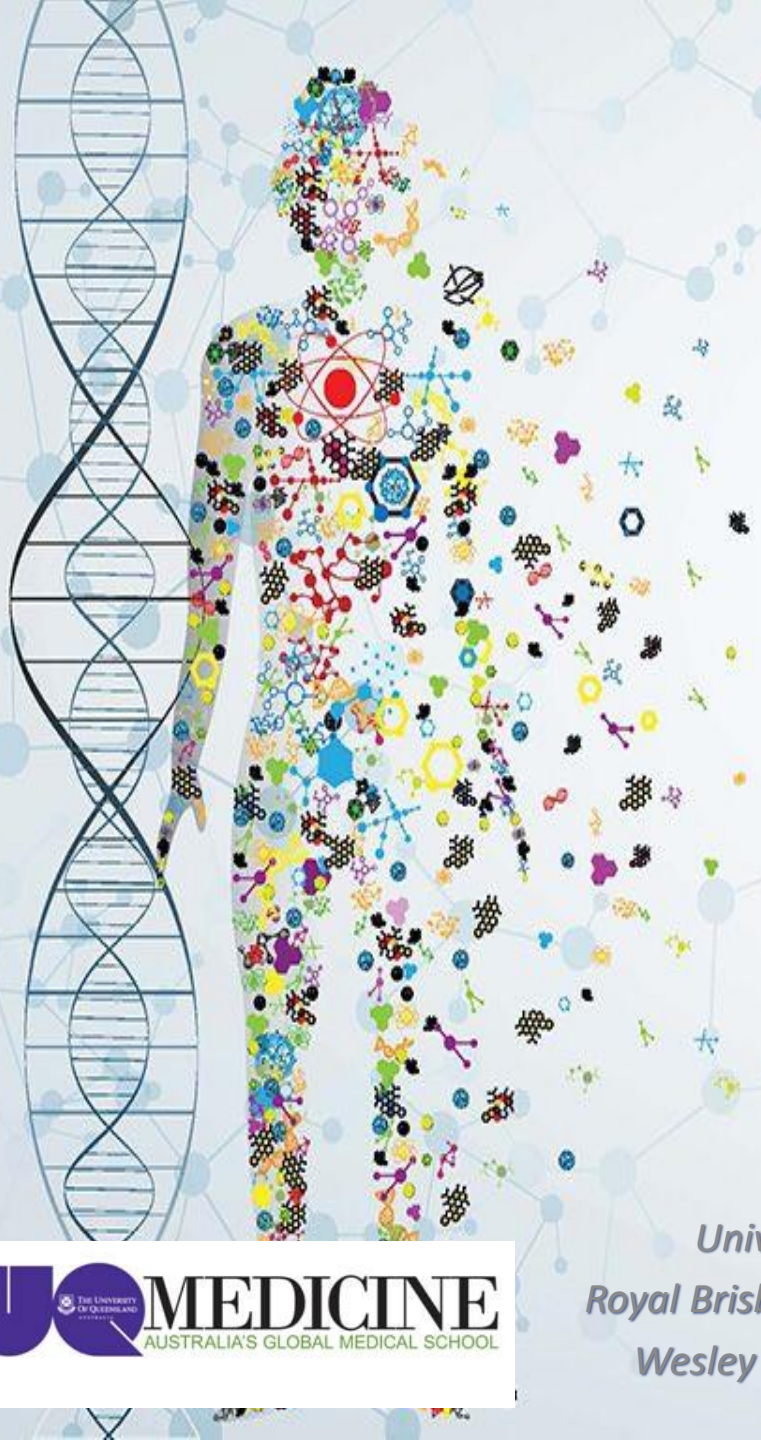


THE SURGEONS ROLE: GOING FORWARD

Owen A Ung

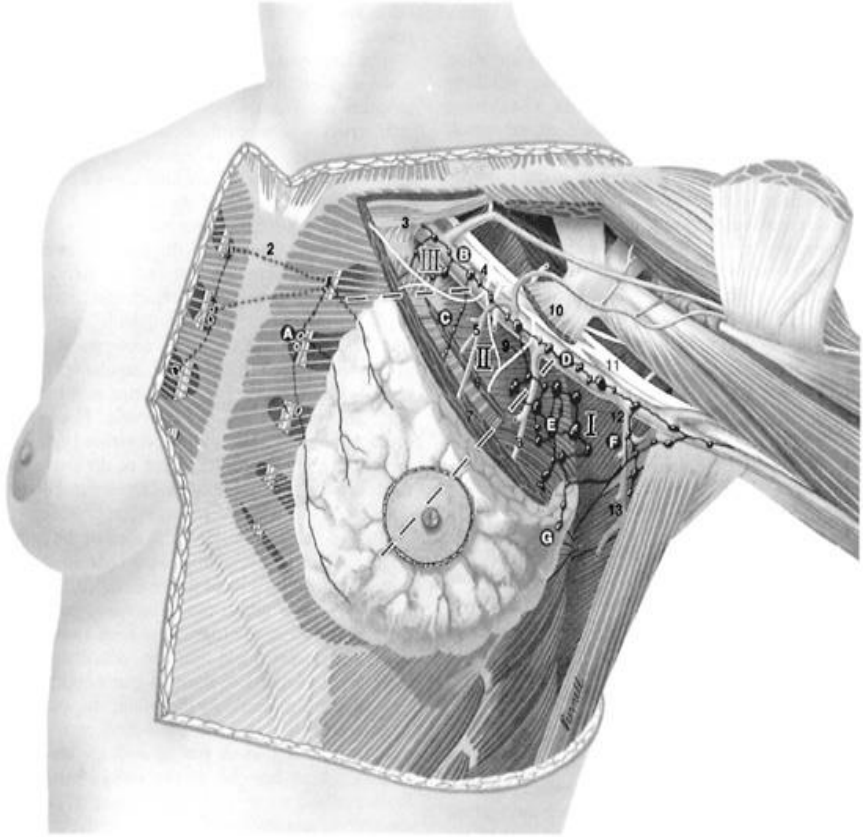
University of Queensland

Royal Brisbane and Women's Hospital

Wesley and St Andrews Hospital

UQ MEDICINE
AUSTRALIA'S GLOBAL MEDICAL SCHOOL

A long time ago in a galaxy far, far away....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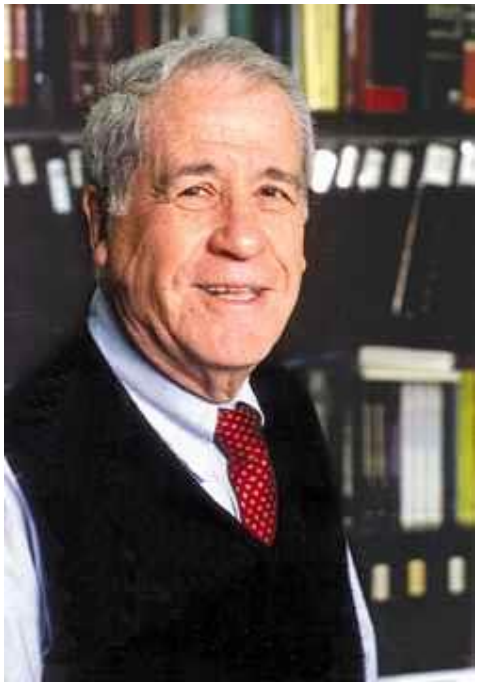
William Halsted

Bernard Fisher



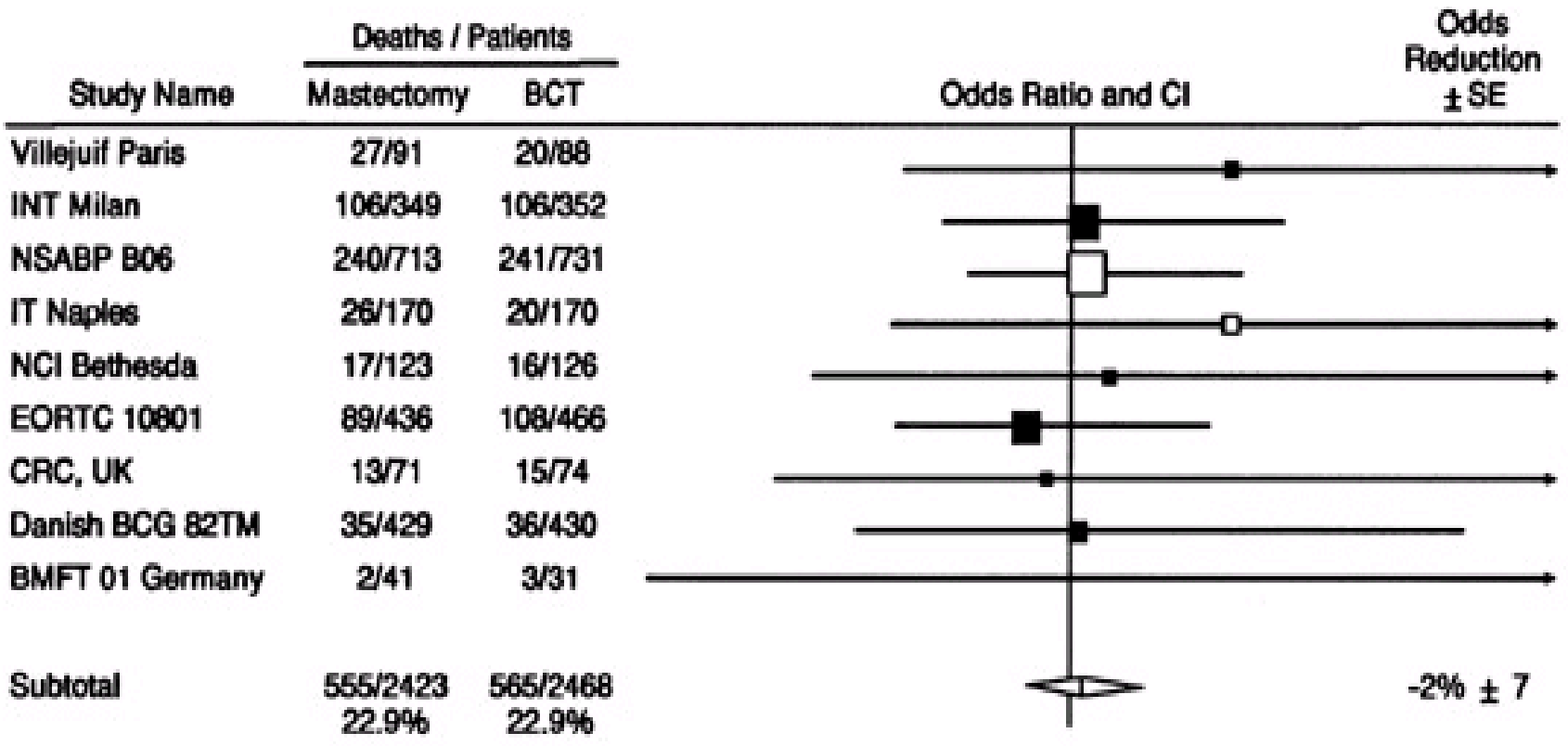
Breast cancer is a local disease

Breast cancer is systemic

Basis of treatment strategy

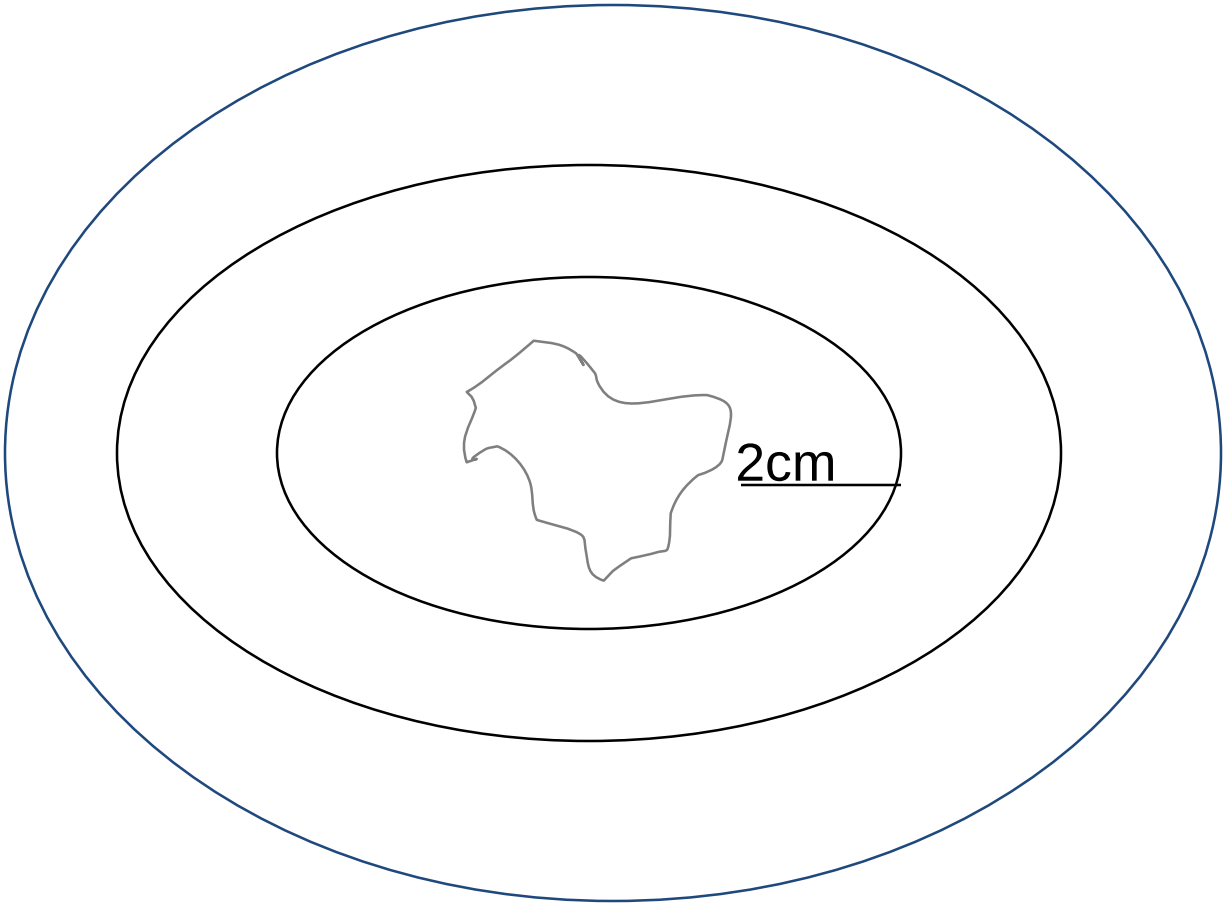
- Early detection and accurate staging
  - Screening for primary breast cancer
- Local control
  - Optimal surgery and XRT
  - Prevent morbid disease recurrence
  - Quality of life
  - Psychological benefit
- Systemic and targeted therapies
  - ALL IMPROVE SURVIVAL
- Minimise side effects of treatment

Nine randomised controlled trials which have compared **breast conservation** to mastectomy have shown equivalent rates of survival



The operation went very well - I got it all

Distribution of cancer in the breast containing a "localised" tumour



Data obtained using correlated specimen radiography and histologic techniques

R. Holland et al. CANCER 56: 979-990, 1985

Probability of finding cancer remaining in the breast after simulated local excision related to distance from the edge of the primary tumour exclusive of LCIS

	>0.5cm	>2cm	>4cm	>6cm	>8cm
Invasive + DCIS	74%	59%	32%	21%	9%
Invasive only	42%	29%	12%	8%	3%
p-value	.00001	.00004	.0009	.01	.09

breast conservation - surgeons don’t get it all most of the time

R. Holland et al. CANCER 56: 979-990, 1985

The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy (n=204)

	Invasive + DCIS		Invasive only		p-value
Final margin	# pts	%IBR	# pts	%IBR	EIC+ vs EIC-
Positive (all)	19	37%	71	7%	0.003
>focally +ve	13	54%	24	8%	0.004
focally +ve	6	0%	44	7%	NS
Close	5	0%	19	5%	NS
Negative	8	0%	66	3%	NS

Schnitt S. et al CANCER 1994 74(6)

Margins – time is the only thing that's changed

Evidence from larger population studies

Effect of Margin Status on Local Recurrence After Breast Conservation and Radiation Therapy for Ductal Carcinoma In Situ

- Meta analysis - 22 trials (9 RCT and 13 observational studies), n=4660
- 2mm margins provide equivalent local control

Margin width	%IBTR (n= Patients)	OR (95%CI) Relapse v >5mm	P value
<1mm	9.4 (n=914)	2.56 (1.1-7.3)	<0.001
1mm	10.4 (n= 1239)	2.89 (1.3-8.1)	<0.001
2mm	5.8 (n= 207)	1.51 (0.51-5.0)	>0.5**
>5mm	3.9% (n=154)	1	

Clive Dunne, John P. Burke, Monica Morrow, and Malcolm R. Kell
March 2, 2009 as 10.1200/JCO

Meta analysis: margin invasive breast cancer

Clinical Investigation: Breast Cancer

Society of Surgical Oncology—American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD,* Stuart J. Schnitt, MD,† Armando E. Giuliano, MD,‡ Jay R. Harris, MD,§ Seema A. Khan, MD,‖ Janet Horton, MD,¶ Suzanne Klimberg, MD,# Mariana Chavez-MacGregor, MD,** Gary Freedman, MD,†† Nehmat Houssami, MD, PhD,‡‡ Peggy L. Johnson,§§ and Monica Morrow, MD‖‖

- Relationship between margin width and ipsilateral breast tumor recurrence (IBTR)
- 33 studies included in meta-analysis; 28162 patients; 5.3% IBTR; median follow-up 79.2months
- Positive margin is associated with 2-fold increase in IBTR

Int J Rad Onc 2014 Vol 88, p 553-564

Summary of Recommendation

Do margin widths wider than no tumour cells at ink margin reduce the risk of IBTR?

- 19 studies; 13081 patients; 753 IBTR; 8.7yr median follow up
- No statistical significant evidence that the odds of IBTR were associated with margin distance
- Nor was their a relationship between distance for negative margin and IBTR
- Even when adjusted for other variables there was no difference in IBTR

Recommendation: Wider margins widths do not significantly lower the risk (i.e. no ink on margin)

Int J Rad Onc 2014 Vol 88, p 553-564

Summary of Recommendation

- Other recommendations:
  - Margin width should not be used to determine the delivery technique or fractionation for WBRT or vice versa
  - Wider margins are not indicated for invasive lobular cancer
  - Young age (<40 yrs) is associated with both increased IBTR after BCS or local relapse after mastectomy due to the adverse biology and pathological features.

    Wider margins does not decrease this risk

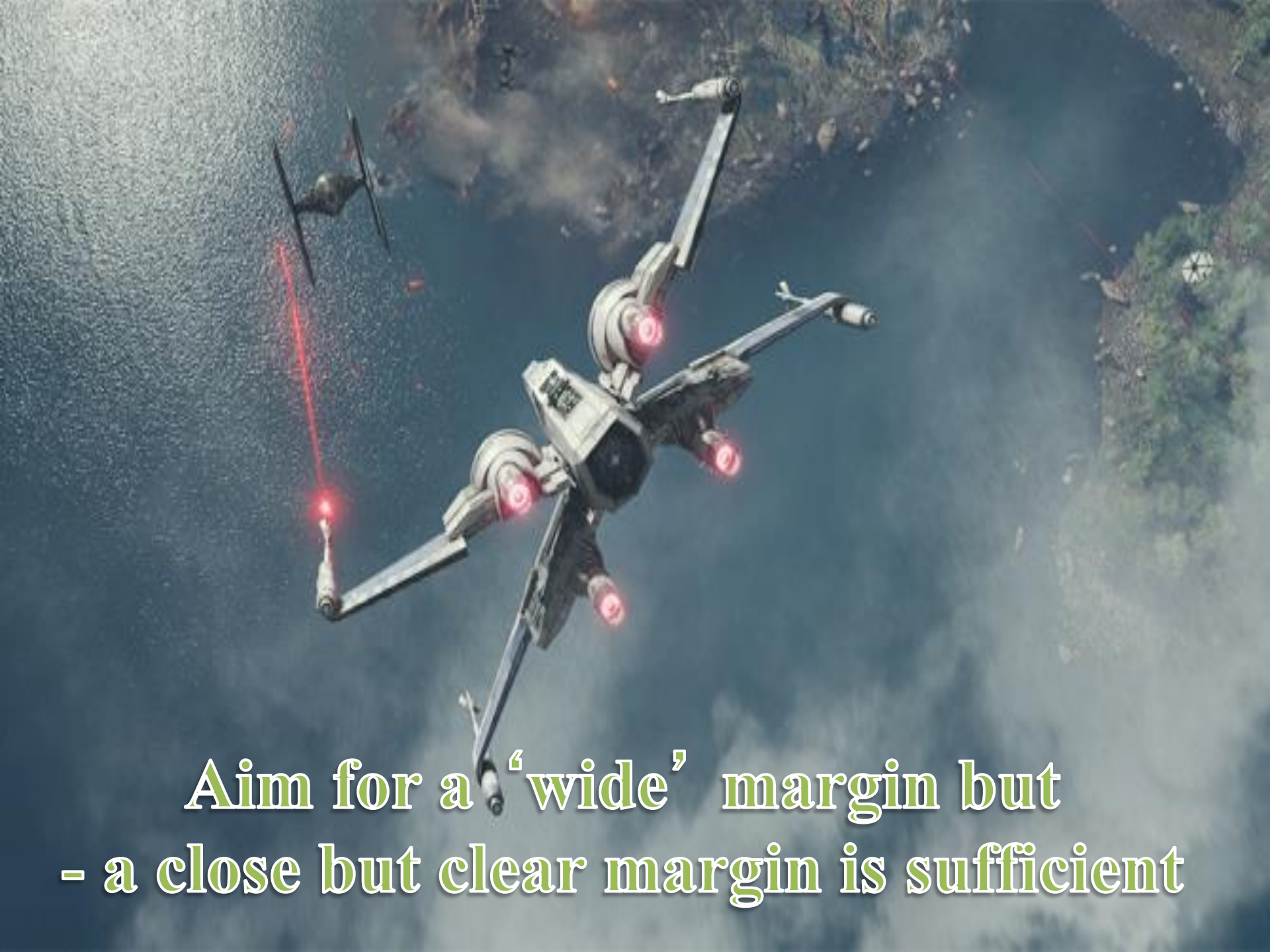
Size of primary is not a factor

Margins - Early exuberance replaced with measured conservatism

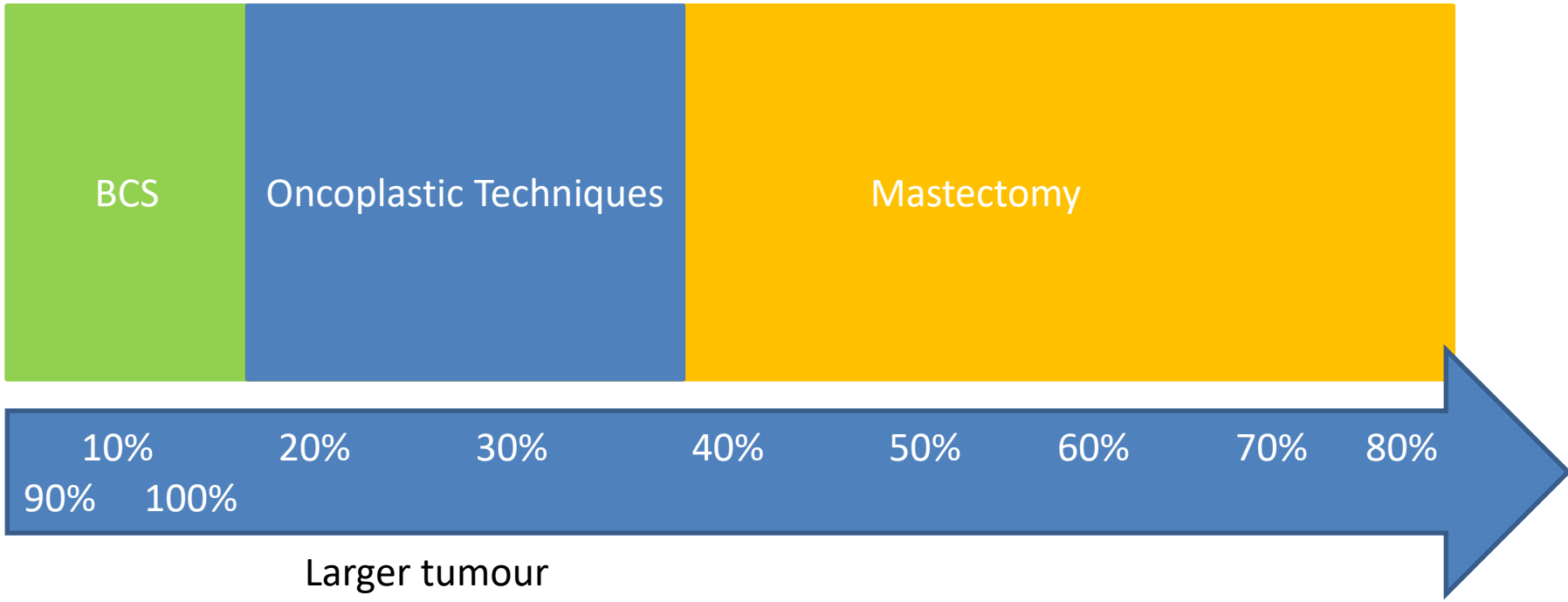
Evolution of better reconstructive techniques but also smaller excisions

Practical implications:

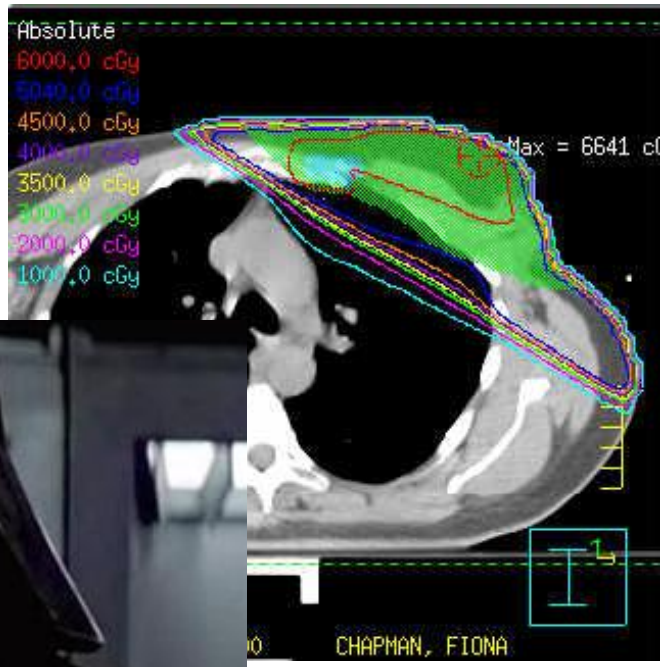
Conservative surgery should be extensive enough to leave at most a small tumour burden, but limited enough to preserve a good cosmetic result

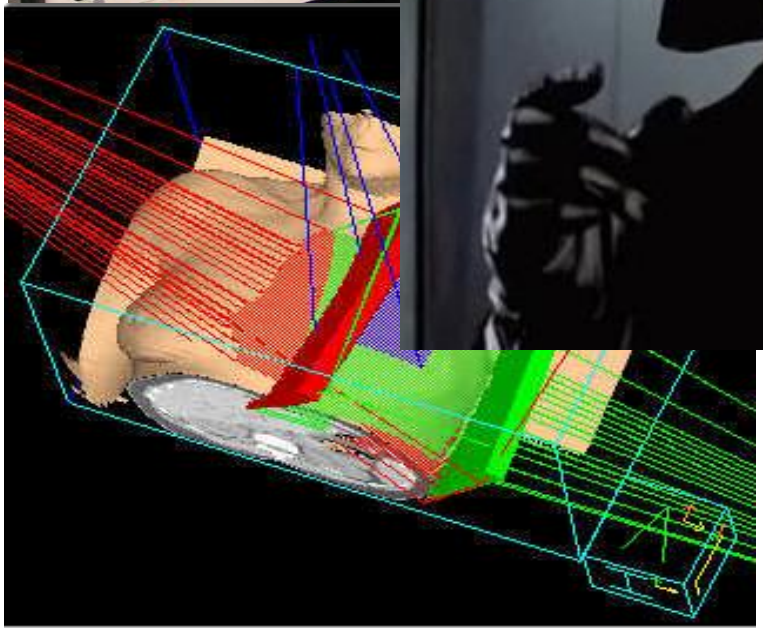

Aim for a ‘wide’ margin but
- a close but clear margin is sufficient

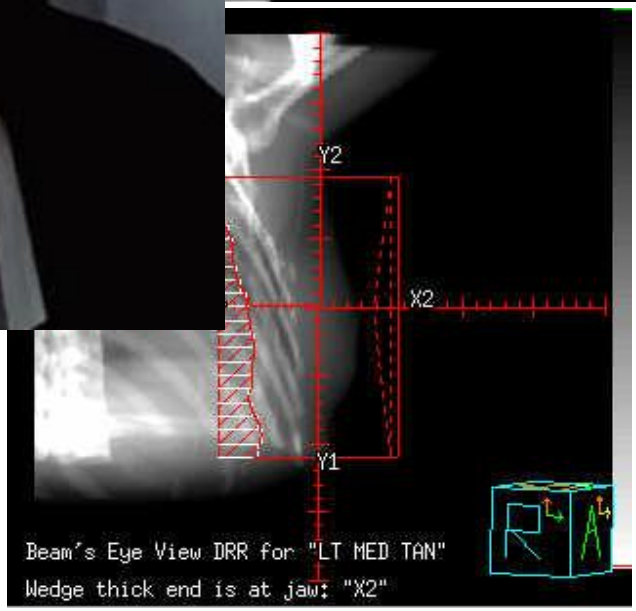
The role of ‘oncoplastics’ Extending Breast Conservation capability



Radiation – we need the dark side!







Role of post-operative radiotherapy in breast conserving surgery

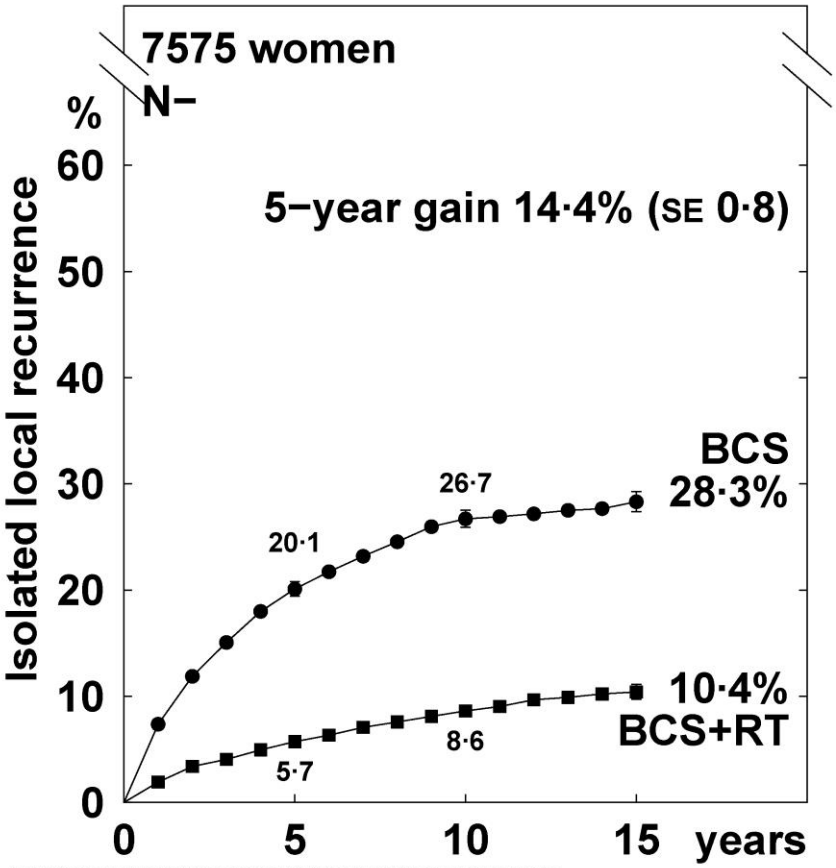
Advantages

- conserve breast – 80-90% patients, 5 x lower risk of local recurrence
- good - excellent cosmesis ~ 90% patients
- psychosocial benefits
- mastectomy for salvage

Disadvantages

- treatment time
- follow-up more difficult
- complications of radiation therapy treatment
  - Acute skin reddening, blistering
  - Chronic darkening, contraction, pain
  - Tiredness
  - Late – rib fracture, pneumonitis, pericarditis, sarcoma

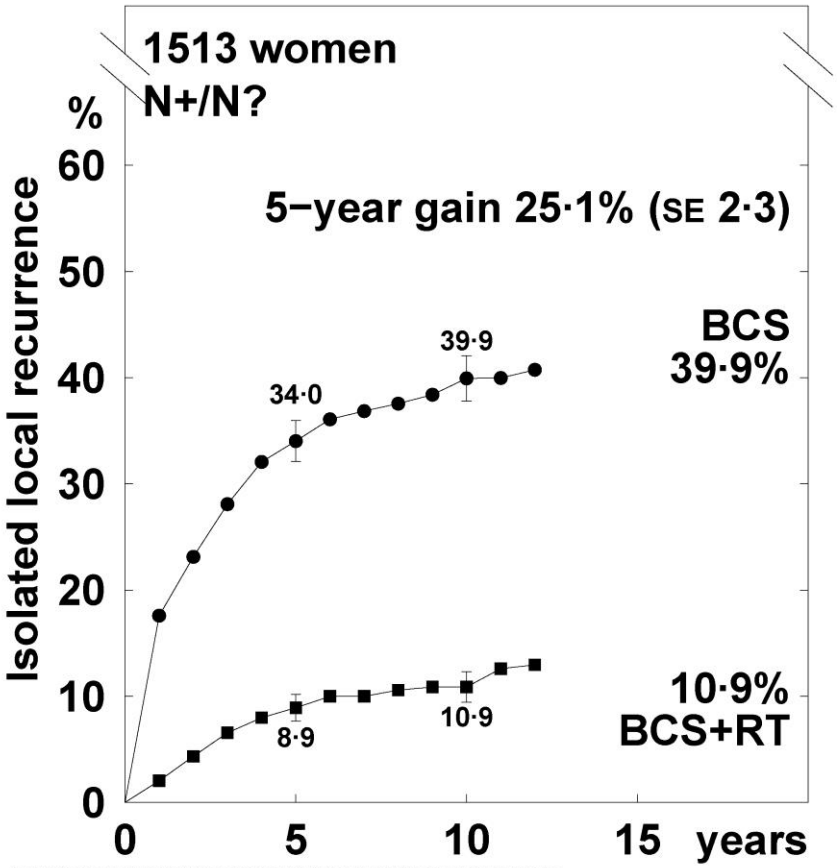
Breast conservation ± RT
ISOLATED LOCAL RECURRENCE
N−



Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 − 4	Years 5 − 9	Years 10 − 14	Year 15+
BCS+RT	1·38 (233 / 16871)	0·72 (82 / 11415)	0·43 (18 / 4190)	0·13 (2 / 1516)
BCS	4·61 (701 / 15205)	1·80 (168 / 9342)	0·39 (13 / 3320)	0·35 (4 / 1137)
Rate ratio, from	0·30 SE 0·04	0·38 SE 0·08	1·13 SE 0·40	0·51 SE 0·78
(O−E) / V	−255·7 / 213·9	−57·2 / 59·7	0·9 / 7·2	−0·6 / 0·9

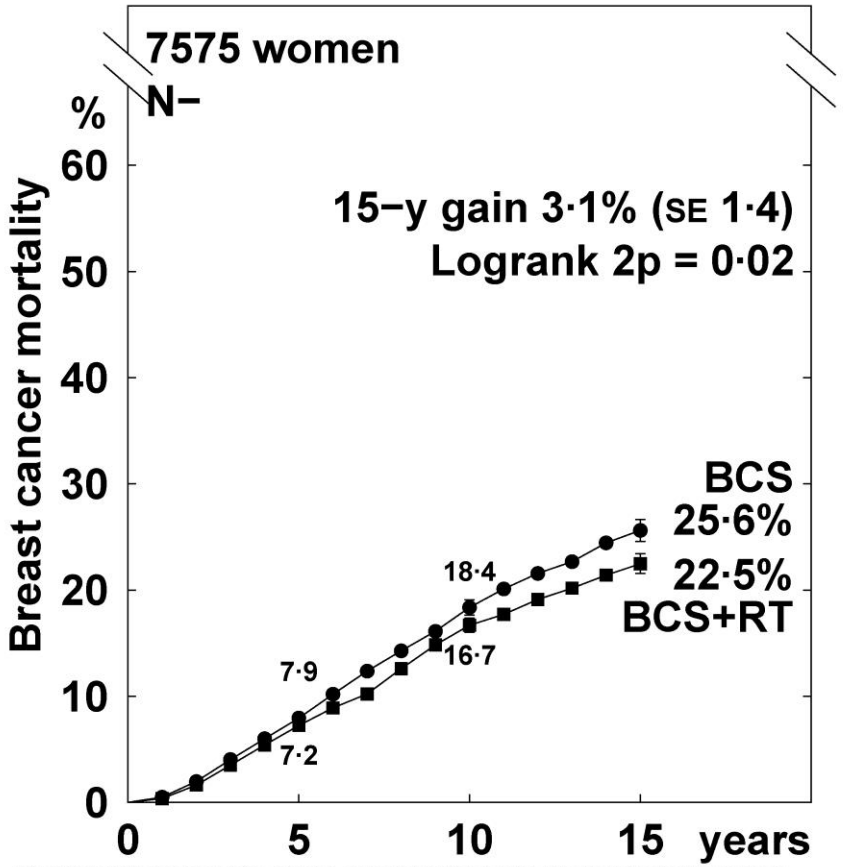
Breast conservation ± RT
ISOLATED LOCAL RECURRENCE
N+/N?



Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 − 4	Years 5 − 9	Year 10+
BCS+RT	2·34 (69 / 2947)	0·61 (10 / 1652)	0·34 (4 / 1178)
BCS	9·08 (226 / 2490)	1·92 (24 / 1247)	0·37 (3 / 819)
Rate ratio, from	0·26 SE 0·07	0·30 SE 0·22	0·81 SE 0·71
(O−E) / V	−85·6 / 62·9	−8·8 / 7·3	−0·3 / 1·6

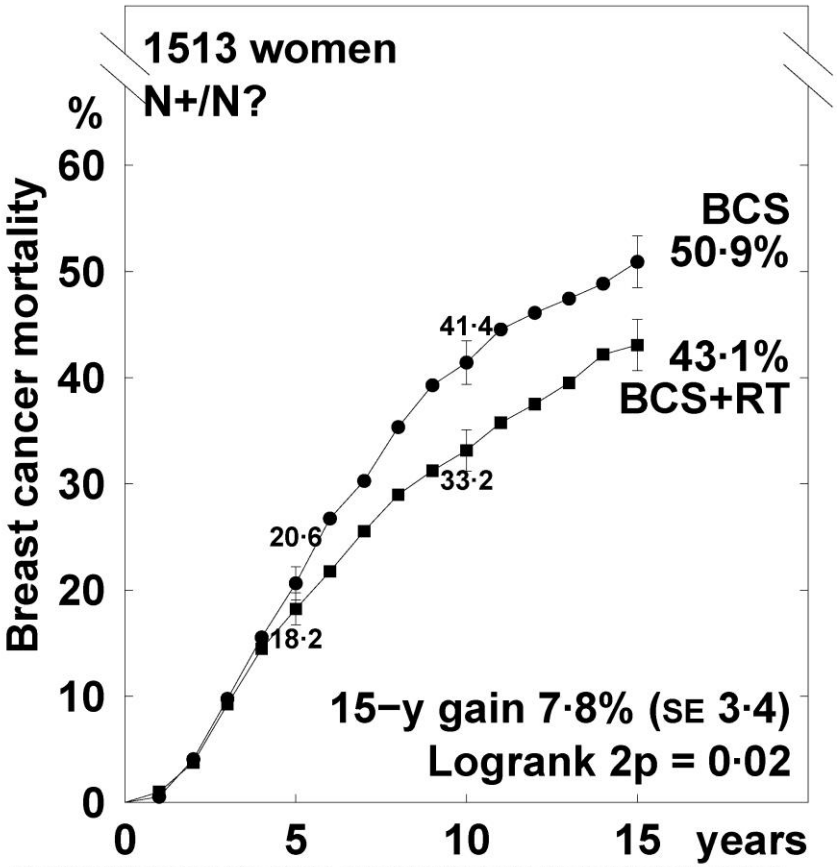
Breast conservation ± RT
BREAST CANCER MORTALITY
N−



After−recurrence or possible−breast−cancer death rates (% / year) and logrank analyses

	Years 0 − 4	Years 5 − 9	Years 10 − 14	Year 15+
BCS+RT	1·46 (263 / 17967)	2·07 (270 / 13043)	1·31 (67 / 5103)	2·24 (48 / 2140)
BCS	1·65 (291 / 17627)	2·44 (308 / 12631)	2·03 (100 / 4918)	2·71 (56 / 2066)
Rate ratio, from	0·91 SE 0·08	0·88 SE 0·08	0·75 SE 0·14	0·93 SE 0·20
(O−E) / V	−13·1 / 132·4	−18·2 / 137·2	−11·4 / 39·4	−1·7 / 24·3

Breast conservation ± RT
BREAST CANCER MORTALITY
N+/N?



After−recurrence or possible−breast−cancer death rates (% / year) and logrank analyses

	Years 0 − 4	Years 5 − 9	Years 10 − 14	Year 15+
BCS+RT	3·96 (130 / 3284)	4·12 (85 / 2062)	3·20 (27 / 844)	3·12 (23 / 738)
BCS	4·40 (145 / 3293)	6·41 (124 / 1935)	3·78 (30 / 793)	2·90 (20 / 690)
Rate ratio, from	0·88 SE 0·12	0·66 SE 0·12	0·88 SE 0·26	1·18 SE 0·34
(O−E) / V	−8·1 / 60·8	−19·3 / 46·8	−1·6 / 12·9	1·7 / 10·3

Effect of radiotherapy after breast-conserving surgery (10 trials of BCS ± RT) on local recurrence and on breast cancer mortality
6097 women with node-negative disease

Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Lancet 2005; 366: 2087–2106

Patient perspective:

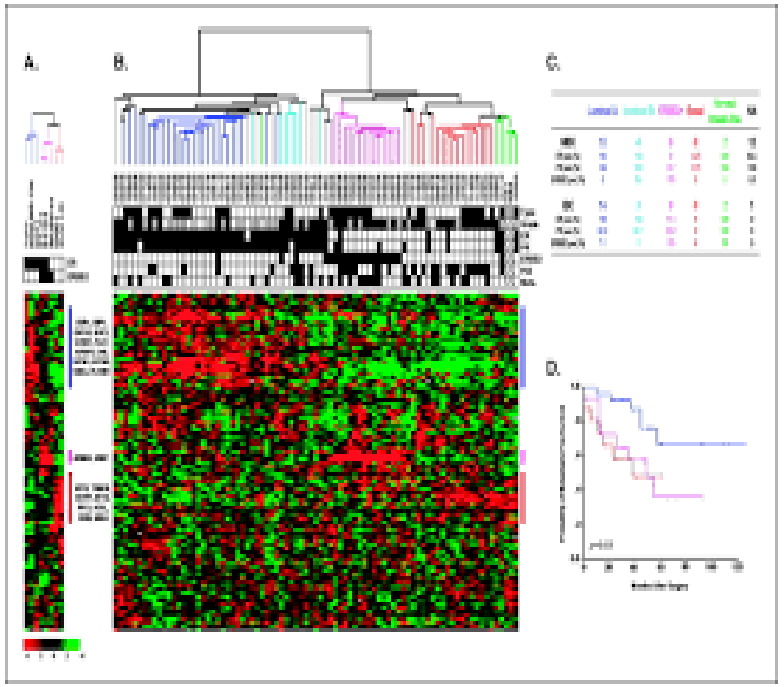
- Is breast conservation a safe choice?
- I just want the best treatment
- Survival is more important to me than my breast

but….

- I refuse to have treatment if it means a mastectomy

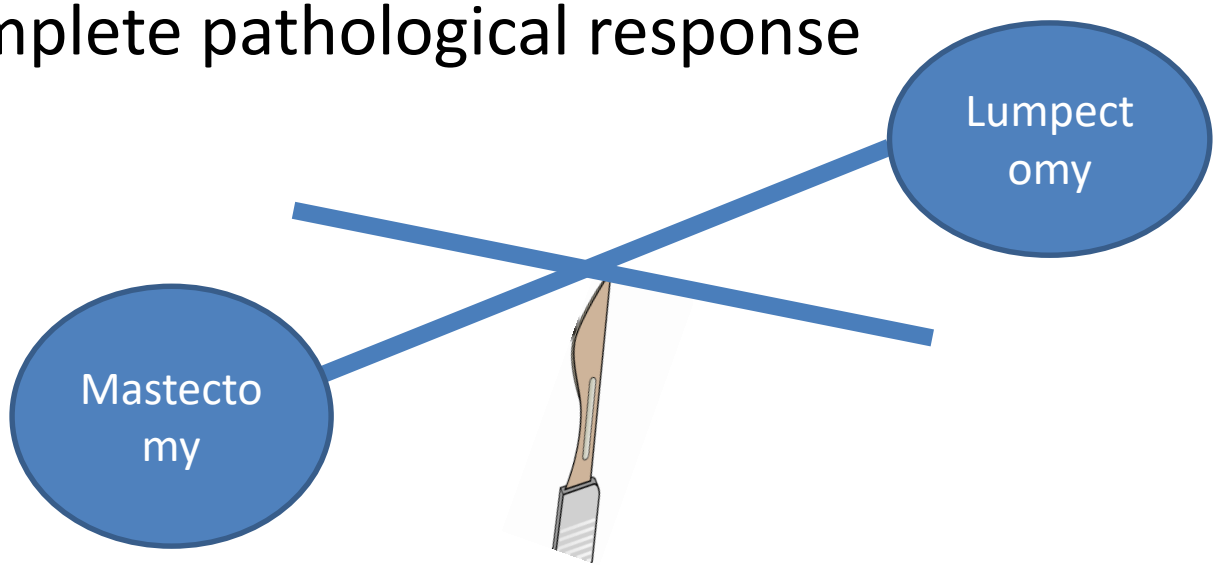
Neoadjuvant therapy to increase likelihood of conservation

- Neoadjuvant therapy
  - Complete pathological response
  - Tumour shrinkage to facilitate BCS
- Aggressive subtypes
  - TNBC
  - Her2 Positive
  - ER-
  - Grade 3



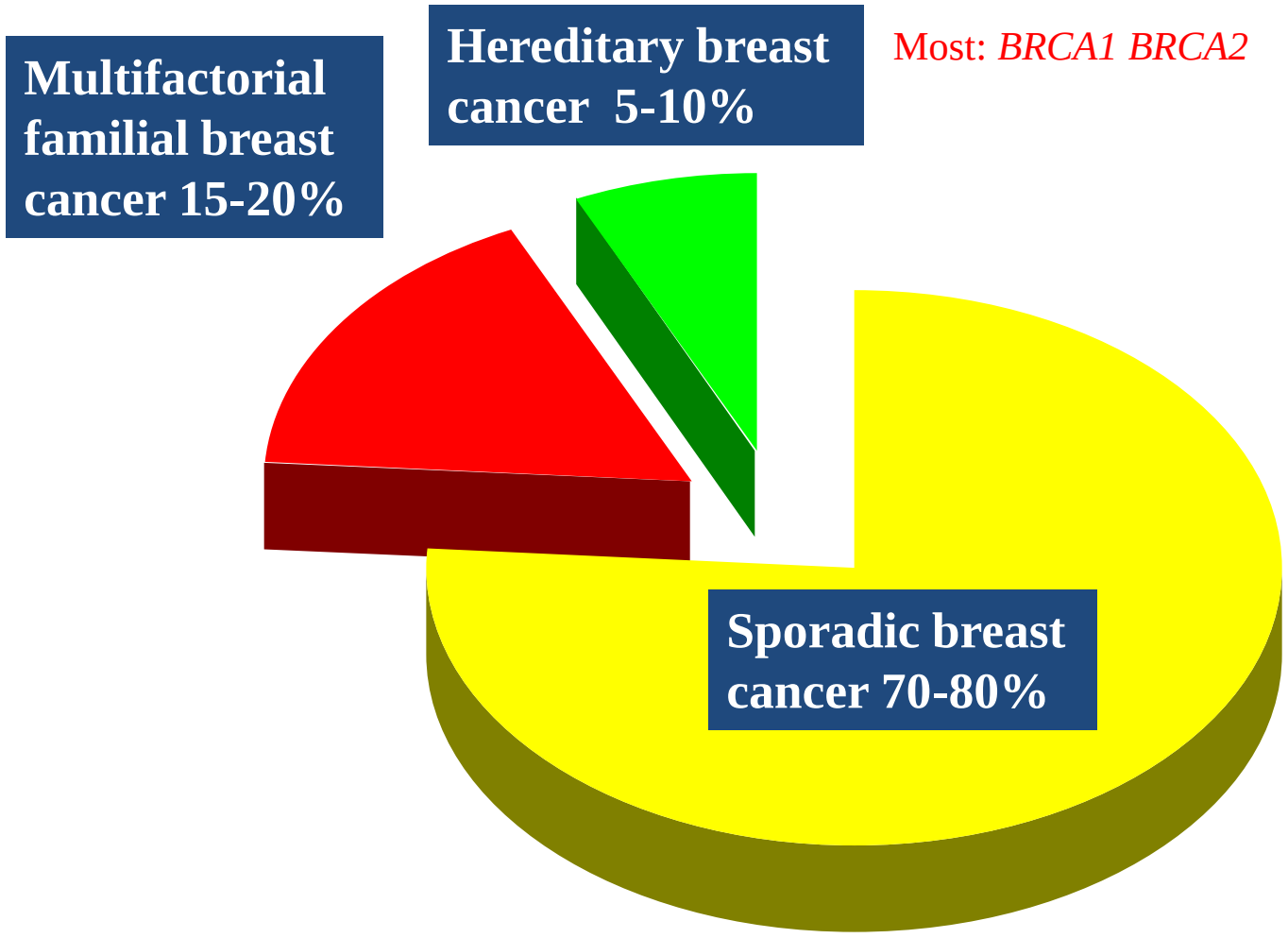
Neoadjuvant Chemotherapy

- Down staging
  - 30-80% complete pathological response



What influences conservation vs mastectomy rate?

Breast and ovarian cancer aetiology



BRCA1 discovered 1994

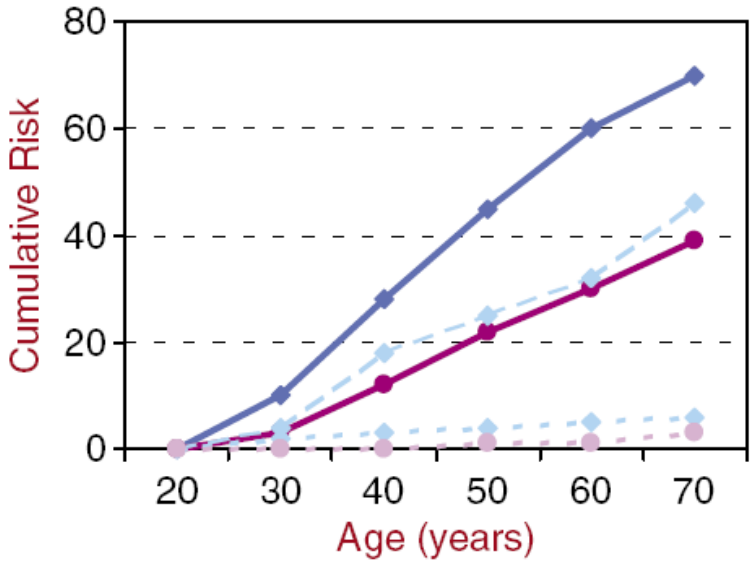
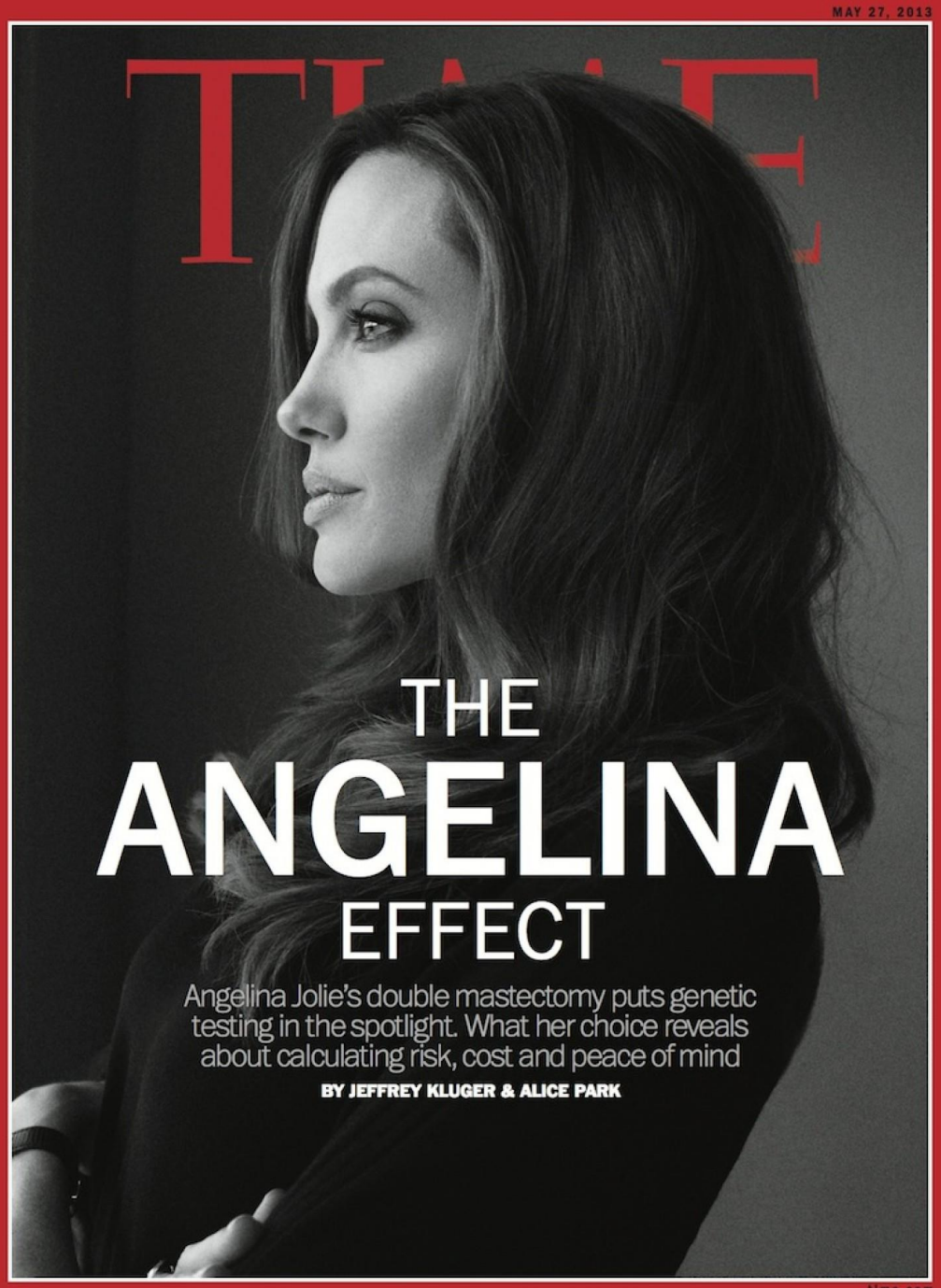
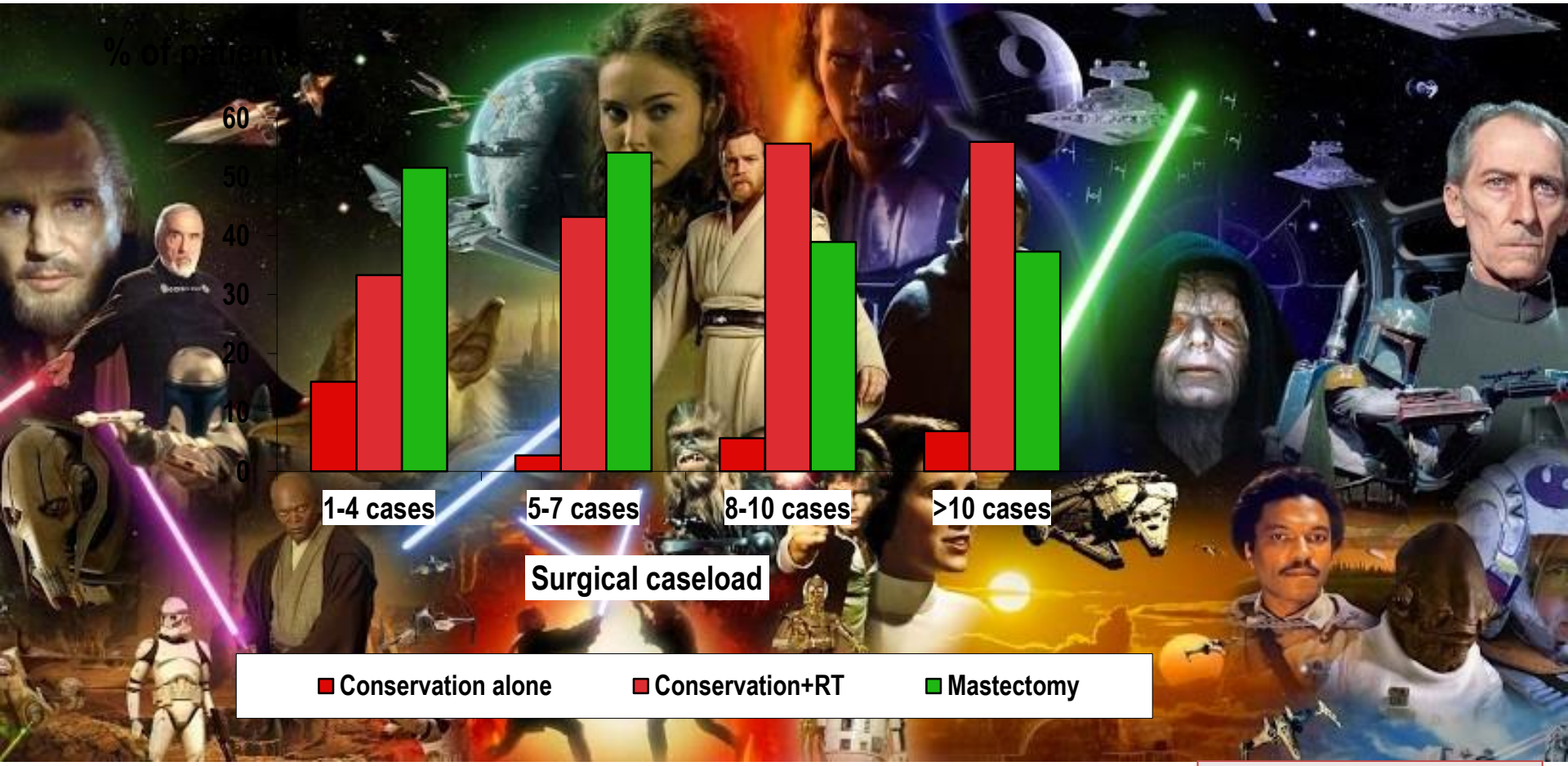


Figure 1 Cancer risk reduction with proph

Prophylaxis and reconstructive options

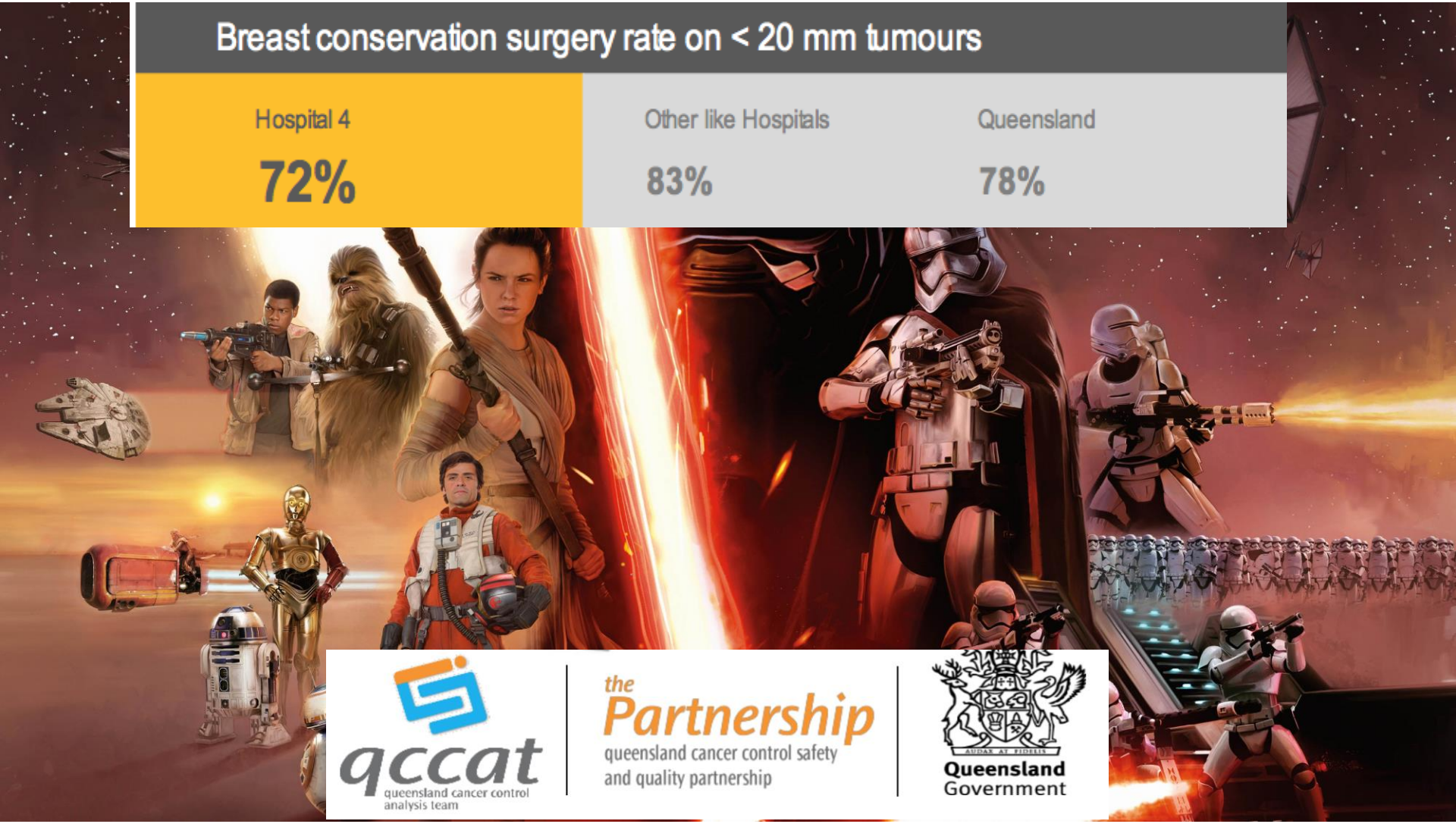


Conservation vs Mastectomy
Treatment of tumours ≤ 2 cm



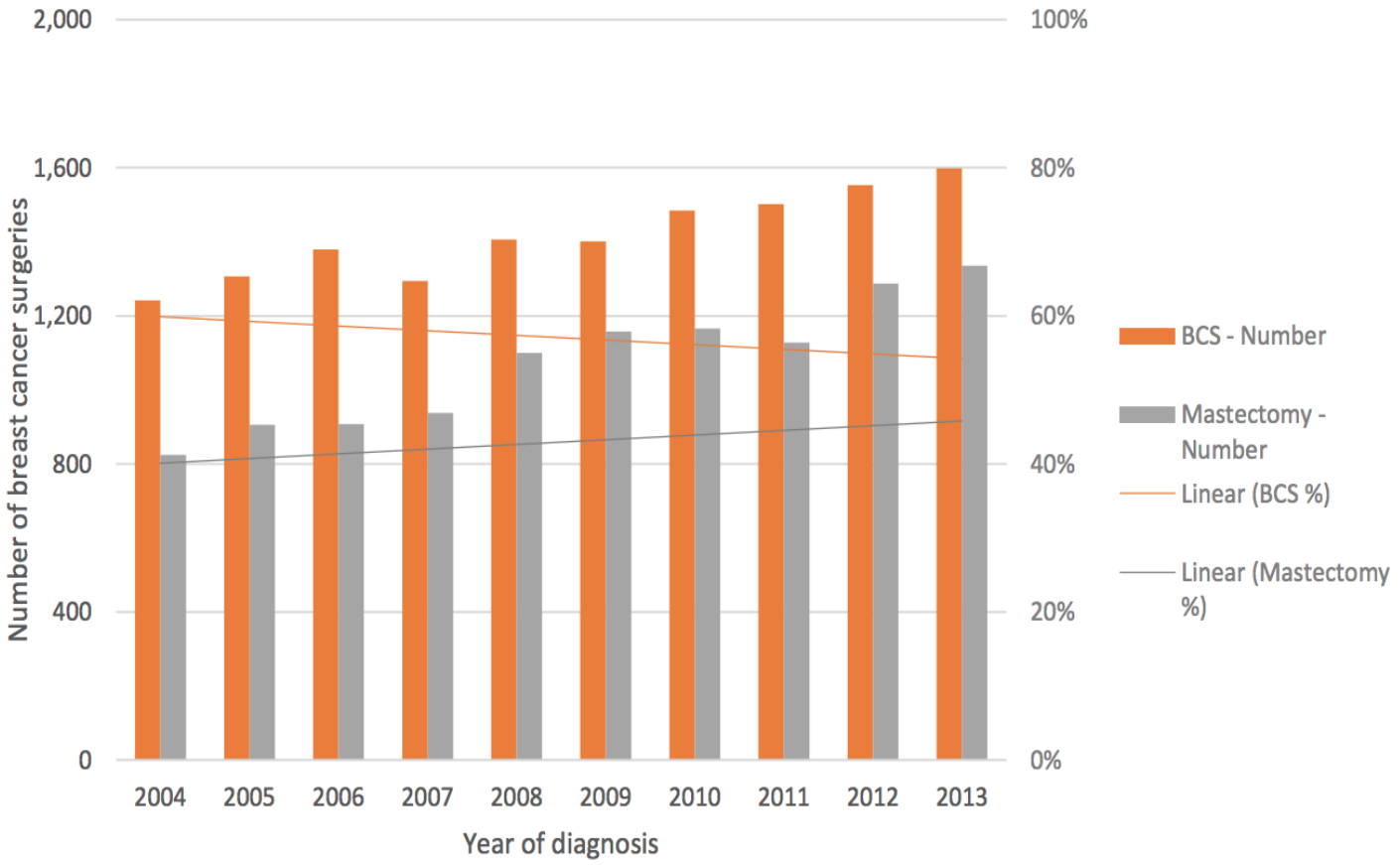
GWRS, 1992

Are breast conservation rates a correct measure of success in 2018?

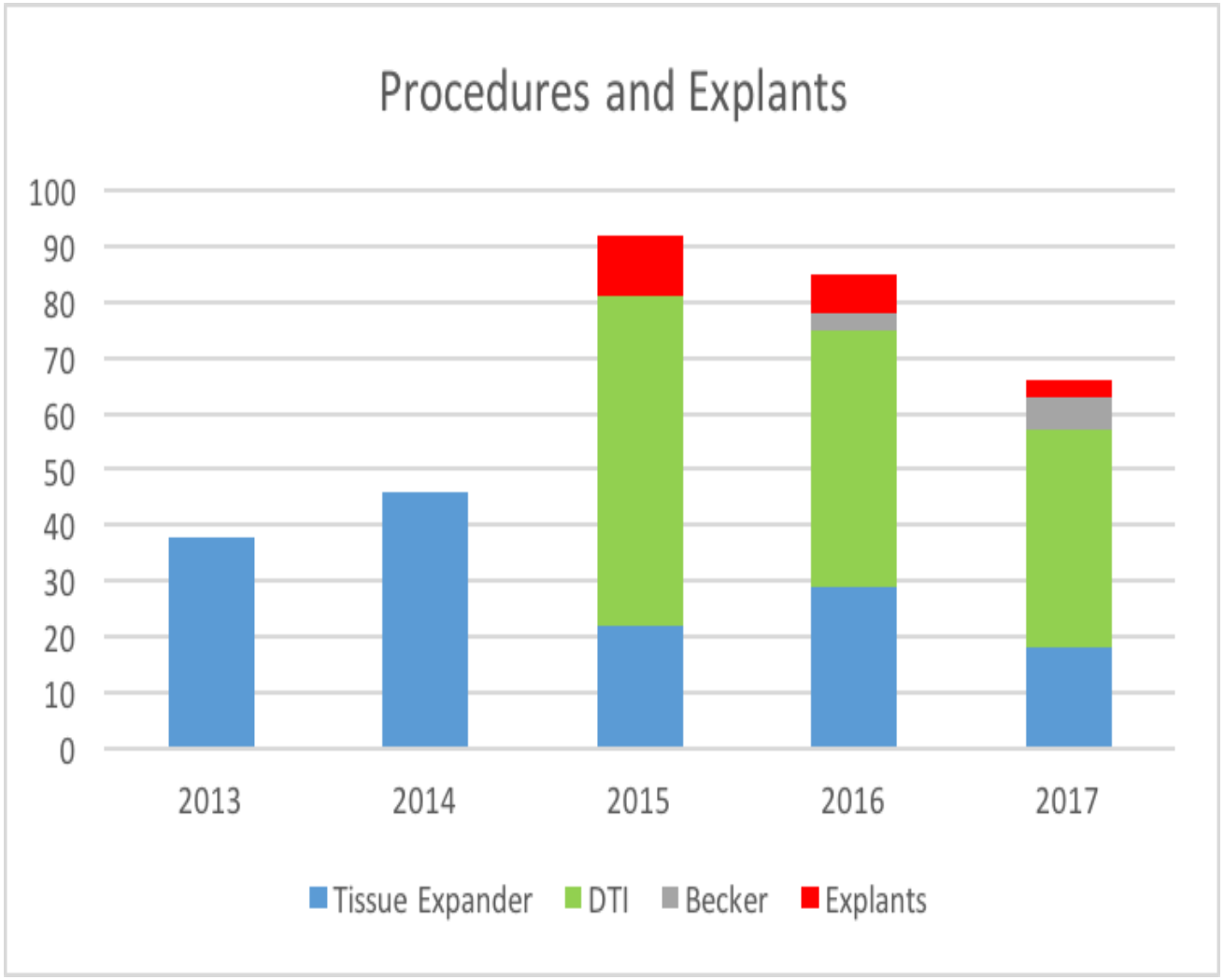


Increasing Trend Towards Mastectomy

Figure 2: Queensland female breast cancer definitive surgery change over time for BCS and Mastectomy 2004 – 2013



RBWH -post Mx reconstruction rates



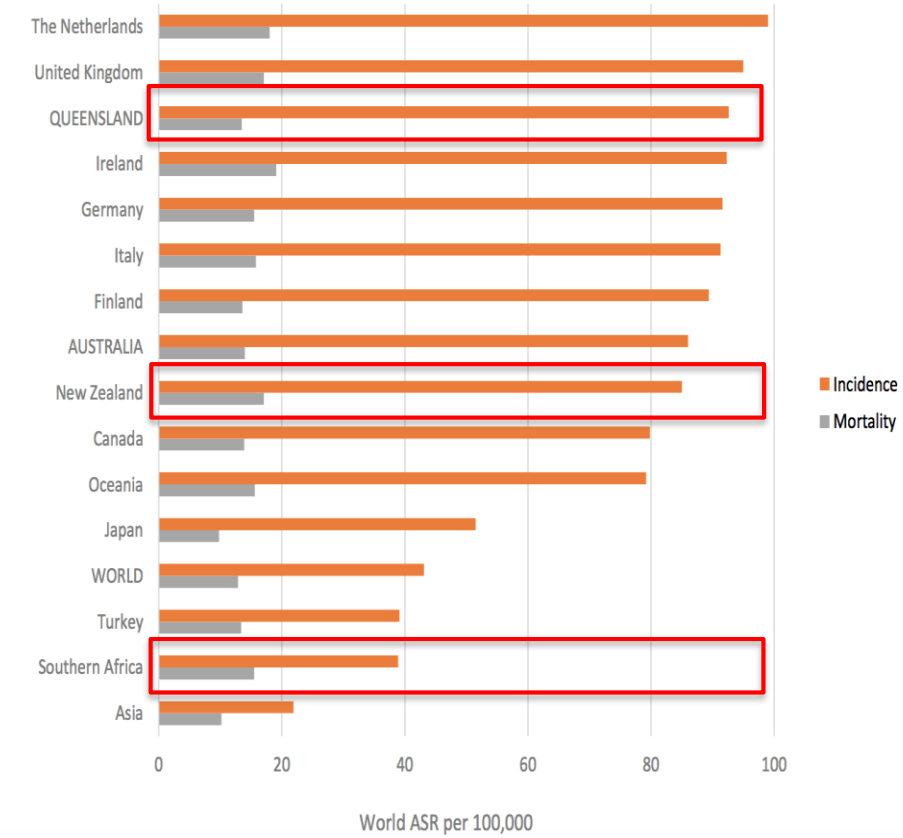
RBWH
Post Mastectomy
Reconstruction Rate

>30 – 40%

Queensland Breast Cancer Incidence

1.1 Breast cancer national and international comparisons

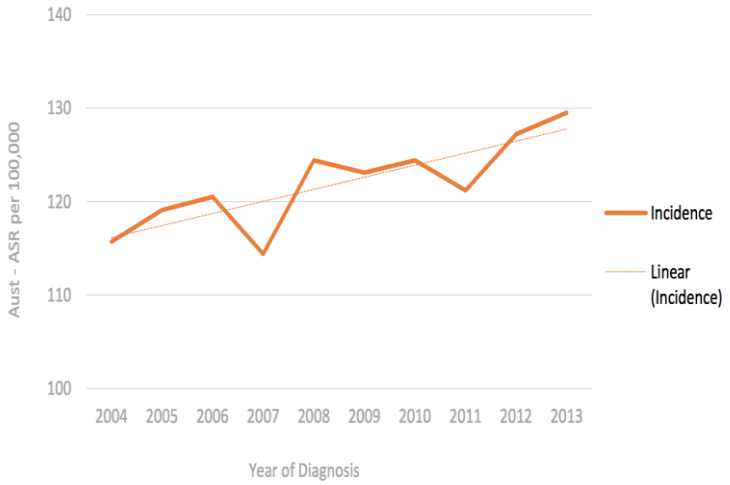
Figure 1.1a: Incidence and Mortality World ASR, Year of diagnosis 2012



Increasing incidence

2017 – 3300
2021 – 4200 per year

Figure 1.0a: Queensland female invasive breast cancer incidence ASR trends 2004 - 2013



ASR –Age standardised rate - Australian population in 2001
Source: Oncology Analysis System (OASys), Queensland Cancer Control Analysis Team

Importance of Clinical Databases

You need your own clinically verified data

- Integrate clinical, pathological and treatment data
- Quality clinical and Translational research
- Precise and effective treatment to improve patient outcomes
- Opportunities for international collaborative projects

Importance of Clinical Databases

- Shift towards value-based reimbursement models and healthcare digitization
- Outcome-based targeted therapies – patient treatment based on successful outcomes rather than a trial-and-error approach
- Clinical trial approach to new therapies

RBWH
Metro North Hospital and Health Service
Queensland Government

Brisbane Breast Bank
Building research resources to fight breast cancer for all generations

Collaboration

RBWH
Metro North Hospital and Health Service
Queensland Government

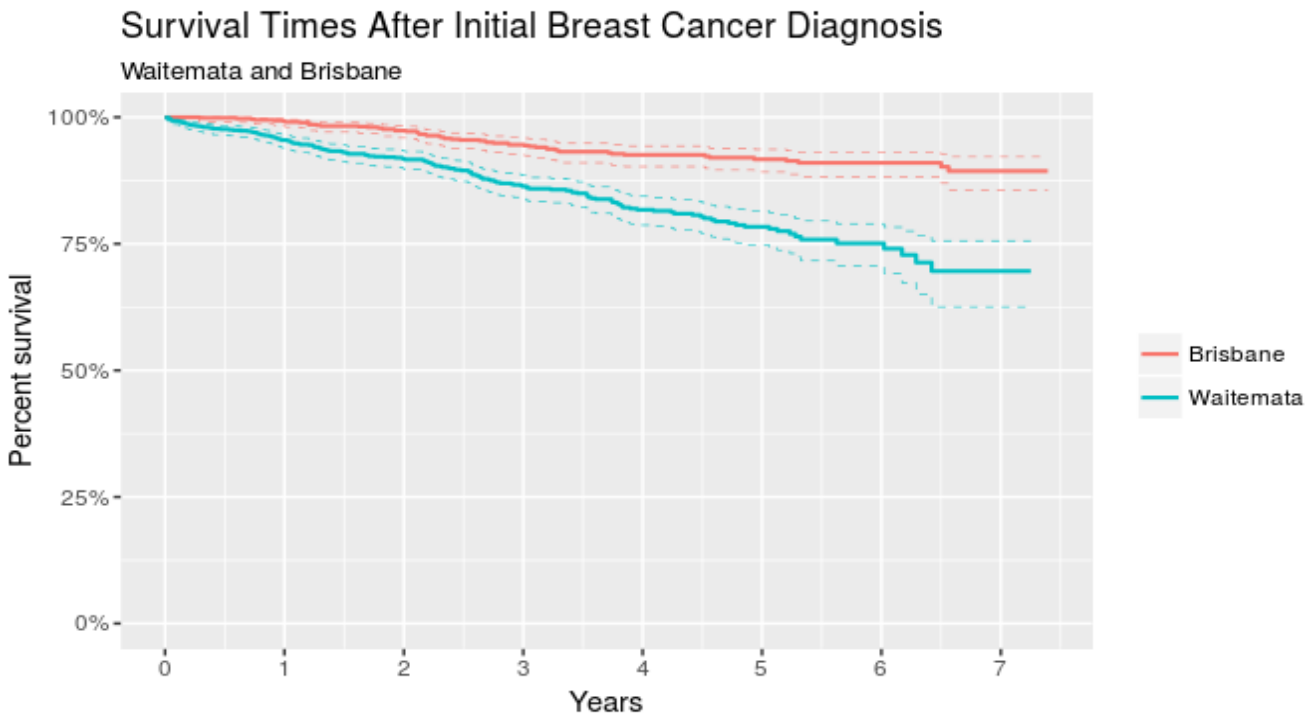
Brisbane Breast Bank
Building research resources to fight breast cancer for all generations

Trans-Tasman Study
Australia – New Zealand

Why do Australian women have appear to have a better breast cancer survival rate?

- Breast cancer patients treated at two large hospitals in Auckland (Royal North Shore Hospital) and Queensland (RBWH) - June 2008- May 2013
  - Matched databases
  - Exclude stage IV disease
- Comparisons of diagnosis, tumour pathology and treatment impact upon survival

Preliminary results



The log-rank p-value: 1.327160610^{-12}

	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Brisbane	99% (98, 100)	97% (96, 98)	95% (93, 96)	93% (90, 94)	92% (89, 94)	91% (88, 93)	89% (86, 92)
Waitemata	95% (94, 97)	92% (90, 93)	86% (84, 88)	82% (79, 84)	78% (75, 82)	75% (71, 79)	70% (63, 76)

Absolute and Relative Survival

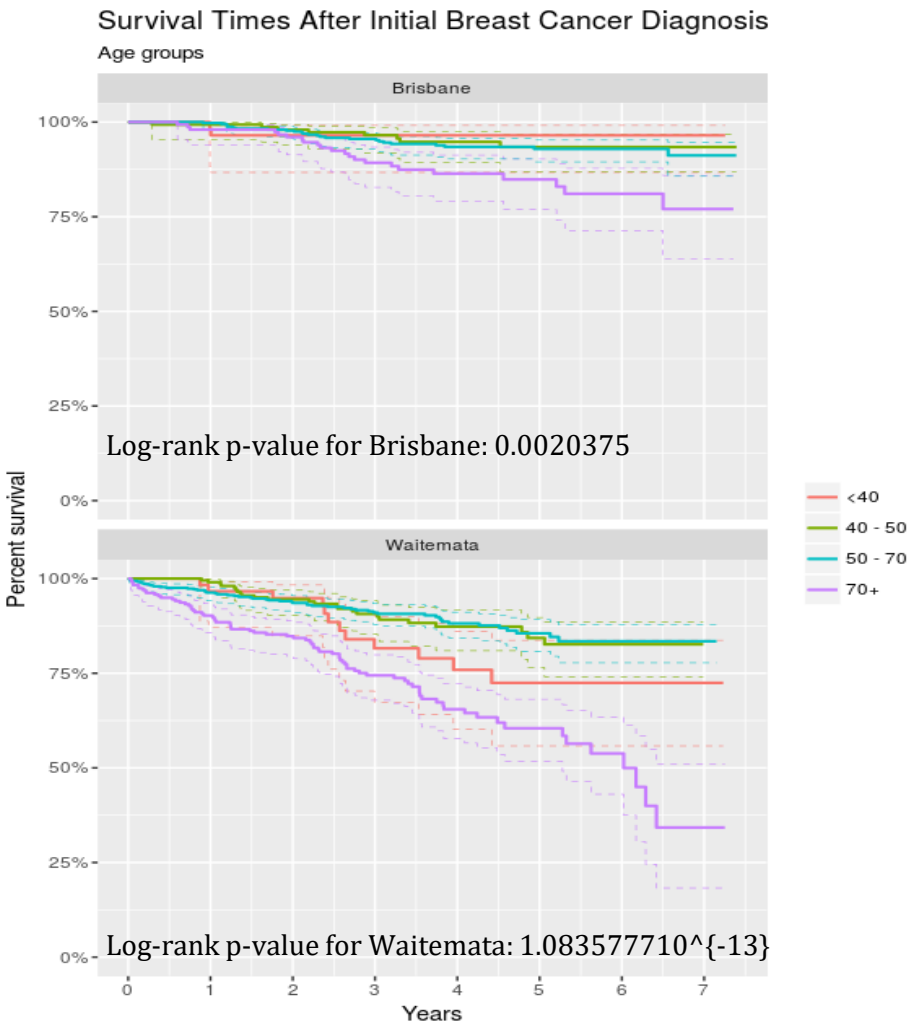
Absolute 5yr:

- Waitemata: 78% (if non breast cancer related deaths are excluded, this figure rises to 90%)
- RBWH: 92%

Relative 5yr:

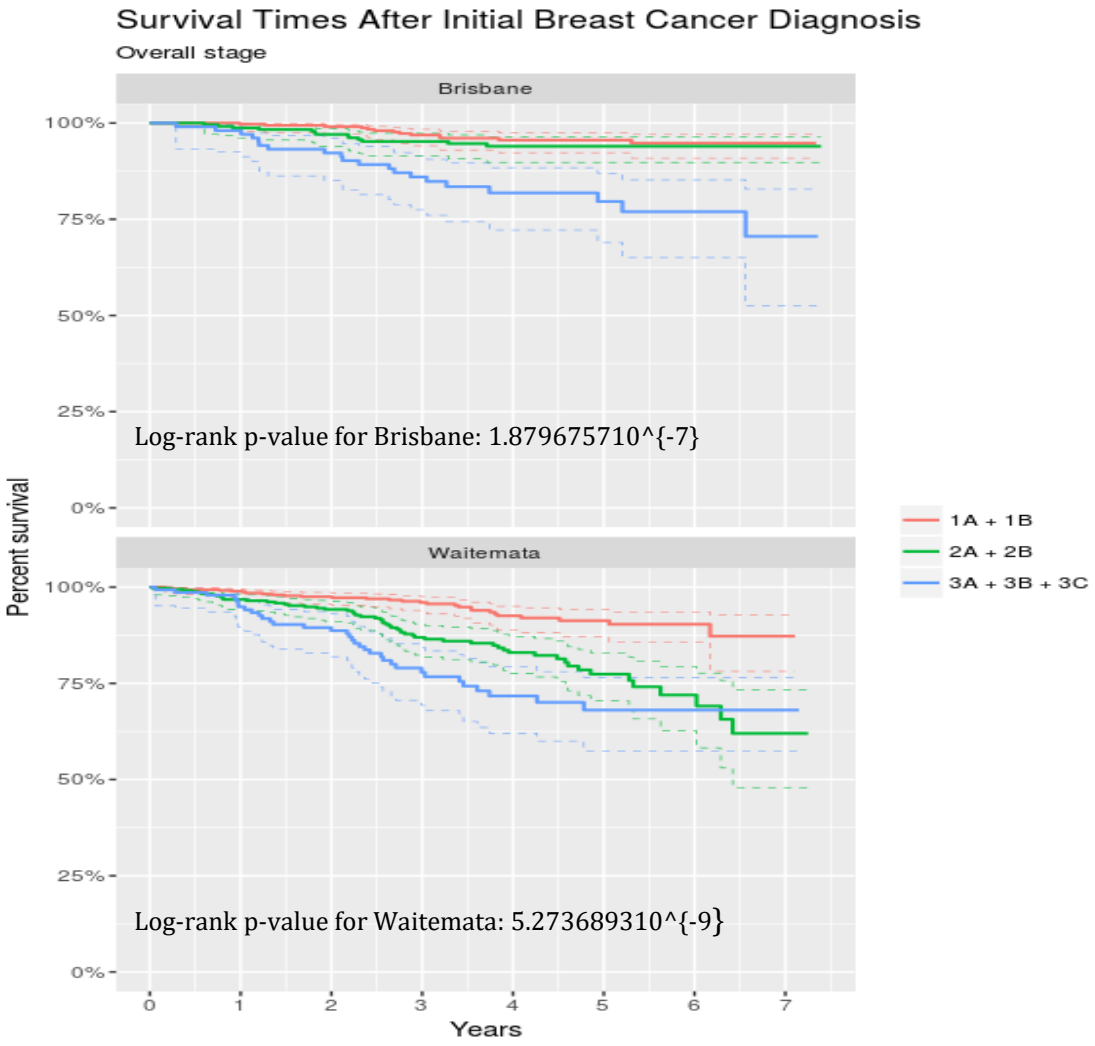
- Waitemata: 84.1%
- RBWH: 98.5%

Survival by Age at Diagnosis



	5YS (95% CI)		5YS Difference (p-value)
	Waitemata	RBWH	
<40 yrs	72% (56,84)	96% (87,99)	-24% (0.039)
40-50yrs	84% (77,90)	93% (87,97)	-9% (0.105)
50-70yrs	86% (81,89)	93% (89,95%)	-7% (0.024)
70+ yrs	60% (52,68)	85% (77,90)	-25% (0.005)

Survival by Stage at Diagnosis



	5YS (95% CI)		5YS Difference (p-value)
	Waitemata	RBWH	
Stage 1	91% (92,97)	96% (92,97)	-5% (0.101)
Stage 2	77% (70,83)	94% (90,96)	-17% (0.0004)
Stage 3	68% (57,77)	80% (69,87)	-12% (0.312)

GOING FORWARD

- Breast Cancer mortality is improving
- We are making a difference
- New and better drugs are contributing
- Many new promising agents in the pipeline
- Individualised treatment – direction we are heading

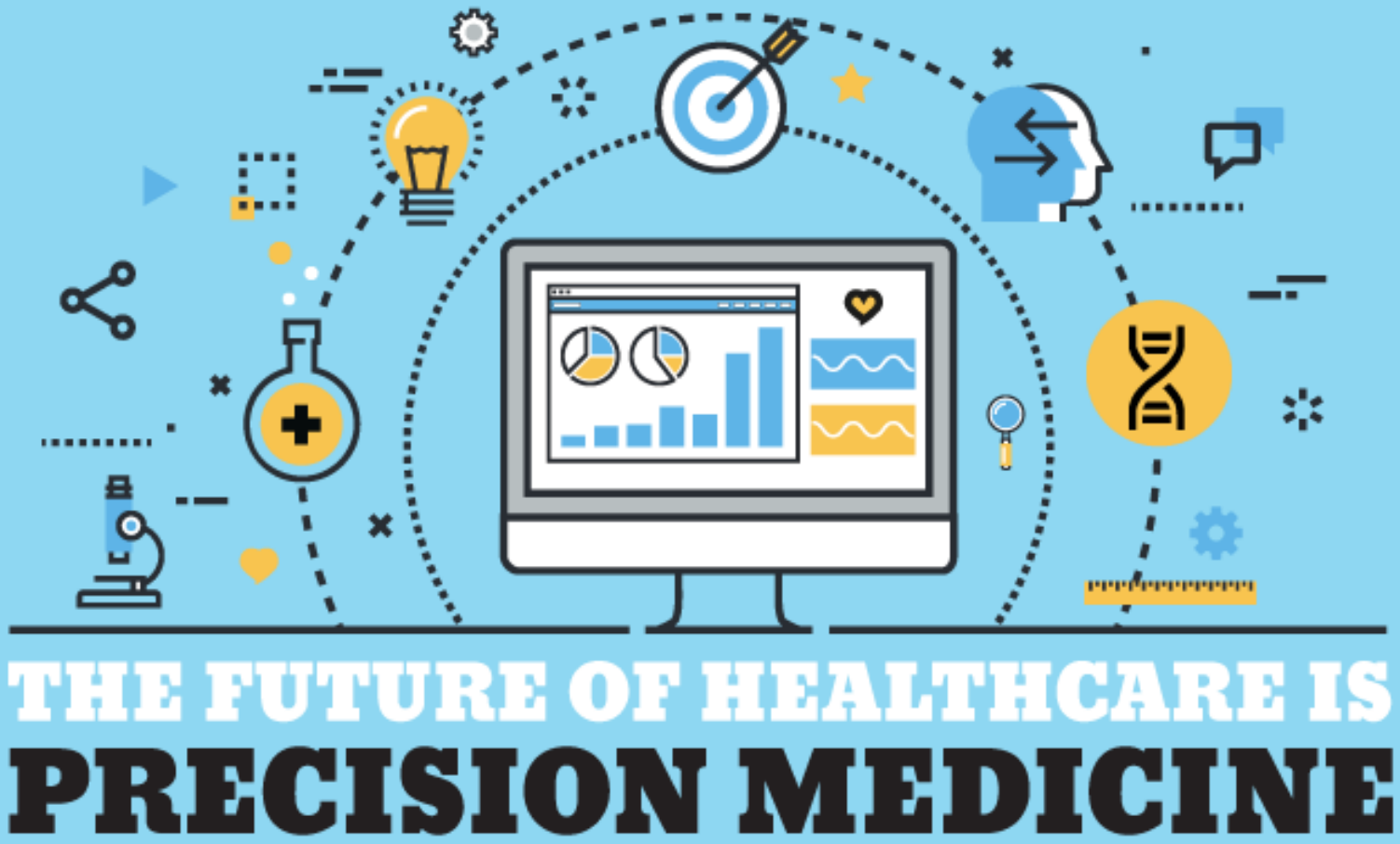

ONE-SIZE FITS ALL
STORE
SALE

RBWH
Metro North Hospital and Health Service
Queensland Government

Personalised Breast cancer management

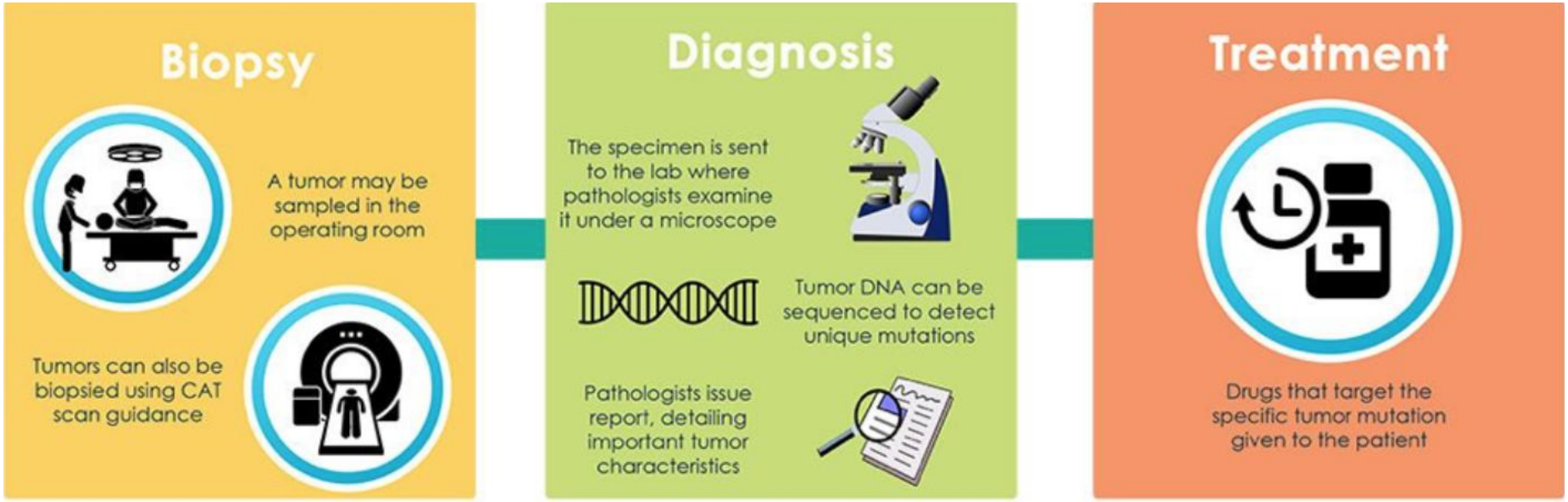
Brisbane Breast Bank
Building research resources to fight breast cancer for all generations

Surgery:



Precision Medicine

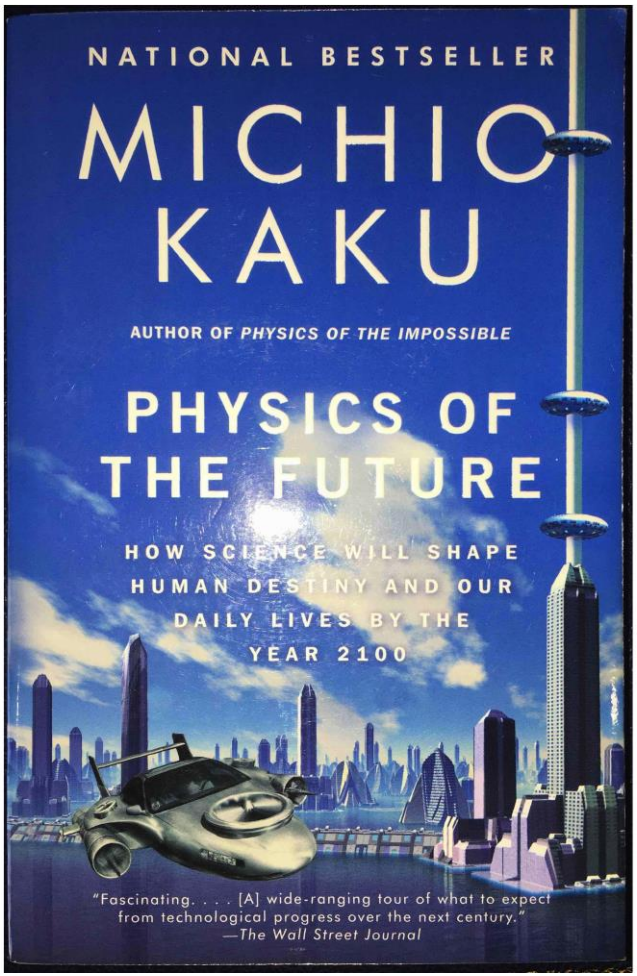
- Treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics



Personalised Medicine

- Creation of drugs or medical devices that are unique to a patient
- Biopharmaceutical companies alike have doubled their investment in Personalized Medicine in the past five years

Three Stages of Medicine



- Thousands of years
  - Superstition, witchcraft, hearsay
  - Secret potions and chants
- 19th century
  - Germ theory and better sanitation
  - Medical experiments, reproducible results
- 21st century
  - Molecular genetics, merge physics & medicine

The next 25 years

- Quantum theory & the computer revolution
  - Gene sequencing, individual blueprints
  - Bioinformatics & gene therapy (somatic & germ-line)
  - Biological sensors
  - DNA chips, nanoparticles, nanobots
- Tissue engineering
- Stem cell advancements, organogenesis

Paradigm shift in Axillary management

- Less axillary surgery
- Adjuvant therapy chosen based on tumour biology
- Prognostication based on molecular subtypes

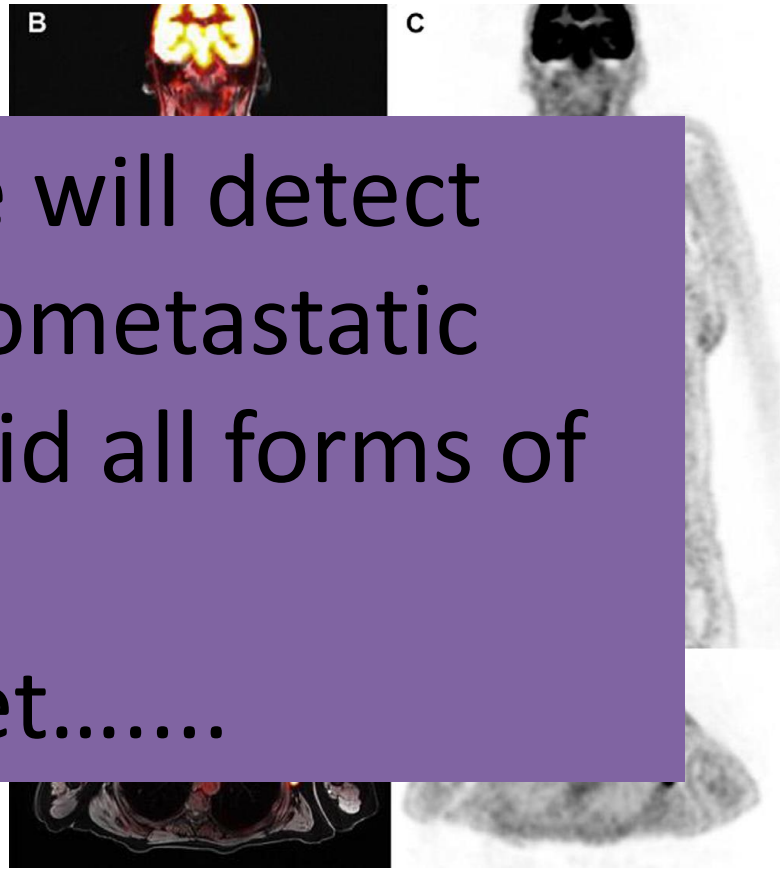
- Latest controversies: Omission of ALND in SLN positive
  - Z0011 trial: T1-2 tumours (BCS), SLN+ no axillary clearance
    - 21% had ≥ 3non SLN positive
  - AMAROS : T1-2 tumours, SLN+ treated with radiotherapy (Axilla and SC)
    - 33% had ≥ 3non SLN positive
  - Both trials have multiple shortcomings and applicable to minority group of patients.
  - POSNOC trial underway

HIRF

HERSTON IMAGING RESEARCH FACILITY

In the future we will detect and target micrometastatic disease and avoid all forms of local therapy

But not there yet…….



PET showing multiple hypermetabolic right axillary lymph nodes in a patient with grade 3 IDC of the ipsilateral breast

Future Directions

- Pilot study - most accurate current method for identifying node positivity = SNBX + OSNA
  - Intraoperative assessment
- Advanced diagnostic imaging to accurately identify node +ve axilla
  - Extent of primary
  - Distant metastasis
- Biological therapies “theranostics” the future
  - Tracers currently under development may profoundly affect breast cancer management in the future allowing personalized treatments
  - Hybrid acquisition PET/MR is a promising emerging technology – more data are needed

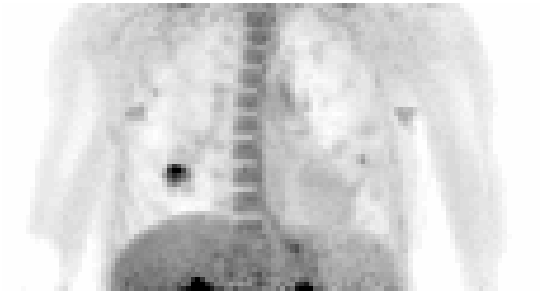
PETAL Study

Role of 18 F-FDG PET-MRI in Axillary staging for Breast Cancer patients who are clinically node negative: Pilot study

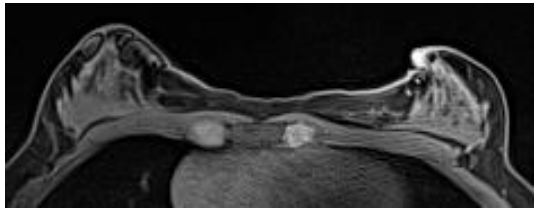
- Prospective pilot study will recruit 20 participants in 6 months
  - High risk women
- The PET and MRI images will be acquired simultaneously using a state-of-the-art 'hybrid' scanner located at the Herston Imaging Research Facility (HIRF) at the Royal Brisbane and Women's Hospital

PET/MRI

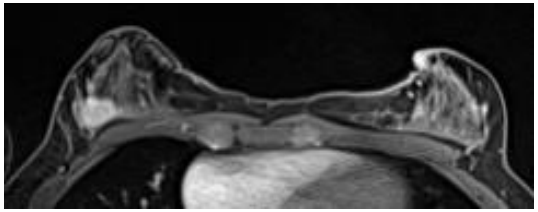
- Carcinoma (39 year old patient)



Attenuation-corrected PET

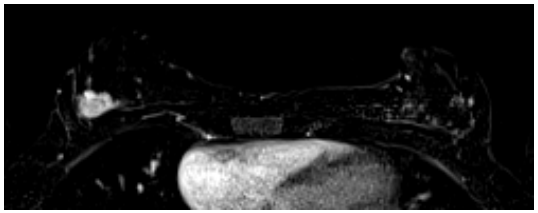


Pre contrast

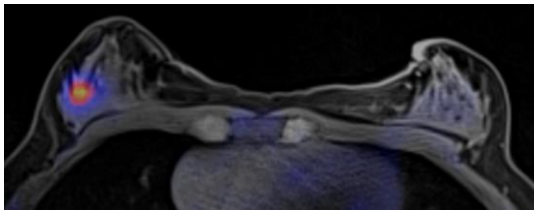


Post contrast

DCE MRI



Subtraction



Overlay of metabolic information

- Scan time (15 mins)

Siemens and
NYU Langone Medical Center,
New York, NY, U.S.

RBWH
Metro North Hospital and Health Service
Queensland Government

Brisbane Breast Bank
Building research resources to fight breast cancer for all generations

PET MRI in Axillary staging

Primary Objective:

- Determine the accuracy of ^{18}F-FDG PET-MRI scan in detecting the extent of metastatic axillary lymph nodes in patients with clinically node negative breast cancer

Secondary Objectives:

- Stratify and define patients into low and high volume axillary disease and tailor management accordingly
- Evaluate long term outcomes of tailored axillary management based on tumour burden in axilla

RBWH FOUNDATION

HIRF
HERSTON IMAGING RESEARCH FACILITY

Future Benefits

- Outcomes from this study will be used for future theranostic projects
  - Identification and Delivering targeted treatment to axillary metastasis using nanotechnology
  - Precise axillary surgery to remove metastatic nodes

RBWH
Metro North Hospital and Health Service
Queensland Government

Brisbane Breast Bank
Building research resources to fight breast cancer for all generations

Brisbane Breast Bank (BBB)

- Bio-bank established – 2005
- Collect tissue sample from breast surgery patients treated at RBWH.
  - Inclusive of benign, pre-invasive and invasive diagnoses.
- BBB Biobank consist of
  - 2520 breast patient tissue sample
    - 1418 invasive cases; 310 pre-invasive cases; 657 Benign cases; 135 cases of brain metastases

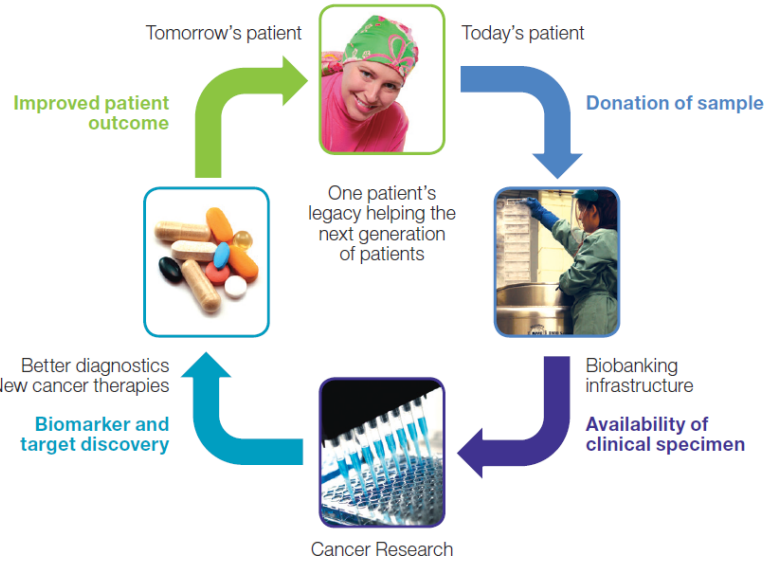
RBWH
Metro North Hospital and Health Service
Queensland Government

Brisbane Breast Bank
Building research resources to fight breast cancer for all generations

Brisbane Breast Bank (BBB)

Contributes to Breast cancer research at local, national and international levels

- International Cancer Genome Consortium (ICGC): Whole genome sequencing of Breast cancer
- Genomic and transcriptomic analysis of Brain metastases
- Circulating Biomarkers of Relapse in Breast Cancer (Circ.BR study currently in progress)
- >60 other studies have utilised BBB and numerous studies published



Regenerative Medicine

collaboration with QUT Centre for Biomedical Innovation

Scaffold

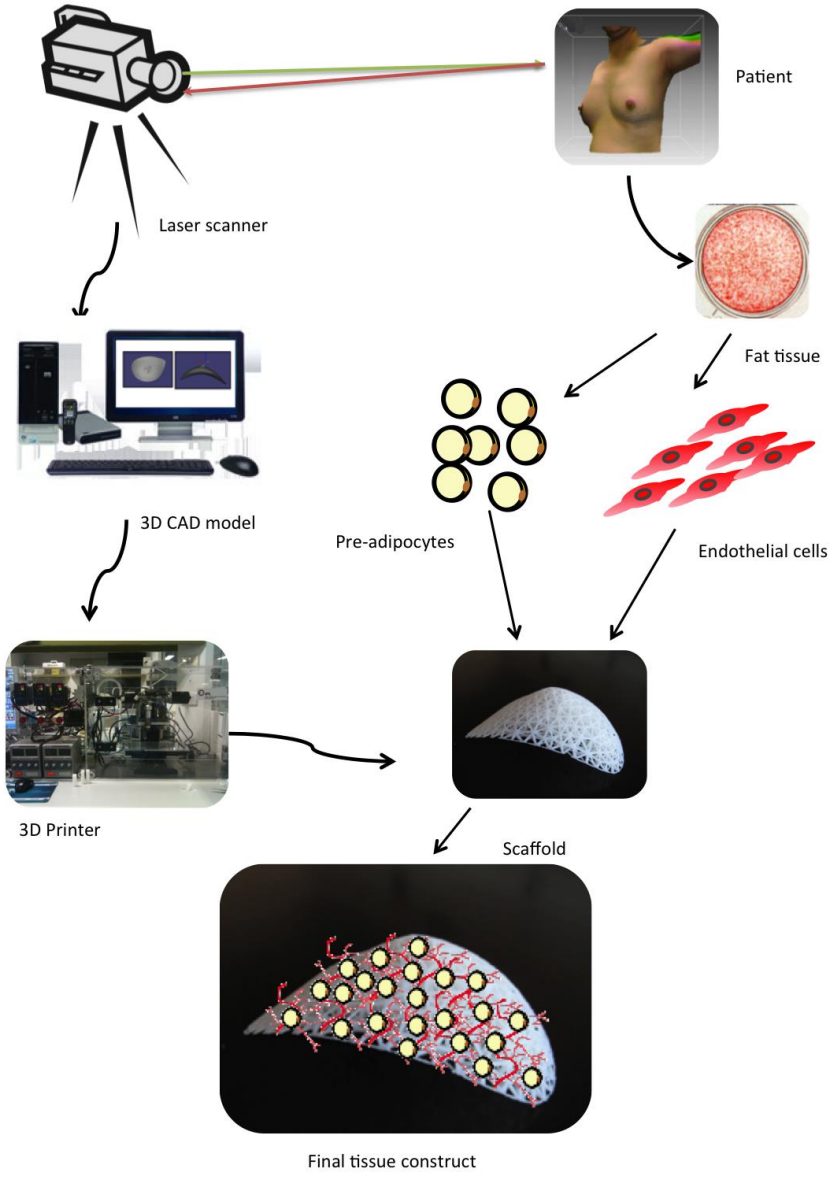
- Cell delivery (tissue engineering)
- Drug delivery

Additive manufacturing (3D printing) (Puskas & Luebbers, 2012)

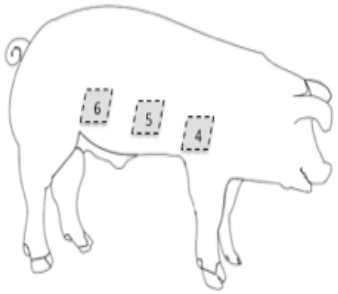
- Biodegradable
- Biocompatible

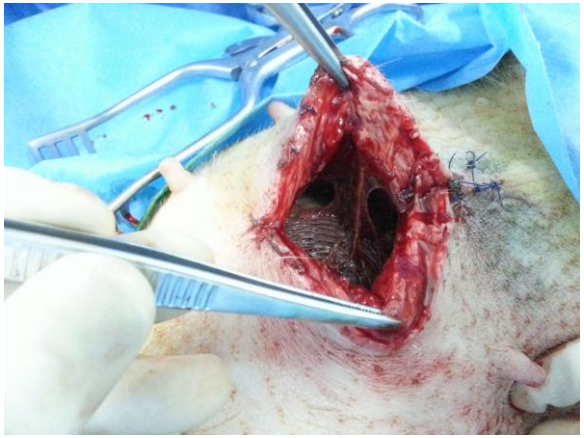
Novel new techniques

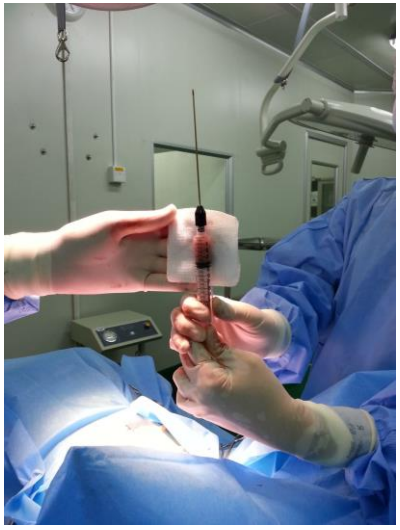
3D printed biodegradable scaffolds

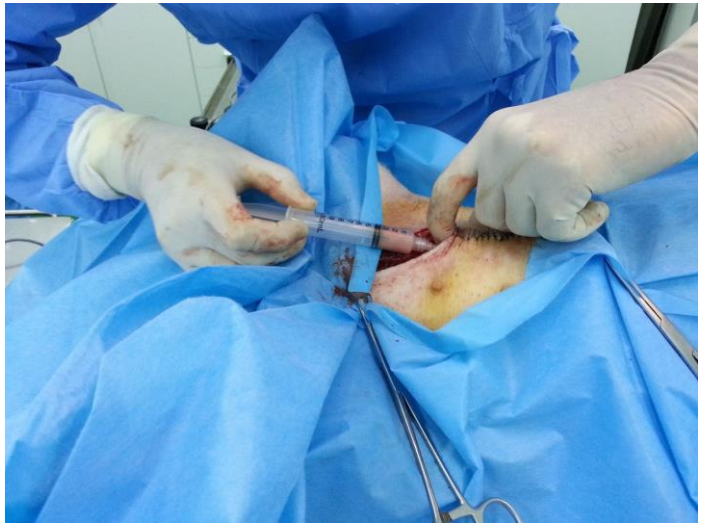


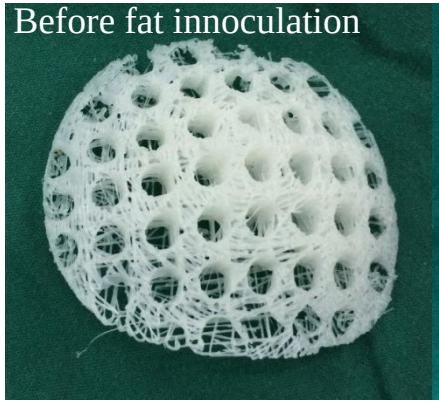
Treatment Site Allocation
Study Group
Fat graft only
Scaffold only
Scaffold + immediate fat graft
Scaffold + immediate PRP
Scaffold / delayed fat graft
Scaffold + PRP / delayed fat graft

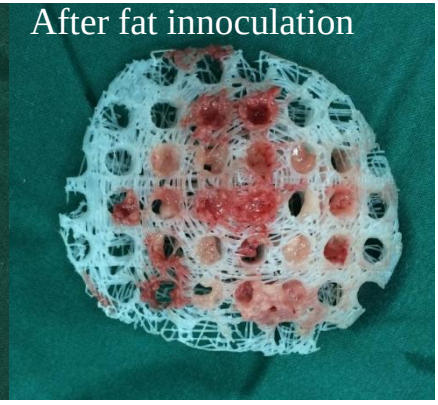


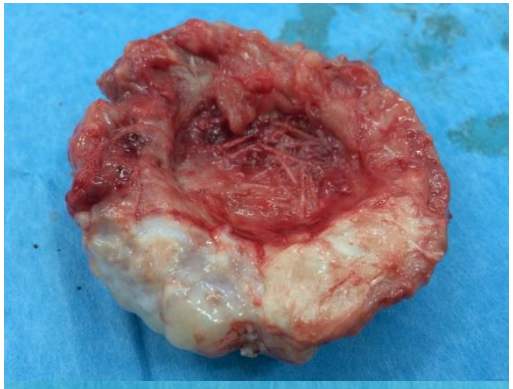


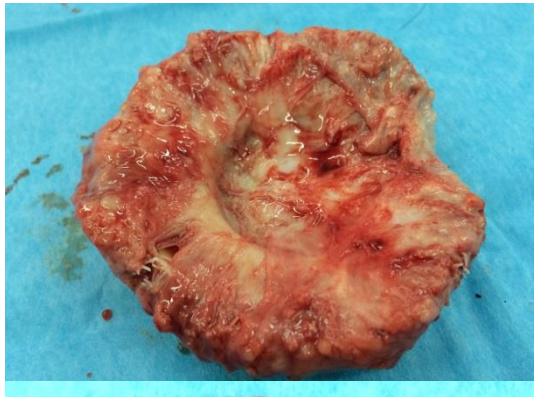


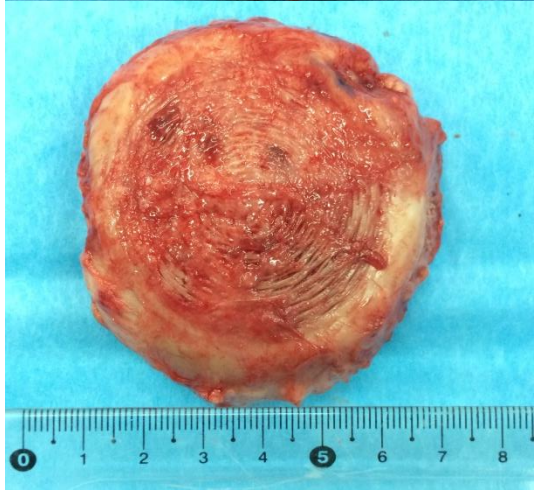








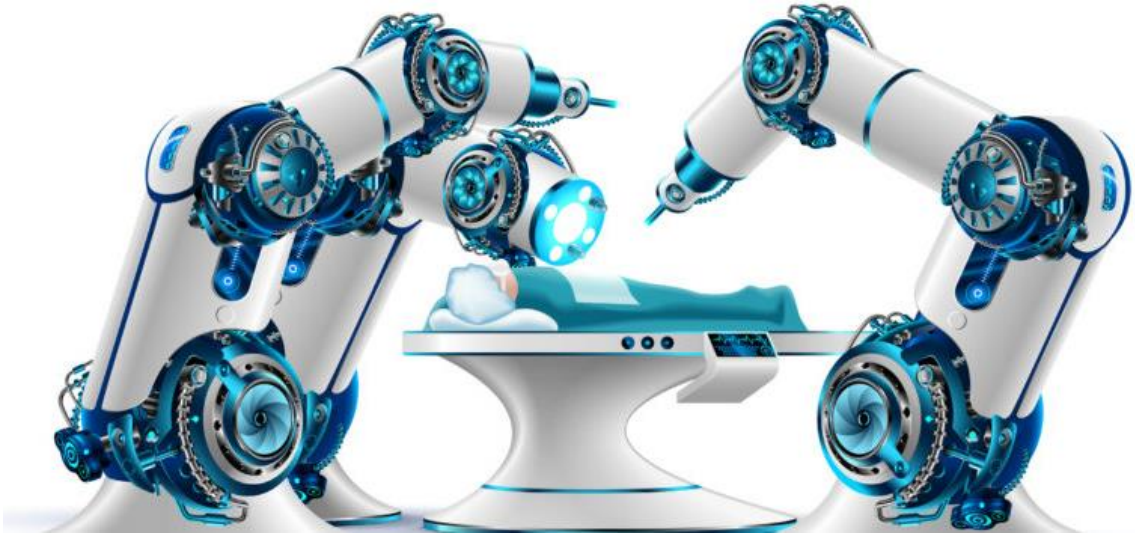




Acknowledgements:
Prof Dietmar Hutmacher QUT

The next 25 years

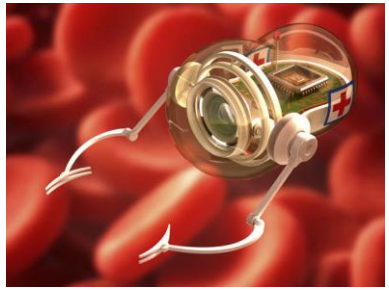
- Advancement in robotics



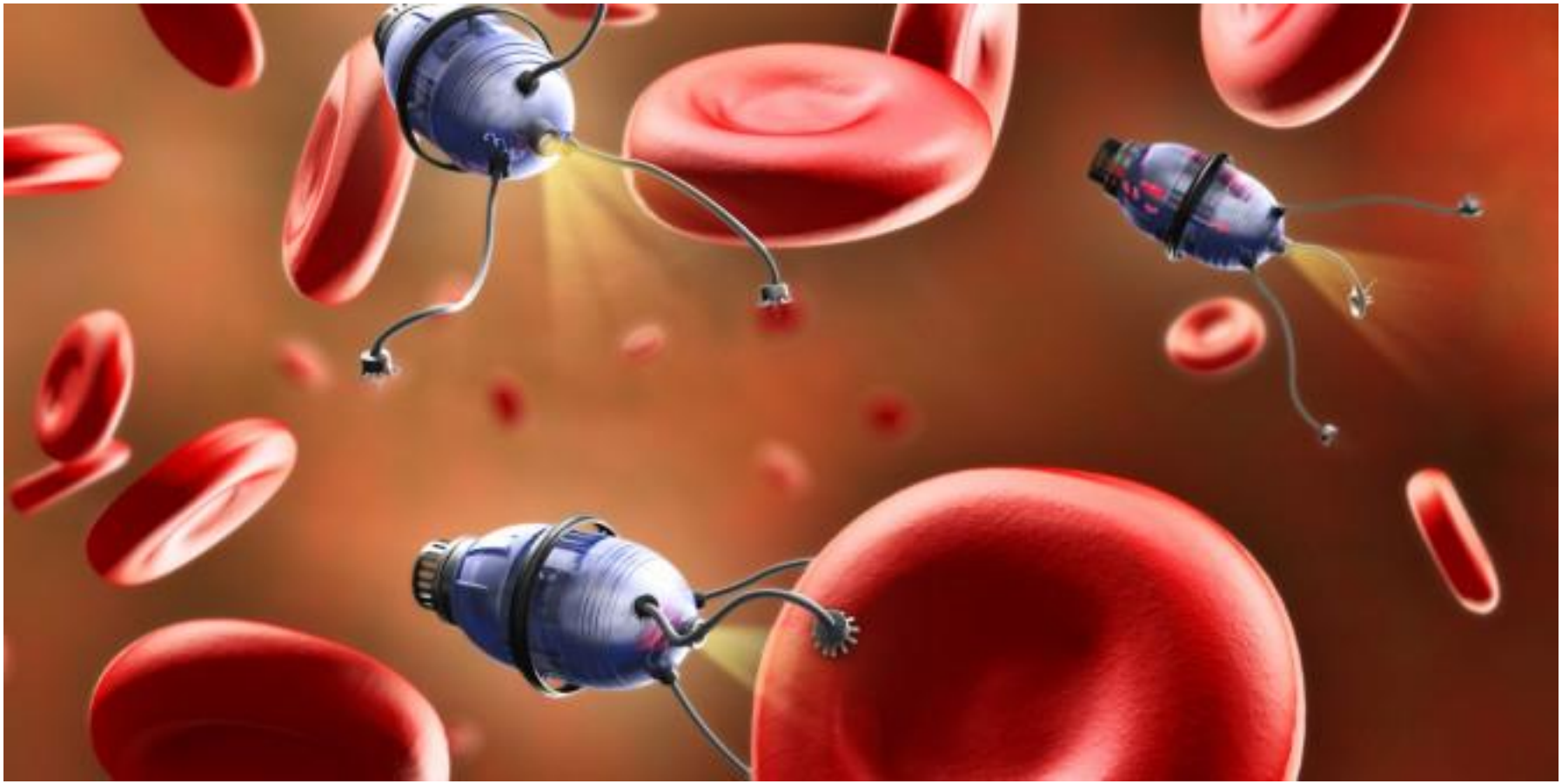
The next 25 years

- Biological sensors

The next 25 years



- DNA chips, nanoparticles, nanobots



Mid Century

- Gene therapy
  - Target diseases that cause mutations in single genes
  - Cancer - oncogenes and tumour suppressors
- Designer children

The price of success is increasing complexity

…and teamwork

RBWH – Breast Endocrine Surgery Unit

"GOING FORWARD"

- Projects
  - TransTasman collaborative
  - Breast Cancer Management Patterns public/private
  - Axillary Levels Study
  - Biodegradable scaffolds for breast reconstruction/3D printing
- Facilitating Clinical Research
  - Patient volumes
  - Clinical excellence & teamwork
  - Innovation
  - Great collaborations