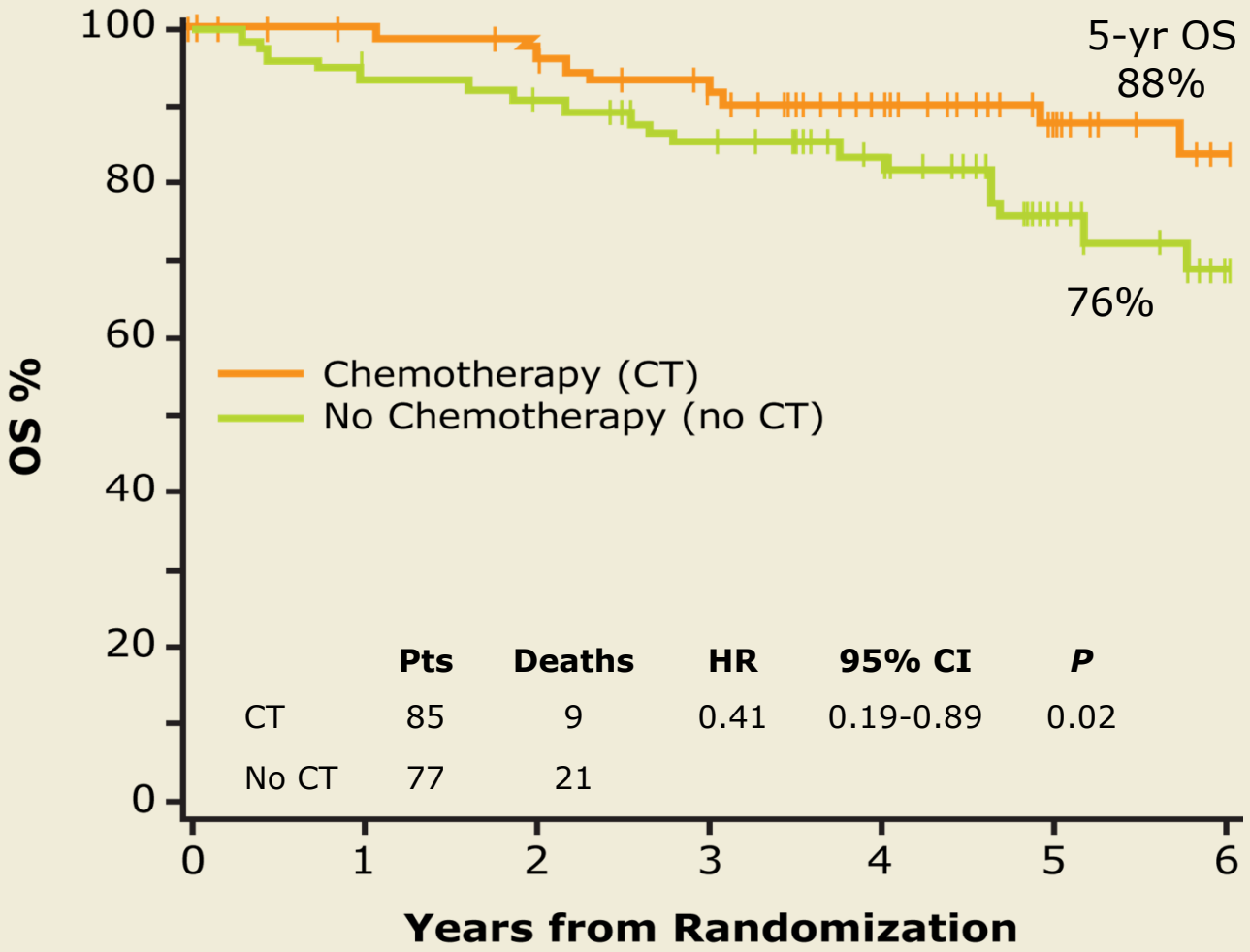
Multivariate Analysis of DFS

	Hazard ratio	*p*-value
ER status (positive/negative)	0.76	0.32
Location of ILRR		
Breast	Reference	Reference
Mastectomy scar or chest wall	0.90	0.79
Lymph nodes	0.99	0.99
Prior chemotherapy (yes/no)	1.002	0.99
Interval from primary surgery (per y)	0.91	0.002
Treatment (chemotherapy/none)	0.50	0.01

- Interaction term:
  - Treatment x ER in ILRR: $p = 0.05$

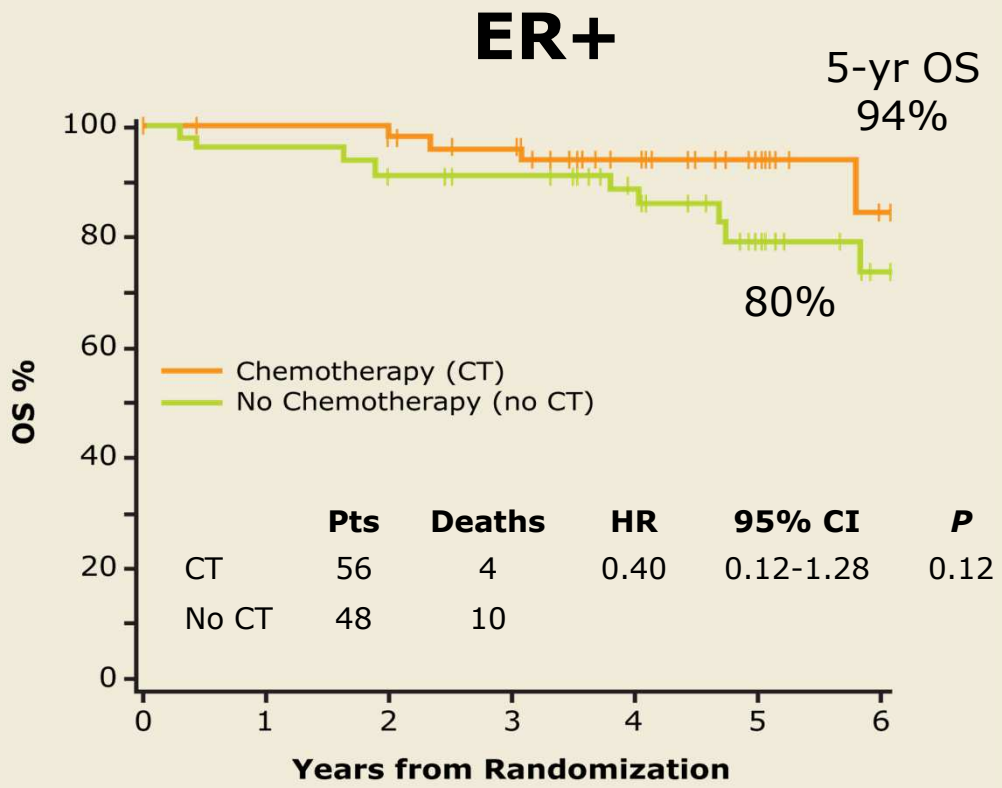
Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

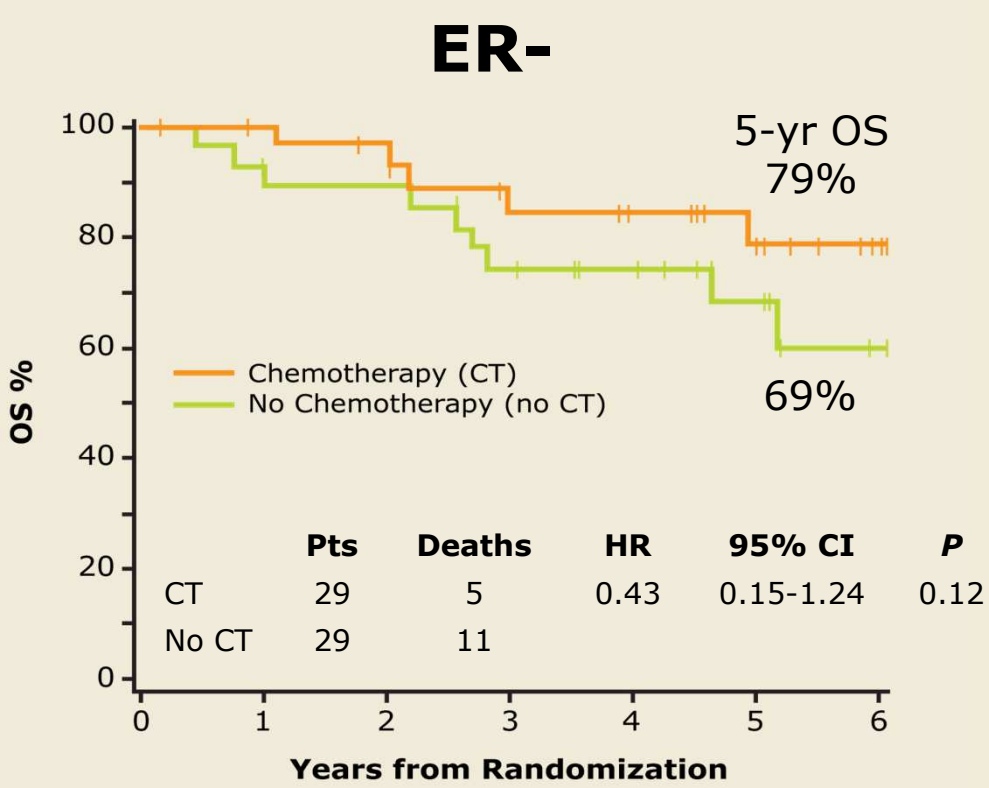
OS: Overall Population



With permission from Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

OS by ER Status





With permission from Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Multivariate Analysis of OS

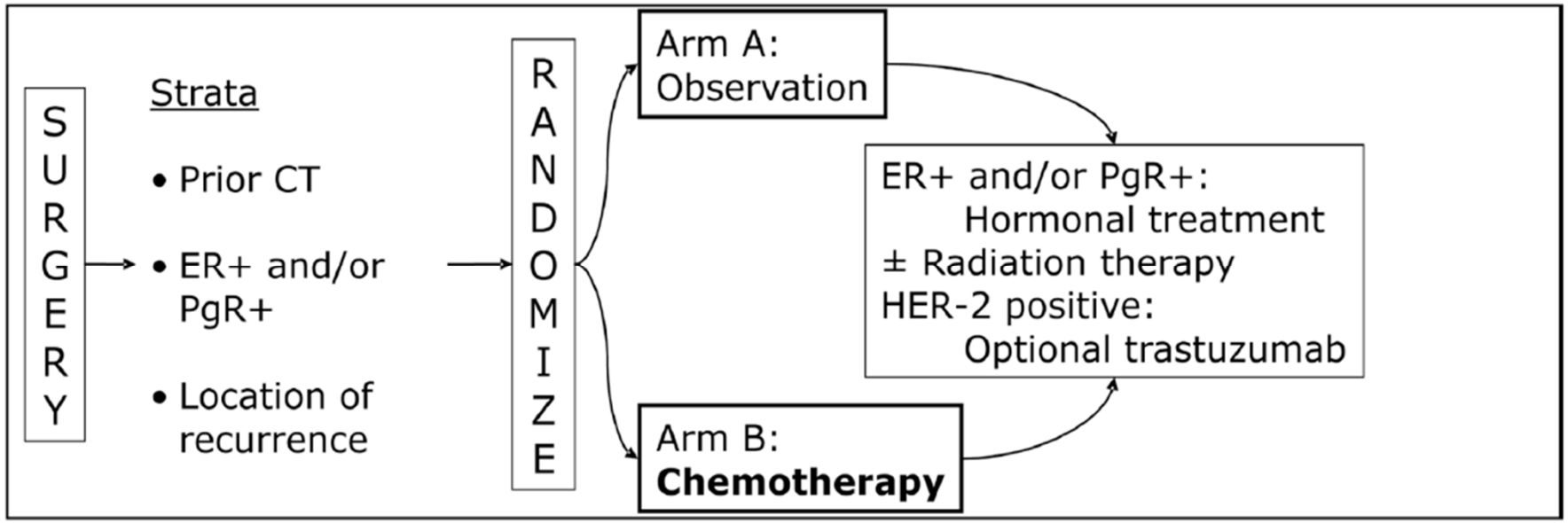
	Hazard ratio	*p*-value
ER status (positive/negative)	0.76	0.49
Location of ILRR		
Breast	Reference	Reference
Mastectomy scar or chest wall	0.73	0.55
Lymph nodes	0.75	0.65
Prior chemotherapy (yes/no)	1.97	0.12
Interval from primary surgery (per y)	0.80	0.0008
Treatment (chemotherapy/none)	0.37	0.02

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Progress on BIG 1-02/IBCSG 27-02/ NSABP B-37, A Prospective Randomized Trial of Evaluating Chemotherapy after Local Therapy for Isolated Locoregional Recurrences of Breast Cancer

Irene L. Wapnir, MD[1,2], Stefan Aebi, MD[3], Shari Gelber, MS[4,5], Stewart J. Anderson, PhD[1,6], István Láng, MD[7], André Robidoux, MD[8], Eleftherios P. Mamounas, MD, MPH[1,9], and Norman Wolmark, MD[1,10]

Ann Surg Oncol. 2008 November ; 15(11): 3227–3231.



Conclusions 3

- Aucune étude de niveau de preuve 1
- Un traitement antihormonal en situation « adjuvante » semble réduire le risque de seconde rechute en cas de rechute locorégionale
  - Il s'agit du tamoxifène
  - Il y a essentiellement un impact sur les rechutes locales
- Un traitement par chimiothérapie en situation « adjuvante » réduit le risque de seconde rechute en cas de rechute locorégionale
  - Pas de chimiothérapie standard
  - Essentiellement dans la population RH-
- Aucune données sur les rechutes HER2 positives

LES RECOMMANDATIONS ACTUELLES

Ipsilateral Recurrence after R0-Resection Systemic Treatment

	Oxford LoE	AGO GR	
➢ Endocrine therapy in endocrine responsive tumors after patho-histological re-evaluation of the recurrent tumor (ER, PgR, HER2)	2b	B	++
➢ Chemotherapy	3b	C	+/-
➢ HER2-targeted therapy in HER2 overexpressing tumors	5	D	+/-
➢ Trastuzumab in trastuzumab-naïve pts.	5	D	+

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Systemic Treatment

Guidelines Breast
Version 2012.1

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)	**Oxford LoE**	**AGO GR**	
➢ **Endocrine therapy in endocrine responsive tumors**			
➢ **Postmenopause**	2b	B	++
➢ **Premenopause**	4	C	++
➢ **Chemotherapy (pre- or postoperatively)**			
➢ **Resectable endocrine non-responsive tumors**	3b	C	+/-
➢ **Resectable endocrine responsive tumors**	5	D	+/-
➢ **In non-resectable tumors**	2b	B	++
➢ **HER2-targeted therapy in HER2-overexpressing tumors**			
➢ **In resectable tumors**	5	D	+/-
➢ **Trastuzumab in trastuzumab-naïve pts.**	5	D	+
➢ **In non-resectable tumors (+ chemotherapy)**	1b	A	++

RPC

Nice St Paul de Vence 2011

Cancers du sein
Soins de support

Prise en charge d'une récidive homolatérale d'un cancer du sein:

Prise en charge thérapeutique

B. BARREAU, F. ETTORE, S. GIARD,
J.M. HANNOUN-LEVI, K. KHALDOUN, O. TREDAN

Recommandations pour le traitement systémique

Niveau 4 Grade C

Facteurs décisionnels

- Facteurs pronostiques et prédictifs validés
- Intervalle libre [primo-tumeur – récidive]
- TTT adjuvant réalisé pour la primo-tumeur

Recommandations traitement systémique (1)

- **RL RH+ et IL > 2 ans :**
  - (re) mise en place d'une HT si :
    - non prescrite initialement
    - patiente non-observante
    - RL survenant >1 an après la fin de l'HT initiale
  - changement d'HT si :
    - RL survenant pdt l'HT ou < 1 an après la fin de celle-ci
- **Durée de traitement à partir de la RL = 5 ans**

Recommandations traitement systémique (2)

- **RL RH+ et IL < 2 ans et TTT adjuvant initial adapté (HT ou CT) :**
  - pas de CT systématique
  - discuter le changement d'HT

Recommandations traitement systémique (3)

- **RL RH- :**
  - pas d'HT
  - proposer une CT si pas de CT adjuvante initiale
  - discuter la prescription de taxanes ou d'anthracyclines si CT adjuvante initiale sans taxane ou sans anthracycline
  - si CT initiale avec taxanes et anthracyclines:
    - discuter CT si IL > 2 ans

Recommandations traitement systémique (4)

- **RL et HER2+++ :**
  - TTT par trastuzumab peut être proposé pour une durée de 1an
  - Pas de recommandation en cas de RL sous trastuzumab

Vraie RL ou 2ème cancer ?

Pas de données suffisantes pour proposer

une prise en charge diagnostique et thérapeutique, locale et générale, différente

entre vraie RL et nouveau cancer

Conclusions 4

- La prise en charge systémique après une rechute locorégionale repose à ce jour sur des considérations de « bon sens » mais non sur des niveaux de preuve scientifique

- En cas de rechute tardive de bon pronostic
  - Second cancer à traiter en fonction des paramètres pronostiques

- En cas de rechute précoce de mauvais pronostic
  - S'assurer de l'absence de maladie métastatique
  - Indiquer un traitement systémique en fonction des paramètres prédictifs de réponse

MERCI