Oncotherapy for urological cancer
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Place of oncotherapy in the treatment of urological tumours

- Prostate cancer
- Bladder cancer
- Penile cancer
- Testicular cancer
- Kidney cancer

Prognostic factors in prostate cancer (PCA)

- PSA (prostate specific antigen)
- TNM status
- Gleason score

- Other compounds
  - PSA doubling time!!
    - <3 y, >3 y
  - Number of positive biopsy cores
  - Percent of positive tissue on biopsy
  - Perineural invasion
  - Se testosterone

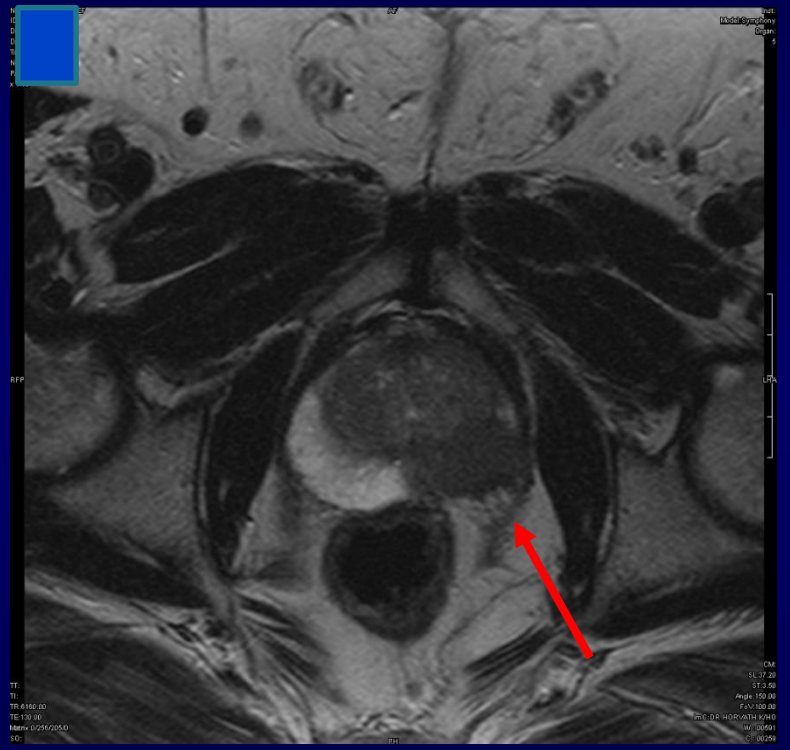
Risk groups in PCA-ban according to D'Amico, NCCN

- Organ confined disease
  - Very low risk
    - T1c GS<6, PSA<10, <3/10 cores, <50 % rate
  - Low risk
    - T 1,2a and PSA<10ng/ml and Gleason sc.≤ 6
  - Intermediate risk
    - T2b, GS7, PSA≥10-20 ng/ml
  - High risk
    - T3-4, PSA>20ng/ml, (N+)
- Locally advanced PCA (T3-T4N0M0)
- Lymph node positive tumour (N1)
- Metastatic / Advanced (M1)

Organ confined disease
Active surveillance

- Indication
  - Organ confined
  - Very low, low or selected intermediate risk
  - >70-75 y
  - <4 cores positive (low volume)

- Action
  - PSA in every three months
  - Rebiopsy at 1y, than at every 2-3y
  - Multiparametric MRI



Localized, locally or regionally advanced PCA
Radical prostatectomy

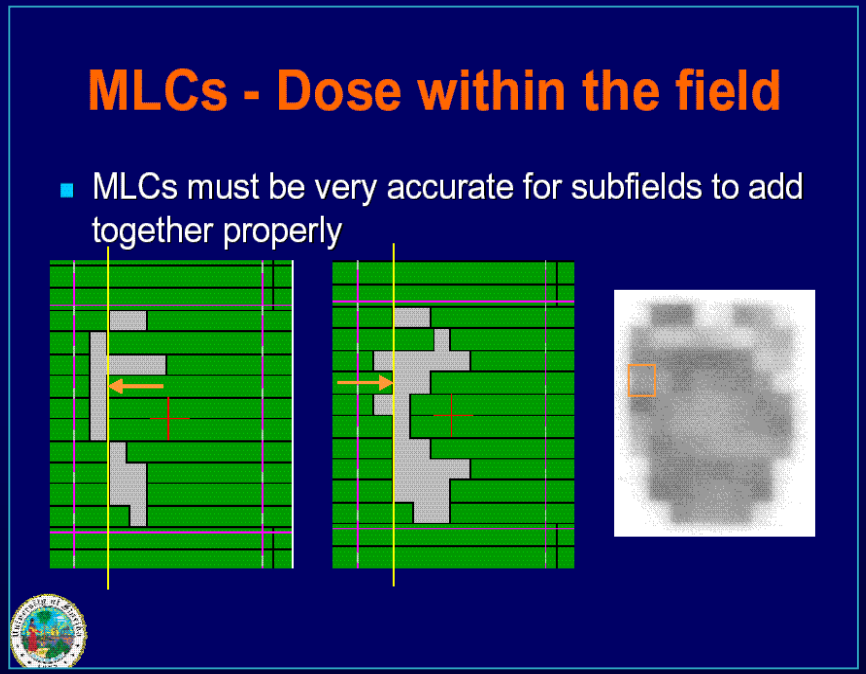
- Indication
  - T1-2N0
  - T3, N1 selected cases
- Action (radical prostatectomy)
  - Removal of prostate and vesicles and pelvic lymph node dissection
  - Open, laparoscopic, robot assisted (DaVinci)
  - Adjuvant treatment (radiotherapy, endocrine th.) depending on histolgy
- Side effects
  - Incontinence
  - Impotence

Localized, locally or regionally advanced PCA
Radical (definitive/primer/curative) radiotherapy

- Indications
  - T1-2N0
  - T3, N1
  - pT3, pN1
- Process
  - According to risk group irradiation of the prostate, vesicles, pelvic lymph nodes
  - In intermediate risk short tem (4-6months), in high risk and in locally or locoregionally advanced tumour long term endocrine therapy (2-3y)
- Side effects
  - Acute irritative complaints, bowel-, bladder- prostate inflammation
  - Impotence, fibrosis, bleeding of the mucus of the rectum or bladder, secondary cancer

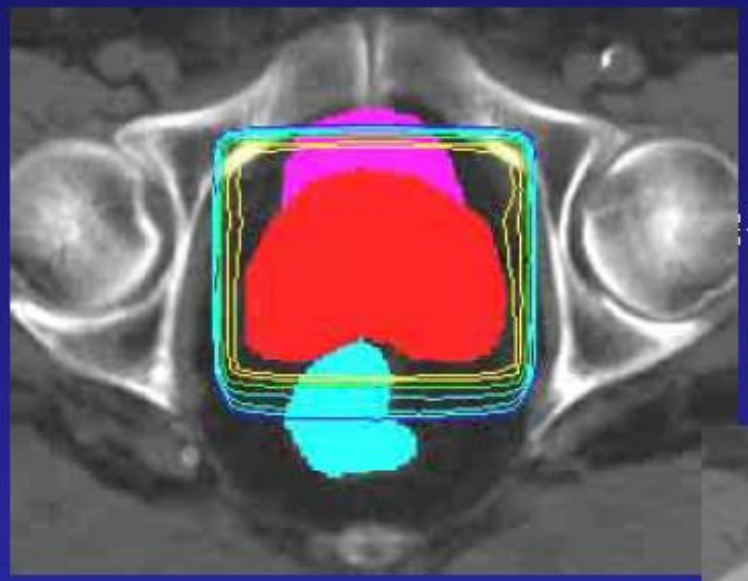
Intensity modulated radiotherapy (IMRT)

- Treatment planning and radiotherapy from several fields according to the shape and localisation of the target volume. The dose intensity is different inside the field



Since 1990

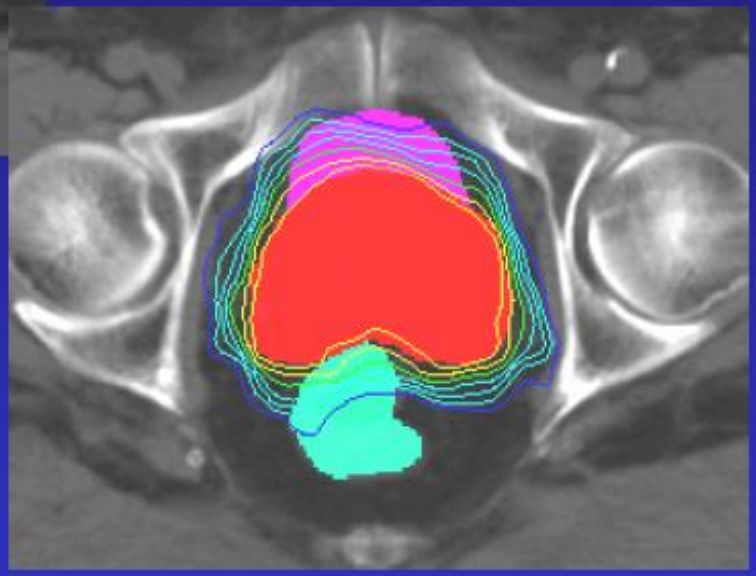
Benefit from IMRT in localised PCA



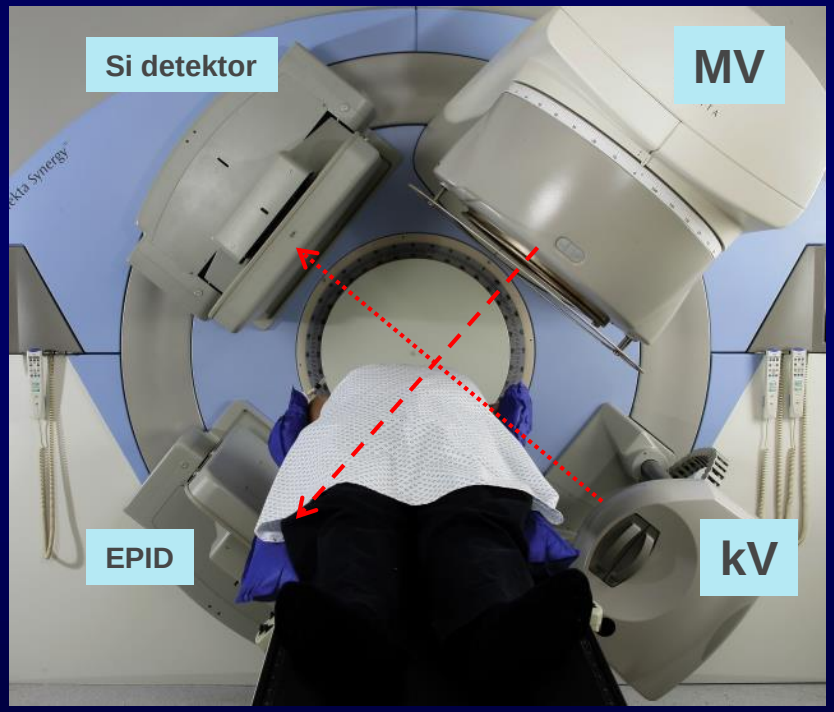
3D-Confomal

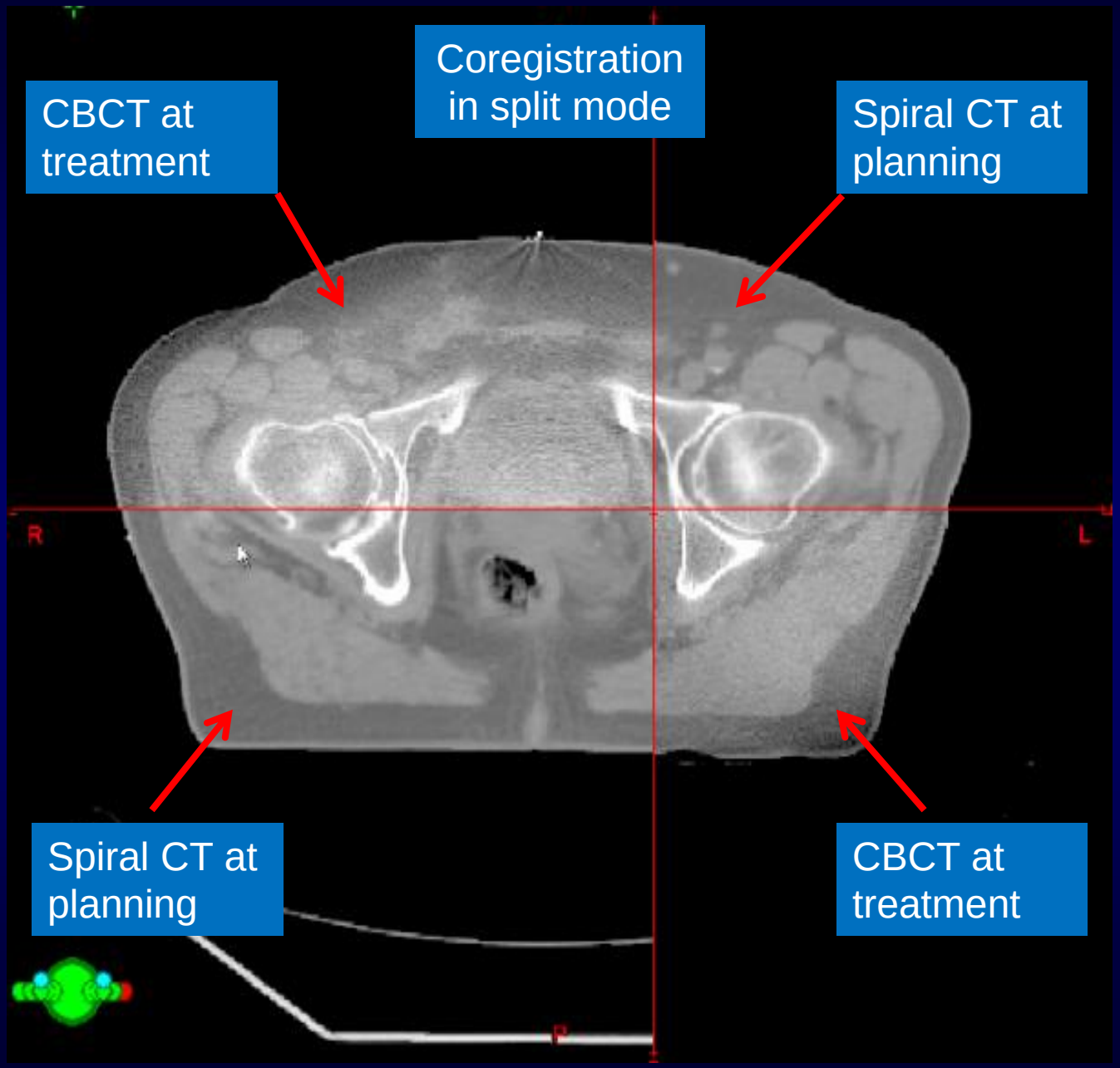
vs.

IMRT

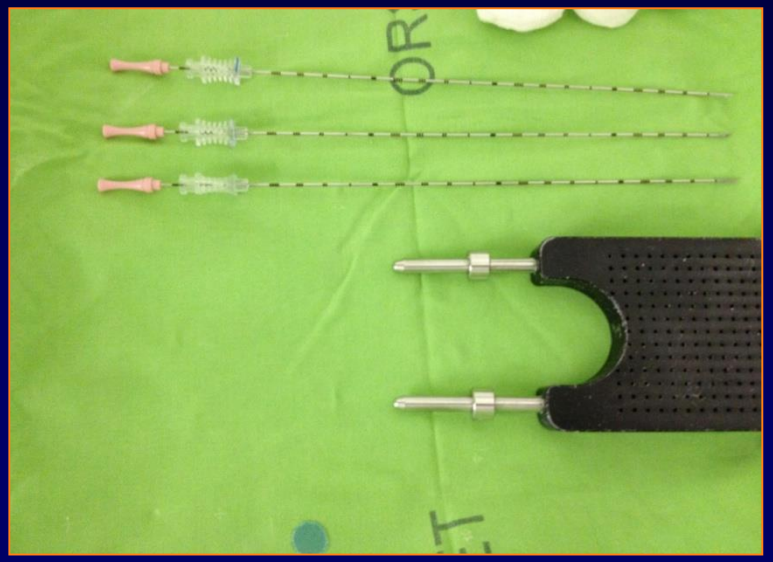


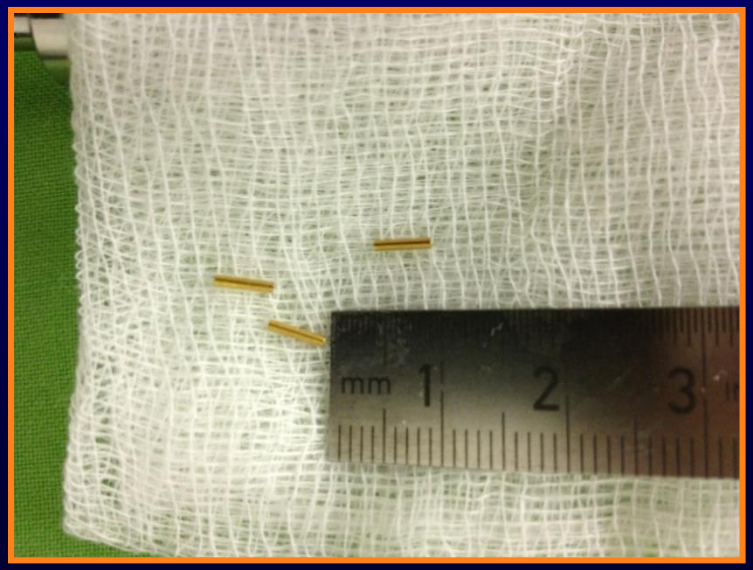
Linear accelerator with EPID and, cone beam CT’



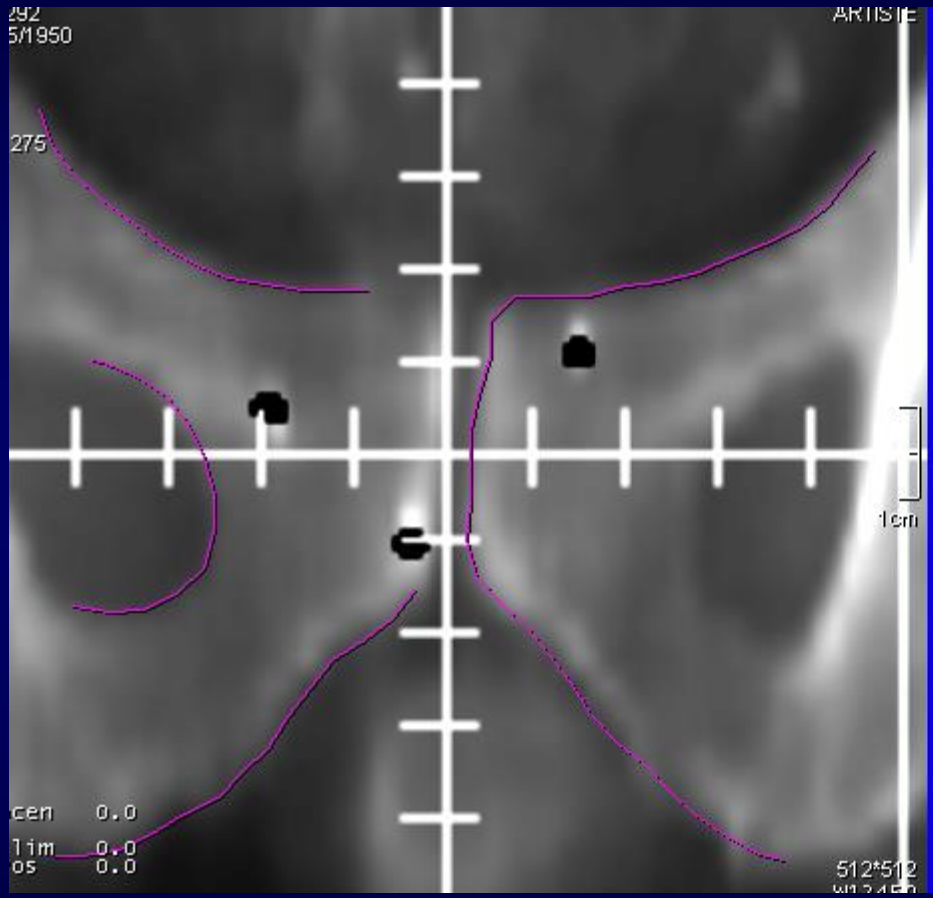

Coregistration in split mode
CBCT at treatment
Spiral CT at planning
Spiral CT at planning
CBCT at treatment
R
L

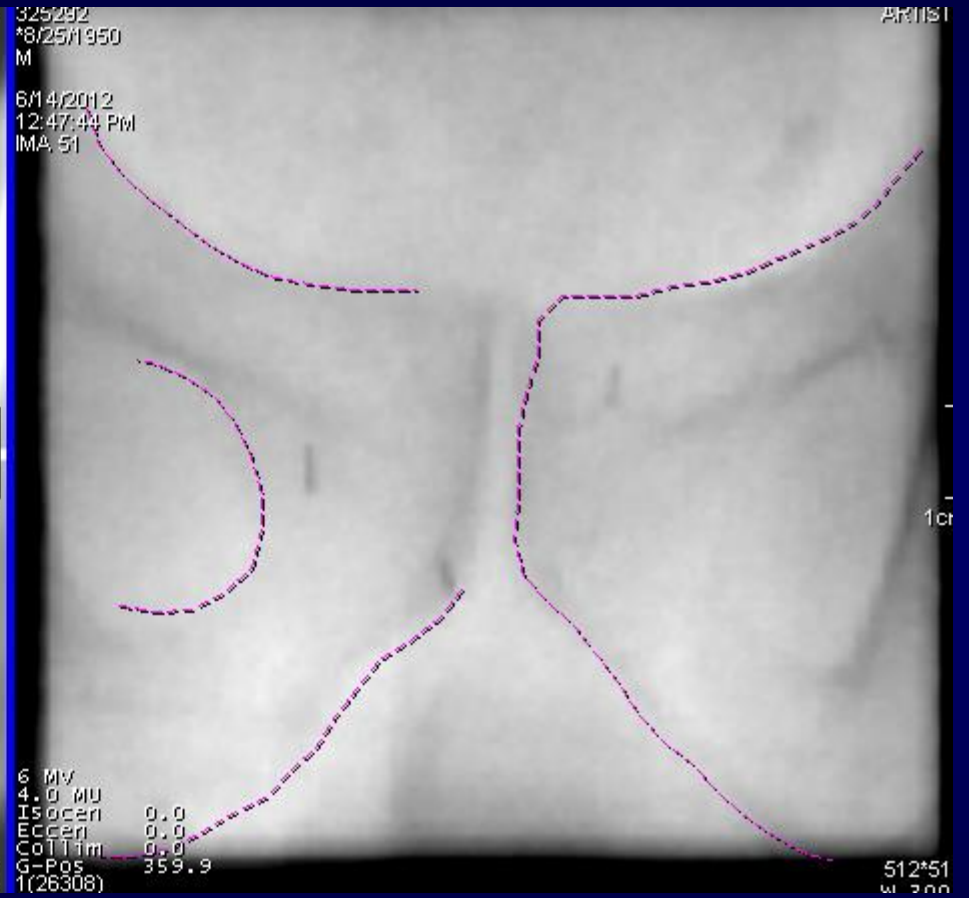
IGRT (image guided radiotherapy)
Implantation of radiopaque markers into the prostate





Patients' set up based on bony structures AP

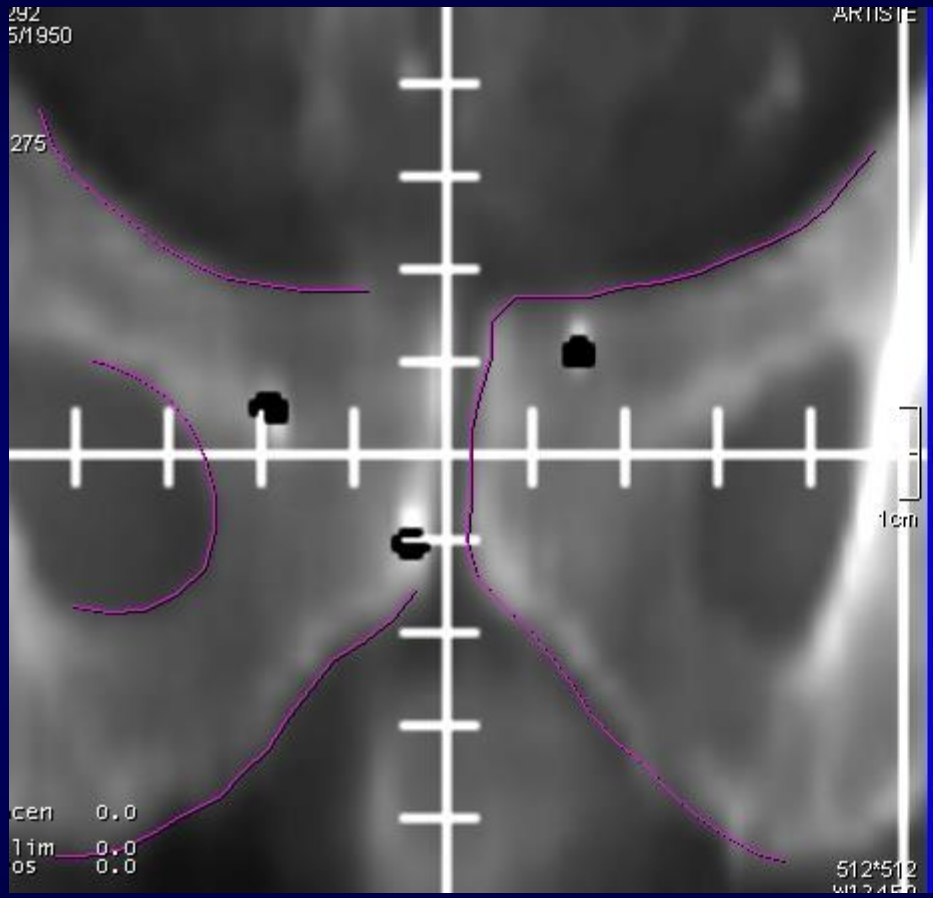


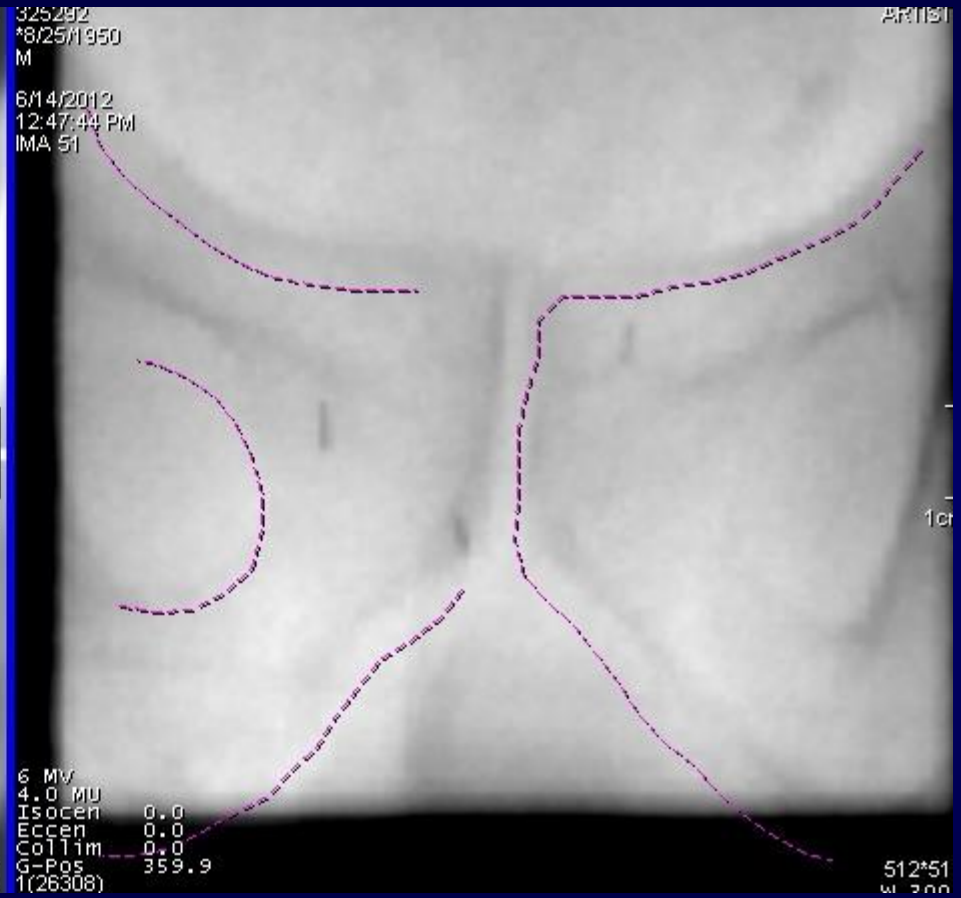


Shifts to skin marks: LAT: 0.0 cm

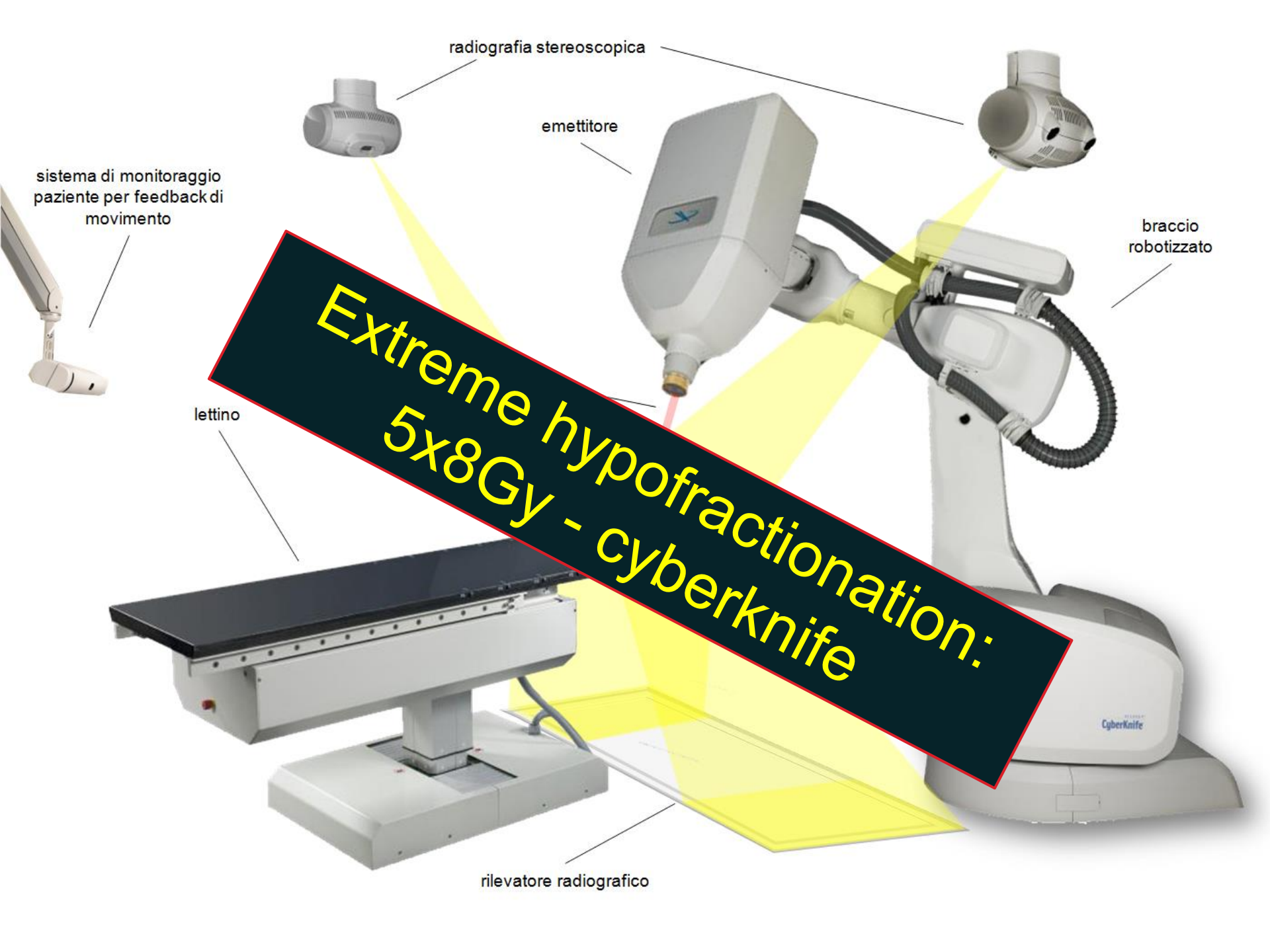
LONG: + 0.5 cm

Patients' set up based on fiducial markers - AP



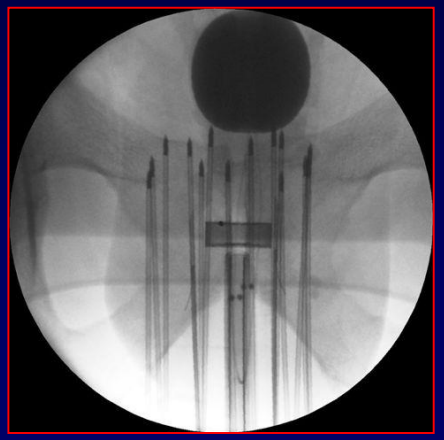


Shifts to skin marks: LAT: + 0.1 cm
LONG: +1.0 cm

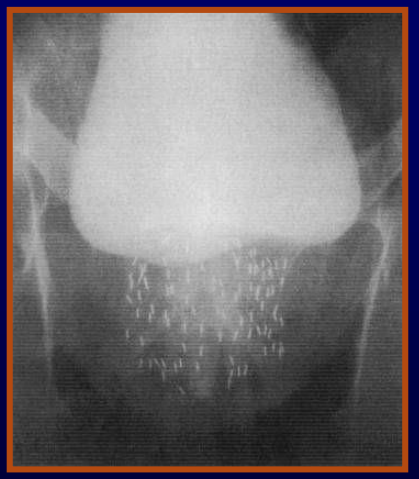

radiografia stereoscopica
emettitore
sistema di monitoraggio paziente per feedback di movimento
braccio robotizzato
lettino
rilevatore radiografico
Extreme hypofractionation:
5x8Gy - cyberknife

Prostata brachytherapy (BT)

- Temporary implant
  - High dose rate (HDR)



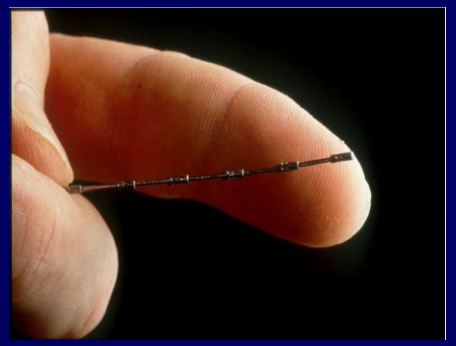
- Permanent („seed”) implant
  - Low dose rate (LDR)

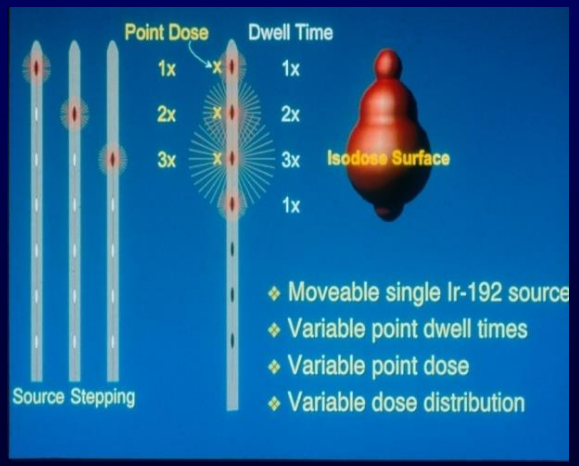


- Monotherapy or in combination with external beam RT

Temporary implant (HDR)

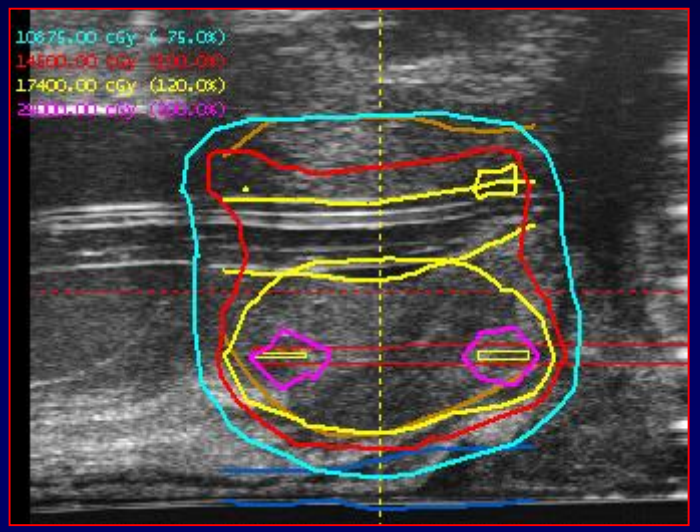
- Best tool for dose escalation
  - Added to external beam therapy (boost)
  - Organ confined high risk, locally advanced
- High dose rate – Ir192
  - Treatment time: 10-15 min
  - Implant time: 2-2,5 hours
- One stepping source – after-loading
  - Intraoperative, real time treatment planning
- Monotherapy: phase II-III clinical trials



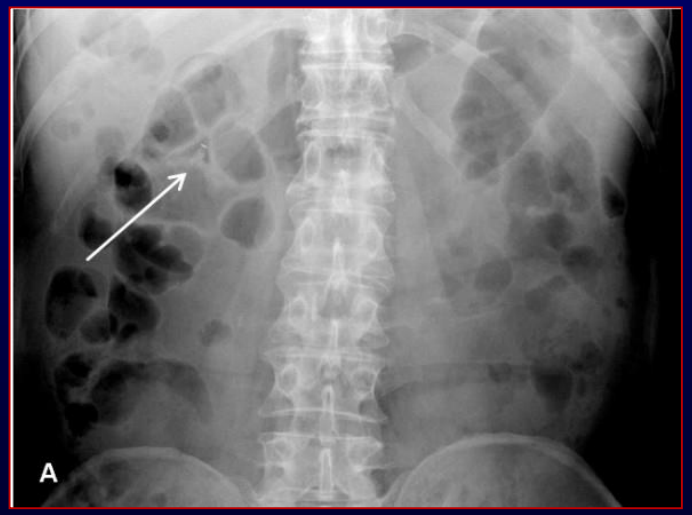


Permanent implant

- Best comfort and low toxicity profile for the patient
- Monotherapy - 2 days in hospital
- Low dose rate – I-125
  - Treatment time: months
  - Implant time: 2-2,5 hours
  - Dose to the prostate: 145 Gy !!



- Number of seeds: 50-80
  - intraoperative dose planning
  - Postimplant dose planning (CT)
- Consider radiation safety and protection
- Seed migration



Toxicity of RT of prostate cancer

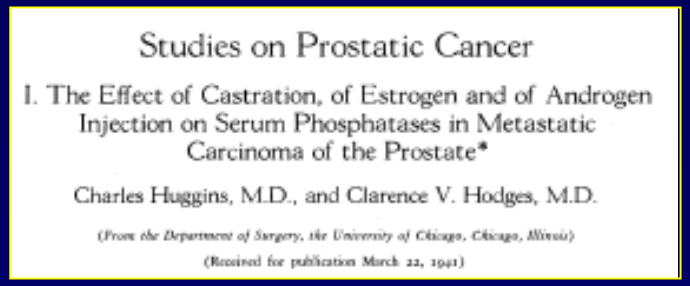
Early	Probability (%)
Diarrhoe	20-30
Proctitis	30
Cystitis	30
Late	
Pollakisuria, urethal stricture	3-7
Rectal teleangiectasia, bleeding	5-20
Rectal ulcer	1-3
Haematuria, bladder teleangiectasia	3-5
Erectile dysfunction	50

Inflammation

Fibrosis

RT in combination with hormonal treatment
Why they started hormonal treatment?

- Huggins és Hodges 1941.
  - Prostate cells are androgen dependent



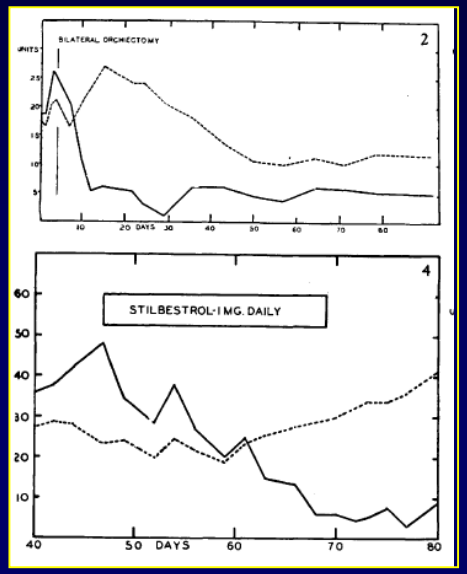
Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

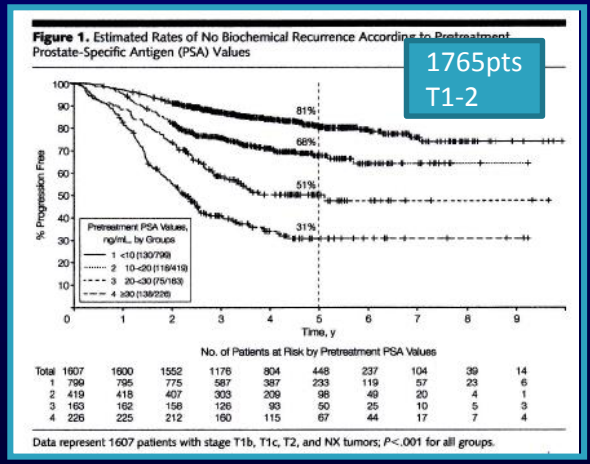
Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)



- Shipley et al. *JAMA 281(17):1598-63, 1999.*
  - Harvard, Boston; 1988-1995.
  - Retrospektív, non randomized trial
  - Sole EBRT median Dose:65Gy!
  - Not optimal results: 5-y bNED: 65,8%! ☹



RT + HT
antiandrogens, LHRH analogues and antagonists

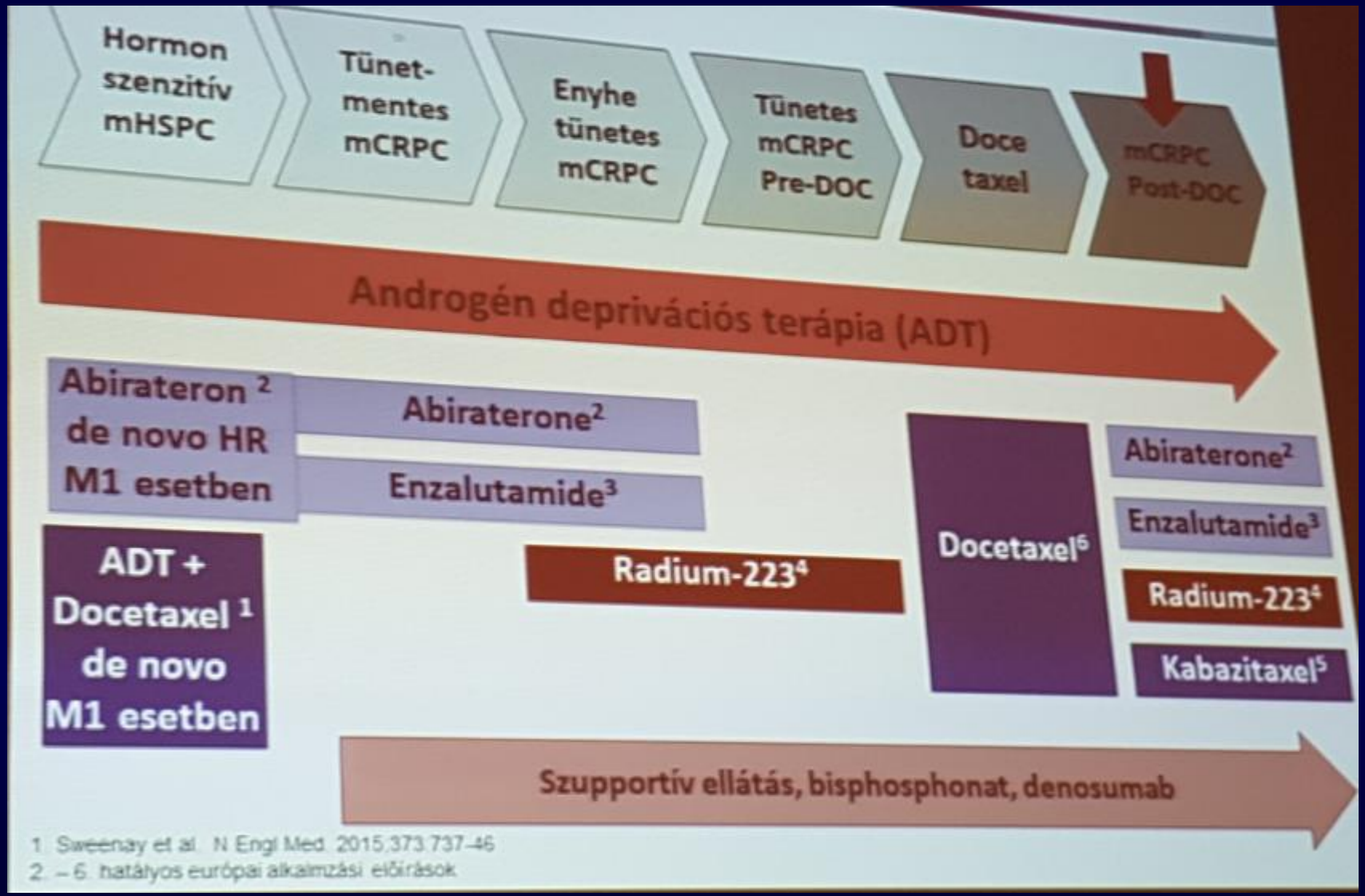
- HT (=Androgen deprivation therapy- ADT) decreases
  - The target volume,
  - The repopulation of tumour cells during RT
  - The local recurrence and consequent distant metastases
  - Occult distant metastases

Follow up after RT

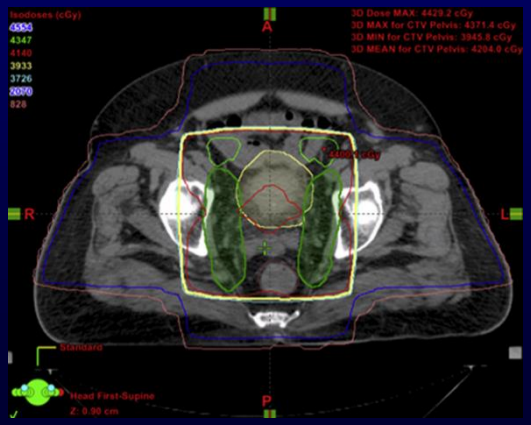
- PSA, kidney, liver function, ALP, physical exam
- PSA slowly decreases, sometimes with bounces
- PSA increase is a first sign of relapse

- Definition of biochemical (PSA) relapse (2006):
  - More than 2 ng/ml increase after PSA nadir (minimum)

Treatment of metastatic prostate cancer

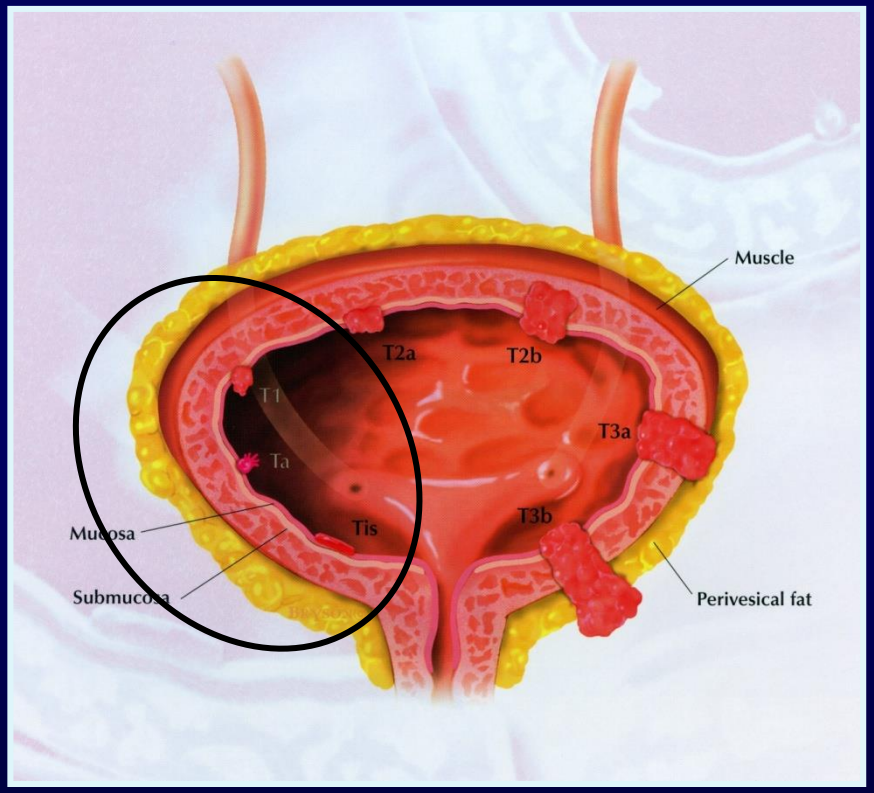


Bladder cancer



Treatment of bladder cancer
Non muscle invasive bladder cancer (pTis, pTa, pT1)

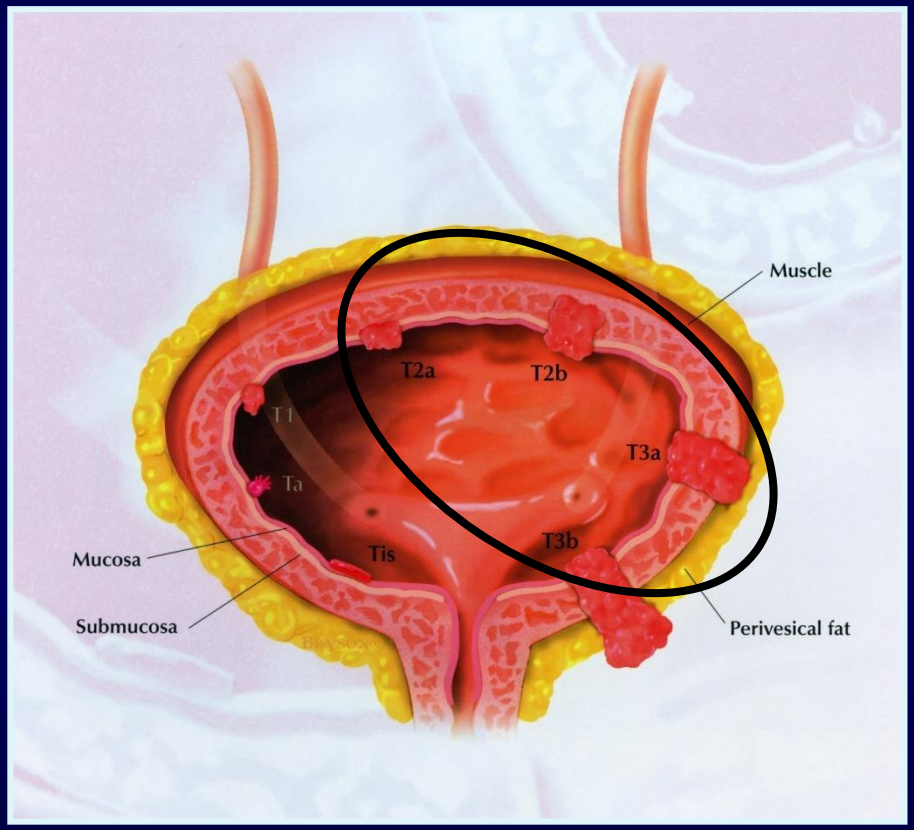
- TUR (transurethral resection)
- Causes of relapse
  - CIS, multiple tumour, high grade
- reTUR
- Instillation (BCG, ADM, MMC)



Treatment of muscle invasive bladder cancer (pT2-4)

- **Cystectomy**
  - Partial
  - Simplex
  - Radical (+ext LND)
  - Urine deviation, neobladder
  - Uretero-cutaneostoma

- Organ preserving trimodal treatment

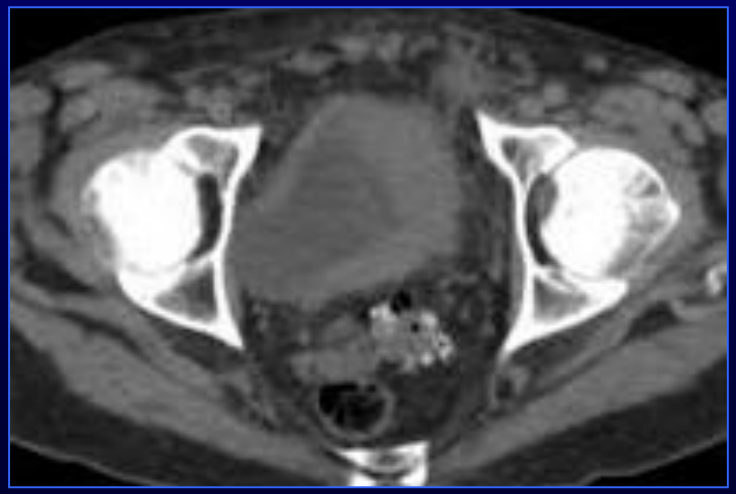


Organ preserving trimodal treatment

- Possible maximal TURB
- Concomittant radio-chemotherapy
  - (Cisplatin based)
  - 60-65 Gy to the bladder
- Cystoscopic revision, TUR or cystectomy in case of relapse

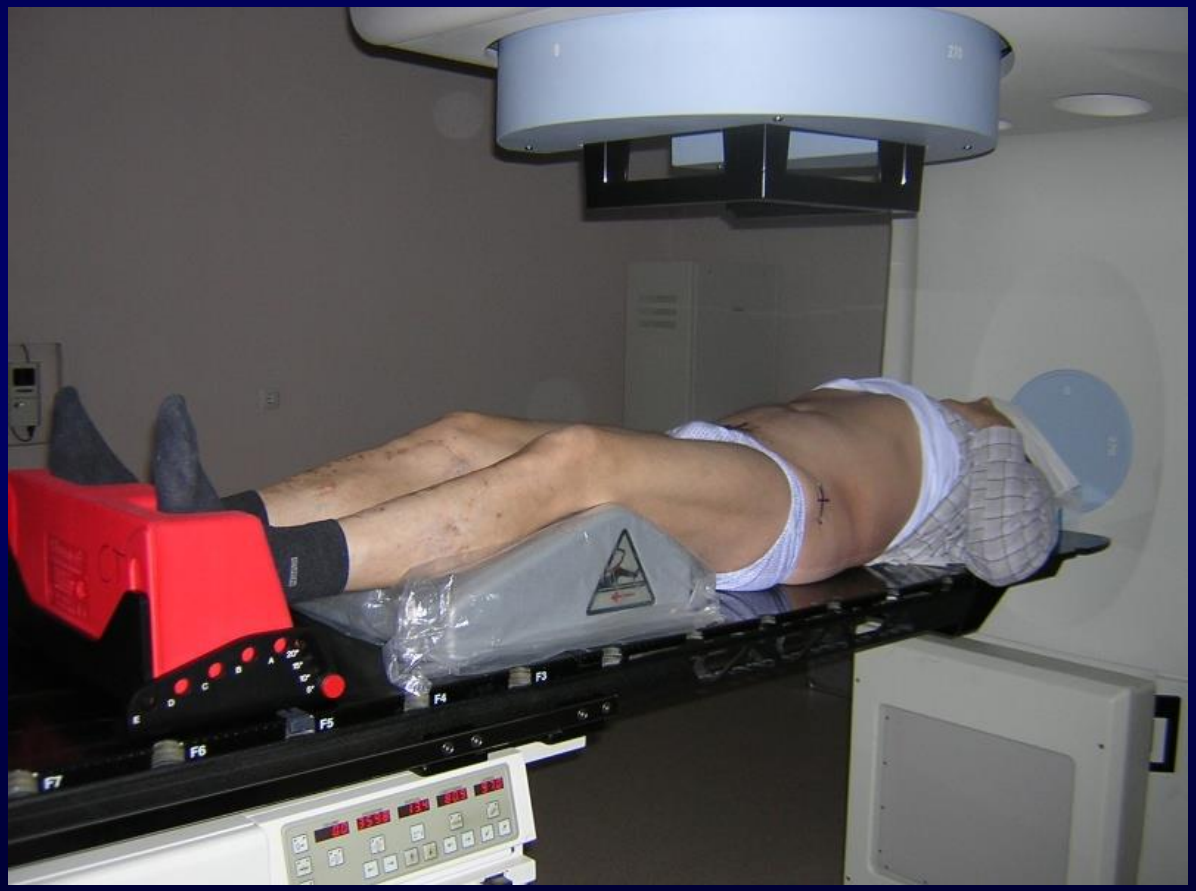
Organ preserving trimodal treatment Indications

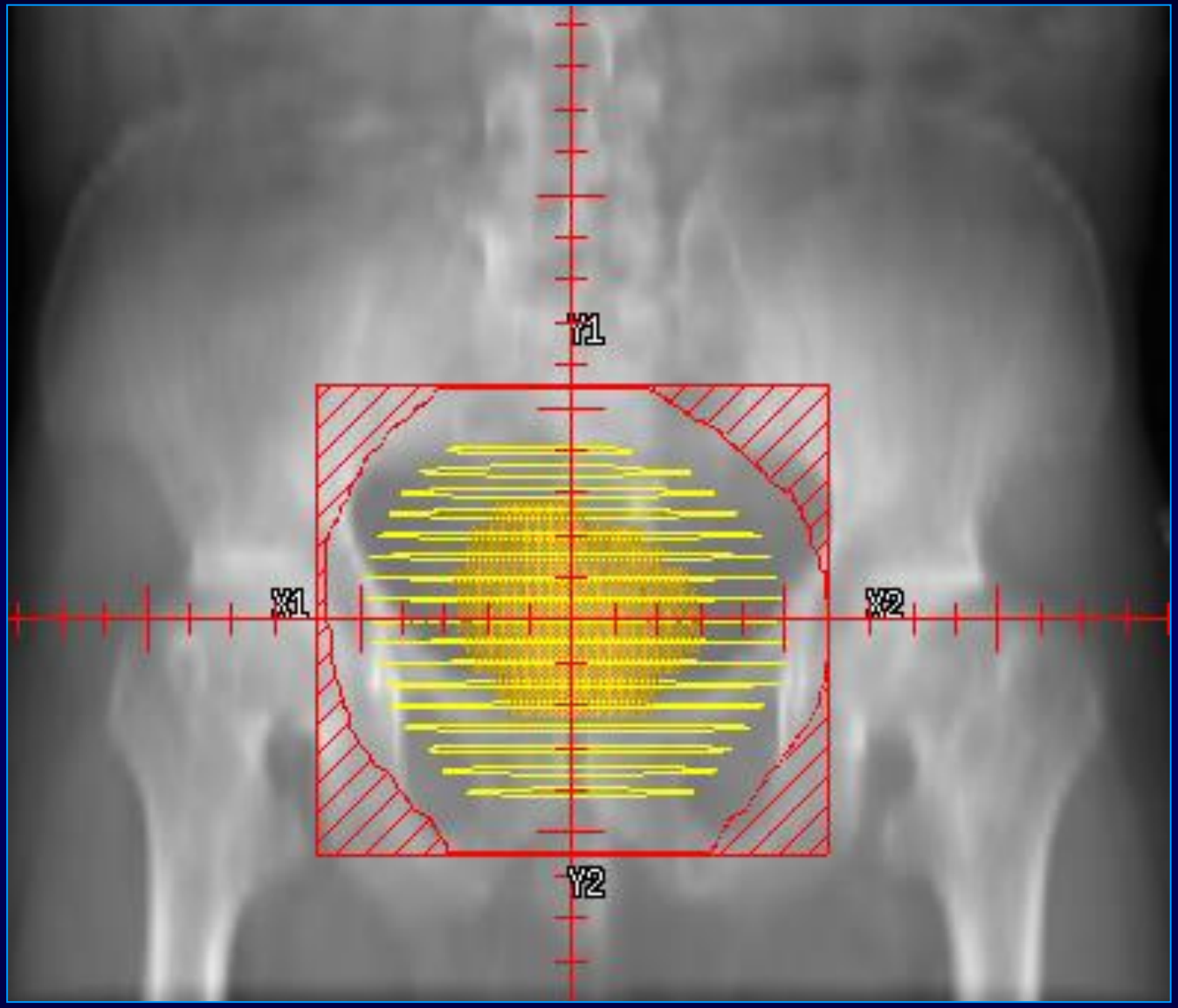
- Inoperable patients or irresectable tumours
  - T1-3N0-1M0
- Patients fit for radical cystectomy, who resist the operation
- Bladder sparing in 80% of the long term survivors



Radiotherapy for bladder cancer

Knee –ankle support system (four field conformal box technique)





Conformal treatment in bladder radiotherapy
Irregular fields according to the shape of the bladder
Digitally reconstructed AP field with the bladder and the target volume

Quality of life in organ sparing protocol

Lagrange JL,et al (GETUG).2010;57:213-234.

- Median follow up: 8y
- R0 TUR: 66%
- Bladder preservation: 67%
- 8y local control: 67%
- 8y Locoregional control: 46%
- 8y Overall survival: 36%

Table 4. Late effects evaluated by investigators according to the LENT-SOMA scale, subjective functions, for patients treated without cystectomy

Late effect	Grade 0		Grade 1		Grade 2		Grade 3	
Dysuria								
6 mo (3-9)	33	(80.5)	5	(12.2)	3	(7.3)	0	
12 mo (9-18)	27	(90)	3	(10)	0		0	
24 mo (18-30)	18	(100)	0		0		0	
36 mo (30-42)	9	(100)	0		0		0	
Frequency								
6 mo (3-9)	16	(39)	11	(26.8)	9	(22)	5	(12.2)
12 mo (9-18)	19	(65.5)	4	(13.8)	4	(13.8)	2	(6)
24 mo (18-30)	12	(66.7)	3	(16.7)	1	(5.5)	2	(11.1)
36 mo (30-42)	6	(66.7)	1	(11.1)	1	(11.1)	1	(11.1)
Hematuria								
6 mo (3-9)	39	(95.1)	2	(4.9)	0		0	
12 mo (9-18)	30	(100)	0		0		0	
24 mo (18-30)	17	(94.4)	1	(5.6)	0		0	
36 mo (30-42)	9	(100)	0		0		0	
Incontinence								
6 mo (3-9)	38	(92.7)	2	(4.9)	1	(2.4)	0	
12 mo (9-18)	27	(90)	3	(10)	0		0	
24 mo (18-30)	17	(94.4)	1	(5.6)	0		0	
36 mo (30-42)	9	(100)	0		0		0	

Abbreviation: LENT-SOMA = Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic.
Values are number (percentage).

Systemic treatment of bladder cancer

- Perioperative systemic treatment in muscle invasive BC

- Neoadjuvant chemotherapy
  - 8 % overall survival benefit
  - GC, MVAC

- Adjuvant chemotherapy
  - Small overall survival benefit
  - Many patients are unfit to chemotherapy after operation

Systemic treatment of metastatic bladder cancer

- First line treatment
  - Cisplatin based chemotherapy
    - GC, MVAC, CAP
  - Unfit to Cisplatin
    - eGFR<30, ECOG>1, loss of hearing, neutropenia
    - 5FU, MMC, Gem-Carboplatin

- Second line treatment
- Immunetherapy (new!!)
  - PD1 inhibitors
  - PD-L1 inhibitors (atezolizumab)
  - Progression after Cisplatin based chemotherapy

Testicular cancer

Histological classification of testicular cancer

TABLE 67.1 CLASSIFICATION OF TUMORS OF THE TESTIS

Germ cell tumors

Intratubular germ cell neoplasia (IGCN)

Seminoma
- Classic type
- Spermatocytic type

← RT

Nonseminomatous germ cell tumors
- Embryonal carcinoma
- Yolk sac (endodermal sinus) tumor
- Teratoma
  - Mature
  - Immature
  - Teratoma with malignant transformation (with somatic carcinoma or sarcoma)
- Choriocarcinoma
- Mixed germ cell tumors

95%

Sex Cord–Stromal Tumors

Leydig cell tumor

Sertoli cell tumor

Granulosa cell tumor

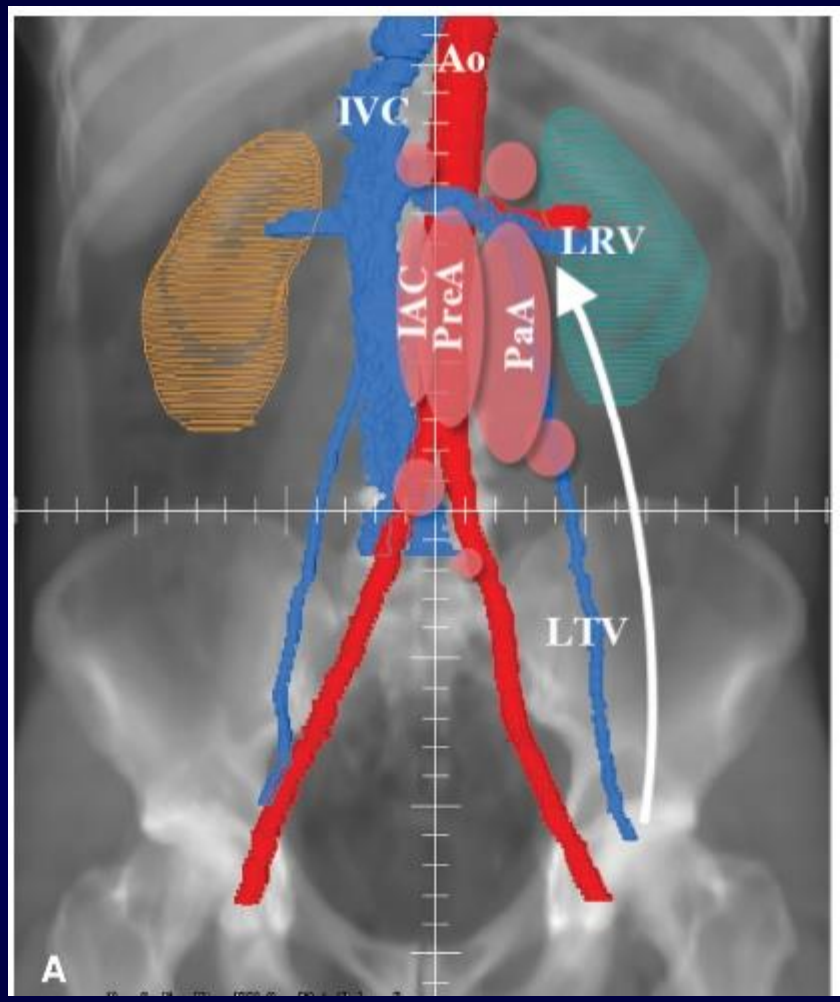
Fibroma-thecoma stromal tumor

Sex cord–stromal tumor with annular tubules

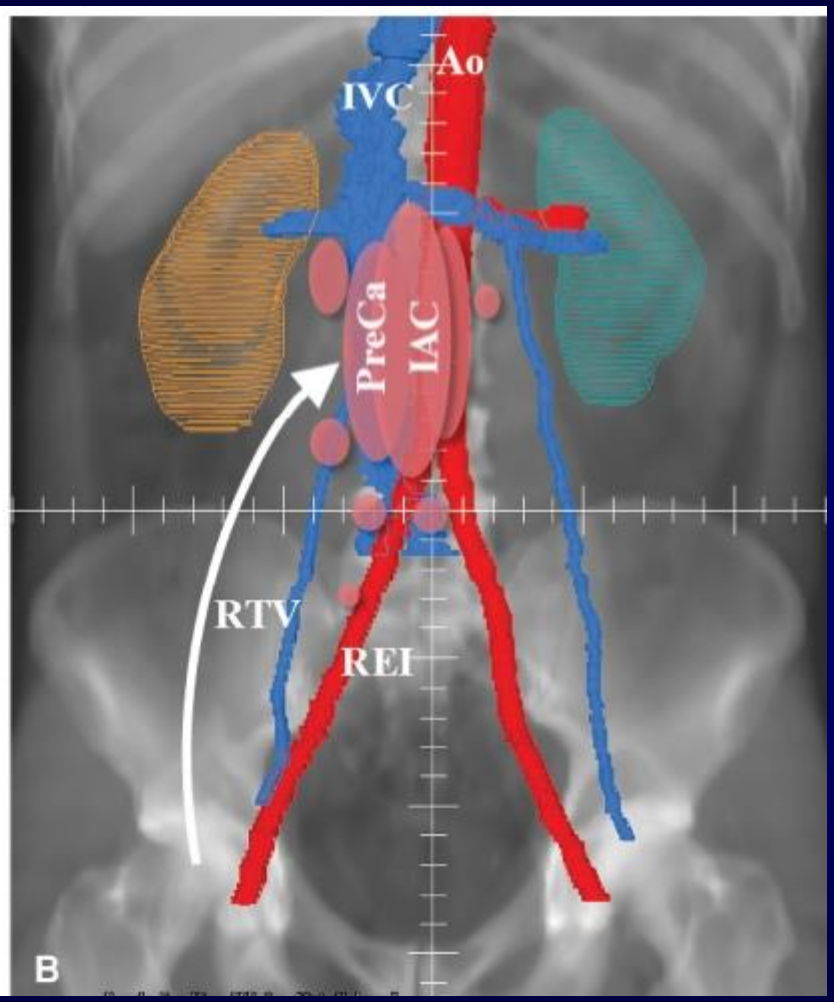
Gonadoblastoma

Sex cord–stromal tumor unclassified type

Natural behaviour, lymphatic drainage



Lymphatic drainage
of left side tumour



Lymphatic drainage of
right side tumour

Treatment in genral

- Suspicious tumour
- Markers
- High castration
- Staging
- Seminoma: RT vs ChT vs AS
- Non-seminoma : ChT vs. S vs. AS

Seminoma, stage I

- PAO irradiation with 20 Gy

- 1. cycle carboplatin

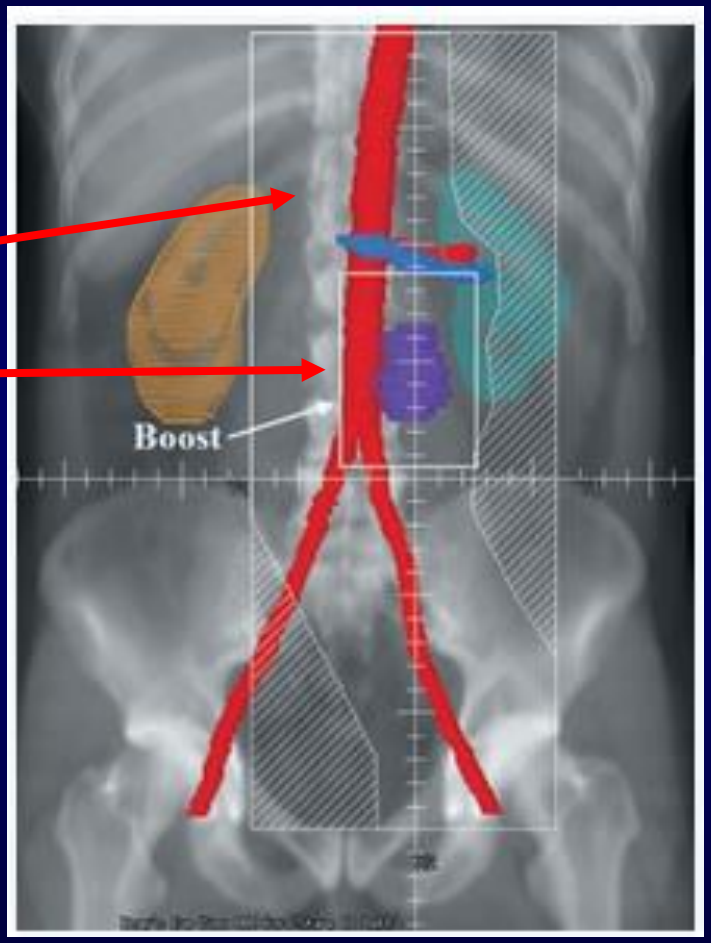
- WW
  - ≤4 cm tumour,
  - rete testis, epidydimis, tunica albuginea, funiculus spermaticus are not involved,
  - Staging abdominal CT, MR, UH are negative

Seminoma stage II/A,B
(<5 cm retroperitoneal lymph nodes)

!

- RT
  - 30Gy / 2 Gy to the PAO and ipsilateral PIL region,
  - 6 Gy boost to the tumour
    - RFS: 92%, 90%
    - OS: ≈100%

- 4 cycle EP or 3 cycle BEP
    - Similar tumour control



Toxicity of RT

- Transient diarrhoe nausea
- Late peptic ulcer
- Aspermiogenesis (above 0,5 Gy scattered dose)
- Secondary cancer due to radiation (15-20 y later)

Treatment of non seminoma tumours

- In stage I castration followed by active surveillance
  - Elevated markers in 60-80% (AFP, hCG)
  - Marker status: S1-3 status stage deciding
- Above stage II castration, followed by Cisplatin based chemotherapy
  - In most cases BEP
  - Bleomycin, Etopozid, cisPlatina
- In case of residual tumour retroperitoneal lymphadenectomy (salvage RLA)
- Advanced cases: polychemotherapy

Treatment of patients with testicular cancer

- Excellent 5-y survival
  - Good progn: 85-90%,
  - interm. progn.: 70-80%,
  - unfavorable progn: 50%
- Active surveillance is more and more common for stage I
- Management should be done in centres
- Needs follow up for long
  - Lung fibrosis
  - Increased cardiovascular risk
  - Secondary cancer

Penile cancer
Surgery of the primary tumour

- Localised:
  - CIS
    - 5 % 5FU cream or imiquimod cream (70% cure rate)
    - Organ sparing surgical techniques
  - T1, G1-2
    - Glansectomy, partial penectomy (>4 cm stump)
  - T1-G3 or T≥2
    - Partial or total penectomy

Penile cancer
Surgery of the regional lymph nodes

- N0
  - CIS T1, G1-2
    - Lymphadenectomy is not necessary
  - T1-G3 or T≥2
    - Sentinel lymph node biopsy
      - positive: dissection
      - negative: observation
- N+
  - Bilateral inguinal lymph node dissection
  - >2 positive – pelvic LA
  - cN3, fixed lymph nodes: neoadjuvant chemotherapy followed by dissection

Penile cancer RT

- T1-T2N0 tumour <4 cm
  - After circumcision

- Brachytherapy
  - Mostly interstitial treatment,
  - Or mould brachytherapy

or

- External beam therapy
  - Applying bolus, 2 cm safety margin around the tumour
  - 60-70 Gy dose
  - Radiation of inguinal lymph node region in those in whom lymph node dissection is not an option

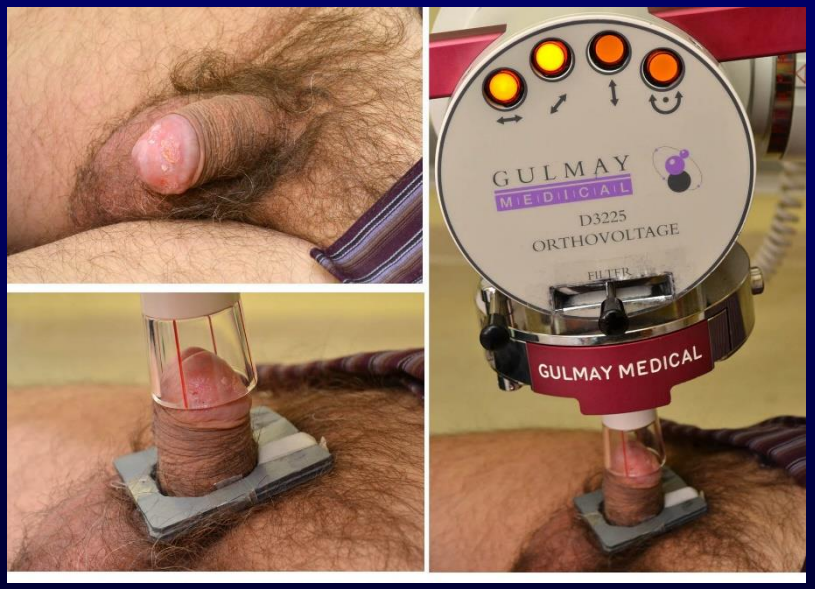


Fig. 1. Intraoperative photograph of two-plane, six-needle implant. Catheter *in situ*. Styrofoam collar around penis.

Side effects:
Urethral stricture necrosis

Radioterhapy for penile cancer
RT for regional lymph nodes

- Following bilateral inguinal lymph node dissection
  - if >2 positive lgl. or extracapsular extension
  - Postoperative inguinal radiotherapy

- In case of positive inguinal lymph nodes, pelvic lymph nodes should be treated, than the fields are narrowed to inguinal region

Systemic treatment of penile cancer

- Indication:
- Locoregionally advanced or metastatic tumour
- Combined chemotherapy
  - MTX, Vin, Belo, Cis
- Palliative in most cases

Surgery for kidney cancer

- The primer treatment for non metastatic kidney cancer is radical nephrectomy
  - Radical nephrectomy
    - Removal of the kidney,
    - Removal of the met. in adrenal gland or lymph node met
  - Partial nephrectomy (nephron sparing)
    - <7cm tumour
    - Soliter kidney
    - relapse 2-10 %
  - Radical nephrectomy is indicated despite metasteses

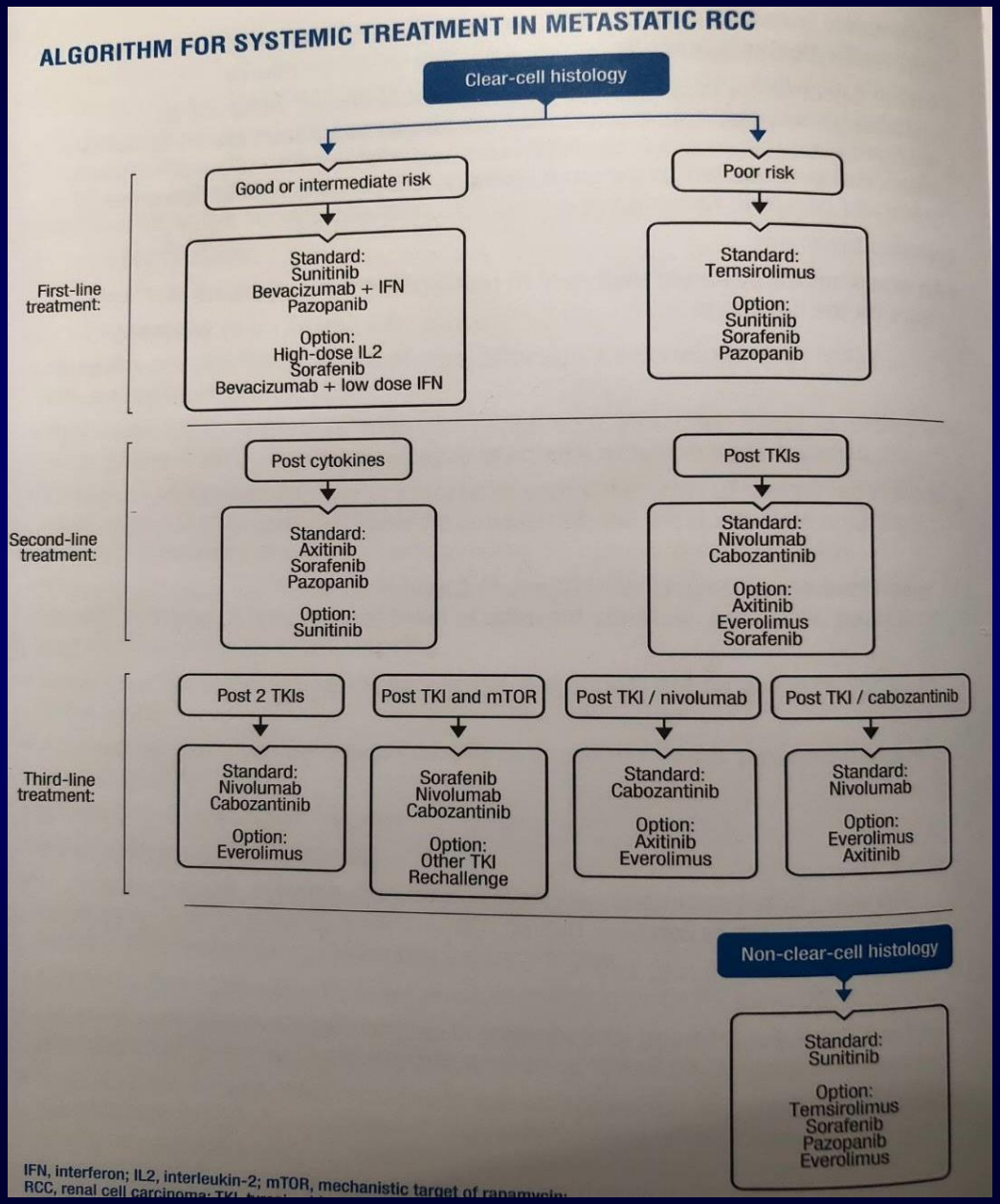
Treatment of kidney cancer Radiotherapy

- **No adjuvant radiotherapy is indicated in operable kidney cancer**
- **Palliative RT to bone metastases or other metastases**
- Palliative RT to the local relapse

Systemic treatment metastatic kidney cancer

- Former treatments
  - Chemotherapy, hormonal treatment, immuntherapy (INF, IL)
- Targeted therapies
  - Antiangiogenetic treatments
    - VEGF inhibitors (Avastin)
    - Tirozin kinase inhibitors (sunitinib, sorafenib, pazopanib, cabozantinib)
  - mTOR inhibitors (mammarian target of rapamycin complex kinase)
    - temsirolimus, everolimus
- Immuntherapy (new):
  - PD-1-inhibitors (nivolumab, pembrolizumab)
  - PD-L1 inhibitors (atezolizumab, durvalumab)

Systemic treatment in metastatic kidney cancer



Thank you for your attention!