Role of Multidisciplinary Care and Regional Centres of Excellence in Cancer Control and Cancer Management in the 21st Century

KC Soo
National Cancer Centre Singapore

Cancer Trends in Singapore

- Rising incidence especially in females
- Cancer mortality rates
- Aging population demographics
- Changing cancer trends

Fig. 8.3(b): TRENDS IN AGE-STANDARDIZED INCIDENCE FOR SELECTED CANCER SITES IN FEMALES, 1968-2002

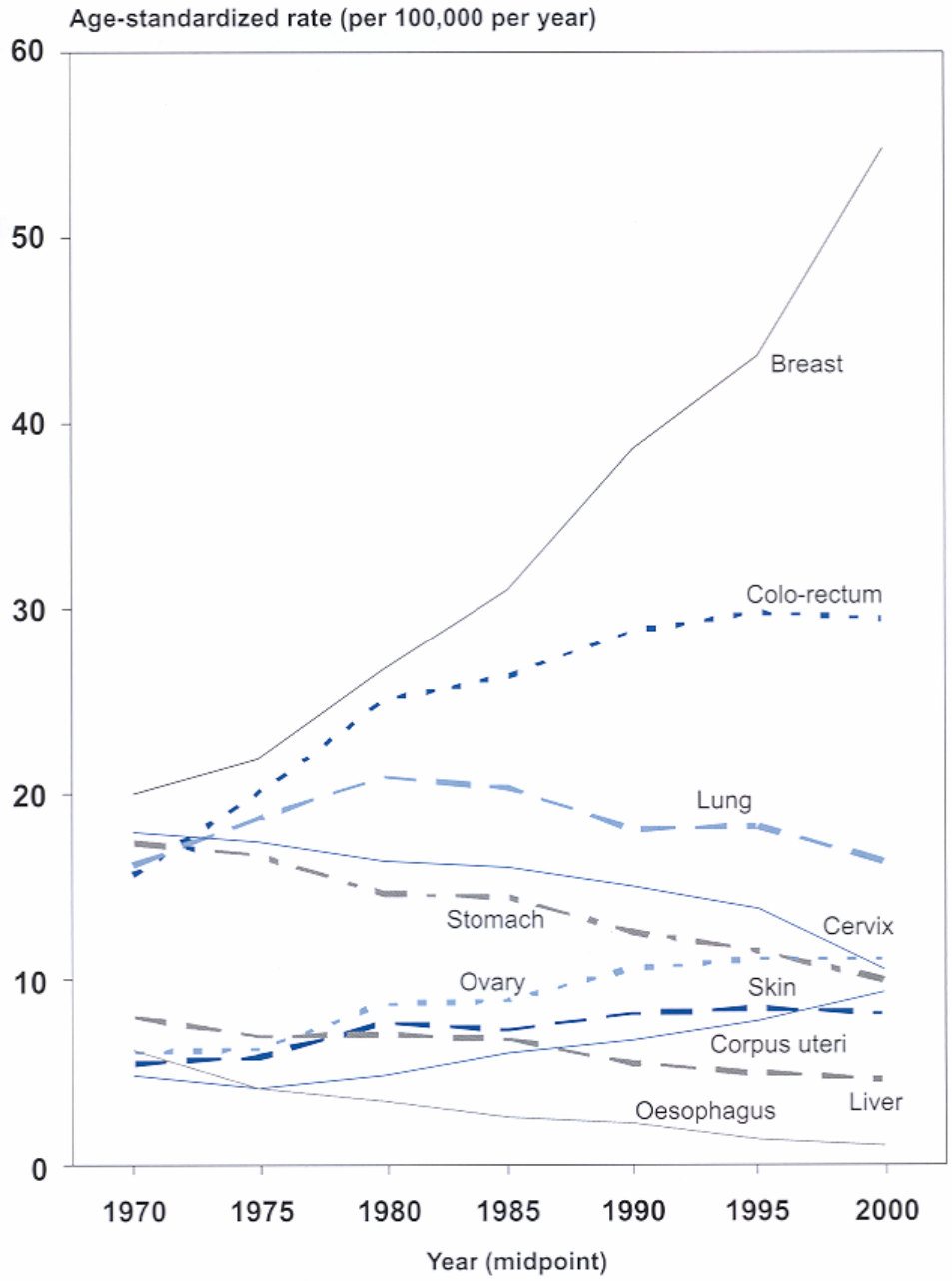
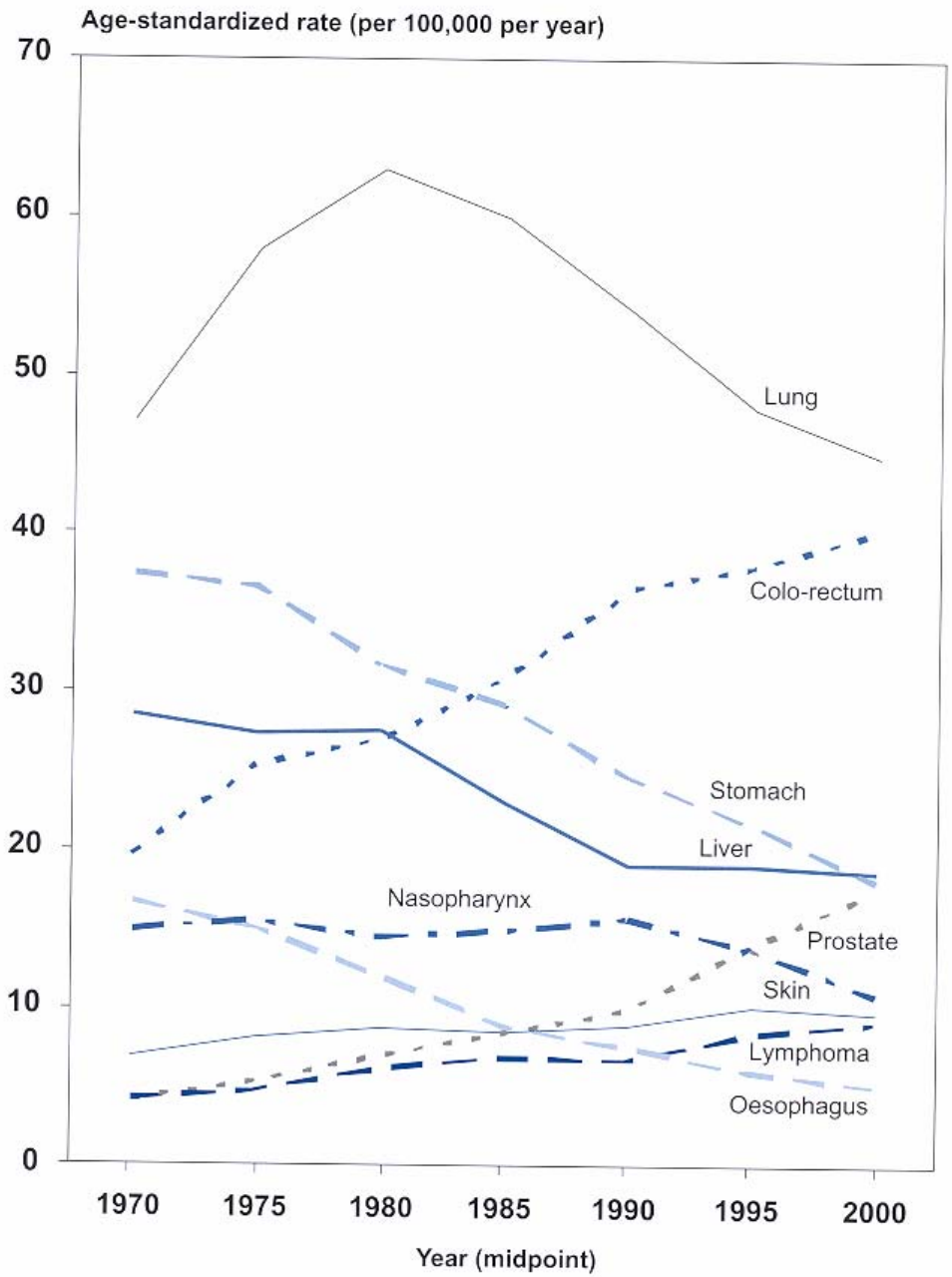


Fig. 8.3(a): TRENDS IN AGE-STANDARDIZED INCIDENCE FOR SELECTED CANCER SITES IN MALES, 1968-2002



- Cancer is the number one killer in Singapore accounting for 30% of all deaths annually.
- At least one in three will have cancer in their lifetime.

WHO / IARC Estimates

- Doubling of incidence over next 2 decades
- Year 2020 – cancer deaths 12 million worldwide

Cancer Control = Reduction in Cancer Mortality

- **Reduction in cancer incidence**
- Early detection and screening
- Improved therapy

Tobacco is the single largest avoidable cause of premature death internationally and the most important known carcinogen to human.

US	443,000 deaths from tobacco 112,000 from lung cancer
Japan	Lung cancer mortality has increased 10 fold in men and 8 fold in women since 1950s

- Ban on advertising and promotion of tobacco products
- Effective government health warnings
- Low tar and nicotine policy
- Tax and pricing policy
- Protection of young people from promotion and sales
- Protection of non smokers and smoke free environment
- Wide availability of help to help smokers stop

Diet and Cancer Prevention

- High dietary fat is associated with increased risk of breast cancer (Boyd 1993)
- High consumption of fruits and vegetables which reduced risk of cancer of aerodigestive tract, stomach, pancreas etc (Steinmetz 1991)

Estimate of the proportion of cancer deaths that will be found to be attributable to various factors

	Best Estimate	Range
Tobacco	30	25 - 40
Alcohol	3	2 - 4
Diet	35	10 - 70
Food additives	<1	5 - 2
Sexual behaviour	1	1
Yet to be discovered hormonal analogies of reproductive factors	Up to 6	0 - 12
Occupation	4	2 - 8
Pollution	2	1 - 5
Industrial products	<1	< 1 - 2
Medicines and procedures	1	0.5 - 3
Geographical factors	3	2 - 4
Infective processes	10	1 - ?

- Reduction in cancer incidence
- **Early detection and screening**
- Improved therapy

Proven Value

- Pap Smear
- Mammography
- Colorectal Cancer

Research Interests/ Selective Screening

- Cancer Families
- Hep B carriers
- High Risk Behaviour

- Reduction in cancer incidence
- Early detection and screening
- **Improved therapy**

Worldwide Trends in Cancer Diagnosis and Management

- Tumour biology
  - **Classical Halstedtian concept**
  - **Disease is systemic at presentation**
  - **Disease is predominantly local**

Worldwide Trends in Cancer Diagnosis and Management

- Tumour biology
- **Multisdisciplinary care**

- Head & neck SCC
- Breast cancer
- Sarcomas

Multidisciplinary Care

H & N, SCC Esophageal, SCC	Radical Surgery & DXT	→	Neoadjuvant Chemo RT ± Salvage Surgery
Breast Ca	Radical Mastectomy	→	Lumpectomy + DXT + Adjuvant Chemo or Neoadjuvant Chemo RT ± Salvage Surgery
Sarcomas	Amputation	→	Compartmental Resection ± Adjuvant DXT

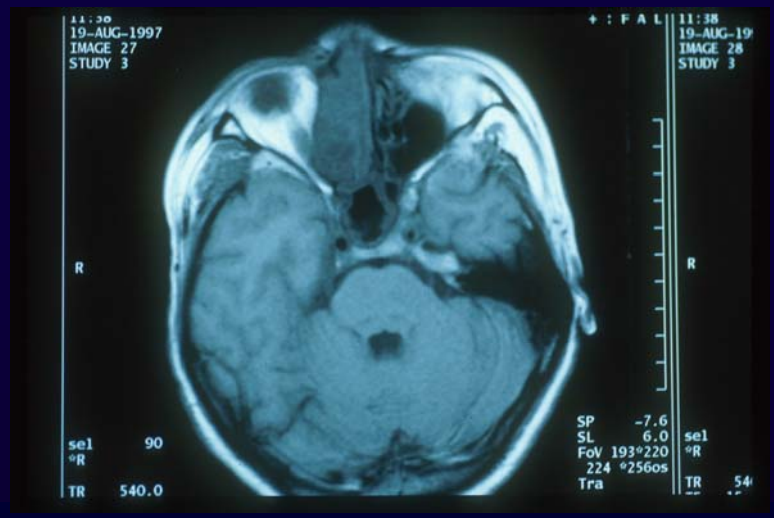
Worldwide Trends in Cancer Diagnosis and Management

- Tumour biology
- Multidisciplinary care
- **Subspecialisation**

- Neurosurgery
- Head & Neck Surgery
- Upper GIT, Lower GIT
- Hepatobiliary
- Breast
- Gynaecology
- Urology
- Musculoskeletal
- Paediatric Surgery
- Thoracic Surgery

Worldwide Trends in Cancer Diagnosis and Management

- Tumour biology
- Multidisciplinary care
- Subspecialisation
- **Increasing reliance on technology e.g. CT scans, MRI, PET scans**



Worldwide Trends in Cancer Diagnosis and Management

Tumour biology

Multidisciplinary care

Subspecialisation

Increasing reliance on technology e.g. CT scans, MRI, PET scans

Comprehensive Cancer Centres

National Cancer Centre - 1999

5 Clinical Departments
Medical Oncology, Radiation Oncology, Surgical Oncology, Palliative Medicine, Oncologic Imaging

Translational Research Divisions
Cellular & Molecular Research, Medical Sciences, Clinical Trials and Epidemiological Sciences

Cancer Registry
Patient and treatment based registry
Population based Singapore Cancer Registry

Department of Cancer Information and Education
Public cancer education, Behavioural science research, Cancer support, Cancer information network and website

Comprehensive Cancer Centres – Consumers' Perspective

- Appropriate referrals
- Coordinated multidisciplinary care
- Access to evidence based care and clinical trials
- Support through cancer journey

Anderiesy C, Elwood M, Hill D, 2006

Multidisciplinary Clinics in Comprehensive Cancer Centres

- Balanced opinions
- Appropriate diagnostic cascade
- Rationalised treatment sequence
- Subspecialisation - lower morbidity and mortality rates
  - improved long term survival
- Wholistic and patient centered
- Efficiency
- Cross discipline educational process
- Access to new therapy / clinical trials
- Research opportunities

Is there data to suggest superior care from multidisciplinary team or regionalisation of cancer care?

533 cases of ovarian cancer, adjustment for age, stage, pathology, degree of differentiation and ascites

Survival improved when patients

(i) 1st seen by gynaecologist ($p < 0.05$)

(ii) operated by gynaecologist ($p < 0.05$)

(iii) were prescribed platinum chemotherapy (p 0.05)

(iv) were referred to a joint clinic ($p < 0.001$)

Management of ovarian cancer: referral to multidisciplinary team matters. B J Cancer 1994 Aug, 70 (2) : 363-70

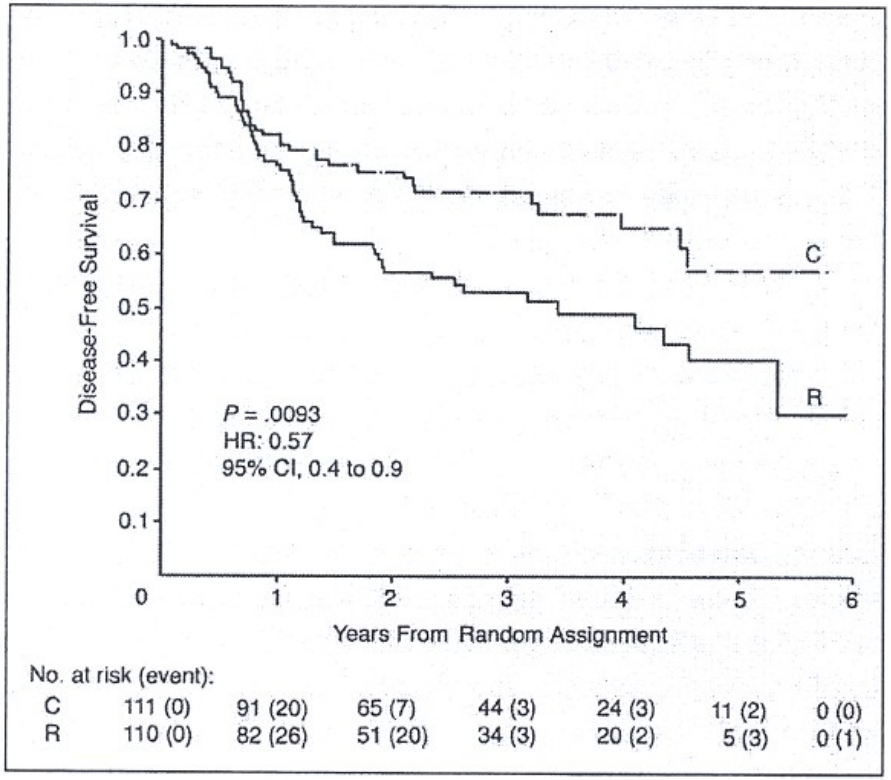


Fig 3. Disease-free survival by treatment.

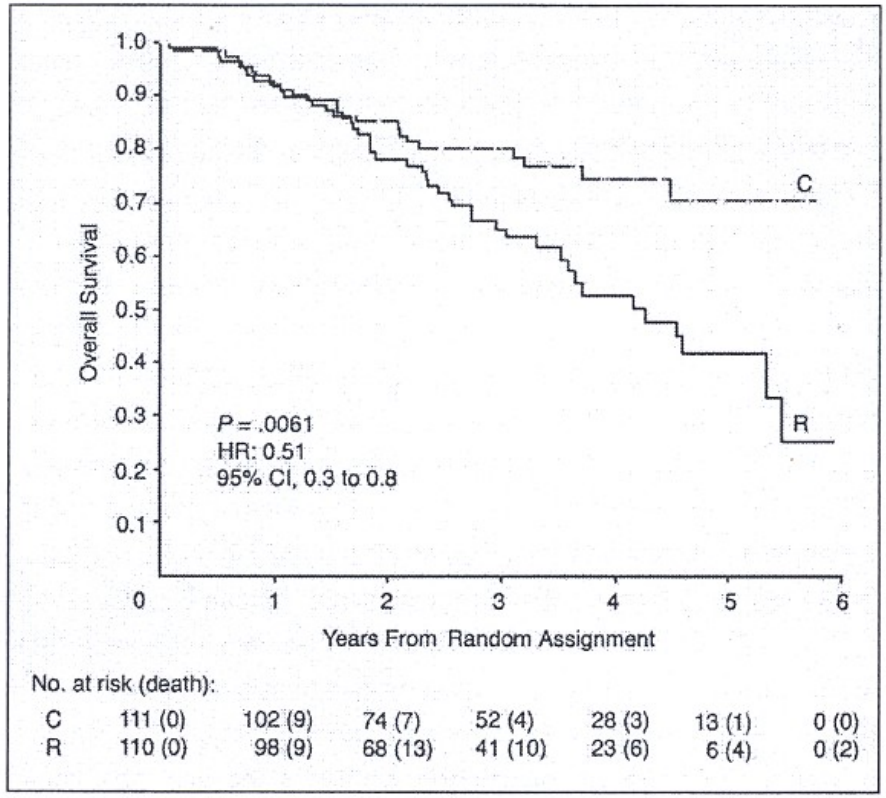
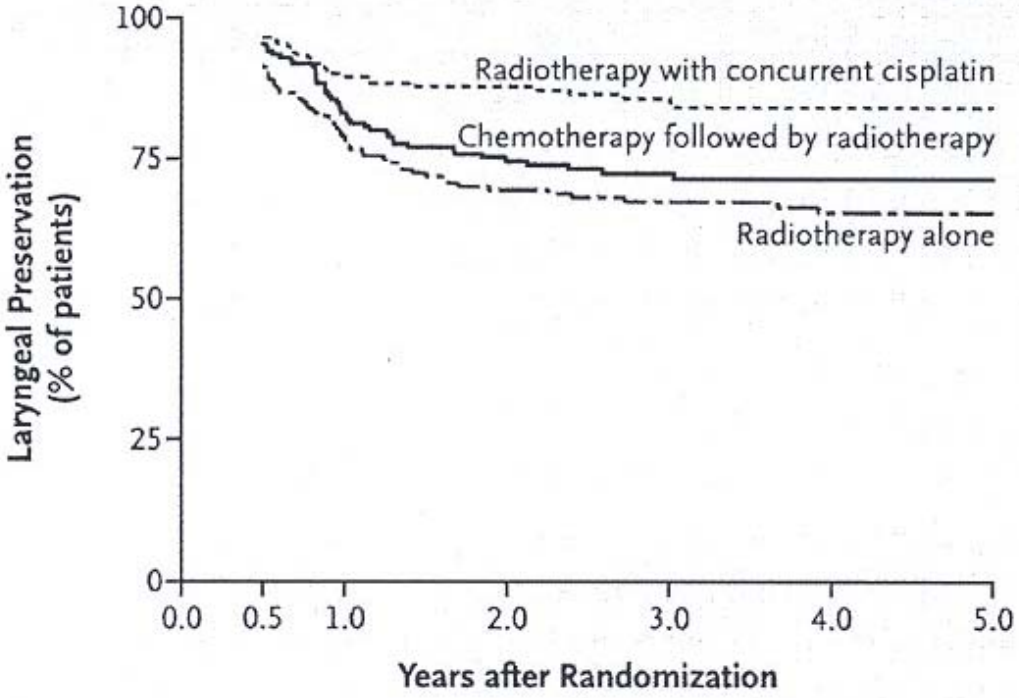


Fig 4. Overall survival by treatment.

Randomized Trial of Radiotherapy vs Concurrent Chemoradiotherapy followed by Adjuvant Chemotherapy in Patients with American Joint Committee on Cancer/International Union Against Cancer Stage III and IV Nasopharyngeal Cancer of the Endemic Variety

J Wee, EH Tan, BC Tai, et al
Lancet 2005, 365 : 1927-1906

Rates of Laryngeal Preservation according to the Treatment Group



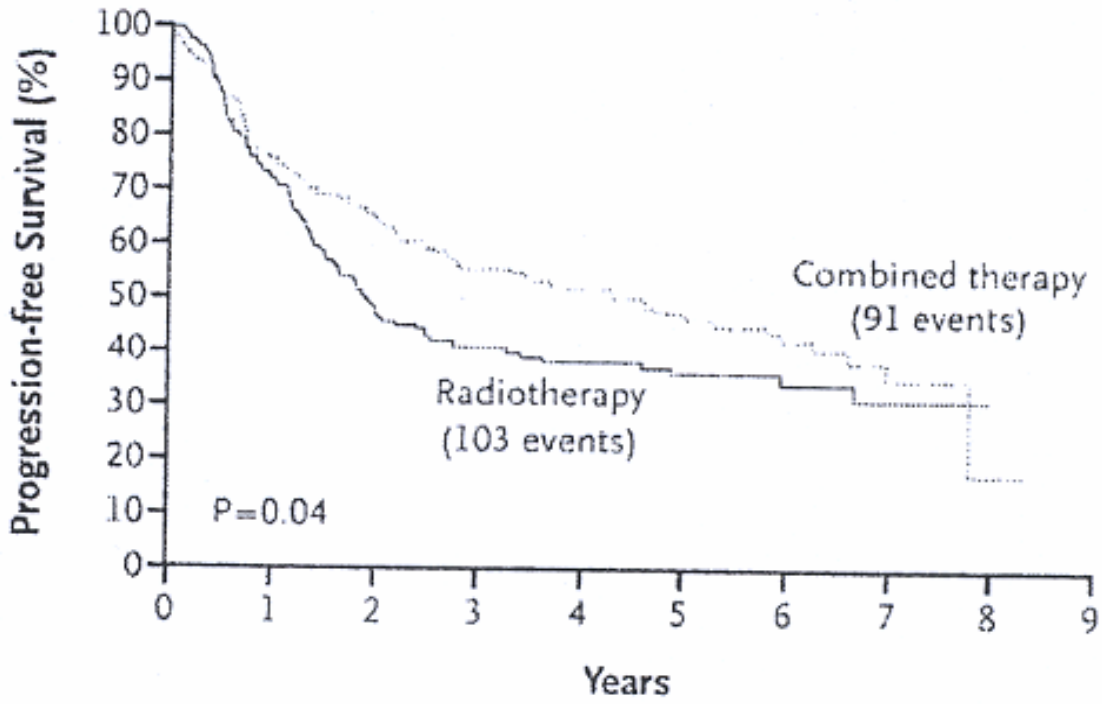
No. at Risk			
Chemotherapy followed by radiotherapy	158	94	20
Radiotherapy with concurrent cisplatin	154	107	28
Radiotherapy alone	146	87	20

Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

AA Forastiere, H Goepfert, M Maor, et al

NEJM 2003, 349 (22) : 2091-8

Kaplan-Meier Estimates of Progression-Free Survival



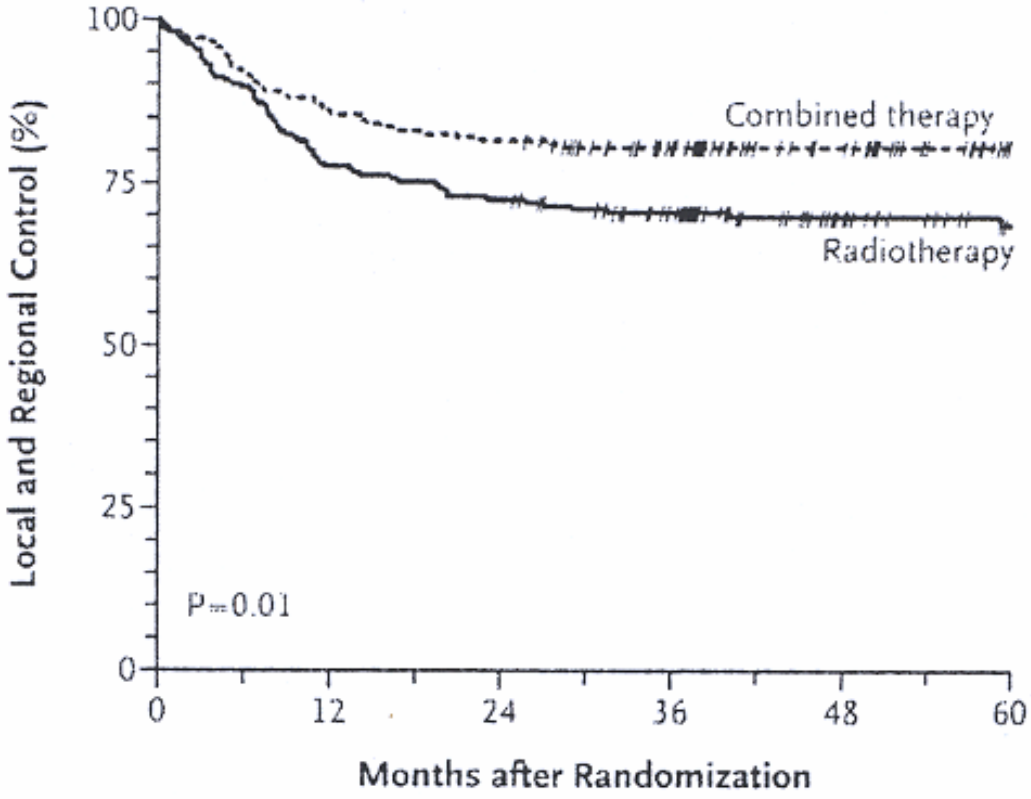
No. at Risk									
Radiotherapy	167	119	73	57	45	30	18	9	0
Combined therapy	167	125	105	85	66	42	29	10	1

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

J Bernier, C Domenge, M Ozsahin, et al

NEJM 2004, 340 (19) : 1945-52

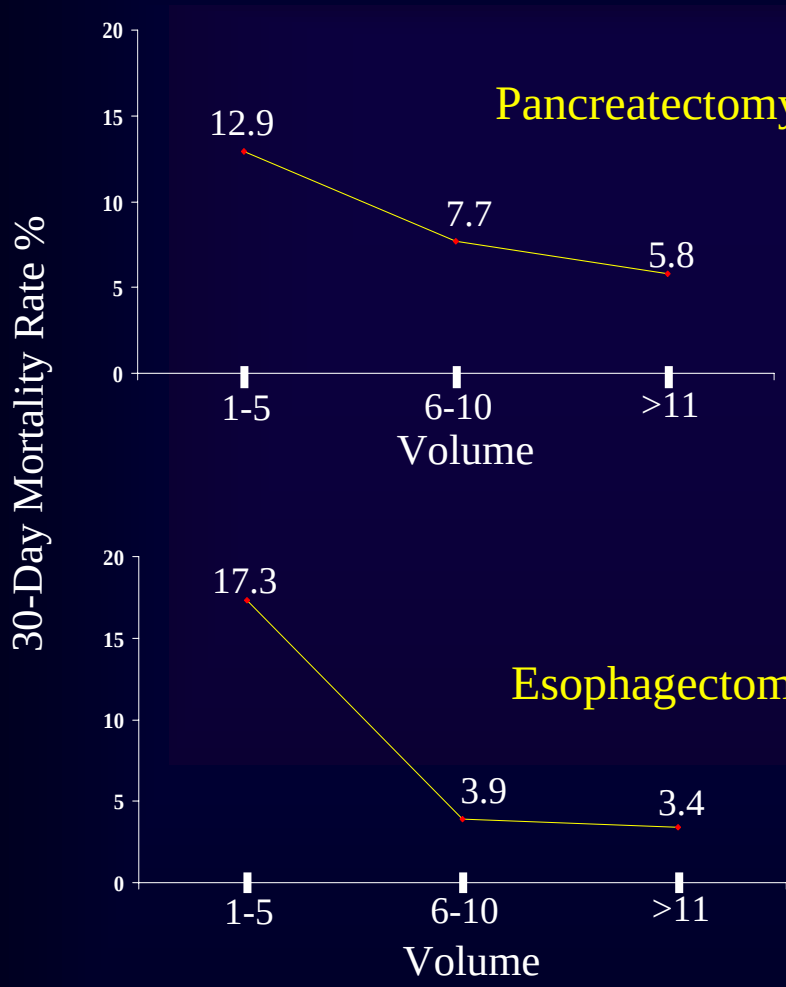
Rates of Local and Regional Control

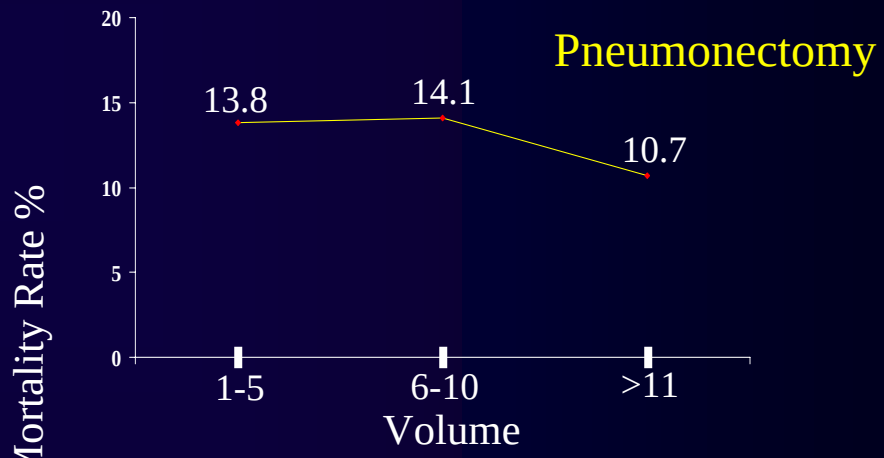


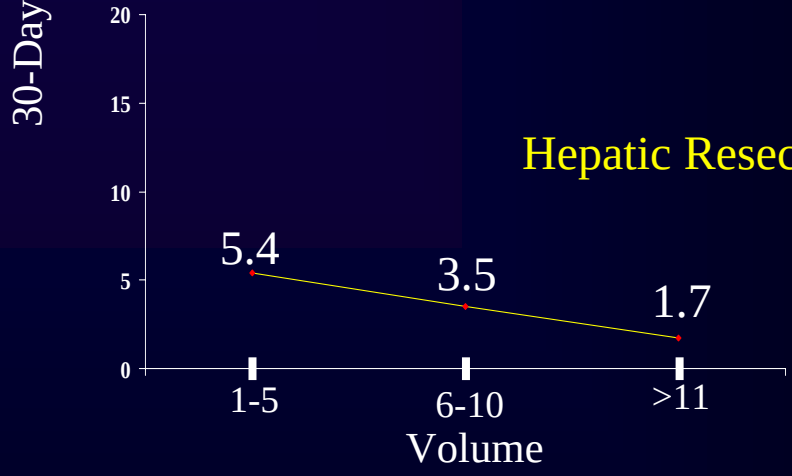
No. at Risk			
Combined therapy	206	123	26
Radiotherapy	210	108	24

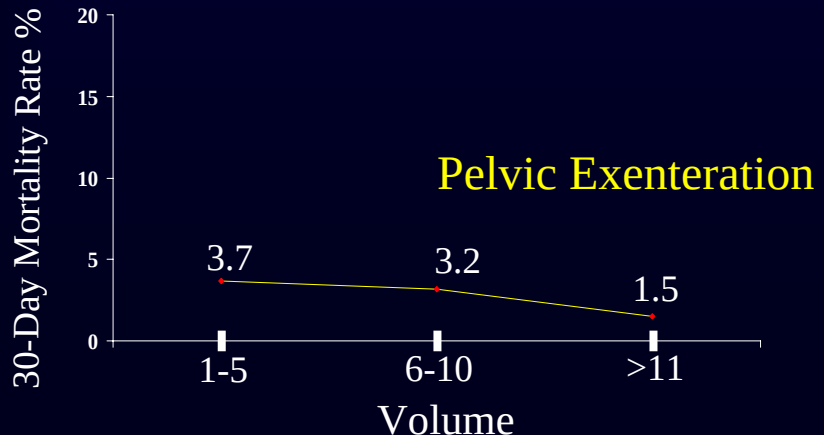
Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamour-Cell Carcinoma of the Head & Neck

JS Cooper, TF Pajak, AA Forastiere, et al
NEJM 2004, 350 (19) : 1937-44



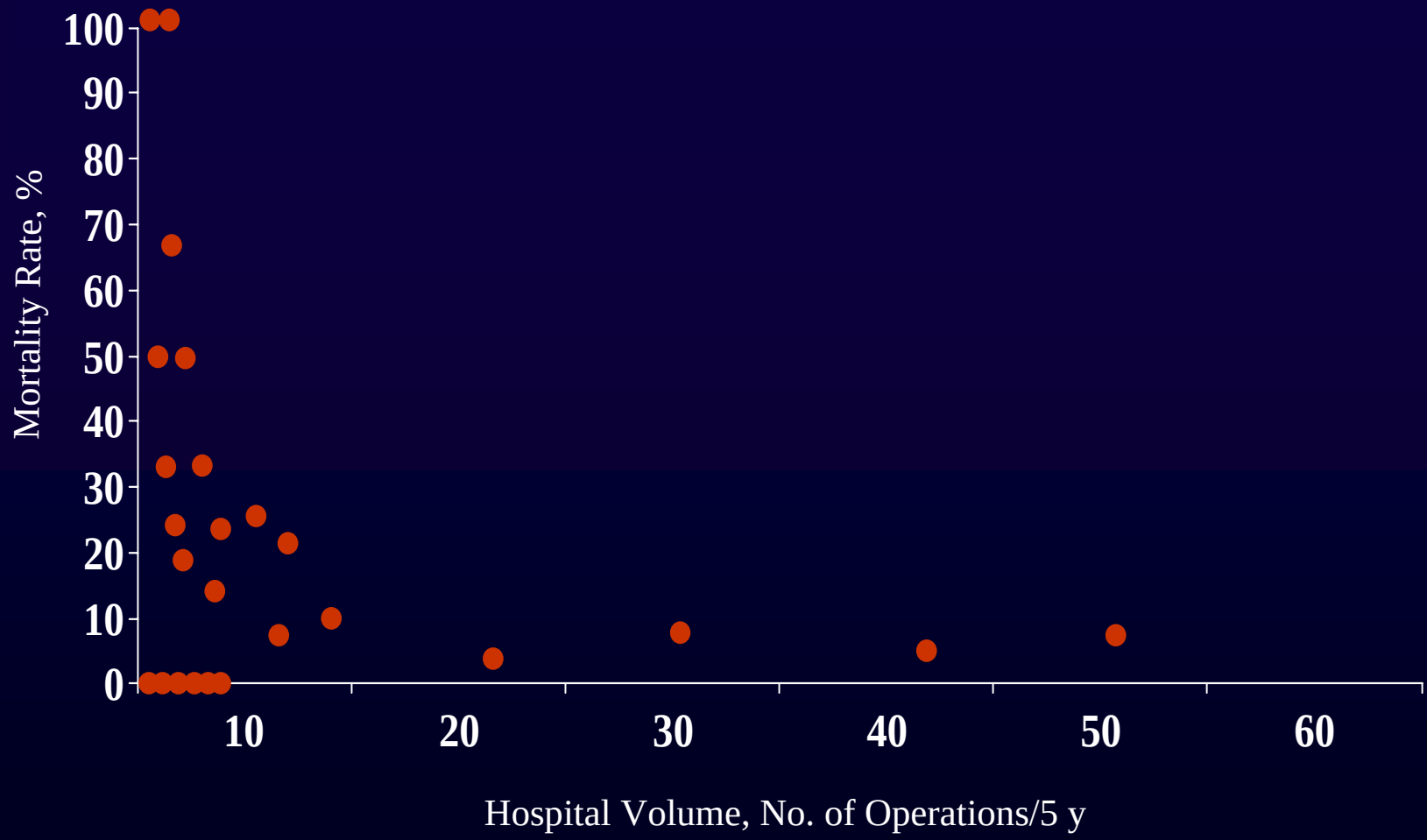






Impact of hospital volume on operative mortality for major cancer surgery. Begly CB, Cramer LD et al. JAMA Nov 25 1998, 280 (20) : 1747-51

Scatterplot Diagram of Hospital Volume Plotted Against Operative Mortality Rate

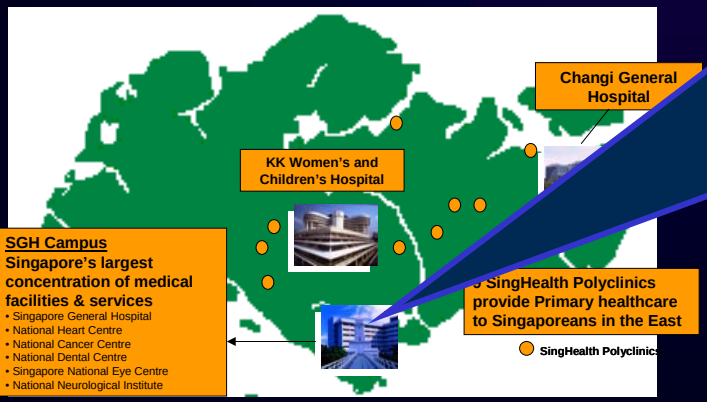


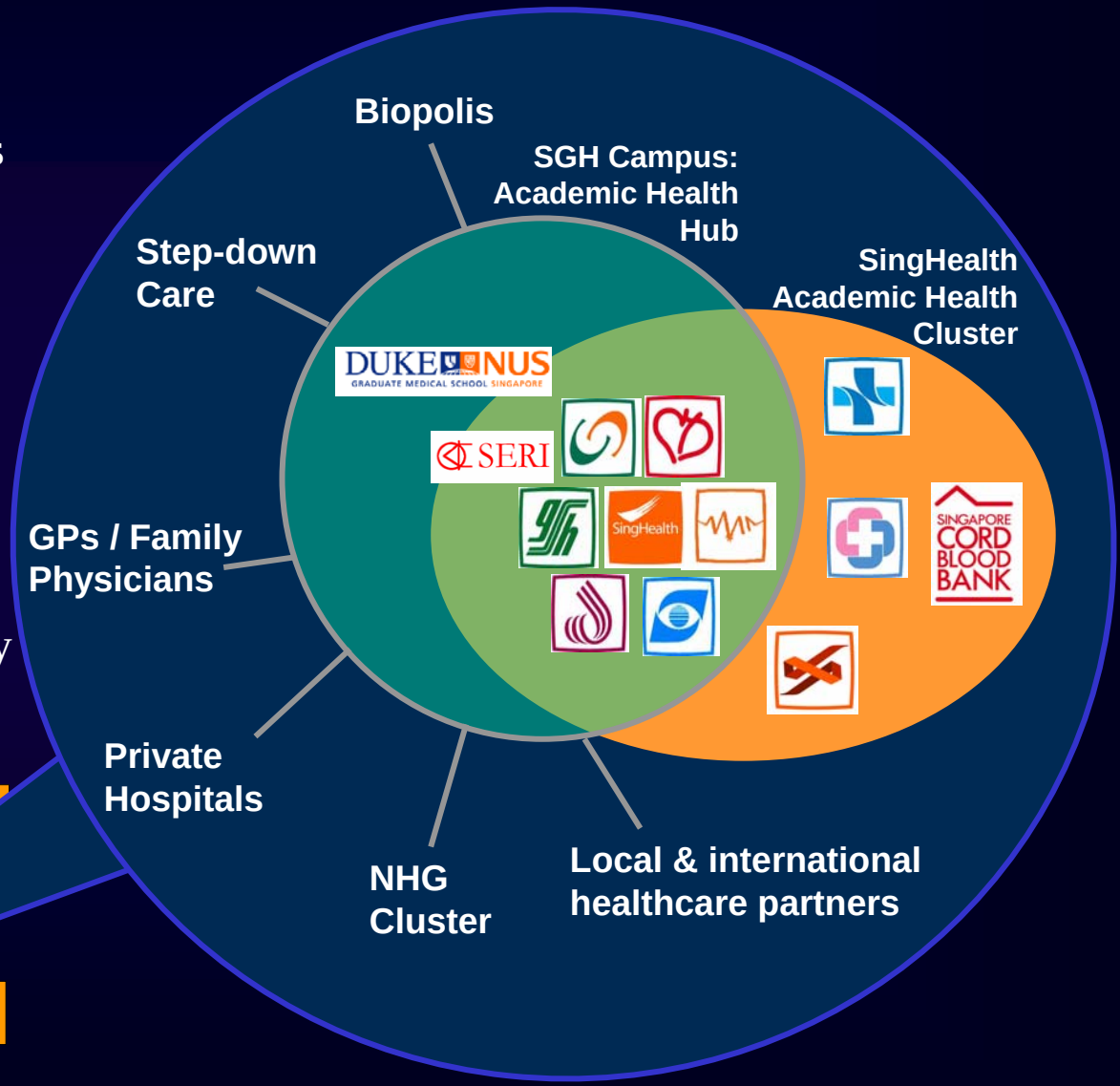
The Relationship between Hospital Volume and Outcomes of Hepatic Resection for Hepatocellular Carcinoma. Glasgow RE, Showstack JA, Katz PP. Arch Surg 1999, 134 : 30-35

- Academic Biomedical Centre
- Comprehensive Cancer Centre
- Institutional home for the highly trained
- Career pathway for clinician scientists
- Collaboration with basic scientists
- Comprehensive IT network and Databased Electronic Medical Records
- Asian Pacific Cancer Network

• Academic Biomedical Centre

3 hospitals
5 national Specialty Centres
3,400 beds
42 specialties
2,000 doctors
3 million patient visits per year
175,000 surgeries per year
51% of all day surgeries in Singapore
… and a network of primary healthcare clinics





- Academic Biomedical Centre
- **Comprehensive Cancer Centre**

- The nation's institutional home for cancer experts
- Holistic range of cancer specialties
- Training for renewal
- System to allow for multidisciplinary approach to cancer management
- Quality yet affordable cancer care

- Academic Biomedical Centre
- Comprehensive Cancer Centre
- **Institutional home for the highly trained**
- **Career pathway for clinician scientists**

NCC/SGH MANPOWER DEVELOPMENT

Clinicians	Department	Academic Pursuits
Philip Karuman FRCS	Surgical Oncology	PhD Harvard University
Susan Loong FFR	Therapeutic Radiology	MD Edinburgh University
Lucien Ooi FRCS	Surgical Oncology	MD NUS
Ho Gay Hui	Surgical Oncology	MD NUS
Tan Hiang Khoon FRCS	Surgical Oncology	PhD Bristol University
Chan Ching Wan FRCS	Surgical Oncology	PhD Bristol University
Ong Kong Wee MBBS	Surgical Oncology	PhD Bristol University
Gopel Iyer MBBS (Hons)	Surgical Oncology	PhD Cambridge University
Pierce Chow FRCS	General Surgery	PhD NUS
Goh Yaw Chong FRCS	General Surgery	PhD Edinburgh
Matthew Sebastian	General Surgery	MD candidate NUS

Training Clinicians in BioInformatics :

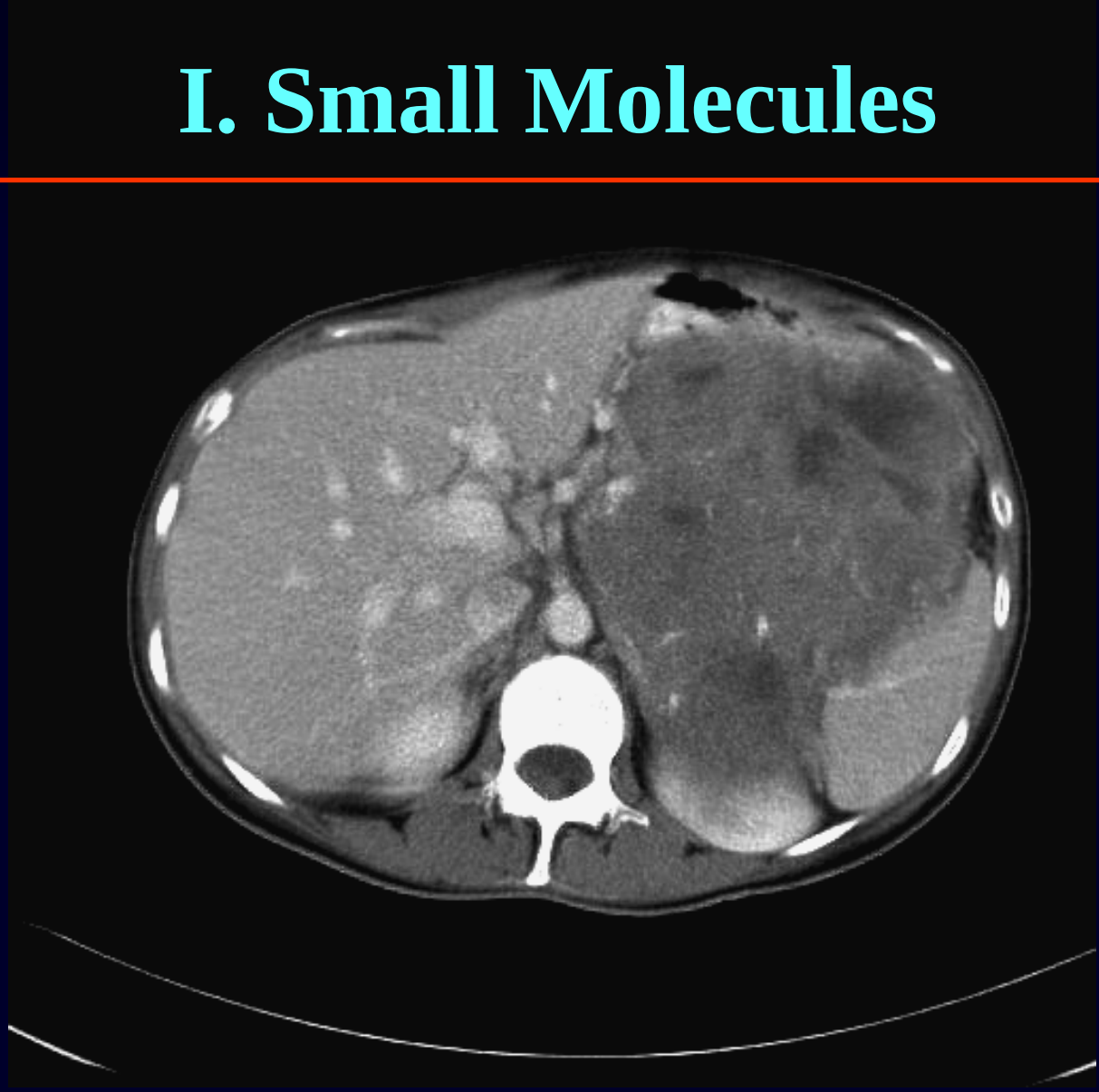
Clinicians	Department	Institution
Benjamin Chua MBBS	Surgical Oncology	MSc Duke University
Victor Lee MRCS	Surgical Oncology	MSc candidate NTU

- Academic Biomedical Centre
- Comprehensive Cancer Centre
- Institutional home for the highly trained
- Career pathway for clinician scientists
- **Collaboration with basic scientists**

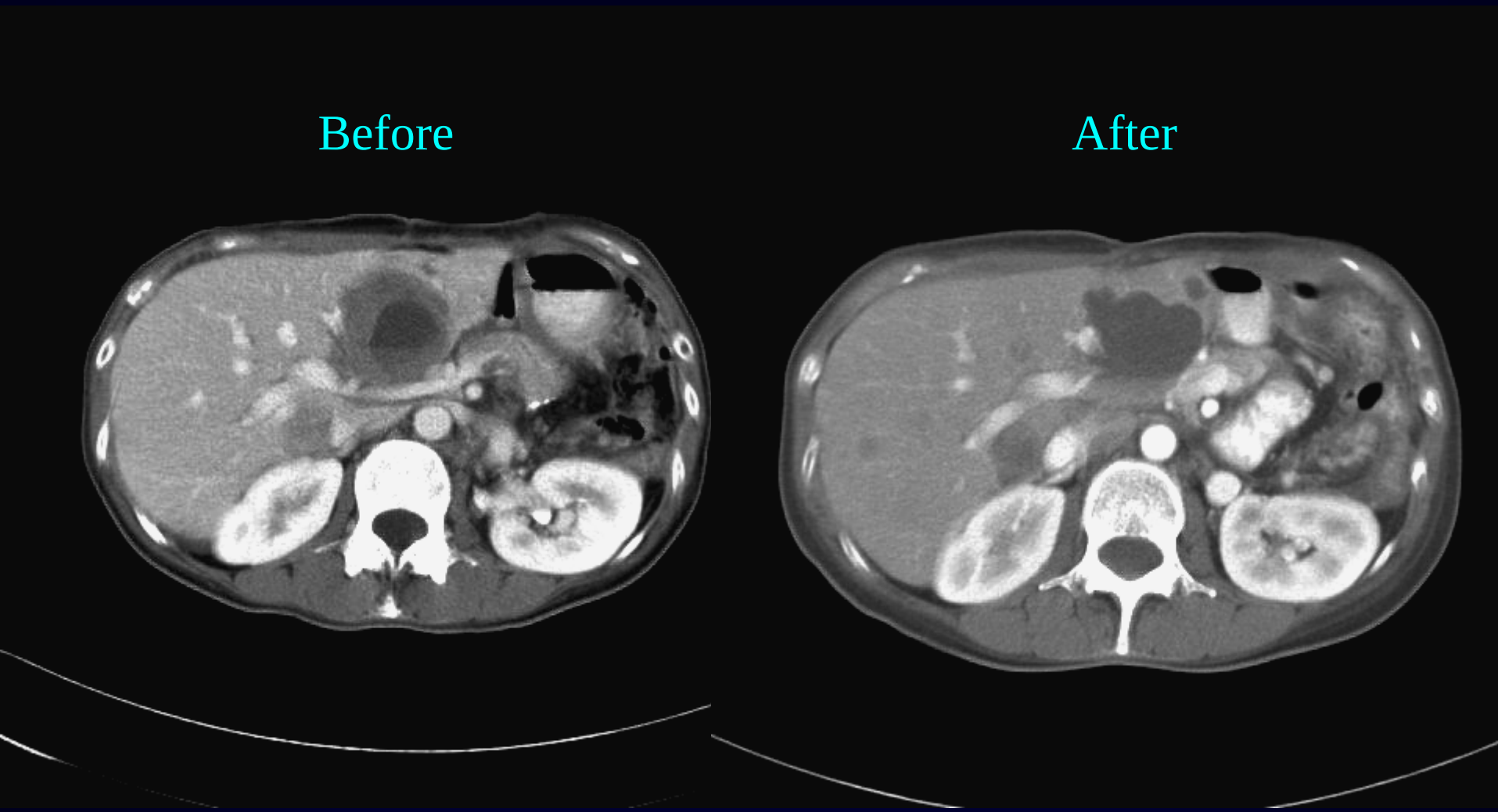
Targeted Cancer Therapies

- Small molecules against biological targets
- Biomarkers to predict tumour aggressiveness and recurrence
- Molecular diagnosis to augment histopathology
- Targeted therapy using xenografts
- Intra-tumoural targeting
- Photodynamic immunotherapy

I. Small Molecules



42 year old female with indigestion, heartburn and indigestion



Commenced on Glivec (Imatinib Mesylate) therapy

Phase III Dose Randomised Study of Imatinib for GIST: Intergroup S0033 Early Results

"Confirming its extraordinary anti-tumour activity in patients with metastatic GIST".

II. Molecular Biomarkers

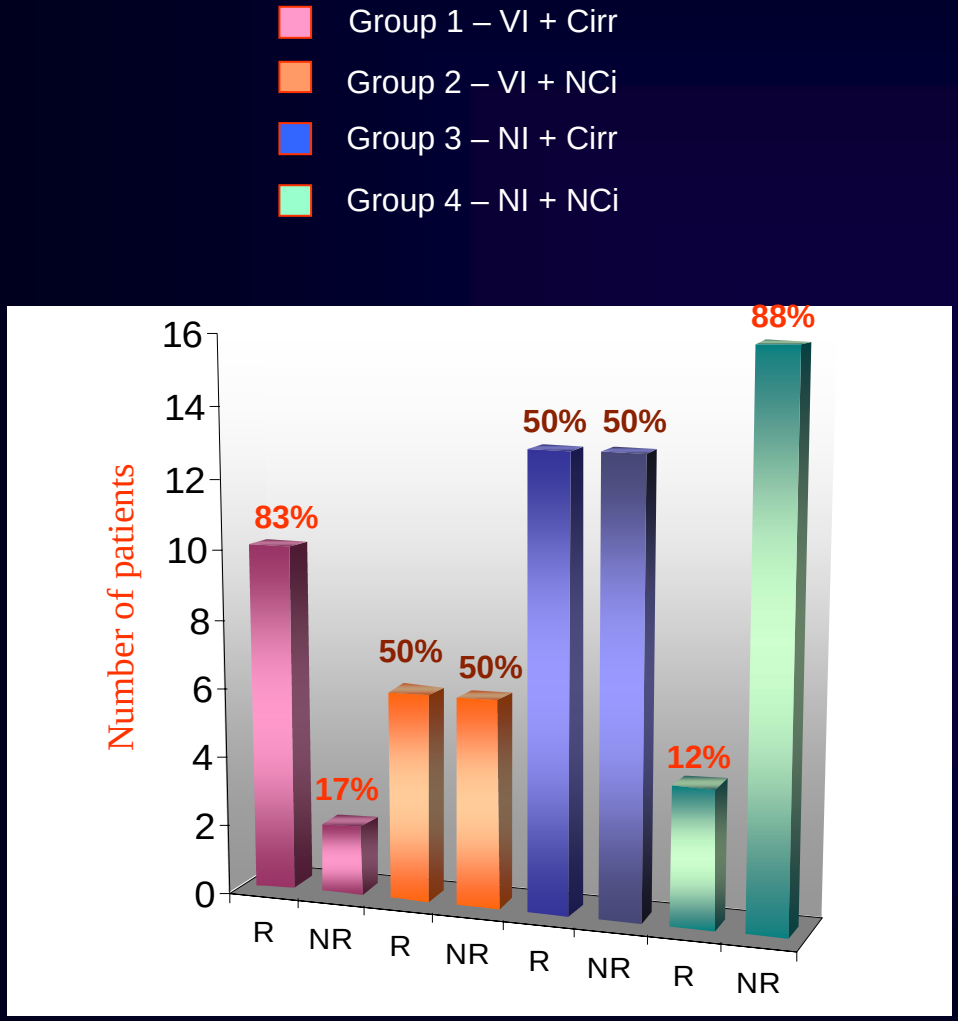
Clinical Problem

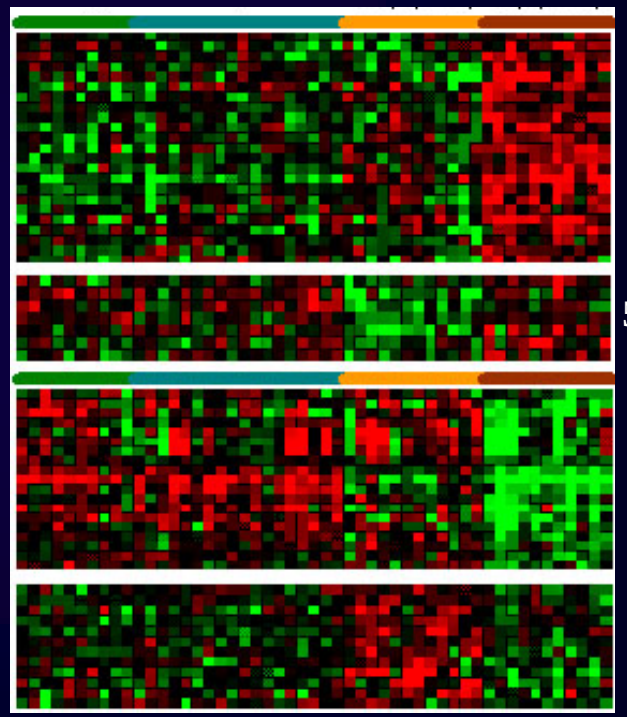
High risk of recurrence after resection of Hepato-cellular carcinomas

- 40% - 1st year
- 80% - lifelong

Hui KM, et al. Clinical Cancer Research (under revision)

By combining conventional prognostic markers and molecular signatures, we could predict the recurrent HCC for up to 88% accuracy.





57 genes

Comparison With Known Signatures?

	Lee et al., Hepatol 2004	Ye et al., Nat Med 2003	Lizuka et al., Lancet 2003	Kurokawa et al., J Hepatol 2004
Aim	Prediction of long- & short term survival of patient after partial hepatectomy	Prediction of HCC with and without intrahepatic metastasis	Prediction of early IHR within 1 year after hepatectomy and non-recurrence	Prediction of early IHR within 2 year after Hepatectomy and non-recurrence
Microarray	Oligonucleotide (21329 genes)	cDNA microarray (9180 genes)	Oligonucleotide array (7070 genes)	PCR-based array (3072 genes)
Sample	Total 91 primary HCC; 56 HBV +ve; 45 with liver cirrhosis	Total 40 primary HCC; all HBV +ve	Total 60 primary HCC; 40 HCV +ve; 36 with liver cirrhosis	Total 100 primary HCC; Training set has 41 HCV +ve & 33 with liver cirrhosis
Study design	45 training samples; 44 independent set	20 training samples; 20 independent set	33 training samples; 27 independent set	60 training samples; 40 independent set
Algorithm	5 type predictors with **406 genes**	Compound covariate predictor with **153 genes**	Fisher linear classifier with **12 genes**	Weighted voting with **20 genes**
Predictive accuracy	P=0.008-0.036	17 of 20 (85%)	25 of 27 (93%)	29 of 40 (73%)
Train: Test:	20R vs 22NR 10R vs 13NR	20R vs 22NR 10R vs 13NR	15R vs 22NR 10R vs 13 NR	18R vs 22NR 10R vs 13NR
Prediction accuracy in our database	**65%** (50%, 77%)	**57%** (80%, 39%)	**61%** (70%, 54%)	**48%** (30%, 62%)

III. Molecular Diagnosis

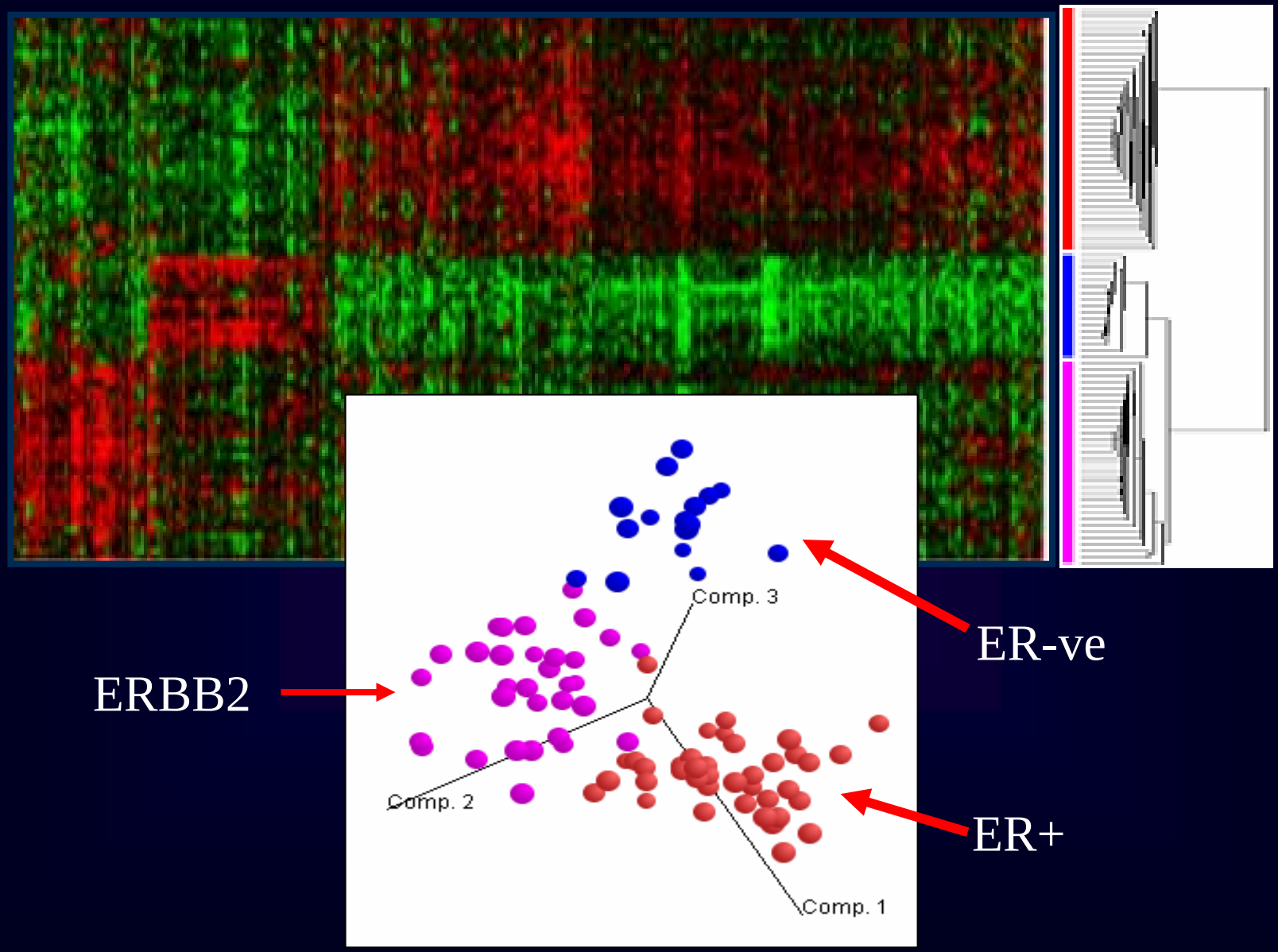
Clinical Problem

Herceptin as adjuvant in early and advanced breast cancer

- Useful only in ERB B2 positive tumours
- Heart failure in 1 – 5% of treated patients
- High cost of therapy

Challenge

Use of robust molecular diagnostics to augment histopathology and immuno-histo chemistry


Comp. 3
Comp. 2
Comp. 1
ERBB2
ER-ve
ER+

Clinical Staging Systems and Gene Expression Surrogates

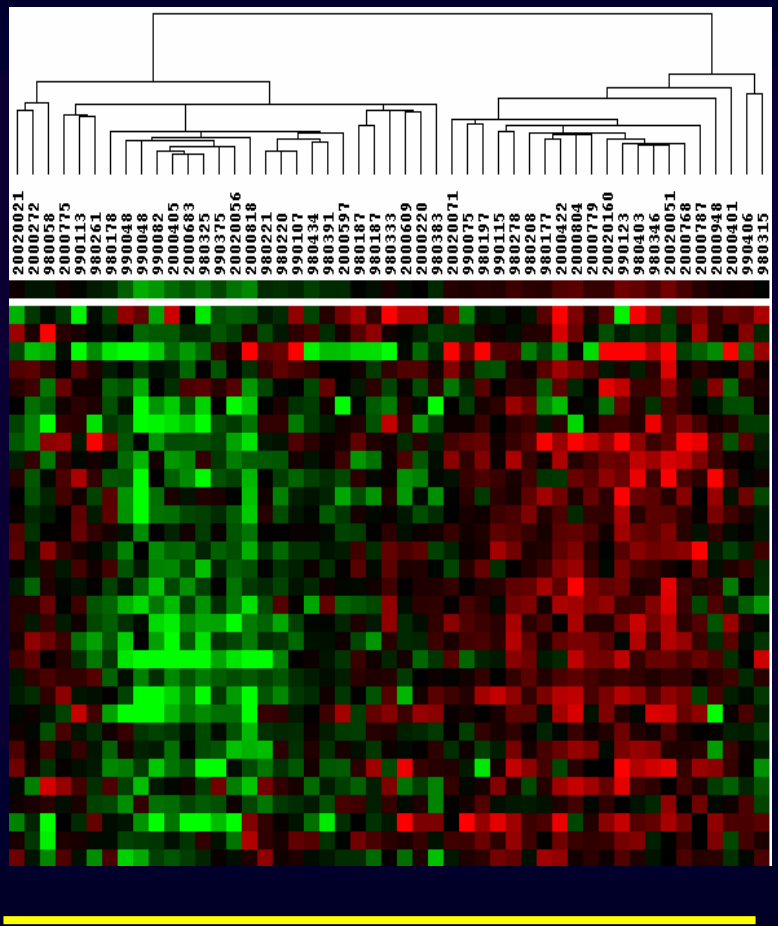
The Nottingham Prognostic Index : Tumor Size + Lymph Node Status + Tumor Grade

Categories : Good (NPI<3.4), Moderate (3.4-5.4), Poor (>5.4)

Challenges : Inter-observer variability
Cut-off Points

Low NPI

High NPI



B

C

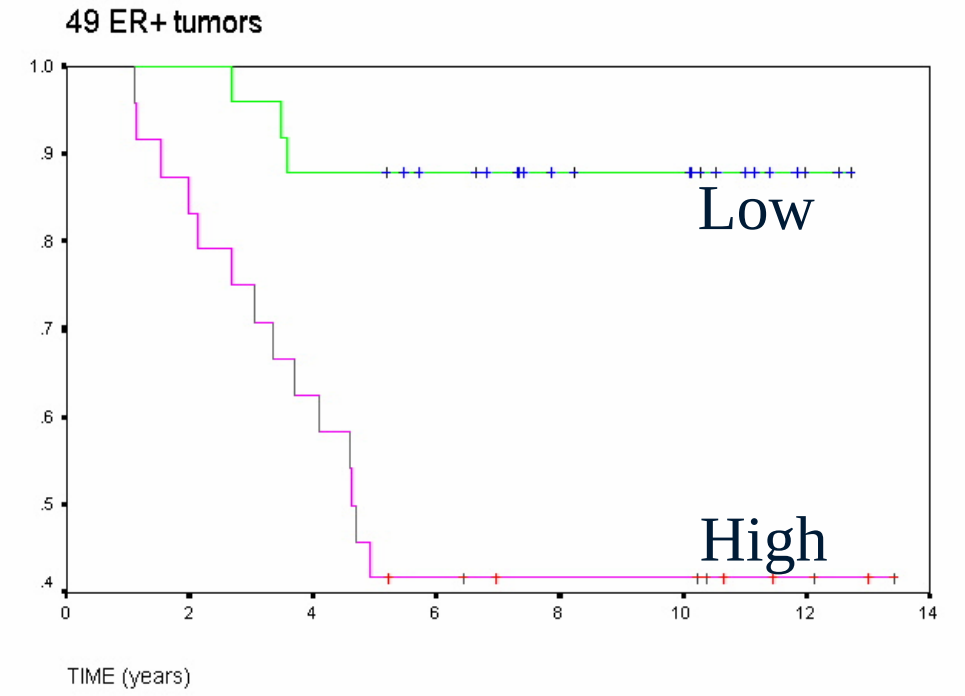
D

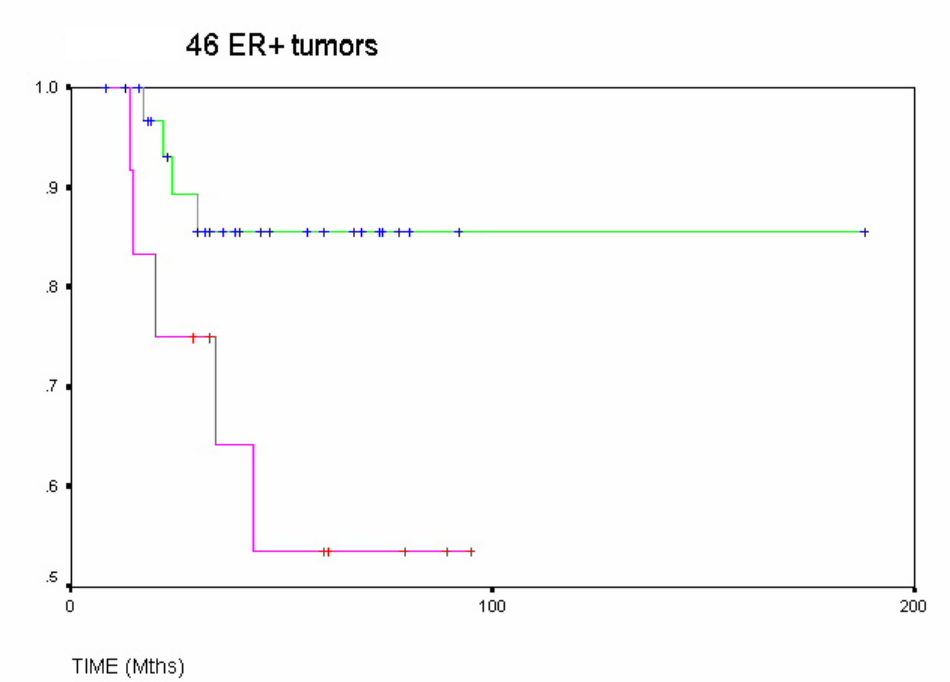
E

NPI Expression Signature

ER+ Samples

Clinical Significance of the NPI-ES (Retrospective)





Disease-Free Survival
Independent Set 1 ($p<0.001$)

Overall Survival
Independent Set 2 ($p<0.05$)

Low NPI-ES

High NPI-ES

Yu et al (2004) *Cancer Research* 64, 2962

IV. Targeted Therapy Using Xenografts

Clinical Problem

- Low response rate to chemotherapy for most solid tumours
- Need for in vivo model of response

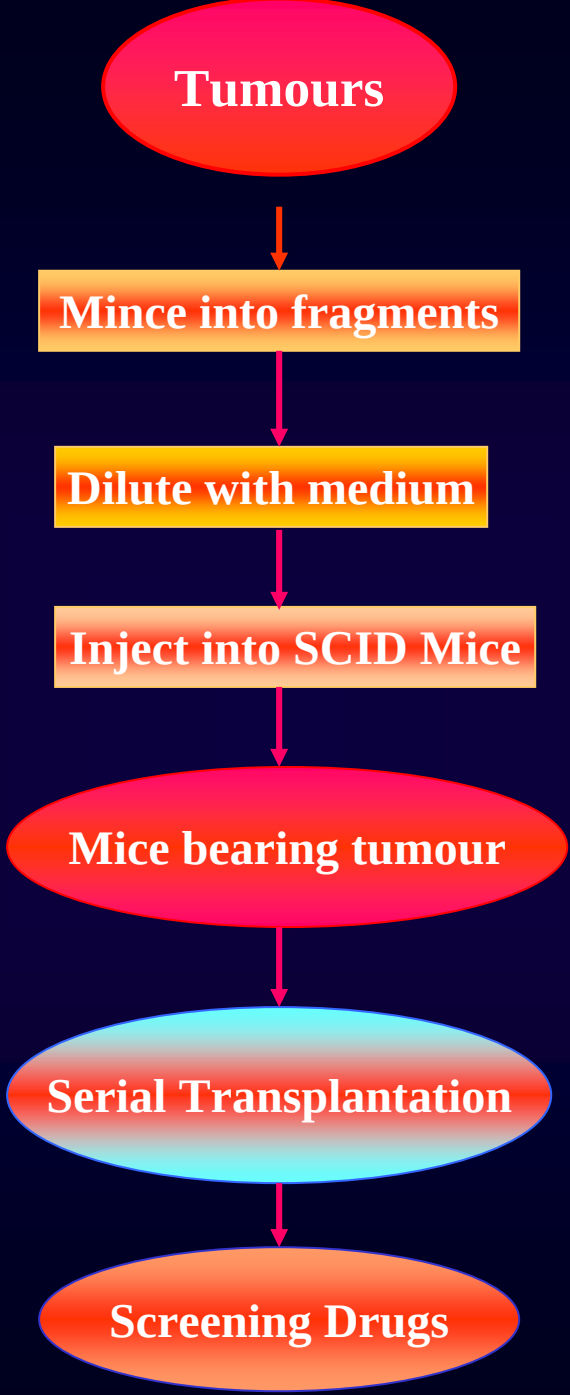
Xenografts of human solid tumors: A tool for screening drugs and molecular targeted therapy

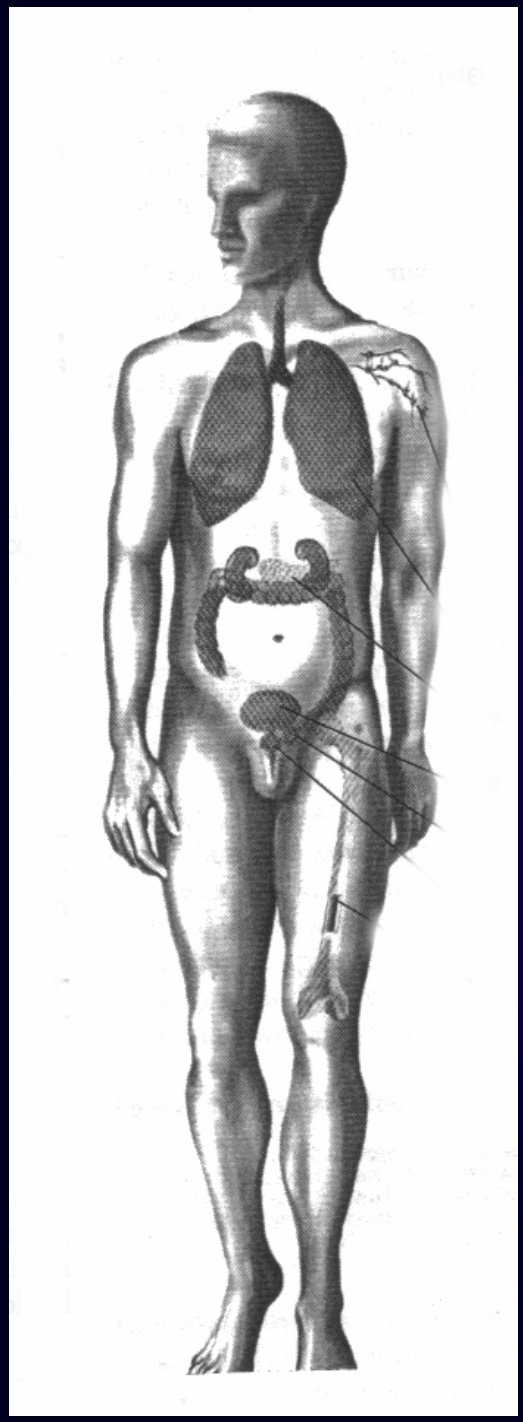
A/Prof. Hung Huynh

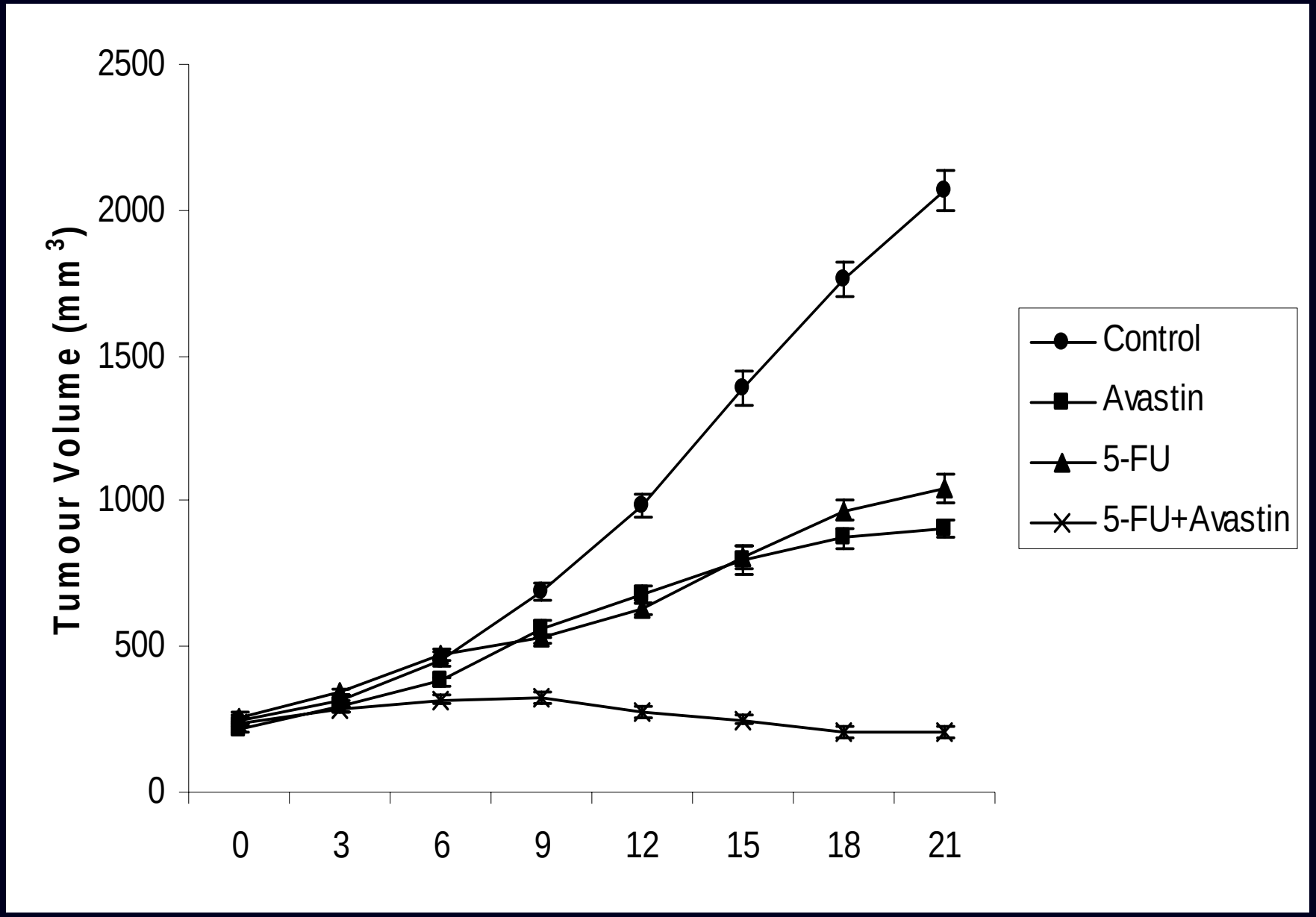
Laboratory of Molecular Endocrinology

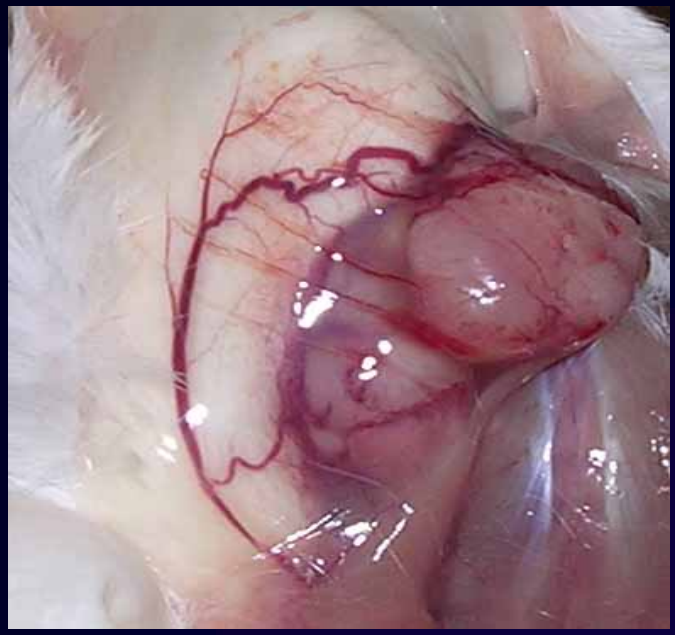
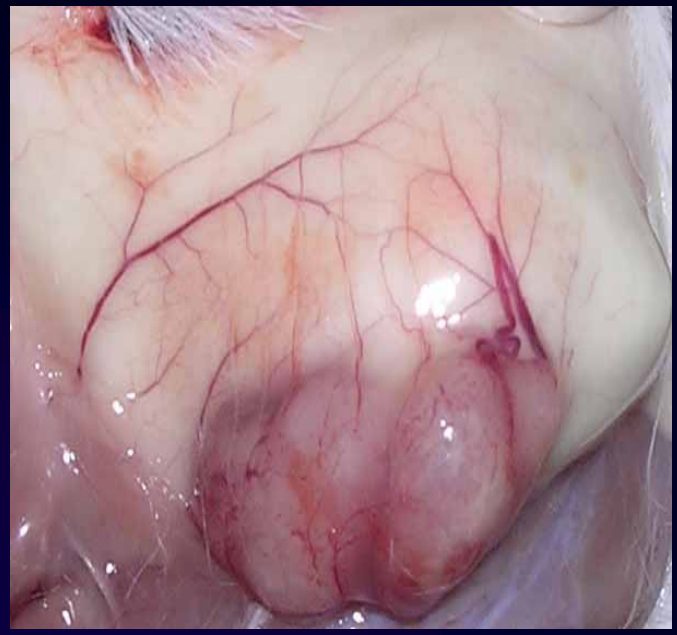
Division of Cellular and Molecular Research

National Cancer Centre


Tumours
Mince into fragments
Dilute with medium
Inject into SCID Mice
Mice bearing tumour
Serial Transplantation
Screening Drugs




2500
2000
1500
1000
500
0
Tumour Volume (mm3)
0
3
6
9
12
15
18
21
Control
Avastin
5-FU
5-FU+Avastin

- We have successfully established and characterized a series of primary human HCC, oral cancer, NK, metastatic CRC, prostate cancer, tongue cancer, GIST, breast cancer which have grown in SCID mice to allow serial transplantation.

- These primary Xenografts are useful for:
  1 - Screening preclinical drugs used in treatment and/or prevention of the disease.
  2 - Improving our current treatment.
  3 - Molecular targeted therapy.

- Establishment of xenografts from primary tumors may also allow individualized therapy to be carried out.

V. Intratumoral Targeting

Non-surgical ablative techniques for HCC

- Extreme temperature changes (cryosurgery, RFA)
- Pharmacologic/biochemical (chemoembolisation, ethanol)
- Radionuclide therapy (intra-arterial, intra-tumoural)

^{32}P BioSilicon (BrachySil ®)

Favourable properties for intra-tumoural brachytherapy:

High-energy beta emission, intermediate half-life.

Carrier particles are biologically inert.

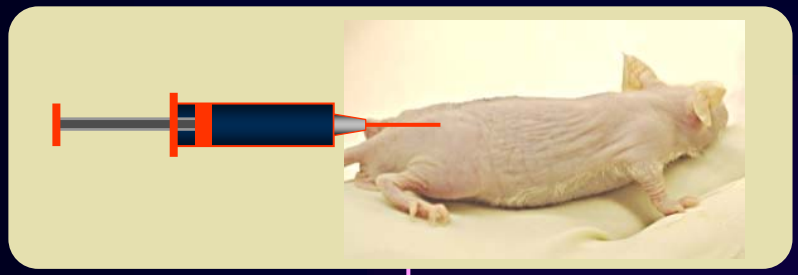
High mechanical stability, resistant to breakdown.

Chemical stability

Uniform size range

Pre-clinical study in mice

In vitro culture of human tumour cells
(HepG2 pancreatic adenoCa)



Implantation of cultured tumour cells to nude mice (5 x 10^5 cells/mouse)

14 days

5 – 8 mm Ø tumours

Intra-tumoural injection of ^{32}P BioSilicon

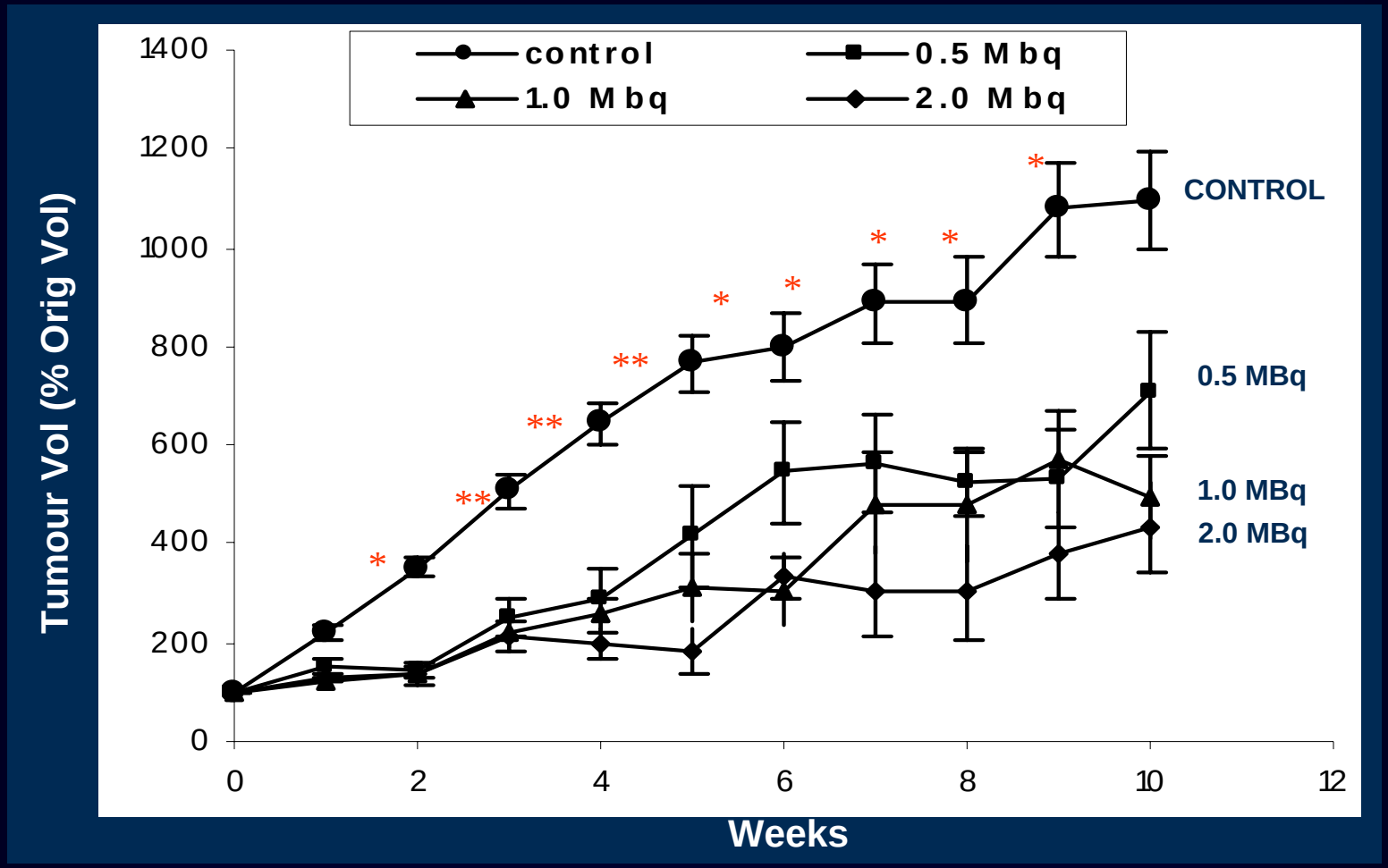
Controls,
0.5, 1.0 and 2.0 MBq

^{32}P activity in blood, liver, & tumour

Histological studies

Tumour volumetrics

^{32}P BioSilicon Effect on growth of liver cancer xenografts



Points are mean±SEM/2

* compared to ^{32}P-biosilicon treated groups $p< 0.05$

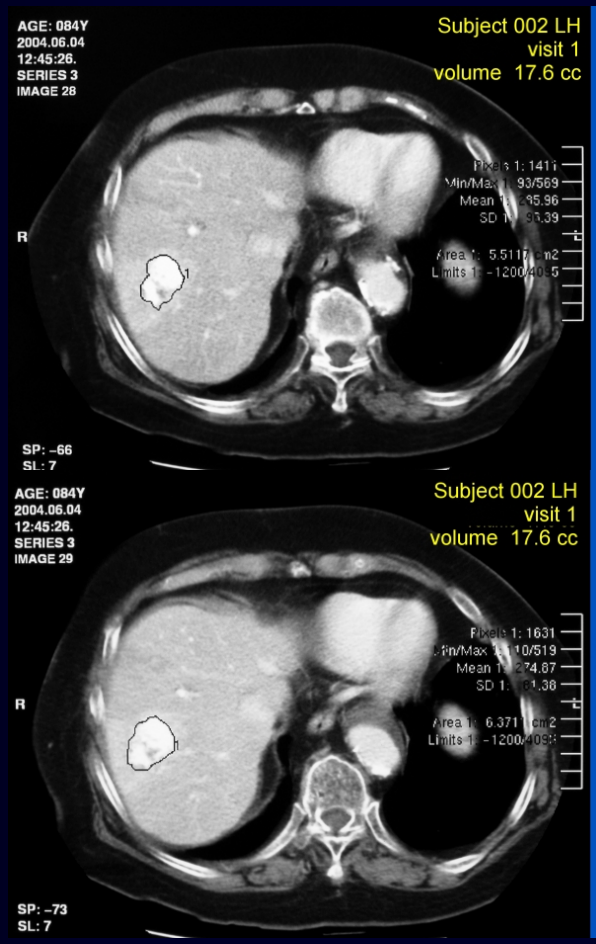
** compared to ^{32}P-biosilicon treated groups $p< 0.01$

Pre-clinical study in large animal model

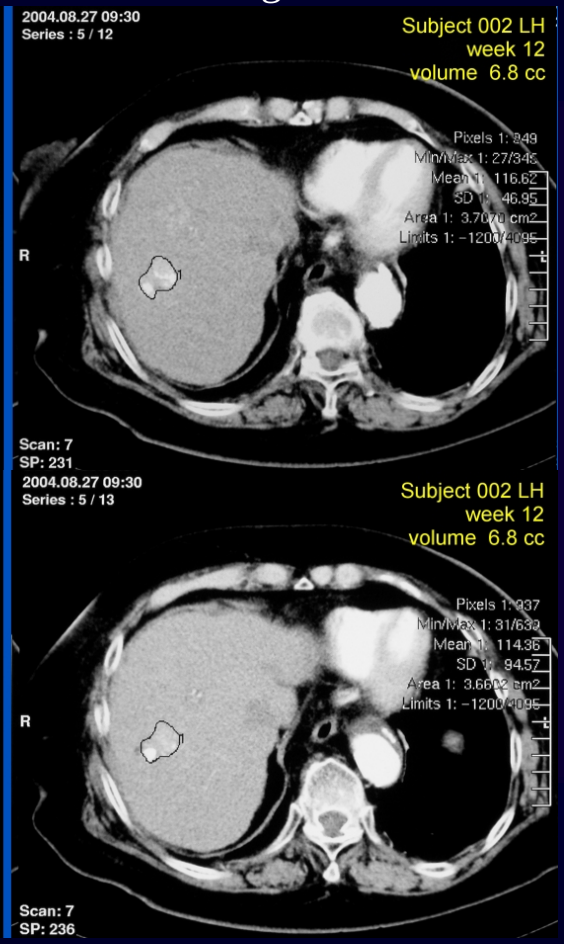
- Ultrasound-guided percutaneous intra-hepatic injection of ^{32}P-BioSilicon in 75-95 kg pigs
- Experienced interventional radiologist
- Assisted by nuclear physician, radiopharmacist, & physicist

Results – tumour regression

4 Jun 2004



27 Aug 2004



All target lesions showed reduction in tumour volumes by 11-100% at week 12, and further reduction was seen in 4 patients at week 24.

Conclusions

No significant toxicity or safety issues arose from ^{32}P BioSilicon implantation.

The technique appears safe in comparison with RFA or TACE. Minimal patient discomfort or pain.

No technical difficulties encountered:
^{32}P dose preparation by nuclear med staff, or
^{32}P administration by interventional radiologist.

All targeted lesions showed a decrease in tumour size, but further follow-up is required.

PDT for Recurrent Angiosarcoma

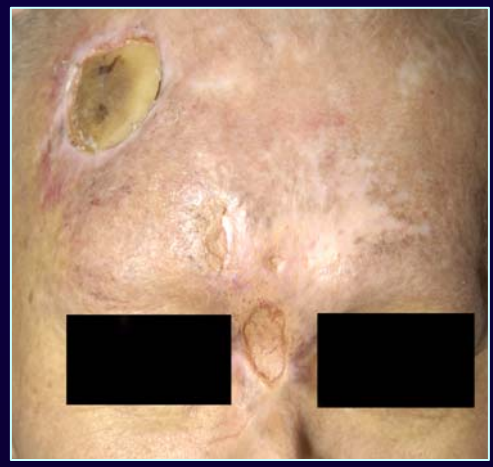
- Subject: Elderly male with multi-focal angiosarcoma
- Previously treated with radiotherapy
- Recurrence within one year

48 h and 1 month post-PDT

48 h – necrosis

1 month – healing

6- and 12 months post-PDT



6 months – soft tissue healed

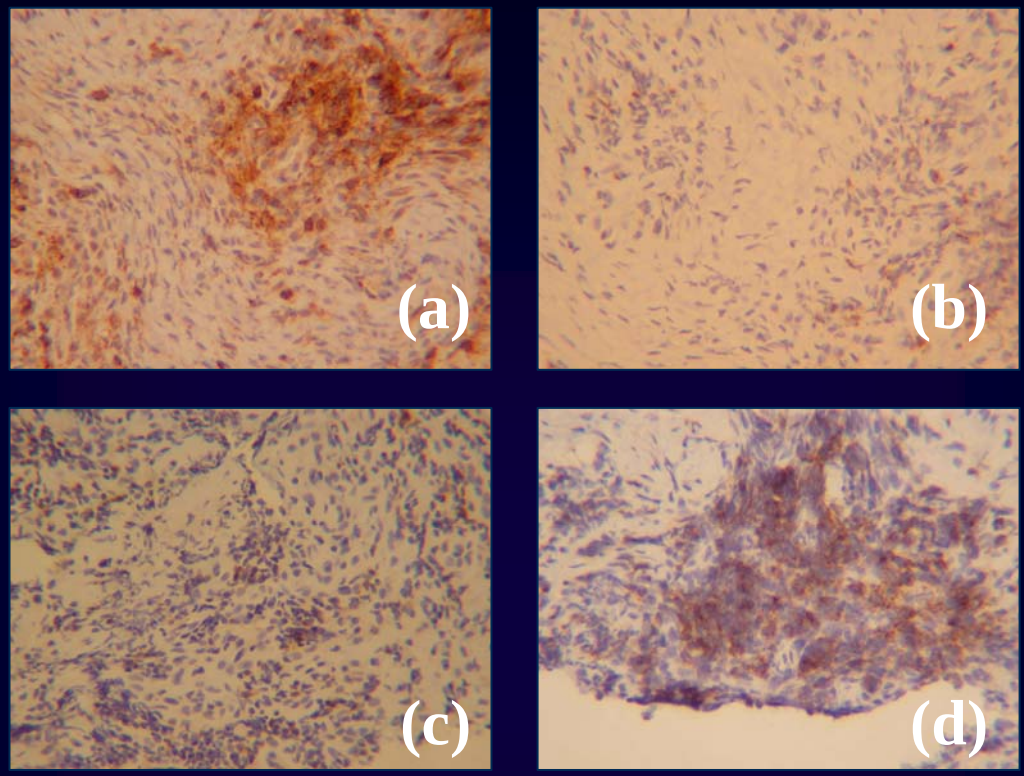
12 months – local control

(a) Angiosarcoma on right upper limb with main cluster (circled) before PDT.

(b) Scarring at PDT treated site as well as spontaneous regression of untreated lesions on right upper limb 2 months post-PDT.

(c) Lesions on left upper limb before PDT.

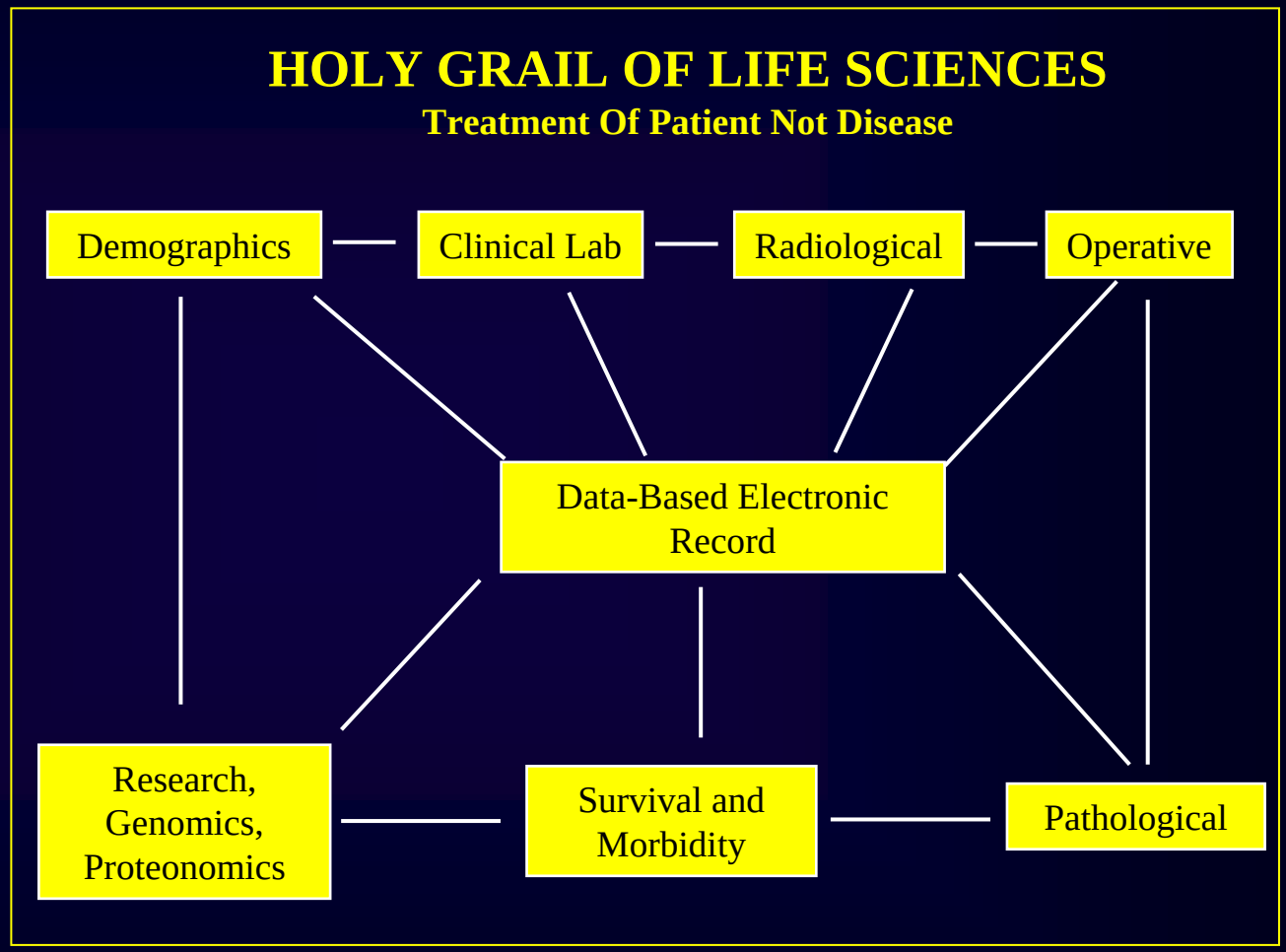
(d) Spontaneous regression of untreated lesions on left upper limb 4 months after PDT.

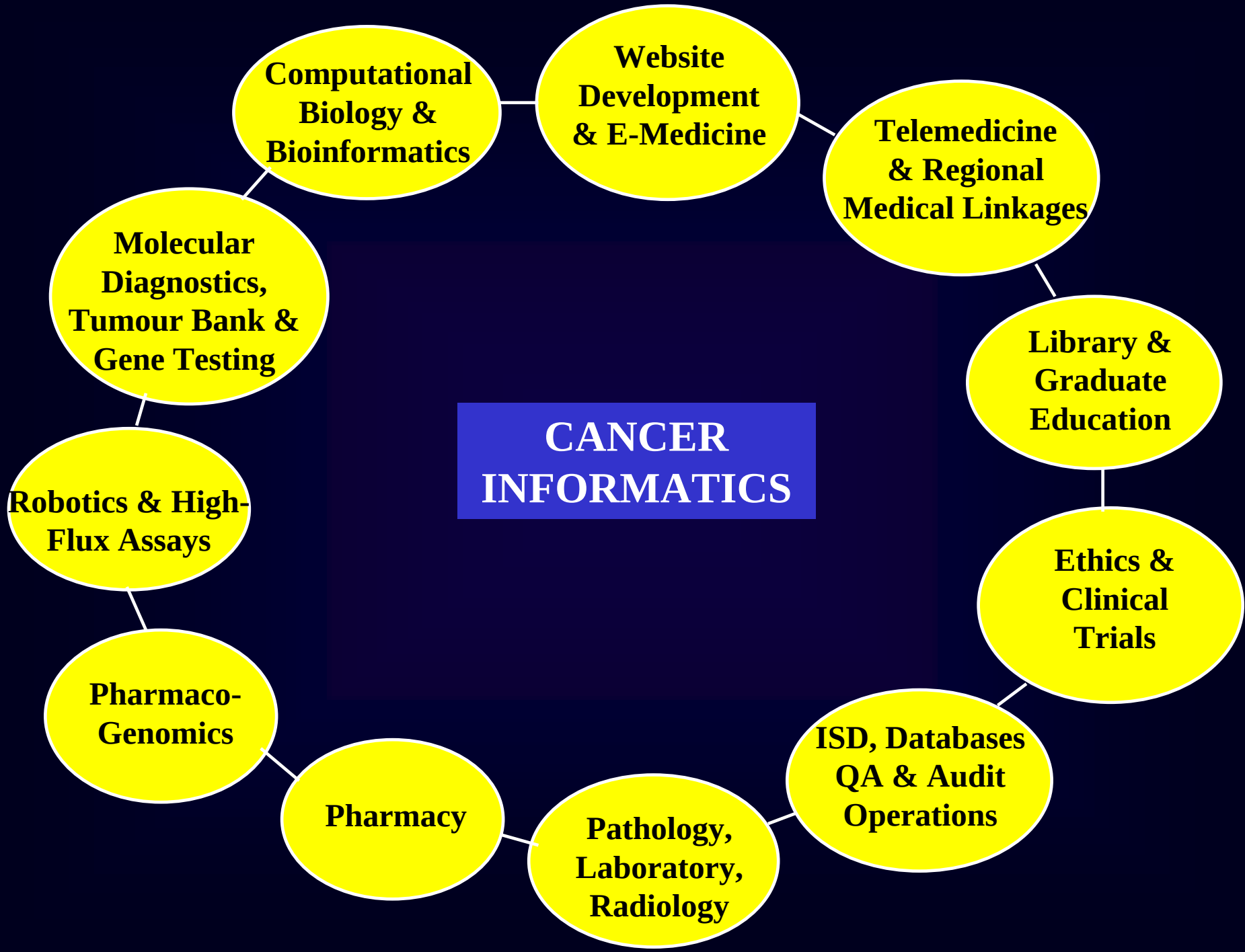


Biopsy from right occiput showing heavy CD4+ T cell infiltrate 48 h after PDT (a; mag x 100), with few CD8+ T cells found (b; mag x 100). Repeat biopsy of the same site one month after PDT was negative for CD4+ T cells (c; mag x 100), while staining strongly for CD8+ T cells (d; mag x 200).

PSP Thong, KW Ong, NSG Goh, KW Kho, V Manivasager, R Bhuvaneswari, M Olivo, KC Soo. ***Photodynamic-therapy-activated immune response against distant untreated tumours in recurrent angiosarcoma.*** Lancet Oncol 2007, 8 : 950–52

- Academic Biomedical Centre
- Comprehensive Cancer Centre
- Institutional home for the highly trained
- Career pathway for clinician scientists
- Collaboration with basic scientists
- **Comprehensive IT network and Databased Electronic Medical Records**




CANCER INFORMATICS
Computational Biology & Bioinformatics
Website Development & E-Medicine
Telemedicine & Regional Medical Linkages
Library & Graduate Education
Ethics & Clinical Trials
ISD, Databases QA & Audit Operations
Pathology, Laboratory, Radiology
Pharmacy
Pharmaco-Genomics
Robotics & High-Flux Assays
Molecular Diagnostics, Tumour Bank & Gene Testing

- Academic Biomedical Centre
- Comprehensive Cancer Centre
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- Career pathway for clinician scientists
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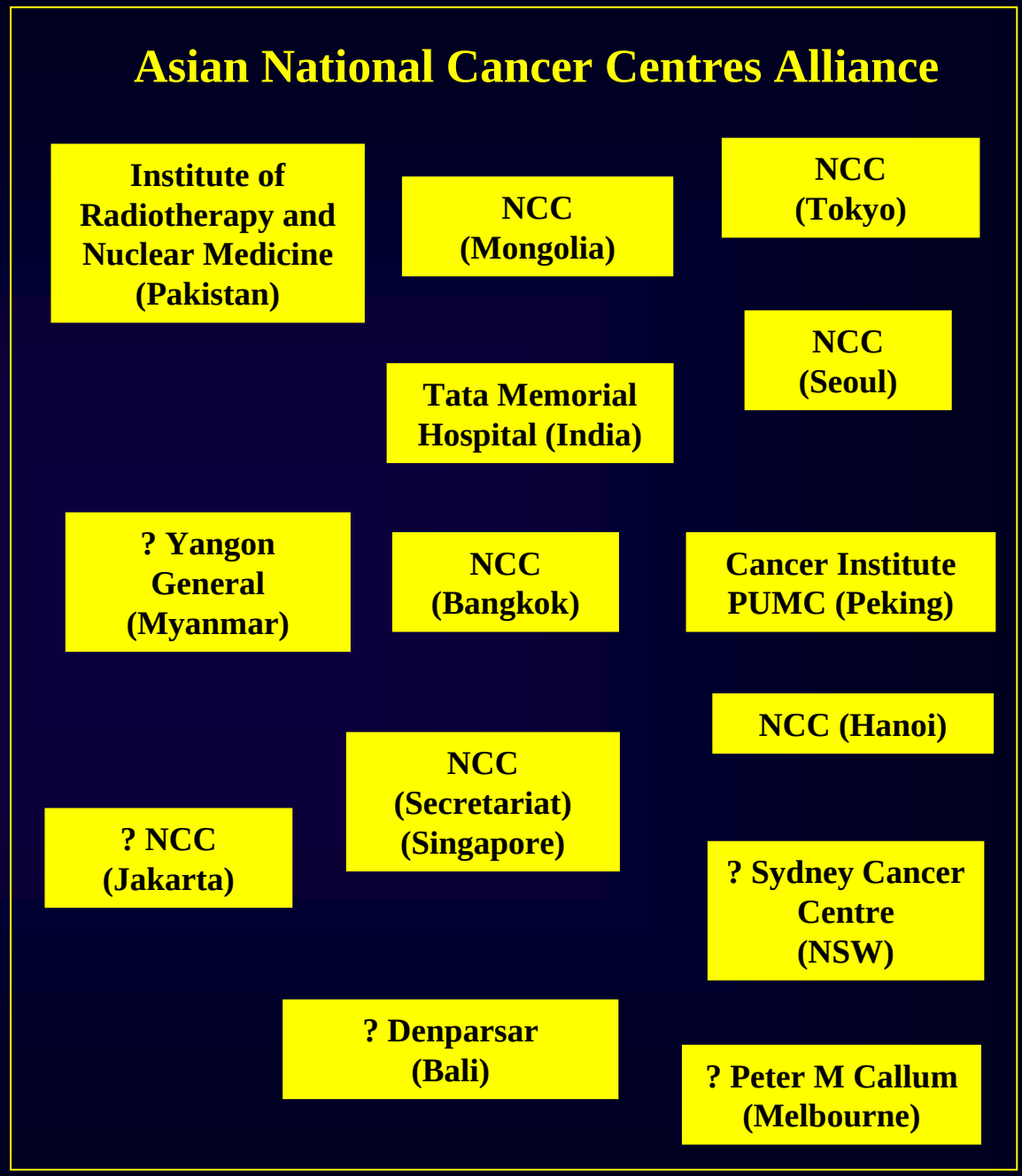
- Comprehensive IT network and Databased Electronic Medical Records
- **Asian Pacific Cancer Network**



- Fellowships for training of oncologists
- Visiting experts for centralised training
- Research collaboration and multi-institutional clinical trials