Reducing delays in the bladder cancer pathway

Hugh Mostafid FRCS(urol) FEBU
Consultant Urologist, Royal Surrey County Hospital and Honorary Senior Lecturer, University of Surrey
<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>May</td>
<td>Incident finding - Lesion on CT</td>
</tr>
<tr>
<td>June</td>
<td>Seen in clinic to discuss</td>
</tr>
<tr>
<td>July</td>
<td>Cystoscopy and Biopsy</td>
</tr>
<tr>
<td>August</td>
<td>G3 pT1 at least but equivocal DM</td>
</tr>
<tr>
<td>Sept</td>
<td>Local MDT: G3 pT1 at least but equivocal DM</td>
</tr>
<tr>
<td>Oct</td>
<td>Up to date CT scan: Rt H/N and Rt BW thickening</td>
</tr>
<tr>
<td>Nov</td>
<td>Seen in spoke DGH to explain Dx</td>
</tr>
</tbody>
</table>

71 y.o F
When carrying out a TURBT when the intention is to eradicate or substantially debulk the tumour it can be considered first definitive treatment. TURBT remains the first definitive treatment even for patients who require further treatment such as cystectomy or radiotherapy.
71 y.o F

May
- Incidental finding - Lesion on CT
- Seen in clinic to discuss

June
- Cystoscopy and Biopsy
- G3 pT1 at least but equivocal DM

July
- Re-TURBT

August
- Local MDT: G3 pT1 at least but equivocal DM
- Central sMDT path review: G3 pT2

Sept
- Up to date CT scan: Rt H/N and Rt BW thickening
- sMDT review

Oct
- Seen in spoke DGH to explain Dx

Nov
Median number of days between referral and diagnosis

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2004</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis/Ureter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Times to Definitive Treatment in Days by Organ – 2010 and 2004
Excluding tumours diagnosed or treated before referral

<table>
<thead>
<tr>
<th>Organ</th>
<th>Median Time between Referral and Definitive Treatment in days</th>
<th>Median Time between Diagnosis and Definitive Treatment in days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
<td>2010</td>
</tr>
<tr>
<td>Prostate</td>
<td>112</td>
<td>54</td>
</tr>
<tr>
<td>Bladder</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>Kidney</td>
<td>65</td>
<td>54</td>
</tr>
<tr>
<td>Testis</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Pelvis/Ureter</td>
<td>117</td>
<td>83</td>
</tr>
<tr>
<td>Penis</td>
<td>41</td>
<td>57</td>
</tr>
</tbody>
</table>
Time from TURBT to RC

- 0-30days
- 31 to 60
- 61-90
- 91-180
- 181-360
- >360

How quickly are we treating muscle invasive bladder cancer? Trends over a 17 year period

M. Mantle, A.J. Dickinson, M. Moody, R. Cox

Waits for TURBT have come down over... the subsequent delay from TURBT to definitive treatment has lengthened with no change in total time to treatment.

BJMSU 2009

Delays in the diagnosis and treatment of muscle invasive bladder cancer: A pilot project mapping the pathway

M Shahid Iqbal, R Pickles, I Pedley, J Frew, A Azzabi, R Heer, A Thorpe, M Johnson, L Robson and R McMenemin

After implementing the strategies, the median time to TURBT improved to 23 days and from TURBT to subsequent treatment to 66 days [89 days total]

JCU 2015
Does it matter?

Significance of the interval between first and second transurethral resection on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer treated with maintenance intravesical Bacillus Calmette-Guerin

Sümer Balcıoğlu, Murat Bozlu*, Asif Yıldırım1, Mehmet İlkı Gökoğlu, İlker Tınay1, Guven Aslan6, Cavit Can5, Levent Turkeri2, Uğur Kuyumcuoglu2, * and Aydin Mungan11

Department of Urology, Ankara University School of Medicine, Ankara, 1Department of Urology, University of Mersin School of Medicine, Mersin, 2Department of Urology, Istanbul Medipol University School of Medicine, 3Department of Urology, Marmara University School of Medicine, Istanbul, 4Department of Urology, Dalıa Züley University School of Medicine Incirli, Erzurum, 5Departments of Urology, Medical Faculty, Eskişehir Osmangazi University, Eskişehir, 6Department of Urology, Trabzon University School of Medicine, Edremit, and 7Department of Urology, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

Mortality Increases When Radical Cystectomy Is Delayed More Than 12 Weeks

Results From a Surveillance, Epidemiology, and End Results–Medicare Analysis

John L. Gore, MD1,2,3, Julie Lai, MS3, Claude M. Setodji, PhD5, Mark S. Litwin, MD, MPH3,4, Christopher S. Saigal, MD, MPH3,4, and the Urologic Diseases in America Project

Delays in Diagnosis and Bladder Cancer Mortality

Brent K. Hollenbeck, MD, MS1,2,3; Rodney L. Dunn, MS2; Zaojun Ye, MS2; John M. Hollingsworth, MD, MS2,4; Ted A. Skolarus, MD2; Simon P. Kim, MD, MPH2; James E. Montie, MD1,5; Cheryl T. Lee, MD1; David P. Wood, Jr., MD1; and David C. Miller, MD, MPH1,2,3

A delay in the diagnosis of bladder cancer increased the risk of death from disease independent of tumor grade and or disease stage.

Cancer 2010

The interval to second TUR was found to be a predictor of both recurrence and progression... The interval between first and second TUR should be ≤42

BJUI 2015

Delay in definitive surgical treatment beyond 12 weeks conferred an increased risk of disease-specific and all-cause mortality among subjects with stage II bladder cancer

Cancer 2009
The rollercoaster
Strategies to reduce pathway delays

- Referrals
- Haematuria Clinic
- Theatre
- MDT
- BCG therapy
- MIBC
Referrals

NICE referral criteria for pts with suspected bladder cancer

- PPV threshold 3%

<table>
<thead>
<tr>
<th>Condition</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVH</td>
<td>0.8</td>
</tr>
<tr>
<td>40-59</td>
<td>1.8</td>
</tr>
<tr>
<td>NVH + Dysuria</td>
<td>4.5%</td>
</tr>
<tr>
<td>NVH + ↑ WCC</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Aged >60 and unexplained NVH and either dysuria or ↑ WCC
Implications of rejecting referrals for asymptomatic NVH: A single centre experience

- aNVH referrals were rejected

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>352</td>
<td>324</td>
</tr>
<tr>
<td>VH</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>NVH</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>aNVH</td>
<td>85</td>
<td>76 rejected</td>
</tr>
<tr>
<td>BC</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>HR NMIBC/MIBC</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>RTT</td>
<td>39d</td>
<td>18d</td>
</tr>
<tr>
<td>OSHC slots</td>
<td>136</td>
<td>90</td>
</tr>
</tbody>
</table>

Carter et al. Global Congress on Bladder Cancer 2016
Time to abandon testing for microscopic haematuria in adults?

Per-Uno Malmström

Although there is no doubt that macroscopic haematuria is serious, the clinical significance of asymptomatic microscopic haematuria is controversial. Should it still be tested for?

BMJ 2003

‘National Board of Health and Welfare in Sweden recommended that testing for MH should be abandoned in 1999’
Prediction of histological stage based on cytoscopic appearances of newly diagnosed bladder tumours

VA During¹, GM Sole², AK Jha², JA Anderson², RT Bryan¹

¹University of Birmingham, Edgbaston, UK
²The County Hospital, Hereford, UK

CONCLUSIONS We find that visual assessment is accurate in predicting the presence of MIBC. This supports the practice of stratifying patients at the time of initial cystoscopy for those requiring further radiological staging pre-TURBT.

1.2.2 Consider CT or MRI staging before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected at cystoscopy.

• If H/nephrosis on U/S ➔ CT scan
In Theatre
HR NMIBC or MIBC?

MIBC ➔ Radical treatment

Re-TUR?

➔ BCG
Time to re-evaluate and refine re-transurethral resection in bladder cancer?

‘As failure to obtain DM results in the patient having a second operation and delays their treatment, perhaps we should start to think of this in much the same way as positive margin rates are used as a measure of the quality of RP and by inference, the skill of the surgeon.’
1st TURBT

- Team Brief  
  Largest TURBT first on list  
  D/C cystoscopies can wait

DM

- Separate deep biopsy of tumour base
- If not sure, try again until you are
- Path form: ‘Is there DM in the specimen?’
MDT

• No mention of DM:
  Pathologist re-examine and rewrite report

• Equivocal DM:
  sMDT path review *and* book re-TUR
Who needs Re-TUR?

Perform a second TURB in the following situations:
- after incomplete initial TURB;
- if there is no muscle in the specimen after initial resection, with the exception of TaG1 tumours and primary CIS;
- in all T1 tumours;
- in all G3 tumours, except primary CIS.

EAU NMIBC Guidelines 2016
The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette-Guérin

- 2451 pts with HG/G3 T1 Rx’d with BCG
- 935 (38%) had re-TUR
- Re-TUR in the presence of DM did not improve the outcome of Rec, Prog, CSS or OS
- ‘Re-TUR may not be necessary in pts with HG/G3 T1 if muscle is present’
Significance of the interval between first and second transurethral resection on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer treated with maintenance intravesical Bacillus Calmette-Guerin

Sümer Baltacı, Murat Bozlu*, Asif Yıldırım¹, Mehmet İker Gökçe, İlker Tinay⁵, Güven Aslan⁶, Cavit Can⁷, Levent Turkeri⁸, Uğur Kuyumcuoğlu** and Aydın Mungan††

Department of Urology, Ankara University School of Medicine, Ankara, ¹Department of Urology, University of Mersin School of Medicine, Mersin, ²Department of Urology, Istanbul Medeniyet University School of Medicine, ³Department of Urology, Marmara University School of Medicine, Istanbul, ⁴Department of Urology, Dokuz Eylül University School of Medicine Inciralti, İzmir, ⁵Department of Urology, Medical Faculty, Eskişehir Osmangazi University, Eskişehir, ⁶Department of Urology, Trakya University School of Medicine, Edirne, and ⁷Department of Urology, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

‘The interval to re-TUR was found to be a predictor of both recurrence and progression...
The interval between first and re-TUR should be < 7 weeks’

BJUI 2015

Time to re-evaluate and refine re-transurethral resection in bladder cancer?

‘It therefore seems logical to reserve re-TUR only for those who truly need it, so that limited resources are focused on ensuring that they receive their operation in a timely manner... whilst for those that do not, essential intravesical treatment is not delayed’

BJUI 2016
Perform a second TURB in the following situations:
• after incomplete initial TURB;
• if there is no muscle in the specimen after initial resection, with the exception of TaG1
tumours and primary CIS;
• in all T1 tumours;
• in all G3 tumours, except primary CIS.

No need to re-TUR G3 pTa if DM in specimen

IPD meta-analysis of re-TUR to determine role of re-TUR in T1
Reducing delays during BCG therapy

‘Wait until 6 month cystoscopy to identify true BCG failures: An additional 25-67% who do not respond to an induction course will respond to a second course of BCG

JCO 2016
Reducing delays during BCG therapy

Definitions, End Points, and Clinical Trial Designs for Non–Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group

Ashish M. Kamat, Richard J. Sylvester, Andreas Böhle, Joan Palou, Donald L. Lamm, Maurizio Brausi, Mark Soloway, Raj Persad, Roger Buckley, Marc Colombel, and J. Alfred Witjes

‘Wait until 6 month cystoscopy to identify true BCG failures: An additional 25-67% who do not respond to an induction course will respond to a second course of BCG

JCO 2016

Flexi, not GA. Don’t biopsy red patches
Reducing delays in MIBC

Could a streamlined pathway improve outcomes?
Can we more accurately stage BC?

- Yes, by MRI:
Magnetic Resonance Imaging
Discriminating NMIBC from MIBC

Sensitivity
• T2-weighted: **88%**
• T2+DWI: **88%**
• T2+DCE: **94%**
• All 3: **94%**

Specificity
• T2: **74%**
• T2+DWI: **100%**
• T2+DCE: **86%**
• All 3: **100%**

TURBT pathological upstaging at cystectomy: **40%**...
The ideal new pathway?

NMIBC
• Diagnose on flexi & biopsy or cytology
• Fast-track to TURBT and subsequent therapy.

MIBC
• Diagnose with flexi & biopsy
• Stage by MRI
• Fast-track to definitive therapy
• TURBT only if urgently needed for symptoms or palliation.
Newly presented haematuria patients

PIS given with Haematuria Clinic appointment letter

Haematuria Clinic
- Informed consent 1
- Flexible cystoscopy + cytology + imaging + biopsy
- Diagnosis given
- Informed consent 2

Randomisation

Pathway 1 (standard)
- Probable NMIBC
- Possible MIBC
  - TURBT
  - E: NMIBC
    - Adjuvant treatment
      - Chemo
      - RT
      - Surgery
        - 1st Definitive Treatment for F (DT-F)
  - MIBC

Pathway 2
- Probable NMIBC
- Possible MIBC
  - TURBT
  - MRI
  - G: NMIBC
  - H: MIBC
    - 1st Definitive Treatment for H (DT-H)

Feasibility test: H/D > 80%
Intermediate test: Time from first consent to DT-F vs Time from first consent to DT-H

Patients without diagnosis of bladder cancer are excluded from study

Informed consent 1: Consenting all patients to biopsy (not standard) and collection of urine sample

Informed consent 2: Consenting bladder cancer patients to the trial
MARGINAL GAINS

HOW THE PROFESSIONALS MAKE SMALL CHANGES TO IMPROVE THEIR PERFORMANCE

LIMITING NUMBER OF CAKE SLICES AT EACH CAFE STOP

SAWING OFF UNNECESSARY SECTION OF SEAT POST (NOT VISIBLE)

CHANGING GREAT BIG KNOBBLY TYRES FOR SOMETHING SLICKER

CHOOSING CLOTHING WITHOUT A LARGE FLAPPY HOOD

WEARING A MORE ELABORATE-LOOKING HELMET

REMOVING SPOKE REFLECTORS

REDUCING BEER BELLY

FITTING A CARBON BOTTLE CAGE
Prioritise tumours from OSHC and order imaging

Put larger tumours first on op list

Take separate biopsies from tumour base

Write ‘is there DM in the specimen?’ on path form

If DM equivocal, sMDT path review and put on re-TUR list

G3 pTa with DM in specimen doesn’t need a re-TUR

Flexi cysto not GA following induction BCG

Review aNVH TWR referrals