Associazione Italiana Radioterapia Oncologica

Local treatments for local and metastatic disease: only palliation?

Dr. Berardino De Bari

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The clinical problem...

Associazione Italiana Radioterapia Oncologica

Why to discuss about local relapse in local relapse after EBRT??

The clinical problem...

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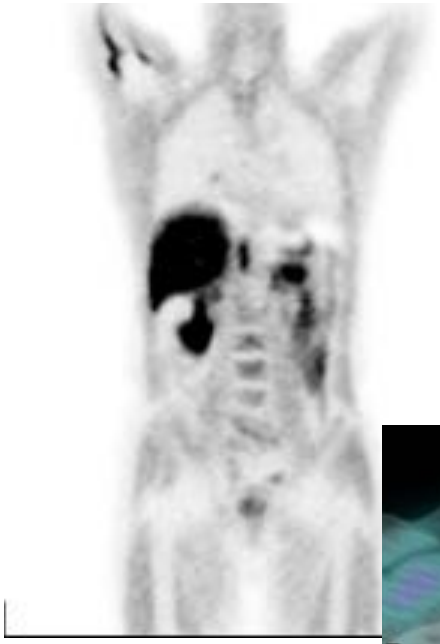

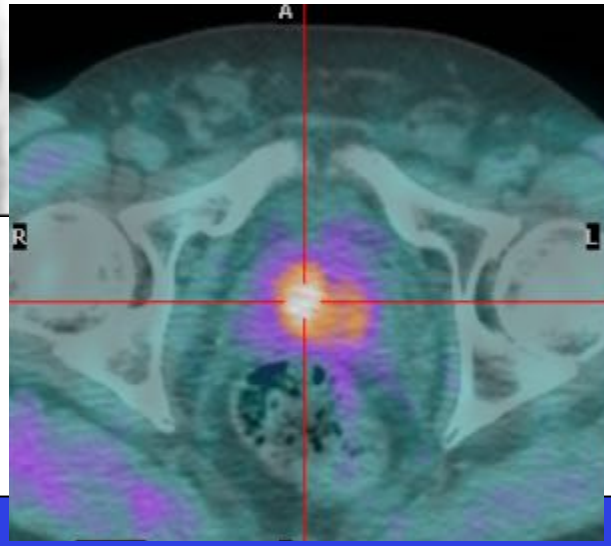

What we can propose to our patients?

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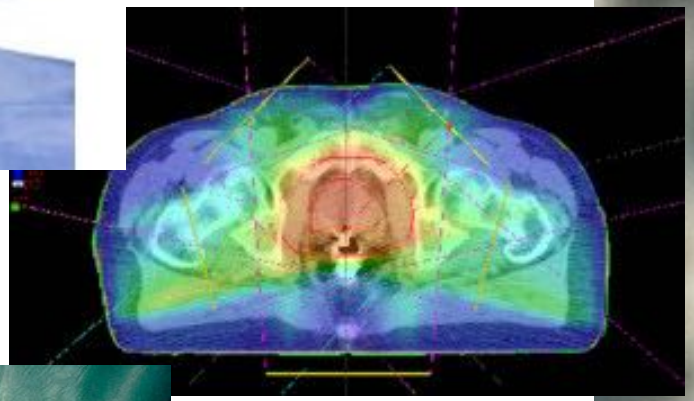

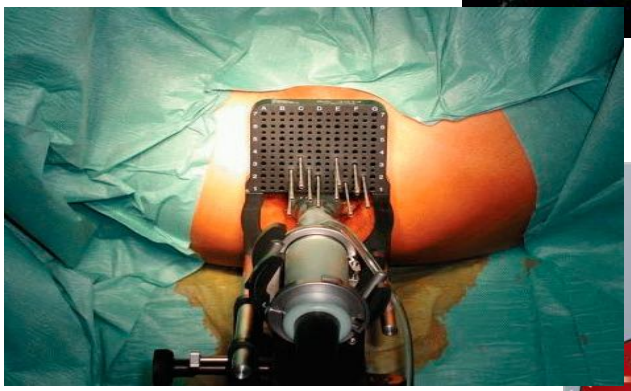

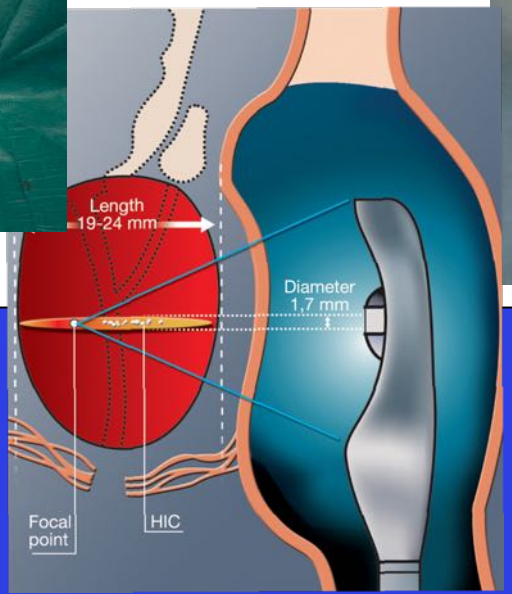

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Agarwal: Treatment failure after primary and salvage therapy for prostate cancer. Cancer 2008;112:307-314

Although there is no well-defined standard salvage therapy for prostate confined recurrences, **hormonal therapy** is the mainly used option

Types of salvage therapy after EBRT (CaPASURE, 430 pts)

Androgen deprivation therapy *93.5%*

- Cryotherapy 3%
- EBRT 1.9%
- Radical prostatectomy 0.9%
- Unknown 0.5%
- Brachytherapy 0.2%

The guidelines?

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Recommendations	GR
Local recurrences may be treated by salvage RP in carefully selected patients, who presumably demonstrate organ-confined disease, i.e. PSA < 10 ng/mL, PSA DT > 12 months, low-dose-radiation brachytherapy, biopsy Gleason score < 7.	B
Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery.	B
High-intensity-focused ultrasound may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality due to the short follow-up periods reported.	
In patients with presumed systemic relapse, ADT may be offered.	B

European Association of Urology

Guidelines

2012 edition

RP....The standard of care?

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Ref.	Pts	Median Interval RT - SRP	Median FUP after SRP	BRFS (%)	CSS (%)	PSM (%)	Rectal injury (%)	Anast. Sten. (%)	Urinary Incont. (%)
Pontes 1993	35	-	12-120 months	28	79	70	9	11	46
Ahlering 1992	11	-	53.5 months	71	71		0	0	64
Lerner 1995	79	-	50 months	53	72		6	12	39
Garzotto 1998	29	4.9 years	5.1 months	69		31	6.9	22	67
Amling 1999	108	36 months	Min. >10y.	43	70	36	6	21	51

RP....The standard of care?

Associazione Italiana Radioterapia Oncologica

Ref.	Pts	Median Interval RT - SRP	Median FUP after SRP	BRFS (%)	CSS (%)	PSM (%)	Rectal injury (%)	Anast Sten. (%)	Urin. Inc. (%)
Stephenson 2004	100	47 months	58 months	66		10	1	30	32
Bianco 2005	100	10 Years	5 years	55	73	21			
Ward 2005	138	-	84		77		10	22	44
Darras 2006	11	36.9 months	83	55	91	0			
Sanderson 2006	51	-	7.2 years	47		36			30
Paparel 2009	146	4.6 years	3.8 years	54		16			
Chade 2011	404	41 months	55	37	83	25			

Cryotherapy...The standard of care?

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Ref.	Pts	FUP	BRFS (%)	Definition of failure	Incontin.	Rectal Tox. (Fistulas)
Cohen 2008	279	5 y	58.9	3 consecutive rises	4.4%	3.2%
Chin 2001	118	18.6 mos	34	PSA ≥0.5	6.7 %	3.3%
Bahn 2003	59	7 y	59	PSA ≥0.5	8%	3.4%
Williams 2011	176	7.5 y	39% (@ 10y)	PSA nadir + 2	-	-
Cheetham 2010	51	10.1 y	61	PSA≥0.5	-	-
Clarke 2007	58	2 y	70	PSA≥0.5	-	-
Spiess 2010	797	3.4 y	66	PSA≥0.5	-	-
Ismail 2007	100	33.5 mos	59 (@ 3 y)	3 consecutive rises	13%	1%

HIFU...The standard of care?

Associazione Italiana Radioterapia Oncologica

Ref.	Pts	FUP (mos)	BRFS (%)	Definition of failure	Incont.	Bladder neck stenosis /Urethral stricture
Gelet 2001	31	7.5	50	PSA<0.2	7%	36%
Murat 2009	167	18.1	17 (at 5 years)	PSA≥1	49.5%	7.8%
Gelet 2004	71	14.8	61	PSA≥0.5	7%	17%
Crouzet 2012	290	48	Not reported	Phoenix ASTRO consensus definition and/or prescription of hormonal therapy	19.5%	16%

The clinical problem...

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Who is the best candidate??

The guidelines!

Associazione Italiana Radioterapia Oncologica

Recommendations	GR
Local recurrences may be treated by salvage RP in carefully selected patients, who presumably demonstrate organ-confined disease, i.e. PSA < 10 ng/mL, PSA DT > 12 months, low-dose-radiation brachytherapy, biopsy Gleason score < 7.	B

European Association of Urology

Guidelines

2012 edition

The clinical problem...

Associazione Italiana Radioterapia Oncologica

What is the
role of RT
in this clinical setting??

The role of SBRT...

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- 15 patients with biopsy-proven isolated intraprostatic recurrence

- CyberKnife SBRT schedule: 30Gy / 5 fractions over 5 consec. days

- 6/15 received also systemic therapy

- Complete biochemical response 6/9 patients (SBRT only)

- Pattern of failure was predominantly out-field (4 out of 5 events).

- Actuarial 3-year progression free survival was 22%.

Jereczek-Fossa BA et al.Int J Radiat Oncol Biol Phys 2012;82:889-97.

The role of SBRT...

Associazione Italiana Radioterapia Oncologica

- Complete biochemical response 6/9 patients (SBRT only)
- Pattern of failure was predominantly out-field (4 out of 5 events).
- Actuarial 3-year progression free survival was 22%.

- No acute or late rectal toxicity was registered.

- Urinary toxicity
  - 5 acute events (only one grade 3)
  - 3 late urinary events (only one grade 3).

Jereczek-Fossa BA et al.Int J Radiat Oncol Biol Phys 2012;82:889-97.

The role of BRT...

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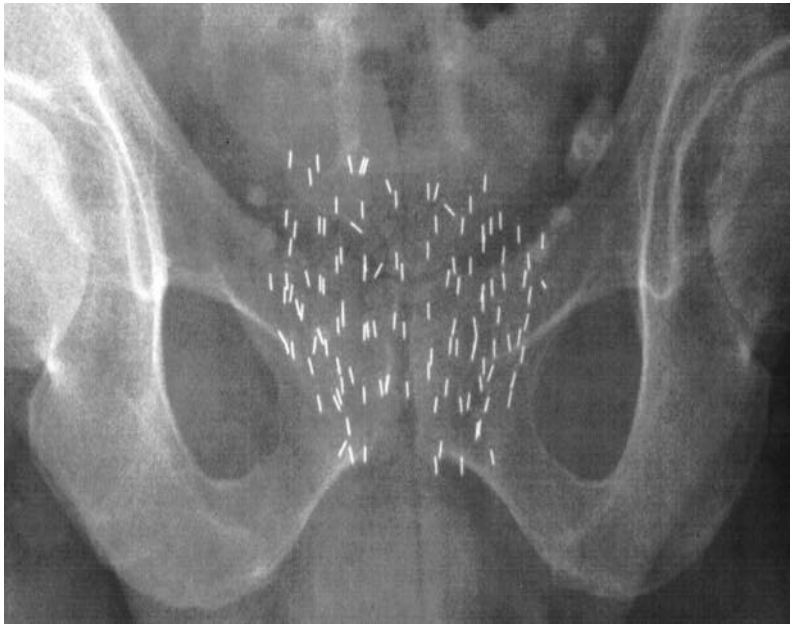

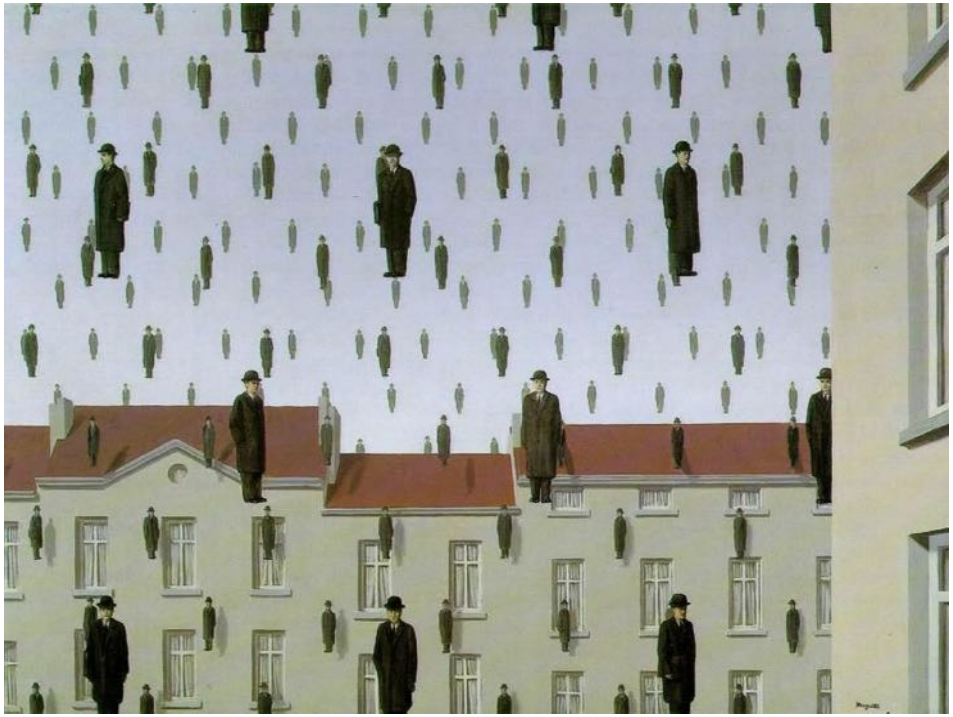

The role of BRT...

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The earliest report of salvage BRT

14 pts between 1975 and 1979 (Stanford Un.)

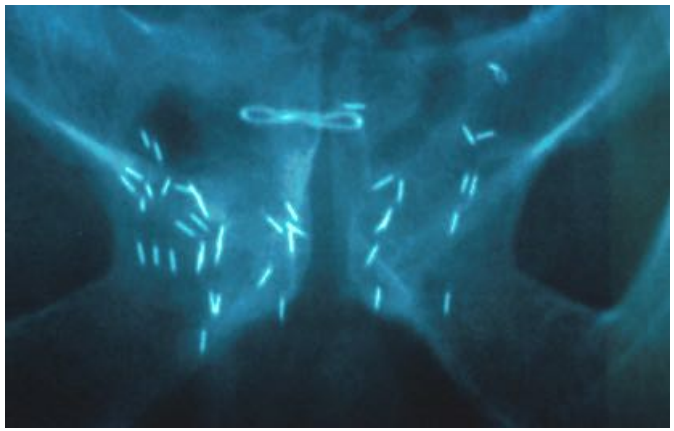
I-125 via a retropubic approach

Clinical local control = 79% (follow-up 6-36 m.)

57% clinically disease-free

4 pts (28.5%): cystoproctitis
urinary incontinence
vesicorectal fistula

Because this study was performed in the pre-PSA era, outcomes are difficult to compare with modern treatment



Goffinet DR. Cancer 1980;45:2717–2724

The role of BRT...

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- Globally, 5-year biochemical disease free survival (bDFS): 20 - 87%

The major experiences:

- Only 5 studies presenting results of >30 patients
- Only 3 of these 5 reports presenting mature results with >60 months of median follow-up
- In these 3 studies, a total of 117 patients has been enrolled, accounting for 40% of the patients treated by salvage BRT.
- After a median follow-up of 64-108 months, the reported 5-years bDFS ranges from 20 to 64%.

The role of BRT...

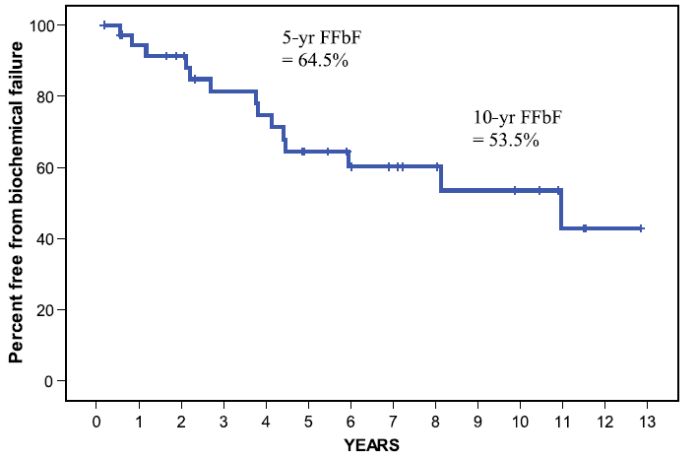
Associazione Italiana Radioterapia Oncologica

37 pts (103-Pd or 125-I) → median dose 122 Gy
(range 67-160 Gy)

Median follow-up: 86 months

Cause-specific survival: 96% @ 10-yy

Freedom from biochemical failure: 65% @ 5-yy
54% @ 10-yy



Improved FFbF was associated with a presalvage PSA <6 ng/mL (p = 0.046)

17 pts toxicity ≥G2
- 2 pts developed obstructive uropathy requiring TURP
- 1 pt required fulguration for gross hematuria
- 1 pt developed a "prostato-rectal" fistula

Burri RJ. IJROBP 2010;77:1338–1344

The role of BRT...

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- Globally, 5-year biochemical disease free survival (bDFS): 20 - 87%

Limits:

- Different definitions of BF
- The use of neo- and/or adjuvant HT that is not always clearly reported.
- Number of patients is often limited (from 13 to 49).

The role of BRT...

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Ref.	Pts	Type BRT	Dose BRT	Adj. ADT (%)	Median FUP (months)	BRFS (years)	Definition of failure	Urinary Incont.	GU 3-4 Tox.	GI 3-4 Tox.	Erectile Dysfun.
Wallner 1990	13	LDR	125I: 170Gy (median)	NR	36	51% (5)	Metast. free survival	31%	NR	15%	NR
Loening 1993	31	LDR	198Au: 100-200Gy	NR	23	67% (5)	Overall Survival	0	NR	NR	NR
Nguyen 2007	25	LDR	125I: 135Gy	0	47	70% (4)	Phoenix criteria	0	16%	24%	NR
Koutrouvelis 2003	31	LDR	103Pd: 120Gy 125I: 144Gy	97	30	87% (5)	ASTRO criteria	0	NR	5%	NR
Beyer 1999	17	LDR	103Pd: 90Gy 125I: 120Gy	47	62	53% (5)	ASTRO criteria	24%	24%	0	NR
Wong 2006	17	LDR	103Pd: 120-126Gy 125I: 103.5-112.5Gy	71	44	57% (4)	ASTRO criteria	6%	47%	6%	NR

The role of BRT...

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Ref.	No. Pts	Type BRT	Dose BRT	Adj. ADT (%)	Median FUP (months)	BRFS (years)	Definition of failure	Urinary Incont.	GU 3-4 Tox.	GI 3-4 Tox.	Erectile Dysfunc.
Moman 2010	31	LDR	125I: 145Gy	-	108	20% (5)	Phoenix criteria	NR	19% (late)	6% (late)	NR
Burri 2010	37	LDR	103Pd or 125I: 122Gy (median to 90% of the volume)	84	86	54 (10)	Phoenix criteria	NR	11%	NR	85%
Grado 1999	49	LDR	103Pd: 170Gy 125I: 160Gy (median)	NR	64	34% (5)	2 rises above nadir	6%	14% (TURP)	2%	NR
Hsu 2012	15	LDR	103Pd: 125Gy 125I: 144Gy	0	23	71% (3)	Phoenix criteria	0	0	0	13%
Jo 2012	10	HDR	11Gy X 2 fr.	0	NR	NR*	ASTRO criteria	0	0	0	NR
Lee 2007	21	HDR	6Gy X 6 fractions	52	19	89% (2)	ASTRO criteria	0	14%	0	100% (G2)

The role of BRT...

Associazione Italiana Radioterapia Oncologica

- Globally, 5-year biochemical disease free survival (bDFS): 20 - 87%

Despite these biases:

- Results are comparable to surgery

- It is not more toxic than surgery

Salvage BRT can have an interesting role in the treatment of locally relapsing prostate cancers

The clinical problem...

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Why to discuss about the role of EBRT in nodal relapse??

The clinical problem...

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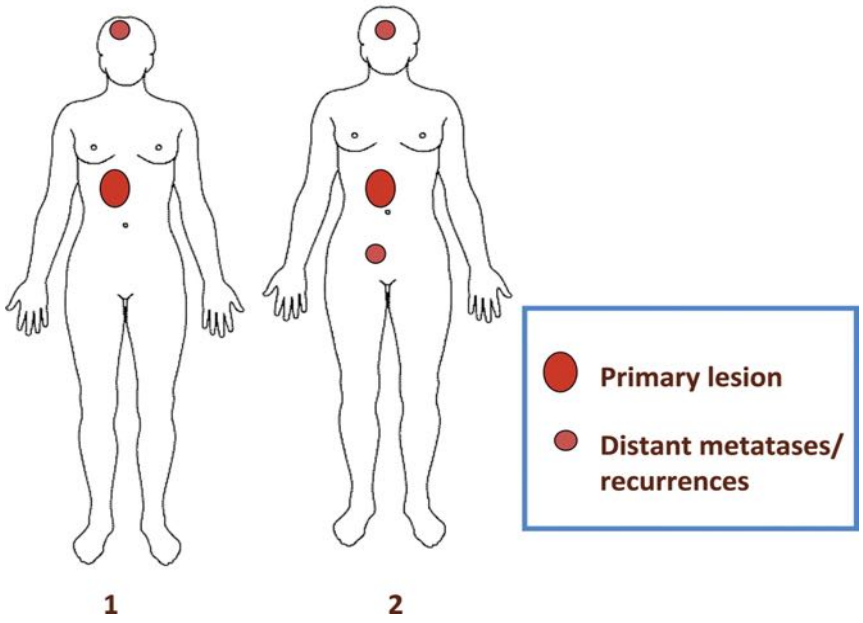
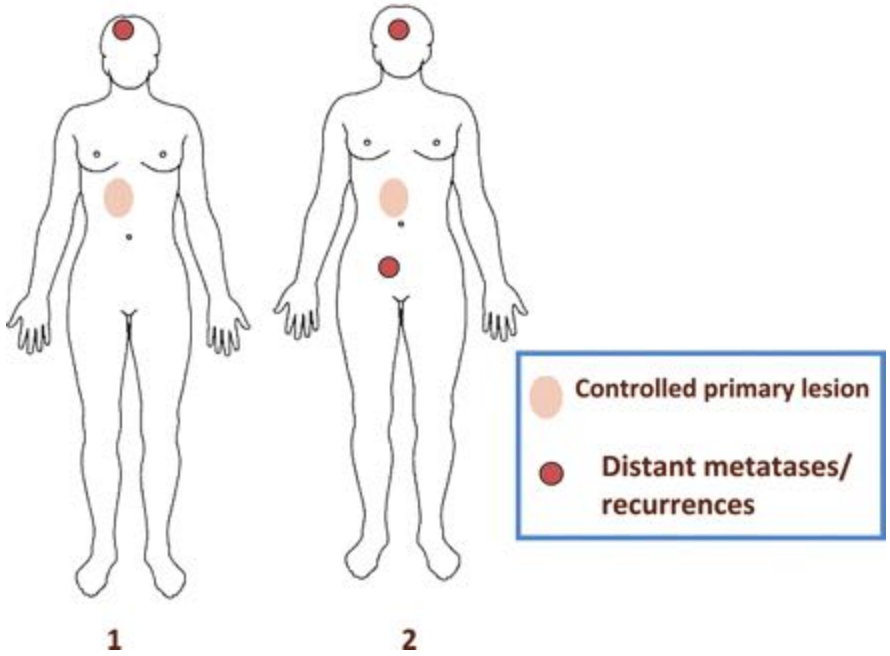
Schema of oligometastases



T and M are sincronous

Schema of oligo-recurrence



T and M are metachronous

The clinical balance in oligorecurrent disease...

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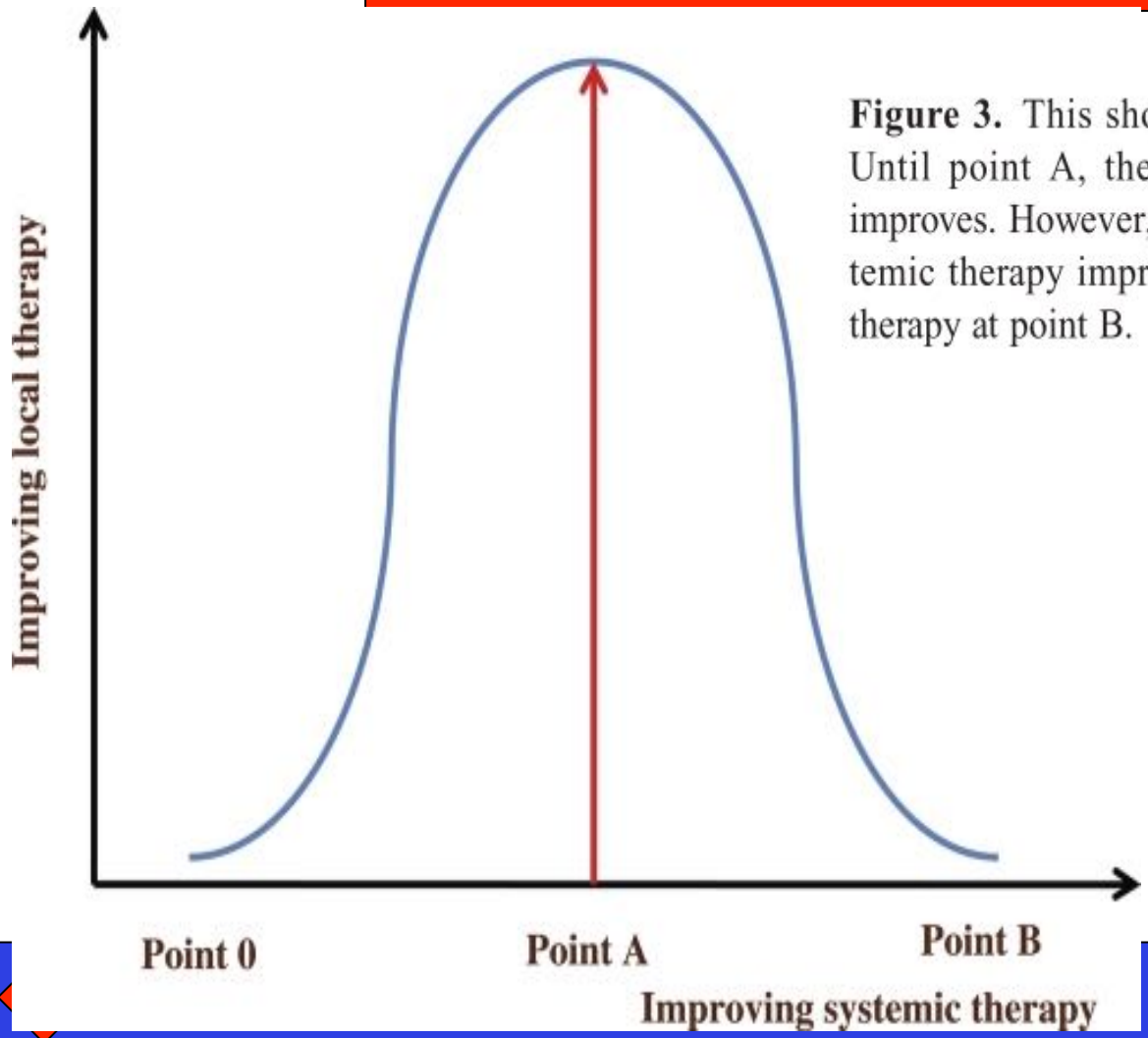

Figure 3. This shows correlations between systemic and local therapies. Until point A, the role of local therapy increases as systemic therapy improves. However, after point A, the role of local therapy decreases as systemic therapy improves, as all cancerous lesions can be cured by systemic therapy at point B.

Niibe Y, Jpn J Clin Oncol 2010;40(2)107– 111

The clinical problem...

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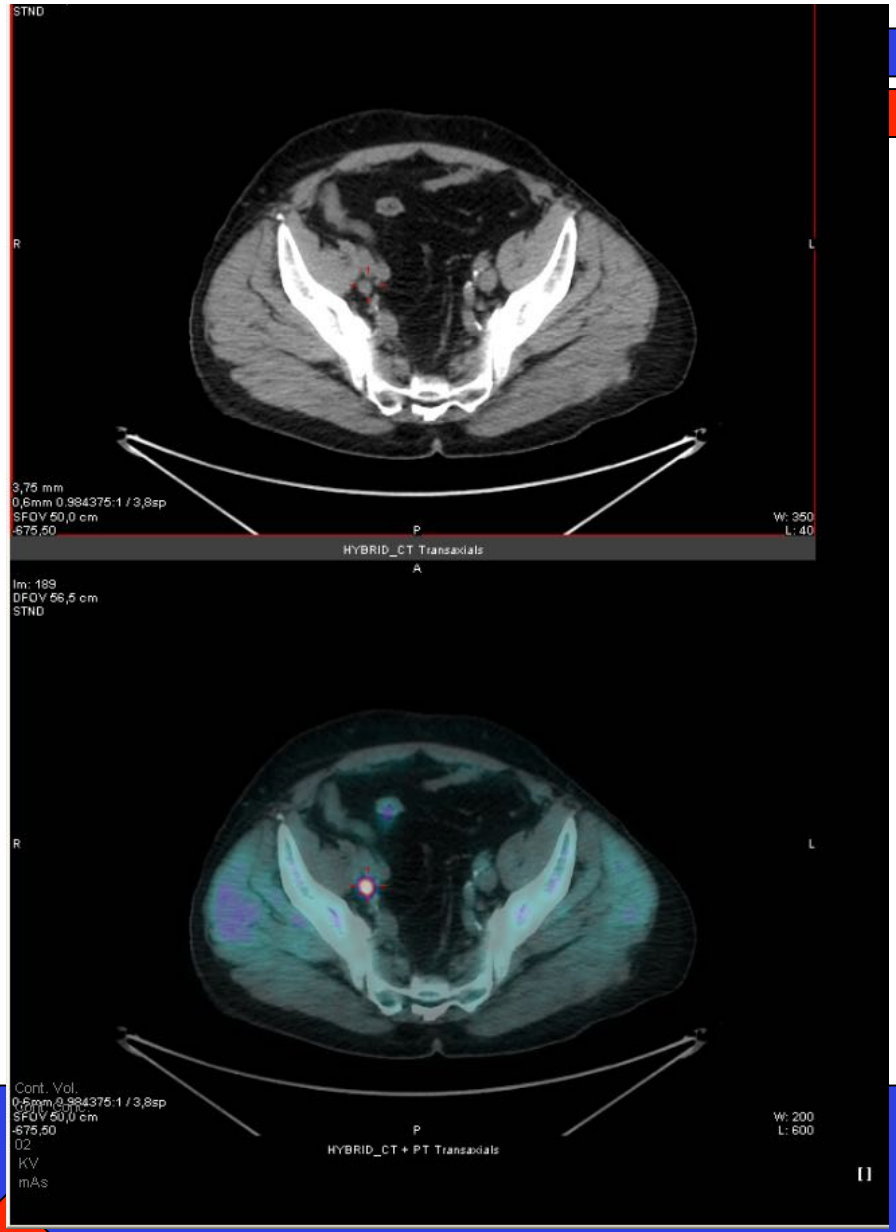

What we can propose to our p

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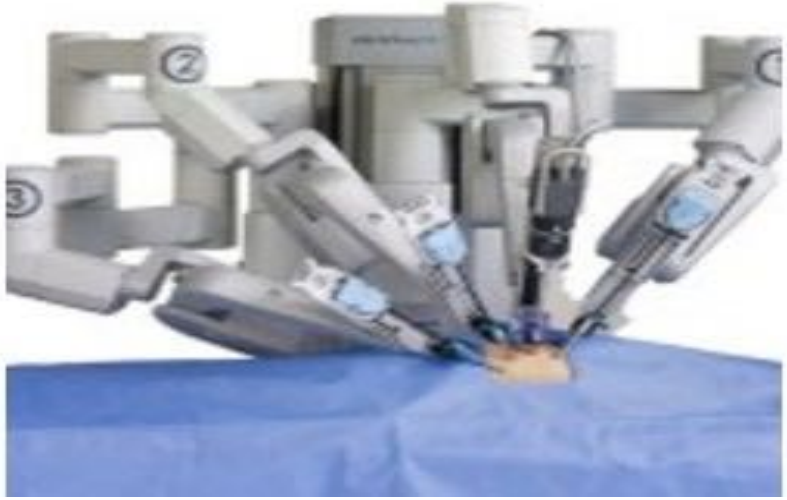

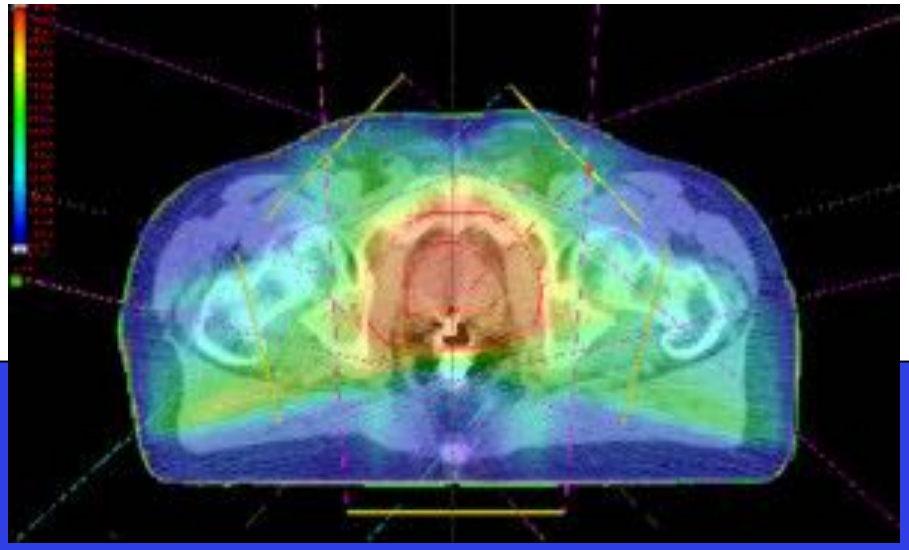

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Although there is no well-defined standard salvage therapy for oligometastatic nodal recurrences, **hormonal therapy** is the mainly used option

M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathologic fractures, ureteral obstruction, extraskeletal metastasis).	1
	Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence.	1
	LHRH antagonists might be used with rapid decrease of serum testosterone.	1
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious complications related to disease progression.	1b
	An active clinical surveillance protocol might be an acceptable option in clearly informed patients if survival is not the main objective.	3

EUROPEAN UROLOGY 59 (2011) 572–583

The clinical problem...

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Who is the best candidate??

Surgeons could help us...

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- 15 patients with 1+ nodal metastases (PET +)

- All patients underwent open salvage pelvic/retroperitoneal extended lymph node dissection

- Mean n. of removed N: 14 (range: 3-45)

- 7/15 were N0.....

- 8/15 were N+

Rinnab L, Urol Int 2008; 81:191-197.

Surgeons could help us...maybe...

Associazione Italiana Radioterapia Oncologica

- Mean followup time : 13.7 months

- Only 1/15 patients had a PSA nadir < 0.1 ng/ml after salvage surgery

- 3/15...developed bone M+

- "....despite the potential of the [(11)C]choline-PET/CT in detection of lymph node metastases when rising PSA occurs, the benefit that can be achieved through 11C-choline PET-CT scan and subsequent salvage lymph node dissection is rather small"

Rinnab L, Urol Int 2008; 81:191-197.

Surgeons could help us...

Associazione Italiana Radioterapia Oncologica

- Prospective phase II trial

- 72 consecutive BR patients with 1+ nodal metastases (PET +, rising postoperative PSA >0.2)

- 18/72 pN1 status.

- Adjuvant RT: 27/72 pts
- Salvage RT: 14/72 pts
- Adjuvant ADT: 40/72 patients prior to salvage LND.

Rigatti P, Eur Urol. 2011 Nov;60(5):935-43.

Surgeons could help us...

Associazione Italiana Radioterapia Oncologica

-Mean PSA at salvage surgery: 3.7 ng/ml (median: 1.5 ng/ml)

-

- Mean number of removed nodes: 30 (median: 9)

- Mean number of positive nodes: 9 (median: 2)

- 41/72 pts with PSA < 0.2 ng/ml (@ 40 days after salvage LND).

The 5-year BCR free survival, clinical recurrence and cancer specific survival rates were 19, 34 and 75%.

Rigatti P, Eur Urol. 2011 Nov;60(5):935-43.

Surgeons could help us...

Associazione Italiana Radioterapia Oncologica

- At multivariable Cox regression analyses:

- PSA at surgery (<4 ng/ml),
- Time to biochemical relapse (<24 months)
- Negative lymph nodes at previous RP to surgery (all p ≤0.04).

→ independent predictors of PSA response (all p = 0.04)

- At multivariable Cox regression analyses:

- PSA >4 ng/ml
- presence of retroperitoneal uptake

→ independent preoperative predictors of clinical recurrence (all p ≤0.03).

Rigatti P, Eur Urol. 2011 Nov;60(5):935-43.

Surgeons could help us...

- At multivariable Cox regression analyses:

  - Presence of pathologic nodes in the retroperitoneum
  - Higher number of positive lymph nodes
  - Evidence of a biochemical response (PSA <0.2 ng/ml)

independent postoperative predictors of clinical recurrence (all p ≤0.03).

THE BEST CANDIDATE (??)

- (p)N0 at diagnosis
- PSA <4 ng/ml at salvage treatment
- >24 months to BR
- pelvic relapse

Rigatti P, Eur Urol. 2011 Nov;60(5):935-43.

And the Choline PET-CT, could help us???

Eur Urol. 2013 Jun;63(6):1040-8. doi: 10.1016/j.eururo.2012.09.039. Epub 2012 Sep 25.

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.

-Studies published in the period 2000 – 01/2012: 18 complete articles
10/18 were selected

- A total of 441 patients.

- Sensitivity 49.2% (95% CI, 39.9-58.4)
- Specificity 95% (95% CI, 92-97.1).

Evangelista L., Eur Urol. 2013 Jun;63(6):1040-8

And the Choline PET-CT, could help us???

^{18}F Choline PET/CT in the Preoperative Staging of Prostate Cancer in Patients with Intermediate or High Risk of Extracapsular Disease: A Prospective Study of 130 Patients

	Whole populaion	N+ ≥ 5mm
sensitivity	45%	66%
specificity	96%	96%
positive predictive value	82%	82%
negative predictive value	83%	92%

Beheshti, M., Radiology. 2010 Mar;254(3):925-33

The clinical problem...

Associazione Italiana Radioterapia Oncologica

What is the role of RT in this clinical setting??

The role of EBRT...

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Author	Pts.	Conc. systemic therapy	EBRT Tech.	Re-irradiat.	Volume	Doses	LC	OS	Tox.
Engels 2009	8	ADT (all pts)	Tomo	Not	PTV1: prostate PTV2: positive LN regions PTV3: pelvic LN	SIB (30fr) PTV1: 70.5Gy PTV2: 60Gy PTV3: 54Gy	?	?	*Acute GI: G2 7%, G3 0% *Acute GU: G2 14% G3 4%
Jereczek-Fossa 2009	14	ADT (7 pts) CHT+ADT (1 pt)	SBRT: Linac (7pts) CBK (7pts)	Yes	PTV:+LN	30Gy/3fr (10Gy/fr)			

The role of Salvage EBRT must still be studied because strong evidences are really lacking.

But...

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"Nessuna umana investigazione si puo' dimandare vera se non passa per matematiche dimostrazioni…"

L. Da Vinci

But...

Associazione Italiana Radioterapia Oncologica

"Quelli che s'innamoran di pratica sanza scienzia son come 'l nocchier ch'entra in navilio senza timone o bussola, che mai ha certezza dove si vada."

L. Da Vinci

But...

Associazione Italiana Radioterapia Oncologica

Da Vinci L., The Atlantic Code, f.381va

Associazione Italiana Radioterapia Oncologica

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

---

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

---

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

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The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

---

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Smith GCS et al. BMJ 2003; 327: 1459-61.


The therapy…
The clinical situation…
Modern Clinical Oncology…

Associazione Italiana Radioterapia Oncologica

Local treatments for local and metastatic disease: only palliation?

GRAZIE PER L'ATTENZIONE!!

Dr. Berardino De Bari