Current Surgical Management of Muscle Invasive Bladder Cancer

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Early Cystectomy

- Several studies have indicated that prognosis is substantially better in patients with low T-stage and negative lymph nodes.
- Few studies have shown that in patients with muscle invasive cancer at diagnosis a delay of 90 days in surgery is associated with advanced disease.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No. of cases</th>
<th>5 year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagano et al. (1991)</td>
<td>261</td>
<td>54</td>
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<tr>
<td>Frazier et. al. (1993)</td>
<td>531</td>
<td>48</td>
</tr>
<tr>
<td>Ghoneim et al. (1997)</td>
<td>1,026</td>
<td>48</td>
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<tr>
<td>Dalbagni et al. (2001)</td>
<td>300</td>
<td>45</td>
</tr>
<tr>
<td>Madersbacher et al. (2003)</td>
<td>507</td>
<td>59</td>
</tr>
<tr>
<td>Quek et al. (2005)</td>
<td>702</td>
<td>51</td>
</tr>
<tr>
<td>Hautmann et al. (2006)</td>
<td>788</td>
<td>57</td>
</tr>
</tbody>
</table>
Survival and nodal involvement

Disease Free Survival

\[ \text{P-value} = 0.001 \]

78.3% Negative

37.8% Positive

Time (Months)

P-value = 0.001

100 80 60 40 20

Disease Free Survival

10 20 30 40 50 60 70

Survival and nodal involvement
Impact of level of nodal involvement

![Graph showing disease free survival with different nodal involvement levels.
- Red line: Endopelvic
- Green line: External iliac
- Blue line: Common iliac

Disease Free Survival

- Endopelvic: 53.6%
- External iliac: 38.8%
- Common iliac: 20.8%

P value = 0.005

Time (Months)
**Extent of Lymphadenectomy**

- There is controversy about extent of lymphadenectomy with cystectomy as seen in the table below.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Extent of Dissection</th>
<th>Mean no. of nodes removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leissner et al. (2000)</td>
<td>Variable</td>
<td>14.6</td>
</tr>
<tr>
<td>Mills et al. (2003)</td>
<td>Pelvic</td>
<td>20</td>
</tr>
<tr>
<td>Stein et al. (2003)</td>
<td>Aortic Bifurcation</td>
<td>30</td>
</tr>
<tr>
<td>Herr et al. (2003)</td>
<td>Pelvic</td>
<td>13</td>
</tr>
<tr>
<td>Vazina et al. (2004)</td>
<td>Aortic Bifurcation</td>
<td>25</td>
</tr>
<tr>
<td>Latif et al. (2004)</td>
<td>Pelvic</td>
<td>18</td>
</tr>
</tbody>
</table>

- Ghoneim study concludes that lymphadenectomy should be done to the level of mid common iliac vessels with a mean of 20 nodes per case. This would cover pN1 and pN2 areas, pN3 involvement was seen in cases with endopelvic disease and hence poor prognosis.
Overall Survival Stratified by Age and Treatment

• Herr et al. and Stein et al. have introduced a concept of Lymph Node density. Patients with less than 20% positive nodes have better prognosis.

• Kassouf et al. conclude that patients with less than 25% positive nodes have better prognosis, nevertheless this index can be used clinically.

• Deserno et al. tested a method of determining with a status of pelvic Lymph Nodes pre-operatively using MRI and Microcolloidal iron particles as a contrast agent. They have reported 95% sensitivity and 96% specificity. Larger studies are needed to assess this method.
Location Of Single +Ve Nodes

Fig. 2. Location of the single positive nodes. Note: (a) Only one node was outside the pelvis (left common iliac). (b) No definitive sentinel node.
Randomised Trials for Neoadjuvant Chemotherapy

- SWOG Trial - 317 patients (cT2 to cT4a) randomised to MVAC + Cystectomy 57% 5 year survival Cystectomy 43% 5 year survival.
- EORTC/MRC Trial - 976 patients from 106 institutions CMV vs. No chemotherapy 5.5% benefit favoured patients with CMV after 7 year follow up.
- GUONE trial Italy no benefit observed.

More benefit seen in cT3b disease as compared to T2 disease

- Meta Analysis of more than 2,000 patients who had neoadjuvant chemotherapy in 10 different trials were evaluated. 5% difference (1% to 9%) has been seen in favour of cisplatinum containing combination chemotherapy. Results of this meta analysis are similar to EORTC/MRC trial.
**Neo adjuvant chemotherapy**

**Advantages**
- Immediate treatment of micro metastasis in relatively fit patient.
- Ability to assess response in clinical setting.
- Potential of bladder preservation in some patients.

**Disadvantages**
- Toxicity (No increased morbidity found in patients undergoing surgery.

  EORTC/MRC study 1% mortality rate attributed to CMV. In comparative study of neo-adjuvant and adjuvant done at M D Anderson cancer centre neo-adjuvant chemotherapy did not increase perioperative morbidity.

- Delay in definitive treatment. Greater than 12 week delay is associated with worse prognosis -Level 3 evidence.

- Unnecessary exposure of some patients to Cyto-toxic therapy.
Pre-operative Radiotherapy

- Radiotherapy can be used in either neoadjuvant or definitive setting, its role in the pre-operative has been assessed by Whitmore et al. These trials have been criticised because they were not carried out in controlled prospective manner.

- Currently the value of pre-operative radiation has been overshadowed by evidence that distant metastases are the principal cause of unsuccessful treatment. This is why neoadjuvant chemotherapy has been found to be useful.
Adjuvant Chemotherapy

Advantages

• Does not cause delay in cystectomy.
• Can be used in only node positive patients.

Disadvantages

• Patient may not be fit after cystectomy for chemotherapy.
• Any opportunity to preserve bladder is lost.
• Meta-analysis of individual patient data done by the advanced bladder cancer meta-analysis collaboration group has revealed a 25% relative risk reduction in death within adjuvant chemotherapy group as compared to cystectomy alone.

The results of EORTC study designed to assess survival after immediate chemotherapy vs. chemotherapy at relapse are eagerly awaited.
1. Nerve Sparing Cystectomy

This procedure requires high ligation of the pedicles of the seminal vesicles and prostate. In an autopsy study Pritchett et al. used a similar dissection and identified remaining lymph nodes in 6 out of 10 specimens. These lymph nodes may be potential first site of metastatic spread. There is concern about this procedure. This procedure may be used in patients with muscle invasive tumour over dome or anterior wall of the bladder.

2. Prostate and Seminal Vesicles Sparing Cystectomy

- Helps to achieve early continence and maintain potency.
- Main concern is adenocarcinoma of prostate in later years.

Hautmann and Stein have reported incidents of carcinoma of prostate in cystoprostatectomy specimens as 29%-46%; they have also reported 30%-50% TCC of the prostate in the specimens. In view of this potential risk this procedure is not justified in most patients.
3. Laproscopic Cystectomy

- Procedure is feasible, 6 ports and a mini laparatomy incision is required. Menon et al. have constructed the reservoir extra corporally and the neobladder was then placed in the pelvis, abdominal incision closed and urethro-ileal anastomosis was done with robotic assistance.

- Procedure does need quality control defined as removal of about 20 lymph nodes and negative surgical margins. Procedure may not be cost effective.
Molecular biology: Potential Therapeutic Role?

• Several Pre-clinical studies in bladder cancer models have confirmed that blocking of epidermal growth factor (EGF) receptors by CETUXIMAB stops the growth and metastasis of human TCC.

• Over expression of chemokine receptor CXCR4 indicated the potential of bladder cancer cells for progression and invasion. Evidence has shown, that CXCR4 antagonists inhibit in vitro bladder cancer migration and invasion.

• ASOs are short DNA sequences that can hybridize selectively to the complementary messenger RNA to form RNA DNA duplexes. The synthesis of encoded proteins is thus inhibited. Liposomal agents are used as a delivery system. Duggan et al. demonstrated that intra vesical administration of these agents is followed by good intracellular uptake. It is suggested that ASO can be used as an intravesical based therapy alone or in combination with standard chemotherapy in the treatment of high grade superficial bladder tumours (G3PT1).
Bladder Sparing Strategies

• The question of radiotherapy vs. cystectomy is still a matter of debate. In the absence of any randomised studies, data from case controlled studies and individual series suggests a small survival advantage for surgery. The possibility of orthotopic bladder makes this a much more attractive option for appropriate patients. After initial cisplatin based chemotherapy complete responders should receive consolidation radiotherapy. Cystectomy should be done in patients who have responded incompletely. Best survival outcomes were reported with radiotherapy for PT1 and PT2 disease that were smaller than 5cm with negative nodes. This is why the society of international radiologists recommend excision of all exophytic disease in the bladder prior to radiotherapy.

• One disadvantage of radical radiotherapy is life long need of endoscopic follow-up as Shipley et al. have reported a recurrence rate of 40%.

• Almost 25% of patients develop significant bladder dysfunction. Zietmann et al. have reported that 15% of patients complain of urgency in continence is seen in 19% and 22% have bowel symptoms.

• Herr et al. suggested that patients with tumour who lack detectable (TP53) are suitable for bladder sparing procedures.
### Bladder Sparing Strategy Trials

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. of patients</th>
<th>Treatment Protocol</th>
<th>5 year survival(%)</th>
<th>5 year survival with intact bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prie et al. (1998)</td>
<td>36</td>
<td>TURBT;radio-chemotherapy</td>
<td>43</td>
<td>?</td>
</tr>
<tr>
<td>Shipley et al. (2002)</td>
<td>190</td>
<td>TURBT;radio-chemotherapy</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>Rodel et al. (2002)</td>
<td>415</td>
<td>TURBT;radio-chemotherapy</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>De Crevoiserier et al. (2004)</td>
<td>58</td>
<td>Radiotherapy; partial cystectomy, brachytherapy</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Nieuwenhuijzen et al. (2005)</td>
<td>108</td>
<td>TURBT;radiotherapy, brachytherapy</td>
<td>62</td>
<td>54</td>
</tr>
</tbody>
</table>
Radical Cystectomy vs. Radical Radiotherapy

Ellison et al. 2008 have published a study comparing radical cystectomy with radical radiotherapy.

10,807 patients were identified from SEERS database between 1992 and 2004 who had muscle invasive TCC and who were treated by radical cystectomy or radiotherapy. These patients were stratified into 4 different age groups.

1. <60
2. 60-69
3. 70-79
4. >79

Kaplan-Meier survival analysis was used to compare treatment strategies by age group.

- In terms of overall survival the benefit of radical cystectomy over radiotherapy was most dramatic among younger patients.
- In terms of cancer specific survival patients who had radical cystectomy had better survival regardless of age. There was a minimal survival benefit in patients above 80 years of age.
Median **Overall Survival stratified by age and treatment**

**FIG. 1.** Kaplan-Meier curves for median overall survival of patients with muscle-invasive bladder cancer stratified by age and treatment. From: Chamie: BJU Int, Volume 102(3).August 2008.284–290
Median Cancer Specific Survival Stratified by Age and Treatment

**a**
Cancer Specific Survival for <60 Cohort
Median Survival NR vs. 43 months
Cox HR 1.69 (1.35–2.11)

**b**
Cancer Specific Survival for 60–69 Cohort
Median Survival 141 vs. 42 months
Cox HR 1.55 (1.32–1.83)

**c**
Cancer Specific Survival for 70–79 Cohort
Median Survival 132 vs. 40 months
Cox HR 1.31 (1.16–1.48)

**d**
Cancer Specific Survival for >79 Cohort
Median Survival 37 vs. 22 months
Cox HR 1.21 (1.07–1.38)

Analysis Time, months

- Blue: Radical Cystectomy
- Pink: Bladder Sparing with Radiotherapy
Key Points

1. Radical Cystectomy remains the gold standard for the treatment of muscle invasive bladder cancer.

2. An early cystectomy after the diagnosis of muscle invasion should be promoted.

3. Neo-adjuvant chemotherapy should be considered standard for high risk patients with adequate renal function.

4. To ensure adequate radical cystectomy with meticulous pelvic lymphadenectomy, removal of about 20 nodes is recommended.

5. Laparoscopic cystectomy should be undertaken with the same quality control criteria.

6. Future bladder sparing trials should be prospective, randomised and adequately powered.

7. Recent developments in molecular biology are promising.