Radiotherapy for Advanced Bladder Cancer

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What is Radiotherapy?
• “電療”：NOT Electricity / Electric Current
• 放射治療：High-Energy Radiation

General Principles for Curative Radiotherapy
• Give as high dose as possible
• Radiotherapy dose limited by dose constraints of surrounding critical structures
• The larger the radiotherapy field, the more surrounding organs likely included, the more difficult it is to give high dose
• Radiotherapy field as small as possible for curative treatment
• Need to give margin to “uncertainties”
  • Patient movement
  • Organ movement / variation in sizes
  • Microscopic disease spread

Radiotherapy as Curative Treatment for Bladder Cancer

Linear Accelerator

http://www3.ha.org.hk/qmh/departmen
t/Clinical%20Department/COD/COD_Webpag_20101019_files/Page998.htm
Curative Radiotherapy

- Stable position of patient
  - Supine
- Empty bladder
  - More consistent volume
  - Smaller treatment field size

Radiotherapy to Pelvis – Side Effects

- Short-Term Side Effects
  - May appear during radiotherapy, but will usually subside a few weeks after completion of treatment
  - Common
    - Nausea, malaise, poor appetite
    - Dryness and redness of irradiated skin, similar to sunburn
    - Hair loss in irradiated area
    - Bladder inflammation causing cramps and diarrhoea
    - Inflammation of the rectum and anus causing pain, irritation, discharge and sometimes bleeding
    - Disturbance of the menstrual cycle (female)
    - Vaginal discharge, irritation, pain, and sometimes bleeding (female)
  - Uncommon
    - Depression of blood counts causing increased risk of infection and bleeding
    - Usually occurs only in patients where large areas are being irradiated
    - More common in those who are also receiving chemotherapy

- Long-Term Side Effects
  - May occur months or years after radiotherapy and may persist
  - Common
    - Skin thickening and discoloration
    - Swelling of the genitalia or legs
    - Radiation damage to the bowel causing chronic diarrhoea or irregular bowel habits
    - Bladder damage with loss of capacity and frequency of urination
    - Ovarian damage causing infertility, sterility or premature menopause (female)
    - Vaginal damage leading to dryness, shrinkage, or sexual dysfunction (female)
    - Testicular damage causing reduced sperm counts, infertility or sterility
    - Impotence or sexual dysfunction (male)
  - Uncommon
    - Permanent hair loss
    - Radiation damage to the bowel causing obstruction, ulceration, bleeding, or poor absorption
    - Bone damage leading to fractures
    - Nerve damage causing pain, loss of strength or feeling in legs and/or loss of control of bladder or rectum
    - Radiation-induced cancer may occur very rarely
    - In rare occasions, patients may develop severe life threatening complications due to radiotherapy
    - During radiotherapy, both male and female patients should take contraceptive measures
What Are the Outcomes of Radical Radiotherapy?

Examples of More Recent Clinical Studies
Components of Successful Radical Radiotherapy

- Concurrent with chemotherapy
  - Cisplatin-based
    - Most common and well-studied
    - Especially if renal function impaired
- Maximal TURBT
  - Incomplete resection being unfavourable prognostic factor for ability to preserve bladder and for survival
- Salvage cystectomy when possible

Purpose

Multiple prospective Radiation Therapy Oncology Group (RTOG) protocols have evaluated bladder-preserving combined-modality therapy (CMT) for muscle-invasive bladder cancer (MIBC), reserving cystectomy for salvage treatment. We performed a pooled analysis of long-term outcomes in patients with MIBC enrolled across multiple studies.

Patients and Methods

Four hundred sixty-eight patients with MIBC were enrolled onto six RTOG bladder-preservation studies, including five phase II studies (RTOG 8802, 9508, 9706, 9900, and 0233) and one phase III study (RTOG 9403). Overall survival (OS) was estimated using the Kaplan-Meier method, and disease-specific survival (DSS), muscle-invasive and non-muscle-invasive local failure (LF), and distant metastases (DM) were estimated by the cumulative incidence method.

Results

The median age of patients was 66 years (range, 20 to 96 years), and 66% were male patients. The percentage of patients with N2 or N3 disease was 29%, T3 in 26%, and T4a in 4% of patients. Complete response to CMT was documented in 41% of patients. With a median follow-up of 34.3 years among patients and 7.8 years among survivors (in 2006), the 5- and 10-year OS rates were 61% and 39%, respectively, and the 5- and 10-year DSS rates were 71% and 60%, respectively. The 5- and 10-year estimates of muscle-invasive LF, non-muscle-invasive LF, and DM were 13% and 14%, 31% and 36%, and 31% and 36%, respectively.

Conclusion

This pooled analysis of multicenter, prospective RTOG bladder-preserving CMT protocols demonstrates long-term DSS comparable to modern immediate cystectomy studies, for patients with similarly staged MIBC. Given the low incidence of late recurrences with long-term follow-up, CMT can be considered as an alternative to radical cystectomy, especially in elderly patients not well-suitied for surgery.
**NICE Guideline 2015**

- Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable
- Include in the discussion
  - prognosis with or without treatment
  - limited evidence about whether surgery or radiotherapy with radiosensitiser is the most effective cancer treatment
  - benefits and risks of surgery and radiotherapy with radiosensitiser, including impact on sexual and bowel function and risk of death as a result of treatment
- Use radiosensitiser when giving radical radiotherapy (e.g. 64Gy in 32 fractions over 6.5 weeks or 55Gy in 20 fractions over 4 weeks)

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*Similarity in survival likely due to prompt salvage cystectomy*
Neoadjuvant Radiotherapy Before Cystectomy?

- Significant downstaging effect
- No significant survival benefit as compared to radical cystectomy alone
- Might be associated with increased risk of postoperative intestinal complications
- Role of neoadjuvant chemotherapy?

Adjuvant Radiotherapy Following Cystectomy?

- Limited data
  - One older randomised study of 236 patients with pT3a to pT4a bladder cancer demonstrated improvement in 5-year disease-free survival and local control compared with surgery alone (Zaghloul et al., IJROBP 1992; 23(3): 511-517)
- Potential significant morbidity
  - Dose-limiting tissues
    - Intestinal epithelium
    - Intact loops of bowel
    - Those of orthotopic neobladder
  - Late responding connective tissues around anastomosis of ureter, urethra, and pelvis
  - Frequency of radiation-induced obstruction of small bowel as high as 37%
- 25% and 10% of patients required surgery or died respectively

General Principles of Palliative Radiotherapy

- Aims of Palliative Radiotherapy
  - Improvement or elimination of symptoms due to incurable cancer
  - Effective in 75% of cases

- General Principles
  - Type of palliative radiation and its complexity must be adapted to each case
  - Wide radiation field but protecting critical areas
  - Short fractions and high doses per fraction preferred
  - Patient must be in most comfortable position while treated
  - Delays should be avoided
    - Use the unit or the treatment available which takes the shortest time

Palliative Radiotherapy for Bladder Cancer

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Multicentre randomised trial
Comparing 21Gy in 7 fractions with 35Gy in 10 fractions
Muscle-invasive bladder cancer causing local symptoms
Unsuitable for chemotherapy or radical radiotherapy (unfit / tumour stage too advanced)
Life expectancy at least 3 months
Assessments
Two weeks after end of radiotherapy
Three months from start of treatment course

Palliative Radiotherapy for Bladder Cancer
Royal College of Radiologists Suggestions (Radiotherapy Dose-Fractionation, June 2006)
For the palliation of local symptoms from bladder cancer, 21Gy in 3 fractions on alternate days in 1 week is the regimen of choice
A single fraction of 6-8Gy may provide useful palliation in patients who are unfit for the recommended regimen
In daily practice, may consider longer course more fractionated radiotherapy hoping for more durable local control
Re-irradiation
Radiation dose usually limited by tolerance of surrounding critical structures
For palliation of recurrent symptoms but can unlikely result in any disease control

Conclusion
For patients who are suffering from muscle invasive bladder cancer, radiotherapy can be an option for those who are keen to consider bladder preservation.
Radiotherapy is more effective when it is given in combination with chemotherapy and after an endoscopic resection that is as complete as possible is performed.
For those patients that are considered not a candidate for curative treatment, radiotherapy can still be offered as a means of local symptom palliation.
Multidisciplinary approach to achieve the best outcome.
Thank You For Your
Attention