National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®)

Prostate Cancer

Version 2.2013

NCCN.org

Continue

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

In the late 1980s and early 1990s, the number of newly diagnosed prostate cancers in U.S. men increased dramatically, and prostate cancer surpassed lung cancer as the most common cancer in men. It is generally accepted that these changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers. For example, the percentage of patients with low-risk disease has increased to 45% in 1999-2001 from 30% in 1989-1992 ($P <$ .0001).[1] The incidence of prostate cancer increased 2% annually from 1995 to 2001, and has since declined. An estimated 241,740 new cases will be diagnosed in 2012, accounting for 29% of new cancer cases in men in 2012.[2,3] Fortunately, the age-adjusted death rates from prostate cancer have also declined (-4.1% annually from 1994 to 2001). Researchers estimated prostate cancer to account for 28,170 deaths in 2012.[2] This comparatively low death rate suggests that unless prostate cancer is becoming biologically less aggressive, increased public awareness with earlier detection and treatment has begun to affect mortality from this prevalent cancer. However, early detection and treatment of prostate cancers that do not threaten life expectancy results in unnecessary side effects, which impair quality of life and health care expenses, while decreasing the value of PSA and digital rectal exam as early detection tests (see below).

To properly identify and manage patients with prostate cancer or any other malignancy, physicians must have an in-depth understanding of the natural history and the diagnostic, staging and treatment options. To this end, an NCCN guideline panel of leading experts from the fields of urology, radiation oncology, and medical oncology at member institutions developed guidelines for the treatment of prostate cancer. The panel representing NCCN member institutions reviews and updates the prostate guidelines every year, which are available on the NCCN web site (www.nccn.org). The treatment algorithms and recommendations represent current evidence integrated with expert consensus regarding acceptable approaches to prostate cancer treatment rather than a universally prescribed course of therapy. Individual physicians treating individual men with prostate cancer are expected to use independent judgment in formulating specific treatment decisions.

Estimates of Life Expectancy

As a result of widespread PSA testing, most patients are diagnosed with asymptomatic, clinically localized cancer. The combination of Gleason score, PSA level, and stage can effectively stratify patients into categories associated with different probabilities of achieving a cure. However, in addition to considering the probability of cure, the choice of initial treatment is influenced greatly by estimated life

Fattori prognostici

- Livello PSA iniziale
- GS
- Stadio

Combinati per generare nomogrammi che predicono la probabilità che la malattia rimanga

confinata alla ghiandola

si estenda:

vescichette seminali

linfonodi

expectancy, comorbidities, potential therapy side effects, and patient preference. The primary management options for initial therapy for clinically localized prostate cancer include active surveillance, radical prostatectomy or radiotherapy.

Estimates of life expectancy have emerged as a key determinant of treatment decision-making, particularly when considering active surveillance (see below). While it is possible to estimate life expectancy for groups of men, it is more difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration Life Insurance Tables.[4] The life expectancy can then be adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.[5] As an example, the Social Security Administration Life Expectancy for a 65 year old American man is 16.05 years. If judged to be in the upper quartile of health, a life expectancy of 24 years is assigned. If judged to be in the lower quartile of health, life expectancy of 8 years is assigned. Thus, treatment recommendations could change dramatically using the NCCN guidelines if a 65 year old man was judged to be in either very poor or excellent health. Life expectancy should be estimated using the Social Security Administration Tables[4] and modified further by a clinician's assessment of overall health. Examples of 5 year increments of age are reproduced from the NCCN Senior Adult Oncology Guidelines. Other prognostic comorbid conditions (including body mass index), and difficulty with 4 functional variables.

Nomograms and Predictive Models

Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or to spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is salvage by adjuvant radiation after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by clinical (TNM) stage determined by digital rectal examination (DRE), Gleason score in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been investigated intensively but have yet to be accepted as essential adjuncts to staging.

Predicting prognosis is essential for patient decision-making, treatment selection, and adjuvant therapy. These NCCN Guidelines incorporate a risk stratification scheme that uses a minimum of stage, grade, and PSA to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered for treatment and to predict the probability of biochemical failure (i.e., probability of a rising PSA, which is also termed *biochemical recurrence* or *PSA failure*) after definitive local therapy.[7] This risk group stratification has been published widely and validated, and it provides a better basis for treatment recommendations than clinical stage alone.[8,9]

SCREENING

Argomento controverso

America Cancer Society e National Cancer Institute

> 50 ANNI

PSA annuale

Visita clinica con ER

Biopsia prostatica

National Comprehensive Cancer Network®

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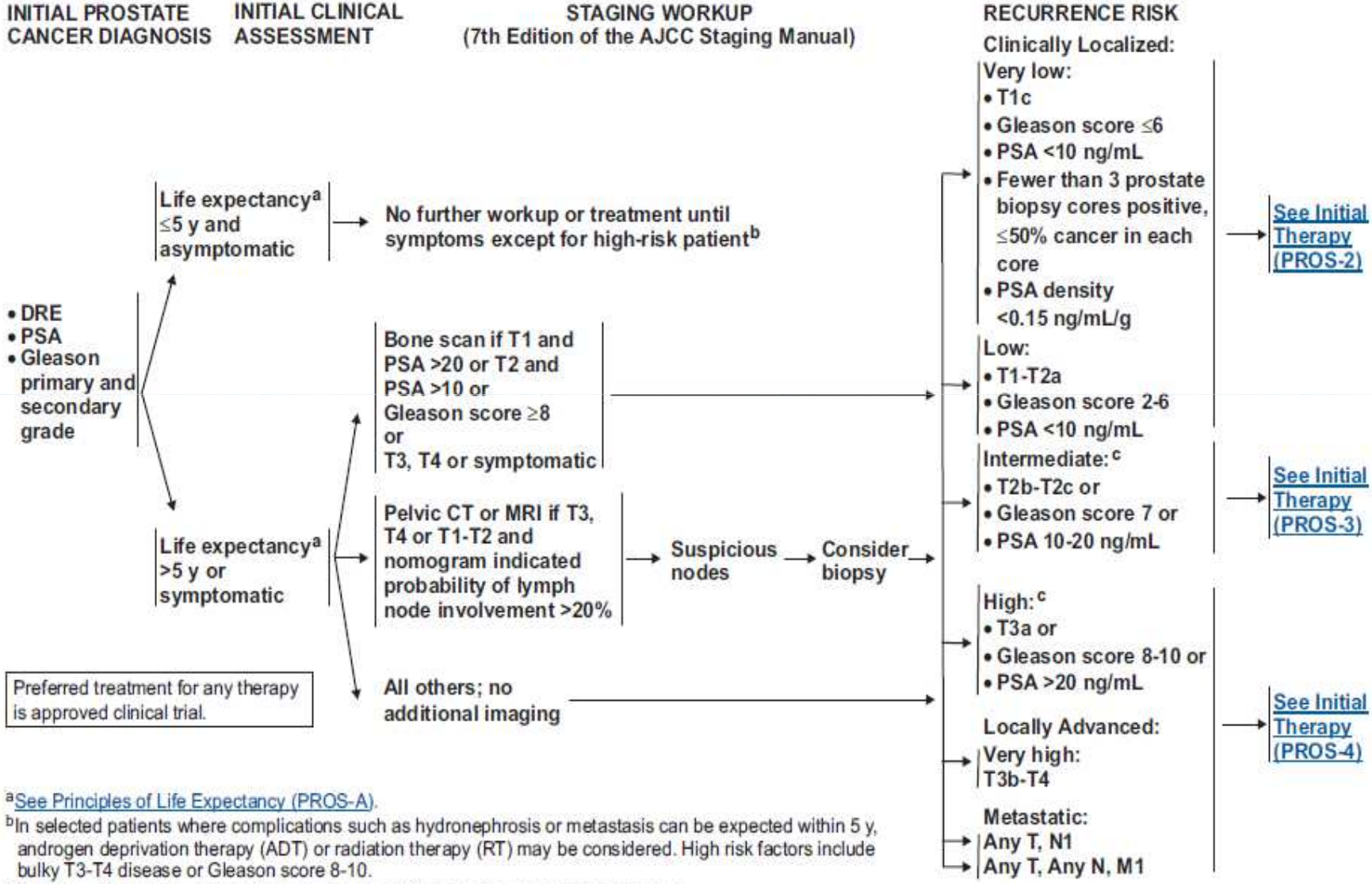

[a] See Principles of Life Expectancy (PROS-A).

[b] In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered. High risk factors include bulky T3-T4 disease or Gleason score 8-10.

[c] Patients with multiple adverse factors may be shifted into the next higher risk group.

Histopathologic Grade (G)

Gleason score is recommended because as the grading system of choice, it takes into account the inherent morphologic heterogeneity of prostate cancer, and several studies have clearly established its prognostic value. A primary and a secondary pattern (the range of each is 1–5) are assigned and them summed to yield a total score. Scores of 2–10 are thus theoretically possible. The vast majority of newly diagnosed needle biopsy detected prostate cancers are graded Gleason score 6 or above. (If a single pattern of disease is seen, it should be reported as both grades. For example, if a single focus of Gleason pattern 3 disease is seen, it is reported as Gleason score 3 + 3 = 6.) In a radical prostatectomy, if a tertiary pattern is present, it is commented upon but not reflected in the Gleason score. It is recommended that radical prostatectomy specimens should be processed in an organized fashion where a determination can be made of a dominant nodule or separate tumor nodules. If a dominant nodule/s is present, the Gleason score of this nodule should be separately mentioned as this nodule is often the focus with highest grade and/or stage of disease.

Gleason X	**Gleason score** cannot be processed
Gleason ≤ 6	Well differentiated (slight anaplasia)
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

Table 1.
TNM Staging System For Prostate Cancer

Primary Tumor (T)

Clinical

TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Clinically inapparent tumor neither palpable nor visible by imaging
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2		Tumor confined within prostate*
	T2a	Tumor involves one-half of one lobe or less
	T2b	Tumor involves more than one-half of one lobe but not both lobes
	T2c	Tumor involves both lobes
T3		Tumor extends through the prostatic capsule **
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumor invades the seminal vesicle(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder, levator muscles, and/or pelvic wall.

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

Pathologic(pT)*

pT2		Organ confined
	pT2a	Unilateral, involving one-half of one side or less
	pT2b	Unilateral, involving more than one-half of one side but not both sides
	pT2c	Bilateral disease
pT3		Extraprostatic extension
	pT3a	Extraprostatic extension or microscopic invasion of the bladder neck**
	pT3b	Seminal vesicle invasion
pT4		Invasion of bladder, rectum

*Note: There is no pathologic T1 classification.

**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Pathologic

PNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional nodes(s)

Distant Metastasis (M)*

M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

ANATOMIC STAGE/PROGNOSTIC GROUPS *

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA < 10	Gleason ≤ 6
	T2a	N0	M0	PSA < 10	Gleason ≤ 6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA < 20	Gleason 7
	T1a-c	N0	M0	PSA ≥10 <20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥ 20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥ 8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*Note: When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

Histopathologic Type

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell carcinoma of the prostate. Adjectives used to describe adenocarcinomas can include mucinous, signet ring cell, ductal, and neuroendocrine including small cell carcinoma. Transitional cell (urothelial) carcinoma of the prostate is classified as a urethral tumor. There should be histologic confirmation of the disease.

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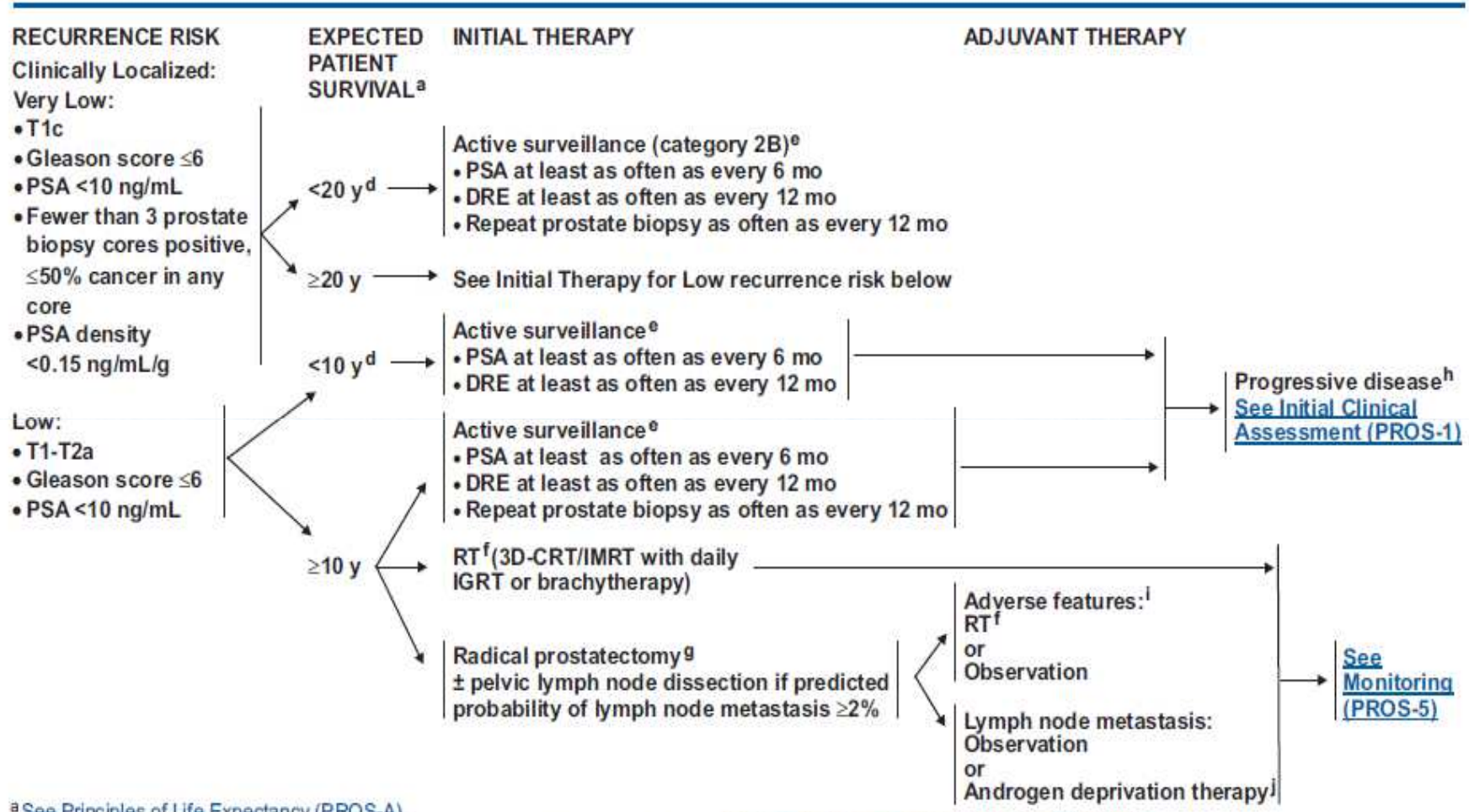

[a] See Principles of Life Expectancy (PROS-A).

[d] The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.

[e] Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses See Principles of Active

[f] See Principles of Radiation Therapy (PROS-C).

[g] See Principles of Surgery (PROS-D).

[h] Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.

[i] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.

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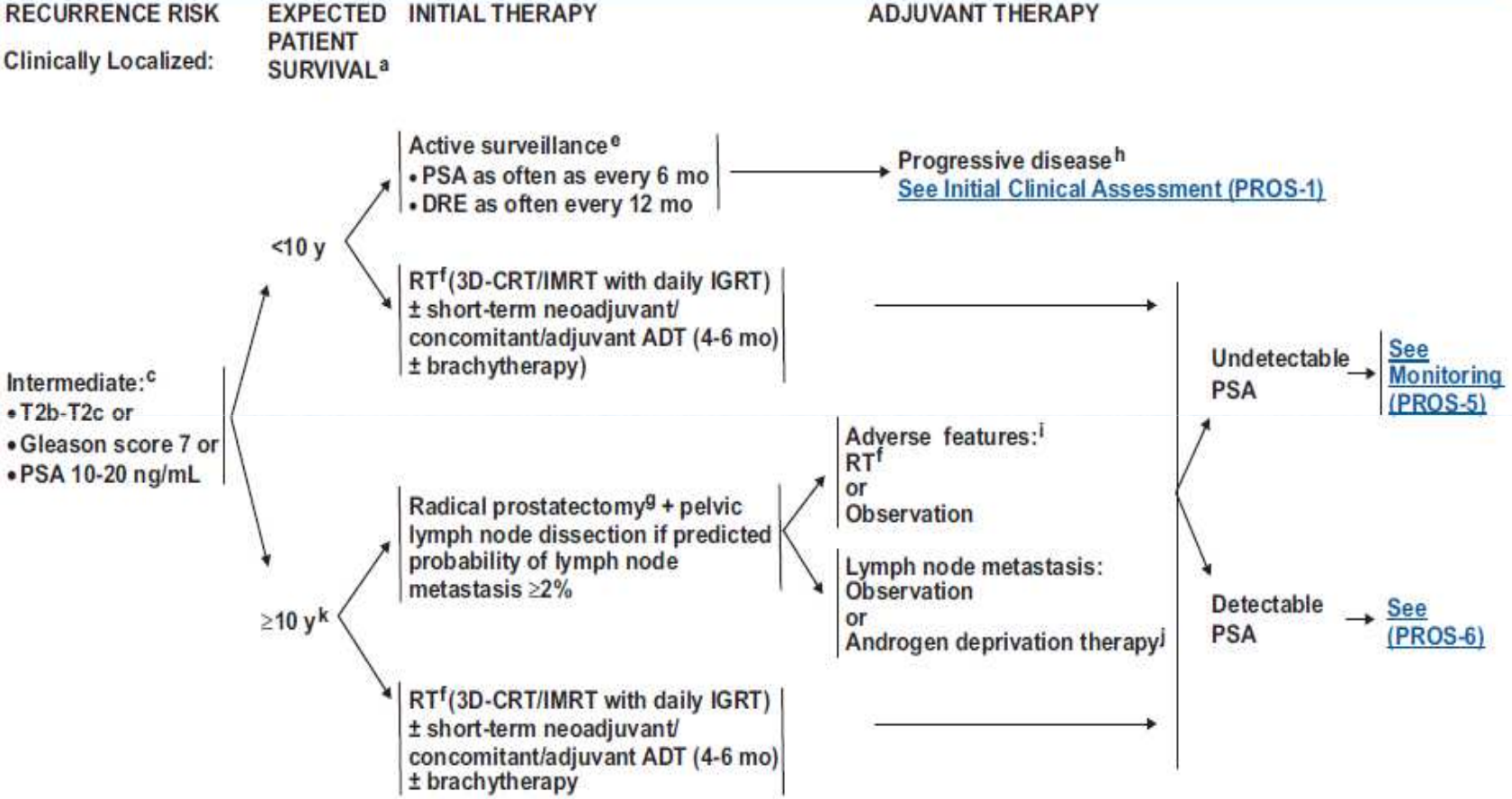

[a] See Principles of Life Expectancy (PROS-A).

[c] Patients with multiple adverse factors may be shifted into the next higher risk group.

[e] Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (PROS-B).

[f] See Principles of Radiation Therapy (PROS-C).

[g] See Principles of Surgery (PROS-D).

[h] Criteria for progression are not well-defined and require physician judgement; however, a

[i] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.

[j] See Principles of Androgen Deprivation Therapy (PROS-E).

[k] Active surveillance of intermediate and high risk clinically localized cancers is not recommended in patients with life expectancy > 10 years

exactly to the shape of the prostate. 3D-CRT allows higher cumulative doses to be delivered with lower risk of late effects.[25, 64-66] The second generation 3D technique, intensity-modulated radiation therapy (IMRT), significantly reduces the risk of gastrointestinal toxicities compared to 3D-CRT.[67, 68] Daily prostate localization using image-guided radiation therapy (IGRT) is essential for target margin reduction and treatment accuracy. Imaging techniques, including ultrasound, implanted fiducials, electromagnetic targeting and tracking, or endorectal balloon, can be helpful in improving cure rates and minimizing complications.

These techniques have permitted safer dose escalation, and results of randomized trials suggested that dose escalation is associated with improved biochemical outcomes.[69-72] Kuban et al[72] recently published an updated analysis on their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. With a median follow-up reaching 8.7 years, the authors reported superior freedom from biochemical or clinical failure in the group randomized to 78 Gy compared to 70 Gy (78% vs 59%, P = 0.004). The difference was even greater among patients with initial PSA > 10 ng/mL (78% vs 39%, P = 0.001). In light of these findings, the conventional 70 Gy is no longer considered adequate. A dose of 75.6-79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses up to 81.0 Gy.[67, 73, 74]

One of the key aspects of RT planning includes identifying which patients will benefit from inclusion of pelvic lymph node irradiation and ADT. Patients with high-risk cancers are candidates for pelvic lymph node irradiation (78-80+ Gy) and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 years or 4-6 months if they have a single high risk adverse factor. Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 months of neoadjuvant/concomitant/adjuvant ADT. Patients with low risk cancers should not receive either pelvic lymph node radiation or ADT. Evidence from randomized trials has emerged that supports the use of adjuvant/salvage RT after radical prostatectomy in men with adverse laboratory or pathologic features or detectable PSA (See Section "Adjuvant therapy for high/very high risk of recurrence").

EBRT for prostate cancer shows several distinct advantages over surgical therapy. RT avoids complications associated with surgery, such as bleeding and transfusion-related effects as well as risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-conformal and IMRT techniques are available widely in community practice and are possible for patients over a wide range of ages. This therapy includes a very low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function.[75] Combined with ADT, radiation offers a survival benefit in locally advanced cancer, because treatments may eradicate extensions of tumor beyond the margins of the prostate.[76] However, the addition of ADT increases the risk for erectile dysfunction.[77]

The disadvantages of EBRT include a treatment course of 8 to 9 weeks. Up to 50% of patients have some temporary bladder or bowel symptoms during treatment, there is a low but definite risk of protracted rectal symptoms from radiation proctitis, and the risk of erectile dysfunction increases over time.[75, 77] In addition, if the cancer recurs, salvage surgery is associated with a higher risk of complications than primary surgical therapy.[78] Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum or a permanent indwelling Foley catheter. Relative contraindications include very low capacity bladder, chronic moderate or severe diarrhea, bladder outlet

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European Association of Urology

Guidelines

EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Treatment of Clinically Localised Disease

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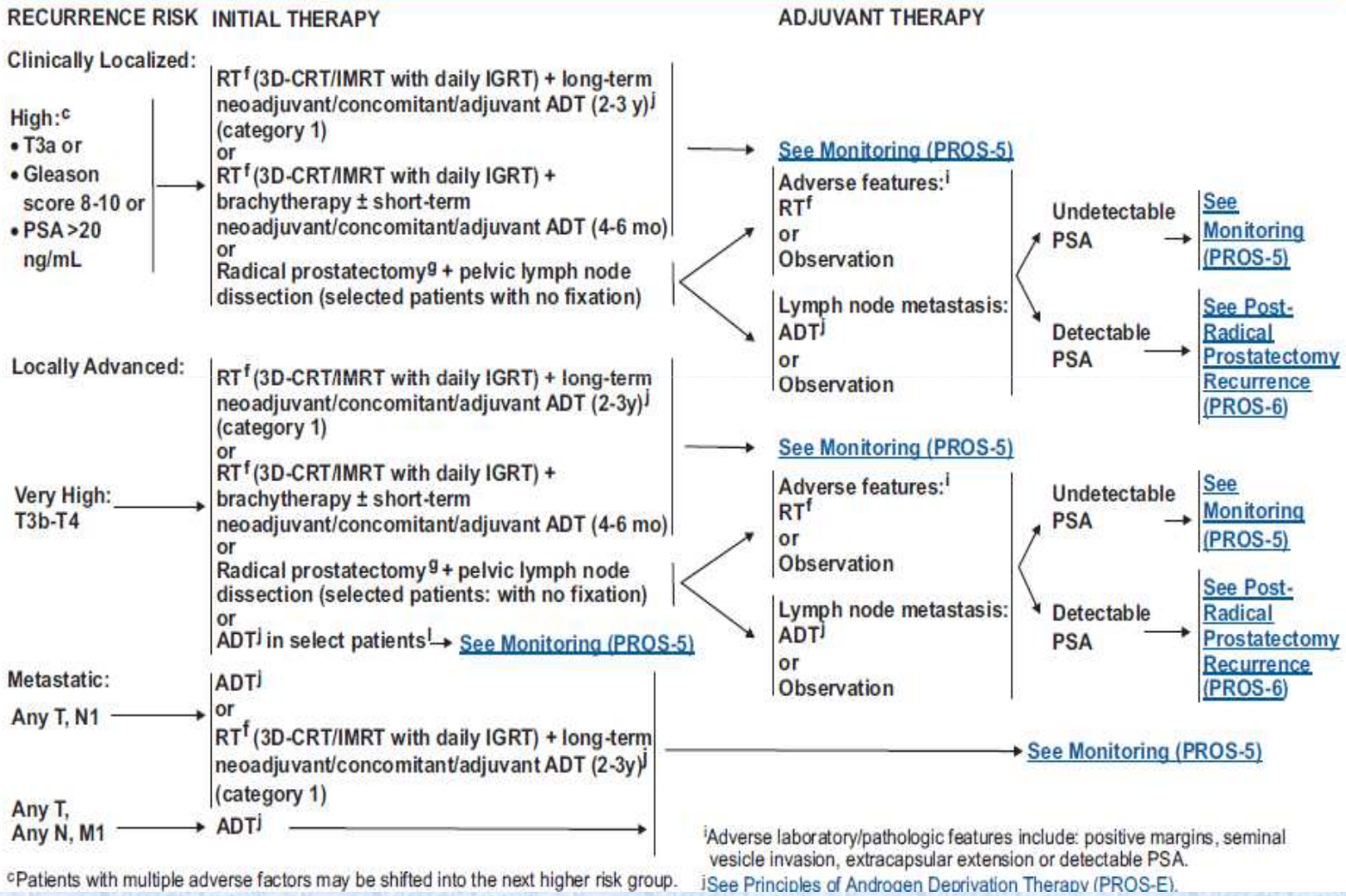

[c]Patients with multiple adverse factors may be shifted into the next higher risk group.

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[j]See Principles of Androgen Deprivation Therapy (PROS-E).

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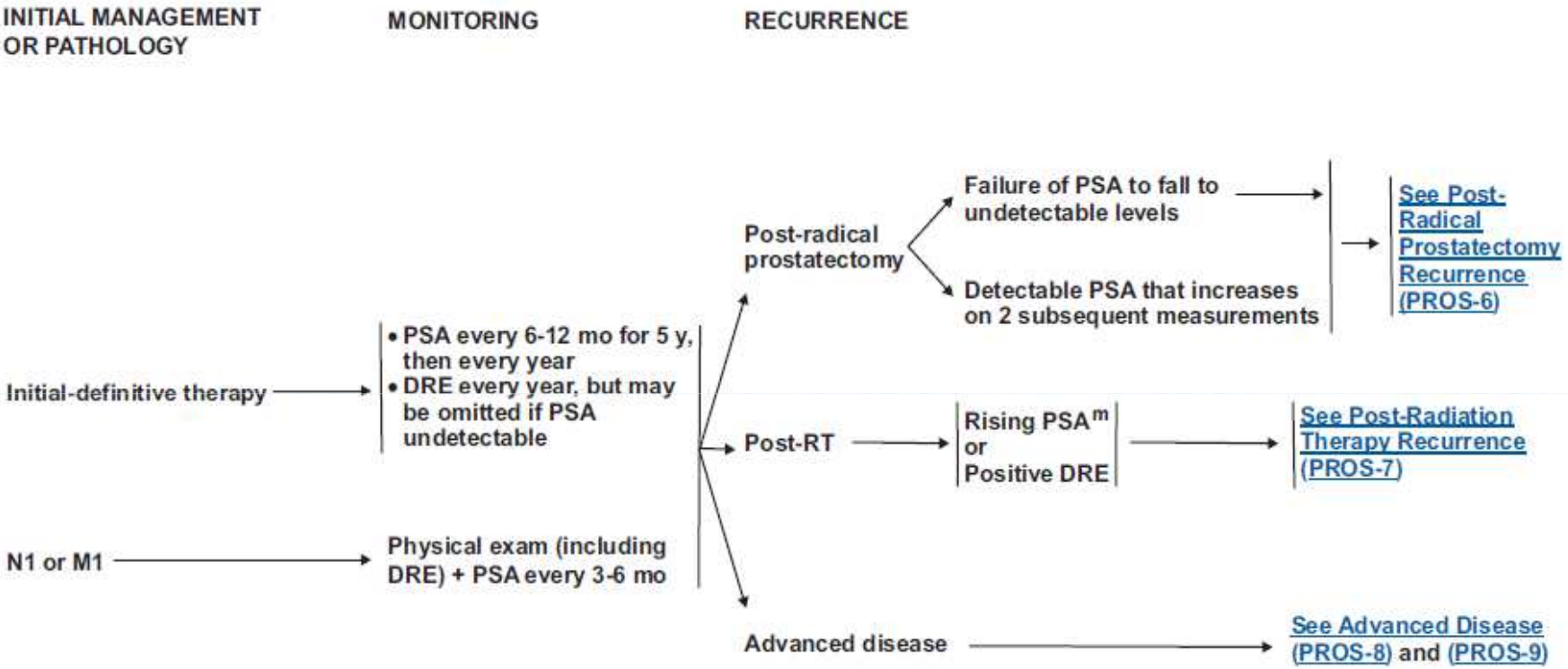
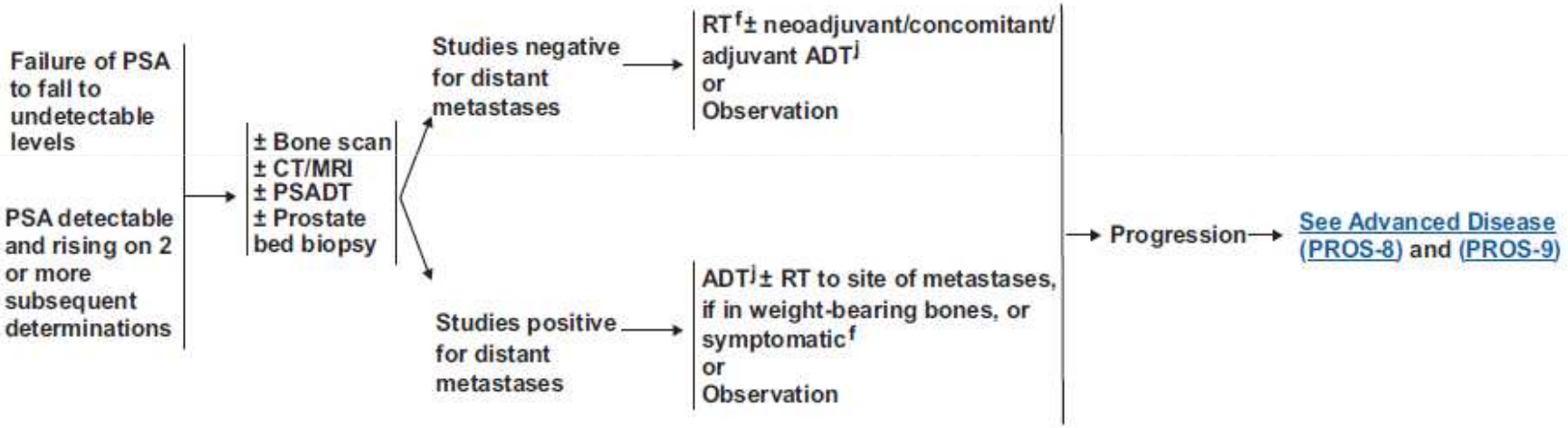


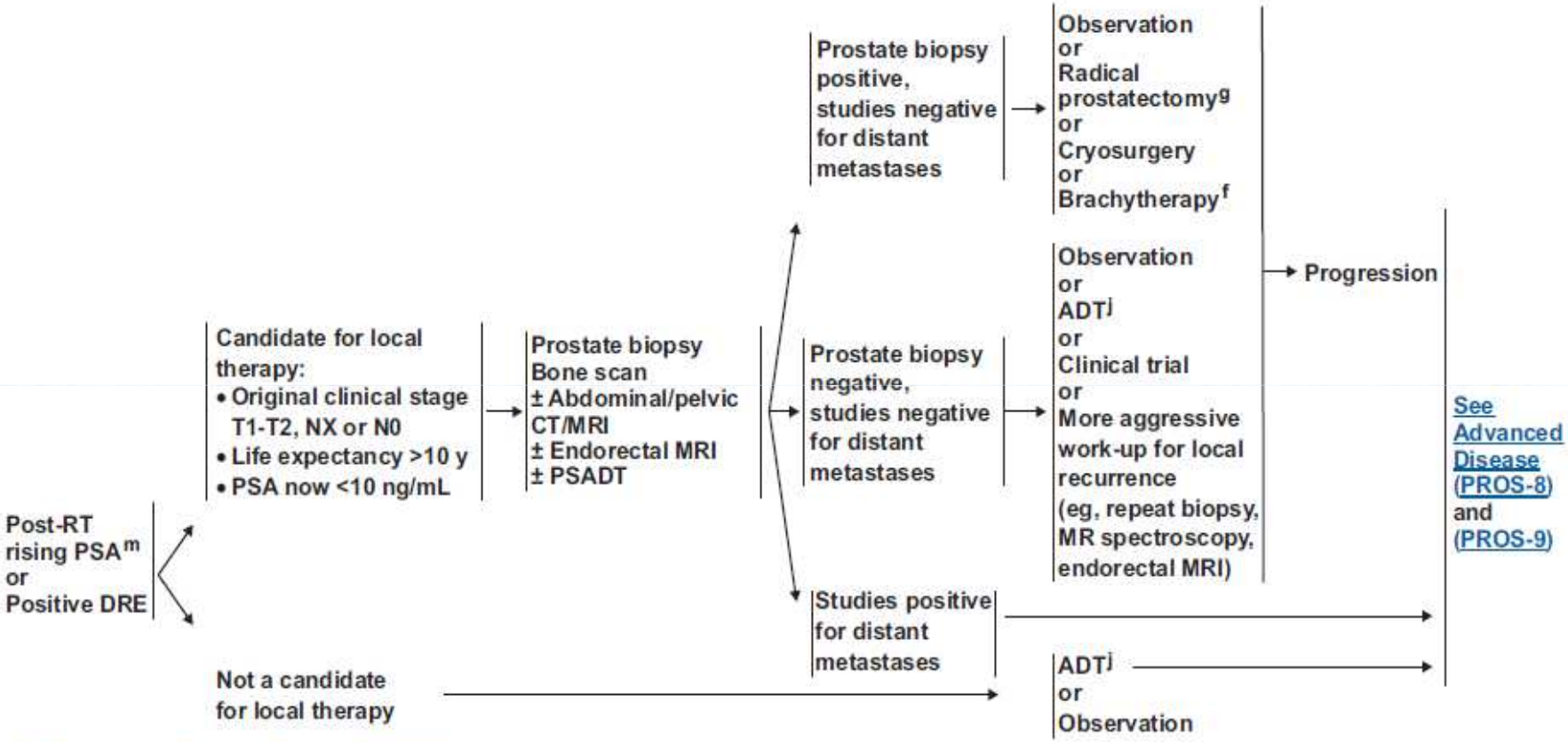
[m]RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - (1) PSA rise by 2 ng/ml or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; (2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.

POST-RADICAL PROSTATECTOMY RECURRENCE



[f] See Principles of Radiation Therapy (PROS-C).
[j] See Principles of Androgen Deprivation Therapy (PROS-E).

POST-RADIATION THERAPY RECURRENCE



[f] See Principles of Radiation Therapy (PROS-C).
[g] See Principles of Surgery (PROS-D).
[j] See Principles of Androgen Deprivation Therapy (PROS-E).
[m] RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - (1) PSA rise by 2 ng/ml or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; (2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.

RADIOTERAPIA

INTENTO RADICALE

A Fasci Esterni:

Convenzionale
3D Conformazionale
IMRT

Brachiterapia

^{125} Iodio
^{108} Palladio
} Impianti permanenti
^{192} Iridio (alto dose-rate)

Radioterapia a fasci esterni + brachiterapia

RADIOTERAPIA

PRINCIPLES OF RADIATION THERAPY

External Beam Radiotherapy:

- 3D conformal and IMRT (intensity modulated radiation therapy) techniques should be employed. Image-guided radiation therapy (IGRT) is required if dose ≥78 Gy.
- Doses of 75.6-79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques such as IGRT using CT, ultrasound implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.

Brachytherapy:

- Permanent low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers consider combining brachytherapy with EBRT (40-50 Gy) ± 4-6 mo neoadjuvant/comcomittant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 4-6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate (TURP) are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant androgen deprivation therapy may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry should be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for 125-Iodine and 125 Gy for 103-Palladium. The corresponding boost dose after 40-50 Gy EBRT are 110 Gy and 90-100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5-10.5 Gy x 2 fractions, 5.5-7.5 Gy x 3 fractions, and 4.0-6.0 Gy x 4 fractions.

Palliative Radiotherapy:

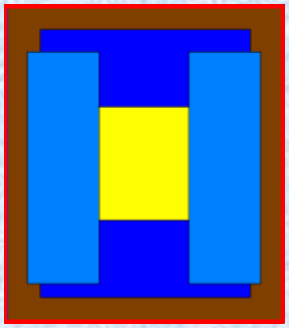
- 800 cGy as a single dose should be used instead of 3000 cGy in 10 fractions for non-vertebral metastases.
- Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external beam radiation.

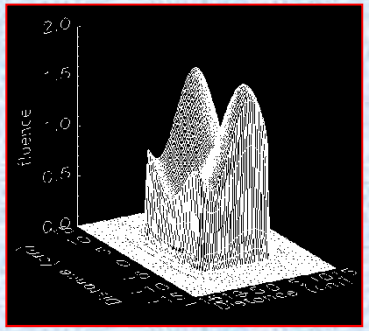
Evoluzione Tecnologica in Radioterapia

1980s Fine 1990s 2000s

TREND – Miglioramento della Precisione

2D **3D-CRT** **IMRT**





INTENTO RADICALE
Piani di trattamento in 2D

utilizzano simulatori convenzionali per disegnare le dimensioni campi di irradiazione

arrangiamenti del fascio standard, basati su reperi ossei visibili sulle radiografie

CARCINOMA OF PROSTATE - PORTALS

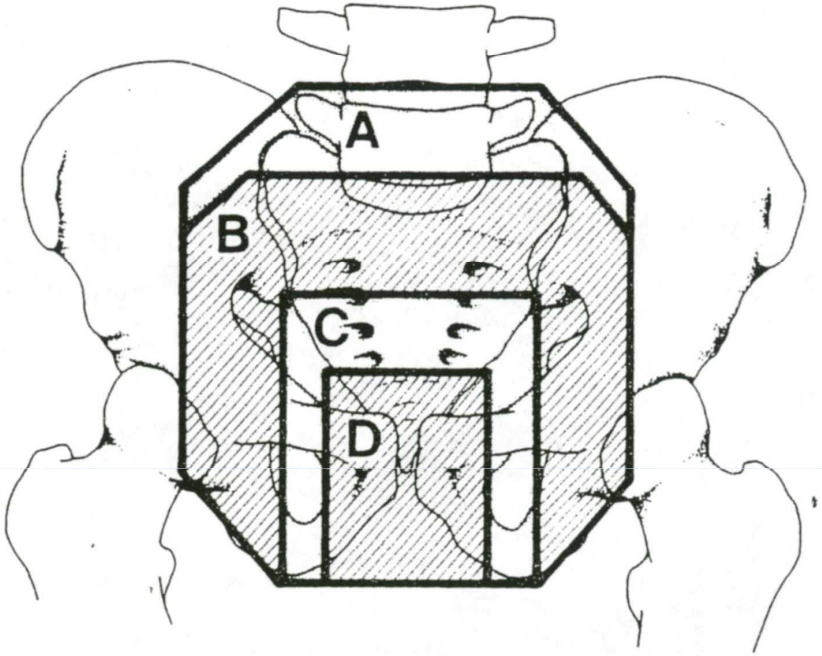


FIGURE 58.11. Diagrams of the pelvis showing volumes used to irradiate the prostate and pelvic lymph nodes. Lower margin is at or 1 cm below ischial tuberosities. At the Mallinckrodt Institute of Radiology, 15 × 15 cm portals at source–skin distance are used for stage A2 and B disease and for selected postoperative patients, whereas for stage C or D1 disease, 18 × 15 cm portals are used to cover all common iliac lymph nodes up to the bifurcation of the common iliac lymph nodes. Sizes of reduced fields are larger (up to 12 × 14 cm) when seminal vesicles or periprostatic tumor are irradiated compared with prostate boost only (up to 10 × 11 cm).

PROSTATE
LATERAL PELVIC FIELDS

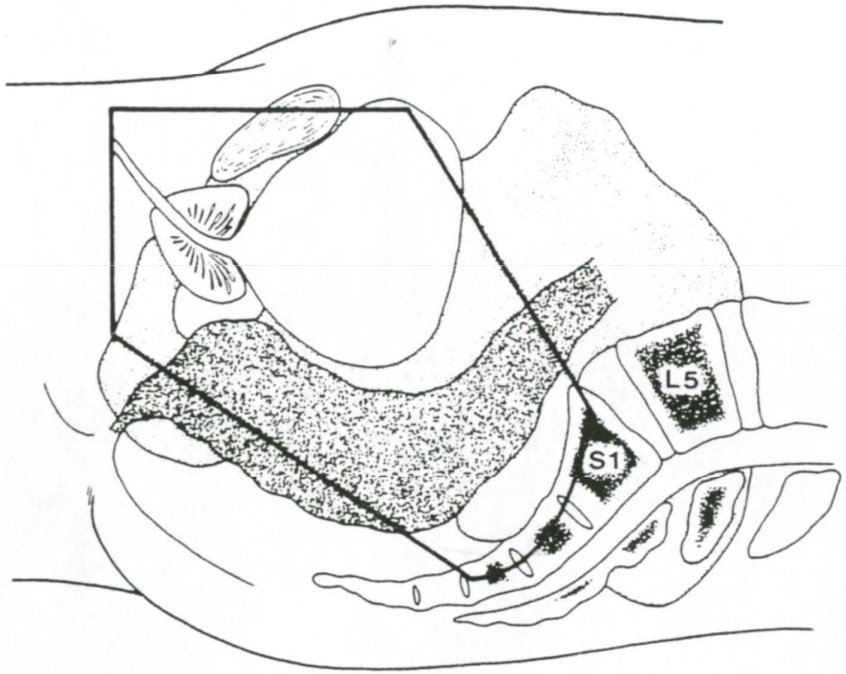


FIGURE 58.12. Lateral portal used in box technique to irradiate pelvic tissues and prostate. The anterior margin is 0.5 to 1 cm posterior to projected cortex of pubic symphysis. Presacral lymph nodes are included down to S3; inferiorly, the posterior wall of rectum is spared.

2D

Dosi > 70 Gy sono state associate ad un rischio di tossicità severa 2 volte + alta rispetto a dosi < 70 Gy

Hanks, Semin Radiat Oncol 1997

Radioterapia 3D conformazionale

Processo nel quale il piano di trattamento, basato su immagini TC, viene elaborato con lo scopo di:

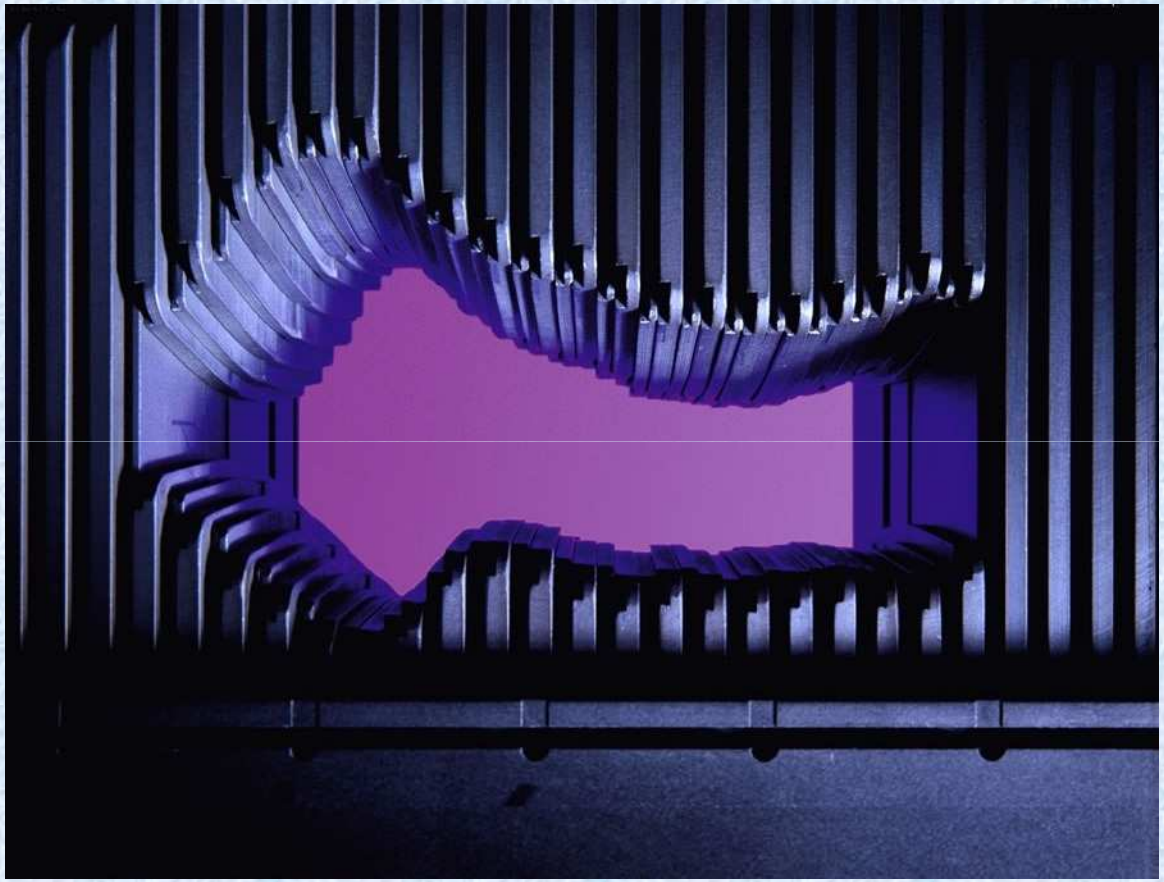
conformare precisamente la prescrizione di dose al volume bersaglio

ridurre o minimizzare la dose ai tessuti sani circostanti

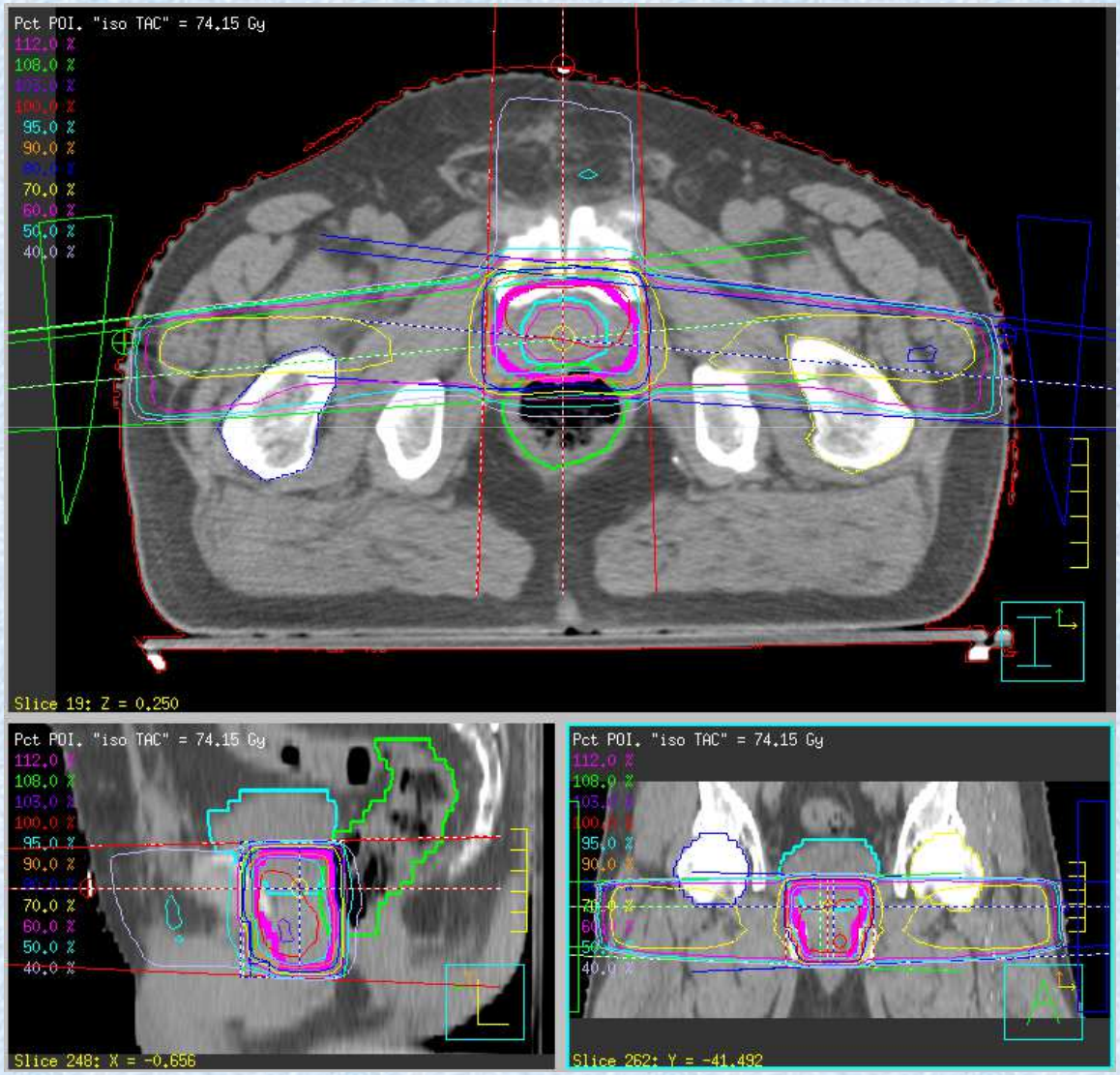
Ai fini di un corretta pianificazione ed esecuzione di un trattamento radiante 3D conformazionale sono necessari:

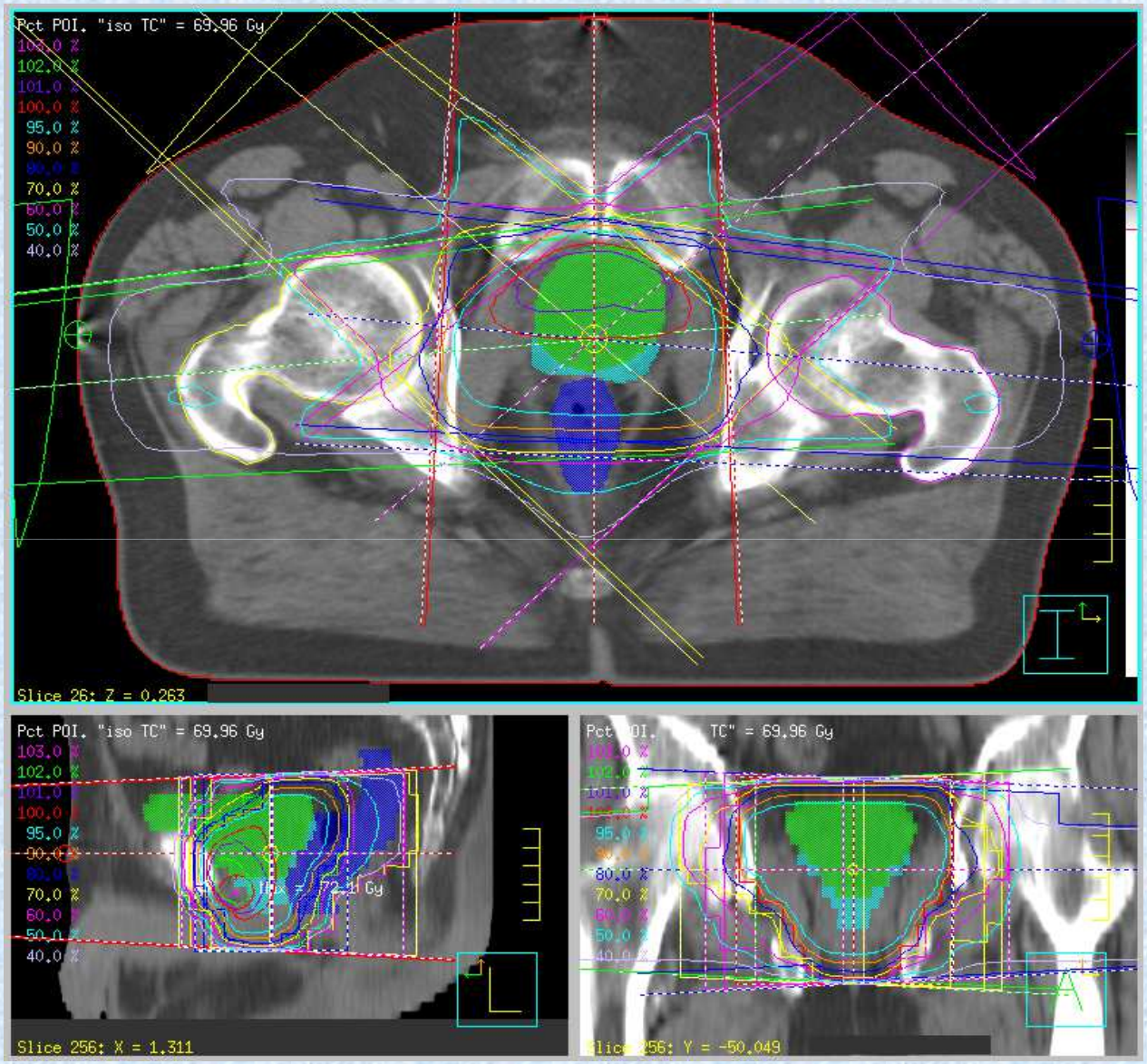
- ✓ **Imaging dettagliato** per poter generare precisamente il volume bersaglio in 3D
- ✓ **3D-TPS** per poter definire il numero di fasci, le dimensioni e la forma di ogni fascio, per coprire adeguatamente il volume bersaglio
- ✓ **Accurati algoritmi di calcolo 3D**
- ✓ **Collimatori multilamellari**

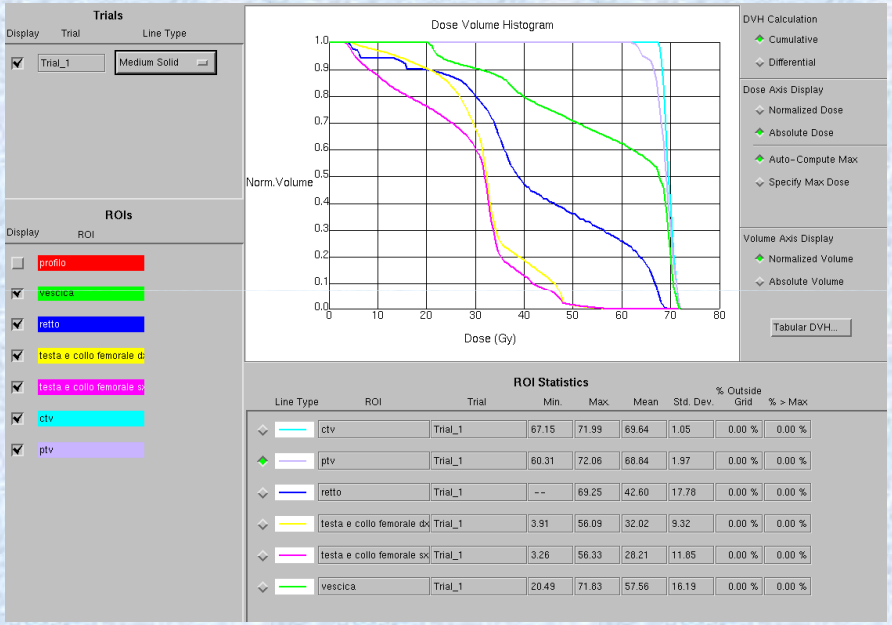
RADIOTERAPIA 3D CONFORMAZIONALE

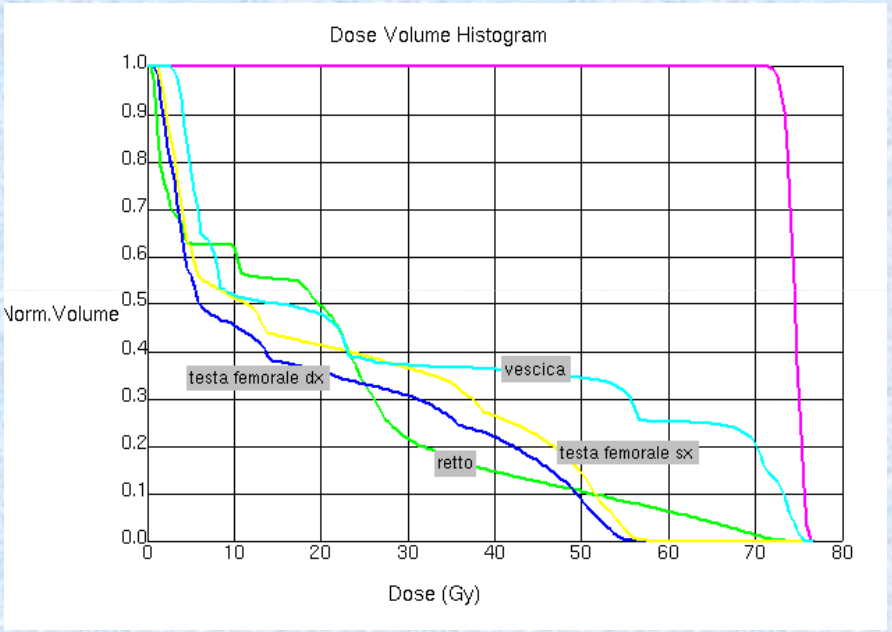


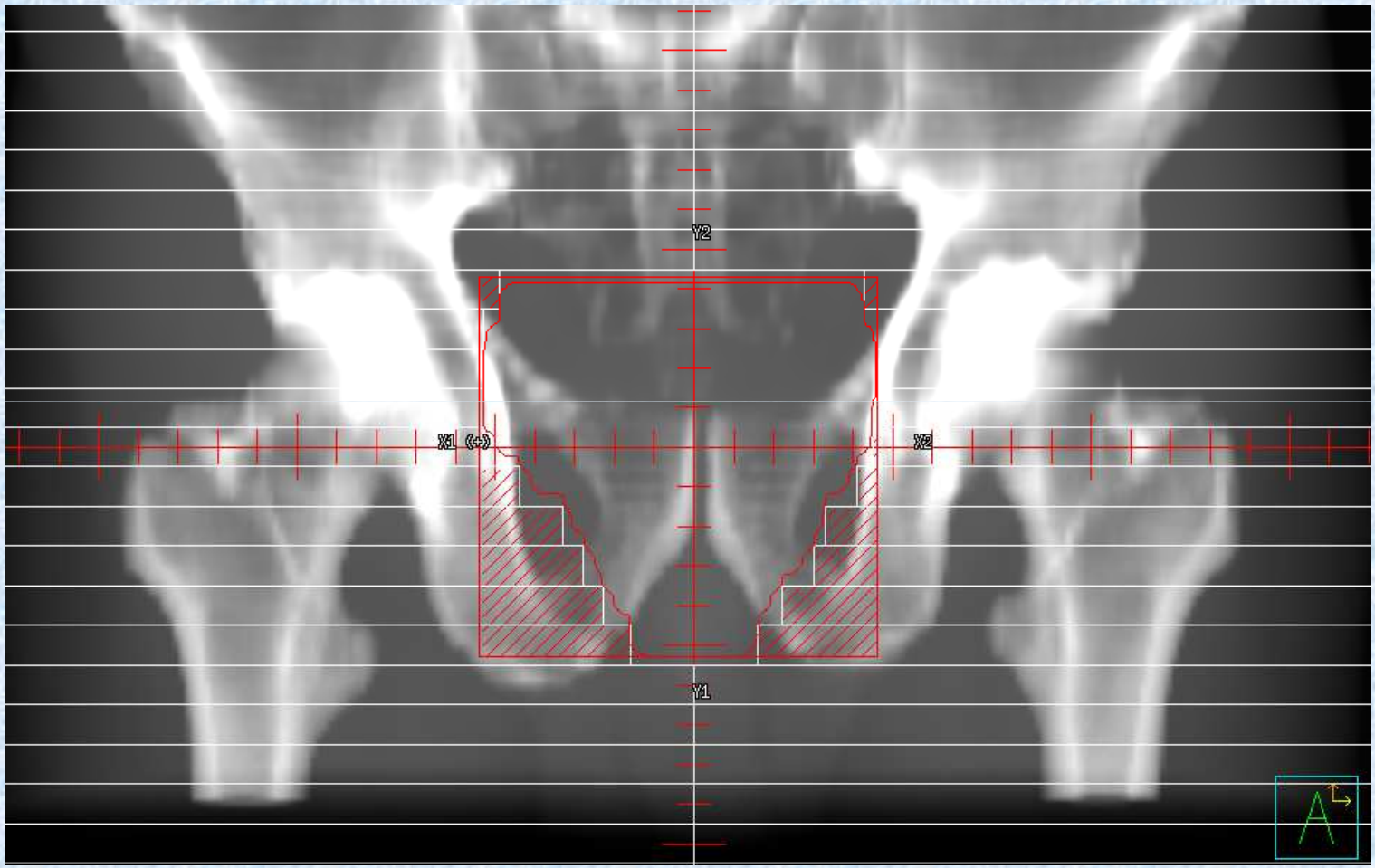
3D CONFORMAZIONALE

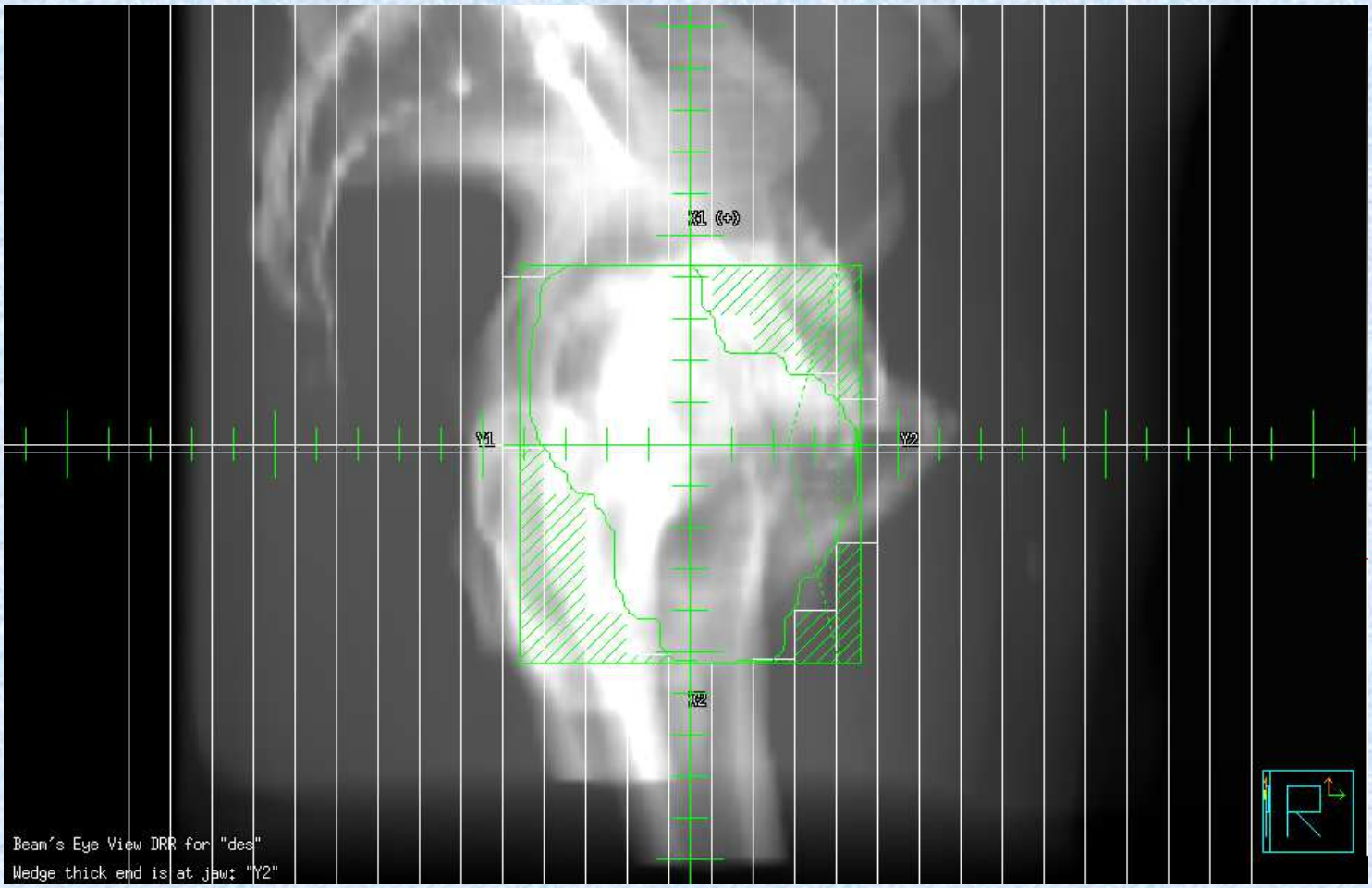


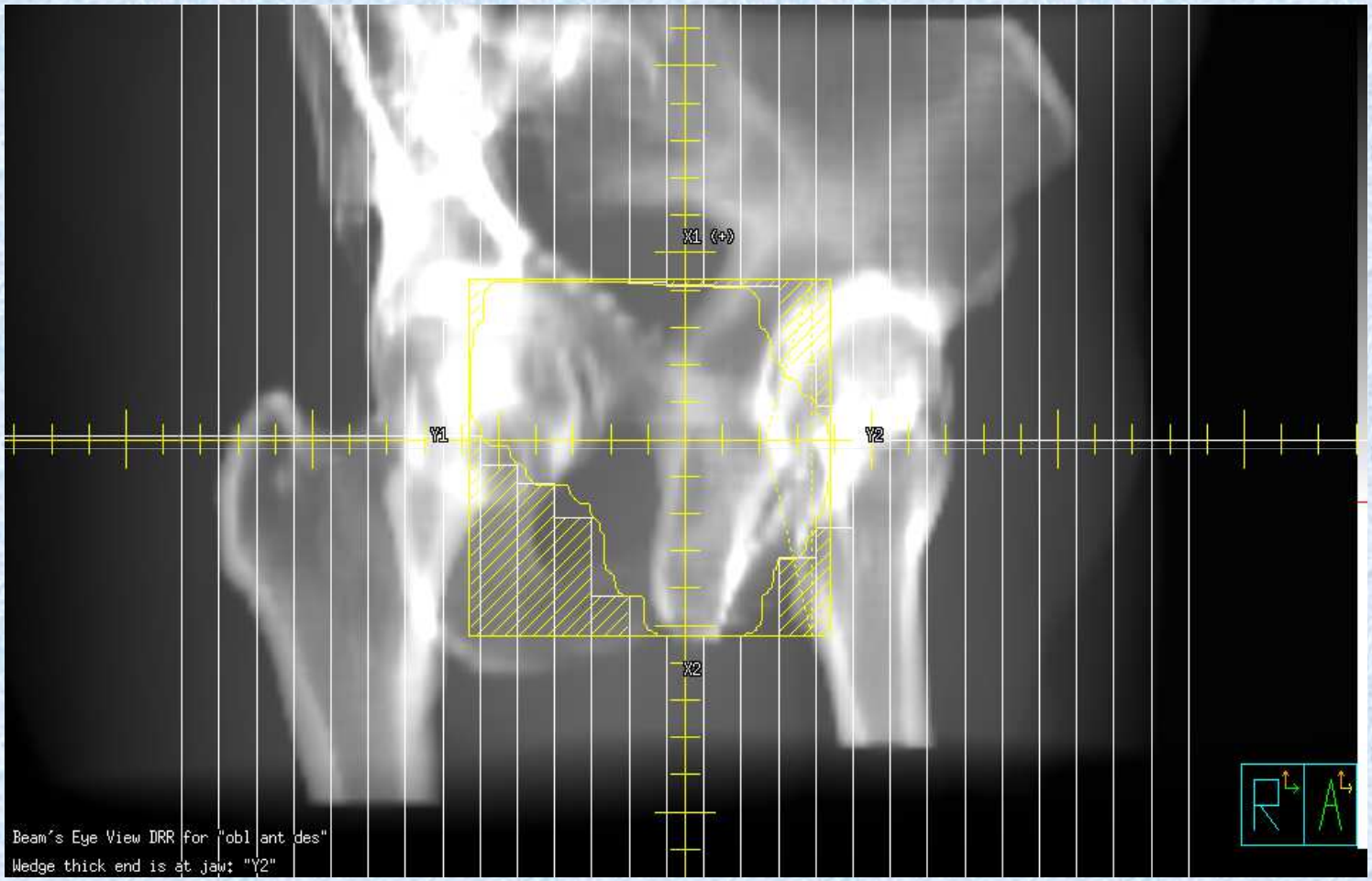

Pct POI. "iso TC" = 69.96 Gy
103.0 %
102.0 %
101.0 %
100.0 %
95.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
Slice 26: Z = 0.263
Pct POI. "iso TC" = 69.96 Gy
103.0 %
102.0 %
101.0 %
100.0 %
95.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
Slice 256: X = 1.311
Pct POI. TC" = 69.96 Gy
95.0 %
80.0 %
70.0 %
50.0 %


Trials
Display
Trial
Line Type
Trial_1
Medium Solid
ROIs
Display
ROI
profilo
vescica
retto
testa e collo femorale dx
testa e collo femorale sx
ctv
ptv
Dose Volume Histogram
Norm.Volume
Dose (Gy)
DVH Calculation
Cumulative
Differential
Dose Axis Display
Normalized Dose
Absolute Dose
Auto-Compute Max
Specify Max Dose
Volume Axis Display
Normalized Volume
Absolute Volume
Tabular DVH...
ROI Statistics
Line Type
ROI
Trial
Min.
Max.
Mean
Std. Dev.
% Outside Grid
% > Max
ctv Trial_1 67.15 71.99 69.64 1.05 0.00 % 0.00 %
ptv Trial_1 60.31 72.06 68.84 1.97 0.00 % 0.00 %
retto Trial_1 -- 69.25 42.60 17.78 0.00 % 0.00 %
testa e collo femorale dx Trial_1 3.91 56.09 32.02 9.32 0.00 % 0.00 %
testa e collo femorale sx Trial_1 3.26 56.33 28.21 11.85 0.00 % 0.00 %
vescica Trial_1 20.49 71.83 57.56 16.19 0.00 % 0.00 %

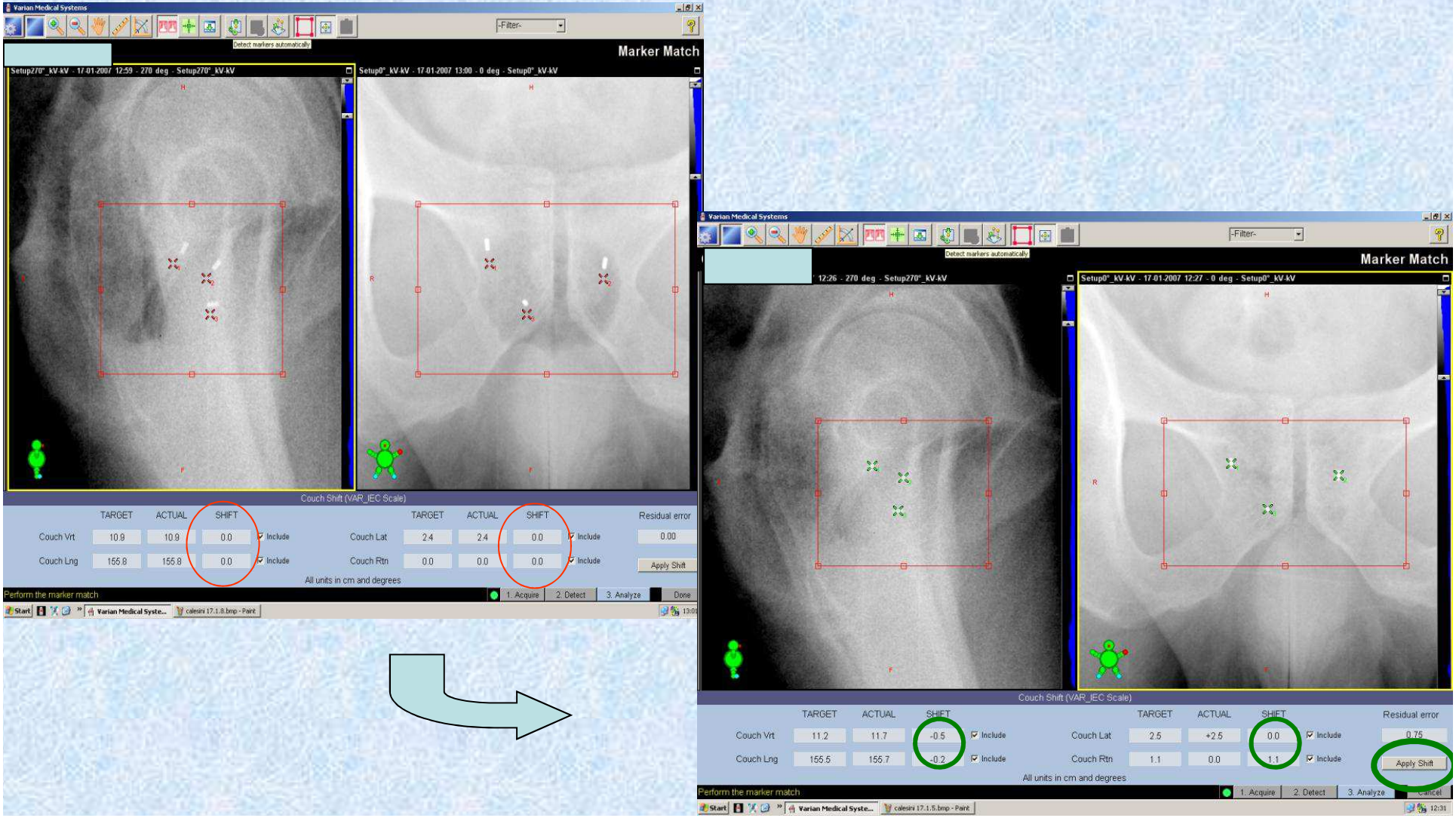

Dose Volume Histogram
Norm.Volume
Dose (Gy)
testa femorale dx
vescica
retto
testa femorale sx


Y2
X1
X2
Y1


X1 (+)
Y1
Y2
X2
Beam's Eye View DRR for "des"
Wedge thick end is at jaw: "Y2"


X1 (+)
Y1
Y2
X2
R
A
Beam's Eye View DRR for "obl ant des"
Wedge thick end is at jaw: "Y2"

MARKER MATCH



RT 3D conformazionale

- Migliore distribuzione di dose nel volume bersaglio
- Riduzione della tossicità
- Incremento di dose

Migliore ratio terapeutico

Tuttavia, anche con 3D-CRT

15% - 35% ≥ G2 tossicità rettale con dosi > 70 Gy

Tossicità tardiva in studi di dose-escalation con 3D-CRT

Studio	Dose (Gy)	GI			GU		
		G2	G3	P	G2	G3	P
Pollack 02’	70 78	11 19	1 7	.006	7 10	1 3	ns
Zietman 05’	70.2 79.2	8 17	1 1	.004	18 20	2 1	ns
Peeters 05’	68 78	23 30	2 5	ns	28 30	5 7	ns
Dearnaley 07’	64 74	14 20	4 6	.005	6 8	2 4	ns
RTOG 9406, 02’	68.4 73.8 79.2	8 8 7	0 0 1	ns	16 14 10	0 1 2	ns

RADIOTERAPIA AD INTENSITÀ MODULATA (IMRT)

- Modalità di somministrazione del trattamento radiante

- Rappresenta una delle maggiori innovazioni tecnologiche in radioterapia

- Evoluzione della RT 3D conformazionale in grado di conformare alte dosi al tumore con risparmio dei tessuti normali.

IMRT

- Caratterizzata dalla possibilità di dividere i fasci di radiazioni in tanti segmenti di ognuno dei quali può essere manipolare l'intensità

- Questo permette una modulazione fine della intensità di dose che è "depositata" in ogni punto specifico ad un livello differente.

IMRT

- In questo approccio vengono selezionati i parametri desiderati, relativi alla distribuzione di dose nel volume bersaglio e ai limiti di dose agli organi a rischio
- Algoritmi specifici permettono di calcolare l'intensità del fascio che consente di ottenere la distribuzione di dose desiderata
- L'intensità del fascio non è uniforme nel campo di irradiazione

IMRT

INDICAZIONI:

1. Volume bersaglio con morfologia irregolare e in prossimità di organi a rischio

2. Volumi target di forma concava

3. Volume di interesse in prossimità di strutture precedentemente irradiate.

4. Necessità di dose escalation.

Fascio modulato in intensità

conformazionale

IMRT

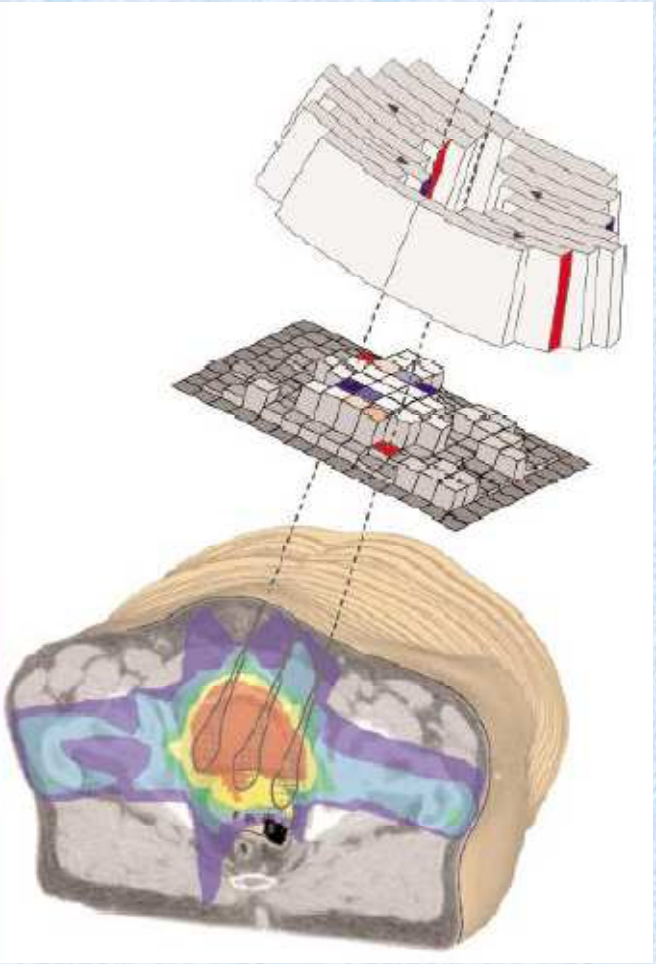
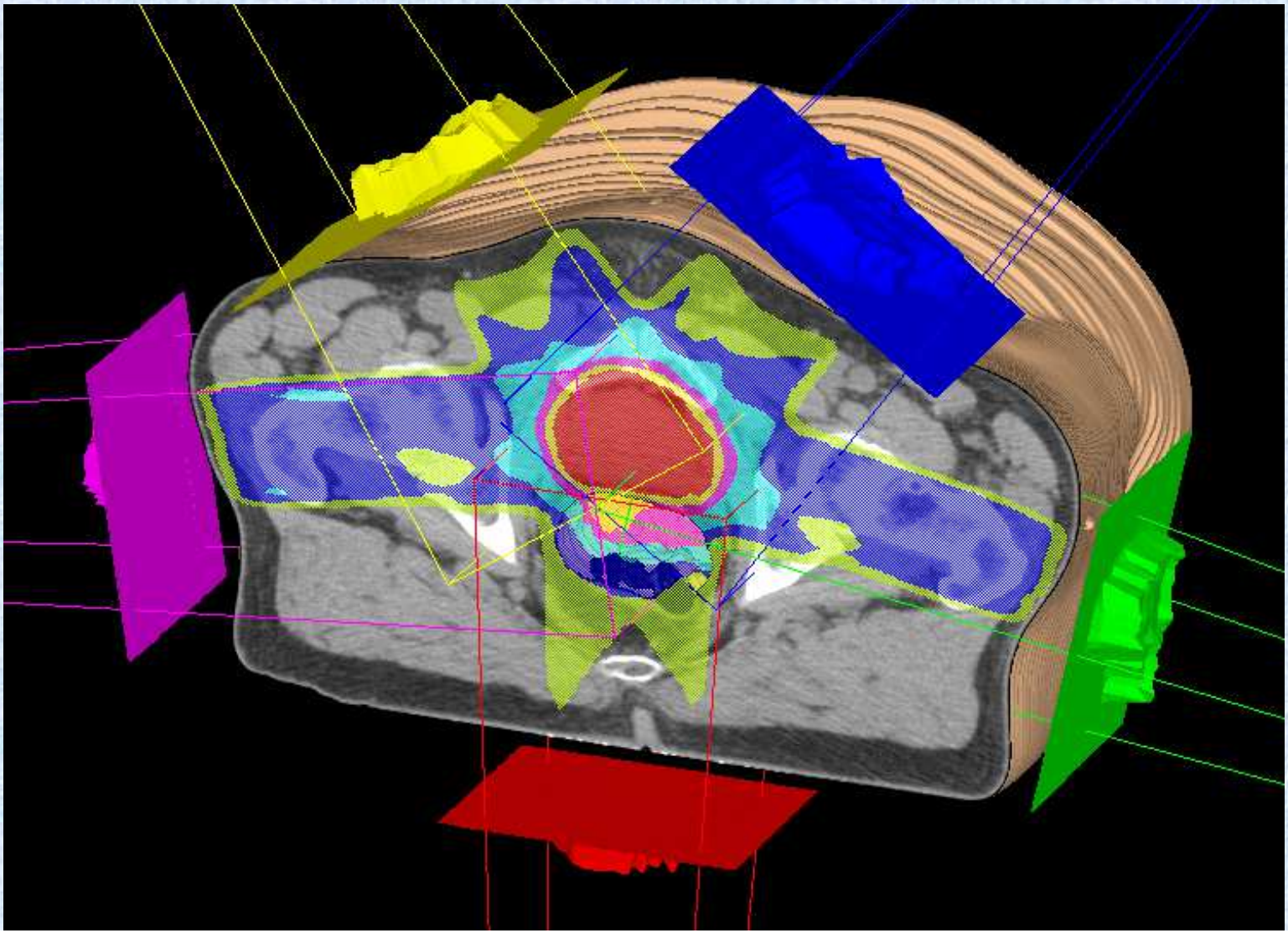
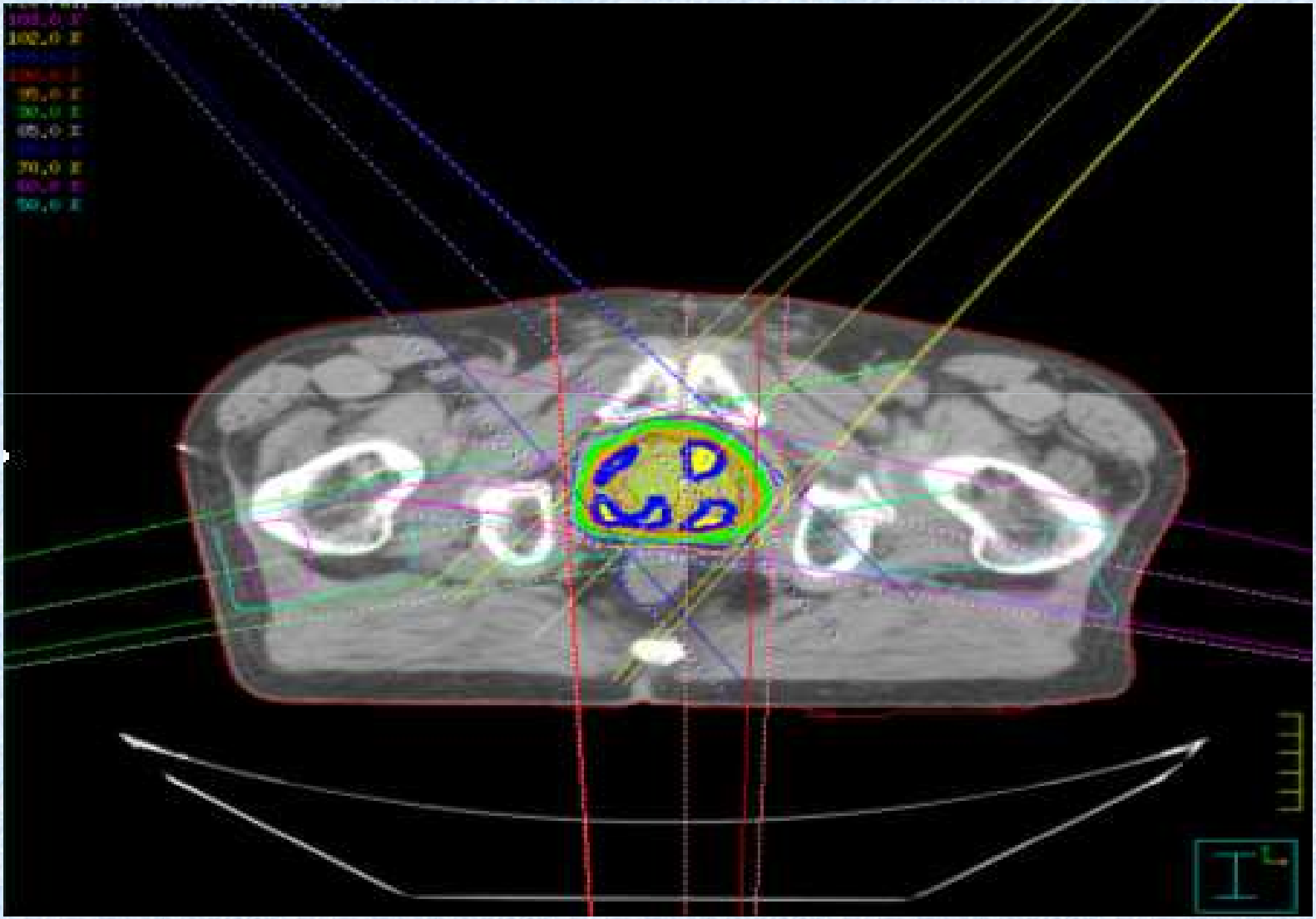


Immagine 3D stilizzata del trattamento IMRT eseguito con i 5 campi di ingresso



Piano di trattamento



Vantaggio IMRT rispetto alla 3D:

migliora la distribuzione di dose al volume bersaglio ed aumenta il differenziale di dose tra target e OR

↓

Permette l'incremento di dose :

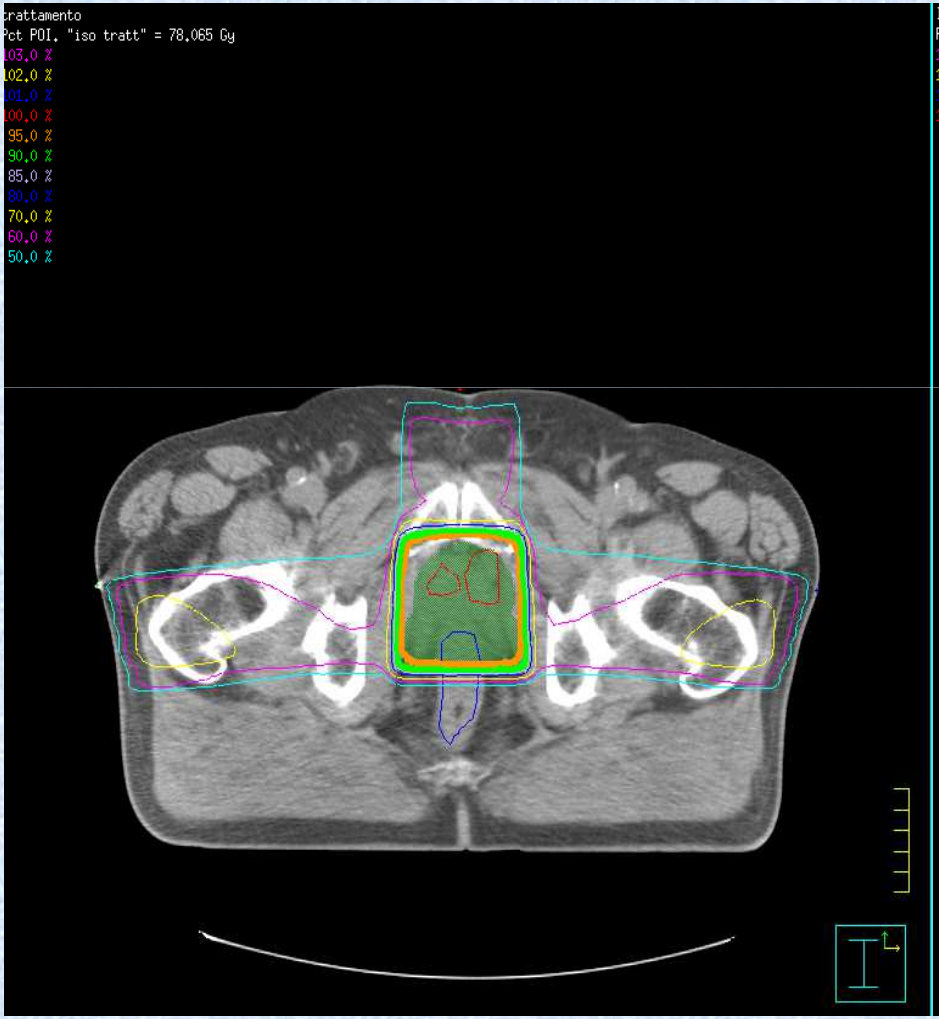
miglior controllo locale

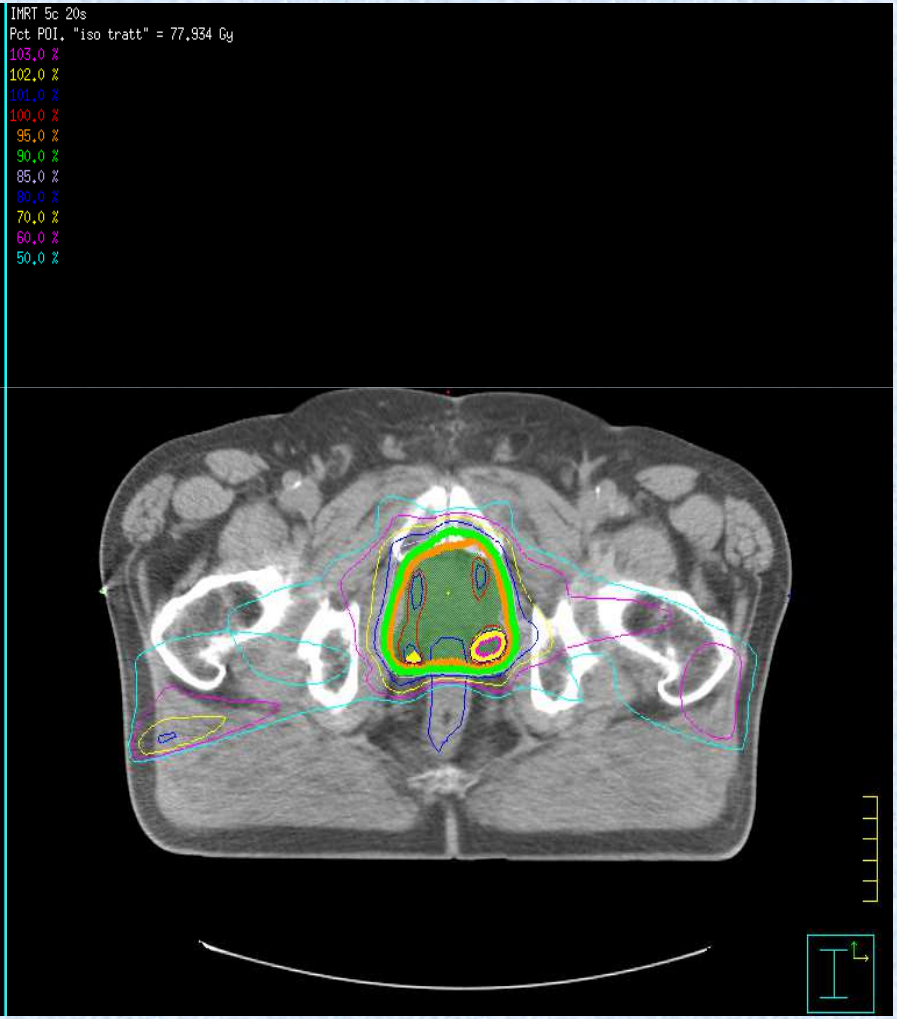
riduce il rischio di effetti collaterali

↓

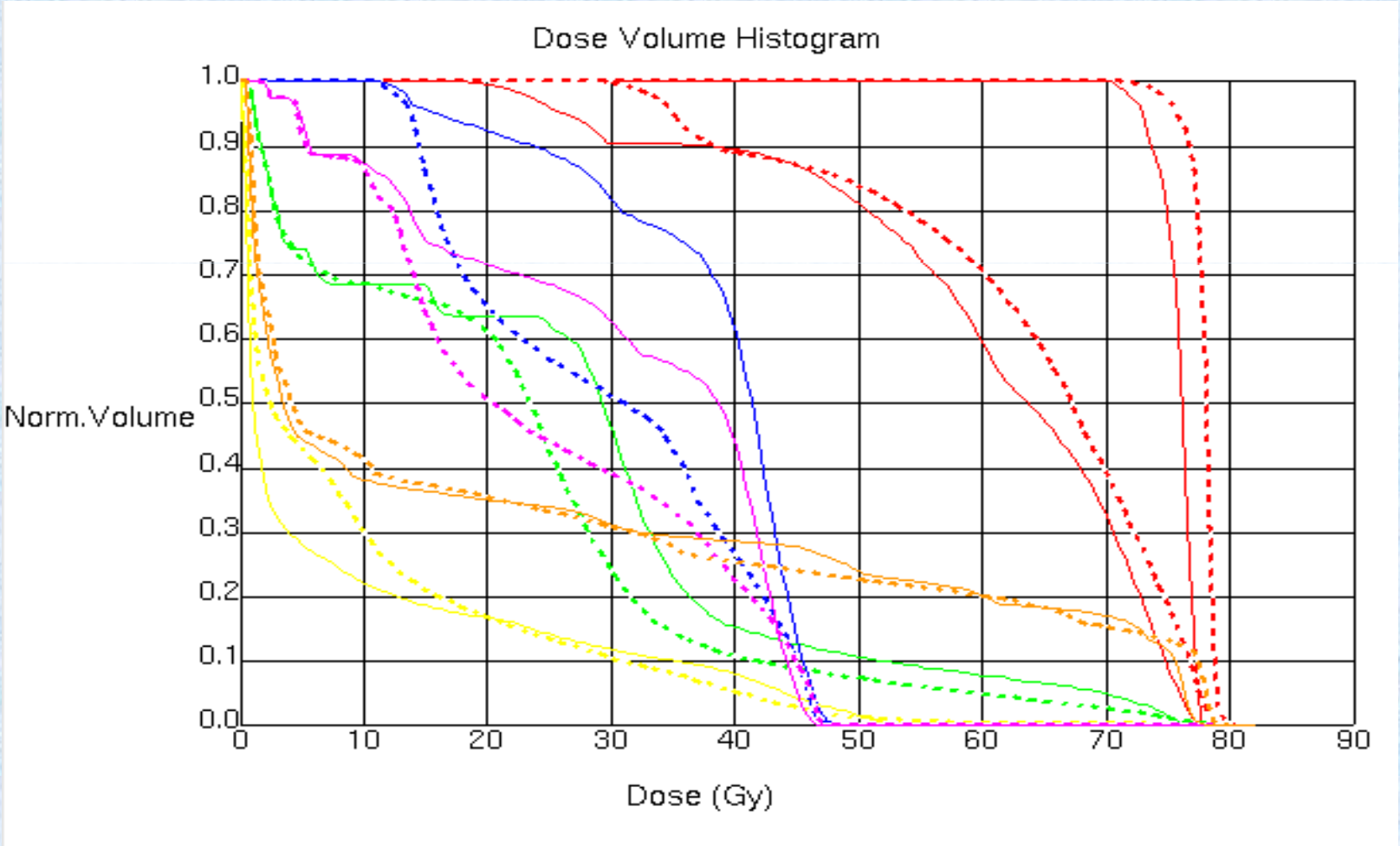
IPOFRAZIONAMENTO

Confronto delle curve di isodose sulle immagini TC ottenute con le due metodiche





Confronto degli istogrammi dose volume ottenuti con le due metodiche: sovrapposizione degli istogrammi 3D-CRT e IMRT



- Studi prospettici e retrospettivi hanno dimostrato una correlazione tra controllo biochimico, controllo locale e dose di RT.

- Non è stata definita la dose ottimale di RT

Necessità di studi randomizzati

- Non è stata dimostrata una chiara correlazione tra dose di RT e sopravvivenza

Perchè somministrare alte dosi?

- È stata dimostrata una correlazione dose-risposta

Pollack, JCO 2000
Hanks, IJROBP 2002
Peeters, JCO 2006
Dearnaley, Lancet Oncol 2007
Kuban, IJROBP 2008

Tuttavia la dose necessaria ad ottenere il miglior risultato nel controllo di malattia non è stata definita

DOSE-ESCALATION

- Dosi 74-80 Gy $\Rightarrow$ migliore controllo biochimico ($\uparrow$ del 15-20 %) rispetto a dosi < 70 Gy

  Studi random: Pollack 00', Zietman 05', Peeters 06', Dearnley 07'

- Miglioramento nella SVV libera da metastasi

  Hanks 02',Pollack 04', Jacob 04',Zelefsky 08'

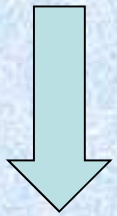
- Dosi > 80 Gy $\Rightarrow$ controllo tumorale ottimale?

  Eade 07',Morgan 07', Zelefsky 08', Cahlon 08'

  ….non è nota la dose massima ottimale

Dosi ≥ 80 Gy

Heade, IJROBP 2007

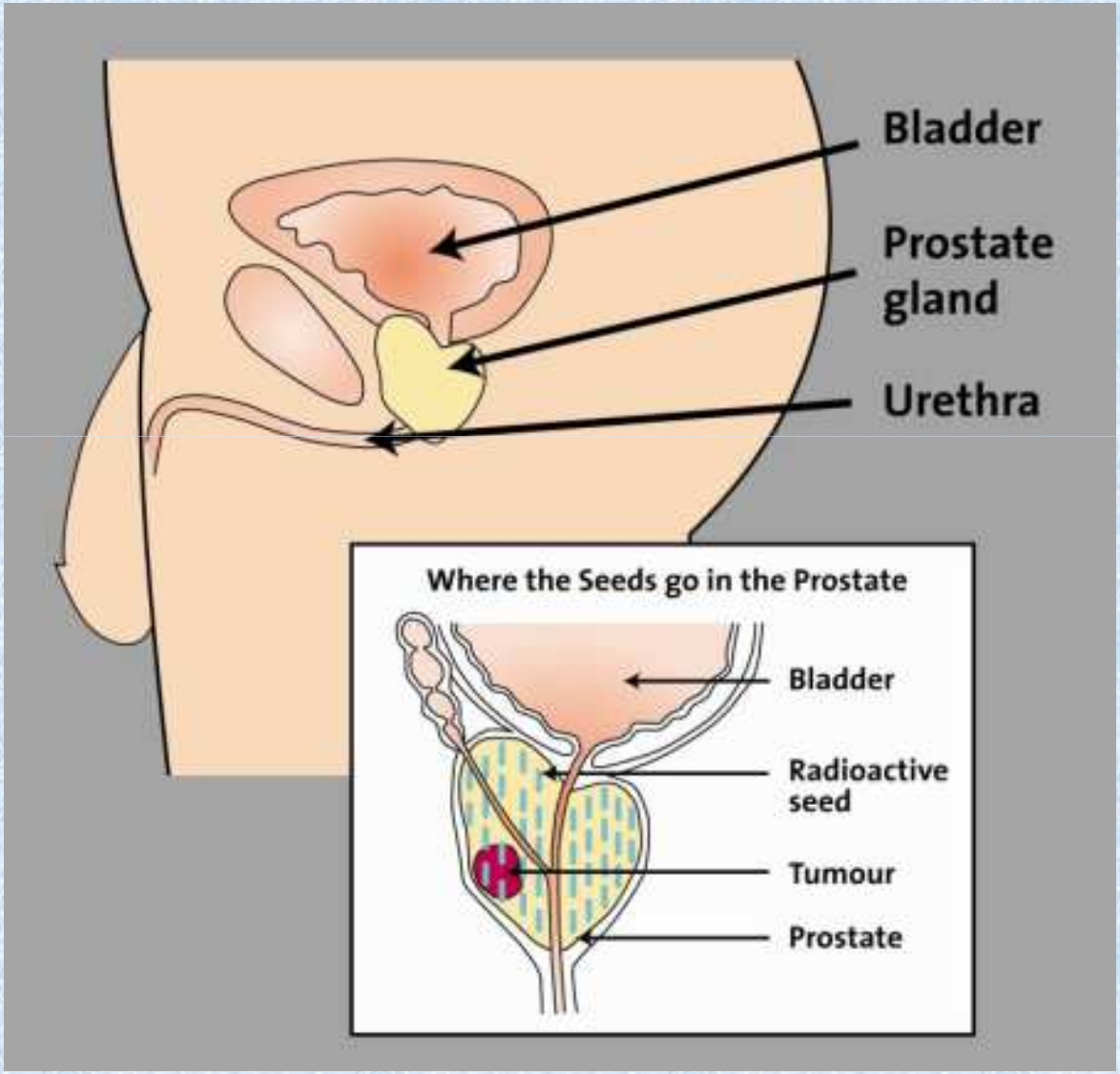


Ma per quale malattia?

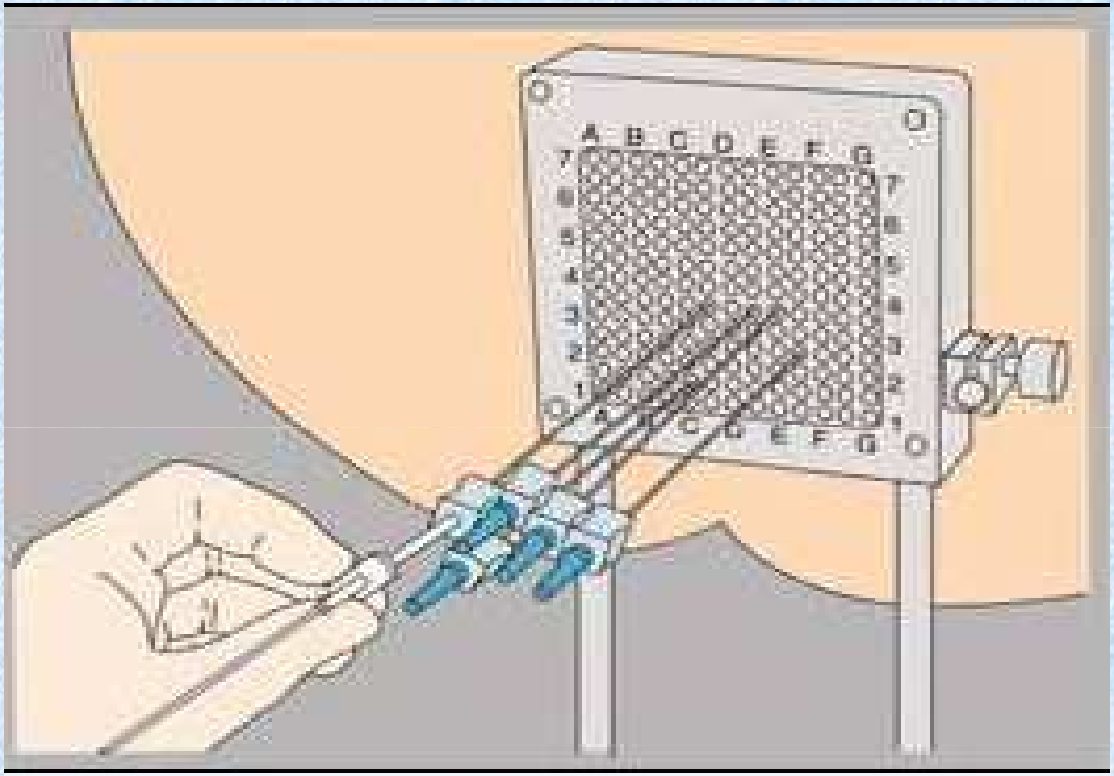
Tossicità tardiva in studi di IMRT

Studio	Dose (Gy)	N	FU ms	GI			GU		
				G2	G3	G4	G2	G3	G4
Zelefsky 06’	81-86.4	561	84	1.5	<1	0	9	3	0
Jani 06”	76	106	29	3	3	0	19	4	0
De Meerleer 07’	74-76	133	36	17	1	0	19	3	0
Vora 07’	75.6	145	48	23	1	0	27	23	6
Kupelian 07’	70 (2.5Gy/fr)	770	45	3	1	1	5	1	0
Cahlon 08’	86.4	478	53	3	<1	0	13	3	0

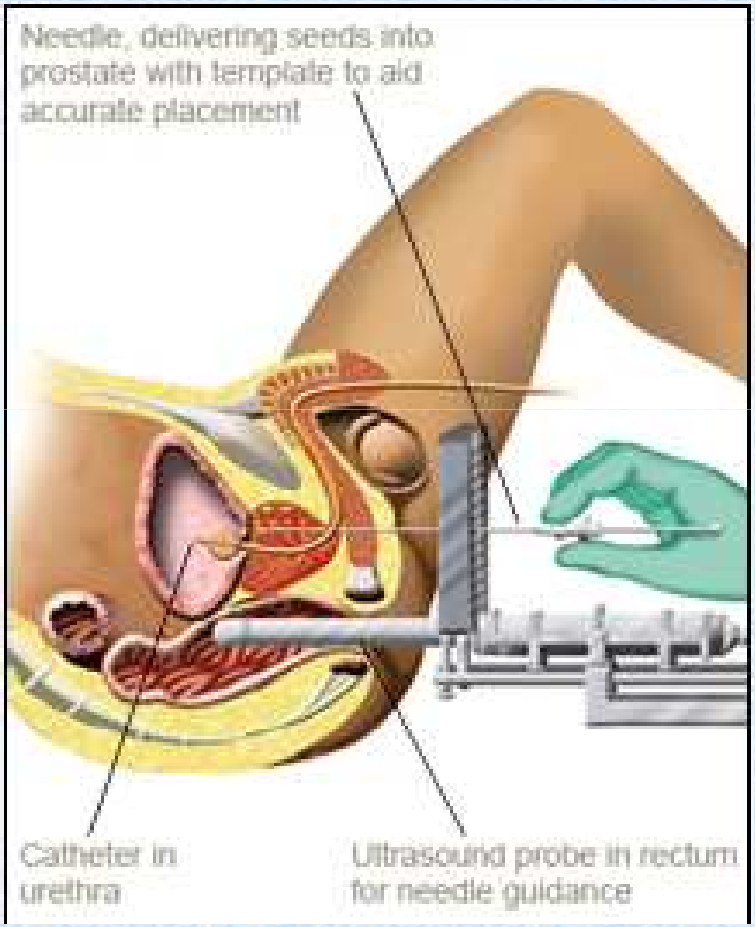
BRACHITERAPIA



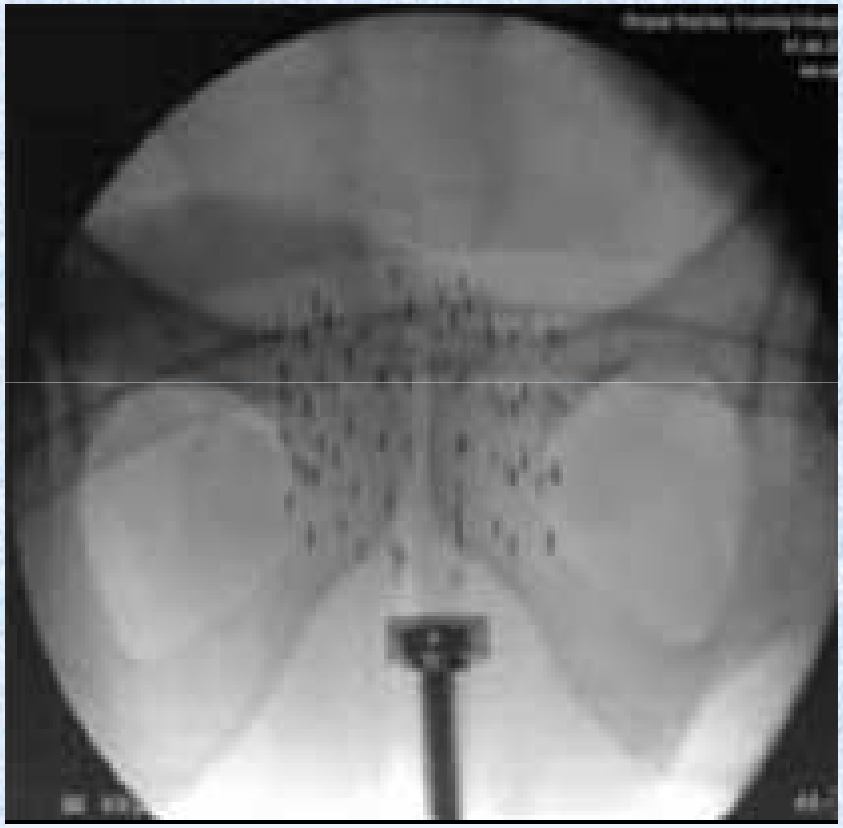
BRACHITERAPIA



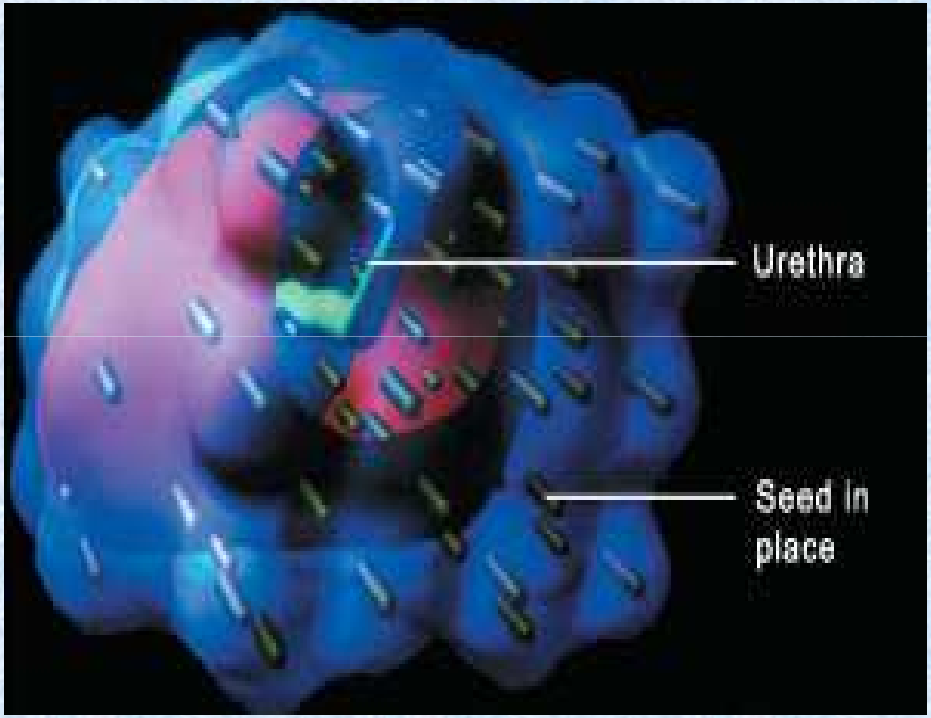
BRACHITERAPIA



BRACHITERAPIA



BRACHITERAPIA



Terapia della malattia recidivata

- **Dopo CH: RT**
- **Dopo RT: OT**

  RT con brachiterapia

  EBRT

IGRT

SOPPRESSIONE ANDROGENICA

- Monoterapia
- Blocco androgenico totale

RAZIONALE PER L'IMPIEGO DELLA SOPPRESSIONE ANDROGENICA

Azione su:

popolazioni cellulari ormonosensibili

micrometastasi

cellule radioresistenti

Effetto sinegico con la RT

- AD ha migliorato la BNED, il controllo locale e in alcuni studi o sottogruppi di pazienti la sopravvivenza globale.

- È necessaria la dose escalation nell'associazione RT-AD o gli stessi risultati potrebbero essere raggiunti con RT a dosi standard?

- Qual è la durata ottimale della terapia?

T3, GS ≤ 6	AD short course x 4 mesi
ogni T, GS ≥ 8	AD a lungo termine (≥ 2 anni)
T3, GS 7	

Lawton, Semin Radiat Oncol, 2003

L' Imaging nella Definizione del Volume Bersaglio

Piani di trattamento basati su immagini **TC**

Le informazioni TC sono importanti per due aspetti del piano di trattamento

1. **Delineare il GTV (o CTV)**
2. **Applicare le correzioni per le disomogeneità dei tessuti**

RM NEI PIANI DI TRATTAMENTO

	TC	RM
Segnale	Numero atomico tessuti Difficoltà nel visualizzare tumori la cui densità è poco differente da quello dei tessuti vicini	Comportamento dei protoni nel campo magnetico
Artefatti da presenza di osso	**SI**	**NO**

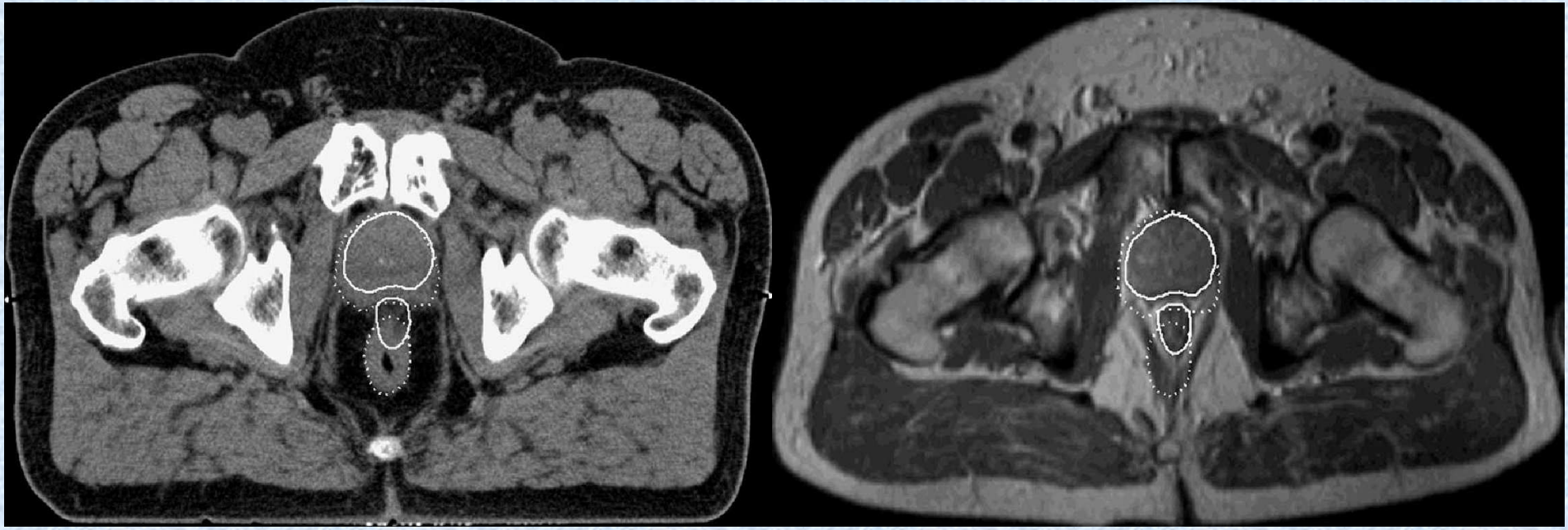
RM NEI PIANI DI TRATTAMENTO

Migliore definizione rispetto alla TC:

Tumori encefalo
midollo spinale
rinofaringe
} **Vicini a strutture ossee**

Tumore prostata: **migliore definizione del contorno della ghiandola**

TC RM



VOLUME TC 63.7 cc

RM 44.5 cc

Fusione di immagini

Utilizza immagini derivate da **modalità di imaging più sensibili e specifiche** rispetto alla TC per la diagnosi e per contornare il/i volume/i bersaglio

Migliore prescrizione del trattamento rispetto alla sola TC

TC è l'unica modalità che consente di misurare la densità elettronica dei tessuti, necessaria per il calcolo della distribuzione di dose

PET CON COLINA PER TRATTAMENTO DELLE RECIDIVE