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Cancer research investment should shift from late stage treatment to early stage detection – No!

KC Soo
National Cancer Centre Singapore
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3 caveats

1. The primacy of cancer prevention and related research
2. The importance of early detection but not an overemphasis on cancer screening
3. Research on late stage treatment is not necessarily all bench based

WHO guidelines (2015) on cancer control

- Reduce the incidence and mortality of cancer by prevention
- Improve the quality of life of cancer patients

WHO guidelines on early detection

- Education to promote early diagnosis of cancer (symptomatic), cancer screening (asymptomatic)

- **Early stage**
  - Carcinoma in-situ, stage I, stage II → local disease

- **Late stage**
  - Stage III → loco-regional disease
  - Stage IV → systemic disease

- Health planners from LMICs prioritizing their limited resources for funding of cancer control. Even so for HICs.

- Cancer Research Institute prioritizing its research agenda

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10 reasons why I disagree with the proposition.

1. A wise cancer control programme should invest in the full spectrum of cancer research and treatment relevant to the country i.e. cancer registry, prevention, early detection, treatment, palliative care, cancer rehabilitation and research to inform all the above.

Holistic funding for cancer control

- Resources are never enough but are not as important as strategy and marshalling of limited resources
- Evolution and increasing sophistication in cancer control rather than a ‘big bang’ approach
- Institutionalize a central core of concerned healthcare workers/researchers to champion the cause
- Governments have broad agenda. The cancer centre has to mobilise the community to focus on cancer control

KC Soo. Foundation of Cancer Control in Asia-Pacific Region Brisbane April 2016

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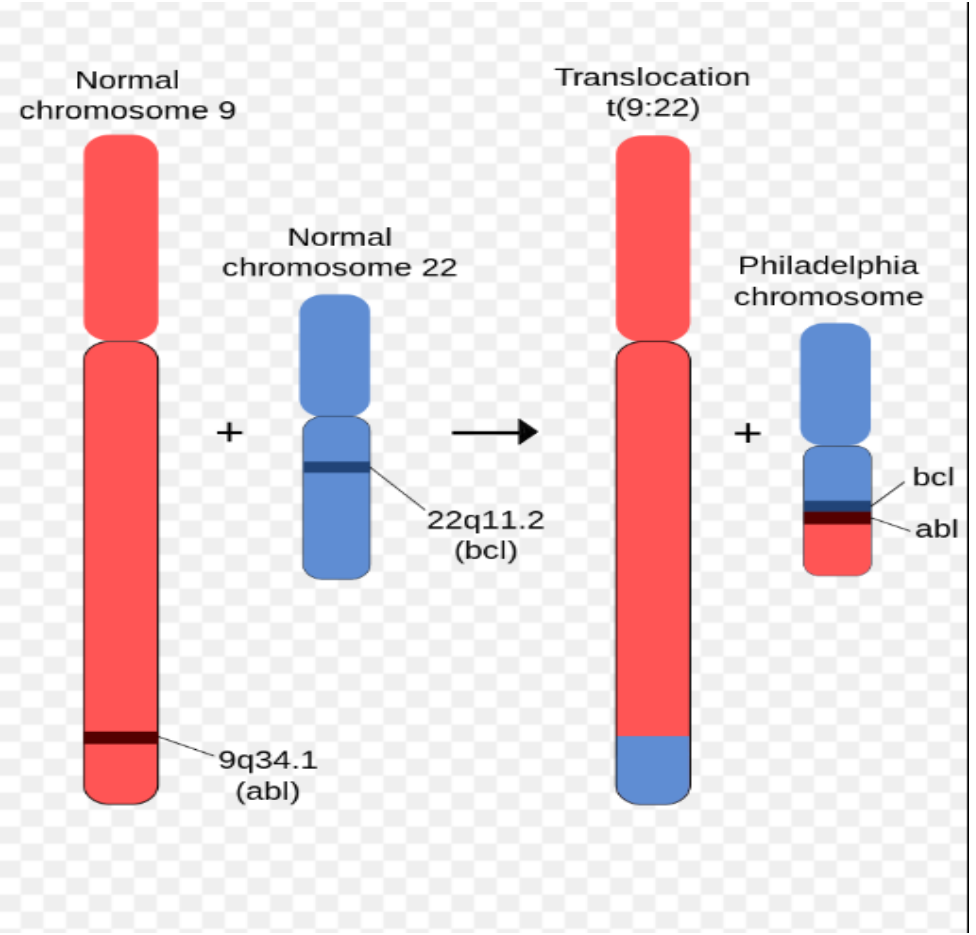
2. Research in late stage treatment provides deep insights into cancer biology, in addition to curing many patients.

Targeted Therapy

Imatinib in Chronic Myeloid Leukemia

- Fusion gene bcr-ab1 produces abnormal protein kinase
- Abnormal protein kinase results in proliferation and accumulation of immature wbc → CML



Development of Imatinib (Druker)

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- In silico modelling of ATP binding sites for bcR-abl fusion protein
- Cell culture assessment of putative drug candidates. One compound 92-98% ↓ in bcR-abl cell colonies
- Phase I trial 31 patients (1998) – all showed complete remission
- Effective because CML caused by a single aberrant protein

Imatinib in GIST

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- 5 year overall survival 92% vs 82%
- 397 patients post surgery randomized into 12 months vs 36 months of Imatinib. Follow-up 42-48 months
- Relapse 42% vs 25%
- Death 13% vs 6%
- 55% reduction in death risk if treated for 36 months

Tumour Heterogeneity and Evolution

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- Lack of response for some histological and anatomical subtypes
- Dramatic responses in some arms
- Often rapid development of drug resistance and subsequent recurrence and treatment failures
- Usefulness of combination of targeted therapies

Intra-tumoral heterogeneity
Swanton, NEJM 2012

Genome Institute of Singapore
A*STAR

The spatial organization and implication of intratumor heterogeneity in Hepatocellular Carcinoma

Weiwei Zhai

Senior Research Scientist

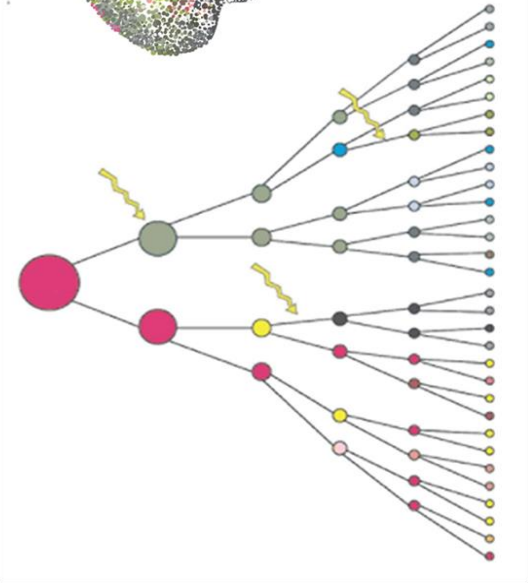
Genome Institute of Singapore

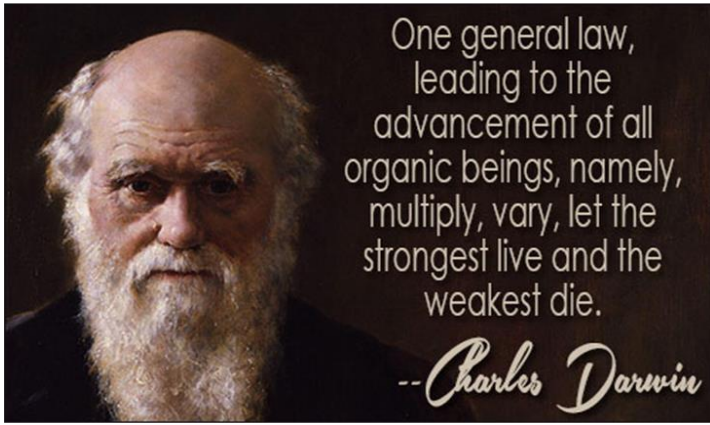
May 29 2015

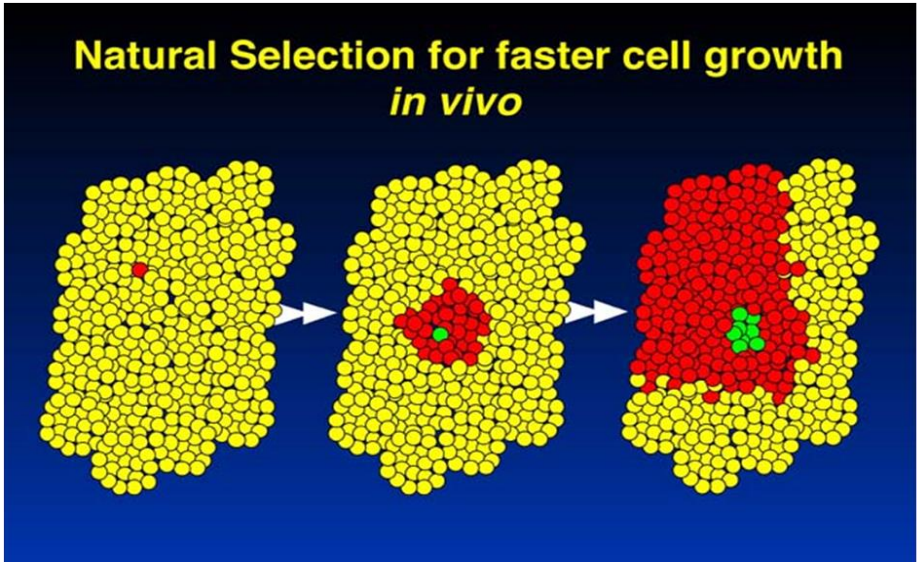
The cost of multi-cellularity

Three major ingredients for Natural Selection

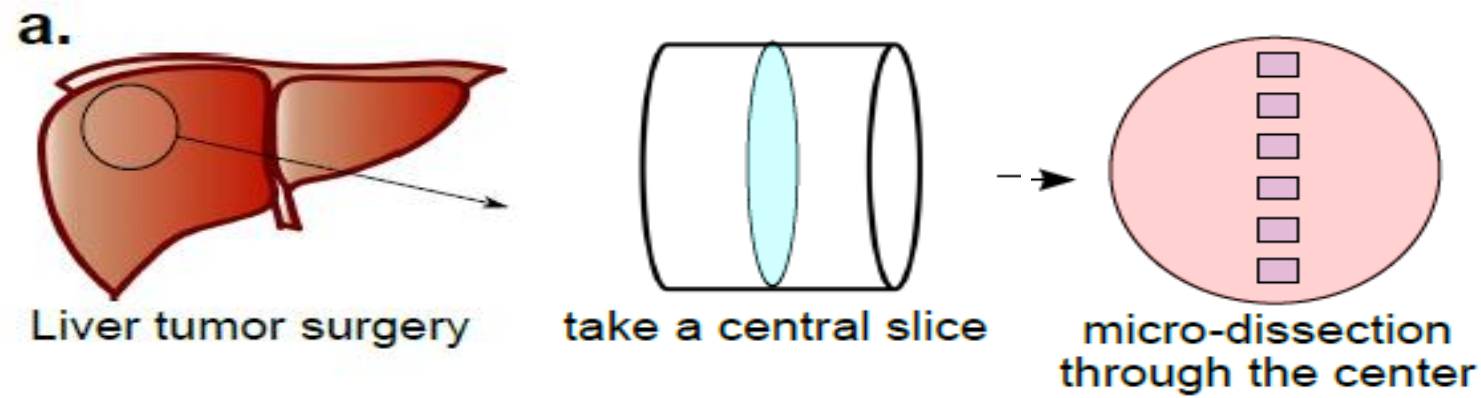
1) Variability
2) Inheritance
3) Selective pressure



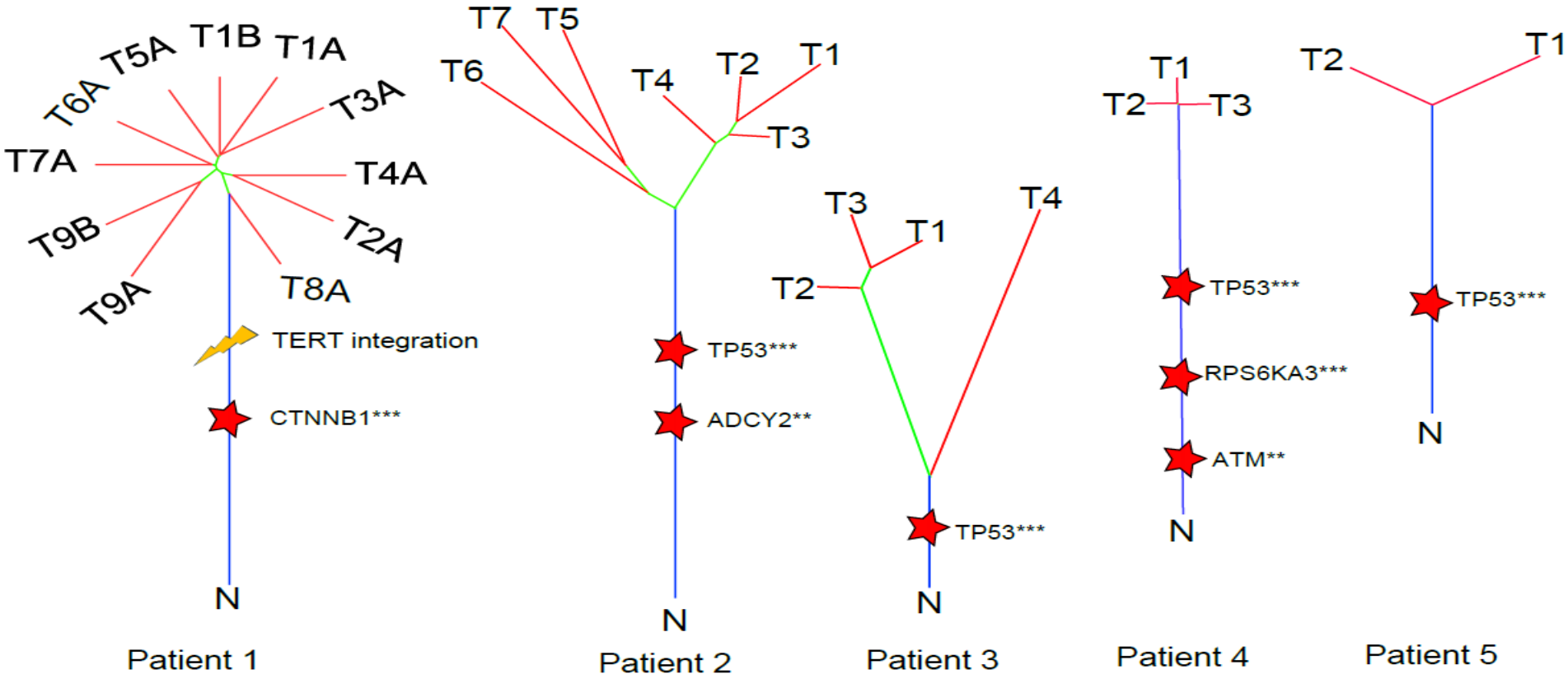




The study design



Liver cancer drivers and intra-tumor heterogeneity ‘palm tree’ and ‘bush’ mutations



Patient treatment?

Sorafenib, Regorafenib, Pazopanib

T6A T5A T1B T1A T3A T7A T4A T9B T2A T9A T8A

TERT integration

Gleevec

CTNNB1***

KIT

N

Patient 1

Tamoxifen

T7 T5 T6 T4 T2 T1 T3

F2

TP53***

ADCY2**

N

Patient 2

T3 T1 T2 T4

RET

EPHA4

TP53***

EGFR

N

Patient 3

T1 T2 T3

EPHA7

TP53***

RPS6KA3***

ATM**

N

Patient 4

T2 T1

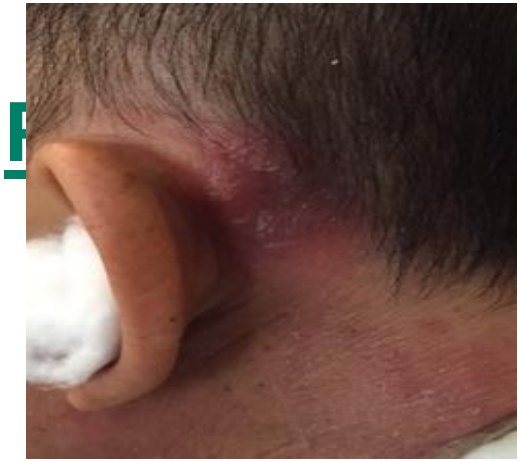
Ponatinib

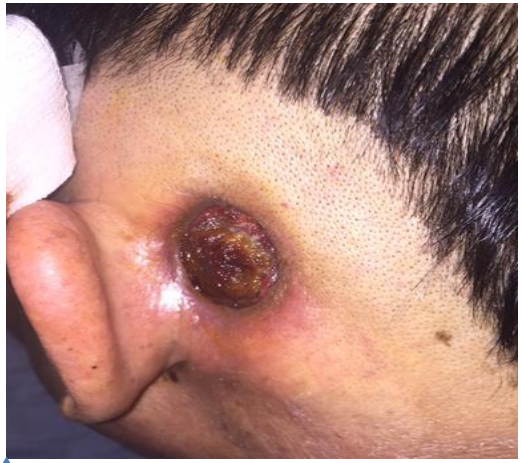
TP53***

N

Patient 5

gefitinib ....





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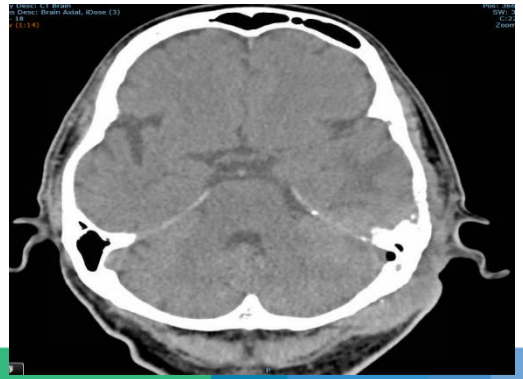
25th Aug

Gefitinib started 1st Sept

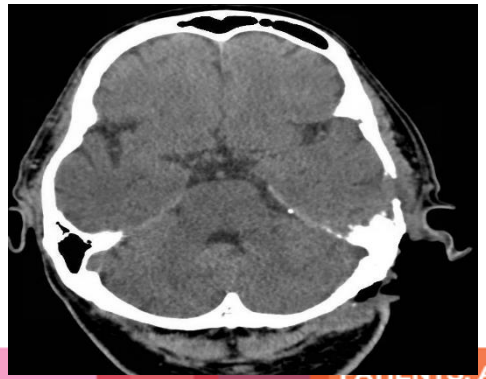
10th Sept

17th Sept

28th Aug



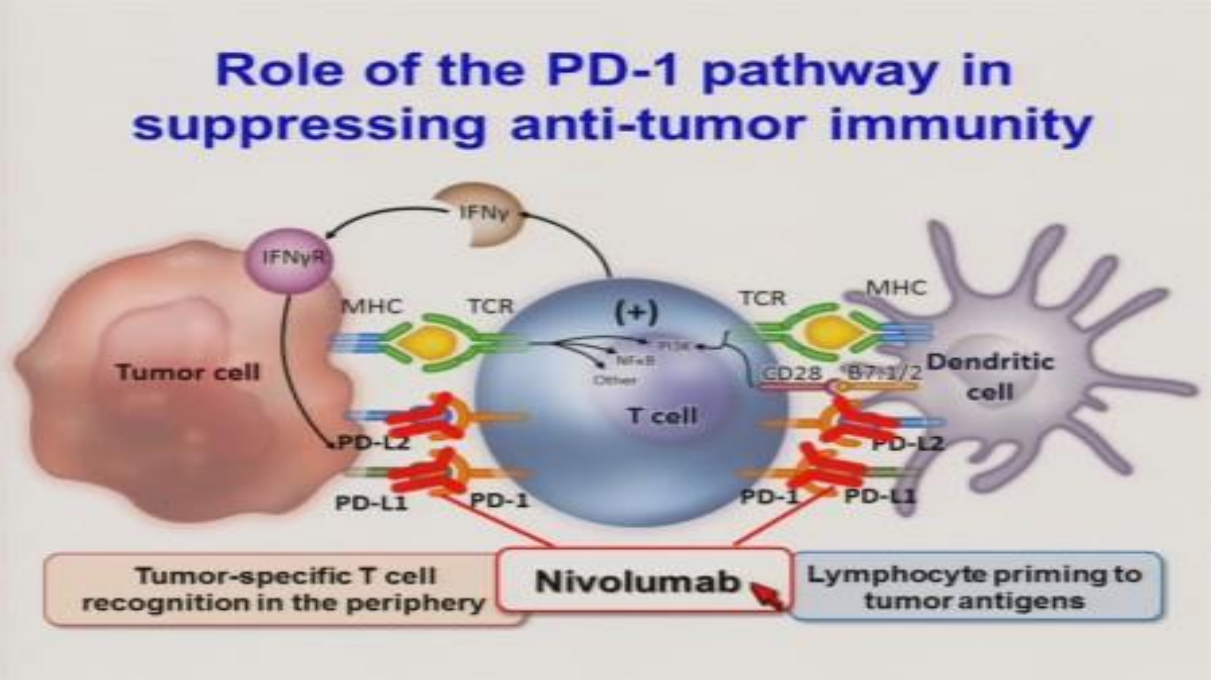
30th Sept



Immuno-Therapy

PD-1 blockade induces responses by inhibiting adaptive immune resistance.

Tumeh et al
Nature 2014, 515 (7528) : 568-71



The Role of T-Regs in Tumour Tolerance

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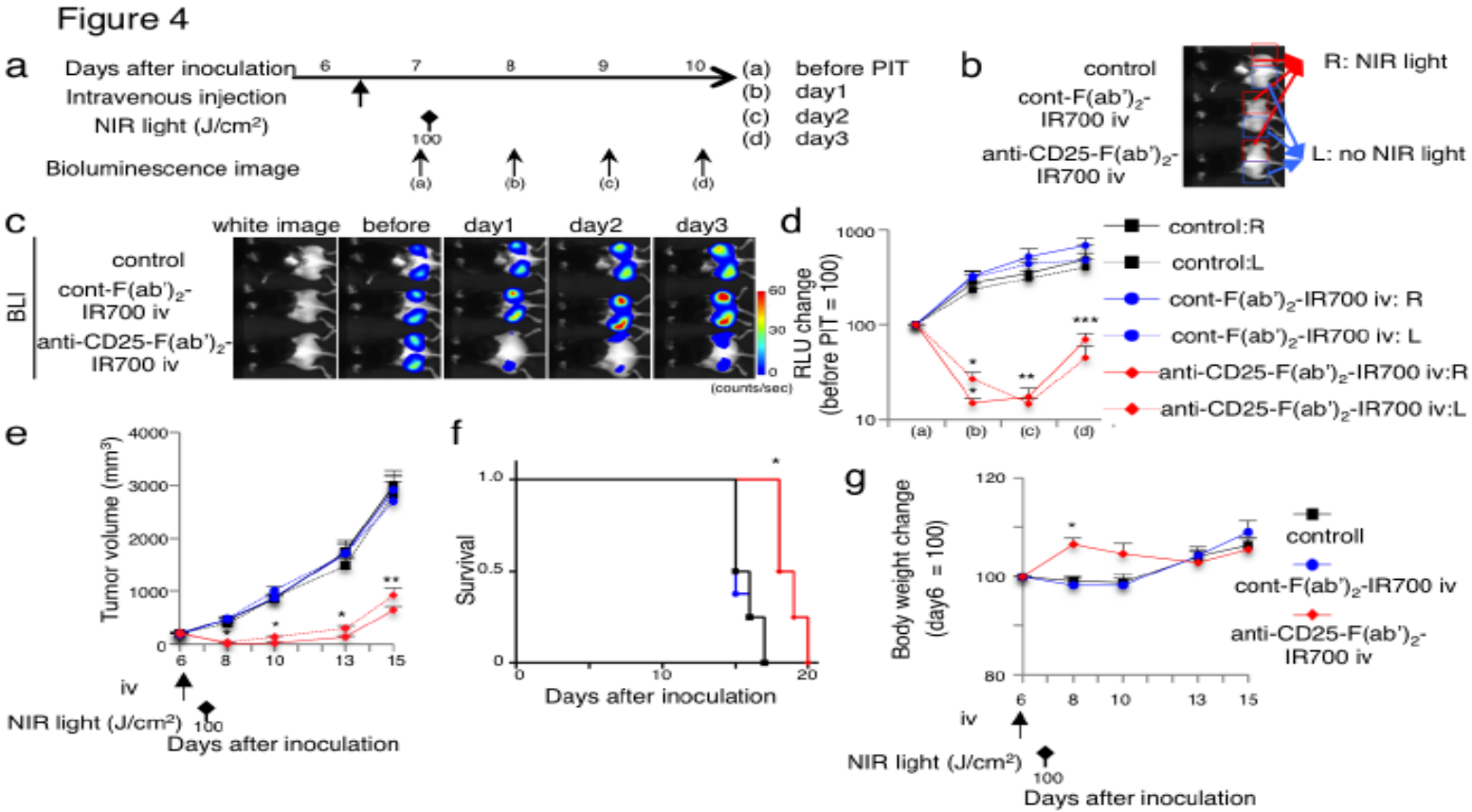

Sato K et al. AACR 2016, #1470

3. While it is good to research on cancer screening/early detection and biomarkers, there is an immediate problem of patients with advanced cancer patients turning up our doorsteps daily, requiring late stage treatment and research initiatives that go with it.

Lymphomas

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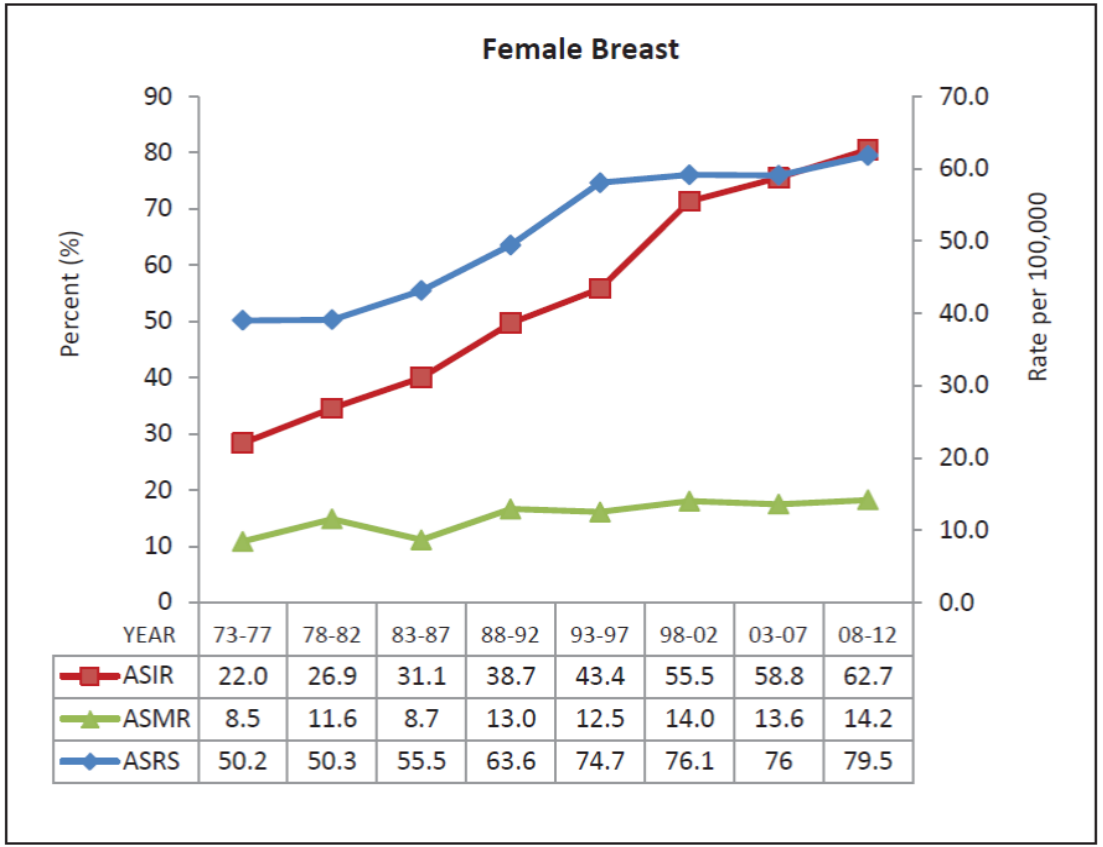
- The overall 5-yr RSR has **increased** for the mature B-cell lymphoma subgroup. The largest increase in 5-year RSR subtypes
  - **FL** from 43.8% in 1998-2002 to 82.3% in 2008-2012
  - **CLL** from 48.1% in 1998-2002 to 77.9% in 2008-2012.
- Improvements in survival have spanned across both genders and all ethnicities

NCCS Data 2015

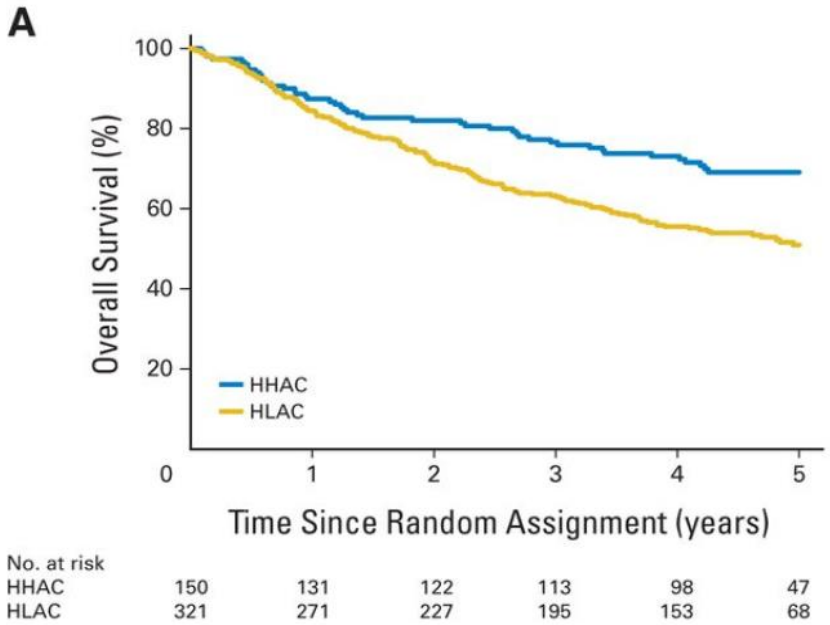
Trends in Incidence, Mortality and 5 years ASRS

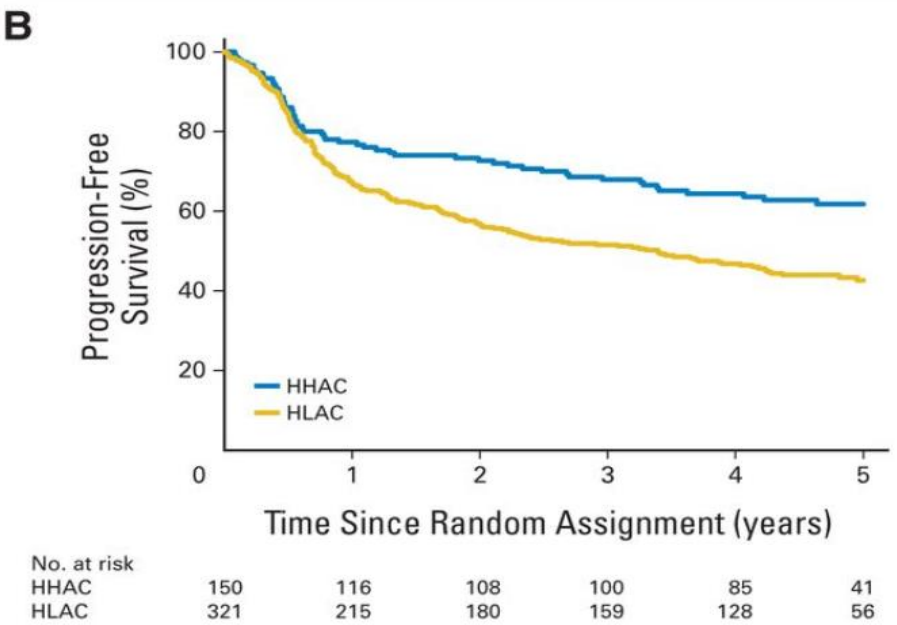


YEAR	73-77	78-82	83-87	88-92	93-97	98-02	03-07	08-12
ASIR	22.0	26.9	31.1	38.7	43.4	55.5	58.8	62.7
ASMR	8.5	11.6	8.7	13.0	12.5	14.0	13.6	14.2
ASRS	50.2	50.3	55.5	63.6	74.7	76.1	76	79.5

The survival of female breast cancer increased steadily over from 1973 to 2012. **The 5-year ASRS were 50.2% and 79.5% in 1973 – 1977 and 2008 – 2012 respectively.** Relative survival for breast cancer in Singapore was higher than that in Europe and China but lower than that in the SEER registries, Japan and Australia. Breast cancer is the most frequent cancer among females in Singapore. The incidence of breast cancer has increased steadily from 22.0 per 100,000 in 1973 – 1977 to 62.7 per 100,000 in 2008 – 2012, though the rate of increase seemed to have slowed after 1998 – 2002. There was no significant trend in stage-specific survival.

SCR 2013





Institutional clinical trial accrual volume and survival of patients with head and neck cancer. Wuthrick EJ et al. JCO 2015 Jan 10, 33(2):156-64

4. Investments in late stage treatment in the form of comprehensive cancer centres for cancer control will ensure that there are enough critical pool of healthcare workers and researchers to drive not only treatment of cancers but early detection and even prevention. The converse is not true.
   - 3-4 cancers have proven effectiveness of cancer screening but what about the other more than 100 cancers?

5. An important corollary of a good detection programme is that there must be facilities available to treat cancers detected, of which a significant proportion are advanced cancers.

Early stage oral cancers treated with elective neck dissection at time of primary surgery vs therapeutic neck dissection after nodal relapse – 80% vs 67.5% 3 years overall survival.

2 observations

1) Research on treatment on early disease, results suggest it is actual treatment for late stage disease
2) Clinical research may not need elaborate or expensive molecular biology facilities

Elective vs therapeutic neck dissection in node negative oral cancer

Anil D'Cruz et al

NEJM 2015, 373:521-9

6. ‘So much for so little’ in cancer screening and early detection.
   - 96,517 patients intervention arm vs 95,356 patients control arm
   - 8 year study
   - Intervention arm – 205 cases, 77 deaths vs Control arm – 158 cases, 87 deaths

Effect of screening on oral cancer mortality in Kerala, India: a cluster randomised controlled trial
Rengaswamy Sankaranarayanan et al
Lancet 2005, 365: 1927–33

Anil D'Cruz et al, NEJM Aug 2015

- 245 patients intervention arm vs 255 control arm
- 10 year study
- Intervention arm 81 recurrences, 50 deaths vs
  146 recurrences, 79 deaths in control arm

Postoperative irradiation with or without concomitant chemotherapy for locally advanced head & neck cancer
(Bernier et al. NEJM 2004, 350 : 1945-52)

- 334 patients recruited
- 6 year study
- Radiation alone 167 patients – 90 patients disease progressed, 71 patients died
- Chemoradiation – 69 patients disease progressed, 45 patients died

7. Screening results after so many decades are variable.

- Cervical cancer – opportunistic screening and appears to be likely to be supplanted by HPV vaccination
- Breast cancer screening – increasing by controversial
- Colorectal screening – screening participation suboptimal
- Prostate cancer – over diagnosis with insufficient data to discriminate bad players from PSA measurements

Mammography Controversial

25 years follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial (Miller AB et al. BMJ 2014, 346:6) (consistently judged to be of high quality)

- No reduction mortality for women, aged 40-59 beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available.

Cochrane meta-analysis of screening for prostate cancer. (Ilic D et al. Cochrane Database Syst Review 2013, 31 Jan)

- 5 RCT – total of 341, 342 participants
- No significant decrease in prostate specific mortality
- Significant over diagnosis and over treatment and treatment related harm

Predicted impact of vaccination against human papillomavirus 16/18 on cancer incidence and cervical abnormalities in women aged 20-19 in the UK.
(Cuzick J et al. B J Cancer 2010, 102(5) : 933-9

- 80% vaccination coverage
- 63% reduction in invasive cancer
- 51% reduction CIN
- 27% reduction cervical abnormalities before age of 30

In a vaccinated population cervical cancer will become a rare disease!

Even the study of HPV as the cause of cervical cancer is due to study of advanced cervical cancer (zur Hausen).

8. Problems inherent in early detection
   - Lead time bias
   - Length time bias
   - Over diagnosis and related treatment harm

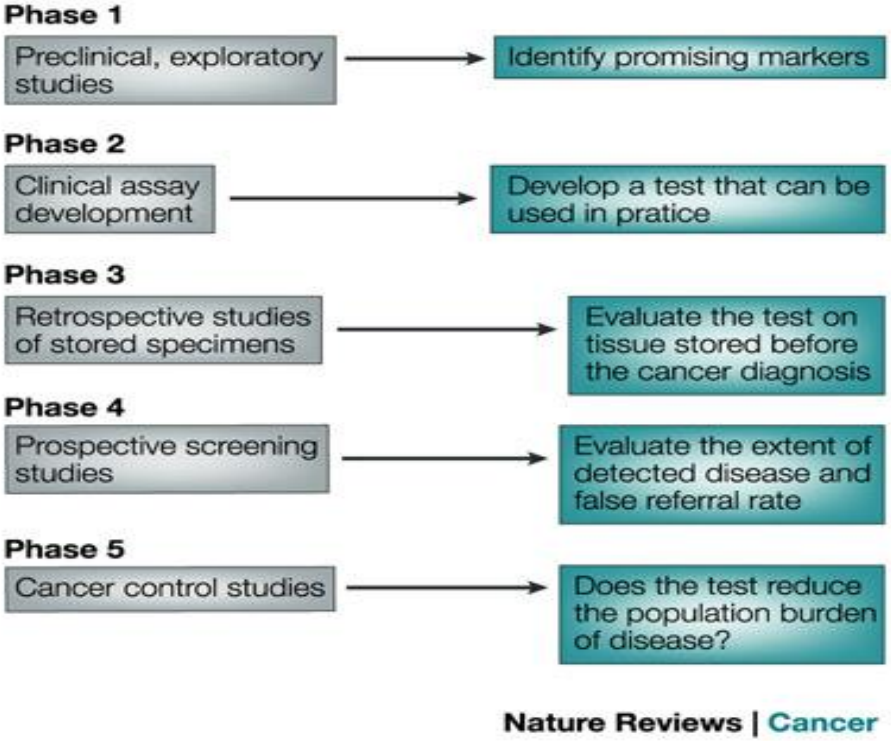
Early detection of disease - statistical challenges

Marvin Zelen. R.A. Fisher Memorial Lecture. Aug 1, 2007

9. Early detection research programme is “an extreme programme”

National Cancer Singapore | Health

Stages in early detection by biomarkers



The case for early detection

Etzioni R et al. Nature Reviews 2003 April, 3:1-10

Early detection research programme is “an extreme programme”

An early-detection RCT is extreme in many aspects — extremely time consuming, extremely expensive and extremely vulnerable to irrelevance due to either technological advancement or adoption of the intervention by an impatient clinical community and public. Additionally, screening trials, like prevention trials, can only test a minimal number of intervention strategies. Finally, screening trials test interventions in a highly rigorous and controlled environment.

The case for early detection
Etzioni R et al. Nature Reviews 2003 April, 3:1-10

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10. From the leading world authority on cancer screening / early detection
    - Options for breast cancer detection in lower and medium resource countries

R Sankaranarayanan: IARC Monograph

Feasible options for breast cancer control

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- Low-income countries: breast awareness, early clinical diagnosis and adequate basic treatment
- Low-middle income countries: breast awareness, early clinical diagnosis and adequate basic treatment
- High-middle income countries: breast awareness, early clinical diagnosis and adequate treatment; ?!mammography-based screening

R Sankaranarayanan

Options for breast cancer early detection in low- and medium- resource countries

- Establish cancer registry
- Awareness and advocacy for prevention and early diagnosis
- A comprehensive cancer centre (hub) and associated facilities in the community (spoke) for cancer control
- Varying investment in cancer research

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Thank You