COMBINED DRUG RADIATION TREATMENT:
URINARY BLADDER CANCER

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ESTRO course, Yogyakarta 2014
- 65-year old male, no significant medical problems, moderate smoker,
- 6-month history of hematuria, voiding problems
- **PSA:** 1.7 ng/ml
- **DRE:** normal
- **Cystoscopy and TURBT:**
  TCC T2 G3
Worldwide health problem

The 4th most common malignancy in men (10th in women): white male>

The majority are transitional (urothelial) cancers

Squamous cell carcinoma (schistosomal infection)
Crude incidence: 19.5/100,000/year
Mortality: 7.9/100,000/year
70% of patients are > 65 years of age
20% are muscle invasive cancers

Bellmunt et al. 2010
TREATMENT OPTIONS

**NON INVASIVE \( \leq T1 \)**

- **TURBT**
- Intravesical ChT
- or immunotherapy
- Cystectomy \((T1 \ G3, \ \text{multifocal, residual, recurrent})\)

**MUSCLE INVASIVE \( \geq T2 \)**

- **SURGERY**
- or
- ORGAN PRESERVATION
  - (Multimodality treatment)

TURBT: Transurethral Resection of Bladder Tumor
Patients with muscle invasive bladder cancer M0

- **Fit for surgery:**
  bladder preservation as an alternative to cystectomy

- **Unfit for surgery:**
  bladder preservation as an alternative to cystectomy palliation
Breast carcinoma
Anal carcinoma
Laryngeal carcinoma
Esophageal carcinoma
Limb sarcomas
Prostate cancer
OPTIONS OF BLADDER SPARING IN T2/T3A TCC

- TURBT alone
- RT alone
- Chemotherapy alone
- Combined modality strategies:
  - Chemotherapy followed by partial cystectomy
  - Chemoradiotherapy
  - TURBT and RT BIMODALITY
  - TURBT and chemo-radiotherapy TRIMODALITY
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EVOLUTION OF MULTIMODALITY
BLADDER PRESERVATION

1974-81
Radiation

1981-86
Radiation sensitizer
TURBT

1986-93
Neoadjuvant chemo
Response evaluation

1994-98
Accelerated radiation
Adjuvant chemo

1999-09
Enhanced radiation sensitizer

RT → RT + C → RT + C → bidRT+C/5Fu → bidRT+C/Tax

MCVx2 → MCVx3 → Novel
ENHANCING THERAPEUTIC RATIO

- Neutrons NS
- Hyperbaric oxygen NS
- Hyperthermia NS
- Misonidazole NS
- Dose escalation and partial bladder RT (UK trial) NS
- RT vs. Carbogen + RT: better overall survival (Hoskin 2010)
- Brachytherapy needs expertise
- New radiosensitizers (gemcitabine, taxanes?)
- Novel drugs (trastuzumab): under investigation

Carbogen: mixture of 95% oxygen and 5% carbon dioxide
Doses ranged between 54-70 Gy

Multivariate analysis: poorer outcome if < 57.5-60 Gy
BLADDER PRESERVATION: TRIMODALITY

No randomized trial TRIMODALITY vs. surgery is available

All conclusions are of level 2b-3 evidence
Expertise:

1. Trento, Italy
2. University of Erlangen, Germany
3. University of Paris, France
4. Massachusetts General Hospital MGH, MA, USA
5. RTOG
Maximal TURBT

- Concomitant chemo-radiotherapy to whole bladder+pelvis (40-50 Gy)
- Concomitant CHT-RT Boost to bladder (to 60-66 Gy)

Cystoscopic assessment + urine cytology +/- biopsy or TUR

- CR: Adjuvant chemotherapy
- > T0: Cystectomy

And the winner is: Upfront CHT-RT
5-year survival rates 39-63% (as surgery)

OS and distant control as after surgery: the need to improve systemic therapies!

60% of surviving patients maintain well-functioning bladder (40% of all patients)

79% delighted with their bladder function

The incidence of cystectomy for palliation or treatment-related toxicity is low.

Initial maximum TURBT and post-RT tumor response – strong prognostic factors for OS and bladder preservation.

No impact of age and gender.

Prognostic factors for local control and function:

- Solitary tumor
- Away from the bladder dome
- < 5 cm
- Visibly complete TURBT
- No in situ component
- No hydronephrosis
- Hb >10 g/dl
- Negative lymph nodes
- Good bladder capacity

Fung CY 1991, Shipley WU 1997
Trimodality bladder preservation with conventional schedules:

TURBT → radiochemotherapy -/+ adjuvant chemotherapy

or

RADIATION THERAPY ONCOLOGY GROUP
RTOG 0524
A PHASE I/II TRIAL OF A COMBINATION OF PAACLITAXEL AND TRASTUZUMAB WITH DAILY IRRADIATION OR PAACLITAXEL ALONE WITH DAILY IRRADIATION FOLLOWING TRANSURETHRAL SURGERY FOR NON-CYSTECTOMY CANDIDATES WITH MUSCLE-INVASIVE BLADDER CANCER
NCI-supplied agent: trastuzumab (NSC 688097, IND 6667)
56 pts:

45% refused cystectomy
34% unresectable tumor
21% medically unfit for surgery
57% completed planned trimodality

unresectable tumor 63%
refused cystectomy 60%
medically unfit for surgery 42%
Bimodal: TURBT + RT

Maximum TURBT

Radiotherapy to at least 60 Gy (limited volumes?)

- Normal tissue sparing technologies: IG-IMRT

- Careful patient monitoring and supportive care
Results of radical radiotherapy alone in patients with muscle invasive bladder cancer

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Candian experience: Randomized trial

PMH 1991: 99 pts TURBT + RT with or without CDDP

Coppin JCO 1996
Table 6. Comparison of four different treatment regimens for bladder cancer over the past 25 years

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Acute toxicity ≥Grade 3 (%)

- Leucocytopenia: 0, 26.3, 25.4, 15.3
- Thrombocytopenia: 0, 12.6, 7.6, 12.5
- Anemia: 0, 1.1, 2, 1.8
- Gastrointestinal: 0.8, 2, 3.4, 9.8
- Genitourinary: 9.6, 5.5, 8.2, 8

Late toxicity ≥Grade 3 (%)

- Gastrointestinal: 1.6, 2.2, 7.7, 4
- Genitourinary: 4, 5.6, 9.8, 3.6

Abbreviations: CR = complete response; OS + bladder = overall survival with bladder preserved after 5 years; RT = radiotherapy.
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cT2-T4 N0 M0

Medically operable
- High risk
  - cT4: Multifocal tumour
  - CIS: Incomplete TUR
  - Hydronephrosis
- Average risk
  - cT2-T3: Unifocal tumour
  - No CIS: Complete TUR
  - No hydronephrosis

Medically inoperable
- Definitive chemoradiotherapy

Palliative dose RT

TURBT+ full dose RT

Radical cystectomy

Selective bladder preservation
Palliative radiotherapy

Indications: hematuria, pain

Schedules: 30 Gy in 10 fractions

1. Advances in surgical TURBT, chemotherapy and radiotherapy have made **trimodality bladder treatment** an effective and safe alternative to radical cystectomy in selected patients.

2. In less fit patients **bimodality approach** might be considered.

3. In other patients **RT** still can offer good palliation.
Patients with muscle invasive bladder cancer

- **Fit for surgery:**
  trimodality bladder preservation as an alternative to cystectomy

- **Unfit for surgery:**
  trimodality bladder preservation as an alternative to cystectomy
  bimodality bladder preservation as an alternative to cystectomy
  palliation

Smith et al. BJU Int 2013
1. Advances in surgical transurethral resection of bladder tumors, chemotherapy and radiotherapy have made trimodality bladder treatment **an effective and safe alternative to radical cystectomy**

2. **All non-complete** responders or those who relapse in the muscle layer should be salvaged by **cystectomy**

3. **High precision radiotherapy** is necessary in order to improve therapeutic index:
   - tumor definition
   - dose delivery and verification (tumor tracking due to organ motion)