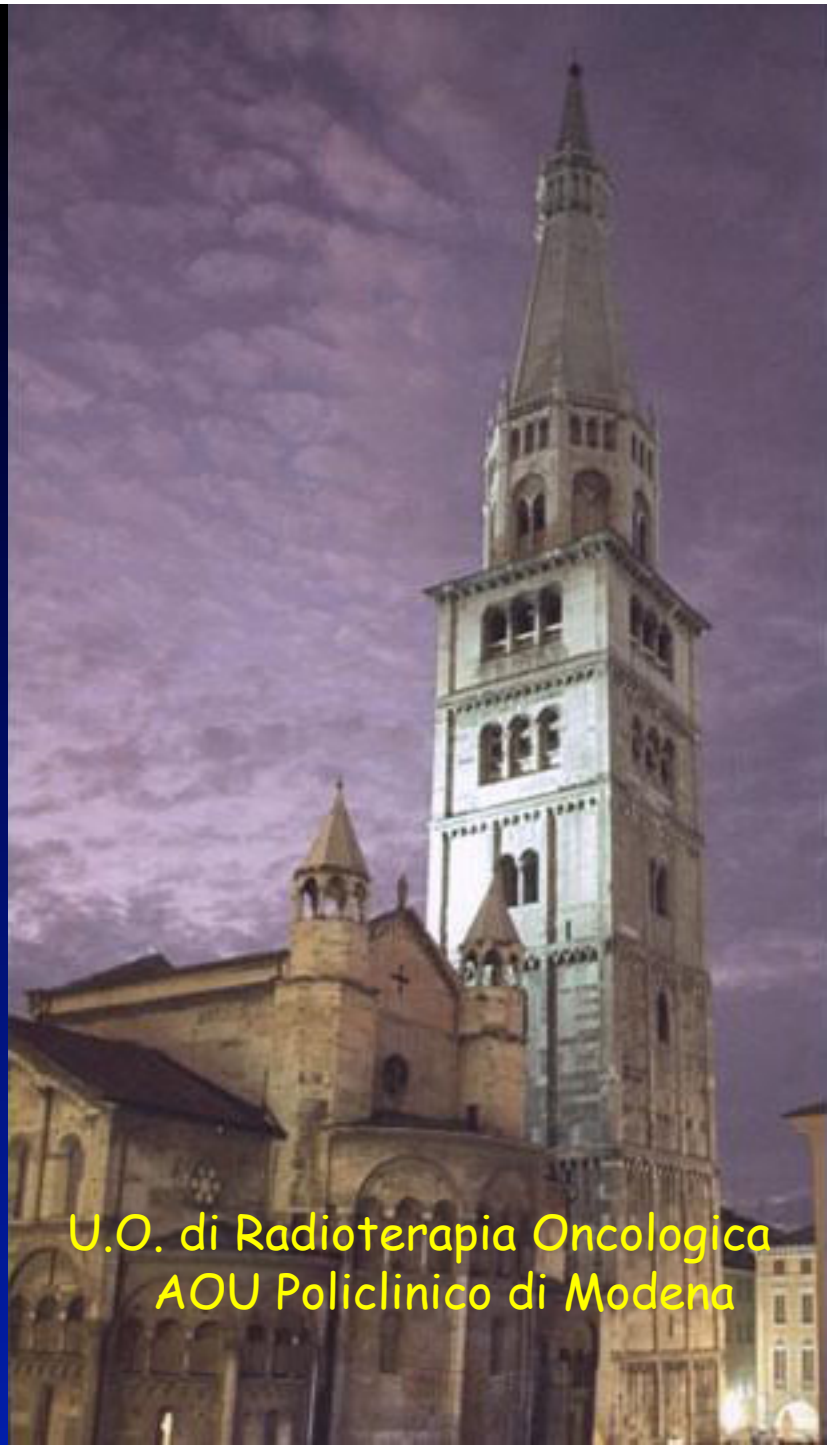
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliera Policlinico di Modena

IL CARCINOMA PROSTATICO AD INTERMEDIO ED ALTO RISCHIO

F. Bertoni, A. Bruni, E. Mazzeo

Taormina 27/10/2013



Tab 1. Sintesi dei dati di incidenza e mortalità

	Incidenza	Mortalità
Numero casi	544	91
% sul totale dei casi	22,1	8,3
Tasso grezzo*	163,8	27,4
Tasso STD* (eur)	114,9	15,0
IC95% STD	*105,0-124,8*	*11,8-18,1*
Rischio cumulato (0-74 aa), %	10,9	0,5
Età mediana	69	81

** x 100 000*

Fig 1. Distribuzione per fascia d'età

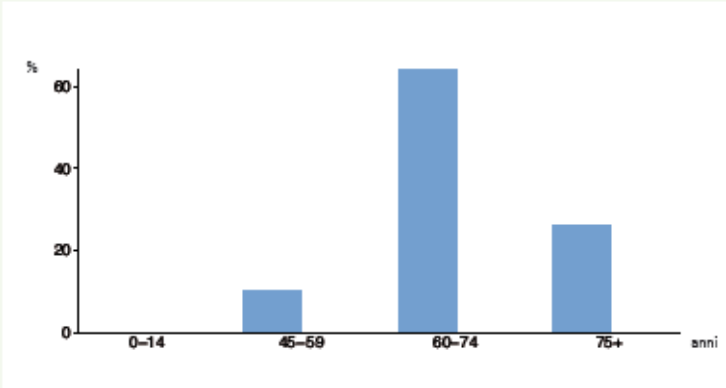
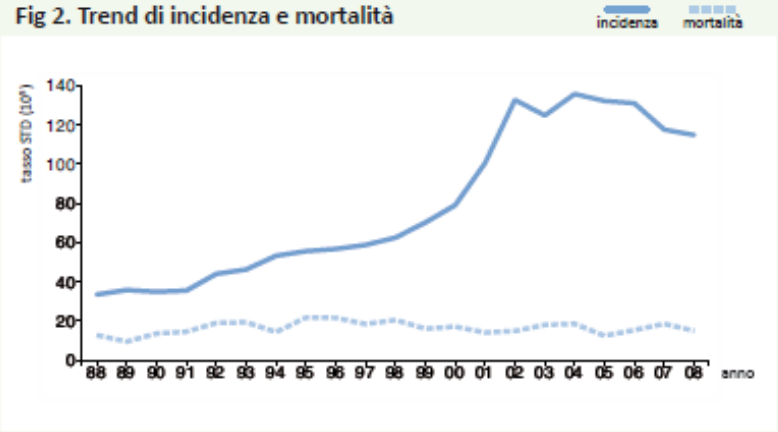
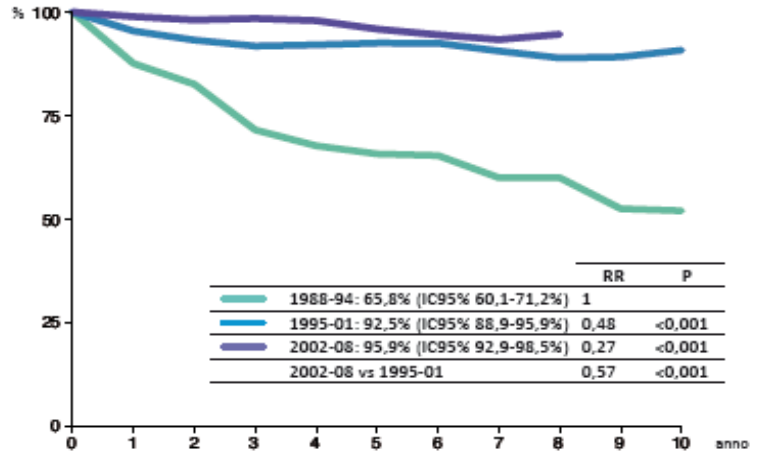


Fig 2. Trend di incidenza e mortalità



APC incidenza: 10,36 -3,70 (2004)*
APC mortalità: 0,10
** APC significativo (anno di cambio)*

Fig 3. Sopravvivenza relativa STD a 5 anni per periodo di diagnosi



PDTA e Linee Guida nelle neoplasie prostatiche

.....dalla diagnosi precoce (e screening?)

agli algoritmi diagnostici e terapeutici

..."Prostate Cancer Unit"...

R.Valdagni, et al.: Eur.J.Cancer 2011, 47: 1-7

Governo Clinico: la qualità dell'assistenza

garantire una
assistenza sanitaria efficace nell'ambito delle risorse disponibili

….condivisione di un problema……

….negoziazione per una soluzione.

EBM: metodo GRADE (AIOM 2012)

Grading of Recommendation, Assessment, Development and Evaluation for the production and grading of clinical recommendations on the effects of health care interventions

Percorso rigoroso ed esplicito a più fasi per la valutazione di nuove tecnologie contraddistinte da un sicuro alto costo a fronte di un incerto profilo beneficio-rischio :

1. definizione del quesito clinico sul quale deve essere formulata la raccomandazione
2. individuazione di tutti gli *outcome* relativi al quesito clinico e valutazione della loro importanza relativa per una adeguata valutazione dell'intervento specifico
3. ricerca dei dati relativi agli effetti positivi o negativi dei diversi interventi oggetto di valutazione
4. sintesi delle prove per singolo *outcome* ritenuto "essenziale" o "importante"
5. valutazione della qualità delle prove per ciascun *outcome*
6. valutazione della qualità globale delle prove
7. bilancio tra benefici e danni attribuibili all'intervento
8. definizione della forza della raccomandazione
9. formulazione della raccomandazione
10. implementazione e verifica di impatto

Governo clinico: metodo AGREE

APPRAISAL OF **G**UIDELINES
FOR **RE**SEARCH & **E**VALUATION **II**

AGREE II

INSTRUMENT

The AGREE Next Steps Consortium

May 2009

Struttura e contenuto di AGREE

AGREE consiste di 23 criteri *(item)* suddivisi in sei aree. Ciascuna area è rivolta a uno specifico aspetto della qualità di una linea guida.

***Obiettivo e motivazione (item* 1-3)**

riguarda gli obiettivi generali della linea guida, gli specifici quesiti clinici affrontati e la popolazione di pazienti cui si rivolge.

***Coinvolgimento delle parti in causa (item* 4-7)**

riguarda la misura in cui la linea guida rappresenta le opinioni dei suoi potenziali utilizzatori.

***Rigore della elaborazione (item* 8-14)**

si riferisce al processo utilizzato per identificare e sintetizzare le informazioni scientifiche, per formulare le raccomandazioni e per mantenerle aggiornate.

***Chiarezza e presentazione (item* 15-18)**

riguarda la formulazione e il formato della linea guida.

***Applicabilità (item* 19-21)**

si riferisce alle possibili implicazioni organizzative, economiche e sui comportamenti professionali attese dall'applicazione della linea guida.

***Indipendenza editoriale (item* 22-23)**

riguarda l'indipendenza delle raccomandazioni e l'esplicito riconoscimento di possibili conflitti di interesse da parte del gruppo che ha elaborato la linea guida.

Tabella 1. Confronto tra gli item dello strumento AGREE originale e quelli di AGREE II

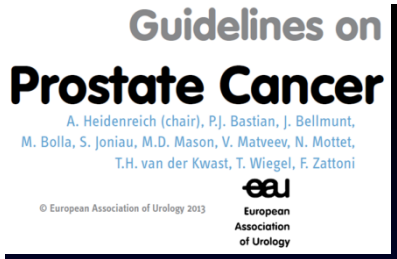
Item AGREE originale	Item AGREE II
Dimensione 1. Obiettivi e ambiti di applicazione	
1. Gli obiettivi generali della linea guida sono descritti in modo specifico	Non modificato
2. I quesiti clinici trattati dalla linea guida sono descritti in modo specifico	I quesiti sanitari trattati dalla linea guida sono descritti in modo specifico
3. I pazienti ai quali applicare la linea guida sono descritti in modo specifico	La popolazione target (pazienti, cittadini, etc.) a cui applicare la linea guida è descritta in modo specifico
Dimensione 2. Coinvolgimento dei soggetti portatori di interesse (*stakeholders*)	
4. Il gruppo che ha elaborato la linea guida include tutte le categorie professionali rilevanti	Non modificato
5. Sono stati presi in considerazione i punti di vista e le preferenze dei pazienti	Sono stati presi in considerazione i punti di vista e le preferenze della popolazione target (pazienti, cittadini, etc.)
6. La linea guida identifica con chiarezza gli utenti target	Non modificato
7. I potenziali utenti hanno effettuato una sperimentazione pilota della linea guida	Item eliminato. Integrato nella descrizione dell'item 19
Dimensione 3. Rigore Metodologico	
8. Sono stati utilizzati metodi sistematici per ricercare le evidenze scientifiche	Non modificato. Item rinumerato (7)
9. La linea guida descrive con chiarezza i criteri utilizzati per selezionare le evidenze scientifiche	Non modificato. Item rinumerato (8)
	NUOVO Item 9. La linea guida descrive con chiarezza i punti di forza e i limiti delle evidenze scientifiche
10. La linea guida descrive con chiarezza i metodi utilizzati per formulare le raccomandazioni	Non modificato
11. Nella formulazione delle raccomandazioni sono stati presi in considerazione benefici e rischi conseguenti alla loro applicazione	Non modificato

Dr. M. Leoni ASR - R.E.R. : 2013

EBM e Linee Guida

..... Livelli di evidenza....

...grado e forza della raccomandazione.....



EAU 2013

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2013
Prostate Cancer

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.

ESMO Guidelines 2012

Table 1. Level of evidence [3]

I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Linee guida

CARCINOMA DELLA PROSTATA

AIOM 2012 / 2013

AIOM 2012

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Grado di raccomandazione SIGN

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

La forza della raccomandazione è stata adattata dal metodo GRADE (Grading of Recommendations Assessment, Development and Evaluation) , come sotto riportato:

A: Raccomandazione positiva forte (tutti i pz dovrebbero ricevere questo intervento/trattamento/percorso diagnostico/ etc.)-> Studi a basso rischio di bias, con bilancio beneficio/rischio nettamente a favore del BENEFICIO.

B: Raccomandazione positiva debole (essere preparati a discutere con il pz il bilancio tra beneficio e rischio)-> Assenza di elevata qualità delle evidenze, bilancio beneficio/rischio moderatamente a favore del BENEFICIO ma con presenza di incertezza nel risultato.

C: Raccomandazione negativa debole: (essere preparati a discutere con il pz il bilancio tra beneficio e rischio)-> Assenza di elevata qualità delle evidenze, bilancio beneficio/rischio moderatamente a favore del RISCHIO ma con presenza di incertezza nel risultato.

D: Raccomandazione negativa forte: (tutti i pz dovrebbero ricevere questo intervento/trattamento/percorso diagnostico/ etc.)-> Studi a basso rischio di bias, con bilancio beneficio/rischio nettamente a favore del RISCHIO.

PDTA

e Livelli di rischio IR – HR

Screening ?

Trial Disponibili:

ERSPC (europa)

(European Randomized Study of Screening for Prostate Cancer)

- 162243 paz. ; 9 aa F.U.
- Ca : 8,2% vs. 4,8%
- Con lo Screening:
  - RR morte x Ca 0.80 per screening
  - Absolute risk difference: 0.71 / 1000 men.

PLCO (USA)

(Prostate, Lung,Colorectal, and Ovarian Cancer Screening Trial)

- 76693 paz ; 10 aa F.U.
- Incidenza R.R. 1,22
- Morte R R : 1,13

1410 uomini screenati (+48 Ca trattat) 1 morto in meno

- **ERSPC** : PSA-based screening reduced the rate of death from PCa by 20%, but was associated with a high risk of over-diagnosis **(level of evidence: 1b).**
- **PLCO** project team: Pca related mortality was very low and not significantly different between the two study groups **(level of evidence:1b).**

Original Article

The Cost Implications of Prostate Cancer Screening in the Medicare Population

Characteristics of the Study Population (n = 94,652)

Patient Characteristics	n	Percent
Age in years on January 1, 2007		
66-69	23,827	25.2
70-74	25,401	26.8
75-79	20,112	21.3
80-84	14,440	15.3
85-99	10,872	11.5
Race		
White	79,824	[illegible]
Black	[illegible]	6.2
Other	[illegible]	9.4
Median household income		
<$33,000	18,968	20.0
$33,000-$39,999	15,790	16.7
$40,000-$49,999	19,757	20.9
$50,000-$62,999	17,577	18.6
≥$63,000	19,256	[illegible].3
Unknown	3,304	3.5
Comorbid conditions		
0	48,347	51.1
1 to 2	32,260	34.1
≥3	14,045	14.8
Stage and risk classification[a]		
Localized, low-risk	388	17.2
Localized, intermediate-risk	877	38.9
Localized, high-risk	468	20.7
Regional/metastasized	138	6.1
Unknown	386	17.1

[a]Number of prostate cancer patients for stage and risk classification = 2257.

Regional-Level Prostate Cancer Incidence According to Regional Screening Expenditures

HRR-Level Screening Expenditures	All Men		Aged 66-74 y		Aged 75-99 y	
	Annual Incidence (per 100,000)	IRR (95% CI)[a]	Annual Incidence (per 100,000)	IRR (95% CI)[a]	Annual Incidence (per 100,000)	IRR (95% CI)[a]
Overall						
1st quartile	761	REF	870	REF	655	REF
2nd-3rd quartiles	[illegible]	1.09 (0.98-1.21)	952	1.04 (0.91-1.19)	723	1.05 (0.89-1.25)
4th quartile	[illegible]20	1.20 (1.07-1.35)	1140	1.24 (1.06-1.44)	942	1.31 (1.08-1.58)
Localized, low-risk						
1st quartile	[illegible]3	REF	155	REF	70	REF
2nd-3rd quartiles	149	1.19 (0.91-1.56)	209	1.25 (0.91-1.71)	71	0.93 (0.55-1.57)
4th quartile	202	1.52 (1.15-2.01)	283	1.71 (1.22-2.[illegible])	94	1.13 (0.64-2.01)
Localized, intermediate-risk						
1st quartile	285	REF	344	REF	245	REF
2nd-3rd quartiles	341	1.13 (0.95-1.34)	397	1.05 (0.85-1.30)	234	0.92 (0.69-1.22)
4th quartile	404	1.24 (1.03-1.49)	475	1.27 (1.00-1.62)	375	1.39 (1.03-1.88)
Localized, high-risk						
1st quartile	167	REF	184	REF	125	REF
2nd-3rd quartiles	171	[illegible]9 (0.78-1.[illegible])	172	0.88 (0.65-1.20)	183	1.41 (0.97-2.06)
4th quartile	215	1.[illegible]2 (0.[illegible]3-1.52)	204	1.04 (0.73-1.47)	233	1.70 (1.13-2.55)
Regional/metastasized						
1st quartile	[illegible]4	REF	29	REF	85	REF
2nd-3rd quartiles	[illegible]7	1.40 (0.91-2.14)	43	1.57 (0.77-3.22)	71	0.85 (0.52-1.41)
4th quartile	57	1.31 (0.81-2.11)	46	1.66 (0.74-3.75)	55	0.65 (0.35-1.24)

Abbreviations: [illegible], confidence interval; HRR, hospital referral region; IRR, incidence rate ratio.
[a]IRR and CI were both derived from multivariate Poisson models that adjusted for age group (66-69, 70-74, 75-79, 80-84, 85-99 years), race (white, black, and other), median household income at the ZIP code level (in quintiles), and Elixhauser comorbidity score (0, 1-2, ≥3).

I R - H R: 60 – 70% dei CaP

1,4 – 1,7% dei pazienti screenati

(CaP 1871/2257) /94652 paz. screenati

LR : 17 - 21%

IR: 39 - 47 %

HR: 21 - 25%

X. Ma et al. : Cancer 2013

…..un dato variabile in funzione di…

Definizione della Classe di Rischio

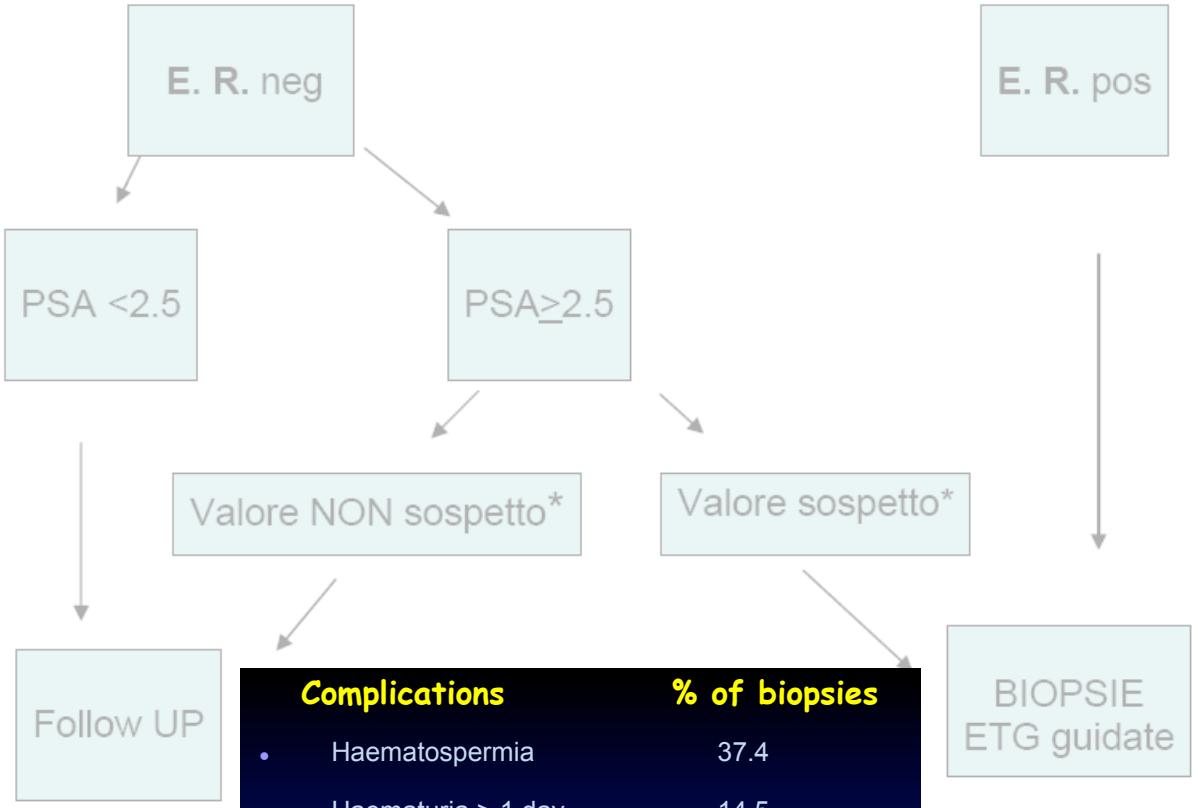
Delle modalità diagnostiche

Quale Rischio ?

Quale Scopo ?

Quanti Prelievi bioptici?

ALGORITMO DIAGNOSTICO (AIOM 2009 – 2012)



Complications	% of biopsies
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Other complications	0.3 – 0.7

N° prielievi

- 6 biopsie in sei sestanti
- 10-12 prelievi: migliora diagnosi ma...

non esiste evidenza scientifica che dimostri che >di 6 biopsie si traducano in vantaggio per il paziente

Guidelines on

Prostate Cancer

A. Heidenreich (chair), P.J. Bastian, J. Bellmunt,
M. Bolla, S. Joniau, M.D. Mason, V. Matveev, N. Mottet,
T.H. van der Kwast, T. Wiegel, F. Zattoni

European Association of Urology

EAU 2013

Diagnosis of PCa - Recommendations	GR
Biopsy and further staging investigations are only indicated if they affect the management of the patient.	C
Transrectal ultrasound (TRUS)-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 8 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volume prostates.	B
Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates.	C
One set of repeat biopsies is warranted in cases with persistent indication for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy).	B
Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	C

CUAJ • April 2012 • Volume 6, Issue 2

- **Esistono > 20 modelli predittivi** che nascono dalla combinazione tra classe T, PSA alla diagnosi, GS
  - Grafici per predire probabilità
  - Nomogrammi
  - Look-up tables
  - Reti neurali

.... il problema degli endpoint...

Original Contributions

Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer

Level of Risk	No. (%) of Patients Receiving Treatment*			
	Radical Prostatectomy at the Hospital of the University of Pennsylvania	External Beam Radiation Therapy at the Joint Center for Radiation Therapy	Interstitial Radiation (Implant)	Interstitial Radiation (Implant) Plus Neoadjuvant Androgen Deprivation Therapy
Low	(n = 402)	(n = 225)	(n = 32)	(n = 91)
PSA >0-4	68 (17)	42 (19)	4 (13)	12 (13)
PSA 4.1-10	334 (83)	183 (81)	28 (87)	79 (87)
Biopsy Gleason score 2-4	104 (26)	53 (24)	4 (12)	7 (8)
Biopsy Gleason score 5-6	298 (74)	172 (76)	28 (88)	84 (92)
American Joint Commission on Cancer Staging (AJCC) T1c, T2a	402 (100)	225 (100)	32 (100)	91 (100)
Intermediate	(n = 247)	(n = 232)	(n = 15)	(n = 38)
PSA >0-4	9 (4)	23 (10)	1 (7)	1 (3)
PSA 4.1-10	100 (40)	82 (35)	4 (27)	19 (50)
PSA 10.1-20	138 (56)	127 (55)	10 (66)	18 (47)
Biopsy Gleason score 2-4	31 (13)	31 (13)	3 (20)	3 (8)
Biopsy Gleason score 5-6	126 (51)	91 (39)	6 (40)	12 (32)
Biopsy Gleason score 7	90 (36)	110 (48)	6 (40)	23 (60)
AJCC T1c, T2a	179 (72)	138 (59)	12 (80)	31 (82)
AJCC T2b	68 (28)	94 (41)	3 (20)	7 (18)
High	(n = 239)	(n = 309)	(n = 19)	(n = 23)
PSA >0-4	8 (3)	12 (4)	0 (0)	3 (13)
PSA 4.1-10	76 (32)	64 (21)	5 (26)	13 (57)
PSA 10.1-20	72 (30)	71 (23)	6 (32)	6 (26)
PSA >20	83 (35)	162 (52)	8 (42)	1 (4)
Biopsy Gleason score 2-4	29 (12)	25 (8)	0 (0)	0 (0)
Biopsy Gleason score 5-6	93 (39)	113 (36)	12 (63)	14 (61)
Biopsy Gleason score 7	43 (18)	82 (27)	4 (21)	6 (26)
Biopsy Gleason score 8-10	74 (31)	89 (29)	3 (16)	3 (13)
AJCC T1c, T2a	63 (26)	105 (34)	6 (31)	3 (13)
AJCC T2b	25 (11)	47 (15)	2 (11)	0 (0)
AJCC T2c	151 (63)	157 (51)	11 (58)	20 (87)

*n indicates sample sizes stratified by risk and treatment.

D'Amico et al JAMA September 16, 1998-Vol280 N° 11

Original Contributions

Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer

Classe di rischio	Definizione	Rischio di PSA failure a 5 anni dalla terapia
Basso rischio	T-T2a e GS ≤6 e PSA ≤ 10 ng/ml	<25 % a 5 anni
Rischio intermedio	T2b o PSA 10 – 20 ng/ml o GS 7	25 % – 50% a 5 anni
Alto rischio	T2c o GS > 8 o PSA > 20 ng/ml	> 50 % a 5 anni

D'Amico et al *JAMA* September 16, 1998-Vol280 N° 11

An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011

John B. Eifler, Zhaoyang Feng, Brian M. Lin, Michael T. Partin, Elizabeth B. Humphreys, Misop Han, Jonathan I. Epstein, Patrick C. Walsh, Bruce J. Trock and Alan W. Partin

Table 2 Predicted probability (95% confidence interval) of pathological stage according to clinical stage (TNM), PSA level, and biopsy Gleason score (Johns Hopkins RP patients 2006–2011).

PSA	Pathological stage	Biopsy Gleason Score				
		6	3+4	4+3	8	9–10
Clinical stage T1c ($n = 4380$)						
0–2.5	OC ($n = 289$)	93 (91–95)	83 (78–87)	80 (74–85)	79 (72–85)	74 (61–83)
	EPE ($n = 21$)	7 (5–8)	15 (11–20)	17 (12–22)	18 (12–24)	20 (12–29)
	SV+ ($n = 4$)	0 (0–1)	2 (0–3)	3 (1–6)	3 (1–6)	5 (1–12)
	LN+ ($n = 0$)	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–2)	2 (0–6)
2.6–4.0	OC ($n = 751$)	87 (85–89)	71 (67–75)	66 (60–71)	65 (57–72)	56 (44–67)
	EPE ($n = 133$)	12 (10–14)	25 (22–29)	27 (22–32)	28 (22–34)	29 (20–40)
	SV+ ($n = 10$)	0 (0–1)	2 (1–4)	4 (2–7)	4 (2–8)	7 (3–12)
	LN+ ($n = 4$)	0 (0–0)	1 (0–2)	3 (1–5)	3 (1–6)	8 (3–16)
4.1–6.0	OC ($n = 1439$)	84 (83–86)	66 (63–69)	60 (55–65)	59 (51–66)	50 (38–60)
	EPE ($n = 371$)	15 (13–16)	29 (26–33)	31 (26–36)	32 (25–38)	32 (23–42)
	SV+ ($n = 37$)	1 (0–1)	4 (2–5)	6 (4–9)	6 (4–10)	10 (5–16)
	LN+ ($n = 11$)	0 (0–0)	1 (0–2)	3 (2–5)	3 (1–6)	8 (4–15)
6.1–10.0	OC ($n = 686$)	80 (78–82)	59 (55–63)	53 (47–58)	52 (44–59)	42 (31–52)
	EPE ($n = 226$)	18 (16–20)	34 (30–38)	35 (30–40)	36 (29–43)	36 (26–46)
	SV+ ($n = 36$)	1 (1–2)	6 (4–8)	9 (6–13)	9 (5–14)	14 (8–21)
	LN+ ($n = 8$)	0 (0–0)	1 (0–2)	3 (1–5)	3 (1–6)	8 (4–14)
>10.0	OC ($n = 191$)	69 (64–74)	42 (36–48)	34 (28–40)	33 (26–40)	23 (15–32)
	EPE ($n = 121$)	27 (22–31)	42 (36–47)	28 (32–45)	39 (31–47)	33 (24–44)
	SV+ ($n = 28$)	3 (2–5)	13 (9–18)	20 (14–27)	20 (12–28)	25 (15–36)
	LN+ ($n = 14$)	0 (0–1)	3 (1–5)	8 (4–14)	8 (3–14)	18 (9–30)

J.B. Eifler et al: BJU International, 2012

T1c N0 M0 → T3a N0 M0

T1c

PARTIN TABLES

PSA: 6.1-10

Gleason Score: 3+4

Clinical Stage: T1c

Find Results

Caso a rischio intermedio → rischio alto

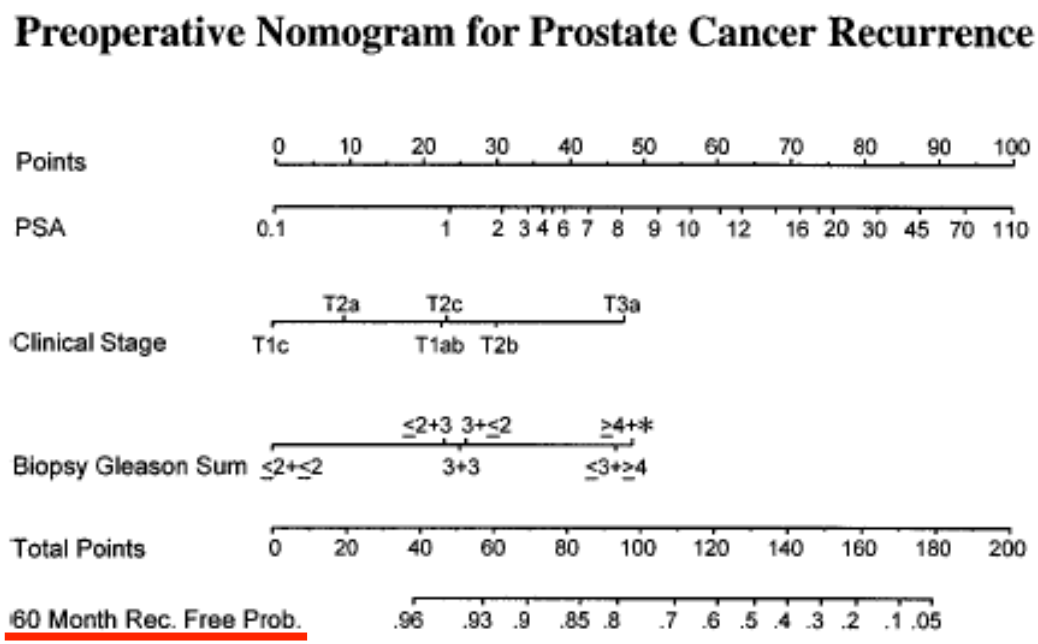
OC: *organ confined* (686)	EPE: *extraprostatic extension* (226)	SV+: *seminal vesicle involvement* (36)	LN+: *lymph node involvement* (8)
59(55-63)	34(30-38)	6(4-8)	1(0-2)

T2

OC: *organ confined* (25)	EPE: *extraprostatic extension* (36)	SV+: *seminal vesicle involvement* (7)	LN+: *lymph node involvement* (5)	
31(25-37)	52(46-59)	12(8-18)	4(2-7)	3+4
OC: *organ confined* (25)	EPE: *extraprostatic extension* (36)	SV+: *seminal vesicle involvement* (7)	LN+: *lymph node involvement* (5)	
24(19-31)	47(40-55)	19(12-25)	10(5-16)	4+3

….Noi x stimare N utilizziamo Roach (LN + = 2/3 PSA + (GS – 6) x 10)

Kattan's nomogram



Instructions for Physician: Locate the patient's PSA on the **PSA** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the **Clinical Stage** and **Biopsy Gleason Sum** axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for radical prostatectomy. You can use this only on a man who has already selected radical prostatectomy as treatment for his prostate cancer.

Instruction to Patient: "Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram – 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare."

Scott Department of Urology

A Preoperative Nomogram for Disease Recurrence Following Radical Prostatectomy for Prostate Cancer

*Michael W. Kattan, James A. Eastham, Alan M. F. Stapleton, Thomas M. Wheeler, Peter T. Scardino**

REPORT 771
Journal of the N.C.I.
Vol. 90, No. 10, May 20, 1998

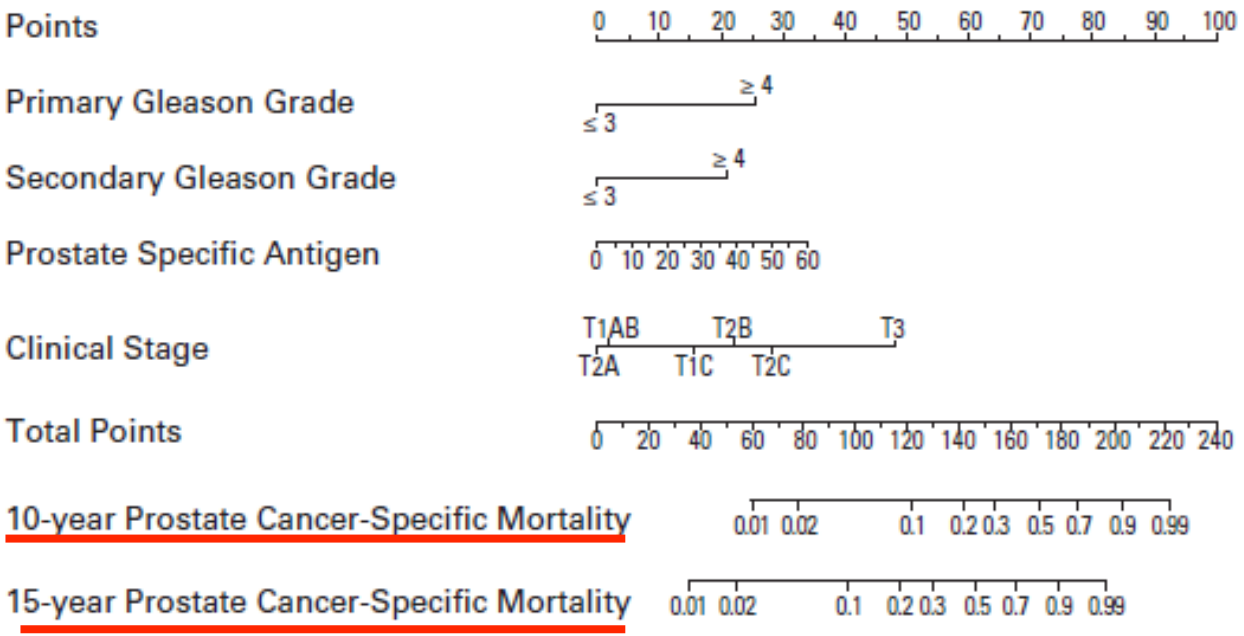
Stephenson's nomogram

VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

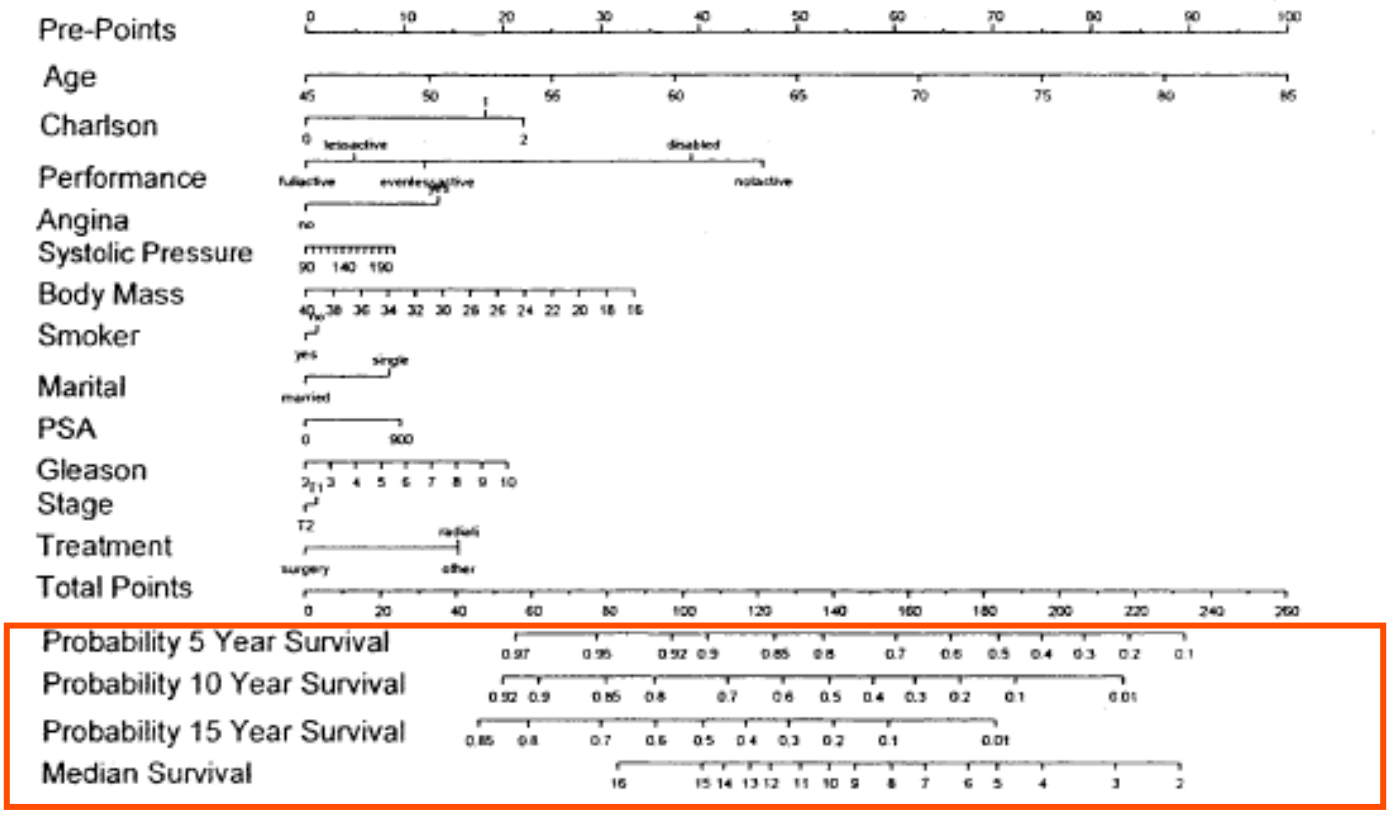
Prostate Cancer–Specific Mortality After Radical Prostatectomy for Patients Treated in the Prostate-Specific Antigen Era

Andrew J. Stephenson, Michael W. Kattan, James A. Eastham, Fernando J. Bianco Jr, Ofer Yossepowitch, Andrew J. Vickers, Eric A. Klein, David P. Wood, and Peter T. Scardino



Predicting Life Expectancy in Men With Clinically Localized Prostate Cancer

Mark E. Cowen,* Lakshmi K. Halasyamani and Michael W. Kattan†



THE JOURNAL OF UROLOGY Vol. 175, 99-103, January 2006

Pre-treatment risk stratification of prostate cancer patients: A critical review

George Rodrigues, MD, FRCPC, MSc;[*] Padraig Warde, FRCPC, MB;[†] Tom Pickles, MD, FRCPC;[‡] Juanita Crook, MD, FRCPC;[±] Michael Brundage, MD, FRCPC, MSc;[§] Luis Souhami, MD, FRCPC;[¥] Himu Lukka, MD, FRCPC;[¶] on behalf of the Genitourinary Radiation Oncologists of Canada

Table 1. Organizational pre-treatment prostate cancer risk stratification systems

Institution/organization	Low risk	Intermediate risk	High risk
Harvard (D'Amico)[12] AUA[33] EAU[34]	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	≥T2c or PSA >20 or GS 8-10
GUROC*[3] NICE[31]	T1-T2a and GS ≤6 and PSA ≤10	T1-T2 and/or Gleason ≤7 and/or PSA ≤20 not low-risk	≥T3a or PSA >20 or GS 8-10
CAPSURE*[41]	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	T3-4 or PSA >20 or GS 8-10
NCCN[30]	T1-T2a and GS 2-6 and PSA ≤10 not very low-risk AND very-low risk category: T1c and GS ≤6 and PSA <10 and Fewer than 3 biopsy cores positive and ≤50% cancer in each core	T2b or T2c and/or GS =7 and/or PSA >10-20 not low-risk	T3a or PSA >20 or GS 8-10 not very high risk AND very high-risk category: T3b-4
ESMO[32]	T1-T2a and GS ≤6 and PSA <10	Not high risk and not low risk (the remainder)	T3-4 or PSA >20 or GS 8-10

AUA: American Urological Association; EAU: EAU = European Association of Urology; GUROC: Genitourinary Radiation Oncologists of Canada; NICE: National Institute for Health and Clinical Excellence; CAPSURE: Cancer of the Prostate Strategic Urologic Research Endeavour; NCCN: National Comprehensive Cancer Network; ESMO: European Association of Urology; T: T stage; GS: Gleason score; PSA: prostate-specific antigen; *Use of the 1997 TNM staging system (T2a one lobe involvement, T2b two lobes involvement, no T2c category).

Pre-treatment risk stratification of prostate cancer patients: A critical review

DUE PROBLEMATICHE FONDAMENTALI

- Come per la classificazione NCCN si rende necessaria una classe di rischio **"very low"** per pazienti da avviare a sorveglianza attiva
- La classe di rischio intermedia dovrebbe essere ulteriormente suddivisa in una **low-intermediate risk** e in una **high-intermediate risk**

Rodrigues G. et al *Can Urol Assoc J* 2012;6(2):121-7

EURURO-5036; No. of Pages 8

ARTICLE IN PRESS

EUROPEAN UROLOGY XXX (2013) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

A New Risk Classification System for Therapeutic Decision Making with Intermediate-risk Prostate Cancer Patients Undergoing Dose-escalated External-beam Radiation Therapy

Zachary S. Zumsteg[a], *Daniel E. Spratt*[a], *Isaac Pei*[a], *Zhigang Zhang*[b], *Yoshiya Yamada*[a], *Marisa Kollmeier*[a], *Michael J. Zelefsky*[a,*]

[a] *Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [b] *Department of Epidemiology-Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

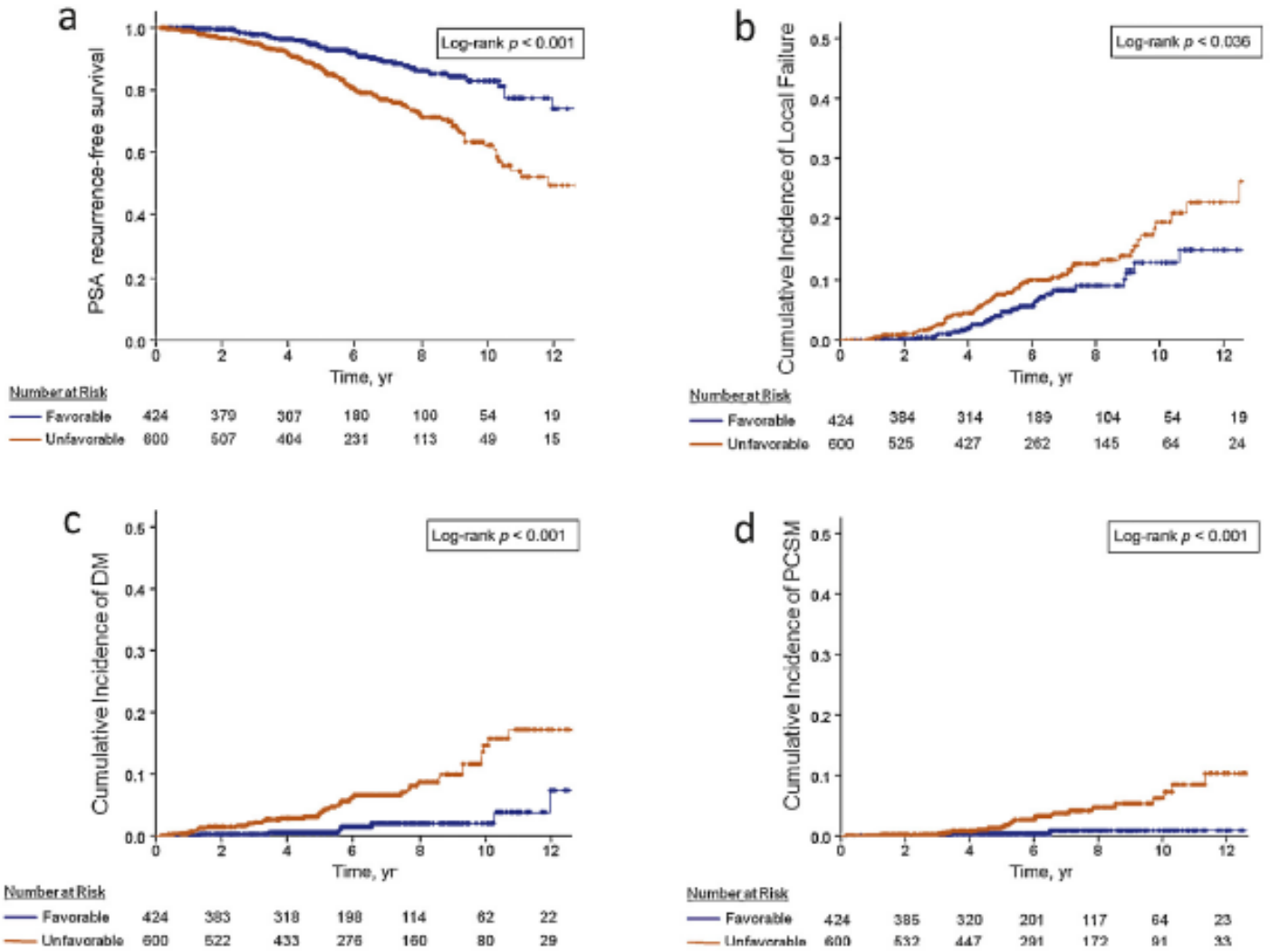


Fig. 1 – A comparison of favorable versus unfavorable intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy showing significant differences in (a) prostate-specific antigen (PSA) recurrence-free survival, (b) local failure, (c) distant metastasis (DM), and (d) prostate cancer–specific mortality (PCSM).

Zumsteg ZS. et al *European Urology, 2013* in press

Multiparametric 3T Prostate Magnetic Resonance Imaging to Detect Cancer: Histopathological Correlation Using Prostatectomy Specimens Processed in Customized Magnetic Resonance Imaging Based Molds

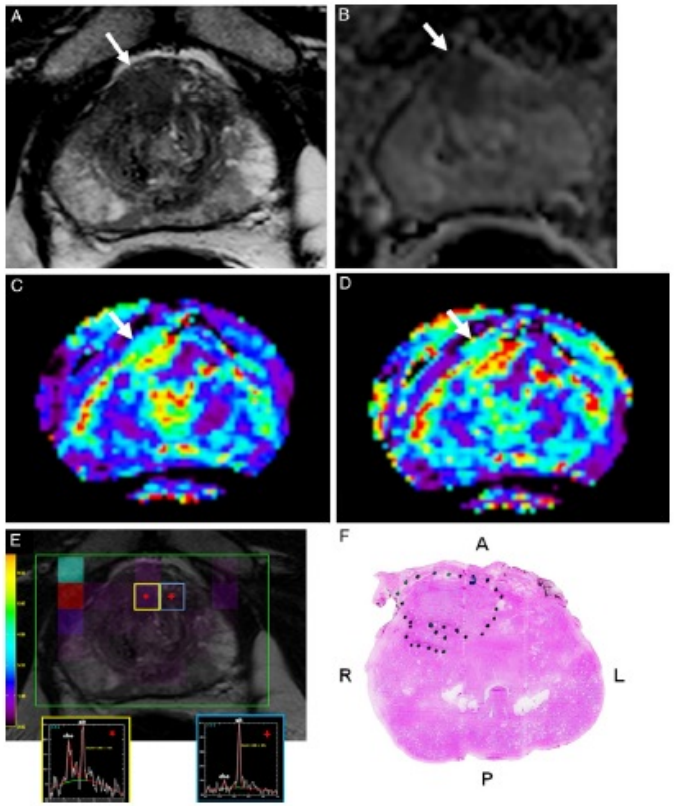


Figure 2. Prostate cancer in 52-year-old man. Axial T2-weighted and ADC map (*A*) of diffusion weighted (*B*) MRI demonstrates low signal intensity lesion (arrows) in right mid anterior central gland lesion suspicious for cancer. K^{trans} (*C*) and k_{ep} (*D*) maps of dynamic contrast enhanced MRI localize tumor (arrows). MRS (*E*) demonstrates increased ratio of choline (*cho*)-to-citrate (*cit*) in right mid anterior central gland lesion (asterisk) compared with normal adjacent left side (plus sign). Histopathological slide (*F*) at mid prostate level confirms presence of tumor (Gleason score 7, broken line) detected on multiparametric MRI. *A*, anterior. *L*, left. *P*, posterior. *R*, right. Reduced from ×100.

CONCLUSIONS

Prostate MRI at 3T allows for the detection of prostate cancer. In particular, a multiparametric approach increases the predictive power of MRI for diagnosis. The patient specific mold provides evenly spaced tissue blocks of uniform thickness which correspond directly to the MRI slice planes, leading to improved co-registration with histology compared with prior freehand methods. MRI may provide the urologist an imaging modality to better treat patients with prostate cancer. With continued research this imaging platform may also allow a more accurate method for cancer detection than traditional systematic nonguided biopsies. Compared to the traditional biopsy method, multiparametric imaging may allow earlier diagnosis of anterior prostate lesions and can guide needle biopsies more accurately than systematic methods. These findings may also provide the basis for image guided, minimally invasive, focal treatments of prostate cancer.

THE JOURNAL OF UROLOGY® Vol. 186, 1818-1824, November 2011

Multiparametric Magnetic Resonance Imaging and Ultrasound Fusion Biopsy Detect Prostate Cancer in Patients with Prior Negative Transrectal Ultrasound Biopsies

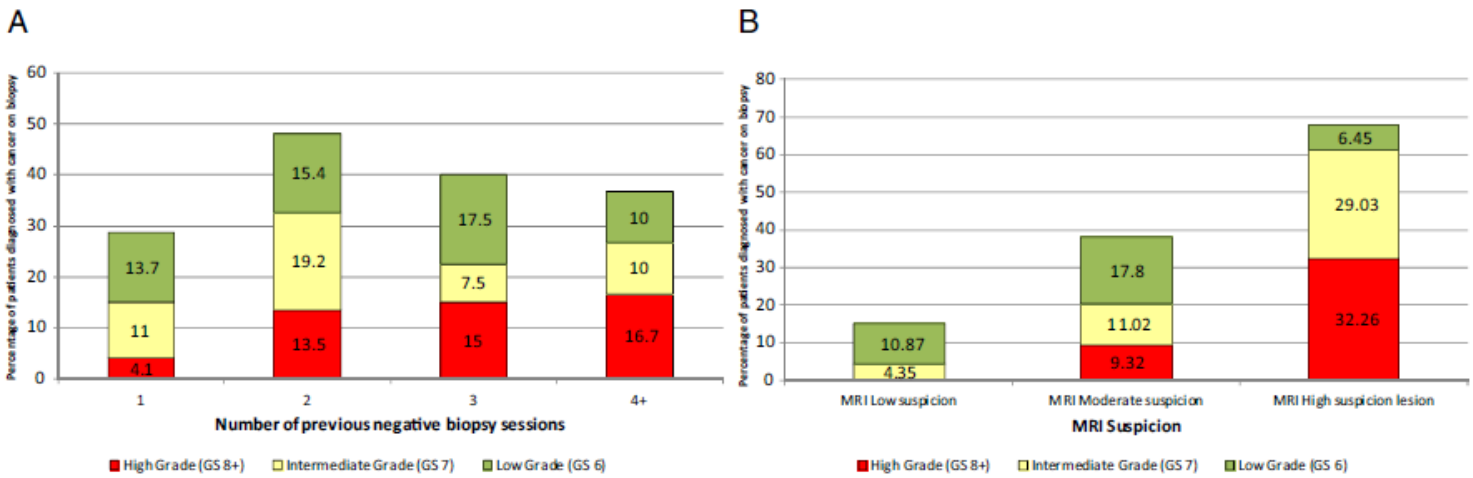


Figure 1. Diagnostic yield stratified by number of previous negative biopsies (*A*) and by MRI suspicion level (*B*). Diagnostic yield is further broken down into Gleason grade (low grade GS 6, intermediate grade GS 7 and high grade GS 8–10).

CONCLUSIONS

MRI/US fusion biopsy specifically targets clinically suspicious cancers throughout the prostate, including the anterior gland. This biopsy technique delivers a significant diagnostic yield in patients with prior negative TRUS biopsies and is not degraded by the number of previous biopsy sessions. Therefore, in contrast to nontargeted diagnostic strategies, we believe that MRI/US fusion biopsy is ideally suited for those men with persistent clinical suspicion of cancer but negative biopsy.

Vourganti S. et al
THE JOURNAL OF UROLOGYVol. 188, 2152-2157, December 2012

Platinum Priority – Editorial

Referring to the article published on pp. x–y of this issue

Personalizing the Management of Men with Intermediate-risk Prostate Cancer

Anthony V. D'Amico *

Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA

New treatment algorithm for men with UIR PCa who are planning to undergo RT

Imaging e biopsie image-guided per decidere su Ormonoterapia !

1. Obtain a 3T multiparametric MRI in men with biopsy GS 7 UIR PCa and assess whether areas suspicious for GS 8–10 PCa exist.
2. If suspicious areas are noted, then biopsy those areas using an MRI/TRUS fusion platform [9] or take additional cores from the suspicious areas using a TRUS-based approach.
3. If the biopsy is negative for GS 8–10 PCa, then treat with RT and 6 mo of AST.
4. If the biopsy is positive for GS 8–10 PCa, then treat with **RT and 28–36 mo of AST.**

In summary, three clinical factors have been identified in men with intermediate-risk PCa that are known to be associated with upgrading as well as increased risk of PSA recurrence, DM, and PCSM following RT with or without short-course AST [3–5], leading to the designation of these cancers by Zumsteg and colleagues [6] as UIR PCa. These three factors include biopsy GS 4 + 3, at least 50% PPB, and having more than one determinant of intermediate-risk PCa.

Ascertaining who with biopsy GS 7 UIR PCa harbors occult GS 8–10 PCa through the use of modern imaging and image-guided biopsy techniques may be one way to personalize the care of these men and improve their outcomes.

Staging for Prostate Cancer

CANCER January 15, 2007 / Volume 109 / Number 2

Time to Incorporate Pretreatment Prostate-specific Antigen and Gleason Score?

Prostate- 7th edition

T1 Not palpable or visible
- T1a ≤5% or less
- T1b >5%
- T1c Detected by needle biopsy

T2 Confined within prostate
- T2a ≤ half of one lobe
- T2b > half of one lobe
- T2c Both lobes

T3 Through prostate capsule
- T3a Extracapsular
- T3b Seminal vesicle(s)

T4 Fixed or invades adjacent structures

No change from 6th

STAGE GROUPING (ANATOMIC)

(UICC)

Stage I	T1, T2a	N0	
Stage II	T2b-2c	N0	
Stage III	T3	N0	
Stage IV	T4	N0	
	Any T	N1	
	Any T	Any N	M1

TNM 2010

Change from 6th

Grade was in 6th

Prostate- 7th ed

PROGNOSTIC GROUPING

I	T1a – c	N0	PSA <10	Gle ≤ 6
	T2a	N0	PSA <10	Gle ≤ 6
IIA	T1 a – c	N0	PSA < 20	Gle 7
	T1 a – c	N0	PSA ≥10 <20	Gle <6
	T2a,b	N0	PSA ≥10 < 20	Gle ≤ 7

If PSA or Gleason is missing, use whatever is available

IIB	T2c	N0	Any PSA	Any Gle
	T 1-2	N0	PSA ≥20	Any Gle
	T 1-2	N0	Any PSA	Gle ≥ 8
III	T3a-c	N0	Any PSA	Any Gle
IV	T4	N0	Any PSA	Any Gle
	Any T	N1	Any PSA	Any Gle
	Any T	Any N	M1 Any PSA	Any Gle

If both missing, no prognostic grouping is possible

Gx

G1 :	ben differenz.	(GPS 2-4)
G2:	moderat differenz.	(GPS 5-6)
G3-4:	scarsam./indifferenz.	(GPS 7-10)

….quali esami per la stadiazione ?...

Guidelines on
Prostate Cancer
A. Heidenreich (chair), P.J. Bastian, J. Bellmunt, M. Bolla, S. Joniau, M.D. Mason, V. Matveev, N. Mottet, T.H. van der Kwast, T. Wiegel, F. Zattoni

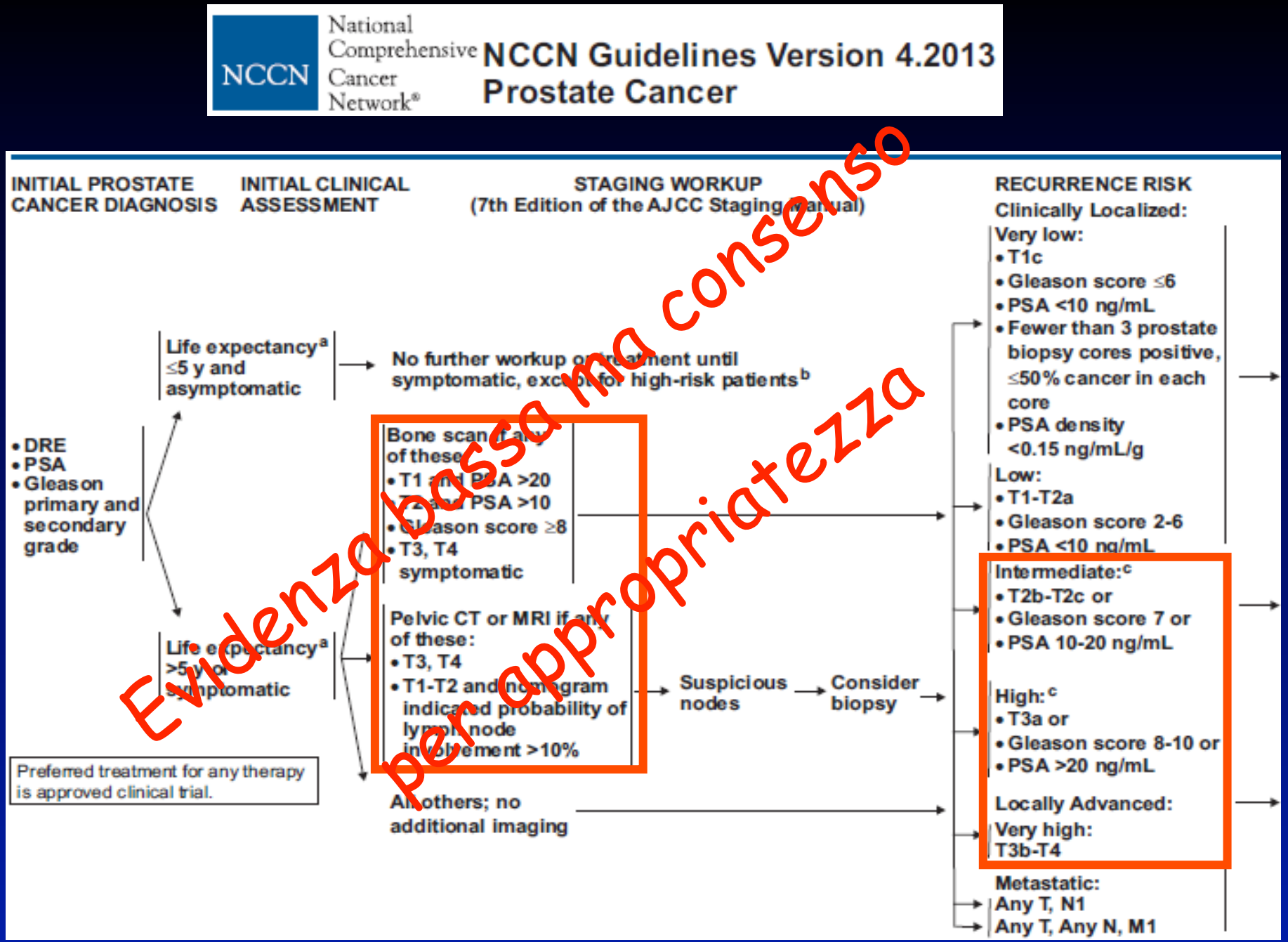
European Association of Urology

EAU 2013

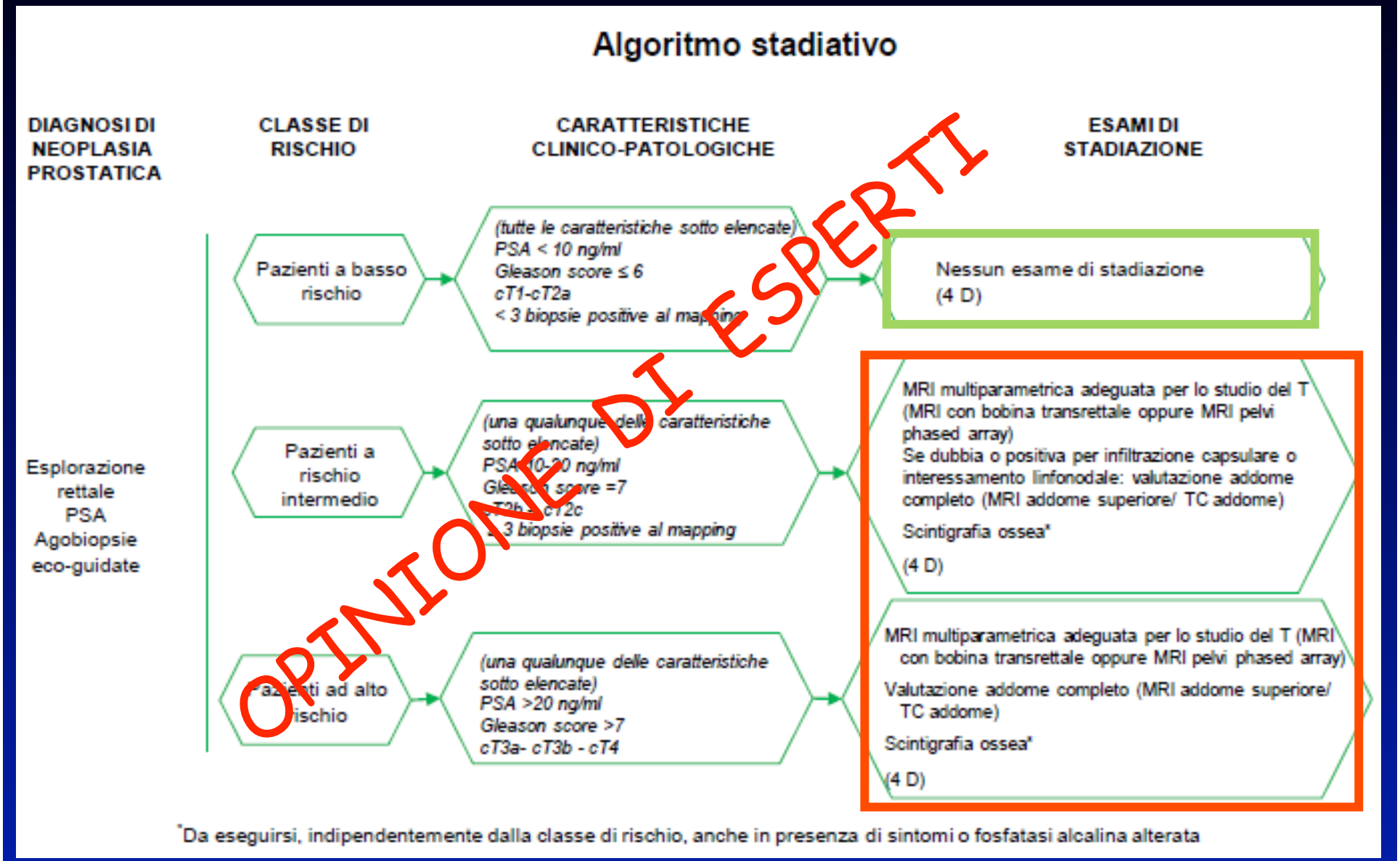
RMI multiparametrica ?? Valutazione N ?? Scintigrafia ?? PET ??

1.	Local staging (T-staging) of PCa should be based on magnetic resonance imaging (MRI). Further information is provided by the number and sites of positive prostate biopsies, the tumour grade and the level of serum PSA.	C
	Despite its high specificity in the evaluation of extraprostatic extension (EPE) and seminal vesicle invasion or involvement (SVI), TRUS is limited by poor contrast resolution, resulting in low sensitivity and a tendency to understage PCa. Even with the advent of colour- and power Doppler to assist in identifying tumour vascularity, the accuracy of TRUS in local staging remains inadequate. In comparison with DRE, TRUS and computed tomography (CT), MRI demonstrates higher accuracy for the assessment of uni- or bi-lobar disease (T2), EPE and SVI (T3), as well as the invasion of adjacent structures (T4). The addition of dynamic contrast-enhanced MRI (DCE-MRI) can be helpful in equivocal cases. The addition of magnetic resonance spectroscopic imaging (MRSI) to MRI also increases accuracy and decreases inter-observer variability in the evaluation of EPE.	C
2.	Lymph node status (N-staging) is only important when potentially curative treatment is planned. Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score ≤ 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation.	B
	Given the significant limitations of pre-operative imaging in the detection of small metastases (< 5 mm), pelvic lymph node dissection (PLND) remains the only reliable staging method in clinically localised PCa.	
	Currently, it seems that only methods of histological detection of lymph node metastases with high sensitivity, such as sentinel lymph node dissection or extended PLND, are suitable for lymph node staging in PCa.	C
3.	Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is < 20 ng/mL in the presence of well or moderately differentiated tumours.	B
	In equivocal cases, ^{11}C-choline-, ^{18}F-flouride-PET/CT or whole body MRI are an option.	C

B = studi buoni ma non RCT
C = data senza studi buoni o direttamente applicabili


NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 4.2013
Prostate Cancer
INITIAL PROSTATE CANCER DIAGNOSIS
INITIAL CLINICAL ASSESSMENT
STAGING WORKUP
(7th Edition of the AJCC Staging Manual)
RECURRENCE RISK
Clinically Localized:
Very low:
• T1c
• Gleason score ≤6
• PSA <10 ng/mL
• Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
• PSA density <0.15 ng/mL/g
Low:
• T1-T2a
• Gleason score 2-6
• PSA <10 ng/mL
Intermediate:c
• T2b-T2c or
• Gleason score 7 or
• PSA 10-20 ng/mL
High:c
• T3a or
• Gleason score 8-10 or
• PSA >20 ng/mL
Locally Advanced:
Very high:
T3b-T4
Metastatic:
Any T, N1
Any T, Any N, M1
Life expectancy[a] ≤5 y and asymptomatic
No further workup or treatment until symptomatic, except for high-risk patients[b]
• DRE
• PSA
• Gleason primary and secondary grade
Life expectancy[a] >5 y or symptomatic
Bone scan if any of these:
• T1 and PSA >20
• T2 and PSA >10
• Gleason score ≥8
• T3, T4 symptomatic
Pelvic CT or MRI if any of these:
• T3, T4
• T1-T2 and nomogram indicated probability of lymph node involvement >10%
Suspicious nodes
Consider biopsy
All others; no additional imaging
Preferred treatment for any therapy is approved clinical trial.
Evidenza bassa ma consenso per appropriatezza

ALGORITMO STADIATIVO AIOM 2012



*Da eseguirsi, indipendentemente dalla classe di rischio, anche in presenza di sintomi o fosfatasi alcalina alterata

ESMO 2012 per staging N

5. Which patients should have staging of pelvic lymph nodes?

Recommendation 5a: High-risk patients having a radical prostatectomy should have an extended bilateral lymph node dissection unless prior imaging shows gross multiple lymph node involvement

Level of evidence: III

Strength of recommendation: B

Recommendation 5b: Intermediate risk patients having a prostatectomy should have discussion about risk/benefit of lymph node dissection informed by nomogram estimates.

B= generalmente raccomandabile

Level of evidence: III

Strength of recommendation: B

Recommendation 5c: Low-risk patients should not routinely have a pelvic lymph node dissection.

D = non raccomandabile

Level of evidence: III

Strength of recommendation: D

Recommendation 5d: Intermediate and high-risk patients to be treated with radiotherapy should have pelvic imaging unless they have had surgical lymph node staging.

Level of evidence: IV

Strength of recommendation: B

B= generalmente raccomandabile

Recommendation 5e: Patients evaluated for salvage radiation therapy after prostatectomy should have pelvic imaging, unless low volume and low risk (PSA < 1.0, Gleason score < 7 and slow PSA progression [PSA DT > 15 months]).

Level of evidence: IV

Strength of recommendation: B

A. Horwich et al : Annals of Oncology: 2013

RMN Multiparametrica ?

Whole-body RMN? PET?

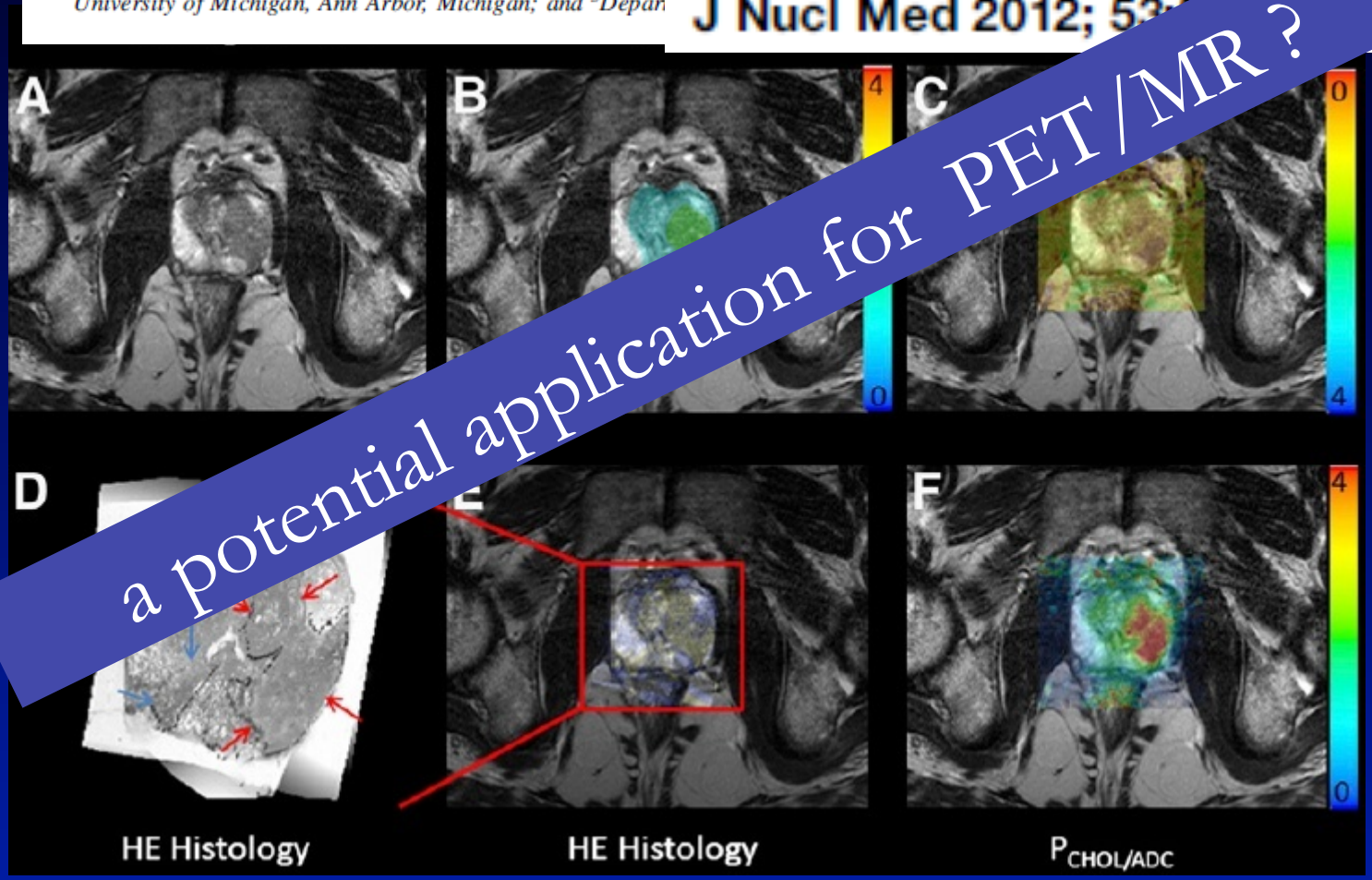
Introducing Parametric Fusion PET/MRI of Primary Prostate Cancer

Hyunjin Park[1,2], David Wood[3], Hero Hussain[1], Charles R. Meyer[1], Rajal B. Shah[4], Timothy D. Johnson[5], Thomas Chenevert[1], and Morand Piert[1]

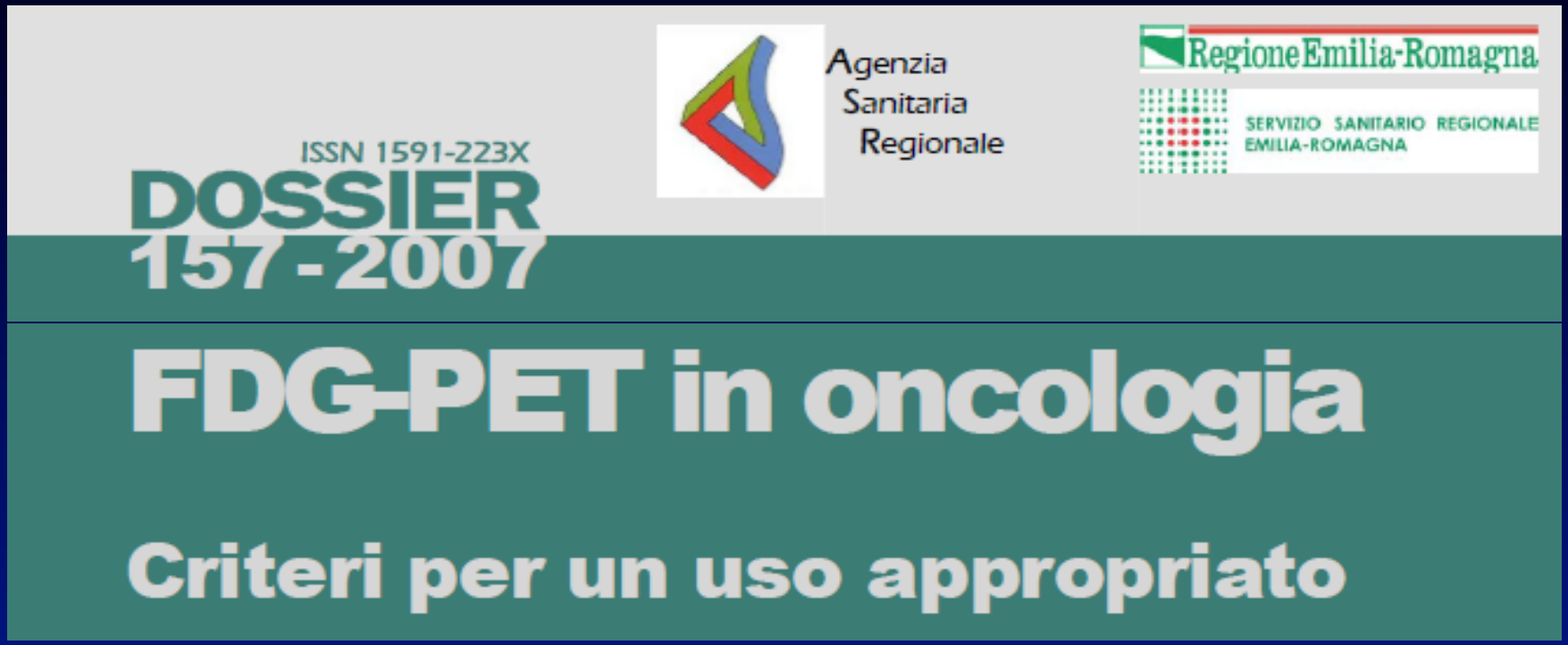
[1]Department of Radiology, University of Michigan, Ann Arbor, Michigan; [2]Department of Biomedical Engineering, Gachon University, Incheon, South Korea; [3]Department of Urology, University of Michigan, Ann Arbor, Michigan; [4]Department University of Michigan, Ann Arbor, Michigan; and [5]Depar

J Nucl Med 2012; 53:

a potential application for PET/MR ?



FDG-PET nelle neoplasie prostatiche



Commento

Gli studi disponibili documentano una accuratezza diagnostica della PET con 18 FDG inferiore alla diagnostica per immagini tradizionali.

The Role of 11C-Choline and 18F-Fluorocholine Positron Emission Tomography (PET) and PET/CT in Prostate Cancer: A Systematic Review and Meta-analysis

Martin H. Umbehr [a,b,*], *Michael Müntener* [c], *Thomas Hany* [d], *Tullio Sulser* [b], *Lucas M. Bachmann* [a]

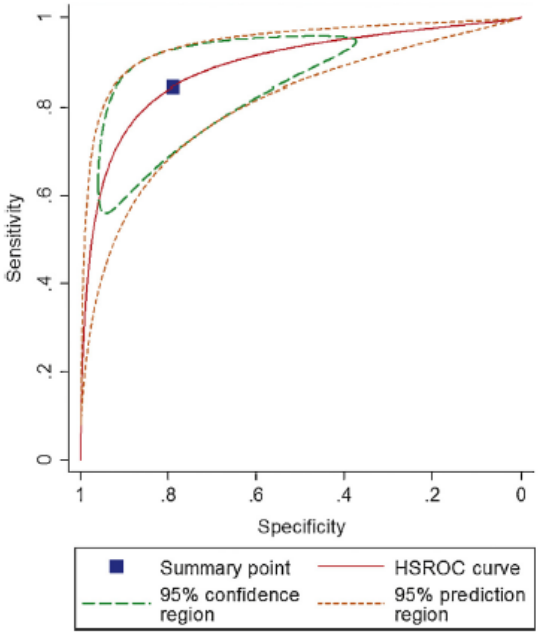


Fig. 2 – Receiver operating characteristic curve for patients with proven but untreated prostate cancer on per-patient analysis. HSROC = hierarchical summary receiver operating characteristic.

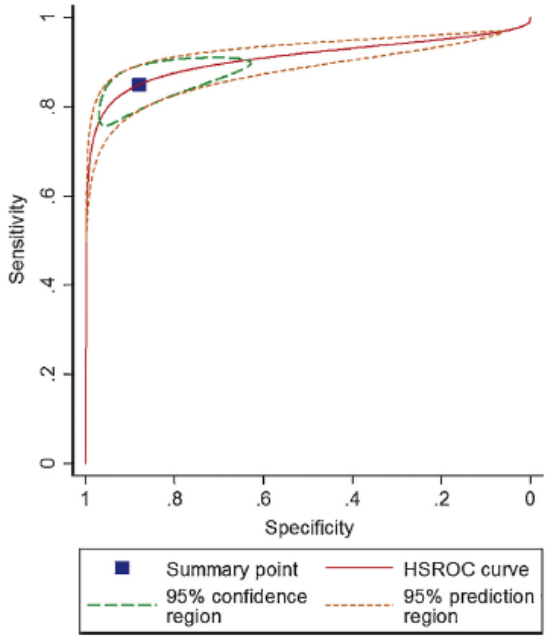


Fig. 4 – Receiver operating characteristic curve for patients with biochemical failure after local treatment with curative intention on per-patient analysis. HSROC = hierarchical summary receiver operation characteristic.

4. Conclusions

Our results strengthen the current evidence of the usefulness of PET and PET/CT using 11C-choline or 18F-FCH as tracers in PCa work-up, whereby the diagnostic evidence is stronger in restaging than in staging settings. In general, proper patient selection, by considering predictive clinical parameters like PSA level, PSA doubling time, and initial tumor stage, is the key to avoiding FN results up front. The current evidence, although promising, has crucial limitations in terms of its applicability in common clinical scenarios.

Review – Prostate Cancer

Utility of Choline Positron Emission Tomography/Computed Tomography for Lymph Node Involvement Identification in Intermediate- to High-risk Prostate Cancer: A Systematic Literature Review and Meta-analysis

Evidence synthesis: From the year 2000 to January 2012, we found 18 complete articles that critically evaluated the role of choline PET and PCa at initial staging. The meta-analysis was carried out and consisted of 10 selected studies with a total of 441 patients. The meta-analysis provided the following results: pooled sensitivity 49.2% (95% confidence interval [CI], 39.9–58.4) and pooled specificity 95% (95% CI, 92–97.1). The area under the curve was 0.9446 ($p < 0.05$). The heterogeneity ranged between 22.7% and 78.4%. The diagnostic odds ratio was 18.999 (95% CI, 7.109–50.773).
Conclusions: Choline PET and PET/CT provide low sensitivity in the detection of lymph node metastases prior to surgery in PCa patients. A high specificity has been reported from the overall studies. Studies carried out on a larger scale with a homogeneous patient population together with the evaluation of cost effectiveness are warranted.

Pooled diagnostic accuracies for 18F-choline and 11C-choline positron emission tomography (PET)-PET/computed tomography

	18F-choline		11C-choline	
	Pooled value (95% CI)	Chi-square/I^2, %	Pooled value (95% CI)	Chi-square/I^2, %
Sensitivity	0.40 (0.27–0.53)	11.35/73.6	0.58 (0.45–0.70)	16.37/69.5
Specificity	0.96 (0.91–0.98)	6.63/54.7	0.94 (0.90–0.97)	4.77/0
Positive likelihood ratio	6.44 (1.64–25.30)	1.05/56.9	8.99 (4.43–18.27)	5.52/9.4
Negative likelihood ratio	0.74 (0.45–1.21)	12.19/75.4	0.39 (0.16–0.92)	33.31/85
Diagnostic odds ratio	10.64 (1.32–85.91)	3/65	29.19 (10.44–81.57)	5.70/12.3

CI = confidence interval.

45% of metastatic lymph nodes are <0.4 cm in diameter , a value below the spatial resolution of PET/CT and below the adopted criteria of anatomic imaging tools such as MRI and CT

L. Evangelista et al: EURURO 2013

CURRENT OPINION

Novel imaging techniques reshape the landscape in high-risk prostate cancers

Frederic E. Lecouvet[a], Renaud Lhommel[b], Vasiliki Pasoglou[a], Ahmed Larbi[a], François Jamar[b], and Bertrand Tombal[c]

Recent findings

In contrast to the progress that has been made in PCa treatment, diagnostic strategies have not much evolved. Most guidelines still recognize ^{99m}Tc bone scintigraphy and computed tomography (CT) as cornerstone modalities to assess metastatic spread in bones and lymph nodes. Therefore, modern imaging techniques should primarily focus on these two targets. PET with various tracers, including ^{11}C or ^{18}F-choline and ^{18}F-sodium fluoride, and MRI with or without diffusion-weighted imaging are competing to supplant bone scan and CT scan as reference imaging techniques. This review focuses on the latest development of these techniques and analyses their potential impact in everyday urology practice.

Summary

Although certain hurdles remain, PET and whole-body MRI have the ability to supplant ^{99m}Tc bone scan and CT as upfront test to assess metastatic spread in high-risk PCa.

Table 1. Diagnostic performance of ^{11}C-choline PET for node assessment, with eLND as comparator

Author, year	Analysis	*n*	Sensitivity	Specificity	PPV	NPV
Poulsen, 2012 [24]	Patient based	210	73.2%	87.6%	58.8%	93.1%
	LN based	1093	56.8%	94%	40%	96.8%
Schiavina, 2008 [25]	Patient based	57	60.0%	97.6%	90%	87.2%
	LN based	892	41.4%	99.8%	94.4%	97.2%
Budiharto, 2011 [21▪▪]	Patient based	36	18.8%	95.0%	75.0%	59.4%
	LN based	773	9.4%	99.7%	75%	91.0%

eLND, extended lymph nodes dissection; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value.

Are these results sufficient to definitively state that PET/CT or whole-body DWI-MRI should replace 99mTc bone scintigraphy and CT as initial and sole imaging modality for staging of high-risk PCa patients?

The answer is no !

F. Lecouvet et al. : Curr Opin Urol 2013

Programmi terapeutici
per IR e HR

Linee Guida

L'outcome di

RTT, Brachiterapia e Chirurgia è simile;

l'evidenza di efficienza clinica

per le terapie dei tumori localizzati è scarsa.

European Urology 44: 40-46, 2003

Results from the Prostate Cancer Results Study Group

Low Risk

(NCCN and D'Amico) - PSA < 10.0
And Gleason Score < 7
cT1c-T2a

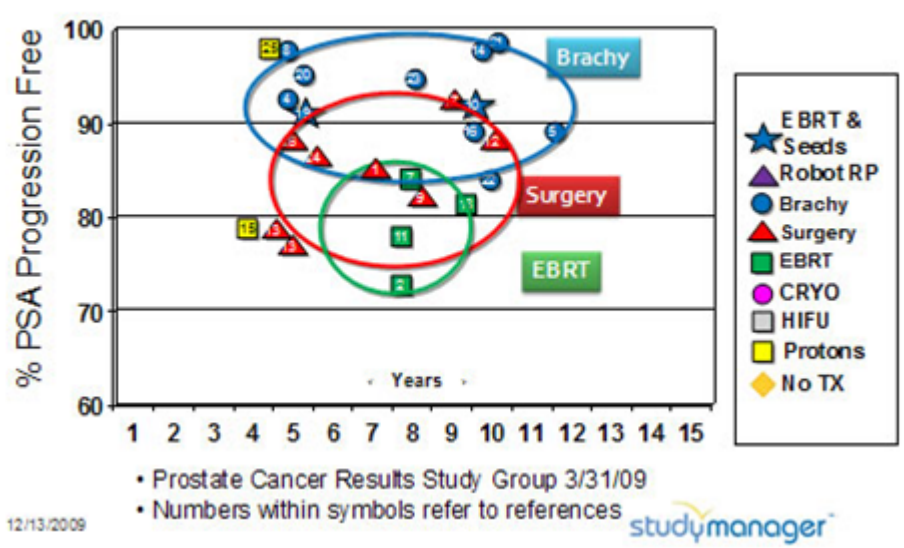
Intermediate Risk

NCCN - PSA > 10.0 < 20.0
And/Or Gleason = 7
And/Or cT2b-c
D'Amico - PSA > 10.0 < 20.0
And/Or Gleason = 7
And/Or cT2b

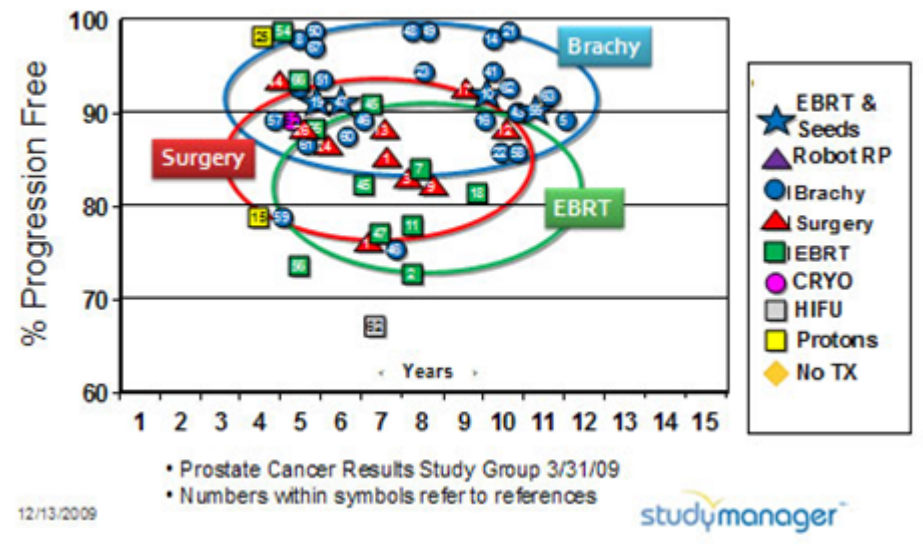
High Risk

NCCN - PSA > 20.0
And/Or Gleason 8-10
And/Or cT3
Or 2 or More Intermediate Risk Features
D'Amico - PSA > 20.0
And/Or Gleason 8-10
And/Or cT2c-T3

Low Risk PCSG Criteria



Low Risk > 40 mo Med F/U or < 100 pts



PCRSG , P.Grimm et al : 2009

Low Risk

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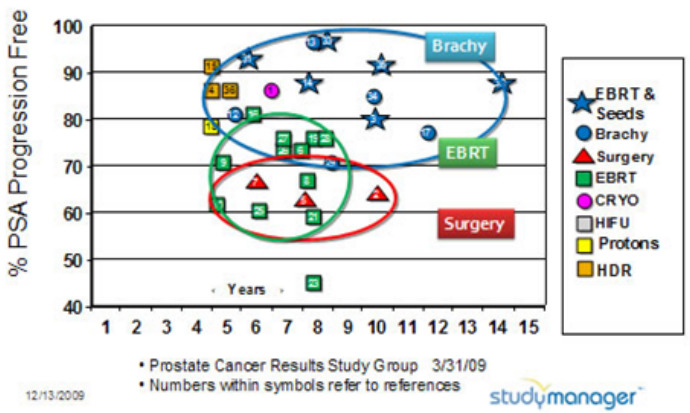
D'Amico - PSA > 10.0 < 20.0
And/Or Gleason = 7
And/Or cT2b

High Risk

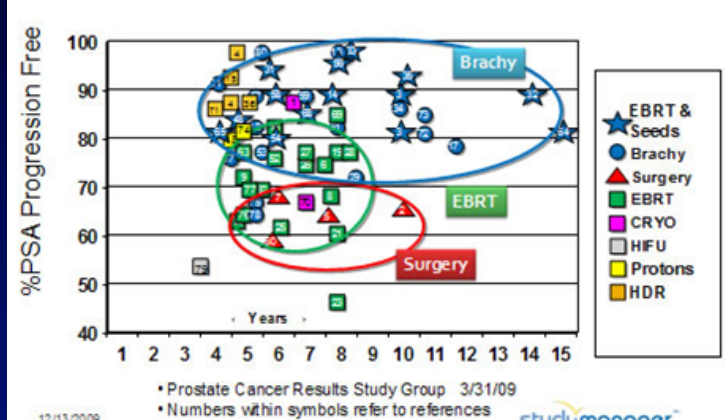
NCCN - PSA > 20.0
And/Or Gleason 8-10
And/Or cT3
Or 2 or More Intermediate Risk Features
D'Amico - PSA > 20.0
And/Or Gleason 8-10
And/Or cT2c-T3

PCRSG , P.Grimm et al : 2009

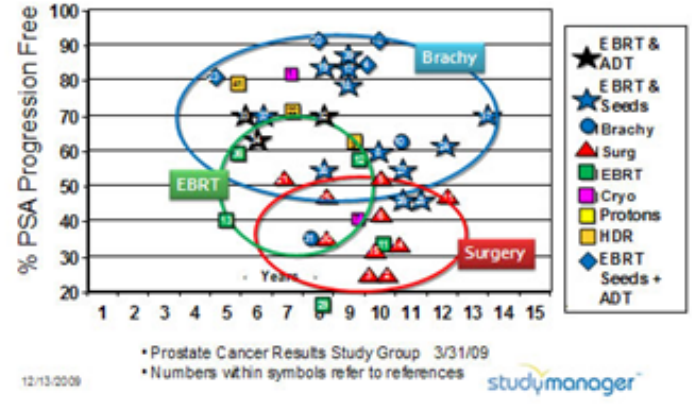
Intermediate Risk PCRSG Criteria



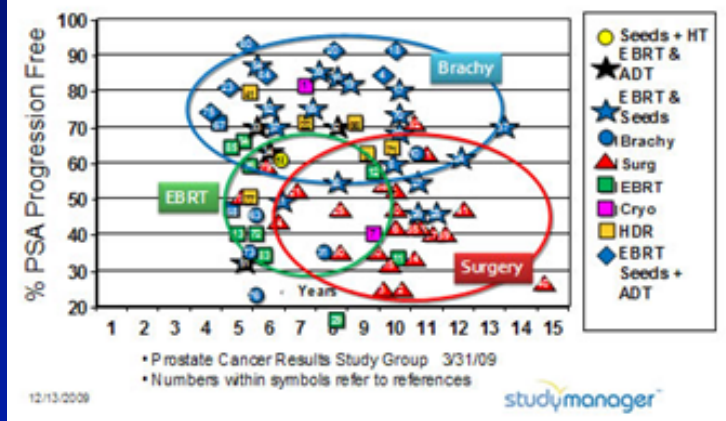
Int. Comparison >40 mo Med F/U or <100 pts

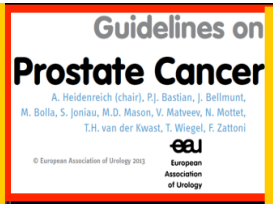


High Risk PCRSG Criteria



High Risk >40 mo Med F/U or <50 pts

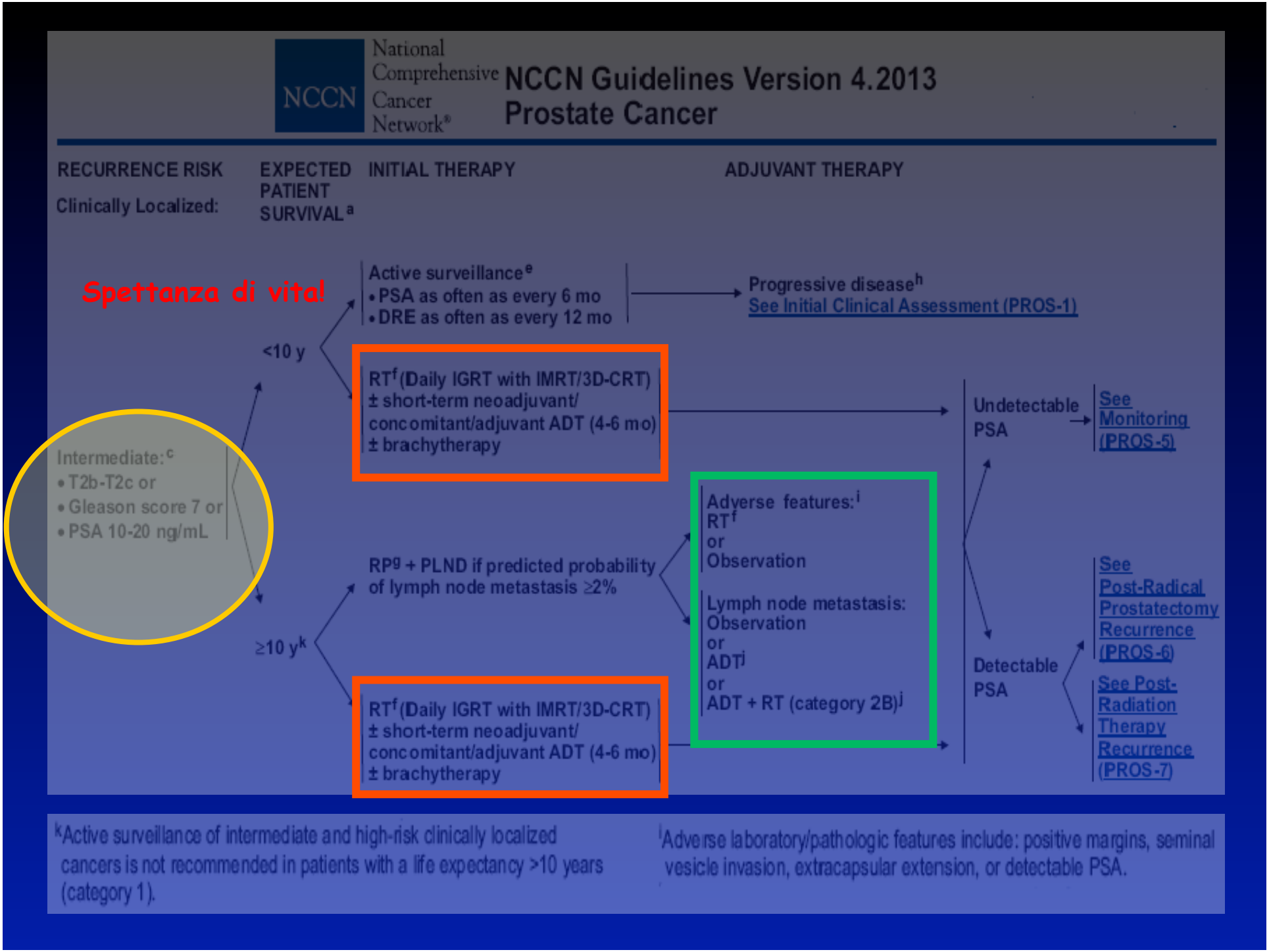




T1a-T2c	Radical prostatectomy	Optional in patients with pT1a PCa.	A
		Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.	
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications.	B
		Patients with contraindications for surgery.	
		Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below).	
	Brachytherapy	Low-dose rate brachytherapy can be considered for low risk PCa patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.	B
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.	C
		Anti-androgens are associated with a poorer outcome compared to 'active surveillance' and are not recommended.	A
	Combination	For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A
T3- T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately-differentiated tumours, and a life expectancy < 10 years who are unfit for local treatment.	C
	Radical prostatectomy	Optional for selected patients with T3a, PSA < 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy > 10 years.	C
		Patients have to be informed that RP is associated with an increased risk of positive surgical margins, unfavourable histology and positive lymph nodes and that, therefore, adjuvant or salvage therapy such as radiation therapy or androgen deprivation might be indicated.	
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation of > 74 Gy seems to be of benefit. A combination with hormonal therapy can be recommended (see below).	A
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSA-Doubling Time (DT) < 1 year.	A
		Patient-driven, unfit patients.	
		Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.	
	Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation.	A
		NHT plus radical prostatectomy: no indication.	B

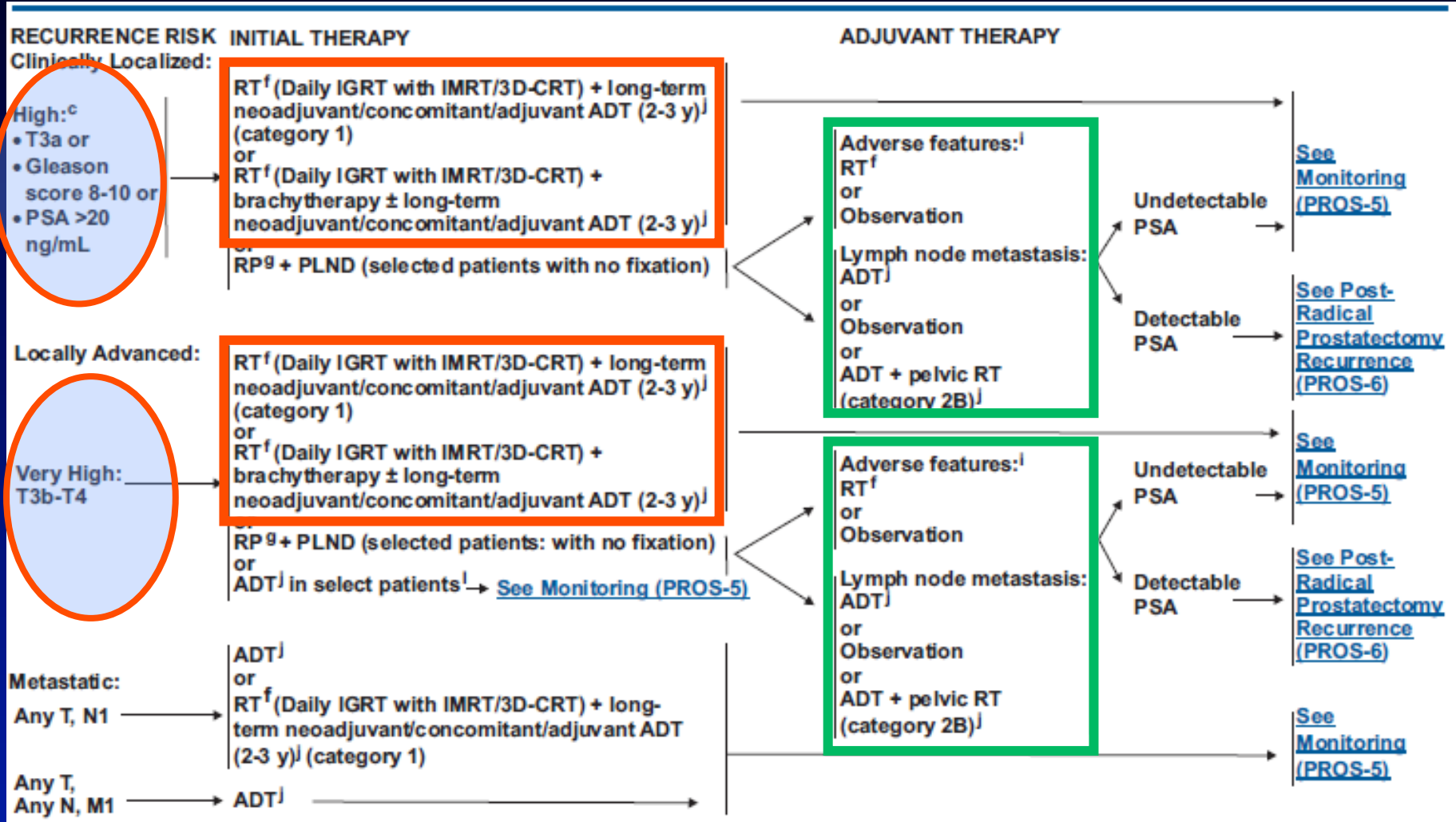
T 1-2

T 3-4


NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 4.2013
Prostate Cancer
RECURRENCE RISK
Clinically Localized:
EXPECTED PATIENT SURVIVAL[a]
INITIAL THERAPY
ADJUVANT THERAPY
Spettanza di vita!
Intermediate:[c]
• T2b-T2c or
• Gleason score 7 or
• PSA 10-20 ng/mL
<10 y
≥10 y[k]
Active surveillance[e]
• PSA as often as every 6 mo
• DRE as often as every 12 mo
Progressive disease[h]
See Initial Clinical Assessment (PROS-1)
RT[f] (Daily IGRT with IMRT/3D-CRT)
± short-term neoadjuvant/
concomitant/adjuvant ADT (4-6 mo)
± brachytherapy
RP[g] + PLND if predicted probability of lymph node metastasis ≥2%
RT[f] (Daily IGRT with IMRT/3D-CRT)
± short-term neoadjuvant/
concomitant/adjuvant ADT (4-6 mo)
± brachytherapy
Adverse features:[i]
RT[f]
or
Observation
Lymph node metastasis:
Observation
or
ADT[j]
or
ADT + RT (category 2B)[j]
Undetectable PSA
See Monitoring (PROS-5)
Detectable PSA
See Post-Radical Prostatectomy Recurrence (PROS-6)
See Post-Radiation Therapy Recurrence (PROS-7)
[k]Active surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).
[i]Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

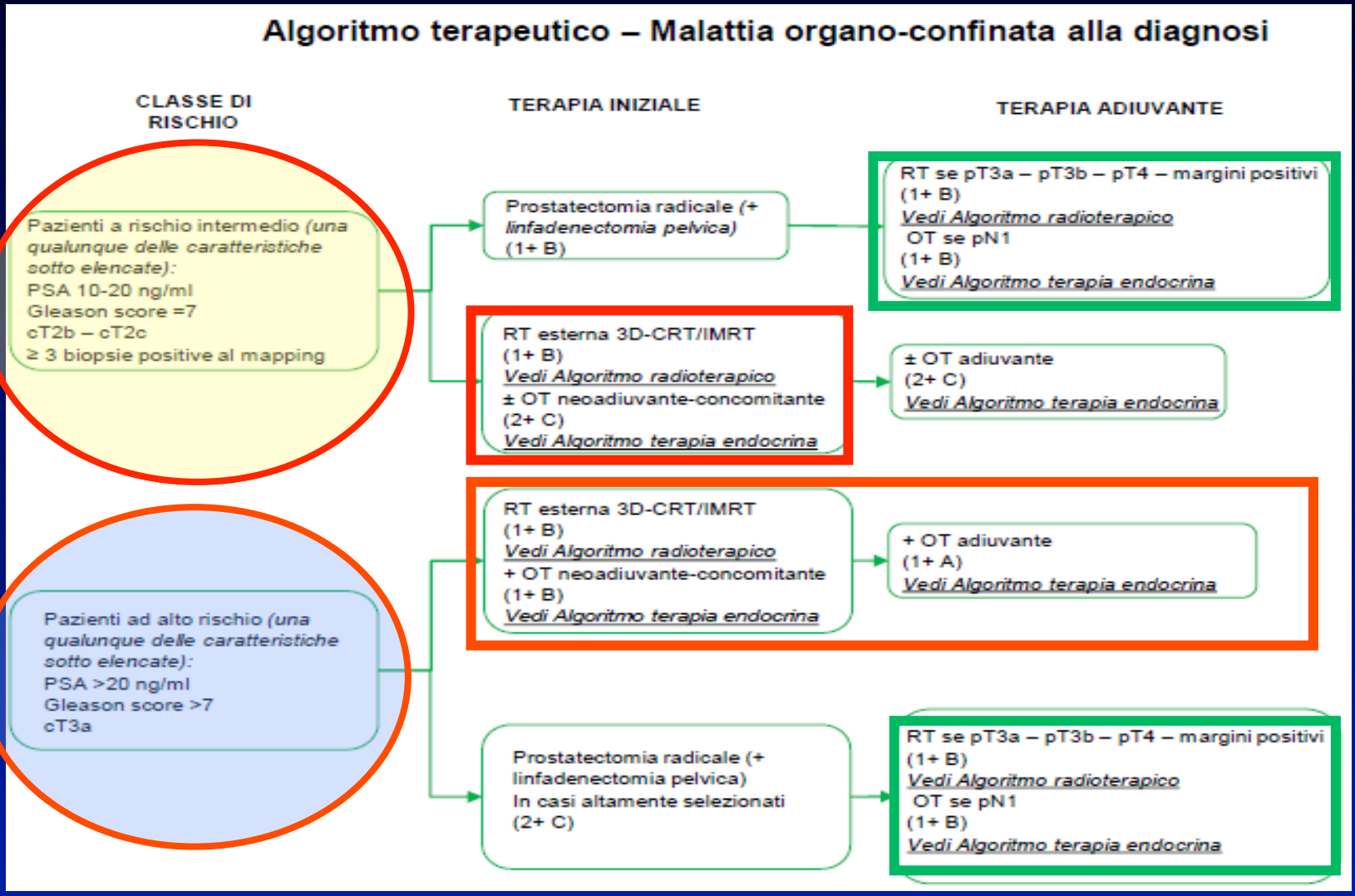
National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2013
Prostate Cancer



AIOM 2012

Sempre 1+B per la RT



CHIRURGIA

EAU 2013 : raccomandazioni per Prostatectomia Radicale

Indications	LE
In patients with low and intermediate risk localised PCa (cT1a-T2b and Gleason score 2-7 and PSA ≤ 20 ng/mL) and life expectancy > 10 years.	1b
Optional	
Patients with stage T1a disease and a life expectancy >15 years or Gleason score 7.	3
Selected patients with low-volume, high-risk, localised PCa (cT3a or Gleason score 8-10 or PSA > 20 ng/mL).	3
Highly selected patients with very-high-risk, localised PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.	3
Short-term (3 months) or long-term (9 months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is NOT recommended for the treatment of stage T1-T2 disease.	1a
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables/nomograms).	3
Unilateral nerve-sparing procedures are an option in stage T2a-T3a disease.	4

Complication	Incidence (%)
• Peri-operative death	0.0-2.1
• Major bleeding	1.0-11.5
• Rectal injury	0.0-5.4
• Deep venous thrombosis	0.0-8.3
• Pulmonary embolism	0.8-7.7
• Lymphocoele	1.0-3.0
• Urine leak, fistula	0.3-15.4
• Slight stress incontinence	4.0-50.0
• Severe stress incontinence	0.0-15.4
• Impotence	29.0-100.0
• Bladder neck obstruction	0.5-14.6
• Ureteral obstruction	0.0-0.7
• Urethral stricture	2.0-9.0

- **Intermediate-risk, localised PCa: cT2b-T2c or GPS = 7 or PSA 10-20 ng/mL** : patients should be informed about the results of two randomised trials:
  - PCG-4 study: the survival benefit was confined to men < 65 years of age. The number needed to treat to avert one death was 15 overall and seven for men < 65 years of age.
  - PIVOT-trial: in men with intermediate-risk tumours, RP did significantly reduce all-cause mortality.
- **High-risk localised and loc.advanced Pca: cT3a or GPS 8-10 or PSA > 20 ng/mL**: no consensus regarding the optimal treatment (management decisions should be discussed by a multidisciplinary and pts).

Prostate Intervention Versus Observation Trial
PIVOT Trial

- 731 pazienti reclutati dal 1994 al 2002
- Prostatectomia radicale vs. Watchful Waiting o Active monitoring
- Risultati a 12 aa **(non differenze in mortalità : differenza assoluta 1%)**

Low Risk Prostate Cancer

"In men with low risk prostate cancer, disease mortality occurred in less than 3% and did not differ between radical prostatectomy and observation" (HR=1.48; ARR=1.4, P=0.54). **This favored observation**."

High Risk Prostate Cancer

"Among men with high risk tumors, prostate cancer mortality occurred in approximately 13%. Radical prostatectomy produced a 60% relative risk reduction (HR = 0.4, ARR = 8.4) **of borderline significance** (P=0.04).

Intermediate Risk Prostate Cancer

"Among men with intermediate risk prostate cancer, we found **a non-significant reduction** of 4.6%."

T.J. Wilt: EAU Congeress, Parigi, 6 marzo 2012
T.J.Wilt et al. NEJM: luglio 19: 2012

EAU 2013 :
Raccomandazioni per la PR, extended LND nell'alto rischio

RP is a reasonable treatment option in selected patients with cT3a PCa, Gleason score 8-10 or PSA > 20. Furthermore, RP is optional in highly selected patients with cT3b-4 N0 or any cT N1 PCa in the context of a multimodality approach.
Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.
If RP is performed, pelvic eLND must be performed, because lymph node involvement is common.
The patient must be informed about the likelihood of a multimodal approach. In case of adverse tumour characteristics (positive section margin, extraprostatic extension, or seminal vesicle invasion), adjuvant radiotherapy may reasonably be used after recuperation from surgery.
When nodal involvement is detected after surgery, adjuvant ADT may be selected.
Extended LND is not necessary in low-risk, localised PCa, because the risk for positive lymph nodes does not exceed 5%.
Extended LND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 5%, as well as in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15-40%.
Limited LND should no longer be performed, because it misses at least half the nodes involved.

Ext. LND: includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal ileac artery. (a mean of 20 lymph nodes should be removed)

CHIRURGIA in IR – HR

VANTAGGI

- Accurata valutazione patologica
- Follow – up biochimico con PSA meno ambiguo
- Possibilità di attuare radioterapia di salvataggio

SVANTAGGI

- Incontinenza urinaria nel 2-5% dei casi a 6 mesi dalla chirurgia
- Impotenza nel 10-90% (media 30%)
- Rischi operatori

Il ca. prostatico non sempre è confinato alla ghiandola: **30 – 50%** degli adenoca. IR – HR di nuova diagnosi ***si estendono oltre la capsula*** o ai linfonodi

D. Boehmer et al. / Radiotherapy and Oncology 79 (2006) 259-269

Il rischio di recidiva in pazienti con margini positivi e ECE^+ è > 50% e la RTT adiuvante può ridurre il rischio del 30-50%.

15-Year b-NED (%) in Men Treated with Radical Prostatectomy in the PSA era

(adapted from Mullins)

Pathology Finding	Pathological Gleason Score		
	3 + 3	3 + 4	≥ 4 + 3
Organ-confined	99	86	79
No EPE; Margin +	94	75	67
EPE; Margin -	89	72	41
EPE; Margin +	75	45	27 (at 14 years)
SVI	39	39	15

Recidiva biochimia in IR e HR :

SV+ : 60 - 85%

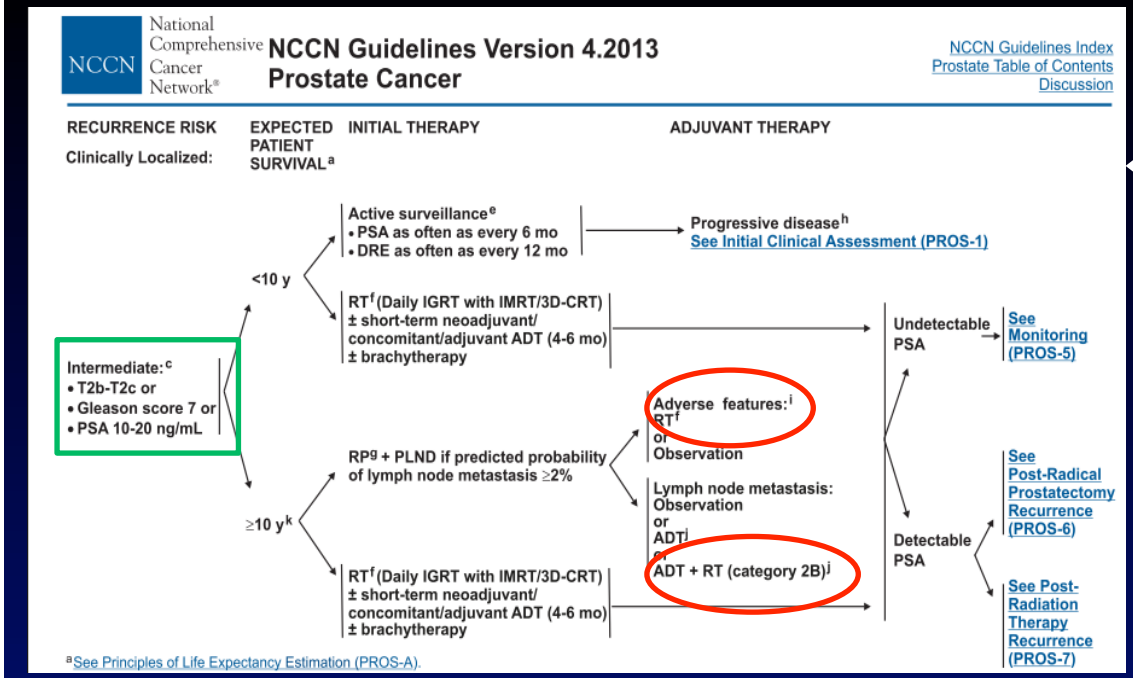
M+ : 25 – 33%

ECE+ : 65 – 72%

I.M. Thompson et al.: THE JOURNAL OF UROLOGY 2013

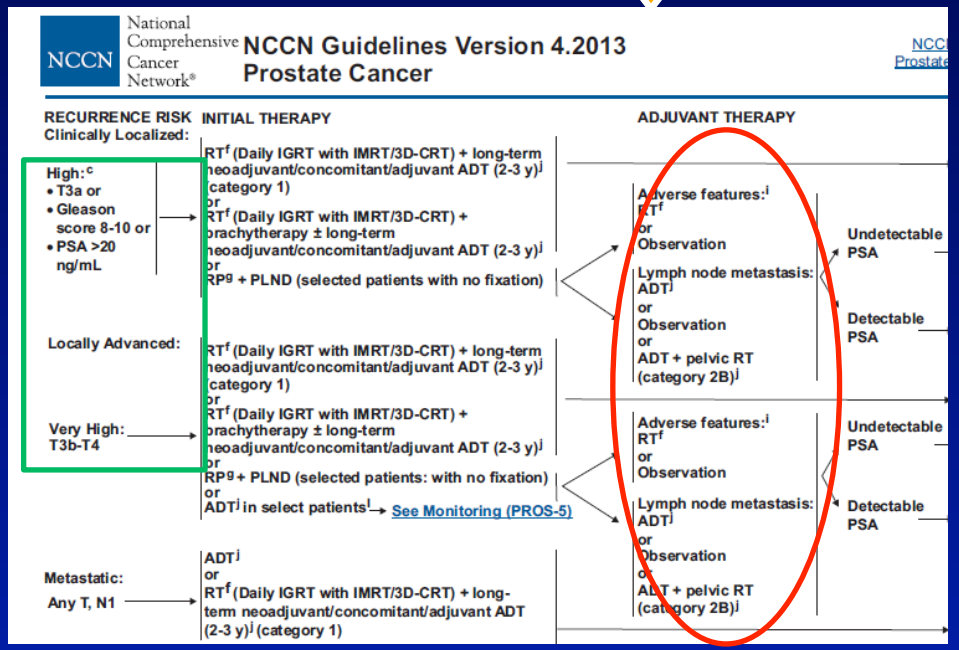
RT POST-OPERATORIA

ADIUVANTE O DI NECESSITA'?



Rischio Intermedio

Rischio Alto



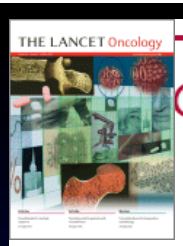
Fattori prognostici negativi :

- Margini Chirurgici +
- Interessamento VS
- Estensione Extracapsulare
- Non azzeramento del PSA

European Association of Urology

EAU 2013

	LE	GR
In localised prostate cancer, T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended, even for young patients who decline surgical intervention.	1b	B
For high-risk patients, long-term ADT before and during radiotherapy is recommended, as it results in increased overall survival.	2a	B
In patients with locally advanced prostate cancer (T3-4, N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.	1b	A
In patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.	2a	B
In patients with pathological tumour stage T3 N0 M0, immediate postoperative external irradiation after RP may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.	1b	A
In patients with pathological tumour stage T2-3 N0 M0, salvage irradiation is indicated in case of persisting PSA or biochemical failure, but before the PSA level rises above 0.5 ng/mL.	3	B
In patients with locally advanced prostate cancer, T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.	1b	A



Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911)

Michel Bolla, Hein van Poppel, Bertrand Tombal, Kris Vekemans, Luigi Da Pozzo, Theo M de Reijke, Antony Verbaeys, Jean-François Bosset, Roland van Velthoven, Marc Colombel, Cees van de Beek, Paul Verhagen, Alphonsus van den Bergh, Cora Sternberg, Thomas Gasser, Geertjan van Tienhoven, Pierre Scalliet, Karin Haustermans, Laurence Collette, for the European Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups

- PR+ W&S (RTT di salvataggio o OT) vs PR+ RT postop. entro 16 sett.
- Ruolo della RTT adiuvante in cT0-3 N0-M0 (cT_{0-2} : 83%), pT2-3 N0 con fattori di rischio:
  - Superamento capsulare (26%)
  - Margini + (16%)
  - V+ (4%)
  - Più di un fattore (54%)
- 1005 pazienti (503 wait and see ; 502 RTT); età 61 – 69 aa :
  - RTT su loggia prostatica(vesc. – apice), 50 Gy + 10 Gy di boost su R1-x
  - Tecnica a 4 campi, X da 5 – 25 MV
  - Inizio RT : 90 gg dopo chirurgia
  - Durata RT : 44 gg
  - Dose prevista per RTT di salvataggio nel gruppo W&S : 70 Gy

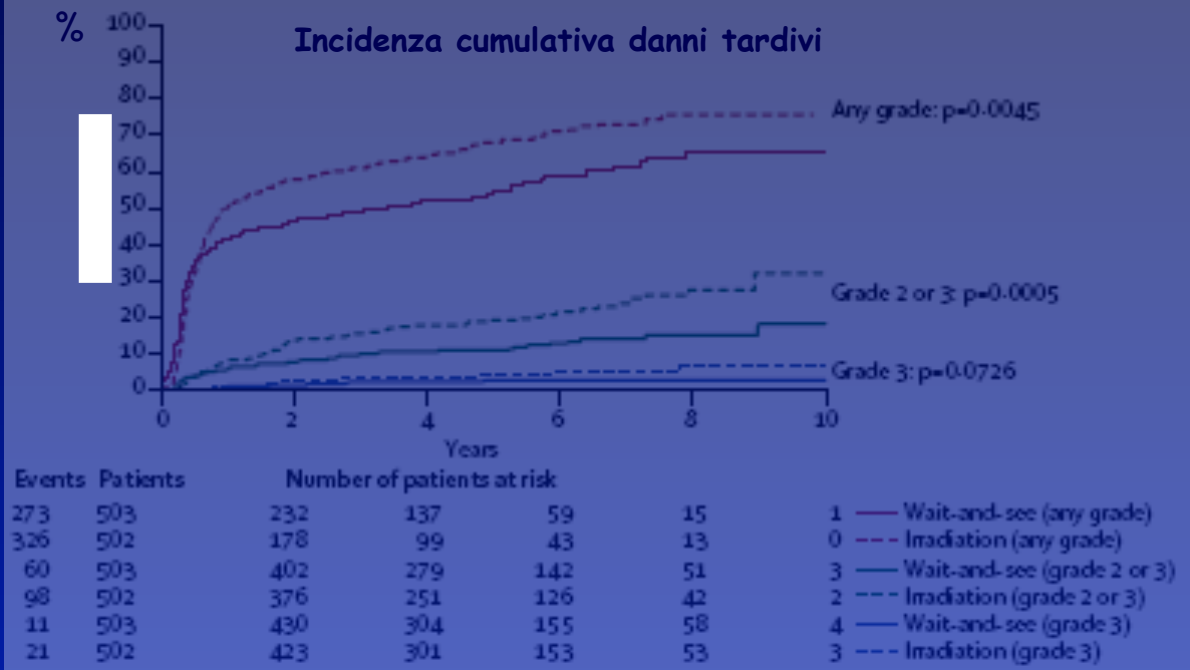
(M. Bolla et al : The Lancet Oncol 2013)

EORTC 22911 : TOSSICITA'

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Nausea or vomiting	434 (95·0%)	19 (4·2%)	1 (0·2%)	0 (0·0%)	0 (0·0%)	3 (0·7%)
Diarrhoea	174 (38·1%)	175 (38·3%)	81 (17·7%)	24 (5·3%)	0 (0·0%)	3 (0·7%)
Frequency passage of urine	151 (33·0%)	205 (44·9%)	79 (17·3%)	15 (3·3%)	2 (0·4%)	5 (1·1%)
Dysuria	229 (50·1%)	173 (37·9%)	47 (10·3%)	5 (1·1%)	0 (0·0%)	3 (0·7%)
Skin	279 (61·1%)	144 (31·5%)	29 (6·3%)	2 (0·4%)	0 (0·0%)	3 (0·7%)
Haematuria	433 (94·7%)	17 (3·7%)	4 (0·9%)	0 (0·0%)	0 (0·0%)	3 (0·7)

Data are number (%) of 457 patients in irradiation group who were actually irradiated.

Table 2: Adverse effects from acute radiation



Acuta

Tardiva a 10 aa

	W&S	RT
GU G3	2,5%	5,3%
GI G2	1,9%	2,5%
Sten. uretr.	1,4%	1,4%

(M. Bolla et al : Lancet 2005 e 2012)

Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911)

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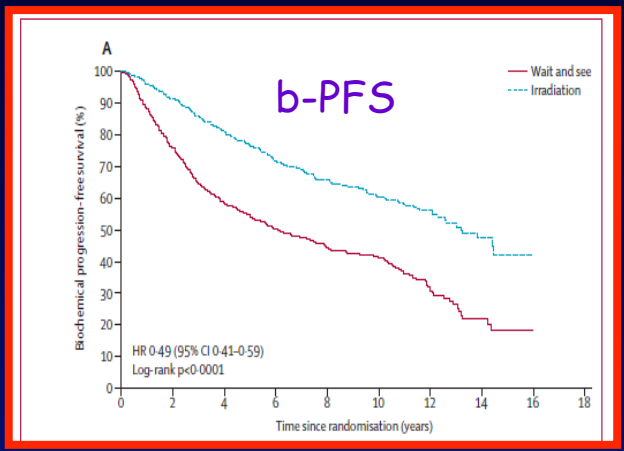
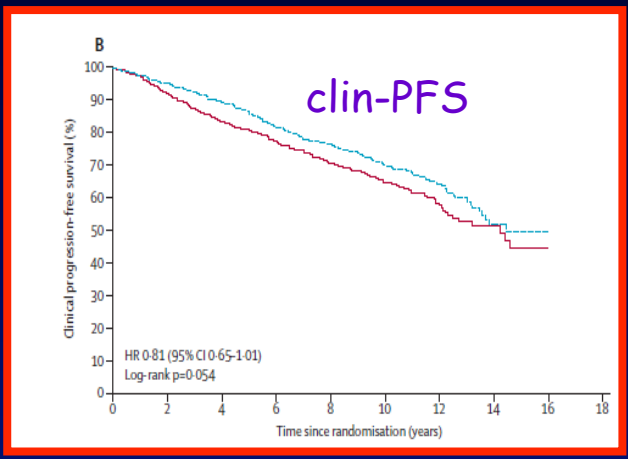
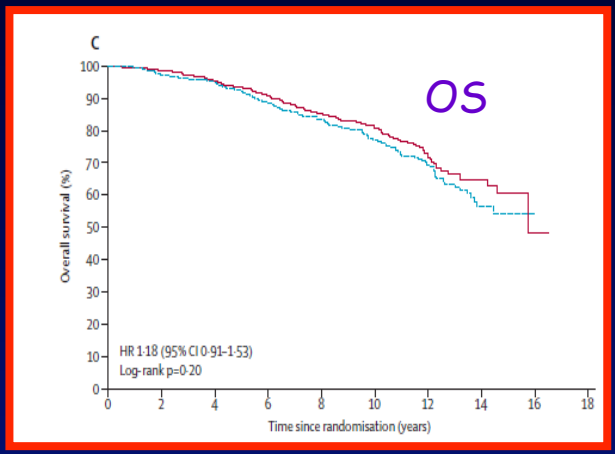






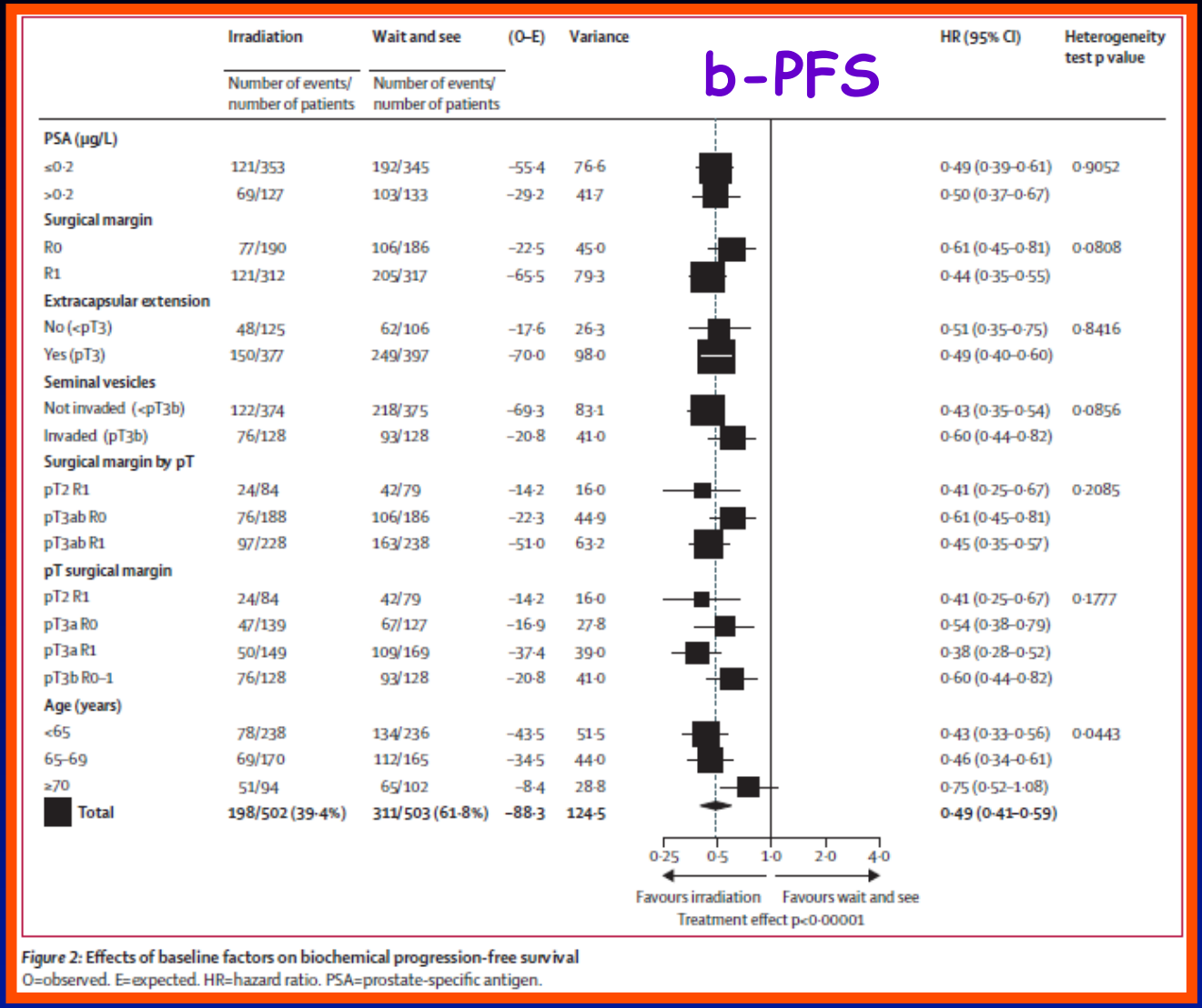
Endpoint a 5 anni	W&S	ART	HR	p
bPFS	52%	74%	0.48	0,0001
cPFS	81%	91%	0,6	0,0001
Distant failure	6,3%	6,1%	1	0,6
OS	92%	93%	1	-

HR variabili da 0,45 – 0,66 a favore della RTT

M. Bolla : Lancet 2005

M. Bolla et al : The Lancet Oncol 2013

EORTC 22911 : Risultati in funzione dei fattori prognostici



	Irradiation	Wait and see	(O–E)	Variance	HR (95% CI)	Heterogeneity test p value
	Number of events/ number of patients	Number of events/ number of patients				
PSA (µg/L)						
≤0·2	121/353	192/345	−55·4	76·6	0·49 (0·39–0·61)	0·9052
>0·2	69/127	103/133	−29·2	41·7	0·50 (0·37–0·67)	
Surgical margin						
R0	77/190	106/186	−22·5	45·0	0·61 (0·45–0·81)	0·0808
R1	121/312	205/317	−65·5	79·3	0·44 (0·35–0·55)	
Extracapsular extension						
No (<pT3)	48/125	62/106	−17·6	26·3	0·51 (0·35–0·75)	0·8416
Yes (pT3)	150/377	249/397	−70·0	98·0	0·49 (0·40–0·60)	
Seminal vesicles						
Not invaded (<pT3b)	122/374	218/375	−69·3	83·1	0·43 (0·35–0·54)	0·0856
Invaded (pT3b)	76/128	93/128	−20·8	41·0	0·60 (0·44–0·82)	
Surgical margin by pT						
pT2 R1	24/84	42/79	−14·2	16·0	0·41 (0·25–0·67)	0·2085
pT3ab R0	76/188	106/186	−22·3	44·9	0·61 (0·45–0·81)	
pT3ab R1	97/228	163/238	−51·0	63·2	0·45 (0·35–0·57)	
pT surgical margin						
pT2 R1	24/84	42/79	−14·2	16·0	0·41 (0·25–0·67)	0·1777
pT3a R0	47/139	67/127	−16·9	27·8	0·54 (0·38–0·79)	
pT3a R1	50/149	109/169	−37·4	39·0	0·38 (0·28–0·52)	
pT3b R0–1	76/128	93/128	−20·8	41·0	0·60 (0·44–0·82)	
Age (years)						
<65	78/238	134/236	−43·5	51·5	0·43 (0·33–0·56)	0·0443
65–69	69/170	112/165	−34·5	44·0	0·46 (0·34–0·61)	
≥70	51/94	65/102	−8·4	28·8	0·75 (0·52–1·08)	
Total	**198/502 (39·4%)**	**311/503 (61·8%)**	**−88·3**	**124·5**	**0·49 (0·41–0·59)**	

b-PFS

0·25 0·5 1·0 2·0 4·0

Favours irradiation Favours wait and see

Treatment effect p<0·00001

Figure 2: **Effects of baseline factors on biochemical progression-free survival**
O=observed. E=expected. HR=hazard ratio. PSA=prostate-specific antigen.

HR variabili da 0,41 – 0,75 a favore della RTT

(M. Bolla et al : The Lancet Oncol 2012)

RT postoperatoria : RCT

Inclusion criteria for the three randomised controlled trials for adjuvant radiation therapy

	n	TNM	Patients with a PSM at prostatectomy, %	Patients with a postoperative PSA >0.2 ng/ml, %	Interval of prostatectomy to adjuvant RT, d	Dose of adjuvant radiation, Gy
ARO-96-02 [5]	307	pT3N0	68	0	81	60
EORTC-22911 [3]	1005	pT2R1–pT3N0	63	11	112	60
SWOG-S8794 [4]	431	pT3N0	67 (with EC)	16	<122	60–64

PSM = positive surgical margin; PSA = prostate-specific antigen; RT = radiation therapy; EORTC = European Organisation for Research and Treatment of Cancer; SWOG = Southwest Oncology Group; EC = extracapsular disease.

Follow-up data for the three randomised controlled trials for adjuvant radiation therapy

	n	Primary end point	Median follow-up, mo	Definition of BCR (PSA, ng/ml)	BCR for adjuvant and control arms, yr	Metastasis development, y	OS
ARO-96-02 [5]	307	BCR	54	0.1	5 (28% vs 46%)	2% vs 3.1%	–
EORTC-22911 [3]	1005	BCR	60	0.2	5 (21% vs 44%)	5 (6.1% vs 6.3%)	90.8% vs 91.5%
SWOG-S8794 [4]	431	Metastasis-free survival	152	0.4	10 (47% vs 70%)	10 (27% vs 35%)	10 (74% vs 66%)

BCR = biochemical recurrence; PSA = prostate-specific antigen; OS = overall survival; EORTC = European Organization for Research and Treatment of Cancer; SWOG = Southwest Oncology Group.

Nel ca. localmente avanzato la RT Adiuvante migliora bNED (+ 20 - 30%) in 3 trial e la Met.FS (+ 8%) in uno studio; Vantaggi più evidenti in Marg. +

La RT di salvataggio dopo ripresa biochimica o recidiva locale è ancora valida in particolare in pazienti con rapido aumento del PSA prima della RT

(RT prima che il PSA raggiunga il valore di **2ng/ml**; in corso studi per PSA < **0,2ng/ml**)

H.G. van der Poel: Eur. Urol 2010

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer

Methodologic quality of eligible trials.

Trial Characteristic	EORTC 22911	SWOG 8794		German Cancer Society ARO 96-02 and AUO AP 09/95	
	Bolla 2005 (6)	Thompson 2006 (10)	*Thompson 2009 (17)*	Wiegel 2007 (14)	*Wiegel 2009 (18)*
Random allocation	Yes	Yes	*Same*	Yes	*Same*
Allocation concealment	Yes	Yes	*Same*	Unclear	Yes
Description of withdrawals	Yes	Yes	*Same*	Unclear	Yes
Intention-to-treat analysis	Yes	Yes	*Same*	No	Yes

Pathologic characteristic		Biochemical Progression-Free Survival SWOG, EORTC, ARO/AUO n=1627 Summary HR (95% CI) (27,28)	Overall Survival SWOG 8794 n=416 HR (95% CI) (27,28)
Surgical margin status	Positive	0.45 (0.36-0.57)	0.68 (0.49-0.94)
	Negative	0.61 (0.44-0.85)	0.75 (0.44-1.28)
Extracapsular extension	Present	0.50 (0.41-0.60)	0.62 (0.46-0.84)
	Absent	0.49 (0.31-0.75)	1.32 (0.66-2.63)
Seminal vesicle invasion	Present	0.52 (0.40-0.68)	0.57 (0.35-0.93)
	Absent	0.47 (0.37-0.60)	0.78 (0.55-1.10)

Abbreviations: CI - confidence interval; EORTC - European Organization for the Research and Treatment of Cancer; HR - hazard ratio; NR - not reported; SWOG - Southwest Oncology Group.

HR in presenza di fattore rischio : per BF= 0,36 – 0,85; OS= 0,35 – 0,95

Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

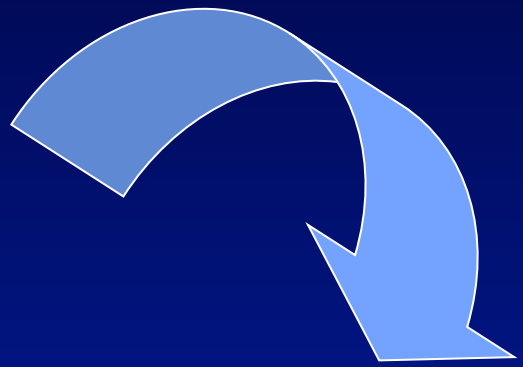
Ian M. Thompson,* Richard K. Valicenti,* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the American Society for Radiation Oncology, Fairfax, Virginia

"A systematic review identified articles relevant to the use of RT after prostatectomy as adjuvant or salvage therapy"
(SWOG 8794, EORTC 22911 and ARO 96-02,....)

Definitions

Adjuvant radiotherapy is the administration of radiotherapy post-prostatectomy to patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence (i.e., with an undetectable PSA). Salvage radiotherapy is the administration of radiotherapy to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patient with a PSA recurrence after surgery but no evidence of distant metastatic disease. Biochemical (PSA) recurrence after surgery is defined as a detectable PSA level >0.2 ng/ml with a second confirmatory level >0.2 ng/ml.



In the Panel's view, 64–65 Gy is the minimum dose that should be delivered post-RP but decisions regarding dose should be made by the treating physician who has full knowledge of the patient's functional status, history and toxicity tolerance.

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Acute Toxicity Effects of Radiotherapy After Prostatectomy

(Ranges based on RTOG or CTCAE Grading Systems)				
	Genitourinary		Gastrointestinal	
Study Arm Type	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Adjuvant	10.5 - 26%	2.0 - 8.0%	22.0 – 25.0%	0.0 – 2.0%
Salvage	3.0 - 82.0%	0.0 – 6.0%	2.9 – 96.0%	0.0 – 2.2%
Mixed	5.0 – 92.0%	0.0 – 3.0%	4.3 – 87.0%	0.0 – 1.3%

Late Toxicity Effects of Radiotherapy After Prostatectomy

(Ranges based on RTOG/EORTC or CTCAE Grading Systems)				
	Genitourinary		Gastrointestinal	
Study Arm Type	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Adjuvant	2.0 – 22.0%	0.0 - 10.6%	1.0 – 12.7%	0.0 – 6.7%
Salvage	1.0 – 49.0%	0.0 – 6.0%	0.0 – 66.0%	0.0 – 18.0%
Mixed	1.3 – 79.0%	0.0 – 17.0%	2.0 – 59.0%	0.0 – 4.3%

Tossicità acuta e tardiva sovrapponibili

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Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

Ian M. Thompson,* Richard K. Valicenti,* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the American Society for Radiation Oncology, Fairfax, Virginia

- **Pts with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant RT, compared to radical prostatectomy only, reduces the risk of PSA recurrence, local recurrence, and clinical progression of cancer.**

- **They should also be informed that the impact of adjuvant RT on subsequent metastases and OS is less clear; one of two RCTs that addressed these outcomes indicated a benefit but the other trial did not demonstrate a benefit»**

(Clinical Principle)

Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including SV+, M+, ECE+ because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression»

(Standard; Evidence Strength: Grade A)

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C'è altro da affrontare ?

...Si !!

STUDIO RTOG 8531 (fase III)
RTT o RT POST-OPERATORIA CON LHRH

(M. Pilepich Int.J. Radiat.Oncol.Biol.Phys. 1999)

valutabili 945 / 977 pazienti reclutati
follow up medio 5.6 aa ; sopravvivenza a 5 aa
T3 , N+, post-prostatectomia con margini chirurgici positivi e SV+
RT vs RT+ Goserelin , in adiuvante a lungo termine

GRUPPI	rec. L.	Met	NED	bNED (PSA <1.5)	OS
RT	31%	29%	44%	21% (42%)	71%
RT+ORM	15%	15%	62%	54% (65%)	75%
Val. p	.001	.001	.001	.001 (0.002)	N.S.

Globalmente : chiaro vantaggio su controllo locale e M1 ma nessun vantaggio in sopravvivenza , bruta e determinata

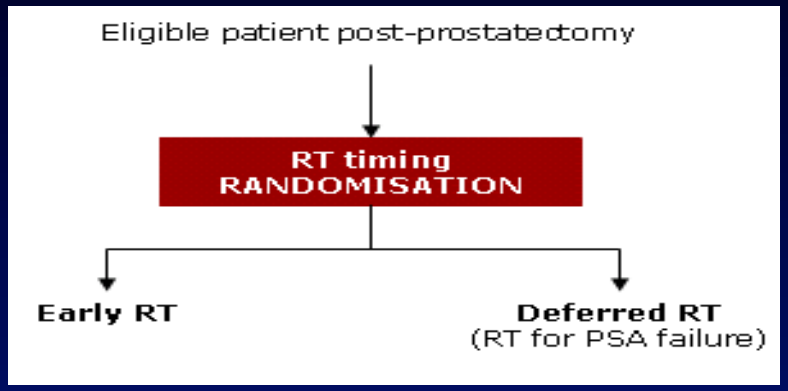
Sottogruppo RT postop. (139/977): differenze solo per bNED (****)

RT postop: ongoing trial:

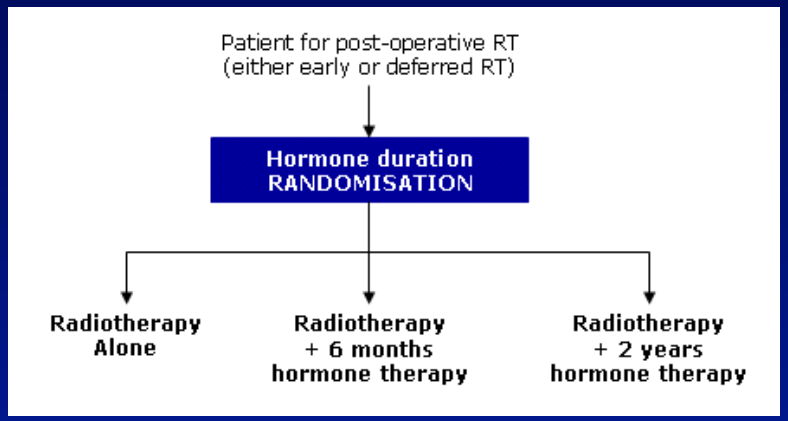
NMRC - NCT00541047 (RADICALS) chiusura prevista (1/11/2013 ?)

Radiotherapy and **A**ndrogen **D**eprivation **I**n **C**ombination **A**fter **L**ocal **S**urgery

Protocol ID	Title and details of trial
MRC-RADICALS-PR10	Phase III randomized study of immediate vs. early salvage radiotherapy (RT) and short- vs. long-term androgen deprivation therapy in patients who have undergone local surgery for non-metastatic adenocarcinoma of the prostate. Treatment groups: Arm I - immediate RT; Arm II - early salvage RT in case of PSA failure; before postoperative RT, patients randomized to one of three hormone therapy (HT) arms: Arm III - no HT; Arm IV - short-term HT; Arm V - long-term HT.



- Elegibili:
  - Post-operative serum PSA ≤0.2ng/ml
  - More than 4 weeks and less than 22 weeks after radical prostatectomy
  - One or more of:
    - pT3/T4
    - Gleason 7-10 (biopsy or surgical sample)
    - Pre-operative PSA ≥10ng/ml
    - Positive margins



- **Due randomizzazioni; 127 centri ; Reclutati (15/7/2013) 2348 / 4000 paz.**
- **HT:** LHRH agonist (gonadotrophin-releasing hormone analogue [GnRHa] [e.g., goserelin or leuprolide acetate]) or bicalutamide daily.

NCI: open 15/10/2013

THE JOURNAL of UROLOGY® American Urological Association Education and Research, Inc.

2013

Health Outcomes Research

Variation in Treatment Recommendations of Adjuvant Radiation Therapy for High-risk Prostate Cancer by Physician Specialty

Simon P. Kim, Jon C. Tilburt, R. Jeffrey Karnes, Jeanette Y. Ziegenfuss, Leona C. Han, Nilay D. Shah, Igor Frank, Marc C. Smaldone, Cary P. Gross, James B. Yu, Quoc-Dien Trinh, Maxine Sun, Rebecca L. O'Malley, and Paul L. Nguyen

Table 2. Adjusted odds ratios in the treatment recommendation of adjuvant radiotherapy from radiation oncologists*,†

Adverse Pathologic Features	OR (95% CI)	*P* Value
pT3a Gleason 7 MN	7.82 (4.85-12.60)	<.001
pT3a Gleason 7 MP	9.40 (5.86-15.07)	<.001
pT3b Gleason 7 MN	1.98 (1.40-2.81)	<.001
pT3b Gleason 7 MP	4.65 (2.54-8.51)	<.001
pT3a Gleason 8-10 MN	3.40 (2.38-4.85)	<.001
pT3a Gleason 8-10 MP	4.18 (2.19-8.00)	<.001
pT3b Gleason 8-10 MN	3.40 (2.38-4.85)	<.001
pT3b Gleason 8-10 MP	2.46 (1.29-4.71)	<.001

Table 3. Adjusted odds ratios in the treatment recommendation of salvage radiotherapy from urologists*,†

Adverse Pathologic Features	OR (95% CI)	*P* Value
pT3a Gleason 7 MN	7.72 (4.79-12.44)	<.001
pT3a Gleason 7 MP	9.52 (5.90-15.36)	<.001
pT3b Gleason 7 MN	1.97 (1.39-2.81)	<.001
pT3b Gleason 7 MP	4.40 (2.40-8.06)	<.001
pT3a Gleason 8-10 MN	3.32 (2.23-4.74)	<.001
pT3a Gleason 8-10 MP	3.81 (1.99-7.39)	<.001
pT3b Gleason 8-10 MN	3.32 (2.32-4.74)	<.001
pT3b Gleason 8-10 MP	2.22 (1.15-4.28)	<.001

- In this national survey, urologists and radiation oncologists differ markedly in the treatment recommendations for adjuvant radiotherapy in prostate cancer with adverse pathologic features.
- Urologists were less likely to recommend adjuvant radiotherapy compared with radiation oncologists.

Patients with adverse pathologic features after radical prostatectomy should consult with both a urologist and radiation oncologist to hear a diversity of opinions to make the most informed decision possible.

PERCHE' NON RADIOTERAPIA ESCLUSIVA ?

Results from the Prostate Cancer Results Study Group

Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy.

TABLE 2 Criteria for inclusion of a study on treatment of localized prostate cancer

- Patients must be stratified into recognizable pretreatment risk groups, low, intermediate and high risk, using D'Amico, Zelefsky or NCCN stratification
- Standard endpoint used to measure biochemical relapse-free survival: ASTRO, Phoenix and PSA < 0.2 ng/mL (for surgery)
- Clinical staging conducted and not pathological staging alone
- EBRT must be minimum 72 Gy IMRT/conformal
- All treatment modalities considered: brachytherapy (including HDR), surgery, IMRT, HIFU, cryotherapy, protons
- Results published in peer-reviewed journals only
- Low risk accepted minimum number of patients was 100
- Intermediate risk accepted minimum number of patients was 100
- High risk accepted minimum number of patients was 50
- Minimum median follow-up was 5 years

NCCN, National Comprehensive Cancer Network; ASTRO, American Society for Radiation Oncology; IMRT, intensity modulated radiotherapy; HDR, high dose rate; HIFU, high intensity focused ultrasound.

TABLE 3 Number of patients in each treatment group and according to risk group category

	No. of patients (no. of studies)		
Treatment type	Low risk	Intermediate	High
RP	6447 (6)	3696 (4)	5149 (11)
Robotic RP	706 (1)	479 (1)	200 (1)
Seeds alone	8133 (17)	5808 (15)	295 (1)
Seeds + EBRT	726 (1)	1554 (6)	2864 (15)
EBRT + seeds + ADT	–	–	1231 (6)
HDR (seeds)	226 (2)	607 (4)	869 (5)
Protons	388 (2)	162 (1)	–
EBRT alone	4735 (9)	2969 (10)	3828 (11)
HIFU	227 (1)	–	–
Cryotherapy	–	175 (1)	357 (2)
Seeds + ADT	–	165 (1)	–

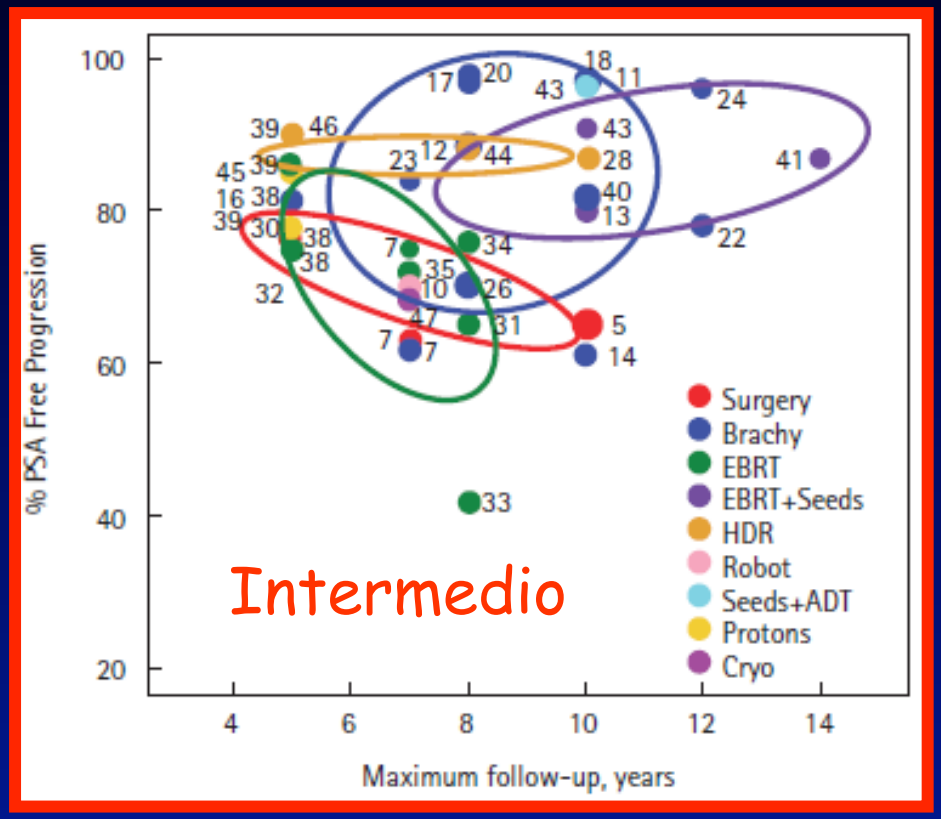
ADT, androgen deprivation therapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiation.

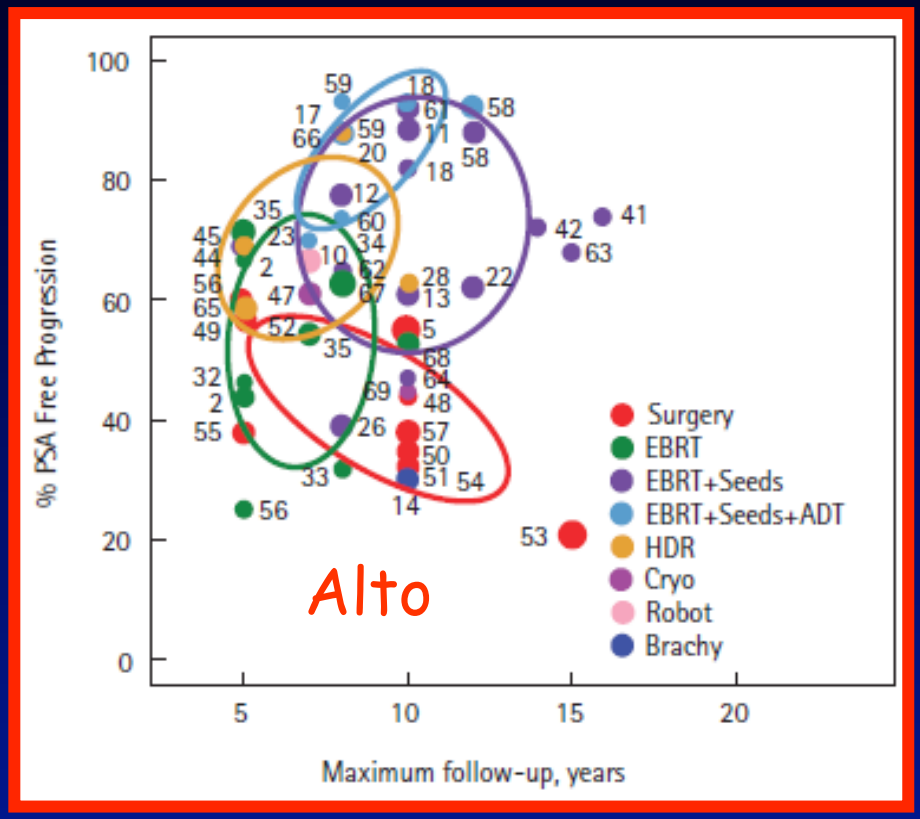
140/ 18000 abstracts→ 52087 pts (30405 IR/HR pts.)

PCRSG criteria was as follows: high intensity focused ultrasound 1/30 (3%); robotic radical prostatectomy 3/59 (5%); radical prostatectomy 24/260 (9%); proton therapy 2/13 (15%); cryotherapy 5/31 (16%); EBRT 39/222 (18%)

P.Grimm et al. : BJUI supp: 1 , 22-29 2012

b-NED





P.Grimm et al. : BJUI supp: 1 , 22-29 2012

Linee guida

QUALE RT PER IR/HR ?

Prostate Cancer Results Study Group

- Risk group definition was uniformly consistent only in the low-risk group. Intermediate- and high-risk group definitions demonstrated some variability.

- In terms of biochemical (PSA) free progression:

  - Brachytherapy approaches provide superior outcome in patients with low-risk disease.

  - EBRT and brachytherapy appear equivalent to brachytherapy alone and appear superior to EBRT or surgery for intermediate-risk disease; however, selection issues may play a large role in outcomes between these treatment options.

  - EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT, **for high-risk patients**

It is unlikely that large randomized studies will be conducted, physicians and patients will rely largely upon the use of retrospective studies to compare treatment results.

P.Grimm et al. : BJUI supp: 1 , 22-29 2012

Guidelines for definitive radiotherapy

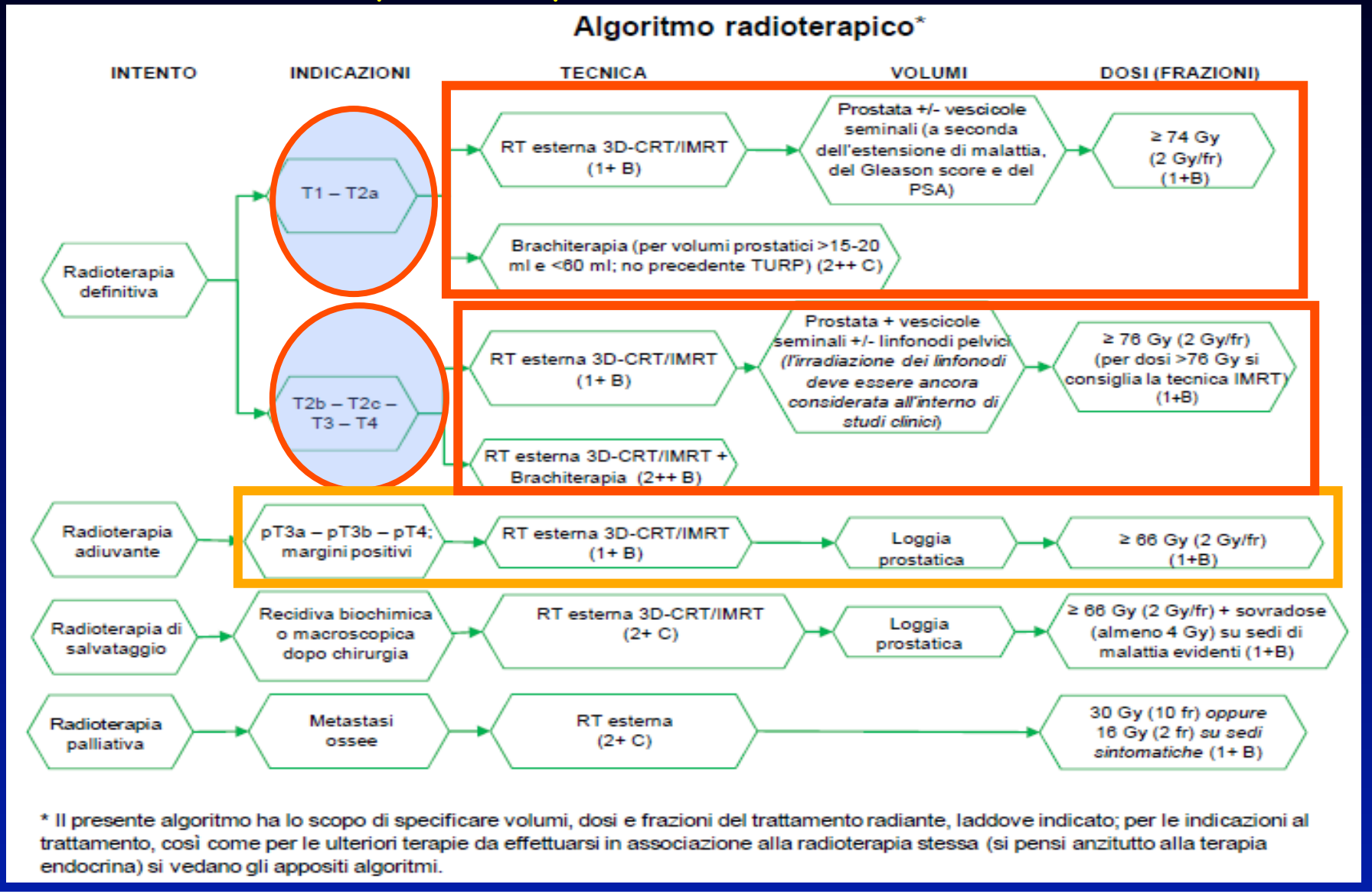
	LE	GR
In localised prostate cancer, T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended, even for young patients who decline surgical intervention.	1b	B
For high-risk patients, long-term ADT before and during radiotherapy is recommended, as it results in increased overall survival.	2a	B
In patients with locally advanced prostate cancer (T3-4, N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.	1b	A
In patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.	2a	B
In patients with pathological tumour stage T3 N0 M0, immediate postoperative external irradiation after RP may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.	1b	A
In patients with pathological tumour stage T2-3 N0 M0, salvage irradiation is indicated in case of persisting PSA or biochemical failure, but before the PSA level rises above 0.5 ng/mL.	3	B
In patients with locally advanced prostate cancer, T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.	1b	A
In a subset of patients with T2c-T3 N0-X and a Gleason score of 2-6, short-term ADT before and during radiotherapy can be recommended, as it may favourably influence the overall survival.	1b	A
In patients with very high-risk prostate cancer, c-pN+ M0, with no severe comorbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended as it will improve overall survival, disease-specific failure rate, metastatic failure rate and biochemical control.	2b	B

CRT = conformal radiotherapy; IMRT = intensity-modulated radiotherapy; ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; PSA = prostate-specific antigen; TURP = transurethral resection of the prostate; IPSS = international prostatic symptom score; RP = radical prostatectomy; TURP = International Prostatic Symptom Score.

per IR/HR:
sempre EBRT (3D-CRT/IMRT)
in assenza di comorbilità

AIOM 2012

Sempre 1+B per la EBRT (3D-CRT/ IMRT)



NCCN 2013 : RT (3D-CRT/IMRT → IGRT)

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2013
Prostate Cancer

PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy (EBRT) :

- 3-D conformal RT or IMRT techniques should be used to treat prostate cancer. IGRT is required if dose is ≥ 78 Gy. IMRT, if available, is preferred.
- Doses of 75.6 to 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 to 3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4 to 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 of IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Treatment results appear better when disease burden is lower. Radiation should be administered before PSA exceeds 0.5 ng/mL.

Primary/Salvage 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 to 6 mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 4 to 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 are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 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 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

ESMO 2012 RT

IMRT +/- IGRT ??: livello III-B

12. Is brachytherapy as effective as external beam radiotherapy in early prostate cancer?

Recommendation 12: Brachytherapy is an effective treatment option for localized prostate cancer

Level of evidence: III

Strength of recommendation: B

13. Are sophisticated radiation planning and delivery techniques required for dose-escalated external beam radiotherapy?

Recommendation 13a: To reduce the adverse effects following radiotherapy, conformal radiotherapy should be used.

Level of evidence: I

Strength of recommendation: A

3D-CRT (IA)

Recommendation 13b: Intensity-modulated with or without image-guided treatment techniques can be used to reduce normal tissue irradiation

Level of evidence: III

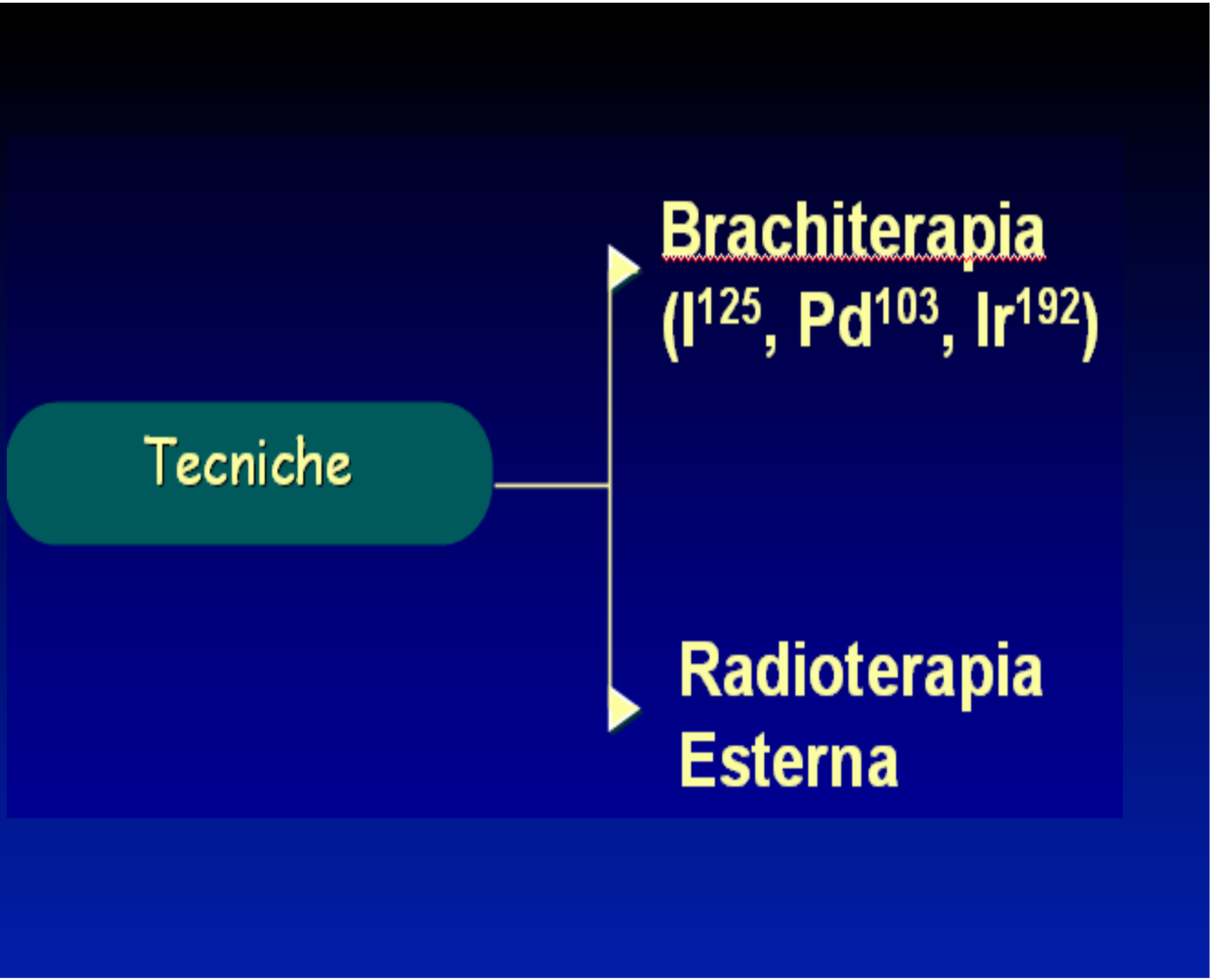
Strength of recommendation: B

14. Is radical prostatectomy an option for patients with T3/T4 prostate cancer?

Recommendation 14: A decision to recommend radical prostatectomy in locally advanced T3-4 prostate cancer should be made only after careful staging and discussion in a multidisciplinary team

Level of evidence: III

Strength of recommendation: C


Tecniche
Brachiterapia
(I^{125}, Pd^{103}, Ir^{192})
Radioterapia
Esterna

BRACHITERAPIA

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2013
Prostate Cancer

Primary/Salvage 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 to 6 mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 4 to 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 are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 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 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

Rischio basso – intermedio (+/- EBRT) – alto (+EBRT)

LDR – HDR

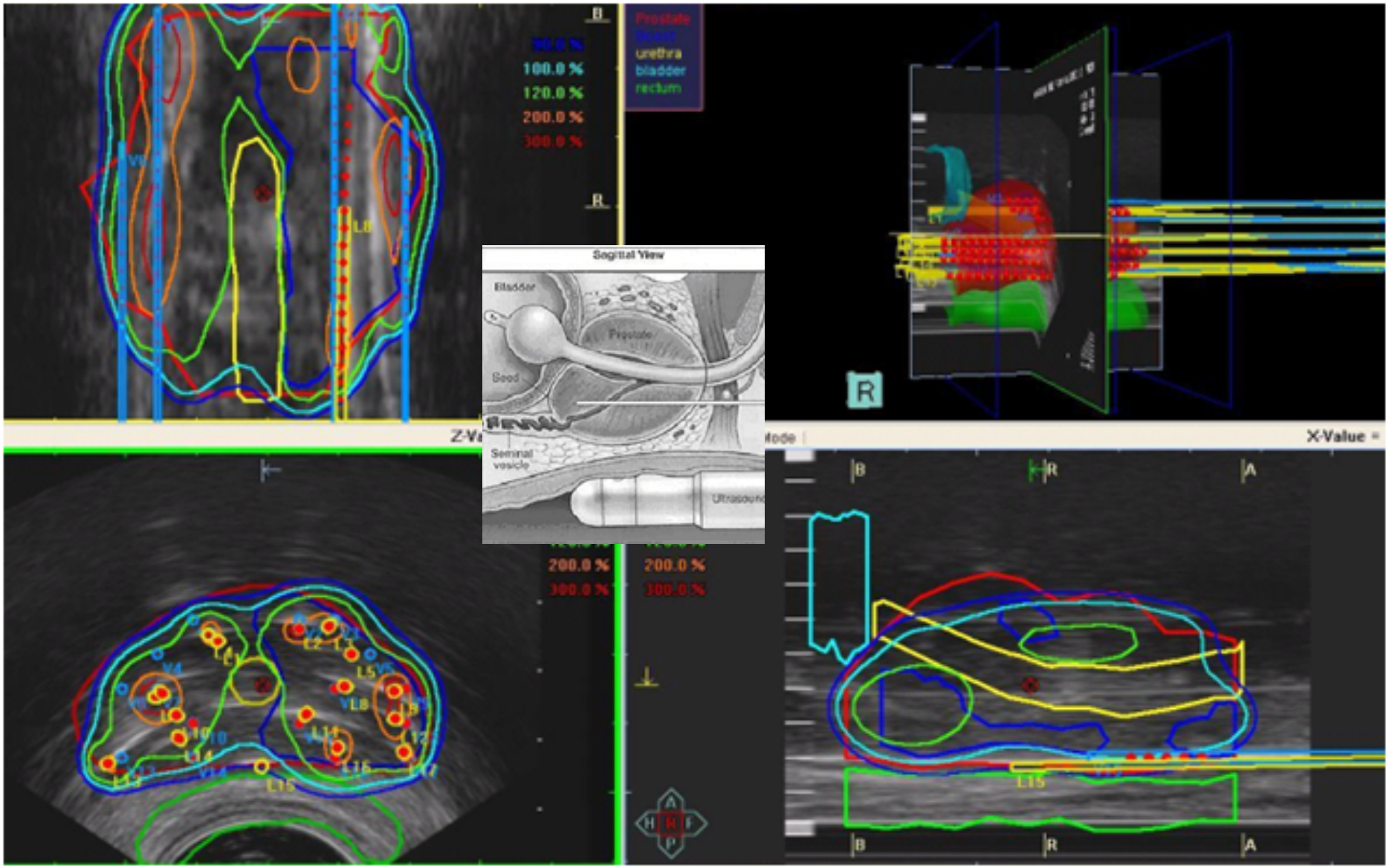
BRACHITERAPIA (trans-perineale)

- Sorgenti radioattive inserite direttamente nella prostata
- LDR - HDR
- Radioisotopi utilizzati: Iridio192, Iodio125 e Palladio 103
- Dosi proposte :
  - 145 Gy x ^{125} I
  - 125 Gy x ^{103}Pd
  - 110-100 Gy x boost dopo 40-50 Gy RTT
- I migliori candidati per la brachiterapia sono i migliori candidati per la chirurgia

T1-2, GPS < 7, PSA =< 10, non TURP precedente, volume < 60 ml

Dispositivo di puntamento per impianto ecoguidato
Template for ultrasound guided implant

Brachiterapia HDR



Courtesy of G. Tolento: Bologna 2013

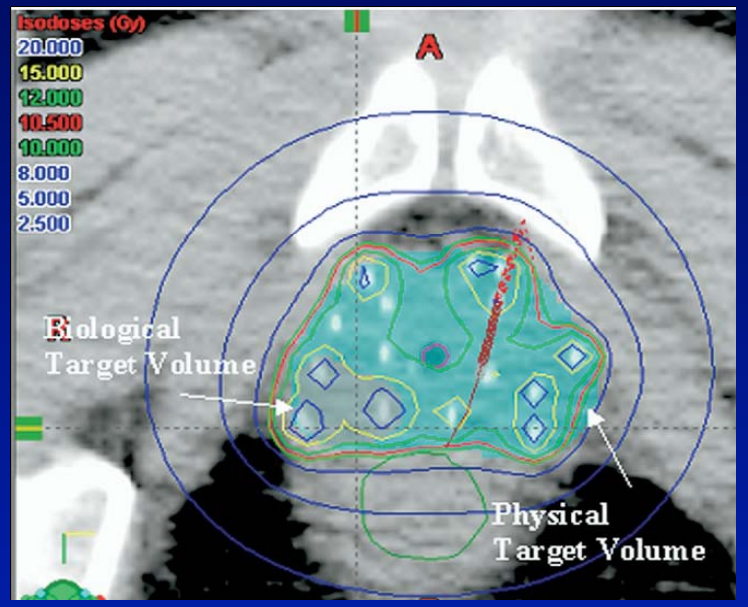
Impianti temporanei HDR

- Razionale radiobiologico: α/ß basso
- Indicazione:

  boost dopo EBRT (45-50 Gy): 11,5Gyx2/4Gyx4

  monoterapia: 36-43 Gy in 3 frazioni

- Flessibilità degli impianti (estensioni EC e VS) Impianto in anestesia generale
- Planning con TC 3D per definire la sede dei cateteri ed il PTV
- Impianto temporaneo con rimozione alla fine del trattamento
- Dati preliminari: < tox GU



VANTAGGI

- Non problemi protezionistici
- Conformabilità
- Reversibilità dell'impianto

RT TRANSCUTANEA

Tecniche e Dosi

…..consolidate….

RADIOTERAPIA TRANSCUTANEA

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2013
Prostate Cancer

PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy (EBRT) :

- 3-D conformal RT or IMRT techniques should be used to treat prostate cancer. IGRT is required if dose is ≥ 78 Gy. IMRT, if available, is preferred.
- Doses of 75.6 to 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 to 3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4 to 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 of IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Treatment results appear better when disease burden is lower. Radiation should be administered before PSA exceeds 0.5 ng/mL.

Basso rischio : 76 – 79 GY

Rischio intermedio/alto : 79 → 81 Gy

IGRT se > 78 Gy

RTT su linfonodi pelvici e Ormono per rischio intermedio e alto

..... ma .....

PROBLEMI DA AFFRONTARE

- Vantaggi con dosi elevate?
- Ruolo della ormonoterapia ?
- RTT sulle stazioni linfonodali ?
- Tecnologie e RT ipofrazionata ?

..... Lo studio R.E.R. .....

PROBLEMI DA AFFRONTARE

- Vantaggi con dosi elevate? SI
- Ruolo della ormonoterapia ? SI
- RTT sulle stazioni linfonodali ? NI
- Tecnologie e RT ipofrazionata ? NI

..... Lo studio R.E.R. .....

RT a dosi elevate: RTT + Brachiterapia ?

Martinez: 579 pazienti trattati con RTT(anche sulla pelvi) + brachiterapia con HDR (boost) (dosi equivalenti > 95 Gy)

Almeno un fattore prognostico sfavorevole:

- Stadio >T2b
- Gleason score > 7
- PSA > 10

Risultati eccellenti :

Overall Survival	90%
Cause Specific Survival	98%
Disease Free Survival	71%
Biochemical Control	79%
Clinical Local Control	93%

L'aggiunta di Ormono- neoadiuvante o concomitante < a 6 mesi non sembrava dare un vantaggio terapeutico

Educational review

Evidence-based radiation oncology: Definitive, adjuvant and salvage radiotherapy for non-metastatic prostate cancer☆

Barbara Alicja Jereczek-Fossa*, Roberto Orecchia

Table 4
Phase III dose escalation studies

Author, year, reference	Patients	Study design	Study conclusions	Comments
Shipley et al. 1995[197]	201 pts, T3–4 any N	67.2 GyE vs. 75.6 GyE (perineal proton boost in both arms)	No difference in OS, DSS, TRFS, LC between arms	Subgroup analysis: increased LC in high Gleason tumors
Pollack et al. 2002 [165]	305 pts, T1–T3	EBRT: 70 Gy vs. 78 Gy (with 3DCRT boost)	Higher dose improved FFF	Subgroup analysis: benefit if PSA >10 ng/mL
Lukka et al. 2005 [121]	936 pts, T1–2	66 Gy/33 fr vs. 52.5 Gy/20 fr	Lower dose tended to do worse* (BCF)	Low dose in both arms
Zietman et al. 2005 [248]	393 pts, T1b–2b PSA < 15 ng/mL	70.2 GyE vs. 79.2 GyE (proton boost in both arms)	Higher dose improved PSA control rates	
Sathya et al. 2005 [190]	104 pts, T2–3	EBRT 66 Gy/33 fr vs. Iridium implant 35 Gy + EBRT 40 Gy/20 fr	Higher dose (Iridium + EBRT) improved PSA control rates and post-RT biopsy	Low dose in standard arm
Dearnaley et al. 2005 [51]	126 pts, T1b–T3b	64 Gy vs. 74 Gy, neoadjuvant and concomitant androgen suppression in both arms	Higher dose improved PSA control rates*	2×2 factorial design to study the impact of dose escalation and target volume: 1.5 cm margin is unnecessary
Peeters et al. 2006 [155]	669 pts, T1b–T4	68 Gy vs. 78 Gy	Higher dose improved PSA control rates	Subgroup analysis: benefit in intermediate and high-risk groups

"Many randomized trials consistently support a benefit from higher doses in the intermediate- and high-risk patients (*level 1 evidence*)"

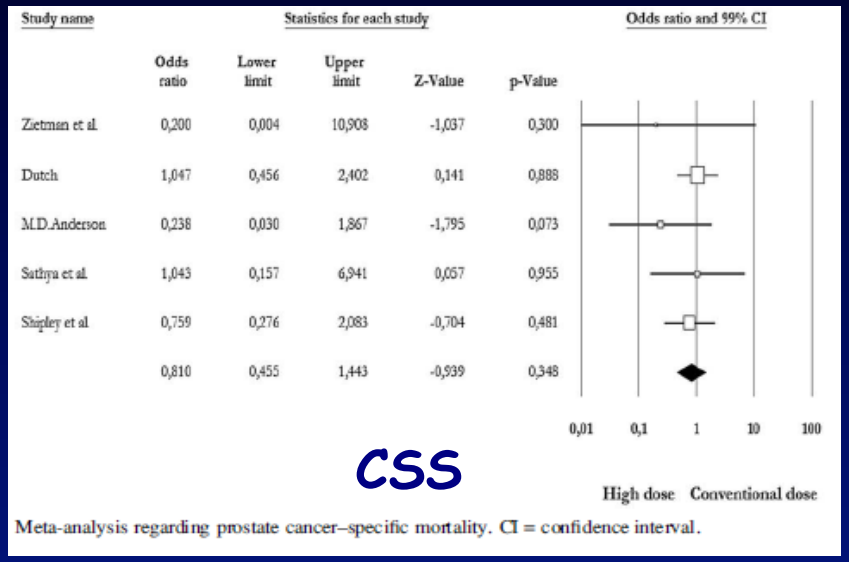
Jereczek-Fossa BA, Radiot Oncol 2007

ASTRO Online CME

CLINICAL INVESTIGATION — **Prostate**

HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.



CSS

Meta-analysis regarding prostate cancer–specific mortality. CI = confidence interval.

Late Tox.

Table 2. Gastrointestinal and genitourinary late toxicity in the trials included in the meta-analysis

Study (reference)/toxicity criteria	GI *		GU*	
	High dose	Conventional	High dose	Conventional
Zietman *et al.* (23)/RTOG scale	43% G1	36% G1	43% G1	43% G1
	17% G2	8% G2	20% G2	18% G2
	1% G3	1% G3	1% G3	2% G3
Dutch (25)/RTOG/EORTC	32% G≥2	27% G≥2	39% G≥2	41% G≥2
	5% G≥3	4% G≥3	13% G≥3	12% G≥3
MRC RT01 (27)/RTOG scale	60% G≥1	58% G≥1	26% G≥1	22% G≥1
	33% G≥2	24% G≥2	11% G≥2	8% G≥2
	10% G≥3	6% G≥3	4% G≥3	2% G≥3
M. D. Anderson (22)/RTOG/EORTC	42% G1	66% G1	35% G1	21% G1
	28% G2	42% G2	7% G2	11% G2
	10% G3	3% G3	7% G3	5% G3
GETUG (28)/RTOG modified	57% G1	42% G1	65% G1	67% G1
	43% G2	28% G2	46% G2	48% G2
	3% G3	10% G3	11% G3	8% G3
Sathya *et al.* (24)/CTC scale	3.9% G3 or G4	1.9% G3 or G4	13.7% G3 or G4	3.8% G3 or G4
Shipley *et al.* (26)/RTOG scale	27% G≥2	9% G≥2	14% G≥2	6% G≥2

Abbreviations: GI = gastrointestinal; GU = genitourinary; RTOG = Radiation Therapy Oncology Group; G = grade; EORTC = European Organization for Research and Treatment of Cancer; MRC = Medical Research Council; CTC = Common Toxicity Criteria.
* Some patients had Grade 1 then Grade 2 toxicity; thus for some trials the sum of Grade 1–3 toxicities exceeds 100%.

(1997 – 2007)

7 RCT utili / 137 valutabili

- 2812 pazienti
- 3D-CRT
- HDRT (fotoni o protoni o ERTT+ Brachi) + vs CDRT (Convenszionali)
- Correlazione lineare tra dose e Controllo biochimico

BC = - 67.3 + (1.8 x RT total dose in Gy)

p = 0.04

G.A. Viani et al.: IJROBP: 2013

ASTRO Online CME

CLINICAL INVESTIGATION — Prostate

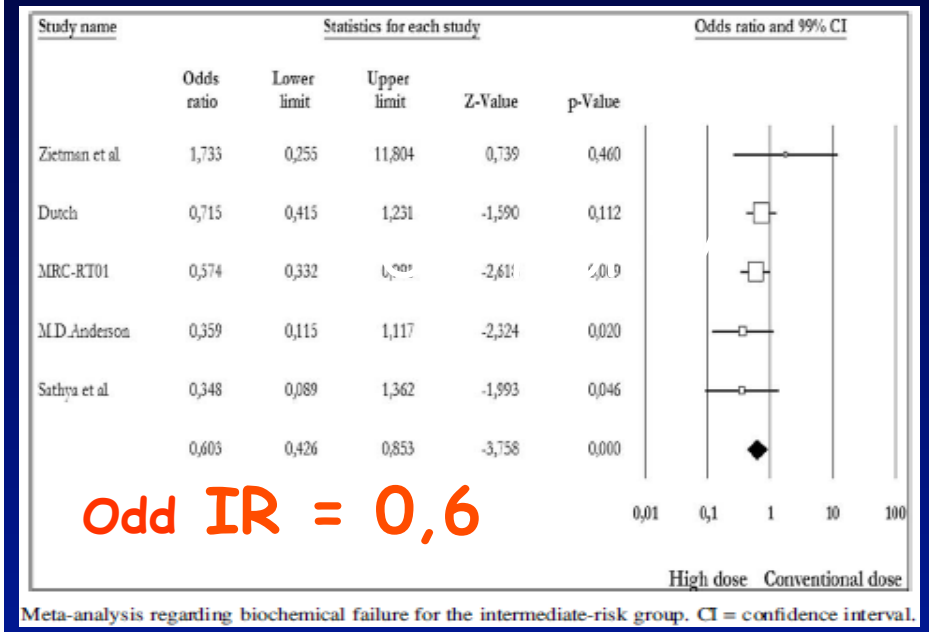
HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.

7 RCT / 137 valutabili, 2812 pazienti

Odd Ratio HDRT/CDRT per **Ripresa Biochimica**

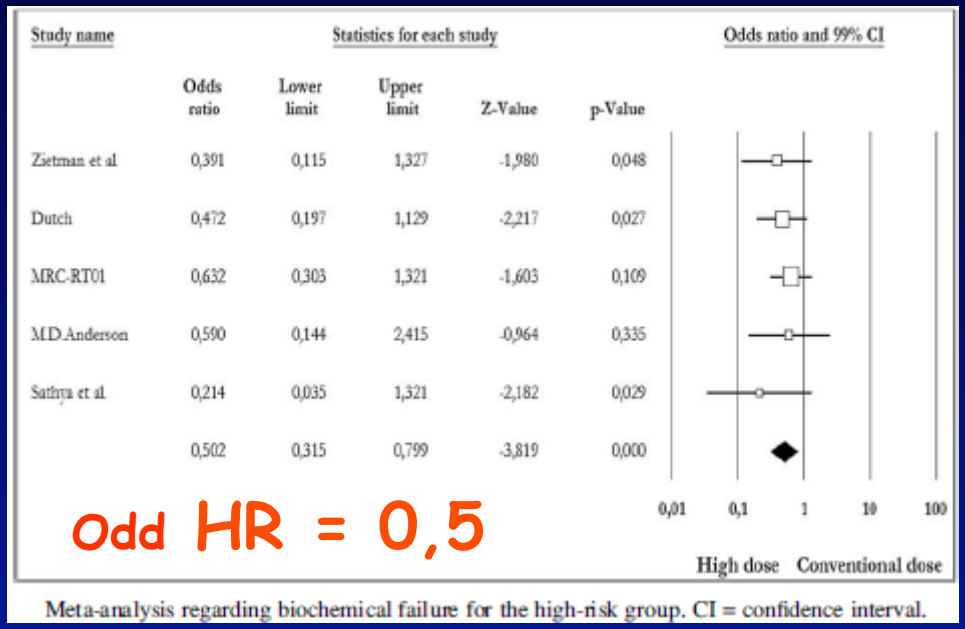
Riprese biochimiche: HDRT (312 / 1255, 24.8%) vs CDRT arm (434 / 1251, 34.6%)



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zietman et al	1,733	0,255	11,804	0,739	0,460
Dutch	0,715	0,415	1,231	-1,590	0,112
MRC-RT01	0,574	0,332	[illegible]	-2,61[illegible]	[illegible]0,0[illegible]9
M.D.Anderson	0,359	0,115	1,117	-2,324	0,020
Sathya et al	0,348	0,089	1,362	-1,993	0,046
	0,603	0,426	0,853	-3,758	0,000

Odd IR = 0,6

Meta-analysis regarding biochemical failure for the intermediate-risk group. CI = confidence interval.



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zietman et al	0,391	0,115	1,327	-1,980	0,048
Dutch	0,472	0,197	1,129	-2,217	0,027
MRC-RT01	0,632	0,303	1,321	-1,603	0,109
M.D.Anderson	0,590	0,144	2,415	-0,964	0,335
Sathya et al	0,214	0,035	1,321	-2,182	0,029
	0,502	0,315	0,799	-3,819	0,000

Odd HR = 0,5

Meta-analysis regarding biochemical failure for the high-risk group. CI = confidence interval.

Vantaggi per tutti i sottogruppi

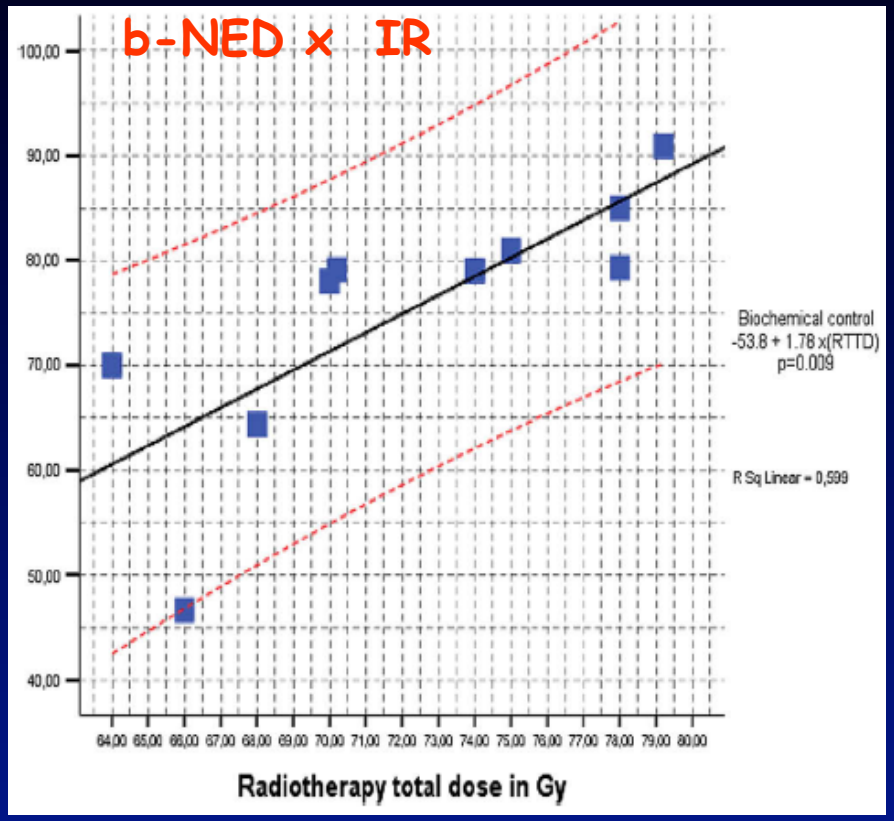
G.A. Viani et al.: IJROBP: 2013

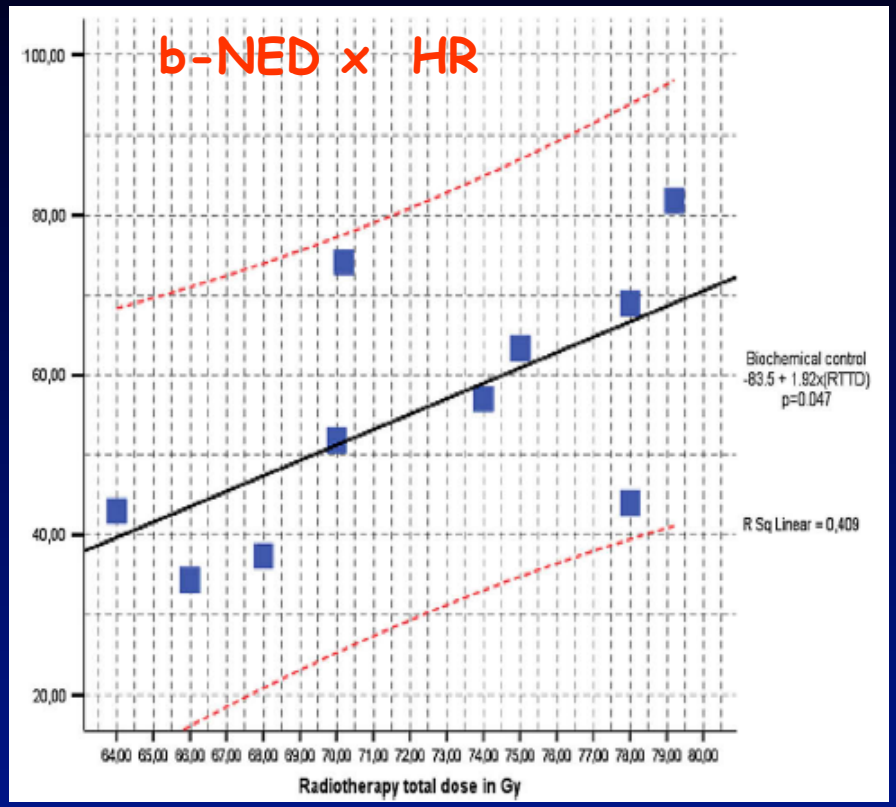
ASTRO Online CME

CLINICAL INVESTIGATION **Prostate**

HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.





- Il controllo biochimico per dosi totali tra 64 to 79.2 Gy con la 3D-CRT, cresce uniformemente
- La presenzsa di una dose risposta supporta l'impiego di dosi alte.
- IMRT e IGRT sono due metodiche che possono consentire la somministrazione di dosi superiori

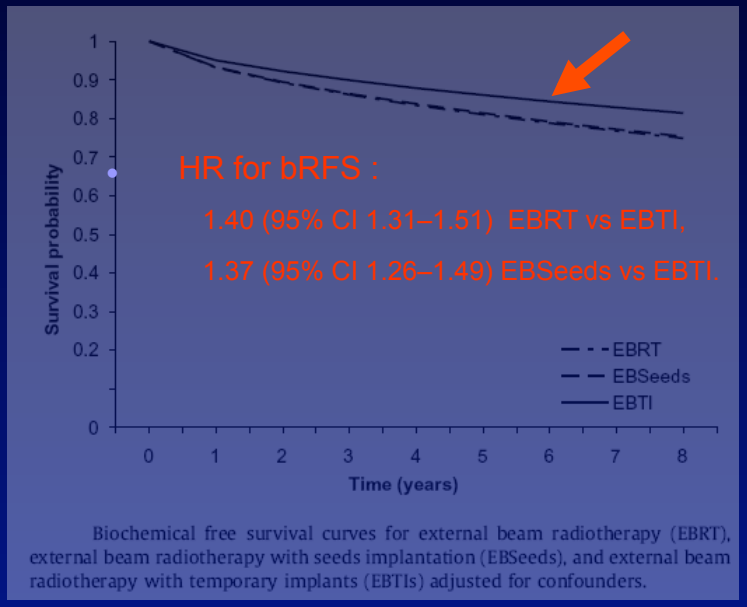
Sono necessari studi ulteriori con IGRT / IMRT per erogare dosi maggiori di 80 Gy

G.A. Viani et al.: IJROBP : 2009

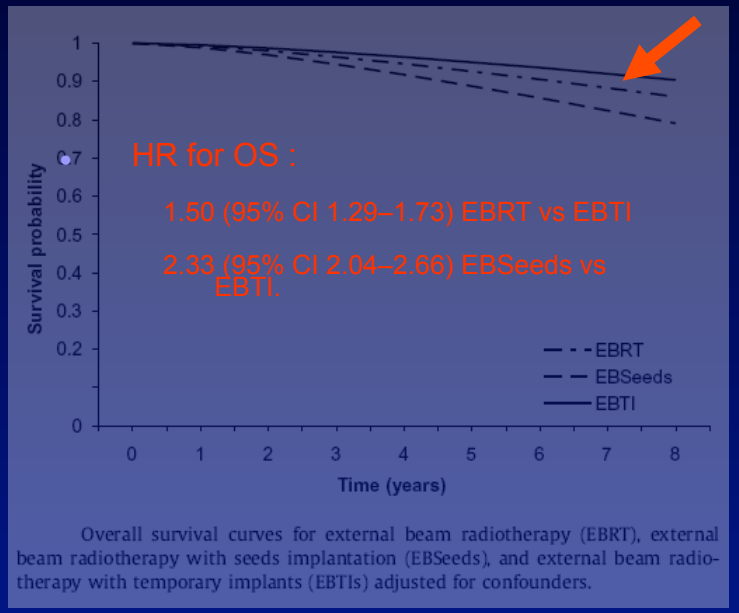
Systematic review

Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: A systematic review

Bradley R. Pieters [a,*], Djuna Z. de Back [a], Caro C.E. Koning [a], Aeilko H. Zwinderman [b]



Biochemical free survival curves for external beam radiotherapy (EBRT), external beam radiotherapy with seeds implantation (EBSeeds), and external beam radiotherapy with temporary implants (EBTIs) adjusted for confounders.



Overall survival curves for external beam radiotherapy (EBRT), external beam radiotherapy with seeds implantation (EBSeeds), and external beam radiotherapy with temporary implants (EBTIs) adjusted for confounders.

La combinazione RTT + brachiterapia HDR offre vantaggi in termini di bNED e OS

Radiother. Oncol. 2009

POINT/COUNTERPOINT

(Nei pazienti a rischio intermedio lo standard è RTT + OT)

E' necessaria EBRT con Brachi per erogate alte dosi ? Solo HDR ?


ELSEVIER

BRACHYTHERAPY

Brachytherapy 12 (2013) 389–392

Point/Counterpoint

Point: There is a need for supplemental XRT with brachytherapy in the treatment of intermediate-risk prostate cancer patients

Daniel E. Spratt, Michael J. Zelefsky*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BRACHYTHERAPY

Brachytherapy 12 (2013) 393–397

Point/Counterpoint

Counterpoint: Is there a need for supplemental XRT in intermediate-risk prostate cancer patients?

Nelson N. Stone[1,2,*]


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BRACHYTHERAPY

Brachytherapy 12 (2013) 400

Point/Counterpoint

Rebuttal to Drs. Spratt and Zelefsky

Nelson N. Stone[1,2,*]


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BRACHYTHERAPY

Brachytherapy 12 (2013) 398–399

Point/Counterpoint

Rebuttal to Dr. Stone

Daniel E. Spratt, Michael J. Zelefsky*

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

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BRACHYTHERAPY

Brachytherapy 12 (2013) 389–392

Point/Counterpoint

Point: There is a need for supplemental XRT with brachytherapy in the treatment of intermediate-risk prostate cancer patients

Daniel E. Spratt, Michael J. Zelefsky*

Benefits of supplemental external beam radiotherapy
Dose escalation
Intraprostatic dose escalation
Extracapsular extension ≤5 mm from capsule and proximal seminal vesicles dose escalation
Improved coverage
Ability to cover extracapsular extension >5 mm from prostate
Ability to treat entire seminal vesicles
Ability to treat pelvic lymph nodes
Compensate for an inadequate implant

Ultimately, the resolution of our point counterpoint debate will be addressed when the results of RTOG 0232 become available in the future.

- Favorable intermediate-risk patients (low volume of disease and few intermediate-risk features may have adequate tumor control with a brachytherapy alone.
- Bulky disease or GPS 4 + 3 are at high risk of recurrence and ECE and warrant more aggressive combination therapy.

ELSEVIER

BRACHYTHERAPY

Brachytherapy 12 (2013) 400

Point/Counterpoint

Rebuttal to Drs. Spratt and Zelefsky

Nelson N. Stone[1,2,*]

- Mixed dosimetry results
- High BED can be achieved with implant alone
- Seed just undee the capsule to get dose 5 mm and more outside the gland
- High dose conformity an fewer rectal complications combination therapy.

A well done implant should be the treatment o choice for intermediate-risk prostate cancer patients

EXPERT REVIEWS

Do theoretical potential and advanced technology justify the use of high-dose rate brachytherapy as monotherapy for prostate cancer?

La brachiterapia HDR può sostituire quella a LDR come monoterapia in pazienti selezionati a rischio intermedio/alto ?

17 studi / 131 eligibili (2435 pazienti)

HDR monotherapy ?

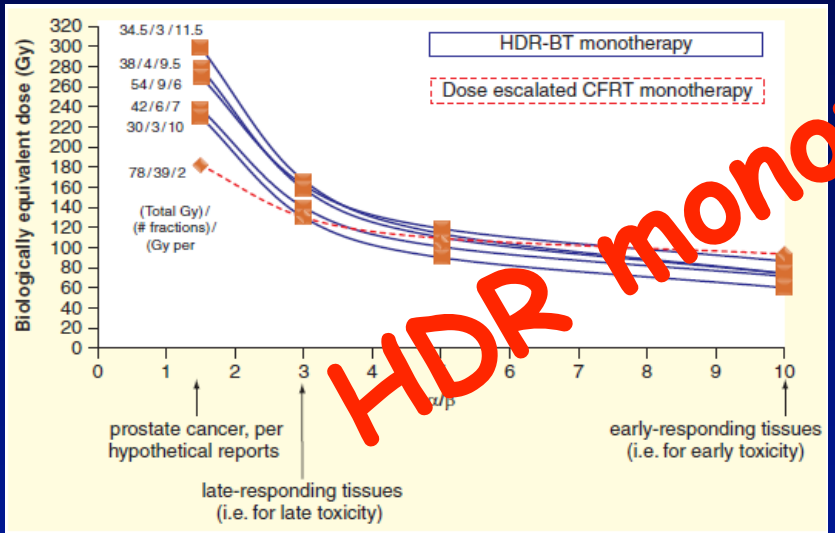
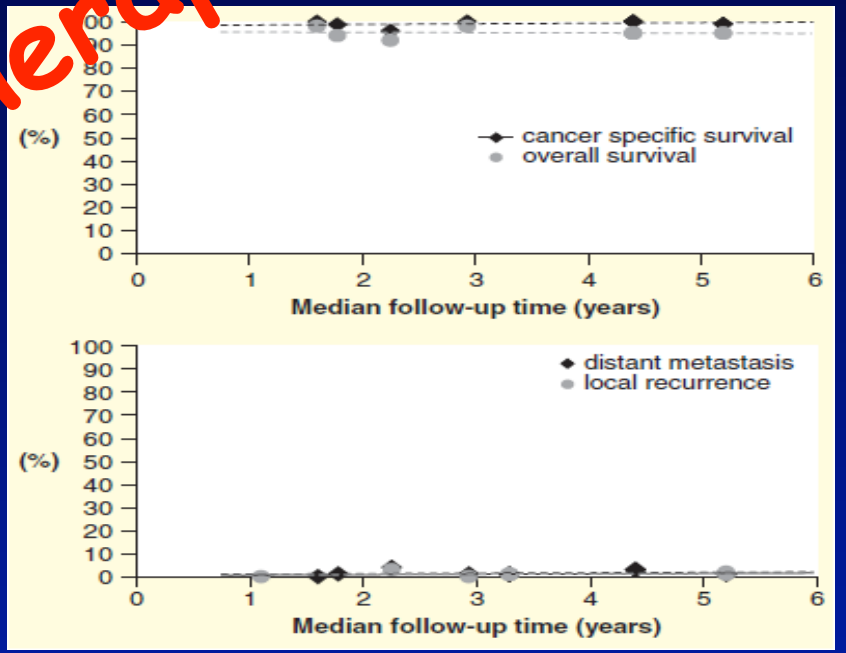


Figure 2. BED versus α/β ratios for HDR-BT and CFRT. The BEDs from commonly used HDR-BT monotherapy regimens at different α/β ratios are juxtaposed to those of CFRT.
BED: Biologically equivalent dose; CFRT: conventionally fractionated radiation therapy; HDR-BT: High-dose rate brachytherapy.



N. G. Zaorsky et al: Expert Rev. Anticancer Ther. 2013

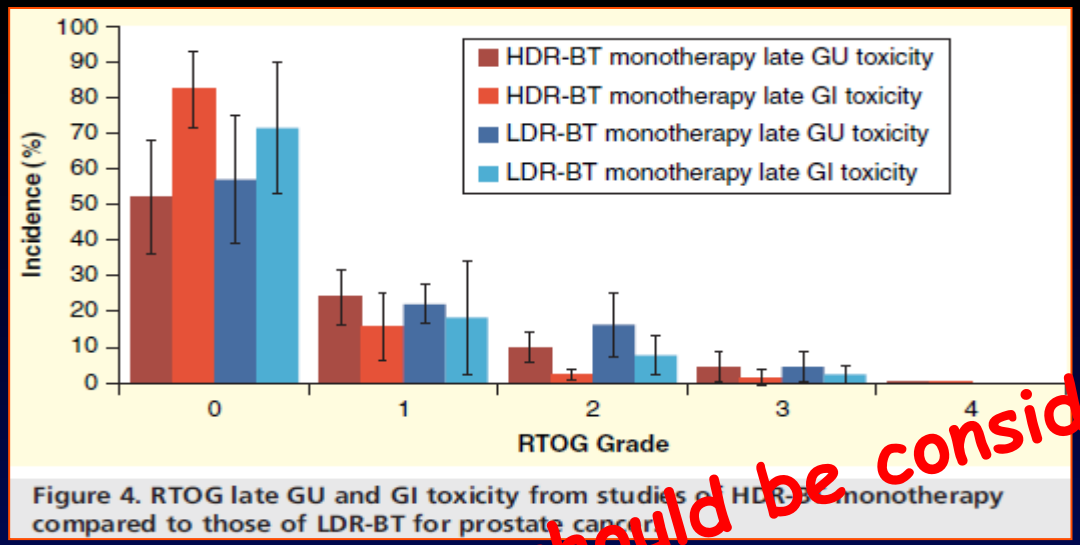


Figure 4. RTOG late GU and GI toxicity from studies of HDR-BT monotherapy compared to those of LDR-BT for prostate cancer.

HDR-BT monotherapy should be considered experimental at present...

Table 4. Current clinical trials including HDR-BT as definitive monotherapy for prostate cancer.

Short title and ClinicalTrials.gov identifier	n	Phase	Risk groups	Plan	Total BT dose (Gy)	Gy/fraction	Primary outcome
Dose Escalation to Dominant Intra-prostatic Nodule; British Columbia; NCT01605097	15	II	I, I	TCE-MRI; US	20–25	10–12.5	Dosimetric constraints
HDR-BT and/or IM-EBRT; Virginia Commonwealth University; NCT00[illegible]2	X	I/II	L, I	NR	6	6	Dose-limiting toxicities
Natural history of patients with cancer (including prostatic) receiving HDR-BT; National Cancer Institute; NCT00924027	112	N/A	L, I, H	NR	NR	NR	Dosimetric constraints

BT: Brachytherapy; CT: Computerized tomography; DCE: dynamic contrast enhanced; GI: Gastrointestinal; GU: Genitourinary; H: High-risk; I: Intermediate risk; L: Low risk; MRI: Magnetic resonance imaging; N/A: Not applicable; NR: Not reported; SBRT: Stereotactic body radiation therapy.

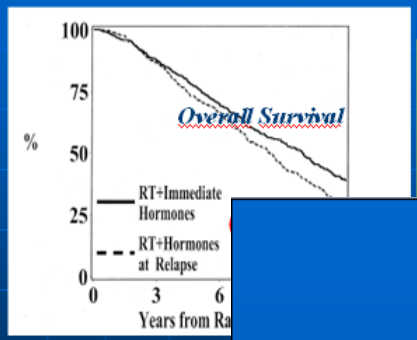
Vi sono limiti che precludono l'impiego della Brachi HDR come monoterapia fuori da trial clinici

PROBLEMI DA AFFRONTARE

- Vantaggi con dosi elevate? SI
- Ruolo della ormonoterapia ? SI
- RTT sulle stazioni linfonodali ? NI
- Tecnologie e RT ipofrazionata ? NI

..... Lo studio R.E.R. e altro.....

RTOG 8531



ARM 1 : Zoladex® alone (from last week of up to relapse)

ARM 2 Zoladex started only at first relapse

ONCH-1489; No. of Pages 5 ARTICLE IN PRESS

ELSEVIER

Critical Reviews in Oncology/Hematology xxx (2010) xxx–xxx

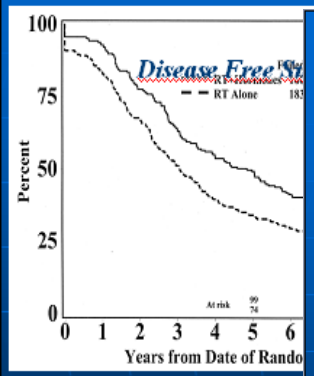
CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Combined hormone therapy and radiation therapy for locally advanced prostate cancer

M. Bolla [a,b,*], M. Laramas [a,b]

RTOG 86-10



Overal
Loca

Local Control →
Disease
Overall

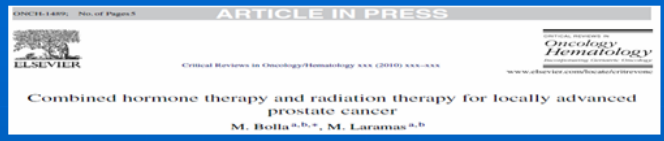
RTOG 92-02

- 1554 patients -

- **ARM 1 (STAS)** : two months of Complete Androgen Suppression (CAS) before RT followed during radiotherapy (WPRT up to 44-46 Gy followed by boost to prostate up to 20-29 Gy for a total dose of max 70 Gy)
- **ARM 2 (LTAS)** : two months of CAS before RT followed during RT and additional therapy of 24 months wit

LTAS showed a significant improveme
except 5-year OS; in a subset of patient
arm had significantly better OS : 81%vs

In a subset analysis the overall survival
patients with GS 8–10 ($P = 0.006$).



RTOG 94-13

- ***Four Arm Trial*** -

First Randomization

ARM 1 : neoadjuvant concurrent HT (NCHT) – 2 months before and 2 months during RT

ARM 2 : 4-month adjuvant hormone therapy (AHT) after RT

Second randomization

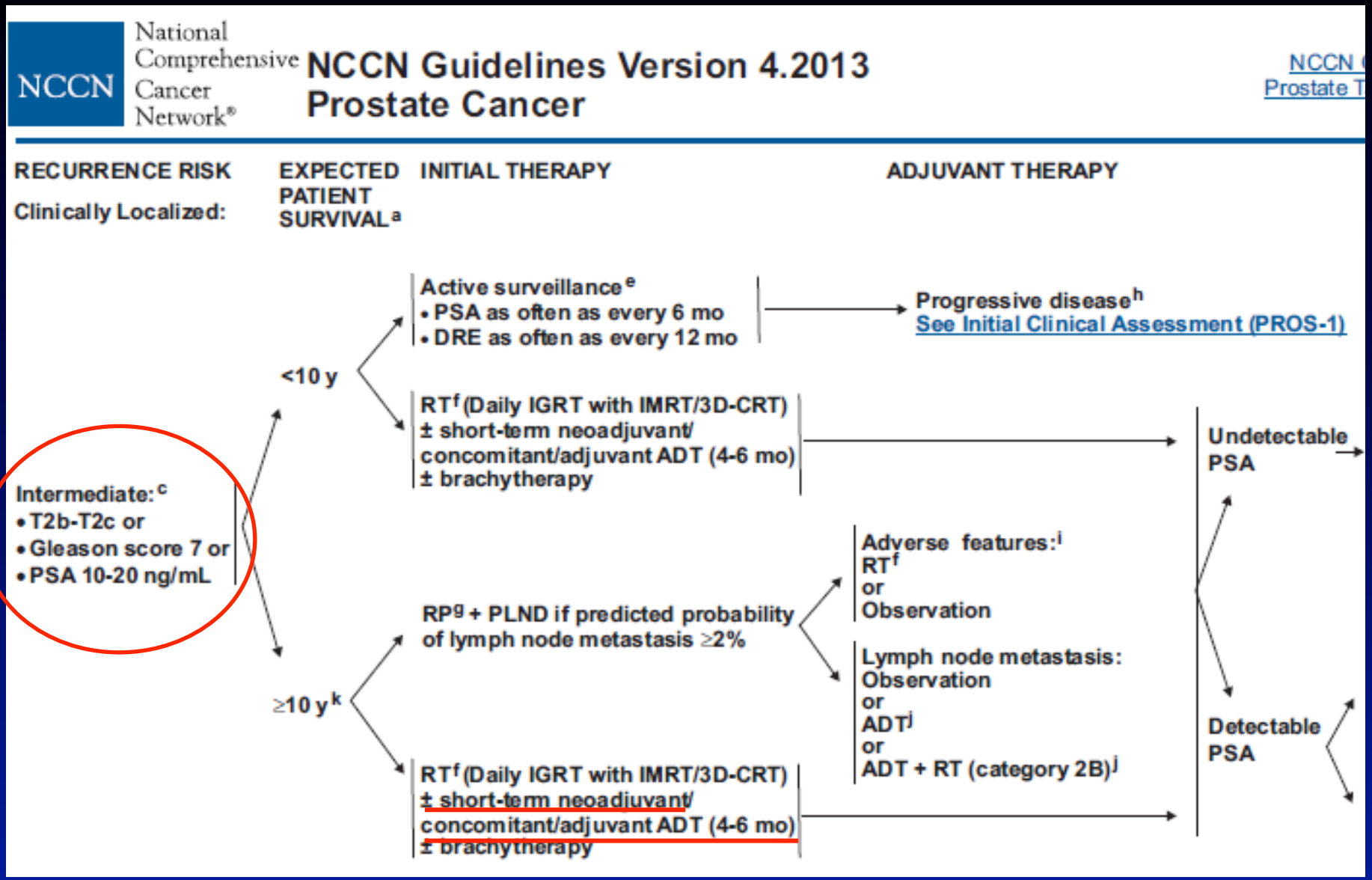
ARM 3 : Whole Pelvis RT (WPRT up to 50 Gy) followed by a boost to the prostate (ICRU dose 70.2 Gy)

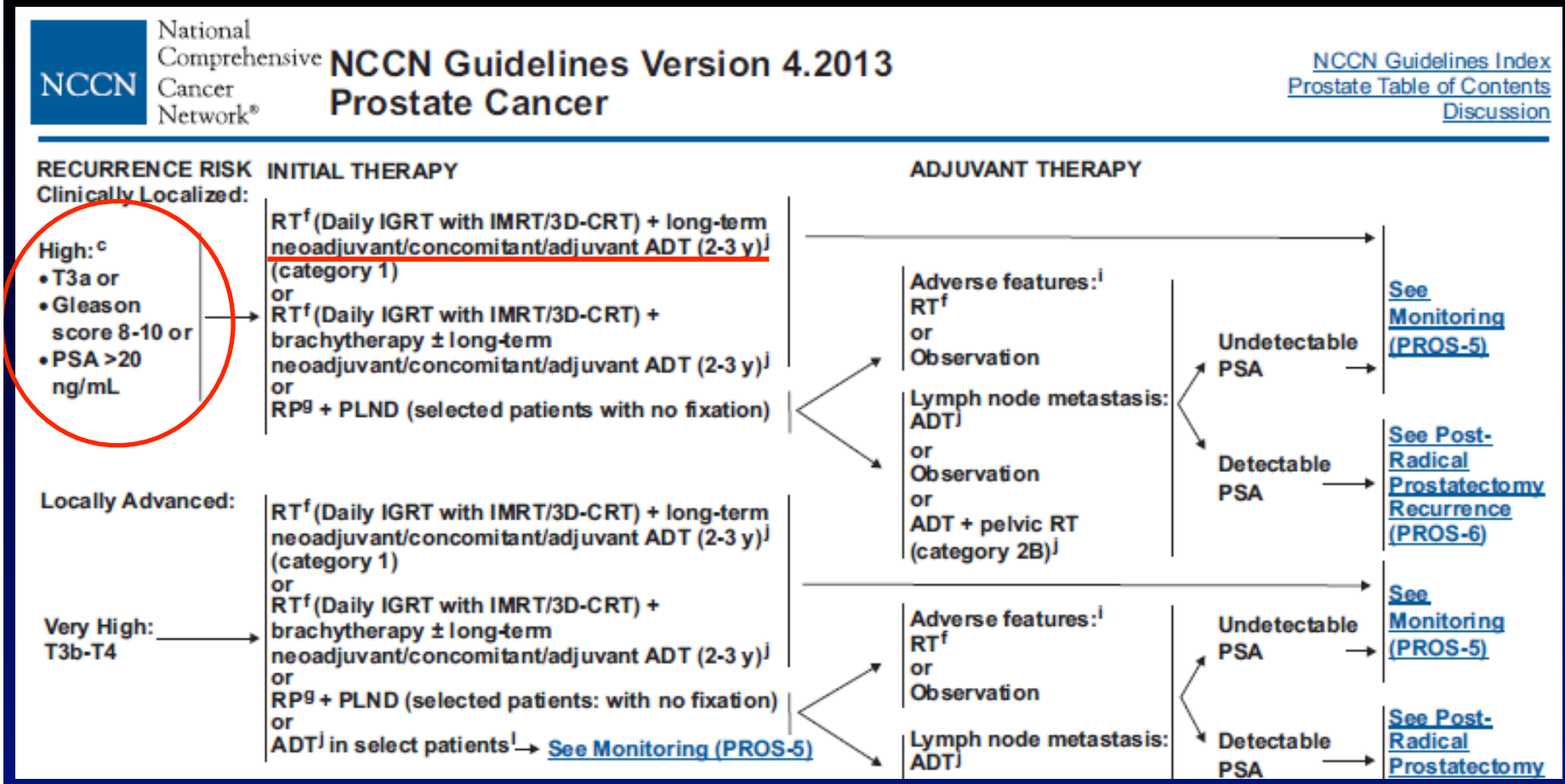
ARM 4 : prostate RT (PORT up to 70.2 Gy).

Particularly WPRT seems to be needed in patients with an estimated risk of lymph node involvement >15%.

Crit Rev Oncol Hemat, 2010

....tutte le Linee guida concordano....


NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 4.2013
Prostate Cancer
NCCN
Prostate T
RECURRENCE RISK
Clinically Localized:
EXPECTED PATIENT SURVIVAL[a]
INITIAL THERAPY
ADJUVANT THERAPY
Intermediate:[c]
• T2b-T2c or
• Gleason score 7 or
• PSA 10-20 ng/mL
<10 y
Active surveillance[e]
• PSA as often as every 6 mo
• DRE as often as every 12 mo
Progressive disease[h]
See Initial Clinical Assessment (PROS-1)
RT[f] (Daily IGRT with IMRT/3D-CRT)
± short-term neoadjuvant/
concomitant/adjuvant ADT (4-6 mo)
± brachytherapy
Undetectable PSA
≥10 y[k]
RP[g] + PLND if predicted probability of lymph node metastasis ≥2%
Adverse features:[i]
RT[f]
or
Observation
Lymph node metastasis:
Observation
or
ADT[j]
or
ADT + RT (category 2B)[j]
RT[f] (Daily IGRT with IMRT/3D-CRT)
± short-term neoadjuvant/
concomitant/adjuvant ADT (4-6 mo)
± brachytherapy
Detectable PSA



High risk ***(T1-2 N0-X M0 with either a baseline PSA value > 20 ng/mL and/or a Gleason score of 8-10) plus short-term ADT, suggested by the Boston and 94-08 RTOG trials, did not show any impact on OS in the high-risk cohort.*** The high risk of relapse outside the irradiated volume makes a combined modality approach mandatory, consisting of dose-escalated IMRT including the pelvic lymph nodes plus long-term ADT. The duration of ADT has to take into account WHO performance status, comorbidities, and the number of poor prognostic factors: cT stage (> T2c), Gleason score 8-10, and PSA > 20 ng/mL.

ASTRO 2013

durata Ormonoterapia (BAT) per IR

8 sett. + 8 sett.

Neoad. Concom

Durata per HR ???.....

RESEARCH ARTICLE Open Access

Impact of hormonal treatment duration in combination with radiotherapy for locally advanced prostate cancer: Meta-analysis of randomized trials

Targets

- Optimal hormone therapy duration

- Impact of volume and RT dose on outcome and local control.

Outcomes	Pts (RCTs)	RR (95% CI)	*p-value*	Het. (*p*)	AD (%)	NNT
BF	3,424 (5)	1.32 (1.09, 1.60)	*0.004*	*0.003*	10.1	9-10
CSS	3,128 (4)	1.21 (0.82, 1.79)	*0.32*	*0.09*	-	-
OS	3,128 (4)	1.09 (0.92, 1.28)	*0.28*	*0.15*	-	-
DM	2,852 (3)	1.77 (1.16, 2.69)	*0.007*	*0.06*	11.5	9
LR	2,852 (3)	1.87 (1.22, 2.86)	*0.004*	*0.10*	11.7	9

Pts: patients; RCTs: randomized clinical trials; RR: relative risk; CI: confidence intervals; Het.: heterogeneity; p: p-value; AD: absolute difference; NNT: number needed to treat; BF: biochemical failure; CSS: cancer specific survival; OS: overall survival; LR: local relapse; DM: distant metastases.

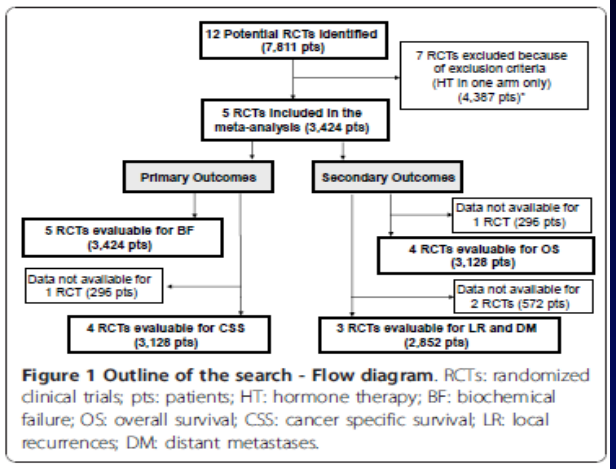


Figure 1 Outline of the search - Flow diagram. RCTs: randomized clinical trials; pts: patients; HT: hormone therapy; BF: biochemical failure; OS: overall survival; CSS: cancer specific survival; LR: local recurrences; DM: distant metastases.

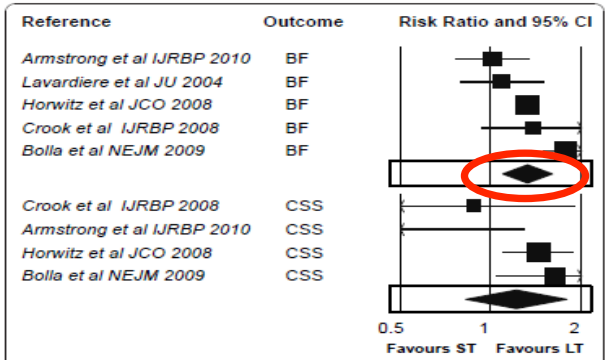


Figure 2 Combined Results - Primary Outcomes (BF, CSS). CI: confidence intervals; BF: biochemical failure; CSS: cancer specific survival; ST: shorter therapy; LT: longer therapy.

LT HT should be the strategy for pts affected by LA prostate cancer

Cuppone et al. BMC Cancer 2010

Review

…sono possibili nuove proposte per il Rischio-Intermedio ?

Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care?

Zachary S Zumsteg, Michael J Zelefsky

Lancet Oncol 2012; 13: e259–69

Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care?

Review

Zachary S Zumsteg, Michael J Zelefsky

Lancet Oncol 2012; 13: 259–69

	Favourable intermediate-risk prostate cancer*	Unfavourable intermediate-risk prostate cancer†
Clinical characteristics	One intermediate risk factor Gleason score of 3+4=7 or less <50% positive biopsy cores	Several intermediate risk factors[3,7] Gleason score of 4+3=7[14] ≥50% positive biopsy cores[11]
Recommended radiation options	Dose-escalated external beam radiotherapy alone Brachytherapy alone in select cases (eg, ≤3 positive cores, none with >50% involvement)	Dose-escalated external beam radiotherapy and short-term androgen deprivation therapy Combined brachytherapy and external beam radiotherapy with or without short-term androgen deprivation therapy

*All these criteria are required. †Any of these criteria can be met.

Table 5: Memorial Sloan-Kettering Cancer Center treatment algorithm for definitive radiotherapy in patients with intermediate-risk prostate cancer

...pochi RCT, scarsa qualità degli studi retrospettivi...

...addition of short-term androgen deprivation for patients with unfavourable features **could be considered on the basis of extrapolation** of data from trials of external beam radiotherapy.

PROBLEMI DA AFFRONTARE

- Vantaggi con dosi elevate? SI
- Ruolo della ormonoterapia ? SI
- RTT sulle stazioni linfonodali ? **NI**
- Tecnologie e RT ipofrazionata ? NI

..... Lo studio R.E.R. e altro .....

The role of whole pelvic radiotherapy in locally advanced prostate cancer

Piet Dirix[a], Karin Haustermans[a,*], Sara Junius[a], Rodney Withers[b], Raymond Oyen[c], Hendrik Van Poppel[d]

Study	Population	Field	D F S (%)	P value
Ploysongsang (1991)	T3	WPRT PORT	63 30	.0004
Seaward (1998)	LN+ >15%	WPRT PORT	34.3 21	.0001
Seaward (1998)	15<LN+<35	WPRT PORT	39.5 22.5	.0001
	LN+ >35%	WPRT PORT	27.2 20.8	NS
Pan et al. (2002)	LN+ >5%	WPRT PORT	79.3 79.0	NS
	5%<LN+<15%	WPRT PORT	60.2 47.9	0.02
	LN+ >15%	WPRT PORT	45.7 45.3	NS
Roach et al. (2003)	+LN >15%	WPRT +NCH PORT + NCH WPRT + AH PORT + AH	60 44 48 50	0.008

Study	Population	Field	DFS (%)	P value
Aristizabal (1984)	All Stages	WPRT PORT	NA	NA
Rosen (1985)	T2	WPRT PORT	60 60	NS
	T3	WPRT PORT	45 65	
Zagars (1987)	T3	WPRT PORT	54 43	NS
Rasp (1996)	+LN >15%	WPRT PORT	35 29	NS

Dirix et al, Review Radiot Oncol 2006

RTT sulla pelvi ?

- Trial RTOG 9413 di FASE III (dal '95 – '99) : 1323 paz. cN0 ma con rischio di N+ > 15%.
- 50.4 Gy + boost 70.2 Gy +/- BAT 2 mesi prima – durante - immediatamente dopo per 4 mesi (Zoladex, flutamide)

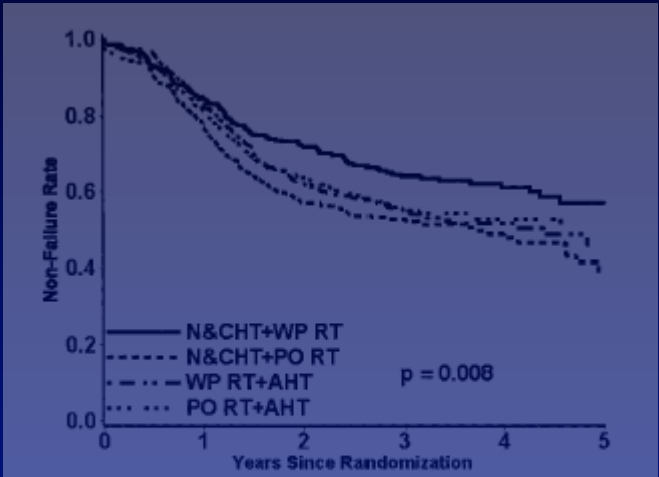
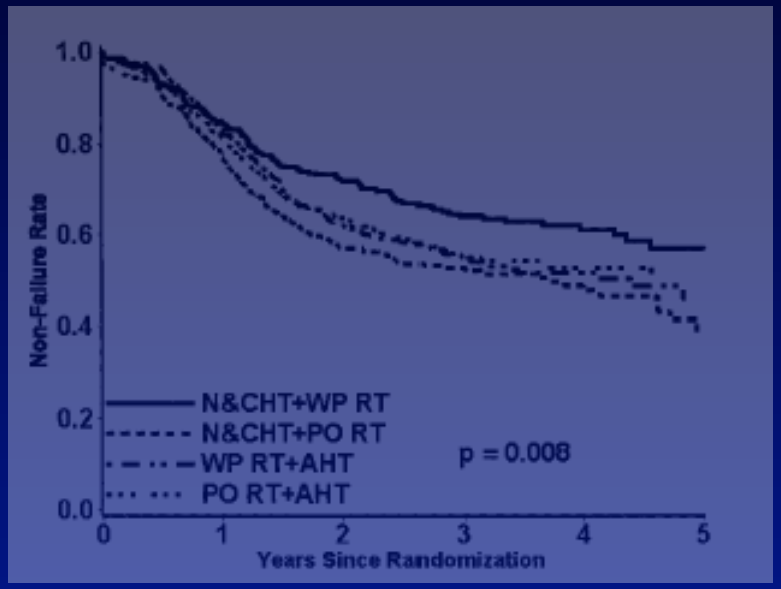


Fig 3. Four-year progression-free advantage for whole pelvic (WP) radiotherapy (RT) and neoadjuvant and concurrent hormonal therapy (NCHT) compared with prostate only (PO) RT and NCHT, and WP RT or PO RT and adjuvant hormonal therapy (AHT; 60 v 44, 49% and 50% respectively, $P = .008$).



Treatment Arm	Disease Progression (includes death due to any cause) RR*	95% CI	Death Due to Any Cause RR*	95% CI	Biochemical Failure RR*	95% CI
WP RT + N & CHT	1.00		1.00		1.00	
PO RT + N & CHT	1.52	1.19 to 1.93	1.35	0.87 to 2.09	1.52	1.15 to 2.01
WP RT + AHT	1.32	1.03 to 1.68	1.54	1.00 to 2.36	1.30	0.97 to 1.73
PO RT + AHT	1.29	1.01 to 1.65	1.21	0.78 to 1.90	1.24	0.92 to 1.65

Roach J Clin Oncol 2003

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 5, pp. 1344–1349, 2009

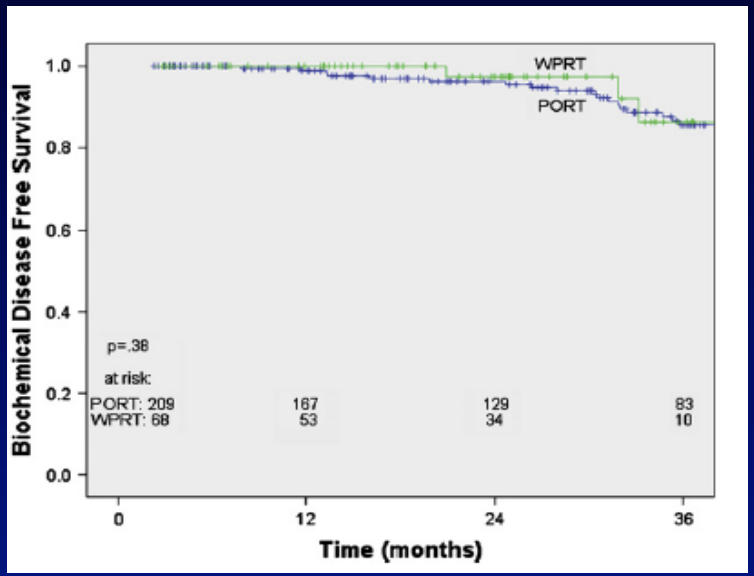
0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.12.082

CLINICAL INVESTIGATION **Prostate**

WHOLE PELVIC RADIOTHERAPY VERSUS PROSTATE ONLY RADIOTHERAPY IN THE MANAGEMENT OF LOCALLY ADVANCED OR AGGRESSIVE PROSTATE ADENOCARCINOMA

Ayal A. Aizer, B.S.,* James B. Yu, M.D.,* Anne M. McKeon, B.S.,* Roy H. Decker, M.D., Ph.D.,*
John W. Colberg, M.D.,† and Richard E. Peschel, M.D., Ph.D.*



After adjustment, the pretreat **PSA level** (p<. 001), **Gleason score** (p < .001), the presence of **HT** (p = .002), and **WPRT** (vs. PORT, p = **.006**) were predictive of BDFS.

Table 3. Acute and late toxicities

Toxicity	Grade	PORT (%)	WPRT (%)	p*
Acute genitourinary				.09
	1	41.6	44.1	
	2	25.4	33.8	
	3	5.7	10.3	
	≥4	0	0	
Late genitourinary				1.0
	1	3.3	1.5	
	2	1.4	1.5	
	3	0	0	
	≥4	0	0	
Acute gastrointestinal				.048
	1	49.3	75.0	
	2	7.2	17.6	
	3	2.9	1.5	
	≥4	0	0	
Late gastrointestinal				.23
	1	4.8	2.9	
	2	1.9	4.4	
	3	0	1.5	
	≥4	0	0	
Fatigue				.50
	1	27.8	26.5	
	2	11.5	8.8	
	3	1.9	1.5	
	≥4	0	0	

WPRT può essere raccomandata in pazienti affetti da adenoca prostatico localmente avanzato **(+LF% >15%)**

ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Pelvic Lymph Node Irradiation for Prostate Cancer: Who, Why, and When?

Dian Wang, MD, PhD, and Colleen Lawton, MD

Prostate cancers are best characterized by their clinical (TNM) stage, Gleason score, and serum prostate-specific antigen (PSA) level. These 3 factors are known to influence the risk of pelvic nodal involvement. By combining these prognostic factors, nomograms and equations have been developed and are widely used in clinical practice as an accurate way of predicting the probability of a given pathological stage. Patients who have a significant risk of pelvic nodal metastasis will likely have higher biochemical failure rates. Results from the multi-institutional prospective trials have shown that patients at an intermediate to high risk for pelvic nodal involvement experience disease progression-free survival benefits from the use of whole pelvic radiotherapy combined with hormone therapy. Yet, significant biological interactions between radiation treatment volumes and timing of hormone therapy have been shown. Further study of these issues is necessary to define the best treatment for patients at significant risk of pelvic lymph node involvement.
Semin Radiat Oncol 18:35-40

Multi-institutional prospective trials have shown that patients at intermediate/ high risk for pelvic nodal involvement experience disease progression-free survival benefits from the use of whole pelvic radiotherapy combined with hormone therapy

CLINICAL INVESTIGATION **Prostate**

RTOG GU RADIATION ONCOLOGY SPECIALISTS REACH CONSENSUS ON PELVIC LYMPH NODE VOLUMES FOR HIGH-RISK PROSTATE CANCER

Colleen A. F. Lawton, M.D.,* Jeff Michalski, M.D.,† Issam El-Naqa, Ph.D.,‡ Mark K. Buyyounouski, M.D.,§ W. Robert Lee, M.D.,|| Cynthia Menard, M.D.,¶ Elizabeth O'Meara, M.D.,** Seth A. Rosenthal, M.D.,†† Mark Ritter, M.D.,‡‡ and Michael Seider, M.D.§§

1. Commence contouring the pelvic CTV lymph node volumes at the L5/S1 interspace (the level of the distal common iliac and proximal presacral lymph nodes). (Fig. 2a).
2. Place a 7-mm margin around the iliac vessels connecting the external and internal iliac contours on each slice, carving out bowel, bladder, and bone (Fig. 2b, 2c).
3. Contour presacral lymph nodes (subaortic only) S1 through S3, posterior border being the anterior sacrum and anterior border approximately 10 mm anterior to the anterior sacral bone carving out bowel, bladder, and bone (Fig. 2a, 2b).
4. Stop external iliac CTV lymph node contours at the top of the femoral heads (bony landmark for the inguinal ligament) (Fig. 2d).
5. Stop contours of the obturator CTV lymph nodes at the top of the pubic symphysis (Fig. 2e).

DVH Consensus: Organs At Risk (OARs)

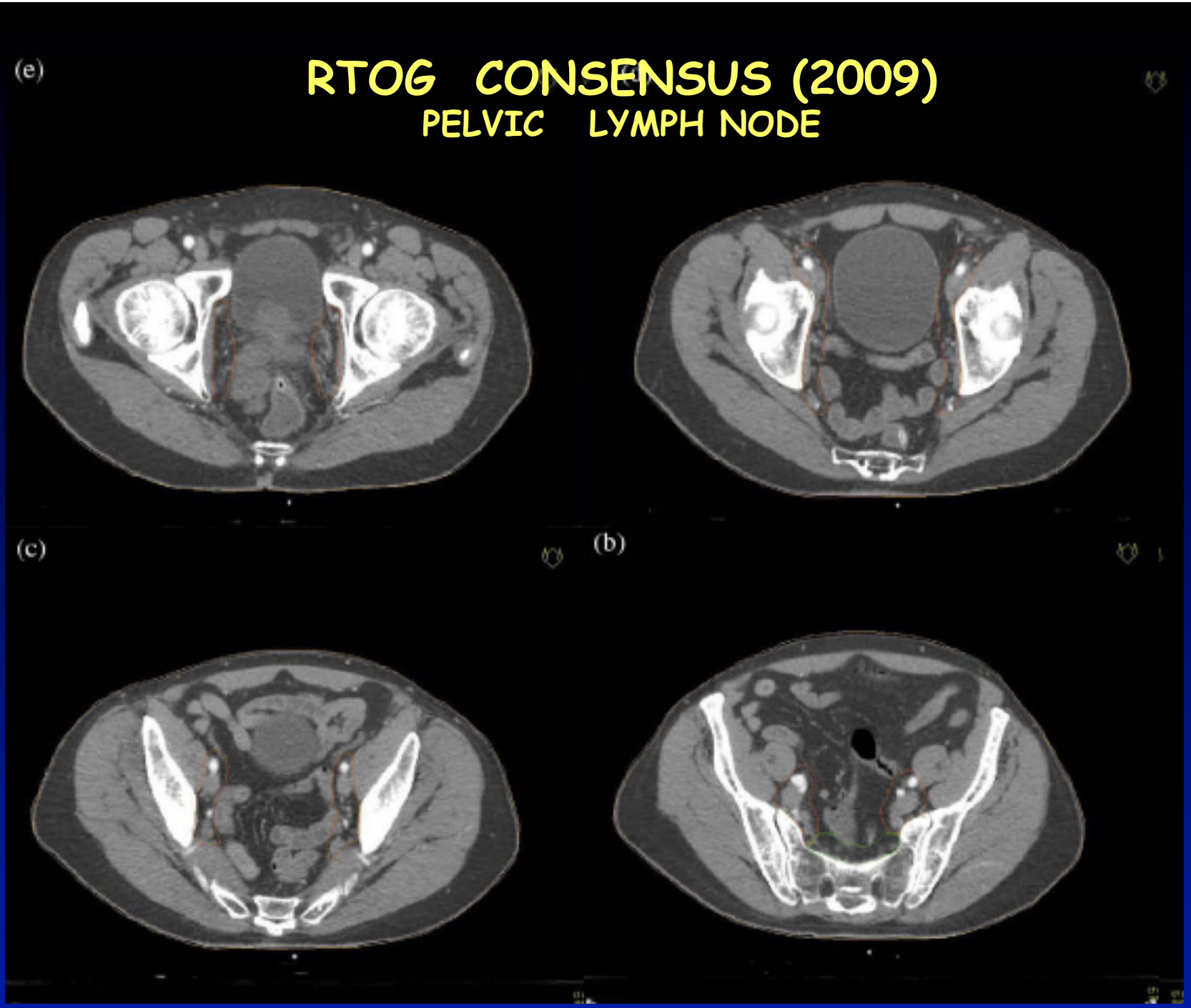
- Rectum: 2 data points:
  - 50 Gy ≤ 50%
  - 70 Gy ≤ 20%
- Bladder: 2 data points:
  - 55 Gy ≤ 50%
  - 70 Gy ≤ 30%
- Femoral Heads <5% @ 50Gy
- Small Bowel 0% @ 52Gy
- Large Bowel Same as Rectum
- Penile Bulb No Constraints
- Iliac Crests No Constraints

Fig 3. Dose–volume histogram constraints for organs at risk.

Consensus on pelvic lymph node CTVs for radiation therapy to address high-risk prostate cancer was attained and is available as web-based

C.A.F. Lawton: IJROBP , 2009

RTOG CONSENSUS (2009)
PELVIC LYMPH NODE



PROBLEMI DA AFFRONTARE

- Vantaggi con dosi elevate? SI
- RTT sulle stazioni linfonodali ? NI
- Ruolo della ormonoterapia ? SI
- Tecnologie e RT ipofrazionata ? NI/SI

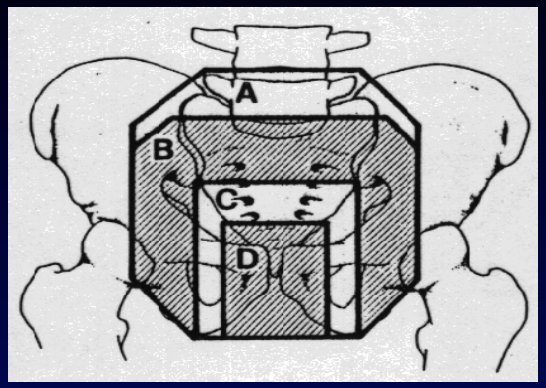
..... Lo studio R.E.R. e altro.....

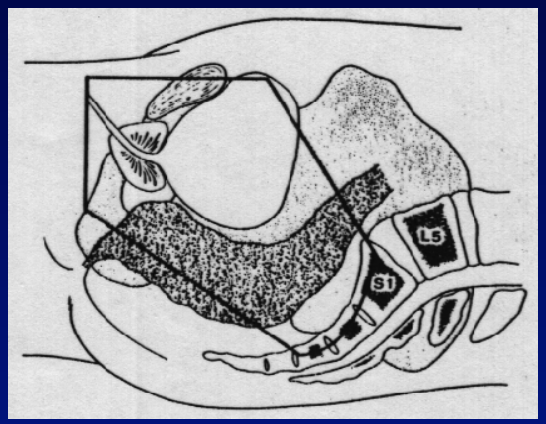
EVOLUZIONE TECNICA DELLA RTT

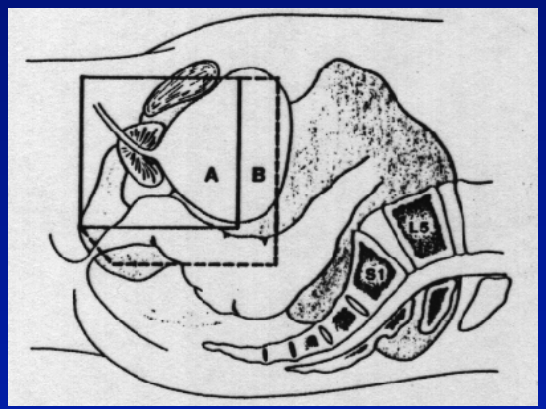
....a partire dal 1970 sviluppo di una RTT di precisione:

RT Convenzionale

VOLUME PROSTATICO E LINFONODI







- **MODALITA' :**
  - *Tecnica multiportale con fotoni 6 -10 MV*
  - *Dose : 45-50 Gy +/- boost di 15-25 su loggia prostatica , 2 Gy/f*
  - *Piano di cura : studio TC, simulatore, TPS (2D - 3D)*

- **MODALITA' :**
  - Tecnica multiportale con fotoni 6 -10 MV
  - Dose 65 - 70 Gy o più , 2 Gy/f
  - Studio TC, Simulatore, TPS (2D - 3D) ,

SEQUELE TARDIVE DELLA RTT

	Review	RTOG
• Mortalità	0.2%	0%
• Complicazioni severe	1.9%	0%
• Incontinenza	0.9%	0.4%
• Stenosi uretrali	2%	1.2%
• Ematuria persist.		0.9%
• Rettorragie pers.		0.6%

L' incidenza di rettosigmoidite (G2- 3) : 10 % per RTT su pelvi in toto e 3% per RTT sulla sola prostata / Fistole e cistiti emorragiche : 0.4 - 0.2 %

Potenza sessuale è mantenuta nel 33 - 60 % dei casi **(sino al 90%)**

minori incertezze nel definire i volumi di trattamento e gli organi pelvici

piani di trattamento con risparmio dei tessuti sani

elevata precisione nell'esecuzione del trattamento

RT convenzionale (4 campi APPA e LL)

RTT conformazionale 3D (standard)

RTT ad intensità modulata del fascio IMRT

IMAT - VMAT - IMRT Elicoidale

IGRT

Adroterapia

NUOVI STANDARD RADIOTERAPICI

3D > 2D?

Associazione Italiana di Radioterapia Oncologica

Less toxicity and better survival results wit
the diffusion of 3DCRT techniques?

Courtesy of S.M. Magrini: Brescia 2013

Title: Changes in patterns of practice for prostate cancer radiotherapy in Italy 1995-2003. A survey of the Prostate Cancer Study Group of the Italian Radiation Oncology Society (AIRO).

Therapeutic feature	Historical series [12], 1995-1998 1005 patients (n, %)	Actual series, 1999-2003 3001 patients (n, %)
Dose to prostate		
<70Gy	315 (31)	218 (7)
70-75.9Gy	689 (69)	2531 (84)
>76Gy	1 (<1)	252 (9)
Treated Volume		
No pelvic irradiation	784 (78)	2497 (83)
Pelvic irradiation	221 (22)	504 (17)
Beam Energy		
<10MV	62 (6)	174 (6)
10-18MV	421 (42)	2026 (68)
>18MV	522 (52)	252 (8)
Not Known	-	549 (18)
Conformal techniques		
2D-RT	593 (59)	725 (24)
Static 3D-CRT	412 (41)	2174 (72)
Dynamic 3D-CRT	-	95 (3)
IMRT	-	7 (<1)

In press, September 20

3D > 2D?

	1995-1998 1005 pts (5-yr results)	1999-2003 2585 pts (5-yr results)
Overall survival	79 %	88 %
Disease specific survival	90 %	96 %
Clinical relapse free survival	67 %	96 %
B- RFS	-	88 %

	N	OS	DSS	RFS	BRFS
D'Amico category risk [16]					
Low	459	92%	99%	98%	87%
Intermediate	921	89%	98%	97%	83%
High	1205	85%	94%	94%	73%
P		< 0.001	< 0.001	<0.001	< 0.001
RT Dose					
< 70 Gy	121	82%	93%	96%	76%
70-75.9 Gy	2241	87%	96%	96%	78%
≥76 Gy	223	97%	98%	99%	87%
P		<0.001	0.03	NS	0.012
Pelvic irradiation					
Yes	448	84%	93%	91%	96%
No	2137	89%	97%	95%	97%
P		<0.001	<0.001	0.003	NS
Conformal techniques					
No	325	87%	96%	93%	76%
Yes	2260	88%	96%	96%	79%
P		NS	NS	NS	NS

Miglioramento della Clin-RFS
Differenze per dosi

Courtesy of S.M. Magrini: Brescia 2013

2D > 3D?

Radiotherapy and Oncology 107 (2013) 134–139

Phase III randomised trial

Radiotherapy with rectangular fields is associated with fewer clinical failures than conformal fields in the high-risk prostate cancer subgroup: Results from a randomized trial

Wilma D. Heemsbergen [a,*], Abrahim Al-Mamgani [b], Marnix G. Witte [a], Marcel van Herk [a], Joos V. Lebesque [a]

[a] Department of Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam; and [b] Department of Radiation Oncology, Erasmus Medical Center – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

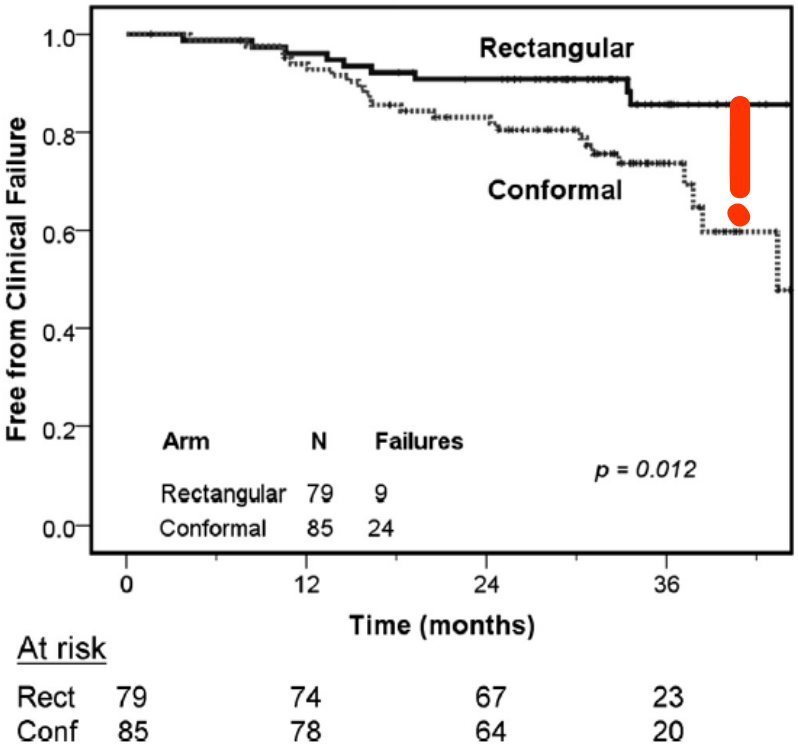
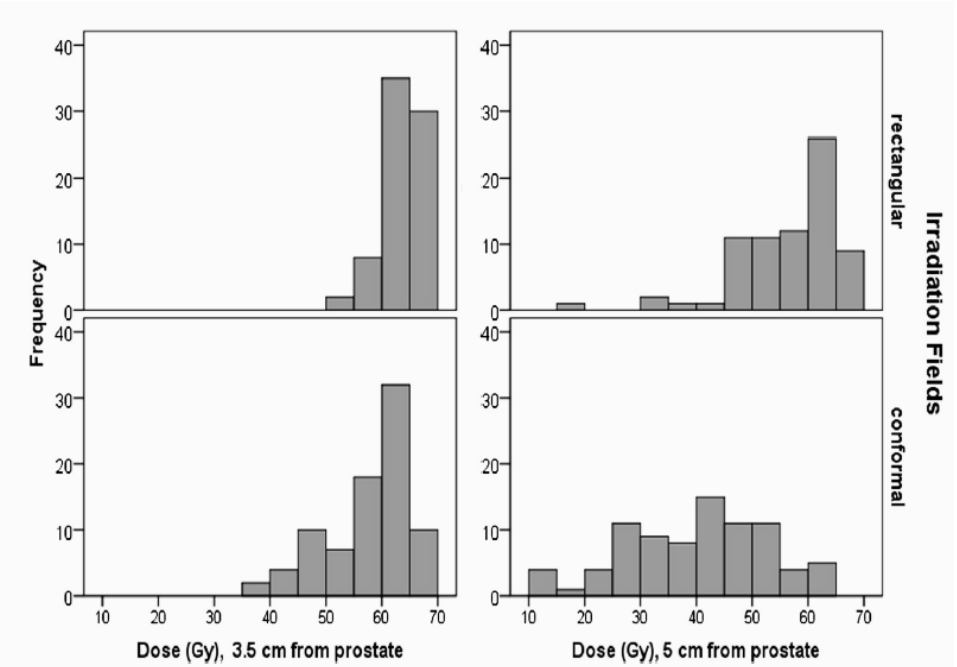


Fig. 2. Freedom from clinical failure for high-risk prostate cancer patients: rectangular arm versus conformal arm.

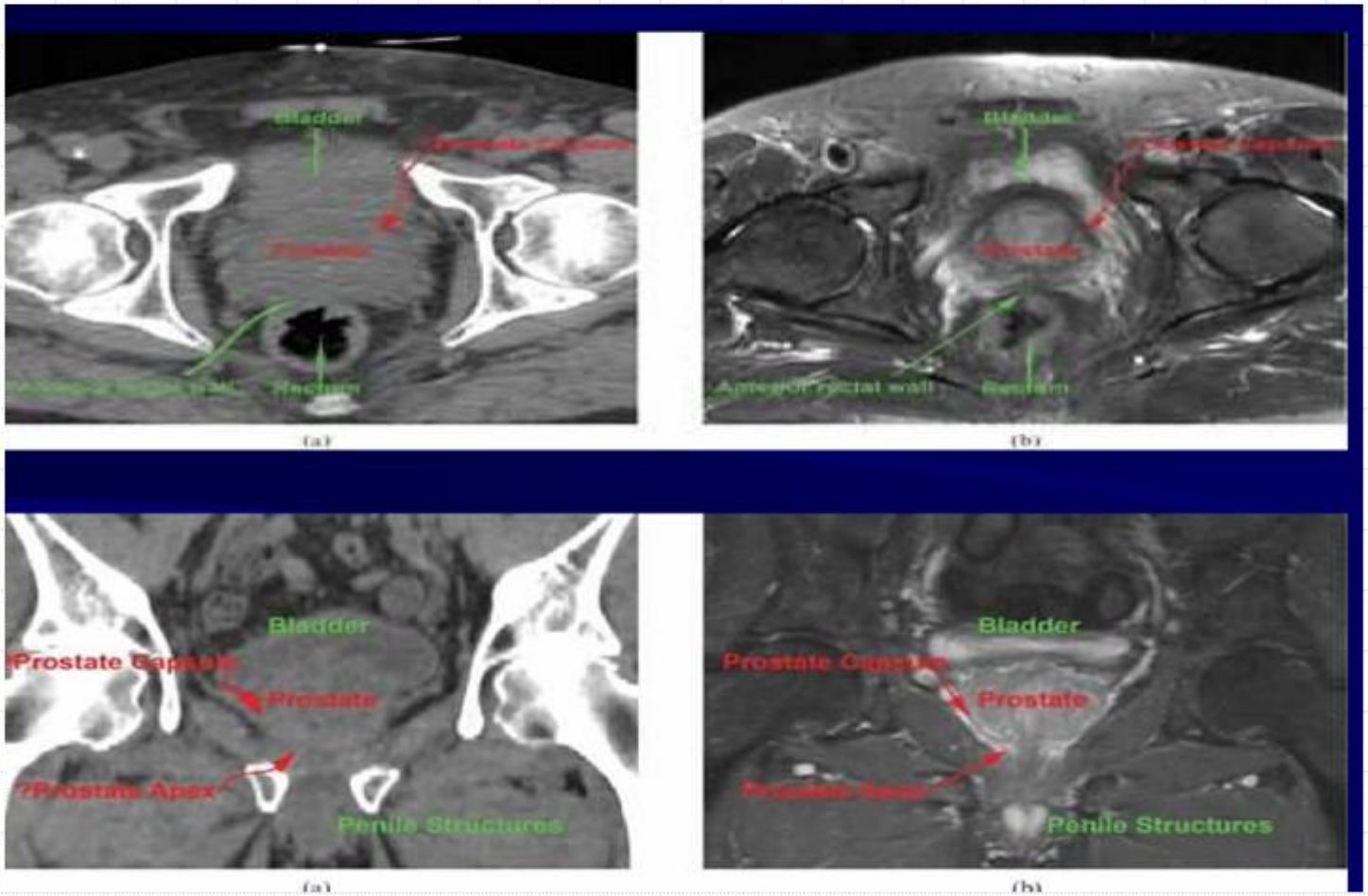


Courtesy of S.M. Magrini : 2013

3D-CRT e IMRT ?

.....problemi di imaging e contouring…

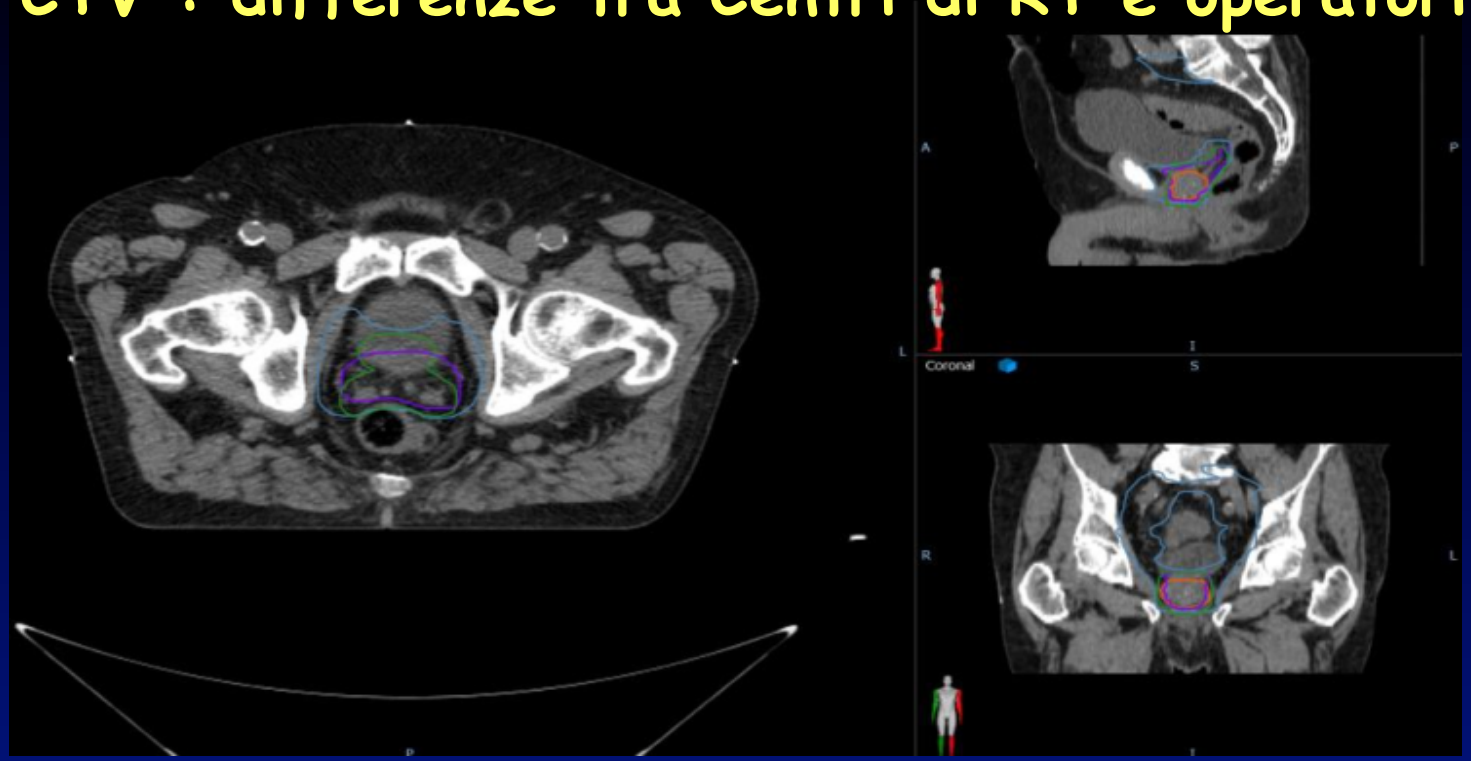
Lo standard per la pianificazione è la TC

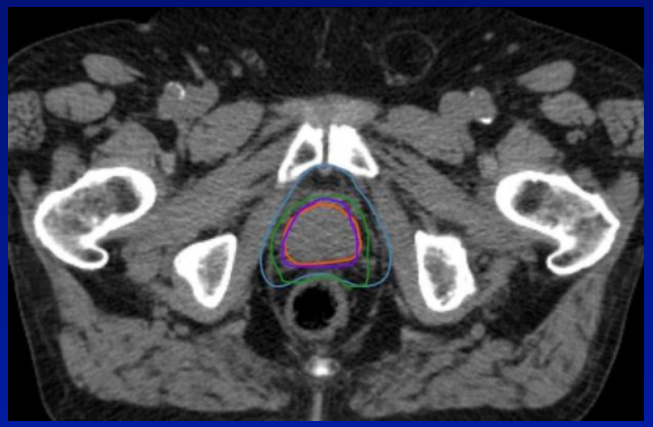


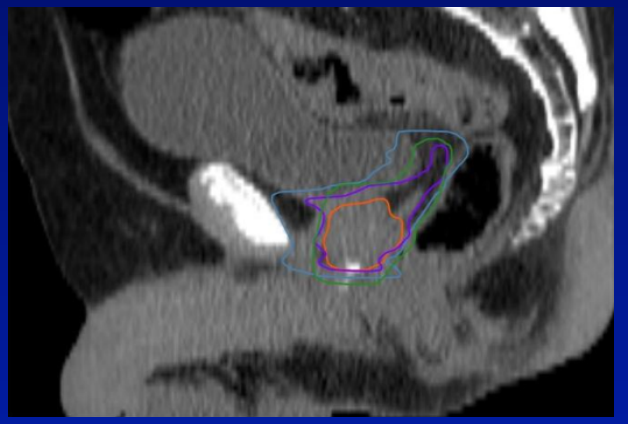
CT **MRI**

Courtesy of D. Genovesi: Brescia 2013

CTV : differenze tra Centri di RT e operatori

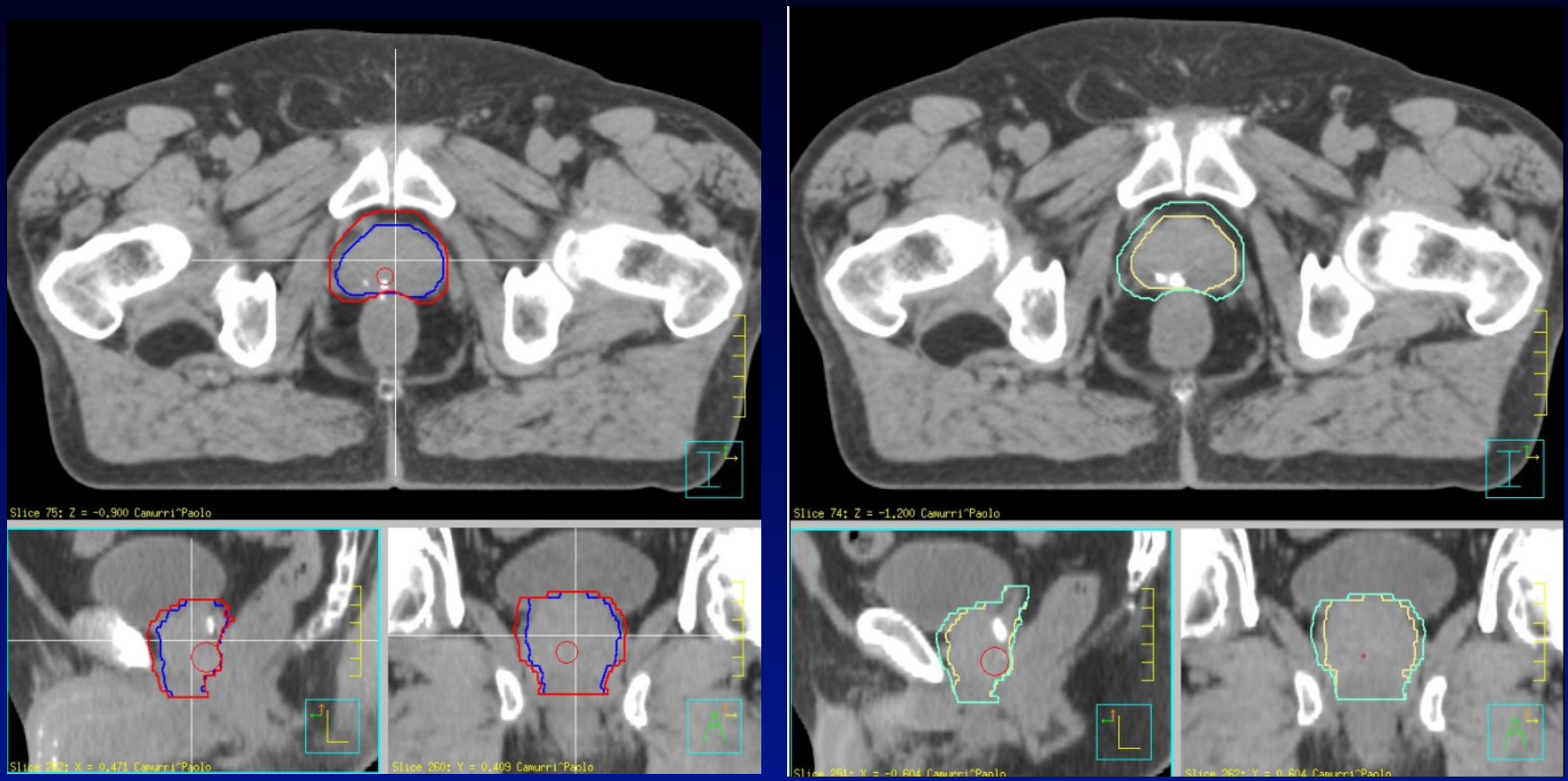






F. Bertoni, D. Genovesi, S.M.Magrini, L. Spiazzi: Brescia 2013

CTV volume prostatico secondo EORTC



- CTV Rischio intermedio (rosso)
- Prostata +5 mm
- VS 1 cm

- CTV Alto Rischio (verde)
- Prostata + 5 mm
- VS 2 cm

D. Boehmer et al : Radiotherapy and Oncology 79 (2006) 259-269

3D-CRT e IMRT

……come gestire i movimenti d'organo e le co-registrazioni ….

4D-RT ? ART ?

Prostate radiotherapy

An evaluation of intrafraction motion of the prostate in the prone and supine positions using electromagnetic tracking

Amish P. Shah*, Patrick A. Kupelian, Twyla R. Willoughby, Katja M. Langen, Sanford L. Meeks

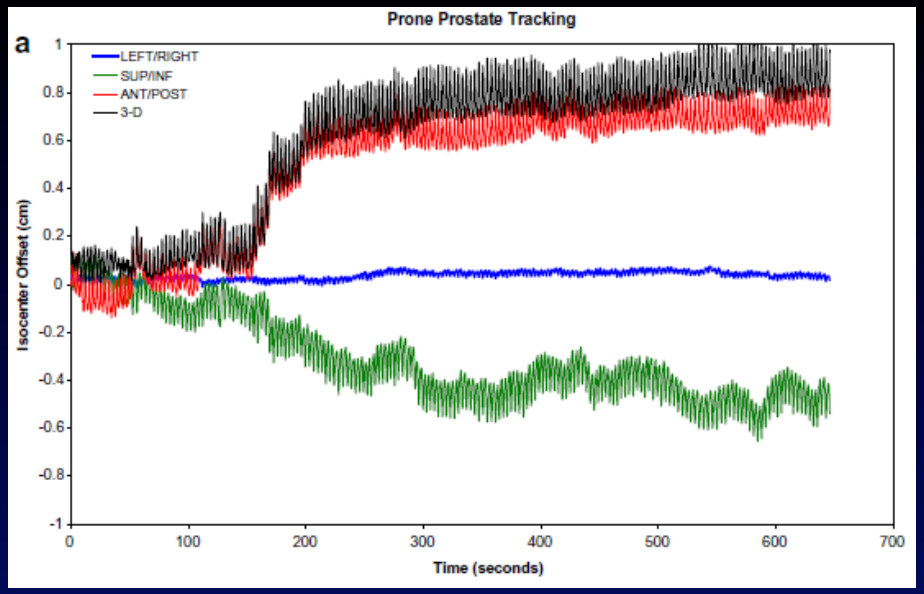
- 20 prostate pts (400 tracking sessions).
- supine treatment position with no immobilization beyond a knee cushion. Additional immobilization, bladder filling, or bowel preparation was intentionally excluded during prone tracking sessions,
- The fraction of time that the prostate was displaced by >3, 5, 7, and 10 mm was calculated for each patient, for both positions

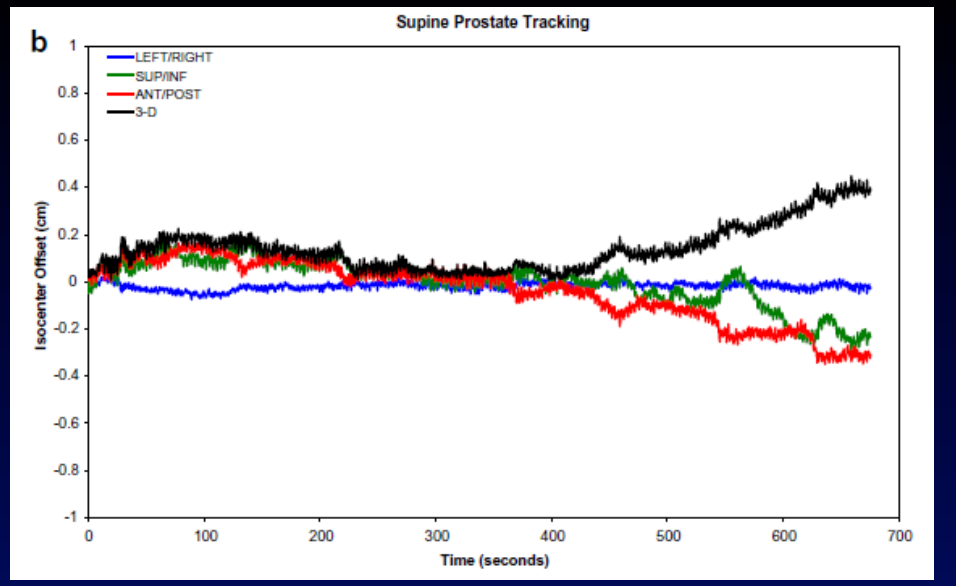
Results: Clear patterns of respiratory motion were seen in the prone tracks due to the influence of increased abdominal motion. Averaged over all patients, the prostate was displaced >3 and 5 mm for 37.8% and 10.1% of the total tracking time in the prone position, respectively. In the supine position, the prostate was displaced >3 and 5 mm for 12.6% and 2.9%, respectively. With both patient setups, inferior and posterior drifts of the prostate position were observed. Averaged over all prone tracking sessions, the prostate was displaced >3 mm in the posterior and inferior directions for 11.7% and 9.5% of the total time, respectively.

Conclusions: With real-time tracking of the prostate, it is possible to study the effects of different setup positions on the prostate mobility. The percentage of time the prostate moved >3 and 5 mm was increased by a factor of three in the prone versus supine position. For larger displacements (>7 mm) no difference in prostate mobility was observed between prone and supine positions. To reduce rectal toxicity, radiotherapy in the prone position may be a suitable alternative provided respiratory motion is accounted for during treatment. Acute and late toxicity results remain to be evaluated for both patient positions.

 Radiotherapy and Oncology 99 (2011) 37–43

A.P.Shah et al : Radiat Oncol 2011





Fraction of time prostate displaced by >10, >7, >5, and >3 mm calculated from the total tracking time for each patient.

	Prone		Supine	
	Average	Standard deviation	Average	Standard deviation
3D >3 mm (%)	37.8	17.2	12.6	14.5
3D >5 mm (%)	10.1	10.9	2.9	9.6
3D >7 mm (%)	2.4	4.2	1.5	5.5
3D >10 mm (%)	0.2	0.6	0.3	1.2

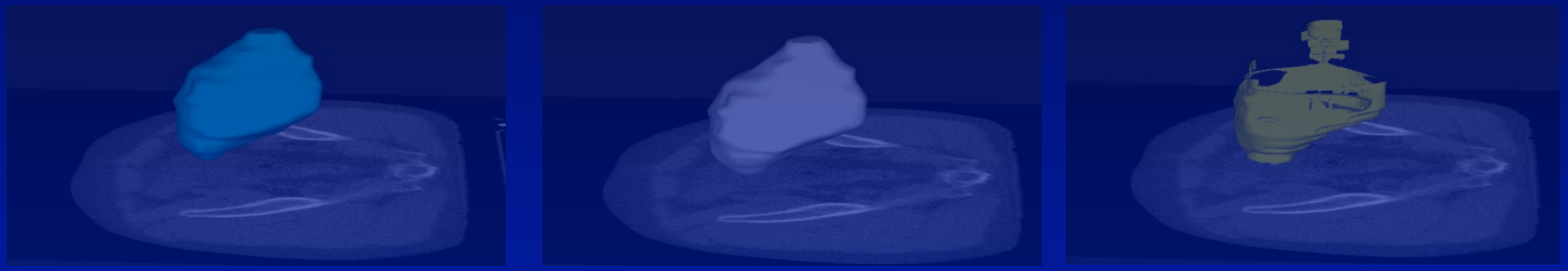
Rari gli spostamenti intra-frazione > 7 mm

A.P.Shah et al : Radiat Oncol 2011

Differenze volumi OAR tra KVCT di pianificazione e MVCT terapia

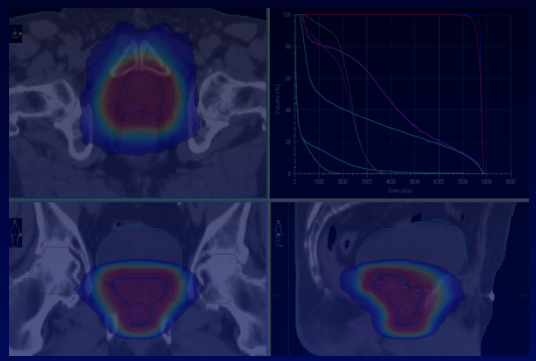
- Retto CT0 MVCT13 diff.: 39%

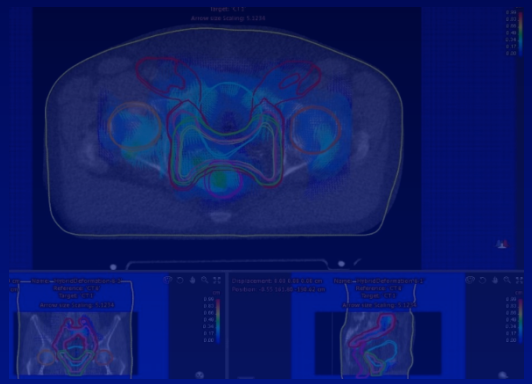
- Vescica CT0 MVCT8 diff.: 35%

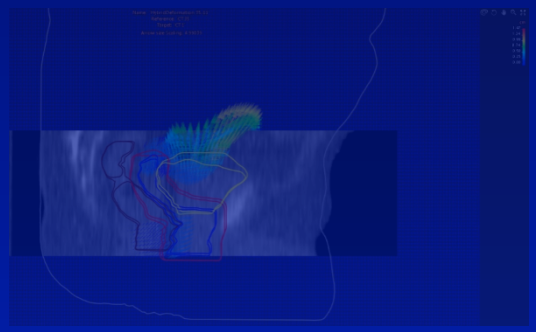


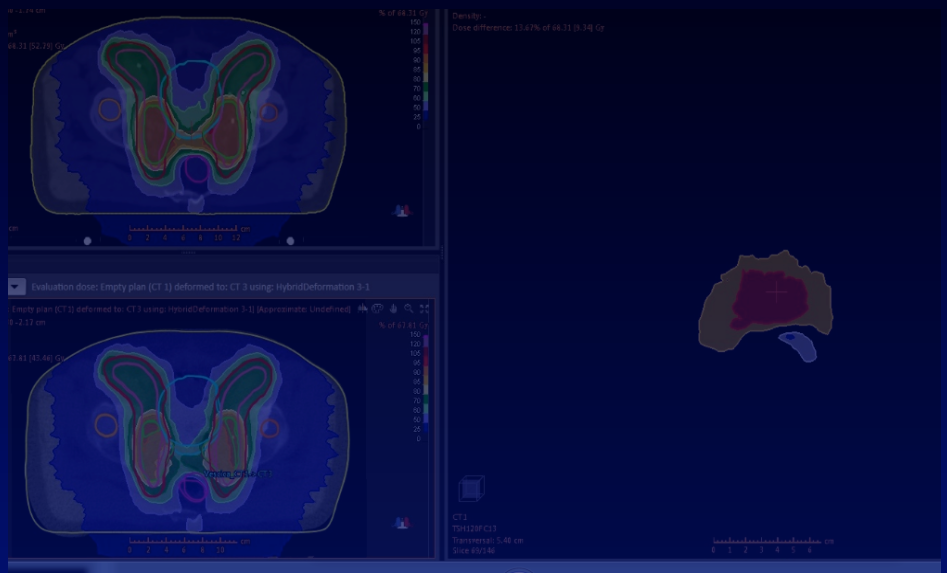
Courtesy of G. Guidi, N. Maffei, C. Vecchi : Modena 2013

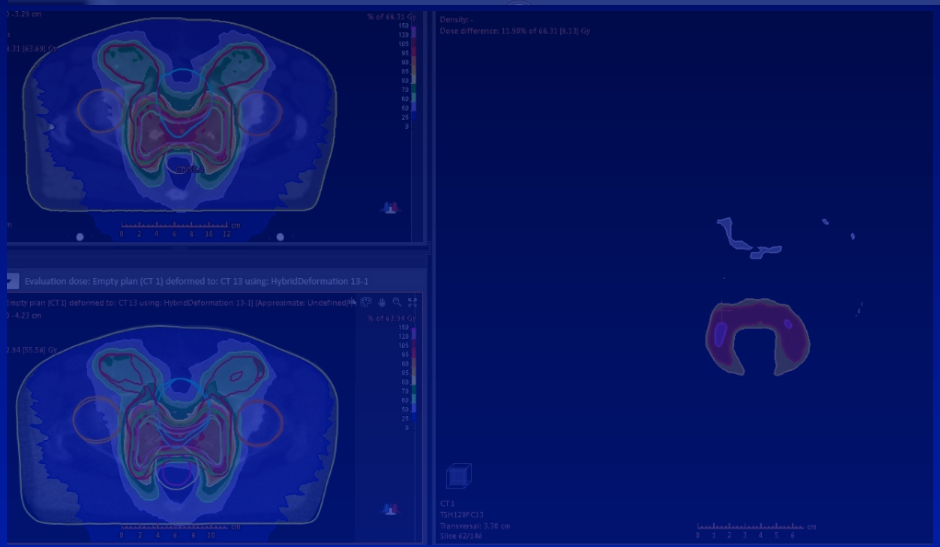
Deformazioni volumi e dosi
Vescica : -9 Gy rispetto ai previsti 53 Gy











Courtesy of G. Guidi, N. Maffei, C. Vecchi : Modena 2013

3D-CRT e IMRT

.....risultati e costi ....

SEER Medicare database 2002-2004

12598 paz. => 65 aa M0 (5845 IMRT , 6753 3D-CRT)

Tossicità GI (proctite, emorragia rettale) e GU (cistite, ematuria) a 24 mesi:

	IMRT	3D-CRT
GI globali	18,8%	22,2%
Rettali	3,5%	4,5%
GU	=	=
Disf. erettile	=	=

….IMRT is associated with fewer gastrointestinal problems after treatment…

J. Bekelman: ASTRO meeting, nov. 2010

Prostate cancer: ESMO Consensus Conference Guidelines 2012

13) Are sophisticated radiation planning and delivery techniques required for dose-escalated external beam radiotherapy?

Recommendation 13a: To reduce the adverse effects following radiotherapy, conformal radiotherapy should be used.
Level of evidence: I
Strength of recommendation: A

Recommendation 13b: Intensity-modulated with or without image-guided treatment techniques can be used to reduce normal tissue irradiation.
Level of evidence: III
Strength of recommendation: B

Annals of Oncology 2013

ASTRO
TARGETING CANCER CARE

Official Statement

FOR IMMEDIATE REVIEW

Renowned urologist Dr. Patrick Walsh and esteemed radiation oncologist Dr. Theodore DeWeese join ASTRO in denouncing physician self-referral and recommending passage of Promoting Integrity in Medicare Act (PIMA) by Congress

"As a urologist and a radiation oncologist, we collaborate every day to provide high quality prostate cancer care to our patients. Today, we are proud to continue our work together on behalf of patients by pressing for an end to the wasteful overtreatment of prostate cancer resulting from the physician self-referral law's loophole for radiation therapy services.

Urology-ownership of radiation therapy presents a clear conflict of interest, often with a for-profit motive, that risks overuse of intensity modulated radiation therapy (IMRT).

This activity is an affront to the vast majority of urologists and radiation oncologists who partner every day to provide well-coordinated care in community practices and hospitals without self-referral's additional financial incentives....."

ASTRO settembre 2013

…… il futuro prossimo …….

IMRT/IGRT

ipofrazionata come standard ?

ASTRO 2013

1,8- 2Gy/f è ancora lo standard !!

IMRT - IGRT- ART

RapidArc

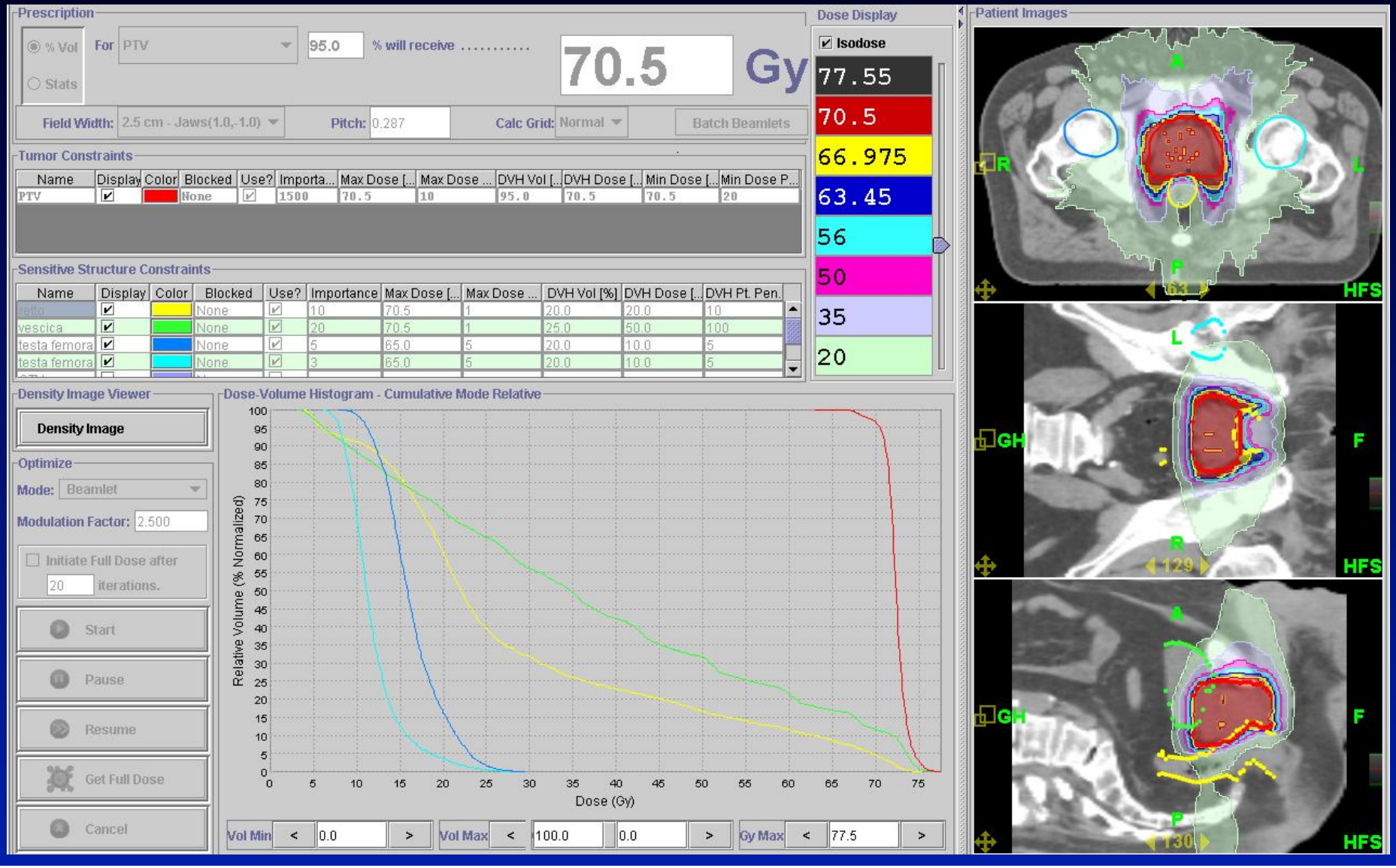
DAO

Tomotherapy

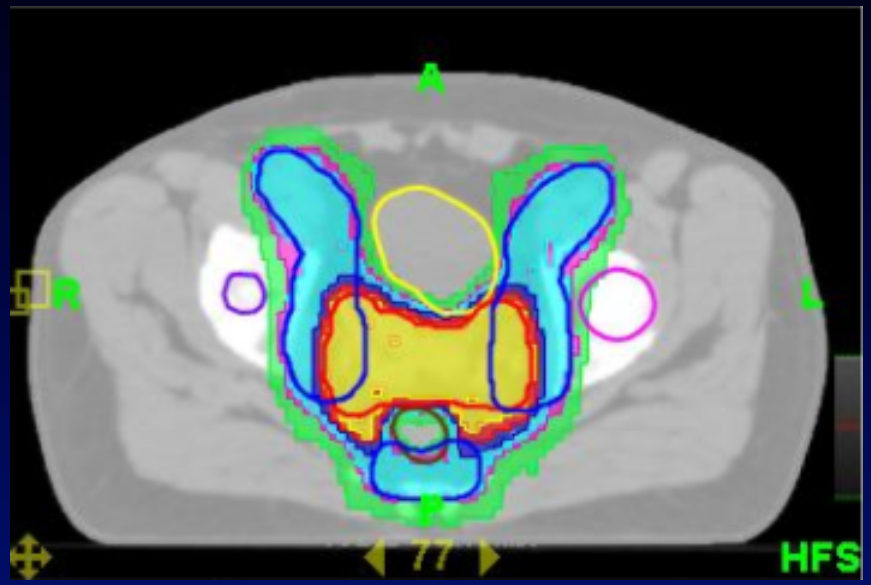
CyberKnife

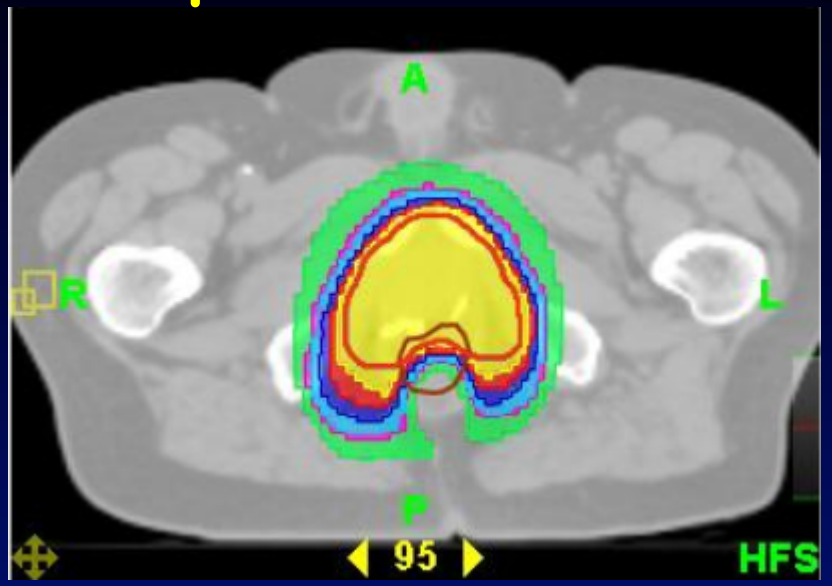
Vmat

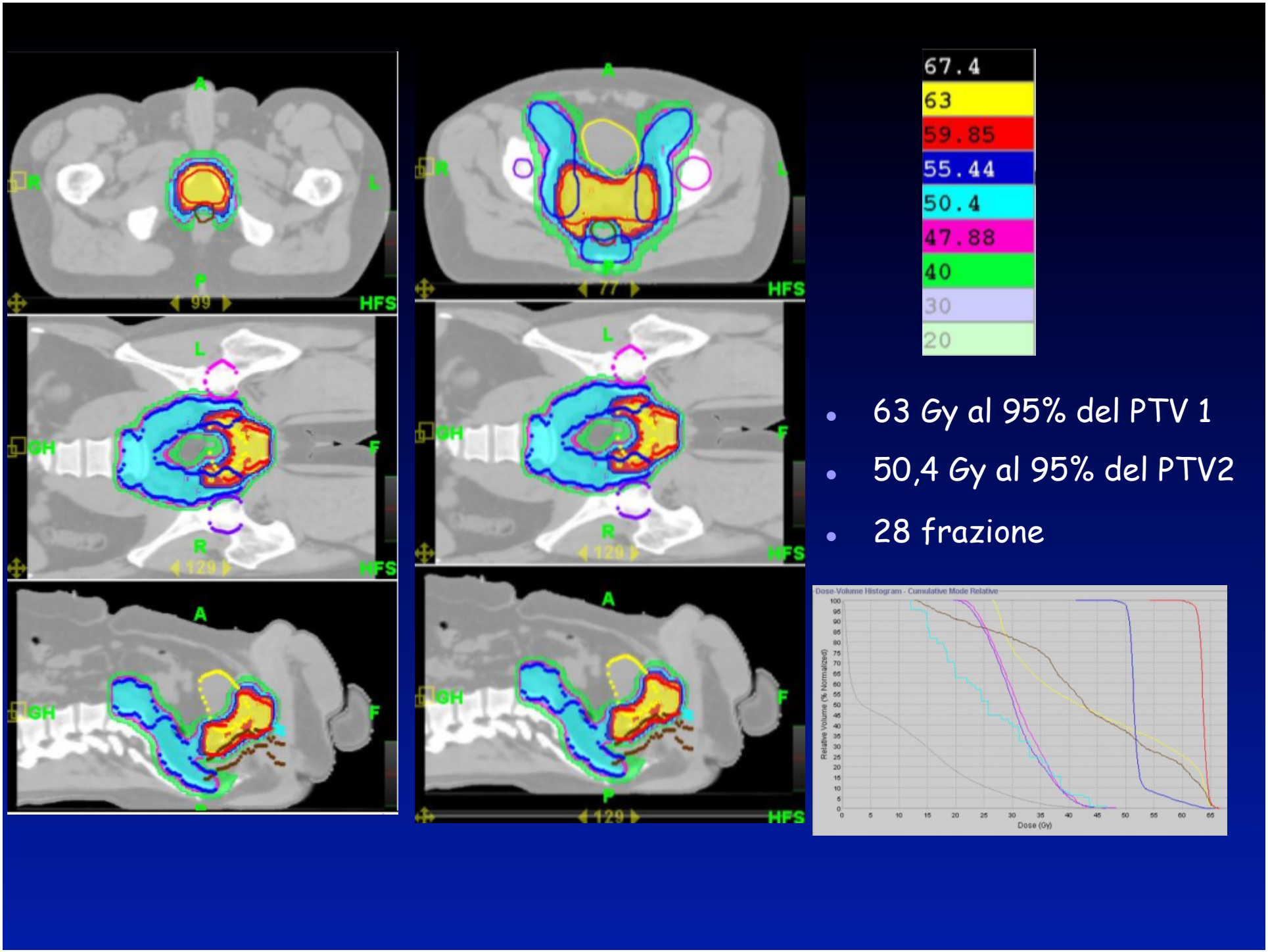
Adenoca prostatico con basso rischio di interessamento dei linfonodi pelvici
DF 2,5 Gy - DT 70 Gy x 28 frazioni (4,5 settimane di trattamento)
(**equivalenti a circa 80 Gy con frazionamento standard di 2 Gy** a frazione con LINAC, tempo di trattamento 8 settimane)



Tomotherapy – VMAT – RapidArc - DAO







- 63 Gy al 95% del PTV 1
- 50,4 Gy al 95% del PTV2
- 28 frazione

RT ipofrazionata e IGRT

Hypofractionated radiotherapy for localised prostate cancer. Review of clinical trials

Clin Transl Oncol (2009)

Víctor Macías · Albert Biete

ELSEVIER

Seminars in RADIATION ONCOLOGY

Hypofractionation for Prostate Cancer: A Critical Review

2008)

Edward F. Miles, MD, and W. Robert Lee, MD, MS, Med

.....Molti studi in corso...

Table 2 Ongoing Randomized Trials of Hypofractionation

Study	Eligible Patients	Randomization Arms	NTD_{2Gy} if α/β is: 1.5/5/10	Sample Size
Fox Chase*	Intermediate risk	76 Gy at 2 Gy *v*	76 Gy	300
	High risk	70.2 Gy at 2.7 Gy	84.3 Gy/77.2 Gy/74.3 Gy	
MRC	Low risk	70 Gy at 2 Gy *v*	70 Gy	
	Intermediate-risk	57 Gy at 3 Gy *v*	73.3 Gy/65.1 Gy/61.8 Gy	2,100
		60 Gy at 3 Gy	77.2 Gy/68.6 Gy/65 Gy	
NCIC	Intermediate risk	78 Gy at 2 Gy *v*	78 Gy	1,204
		60 Gy at 3 Gy	77.2 Gy/68.6 Gy/65 Gy	
RTOG 0415	Low risk	73.8 Gy at 1.8 Gy *v*	70.1 Gy	1,067
		70 Gy at 2.5 Gy	80 Gy/75 Gy/72.9 Gy	

Abbreviations: MRC, Medical Research Council; NCIC, National Cancer Institute of Canada; RTOG, Radiation Therapy Oncology Group.
*Study completed accrual May 2006.

4 RCT : tossicità acuta e tardiva sovrapponibile alla RT convenzionale

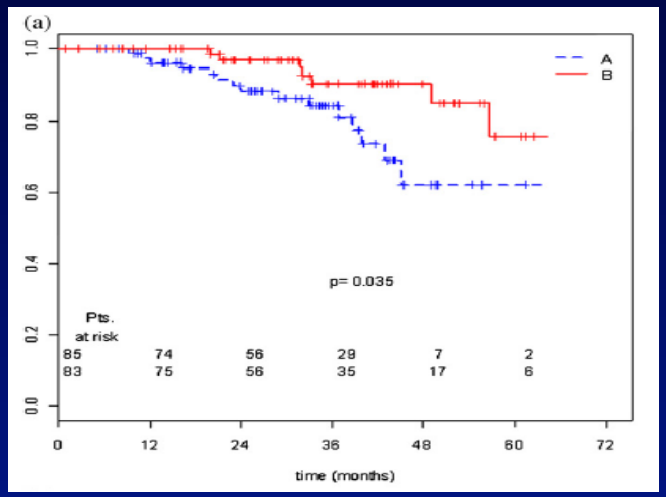
Possibili vantaggi in costi e qualità di vita

CLINICAL INVESTIGATION **Prostate**

A PROSPECTIVE PHASE III RANDOMIZED TRIAL OF HYPOFRACTIONATION VERSUS CONVENTIONAL FRACTIONATION IN PATIENTS WITH HIGH-RISK PROSTATE CANCER

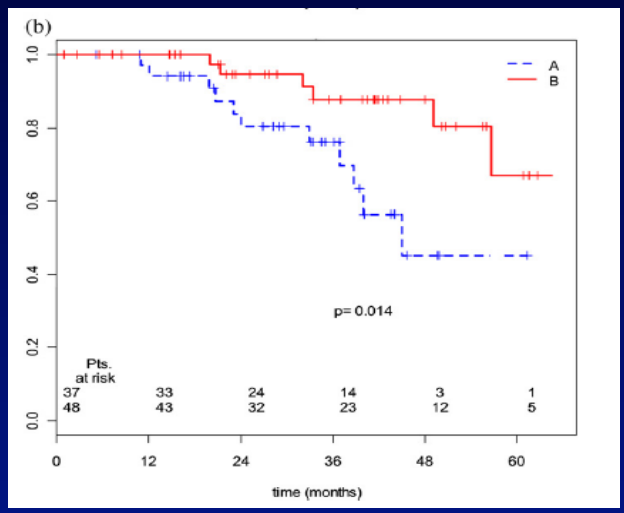
GIORGIO ARCANGELI, M.D.,* BIANCAMARIA SARACINO, M.D.,* SARA GOMELLINI, M.D.,* MARIA GRAZIA PETRONGARI, M.D.,* STEFANO ARCANGELI, M.D.,* STENO SENTINELLI, M.D.,‡ SIMONA MARZI, PH.D.,† VALERIA LANDONI, PH.D.,† JACK FOWLER, D.SC., PH.D.,§ AND LIDIA STRIGARI, PH.D.†

"..**hypofractionated (62 Gy/20 fractions/5 weeks, 4 fractions per week)** vs. conventional fractionation RT (80 Gy/40 fractions/8 weeks) in pts with high-risk prostate cancer "



3D-CRT

Mean FUP 32 mths



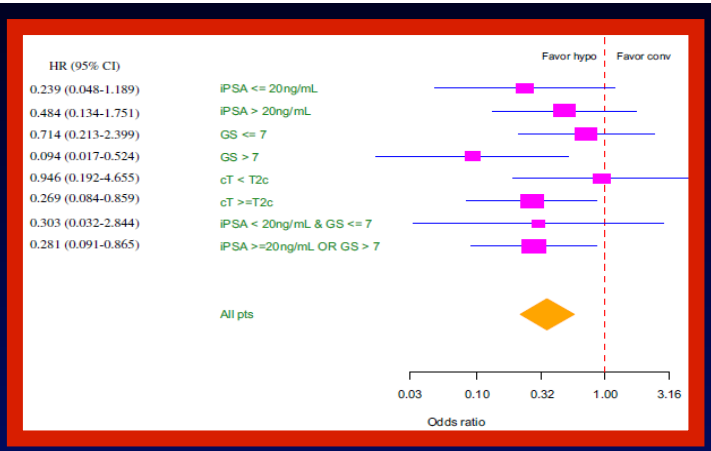
...vantaggi con l' ipofrazionamento con riduzione del 70% del rischio di recidiva biochimica (p = 0.009)

Arcangeli, IJROBP, 2009

CLINICAL INVESTIGATION **Prostate**

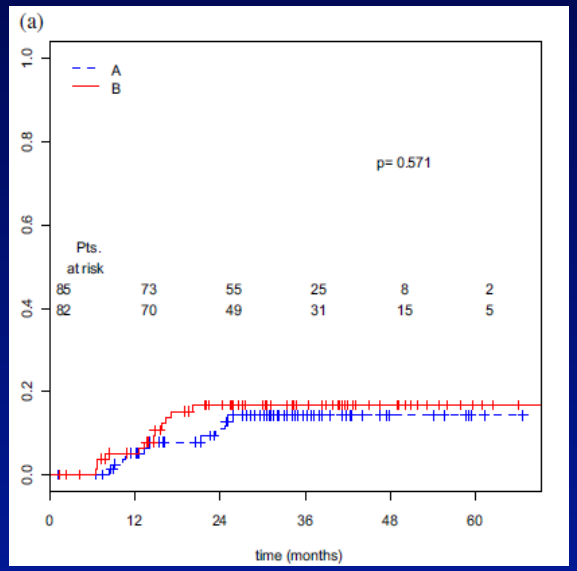
A PROSPECTIVE PHASE III RANDOMIZED TRIAL OF HYPOFRACTIONATION VERSUS CONVENTIONAL FRACTIONATION IN PATIENTS WITH HIGH-RISK PROSTATE CANCER

GIORGIO ARCANGELI, M.D.,* BIANCAMARIA SARACINO, M.D.,* SARA GOMELLINI, M.D.,* MARIA GRAZIA PETRONGARI, M.D.,* STEFANO ARCANGELI, M.D.,* STENO SENTINELLI, M.D.,‡ SIMONA MARZI, PH.D.,† VALERIA LANDONI, PH.D.,† JACK FOWLER, D.SC., PH.D.,§ AND LIDIA STRIGARI, PH.D.†



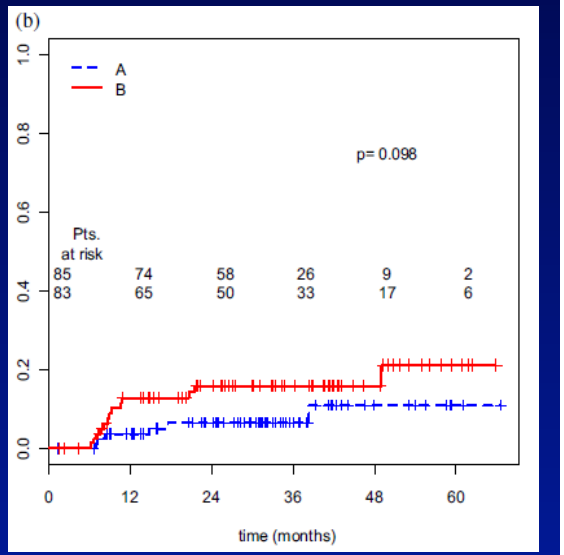
HR = 0.3

Forest Plot in favour of Hypofractionated



Tossicità G2 a 3 aa

- **GI**: 17% vs 14%
- **GU**: 16% vs 11%



.....Tossicità acuta e tardiva NON significativamente differenti.....

.....SBRT ablativa....

Ipofrazianata → Ultraipofrazionata

Table 2 Phase I/II Ultrahypofractionation Trials: Schedules and Equivalent Total Doses in 2 Gy Fractions

Fractionation (tot.dose/fx size/#fx)	Total Dose Equivalent in 2 Gy Fractions (NTD_2) Alpha/Beta = 1.5 (tumor)	Alpha/Beta = 3 (late effects)	No. of PTS	Institution	References
33.5 Gy/6.7 Gy/5 fx	78 Gy	64.9 Gy	40	Virginia Mason	Madsen et al[36]
36.25 Gy/7.25 Gy/5 fx	90.6 Gy	74.3 Gy	25 (ongoing)	Stanford	Pawlicki et al[37]
42.7 Gy/6.1 Gy/7 fx	92.7 Gy	77.7 Gy	105	Umea	Widmark (personal communication, 2008)
35 Gy/7 Gy/5 fx	85.1 Gy	70 Gy	30 (ongoing)	University of Toronto	Tang et al[38]
47.5 Gy/9.5 Gy/5 fx	149 Gy*	118 Gy	15	UTSW, Dallas	Timmerman (personal communication, 2008)
50 Gy/10 Gy/5 fx	164 Gy	130 Gy	10 (ongoing)		
52.5 Gy/10.5 Gy/5 fx	180 Gy	142 Gy	—		

*NTD doses based on linear-quadratic modeling may overpredict NTDs for large fractions, as in the UTSW trial.

...solo nell'ambito di studi controllati !!...

Stereobody: Cyberknife – Tomotherapy - VMAT

41 pazienti a basso rischio
7,25 Gy/fr. X 5 fraz → 36,5 Gy

Ritter 2007

210 pts treated with Tomotherapy or Linac-based IMRT

- 110 pts 64.7 Gy\22 fx of 2.94 Gy
- 50 pts 58.08 Gy\16 fx of 3.63 Gy
- 50 pts 51.6 Gy\12 fx of 4.3 Gy

RT in 16 frazioni

20-30 % with acute grade 2 GU toxicity

5-10 % with acute grade 2 GI toxicity

Risultati incoraggianti anche in termini di tossicità acuta e tardiva

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

Radiotherapy and Oncology 107 (2013) 153–158

Prostate radiotherapy

Prostate stereotactic ablative body radiotherapy using a standard linear accelerator: Toxicity, biochemical, and pathological outcomes

Andrew Loblaw [a,b,d,*,1], Patrick Cheung [a,b,1], Laura D'Alimonte [a,d], Andrea Deabreu [d], Alexandre Mamedov [d], Liying Zhang [a], Colin Tang [e], Harvey Quon [f], Suneil Jain [g], Geordi Pang [a,d], Robert Nam [c,d]

A B S T R A C T

Materials and methods: A phase I/II study was performed where low risk localized prostate cancer received SABR 35 Gy in 5 fractions, once weekly on standard linear accelerators. Common Terminology

Results: As of May 2012, 84 patients have completed treatment with a median follow-up of 55 months (range 13–68 months). Median age was 67 years and median PSA was 5.3 ng/ml. The following toxicities were observed: acute grade 3+: 0% gastrointestinal (GI), 1% genitourinary (GU), 0% fatigue; late grade 3+: 1% GI, 1% GU. Ninety-six percent were biopsy negative post-treatment. The 5-year BC was 98%.

Conclusions: This novel technique employing standard linear accelerators to deliver an extreme hypofractionated schedule of radiotherapy is feasible, well tolerated and shows excellent pathologic and biochemical control.

Radiotherapy and Oncology 107 (2013) 153–158

..... ma erano **Low - Risk**.....

RTOG 0938 Low Risk!!!

A RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED RADIOTHERAPY FOR FAVORABLE RISK PROSTATE CANCER

Patient Population: Histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days of randomization; Gleason scores 2-6; Clinical stage T1-2a; PSA < 10 ng/mL (PSA should not be obtained within 10 days after prostate biopsy).

- GPS: 2-6
- T1-2a (AJCC 7th ed.)
- PSA < 10 ng/mL

SCHEMA

STRATIFY		RANDOMIZE	
	Treatment techniques/machine 1. All linear accelerator based treatment (excluding Cyberknife) 2. Cyberknife 3. Protons		Arm 1 36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days)* Arm 2 51.6 Gy in 12 daily fractions of 4.3 Gy over two and a half weeks (in 16-18 days)*

*For proton doses, see Section 6.1.4.

Document History		
	Version/Update Date	Broadcast Date
Amendment 2	July 24, 2013	August 9, 2013
Update	November 8, 2012	November 8, 2012
Amendment 1	October 22, 2012	November 8, 2012
Update	November 17, 2011	November 17, 2011
Activation	September 1, 2011	September 29, 2011

Previsti: ~~174~~ → 240 dal 24/7/2013 (open)

the center must be credentialed for both IMRT and for prostate (IGRT).

Hindawi Publishing Corporation
Prostate Cancer
Volume 2013, Article ID 103547, 11 pages
http://dx.doi.org/10.1155/2013/103547

Review Article

Hypofractionated External-Beam Radiotherapy for Prostate Cancer

L. Chinsoo Cho,[1] Robert Timmerman,[2] and Brian Kavanagh[3]

Prospective trials of hypofractionated external-beam radiotherapy (5 fractions).

Author	No. of patients	Type of study	Patient characteristics NCCN risk group	HYPO FX Total dose(Gy)/fractional dose(Gy)	Median follow up (months)	PSA control	Late GU toxicity		Late GI toxicity	
Madsen et al. [53, 54]	40	Phase I/II	Low risk	33.5/6.7	60	93%* at 5 years	12.5% 2.5%	Gr-2 Gr-3	12.5% 0%	Gr-2 Gr-3
Tang et al. [55]	30	Phase I/II	Low risk	35/7	12	—	13% 0%	Gr-2 Gr-3	7% 0%	Gr-2 Gr-3
King et al. [56, 57]	67	Phase II	Low risk	36.25/7.25	32	94%* at 4 years	3% 5%	Gr-2 Gr-3	2% 0%	Gr-2 Gr-3
McBride et al. [58]	45	Phase I	Low risk	36.25/7.25 37.5/7.5	44.5	98%* at 3 years	17% 2%	Gr-2 Gr-3	7% 5%	Gr-2 Gr-3
Boike et al. [59]	45	Phase I	Low-Intermediate risk	45/9 47.5/9.5 50/10	12–30	100%*	9% 4% Late toxicity after 90 days	Gr-2 Gr-3	4% 0% 2% Late toxicity after 90 days	Gr-2 Gr-3 Gr-4

No.: Number, HYPO FX: hypofractionation, STD FX: standard, Gy: Gray, FX: fractionation, *: by Phoenix definition, NS: not significantly different, GS: Gleason's score.

IR

..... ma prevalentemente per Low - Risk.....

HUMANITAS
CANCER CENTER

2013

RADIATION ONCOLOGY

RESEARCH Open Access

Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years

Alan J Katz[1*], Michael Santoro[1], Fred Diblasio[2] and Richard Ashley[3]

Pts IR/HR = 30%

Background: Stereotactic body radiotherapy (SBRT) may yield disease control for prostate cancer in a brief, hypofractionated treatment regimen without increasing treatment toxicity. Our report presents a **6-year update from 304 low- (n = 211), intermediate- (n = 81), and high-risk (n = 12) prostate cancer patients** who received CyberKnife SBRT.

Methods: The first 50 patients received a total dose of **35 Gy in 5 fractions of 7 Gy**. The subsequent 254 patients received a total dose of **36.25 Gy in 5 fractions of 7.25** Gy.

Courtesy of M. Scorsetti: Taormina 2013

HUMANITAS
CANCER CENTER

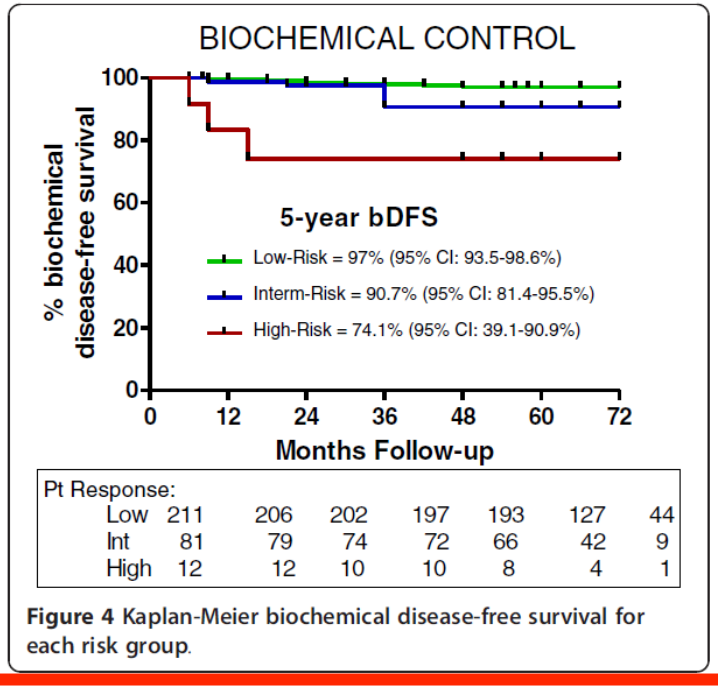


Figure 4 Kaplan-Meier biochemical disease-free survival for each risk group.

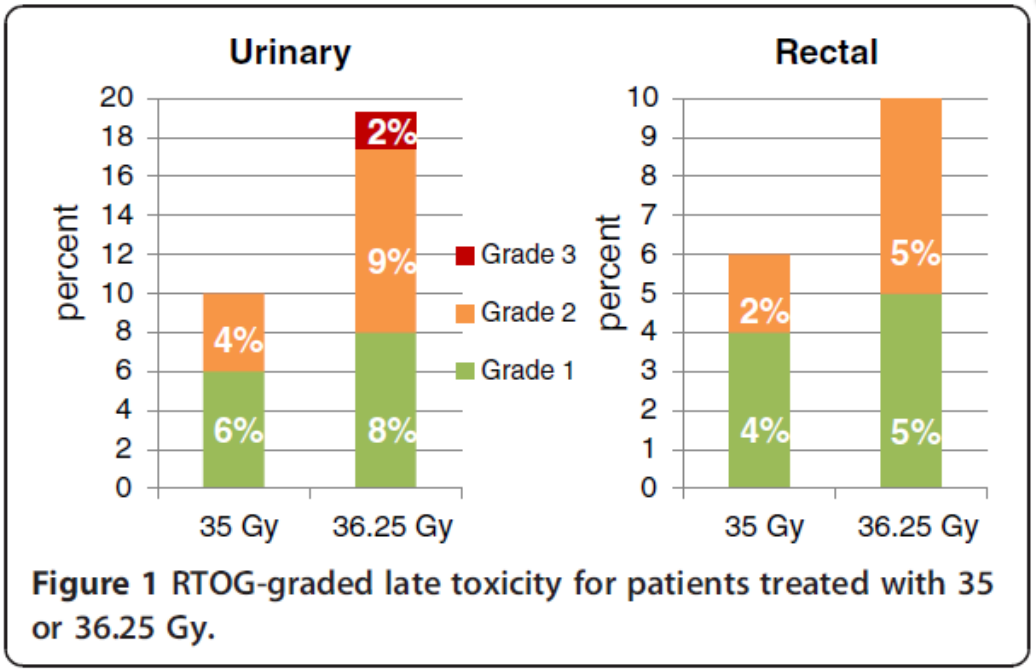


Figure 1 RTOG-graded late toxicity for patients treated with 35 or 36.25 Gy.

Conclusions: In this large series with long-term follow-up, we found **excellent biochemical control rates and low and acceptable toxicity**, outcomes consistent with those reported for from high dose rate brachytherapy (HDR BT).

Provided that measures are taken to account for prostate motion, **SBRT's distinct advantages over HDR BT** include its **non invasiveness and delivery to patients without anesthesia or hospitalization.**

Courtesy of M. Scorsetti: Taormina 2013

Alongi et al. Radiation Oncology 2013, 8:171

RADIATION ONCOLOGY

RESEARCH Open Access

Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: preliminary report of a phase II study

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Abstract

Background: To evaluate the feasibility and early side effects of a short course hypo-fractionated SBRT programme with Volumetric Modulated Arc Therapy (VMAT) and Flattening Filter Free (FFF) beams.

Methods: A prospective phase II study, started on February 2012. Inclusion criteria were: age ≤ 80 years, WHO-PS ≤ 2, PSA ≤ 20 ng/ml, histologically proven prostate adenocarcinoma, T1-T2 stage, no distant metastases, no previous surgery other than TURP, no malignant tumours in the previous 5 years, IPSS 0–7. The schedule was 35 Gy in 5 alternative days. SBRT was delivered with RapidArc VMAT, with 10MV FFF photons. Toxicity assessment was performed according to CTCAE v4.0 scale. EPIC questionnaires assessed Quality-of-Life. Neo-adjuvant/concomitant hormonal-therapy was prescribed according to risk classification. SpaceOAR™ gel was optionally implanted to increase the separation space between the prostate and the rectal wall.

Results: Median follow-up was 11 months (range: 5–16); 40 patients were recruited in the protocol and treated. According to NCCN criteria, 26/40 patients were low-risk and 14/40 were intermediate risk. Median age was 70 years (56–80), median initial PSA was 6.25 ng/ml (0.50-13.43 ng/ml). Median Gleason score was 6 (6–7). All patients completed the treatment as programmed (median 11.8 days (9–22). Acute Toxicities were as follow: Rectum G0: 30/40 cases (75%); G1: 6/40 (15%); G2: 4/40 (10%). Genito-urinary: G0: 16/40 (40%); G1: 8/40 (20%); G2: 16/34 (40%). In two G2 urinary retention cases, intermittent catheter was needed. No acute G3 or greater toxicity was found. Median treatment time was 126 sec (120–136). SpaceOAR™ was implanted in 8 patients. PSA reduction from the pre-treatment value of the marker was documented in all patients.

Conclusions: Early findings suggest that SBRT with RapidArc and FFF beams for prostate cancer in 5 fractions is feasible and tolerated in acute setting. Longer follow-up is needed for assessment of late toxicity and outcome.

Keywords: Prostate, RapidArc, Stereotactic body radiation therapy

Studio Fase I-II

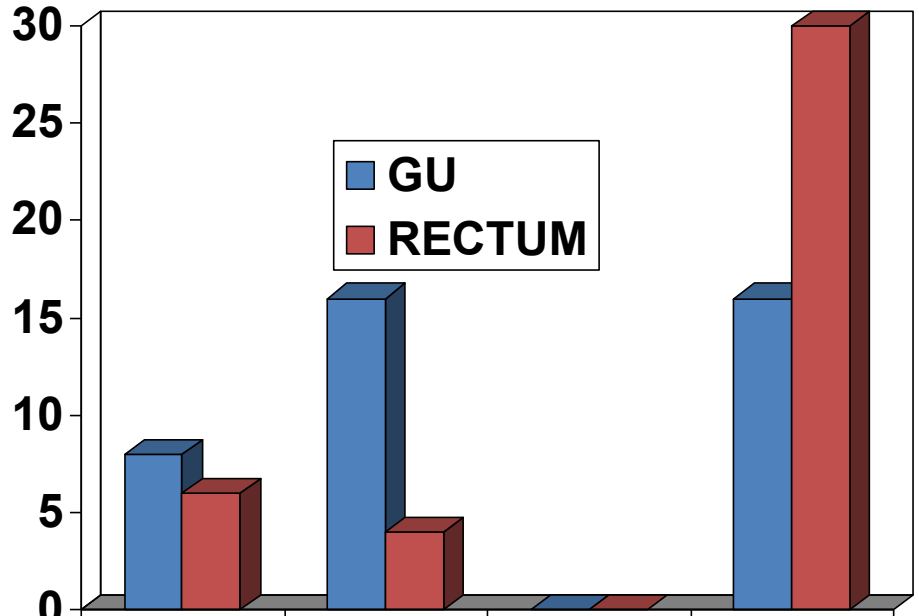
IR: 14/40 pts

HUMANITAS
CANCER CENTER

PRELIMINARY RESULTS (40 pts):

Acute Toxicity

- Dose: 35 Gy in 5 fractions
- Median follow-up: 11 months
- SpaceOAR: 8 pts



	G1	G2	G3	G0
GU	8	16	0	16
RECTUM	6	4	0	30

Courtesy of M. Scorsetti: Taormina 2013

INTERNATIONAL JOURNAL OF UROLOGY

International Journal of Urology (2012) 19, 296–305 doi: 10.1111/j.1442-2042.2012.02961.x

Review Article

Carbon-ion radiation therapy for prostate cancer

Hitoshi Ishikawa,[1,2] Hiroshi Tsuji,[2] Tadashi Kamada,[2] Koichiro Akakura,[2] Hiroyoshi Suzuki,[2] Jun Shimazaki,[2] Hirohiko Tsujii[2] and the Working Group for Genitourinary Tumors

[1]Department of Radiation Oncology, Tsukuba University Faculty of Medicine, Tsukuba, Ibaraki, and [2]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Inage, Chiba, Japan

… anche IR/ HR : 768/927 pazienti

Table 2 Characteristics of patients treated in the protocol 9904

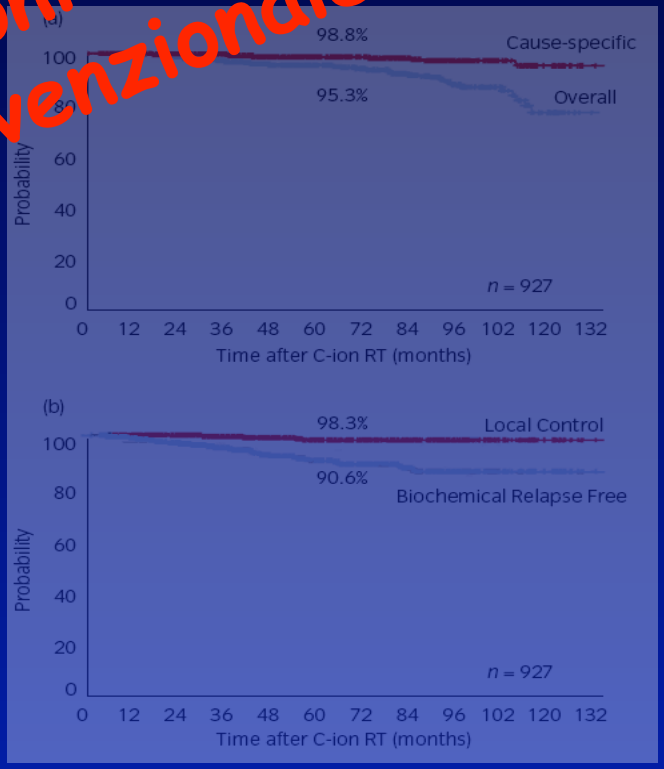
Characteristics	No. patients (%)
Age (years)	47–92 (Average, 67.6)
Risk group	
Low	150 (17.2%)
Intermediate	268 (30.0%)
High	490 (52.8%)
T-stage (1997 UICC)	
T1b–T2a	413 (52.0%)
T2b	152 (19.6%)
T3a–T3b	263 (28.3%)
Initial PSA value (median, 12.0 ng/mL)	
<10 ng/mL	413 (44.6%)
10–19.9 ng/mL	238 (25.7%)
≥20 ng/mL	276 (29.8%)
Gleason score	
5–6	216 (23.3%)
7	453 (48.9%)
8–10	258 (27.8%)

Risultati molto buoni confrontati con RT convenzionale

BED

63 GyE/ 20 fr

57,6 GyE/16 fr



vi è la necessità di studi di fase III !!

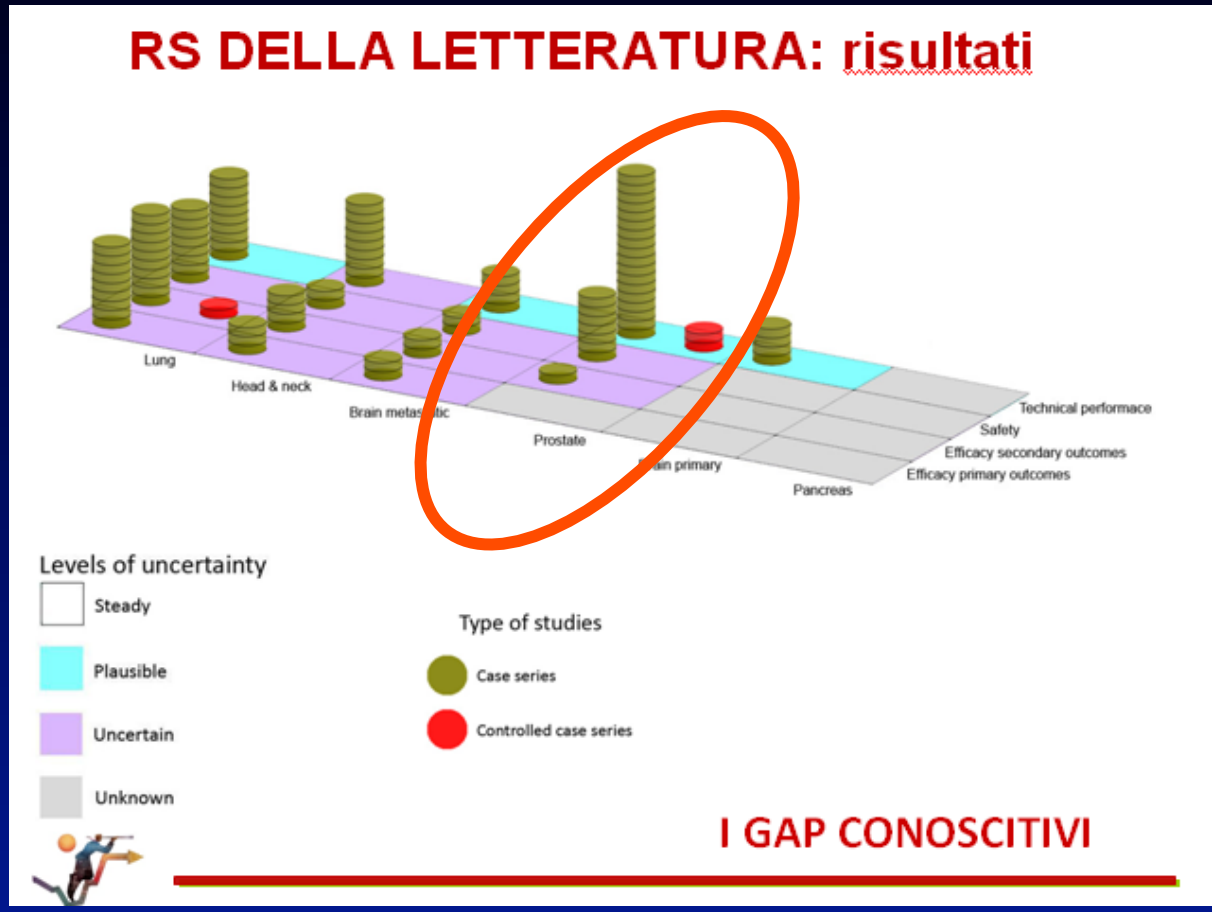
….di Technology assessment….

AMBITI DI DISCUSSIONE E RICERCA

- Vantaggi con dosi elevate? SI
- RTT sulle stazioni linfonodali ? NI
- Ruolo della ormonoterapia ? SI
- Tecniche e RT ipofrazionata ? NI

..... Lo studio R.E.R. .....

Analisi della letteratura sul ruolo e risultati clinici della IMRT/IGRT

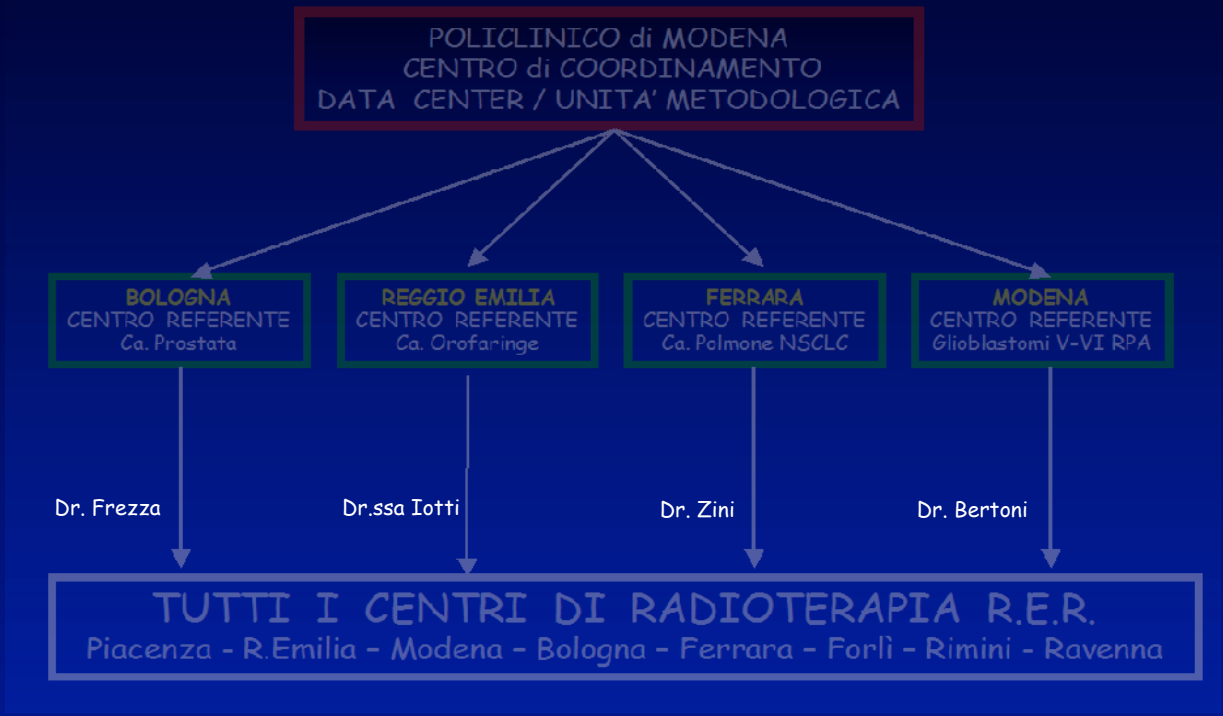


…….Nessuna conclusione possibile su: tossicità, controllo tumorale, efficacia clinica

…..necessari studi appropriati con RCT di confronto con i trattamenti standard con adeguato follow-up

Validità scientifica della proposta : metodologia

Il progetto propone un modello di introduzione controllata nella pratica clinica delle nuove tecnologie, entro la rete del sistema sanitario della R.E.R.

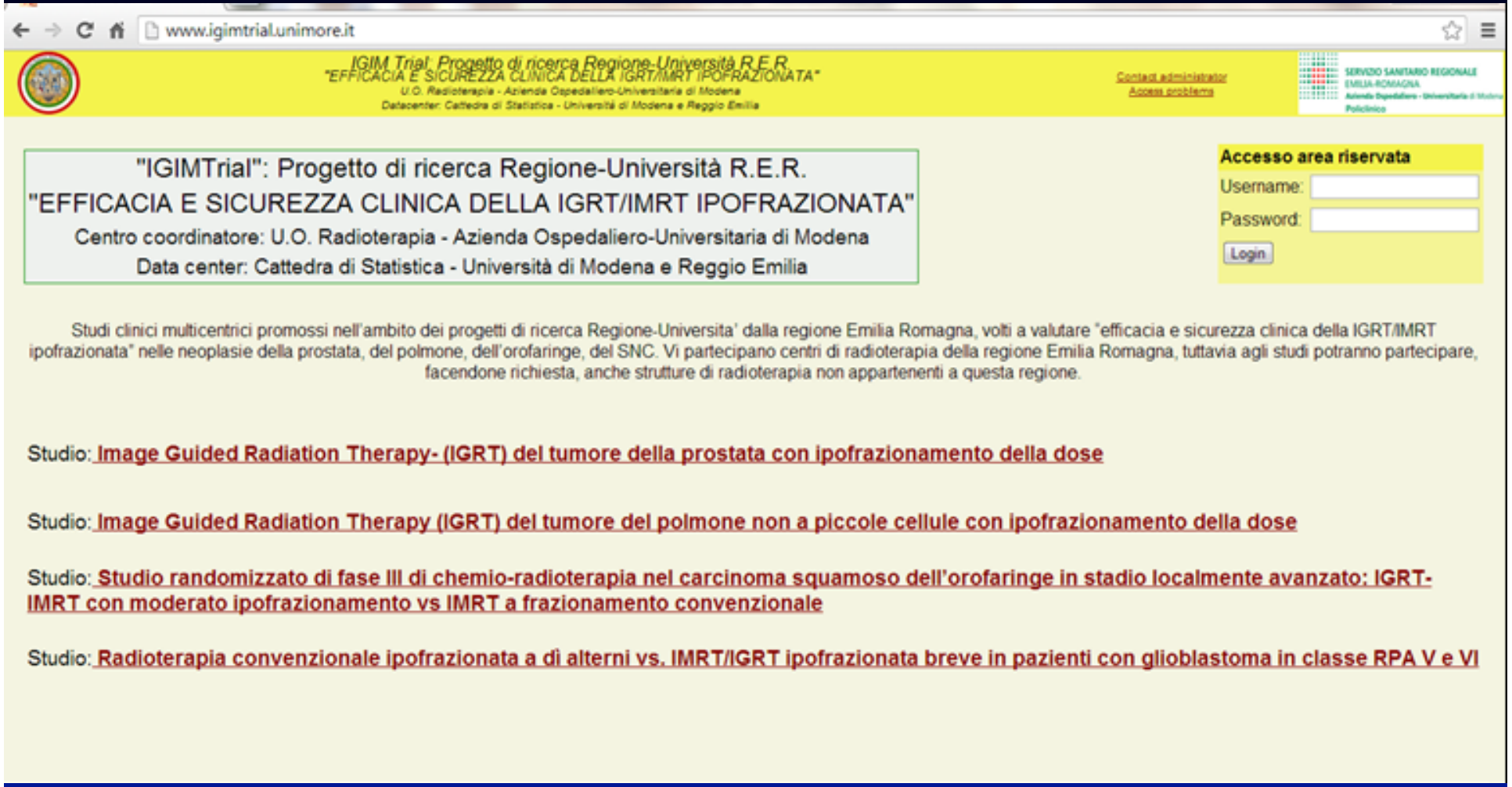


Responsabili Centri RT R.E.R.

- Pr.ssa Barbieri
- Dr. Bertoni
- Dr..Emiliani
- Dr. Frezza
- Dr. Fumagalli
- Dr.ssa Iotti
- Dr. Mazzarotto
- Dr. Perini
- Dr. Polico
- Dr. Vanzo
- Dr. Zini

Previsti **4 studi multicentrici randomizzati**, per colmare i gap conoscitivi su efficacia e sicurezza clinica della IMRT/IGRT IPOFRAZIONATA rispetto a trattamenti radioterapici convenzionali.

www.igimtrial.unimore.it



www.igimtrial.unimore.it

Trattamento

- **Braccio convenzionale (braccio 1) 3D-CRT o IMRT:**

  margine CTV-PTV non inferiore a 5 mm posteriormente e a 6 mm nelle altre direzioni

  Basso rischio: il PTV deve ricevere 74 Gy in frazioni da 2 Gy

  Rischio intermedio: il PTV deve ricevere una dose di 78 Gy in frazioni da 2 Gy

  (Controllo convenzionale del posizionamento con immagini portali secondo le consuetudini del centro).

- **Braccio sperimentale (braccio 2) IMRT con IGRT daily:**

  margine CTV-PTV non superiore a 5 mm posteriormente e a 6 mm nelle altre direzioni

  Basso rischio: il PTV deve ricevere 54,30 Gy in 15 frazioni da 3,62 Gy prevedendo non più di 4 sedute di terapia a settimana.

  Rischio intermedio: il PTV deve ricevere una dose di 57,30 Gy in 15 frazioni da 3,82 Gy prevedendo non più di 4 sedute di terapia a settimana.

  (Verifica quotidiana on-line del posizionamento con IGRT volumetrica o con EPID nel caso siano stati impiantati nella prostata markers fiduciali).

Criteri d'inclusione

Età > 18 anni

Adenocarcinoma della prostata confermato istologicamente

Stadio clinico T1b,T1c, T2a, T2b e T2c

Gleason score ≤ 7

PSA alla diagnosi ≤ 20 ng/ml Performance status < ECOG 2

Nessuna precedente patologia neoplastica negli ultimi 5 anni (tranne tumori cutanei non melanomatosi)

Firma del consenso informato da parte del paziente

Criteri d'esclusione

Precedente radioterapia a livello della pelvi

Precedente prostatectomia

Importanti patologie a carico del retto o del distretto genitourinario che controindichino la radioterapia

Terapia ormonale che abbia avuto una durata superiore ai 2 mesi e interrotta meno di 2 mesi prima dell'inizio del trattamento.

15 frazioni !!!

Grazie

Results From the Scandinavian Prostate Cancer Group Trial Number 4: A Randomized Controlled Trial of Radical Prostatectomy Versus Watchful Waiting

In the Scandinavian Prostate Cancer Group Trial Number 4 (SPCG-4), 347 men were randomly assigned to radical prostatectomy and 348 to watchful waiting. In the most recent analysis (median follow-up time = 12.8 years), the cumulative mortality curves had been stable over the follow-up. At 15 years, the absolute risk reduction of dying from prostate cancer was 6.1% following randomization to radical prostatectomy, compared with watchful waiting. Hence, 17 need to be randomized to operation to avert one death. Data on self-reported symptoms, stress from symptoms, and quality of life were collected at 4 and 12.2 years of median follow-up. These questionnaire studies show an intricate pattern of symptoms evolving after surgery, hormonal treatments, signs of tumor progression, and also from natural aging. This article discusses some of the main findings of the SPCG-4 study.

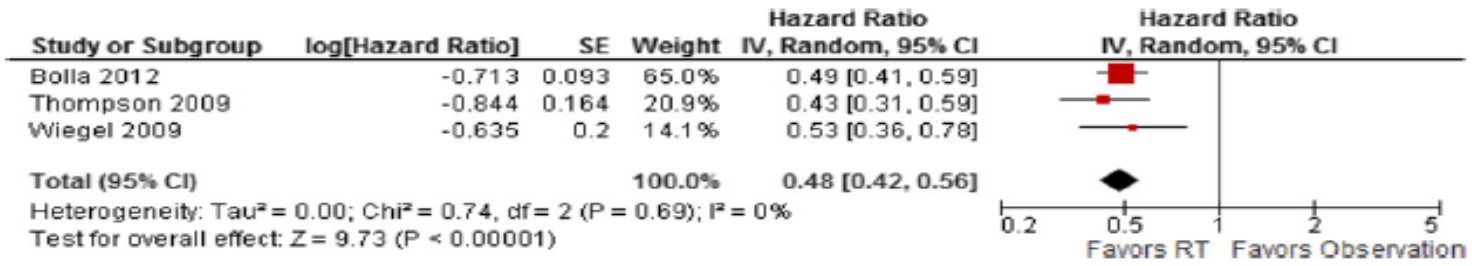
J Natl Cancer Inst Monogr 2012;45:230–233

- 1989 – 1999: 695 paz di età < 75 aa
- It is likely that the absolute mortality reduction following RP will be lower among men with lower risk tumors .....the gains are substantial in younger men with high-risk tumors.
- The lack of a benefit in men older than 65 years, is in a more advanced analysis depending on tumor characteristics, PSA level, and general health status, rather than approaching 70 years.

Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

Ian M. Thompson,* Richard K. Valicenti,* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the American Society for Radiation Oncology, Fairfax, Virginia



Meta-analysis of biochemical recurrence data from SWOG 8794,[26] EORTC 22911[25] and ARO 96–02[15]

- Patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease.
- Physicians should regularly monitor PSA after radical prostatectomy

(Clinical Principle)

Ongoing Trials

RTOG 0534, RTOG9601, RADICALS, RAVES

to clarify the role of ART or SRT and the value of combining RT with other therapies, and which patients are more likely to benefit from specific therapeutic approaches.

Incidence of late toxicity by RTOG grade (from EORTC trial 22863).

Toxicity	Grade 2		Grade 3		Grade 4		Any significant toxicity (> grade 2)	
	No.	%	No.	%	No.	%	No.	%
Cystitis	18	4.7	2	0.5	0	0	20	5.3
Haematuria	18	4.7	0	0	0	0	18	4.7
Urinary stricture	18	4.7	5	1.3	4	1	27	7.1
Urinary incontinence	18	4.7	2	0.5	0	0	20	5.3
Overall GU toxicity	**47**	**12.4**	**9**	**2.3**	**4†**	**1†**	**60**	**15.9**
Proctitis	31	8.2	0	0	0	0	31	8.2
Chronic diarrhoea	14	3.7	0	0	0	0	14	3.7
Small bowel obstruction	1	0.2	1	0.2	0	0	2	0.5
Overall GI toxicity	**36**	**9.5**	**1**	**0.2**	**0**	**0**	**37**	**9.8**
Leg oedema	**6**	**1.5**	**0**	**0**	**0**	**0**	**6**	**1.5**
Overall toxicity*	**72**	**19.0**	**10**	**2.7**	**4**	**1**	**86**	**22.8**

GU = genitourinary; GI = gastrointestinal.

- Radiotherapy affects **erectile function** to a lesser degree than surgery according to retrospective surveys .
  - Recent meta-analysis : the **1-year rate** of probability for maintaining erectile function was 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing radical prostatectomy, and 0.25 after standard radical prostatectomy.
  - Studies with more than **2 years of follow-up** (i.e. excluding brachytherapy): the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches .
- Secondary malignancies : re-analysis of the SEER-data with more than 100,000 patients demonstrated a risk of about 0.16% (i.e. 160 cases per 100,000 patients) of radiation-induced malignant tumours.

NCCN 2013

Intermediate risk. In patients who are suitable for ADT, combined IMRT with short-term ADT (4-6 months) (26,27). In patients who are unsuitable for ADT (e.g., due to comorbidities) or unwilling to accept it (e.g., to preserve their sexual health), IMRT at an escalated dose (80 Gy) or a combination of IMRT and brachytherapy is recommended.

EBRT (3D-CRT/IMRT with daily IGRT with or without brachytherapy) with or without 4 to 6 months of neoadjuvant/concomitant/adjuvant ADT is another treatment option. Overall and cancer-specific survival improved with the addition of short-term ADT to radiation in three randomized trials containing 20% to 60% of men with intermediate-risk prostate cancer (Tran Tasman Radiation Oncology Group [TROG] 9601, Dana Farber Cancer Institute [DFCI] 95096, Radiation Therapy Oncology Group [RTOG] 9408).[219-221] Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610).[182] Overall, the addition of short-course ADT to RT in men with intermediate-risk disease is a viable option.

Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care?

Review

Zachary S Zumsteg, Michael J Zelefsky

Lancet Oncol 2012; 13: 259–69

	Patients (n)	Patients at intermediate risk (n)	Median follow-up (years)	Androgen deprivation therapy comparison arms	Radiotherapy dose (Gy)*	Primary endpoint	Reported outcomes with short-term androgen deprivation therapy
Jones (2011)[1]	1979	1068†	9·1	0 vs 4 months	63·3	Overall survival	Increased overall survival and biochemical progression-free survival, reduced prostate cancer-specific mortality and distant metastasis
D'Amico (2008)[2]	206	153†	7·6	0 vs 6 months	70·35	Biochemical progression-free survival	Prolonged overall survival and decreased prostate cancer-specific mortality
Denham (2011)[3]	818	130†	10·6	0 vs 3 vs 6 months	62·7	Prostate cancer-specific mortality and local control‡	Augmented overall survival and diminished prostate cancer-specific mortality and distant metastasis§
Roach (2008)[20]	456	Not reported¶	11·9–13·2	0 vs 4 months	61·8–66·5	Local control	Reductions in prostate cancer-specific mortality and distant metastasis, increases in biochemical progression-free survival and disease-free survival, but no improvements in overall survival or local control
Lawerdière (2004)[22]	161	Not reported	5	0 vs 3 vs 10 months	64	Biochemical progression-free survival	Prolonged biochemical progression-free survival‖
Dubray (2011)[23]	366	366	3·1	0 vs 4 months	80	Freedom from failure**	Increased biochemical progression-free survival, non-significant rise in freedom from failure (p=0·09)

Table 1: Randomised trials of radiotherapy and short-term versus no androgen deprivation therapy for localised prostate cancer

	Patients (n)	Patients at intermediate risk (n)	Median follow-up (years)	Radiotherapy dose (Gy) comparison arms*	Androgen deprivation therapy	Primary endpoint	Outcomes with dose escalation
Dearnaley (2007)[24]	843	264†	10	70·3 vs 60·8	3–6 months in 100%	Biochemical progression-free survival, local control, distant metastasis-free survival, overall survival, late toxic effects	Prolonged biochemical progression-free survival but not overall survival
Al-Mamgani (2008)[25]	669	182†	5·8	74·1 vs 64·6	6 months or 3 years in 21%	Freedom from failure (combined clinical and biochemical failure)	Rise in freedom from failure but not overall survival
Zietman (2010)[26]	393	144‡	8·9	79·2 vs 70·2	None	Biochemical progression-free survival	Increased biochemical progression-free survival but not overall survival
Kuban (2008)[27]	301	139§	8·7	74·1 vs 66·5	None	Freedom from failure (combined clinical and biochemical failure)	Augmented freedom from failure but not overall survival; distant metastasis-free survival and prostate cancer-specific mortality saw non-significant improvement
Beckendorf (2011)[28]	306	218‡	5·1	70 vs 80	None	Biochemical recurrence	Decreased biochemical recurrence¶, overall survival not reported

*All doses are normalised to the planning target volume to allow more accurate comparisons. For doses prescribed to the centre of the prostate (ie, the isocentre), normalised radiation doses were calculated assuming a 5% dose reduction from the isocentre to the outside of the target. †Chism classification.[4] ‡D'Amico classification.[2] §NCCN classification.[5] ¶Decreased only according to ASTRO definition,[29] not Phoenix.[30]

Table 2: Randomised trials of lower versus higher dose external beam radiotherapy

Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care?

Review

Zachary S Zumsteg, Michael J Zelefsky

Lancet Oncol 2012; 13: 259–69

	Patients (n)	Patients at intermediate risk (n)	Median follow-up (years)	Number at intermediate risk receiving androgen deprivation therapy	Duration of androgen deprivation therapy (months)	Median radiotherapy dose (Gy)	Outcomes for patients at intermediate risk
Zelefsky (2011)[9]	2551	1074	8	456 (42%)	5 (median)	81	Prolonged biochemical progression-free survival with androgen deprivation therapy
Valicenti (2011)[35]	883	291	6·6–7·9	74 (25%)	2–6	≥77·4	No benefit in biochemical progression-free survival, disease-free survival, or overall survival with androgen deprivation therapy
Krauss (2011)[36]*	469	365	4·1	73 (28%)	6 (median)	75·6	No benefit in biochemical progression-free survival, distant metastasis-free survival, or overall survival with androgen deprivation therapy
Ciezki (2004)[37]*	519	237	4	139 (59%)	6 (median)	78	No benefit in biochemical progression-free survival with androgen deprivation therapy

*Only patients treated with external beam radiotherapy alone are included.

Table 3: Retrospective series combining short-term androgen deprivation therapy with dose-escalated external beam radiotherapy

	Patients (n)	Patients at intermediate risk (n)	Median follow-up (years)	Proportion receiving androgen deprivation therapy	Radiotherapy technique	Outcomes with androgen deprivation therapy
Ciezki (2004)[37]*	386	91	4	64%	Low-dose rate	No benefit in biochemical progression-free survival
Lee (2002)[40]	201	66	3·5	66%	Low-dose rate	Prolonged biochemical progression-free survival†
Ash (2005)[41]	667	238	2·6	52%	Low-dose rate	No benefit in biochemical progression-free survival in patients with intermediate-risk disease
Stock (2010)[42]	432	432	4·7	81%	Low-dose rate and external beam radiotherapy	No benefit in biochemical progression-free survival
Dattoli (2010)[43]	321	157	10·6	45%	Low-dose rate and external beam radiotherapy	No benefit in biochemical progression-free survival
Demanes (2009)[44]	411	188	6·4	49%	High-dose rate and external beam radiotherapy	No benefit in biochemical progression-free survival, local control, distant metastasis-free survival, and prostate cancer-specific mortality
Martinez (2005)[45]	934	Not reported	4·4	44%	High-dose rate and external beam radiotherapy	No benefit in biochemical progression-free survival, prostate cancer-specific mortality, and overall survival
Beyer (2005)[46]	2378	787	4·1	20%	Low-dose rate or low-dose rate and external beam radiotherapy	No benefit in prostate cancer-specific mortality, reduced overall survival
Zelefsky (2011)[47]	1466	563	4·1	31%	Low-dose rate or low-dose rate and external beam radiotherapy or high-dose rate and external beam radiotherapy	No benefit in biochemical progression-free survival
Krauss (2011)[36]*	575	417	5	47%	Low-dose rate or high-dose rate or high-dose rate and external beam radiotherapy	Increased biochemical progression-free survival for brachytherapy alone, no benefit for external beam radiotherapy and brachytherapy

*Only patients receiving brachytherapy, or brachytherapy with external beam radiotherapy, are included. †Benefit restricted to patients with low-dose implants (dose to 90% of the prostate <140 Gy for iodine-125, <100 Gy for palladium-103).

Table 4: Retrospective series with short-term androgen deprivation therapy in patients treated with brachytherapy

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Hypofractionation for Prostate Cancer: A Critical Review

Edward F. Miles, MD, and W. Robert Lee, MD, MS, Med

A number of recent publications have suggested that the alpha-beta ratio (α/β) for prostate is low, in the range of 1 to 3 Gy. If α/β is truly low, then hypofractionated schedules using fewer, larger fractions should improve the therapeutic ratio.

Several large randomized trials comparing conventional fractionation to hypofractionation are ongoing and are described. Until these trials are completed and the results submitted for rigorous peer review, the notion that α/β for prostate cancer is low remains an unconfirmed hypothesis.

Semin Radiat Oncol 18:41-47

Table 2 Ongoing Randomized Trials of Hypofractionation

Study	Eligible Patients	Randomization Arms	NTD_{2Gy} if α/β is: 1.5/5/10	Sample Size
Fox Chase*	Intermediate risk	76 Gy at 2 Gy *v*	76 Gy	300
	High risk	70.2 Gy at 2.7 Gy	84.3 Gy/77.2 Gy/74.3 Gy	
MRC	Low risk	70 Gy at 2 Gy *v*	70 Gy	
	Intermediate-risk	57 Gy at 3 Gy *v*	73.3 Gy/65.1 Gy/61.8 Gy	2,100
		60 Gy at 3 Gy	77.2 Gy/68.6 Gy/65 Gy	
NCIC	Intermediate risk	78 Gy at 2 Gy *v*	78 Gy	1,204
		60 Gy at 3 Gy	77.2 Gy/68.6 Gy/65 Gy	
RTOG 0415	Low risk	73.8 Gy at 1.8 Gy *v*	70.1 Gy	1,067
		70 Gy at 2.5 Gy	80 Gy/75 Gy/72.9 Gy	

Abbreviations: MRC, Medical Research Council; NCIC, National Cancer Institute of Canada; RTOG, Radiation Therapy Oncology Group.
*Study completed accrual May 2006.

.....Molti studi in corso...

Possibili vantaggi in costi e qualità di vita

RT ipofrazionata e IGRT

Hypofractionated radiotherapy for localised prostate cancer. Review of clinical trials

Víctor Macías · Albert Biete

Clin Transl Oncol (2009)

Characteristics of randomised trials comparing hypofractionated radiotherapy and normofractionated radiotherapy

		Lukka [1]	Yeoh [4]	Pollack [3]	Dearnaley [53][a]
n		936	217	100	150
Technique		2D	2D/3D$_{(22\%)}$	IMRT+IGRT	IMRT
Toxicity scale		NCIC	mLENT-SOMA	mRTOG	RTOG
Dose/fraction.	HYPORT	2.625	2.75	2.7	3
Overall time (w)	NRT	6.5	6.5	7.6	7.4
	HYPORT	4	4	5.2	4
Total dose (Gy)	NRT	66	64	76*	74
	NTD$_{1.5\text{-}2}$ HYPORT	61.9–60.7	66.8–65.3	84.2–82.5*	78–75
Acute GItox	NRT	≥3: 2.6%		≥2: 8%	≥2: 48%
	HYPORT	≥3: 4.1%‡		≥2: 18%	≥2: 39%
Acute GUtox	NRT	≥3: 4.9%		≥2: 56%	≥2: 38%
	HYPORT	≥3: 8.6%‡		≥2: 48%	≥2: 43%
Median follow-up (years)		5.7	4	–	2.1
Late GItox	NRT	≥3: 1.3%		–	≥2: 11%
	HYPORT	≥3: 1.3%§		–	≥2: 4%
Late GUtox	NRT	≥3: 1.9%		–	≥2: 2%
	HYPORT	≥3: 1.9%§		–	≥2: 12%
Failure**	NRT	52.95%	35.77%	–	–
	HYPORT	59.95%	34.25%	–	–

NTD1.5-2, 2 Gy total dose equivalent if given 2 Gy/fraction (α/β prostate cancer 1.5 and 2 Gy respectively); *NRT*, normofractionated radiotherapy arm; *HYPORT*, hypofractionated radiotherapy arm; *NCIC*, National Cancer Institute of Canada; m, modified; *GI$_{tox}$*, gastrointestinal toxicity; *GU$_{tox}$*, genitourinary toxicity

[a]Clinical results of the 60 Gy at 3 Gy/fraction hypofractionated arm

*Minimum dose to PTV

4 RCT : tossicità acuta e tardiva sovrapponibile alla RT convenzionale

Possibili vantaggi in costi e qualità di vita

Table 5 Prognostic factors of cause-specific survival and biochemical disease control after C-ion RT for prostate cancer

Characteristics	5-year CSS rate	*P*-value	5-year bNED rate	*P*-value
Risk group				
Low ($n = 159$)	100%	<0.01	89.6%	<0.01
Intermediate ($n = 278$)	100%		96.8%	
High ($n = 490$)	97.9%		88.4%	
T-stage (1997 UICC)				
T1–T2 ($n = 664$)	100%	<0.001	[illegible]	<0.001
T3 ($n = 263$)	96.0%		[illegible]	
Initial PSA value				
<20 ng/mL ($n = 649$)	99.5%	0.01	92.4%	0.028
≥20 ng/mL ($n = 278$)	97.4%		87.4%	
Gleason score				
5–6 ($n = 216$)	100%	0.00	92.2%	0.005
7 ($n = 453$)	99.3%		94.5%	
8–10 ($n = 258$)	96.9%		82.6%	

Table 6 Comparison of biochemical relapse-free rates between carbon ion radiation therapy and conventional radiation therapy combined with or without androgen deprivation therapy

Authors	No. of Pts	Stage	Dose (Gy)	ADT	bNED (%)	Overall survival (%)
Bolla, *et al*.[49]	198	T1–4	70	(–)	45†	62†
	203			(+)	76†	78†
Pilepich, *et al*[50]	463	T1–3	65–70	(–)	20†	71†
	477			(+)	53†	75†
Denham, *et al*.[51]	270	T2–4	66	(–)	26‡	58‡
	208			(+)	47‡	71‡
Valicenti, *et al*.[52]	99	High-risk	73.8–84.3	(–)	71†	NA
	69			(+)	75†	NA
Current study	490	T3	57.6–66	(+)	83†	94†

ADT, androgen deprivation therapy; bNED, biological relapse-free †5 years, ‡10 years.

Risultati molto buoni confrontati con RT convenzionale