Prossimità e organizzazione delle cure: la medicina generale di domani tra demografia e cronicità

COSA ORIENTA VERSO LA RADIOTERAPIA NEL TUMORE ALLA PROSTATA ORGANO-CONFINATO

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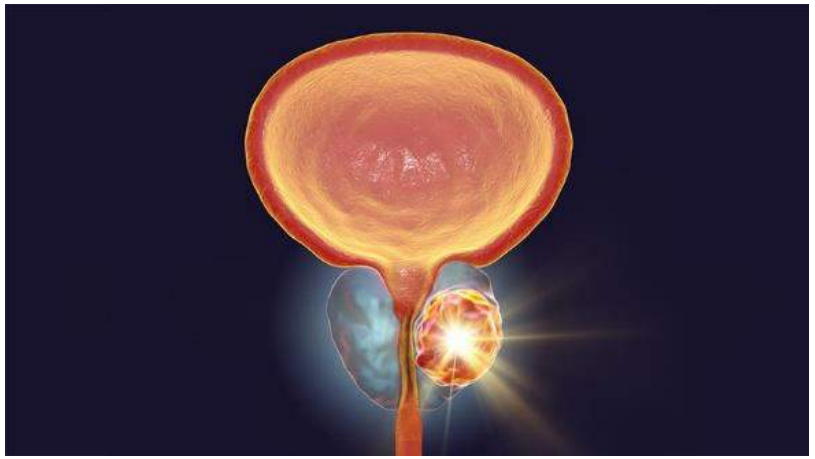
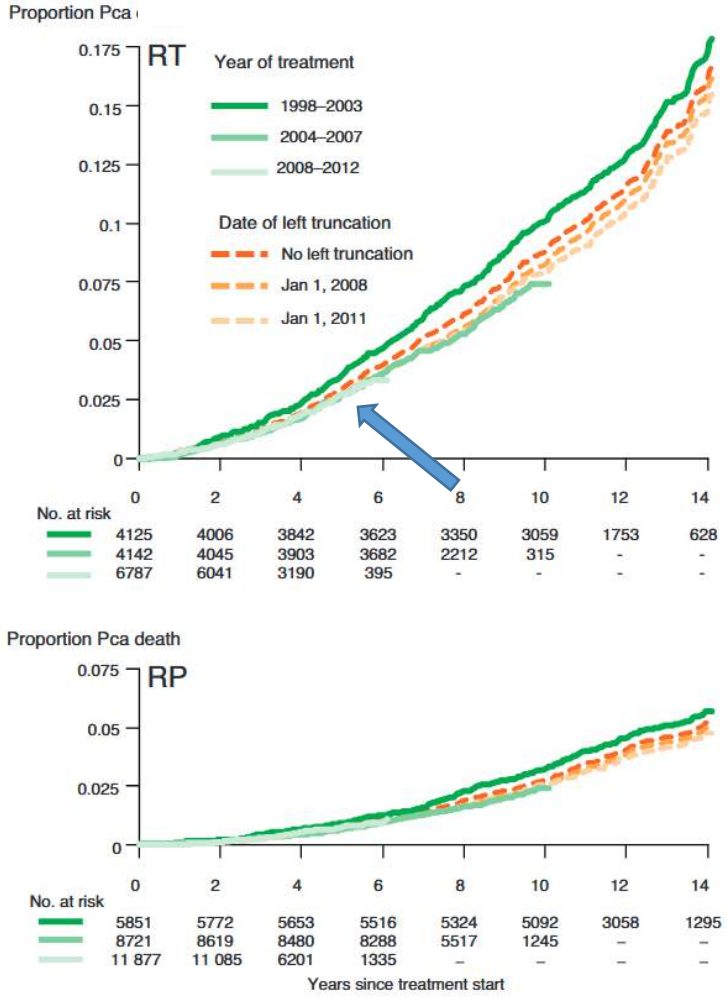
Radioterapia del tumore prostatico organo-confinato

- low risk: clinical local stage T1–T2, PSA<10 ng/ml and GGG 1
- intermediate risk: T1–T2 with PSA level 10–20 ng/ml and/or GGG 2 or 3
- high risk: T3 and/or PSA level 20–99 ng/ml and/or GGG 4 or 5



Famo a mmezzi

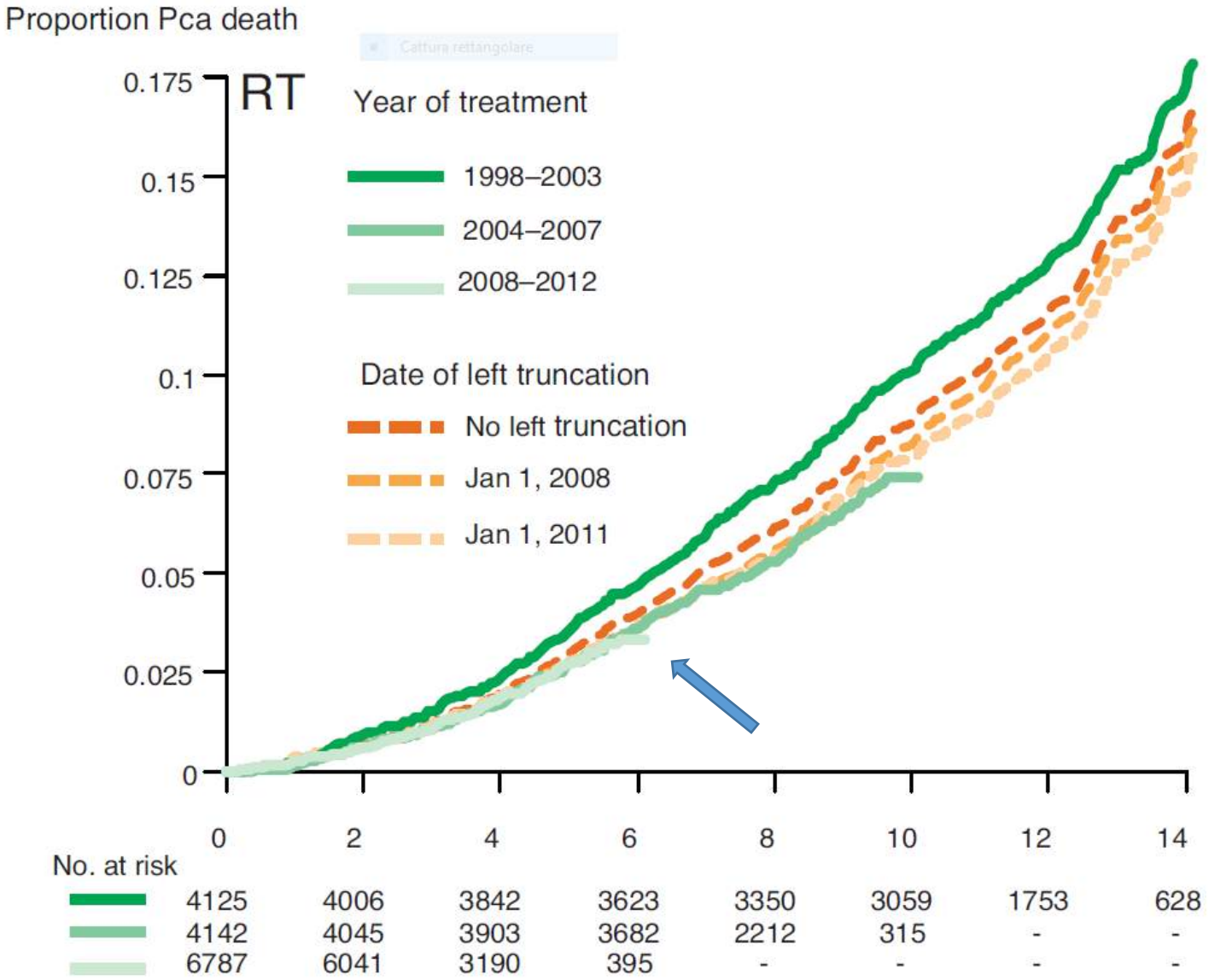
Prostate Cancer Death After Radiotherapy or Radical Prostatectomy: A Nationwide Population-based Observational Study



- A **small difference** in favor of Radical Prostatectomy persisted in men with low-and intermediate-risk Prostate cancer, for high-risk Prostate cancer there was no difference.
- However, **the absolute difference in the risk of Prostate cancer-death within 10 yr was <1% across all risk categories**.
- Thus, **the choice between these two treatments should be guided by the risk of side effects and patient preference rather than by the risk of Prostate cancer death**.

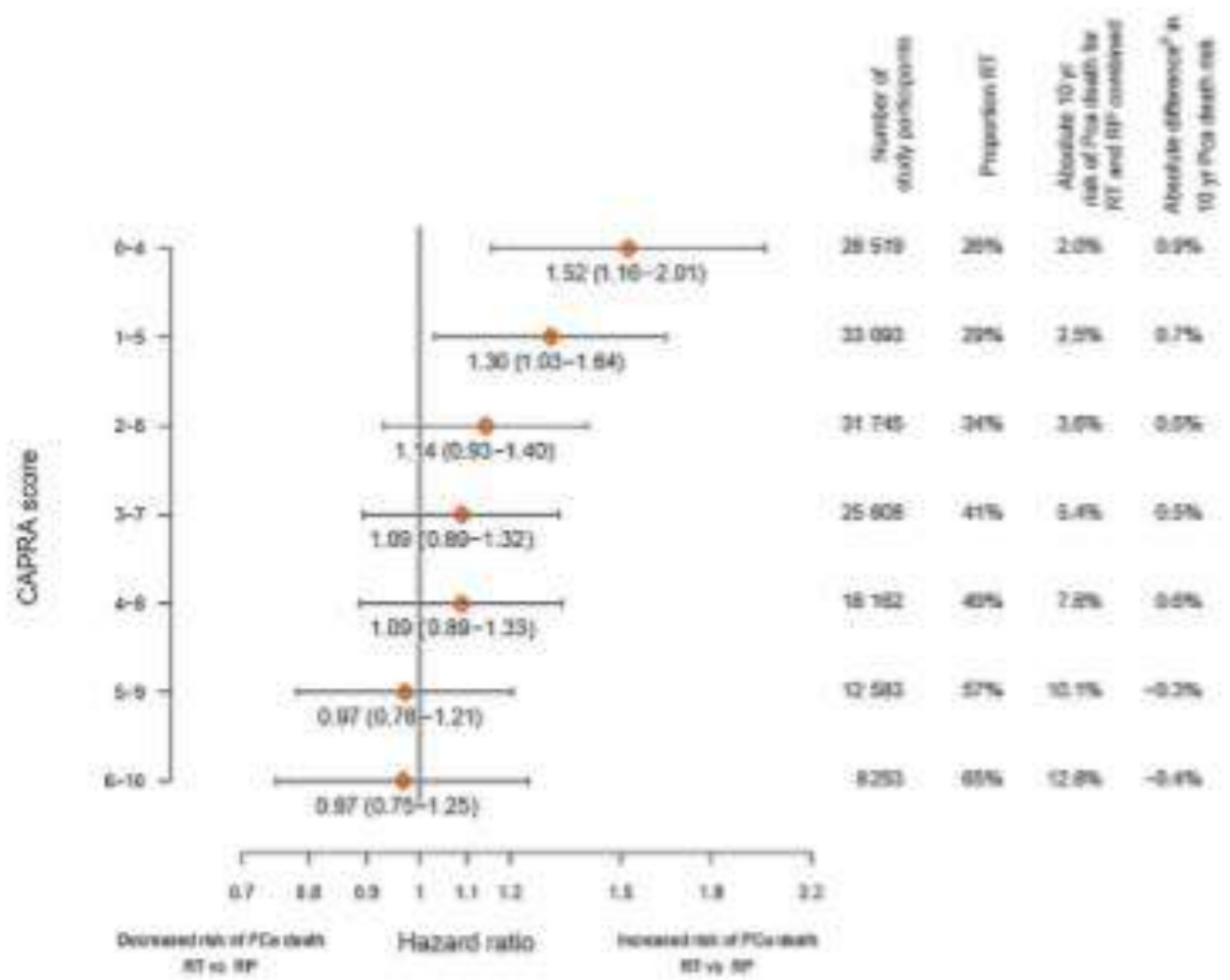
Robinson, 2018

Radioterapia del tumore prostatico organo-confinato



Robinson, 2018

Radioterapia del tumore prostatico organo-confinato



Robinson, 2018

Radioterapia del tumore prostatico organo-confinato

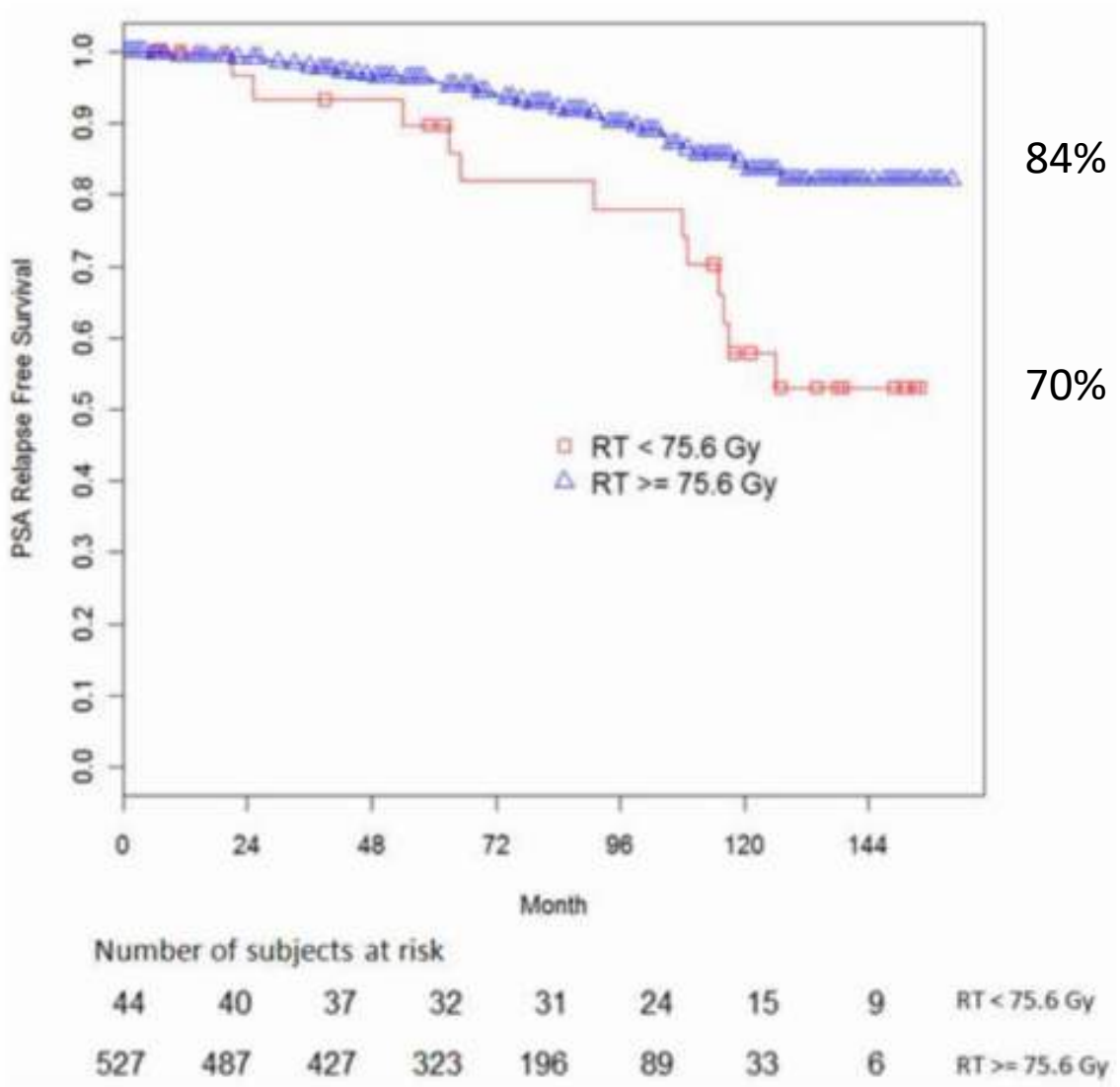
Eur Urol. 2011 December ; 60(6): 1133–1139. doi:10.1016/j.eururo.2011.08.029.

Dose Escalation for Prostate Cancer Radiotherapy: Predictors of Long-Term Biochemical Tumor Control and Distant Metastases–Free Survival Outcomes

Michael J. Zelefsk*, Xin Pei, Joanne F. Chou, Michael Schechter, Marisa Kollmeier, Brett Cox, Yoshiya Yamada, Anthony Fidaleo, Dahlia Sperling, Laura Happersett, and Zhigang Zhang

Dose levels of ≥75.6 Gy for low-risk patients were associated with improved long-term PSA-RFS outcomes, and for higher-risk patients we observed improved biochemical control with ≥81 Gy. These data suggest that given the larger volume of disease and the possibly increased percentage of more resistant clonogens in higher-risk patients, further escalation of the radiation dose is critical to achieve improved outcomes.

Radioterapia del tumore prostatico organo-confinato



84%

70%

Low-risk
10y bRFS

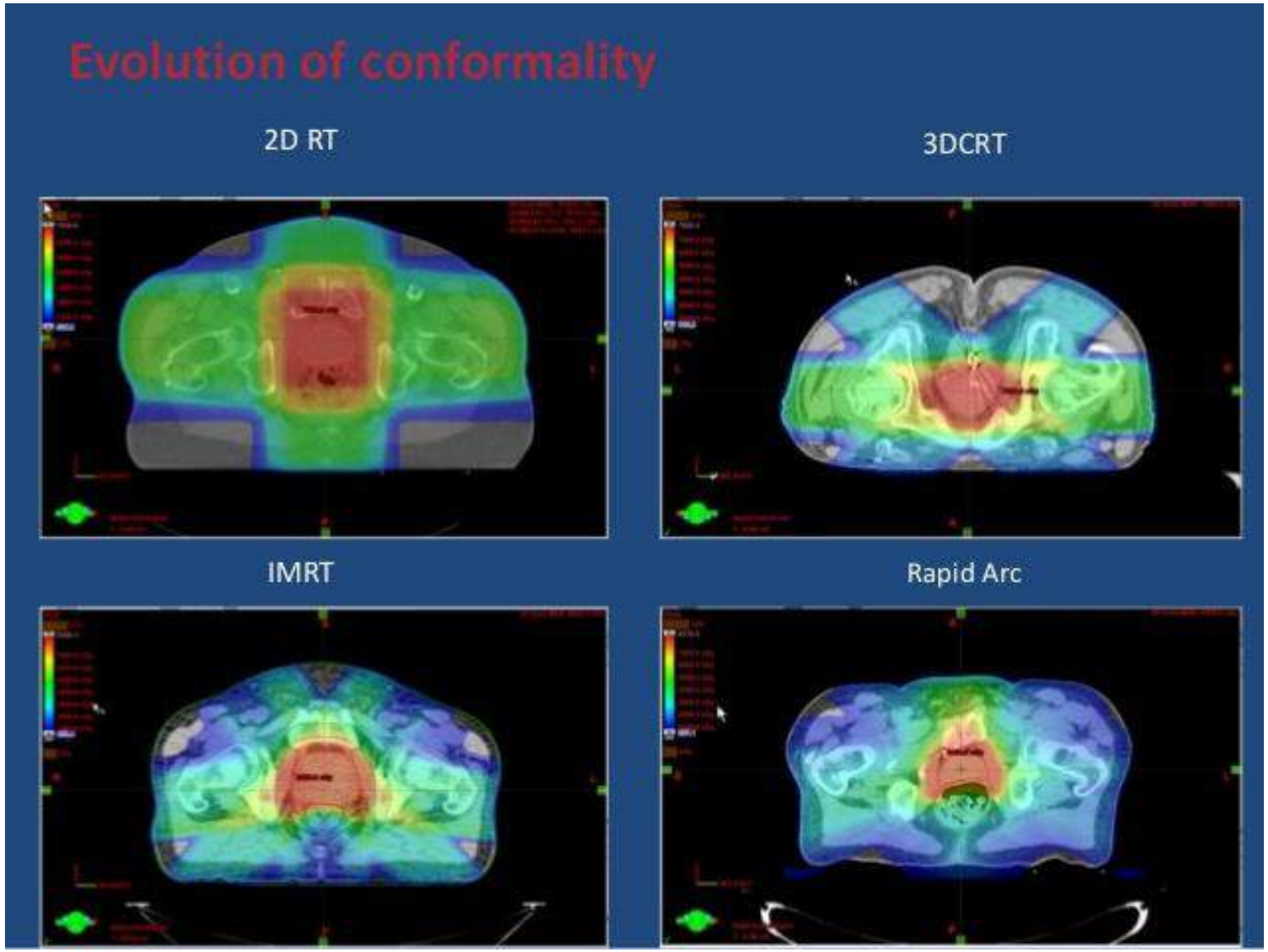
Fig. 1.
Ten-year prostate-specific antigen (PSA) relapse-free survival for low-risk patients was 84% and 70% for patients treated with ≥75.6 Gy and with lower doses, respectively ($p = 0.04$).

Improved outcomes with dose escalation in localized prostate cancer treated with precision image-guided radiotherapy

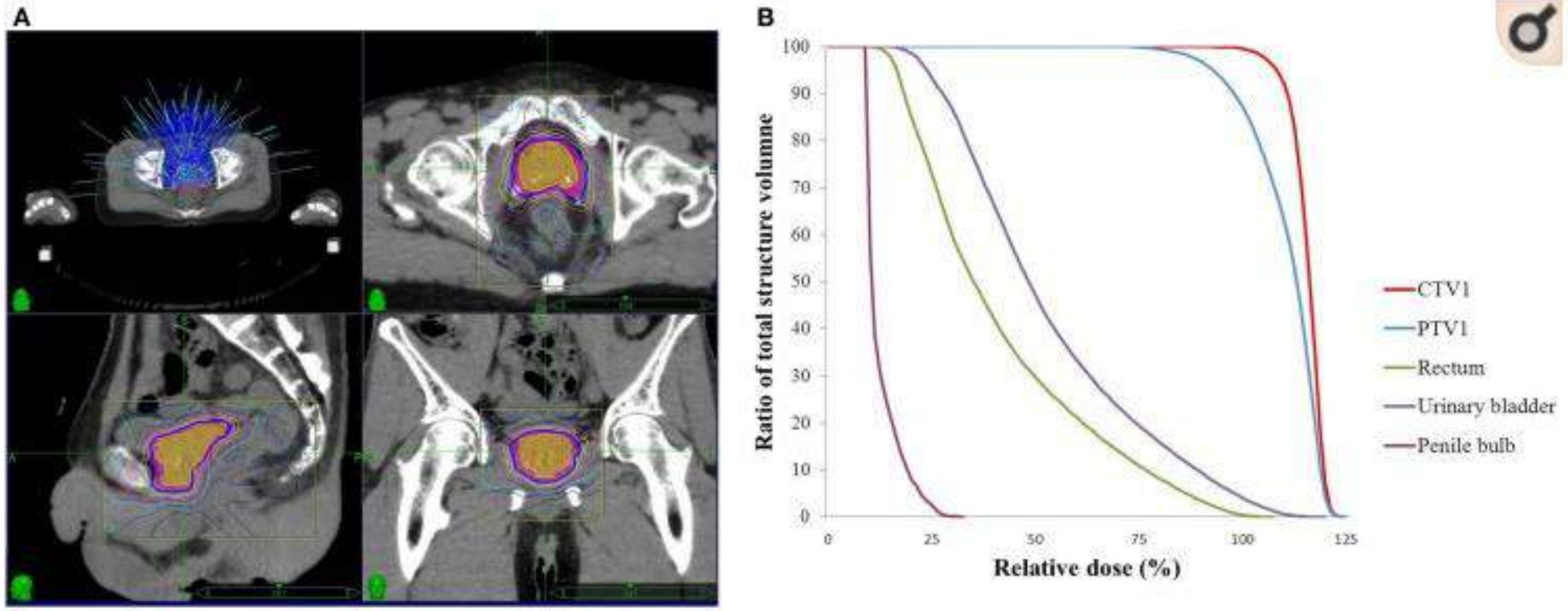
- Three sequential institutional schedules: (A) 75.6Gy, (B) 79.8Gy, (C) 78Gy, with 1.8, 1.9 and 2Gy/fraction, respectively.
- IGRT consisted of fiducial markers and daily EPID (A, B) or CBCT (C).
- Biochemical recurrence was different between A, B and C with 5-year rates of 23%, 17% and 9%
- Continuous Biochemical Recurrence improvement with progressive Dose Escalated-IGRT.

Raziee, 2017

Radioterapia del tumore prostatico organo-confinato

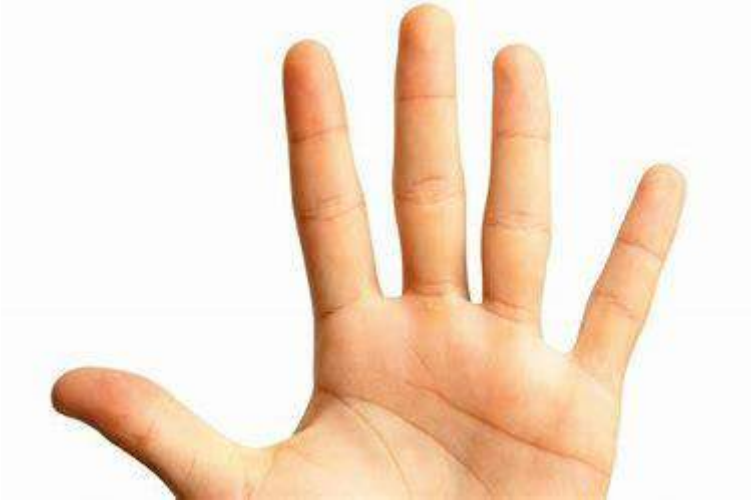


Radioterapia del tumore prostatico organo-confinato



Isodose curves (A) and dose–volume histogram (B) of SBRT boost for the applied CyberKnife in the particular patient. **(A)** The prescription dose (21Gy), blue solid line; CTV1, orange color wash; PTV1, pink color wash.

Poche ma buone: Ipofrazionamento



Moderate hypofractionated radiotherapy vs conventional fractionated radiotherapy in localized prostate cancer: a systemic review and meta-analysis from Phase III randomized trials

There is no significant difference in late GI (RR =0.97, 95% CI: 0.71–1.33, *P*=0.85; Figure 4A) and GU toxicities (RR =1.04, 95% CI: 0.87–1.24, *P*=0.69; Figure 5A) at 5 years. Since severe heterogeneities existed, subgroups were deeply analyzed. Several studies have supported that α/β ratio is 4–6 Gy for GI and GU late toxicities. Therefore,

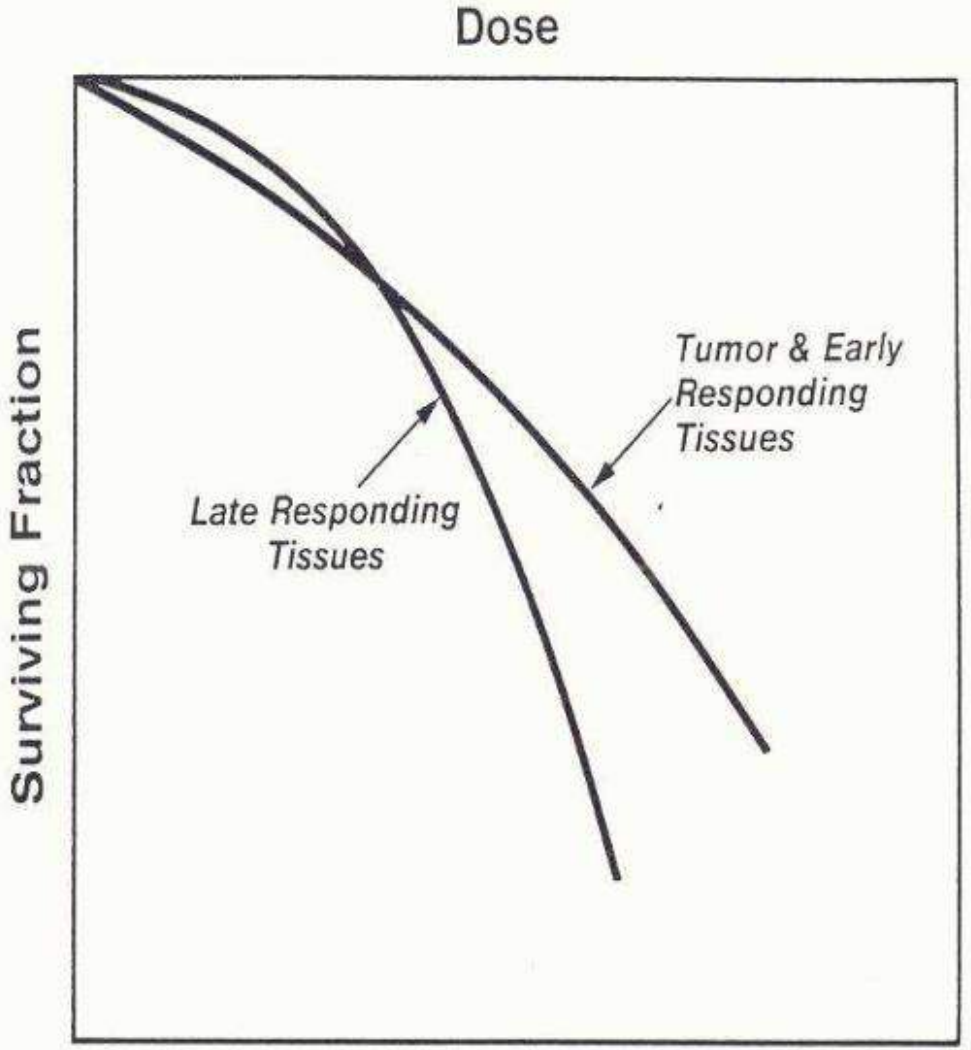
Zhenzhen, 2019

Radioterapia del tumore prostatico organo-confinato

Il modello lineare-quadratico
Alfa/beta

Alfa: letalità cellulare al danno per colpo singolo, lineare
Beta: letalità cellulare per danno da somma di sub-letali

α/β: dose in Gy in cui si osserva uguale letalità da colpo singolo e da sub-letali
Caratteristico di ogni popolazione cellulare



Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline

Definitions

Conventional fractionation is defined as EBRT with a fraction size of 180 to 200 cGy. In this guideline, hypofractionation is subdivided into "moderate hypofractionation" and "ultrahypofractionation." As fraction size is a continuous variable, it is acknowledged that hypofractionation represents a spectrum and that any subdivision is necessarily arbitrary, with no universally accepted definitions. The subdivision chosen by the task force reflects the reality that two distinct approaches to hypofractionation have arisen in clinical practice. Moderate hypofractionation is defined in this guideline as EBRT with a fraction size between 240 cGy and 340 cGy. This is a pragmatic definition, and the dose range chosen has been influenced by the approaches used in a number of recently completed large trials that are discussed in detail later.

Morgan, 2018

Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline

Ultrahypofractionation is defined in this guideline as EBRT with a fraction size ≥500 cGy. The choice of 500 cGy as the cutpoint reflects a body of literature suggesting this is a threshold beyond which the linear-quadratic model ceases to be valid.[10] Ultrahypofractionation has been referred to in the literature alternately as "extreme hypofractionation," "stereotactic body radiation therapy" (SBRT), and "stereotactic ablative body radiation therapy" (SABR), with the latter terms implying particular radiation techniques. Ultrahypofractionation was chosen as a neutral term that stipulates a fraction size but is independent of considerations of technique. The fraction size "gap" created by our definitions (i.e., >340 cGy but <500 cGy) represents a relatively little studied and little used intermediate range that is outside of the scope of the current document.

Morgan, 2018

Grading of Evidence and Recommendations and Consensus Methodology Guideline recommendation statements were developed based on the literature using a modified **Grading of Recommendations Assessment, Development, and Evaluation** (GRADE) methodology.

- **Recommendations were classified as "strong" or "conditional."**
- A strong recommendation indicates the task force was confident the benefits of the intervention clearly outweighed the harms, or vice-versa, and "all or almost all informed people would make the recommended choice for or against an intervention."
- Conditional recommendations were made when the balance between risks and benefits was more even or was uncertain.

The **quality of evidence** underlying each recommendation statement was categorized as high, moderate, low, or very low. These quality levels indicated:

- High: We are very confident that the true effect lies close to that of the estimate of the effect,
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- Very Low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate."

PICO Methodology

P: problem/patient/population

I: intervention

C: comparison/control

O: outcome

Key Question 1

In patients with localized prostate cancer who are candidates for EBRT, **how does moderately hypofractionated EBRT** (240-340 cGy per fraction) **compare to conventionally fractionated EBRT** (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life based on:

- Prostate cancer risk stratification group?
- Patient age, comorbidity, anatomy (e.g., prostate gland volume), and baseline urinary function?

Radioterapia del tumore prostatico organo-confinato

Statement KQ1A:

In men with low-risk prostate cancer who decline active surveillance and receive EBRT to the prostate with or without radiation to the seminal vesicles, *moderate hypofractionation should be offered*.

- Recommendation strength: Strong
- Quality of evidence: High
- Consensus: 100%

Statement KQ1B:

In men with intermediate-risk prostate cancer receiving EBRT to the prostate with or without radiation to the seminal vesicles, *moderate hypofractionation should be offered*.

- Recommendation strength: Strong
- Quality of evidence: High
- Consensus: 100%

Prostate cancer control outcomes: Impact of patient age, comorbidity, anatomy, and urinary function

Statement KQ1D:

In patients who are candidates for EBRT, *moderate hypofractionation should be offered regardless of patient age, comorbidity, anatomy, or urinary function*. However, *physicians should discuss the* ***limited follow-up beyond five years*** *for most existing Randomized CTs evaluating moderate hypofractionation*.

- Recommendation strength: Strong
- Quality of evidence: High
- Consensus: 94%

The efficacy of moderately hypofractionated EBRT does not appear to be impacted by patient age, comorbidity, or anatomy. Baseline characteristics were well-balanced in the arms of all the large prospective RCTs comparing moderately hypofractionated and conventionally fractionated EBRT.

Key Question 3

In patients with localized prostate cancer who are candidates for EBRT, how does **ultrahypofractionated EBRT** (≥500 cGy per fraction) compare to **conventionally fractionated EBRT** (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ3A:

In men with low-risk prostate cancer who decline active surveillance and choose active treatment with EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation.

- Recommendation strength: Conditional
- Quality of evidence: Moderate
- Consensus: 88%

Key Question 3

In patients with localized prostate cancer who are candidates for EBRT, how does **ultrahypofractionated EBRT** (≥500 cGy per fraction) compare to **conventionally fractionated EBRT** (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ3B:

In men with intermediate-risk prostate cancer receiving EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation. The task *force strongly encourages that these patients* ***be treated as part of a clinical trial or multi-institutional registry***.

- Strength of recommendation: Conditional
- Quality of evidence: Low
- Consensus: 94%

Key Question 4

In patients with localized prostate cancer ***who are candidates*** for EBRT, *how do **ultrahypofractionated** EBRT regimens used in clinical trials **compare*** in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ4A: Ultrahypofractionated prostate EBRT of 3500 to 3625 cGy in 5 fractions of 700 to 725 cGy to the planning target volume may be offered to low- and intermediate-risk patients with prostate sizes less than 100 cm3 .

- Recommendation strength: Conditional
- Quality of evidence: Moderate
- Consensus: 88%

Key Question 4

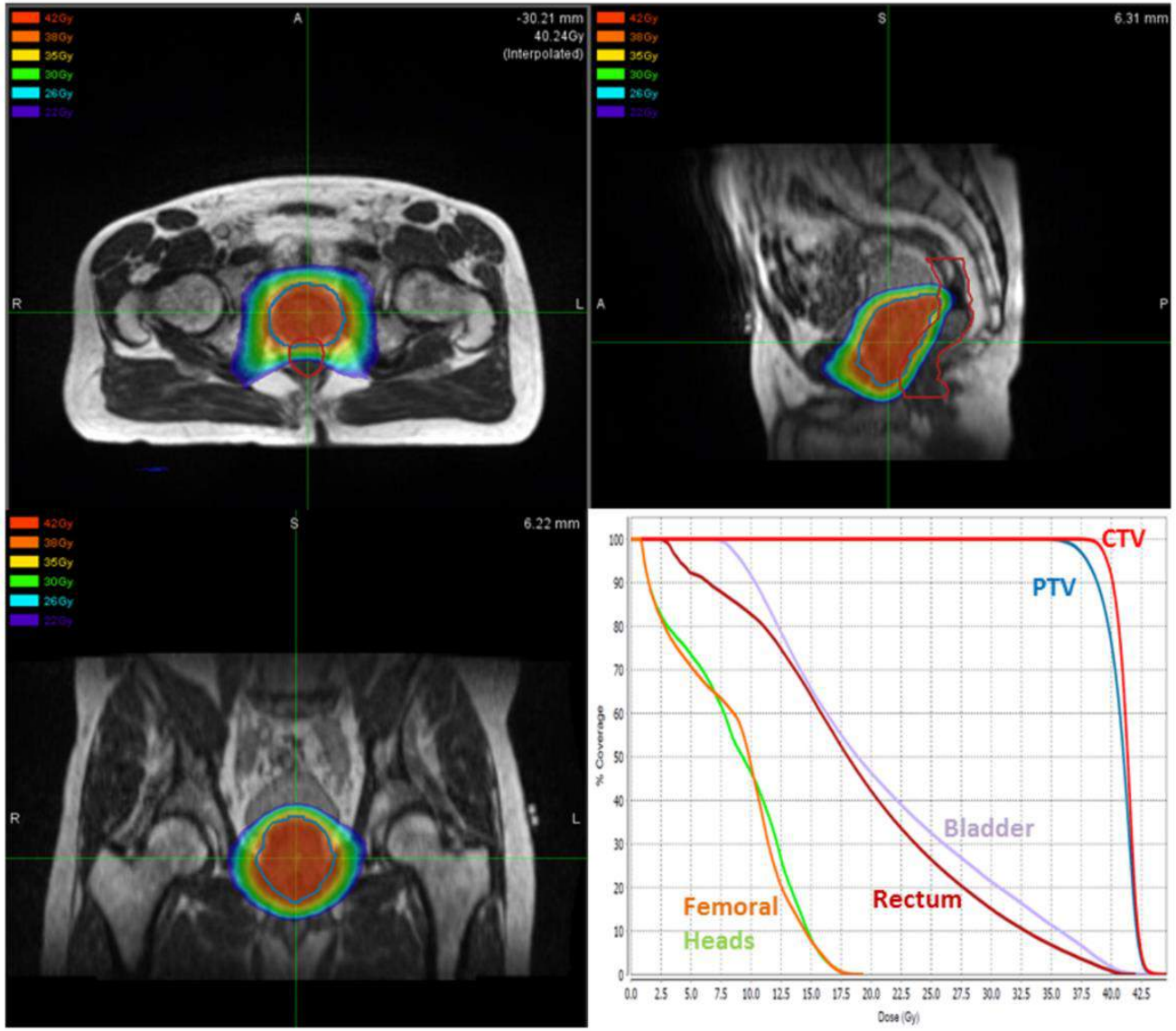
In patients with localized prostate cancer who are candidates for EBRT, *how do **ultrahypofractionated** EBRT regimens used in clinical trials **compare*** in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ4B:

Five-fraction prostate ultrahypofractionation at doses above 3625 cGy to the planning target volume ***is not suggested outside*** the setting of a clinical trial or multi-institutional registry due to risk of late toxicity.

- Strength of recommendation: Conditional
- Quality of evidence: Moderate
- Consensus: 100%

Radioterapia del tumore prostatico organo-confinato



- Compared to conventional fractionation, moderate hypofractionation confers ***similar prostate-cancer-control outcomes, similar rates of late toxicity***, and only a *slight excess in acute gastrointestinal toxicity*.
- Moderate hypofractionation holds *important advantages* in terms of patient convenience and resource utilization.
- Moderately hypofractionated EBRT should be offered to patients choosing EBRT for the treatment of their prostate cancer. This recommendation holds across *all risk groups*.
- The decision to offer *moderate hypofractionation should not be affected by considerations* of age, comorbidity, anatomy, or baseline urinary function.

Moderate Hypofractionation with Simultaneous Integrated Boost in Prostate Cancer: Long-term Results of a Phase I-II Study

- Intermediate- and high-risk patients received 51.8 Gy (1,85 Gy/d) to pelvic lymph nodes and concomitant simultaneous integrated boost to prostate up to 74.2 Gy/28 fractions (2,65 Gy/d) whereas low-risk patients were treated to the prostate only with 71.4 Gy/28 fractions (2,55 Gy/d)
- The overall 5 year bRFS was 93.7% (low risk: 94.6%; intermediate risk: 96.2%; high risk: 91.1%), overall survival and CSS were 88.6% (low risk: 90.5%; intermediate risk: 87.4%; high risk: 87%) and 97.5% (low risk: 98.7%; intermediate risk: 95%; high risk: 94.3%), respectively

Di Muzio, 2016

Radioterapia del tumore prostatico organo-confinato

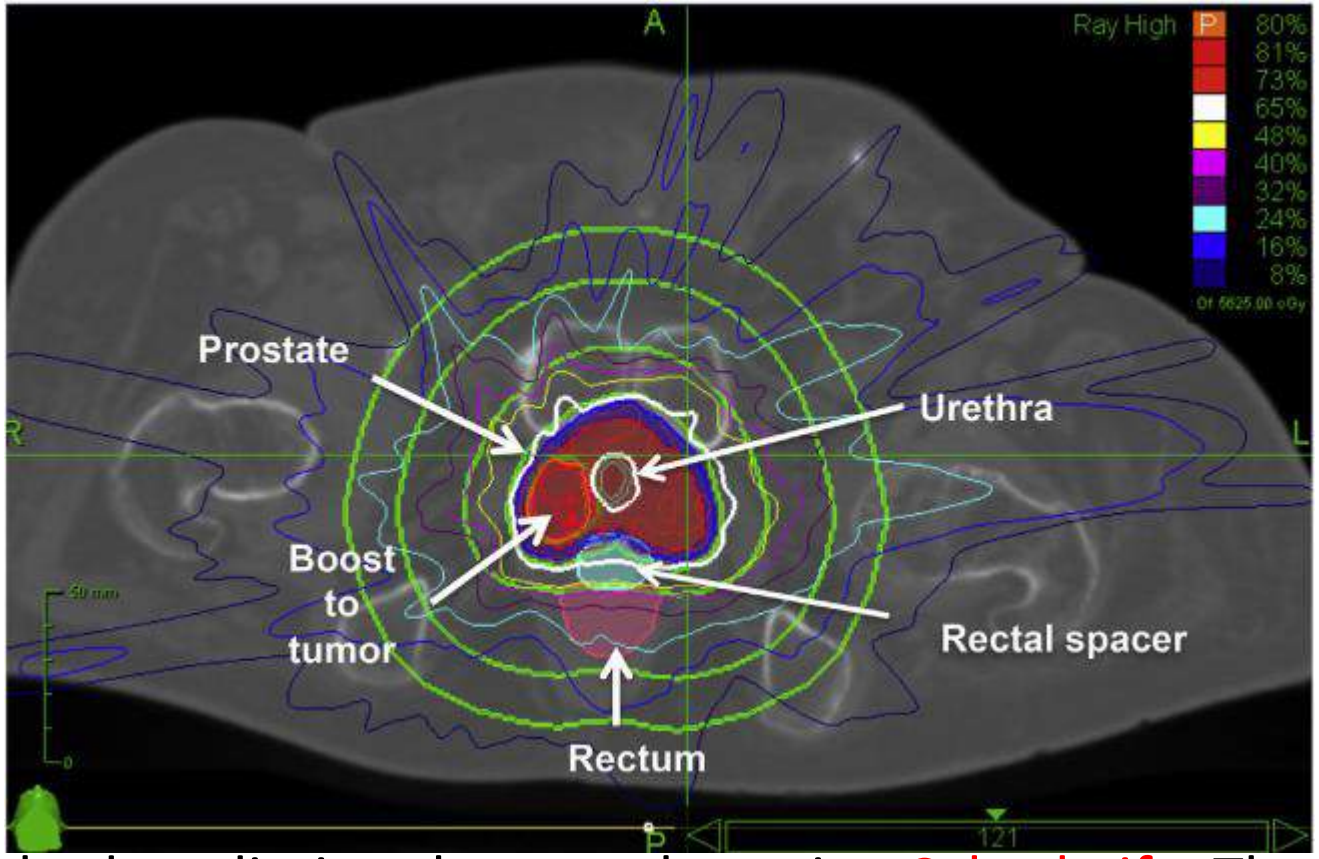
Dominant **I**ntraprostatic **L**esion

Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule: a systematic review

Most of the studies using EBRT prescribed the radiation dose to isocenter to cover homogeneously 98–100% of the prostate PTV. For IMRT series, the mean doses delivered to the PTV boost (PTVb) were 89 Gy (range 80–130 Gy), and the mean dose to the prostate PTV was 74.7 Gy (range 67.9–82.7 Gy). The average differential dose [PTVb–PTV prostate (PTVpr)] was 14.8 Gy (range 3.2–29.9 Gy).

For the VMAT series, the mean dose to the PTVb and PTVpr were 104 Gy (range 92.2–130 Gy) and 78 Gy (range 74–82.7 Gy), respectively. The average differential dose was 26 Gy (range 17–35 Gy).

Radioterapia del tumore prostatico organo-confinato



Stereotactic body radiation therapy plan using Cyberknife. The tumor is located in the right posterior prostate lobule. Fiducial markers are placed in the prostate for robotic-assisted tracking purposes. A rectal balloon spares the rectum from high doses of radiation. The prostate is treated with 36.25 Gy in five fractions of 7.25 Gy with a **boost of 50 Gy** to the intraprostatic dominant nodule.

Short-term high precision radiotherapy for early prostate cancer with concomitant boost to the dominant lesion: Phase II trial AIRC-IG-13218

- Extreme hypofractionated radiotherapy to the prostate (36.25 Gy in 5 fractions; 7,25 Gy/d) and a simultaneous integrated boost to the **dominant intraprostatic lesion** (DIL) to 37.5 Gy (7,5 Gy/d). The DIL was identified by a multiparamentric MRI (mpMRI) co-registered with planning CT

- The **use of mpMRI** to identify and boost the DIL is an innovative and interesting approach to Prostate Cancer. Dose escalation using DIL boost and extremely hypofractionated radiotherapy regimens might be a safe approach, allowing for short and effective treatment of organ-confined Prostate Cancer.

Timon, 2018

Ma la RT non farà male?

Radioterapia del tumore prostatico organo-confinato

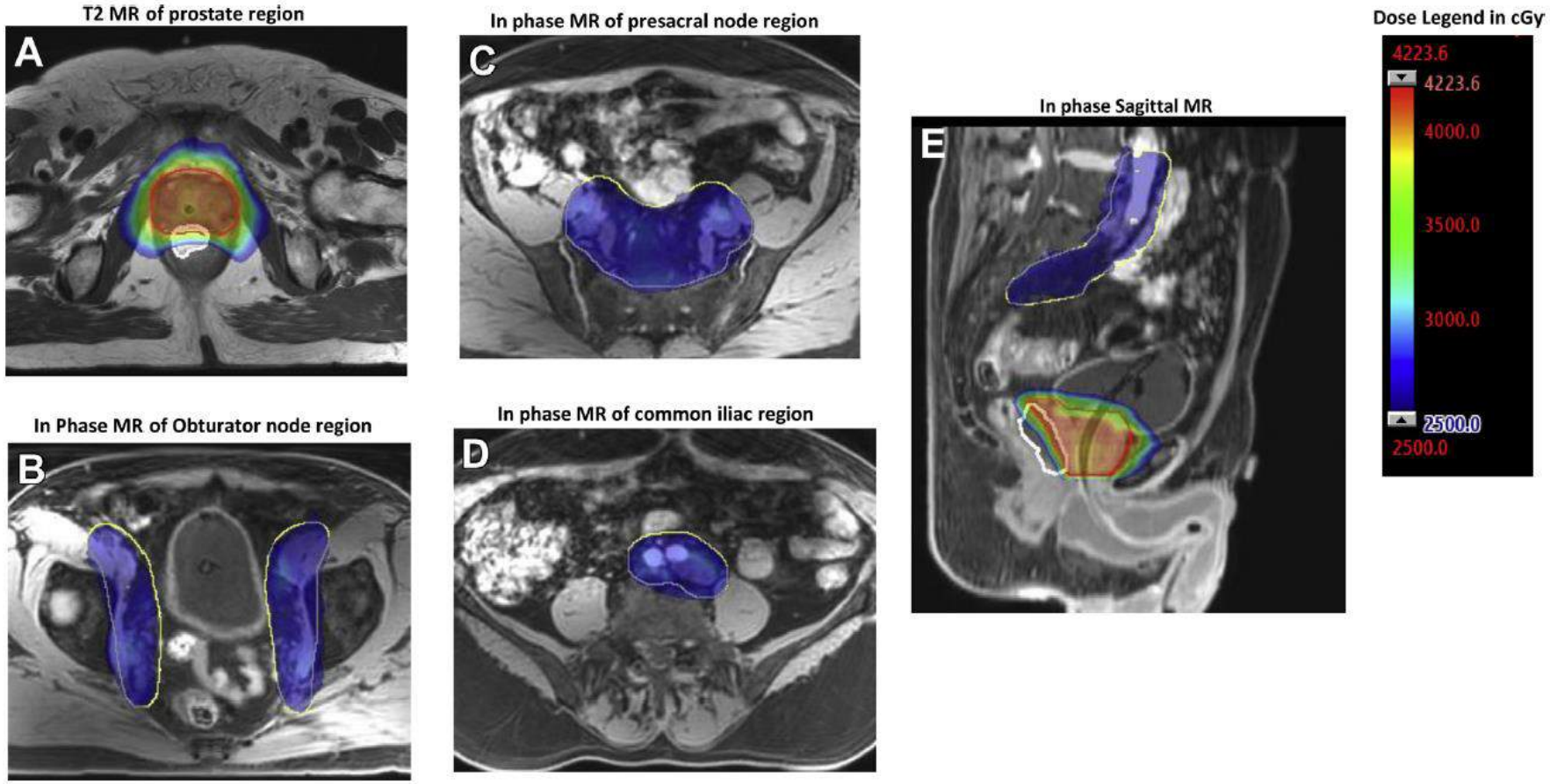


Fig. 1 Example of volumetric arc dose distribution of prostate concomitant with pelvic node radiation overlay on (A) axial T2-weighted, (B-D) axial mDIXON, and (E) sagittal mDIXON water contrast magnetic resonance image. Images are in transverse level of (A) prostate, (B) obturator region, (C) presacral region, and (D) common iliac region. Planning target volume of the prostate plus seminal vesicles, pelvic nodes and rectal spacer are contoured red, yellow, and white, respectively. Highlighted red/pink and blue areas correspond to 40 Gy and 25 Gy, respectively.

Acute and Late Toxicity after Moderate Hypofractionation with Simultaneous Integrated Boost Radiation Therapy for Prostate Cancer in intermediate-high risk patients

- IMRT 50.4Gy in 28 fractions (1.8 Gy/fraction) to the pelvic lymph nodes while simultaneously delivering 57.4 Gy in 28 fractions (2.05 Gy/fraction) to the seminal vesicles and 70 Gy in 28 fractions (2.5 Gy/fraction) to the prostate for high risk patients.
- For intermediate risk patients the same technique was applied, without WPRT.
- The rate of cumulative late grade ≥ 2 GI and GU toxicities were 11% and 17%, respectively.
- Acute grade 3 GI and GU toxicities occurred in 1% and 1%.

Jorgo, Pathol Oncol Res 2019

Disease-specific and general health-related quality of life in newly diagnosed prostate cancer patients: the Pros-IT CNR study

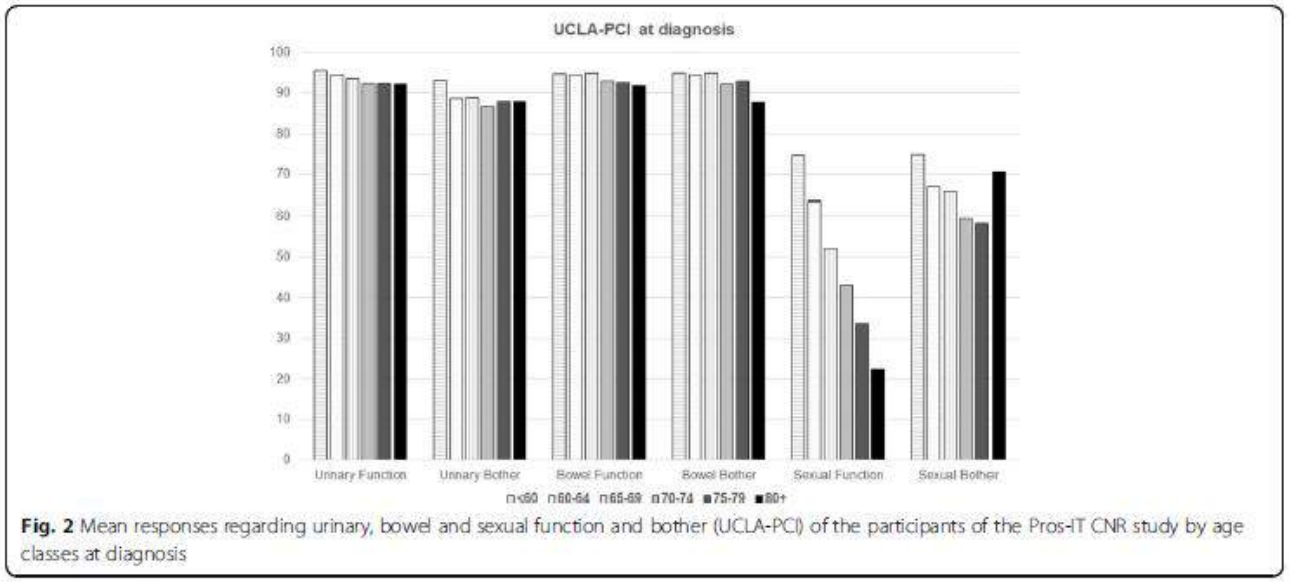
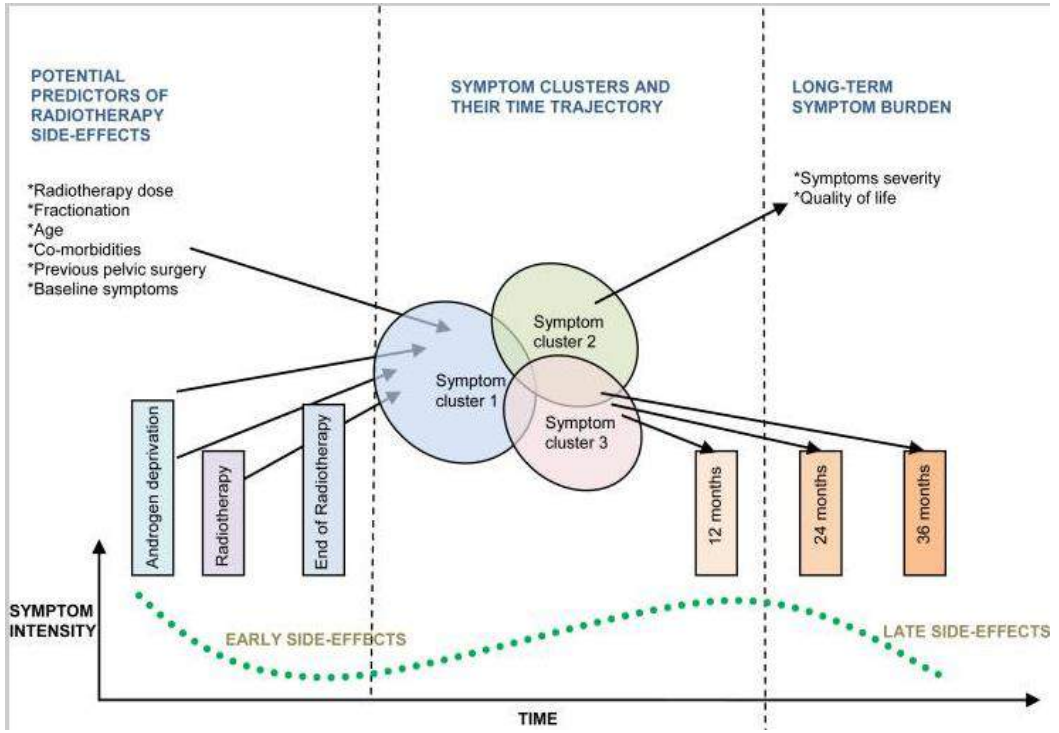


Fig. 2 Mean responses regarding urinary, bowel and sexual function and bother (UCLA-PCI) of the participants of the Pros-IT CNR study by age classes at diagnosis

Older Age, Early Symptoms and Physical Function are Associated with the Severity of Late Symptom Clusters for Men Undergoing Radiotherapy for Prostate Cancer



Porreca, 2018; Lemansk, 2018

Early Tolerance Outcomes of Stereotactic Hypofractionated Accelerated Radiation Therapy Concomitant with Pelvic Node Irradiation in High-risk Prostate Cancer

Table 4 Acute and late toxicity profiles

Acute	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Urinary frequency/urgency	8 (36.4)	7 (31.8)	6 (27.3)	1 (4.5)
Urinary retention	17 (77.3)	1 (4.5)	4 (18.2)	0
Urinary incontinence	22 (100)	0	0	0
Urinary hemorrhage	22 (100)	0	0	0
Diarrhea	20 (90.9)	2 (9.1)	0	0
GI hemorrhage	22 (100)	0	0	0
Late				
Urinary frequency/urgency	7 (31.8)	11 (50.0)	4 (18.2)	0
Urinary retention	16 (72.7)	5 (22.7)	1 (4.5)	0
Urinary incontinence	20 (90.9)	1 (4.55)	1 (4.55)	0
Urinary hemorrhage	20 (90.9)	1 (4.55)	0	1 (4.55)
Diarrhea	21 (95.5)	1 (4.5)	0	0
GI hemorrhage	18 (81.8)	2 (9.1)	2 (9.1)	0

Abbreviation: GI = gastrointestinal.

Pinitpatcharalert et al 2019

Radioterapia del tumore prostatico organo-confinato

Health-related quality of life in men with prostate cancer undergoing active surveillance versus radical prostatectomy, external-beam radiotherapy, prostate brachytherapy and reference population: a cross-sectional study

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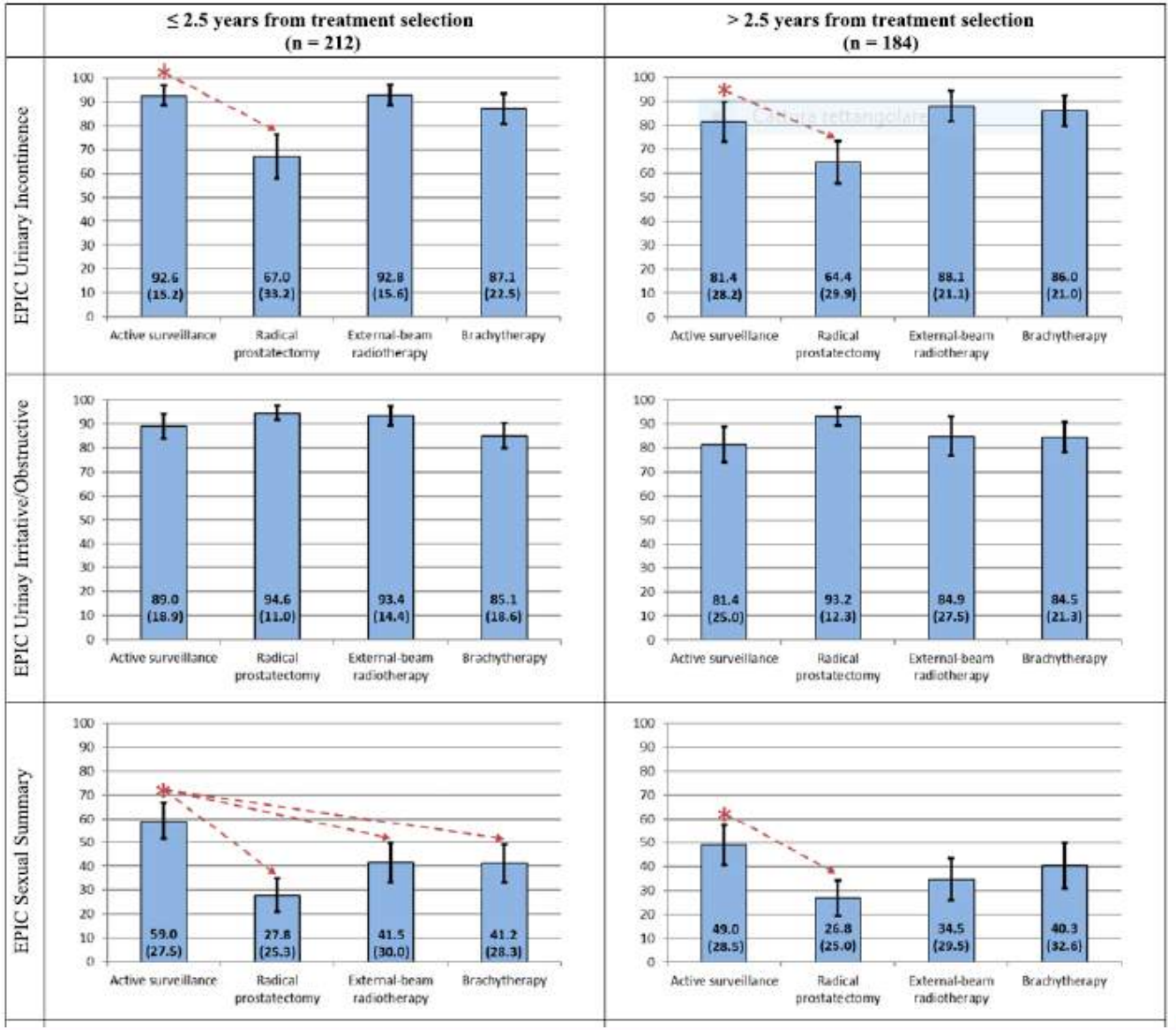


Sureda, 2019

Radioterapia del tumore prostatico organo-confinato

The Natural History of Erectile Dysfunction After Prostatic Radiotherapy: A Systematic Review and Meta-Analysis

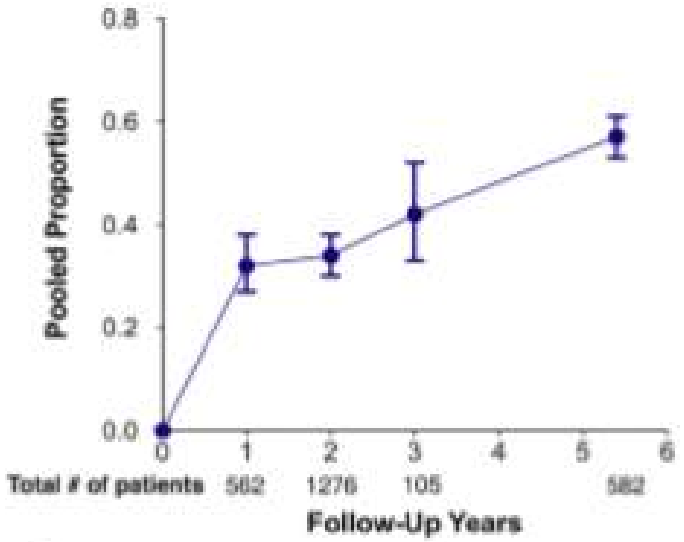
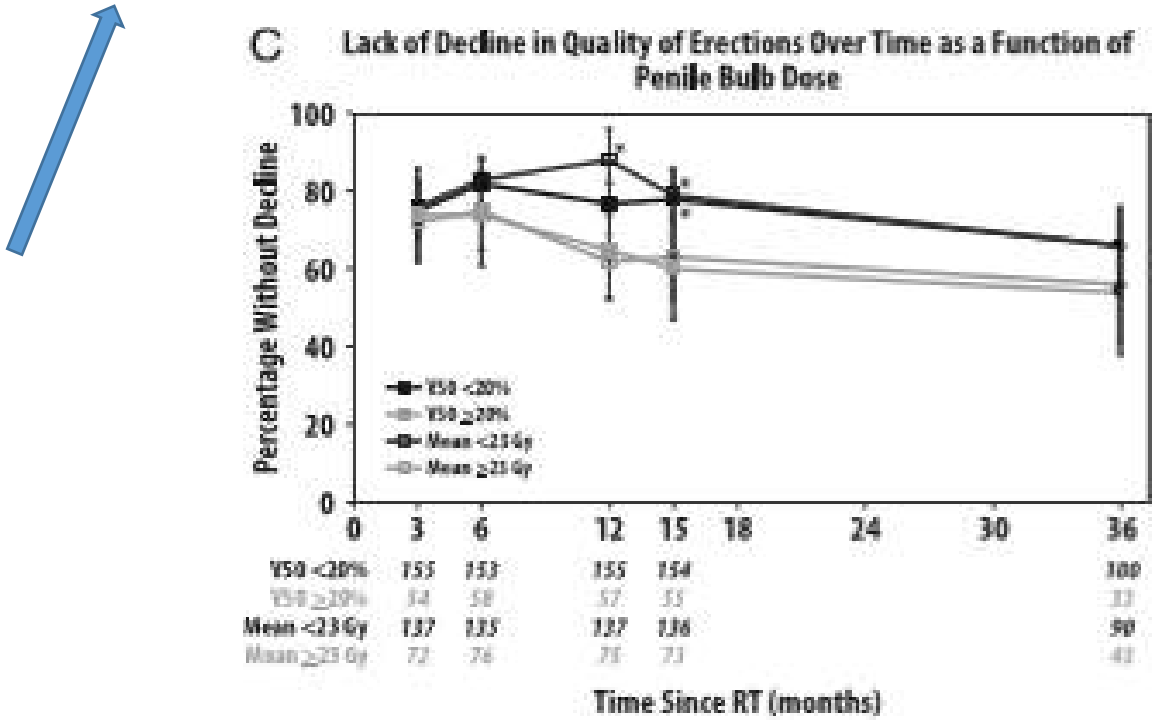


Figure 2. Pooled proportion of erectile dysfunction after radiotherapy confirmed by the Sexual Health Inventory for Men using cutoffs from 10 to 17. Figure 2 is available in color at www.jsm.jsexmed.org.

Definitions and measurements of ED after RT vary considerably in published series and could account for variability in the prevalence of reported ED. Nevertheless, ED is common regardless of RT modality and increases during each year of follow-up. BT plus EBRT is associated with increased ED, whereas the prevalence of ED did not differ between BT and EBRT monotherapies. Using the SHIM, ED is found in approximately 50% patients at 5 years. LTF in studies could bias the results to overestimate ED.

Gaither, 201

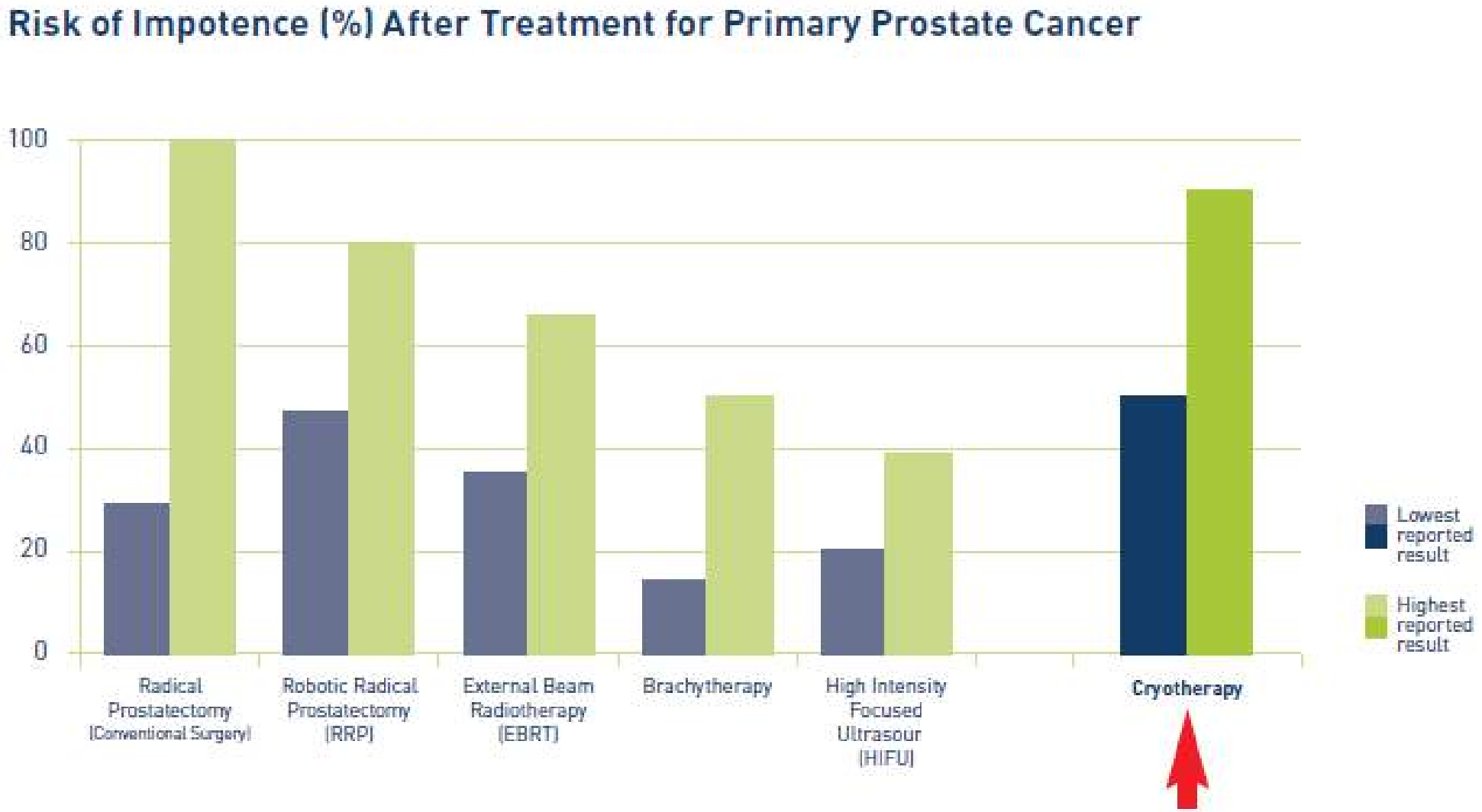
Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/ prostate spacer: Secondary analysis of a phase 3 trial



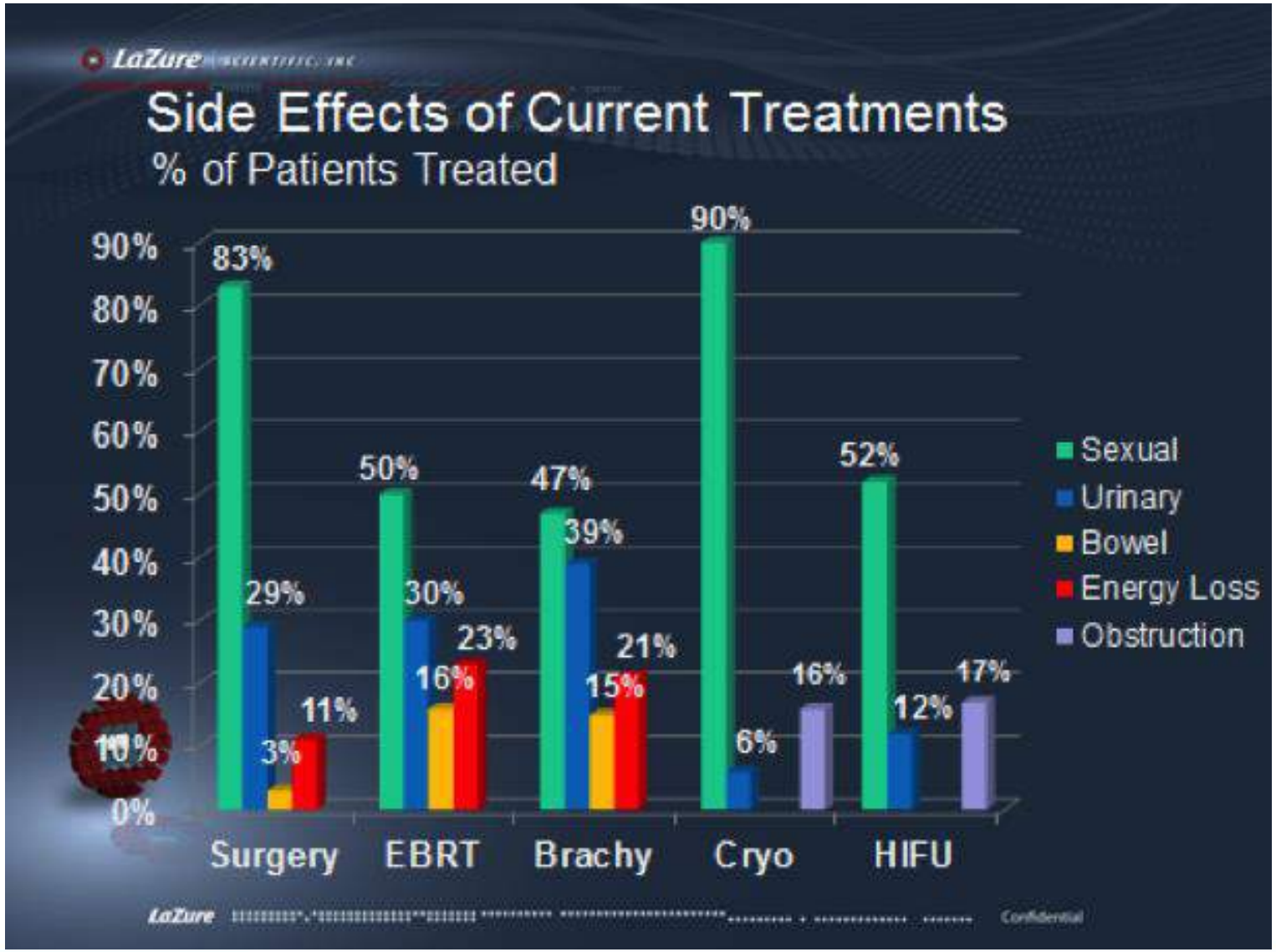
Conclusions: The use of a hydrogel spacer decreased dose to the penile bulb, which was associated with improved erectile function compared with the control group based on patient-reported sexual QOL.

Hamstra, 2018

Radioterapia del tumore prostatico organo-confinato



Radioterapia del tumore prostatico organo-confinato

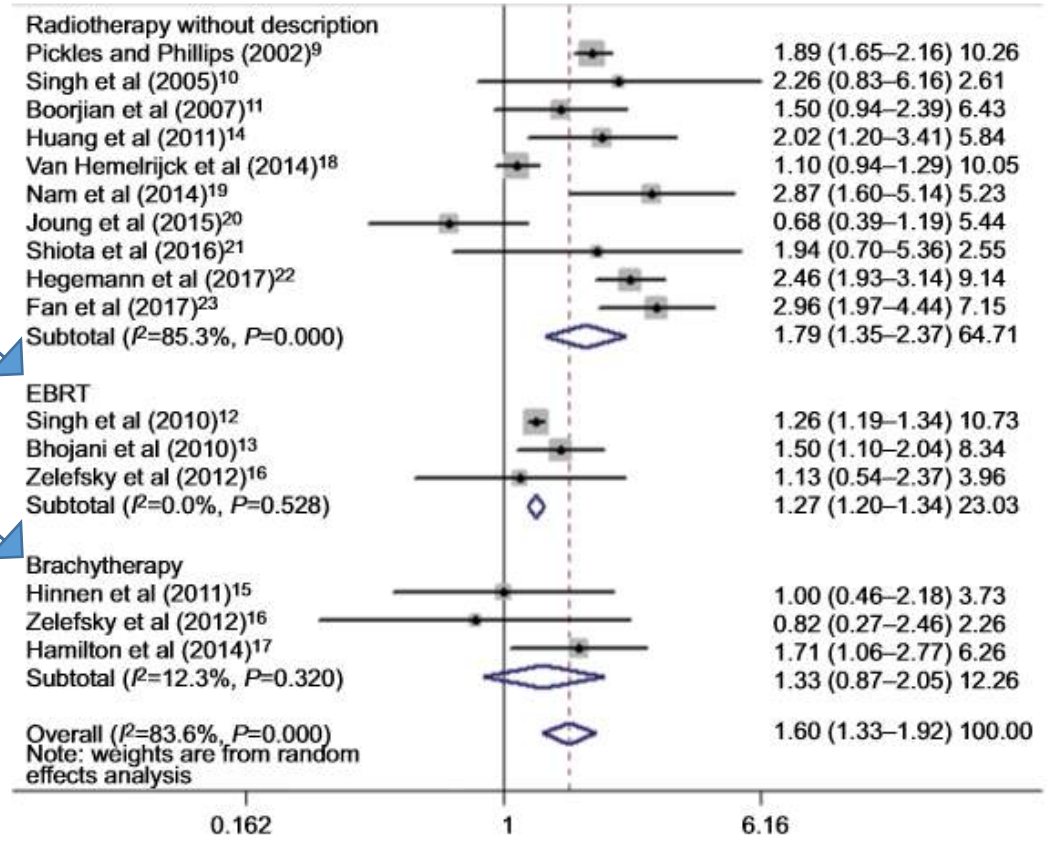


High prevalence of secondary bladder cancer in men on radiotherapy for prostate cancer: evidence from a meta-analysis

619.479 pz

RT was significantly associated with an increased risk of secondary bladder cancer.

The results were consistent when restricted to a period of 5-ye, but not for a 10-year lag period and for Brachytherapy



Zhao, 2019

Nonsurgical Salvage Local Therapies for Radiorecurrent Prostate Cancer: A Systematic Review and Meta-analysis

Evidence synthesis: A total of 64 case-series studies were included, corresponding to a cohort of 5585 patients. The modified Delphi checklist evidenced high methodological quality overall (mean quality score of 80.6%). Biochemical control rates were lowest for patients treated with HIFU (58%, 95% confidence interval [CI] 47–68%) and highest for patients treated with BT (69%, 95% CI 62–76%) and EBRT (69%, 95% CI 53–83%). The lowest prevalence of incontinence was for patients treated with BT (3%, 95% CI 0–6%; $I^2 = 63.4\%$) and the highest was among patients treated with HIFU (28%, 95% CI 19–38%; $I^2 = 89.7\%$).

Ingrosso, 2018

Concludendo

Radioterapia del tumore prostatico organo-confinato

- *La Radioterapia esterna con le sue nuove metodologie è trattamento efficace ed a bassa morbidità per il tumore della prostata in fase iniziale ed intermedia*
- *La Radioterapia volumetrica con verifica quotidiana della posizione delle strutture adiacenti alla prostata ha minimizzato la tossicità acuta e cronica a carico della vescica e del retto*
- *Il trattamento radioterapico può essere realizzato attraverso poche sedute (5), anche se nell'ambito di studi clinici*
- *Il rischio di impotenza potrà essere ulteriormente ridotto con specifica attenzione alle dosi a carico del bulbo penieno*
- *In caso di recidiva locale è ancora possibile intervenire con metodiche non chirurgiche, prime fra tutte la Radioterapia stereotassica*
- *E' raccomandata una particolare attenzione nel follow-up alla integrità della mucosa vescicale*

«Lasciate che le prostate vengano a noi»

LM

Grazie per l'attenzione