Non Muscle Invasive (NMIBC) is, Ta, T1 (Stage I)

Muscle Invasive (MIBC) T2 onwards (Stage II & III)

Metastatic N1, M1 (Stage IV)
Role of Radical Radiation

Stage II & III

Stage IV

Regional lymph Nodes (N)

M1: Distant metastasis

Neoadjuvant chemotherapy followed by Radical cystectomy +/- Radiotherapy

Palliative Radiotherapy and chemotherapy
Pathologist should comment on:

- Size
- Tumor grade
- Depth of tumor invasion,
- Presence of CIS
- Detrusor muscle involvement in the specimen.
- Presence of LVI or unusual (variant) histology

If there is uncertainty over the pathology, a further early re-resection (2-6 wk.) is indicated.
Muscle Invasive Bladder Cancer (MIBC) (20% of cases)

If left untreated 85% of patients will die by 2yrs
Treatment Options

RADICAL CYSTECTOMY WITH URINARY RECONSTRUCTION FOLLOWED BY POST OP RADIATION

BLADDER PRESERVATION PROTOCOLS

RELAPSE (OR) PROGRESSION IN BLADDER

Salvage cystectomy

No difference in OS, Cause Specific Survival & Distant recurrence free survival
Bladder Preservation strategies

Conservative Surgery
- Partial Cystectomy
- TURBT

Radical EBRT alone

Trimodality: Maximum TURBT, RT & Chemotherapy
Survival after radical treatment for transitional cell carcinoma of the bladder

L. Dæhlin*, S. Haukaas*, H. Maartmann-Moe† and P. C. Medby*

*Division of Urology, Department of Surgery and †Department of Pathology, University of Bergen, N-5021 Bergen, Norway

Table 3. Five- and 10-year overall and disease-specific survival rates (%) after cystectomy or high-dose radiotherapy for carcinoma of the bladder with primary stages Ta–T1 and T2–T3

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cystectomy</th>
<th></th>
<th></th>
<th>Radiotherapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>5 years</td>
<td>10 years</td>
<td>n</td>
<td>5 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stages</td>
<td>43</td>
<td>72 (7)</td>
<td>49 (8)</td>
<td>66</td>
<td>29 (6)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Ta–T1</td>
<td>24</td>
<td>88 (7)</td>
<td>67 (10)</td>
<td>27</td>
<td>48 (10)</td>
<td>26 (8)</td>
</tr>
<tr>
<td>T2–T3</td>
<td>19</td>
<td>53 (11)</td>
<td>26 (10)</td>
<td>39</td>
<td>15 (6)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Disease-specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stages</td>
<td>43</td>
<td>74 (7)</td>
<td>61 (8)</td>
<td>66</td>
<td>45 (6)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Ta–T1</td>
<td>24</td>
<td>88 (7)</td>
<td>79 (8)</td>
<td>27</td>
<td>58 (10)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>T2–T3</td>
<td>19</td>
<td>56 (12)</td>
<td>38 (12)</td>
<td>39</td>
<td>35 (9)</td>
<td>21 (9)</td>
</tr>
</tbody>
</table>
Ideal Candidate for Bladder Preservation:

- Primary T2 to T3a tumors that are unifocal
- Tumor size less than 5 cm in maximum diameter
- Tumor not associated with extensive CIS
- No Ureteral obstruction or tumor-associated Hydronephrosis
- Good capacity of the bladder
- Visibly complete TURBT
- Adequate KFT to allow cisplatin to be given concurrently with irradiation
Contraindications of pelvic Radiotherapy

- Patients with active inflammatory bowel disease
- Previous Pelvic irradiation
- Extensive prior pelvic surgery
- Chronic Pelvic infections
- High risk of serious late bowel complications.
- Extensive bladder CIS: high risk for tumor recurrence after RT therefore should be considered for cystectomy
Bladder Conservative Protocols: Two School of Thoughts

- Public university in Erlangen, Germany
- Massachusetts General Hospital, USA

MGH

TUBRT

- Induction RT (40Gy) + Concomitant Chemo
- Cystoscopic response evaluation
- CR Non-CR

Consolidation ChemoRT + Adj Chemo
Radical cystectomy + Adj Chemo

Erlangen

TUBRT

RT+CHT (Whole treatment)

Restaging Cystoscopy

CR

PR

FU

Cystectomy

NED

Recurrence

FU

Cystectomy
Conclusions:

- Combined modality provided better bladder preservation.
- Cisplatin: Best Radio sensitizer, Safe and easily administered
- Accelerated fractionation has given better control rates in Phase II trial
## Cystectomy Vs Trimodality Treatment:

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>Category</th>
<th>No. Patients</th>
<th>5-yr</th>
<th>10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USC</td>
<td>2001</td>
<td>pT2-pT4a</td>
<td>633</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2001</td>
<td>pT2-pT4a</td>
<td>181</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>SWOG/ECOG/CALGB(^*)(^{1,216})</td>
<td>2002</td>
<td>cT2-cT4a</td>
<td>317</td>
<td>49%</td>
<td>34%</td>
</tr>
<tr>
<td>Selective Bladder Preservation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Erlangen(^*)(^{123,234})</td>
<td>2002</td>
<td>cT2-cT4a</td>
<td>326</td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>MGH(^*)(^{233})</td>
<td>2009</td>
<td>cT2-cT4a</td>
<td>348</td>
<td>52%</td>
<td>35%</td>
</tr>
<tr>
<td>RTOG(^*)(^{209})</td>
<td>1998</td>
<td>cT2-cT4a</td>
<td>123</td>
<td>49%</td>
<td></td>
</tr>
</tbody>
</table>
Definitive Radiation Planning

- 2D-Conventional
- 3D-Conformal
- IGRT
RT-Planning

• Explain patient about the procedure
• Positioning
• Immobilization
• Simulation
• Prescription of dose
• Treatment
• Patient care during RT.
Target volume:

- Primary tumor & its local extension,
- Whole bladder,
- Proximal urethra
- Prostate with prostatic urethra.
- In female proximal 2 Cm of urethra
- Regional LNs: External iliac, Internal iliac, Hypogastric & Obturator LNs.
Patient position

Supine
- Easier for set up,
- More comfortable to pt.
- More reproducible for daily set up.

Patient immobilization
- Knee rest – relaxes lower back muscles on rigid treatment couch,
- Foot rest
- Vac lock
  - Reproducibility of patient set up
  - Limits pts. Movement during treatment
- Advanced localization techniques:
  - Implanted markers
Conventional planning

• Give oral contrast 1 hr before
• Ask patient to voiding urine
• Foley’s catheter inserted immediately after voiding urine and measure the residual volume of urine.
• 7CC Hypaque solution to inflate balloon and pull down at base of bladder

• This volume is replaced by an equal volume of hypaque solution plus an additional 25 ml and 10-15 ml of air then clamp the catheter.
• Hypaque solution- Urographin :NS = 1: 3
• Air will rise to the top & define the anterior extension of bladder.
• Pt then transferred to simulator couch & positioned.

• Pt is adjusted so that pelvis is straight, relative to the axes of treatment couch.

• Following simulation & radiographic exposure of anterior fields, rectal contrast may be given & lateral simulation is exposed.

Bladder : Empty or Full  ???

Empty bladder :
  – More reproducible
  – More comfortable to patient
  – Overall irradiated volume is smaller.

Full bladder:
  – Displaces small intestine & some part of rectum out of radiation portals
Significant changes in bladder volume

- Interval between voiding & T/t delivery
- Patient’s state of Hydration
- Use of Diuretic Medications
- Ingestion of diuretic beverages (coffee, soft drinks)
- Extrinsic pressure (rectal filling, tumor mass)
Phase I:

- The whole pelvis, encompassing the pelvic lymph nodes, bladder, and proximal urethra

- Elective irradiation of the pelvic lymph nodes ----still not confirmed (BC 2001 trial treated only bladder with margin in radiologically node negative patients)

Phase II (Boost)

- Then cone-down to boost the bladder alone / partial bladder (where the primary tumor was present- cystoscopy and radiology)
Phase I:

AP-PA field

- Superior: at the L5-S1 disc space
- Inferior: below obturator foramen.
- Laterally: 1.5-2 cm to the bony pelvis at its widest section
Lateral field

- Superior & Inferior border same as in AP-PA portal
- Anterior: anterior to bladder with a margin with 1.5 – 2cm
- Posterior: 2-3 cm posterior to bladder
Phase II (Boost)

PORTALS:
- Anterior – Bladder with a margin of 1-1.5cm
- Lateral – Bladder with a margin of 1-1.5cm
- Oblique – Selected at an angle which spares the rectum completely and encompasses the bladder with 1.5 cm margin

FIELDS: 3 fields
- 2 laterals and one anterior / 2 obliques and one anterior
Conformal Radiotherapy (3D-CRT) :

PLANNING CT :

• Supine, arms on chest

• Knee and Ankle immobilization

• Empty Rectum

• Empty Bladder 15 minutes before

• Scan is performed with 2-3 mm slices from the lower border of L5 to the inferior border of the ischial tuberosities.

• All planning and treatment should be carried out with the bladder empty
Different Target Volume Contouring:

- **GTV** = Primary Bladder tumour
- **CTV Tumour** – Whole bladder and any extra-vesical extension
  - **Men**: entire prostate & Seminal Vesicles
  - **Women**: Proximal 2 cm of urethra is also considered as part of the target field
- **CTV Nodal**
- **CTV Total** = CTV Tumour + CTV Nodal
- **PTV 1** = 1.5-2cm around CTV
- **PTV Boost** = CTV Tumour + 1cm
Vessels: From L5 Lower border – femoral Head upper border
CTV Nodal

Vessels+ 0.7 cm margin

1 cm brush post border of iliopsoas for presacral

join Ext-int iliac with 1.8 cm brush for Hypogastric LN

1.8 cm brush obturator strip up to pelvic floor
CTV Nodal
PTV Total = CTV Total + 1cm
95% Isodose line of prescribed dose
Boost Phase:
4 Fields
In supine position

3 Fields (2 lateral & 1 Ant)
In Prone position

3 Fields (2 post Oblique & 1 Ant)
In Prone position
Radiation Dose:

Phase I: 40 to 46 Gy at 1.8 – 2 Gy per fraction.
Phase II (Boost): 14-20 Gy at 1.8-2 Gy per fraction
Total Dose: 60-66 Gy

Energy: 6-15MV

At PGIMER:

• Phase I: 46 Gy @ 2 Gy/# in 23 fractions.
• Phase II (Boost): 18 Gy @ 2 Gy/# in 9 fractions
• Total Dose: 64 Gy in 32 Fractions
Problems in Bladder Radiation:

- Organ motion
- Delineation errors
- Set up errors
- Treatment verification
- Reproducibility of bladder volume

**Table 2 CTV to PTV Margin Widths Suggested by Muren et al.**

<table>
<thead>
<tr>
<th>Margin</th>
<th>Inferior</th>
<th>Superior</th>
<th>Left</th>
<th>Right</th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set-up margin (SM)</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Internal margin (IM)</td>
<td>1.0</td>
<td>2.0</td>
<td>1.1</td>
<td>0.8</td>
<td>2.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Total CTV to PTV margin</td>
<td>1.6</td>
<td>2.3</td>
<td>1.3</td>
<td>1.1</td>
<td>2.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>
IGRT

• Patient-specific direct anatomic or surrogate variations are assessed before treatment delivery and are used to modify the patient setup and treatment plan potentially multiple times during the treatment course.

• Goal: Accurate dose delivery to targeted areas and avoidance of normal structures by reducing the margins around the CTV.

• Patient-specific variations assessed at treatment console with volumetric 3D imaging modalities fitted to treatment machines, such as kilovoltage CBCT.
Adaptive Planning – I

Online Adaptive Radiotherapy for MIBC: Results of a pilot study; Farshad Foroudi et al.; IJROBP, Vol. 81, No. 3, pp. 765–771, 2011

Fig. 1. Technique used for creation of conventional and three adaptive radiotherapy plans. CBCT = cone-beam computed tomography; CTV = clinical target volume.
Adaptive Planning – II

Adaptive radiotherapy in MIBC – An effective method to reduce the irradiated bowel volume. Laura Tuomikoski et al; Radiotherapy and Oncology 99 (2011) 61–66

- Treatment planning was performed in order to determine the changes of volume and shape of the bladder due to filling.
- The images were acquired by using four to five repeated planning CTs.
- The patients emptied their bladder and drank 2–8 dl of water before the scanning.
- The first series of CT images was acquired shortly (with in 3–15 min).
- The following 3–4 scans were taken with a time interval of 15–30 min between the successive scans to get a sufficient range of bladder volume changes for treatment planning.
• CTVs were then anisotropically expanded with anterior and cranial margins of 10 mm and lateral, posterior and caudal margins of 15 mm to create 3–4 elective PTVs.

• Depending on the range of bladder volumes, 3–4 treatment plans for whole bladder PTVs and 2–4 plans for boost PTVs were created.

• The bladder volume in every day CBCT images was compared to different PTV contours in the planning CT images by the physicist and the oncologist who had performed contouring.

• The plan with the smallest PTV was chosen so that the bladder visible in the CBCT image fitted inside the PTV with margins of at least 3 mm in every direction after optimal matching.

• This additional margin was estimated to account for filling of the bladder during the registration and treatment delivery.
Composite Volume
Dose Constraints

- Small bowel V45 < 195cc
- Femoral head D max < 45GY
- Rectum V40 < 40%

In conclusion: without IGRT, generous margins in the range of 2–3 cm have to be applied in order to account for organ motion, implying large treatment volumes and dose-limiting toxicity.
**Disadvantage**

- IMRT offers increased conformity and potential dosimetric improvements to organs at risk (Van Rooijen et al. Turgeon et al.)

- IMRT can be used in selected cases to boost defined gross disease.

- Organ motion is the dominant source of error in the planning and delivery of radiotherapy to the bladder

- Disadvantages include prolonged treatment delivery time, increased MU, the close delineation of the radiation field to the tumor might lead to higher risk of geographic miss.
Radiation Toxicity

**Acute effects:**
- Dysuria
- Urgency
- Frequency
- Diarrhoea

**Late effects:**
- Chronic irritative cystitis
- Hemorrhagic cystitis
- Bladder contracture
- Rectal stricture
- Small bowel obstruction

79% of patients had normal bladder function at 10 yrs
Take Home Message

- 3DCRT is now standard of care for UB
- With advance of RT techniques bladder preservation can easily achievable with dose escalation
- Trimodality is “The treatment regimen” for organ preservation in which Radiation plays principal role
- Newer technology has reduced normal tissue toxicity significantly with improvement in QOL
- No significant benefit of Elective nodal irradiation in radiologically node negative patients
- IGRT with adoptive technique can deliver higher dose with acceptable toxicity in node negative MIBC
Acknowledgment

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Senior Resident, Department of Radiotherapy, PGIMER, Chandigarh

Thank You