DESESCALADE THERAPEUTIQUE POUR LES CCIS JUSQU'OU PEUT-ON ALLER?

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RAPPELS (1)

- ~ 6500 nouveaux CCIS/an en France
- Survie globale à 10 ans ~ 96%
- Taux de récidives locales (RL):

MASTECTOMIE	~ 2% (> 80% invasives)
CHIR.CONSERV.	~ 20-25% (~ 60% invasives)
CHIR.CONS.+RT	~ 8-12% (~ 50% invasives)

NB: ≤ 5% de RL dans les études récentes (surtout avec TAMOXIFENE associé)

RAPPELS (2)

META-ANALYSE DE BOYAGES

Analyse des taux de RL selon les traitements:

(CANCER 1999; 85: 616-628)

Mastectomie:	*1.4%*
Chir. Cons.:	*22.5%*
CC + RT:	*9%*

PRONOSTIC DES RL invasives:
17% de métastases après RL invasives

(CUTULI B, CANCER-RADIOTHERAPIE; 2013:17: 196-201)

MORTALITE A 15 ANS après RL d'un CCIS: 16%

(SOPIK V, BCRT 2016; 155: 175-185)

- **Dans l'actualisation à 15 ans de l'essai EORTC, la survenue d'une RL invasive diminue dramatiquement la survie, qui passe de 95% à 60%**

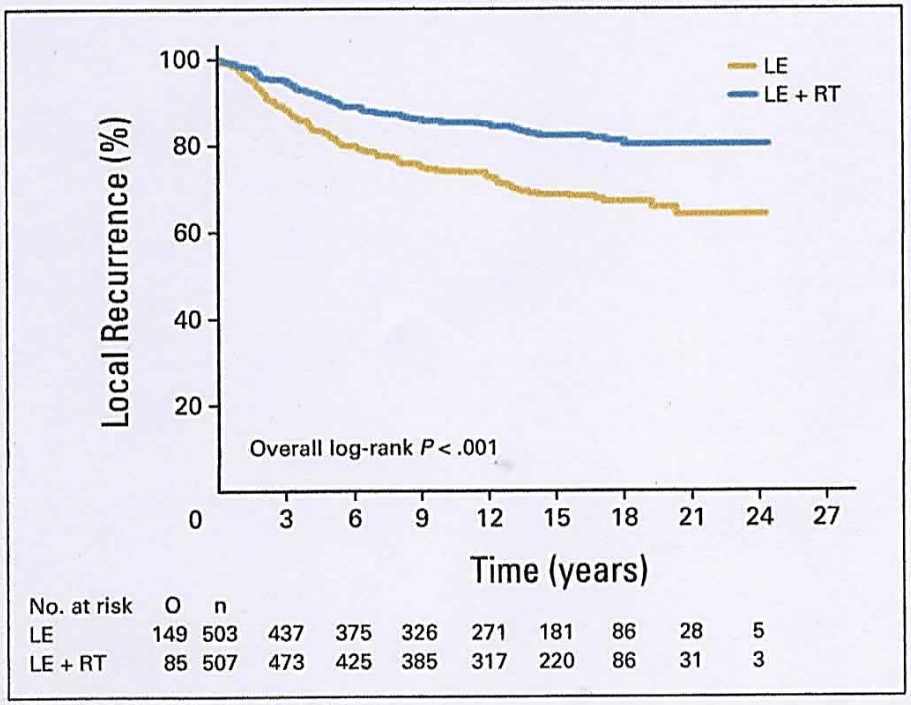


Fig 2. Time to local recurrence by treatment arm. LE, local excision; n, number of patients; O, observed; RT, radiotherapy.

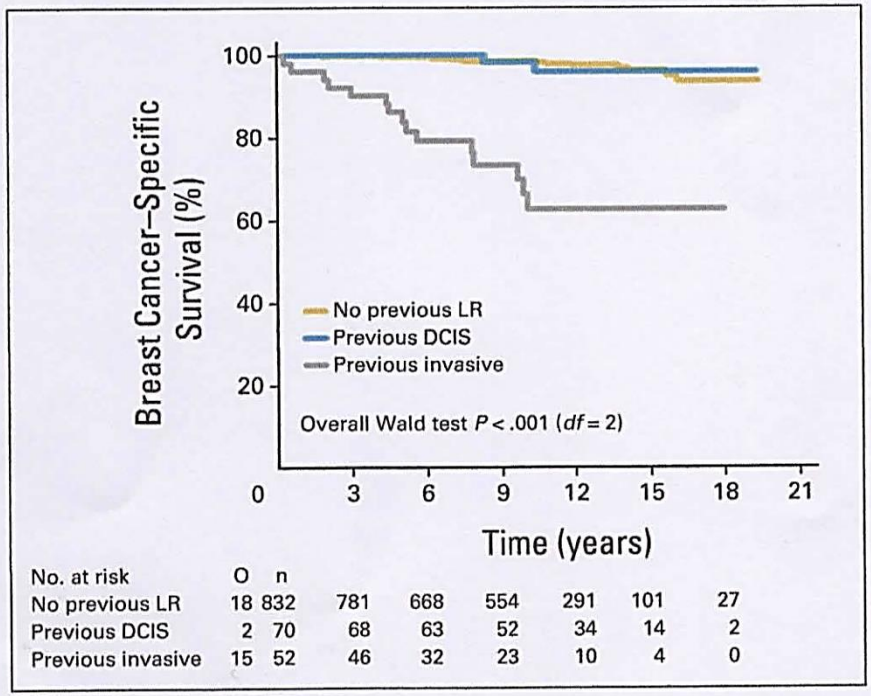


Fig 4. Breast cancer–specific survival after a local recurrence (LR) 5 years after random assignment. DCIS, ductal carcinoma in situ; n, number of patients; O, observed.

NSABP B-17/ B-24 TRIALS CUMULATIVE BC DEATH INCIDENCE AFTER IN SITU AND INVASIVE LR

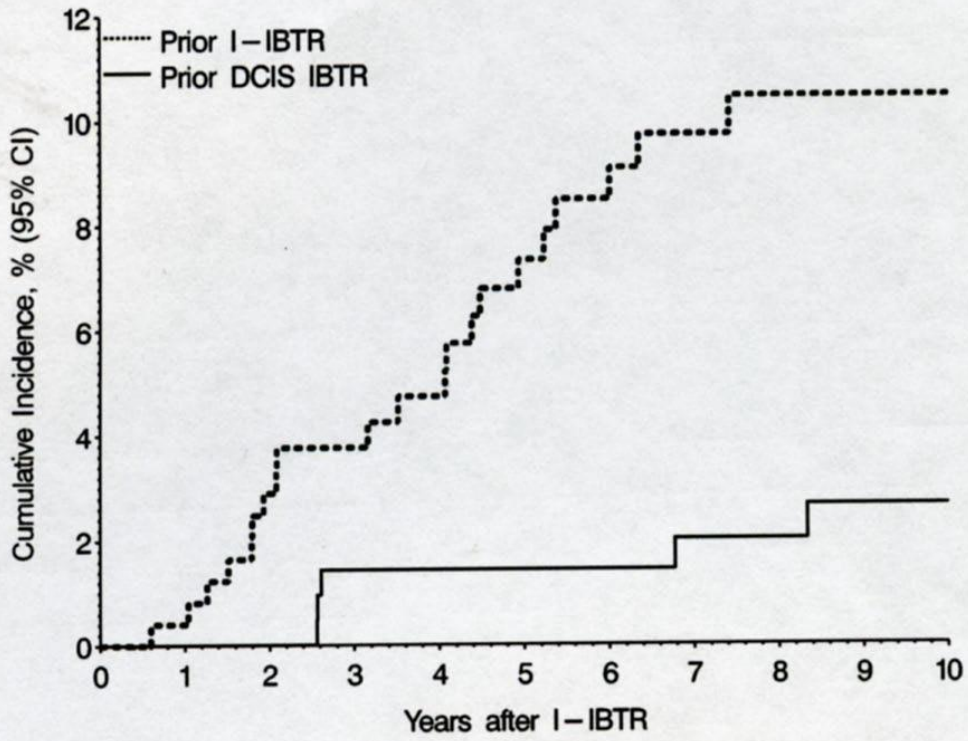


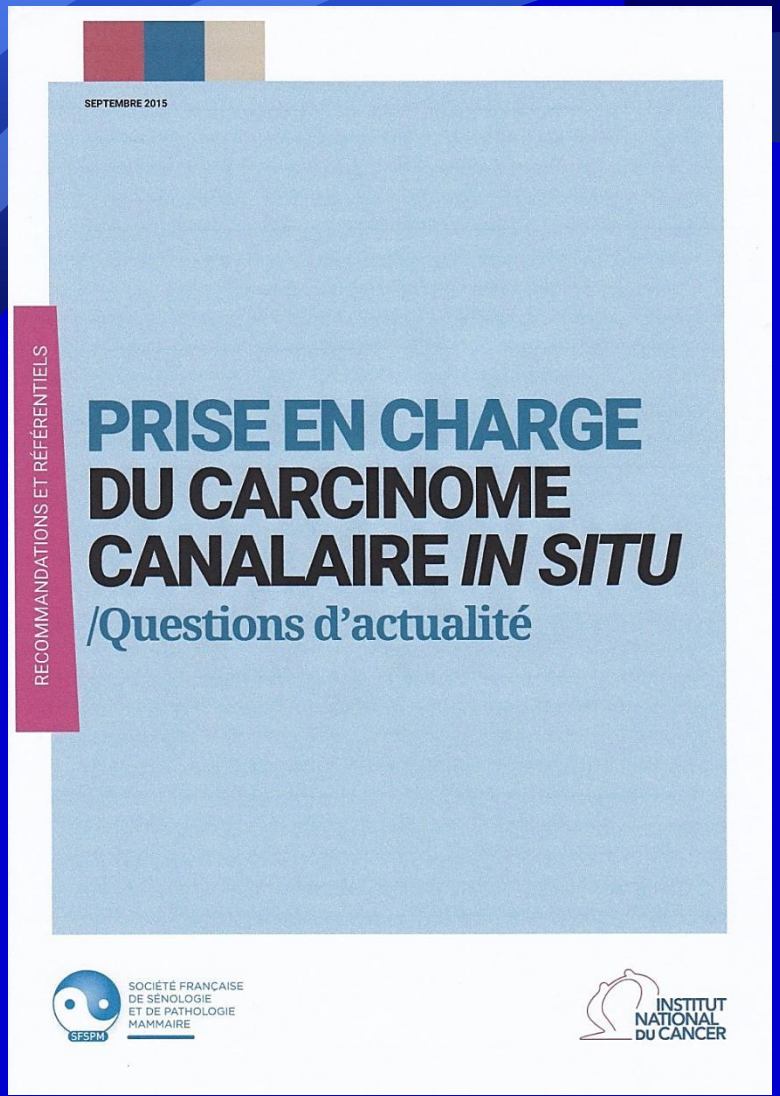
Figure 6. Cumulative incidence of breast cancer deaths after invasive ipsilateral breast tumor recurrences (I-IBTR) or ductal carcinoma in situ (DCIS)-IBTR. The patient cohort includes 263 patients with a prior I-IBTR and 227 patients with a prior DCIS-IBTR as a first failure event.

JNCI 2011, 103 : 486

PLACE DE LA MASTECTOMIE dans les CCIS

Compte tenu de l'extension lésionnelle (~ 15%>4cm) de la multicentricité/multifocalité (~ 15%), des exérèses limites, et parfois du souhait de la patiente, les taux de mastectomie oscillent entre 25 et 40%, dont ~ 60% avec reconstruction immédiate

RECOMMANDATIONS INCA-SFSPM POUR LES CCIS: ACTUALISATION DE 2015



Le traitement radio-chirurgical conservateur reste le standard recommandé pour la majorité des CCIS

(exérèse complète possible et résultat esthétique satisfaisant)

« LA DESESCALADE» …LES GRANDES QUESTIONS

Peut-on faire moins sans faire courir de risques à la patiente?

- *Omission de la radiothérapie?*
- *Omission de la chirurgie?*
- *A-t-on vraiment identifié des « LOW-RISK DCIS »??*
- *Quel taux de RL peut-on accepter??*

RESULTATS DES ETUDES

- *ECOG*

(EASTERN COOPERATIVE ONCOLOGY GROUP)

- *RTOG 9804*

(RADIATION THERAPY ONCOLOGY GROUP)

LOCAL EXCISION ALONE WITHOUT IRRADIATION FOR DCIS OF THE BREAST : A TRIAL OF EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)

HUGHES L, JCO 2009, 27 : 5319-24

- ***Analysis of two cohorts of patients (1997-2002) :***

  A) Grade 1-2 DCIS ≤ 2.5 cm (n=565)

  B) Grade 3 DCIS ≤ 1 cm (n= 105)

- ***In all cases :***

  - Complete excision (≥ 3 mm)

  - Post Op. mammogram

  - Central pathology review (90%)

LOCAL EXCISION ALONE WITHOUT IRRADIATION FOR DCIS OF THE BREAST : A TRIAL OF EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)

HUGHES L, JCO 2009

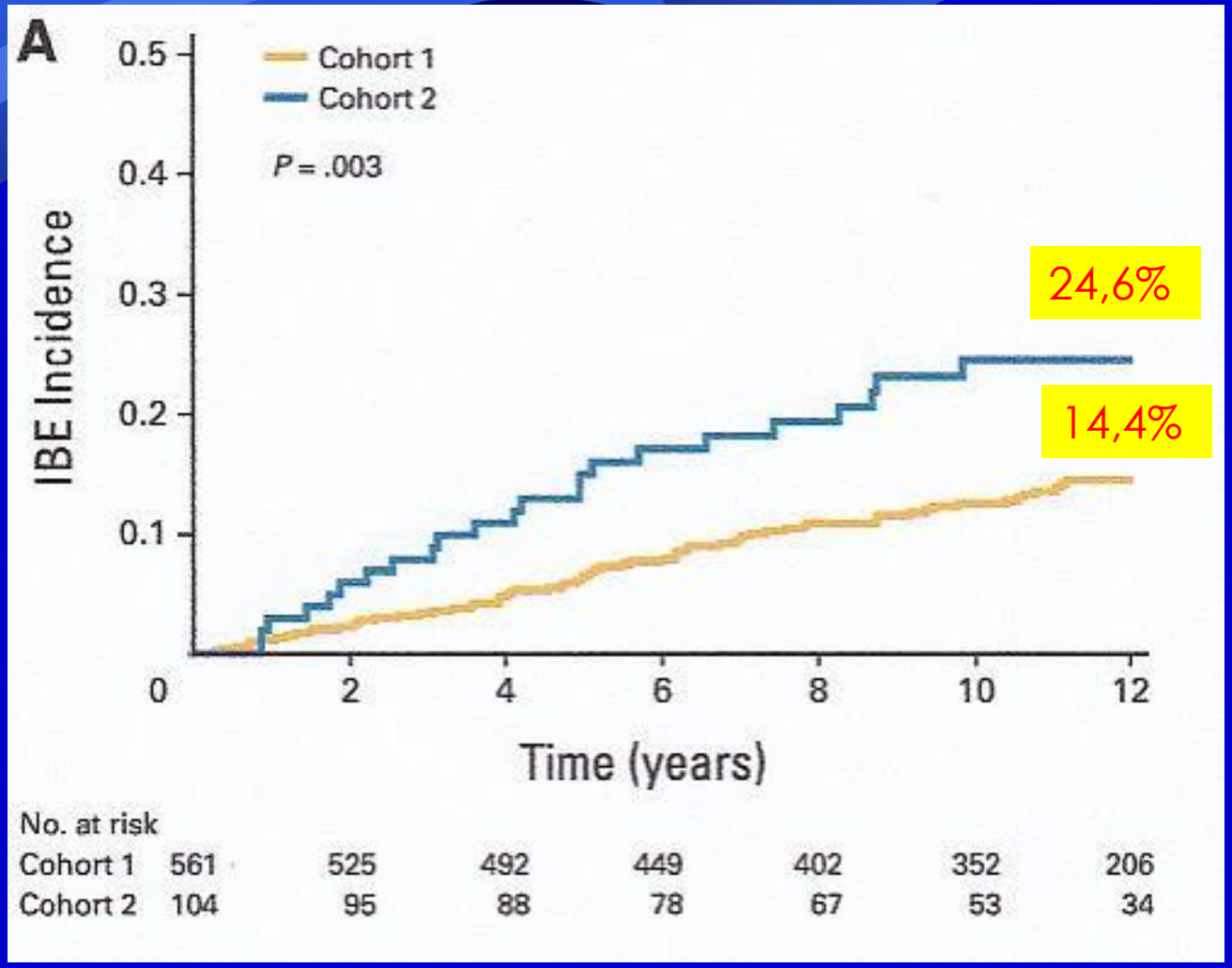
- ***Median*** *:*

  Age : 60y
  F.U : 6.5 y

  Tumor sizes
  - *A) 6 mm (76% < 10 mm) (low / Int. Grade)*
  - *B) 5 mm (88%) < 10 mm) (High Grade)*

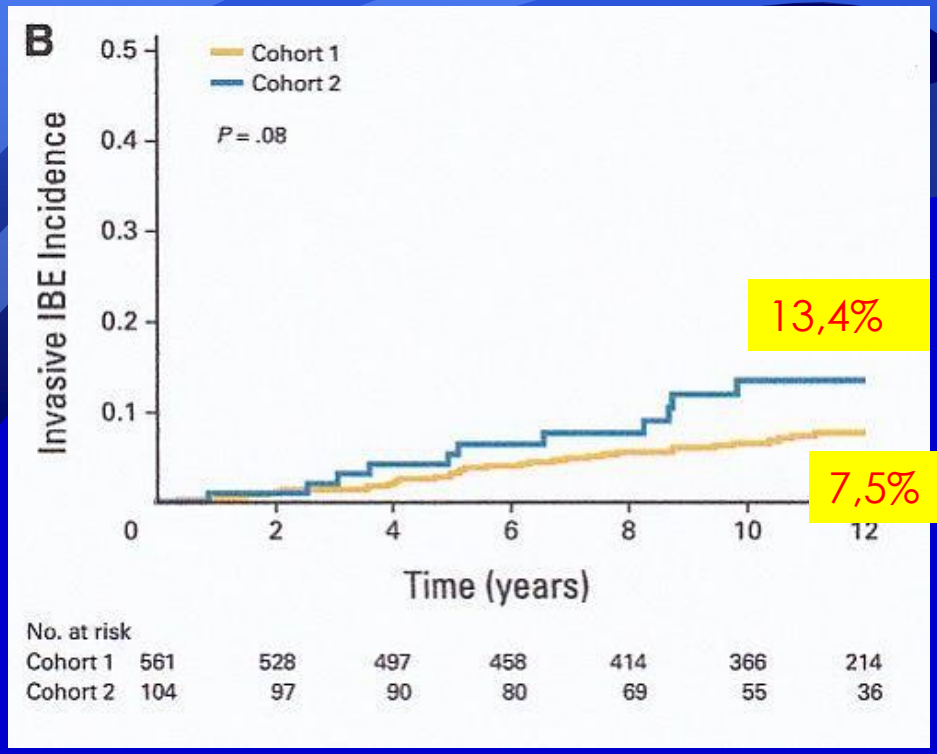
NB *: 1) margins ≥ 5 mm : 83%*
≥ 10 mm : 53%
2) ≅ 30% received Tamoxifen (> 2000)

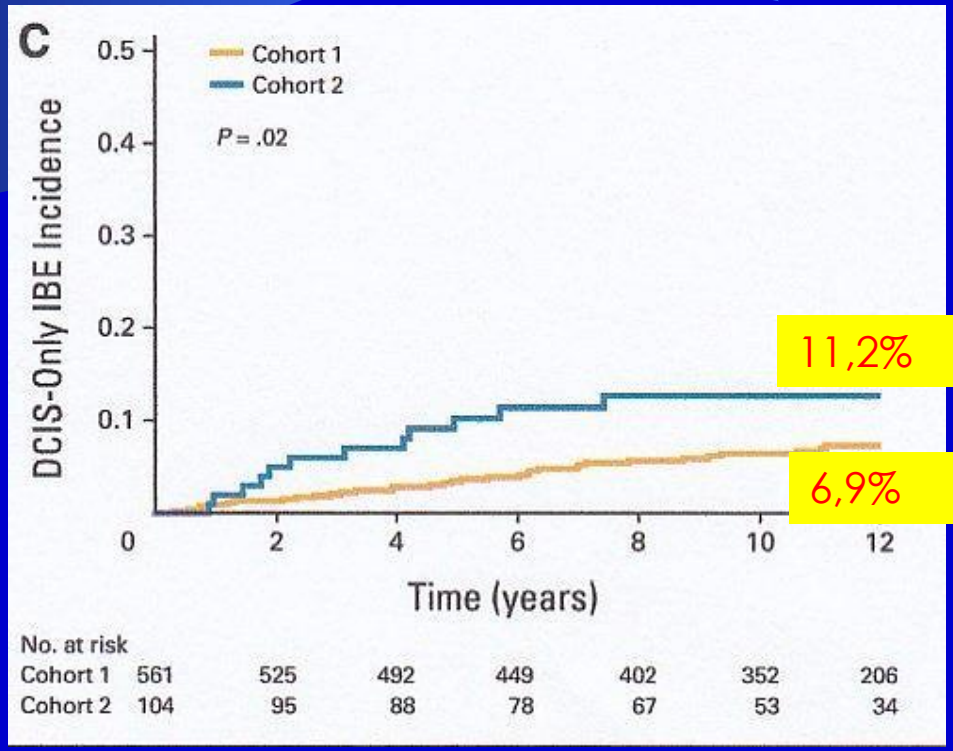
ECOG STUDY : LOCAL RECURRENCE INCIDENCE (12-year follow-up)



SOLIN L. JCO 2015

ECOG STUDY : INVASIVE AND IN SITU LR INCIDENCE





Conclusion:
The risk of LR increased through out 12 year FU, without plateau

SOLIN L. JCO 2015

IMPACT OF WBRT AFTER LUMPECTOMY
A « MODERN »TRIAL

RTOG 9804: A PROSPECTIVE RANDOMIZED TRIAL FOR GOOD-RISK DCIS COMPARING RADIOTHERAPY WITH OBSERVATION

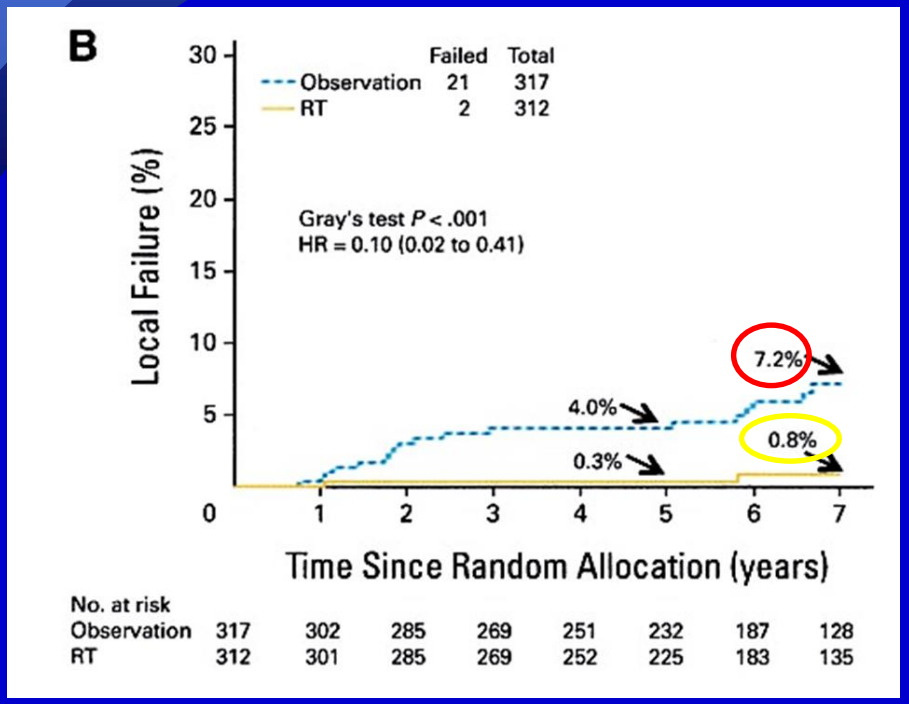
B.MC CORMICK et al
JCO 2015, 33: 709-15

Analysis of 636 patients (from 1998 to 2006)

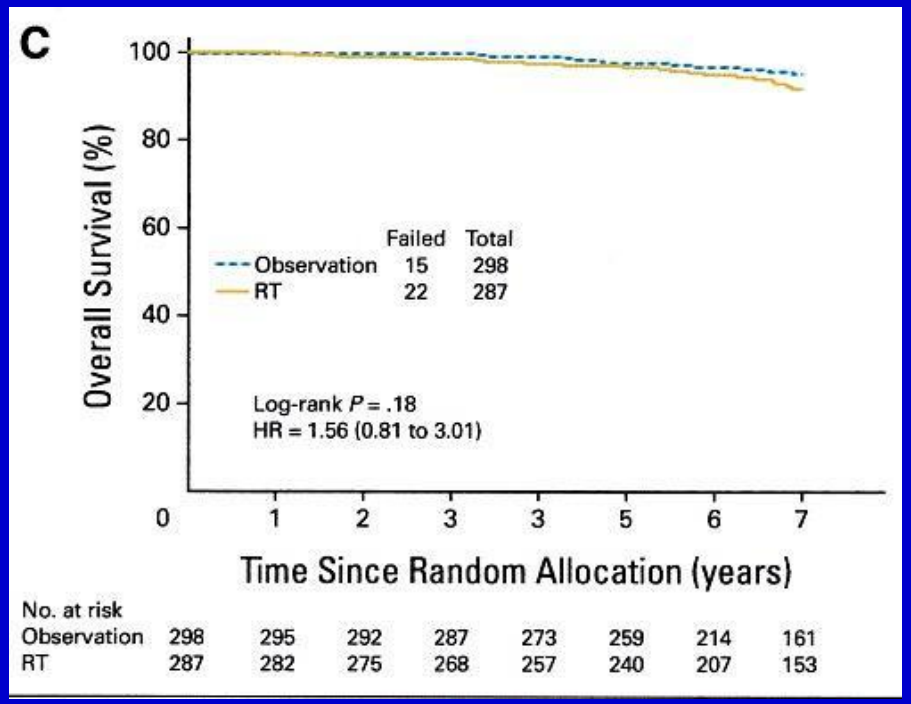
- DCIS NG1-2, < 2.5 cm
- minimal free margins: 3 mm
- 62% underwent TAMOXIFEN
- All patients had post surgical mammography

RTOG 9804 TRIAL: 7-year FU RESULTS

LOCAL RECURRENCE
(INVASIVE: 42%; IN SITU: 58%)



OVERALL SURVIVAL



EST-IL POSSIBLE DE FAIRE MIEUX? LES CARACTERISTIQUES MOLECULAIRES PEUVENT PERMETTRE D'AFFINER LES INDICATIONS?

1. TAILORING TREATMENT FOR DUCTAL INTRAEPITHELIAL NEOPLASIA OF THE BREAST ACCORDING TO KI67 AND MOLECULAR PHENOTYPE

LAZZERONI M et al BJC 2013, 108: 1593-1601

Experience de l'IEO de Milan

- Influence favorable du Ki67 ≤ 14%
- Intérêt du Tamoxifène pour les LUMINAL A/B

2. MOLECULAR PHENOTYPE OF DCIS PREDICT OVERALL AND INVASIVE RECURRENCE

WILLIAMS KE et al ANN ONCOL 2015, 26:1019-1025

Analyse de 314 patientes à MANCHESTER

- Faible taux de RL pour les DCIS LUMINAL A (RE+ RP+Her2-)

3. RISK OF SUBSEQUENT IN SITU AND INVASIVE Breast cancer in Her2 positive DCIS

CURIGLIANO G et al ANN ONCOL 2015, 26:682-7

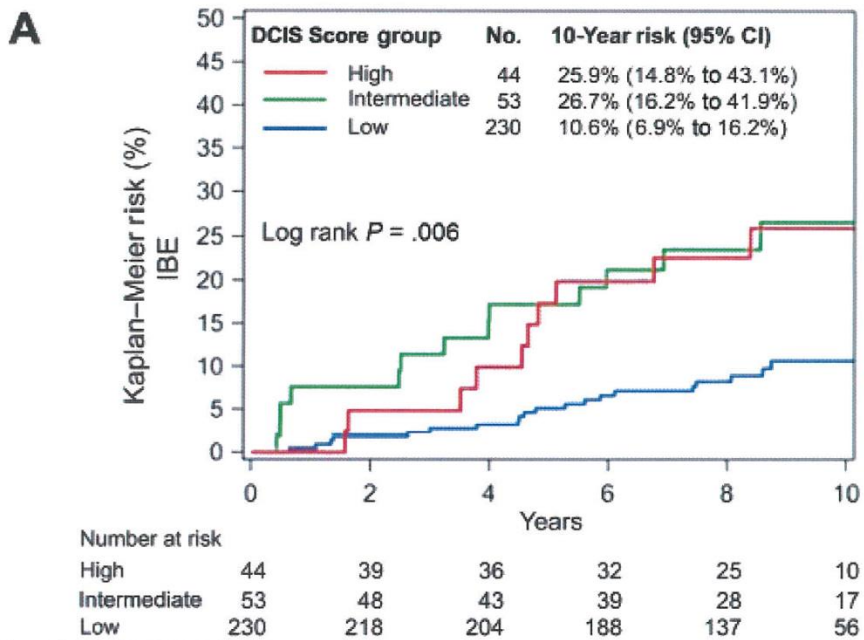
Expérience de l'I.E.O de Milan

- ↗ modérée du taux de RL

DCIS SCORE

Signature prédictive de récidive?

- 327 ptes issues de l'étude ECOG (*sans RT*)
- Test d'expression multigénique (Oncotype Dx®)
- 10 ans de suivi
- Récidive locale dans le groupe à faible risque: 10.6% à 10 ans



Proliferation group
Ki67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

Hormone receptor group
PR

GSTM1

Reference group
ACTB (β-actin)
GAPDH
RPLPO
GUS
TFRC

Solin LJ et al. *J Natl Cancer Inst*, 2013

REMERCIEMENTS: Dr Alain FOURQUET

Essai « ROMANCE »
Omission de la radiothérapie mammaire dans les CCIS de faible risque

- Prospectif multicentrique randomisé type phase II
- Après chirurgie conservatrice
- Critères d'inclusion:
  - Age ≥ 55 ans
  - Taille < 25 mm
  - Grade nucléaire intermédiaire ou bas
  - Unifocal
  - Berges saines avec marge > 2 mm
  - RO+RP+HER2-
  - Ki67 < 15%

UNICANCER R&D

institut Curie

REMERCIEMENTS: Dr Alain FOURQUET

Essai « ROMANCE »
Omission de la radiothérapie mammaire dans les CCIS de faible risque

- 700 patientes
- Résultat concluant si < 3,5 % de récidive mammaire à 5 ans
- Suivi 10 ans
- Evaluation de la toxicité et de la qualité de vie

UNICANCER R&D

institut Curie

REMERCIEMENTS: Dr Alain FOURQUET

LES ESSAIS DE « SURVEILLANCE ACTIVE » EXCLUSIVE:

- LORIS TRIAL (LOW RISK DCIS) (960 patientes prévues)

- LORD STUDY (LOW RISK DCIS) (1240 patientes prévues)

Ce sont 2 essais de phase III de « non infériorité »

LORIS TRIAL

FRANCIS A

Eur J Cancer

2015, 51: 2296-2303

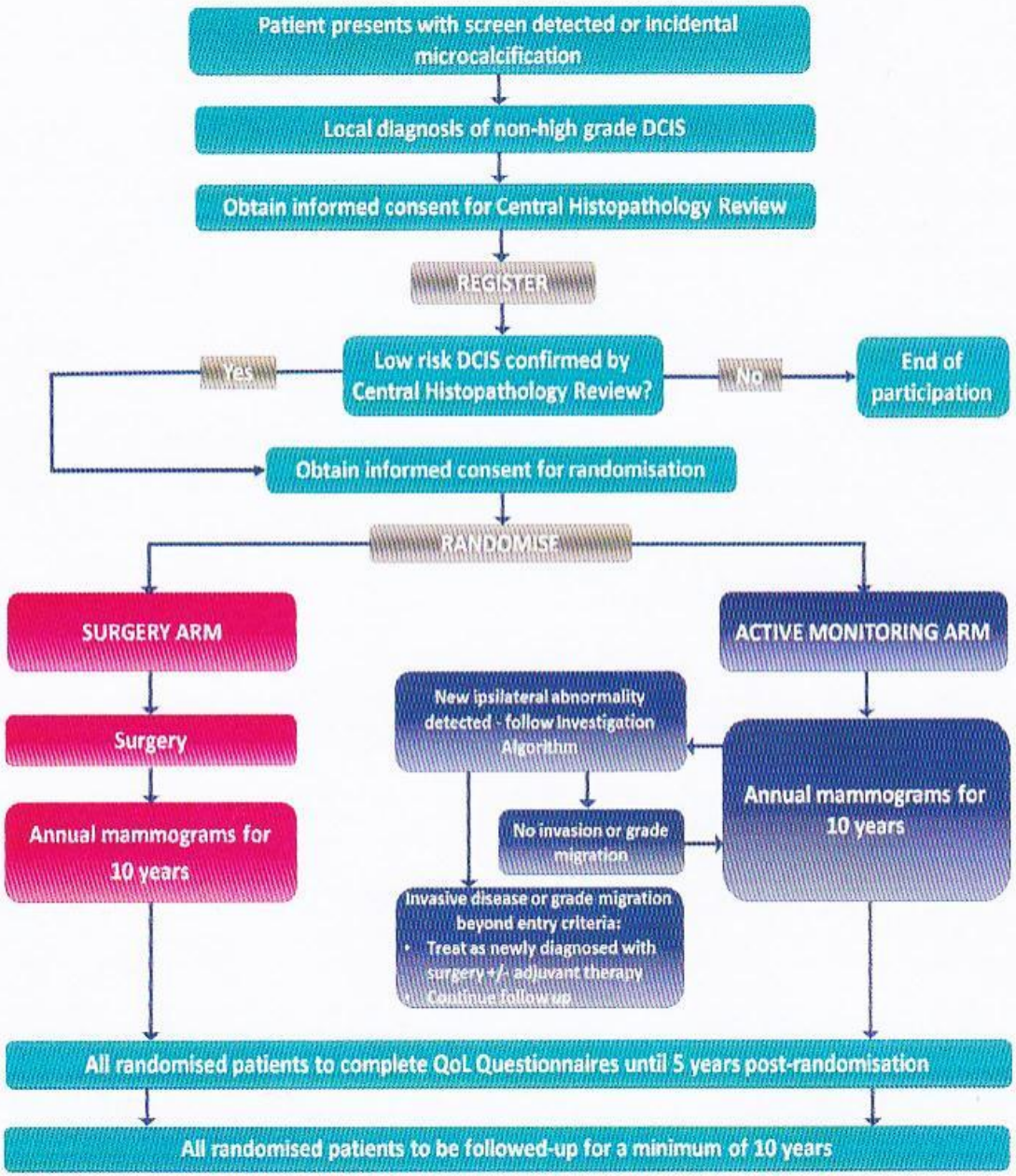


Fig. 1. Low risk DCIS (LORIS) trial flow diagram.

LORD STUDY

ELSHOF LE

Eur J Cancer

2015, 51: 1497-1510

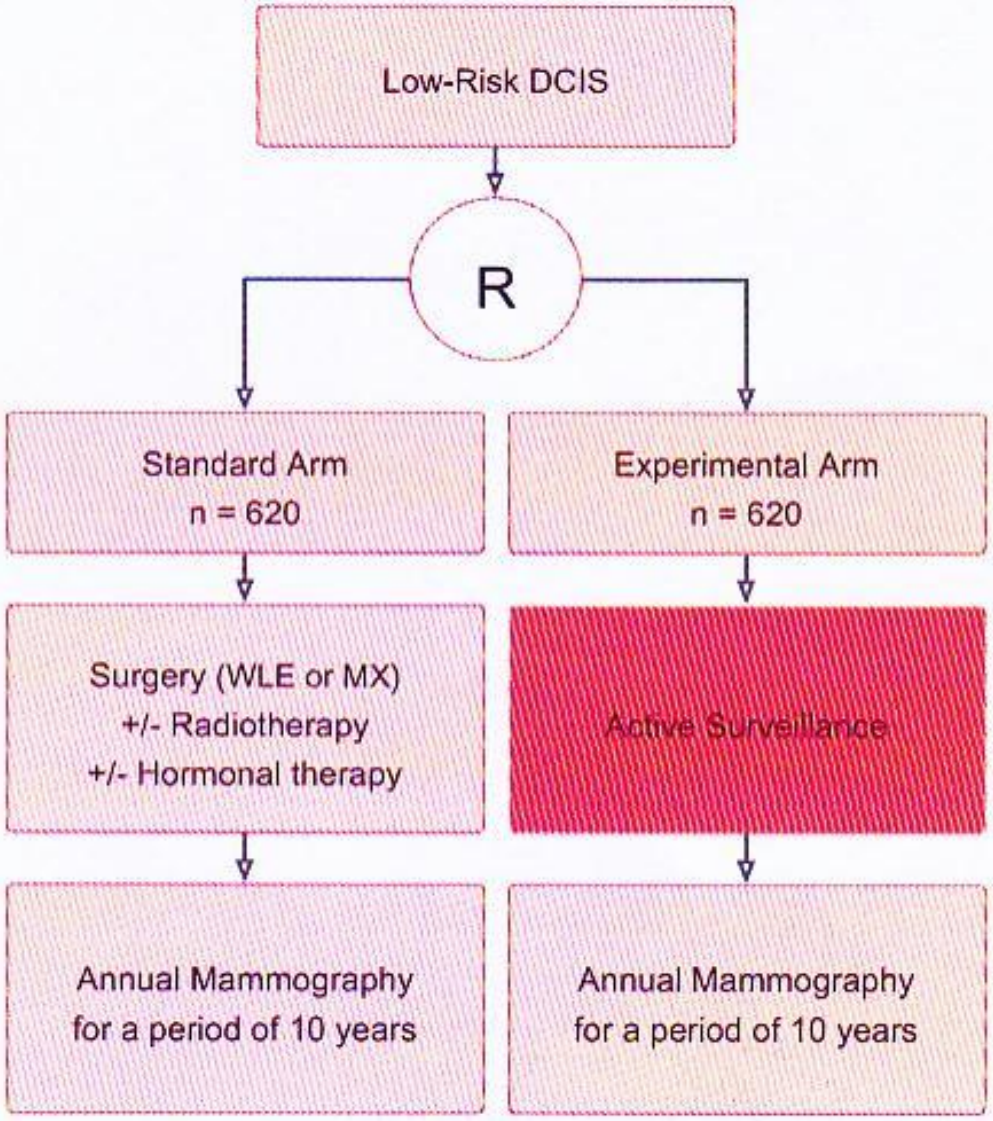
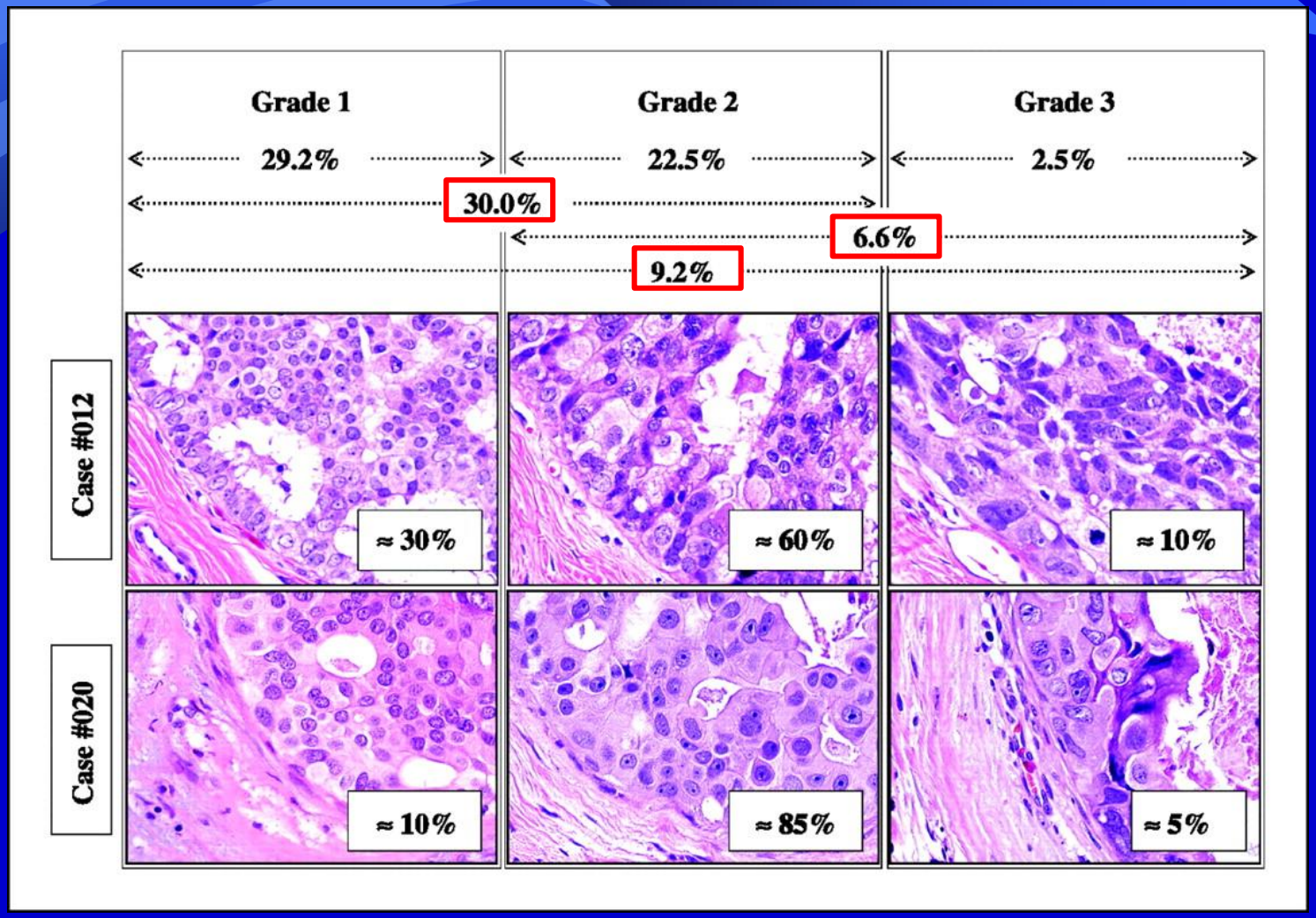


Fig. 2. Flow chart of study design. R = randomisation. WLE = wide local excision. MX = mastectomy.

QUELQUES QUESTIONS…

- *Les CCIS sont des lésions hétérogènes… les formes « mixtes » de grades différents sont fréquentes*
- *Quels est le risque réel de sous-estimation d'une lésion de haut grade, voir d'un cancer microinvasif?*
- *Quel est l'impact « psychologique » d'une telle surveillance?*

HETEROGENEITE DES DCIS



Allred D C et al. Clin Cancer Res 2008;14:370-378

QUELQUES PRECISIONS…

- *Les effets secondaires de la RT moderne sont extrêmement réduits*
- *La toxicité cardiaque de l'irradiation mammaire exclusive est minime*
- *Le Tamoxifène est mal toléré chez ~ 20% des patientes*

CONCERNS ABOUT WBRT (II)
CARDIOVASCULAR MORBIDITY AND MORTALITY
after treatment for DCIS of the breast

BOEKEL N et al JNCI 2014

- ***Analysis of 10468 patients treated between 1989 and 2004 in the NETHERLANDS***

- ***27 % underwent lumpectomy + WBRT***

- ***After 10-year FU:***

➢ ***no increase of CV morbidity or mortality***

➢ ***no difference in left-sided vs right-sided DCIS***

DES INTERROGATIONS OUTRE-ATLANTIQUE…

Memorial Sloan Kettering Cancer Center

Is Low Risk DCIS Really Low Risk?

By **Melissa L. Pilewskie, MD, FACS**,
Thursday, June 23, 2016

The DCIS Treatment Controversy

The appropriate management of women with ductal carcinoma in situ (DCIS) remains an area of ongoing controversy. DCIS is a noninvasive breast lesion diagnosed in more than 60,000 patients annually in the United States, currently accounting for 20 to 25 percent of all breast cancer diagnoses. The standard treatment of DCIS is associated with excellent survival and includes surgical excision by lumpectomy or mastectomy, with or without adjuvant radiation or endocrine therapy. While little data exist on the natural history of untreated DCIS, some small studies suggest that 40 to 50 percent of low-to-intermediate-grade DCIS will progress to invasive carcinoma. [(1), (2), (3)] Given that more than half of patients with DCIS may not progress to a potentially life-threatening disease, there has been growing interest in studying observation and alternative strategies for this patient cohort.

Is "Low-Risk" DCIS Truly Low-Risk?

We recently examined our DCIS patient population at Memorial Sloan Kettering Cancer Center (MSK) and identified patients who met the LORIS trial eligibility criteria. Only 16 percent of our patients with DCIS met these inclusion and exclusion criteria, emphasizing that the observation study results will apply to a minority of our patients. However, even among this highly select cohort of our patients who underwent surgical excision, 20 percent were found to have invasive breast cancer on final pathology. This upgrade rate is very similar to that reported in a meta-analysis of all patients with DCIS at the time of surgical excision, regardless of tumor grade or presentation. [6] Interestingly, the invasive cancers identified in this highly select, "low-risk" population were not all small, estrogen receptor positive, node-negative tumors, but rather were heterogeneous in regards to tumor grade, size, receptor status, and nodal involvement.

CONCLUSIONS (I)

- *Les CCIS restent des lésions de bon pronostic quand leur traitement initial est optimal*
- *Les facteurs de risque de RL doivent être précisément pris en compte dans la décision thérapeutique*

(âge/grade/taille/qualité de l'exérèse)

CONCLUSIONS (II)

- *La radiothérapie garde encore une place majeure après la chirurgie conservatrice pour réduire le taux de RL*
- *Les études de désescalade thérapeutique doivent être très précisément évaluées à long terme*

SE RAPPELER DES RESULTATS ACQUIS…

Radiotherapy and Oncology 112 (2014) 1–8

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Radiotherapy in DCIS, an underestimated benefit?

Bruno Cutuli [a,*], Jacques Bernier [b], Philip Poortmans [c]

[a] Institut du Cancer Courlancy, Reims, France; [b] Genolier Swiss Medical Network, Genolier, Geneva, Switzerland; [c] Dr. Bernard Verbeeten Institute, Tilburg, The Netherlands

Radiotherapy and Oncology 114 (2015) 50–55

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

Cecilia Nilsson [a], Antonis Valachis [b,*]

[a] Center for Clinical Research, Västmanlands County Hospital, Västerås; and [b] Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden