




***RADIOTHERAPY IN THE
MANAGEMENT OF CANCERS OF THE
URINARY BLADDER***



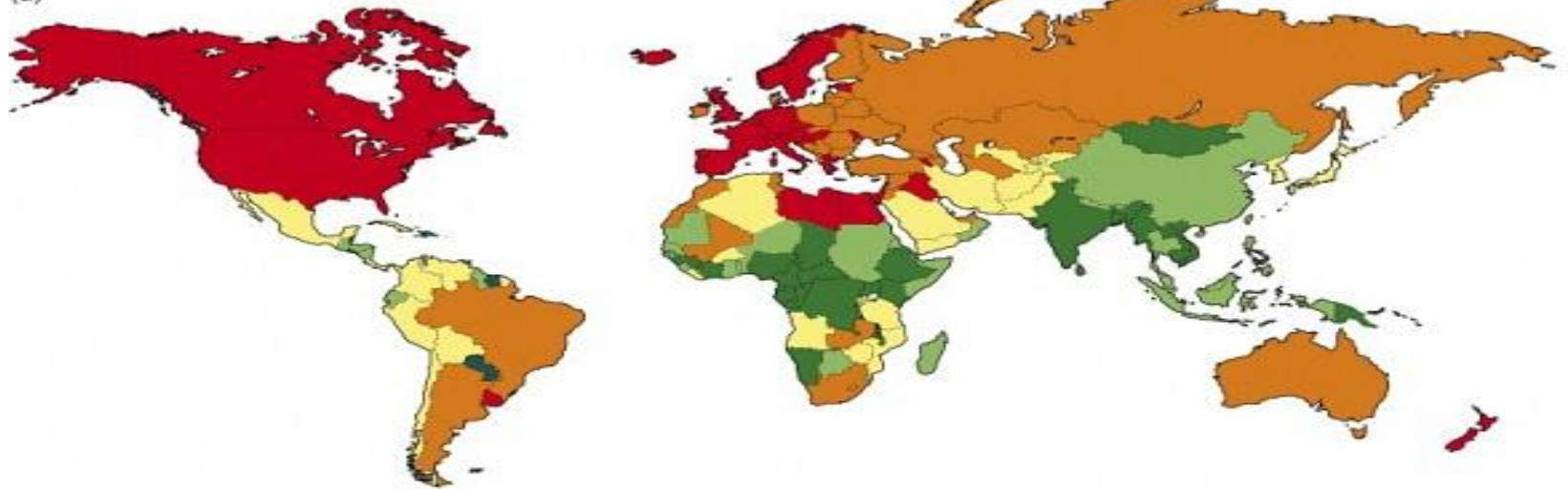
INTRODUCTION

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- Incidence: 20/100000/year (Europe)
 - Mortality: 8-9/100000/year

 - Worldwide fourth most common cancer in men
 - Incidence: 31.1 mortality: 12.1
 - Seventh most common cancer in women
 - Incidence: 9.5 mortality: 4.5

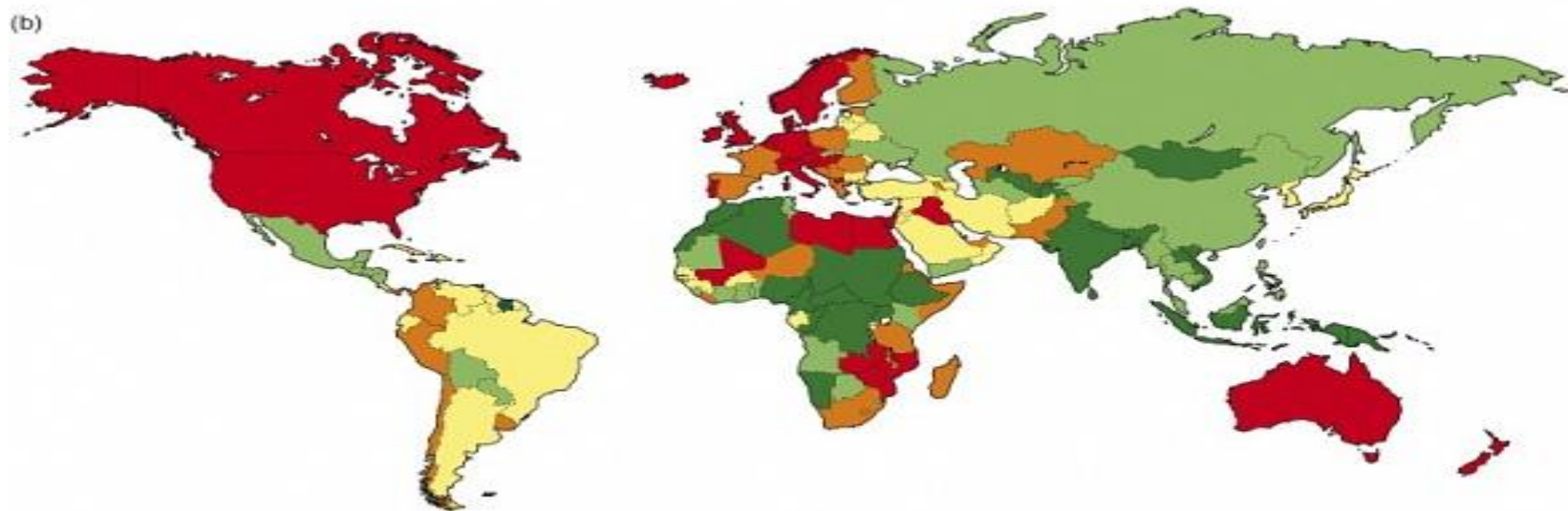
 - At diagnosis >70%: > 65 y of age

(a)



GLOBOCAN, 2002, IARC

(b)



GLOBOCAN, 2002, IARC

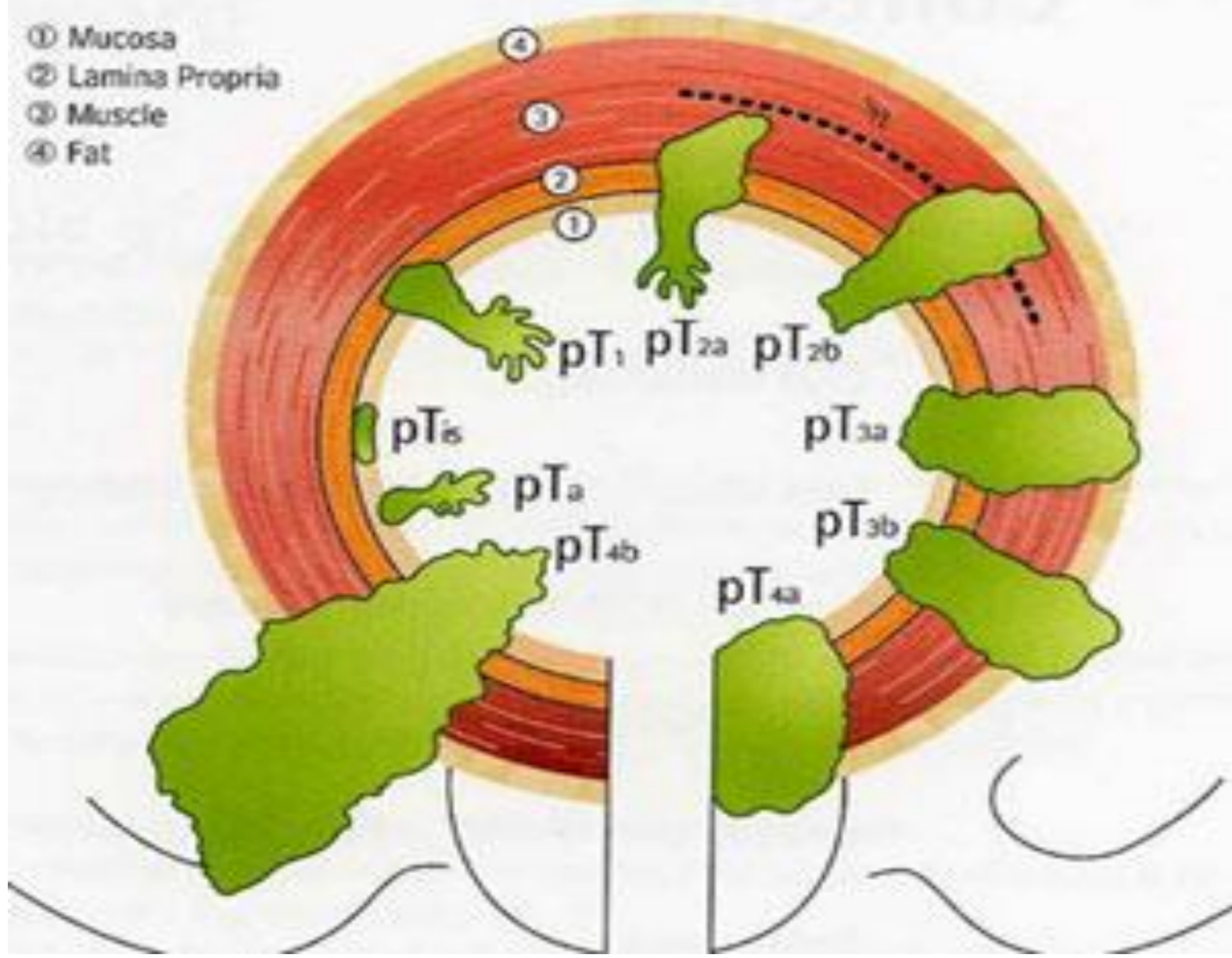
Histology

- 90-95% transitional-cell carcinoma
- 3% squamous-cell carcinoma
- 2% adenocarcinoma
- <1% small-cell carcinoma

Entities

- 75-85% superficial bladder cancer
pTa, pTis, pT1
- 10-15% muscle-invasive bladder cancer
pT2, pT3, pT4
- 5% metastatic bladder cancer
N+, M+

- ① Mucosa
- ② Lamina Propria
- ③ Muscle
- ④ Fat



Stage and Prognosis

Stage	TNM	5-y. Survival
0	Ta/Tis NoMo	>85%
I	T1NoMo	65-75%
II	T2a-b NoMo	57%
III	T3a-4aNoMo	31%
IV	T4bNoMo	24%
	each T N+Mo	14%
	each T M+	med. 6-9 Mo

Treatment of choice for:

Superficial Bladder tumours:

- The most common presentation is of Ta and T1 tumor.
- TURBT is the treatment of choice for Ta, G1 tumors
- High grade lesions may require adjuvant intra-vesical BCG.

Muscle Invasive Bladder cancers:

- **Radical cystectomy has been standard of care for two decades**
- But organ-preserving regimens using multiple-modality therapy, consisting of TUR followed by irradiation and concurrent chemotherapy, emerging as viable alternatives.
- The ultimate goal is to maximize the quality of life by refining the treatment choice.

Results of radical cystectomy

Stage	Recurrence-Free / 5 years	Overall Survival
Organ-confined (\leq pT2pNo)	73%	62%
non-organ-confined ($>$ pT2pNo)	56%	49%
Positive lymph nodes (pT1-4, pN+)	33%	24%

Madersbacher et al JCO 2003;21:690



***RADIOTHERAPY IN BLADDER
CANCERS***

Why radiotherapy?

- In a large series of high risk T1 cancers treated with either TURBT plus RT/RCT (*University of Erlangen*), only 15% of patients progressed to muscle-invasive disease after 5 years and more than 80% of those alive at 5 years preserved their bladder.
- In patients with unifocal T2-T3a disease, <5cm size, no hydronephrosis, good initial bladder function and visibly complete TURBT..... bladder preserving approach is preferred .
- **Radiotherapy alone** is being used **less** frequently in the management of patients with bladder cancer. It became, however, an important **part of a multimodality bladder preservation program**.

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- The five year control ranged from 31% to 45% for the entire population and from 49% to 79% for patients with complete response.

Factors reported as having a significant favorable effect on local control with RT include:

- Early clinical stage (T2 and T3a)
- Absence of ureteral obstruction
- Complete response
- Visibly complete TURBT
- Absence of coexisting CIS
- Small tumor size (<5cm in diameter)
- Solitary tumors
- Tumor configuration (papillary vs. sessile)
- Hemoglobin level (>10g/dl)

When is radiotherapy delivered??

- Radiation therapy for cancers of the urinary bladder can be delivered as external beam or as brachytherapy; and the intent of treatment can be:
- Pre-operative
- Post-operative
- Concurrent chemo-radiation as a part of multi-modality bladder sparing protocol
- Radiotherapy alone especially in elderly patients
- Palliative radiotherapy

Pre-operative Radiotherapy

The aims of preoperative radiotherapy include:

- Tumor size reduction in locally advanced, muscle-invasive disease, resulting in down staging and make surgery easier,
- Decrease in the incidence of local recurrence following radical cystectomy,
- Decrease in the incidence of distant metastasis,
- Improvement of survival
- No increase in the incidence of surgical complications.

Evidence for pre-operative radiation

- Study of 724 bladder cancer patients at M.D. Anderson Hospital. Radiotherapy: 50 Gy/25 #/5 weeks, followed 6 weeks later by radical cystectomy.
- Treatment results in this group (I) were compared with patients who received definitive radiotherapy alone (group II) and postoperative irradiation (group III). The 5- and 10-year survival were 23% and 20%, respectively, for group I; 16% and 8% for group II; and 40% and 14%, respectively, for group III patients.

Benefit seen in:

- Improving overall survival and disease-free survival
- Increase in freedom from distant metastasis
- Recommended in young patients with T3 disease

However when compared to definitive chemo-radiation, there is no significant improvement in bladder preservation.

Post-operative Radiotherapy

- Indicated when there is extravesical disease or positive surgical margins.
- Administration of adjuvant irradiation decreases probability of tumor recurrence following radical cystectomy.
- However morbidity of post operative radiation is high due to small bowel toxicity that occupies pelvis after cystectomy.

TUR and adjuvant Radio-Chemotherapy

- **5 year Survival** **50-65%**
- **Preservation of Bladder** **38-43%**

Radiotherapy in the Elderly

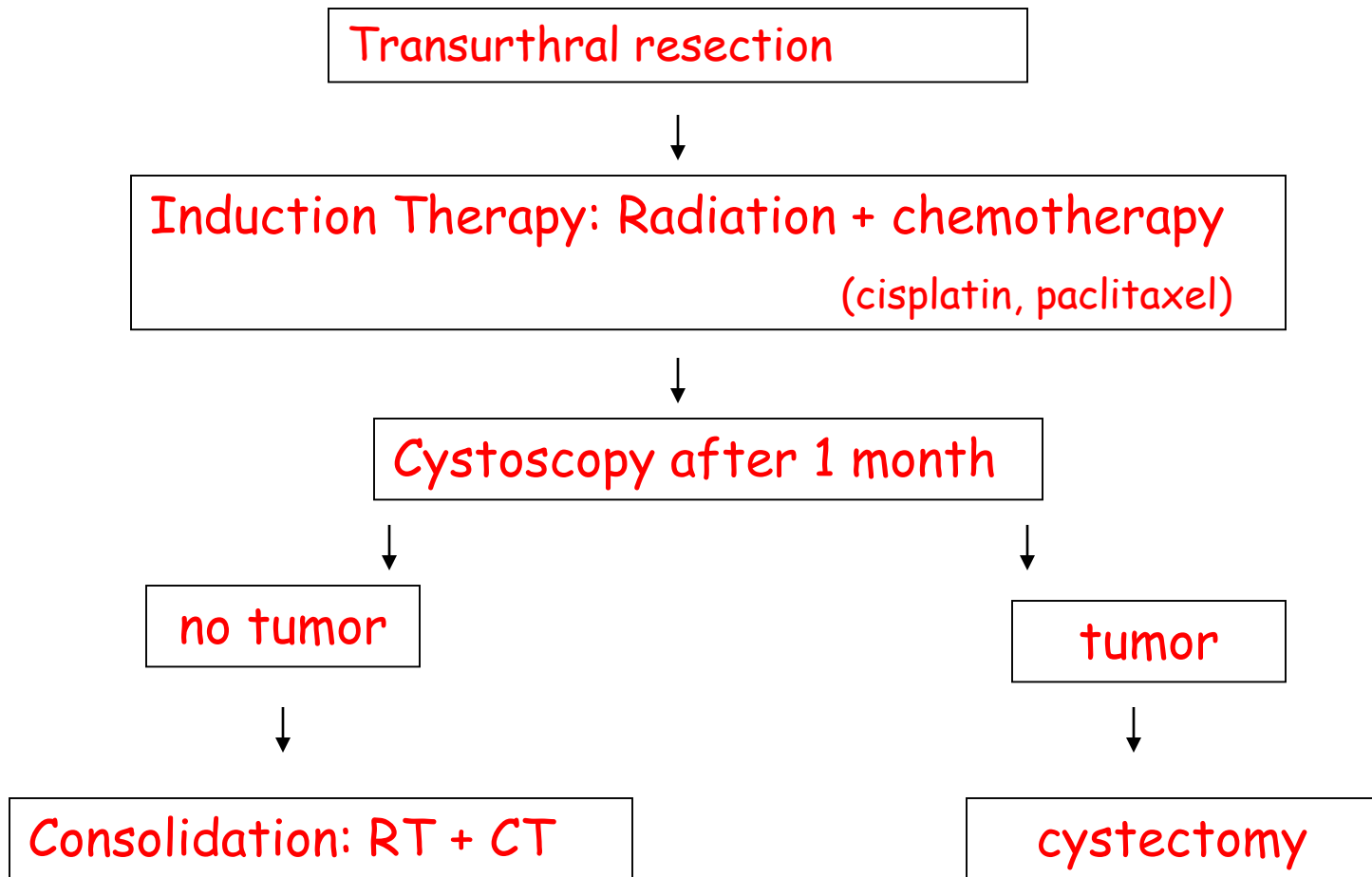
- These patients may also have coexisting medical conditions contraindicating the use of conventional bladder-sparing therapy or radical cystectomy.
- Radiotherapy alone consisting of a 6- to 7-week course of daily treatments may create a hardship on the patient
- On the other hand no-treatment option is likely to lead to distressing symptoms and signs of progressive disease such as pain, gross hematuria, frequency, and dysuria.
- Duchesne et al conducted a prospective randomized trial in 500 patients to compare the outcome in hypofractionated RT. There was no significant difference between the two treatment groups (35 Gy/10 # Vs 21 Gy / 7 #) in important study end points, including palliative effect, toxicity, and survival

Bladder-sparing therapy for invasive bladder cancer

- High probability of subsequent distant metastasis after cystectomy or radiotherapy alone (50% within 2 years)
- Radiotherapy alone in comparison with cystectomy has inferior results (local control 40%)
- Muscle-invasive bladder cancer is often a systemic disease

→HENCE Need for combined modality therapy

Bladder-sparing protocol



Combined Radio- and Chemotherapy

	CR	5y.OS
• Radiotherapy	57%	47%
• RT and cisplatin	85%	69%
• RT and carboplatin	70%	57%

Birkenhake et al. Strahlenther Onkol 1998;174:121

Combined-modality treatment and organ preservation in invasive bladder cancer

Rödel et al. JCO 2002;20:3061

415 patients with T1 high-risk, T1-4, No-1

Treatment: 1. Transurethral resection

2. RT (n=126), RCT (n=289)

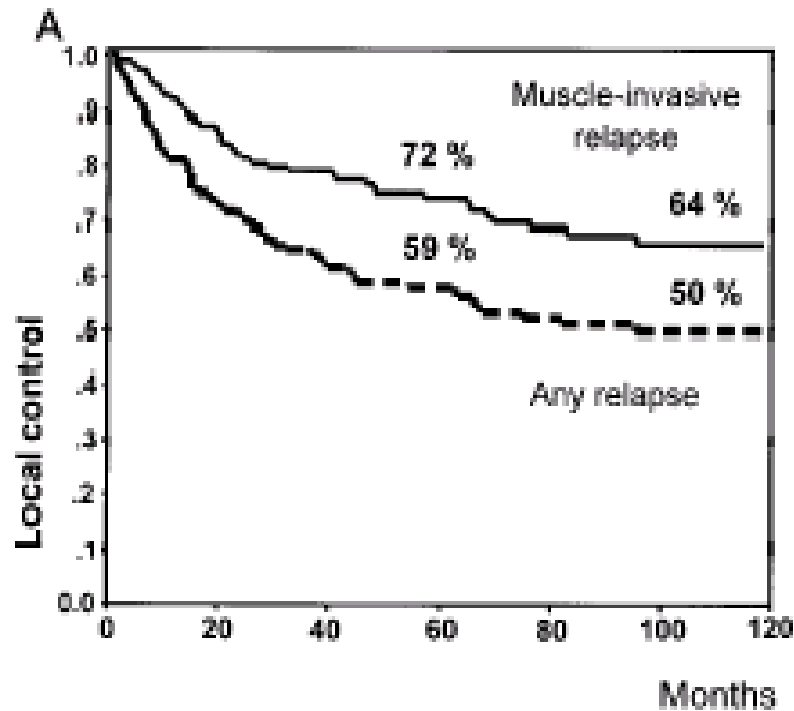
RT median 54 Gy, CT cisplatin week 1, 5

3. Restaging-TUR

Combined-modality treatment and organ preservation in invasive bladder cancer

- Rödel et al. JCO 2002;20:3061
- **Complete remission** **72%**
- **Local control after CR** **64%** (10 y.)
- **distant metastasis** **35%** (10 y.)
- **Disease-specific survival** **42%** (10 y.)
- **Preservation of bladder** **>80%**

Local control



Distant metastasis

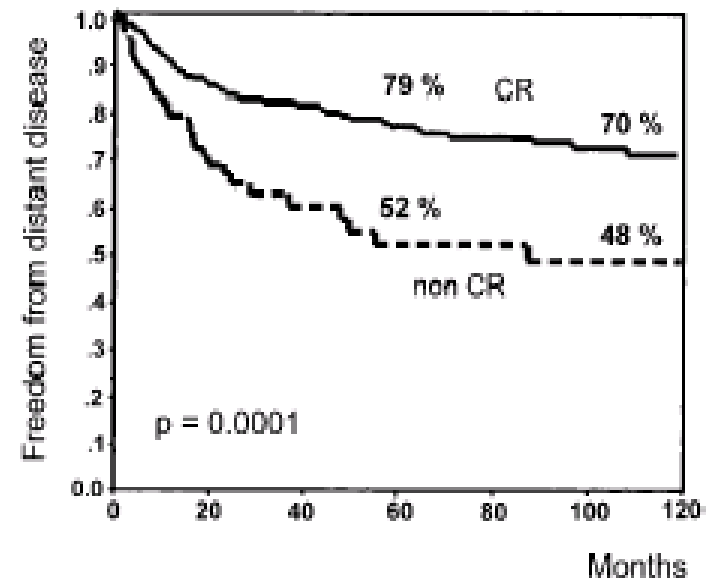


Fig 5. Freedom from distant metastases, stratified by initial tumor response (CR, n = 288; non-CR, n = 110).

Table 1. Trials of Combined Modality Treatment and Selective Organ Preservation

Study/Author (Reference)	Combined Therapy Used	No. of Patients	5-Year Overall Survival (%)	5-Year Survival with Bladder Preservation (%)
Erlangen-Germany/Rodel et al. [27]	TURBT, EBRT ± chemo (Cisplatin, carboplatin, or cisplatin and 5-FU)	415 (RCT: cisplatin, 82; carboplatin, 61; 5FU/cisplatin, 87)	50	42
MGH –Shipley 2003 [28]	TURBT, ± MCV, EBRT + cisplatin	190	54	45
RTOG 8903/Shipley et al. [29]	TURBT, ± MCV, EBRT + cisplatin	123	49	38
Univ. Paris/Housset et al. [30]	TURBT, 5-FU, EBRT + cisplatin	120	63	NA

EBRT, external beam radiotherapy; 5-FU, 5-fluorouracil; MCV, methotrexate, Cisplatin, Vinblastine; MGH, Massachusetts General Hospital; RTOG, Radiation Therapy Oncology Group; TURBT, transurethral resection of bladder tumor.


How is Radiotherapy delivered?


Radiotherapy can be either


- External Beam or Brachytherapy.
- For external beam radiotherapy, initial treatment volume includes the whole bladder, proximal urethra, and, in male patients, the prostate with the prostatic urethra and the regional lymphatics. The regional lymphatics adjacent to the bladder include hypogastric, external iliac, and obturator lymph nodes.
- Boost volume usually includes the bladder or part of bladder with a 2-cm margin.

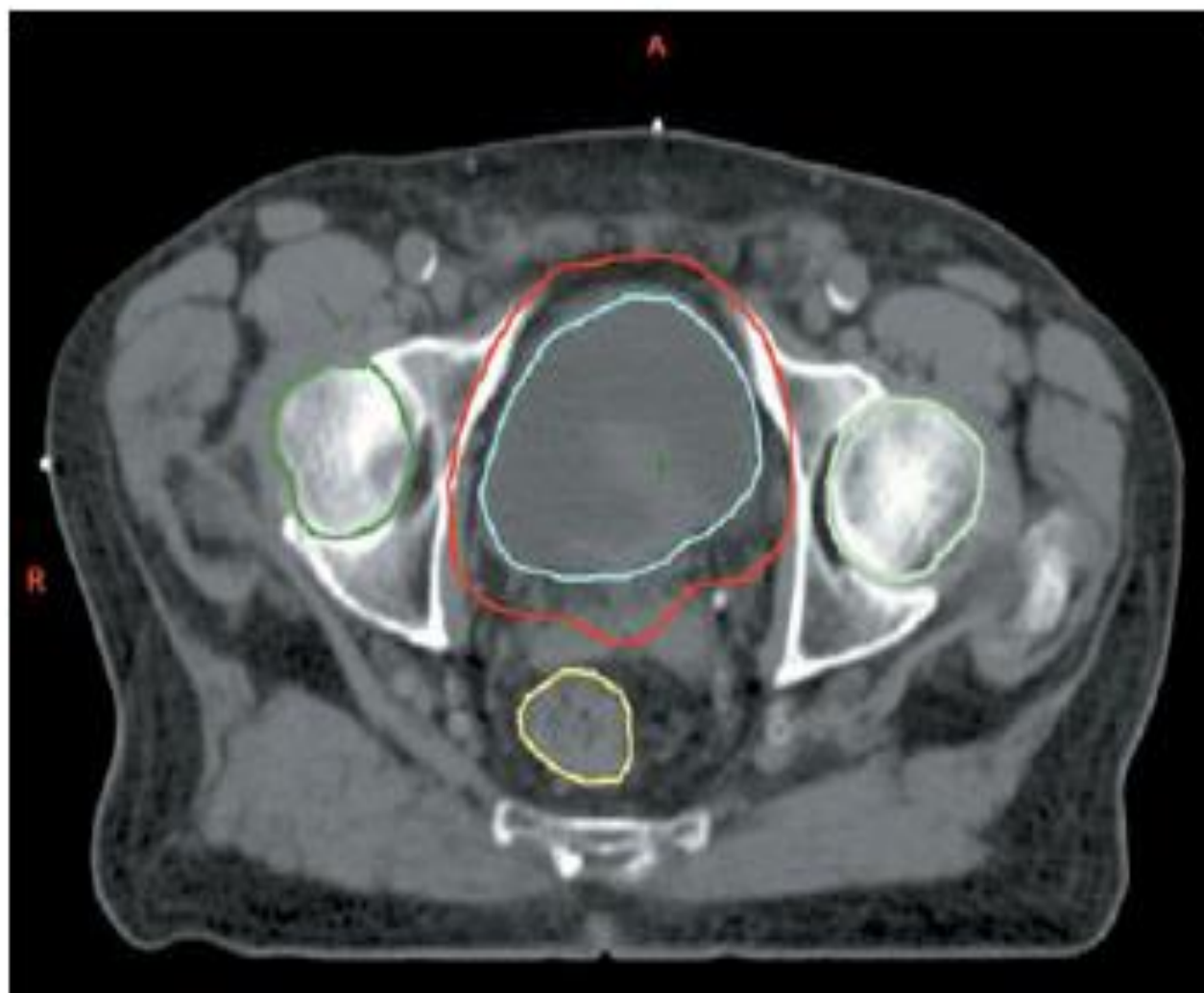
Anatomic extent of the radiation portals:

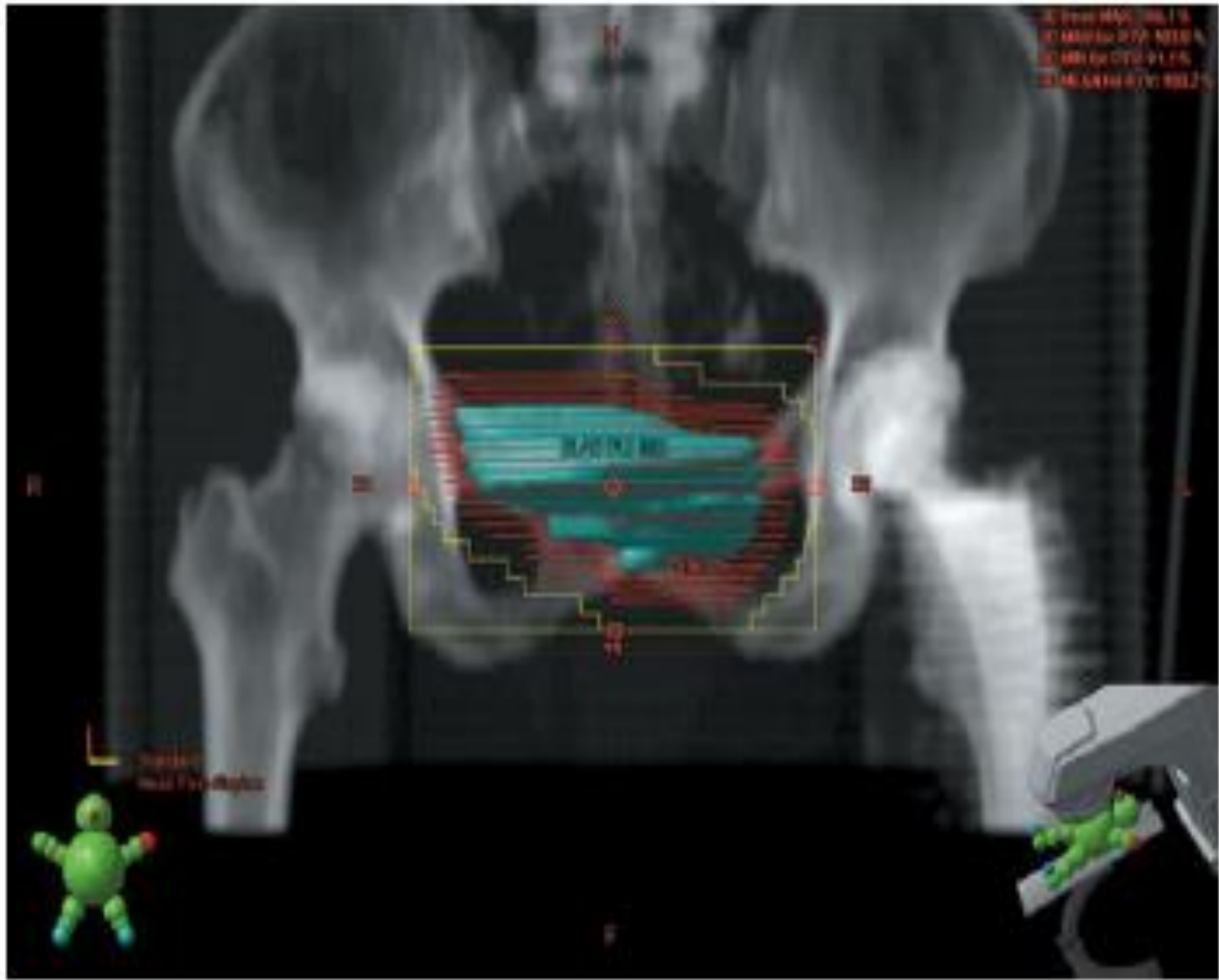
- The anterior–posterior fields extend *laterally* about 1.5 cm to the bony pelvis at its widest section with inferior corners shielded to protect the femoral heads.
- The lateral fields extend *anteriorly* to about 1.5 to 2 cm from the most anterior aspect of the bladder as seen CT.
- The posterior border lies about 2.5 cm posterior to the most posterior aspect of the bladder and falls within the rectum. Inferiorly, the tissue above the symphysis and the anal canal is shielded.
- The inferior border is placed below the middle of the obturator foramen.
- The superior border is usually at the L5-S1 disc space

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- A four-field box technique is used most frequently as it provides a relatively homogeneous dose distribution over the treated volume, while keeping the radiation dose outside this volume to about 50% of the intended tumor dose.
 - Because much of the bladder is anterior to the coronal midplane, anterior weightage is given, relative to the posterior one.
 - The boost fields include either the whole bladder or only the involved part of the bladder with at least a 2-cm margin. Techniques may include 4 field box, two lateral fields, three or four oblique fields, or rotational arc techniques.
 - Commonly accepted treatment schedule is 180-200 cGy per day to a total of 45 to 50 Gy to the whole pelvis, followed by a boost to a smaller volume to a combined total dose of 60 to 65 Gy

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- For treatment planning, a CT scan is performed with the patient supine in the treatment position with arms folded across the chest with ankle supports to stabilise the legs and pelvis, and a knee support for comfort.
 - The bladder should be emptied immediately before scanning and treatment, to reduce the volume irradiated and doses to normal tissues.
 - The rectum should be empty to reduce organ motion and interfractional variations.
 - A small volume of oral contrast is given 1 h before the planning CT scan to show the small bowel.
 - The scan is performed with 3–5 mm slices from the lower border of L5 to the inferior border of the ischial tuberosities.

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- The GTV is the primary bladder tumour
 - CTV is the GTV and the whole bladder. In patients with tumours at the bladder base, the proximal urethra and (in men) the prostate and prostatic urethra is included in the CTV
 - PTV is the CTV with a 1.5–2 cm margin.






Newer treatment techniques


- **Teletherapy**

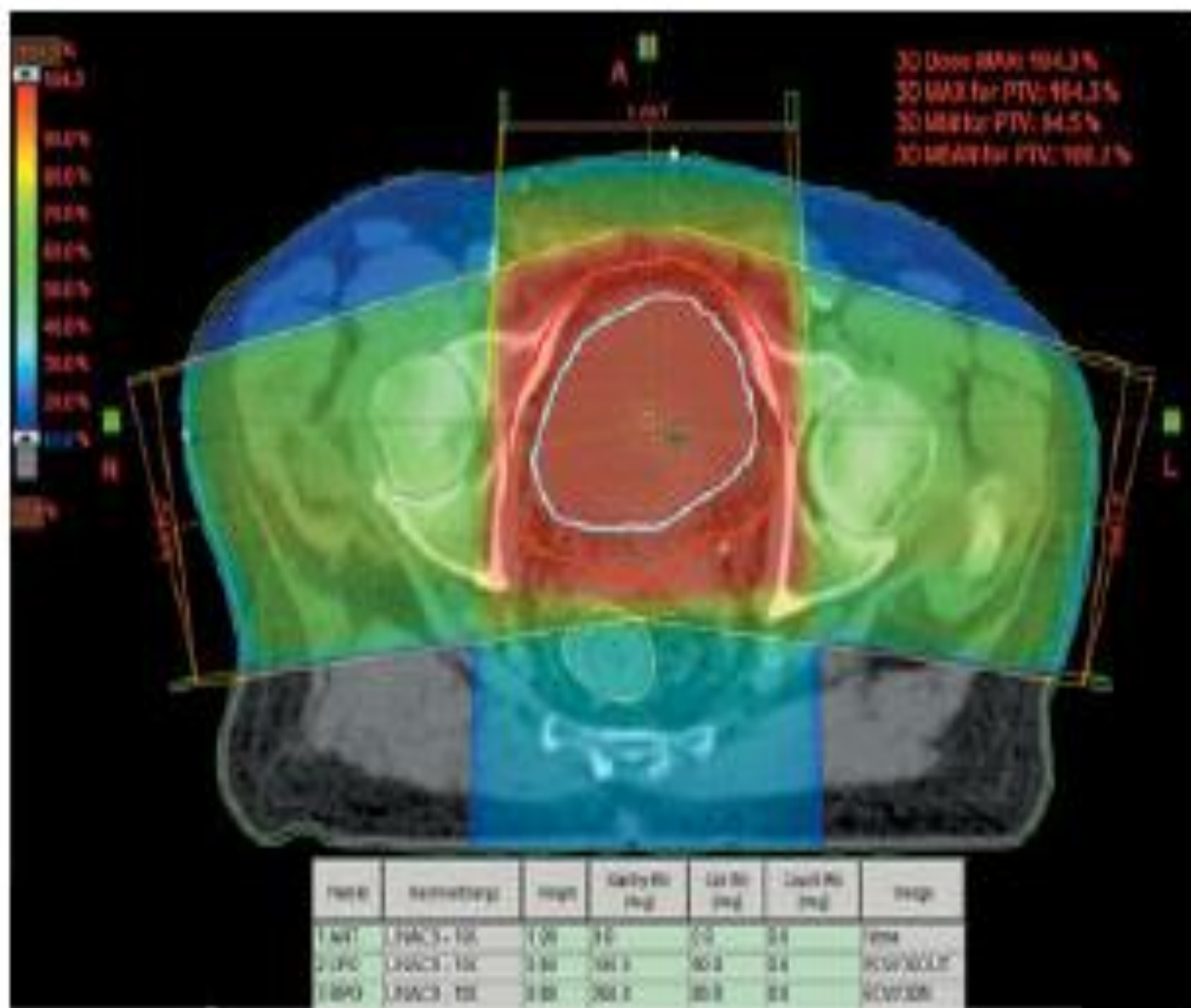
- 3D Conformal Radiotherapy
- Intensity Modulated Radiotherapy (IMRT)
- Image Guided Radiotherapy (IGRT)


- **Brachytherapy**

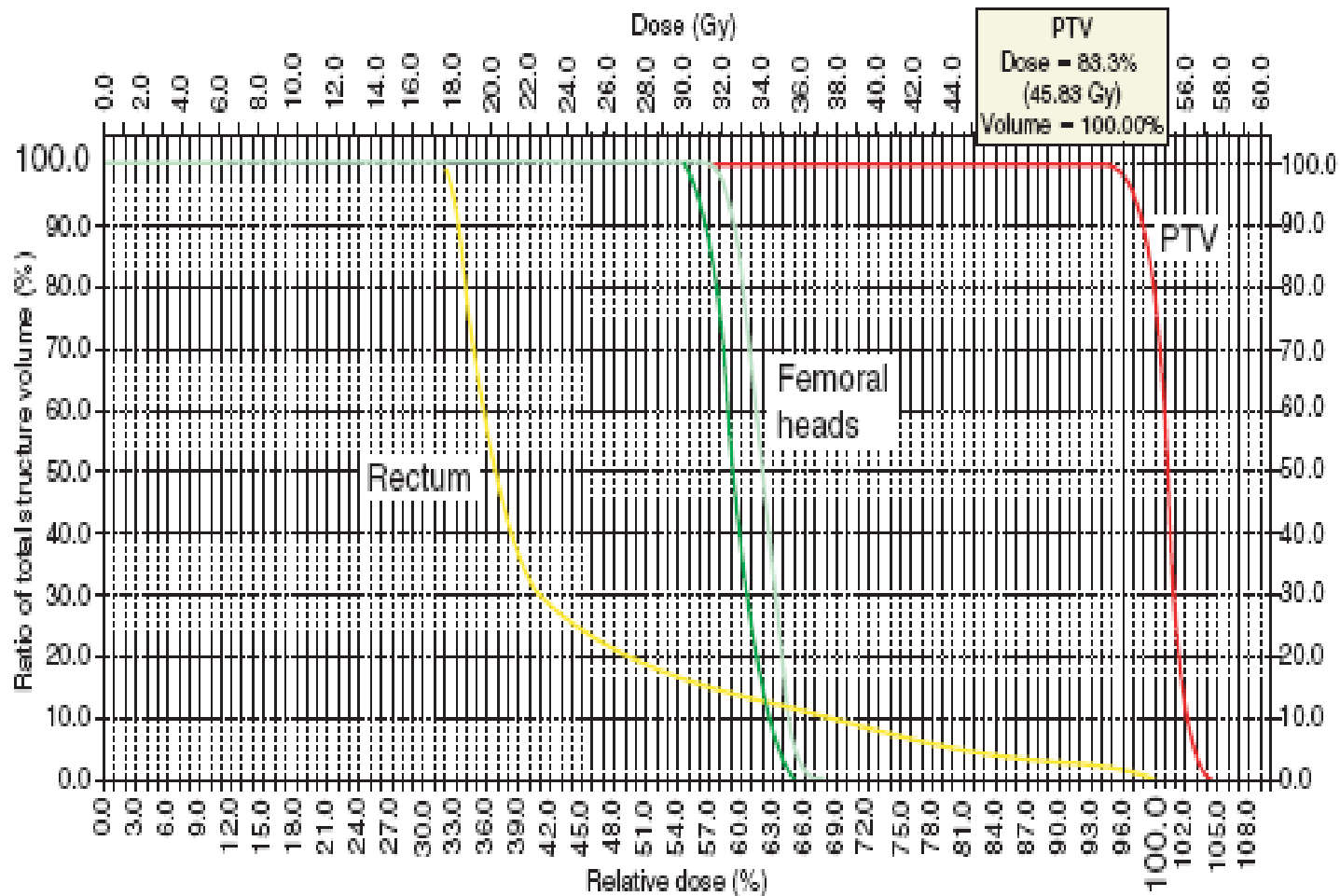
- Advanced High Dose Rate systems

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- Due to the mobility of the bladder, strictly conformal radiotherapy of bladder tumors needs to be given with great care to ensure targeting accuracy for every treatment.
 - Advanced localization techniques such as implanted markers and gating technology may make conformal therapy possible.
 - Portal imaging systems are helpful in real-time monitoring of treatment accuracy.

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- IMRT with inverse planning can reduce the dose to normal tissues, and allow the delivery of a synchronous boost needed for partial bladder irradiation and permit dose escalation to the tumour.
 - However, IMRT for this tumour site requires excellent immobilisation, with IGRT to locate and minimise PTV at the time of treatment.
 - It has been shown that without IGRT an isotropic margin of 3 cm is required, but with IGRT this can be reduced to 12 mm.
 - Organs At Risk (OAR) should be outlined including rectum, femoral heads and small bowel. Recommended dose constraints are: rectum V50 60 per cent, V60 50 per cent; femoral heads V50 50 per cent; small bowel V45 250 cm³.



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- The bladder is mobile and can change shape as well as position during treatment. Verification is therefore very important.
 - The current standard is EPI comparing bony anatomy with the AP and lateral DRRs daily for the first 3–5 days, and then once weekly correcting for systematic errors.
 - Verification that allows visualisation of soft tissues at the time of treatment delivery, such as kV cone beam imaging, MV imaging with tomotherapy and MV imaging of gold seed markers cystoscopically implanted into the bladder, significantly improves accuracy of radiotherapy.
 - Arc RT, which modifies treatment plans to account for variations in individual patients, or gated radiotherapy based on delivery of treatment only when the bladder is in the correct position may be useful techniques.



DVH for conformal plan for bladder cancer showing PTV, rectum and femoral heads.

Brachytherapy

- Interstitial therapy is not a common part of management of patients with bladder cancer.
- Brachytherapy for bladder cancer is limited almost exclusively to afterloaded interstitial therapy with iridium-192 (^{192}Ir) sources.
- A commonly accepted dimension of bladder tumors selected for brachytherapy is <5cm.
- The tumor usually is treated with a single plane implant of three to five line sources: needles or catheters into which the radioactive sources will be loaded (30 Gy at 58 cGy per hour). The distance between line sources is about 1 cm. A single plane implant can be used to treat a 2- to 2.5-cm thick lesion; beyond that two-plane implants may become necessary.

Palliative Radiotherapy

- 21 Gy in 3 fractions given on alternate days in 1 week
or
- 36 Gy in 6 fractions of 6 Gy given once weekly for 6 weeks.
- In most cases 21 Gy in 3 fractions on alternate days over 1 week is as effective as longer schedules for palliation as shown by the MRC BA09 trial.
- A weekly hypofractionated regimen of 6 Gy weekly for 6 fractions has been shown to effectively palliate symptoms in patients unfit for radical treatment and may be preferred by some patients.

Treatment delivery and patient care

- Before radiation starts the patient should be made as fit as possible.
- Urinary infection should be treated, anaemia should be corrected to haemoglobin 12 g/dL and a low residue diet advised.
- Radiation cystitis is common; infection should always be excluded and a high fluid intake advised.
- Catheterisation should be avoided if possible to minimise the risk of infection.

Side effects of Radiotherapy

- Acute complications mainly consist of bladder irritability, resulting from mucositis with decreased bladder capacity, which is manifested by frequency, urge incontinence, dysuria, diarrhea (usually mild) and anal irritation
- Mild proctitis and lethargy are common.
- Late side effects include fibrosis and shrinkage of the bladder, haematuria due to bladder telangiectasia, late bowel damage, vaginal dryness and stenosis in women and impotence in men.

Thank you

