



Medical School - National and Kapodistrian University of Athens - Greece

OPTIMISING TREATMENT IN OLDER BREAST CANCER PATIENTS

Challenges in Screening: the management of DCIS

Christos Markopoulos, MD, MPhil(UK), PhD, FEBS

Professor of Surgery - Medical School

National & Kapodistrian University of Athens - Greece

President: UEMS-EBS-Division of Breast Surgery





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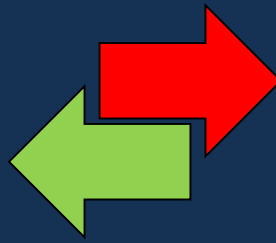
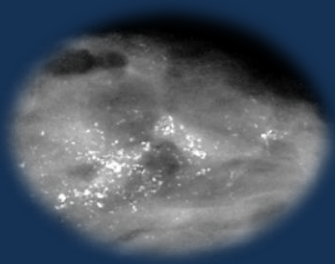
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5th Symposium on Primary Breast Cancer in Older Women

Theme - Optimising treatment in older breast cancer patients: This is precision medicine too!

Disclosures

- Consultant for Genomic Health Inc.
- Educational and research grants from
 - AstraZeneca
 - Pfizer
 - Novartis



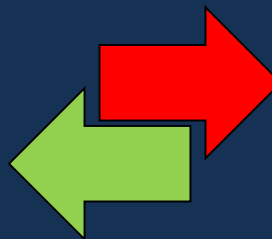
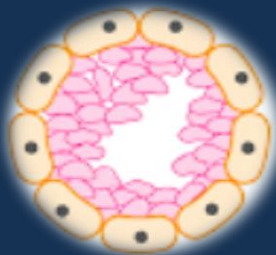
A. Asymptomatic *(detected by screening mammography)*



- a. Microcalcifications (~80%)
- b. Distortion, mass etc. \pm microcalcifications
 - Core biopsy

B. Symptomatic

- a. Lump
- b. Nipple discharge
 - Core biopsy
 - Open biopsy



Diagnosis

Comorbidities

Life expectancy

10~15yrs

**D
C
I
S**

Stable

Progress without invasion

Progress to Invasive disease

+/- Intervention

+/- Intervention

Death

from

other

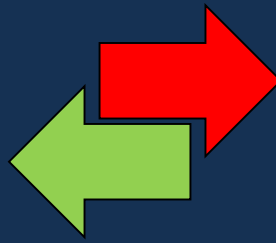
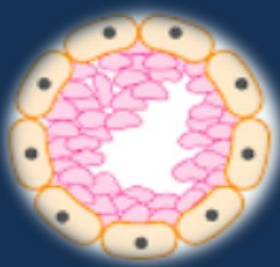
causes

Death

20-30%

Metastasis

QoL



Management of Screen detected DCIS in Old pts

Questions

1. Risk assessment

- what is the chance that this DCIS will progress to or recur with DCIS or Invasive Carcinoma

2. Patient evaluation - CGA

- Life expectancy
- Co-morbidities
- Current QoL

3. Risk *and* Benefits of additional treatment

- benefit of Surgery, RxT, HT or Multimodality treatment
- risk in relation to co-morbidities & current QoL

Facts: DCIS are not all the same

“Currently, most women with DCIS undergo surgical resection ± radiotherapy ± endocrine therapy”

Q.: Cases of over-treatment? YES!

- DCIS is not a single disease process

(clinically, radiologically, histopathologically, biologically, genetically)

- Low- and High-grade DCIS are not equivalent

(different likelihood of progression to invasive disease)

- Medical intervention might not be always necessary

(some DCIS may never progress even without any treatment)

Facts: Risk of Recurrence

Age factor

- **The risk of recurrence** of DCIS decreases with Age, independent of other clinical and pathological factors
- **The risk of invasive recurrence** is also low*

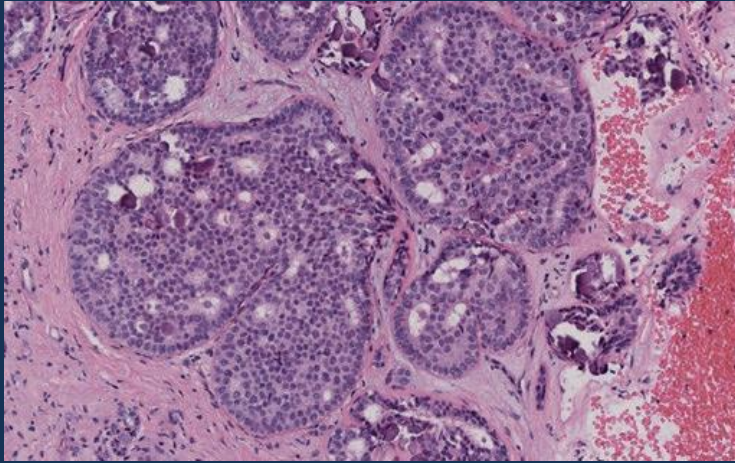
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- **Prediction of recurrence** *with DCIS or invasive BC*

is currently based on pathological factors:

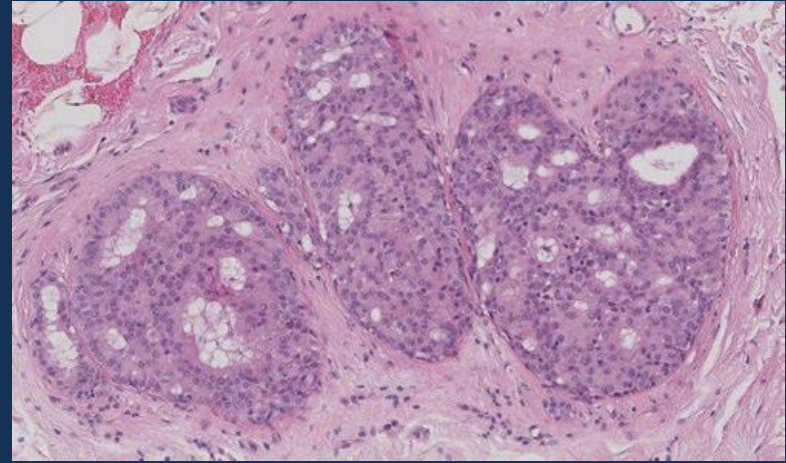
- **Grade**
- **ER and PR status**
- **HER2 status**

* Cronin PA et al. Impact of age on risk of recurrence of ductal carcinoma in situ. Ann Surg Oncol. 2016;23(9):2816–24.

«Low risk» DCIS

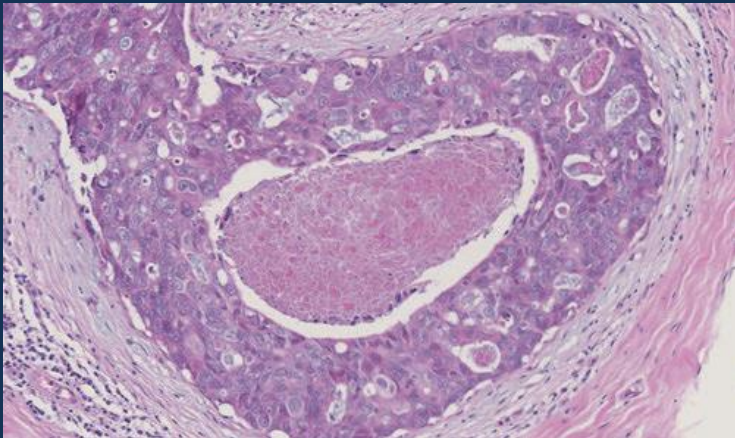


Low-grade DCIS



Intermediate grade DCIS

«High risk» DCIS



High-grade DCIS with central
necrosis

«Low risk» DCIS

Low-Intermediate Grade,
ER/PR positive, HER2 negative

«High risk» DCIS

High-grade, ER/PR negative
and/or HER2 positive

Facts: Risk of Recurrence

- **High-grade** DCIS is more likely to develop invasive disease than Low-grade DCIS¹
- **ER-negative** DCIS has a higher rate of recurrence (12.2%) than ER-positive DCIS (3.7%) at 5 years²
- **HER2-positive** DCIS has an increased risk of recurrence^{3,4}

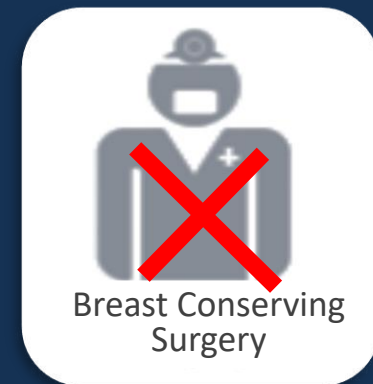
¹Travassoli F, Devilee P. WHO classification of tumours. Washington, DC: IRAC Press; 2003.

²Roka S, et al. Eur J Surg Oncol. 2004;30(3):243–7

³Curigliano G, et al. Ann Oncol. 2015;26(4):682–7

⁴Rakovitch E, et al. Br J Cancer. 2012;106(6):1160–5

Active Surveillance vs Surgery



Surveillance only

- Low grade
- ER / PR positive
- HER2 negative

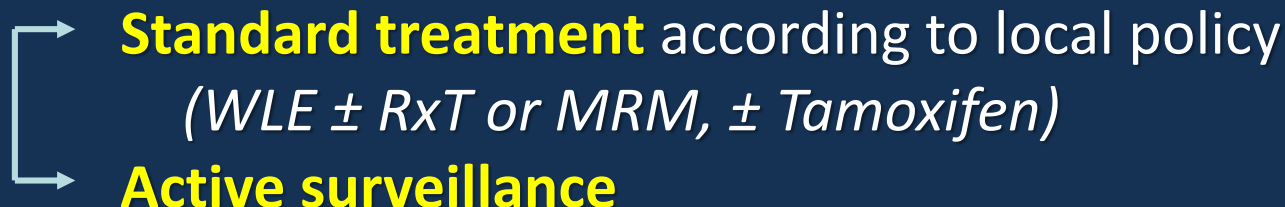
- *Life expectancy*
- *Co-morbidities*

** only 6-7% of screen detected Low grade DCIS cases might have an invasive component*

Active Surveillance Prospective Trials

- **LORD** trial - EORTC
 - **COMET** trial - USA
 - **LORIS** trial - UK
 - **LARRIKIN** trial - AU
- Asymptomatic DCIS, detected by population-based or opportunistic screening mammography*
 - pure low- or non-high grade DCIS
based on vacuum assisted core biopsies

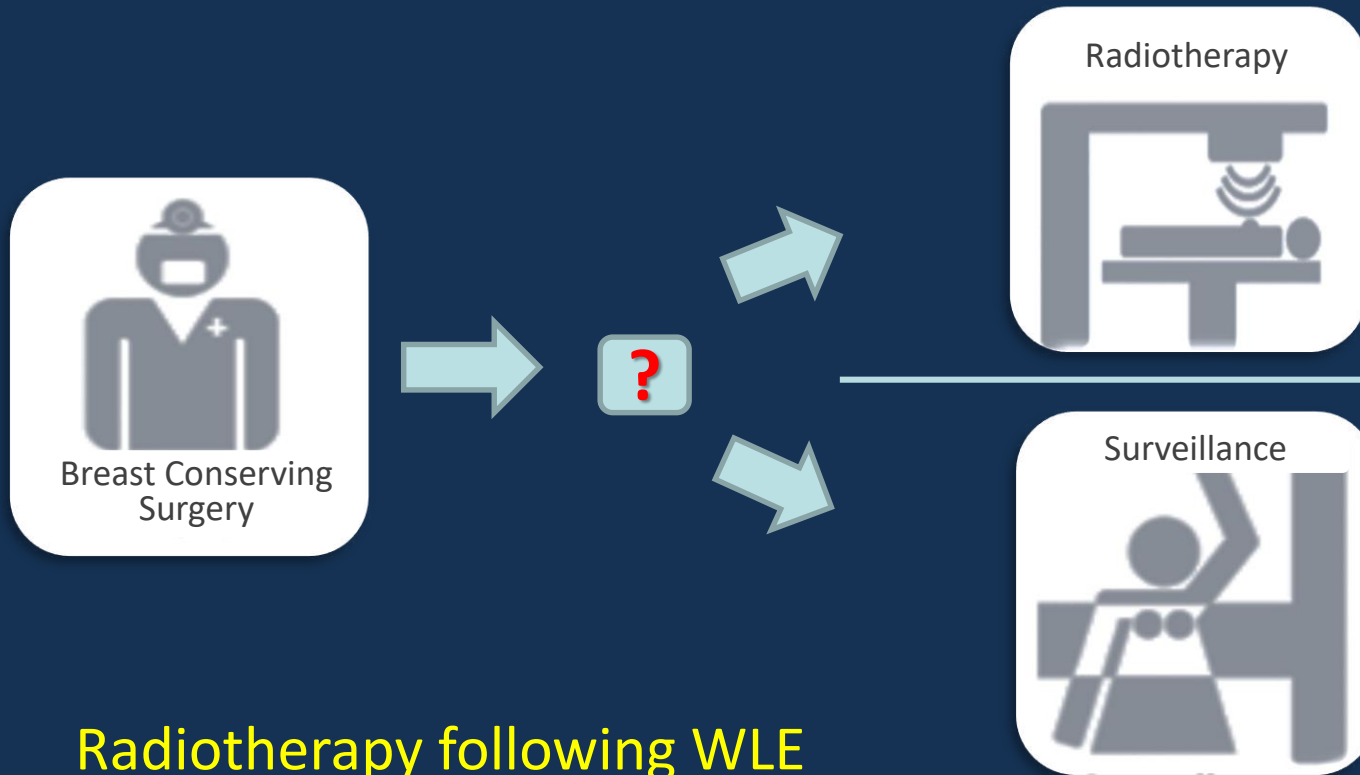
Randomization (1:1)



- **Monitoring:** annual digital mammography for 10 years

* Women ≥40, ≥45 and ≥55 years old

Radiotherapy following WLE



Radiotherapy following WLE
could aim to:

- decrease IBCR with DCIS or Invasive disease
- increase Overall Survival

Facts: Radiotherapy (WBI) following WLE

Reduced IBCR at 10 years¹⁻⁴:

- overall by more than half (28.1% to 12.9%)
- with invasive disease from 11.0% to 5.0%

More recent studies^{5,6} for low-risk DCIS:

- lower benefit, but still a small effect
- Non high grade: 6.7% vs 0.9% with RxT at 10yrs

However, radiotherapy:

- does not affect BC-specific survival⁷
- carries risks: lung, esophagus, cardiovascular¹

¹EBCTCG. J Natl Cancer Inst Monogr. 2010;2010(41):162–77.

³Donker M, et al. J Clin Oncol. 2013;31(32):4054–9.

⁵Wong JS, et al. Breast Cancer Res Treat. 2014;143(2):343–50.

⁷Narod SA, et al. JAMA Oncol. 2015;1(7):888–96.

²Cuzick J, et al. Lancet Oncol. 2011;12(1):21–9.

⁴Holmberg L, et al. J Clin Oncol. 2008;26(8):1247–52.

⁶McCormick B, et al. J Clin Oncol. 2015;33(7):709–15.

Van Nuys Prognostic Index

<i>Parameter</i>	<i>Score 1</i>	<i>Score 2</i>	<i>Score 3</i>
Van Nuys Classification	Group 1	Group 2	Group 3
	Non high nuclear grade without necrosis	Non-high nuclear grade with necrosis	High nuclear grade with or without necrosis
Margins	≥10 mm	1–9 mm	<1 mm
Size	<15 mm	16–40 mm	>40 mm
Age	>60	40–60	<40

Prognosis

Low risk
4 – 5 – 6

Intermediate risk
7 – 8 – 9

High risk
10 – 11 – 12

Modified from Silverstein; Ductal Carcinoma in situ of the breast 2nd ed. 2002.

Prognosis by Treatment Modality

Surgery +/- Radiotherapy

USC/VNPI Score, Margin Width	Patients (N = 1673)	Treatment Needed	12-Year Recurrence
All 4, 5, or 6	420	Excision alone	≤7% ←
7, margins ≥3 mm	196	Excision alone	16% ←
7, margins < 3 mm	117	Excision plus radiation	14% ← -2%
8, margins ≥3 mm	128	Excision plus radiation	14% ←
8, margins < 3 mm	183	Mastectomy	0%
9, margins ≥5 mm	43	Excision plus radiation	17%
9, margins < 5 mm	197	Mastectomy	0%
All 10, 11, 12	389	Mastectomy	7%

- 1673 patients with DCIS with 86 months of follow-up
- M. Silverstein , 2014 Miami Breast Cancer Conference

Radiotherapy



Radiotherapy following WLE
could be omitted in

- Low-risk DCIS
- Low to Intermediate VNPI score
 - *Life expectancy*
 - *Co-morbidities*

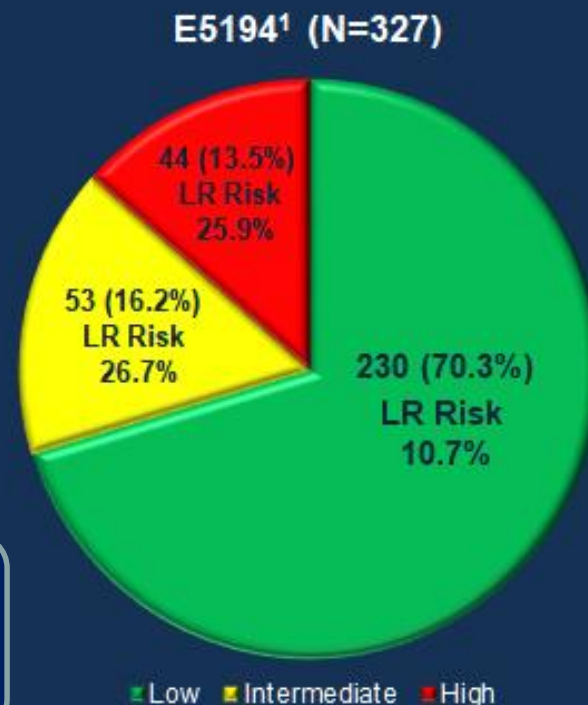
Multi-Gene Assays: Oncotype DX Breast DCIS score

*A Genomic Risk Stratification Tool - Includes 12 genes
Provides individualized risk based on underlying tumor biology*

- *Validation:* ECOG E5194¹ & Ontario Cohort²
- DCIS treated by WLE ± RxT ± Tam, any ER
- Independent predictor of LR at 10 years
 - of
 - any DCIS or invasive LR
 - an invasive LR

- DCIS Score (0-100) risk groups:
Low < 39 **Intermediate** 39 – 54 **High** ≥ 55

- **Clinical implication:** information to omit RxT in Low-risk DCIS



¹ Solin et al. *J Natl Cancer Inst.* 2013.

² Rakovitch et al. *Breast Cancer Res Treat.* 2015.
Rakovitch et al. *J Natl Cancer Inst.* 2017.

Hormonal Therapy

NSABP B-24 *pre- & postM with DCIS, WLE + Radiotherapy* **Tamoxifen**

- reduces the risk of IBCR by 30% and CBC by 50%
- absolute overall risk: 13% placebo vs. 8% Tamoxifen
- Survival: no effect¹

UK/ANZ DCIS trial *postM, WLE of DCIS ± Radiotherapy* **Tamoxifen vs no adjuvant therapy**

- no effect in preventing invasive IBCR
- Survival: not improved by Tamoxifen or RxT²

IBIS II trial *postM, WLE of DCIS ± Radiotherapy* **AI vs Tamoxifen/Placebo**

- no improvement (HR 0.89, $p = 0.49$)

¹Allred DC, et al. J Clin Oncol. 2012;30(12):1268. ²Cuzick J, et al. Lancet Oncol. 2011;12(1):21. ³Forbes JF, et al. Lancet. 2016;387(10021):866.

Could Tamoxifen replace Radiotherapy or add more benefit?

Meta-analysis of 10-year event rates		
DCIS	Locoregional recurrence following BCS	
Study	No radiotherapy	Radiotherapy
Correa ¹	28.1%	12.9%
Stuart ² 9,404 DCIS cases	24.7% with Tamoxifen	14.4%
		9.7% with Tamoxifen

¹ EBCTCG, Correa C, et al. J Natl Cancer Inst Monogr. 2010;2010(41):162–77.

² Stuart KE, et al. BMC Cancer. 2015;15:890.

Hormonal Therapy: Concerns

Benefit

- reduction in contralateral disease
- *potential* reduction of local recurrence

Common Side Effects

- Tamoxifen: hot flashes, DVT, endometrial cancer
- Aromatase Inhibitors: hot flashes, arthralgia

Real world concerns

- Adherence: only 70% of pts in the IBIS II trial at 5 years¹
- Canadian cohort study: only 26% of pts take Tam for DCIS²
- for 1 pt to benefit, 15 need to be treated with HT³

¹Forbes JF, et al. Lancet. 2016;387(10021):866–73.

²Lo AC, et al. Ann Oncol. 2015;26(9):1898–903.

³Staley H, et al. Breast. 2014;23(5):546–51.

Facts: DCIS *and* Survival

- **Death from breast cancer** after a diagnosis of DCIS is rare¹
 - ✓ 1.1% at 10 years and 3.3% at 20 years
 - ✓ increased risk in: ER-negative, high grade, comedo type
- **Surgery**
 - ✓ improves survival for intermediate and high-grade DCIS, *but not for low-grade DCIS*²
 - ✓ not significant difference with Mastectomy vs BCS¹
- **Radiotherapy**
 - ✓ is not associated with a survival advantage¹
- **Tamoxifen**
 - ✓ is not associated with a survival advantage³



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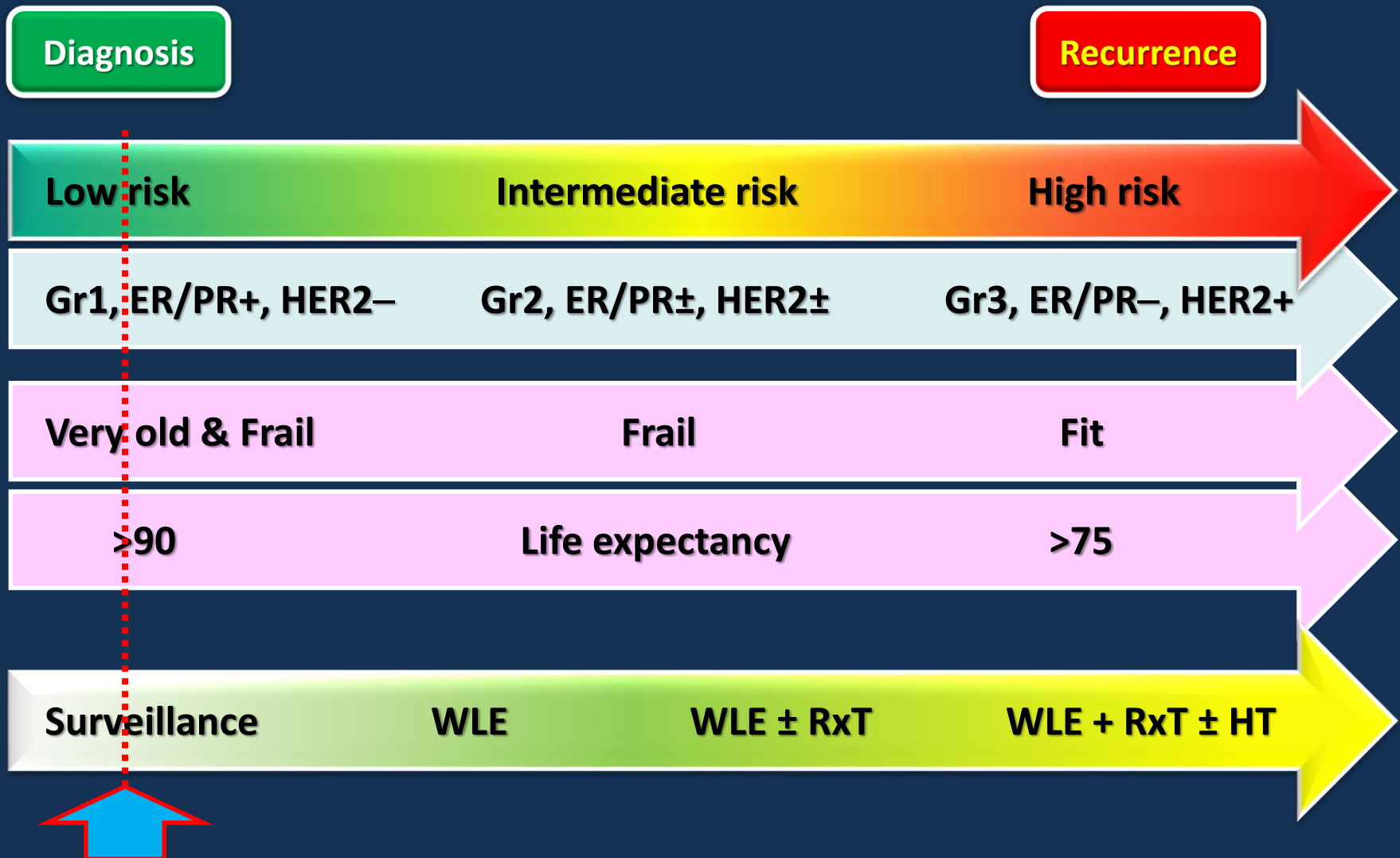
OPTIMISING TREATMENT

IN OLDER BREAST CANCER PATIENTS

Challenges in Screening: the management of DCIS

Conclusion

Management of Screen detected DCIS



DCIS in older patients: take home Message

- **Multidisciplinary** team approach is most important!
- **Assess patient's risk** based on disease parameters
- **Assess patient's** life expectancy, fitness, current QoL
- **Be aware of the risks & benefits** of therapy
- **Find the balance** between over- and under-treatment
- **Treatment** should be oncologically optimum but, **safe**

DO NOT FORGET

- Older women value most: QoL & independence
- Engage them in the decision-making process



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Thank you!

Christos Markopoulos, MD, MPhil(UK), PhD, FEBS

Professor of Surgery - Medical School

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President: UEMS-EBS-Division of Breast Surgery

