Bladder preservation for muscle-invasive bladder cancer

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Controversies in muscle-invasive bladder cancer

• Surgery the optimal treatment strategy for all bladder cancers

• The role of chemotherapy in bladder preservation

• Use of predictive biomarkers to determine treatment
Treatment of muscle invasive bladder cancer (MIBC)

- Depends on TNM staging
- Local v systemic
- Surgery v radiotherapy
- Increasing role of chemotherapy in organ preservation
- 5 year survival ~50%
Patient who have RT are older

Median age
RT: 75 (43-99)
Surg: 68 (37-85)
Patients who have RT have more advanced tumours

Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer.

5yr survival

RT: 35%

Surg: 41%

Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer.


5yr Survival
RT: 57%
Surg: 53%

Disease-specific Survival

Cumulative survival

p-value = 0.507

Years since definitive treatment

The Christie NHS Foundation Trust
The SPARE (Selective bladder Preservation Against Radical Excision) study

- Attempt to answer the question of surgery v radiotherapy

- Opened in July 2007, closed in Jan 2010

- Poor recruitment – only 45 patients recruited

- Reasons for poor recruitment:
  - Patient choice
  - Clinician choice
  - Lack of equipoise
Prognostic factors for MIBC

- Age/performance status
- Stage
- Renal function
- Hydronephrosis
- Unifocal disease – no widespread CIS
Optimal patients for radical radiotherapy treatment

- Localised-disease muscle-invasive cancer
- Maximal Trans-Urethral Resection of Bladder
- Good bladder function
- WHO PS ≤3
Neoadjuvant Chemotherapy for MIBC

- Meta-analysis:
- cisplatin-based regimes
- 5% improved overall survival at 5 yrs
International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy for muscle-invasive bladder cancer

Randomised patients N=976

No CMV N=485
CMV N=491
Neoadjuvant chemotherapy improves overall survival and metastasis-free survival

\( p = 0.04 \)

\( p = 0.001 \)
Adjuvant chemotherapy for bladder cancer

- Meta-analysis of cisplatin-based regimens
- No evidence of benefit
- Cystectomy is a morbid operation – difficult to recruit patients

Standard neoadjuvant chemotherapy

- ¹Gemcitabine/cisplatin 3 weekly
  Cisplatin 70mg/m² D1
  Gemcitabine 1000mg/m² D1+8

- ²Accelerated MVAC 2 weekly with G-CSF
  Methotrexate 30 mg/m², Vinblastine 3 mg/m²
  Doxorubicin 30 mg/m², and Cisplatin 70 mg/m²

Radiotherapy in organ-confined MIBC
A randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy.

5yr Survival
OS: 58%
CSS: 65%
Ongoing questions

- RT dose and fractionation
- RT Volume: pelvic RT vs bladder alone
- RT Technique: adaptive radiotherapy
- Systemic treatment: concurrent chemoradiotherapy
- The role of novel agents
RT Dose and Fractionation

- Two commonly used regimes:
  - 64Gy in 32 fractions and 55 Gy in 20 fractions

- Longer treatment times may lead to less effective treatment

- Shorter course of radiotherapy may have more side-effects
RT Volume: pelvic RT v bladder alone

- No randomised control trials comparing the two
- Increased toxicity with whole pelvis RT due to increased RT to bowel
- Treating bladder alone does not result in decreased survival
UK trials lead the way for bladder preservation in 2011/12

- BC2001
- BCON
Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer BC2001

• 360 patients – PS0/1, 72yrs, T2

• Centre choice of either 55Gy/20# or 64Gy/32#

• Bladder only RT

• D1: Mitomycin (12mg/m\(^2\))
  D1-5 and 16-20: 5FU (500mg/m\(^2\))
BC2001: Loco-regional control is better with chemoradiotherapy

2-yr LRDFS
67% (95% CI: 59%, 74%)
CT = 52/182

54% (95% CI: 46%, 62%)
No CT = 74/178

HR = 0.66 (95% CI: 0.46, 0.95); p=0.02

Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma BCON

• 333 patients – fit for RT, 74yrs, T2 (1:5 T3)

• Either 55Gy/20# or 64Gy/32#

• Bladder only RT

• RT+/- carbogen (2% CO₂/98% O₂ at 15 l/min and nicotinamide (60mg/kg)

Relapse-free survival with CON
Overall survival improves with CON

Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer

GemX

- 50 patients: PS0/1, 67yrs, T2 (1:5 T3)
- 52.5Gy/20#
- RT to bladder only
- Weekly gemcitabine 100mg/m2

GemX: Disease-specific survival

- 3yr disease-specific survival: 82%; 5yr DSS: 78%

GemX does not cause significant patient-reported late toxicity

The Christie Bladder Practice

Bladder cancer ~220

Radical RT ~20

Neoadjuvant chemo ~60

GemX ~60 n~35

Palliative treatment ~70
Optimising bladder preservation – current Christie approach

Urologist: maximal TURBT

PS 0/1 → neoadjuvant chemo

PS 1/2 → GemX

PS 2 → Radical RT: 55/20

3/12 cystoscopy
Neoadjuvant chemotherapy with GemX

- Median age 69 years (range 51-78 years)
- All PS 0 or 1
- 30 patients received cisplatin and gemcitabine
- 3 patients received carboplatin and gemcitabine
- 1 patient received cisplatin and etoposide
- Mean isotope GFR was 89.
No increase in toxicity for patients receiving neo-adjuvant chemotherapy with GemX

<table>
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<th>Toxicity</th>
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<th>Week 4 Urinary</th>
<th>6/52 post radiotherapy Bowl</th>
<th>6/52 post radiotherapy Urinary</th>
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Patients who have salvage cystectomy after bladder preservation have good outcomes.

Novel approaches : New agents and RT

• NCI: Sorafenib + RT Ph I study

• RTOG: Paclitaxel + herceptin in HER2 + bladder cancer PhI/II study

• NCRN: cetuximab with chemotherapy and radiotherapy for muscle invasive bladder cancer (TUXEDO) PhI/II study
Do Predictive Biomarkers have a role in the management of bladder cancer?

- No validated biomarkers predictive for radiotherapy or chemotherapy response or toxicity
- BUT, multiple candidates
MRE11 expression is predictive of cause-specific survival following radical radiotherapy for muscle-invasive bladder cancer.
MRE11 as a predictive factor for RT response

A

Cause-specific survival

Log-rank $P < 0.001$

HR = 0.43 (95% CI: 0.26–0.71)

Survival from RT (mo)

Numbers at risk

Low: 44 15 10 3 1 0

High: 134 88 54 18 8 1

B

Cause-specific survival

Log-rank $P = 0.46$

HR = 1

Survival from cystectomy (mo)

Numbers at risk

Low: 22 15 10 8 6 2

High: 66 35 25 16 9 2

Choudhury et al. Cancer Res; 70(18) September 15, 2010
Further validation of MRE11

Cystectomy Cohort B

Radiotherapy Cohort C

Laurberg et al. BJUi. 2012
Could tumour necrosis be a biomarker for hypoxia and benefit from hypoxia modified treatment?
Necrosis predicts benefit from hypoxia-modifying therapy in patients with high risk bladder cancer enrolled in a phase III randomised trial.

**Tumour necrosis**

<table>
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<th>Deaths/N</th>
<th>HRuv</th>
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<td>58/110</td>
<td>1.30</td>
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Eustace et al. Radiotherapy and Oncology 2012
Ongoing biomarker work

- MOBIBLART – further validation of MRE11
- GemTrans – are gemcitabine metabolites associated with GemX outcomes?
- MCRC biobank
Other markers of interest

- DNA repair
- P53, HERII
- Apoptosis
- Androgen receptor
MRI as a biomarker in MIBC

- Not fully validated
- Multiple parameters
- Multiple protocols
DCE-MRI predicts response to neoadjuvant chemotherapy prior to cystectomy

Relative signal intensity and plasma perfusion are significantly associated with post treatment response, confirmed at cystectomy.
But its more complicated in bladder preservation….

No clear associations between relative signal intensity and plasma perfusion associated with post treatment response
Future directions in the UK
Potential national UK bladder studies

- **RAIDER**
  - Standard v adaptive RT v adaptive RT with concomitant boost
  - Toxicity end point

- **BIOPIC**
Conclusions

• Outcomes with radiotherapy with radiosensitisation are comparable to surgery

• Neoadjuvant chemotherapy further improves treatment outcomes without increasing toxicity

• Further validation of predictive biomarkers is ongoing, but some markers show promise

• Its all about patient selection……
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