Bladder & Kidney Cancer In Western Australia – An update with strategies for improving outcomes

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Lead Clinician, Urology Tumour Collaborative, WACPCN
Chair, Bladder cancer sub-committee ANZUP cancer trials group
• Prostate cancer accounted for 30% of male cancers in WA in 2006 and caused 252 death making it the commonest male cancer and second commonest cause of male cancer death

• ‘In Western Australia, when considering both invasive and pre-invasive /in situ malignancies, excluding SCC and BCC of the skin, urological services deal with more cases than any other speciality (21% of the total)’ Tim Threlfall WACR

• BPH affects 60% of males over 50yrs (40% have LUTS)

• Incidence of urinary incontinence and over-active bladder in women is approximately 20%

• Urologists are really nice people
Bladder Cancer Fast Facts

• Male bladder cancer mortality in WA is similar to melanoma [86 vs. 89 WACR data 2009]

• Audit of Cancer Research in Australia 2008/09: Bladder cancer outcomes are actually getting

• Bladder cancer has the highest lifetime treatment costs per patient of all cancer [NIH Pub 96-4104]

• Cancer registry coding practices exclude Ta disease and carcinoma in situ grossly under-estimating the burden of disease.
Cancer Incidence in WA

Australian Bladder Cancer
5 year survival (%)

Data from WA cancer Registry and the Australian Institute of Health & Welfare
Bladder Tumours
Urothelial Cancer

- Is caused by urine borne carcinogens
- The whole urothelium has been exposed
- Long latent period
- Risk is proportional to duration and intensity of exposure
  - Fluid intake, poor bladder emptying, diverticulae, coffee protective??
- Cigarette smoking the commonest cause
  - Risk >30 pack years
- Male: female ratio = 2.5:1
Models for development of bladder cancer

THE DEVELOPMENT OF BLADDER CANCER

NORMAL → IN SITU CHANGE → PAPILLARY GROWTH → INVASION OF STROMA → METAS
Models for development of bladder cancer
Grading of Bladder Cancer

- WHO 1973
  - Grade 1-3

- WHO 2004
  - High grade
  - Low grade
Staging of Bladder Cancer
Treatment of Bladder Cancer

- Non-muscle invasive tumours pTa & T1
- Carcinoma in situ
- Muscle invasive cancer T2-T4
- Metastatic disease
Survival by tumour stage

\[ \chi^2 = 334.09 \quad p < 0.0001 \]

<table>
<thead>
<tr>
<th>No at risk</th>
<th>pTa</th>
<th>pT1</th>
<th>T2-T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTa</td>
<td>678</td>
<td>652</td>
<td>624</td>
</tr>
<tr>
<td>pT1</td>
<td>300</td>
<td>267</td>
<td>235</td>
</tr>
<tr>
<td>T2-T4</td>
<td>362</td>
<td>216</td>
<td>150</td>
</tr>
</tbody>
</table>

Years from treatment: 0 1 2 3 4 5 6 7 8 9

% Alive: 100 75 50 25 0
Treatment of Low and Moderate Risk Non-Muscle Invasive Bladder Cancer

- Endoscopic Resection
- Intravesical Cytotoxics E.G. Mitomycin C
- Intravesical Immunotherapy With BCG
- Cystectomy (Rarely)
Treatment of Low and Moderate Risk Non-Muscle Invasive Bladder Cancer

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- Intravesical Cytotoxics E.G. Mitomycin C
- Intravesical Immunotherapy With BCG
- Cystectomy (Rarely)
High Risk TCC: EAU Guidelines

- **Low risk (30%)**
  - pTa low grade
  - small (≤ 3 cm)
  - primary (<1 recurrence per year)
- **High risk (20-30%)**
  - any high grade
  - any pT1
  - any Cis
- **Intermediate risk (40-50%)**
  - the rest
Treatment of High Risk Non-Muscle Invasive Bladder Cancer

- Intra-vesical BCG
- Experimental therapies
  - Combination/sequential treatments
  - Intra-vesical gemcitabine
  - EMDA
- Cystectomy
Treatment of Muscle Invasive Bladder Cancer

- Cystectomy
- Radiotherapy
- Systemic chemotherapy
- Combined treatments – Neo-adjuvant CXT prior to cystectomy is the current standard of care
Cystectomy specimen
Urethrectomy
Ileal Conduit Diversion
Formation of Neo-bladder
Suturing urethro-neovesical anastamosis
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>47</td>
<td>14</td>
<td>10745</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td>My series</td>
<td>Single centre</td>
<td>IOG compliant UK centres</td>
</tr>
<tr>
<td><strong>30/90/365 day mortality (%)</strong></td>
<td>0 / 0 /6.4</td>
<td>0 / 0 / unknown</td>
<td>2.1 / 5.2 /21.5</td>
</tr>
<tr>
<td><strong>Complications: Clavien-Dinido I-II (%)</strong></td>
<td>70%</td>
<td>100%</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Complications: Clavien-Dinido III-IV (%)</strong></td>
<td>7%</td>
<td>21%</td>
<td>30% (reintervention)</td>
</tr>
<tr>
<td><strong>Operating time mean (hrs)</strong></td>
<td>6</td>
<td>7</td>
<td>4.9 -&gt; 6.4</td>
</tr>
<tr>
<td><strong>Blood loss (mls) (range)</strong></td>
<td>814 (150-1300)</td>
<td>1550 (500-3000)</td>
<td>600-1700</td>
</tr>
<tr>
<td><strong>Transfusion rate (units)</strong></td>
<td>36% (0-4)</td>
<td>47% (0-4)</td>
<td>1-66%</td>
</tr>
<tr>
<td><strong>Mean lymph nodes (range)</strong></td>
<td>17 (0-35)</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td><strong>Positive margins</strong></td>
<td>6% (T4)</td>
<td>14% (T4)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Tx, Tis, T1</strong></td>
<td>64.50%</td>
<td>50%</td>
<td>-</td>
</tr>
<tr>
<td><strong>T2&amp;T3</strong></td>
<td>17%</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>6%</td>
<td>36%</td>
<td>-</td>
</tr>
<tr>
<td><strong>LOS median (range)</strong></td>
<td>9 (5-27)</td>
<td>16 (8-55)</td>
<td>14</td>
</tr>
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</table>
Treatment of Metastatic Bladder Cancer

- Systemic platinum based chemotherapy
- Palliative radiotherapy
- Palliative surgery

BL-12
Multi-centre randomized phase 2 comparing Nab-paclitaxel (nanoparticle albumin bound paclitaxel -Abraxane) vs. Paclitaxel

Second line for TCC (whole UT) in metastatic or locally advanced inoperable setting after previous platinum containing regime (for metastatic disease)

International collaboration with NCIC, 16 Australian sites

Approx: 105 patients enrolled (10 in Australia)
Kidney Cancer
Kidney cancer

- M:F 2:1
- 30% Mets at presentation
- 25% Locally advanced
- Increasingly detected incidentally on imaging
- Most lethal urological cancer
Kidney Cancer

- Renal mass found on imaging?
  - Is it cystic or solid?
  - If solid does it enhance with iv contrast?
  - If cystic is it simple or complex?
SOLID MASS = RENAL TUMOUR

- Is the other kidney normal?
- Is renal function normal?
- Is there metastatic disease?
- Is there invasion into renal vein or the IVC?
- Is a biopsy indicated – controversial
Large RCC
Obvious RCC? Biopsy?
Surgical options in kidney cancer
Massive RCC with caval extension
Control of intra-caval tumour thrombus
Extensive tumour thrombus removed
Pulmonary metastases
Treatment of metastatic disease

- Radio-resistant tumours
- Chemo-resistant tumours
- Immunotherapy (Interferon and Interleukin – high toxicity with minimal measurable benefit)
- Very depressing until relatively recently...
New Therapies in Metastatic Renal Cell carcinoma

Tyrosine Kinase Inhibitors
- Sutent® (Sunitinib),
- Votrient® (Pazopanib)
- Nexavar® (Sorafenib)
- Avastin® (bevacizumab)
- Affect tumour angiogenesis via VEGF, PDGF and receptor & RAF kinase
- Often tumour static effect
- Vastly superior to interferon

Immune Checkpoint Inhibitors
- Monoclonal antibodies directed against immune checkpoint proteins
  - programmed cell death-1 (PD-1) e.g Pembrolizumab
  - programmed cell death ligand 1 (PD-L1) e.g Nivolumab
  - cytotoxic T-lymphocyte antigen-4 (CTLA-4) e.g. Ipilimumab
- Boost endogenous immune responses directed against tumour cells
MICHAEL CAINE
WHAT'S IT ALL ABOUT?

‘CAINE gives his public value for money, covering his whole life with DAVID NIVENISH charm’
Sunday Telegraph

IMPROVED HEALTH OUTCOMES
How do we improve bladder and kidney cancer outcomes?

- **Prevention**
- **Early diagnosis**
  - Patient awareness (for haematuria)
  - Clinician Education (for haematuria)
  - Rapid Referral pathways for GPs
- **Better treatment**
  - Quality surgery
  - Enhanced recovery
  - Adjuvant therapy
    - Intra-vesical
    - Chemotherapy and Immunotherapy
  - Therapy in relapsed / metastatic disease
- **Measure outcomes**
  - Stage specific recurrence and survival
  - Quality of life
Prevention

SMOKING CAUSES BLADDER CANCER

SMOKING CAUSES BLINDNESS
Early diagnosis

- Patient awareness (for haematuria)
  - Media
- Clinician Education (for haematuria)
  - Undergraduate education
  - GP awareness
  - Investigation reports
- Rapid Referral pathways
  - One Stop haematuria Clinic

Visible Haematuria (referred patients)

15-22% have cancer in the urinary tract

Non-Visible Haematuria (referred patients)

~5% have cancer in the urinary tract
Patient Awareness

Little alternative than to use the media

Have to keep repeating the same message

Go to your doctor

Refer to a urologist for cystoscopy
Undergraduate Education

Urology Learning Modules

Undergraduate curriculum in urology – web based

Ongoing collaboration between USANZ and BAUS office of education UWA and Uni Birmingham
Postgraduate Education and Research

Improve GP understanding of appropriate significance of (particularly visible) haematuria and appropriate referral times

Reinforcing this message
• GP talks
• In GP letters
• Novel mechanisms to deliver this message e.g MSU reports

<table>
<thead>
<tr>
<th>Delay Type</th>
<th>Median delay in days (range)</th>
<th>Target</th>
<th>Number breaching target (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Missed' referral opportunity</td>
<td>0 (0 - 1095)</td>
<td>None</td>
<td>10 (13.9%)</td>
</tr>
<tr>
<td>Patient delay (haematuria - presentation)</td>
<td>1 (0 - 730)</td>
<td>≤ 14 days</td>
<td>16 (22.2%)</td>
</tr>
<tr>
<td>Primary care delay (presentation - referral)</td>
<td>3 (0 - 89)</td>
<td>≤ 14 days</td>
<td>7 (9.7%)</td>
</tr>
<tr>
<td>Clinic delay (referral - haematuria clinic)</td>
<td>23.5 (0 - 207)</td>
<td>≤ 30 days</td>
<td>26 (36.1%)</td>
</tr>
<tr>
<td>TURBT delay (haematuria clinic - TURBT)</td>
<td>20 (1 - 69)</td>
<td>≤ 30 days</td>
<td>18 (25%)</td>
</tr>
<tr>
<td>Total delay</td>
<td>69.5 (9 - 1165)</td>
<td></td>
<td>77 (69%)</td>
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</tbody>
</table>

‘Potential solutions may include: public health campaigns, GP education, national haematuria guidelines, modification of investigation reports to encourage urological referral, local audit, one-stop haematuria clinics, and waiting list target initiatives.’
Imaging Guidelines:

Appropriate investigation of Visible Haematuria

*Any single episode of visible haematuria is considered significant and should be referred for urological assessment.
Rapid Referral Pathways

One Stop Haematuria Clinic
Running since 2008
Seen >1320 patients
Reduces time from referral to cysto
Demand and throughput increasing

Direct personnel salary savings alone (1,000) patients = $73,000
One Stop Haematuria Clinic

F: Further OPA, 10.00%
E: New non-urological cancer, 1.00%
D: Other operation, 14%
C: New urological cancer, 13%
B: Discharged after further investigation, 22%
A: Discharged

Need further OPA, 14%
Operation, 30%
Discharged, 56%

<5% require further consultant follow-up
A multi-disciplinary cooperative cancer trials group

Trials development and infrastructure

Trials development and infrastructure support

Education and training

Travel grants and Fellowships via fundraising

Mission
To conduct clinical trial research to improve treatment of Bladder, Kidney, Testicular and Prostate Cancers
### What trials are we doing?

<table>
<thead>
<tr>
<th>Active Trials (Bladder &amp; Kidney)</th>
<th>Recruitment 1 February 2018</th>
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<tbody>
<tr>
<td><strong>BCG MM</strong></td>
<td>155</td>
</tr>
<tr>
<td>Phase 3 BEP</td>
<td>41</td>
</tr>
<tr>
<td>e-TC</td>
<td>28</td>
</tr>
<tr>
<td>ENZAMET</td>
<td>closed (1125)</td>
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<tr>
<td>ENZARAD</td>
<td>702</td>
</tr>
<tr>
<td>KEYPAD</td>
<td>1</td>
</tr>
<tr>
<td>Pain Free TRUS B</td>
<td>170</td>
</tr>
<tr>
<td>PCR-MIB</td>
<td>4</td>
</tr>
<tr>
<td>TheraP</td>
<td>0</td>
</tr>
<tr>
<td>UNISoN</td>
<td>17</td>
</tr>
<tr>
<td>NMIBC</td>
<td>196</td>
</tr>
<tr>
<td>FASTRAK II</td>
<td>23</td>
</tr>
</tbody>
</table>
BCGMM Trial

Study Population
Adults with resected, high-risk NMIBC (high grade Ta or any grade T1) suitable for intravesical chemotherapy treatment

Stratified by:
- T-stage (pTa or pT1)
- CIS or no CIS
- Site

Randomisation

Arm A (standard)
Intravesical BCG
Induction + maintenance

Arm B (experimental)
Intravesical BCG + MMC
Induction + maintenance

Min. follow-up
3-monthly (end treatment – year 3)
6-monthly (until disease progression / death / 5 years follow-up complete)

Treatment Schema

* Schema displays treatment administration in terms of nominal weeks, and not calendar weeks, and thus accommodates treatment delays.
- **Stage 1** accrued (162) – multi-site feasibility, completion rates, AEs, HRQoL
- **Stage 2** further 345 patients - DFS, TTR, HRQoL, OS
Advanced Renal Cell Cancer Trials

Single arm Phase 2. 6 of 13 sites now open. First patient recruited

**KEYPAD**

*KidnEY* cancer *Pembrolizumab And Denosumab* Denosumab and Pembrolizumab in advanced clear cell renal carcinoma: a phase II trial (ANZUP1601)

- **Study Chair:** Dr. Craig Gedye
- **Project Manager:** Ms Katie Ford, NHMRC CTC

**UNISoN**

Sequential treatment trial of Single Agent nivolumab, then combination ipilimumab & nivolumab in metastatic or unresectable non-clear cell renal cell carcinoma: a phase II trial (ANZUP 1602)

- **ANZUP Study Chair:** Dr Craig Gedye
- **Project Manager:** Ms Laura Galetta BaCT

Single arm Phase 2. 6 of 13 sites now open. 15 patient recruited
BL-12

Multi-centre randomized phase 2 comparing Nab-paclitaxel (nanoparticle albumin bound paclitaxel -Abraxane) vs. Paclitaxel

Second line for TCC (whole UT) in metastatic or locally advanced inoperable setting after previous platinum containing regime (for metastatic disease)

International collaboration with NCIC. 16 Australian sites

Approx: 105 patients enrolled (10 in Australia)
PCR-MIB

Pilot single arm 30 patient study T2-T4a
Funded via Merck

Current Trial status

5 Australian sites

**NSW:** Chris O’Brien Lifehouse
(Due to open March 2016)
Prince of Wales
(Due to open Q2 2016)

**VIC:** Austin Health
(Due to open March 2016)
Peter Mac Callum
(Due to open Q3 2016)

**WA:** Sir Charles Gardiner
(Due to open Q3 2016)
ANZUP Multi-Centre Cystectomy Audit

https://redcap.anzup.org.au
Exercise medicine prior to radical cystectomy: A pilot randomised controlled trial

Led through ECU funded by ANZUP

To examine the preliminary efficacy and feasibility of a pre-surgical exercise intervention in patients scheduled to undergo radical cystectomy

**Prehabilitation**

**Pre-Surgical Exercise**

Increase physical/physiological reserve capacity to prevent falling below functional threshold

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**Advantage:**
- Pre-surgical wait-times
- ‘Teachable moment’
- Better condition compared to acute postoperative period

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Adapted from Santa Mina et al. *Appl Physiol Nutr Metab* 2015;40:966-969
Conclusions

- **Visible haematuria** is a symptom of cancer and requires referral to urology
  - Quality timely referral is essential
- Bladder cancer is a **common lethal cancer**
  - (Male deaths ≥ malignant melanoma)
- Most renal tumours are incidentalomas but RCC remains a lethal disease
- **Quality surgery** and enhanced recovery can drastically improve outcomes
- Laparoscopic or robotic assisted lap surgery is the gold standard in most kidney cancer surgery. Less established in cystectomy.
- There is a **new armamentarium of agents** for the treatment of advanced bladder and kidney cancer especially the immune therapies
- If we going to make things better we have to enrol more patients in **clinical trials**