Case Study:

Prostate cancer with synchronous bone oligometastases: is the radical treatment approach justified?

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Patient characteristics

- 62 year old patient who signed the informed consent for treatment and permission for publication of disease related information.
- April 2010: iPSA= 52.72 ng/ml.
- April 21, GS 8 (4+4) from 10 to 10
- May 10, ion of the tracer a d left ileum and ischium-
- May 20, ic CT: negative. Bone wi ysis and ileum-pubic b
- June 5, 2010: musculoskeletal MRI: metastatic structural alterations of left ischio-pubic branch and horizontal branch of pubis.

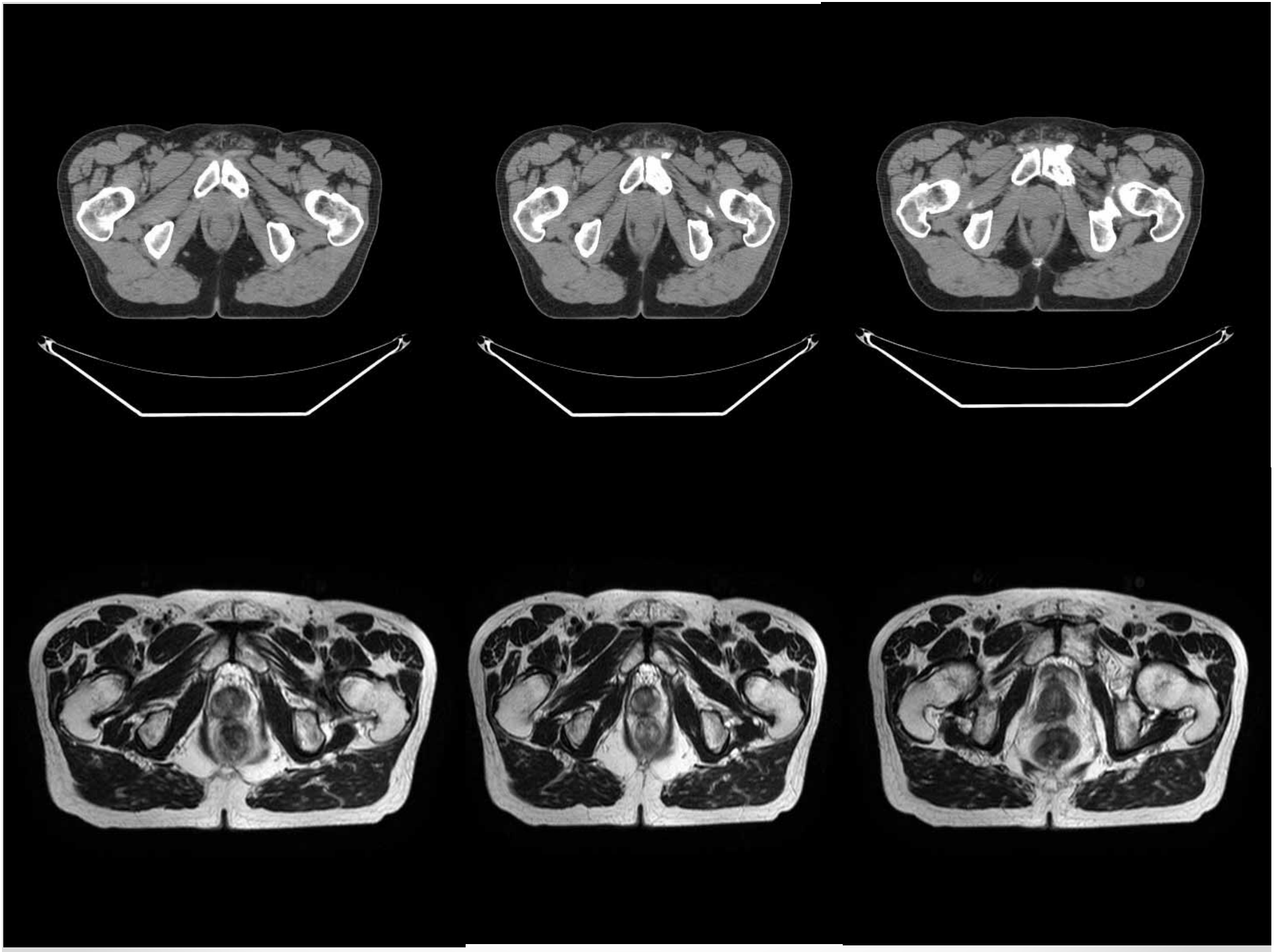
RUOLO DELL'IMAGING:

BONE SCAN ?

PET (COLINA , PSMA)?

RISONANZA MAGNETICA?

TAC?



Imaging

→Corretta individuazione dei pazienti candidabili ad RT con intento di «radicalità»

PET/TC: diversi radiosotopi

- **11C/18F colina:**

Bassa sensibilità (<20%) se PSA < 1 ng/mL

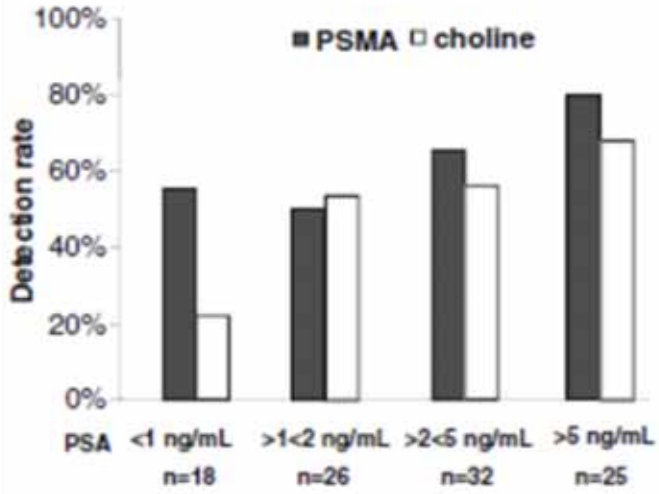
se PSA >2 ng/mL >80%

Author, ref	Choline PET/CT				
	Radioisotope	Site	PSA <1ng/ml (+/tot pts)	PSA 1-2 ng/ml (+/tot pts)	PSA >2ng/ml (+/tot pts)
Giovacchini et al [14]	11C	All	27/144 (19%)	39/85 (46%)	95/132 (72%)
Richter et al [15]	11C	All	1/15 (7%)	6/13 (46%)	36/45 (80%)
Schillaci et al [27]	18F	All	2/10 (20%)	5/9 (56%)	12/15 (80%)
Cimitan et al [35]	18F	All	66/211 (31%)	66/153 (43%)	513/636 (81%)
Median (range)	–	–	20% (7–31)	46% (43–56)	80% (72–81)

PSA cut-offs and detection rates of choline PET/TC in the restaging setting

Evangelista et al, *Eur Urol 2016*

The superiority of 68Ga-PSMA-11 PET was less evident and not statistically significant in patients with higher PSA levels.



Patients PSA <1ng/mL	choline-	choline+
PSMA-	8	0
PSMA+	6	4

McNemar-Test p = 0.031*

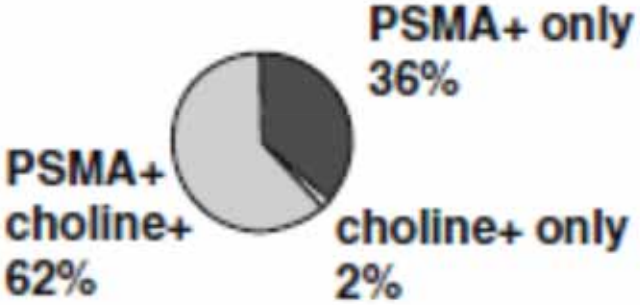
Patients PSA >1<2ng/mL	choline-	choline+
PSMA-	12	1
PSMA+	0	13

Patients PSA >2<5ng/mL	choline-	choline+
PSMA-	11	0
PSMA+	3	18

Patients PSA >5 ng/mL	choline-	choline+
PSMA-	4	1
PSMA+	4	16

Detection rates of patients with suspicious lymph nodes by 68Ga-PSMA-11- and 11C-choline PET at different PSA levels

Bone lesions



Bone lesions	choline-	choline+
PSMA-		8
PSMA+	138	234

McNemar-Test p < 0.001*

Percentage and numbers of bone lesions showing uptake of 68Ga-PSMA and/or 11C-choline.

Johannes Schwenck et al: Imaging Comparison of 68Ga-labelled PSMA-11 and 11C-choline in the detection of prostate cancer metastases by PET/CT - Eur J Nucl Med Mol 2016

- **68 Ga-PSMA PET/TC:** ancora pochi studi a riguardo, risultati promettenti

  Detection rate ~ 50% se PSA <0,5 ng/mL, 90% se = 2 ng/mL !

  → Più utile della PET/TC colina per bassi valori di PSA

Author, ref	Site	68Ga-PSMA PET/CT		
		PSA <0.5 ng/ml (+/tot pts)	PSA 0.5-2 ng/ml (+/tot pts)	PSA >2 ng/ml (+/tot pts)
Afshar-Oromieh et al [58]	All	13/27 (48%)	42/63 (67%)	204/221 (92%)
Morigi et al [61]	All	8/16 (50%)	10/14 (69%)	7/8 (88%)
Median (range)	–	49% (48–50)	68% (67–69)	90% (88–92)

PSA cut-offs and detection rates of 68 Ga-PSMA PET/TC in the restaging setting

- **PET/RM:** vantaggi:

  -migliore risoluzione tessuti molli

  - minore esposizione per paziente

Ancora pochi dati in letteratura !

Patient characteristics

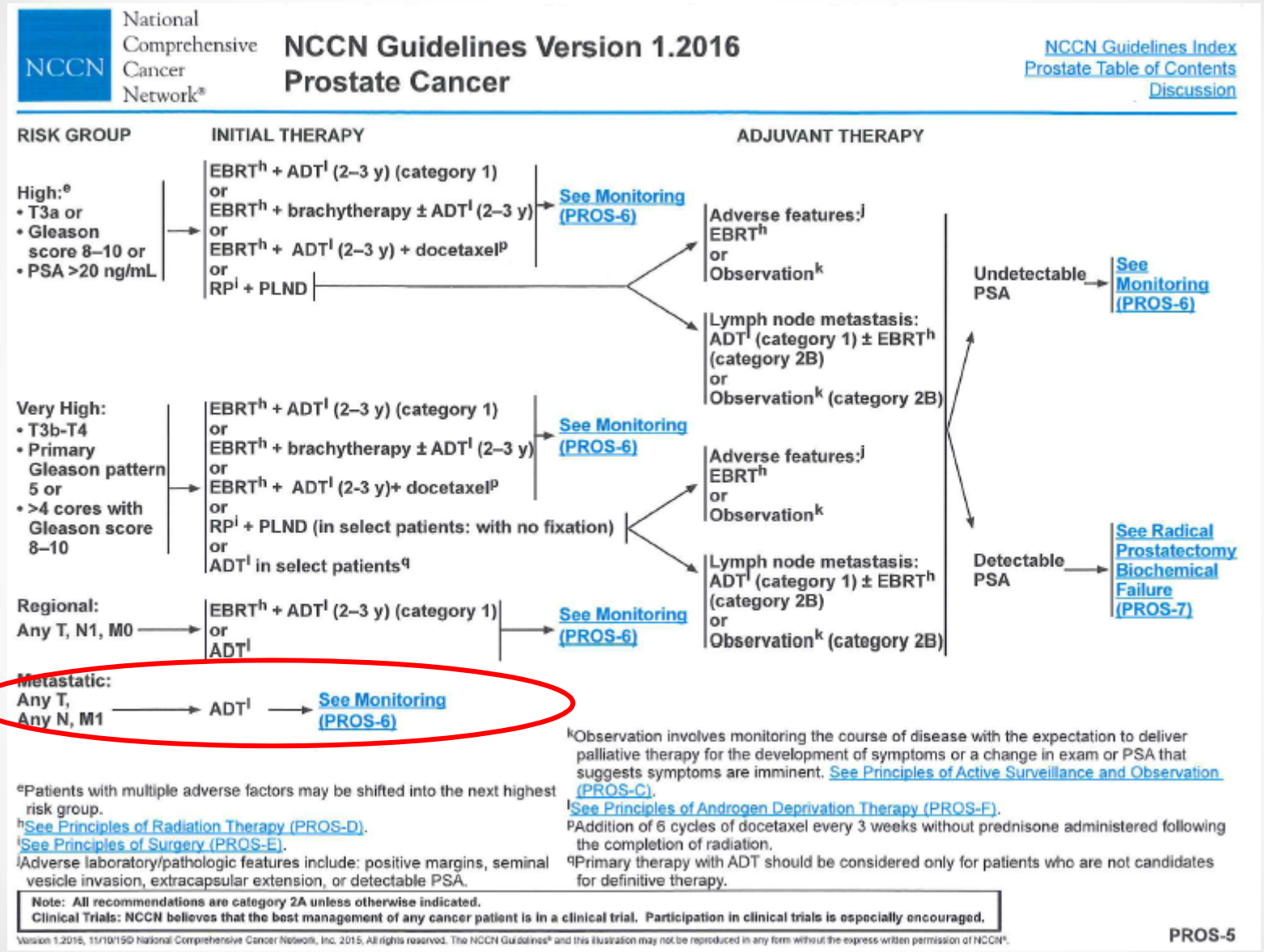
- Starts ADT: Leuprorelin 22,5 mg every 12 weeks and Bicalutamide 50 mg daily.
- Novem… a Radiati…
- Novem… ction of extensi… ation of the tracer at the sacro-iliac synchondrosis and left ileum and ischium-pubic branches. Hyperaccumulation at the upper third of the sternum.

ADT

COME?

QUANDO?

ESISTE UNO SPAZIO PER LA CHEMIOTERAPIA?


National Comprehensive Cancer Network
NCCN Guidelines Version 1.2016
Prostate Cancer
NCCN Guidelines Index
Prostate Table of Contents
Discussion
RISK GROUP
INITIAL THERAPY
ADJUVANT THERAPY
High:e
• T3a or
• Gleason score 8–10 or
• PSA >20 ng/mL
EBRTh + ADTl (2–3 y) (category 1)
or
EBRTh + brachytherapy ± ADTl (2–3 y)
or
EBRTh + ADTl (2–3 y) + docetaxelp
or
RPi + PLND
See Monitoring (PROS-6)
Adverse features:j
EBRTh
or
Observationk
Lymph node metastasis:
ADTl (category 1) ± EBRTh (category 2B)
or
Observationk (category 2B)
Undetectable PSA
See Monitoring (PROS-6)
Very High:
• T3b-T4
• Primary Gleason pattern 5 or
• >4 cores with Gleason score 8–10
EBRTh + ADTl (2–3 y) (category 1)
or
EBRTh + brachytherapy ± ADTl (2–3 y)
or
EBRTh + ADTl (2-3 y)+ docetaxelp
or
RPi + PLND (in select patients: with no fixation)
or
ADTl in select patientsq
See Monitoring (PROS-6)
Adverse features:j
EBRTh
or
Observationk
Lymph node metastasis:
ADTl (category 1) ± EBRTh (category 2B)
or
Observationk (category 2B)
Detectable PSA
See Radical Prostatectomy Biochemical Failure (PROS-7)
Regional:
Any T, N1, M0
EBRTh + ADTl (2–3 y) (category 1)
or
ADTl
See Monitoring (PROS-6)
Metastatic:
Any T,
Any N, M1
ADTl
See Monitoring (PROS-6)
ePatients with multiple adverse factors may be shifted into the next highest risk group.
hSee Principles of Radiation Therapy (PROS-D).
iSee Principles of Surgery (PROS-E).
jAdverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
kObservation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
lSee Principles of Androgen Deprivation Therapy (PROS-F).
pAddition of 6 cycles of docetaxel every 3 weeks without prednisone administered following the completion of radiation.
qPrimary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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PROS-5

6.6 Treatment: Metastatic prostate cancer

6.6.1 *Introduction*

A systematic review of ADT in PCa has recently been published [541].

6.6.2 *Prognostic factors*

In recent years, the median survival of patients with newly diagnosed metastases is 42 months [569]. The M1 population is heterogeneous, with the most convincing data on prognosis produced by the large SWOG 8894 trial [570] discriminating patients into three groups based on the location of metastases (axial bone only compared to appendicular or visceral), the performance status (< 1 compared to ≥ 1), the Gleason score (< 8 compared to ≥ 8) and the PSA (< 65 compared to > 65 ng/mL). Patients with axial bone metastases only or apendicular or visceral metastases, an PS < 1 and a Gleason score < 8 have a median survival of 54 months, compared to those with apendicular or visceral metastases a PS ≥ 1 and a PSA > 65 with only 21 months median survival.

After starting ADT, the PSA level after 7 months of ADT may lead to 3 groups with very different survival expectancy. The median survival is 75 months if the PSA level < 0.2 ng/mL, 44 months if the PSA < 4 ng/mL and only 13 months if the PSA is > 4 ng/mL [571]. Although these predictions are based on data from the large SWOG 9346 cohort, the prognostic use of PSA at 7 months of ADT still requires independent confirmation.

6.6.3 *First-line hormonal treatment*

Primary ADT is the standard of care [541]. There is no level 1 evidence to choose between an LHRH analogue

R. Salujaetal./UrologicOncology:Seminars and Original Investigations 34 (2016)

Chemohormonal therapy trials of castration-sensitive prostate cancer.

Patient population	Treatment arm	GETUG-AFU 15[a]			CHAARTED/E3805[b]			STAMPEDE[c]		
		OS, mo	HR	*P*-value	OS, mo	HR	*P*-value	OS, mo	HR	*P*-value
All patients	ADT	46.5	0.90	0.44	44.0	0.61	<0.001	45.0	0.76	0.005
	ADT + DOC	60.9			57.6			60.0		
	Δ	**+14.4**			**+13.6**			**+15**		
HV disease	ADT	35.1	0.8	0.35	32.2	0.60	<0.001	NR	NR	NR
	ADT + DOC	39.0			49.2			NR		
	Δ	**+3.9**			**+17.0**			**NA**		
LV disease	ADT	NR	1.0	0.87	NR	0.60	0.11	NR	NR	NR
	ADT + DOC	83.1			NR			NR		
	Δ	**NA**			**NA**			**NA**		

DOC = docetaxel chemotherapy; HR = hazard ratio; HV = high-volume disease; LV = low-volume disease; NR = not reported; OS = overall survival; NA = not applicable.

Recent evidence points to a significant survival benefit when ADT is combined with upfront docetaxel chemotherapy as chemohormonal therapy, particularly in patients presenting with high-volume disease.

The high- volume disease state is defined as the presence of visceral metastases or ≥ 4 bone metastases,of which ≥ 1 needs to be beyond the pelvis and the vertebral column

Patient characteristics

- November 22, 2010: Abdomino pelvic contrast enhanced MRI: metastatic structural alterations of left ischio-pubic branch and horizontal pubic branch. Benign cysts of left sacroiliac synchondrosis.

CHIRURGIA??

- December 21, 2010: contrast enhanced thoracic and pelvic CT: negative. Bone windows: stable soft thickening ... pic branch. N...

RT:

QUALI VOLUMI?

QUALI DOSI?

- January 1...

- Prescription of radical radiotherapy on:
  - pelvic lymph-nodes up to TD= 51.8 Gy/ 28 fr,
  - prostate, up to TD = 74.2 Gy, SIB (EQD2Gy= 88 Gy for α/β= 1.5) and
  - the two bone metastases up to 60.2 Gy SIB (EQD2Gy= 62.3 Gy for α/β= 2.2)

PRINCIPLES OF RADIATION THERAPY

Post-Prostatectomy Radiation Therapy

- The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, and PSADT to individualize treatment discussion. The panel also recommends consultation with the American Society for Therapeutic Radiology and Oncology (ASTRO) AUA Guidelines. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-449. Evidence supports offering adjuvant/salvage RT in most men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.
- Indications for adjuvant RT include pT3 disease, positive margin(s), Gleason score 8–10, or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and once any operative side effects have improved/stabilized. Patients with positive surgical margins may benefit the most.
- Indications for salvage RT include an undetectable PSA that becomes detectable and then increases on 2 subsequent measurements. Treatment is more effective when pre-treatment PSA is low and PSADT is long.
- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64–72 Gy in standard fractionation. Biopsy-proven gross recurrence may require higher doses.
- The defined target volumes include the prostate bed and may include the whole pelvis in selected patients.

Radiopharmaceutical Therapy

- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in men who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease greater than 3 to 4 cm. Radium-223 differs from beta-emitting agents, such as samarium 153 and strontium 89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10g/dL.
- Prior to subsequent doses, patients must have absolute neutrophil count ≥1 x 10^9/L and platelet count ≥50 x 10^9/L (per label, although this may be too low in practice). Radium-223 should be discontinued if a delay of 6 to 8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms are likely related to the fact that radium-223 is predominantly eliminated by fecal excretion.
- At the present time, except on a clinical trial, radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression.
- Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of radium-223 on survival.

Palliative Radiotherapy

- 8 Gy as a single dose should be used instead of 30 Gy in 10 fractions for non-vertebral metastases.
- Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external beam radiation.

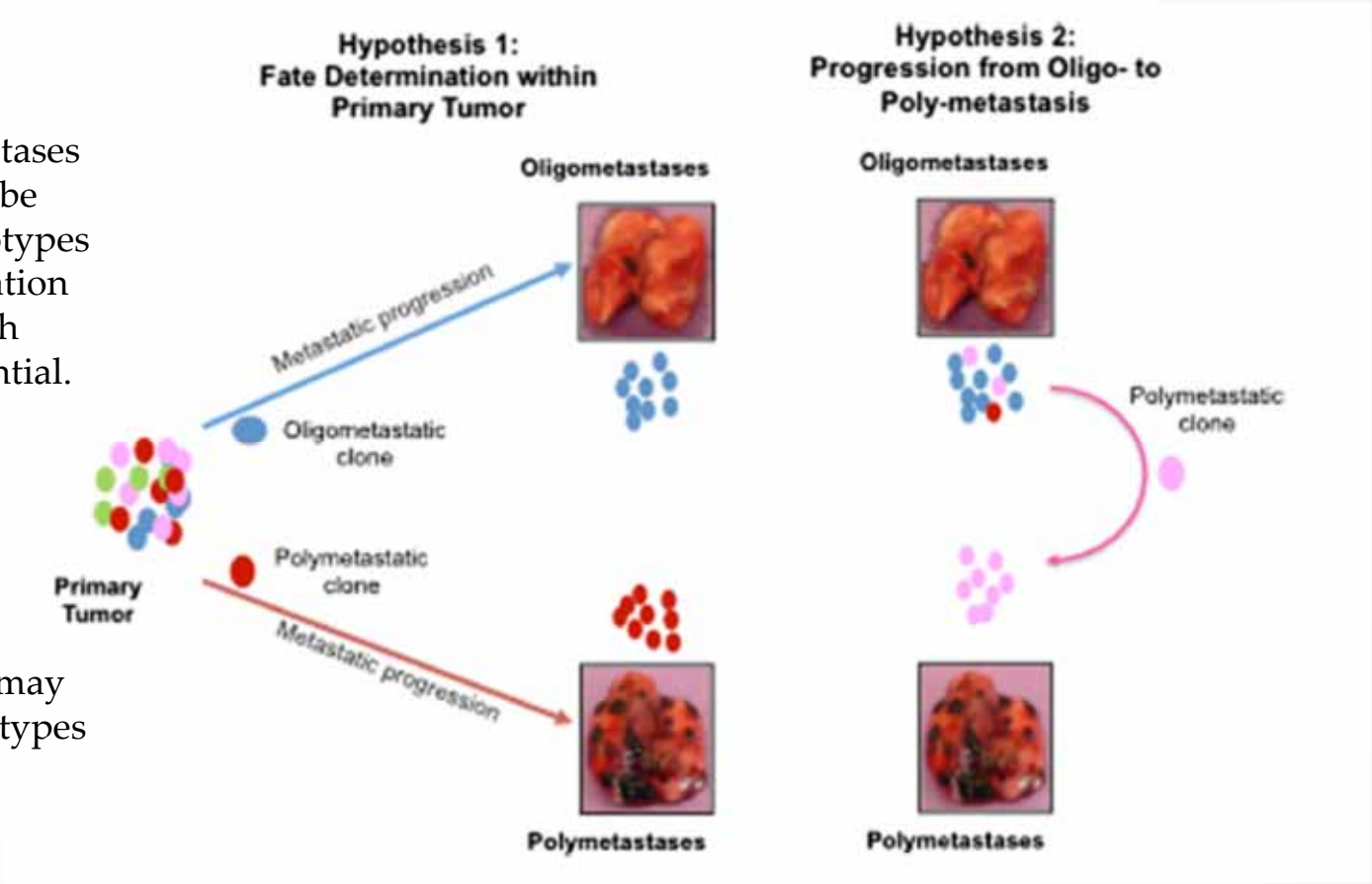
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Pathways of oligo-and polymetastases development. Two hypotheses of Oligometastastic Disease

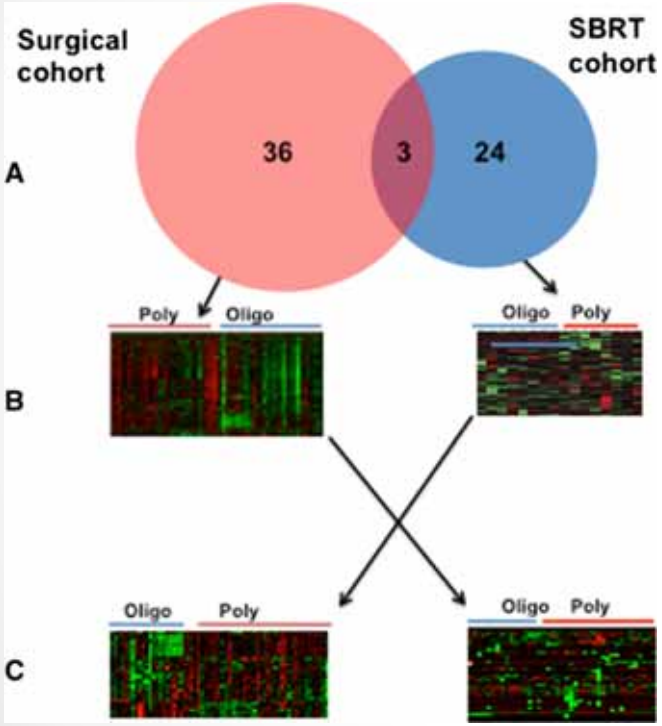
:

Hypothesis 1 Oligometastases and Polymetastases may be distinct metastasis phenotypes determined by dissemination of clonal populations with differing metastatic potential.

Hypothesis 2 Metastasis may be a continuum of phenotypes identified early (oligometastases) or late (polymetastases) in the progression of disease



Cross-talk between micro-RNA patterns obtained in surgical and stereotactic body radiotherapy (SBRT) cohorts.



a Only 3 overlapping micro-RNAs were identified in the surgical and SBRT cohorts (miR-328, miR-502-5p and miR-199b-5p

b Unsupervised clustering of patients in the surgical and SBRT cohorts based on differentially expressed micro-RNAs successfully segregated patients with oligo-and polymetastatic disease independently on clinical parameters of disease progression (heat maps represent normalized CT values; green are up- and red are down-regulated micro-RNAs).

c Application of the SBRT micro-RNA signature to surgical patients successfully separated them into oligo-and polymetastatic
clusters (left panel); the same was true for application of the
surgery micro-RNA signature to SBRT cohort

1071 patients intermediate and high risk prostate cancer cN0- cM0 with T stage 2b and above, or T stage 2a, Gleason score ≥ 7 and baseline PSA levels ≥ 10 ng/mL (2003-2007)
All received 6 months of leuprorelin (22.5 mg i.m. 3 monthly) commencing at randomisation, 5 months before RT to the prostate and seminal vesicles, but excluding pelvic lymph nodes. In the control arm (short term AS [STAS]) participants received no further treatment. In the second AS only treatment arm participants received an additional 12 months of adjuvant leuprorelin (22.5 mg i.m. 3 monthly) (intermediate term AS [ITAS]).
Participants allocated to the two bisphosphonate treatment arms received Z 4 mgs i.v. every 3 months for 18 months starting at randomisation with STAS (STAS + Z) or with ITAS (ITAS + Z).

Important baseline prognostic factors and their relationships with metastatic progression status.

Metastatic progression status		Bone metastases		Number of bone sites at first diagnosis		
		No	Yes	Solitary	2–3 sites	>3 sites
Total number diagnosed		895 (83.6)	176 (16.4)	45 (4.2)	49 (4.6)	82 (7.7)
Non-bone progression* present prior to	No	831 (77.6)	98 (9.2)	28 (2.6)	27 (2.5)	43 (4.0)
or at time of first bone metastases	Yes	64 (6.0)	78 (7.3)	17 (1.6)	22 (2.1)	39 (3.6)
Baseline factors						
T stage:						
T2		594 (55.5)	86 (8.0)	18 (1.7)	19 (1.8)	49 (4.6)
T3/T4		301 (28.1)	90 (8.4)	27 (2.5)	30 (2.8)	33 (3.1)
Gleason score						
≤7		622 (58.1)	78 (7.3)	19 (1.8)	25 (2.3)	34 (3.2)
>7		273 (25.5)	98 (9.2)	26 (2.4)	24 (2.2)	48 (4.5)
PSA ng/ml, median (IQR)		14.0 (9.1–23.0)	19.0 (12.0–33.4)	21.0 (16.0–37.0)	18.0 (10.9–36.0)	17.8 (11.7–27.5)
Age years, median (IQR)		69.1 (63.9–73.0)	68.1 (61.7–73.0)	64.2 (59.8–71.4)	68.9 (61.9–74.2)	69.1 (63.3–73.1)
Allocated treatment:						
STAS		222 (20.7)	46 (4.3)	15 (1.4)	8 (0.7)	23 (2.1)
STAS + Z		211 (19.7)	57 (5.3)	15 (1.4)	17 (1.6)	25 (2.3)
ITAS		231 (21.6)	37 (3.5)	4 (0.4)	16 (1.5)	17 (1.6)
ITAS + Z		231 (21.6)	36 (3.4)	11 (1.0)	8 (0.7)	17 (1.6)

Data are *n* (%) unless otherwise stated. Percentages for each categorical covariate represent proportions of the total 1071 participants.
Abbreviations: STAS, short term androgen suppression; ITAS, intermediate term androgen suppression; Z, zoledronate; IQR, interquartile range; PSA, prostate-specific antigen.
* Local, nodal or soft tissue progression.

Three Fine and Gray competing risk models for PCSM were used to determine the impact of number of bone metastases:
(1) at first presentation,
(2) with or without non-bony progression at, or prior to, first presentation,
(3)for men with <4 bone sites, at subsequent bony progression

S. Sridharan et al. / Radiotherapy and Oncology xxx (2016)

Sridharan S et al. Oligometastatic bone disease in prostate cancer patients treated on the TROG 03.04 RADAR trial. Radiother Oncol (2016),

Table 2
Sub-hazard ratios for time to prostate cancer-specific mortality from randomisation according to number of bone metastases in multivariable models adjusted for baseline age, tumour stage, Gleason score, PSA, and trial arm.

	Adjusted SHR*	95% CI	p-Value
Model 1† (n = 1071)			
No BM	0.02	0.01–0.07	<0.001
Solitary BM	1		
2–3 BM sites	2.32	1.15–4.70	0.019
>3 BM sites	4.98	2.57–9.67	<0.001
Model 2‡,¶ (n = 1071)			
No clinical progression	0.00	0.00–0.00	<0.001
No BM + other progression	0.60	0.23–1.53	0.28
Solitary BM only	1		
Solitary BM + other progression	1.15	0.35–3.82	0.81
2–3 BM sites only	2.06	0.90–4.72	0.09
2–3 BM sites + other progression	2.28	1.00–5.18	0.05
>3 BM sites only	3.32	1.61–6.83	0.001
>3 BM sites + other progression	7.41	3.51–15.65	<0.001
Model 3‡,§ (n = 989)			
No BM	0.10	0.02–0.43	0.002
Solitary BM not progressing	1		
2–3 BM sites not progressing	4.85	1.14–20.58	0.032
Further bone progression	21.60	6.73–69.32	<0.001

Abbreviations: SHR, sub-hazard ratio; CI, confidence interval; BM, bone metastases; STAS, short-term (6 months) androgen suppression and radiotherapy; ITAS, intermediate-term (18 months) androgen suppression and radiotherapy; Z, zoledronic acid.

* Reference group: solitary bone metastases.

† Multivariable competing risks models: number of bone metastases (time-dependent covariate), age (years, continuous), tumour stage (T2, T3/T4), Gleason score (≤7, >7), PSA (continuous), trial arm (STAS, STAS + Z, ITAS, ITAS + Z).

‡ Other progression defined as progression at non-bony sites (i.e. local, nodal or soft tissue) diagnosed prior to or at time of first appearance of bone metastases.

§ The subgroup of men diagnosed with >3 BM sites were excluded from this model due to the difficulty in determining if further bone progression had occurred.

Essential stratification factors:

-number of sites of bone metastases determined using a pre-specified imaging protocol,

-the primary tumour stage, and presence of local or metastatic disease at soft tissue sites.

Most powerful predictor of PCSM:

PSA doubling time

However after PSA progression, baseline factors such as Gleason score, T stage and PSA seem to have reduced prognostic utility

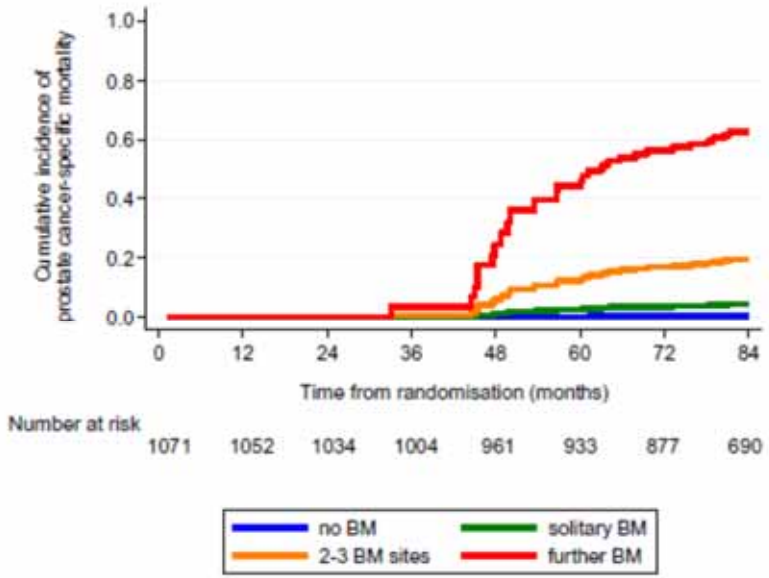


Fig. 1. Evidence of a prostate cancer-specific mortality gradient in men with solitary, two or three, and more than three bony metastatic presentations ($n = 1071$). *Abbreviations:* BM, bony metastasis.

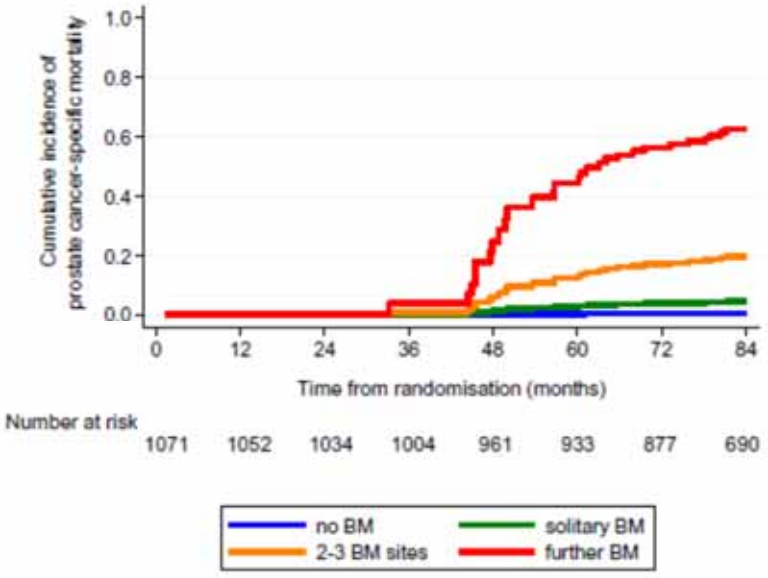


Fig. 3. Evidence that further progression in the bony skeleton of solitary and two or three bony metastatic presentations is associated with a substantial increase in prostate cancer-specific mortality ($n = 989$). *Abbreviations:* BM, bony metastasis.

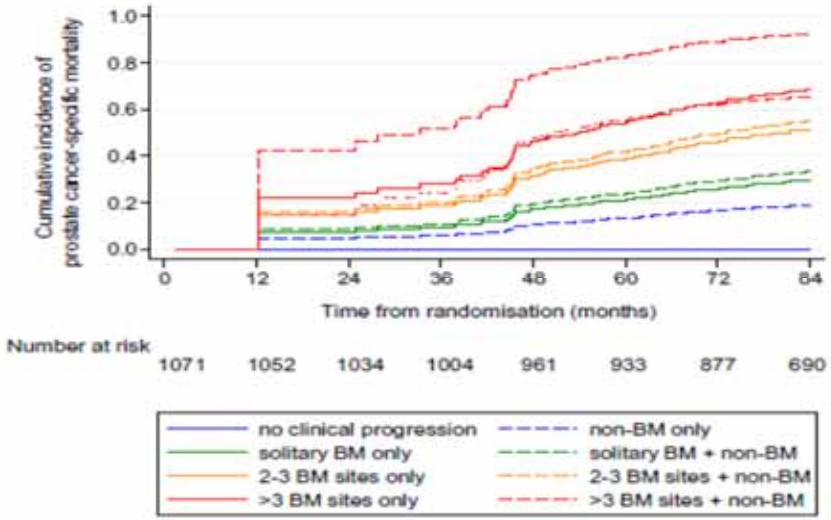
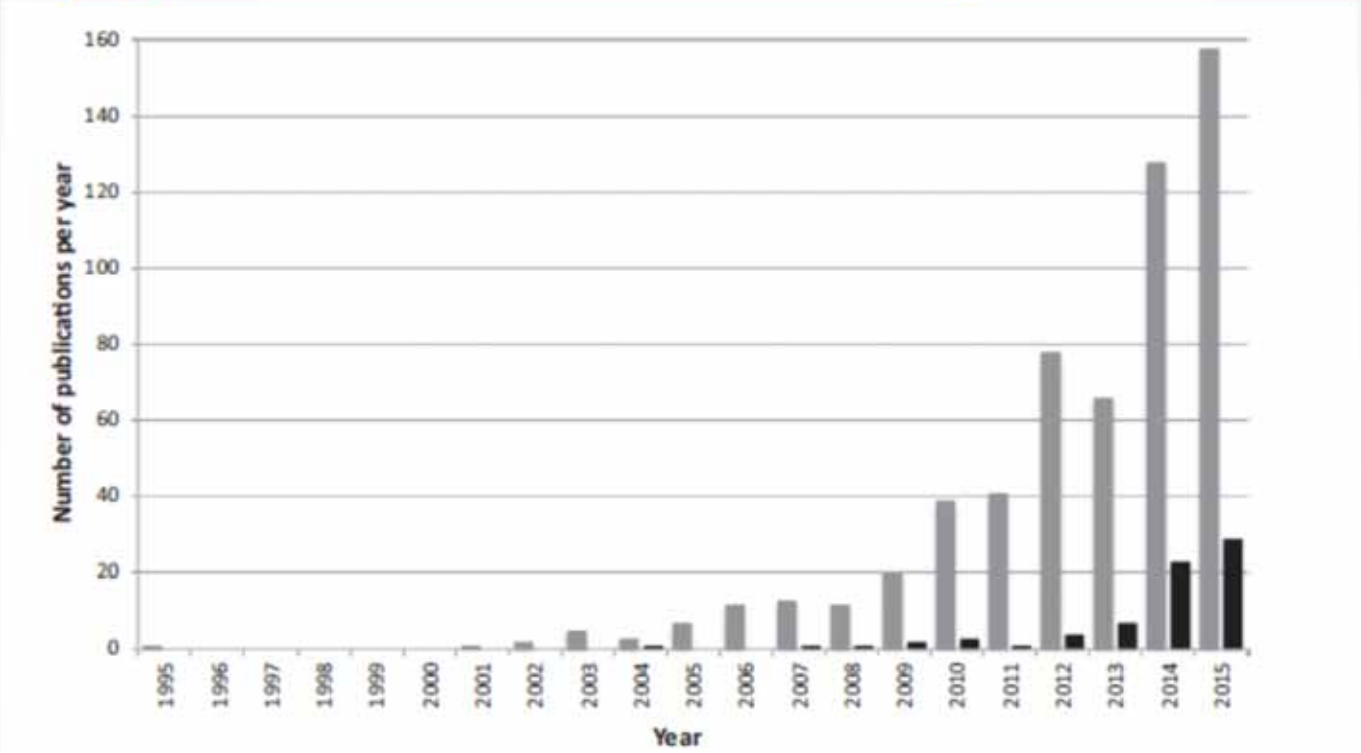


Fig. 2. Evidence that non-bony sites of progression at or prior to diagnosis of bony metastasis also contribute to the prostate cancer-specific mortality gradient ($n = 1071$). *Abbreviations:* BM, bony metastasis.

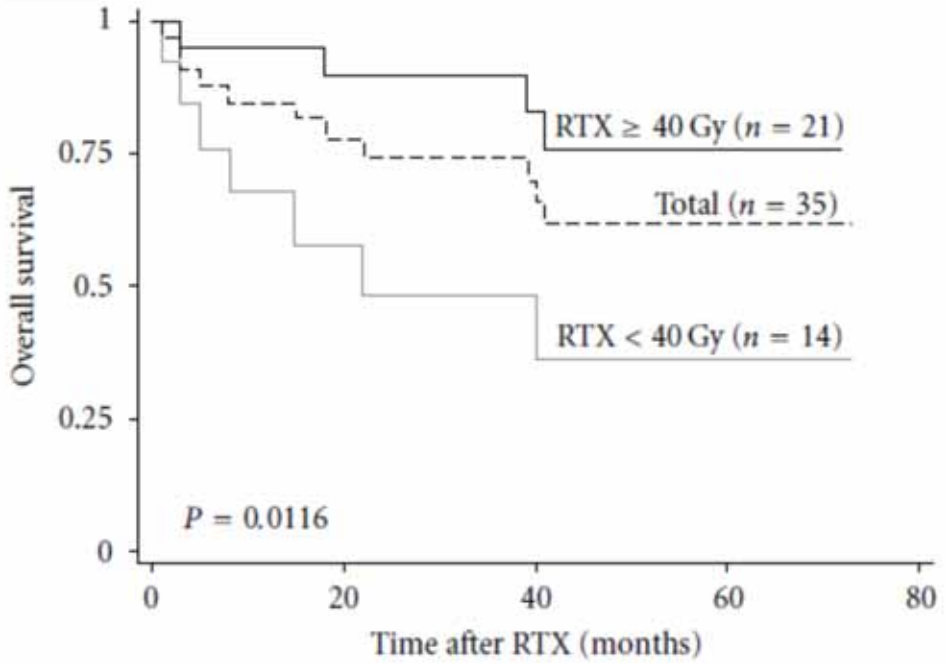
The growing interest in the active management of oligometastases coincides with the emergence of SABR.



Pubmed-listed publications on oligometastases in general by year (gray bars; search strategy used: [oligometastatic OR oligometastasis OR oligometastases]), and number of publications by year relevant to oligometastatic prostate cancer (black bars; search strategy used: [oligometastatic OR oligometastasis OR oligometastases] AND [prostate cancer]).

R. Salujaetal./UrologicOncology:Seminars and Original Investigations 34 (2016)

The overall survival curves for all patients (n = 35) and those that received a total radiotherapy dose of ≥40Gy (n = 21) or <40Gy (n = 14). RTX, radiotherapy



Univariable and multivariable analysis for the effect of radiotherapy on survival.

Factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value*	HR	95% CI	*P* value*
RTX (≥40 Gy versus <40 Gy)	0.231	0.067–0.798	0.021	0.630	0.098–4.285	0.637
Propensity score†	n/d	n/d	n/d	0.300	0.024–3.763	0.351

Abbreviations. HR: hazard ratio; n/d: not done.
*Analyses were performed using Cox proportional hazard regression.
†Multivariable model indicates adjusted effect of RTX by applying propensity score which is a conditional probability of receiving RTX (≥40 Gy) given by other factors including age, baseline PSA, performance status, castration-resistant prostate cancer, and oligostatus.

Ken-ichi Tabata et al : Radiotherapy for Oligometastases and Oligo-Recurrence of Bone in Prostate Cancer
Pulmonary Medicine 2012

Table 1 – Full-text publications of metastasis-directed therapy for oligometastatic prostate cancer recurrence included in the systematic review

Study	No. of patients	Site of metastasis: node/bone/visceral	Median time to metastatic recurrence, mo	Median PSA at time of metastasis	Staging method	Type of MDT	Median follow-up, mo	Median PFS	Adjuvant ADT (%)	Median duration ADT	Prophylactic nodal radiotherapy (%)
Casamassima et al. [23]	25	25/0/0	11.8–36.7	5.65	Choline PET/CT	SBRT	29	24 mo	None	NA	7 (28)
Muacevic et al. [24]	40	0/40/0	NR	5.4	Choline PET/CT	SBRT	14*	NR	27 (68)	NR	NA
Würschmidt et al. [25]	15	15/0/0	NR	1.79	Choline PET/CT	NRT	28	Median not reached; 3-yr PFS: 75%	NR	NR	15 (100)
Ahmed et al. [26]	17	1/15/1	50.4	2.1	Choline PET/CT (n = 9), MRI (n = 6), CT (n = 1), and biopsy (n = 1)	SBRT	6	12 mo	15 (88)	NR	NA
Jereczek-Fossa et al. [27]	19	18/1/0	66	1.77 (pelvic nodes); 10.7 (M1)	Choline PET/CT	SBRT	17	Median not reached; 30-mo PFS: 63.5%	19 (100)	12–17 mo	None
Schick et al. [28]	50	33/15/2	15.6	6.7	Choline PET/CT and bone scintigraphy	SBRT (n = 14) NRT (n = 36)	31	Median not reached; 3-yr PFS: 58.6%	49 (98)	12 mo	25 (50)
Decaestecker et al. [29]	50	27/22/1	57.6	3.8	Choline (n = 18) or FDG (n = 32) PET/CT	SBRT	25	19 mo	35 (70)	1 mo	None
Picchio et al. [30]	83	83/0/0	NR	2.6	Choline PET/CT	HRT	22	NR	58 (70)	NR	77 (93)
Rinnab et al. [31]	15	15/0/0	NR	1.98	Choline PET/CT	LND	13.7*	NR	11 (73)	NR	1 (7)
Schilling et al. [32]	10	10/0/0	NR	8.75	Choline PET/CT	LND	11*	NR	6 (60)	NR	None
Winter et al. [33]	6	6/0/0	NR	2.04	Choline PET/CT	LND	24 mo	NR	None	NA	None
Busch et al. [37]	6	6/0/0	Mean: 79.9	37.6*	Choline (n = 3), MRI (n = 1), CT (n = 2)	LND	NR	15.5 mo	6 (100)	Lifelong ADT	None
Jilg et al. [34]	47	47/0/0	62	11.1*	Choline PET/CT	LND	35.5	27 mo**	34 (65)	NR	27 (52)
Martini et al. [35]	8	8/0/0	NR	1.62	Choline PET/CT	LND	NR	NR	None	NA	None
Suardi et al. [36]	59	59/0/0	NR	2.0	Choline PET/CT	LND	76.6	60 mo**	24 (41)	24 mo	21 (36)

ADT = androgen-deprivation therapy; CT = computed tomography; FDG = fluorodeoxyglucose; HRT = hypofractionated radiotherapy; LND = lymph node dissection; MDT = metastasis-directed therapy; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NRT = normofractionated radiotherapy; PET/CT = positron emission tomography with coregistered computed tomography; PFS = progression-free survival; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy.

* Mean numbers reported instead of median.

** Median estimated from curves.

Piet Ost et al : Metastasis-directed Therapy of Regional and Distant Recurrences After Curative Treatment of Prostate Cancer: A Systematic Review of the Literature EUROPEAN UROLOGY (2015)

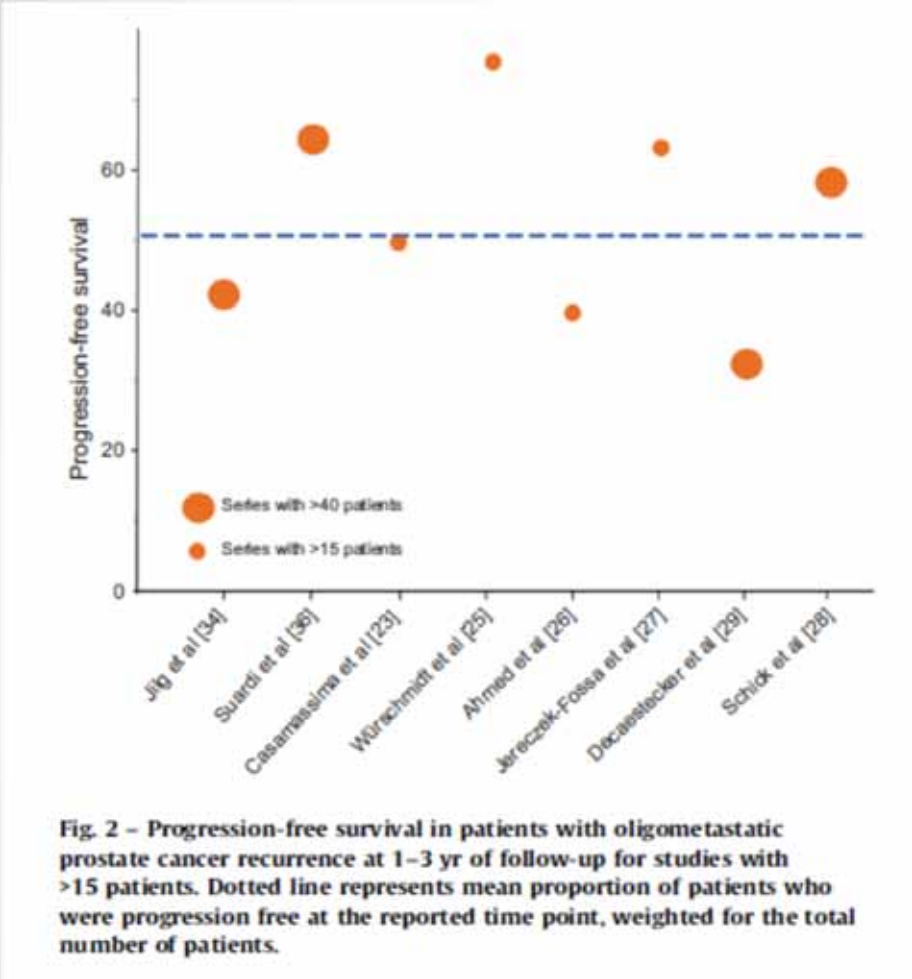


Fig. 2 – Progression-free survival in patients with oligometastatic prostate cancer recurrence at 1–3 yr of follow-up for studies with >15 patients. Dotted line represents mean proportion of patients who were progression free at the reported time point, weighted for the total number of patients.

Apparently, 67% of the patients treated with SBRT only to the lymph nodes relapsed in the pelvis or retroperitoneal nodes, suggesting undertreatment if SBRT is used as a sole treatment modality. However, even extended salvage LND might be insufficient because it appears that the first site of clinical recurrence is again nodal in 47–59% Consequently, the inclusion of prophylactic nodal irradiation in the management of nodal recurrences seems reasonable in this setting.

The pattern of first progression was oligometastatic in 75% in the series of Decaestecker et al. compared with only 10% in the series of Schick et al. A short PSA doubling time before SBRT predicted worse PFS in the study by Decaestecker et al.

approximately 50% of patients remaining disease free at 1–3 yr of follow-up

Piet Ost et al : Metastasis-directed Therapy of Regional and Distant Recurrences After Curative Treatment of Prostate Cancer: A Systematic Review of the Literature EUROPEAN UROLOGY (2015)

R. Salujaetal./UrologicOncology:Seminars and Original Investigations 34 (2016)

Stereotactic ablative radiotherapy for oligometastatic prostate cancer: Study details.

Reference	Study type	No. of patients (no. of metastases)	Prostate cancer stage (no. of patients)	Treated sites	SABR total dose (Gy)/no. of fractions	Comments
Ahmed et al. [30]	Prospective	17 (21)	CRPC (11), CSPC (6)	Bo, LNs, Li	Bo: 8–24/1–3, LNs: 50/5, Li: 60/3	Median follow-up: 6 mo (range: 2–24)
Casamassima et al. [31]	Retrospective	25 (25)	CSPC	LNs	30/3	Median follow-up: 29 mo (range: 14.4–48)
Decaestecker et al. [32]						
Jereczek-Fossa et al. [33]						(range: s DT,
Jereczek-Fossa et al. [34]						; 18/34 nitant
Muacevic et al. [35]						ange: ed tients before
Napieralska et al. [36]						no;

CRPC = castrat

Stereotactic ab

Stereotactic ablative radiotherapy for oligometastatic prostate cancer: Toxicities.

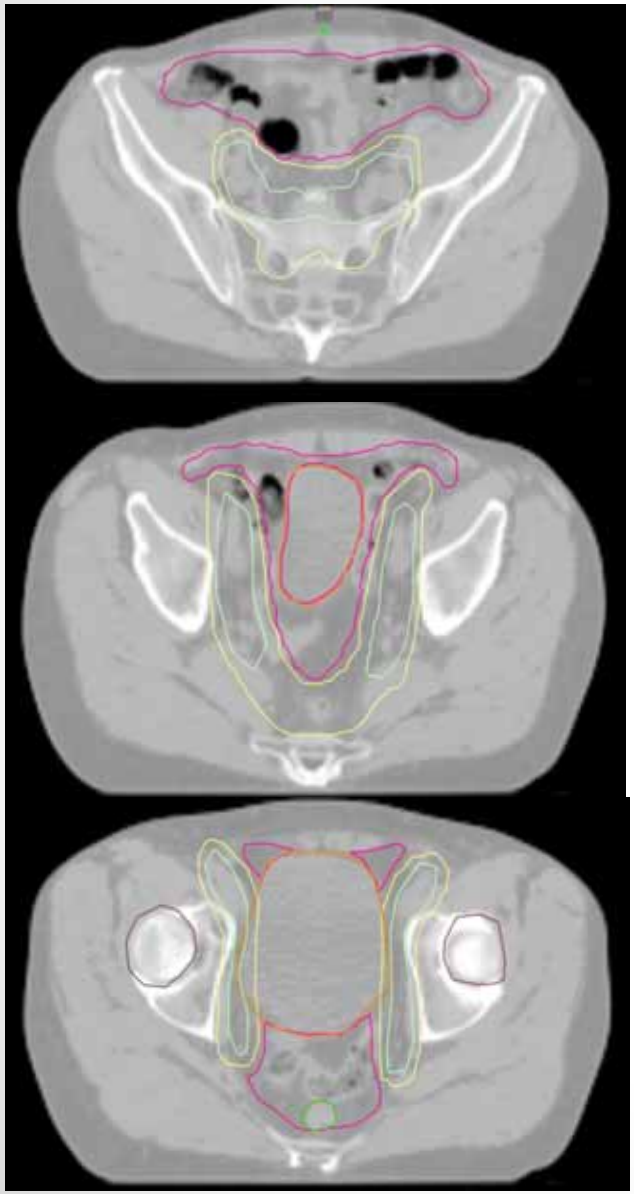
Reference	Acute toxicities	Late toxicities
Ahmed et al. [30]	No ≥ grade 3 toxicities, 3 patients (18%) with grade 1 or 2 toxicites 1 patient grade 2 dyspnea (18 Gy in 1 fraction to left eighth rib) 1 patient grade 2 back pain/nausea (18 Gy in 1 fraction to third thoracic vertebra) 1 patient grade 1 transaminase increase (60 Gy in 3 fractions to liver)	No toxicities reported
Casamassima et al. [31]	No > grade 1 toxicities	No > grade 1 toxicities
Decaestecker et al. [32]	10 patients (20%) developed grade 1 (7 patients) or grade 2 (3 patients) toxicities, including bone pain, asymptomatic ilium fracture, fatigue, diarrhea, and worsening of postradical prostatectomy urinary incontinence[a]	Not reported[a]
Jereczek-Fossa et al. [33]	No toxicities reported	Toxicities evaluable in 13 patients of which 1 (8%) presented with grade 2 rectal tenesmus
Jereczek-Fossa et al. [34]	7 (20%) urinary events, including 2 grade 3 events; 1 (3%) grade 1 rectal event; toxicity rate 0% for metastatic lesions, 6% for lymphnodes, 25% for anastomoses, and 67% for prostate recurrence	7 (20%) urinary events, including 2 grade 3 events; 2 (6%) rectal events, 1 grade 1, 1 grade 2; toxicity rate 0% for treatment of metastatic lesions, 19% for lymphnodes, and 50% for anastomoses
Muacevic et al. [35]	Not reported	Not reported
Napieralska et al. [36]	Not reported	Not reported

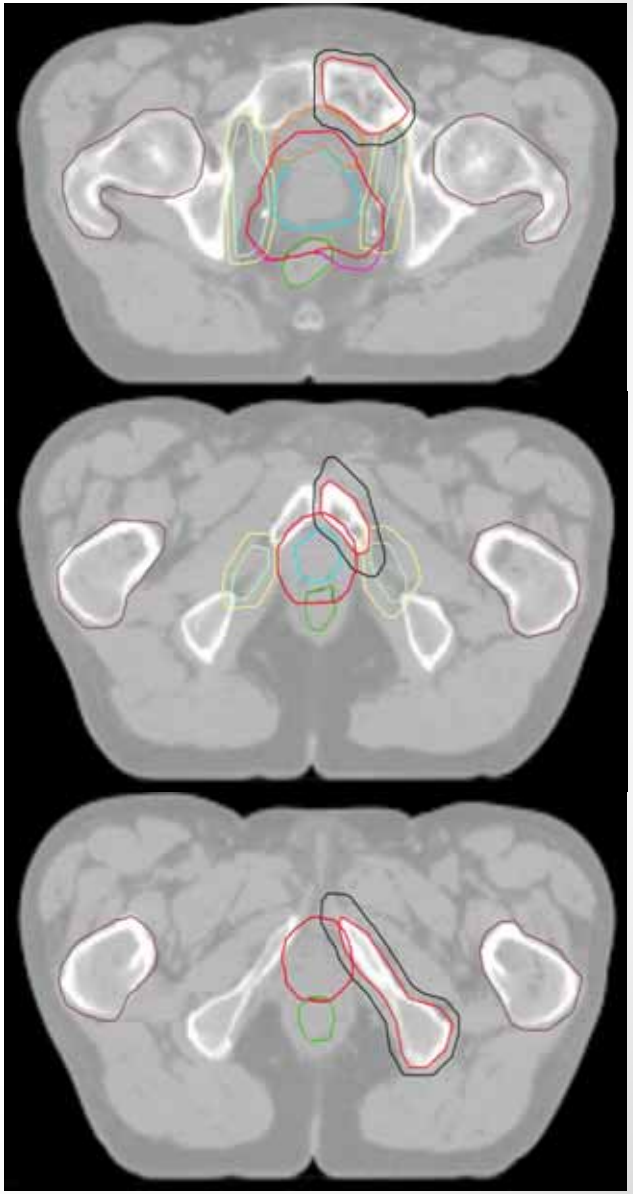
Reference				Overall survival
Ahmed et al. [				NR
Casamassima				92% at 3 y
Decaestecker				NR
Jereczek-Fossa et al. [33]	100% at a median follow-up of 18.6 mo	Mean = 12.7 mo (range: 6.1–19.8)	NR	NR
Jereczek-Fossa et al. [34]	88% at 16.9 mo	42.6% at 30 mo	NR	NR
Muacevic et al. [35]	95% at 2 y (95% CI: 83–98.8)	NR	NR	NR
Napieralska et al. [36]	NR	NR	NR	NR

Ongoing trials of stereotactic ablative radiotherapy for oligometastatic prostate cancer.

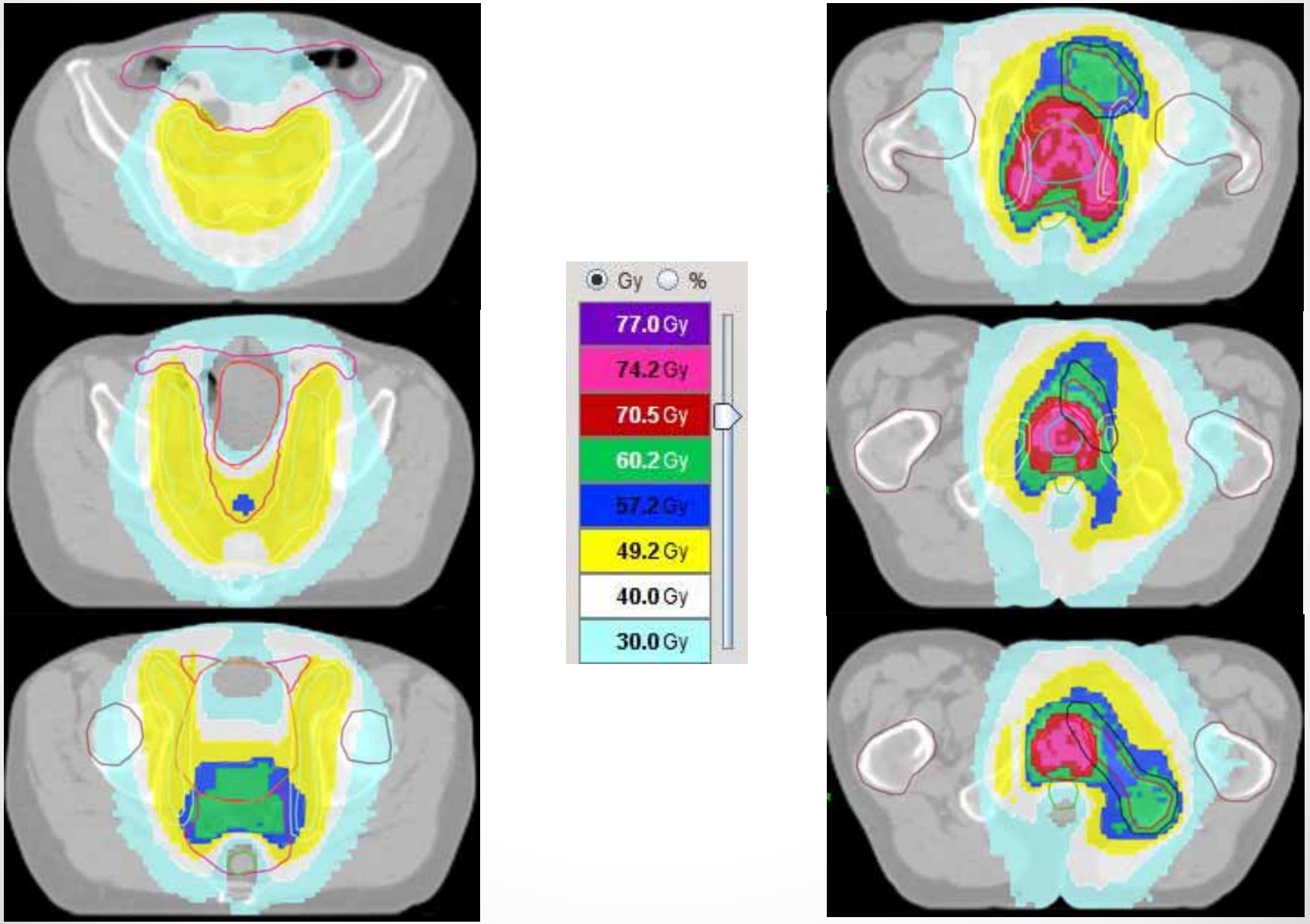
Study identifier	Study type	Patient population[b]	population[b] Intervention(s)	$N = ?$	Primary endpoint	Secondary endpoints
NCT01777802	Observational, prospective	Oligometastatic prostate cancer (**<4 lesions**) amenable to SABR	Monitor antiprostate cancer immunity following SABR	20	Induction of antiprostate cancer immunity	Not reported
NCT0256391	Phase I/II, nonranddomized	Oligometastatic castration-sensitive prostate cancer (**≤ 5 lesions**)	SABR, androgen-deprivation therapy (intermittent therapy allowed after 1 y)	30	Rate of late radiotherapy toxicity	Quality of life, time to castration-resistance, radiological local and distant control, overall survival
NCT01859221	Phase II, nonrandomized	Castration-sensitive or castration-resistant oligometastatic prostate cancer **(not further specified)**	SABR/SHRT	48	Progression-free survival (78 mo)	Overal survival (78 mo); treatment failure rate (78 mo); quality of life (78 mo)
NCT01558427	Phase II, randomized, open label	Low-volume metastatic castration-sensitive prostate cancer (N1 and M1a/b disease on imaging, with a combined **maximum of 3 synchronous lesions**) postradical therapy (surgery or radiotherapy)	Arm 1: active clinical surveillance Arm 2: salvage treatment (surgery or SBRT)	54	ADT-free survival	Quality-of-life assessment
NCT02264379	Observational, prospective	Oligometastatic castration-sensitive prostate cancer (**1–5 lesions**) postlocal therapy (surgery or radiotherapy)	Arm 1: normal fractionated irradiation (25 × 2 Gy, 5 daily fractions/wk) Arm 2: hypofractionated irradiation (3 × 10 Gy, daily, 2–3 d/wk)[a]	60	Toxicity (24 mo)	Acute toxicity (90 d); quality of life (2, 12 and 24 mo); local control (24 mo); therapy-free survival (24 mo); PSA relapse free-survival (24 mo)
NCT02192788	Phase II, nonrandomized	Oligometastatic or oligorecurrent prostate cancer postprimary therapy, defined as **<5 bone or lymphnode metastases**	SABR	68	Progression-free survival (5 y)	Overall survival (5 y); toxicity (3 mo); time to disease progression (5 y); quality of life (3 mo)

Target definition

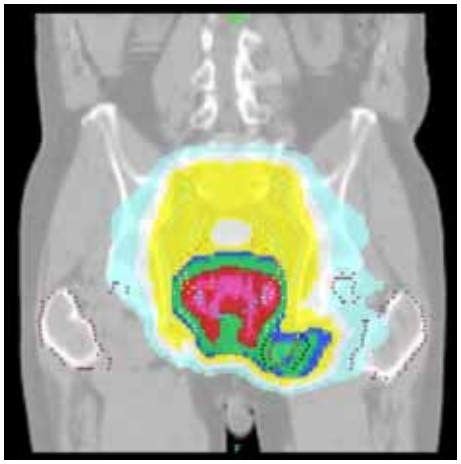


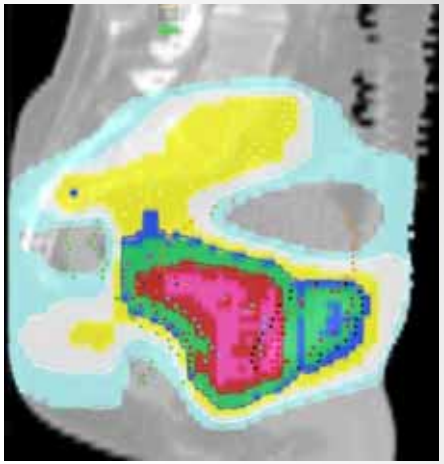


Dose distribution



Dose distribution

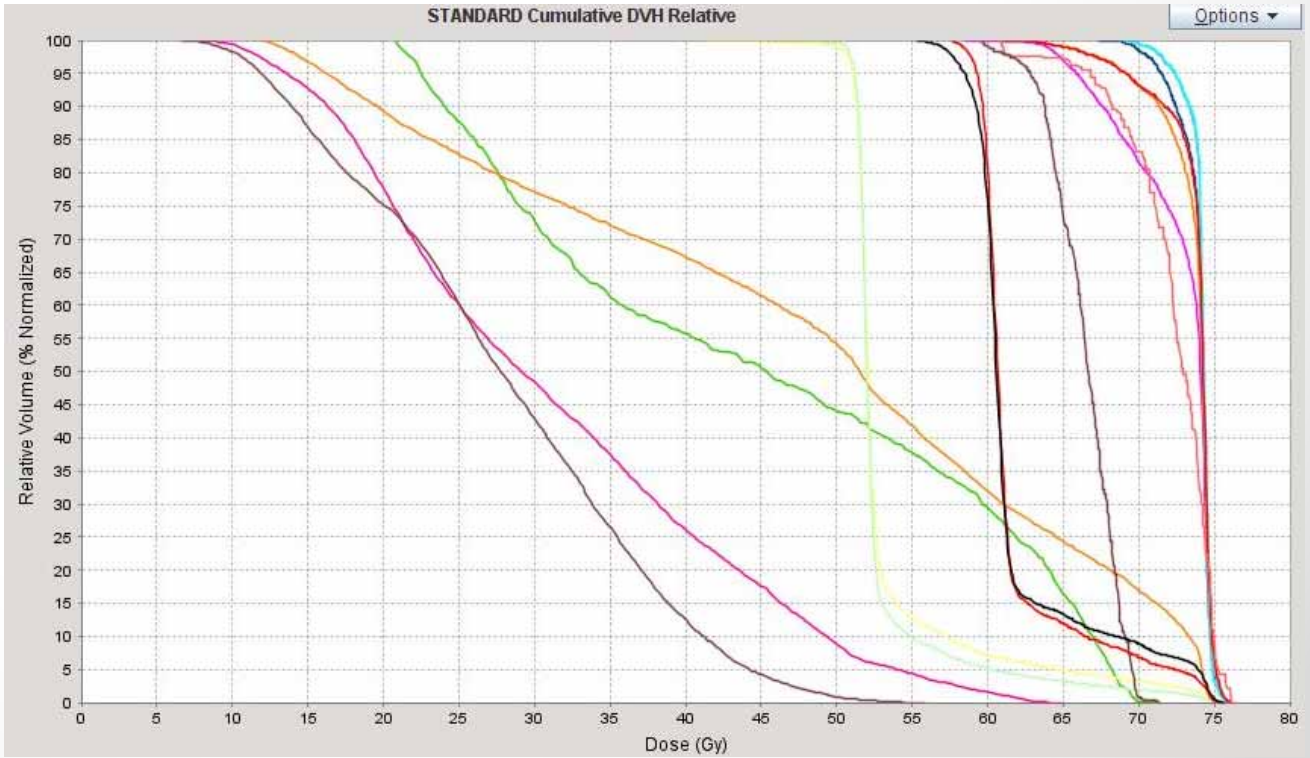




- CTV_p
- CTV_p+1/3vs
- CTV_p+vs
- CTV_Bone
- CTV_LN

- PTV_p
- PTV_p+1/3vs
- PTV_p+vs
- PTV_bone
- PTV_LN
- Ovlp_rectum

- Rectum
- Bladder
- Intestinal cavity
- Femoral heads
- Penile bulb



OAR dose distribution

Rectum
V50=44% *(<35-45%)*
V60=29% *(<25-30%)*
V65=16% *(<15-20%)*
V20=100%; V30=73%; V40=56% *(Reduce V20-40)*
D_{max}=71,3 Gy *(<68-70 Gy)*

Bladder
V60=32% *(<35%)*
V20=90%; V30=77%; V40=67 %; V55=41% *(Reduce V20-55)*
V70=53cc *(<5cc)*

Femoral heads
D_{max}=56 Gy *(<40-45 Gy)*
V40=12%; V45=4% *(V40-45 < low %)*

Intestinal cavity
D_{max}=65 Gy *(<45-48 Gy when far from PTV3-4, otherwise <55Gy)*
D average=29 Gy *(<20-25 Gy)*
V20=651 cc *(<500-700 cc)*
V30= 407 cc *(<150-250 cc)*
V40=219 cc *(<50-100 cc)*
V50=73 cc *(<few thens of cc)*

Penile bulb
D average=72 Gy *(<50 Gy)*
D90%=69 Gy *(optimal<25 Gy; acceptable: 25-50 Gy; not acceptable>50 Gy)*

Acute toxicity

- Treatment carried out from March 7 to April 15, 2011.
- During the treatment he presented G1 dysuria (prescription of Malva sylvestris infusion), G1 GE toxicity (1-2 semi-liquid stool discharges; prescription of lactic ferments) and G2 gluteal erythema (in an area where the dose reached 40 Gy).

Follow up

- Last follow up visit: October 27, 2016.

- He presented an episode of hematuria in May 2014 (GU G2); no other GU, GE or rectal toxicity.
- PSA stable at 0.01 ng/ml during ADT.

- STOP ADT in August 2013.
- PSA stable at 0.01 ng/ml since then.

- He performs annual visits with PSA every 4 months. He was instructed to schedule an earlier visit in case of PSA increase.

First question

Should radical radiotherapy be proposed to a prostate cancer patient with synchronous bone metastases?

a) No.

b) Yes.

c) Yes, in selected patients (oligometastatic disease).

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 1, pp. 3–10, 2004

0360-3016/04/$–see front matter
doi:10.1016/S0360-3016(03)01442-1

CLINICAL INVESTIGATION — **Prostate**

IS THERE A FAVORABLE SUBSET OF PATIENTS WITH PROSTATE CANCER WHO DEVELOP OLIGOMETASTASES?

DEEPINDER SINGH, M.D.,* WON SAM YI, M.D.,* RALPH A. BRASACCHIO, M.D.,*
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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 689–697, 2012

0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2010.11.031

CLINICAL INVESTIGATION — **Genitourinary Cancer**

ROBOTIC IMAGE-GUIDED STEREOTACTIC RADIOTHERAPY, FOR ISOLATED RECURRENT PRIMARY, LYMPH NODE OR METASTATIC PROSTATE CANCER

BARBARA ALICIA JERECZEK-FOSSA, M.D., PH.D.,*† GIANCARLO BELTRAMO, M.D.,‡
LAURA FARISELLI, M.D.,§ CRISTIANA FODOR, M.SC.,* LUIGI SANTORO, M.SC.,‖ ANDREA VAVASSORI, M.D.,*
DARIO ZERINI, M.D.,* FEDERICA GHERARDI, M.D.,*† CARMEN ASCIONE, M.D.,*¶
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Departments of *Radiotherapy, †Urology, and ‡Epidemiology and Statistics, European Institute of Oncology, Milan, Italy; §University of Milan, Milan, Italy; ‖CyberKnife Center CDI, Milan, Italy; ¶Radiotherapy Unit, Carlo Besta Neurological Institute Foundation, Milan, Italy; and #Seconda Università degli Studi di Napoli, Naples, Italy

Original Study

Salvage Stereotactic Body Radiotherapy for Patients With Limited Prostate Cancer Metastases: Deferring Androgen Deprivation Therapy

Patrick Berkovic,[1] Gert De Meerleer,[1] Louke Delrue,[2] Bieke Lambert,[3] Valérie Fonteyne,[1] Nicolaas Lumen,[4] Karel Decaestecker,[5] Geert Villeirs,[2] Philippe Vuye,[1] Piet Ost[1]

Abstract

Patients with metastatic prostate cancer are uniformly treated with castration (surgically or medically), which is associated with numerous side effects such as sexual dysfunction, fatigue, osteoporosis, metabolic syndromes, and others. This single-arm study including 24 patients with limited bone or lymph node prostate cancer (PCa) metastases shows that repeated salvage stereotactic body radiotherapy is well tolerated and defers the necessity to start castration treatment.

Background. this investigated whether repeated stereotactic body radiotherapy (SBRT) of oligometastatic disease is able to defer the initiation of palliative androgen deprivation therapy (ADT) in patients with low-volume bone and lymph node metastases. **Patients and Methods:** Patients with up to 3 synchronous metastases (bone and/or lymph nodes) diagnosed on positron emission tomography, following biochemical recurrence after local curative treatment, were treated with (repeated) SBRT to a dose of 50 Gy in 10 fractions. Androgen deprivation therapy-free survival (ADT-FS) defined as the time interval between the first day of SBRT and the initiation of ADT was the primary end point. ADT was initiated if more than 3 metastases were detected during follow-up even when patients were still asymptomatic or in case of a prostate specific antigen elevation above 50 ng/mL in the absence of metastases. Secondary end points were local control, clinical progression-free survival, and toxicity. Toxicity was scored using the Common Terminology Criteria for Adverse Events. **Results:** We treated 24 patients with a median follow-up of 24 months. Two patients started with ADT resulting in a median ADT-FS of 36 months. The 2-year local control and clinical progression-free survival was 100% and 42%, respectively. Eleven and 3 patients, respectively, required a second and third salvage treatment for metachronous low-volume metastatic disease. No grade 3 toxicity was observed. **Conclusion:** Repeated salvage SBRT is feasible, well tolerated and defers palliative ADT with a median of 36 months in patients with limited bone or lymph node PCa metastases.

Clinical Genitourinary Cancer Vol. 11, No. 1, 37-42 © 2013 Elsevier Inc.
Keywords: Low-volume metastasis, Oligometastases, SBRT

A Prospective Pilot Study of Curative-intent Stereotactic Body Radiation Therapy in Patients With 5 or Fewer Oligometastatic Lesions

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Ann G. Muhs, RN[1]
Abraham Philip, DMD[1]
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BACKGROUND. It is hypothesized that oligometastatic disease represents a state of potentially curable, limited metastases. Stereotactic body radiation therapy (SBRT) is an option for patients who are not amenable to or do not want resection.

METHODS. From 2001 to 2006, 121 patients with ≤5 detectable metastases were enrolled in 2 prospective studies that used curative-intent SBRT. Most patients were treated with 10 fractions of 5 Gray. Stereotactic radiosurgery was offered to patients with brain metastases.

RESULTS. The 2-year overall survival (OS), progression-free survival (PFS), local control (LC), and distant control (DC) rates were 50%, 28%, 67%, and 34%, respectively; and the respective 4-year rates values were 28%, 20%, 60%, and 25%. A greater net tumor volume predicted significantly worse OS, PFS, LC, and DC. Patients with breast cancer fared significantly better with respect to OS, PFS, LC, and DC; and patients with adrenal metastases had significantly worse OS, PFS, and DC despite the small number of such patients enrolled. Neither the number of metastatic lesions nor the number of organs involved was a significant predictor of outcome. Among 45 patients who remained alive at the last follow-up, 29 patients had no evidence of disease, including 23 patients with ≥2 years of follow-up.

CONCLUSIONS. Oligometastatic disease is a potentially curable state of distant cancer spread. In this hypothesis-generating analysis, patients with less volume burden of their metastatic disease and those with primary breast cancer fared better. SBRT delivered with curative intent in patients with limited metastases should be investigated further. The Southwest Oncology Group is developing a prospective protocol to treat women who have limited breast cancer metastases with SBRT. *Cancer* 2008;112:650–8. © *2007 American Cancer Society.*

KEYWORDS: disease burden, local control, oligometastases, stereotactic body radiation.

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum.[1] They hypothesized that, in some patients with a limited number of clinically detectable metastatic tumors, the extent of disease exists in a transitional state between localized and widespread systemic disease. In this model, oligometastatic disease has the potential of progressing to widespread metastatic disease. Thus, local control (LC) of oligometastases may yield improved systemic control.[1,2] An alternative hypothesis is that oligometastatic disease represents a clinical manifestation of few detectable lesions in the setting of widespread occult disease. Such a model argues that local therapy alone

Acta Oncologica, 2013; 52: 1622–1628

informa healthcare

ORIGINAL ARTICLE

Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases

ULRIKE SCHICK[1], SANDRA JORCANO[2], PHILIPPE NOUET[1], MICHEL ROUZAUD[1], HANSJOERG VEES[1], THOMAS ZILLI[1], OSMAN RATIB[3], DAMIEN C.WEBER[1] & RAYMOND MIRALBELL[1,2]

[1]*Department of Radiation Oncology, University Hospital of Geneva, Geneva, Switzerland,* [2]*Department of Radiation Oncology, Institut Oncològic Tèknon, Barcelona, Spain and* [3]*Department of Nuclear Medicine, University Hospital of Geneva, Geneva, Switzerland*

Second question

How many metastases can a patient have and still be considered eligible for radical radiotherapy?

a) 1

b)2-3

c) ≤5

doi:10.1016/S0360-3016(03)01442-1

CLINICAL INVESTIGATION Prostate

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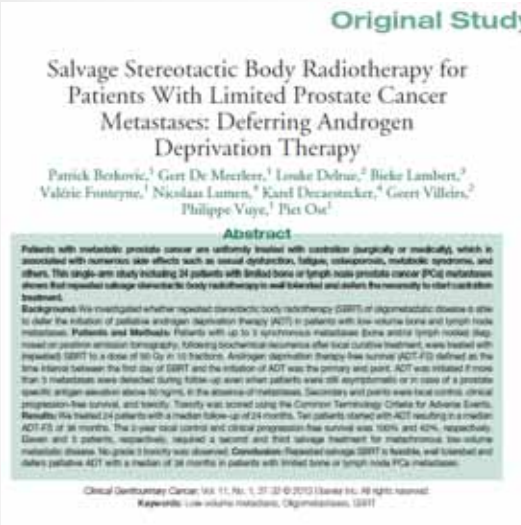
Conclusion: Patients with ≤ 5 metastatic sites had significantly better survival rates than patients with > 5 lesions (73% and 36% vs 45% and 18% at 5 and 10 years respectively, p= 0.02) (2004)



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Keywords: Low-volume metastasis, Oligometastases, SBRT

Patients with up to 3 synchronous metastases (bone and/or lymph nodes) diagnosed on positron emission tomography … (2013)

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ORIGINAL ARTICLE

Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases

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Improved bRFS was found to be significantly associated with the number of OM. The three-year bRFS was 66.5% vs 36.4% for patients with 1 and > 1 OMs (p=0.031) (2013)

Third question

What total dose should be delivered to prostate cancer and bone metastases in an oligometastatic patient?

a) radical dose to prostate cancer and bone metastases,

b) radical dose to prostate cancer and palliative dose to bone metastases,

c) palliative dose to both prostate cancer and bone metastases, because the main treatment is ADT.

2016

REVIEWS

Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations

Jeffrey J. Tosoian[1], Michael A. Gorin[1], Ashley E. Ross[1], Kenneth J. Pienta[1], Phuoc T. Tran[2] and Edward M. Schaeffer[3]

Relative to the no local therapy group, the adjusted hazard ratios associated with radical prostatectomy were 0.18 (95% CI 0.07–0.50, P = 0.0008), 0.22 (95% CI 0.16–0.30, P < 0.0001), and 0.23 (95% CI 0.16–0.35, P < 0.0001) for M1a (metastasis of non regional lymph nodes), M1b, and M1c disease, respectively.

Corresponding values in the brachytherapy cohort were 0.29 (95% CI 0.13–0.64, P = 0.0024), 0.49 (0.36–0.67, P <0.0001), and 0.36 (0.24–0.54, P <0.0001).

On multivariable analysis including :

-sociodemographic factors,

-tu

-C

-u

-b

In prostate radiotherapy group 3-year overall survival was 69% in those who had and 43% in the other groups (P = 0.004). 3-year biochemical-failure-free survival was improved in the prostate radiation cohort (52% versus 16%, P = 0.002). (Choo et al)

the adjusted hazard ratios for PCSM were 0.48 (95% CI 0.27–0.85, P = 0.01) for radical prostatectomy, 0.38 (95% CI 0.24–0.61, P <0.001) for IMRT, and 0.85 (95% CI 0.64–1.14, P = 0.3) for CRT.

After a median follow-up period of 40.6 months in the radical prostatectomy group and 44.0 months in the non-radical-prostatectomy group (P >0.05), men treated with radical prostatectomy demonstrated significantly increased time to castration resistance (median 40 months versus 29 months, P = 0.014) and freedom from clinical progression (median 38.6 months versus 26.5 months, P = 0.032).

Table 2 | **Retrospective data for local consolidative therapy of the primary tumour**

Source	Study design	Inclusion	Intervention	OS*	CSS*	MVA	Additional information
Culp *et al.*[44]	Population-based, *n* = 8,185, median follow-up period: 16 months	M1a–M1c	• RP (*n* = 245) • BT (*n* = 129) • NLT (*n* = 7811)	• 67.4% • 52.6% • 22.5% *P* < 0.001	• 75.8% • 61.3% • 48.7% *P* < 0.001	SHR (CSM) • 0.38 (0.27–0.53; RP) • 0.68 (0.49–0.93; BT) • 1.00 (ref; NLT)	MVA includes: Gleason score ≥8, T4, PSA ≥20 ng/ml, AJCC N1 (versus N0), AJCC M stage (versus M1a), year of diagnosis
Antwi *et al.*[45]	Population-based, *n* = 7,858, median follow-up period: NR	M1a–M1c	• RP (*n* = 222) • BT (*n* = 120) • NSR (*n* = 7516)	• 82.0% • 66.7% • 43.6% *P* < 0.0001	• 84.7% • 71.7% • 54.6% *P* < 0.0001	aHR (CSM) • 0.22 (0.27–0.28; RP) • 0.40 (0.32–0.51; BT) • 1.00 (ref; NSR)	MVA includes: age, race, marital status, tumour grade, PSA level, and cancer registry
Gratzke *et al.*[46]	Population-based, *n* = 1,538, median follow-up period: NR	M1	• RP (*n* = 74) • RT (*n* = 389) • ADT (*n* = 635) • Other (*n* = 440)	• 55% (RP) • 21% (other therapy) *P* < 0.01	• NR	NR	Overall survival compared between RP patients and non-RP patients (including RT, ADT, and other)
Satkunasivam *et al.*[47]	Population-based, *n* = 4,069, median follow-up period: NR	• M1 • Age ≥65 years	• RP (*n* = 47) • IMRT (*n* = 88) • CRT (*n* = 107) • NLT (*n* = 3827)	• 73% • 72% • 37% • 34%	• 79% • 82% • 49% • 46%	aHR (CSM) • 0.48 (0.27–0.85; RP) • 0.38 (0.24–0.61; IMRT) • 0.85 (0.64–1.14; CRT) • 1.00 (ref; NLT)	• MVA includes: sociodemographics, primary tumour characteristics, CCI, ADT, and bone radiation within 6 months of diagnosis. • On CRR: SHR (95% CI) for PCSM versus NLT: • RP 0.58 (0.35–0.95), IMRT 0.43 (0.27–0.68)
Heidenreich *et al.*[48]	Case-control, *n* = 61, median follow-up period: • 40.6 months (RP) • 44.0 months (no RP)	Limited M1	• RP (*n* = 23) • No RP (*n* = 38)	• 91.3% • 78.9% *P* = 0.048	• 95.6% • 84.2% *P* = 0.043	• NR	Inclusion criteria: ≤3 lesions on bone scan; absence of visceral or extended LN metastases; PSA nadir < 1 ng/ml after 6 months of neoadjuvant ADT
Cho *et al.*[49]	Case-control, *n* = 140 (38 cases), median follow-up period: 34 months	M1	• RT (*n* = 38) • No RT (*n* = 102)	• 69% • 43%	• NR	HR (OM) • 0.43 (*P* = 0.015)	MVA includes: ECOG status, site of metastasis

ADT, androgen deprivation therapy; aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; BT, brachytherapy; CCI, Charlson comorbidity index; CRR, competing risk regression; CRT, conformal radiation therapy; CSM, cancer-specific mortality; CSS, cancer-specific survival; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; IMRT, intensity-modulated radiation therapy; LN, lymph node; MRI, magnetic resonance imaging; MVA, multivariable analysis; NLT, no local treatment; NR, not reported; NS, not specified; OM, overall mortality; OS, overall survival; PCSM, prostate-cancer-specific mortality; RP, radical prostatectomy; RT, radiation therapy; SHR, subhazard ratio. *In cases of unspecified time frame, values refer to proportion experiencing outcome during total follow-up period.

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CLINICAL INVESTIGATION **Prostate**

IS THERE A FAVORABLE SUBSET OF PATIENTS WITH PROSTATE CANCER WHO DEVELOP OLIGOMETASTASES?

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 889–897, 2012

0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2010.11.031

CLINICAL INVESTIGATION **Genitourinary Cancer**

ROBOTIC IMAGE-GUIDED STEREOTACTIC RADIOTHERAPY, FOR ISOLATED RECURRENT PRIMARY, LYMPH NODE OR METASTATIC PROSTATE CANCER

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Original Study

Salvage Stereotactic Body Radiotherapy for Patients With Limited Prostate Cancer Metastases: Deferring Androgen Deprivation Therapy

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Abstract

Patients with metastatic prostate cancer are uniformly treated with castration (surgically or medically), which is associated with numerous side effects such as sexual dysfunction, fatigue, osteoporosis, metabolic syndrome, and others. This single-arm study including 24 patients with limited bone or lymph node prostate cancer (PCa) metastases shows that repeated salvage stereotactic body radiotherapy is well tolerated and defers the necessity to start castration treatment.

Background: This investigated whether repeated stereotactic body radiotherapy (SBRT) of oligometastatic disease is able to defer the initiation of palliative androgen deprivation therapy (ADT) in patients with low-volume bone and lymph node metastases. **Patients and Methods:** Patients with up to 3 synchronous metastases (bone and/or lymph nodes) diagnosed on positron emission tomography, following biochemical recurrence after local curative treatment, were treated with repeated SBRT to a dose of 50 Gy in 10 fractions. Androgen deprivation therapy-free survival (ADT-FS) defined as the time interval between the first day of SBRT and the initiation of ADT was the primary end point. ADT was initiated if more than 3 metastases were detected during follow-up even when patients were still asymptomatic or in case of a prostate specific antigen elevation above 50 ng/mL in the absence of metastases. Secondary end points were local control, clinical progression-free survival, and toxicity. Toxicity was scored using the Common Terminology Criteria for Adverse Events. **Results:** We treated 24 patients with a median follow-up of 24 months. Ten patients started with ADT resulting in a median ADT-FS of 36 months. The 2-year local control and clinical progression-free survival was 100% and 42%, respectively. Eleven and 3 patients, respectively, required a second and third salvage treatment for metachronous low-volume metastatic disease. No grade 3 toxicity was observed. **Conclusion:** Repeated salvage SBRT is feasible, well tolerated and defers palliative ADT with a median of 36 months in patients with limited bone or lymph node PCa metastases.

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A Prospective Pilot Study of Curative-intent Stereotactic Body Radiation Therapy in Patients With 5 or Fewer Oligometastatic Lesions

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BACKGROUND. It is hypothesized that oligometastatic disease represents a state of potentially curable, limited metastases. Stereotactic body radiation therapy (SBRT) is an option for patients who are not amenable to or do not want resection.

METHODS. From 2001 to 2006, 121 patients with ≤5 detectable metastases were enrolled in 2 prospective studies that used curative-intent SBRT. Most patients were treated with 10 fractions of 5 Gray. Stereotactic radiosurgery was offered to patients with brain metastases.

RESULTS. The 2-year overall survival (OS), progression-free survival (PFS), local control (LC), and distant control (DC) rates were 50%, 28%, 67%, and 34%, respectively; and the respective 4-year rates values were 28%, 20%, 60%, and 25%. A greater net tumor volume predicted significantly worse OS, PFS, LC, and DC. Patients with breast cancer fared significantly better with respect to OS, PFS, LC, and DC; and patients with adrenal metastases had significantly worse OS, PFS, and DC despite the small number of such patients enrolled. Neither the number of metastatic lesions nor the number of organs involved was a significant predictor of outcome. Among 45 patients who remained alive at the last follow-up, 29 patients had no evidence of disease, including 23 patients with ≥2 years of follow-up.

CONCLUSIONS. Oligometastatic disease is a potentially curable state of distant cancer spread. In this hypothesis-generating analysis, patients with less volume burden of their metastatic disease and those with primary breast cancer fared better. SBRT delivered with curative intent in patients with limited metastases should be investigated further. The Southwest Oncology Group is developing a prospective protocol to treat women who have limited breast cancer metastases with SBRT. *Cancer* 2008;112:650–8. © *2007 American Cancer Society.*

KEYWORDS: disease burden, local control, oligometastases, stereotactic body radiation.

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum.[1] They hypothesized that, in some patients with a limited number of clinically detectable metastatic tumors, the extent of disease exists in a transitional state between localized and widespread systemic disease. In this model, oligometastatic disease has the potential of progressing to widespread metastatic disease. Thus, local control (LC) of oligometastases may yield improved systemic control.[1,2] An alternative hypothesis is that oligometastatic disease represents a clinical manifestation of few detectable lesions in the setting of widespread occult disease. Such a model argues that local therapy alone

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A growing body of retrospective literature suggests RT for oligometastatic prostate cancer is feasible, effective, and without significant toxicity.

Although unproven, its role as a solitary therapy or in conjunction with systemic and/or surgical strategies is evolving, as is the goal and ultimate intent (i.e., aggressive palliation vs. durable control vs. eradication and cure) of its use.

Whether the primary function of radiation in the oligometastatic setting to primary (if intact) and/or metastasis is to delay time to ADT, to consolidate potentially curative multimodal approaches, or both, is to be determined.

Important role of imaging

Numerous clinical trials are currently in development that will provide prospective data to better answer this question