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Tri-modality treatment in Muscle Invasive Bladder Cancer- What is the current status?
K. Beena, Vishnu Rajan Nambiar, Makuny Dinesh

ABSTRACT
Standard of care for muscle invasive bladder cancer (MIBC) is radical cystectomy and now bladder preserving approach with tri-modality treatment (maximal transurethral resection followed by concurrent chemo radiation) is being increasingly tried. The careful selection of complete responders, for bladder preservation after neo-adjuvant chemo radiation is the key to the success of such programmes. Tri-modality treatment with salvage cystectomy for non responders has been shown to produce survival rates comparable to radical cystectomy with 75% of surviving patients retaining a functional native bladder. In the present era with improved surgical and radiation techniques salvage cystectomy is not associated with significant increased morbidity and mortality as dreaded in the past. Advancements in radiotherapy techniques such as intensity modulated and volume modulated radiotherapy with fiducial tracking offers the interesting prospect of dose escalation to the tumour favoring better tumour control with lesser normal tissue morbidity. Translational research to identify markers to predict poor responders to chemo radiation will facilitate tailor made treatment for MIBC.

Introduction
Bladder is the 9th most common cancer worldwide accounting for 2% of the all cancer deaths.1 In India the incidence is 1.7/100,000/year2. Majority of patients present above the age of 60 years and the median age at diagnosis is around 65 years. Naturally it follows that medical co-morbidities are frequent compounding problems in the management of bladder cancer. The usual method of diagnosis of carcinoma of the bladder is by transurethral resection of bladder tumour (TURBT). Pre-cystectomy ‘T’ staging depends on the extent of bladder wall invasion in the biopsy specimen. Transitional cell carcinoma (TCC) is the most common histological subtype, accounting for more than 90% of the cases. Superficial bladder tumours account for 65-70% of the presentation, and are mostly managed conservatively, whereas muscle invasive bladder tumours (MIBC) are managed more aggressively. The standard of care for MIBC in the US, for a long time, was radical cystectomy with pelvic lymph node dissection, whereas in Europe it was radical radiotherapy. As a single modality, radical cystectomy always had a better survival than radical radiotherapy. Hence, tri-modality treatment, with maximal TURBT, radiation therapy and concurrent chemotherapy has been tried, and this has shown to produce 5 year and 10 year overall survival rates comparable to radical cystectomy. There are no randomized phase III clinical trial data directly comparing radical cystectomy versus radiotherapy or concurrent chemo radiotherapy (chemo RT) in MIBC. Current dogma states that radiotherapy based protocols are inferior to cystectomy, in the absence of careful patient selection for radiotherapy3. Now in the US, tri-modality treatment is being increasingly tried in selected cases and in the UK, the practice has moved away from radical radiotherapy alone, towards tri-modality approach or cystectomy for selected patients. This article is an attempt to review the evidence for tri-modality treatment in MIBC with details regarding patient selection, bladder preservation rate, survival outcome, toxicities and impact on quality of life.

Treatment of MIBC – Surgical approach
Radical cystectomy with pelvic node dissection is the gold standard treatment for MIBC and all modalities of treatment have to be compared with this for assessing efficacy, survival and quality of life. More recently, extended lymph node dissection has also shown some survival advantage.4 The probability of survival following cystectomy is determined by the pathologic stage of the disease5,6,7,8,9.

| Table : 1. Survival in radical cystectomy series. |
|---|---|---|
| Stage | 10Yr DFS | 10Yr OS |
| PT₂N₀ | 73% | 49% |
| PT₃T₁a or N₁N₂ | 33% | 23% |

DFS: disease free survival, OS: overall survival.

Dept. of Radiation Oncology, Amrita Institute of Medical Sciences and Research Center, Kochi
Chemotherapy, especially neo-adjuvant to surgery, has been recommended by National Cancer Comprehensive Network 2012, in locally advanced cases, for a 5yr survival advantage of 5% as evidenced by the meta analysis of neo adjuvant trials\textsuperscript{10, 11, 12, 13, 14, 15}.

A major deciding factor in selection of patients for radical surgery, are the co-morbidities and issues with urinary diversion. Furthermore, early and late morbidity after radical cystectomy can be problematic and can include risks of hemorrhage, infection, urinary leaks, pelvic lymphocele.\textsuperscript{16, 17} Even the construction of a neo-bladder cannot be a substitute for a person’s original bladder and is also associated with both acute and long term metabolic and neuro-mechanical complications. There are also a few retrospective reports of increased sexual dysfunction in radical cystectomy series compared to radical radiotherapy\textsuperscript{18}. Partial cystectomy as a bladder preserving approach is seldom tried, because it is possible only in a highly select group with small unifocal tumour well away from ureteric orifice and bladder neck with random bladder biopsies negative for multifocality and Carcinoma in situ (Cis).

Radical cystectomy with pelvic node dissection is the gold standard treatment for MIBC and all modalities of treatment have to be compared with this for assessing efficacy, survival and quality of life. More recently, extended lymph node dissection has also shown some survival advantage.\textsuperscript{4} The probability of survival following cystectomy is determined by the pathologic stage of the disease.

**Tri-modality approach in MIBC.**

Over the past 50 years, the field of oncology has embraced organ preserving therapies in malignancies of breast, anal, head and neck, gynecologic and prostate with success rates equivalent to radical surgery. Organ preservation approaches in MIBC, were initially with radiation alone, with inferior results, and subsequently with tri-modality approach (maximal TURBT, radiation and chemotherapy) which showed equivalence in properly selected patient subgroups. This approach requires close coordination among all disciplines involved (urologists, radiation and medical oncologists). Tri-modality treatment has been shown to produce 5-year and 10-year overall survival (OS) rates comparable to those of radical cystectomy. The current 5-year OS rates, that range from 50-67% with this approach, and 75% of surviving patients preserve their bladder. After tri-modality approach, a complete response (CR) is obtained in more than 70% of patients\textsuperscript{19}.

In Europe, from the 1950s to the 1980s, radiotherapy was extensively used and local control was found to be inferior to radical cystectomy, with multiple studies having documented local control rates of 30-40%. Shelley et al, in a meta analysis of three randomized trials examined the efficacy of pre-operative radiotherapy followed by surgery, versus radiation therapy in 439 patients, 221 of whom were randomized to surgery and 218 to radical radiotherapy, showed 36% 5-year survival for surgery versus 20% 5-year survival for radiation alone\textsuperscript{20}.

Bladder preservation approaches became increasingly favored, and became successful, essentially after the emergence of concurrent chemo-radiation protocols with cisplatin. The National Bladder Cancer Group first demonstrated the safety and efficacy of cisplatin, as a radiation sensitizer, in patients with MIBC who were unsuitable for cystectomy\textsuperscript{21}. The National Cancer Institute, Canada randomized trial, was instrumental in proving the survival benefit of cisplatin in the concurrent setting.\textsuperscript{22} In addition several single institution studies also showed improvement with combined modality approach with TURBT and concurrent chemo-radiation. These encouraging results led RTOG to develop protocols for bladder preservation with maximal TURBT followed by concurrent chemo radiation (CTRT). The careful selection of complete responders, for bladder preservation after neo-adjuvant CTRT is the key to the success of such programmes.

Centers like Massachusetts General Hospital (MGH), the University of Erlangen and the University of Paris have considerable experience in bladder preservation strategies with the tri-modality approach\textsuperscript{23}.

<table>
<thead>
<tr>
<th>Center</th>
<th>No.of patients</th>
<th>T-stage</th>
<th>Protocol</th>
<th>DSS with bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH (Shipley et al)</td>
<td>190</td>
<td>T2-T4a</td>
<td>TURBT + CTRT(Cisplatin)</td>
<td>45%at 10yrs</td>
</tr>
<tr>
<td>200223</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University Erlangen</td>
<td>415 (1982-2000)</td>
<td>T1-T4</td>
<td>TURBT + CTRT(Cisplatin)</td>
<td>42% at 5 yrs</td>
</tr>
<tr>
<td>(Rodel et al)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200224</td>
<td>RT=126</td>
<td>(T1 = 89)</td>
<td>or carboplatin or cisplatin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>chemoRT=289</td>
<td></td>
<td>5FU)</td>
<td></td>
</tr>
</tbody>
</table>

DSS: Disease specific survival.
In the Erlangen series, interval cystoscopy was not done and reassessment was done at the completion of concurrent chemo radiotherapy with restaging TURBT. Complete responders were kept on follow up and patients with persistent or recurrent disease went for re-TURBT + intravesical treatment, or cystectomy depending on depth of invasion. The investigators concluded that chemoradiation was more effective than radiotherapy alone, in terms of complete response (CR) and overall survival (OS). Salvage cystectomy for failure was associated with 45% 10yr DFS, with 80% bladder preservation in survivors. Multivariate analysis of prognostic factors revealed that T stage and a completeness of TURBT were the strongest predictors of OS. The data also suggested that adjuvant radiotherapy is of benefit even among selected patients who had complete TURBT. In this latter group, the incidence of bladder preservation was 85%, compared with 75% reported by Herr for highly selected patients with muscle-invasive tumors treated with TURBT alone.

Radiation Therapy Oncology Group (RTOG) has just as well extensively investigated bladder preservation protocols in MIBC. During the years 1985-2001 the RTOG conducted 6 trials, of which 5 were phase I and II and the 6th a phase III trial, which tested the role of adjuvant chemotherapy with tri-modality treatment. A total of 415 patients were enrolled in these trials. The five year OS was approximately 50%, with 75% of surviving patients retaining a functionally preserved bladder.

The tri-modality approach, used in all of these RTOG protocols, is more effective compared to radiation monotherapy used in the 1950s.

The primary objective of RTOG has been to improve cure rates, with a secondary objective to improve bladder preservation rates and an additional objective was to evaluate the tolerance and advantage of newer chemotherapeutic agents. Results of these trails are summarized in Table 3.

<table>
<thead>
<tr>
<th>Study RTOG</th>
<th>Number (N)</th>
<th>Stage</th>
<th>Neo adj</th>
<th>CTRT</th>
<th>CR %</th>
<th>Consoliation in CR</th>
<th>5yr OS %</th>
<th>Intact bladder %</th>
</tr>
</thead>
<tbody>
<tr>
<td>85-1228</td>
<td>42</td>
<td>T2-T4a</td>
<td>TURBT</td>
<td>40Gy CDDP</td>
<td>66</td>
<td>24Gy CDDP</td>
<td>52</td>
<td>42(5yrs)</td>
</tr>
<tr>
<td>88-0229</td>
<td>91</td>
<td>T2-T4a</td>
<td>TURBT +2 cycles MCV</td>
<td>39Gy CDDP</td>
<td>75</td>
<td>25.2Gy CDDP</td>
<td>62(4yrs)</td>
<td>44(4yrs)</td>
</tr>
<tr>
<td>89-0330</td>
<td>123</td>
<td>T2-T4a</td>
<td>TURBT +2 cycles MCV vs no chemo</td>
<td>39.6Gy CDDP</td>
<td>61.55</td>
<td>25.2Gy CDDP</td>
<td>36vs48</td>
<td>49vs40 (5yrs)</td>
</tr>
<tr>
<td>95-0631</td>
<td>34</td>
<td>T2-T4a</td>
<td>TURBT</td>
<td>24Gy,5FU CDDP</td>
<td>67</td>
<td>20Gy CDDP,5 FU</td>
<td>83(3yr)</td>
<td>66(3yrs)</td>
</tr>
<tr>
<td>97-0632</td>
<td>47</td>
<td>T2-T4a</td>
<td>TURBT</td>
<td>40.8Gy CDDP</td>
<td>74</td>
<td>24Gy CDDP,3 Adj MCV</td>
<td>61(3yr)</td>
<td>48(3yrs)</td>
</tr>
<tr>
<td>99-0627</td>
<td>73</td>
<td>TURBT</td>
<td>Acc RT+TAX,CDDP</td>
<td>81%</td>
<td>RT+adj Gem,CDDP</td>
<td>56%</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

MCV:methotrexate, Cisplatin, vinblastine, TAX: taxol, OS: overall survival, CR: complete response.
RTOG 97-06, phase III trial with adjuvant chemotherapy failed to show the survival benefit of neo adjuvant chemotherapy with tri-modality. This trial stopped accrual prior to the planned 174 patients because of the poor tolerance of MCV regimen and 3 treatment related deaths. Trials using neo-adjuvant or adjuvant chemotherapy, showed more grade 3-4 acute toxicities but late effects were similar. It seems reasonable to conclude from the RTOG data that, tri-modality treatment is an effective bladder preservation approach in a highly select group of patients with MIBC, with the understanding that radical cystectomy is an available option for those who fail combined modality, with no decrease in survival due to delay in cystectomy.

RTOG 0233, examined the role of accelerated twice-daily radiation therapy in combination with either paclitaxel/cisplatin or 5-FU/cisplatin. Both cohorts also received four cycles of adjuvant gemcitabine/paclitaxel/cisplatin chemotherapy. Both regimens had high rates of response, completion and bladder preservation. 73% and 69% of patients had their bladder preserved at 4 years.

A diverse approach tried by Memorial Sloan-Kettering in MIBC is radical TURBT alone for a select group of patients who have no residual tumour on a repeat resection. But whether the good results with this approach can be reproduced is a question, and the answer to which will be clear only after multi institutional studies.

Newer chemotherapeutic agents tried in Concurrent setting

After RTOG 85-12 and NCIC trials the efficacy and safety of cisplatin in CTRT bladder was proved. Newer agents and combination regimens with taxanes, gemcitabine and platinum is being increasingly used in neo adjuvant, concurrent and adjuvant settings with some increase in response rates compared with platinum monotherapy. But as of now, there are no definite recommendations for any particular combination chemotherapy in tri-modality setting. RTOG 0524 is ongoing and will evaluate the role of concurrent trastuzumab/paclitaxel in patients with human epidermal growth factor receptor 2 (her2)/neu over expression.

Prognostic factors for bladder preservation

From the available data a few prognostic factors can be identified for bladder preservation. Tumor stage, as expected, affects both local control and survival. Other factors associated with increased preservation rates are complete TURBT, a complete response (CR) to chemo radiation, solitary tumour without carcinoma in situ, and absence of hydronephrosis and nodal disease. On multivariate analysis of Erlangen series completeness of TURBT was found to be one of the strongest predictors of OS. Anemia has been shown to produce reduced local control and increase in distant metastasis. In addition to T stage, actual T size also is an important predictor of disease recurrence. The Boston experience shows that in the presence of hydronephrosis CR rate was 37 % as compared with 68% in the absence of hydronephrosis, which led to hydronephrosis being an exclusion criterion for their bladder preservation protocols. Presence of Tis has also shown aggressive behavior with increased local recurrence as well as metastasis. Chung et al showed that even in a subset of T2NOM0 patients, those with a T size of less than 2 cm had lesser chance of local failure indicating that not only the T stage, but even the actual size of the tumor was im-portant.

So patient selection criteria helpful for selection of patients for successful bladder preservation include T size < 2cm, T2-T3 disease, a visibly or microscopically negative TURBT, absence of hydronephrosis and pelvic node metastases, absence of Tis, good renal function and performance status. They should also undergo a good TURBT, examination under anaesthesia and metastatic work up.

Recent studies have identified EGFR over expression as a prognostic factor but data regarding this is conflicting with EGFR expression associated with better outcome and Her2neu over expression associated with reduced complete response with tri-modality treatment.

Morbidity of tri-modality treatment.

Tri-modality treatment is well tolerated in patients with good performance status and is associated with slightly increased acute toxicities when compared to RT alone. These acute toxicities are usually self limiting or can be managed with symptomatic measures. Another concern is the increase in peri-operative morbidity for non responders going for radical cystectomy after tri-modality treatment. Early reported series in the 1960s and 70s had shown an increase in mortality and significant peri-operative morbidity with urinary leak and intestinal complications, but recent series failed to demonstrate this increase probably due to better radiation and surgical techniques. A recent retrospective comparison from Japan in 192 patients (treated between1989-2010) revealed a slight increase in anastomotic leak, in the post chemo-RT cystectomy arm compared to radical cystectomy arm (11% vs 2%), but no significant increase in severe complications or mortality. Christie hospital also had analyzed their morbidity and mortality in cystectomy patients with or without pre-op chemo - RT in 420 primary and 426 salvage cystectomy cases, treated between 1970 and 2005. They also reported no significant increase in peri-operative mortality or medical or surgical morbidity between the two groups except anastomotic site stenosis which was slightly higher in the RT group. So their conclusion was that 40-45 Gy pelvic irradiation is safe as far as salvage cystectomy is concerned.
Quality of life (QOL) after tri-modality treatment.

One of the frequent arguments against tri-modality approach is the lack of prospective QOL data. Recently, the Study Group on Genito-Urinary Tumours (GETUG97-015) study provided results of a prospective evaluation both by investigators and patients on quality of bladder preservation. This study reported 67% bladder preservation rate with good quality of bladder function and data was in concordance with the retrospective bladder quality data from MGH and Erlangen series and the retrospective QOL comparison data of Hennigsohn et al18,23,44. According to GETUG97-015, sexual function was also preserved in 79% of the patients at 18 months44. Urodynamic study in preserved bladder by Zietman et al also showed good bladder function (75%) after trimodality45 treatment.


The RTOG and other tri-modality protocols, have shown that, the most effective way of bladder preservation without compromising survival seems to be interval cystoscopy evaluation and early cystectomy in non responders.

Radiation Treatment.

Conventional fractionation treatment with a whole pelvis dose of 40-45 Gy, followed by reassessment and boost to the entire bladder or bladder tumour with margin, to a dose of 20 -24 Gy is the most common regimen used in tri-modality treatment. Altered fractionation regimens have been evaluated in trial setting with slightly increased acute toxicity rates, with similar or moderate increase in response rates. With improvements in radiation techniques tolerance of radiation with...
concurrent chemotherapy has increased and now image guided and adaptive radiotherapy is being increasingly used in bladder tumour radiotherapy with a hope to decrease the morbidity further.

Advancements in radiotherapy, with techniques like intensity modulated radiotherapy and adaptive radiotherapy with implanted fiducials, offers the interesting prospect of increasing the radiation dose favoring better tumor control with lesser normal tissue morbidity47.

**Conclusion**

Data from various randomized and single institution studies appear to indicate that bladder preservation strategies with tri-modality approaches in bladder cancer has come of age and should be considered as an alternative first line treatment to radical surgery in selected group of patients with MIBC. Five year survival rates of 50% are achievable, with 70-75% of long term survivors having a native and normal functioning bladder. Many newer chemotherapy agents are making their way to the therapeutic arena, hitherto ruled by platinum agents and the taxanes. Gemcitabine is a promising agent, with good tolerance and bladder preservation rates in studies. Proper patient selection, patient education regarding realistic goals in bladder preservation and multidisciplinary coordination and cooperation are all vital in producing the best possible outcome and survival. Translational research would help to identify molecular predictors of poor response to chemo-radiation facilitating tailor made treatment for bladder cancer patients.

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