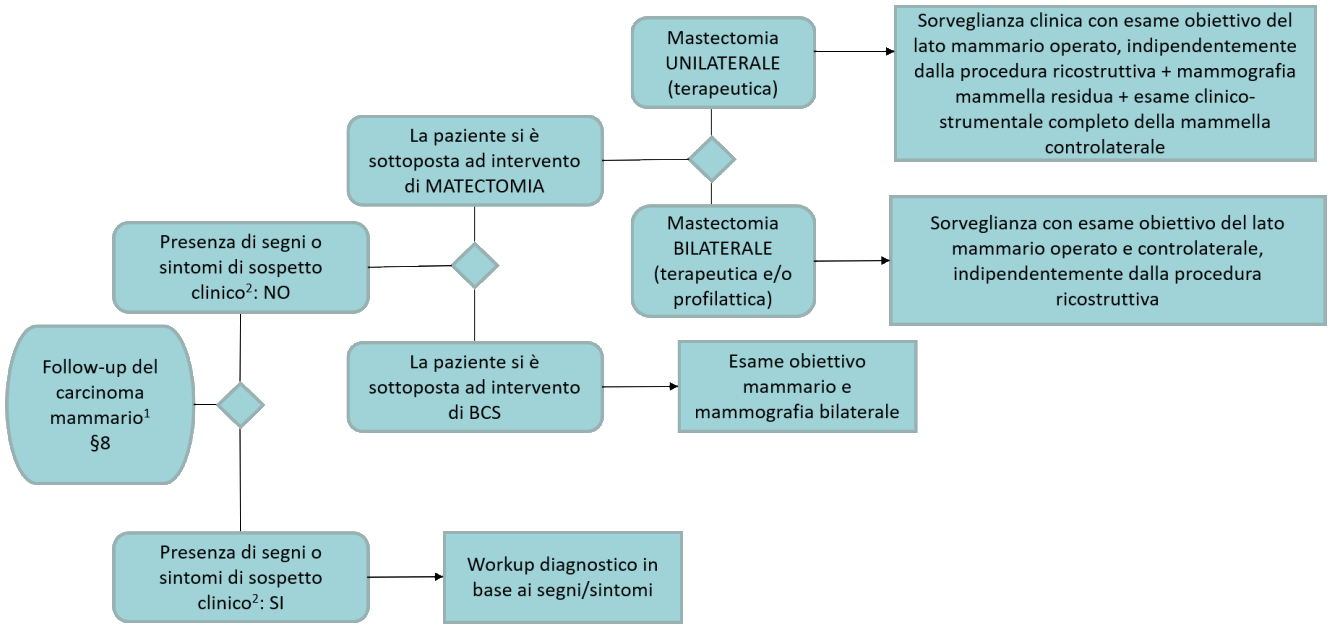
Il follow up nel carcinoma mammario: quali obiettivi? Quali evidenze della letteratura scientifica?

Alberto Zambelli
IRCCS Istituto Clinico Humanitas
Humanitas University – Rozzano (Mi)

Disclosure

Honoraria for advisory board and consultancy: Roche, Novartis, Lilly, Seagen, Daiichi Sankyo, Astra Zeneca, Merck, Exact Sciences

BC Follow up according to the AIOM GLs



Nota 1- i pazienti sono valutati con visita ed anamnesi clinica ad intervalli periodici. Il follow-up dovrebbe includere: educazione del paziente al riconoscimento di sintomi di rilevanza oncologica, il counselling genetico (se impronta eredo-familiare), l'assunzione di stili di vita protettivi, il counselling per la salute sessuale e per la protezione della fertilità. Inoltre, è raccomandata la valutazione della salute dell'osso e gli interventi terapeutici antiriassorbitivi (denosumab/bifosfonati) nei casi di menopausa prematura, uso di AI, età > 65 anni. La sorveglianza cardiologica è indicata in casi selezionati.
Nota 2 - Possibili sintomi clinici meritevoli di workup diagnostico: inspiegato calo ponderale; inspiegato dolore osseo ad eziologia incerta che persiste nel tempo nonostante i trattamenti antalgici: inspiegato dolore addominale; modifiche nelle abitudini intestinali; inspiegato dolore toracico o dispnea; cefalea di nuova insorgenza e/o sintomi neurologici.
BCS, chirurgia mammaria conservativa

LINEE GUIDA 2021

AIOM recommendations

LINEE GUIDA 2021

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
MOLTO BASSA	Nel programma di follow up del carcinoma mammario operato l'esame obiettivo può essere eseguito ogni 3-6 mesi durante i primi 3 anni e quindi ogni 6-12 mesi per i due anni successivi e quindi annualmente[1-7]	**Condizionata a favore**

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
BASSA	Nel programma di follow up del carcinoma mammario operato la mammografia, per la ghiandola residua e/o controlaterale, dovrebbe essere eseguita con regolarità e a cadenza annuale[8-13]	**Forte a favore**

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
ALTA	In assenza di sospetti clinici individuali o di programmi personalizzati, il cosiddetto follow up "intensivo" non dovrebbe essere raccomandato. In particolare, l'uso di indagini strumentali quali la radiografia del torace; l'ecografia addominale, la TC encefalo-torace-addome; la TC-PET con FdG; la scintigrafia ossea, come anche la determinazione dei marcatori tumorali (CEA, CA 15.3) non dovrebbero fare parte delle indagini routinarie di follow up in assenza di sospetto clinico di ripresa di malattia[26-33,37,38,40].	**Condizionata a sfavore**

AIOM recommendations (cont.)

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
ALTA	Nei casi di trattamento adiuvante con *antiaromatasi*, dovrebbe essere valutata la salute dell'osso, con mineralometria ossea e test endocrinologici e considerata la terapia con anti-riassorbitivi ossei (denosumab/bifosfonati) per ridurre il rischio di eventi fratturativi durante il trattamento anti-estrogenico[64-73]	**Forte a favore**

durante la terapia e a 18 e 24 mesi dall'inizio della cura

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
BASSA	Nei casi di trattamento (neo)adiuvante a base di *trastuzumab*, la sorveglianza della funzionalità cardiaca dovrebbe essere eseguita prima dell'inizio del trattamento e quindi ogni 3 mesi	**Condizionata a favore**

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
ALTA	In caso di trattamento con tamoxifene, la valutazione ginecologica iniziale e quindi a cadenza annuale dovrebbe essere raccomandata, associando l'ecografia transvaginale solo in casi selezionati[116,118-122,124-126]	**Forte a favore**

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	L'adozione di uno stile di vita protettivo, che comprenda interventi dietetici (per il controllo del sovrappeso/obesità) e l'esercizio fisico regolare, può essere suggerito a tutte le pazienti operate di tumore al seno, per il miglioramento della qualità di vita e la riduzione del rischio di recidiva tumorale[139,142,143-152,154,155,158,159,165,166,170-172].	**Condizionata a favore**

A global minimalist approach

	ASCO	ESMO	AIOM
Hx & physical exam	Every 3-6m (yrs 1-3) Every 6m (yrs 4-5) Every 1yr (yrs >5)	Every 3-6m (yrs 1-3) Every 6m (yrs 4-5) Every 1yr (yrs >5)	Every 3-6m (yrs 1-3) Every 6m (yrs 4-5) Every 1yr (yrs >5)
Self exam **MX (Breast US/MRI)**	No Yearly (only selected pts)	No Yearly (only age <35y, BD/strong family Hx, genetics)	No Yearly (selected pts/strong family Hx, genetics)
Chest Xray **CT scan** **Pelvic exam**	No No No	No No Yearly on TAM	No No Yearly on TAM
Blood test **Tumor markers** **DXA**	No No Limited to AI (TAM in OFS)	Limited to pts in ET No Limited to AI (or OFS)	No No Limited to AI
Abdominal US **Bone scan** **PET-CT/WB MRI**	No No No	No No No	No No No

Why the FU is minimalist ?

The GIVIO Trial was launched in 1986

N 1320 pts eBC up to 70y; mFU 71 m

Asymptomatic[b]	39	31	26	21
Symptomatic at routine visit	46	37	47	38
Symptomatic between routine visits	40	32	50	41

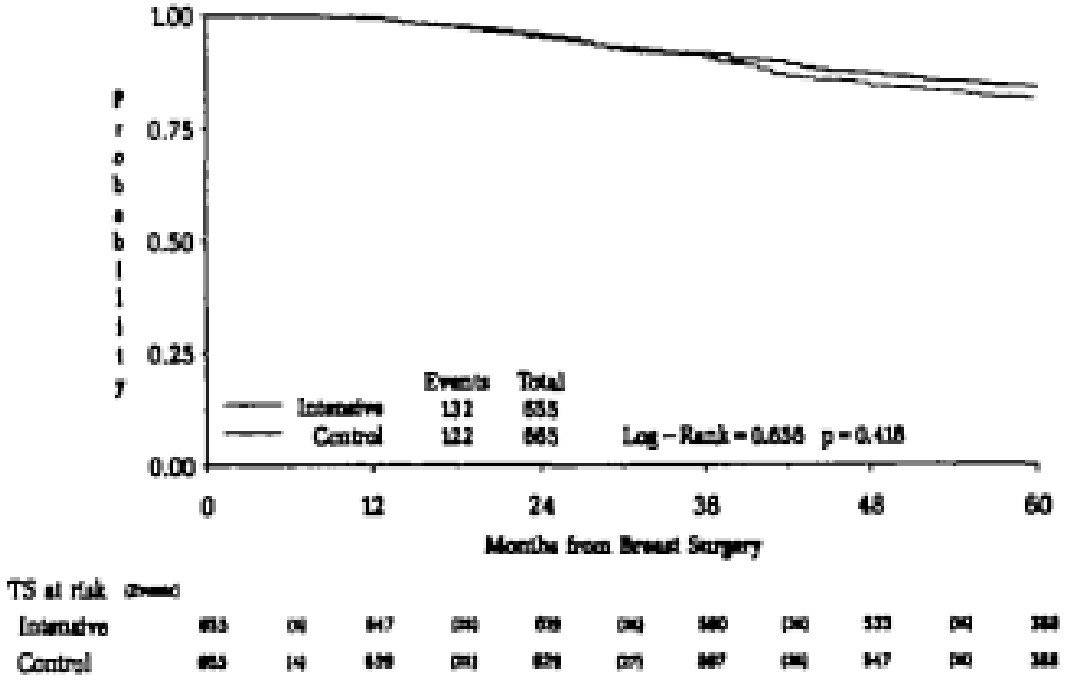
[a] In six cases (2%) modalities of patients' presentation were unknown.

[b] Method of detection: Intensive arm: physical examination (5 cases), chest X-ray (17), bone scan (8), liver echography (7), blood tests (2); Control arm: physical examination (17 cases), chest X-ray (5), liver echography (2), blood tests (2).

Similar QoL perception in experimental vs standard arm

OS (mFU 7y): 20% detahs incontrol vs 18% in intensive

The mean time to detection DM: 53m in intensive *vs* 54m for controls



A Liberati Ann Oncol 1995

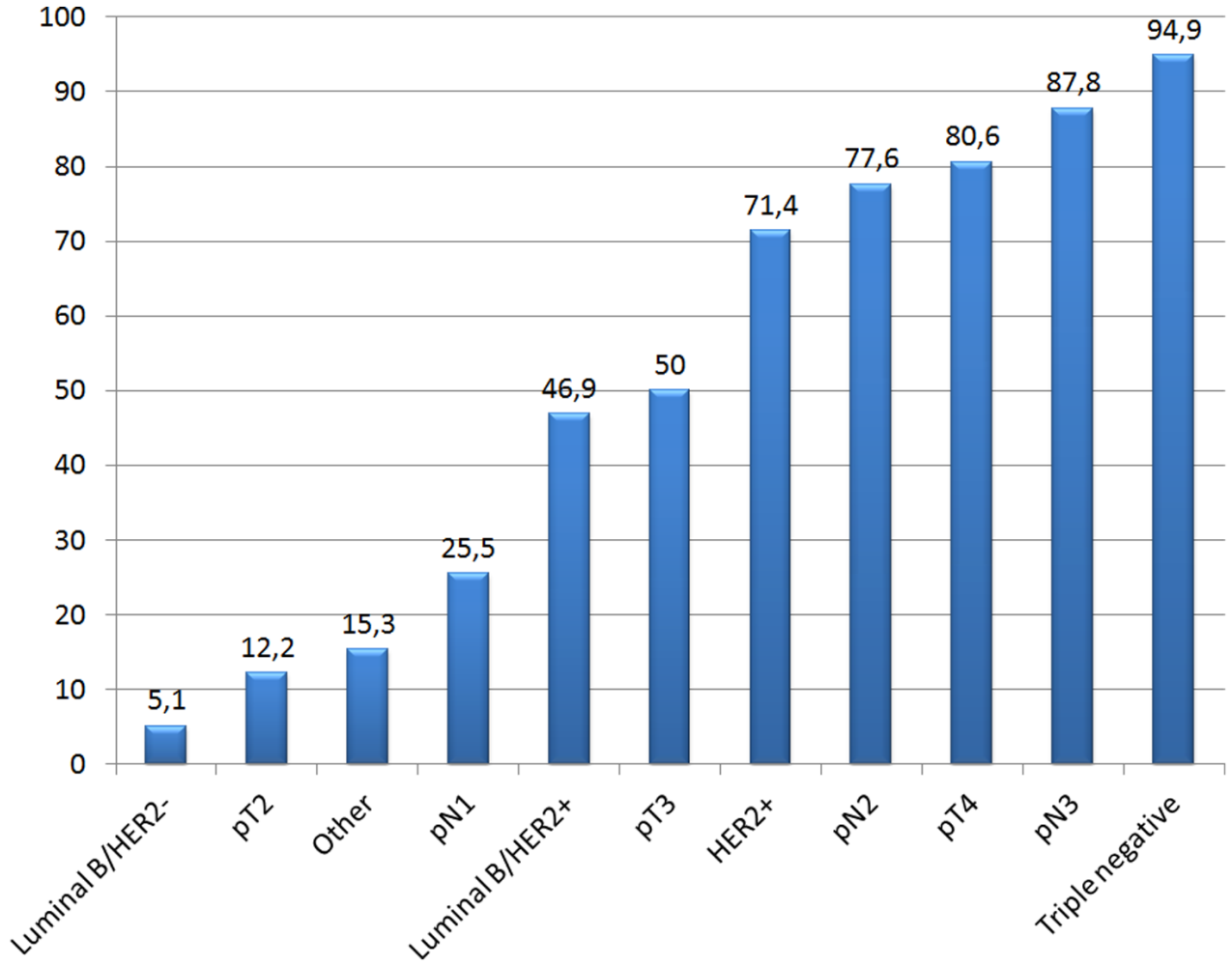
+ Rosselli Del Turco JAMA 1994

Do the physicians apply the minimalist approach?

BC “Tailored Follow-up’’ in Italian Oncology Units

Tumor stage (pT4, pN2-pN3), HER2-pos and TNBC for patients at high risk definition

90% of participating Italian oncology units declare they do not apply the minimal BC follow-up



Natoli Plos one 2014

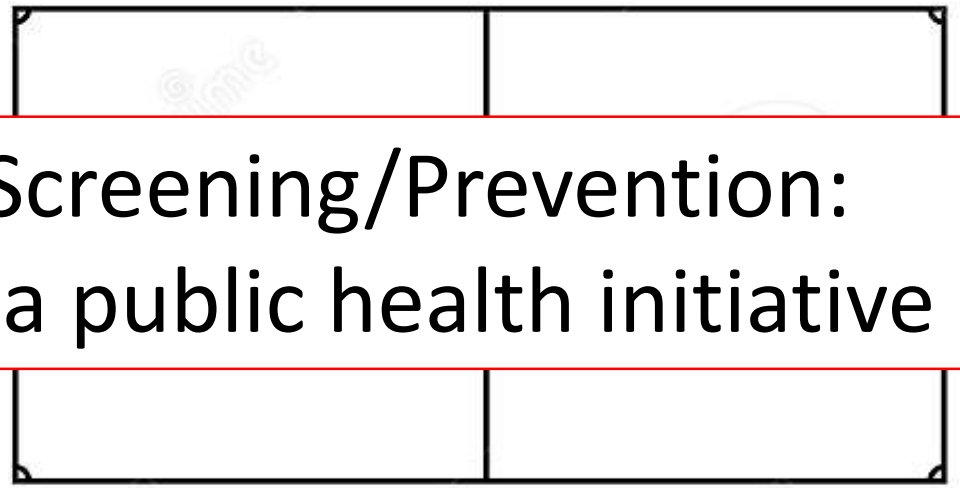
BC “Tailored Follow-up’’ in Italian Oncology Units

80% of interviewed referents performs the so called ‘‘tailored follow-up’’:
- high intensity for high risk, -
- low intensity for low risk

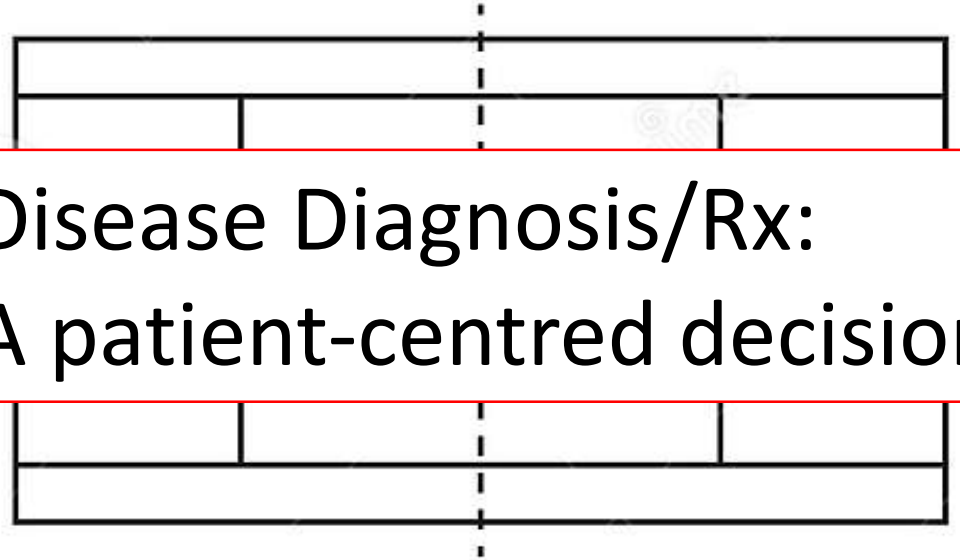
FU survey in 125 Italian medical oncology units (2013)

	At diagnosisAt			*At follow-up*		
	At diagnosis					
	NO	*YES*	*p value*	*NO*	*YES*	*p value*
	No. (%)	**No. (%)**		**No. (%)**	**No. (%)**	
Blood chemistry tests						
Low risk	9 (9.4)	87 (90.6)	0.25	14 (14.6)	82 (85.4)	0.16
High risk	4 (4.2)	92 (95.8)		7 (7.3)	89 (92.7)	
Tumor markers						
Low risk	21 (21.7)	76 (78.3)	0.002	15 (15.5)	82 (84.5)	0.03
High risk	6 (6.2)	91 (93.8)		5 (5.5)	92 (94.5)	
Chest radiograph						
Low risk	7 (7.3)	89 (92.7)	0.23	36 (37.5)	60 (62.5)	0.005
High risk	12 (13.0)	81 (87.0)		17 (18.3)	76 (81.7)	
Liver ultrasound						
Low risk	9 (9.4)	87 (90.6)	0.99	29 (30.2)	67 (69.8)	<0.0001
High risk	8 (8.6)	85 (91.4)		8 (8.6)	85 (91.4)	
Bone scan						
Low risk	40 (41.3)	57 (58.7)	<0.0001	69 (73.4)	25 (26.6)	0.006
High risk	3 (3.1)	94 (96.9)		50 (53.2)	44 (46.8)	
Whole-body CT scan						
Low risk	88 (91.7)	8 (8.3)	<0.0001	87 (93.5)	6 (6.5)	<0.0001
High risk	64 (66.7)	32 (33.3)		61 (63.6)	32 (34.4)	
Whole-body PET/CT scan						
Low risk	94 (98.9)	1 (1.1)	0.007	81 (96.4)	3 (3.6)	0.08
High risk	75 (89.3)	9 (10.7)		75 (89.3)	9 (10.7)	

Is this clinical attitude a «malpractice» ?



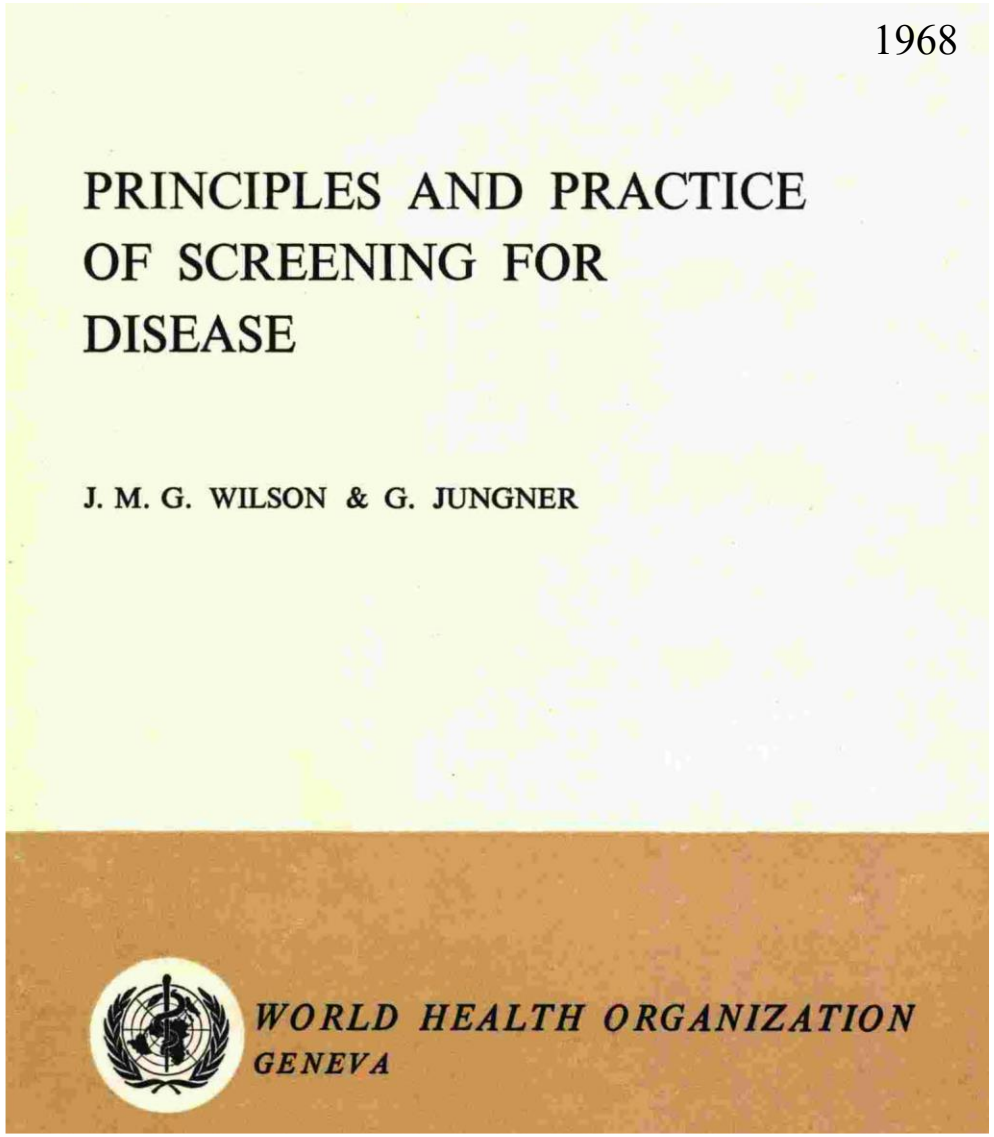
Screening/Prevention:
a public health initiative



Disease Diagnosis/Rx:
A patient-centred decision

The playing filed and the rules

Screening and prevention for disease



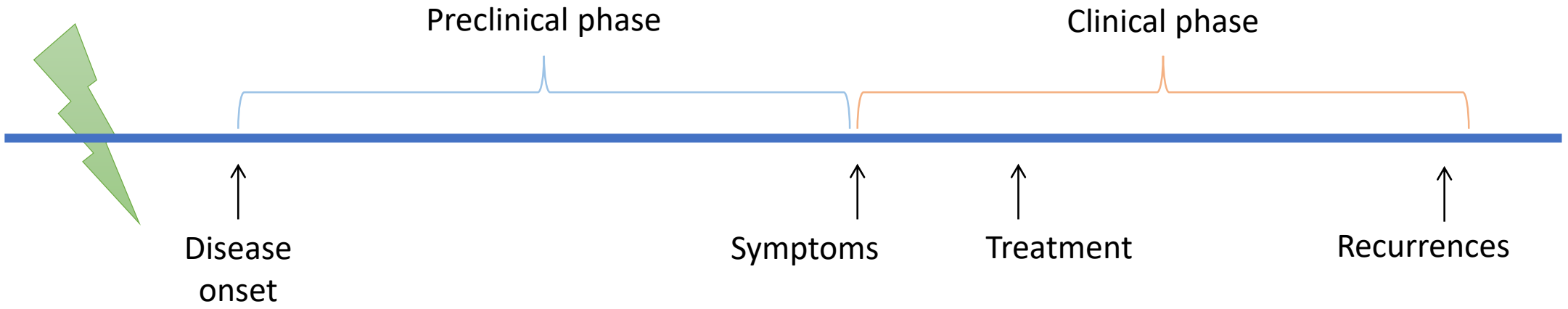
”…the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly.

Screening tests sort out apparently well persons who probably have a disease from those who probably do not.

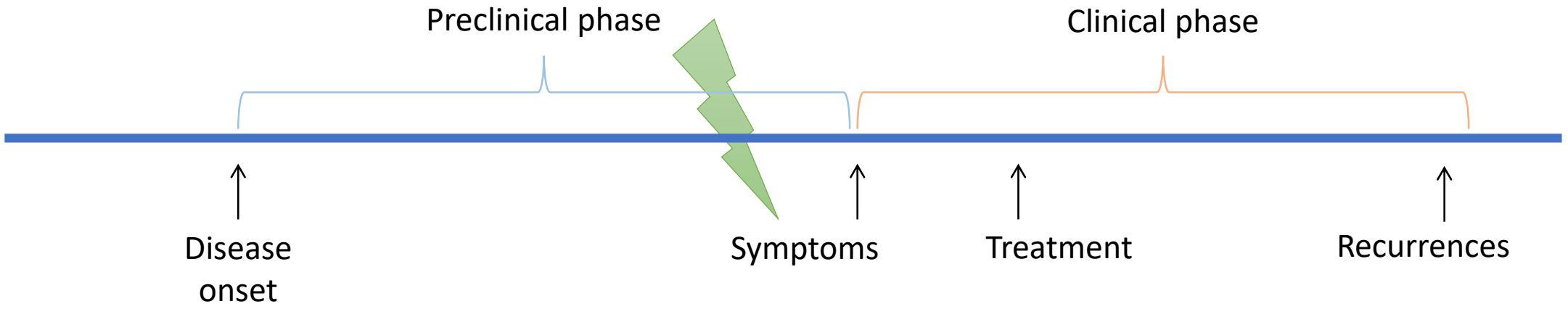
A screening test is not intended to be diagnostic.

Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment…”

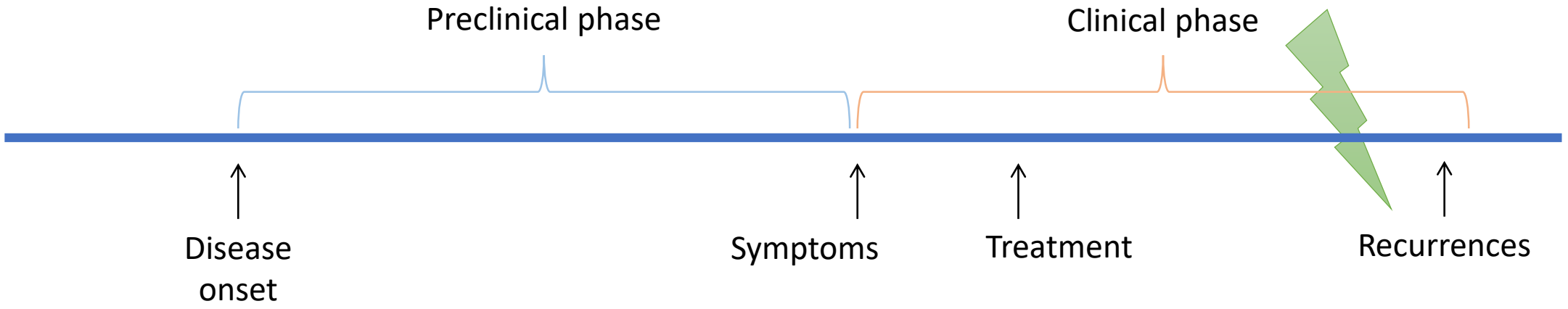
Primary Prevention: **Life styles**



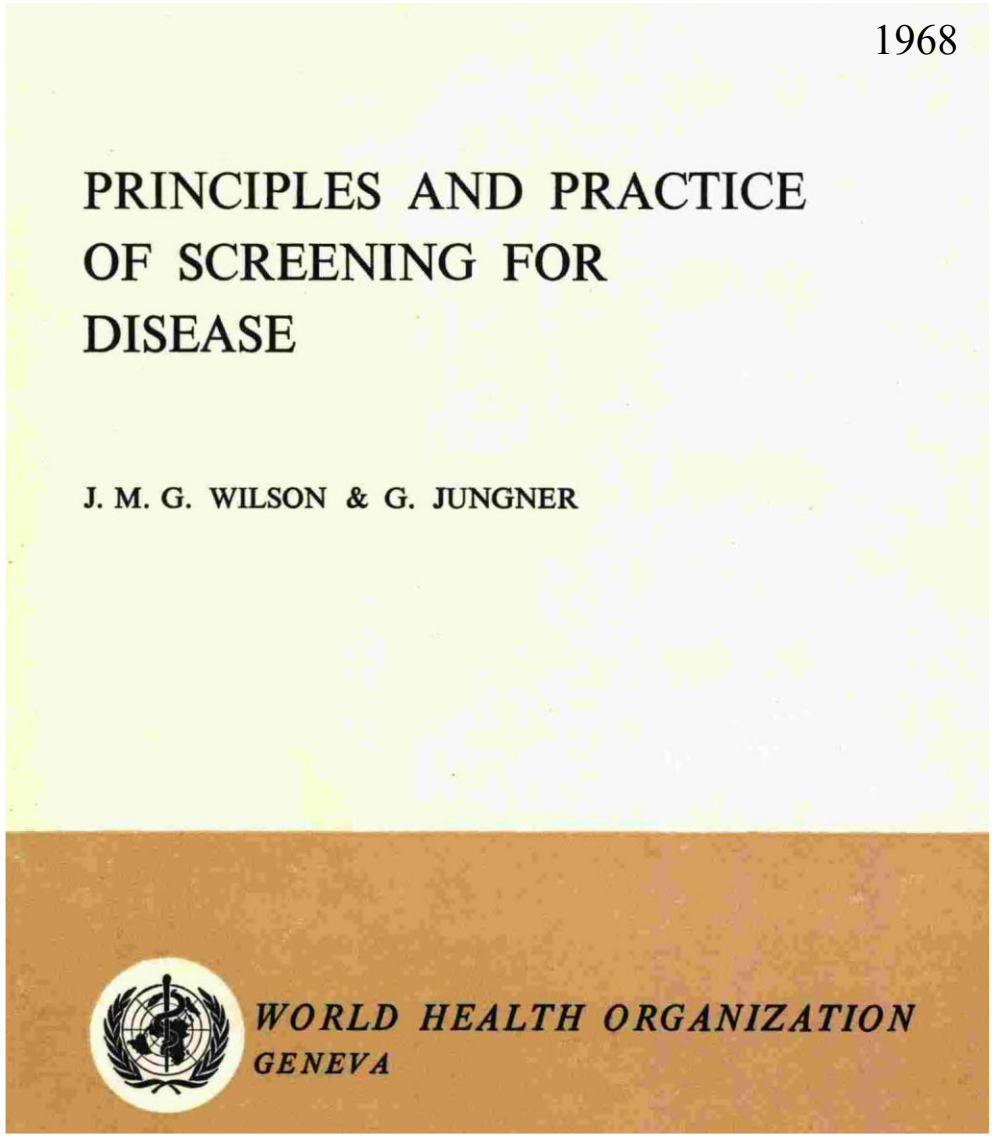
Secondary Prevention: **Screening**



Tertiary Prevention: **Follow up**



Screening and Prevention: Rules and Regs



The screening/prevention approach requires:

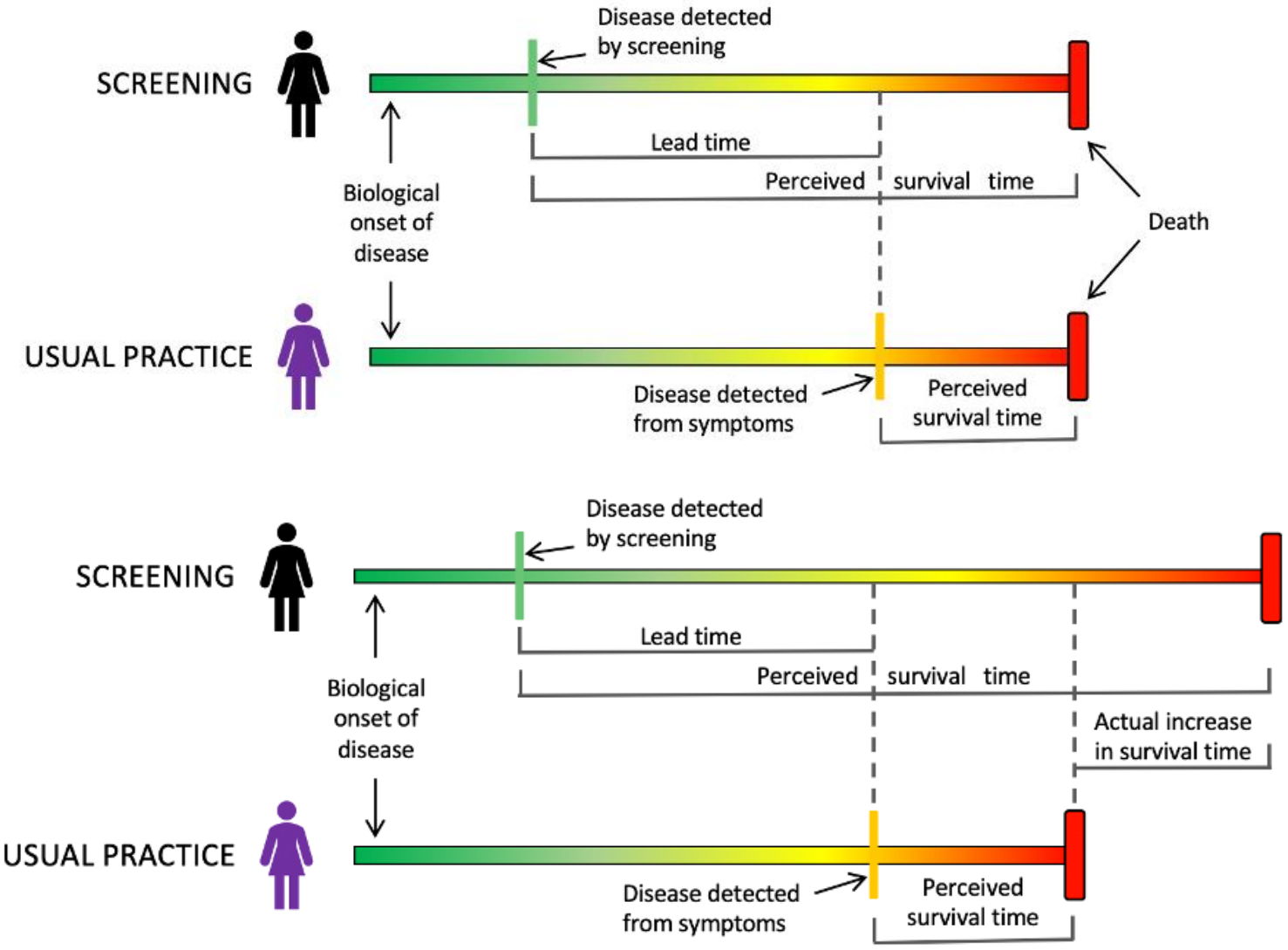
1) **A prevalent disaese** (i.e. 10%)

2) **An accurate, acceptable & sustainable** test

3) **A predicted survival gain**

A gain in survival vs. diagnostic anticipation

Overdiagnosis and Lead/Length-time bias



Lead time: early detection simply increases the period over which a metastasis is observed

Length time bias cases with a long preclinical phase and therefore presumably less aggressive are more likely to be detected by a screening program.

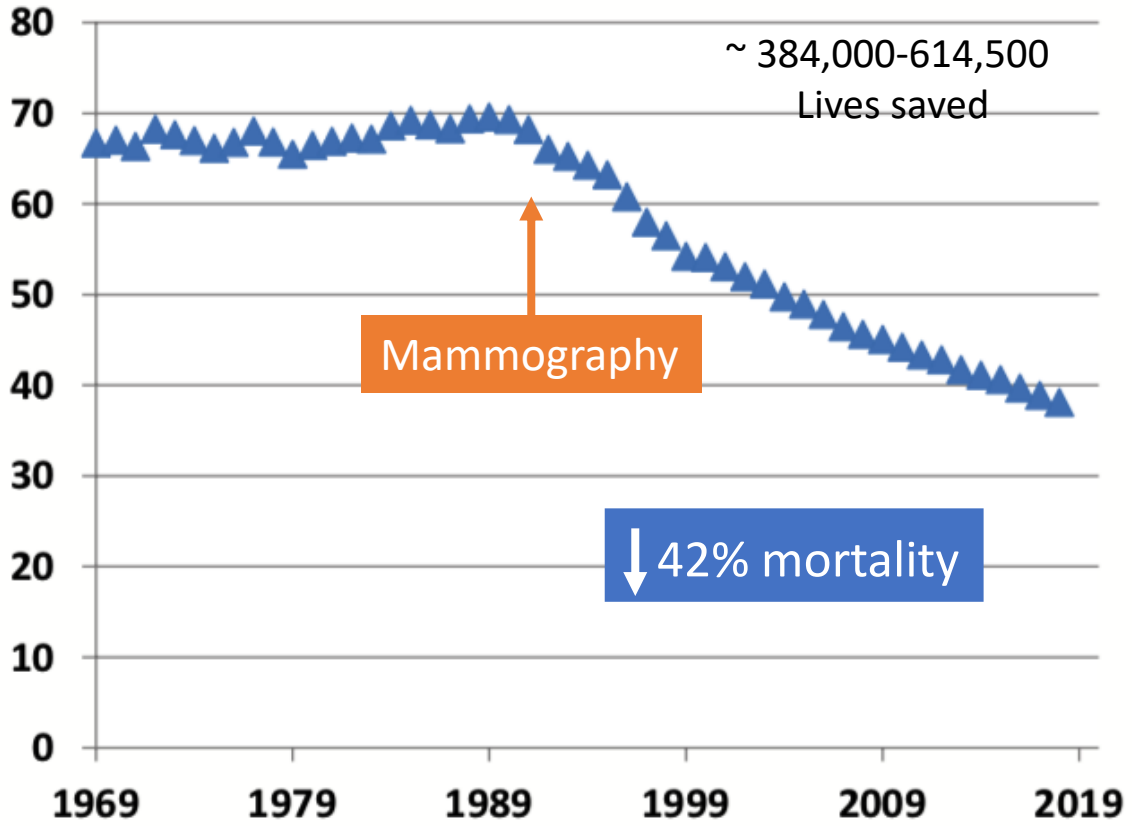
Some common belifs around FU

A common belif #1

The FU is intended to seek and cure BC recurrences

Intensive BC FU has failed to anticipate diagnosis and gain in survival based on 2 main dated RCTs

Mammography Screening has reduced BC deaths

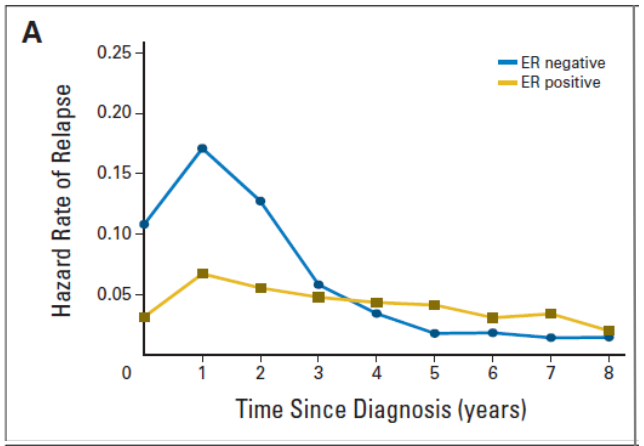


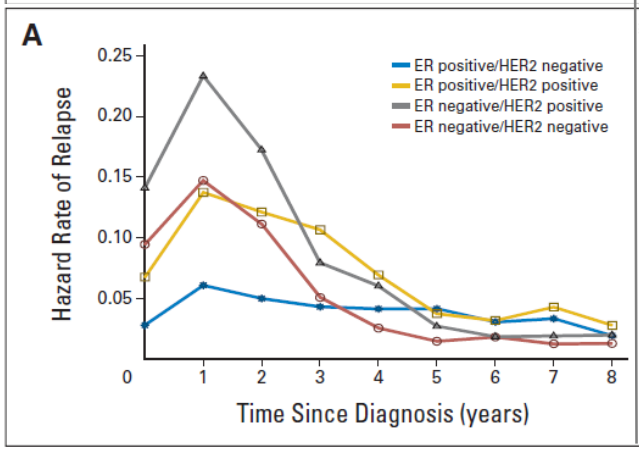
Hendrick RE, Baker JA, and Helvie MA. Breast Cancer Deaths Averted Over 3 Decades. Cancer 2019;0:1-7.

A common belif #2

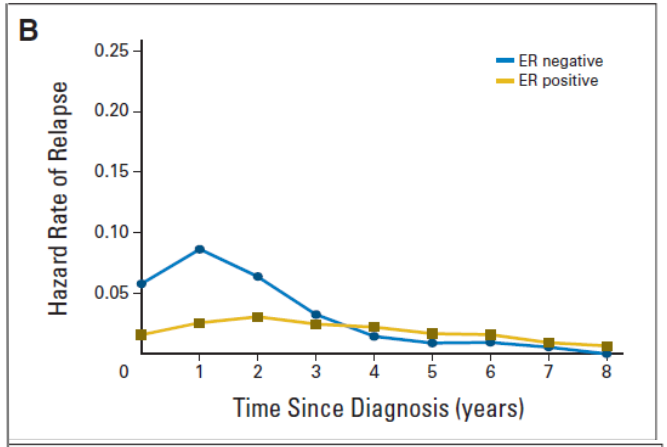
The new drugs provide unprecedented opportunities to cure BC

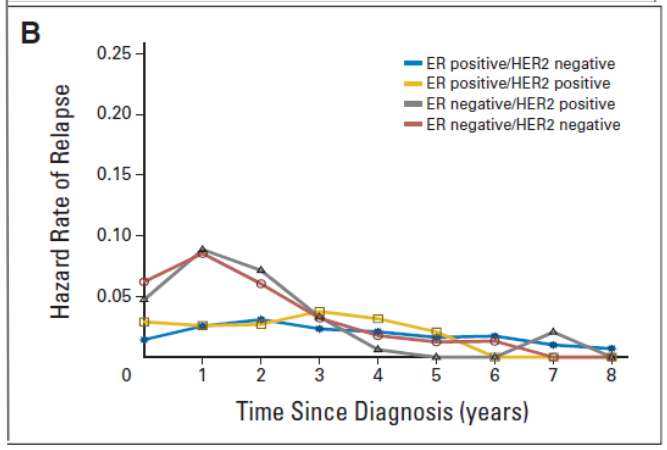
1986-1992





2004-2008





2015-2022

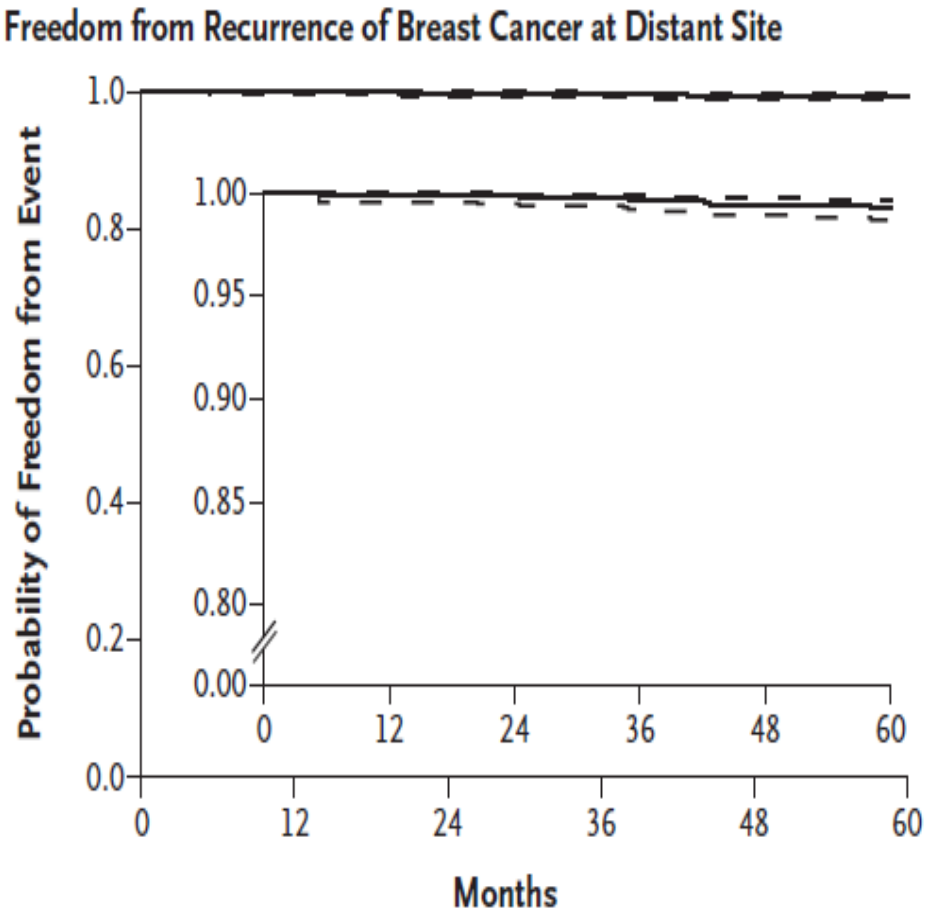
Best modern drugs tend to move to the adj setting

- T-DM1 in postNAC HER2+
- Pertuzumab in adj HER2+
- Abemaciclib in adj HR+
- Olaparib in adj gBRCAm
- Pembro in (neo)adj TN

Cossetti et al. J Clin Oncol 33; 65, 2017

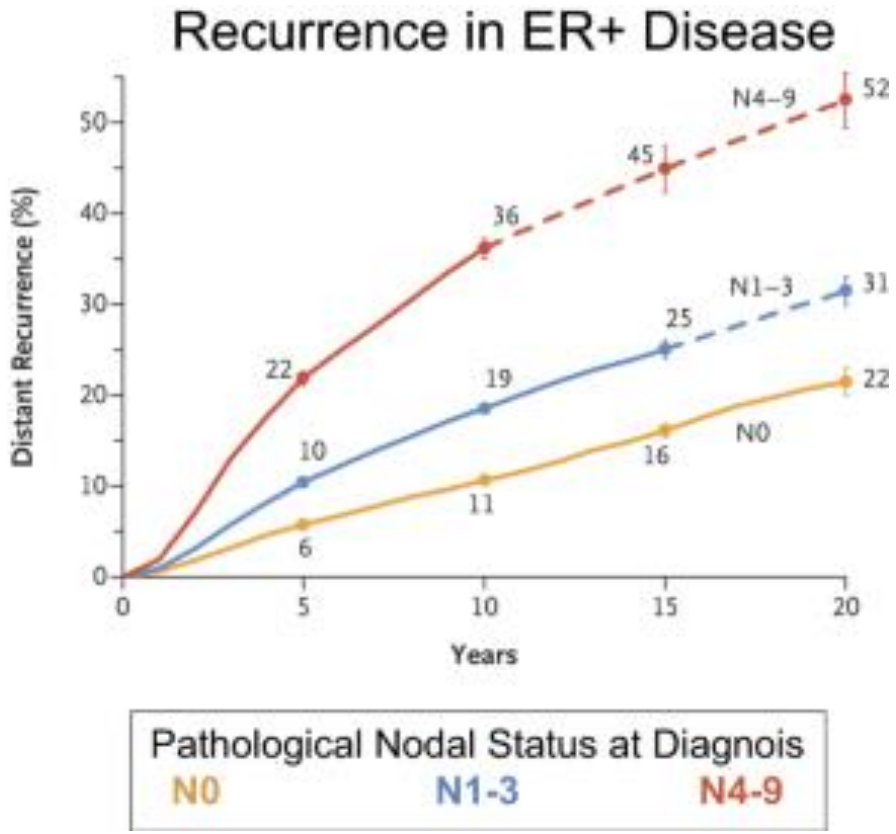
A common belif #3

All BC need to be surveilled up to 5 year from diagnosis



Sparano NEJM 2018

BCs need 17 yrs of DFS to be called cured



Pan NEJM 2019

A common belif #4

The BC follow up has to be managed by medical oncologists

Radiol med (2016) 121:891–896
DOI 10.1007/s11547-016-0676-8

CrossMark

BREAST RADIOLOGY

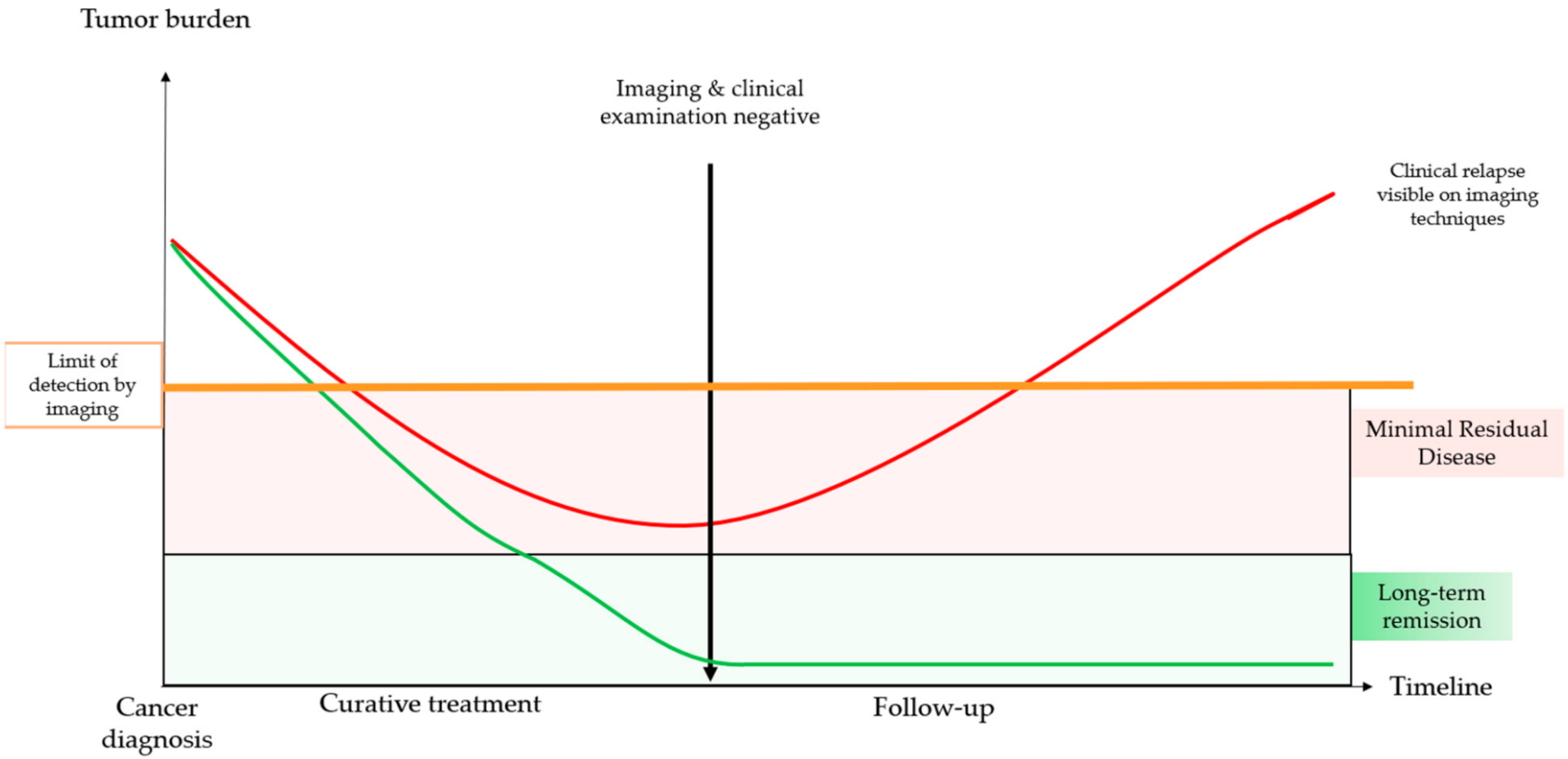
Recommendations for breast imaging follow-up of women with a previous history of breast cancer: position paper from the Italian Group for Mammography Screening (GISMa) and the Italian College of Breast Radiologists (ICBR) by SIRM

Lauro Bucchi[1] · Paolo Belli[2] · Eva Benelli[3] · Daniela Bernardi[4] · Beniamino Brancato[5] · Massimo Calabrese[6] · Luca A. Carbonaro[7] · Francesca Caumo[8] · Beatrice Cavallo-Marincola[9] · Paola Clauser[10,11] · Chiara Fedato[12] · Alfonso Frigerio[13] · Vania Galli[14] · Livia Giordano[15] · Paola Golinelli[16] · Giovanna Mariscotti[17] · Laura Martincich[18] · Stefania Montemezzi[19] · Doralba Morrone[5] · Carlo Naldoni[20] · Adriana Paduos[15] · Pietro Panizza[21] · Federica Pediconi[9] · Fiammetta Querci[22] · Antonio Rizzo[23] · Gianni Saguatti[24] · Alberto Tagliafico[25] · Rubina M. Trimboli[7] · Chiara Zuiani[11] · Francesco Sardanelli[7,26]

BC follow-up should be planned taking in consideration a 1 % annual rate of LR recurrences and new IBCTs during 20 yrs and be based on a regional/ district invitation system, as for the screening in healthy population

A common belif #5

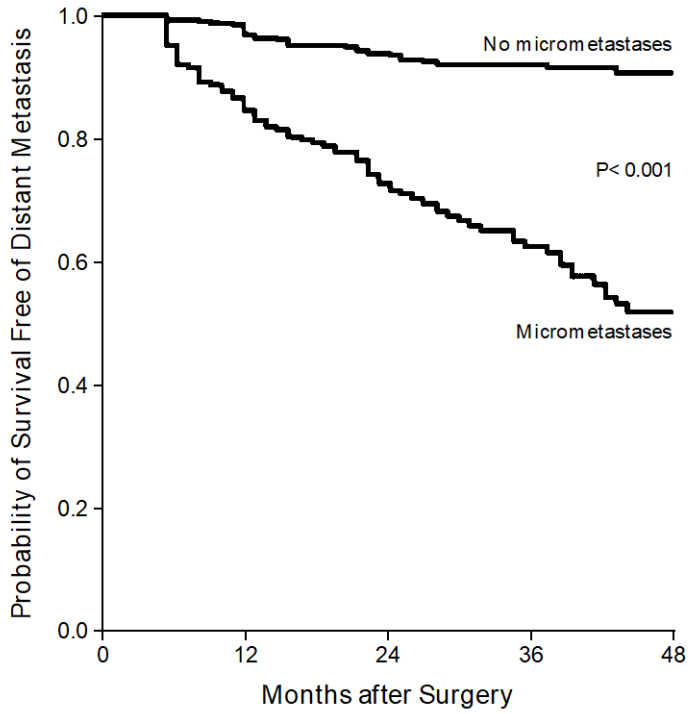
Serial Rx imaging represents the mainstay of BC follow up



DCT: German trial

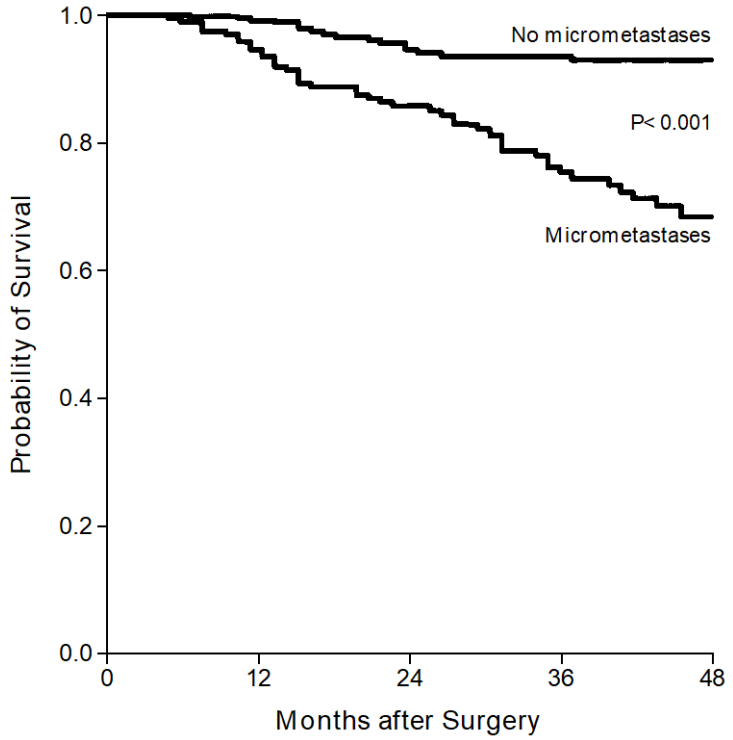
Disseminated tumor cells in the bone morrow of eBC, with no otherwise overt metastasis, are predictive of poor patients outcomes

A



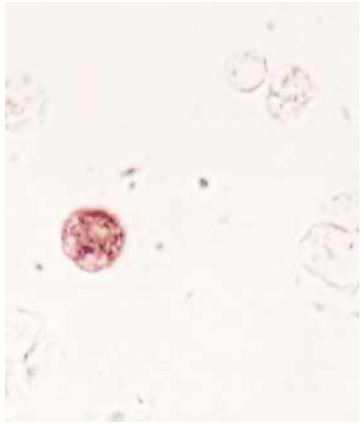
No. at Risk					
No micrometastases	353	346	275	191	92
Micrometastases	199	170	121	75	34

B



No. at Risk					
No micrometastases	353	350	280	193	95
Micrometastases	199	189	138	91	44

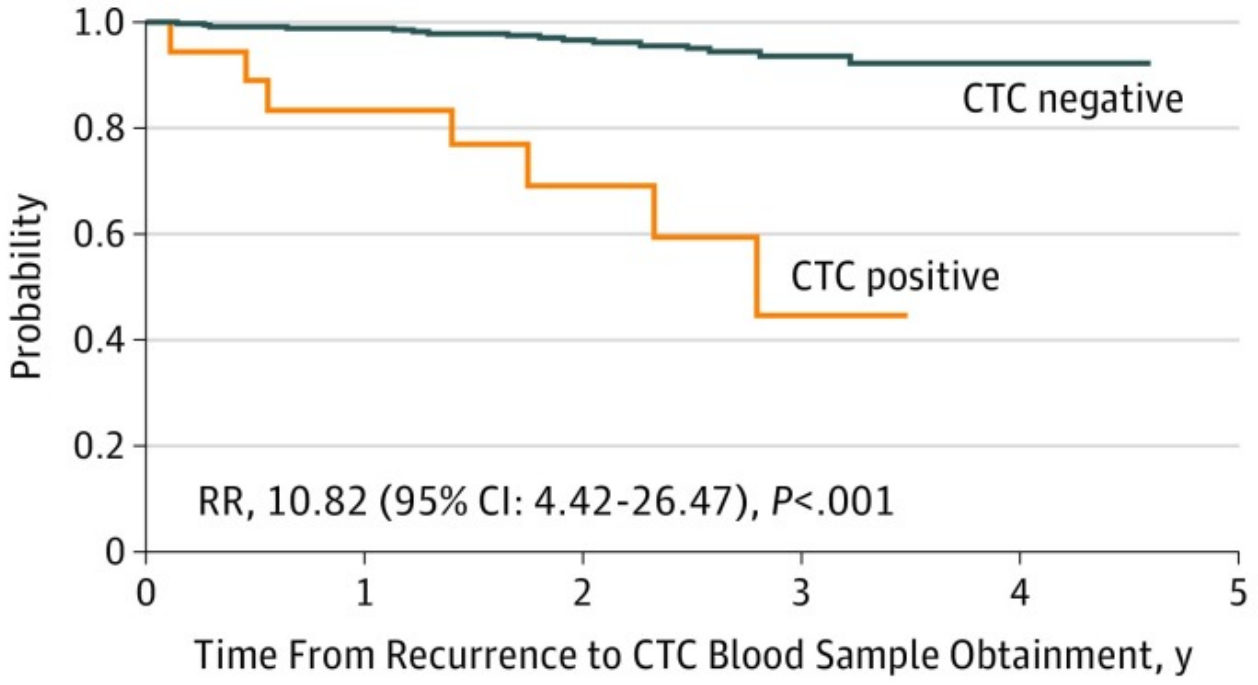
A cluster of eight micromets cells



Braun NEJM 2005

CTC: French trial (SUCCESS)

CTC were detectable in 5% of eBC after diagnosis (>5y) and were associated with a higher risk of recurrence among pts with HR-pos BC.



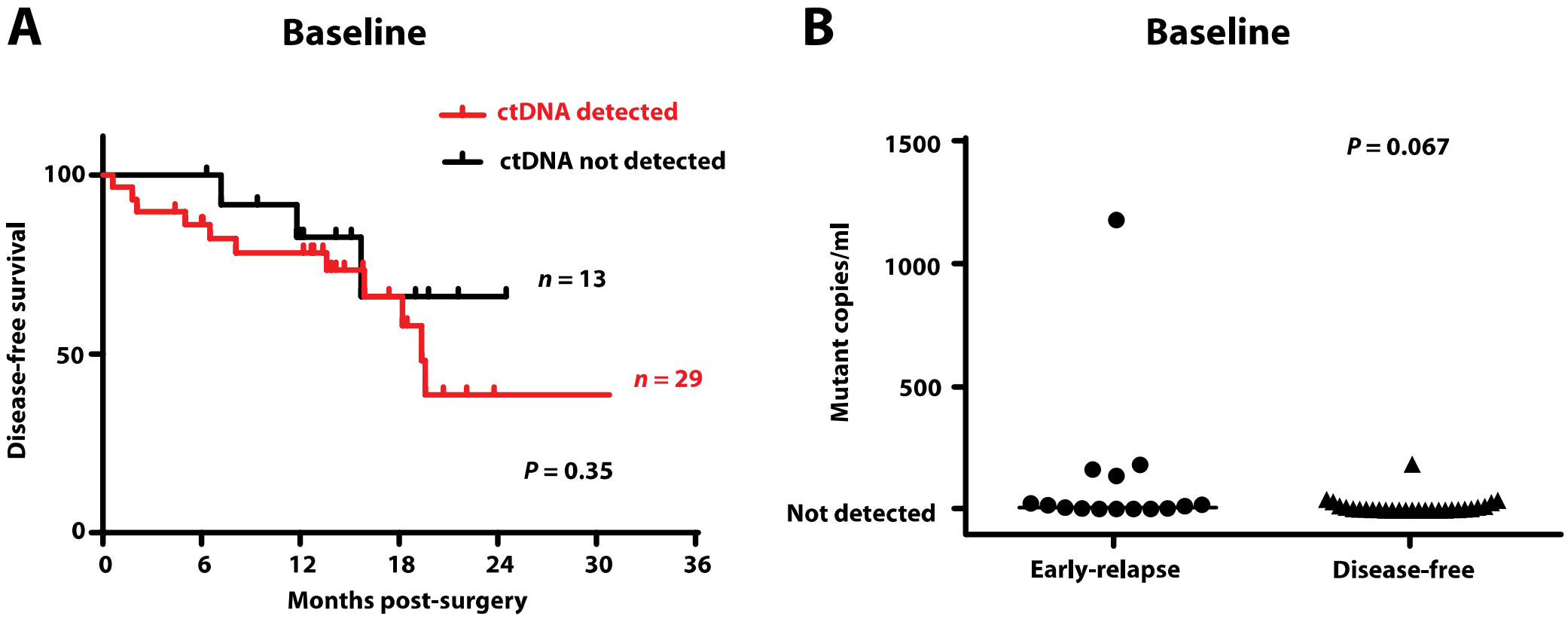
No. at risk						
CTC negative	335	306	211	102	16	0
CTC positive	18	13	7	3	0	0

Bidard, JAMA Oncol. 2018

ctDNA: UK Trial

Tissue-informed ctDNA can be detected in blood in the early phase of BC

Early relapse is not predicted by analysis of baseline ctDNA (N:55 receiving NAC)

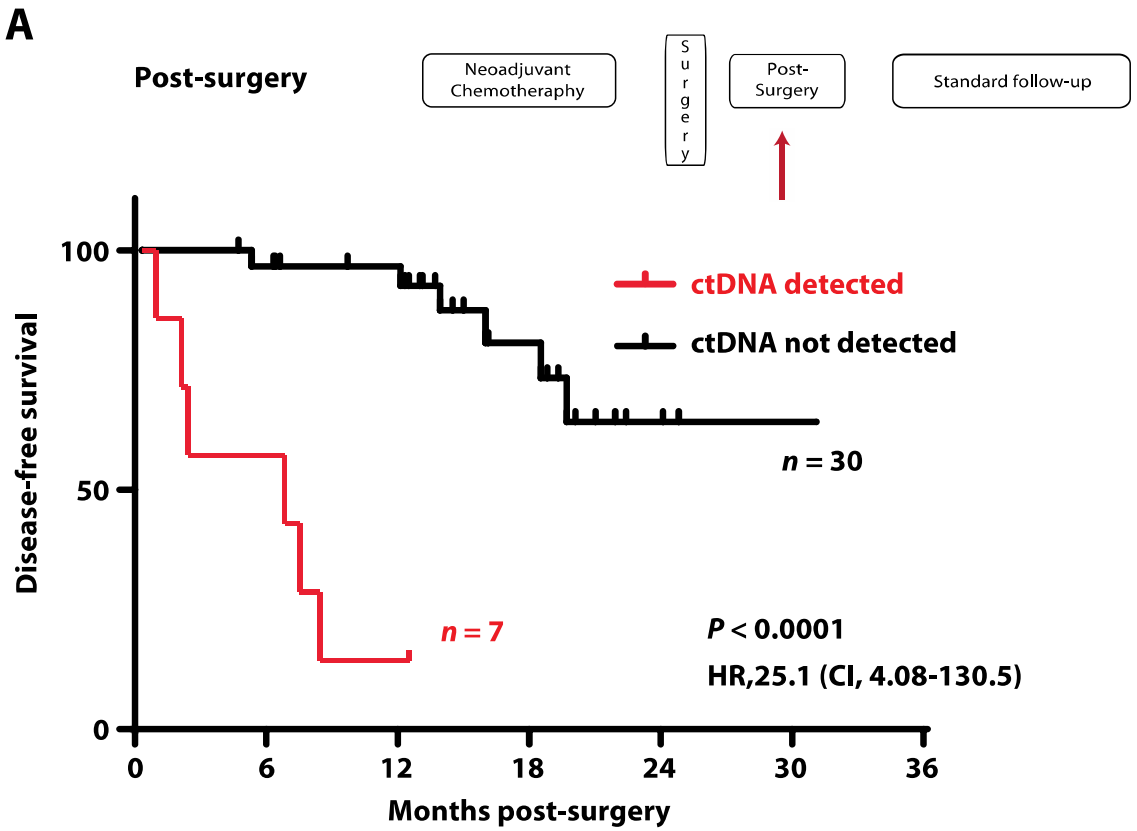


Isaac Garcia-Murillas
ScienceTranslationalMedicine 2015

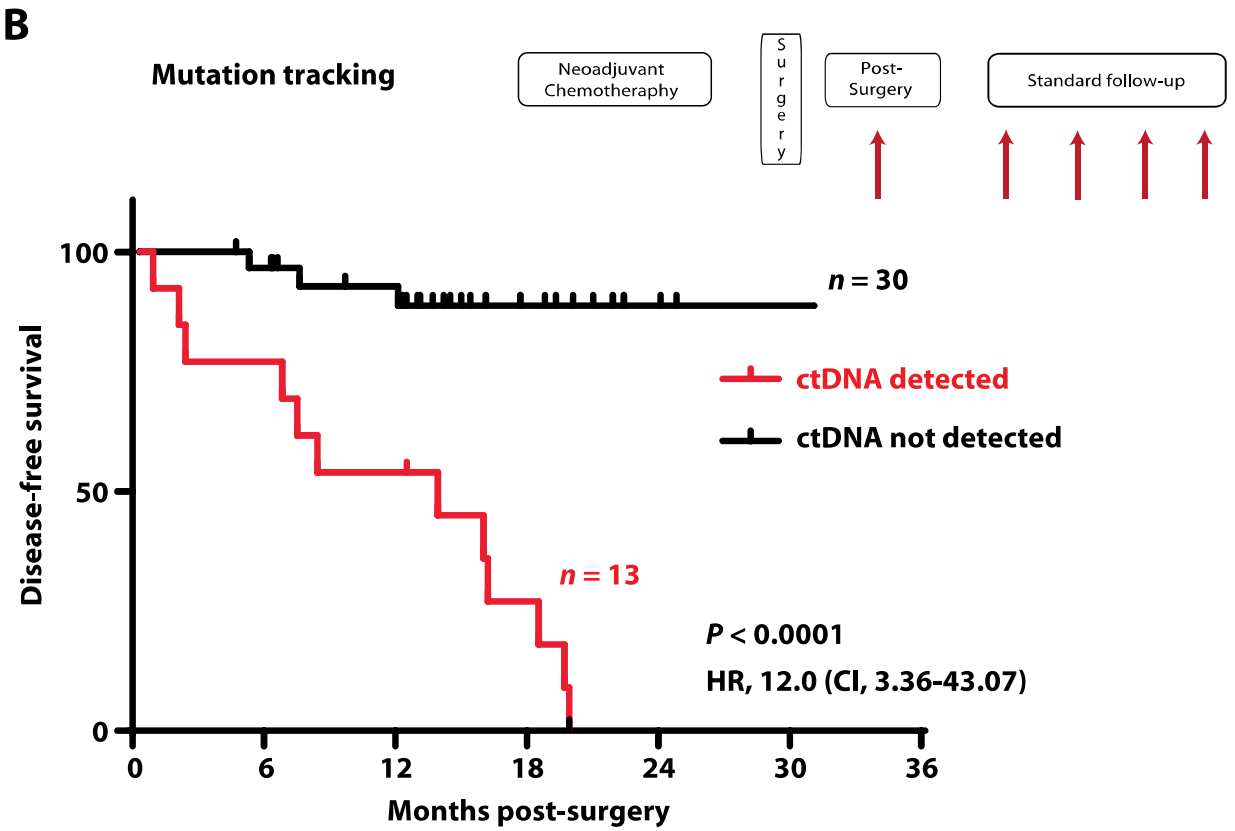
ctDNA UK Trial

Mutation tracking in serial plasma samples predicts early relapse: median lead-time 7.9m

DFS according to the detection of ctDNA in the first postsurgical plasma sample



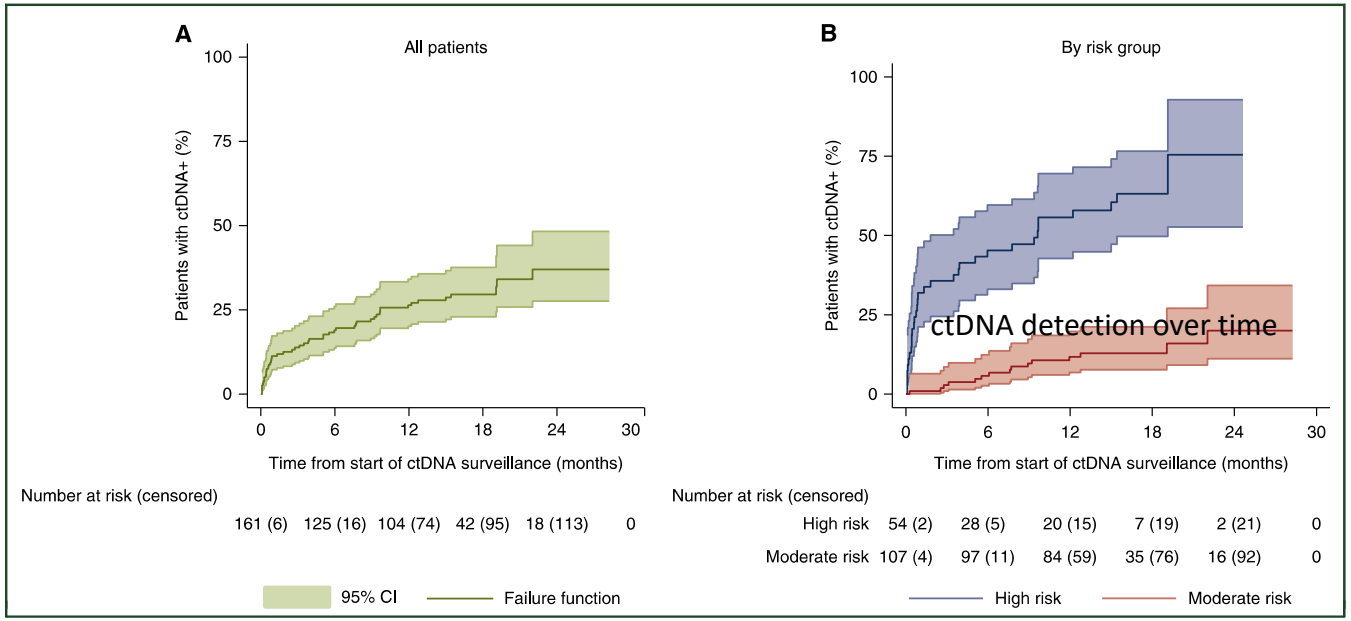
Disease-free survival according to the detection of ctDNA in serial follow- up samples



c-TRAK TN Trial (firts prospective Ph2 study testing the clinical utility of ctDNA in guiding Rx)

ctDNA mutation to detect MRD and trigger intervention (Pembro) in pts with moderate/high risk eTNBC

ctDNA detection over time (digitalPCR every 3m) N:208 92% with trackable mutation



ctDNA was detected at the rate anticipated, with 27% (44/161) of patients having ctDNA detected during the first 12 months

Of the 45 patients allocated to intervention (Pembro), 72% (23/32) had metastatic disease on staging at the time of ctDNA detection with little difference between high vs moderate risk groups

Turner Ann Oncol 2022

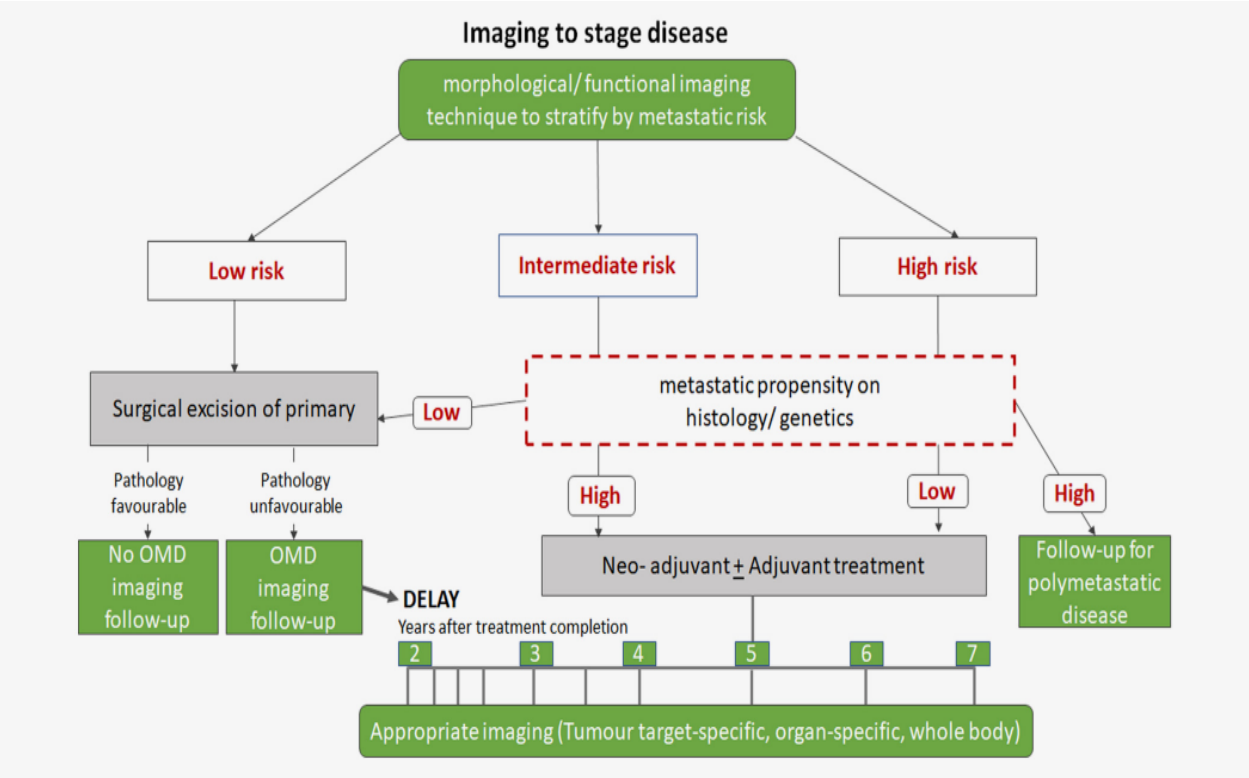
Early BC trials monitoring ctDNA in the (neo)adjuvant

Study	Technique	Method	ctDNA/Total SAMPLES	Main Findings
Riva et al. (2017)	ddPCR	Customized panel to track TP53 mutations previously characterized in tumor tissue	38/41	Customized panel detected 75% at baseline; Slow decrease in ctDNA during neoadjuvant chemotherapy was associated with shorter survival
Garcia-Murillas et al. (2019)	ddPCR	Primary tumor was sequenced and personalized tumor-specific ddPCR was used	101/170	ctDNA detection during follow up was associated with a high rate of relapse
Rothé et al. (2019) (NeoAllto trial)	ddPCR	PIK3CA and/or TP53 mutations	69/455	ctDNA detection before neoadjuvant anti-HER2 therapy was associated with low pCR rates
McDonald et al. (2019)	Targeted digital sequencing (TARDIS)	Exome sequencing of tumor biopsies and analysis of dozens to hundreds of mutations in serial plasma samples	33/33	TARDIS results were informative in 100% of the samples; Patients with pCR showed a large decrease in ctDNA concentration during therapy
Radovich et al. (2020)	NGS	Commercial platform covering multiple genes. (FoundationACT® or FoundationOneLiquid Assay®)	142/196	Detection of ctDNA and CTCs in triple-negative breast cancer patients after neoadjuvant therapy was associated with disease recurrence
Magbanua et al. (2021)	NGS	Personalized ctDNA test to detect up to 16 patient-specific mutations	61/84	Lack of ctDNA clearance predicted poor response and metastasis
Po-Han Lin et al. (2021)	NGS	Deep sequencing of a target gene panel (14 genes)	60/90	The presence of ctDNA after neoadjuvant therapy was a robust marker for predicting relapse in stage II-to-III breast cancer patients

M Sant Cancers 2022

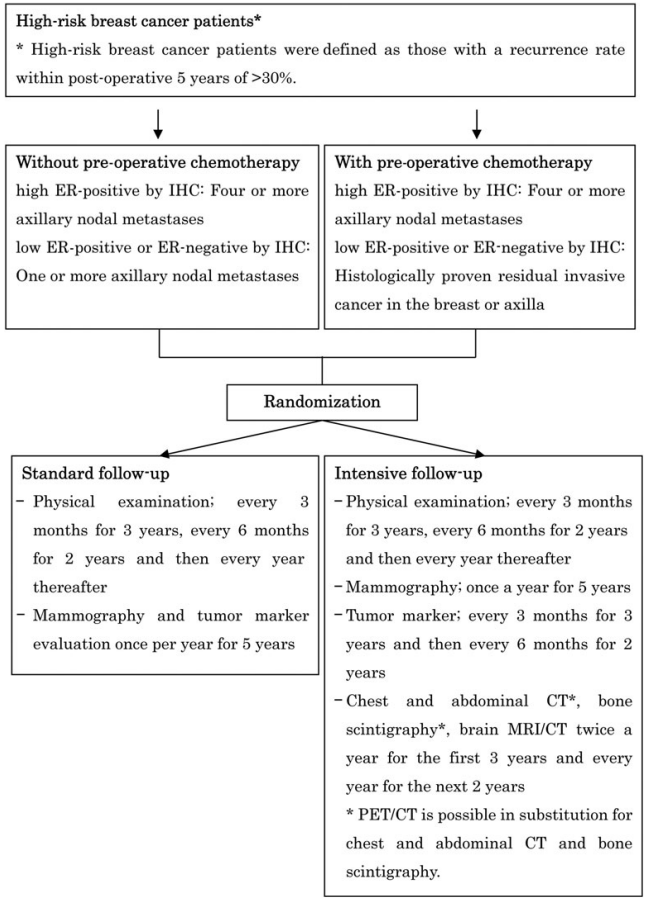
A risk-based approach for order imaging FU

An imaging workflow for detection of oligometastatic disease



Int. J. Cancer: 144, 422–430 (2019)

INSPIRE trial (Japan)



Japanese Journal of Clinical Oncology, 2015

To conclude

Nowdays, the aims of the FU are:

- To detect early local recurrences or contralateral breast cancer;
- To evaluate and treat therapy-related complications (such as menopausal symptoms, osteoporosis and second cancers);
- To motivate patients continuing adjuvant ET;
- To provide support and information in order to enable a return to normal life after BC.

To conclude (cont.)

In perspective

- BC FU is intended as a preventive public health initiative with the final goal to improve survival in apparently healthy women with Hx of BC
- Few and dated evidence suggest a minimalist BC FU approach: modern trial are expected to confirm/reconsider this attitude
- The current «one fits all solution» may be sub-optimal and targeted FU solution should be investigated
- The promise of new diagnostics and therapeutics should be challanged in a innovative FU model