CHEMO-RADIOThERAPY FOR BLADDER CANCER

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At the urologist's

There's something wrong with my Wii.
AIMS

- Muscle invasive disease
- Current ‘Gold-Standard’
- Rationale behind Chemo-Radiotherapy
- Evidence in Bladder cancer
Current ‘Gold-Standard’

- Radical cystectomy
Radical Cystectomy

- 2-3% procedural mortality
  - Elderly
  - Smokers
  - Co-morbidities

- Long-term complications

- Effect on Quality of Life
  - Urinary toxicity
  - Gastrointestinal toxicity
  - Sexual dysfunction
  - Body image
Radical Cystectomy

- How effective is it?
### Table 3. Comparison of 5-year survival for radical cystectomy series based on pathologic stage

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>No Residual Disease at Cystectomy (%)</th>
<th>Operative Mortality (%)</th>
<th>Survival by Pathologic Stage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritchie et al. (1975)</td>
<td>134</td>
<td>8</td>
<td>8.5</td>
<td>40</td>
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<td>Breda et al. (1980)</td>
<td>174</td>
<td>4</td>
<td>4.2</td>
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<td>Mathur et al. (1981)</td>
<td>58</td>
<td>7</td>
<td>3.4</td>
<td>77</td>
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<td>Skinner and Lieskovsky (1984)</td>
<td>197</td>
<td>10</td>
<td>2</td>
<td>64</td>
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<tr>
<td>Montie et al. (1984)</td>
<td>99</td>
<td>10</td>
<td>9</td>
<td>69</td>
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<td>Giuliani et al. (1985)</td>
<td>202</td>
<td>12</td>
<td>1.9</td>
<td>56</td>
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<td>Roehrborn et al. (1991)</td>
<td>280</td>
<td>25</td>
<td>1.8</td>
<td>63</td>
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<tr>
<td>Pagano et al. (1991)</td>
<td>261</td>
<td>15</td>
<td>6</td>
<td>57</td>
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<td>Wishnow and Tenney (1991)</td>
<td>188</td>
<td>5</td>
<td>1.1</td>
<td>79</td>
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<td>Waehre et al. (1993)</td>
<td>227</td>
<td>25</td>
<td>3</td>
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<tr>
<td>Vieweg et al. (1999)</td>
<td>686</td>
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<td>2</td>
<td>58</td>
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<tr>
<td>Stein et al. (2001)</td>
<td>633</td>
<td>6</td>
<td>3</td>
<td>72</td>
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<tr>
<td>Dalbagni et al. (2001)</td>
<td>284</td>
<td>10.7</td>
<td>3</td>
<td>59</td>
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<tr>
<td>Madersbacher et al. (2003)</td>
<td>507</td>
<td>15</td>
<td>4.5</td>
<td>74</td>
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<tr>
<td>Grossman et al. (2003)</td>
<td>154</td>
<td>15</td>
<td>0.6</td>
<td>75</td>
</tr>
</tbody>
</table>

* SouthWest Oncology Group (SWOG) 8710 trial cystectomy-alone arm.

† Pathologic stage T3 and T4a combined.

5yr overall survival --- 66 35 27
Radical Cystectomy

- 5-year survival
  - T2 66%
  - T3 35%
  - T4 27%  
    - unchanged over the last 10 years

- Systemic disease.
- Occult metastatic disease at time of surgery.
- Improved surgery
- Improvements in continent urinary diversions.
Continent Urinary Diversions

Complications

- Stomal stenosis
- Incontinence
- Infection
- Calculi
- Anastamotic leakage
- Anastamotic stricture
- Incomplete Voiding
- Metabolic complications
  - Hyperchloeraemic metabolic acidosis
  - Hypokalaemia and other electrolyte abnormalities
  - Disorders of hepatic metabolism
  - Abnormal drug metabolism
  - Vitamin B12 deficiency
  - Bone demineralisation
  - Mucus production

- Recurrence!
Metastatic disease
Neo-adjuvant chemotherapy

- Occult ‘micro-metastatic’ disease

- Neo-adjuvant ≡ ‘prior to definitive treatment’
  - Potential for limited micro-metastatic disease
  - Patients fitter prior to surgery
  - Tolerate chemotherapy better.
Neo-adjuvant chemotherapy

- “Delay definitive therapy”
- “Death as a consequence of therapy”
  - 1% toxic death rate with CMV (EORTC)
  - 0% toxic death rate with MVAC (SWOG)
- “Increase post-operative morbidity”
  - MD Anderson – ‘Neo-adjuvant chemotherapy does not increase peri-operative morbidity’
<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant Arm</th>
<th>Standard Arm</th>
<th>Patients (N)</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td><strong>Cisplatin chemotherapy</strong></td>
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<td></td>
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<tr>
<td>Australia/UK(^{17})</td>
<td>Cis/RT</td>
<td>RT</td>
<td>255</td>
<td>No difference</td>
</tr>
<tr>
<td>Canada/NCI(^{18})</td>
<td>Cis/RT or preop RT+cytectomy</td>
<td>RT or preop RT+cytectomy</td>
<td>99</td>
<td>No difference</td>
</tr>
<tr>
<td>Spain (CUETO)(^{19})</td>
<td>Cis/cytectomy</td>
<td>Cystectomy</td>
<td>121</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC/MRC(^{11})</td>
<td>CMV/RT or cytectomy</td>
<td>RT or cytectomy</td>
<td>976</td>
<td>5.5% difference in favor of CMV</td>
</tr>
<tr>
<td>SWOG Intergroup(^{20})</td>
<td>M-VAC/cytectomy</td>
<td>Cystectomy</td>
<td>298</td>
<td>Benefit with M-VAC (P = 0.06)</td>
</tr>
<tr>
<td>Italy (GUONE)(^{15})</td>
<td>M-VAC/cytectomy</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
</tr>
<tr>
<td>Italy (GISTV)(^{21})</td>
<td>M-VEC/cytectomy</td>
<td>Cystectomy</td>
<td>171</td>
<td>No difference</td>
</tr>
<tr>
<td>Genoa(^{22})</td>
<td>Cis/5-FU/RT/cytectomy</td>
<td>Cystectomy</td>
<td>104</td>
<td>No difference</td>
</tr>
<tr>
<td>Nordic I(^{24})</td>
<td>ADM/Cis/RT/cytectomy</td>
<td>RT/cytectomy</td>
<td>311</td>
<td>No difference, 15% benefit with ADM + Cis in T3–T4a</td>
</tr>
<tr>
<td>Nordic II(^{16})</td>
<td>MTX/Cis/cytectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
</tr>
<tr>
<td>Abol-Enein et al.(^{23})</td>
<td>CarboMV/cytectomy</td>
<td>Cystectomy</td>
<td>194</td>
<td>Benefit with CarboMV</td>
</tr>
</tbody>
</table>
Neo-adjuvant Platinum combination chemotherapy improves overall survival at 5 years from 45% to 50%
Bladder preservation

“The aim of bladder preservation is to achieve cancer survival with equivalence to radical cystectomy while retaining an anatomically normal functioning bladder”
Rationale of Chemo-Radiation

- Increase effectiveness of radiation
  - Cytoreductive
  - Radiation sensitizer

- Treat micro-metastatic disease
<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Indication and treatment</th>
<th>Commonly used agents</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper aerodigestive tract cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>Locally advanced HNC—primary or adjuvant treatment</td>
<td>Cisplatin, 5-FU, FHX, cetuximab</td>
<td>Improved organ preservation and survival compared with radiation alone</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>Stage IIIIB, nonoperable nonmetastatic disease</td>
<td>Cisplatin, carboplatin/paclitaxel, cisplatin/etoposide</td>
<td>Curative approach in poor surgical candidates or IIIB disease</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>Limited stage disease</td>
<td>Cisplatin/etoposide</td>
<td>Curative in ~20% of patients</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Locally advanced disease</td>
<td>Cisplatin/5-FU</td>
<td>Survival benefit, increased cure rates, organ preservation</td>
</tr>
<tr>
<td>Gastrointestinal malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Neoadjuvant</td>
<td>5-FU</td>
<td>Improved sphincter preservation, decrease in local and distal failures</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>Mainstay of curative treatment</td>
<td>5-FU, MMC</td>
<td>Improved organ preservation</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Adjuvant</td>
<td>Cisplatin, 5-FU</td>
<td>Some data indicate a survival benefit</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Adjuvant, unresectable locoregionally advanced tumors</td>
<td>5-FU</td>
<td>Improved locoregional control, possibly a survival benefit</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Adjuvant, unresectable locoregionally advanced tumors</td>
<td>5-FU</td>
<td>Some data indicate a survival benefit</td>
</tr>
<tr>
<td>Gynecological and genitourinary cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Primary modality</td>
<td>Cisplatin, 5-FU, hydroxyurea</td>
<td>Improved local and distal control, organ preservation</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Primary modality</td>
<td>Cisplatin</td>
<td>Improved local control</td>
</tr>
<tr>
<td>Other cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Adjuvant</td>
<td>Temozolomide</td>
<td>Survival benefit</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Neoadjuvant</td>
<td>Doxorubicin</td>
<td>Downstaging, improved organ preservation</td>
</tr>
</tbody>
</table>

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This is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHX, 5-FU, hydroxyurea and radiation; HNC, head and neck cancer; MMC, mitomycin C.
Anal Cancer

- Squamous cell carcinoma
  - Surgical results poor
  - Radiotherapy results poor

- Interest in Combined Chemo-radiotherapy
  - 5FU - First week and Last week
  - MMC – First day
Combination Chemo-radiotherapy improved survival by 5%
Now the standard of care.
BC 2001 STUDY

- 360 pt
- Radiotherapy (either 55Gy/20F or 64Gy/32F)
- Randomised 1:1
  - Concurrent Chemotherapy
    - 5FU D1-5, D16-20 + MMC D1
    - No concurrent chemotherapy
- Neo-adjuvant chemotherapy was allowed but not mandatory
BC 2001 STUDY

- 2\textsuperscript{nd} Randomisation
- RT to Whole bladder
  or
- RT to Whole bladder/Partial bladder
Follow-up
- Cystoscopy
  - 3 monthly for year 1
  - 12 monthly to year 5
- CT
  - Year 1 and 2
BC 2001 STUDY

- Toxicity
  - GI
    - Grade 3 in 1\textsuperscript{st} year 9.6% vs 2.7%
  - GU
    - Grade 3 in 1\textsuperscript{st} year 3.3% vs 1.3%
BC 2001 STUDY
Local recurrence free survival

– 2 Yr = 67% vs 54%
BC 2001 STUDY

RESULTS

– 2yr Local Recurrence free survival
  • Salvage cystectomy
    – 11.4% after CRT
    – 16.8% after RT

• 80% for muscle invasive recurrence
• 10% for late toxicity (4 cases)
BC 2001 STUDY

RESULTS

- 5 Yr Overall survival - 48% vs 35%
5yr overall survival range 39% - 74%
Bladder preservation 31% - 60%

Table 1 Series of trimodality bladder-sparing treatment for muscle-invasive bladder cancer

<table>
<thead>
<tr>
<th>Investigator (publication year)</th>
<th>No. patients</th>
<th>Clinical stage</th>
<th>Induction therapy</th>
<th>CRT regimen</th>
<th>CR rate (%)</th>
<th>Consolidative therapy</th>
<th>5-year OS (%)</th>
<th>5-year BIS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housset (1993)</td>
<td>54</td>
<td>T-2-4</td>
<td>–</td>
<td>24 Gy + cisplatin/FU</td>
<td>74</td>
<td>20 Gy + cisplatin/FU</td>
<td>59 (3-year)</td>
<td>NA</td>
</tr>
<tr>
<td>Given (1995)</td>
<td>93</td>
<td>T-2-4</td>
<td>2 or 3 cycles MVAC or MCV</td>
<td>64.8 Gy + cisplatin</td>
<td>63</td>
<td>–</td>
<td>39</td>
<td>NA</td>
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<tr>
<td>Tester (1996)</td>
<td>91</td>
<td>T2-4a</td>
<td>2 cycles MCV</td>
<td>39.6 Gy + cisplatin</td>
<td>75</td>
<td>25.2 Gy + cisplatin</td>
<td>62 (4-year)</td>
<td>44 (4-year)</td>
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<td>Kachnic (1997)</td>
<td>106</td>
<td>T2-4a</td>
<td>2 cycles MCV</td>
<td>39.6 Gy + cisplatin</td>
<td>66</td>
<td>25.2 Gy + cisplatin</td>
<td>52</td>
<td>43</td>
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<tr>
<td>Fellin (1997)</td>
<td>56</td>
<td>T2-4</td>
<td>2 cycles MCV</td>
<td>40 Gy + cisplatin</td>
<td>50</td>
<td>24 Gy + cisplatin</td>
<td>55</td>
<td>41</td>
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<tr>
<td>Shipley (1998)</td>
<td>123</td>
<td>T2-4a</td>
<td>2 cycles MCV vs no chemotherapy</td>
<td>39.6 Gy + cisplatin</td>
<td>61 vs 55</td>
<td>25.2 Gy + cisplatin</td>
<td>49 vs 48</td>
<td>36 vs 40</td>
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<tr>
<td>Rodel (2002)</td>
<td>415</td>
<td>T1-4</td>
<td>–</td>
<td>50.4–59.4 Gy + cisplatin or carboplatin(+ FU)</td>
<td>72</td>
<td>–</td>
<td>50</td>
<td>42</td>
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<td>Danesi (2004)</td>
<td>77</td>
<td>T2-4</td>
<td>2 cycles MCV</td>
<td>69 Gy + cisplatin/FU</td>
<td>90</td>
<td>–</td>
<td>58</td>
<td>47</td>
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<td>Kragelj (2005)</td>
<td>84</td>
<td>T-1-4</td>
<td>–</td>
<td>64 Gy + vincristine</td>
<td>78</td>
<td>–</td>
<td>25 (9-year)</td>
<td>NA</td>
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<td>Dunst (2005)</td>
<td>68</td>
<td>T-2-4</td>
<td>–</td>
<td>50.4–59 Gy + cisplatin or paclitaxel</td>
<td>87</td>
<td>–</td>
<td>45</td>
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<td>Weiss (2007)</td>
<td>112</td>
<td>T1-4</td>
<td>–</td>
<td>55.8–59.4 Gy + cisplatin/FU</td>
<td>88.4</td>
<td>–</td>
<td>74</td>
<td>61</td>
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<td>Perdona (2008)</td>
<td>121</td>
<td>T2-4</td>
<td>2 cycles MCV</td>
<td>69 Gy + no vs cisplatin or carboplatin</td>
<td>74.4 vs 89.7</td>
<td>–</td>
<td>60.4 vs 71.8</td>
<td>46.5 vs 53.8</td>
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<tr>
<td>Gamal El-Deen (2009)</td>
<td>186</td>
<td>T2-4a</td>
<td>No or 2 cycles MCV/MVAC/GC</td>
<td>55–64.8 Gy + no vs cisplatin</td>
<td>58.3 vs 81.6</td>
<td>–</td>
<td>59.7 vs 68.4</td>
<td>NA</td>
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<tr>
<td>Kaufman (2009)</td>
<td>80</td>
<td>T2-4a</td>
<td>–</td>
<td>40.3 Gy + cisplatin/ paclitaxel</td>
<td>81%</td>
<td>24 Gy + cisplatin/ paclitaxel</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>Sabaa (2010)</td>
<td>104</td>
<td>T2-3a</td>
<td>3 cycles GC</td>
<td>60–65 Gy + cisplatin</td>
<td>78.8</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
</tbody>
</table>
• Concurrent Cisplatin
  – (Squamous cell carcinoma)
    • Head and neck
    • Cervix

• Concurrent Gemcitabine
  – Potent radiation sensitizer
Case selection for Trimodality

- Favourable response:
  - Small tumour size (<5cm)
  - Unifocal
  - cT2
  - No hydronephrosis
  - Complete/Near complete TURBT
  - Other
    - No con-comitant CIS
    - Biomarkers?
    - Dynamic imaging?
Limitations of Bladder preservation

- Recurrence – typically at original site.
- Limited coverage of regional lymphatics
- Increased toxicity of salvage cystectomy
- Delay in cystectomy
- Superficial disease
Salvage Cystectomy

- Radiotherapy induced fibrosis and ischemia
  - Ureters
  - Urethra
  - Small bowel
  - Rectum

- Difficult
  - Urinary diversion
  - Anastamotic complications

- Mortality 6%-33%
Future developments

- New radiotherapy technologies
  - IMRT
    - ‘Organ at risk’ sparing
    - Dose intensification
  - Fractionation??

- New Agents
  - Gemcitabine
  - Herceptin
Toxicity of CRT and QoL after CRT

- **Acute**
  - Transient cystitis – typically resolve within 2 weeks of completion
  - Bowel frequency – typically resolve within 2 weeks of completion

- **Late**
  - Bladder function (Normal capacity and flow values in 75% at Harvard)
  - 50% of men maintaining satisfactory erections
  - 20% ‘mild to moderate’ bowel symptoms
  - Second malignancies
Cystectomy vs Trimodality

- Lack of RCT
  - Premature closure of SPARE
  - Despite cystectomy being the Gold Standard treatment, patients declined entry because they preferred the bladder sparing approach.

- Lack of MDT discussion
  - Surgeons taking the lead with the ‘Gold standard’
Summary

- Cystectomy with neo-adjuvant chemotherapy
  - 5 year survival of 50% (ABC meta-analysis)

- Trimodality therapy
  - 5 year survival of 48% (BC 2001)
  - 5 year survival of 39 - 74%
Summary

- Radical cystectomy
  - GOLD STANDARD

- Chemoradiotherapy
  - PLATINUM STANDARD?