Bladder Sparing Strategies in Muscle Invasive Bladder Cancer

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Bladder cancer is a worldwide health risk, with more than 350,000 new cases identified annually.

An estimated 74,690 cases of urinary bladder cancer were diagnosed in the United States in 2014, of which 30% were muscle-invasive.


Radical cistectomy is the best treatment option for patients with muscle invasive bladder cancer (MIBC) and recurrent or refractory NMIBC.

**BUT**

..it remains a morbid procedure with a variable complication rate.

The reported complication rates following open RC vary from 24% to 64%.

*Mortality rate is 0-3% in pts <65 but 7-12% in pts > 75*

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RADICAL CYSTECTOMY RATES IN MIBC BY COUNTRY

Potential Contraindications to RC

• Age : > 75
• Co-morbidities (Patients ASA 4, Frail)
• Patients will
• Inexperienced Surgeon
• Very low volume center
• Strong Radiation Oncology and Medical Oncology setting
Bladder Preservation Modalities in MIBC

- TUR alone
- TUR + Radiation Therapy
- Chemotherapy Alone
- TUR + Chemotherapy
- Partial Cystectomy +/- lymph node dissection

- **TRIMODALITY APPROACH: Tur + Chemo + RT**

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**BLADDER PRESERVATION RATES IN MIBC BY COUNTRY**

<table>
<thead>
<tr>
<th>Country</th>
<th>Preservation Rate</th>
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<tbody>
<tr>
<td>UK</td>
<td>60 %</td>
</tr>
<tr>
<td>USA</td>
<td>10 %</td>
</tr>
<tr>
<td>ITALY</td>
<td>1 %</td>
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Munro, UROBP 2010
Dati AIRO 2012
Strategies for Bladder Preservation: History

Neoadjuvant Chemo + Tur + Re-staging Tur

MSKCC Experience: 10 yr FU

N Pts. = 111 received neo-adjuvant M-Vac + TUR
PT0 = 60/111 (54%)
The majority of them had long term survival with bladder preservation
(Herr et al: J Clin. Onc. ‘98)
Chemo For Bladder Preservation

Neo-adjuvant M-Vac in cT2-T4 N0M0 BC
N Pts. = 104 treated with TUR after M-Vac
Results: 49/104 (49%) were T0.
Responding pts underwent Re-Tur or Partial C
Median Survival = 7.5 yrs
60% of pts. (M-Vac+ TUR) are alive at mean F-Up of 56 mo.
44% of pts. treated with TUR alone maintained their bladder
(Sternberg et al Cancer ’03)

MSKCC Experience
(Herr, Eur Urol 2008)

N pts. = 63 (decline to recive RC) for PT0 after Cis-Platin based chemo + TUR
Results: (median F-up = 86 mo)
40/63 (64%) survived: 54% of them maintained their bladder
The most significant treatment variable predicting better survival was:
*pT0 on Re-staging TUR before starting chemotherapy*
Bladder Sparing Strategies in MIBC

• Bladder Sparing Trimodality Treatment in MIBC .... TUR + Chemo + RT

Tri-Modality Therapy
Requires Close Collaboration Between:

- Urologists
- Medical Oncologists
- Radiation Oncologists

MDT (Multidisciplinary Team)
Bladder Sparing Approach: Review of the Literature
(Ploussard et al. Eur Urol 2014)

- TUR BT + RT + Chemo (most used), Dose of Radiotherapy: varies
  Type of Chemotherapy: Should be cisplatin based

- RC vs Organ-sparing Trimodality Treatment in MIBC:
  A Systematic review of Clinical Trials

- Objective: to compare 5-yr OS from retrospective and prospectives studies of
  RC vs TMT. Material: RC: 10,265 pts. Vs TMT: 3,131 pts
  Results 5-yr OS: RC alone: 52%, RC + Chemo 53% vs TMT 57%
  Absolute benefit of 5% in favour of TMT
**RC Compared to Combined Modality Treatment for MIBC: A Systematic Review and Metaanalysis (2017)**

- **Metanalysis of 8 studies with about 9,000 pts**
- **Results:** No difference in OS, DSS

**Limitations**

* Retrospective studies
* A consistent N of pts. underwent salvage RC in the majority of the studies
* Chemotherapy was not always used
* Selection bias: pts receiving RT were older with more co-morbidities

(Vashistha et al Int J Rad Onc. 2017)

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**Propensity Score Analysis of RC vs TMT in the Setting of a Multidisciplinary BC Clinic (Kulkarni et al J Clin Onc 2017)**

- **Retrospective study including 112 patients:**
  - RC : 56
  - TMT : 56
- Statistical Method: Propensity Score Analysis to reduce at minimum the differences between the 2 groups
- Patients were stratifies according to: TURBT, T stage, IDN, Cis and co-morbidities

**Results:** NO difference in OS and DSS
Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience

Methods: TURBT + RT and Chemo
CR: re-TUR and F-UP  No CR: Cystectomy

Results: (median F-Up 7.21 yrs)
- 5-yr DSS = 66%  10-yr DSS = 59%
- 5-yr OS = 57%  10-yr OS = 39%
RC rate at 5-yr = 29%
Multivariate analysis:
  T2, CR to C/RT , Cis predictors for OS- DSS
  '86-'95  5-yr DSS = 60% vs 84% '00-'13
  5-yr risk of Salvage RC
  '86-'95 = 42% vs 16% '00-'13

Conclusions:
TMT should be discussed and offered to selected pts. with MIBC as treatment option

Ideal Candidates (MGH)

Muscle-Invasive (T2/Early T3) Bladder Cancer with:
- No Hydronephrosis
- No Carcinoma in Situ
- No Multifocal Disease
- s/p Complete TURBT
- Good Bladder function
MGH Nomogram for CR

Coen JJ, IJROBP 2014

83% Chance of CR

MGH Nomogram for DSS

Coen JJ, IJROBP 2014

71% Chance of DSS at 5 yrs
Use of Molecular Markers in Bladder-Preservation Therapy

• ASCO-GU 2018/2019

Molecular Markers to Predict BSTT

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Marker</th>
<th>Results</th>
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<tbody>
<tr>
<td>Chakaravty</td>
<td>HER2 (ERBB2)</td>
<td>Over-expression = &lt; CR</td>
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<tr>
<td></td>
<td>MRE11</td>
<td>High MRE11 expression = better outcome with RT not by RC</td>
</tr>
<tr>
<td></td>
<td>TIP60</td>
<td>High expression = &gt; DSS in RC not in RT</td>
</tr>
<tr>
<td>Laurberg</td>
<td>TIP60 + MRE11</td>
<td>Low MRE11 Exp + High TIP60 Exp = Better DSS with RC and Viceversa</td>
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</table>
**MDACC: 3 molecular subtypes of MIBC**

Validated in 3 independent cohorts.

*Choi et al, Cancer Cell 2014*
p53 pathway activation is associated with cisplatin resistance

MDACC Discovery (p=0.018)  MDACC Validation (p=0.014)

Choi et al, Cancer Cell 2014

• Asco-Gu 2018
S. Francisco
MicroRNA biomarkers for patients with MIBC undergoing selective BS trimodality treatment

- **Material and Methods:**
  40 patients with bladder Tcc were studied using microRNA profiling to identify biomarkers with the ability to predict response to chemo-radiation and survival after bladder preservation therapy

- **Results:**
  miR-23a and miR-27a are associated with complete response to chemo-radiation therapy
  The microRNAs were significantly associated with OS

- **Conclusions**
  miR-23a and miR-27a may help in selecting patients for BS
  Efstathiou MW et al Int J Rad Onc Biol Phys 2018

Impact of Immune and Stromal infiltration on outcomes following BSTT for MIBC

- Signatures of T-cell activation and INF-gamma signaling were associated with improved DSS in a TMT cohort but not in the neoadjuvant chemotherapy + RC cohort.
- Conversely a stromal signature was associated with worse DSS in the neoadjuvant chemotherapy + RC cohort but not in the TMT cohort

- Efstatiou JA et al Eur Urol 2019
Drawbacks of Bladder Sparing Trimodality Treatment

- One of the major weak point of bladder sparing using trimodal therapy:
- No information on the lymphnodes status:
  Lymphadenectomy: In T2s 15-20% of positive nodes
  - Staging
  - Therapy: local recurrence after e-LND is low 4%
- Only 50% of patients will respond to chemo
- Many patients (elderly) cannot tolerate chemo (renal function < 60)
- Costs

RC provides improved survival outcomes and decreased costs compared with trimodal therapy for patients diagnosed with localised MIBC

- Data from Seer Data Base collected and evaluated (2002-2011)
- N Pts.: 3,200
- Median Age: 66 or older
- Stage: T2-T4

- Williams ST, Kamat AM et ASCO-GU 2018
• **Results**

Propensity score matching was used to compare the 2 groups
687 pts treated with Trimodal Therapy (TT) (TUR + Chemo +RT)
687 pts received RC
OS: significantly decreased in pts. who received Trimodal Treatment
(HR 1.49, 95%CI, 1.31-1.69, p< **0.001**)
DSS: same (HR 1.55,95% CI, 1.32-1.83, p<0.001)

• **Costs:**

Median costs significantly higher with Trimodal therapy vs RC
At 180 days : $164.720 vs 98.005 (p < **0.001**)

**Conclusions**

* BP is recommended only in selected, well informed and compliant pts in whom RC is not considered for clinical or personal reasons.

* A T0 status after the first TUR or Chemo is a prognostic positive variable

* Tur alone, chemo or RT alone are not recommended as primary treatment of localized BC for BP strategy

* A multimodality treatment (Tur + Chemo or RT, TUR+ RT + Chemo) is the best choice

* Tertiary Centers should have BS protocols to offer to their patients in MDT setting

*Brausi, Cairo 2019*
Is Bladder Sparing for MIBC Becoming a New Standard?

• **Bladder Sparing with TMT** is becoming more popular in US and Europe for the treatment of localised MIBC …however is not yet the new standard

Brausi : Egypt National Congress Cairo 2019

Thank you
Recommendation for Bladder-Sparing treatments for Localised disease: 2018 EAU Guidelines

- Do not offer TURBT alone as a curative treatment option as most patients will not benefit (SR: Strong)
- Do not offer RT alone as primary therapy for localised BC (SR: Strong)
- Do not offer chemotherapy alone as primary therapy for localised BC (SR: Strong)
- Offer surgical intervention or mutimodality treatments (MMT) as primary curative therapeutic approaches since they are more effective than RT alone (SR: Strong)
- Offer MMT as an alternative in selected, well-informed and compliant patients, especially for whom RC is not an option (SR: Strong)