Cancer Treatment: What’s New?

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Content

• **Prognostication Tools**
  - Multigene Assays

• **Precision Medicine**
  - Immunotherapy

• **Person-alized Cancer Care**
  – Geriatric Oncology
Prognostication Tools

- Multi-gene Assays platforms → multivariate prediction models.
- Allows for **prognostication** for cancers and risk of cancer recurrence
- Aids in decision making process for adjuvant treatment – **predictive** for some
- Used in early stage **Breast Cancer**, Colon Cancer, Prostate Cancer
- **Oncotype DX**, MammaPrint/ColoPrint, Prosigna
Oncotype Dx (Breast CA)

- 21-gene assay to predict risk of distant recurrence
- 16 target genes + 5 housekeeping genes
- Calculates the likelihood of recurrence
- ER+ early stage breast cancers

**Proliferation**
- Ki67
- STK15
- Survivin
- CCNB1 (cyclin B1)
- MYBL2

**Invasion**
- MMP11 (stromolysin 3)
- CTSL2 (cathepsin L2)

**HER2**
- GRB7
- HER2

**Estrogen**
- ER
- PGR
- BCL2
- SCUBE2

**Reference**
- ACTB (β-actin)
- GAPDH
- RPLPO
- GUS
- TFRC

**GSTM1**
**CD68**
**BAG1**
NSABP-B14

• Panel of 21 genes in Oncotype DX

**Definitions**
- Low <18
- Intermediate 18-30
- High ≥ 31

**Conclusion**
- Prognostic in Tamoxifen-treated patients

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**Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Percentage of Patients</th>
<th>Rate of Distant Recurrence at 10 Yr (95% CI) †&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>Rate of Distant Recurrence at 10 Yr (95% CI) †&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>51</td>
<td>6.8 (4.0–9.6)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>22</td>
<td>14.3 (8.3–20.3)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>27</td>
<td>30.5 (23.6–37.4)</td>
<td></td>
</tr>
</tbody>
</table>

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**ER+/LN- ESBC randomised to tamoxifen vs obs**

**RT-PCR analysis performed in 668 of 2715 tamoxifen-treated patients (available paraffin blocks)**

Paik NEJM 2004; 351: 2817
NSABP-B20

Paik JCO 2006; 24: 3726

- ER+/LN- ESBC randomised to tamoxifen vs tamoxifen + CMF/MF
- Tumour blocks available for 651
  - 227 received tamoxifen alone
  - 424 received tam + chemo
- Percentage in each category
  - Low <18 (54%)
  - Intermediate 18-30 (21%)
  - High ≥ 31 (25%)

- Conclusions
  - High-risk benefit but low-risk do not; intermediate -risk inconclusive due to wide CI
INT-0100

- ER+/LN+ post-menopausal Tamoxifen vs Tamoxifen + CAF
- Tumour blocks available for 367
  - 148 received tamoxifen alone
  - 219 received tam + CAF
- Percentage in each category
  - Low <18 (40%)
  - Intermediate 18-30 (28%)
  - High ≥ 31 (32%)
- Conclusions
  - Oncotype DX prognostic in this subgroup of patients
- Oncotype DX again predictive of chemotherapy benefit in high-risk but not low-risk patients
Who is cured by surgery alone and therefore need no systemic adjuvant therapy?

Which ER positive cancers are cured with surgery and adjuvant endocrine therapy and therefore need no systemic chemotherapy?

Which cancers are not cured with surgery endocrine therapy and adjuvant chemotherapy and therefore remain high risk despite current best multimodality therapy? (these patients should be the prime candidates for clinical trials and drug development)

Diagnosis

Primary risk prediction

tumor size, nodal status, grade, ER, HER2, Adjuvant Online,

Secondary risk prediction

Oncotype Dx, Prosigna, EndoPredict, GGI, MammaPrint, BCI, etc.

Tertiary risk prediction

ACES (ref 29), more to come...
# Budget Impact Study Results

**Oncotype DX® budget impact studies**

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost Impact</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Cost saving of CAD 34.5 million</td>
<td>Oncotype DX® is cost saving driven by reduced chemotherapy drug costs</td>
</tr>
<tr>
<td>Hassan et al, 2011</td>
<td></td>
<td>Versus current practice: adoption of Oncotype DX® is approximately cost neutral</td>
</tr>
<tr>
<td>Ireland</td>
<td>0.4% increase in direct cost</td>
<td>47% probability of being cost saving</td>
</tr>
<tr>
<td>Lacey et al 2010</td>
<td></td>
<td>Main driver was reduction in chemotherapy expenditure</td>
</tr>
<tr>
<td>Canada and USA</td>
<td>Cost saving of USD 330.8 Million in USA</td>
<td>Oncotype DX® is cost saving in both USA and Canada</td>
</tr>
<tr>
<td>Ragaz et al 2011</td>
<td>Cost saving of USD 46.2 Million in Canada</td>
<td>Cost savings are driven by reduced expenditure on chemotherapy</td>
</tr>
<tr>
<td>Ireland</td>
<td>EUR 666,844 cost saving if chemotherapy only given to high risk patients, over the 140 patients included in this analysis</td>
<td>Versus current practice: Oncotype DX® will result in cost-savings in European health systems</td>
</tr>
<tr>
<td>Wilson et al, 2010</td>
<td></td>
<td>Only the cost of chemotherapy and the assay were included in this analysis</td>
</tr>
</tbody>
</table>
Conclusion

• Oncotype Dx
  - Stage I-II ER+ breast CA
• Prognostication tool to help with making an informed decision about role of adjuvant treatment
• Cost considerations and effectiveness
• Discussions must be held with oncologist before ordering the test.
IMMUNOTHERAPY
Cancer Immunotherapy
Former President Jimmy Carter’s announcement earlier this week that he is free of the melanoma that had spread to his liver and brain may be the highest-profile example yet of the promise of a new form of cancer treatment that unleashes an immune system attack on the disease.

Carter, 91, was treated with radiation therapy and the drug pembrolizumab (Keytruda), which releases a biological “brake” that can prevent the immune system from besieging and destroying tumor cells. Although doctors cannot be certain that the treatment is responsible for the remission of the disease, the improvement in Carter’s condition since beginning therapy is heartening physicians and patients around the world.
Definition of immunotherapy

• “A type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way. “
• “Types of immunotherapy include cytokines, vaccines, bacillus Calmette-Guerin (BCG), and some monoclonal antibodies.”
Homeostasis of the immune system
Madman alert!

• In 1891, a man could plunge a syringe loaded with toxic bacteria into the neck of another man — simply on a hunch.

• In May of that year, William B. Coley was the man holding that dubious syringe in the apartment of a 35-year-old Italian immigrant and drug addict named Zola.
Enthusiasm phase: Coley’s toxin

- Coley's interest in the area stemmed from a cancer patient who had a complete remission of their cancer following two attacks of erysipelas caused by acute infection with the bacteria Streptococcus pyogenes.

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THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPelas: WITH A REPORT OF TEN ORIGINAL CASES.

BY WILLIAM B. COLEY, M.D.,
ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY
IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

MAY, 1893.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Surgeon</th>
<th>Age</th>
<th>Date</th>
<th>Character of tumor</th>
<th>Erysipelas, accidental or inoculated</th>
<th>Immediate results</th>
<th>Final results</th>
</tr>
</thead>
</table>
For Zola (left), Coley’s toxin-triggered infection liquefied the tumor in days. But toxin-induced infections were unpredictable; the patient at right had 63 injections before his tumor shrunk. Some patients died.

Cancer Research Institute/Proceedings of the Royal Society of Medicine 01/1910/3 (Surg Sect): 1-48
Father of immunotherapy

- During the next 43 years Coley treated almost 900 cancer patients with his bacterial preparation which became known as 'Coley's toxin'
- Not widely adopted
- But his early works led to the use of BCG for early bladder cancer
1. Normal work of the immune system

T lymphocytes are the cells of the immune system that identify tumor cells and destroy them.
Immune escape

2. Camouflage of tumour cells

Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.

PD-L1 molecules

The tumours become invisible to our defences and they spread.
Avoiding immune destruction is a hallmark of cancer

“Waking up” immune system

I fear all we have done is to awaken a sleeping giant and fill him with a terrible resolve.

— Isoroku Yamamoto —
Blockade of PD-L1 or PD-1 can inhibit PD-L1/PD-1 signalling

Targeting PD-L1 blocks signalling between the tumour cell and both PD-1 and B7.1, preventing down-regulation of T cell activity. PD-L2/PD-1 interaction is preserved, potentially minimising effects on immune homeostasis.

Targeting PD-1 blocks signalling between the tumour cell and PD-1, sparing the interaction between the tumour cell and B7.1. PD-L2/PD-1 interaction is blocked, potentially increasing autoimmunity.

Is Immunotherapy suitable for all types of cancer?
FDA approved indications for PD1 inhibitors – by tumor subtype

- Non-small cell Lung carcinoma (NSCLC)
- Melanoma
- Renal Cell Carcinoma
- Transitional Cell Carcinoma
- Hodgkin’s Lymphoma
- Head & Neck Cancer
Biomarkers

- PDL1
PD-L1 expression pattern is diverse

Tumour (diffuse)

Tumour (focal)

Tumour* (membrane, cytoplasm, 1+, 2+, 3+)

Immune cells (macrophages, TILs)

MedImmune, images provided courtesy of Ross Stewart, presented at the Immuno-oncology Masterclass 25 March 2015

*1+, 2+ and 3+ represent different intensities of staining observed in different regions within a tumour cell
PD-L1 expression levels within a tumour are heterogeneous
Pattern of response to immunotherapy

1. Response in baseline target lesion (chemotherapy like response)
2. Response after initial increase in total tumor volume
3. Stable disease with slow steady decline in total tumor volume
4. Response in index and new lesions after the appearance of new lesions

Immune-mediated Toxicities

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Enterocolitis
- Dermatitis

- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor and sensory neuropathies
- Arthritis

- Less common: hematologic, cardiovascular, ocular, renal

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A member of the NUHS
Conclusion

• Immunotherapy is a new paradigm shift for the field of oncology
• FDA approved indication for NSCLC, melanoma, Hodgkin’s lymphoma, RCC, Bladder cancer and head & neck Cancer.
• Better biomarkers needed.
• Better understanding and measurement of tumor response.
• Different toxicity profile from cytotoxics.
PERSONALIZED MEDICINE
Ageing Population

Population in Brief 2015: Citizen old-age support ratio, 1970 to 2015
Fewer working-age adults to each citizen aged 65 and above since 1970.

- Citizen aged 65 years & above
- Citizens in working-age band of 20-64 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Elderly (in millions)</th>
<th>Working-age (in millions)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>13.5</td>
<td>107</td>
<td>13.5</td>
</tr>
<tr>
<td>1980</td>
<td>11.4</td>
<td>102</td>
<td>11.4</td>
</tr>
<tr>
<td>1990</td>
<td>10.4</td>
<td>96</td>
<td>10.4</td>
</tr>
<tr>
<td>2000</td>
<td>8.4</td>
<td>88</td>
<td>8.4</td>
</tr>
<tr>
<td>2005</td>
<td>7.2</td>
<td>82</td>
<td>7.2</td>
</tr>
<tr>
<td>2014</td>
<td>5.2</td>
<td>76</td>
<td>5.2</td>
</tr>
<tr>
<td>2015</td>
<td>4.9</td>
<td>77</td>
<td>4.9</td>
</tr>
</tbody>
</table>

SOURCE: Department of Statistics

13.1% of the population are 65+

Birth Rate: 1.25
Cancer Statistics in Singapore

- No.1 cause of mortality
- 1 in 4 Singaporean dies from cancer
- 60% of cancer patients are >65 years of age

**TOP 10 CANCERS diagnosed in Singapore**

**FEMALES** (Total 26,570)

1. Breast 29%
2. Colorectal 14%
3. Lung 8%
4. Corpus uteri 6%
5. Ovarian 6%
6. Skin 4%
7. Stomach 4%
8. Cervical 4%
9. Lymphoma 4%
10. Thyroid 3%

**MALES** (Total 25,087)

1. Colorectal 18%
2. Lung 16%
3. Prostate 11%
4. Liver 8%
5. Stomach 6%
6. Skin 6%
7. Lymphoma 5%
8. Nasopharyngeal 5%
9. Kidney 3%
10. Urinary bladder 3%

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Geriatric Oncology

• **Geriatrics**: Physiological Age + Functional Status $\rightarrow$ optimization of independence

• **Oncology**: Assessment of cancer variables such as tumor biology and stage $\rightarrow$ cancer specific treatment plans

• **Geriatric + Oncology**: Integration of the 2 skill-sets into an individualised care plan to improve the outcomes of the older patient with cancer
Sociocultural considerations

Our elderly patients are:

- More reticent in reporting symptoms – importance of an effective screening tool/CGA
- Deference of decision-making role to family members
- Collusion – non-disclosure of diagnosis
- Unfavourable view of cytotoxics use amongst elderly/family
National Initiatives for Geriatric Oncology

Comprehensive Geriatric Assessment (CGA) based risk factors for increased caregiver burden among elderly Asian patients with cancer

Tanujaa Rajasekaran\textsuperscript{a}, Tira Tan\textsuperscript{a}, Whee Sze Ong\textsuperscript{b}, Khai Nee Koo\textsuperscript{c}, Lili Chan\textsuperscript{a}, Donald Poon\textsuperscript{d,e}, Anupama Roy Chowdhury\textsuperscript{f}, Lalit Krishna\textsuperscript{a,e}, Ravindran Kanesvaran\textsuperscript{a,e,*}

Clinical Services :
- Geriatric Oncology Clinic in NCIS by 2018
- Multi-disciplinary Geriatric Oncology Clinic in NCC in 2020
NCIS Geriatric Oncology Service

- **New Cases** – to assess fitness and support for cancer treatment.
- **Patients on active cancer treatment** – to co-manage other geriatric syndromes and functional limitations.
- **Survivorship** in geriatric oncology patients.
- **Bridge** between active cancer treatment \(\rightarrow\) palliative management
Proposed Workflow

- Internal referrals from NCIS medical oncology, malignant haematology, radiation oncology & surgical oncology for patients 70 & above.
- Trained nurse will administer the screening questionnaire.
- Patients with issues identified will be seen in the Geriatric Oncology Clinic.

#Patient has to fulfill ALL of the criteria
*If patient fulfills any of the above criteria

- Patients who are 70 years old & above diagnosed with cancer
- Geriatric Assessment Screening
  - Nil factors for concern
    - Standard Cancer Treatment
  - Factors for concern present
    - Comprehensive Geriatric Assessment
      - #Independent in IADLs & ADLS
        - No co-morbidities
        - Gd Social Support
        - FIT
      - *Dependent IADLs
        - Some co-morbidities
        - Lack of social Support
        - Vulnerable
      - *Dependent ADLS
        - Serious co-morbidities
        - Geriatric Syndrome
        - Frail
  - Reversible
    - Non-reversible
      - Dose modifications
        - Ensure Care/Support
      - Early initiation of palliative services & supportive care

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