# METASTATIC AT PRESENTATION DISEASE. LOCAL THERAPY?

Assist. Prof. Dr. Nicolae CRISAN

A Comprehensive Review of Contemporary Role of Local Treatment of the Primary Tumor and/or the Metastases in Metastatic Prostate Cancer

Fouad Aoun,[1,2] Alexandre Peltier,[1,2] and Roland van Velthoven[1,2]

BioMed Research International
Volume 2014, Article ID 501213, 12 pages

# METASTATIC PROSTATE CANCER

- < 5% diagnosed with synchronous metastatic disease

- immediate or deferred androgen deprivation therapy
  - delays progression
  - curtails disease-related symptoms
  - prolongs survival

Significant
- morbidity
- mortality

- five-year survival for men with metastatic prostate cancer – 28%

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# EFFECTS OF MOLECULAR AND CLINICAL IMAGING

- significantly improved the detection of distant metastasis in patients who would else have been staged and treated as “non-metastatic”

- choline PET scan
- 18 fluorodihydrotestosterone PET scan
- Ga-labelled prostate-specific membrane antigen (PSMA)
- combined ultrasmall superparamagnetic particles of iron oxide-enhanced MRI

**Prognostic Factors Influencing Prostate Cancer-Specific Survival in Non-Castrate Patients with Metastatic Prostate Cancer**

Piet Ost,[1]* Karel Decaestecker,[2] Bieke Lambert,[3] Valérie Fonteyne,[1] Louke Delrue,[4] Nicolaas Lumen,[2] Filip Ameye,[5] and Gert De Meerleer[1]

The Prostate 74:297–305 (2014)

**TABLE II. Primary Site of Noncastrate Metastases**

| | |
|---|---|
| Lymph nodes | 47 (59%) |
| Pelvic | 27 |
| Extrapelvic | 8 |
| Both | 12 |
| Bones | 40 (50%) |
| Axial | 7 |
| Appendicular | 20 |
| Both | 13 |
| Viscera | 2 (3%) |
| Lung | 1 |
| Liver | 1 |

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# METASTATIC PROSTATE CANCER

| | OS |
|---|---|
| • Lymph node metastases alone | 27.0 months |
| • Bone metastases alone | 20.3 months |
| • Bone metastases with lymph node | 16.5 months |
| • Lung and liver metastases | 12.1 months |

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# OLIGOMETASTATIC PROSTATE CANCER: IS THERE A DEFINITION?

- limited numbers and sites
  - extent of lymph node and bone involvement
- ! no prospective trials on overall survival for the primary control of oligometastases
- Singh et al. – oligometastatic prostate cancer – 5 or fewer sites

# SYNCHRONOUS METASTATIC DISEASE

**Local therapy**

**+**

**Lymph node dissection ( for N+)**

**+**

**androgen deprivation therapy**

# SYNCHRONOUS METASTATIC DISEASE

**Local therapy**

**+**

**Salvage stereotactic body radiotherapy (SBRT)**

**(oligometastatic )**

**+**

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# LOCAL THERAPY

## How does the local control of the primary tumor affect regional and distant metastases?

## Which local therapy?

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# FIRST (ABSCOPAL EFFECT)

**By eliminating the primary site, a better local control is achieved through the self-seeding multidirectional hypothesis**

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# SECOND

- Intratumoral synthesis → protect primary prostate cancer cells from ADT → prostate cancer cells to progress to castrate resistance

- use of early local treatment eliminates androgen independent clones with the potential to
  - delay time to castrate resistance
  - prolong disease control

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# THIRD

- increased circulating tumor cells
  - tumor progression
  - reduced survival

- removal of the prostate reduces the number of circulating tumor cells and prolongs survival

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# THE ABSCOPAL EFFECT VERSUS THE FISHER AND FOLKMAN EFFECTS

Surgical manipulation of the tumour and its vascular supply may mechanically introduce circulating cancer cells into the circulation

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# THE ABSCOPAL EFFECT VERSUS THE FISHER AND FOLKMAN EFFECTS

Removal of the primary tumor, which may be a source of antimetastatic and antiangiogenesis factors, may disturb the equilibrium and accelerate the metastatic and angiogenic process

**Might Men Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor? A SEER-Based Study**

*Stephen H. Culp[a,*], Paul F. Schellhammer[b], Michael B. Williams[b]*

EUROPEAN UROLOGY 65 (2014) 1058–1066

8185 patients M1a, b, c

No SR (n = 7811) | RP (n = 245) | BT (n = 129)

| 5-yr OS | DSS | 5-yr OS | DSS | 5-yr OS | DSS |
|---|---|---|---|---|---|
| 22.5% | 48.7% | 67.4% | 75.8% | 52.6 | 61.3% |

RP or BT were each independently associated with decreased CSM (p <0.01)

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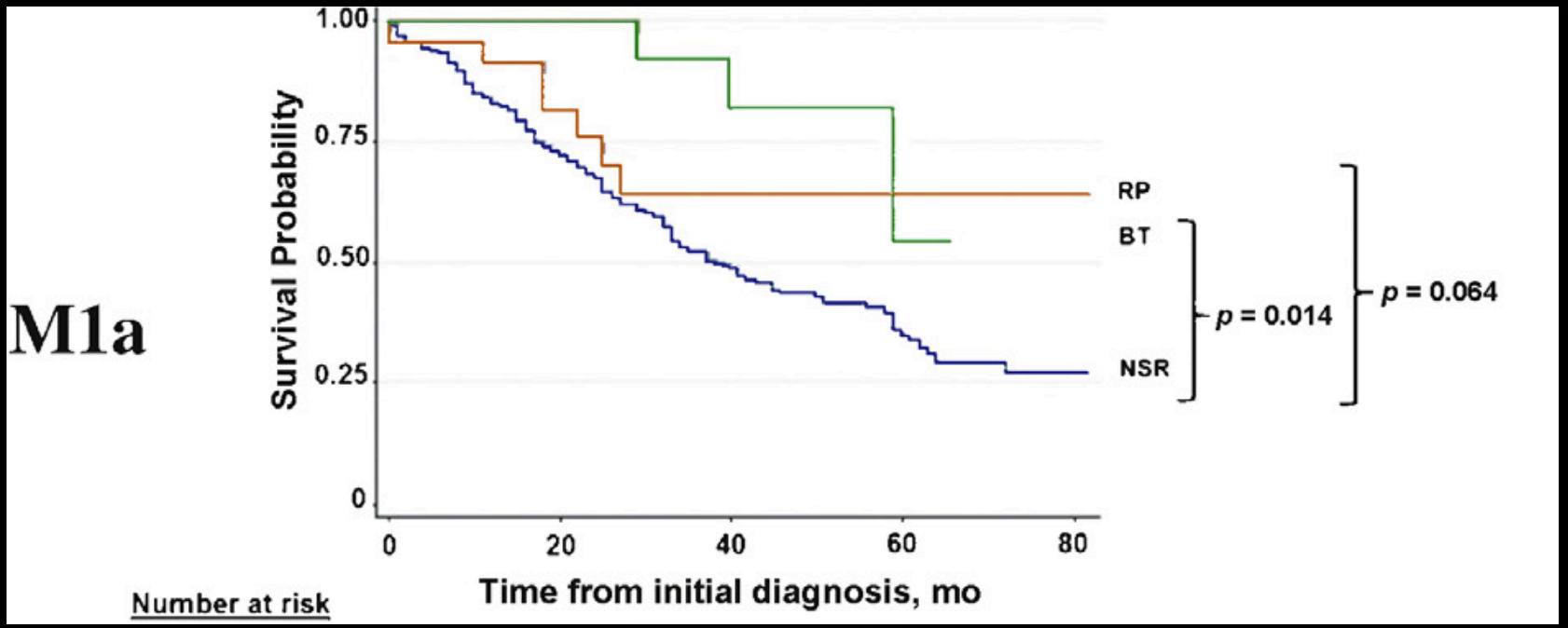

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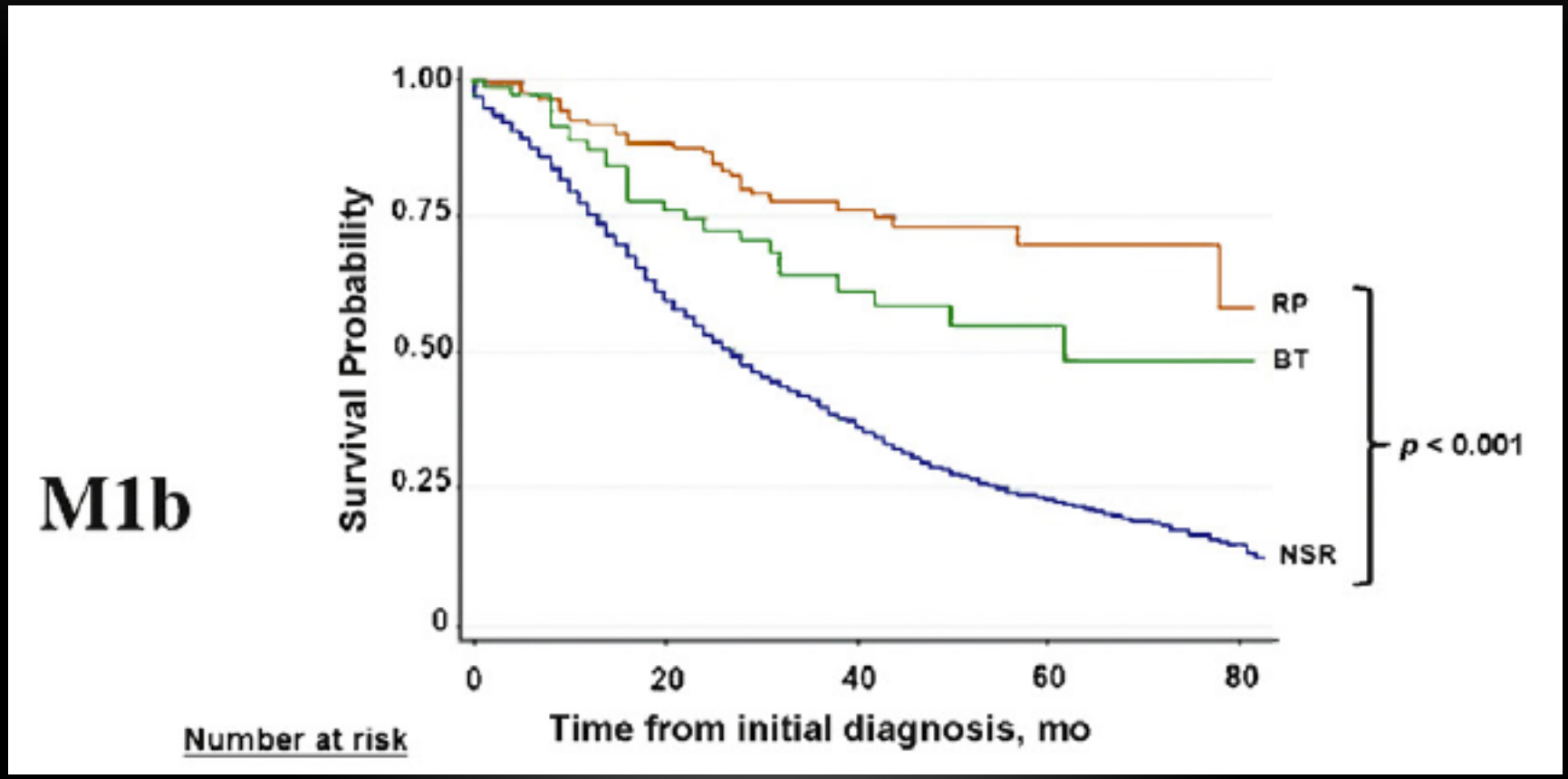

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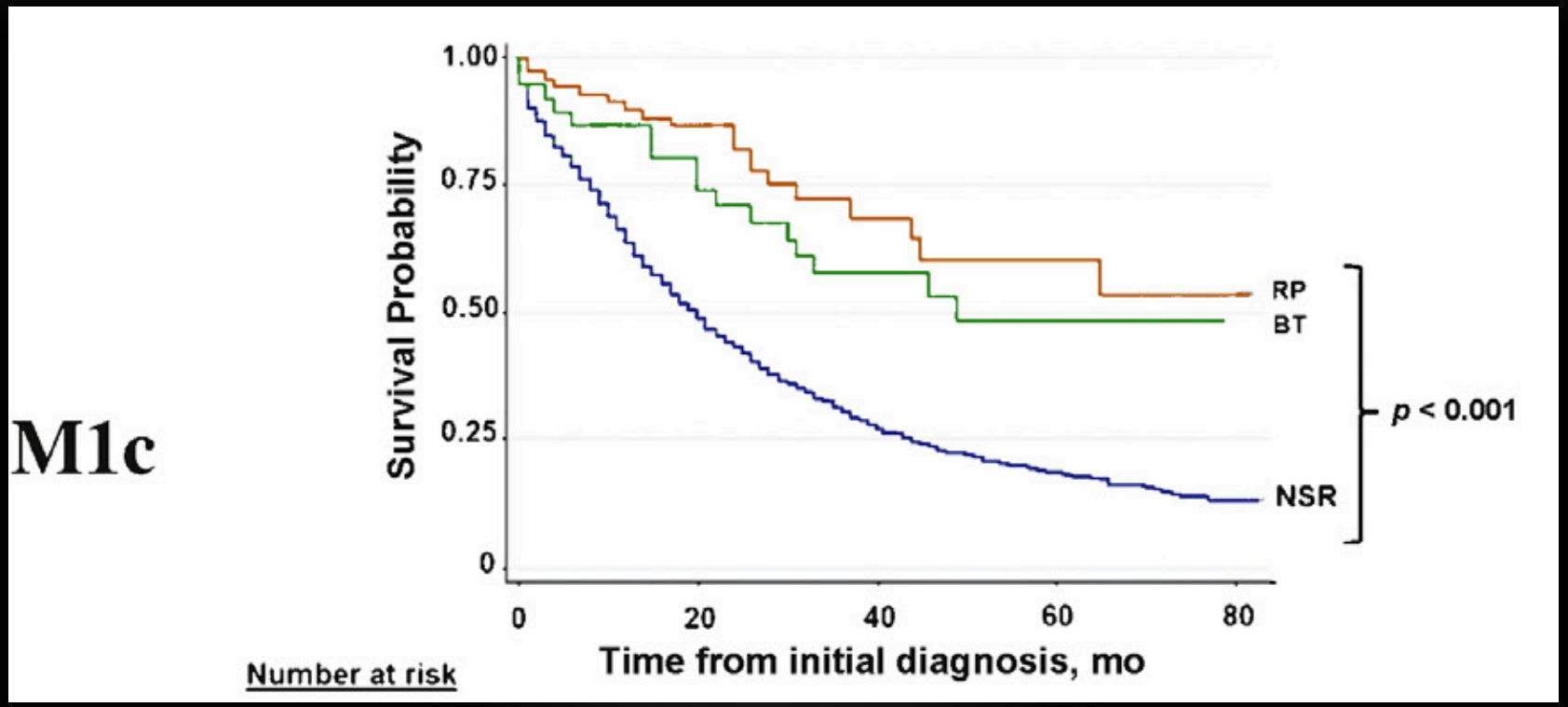
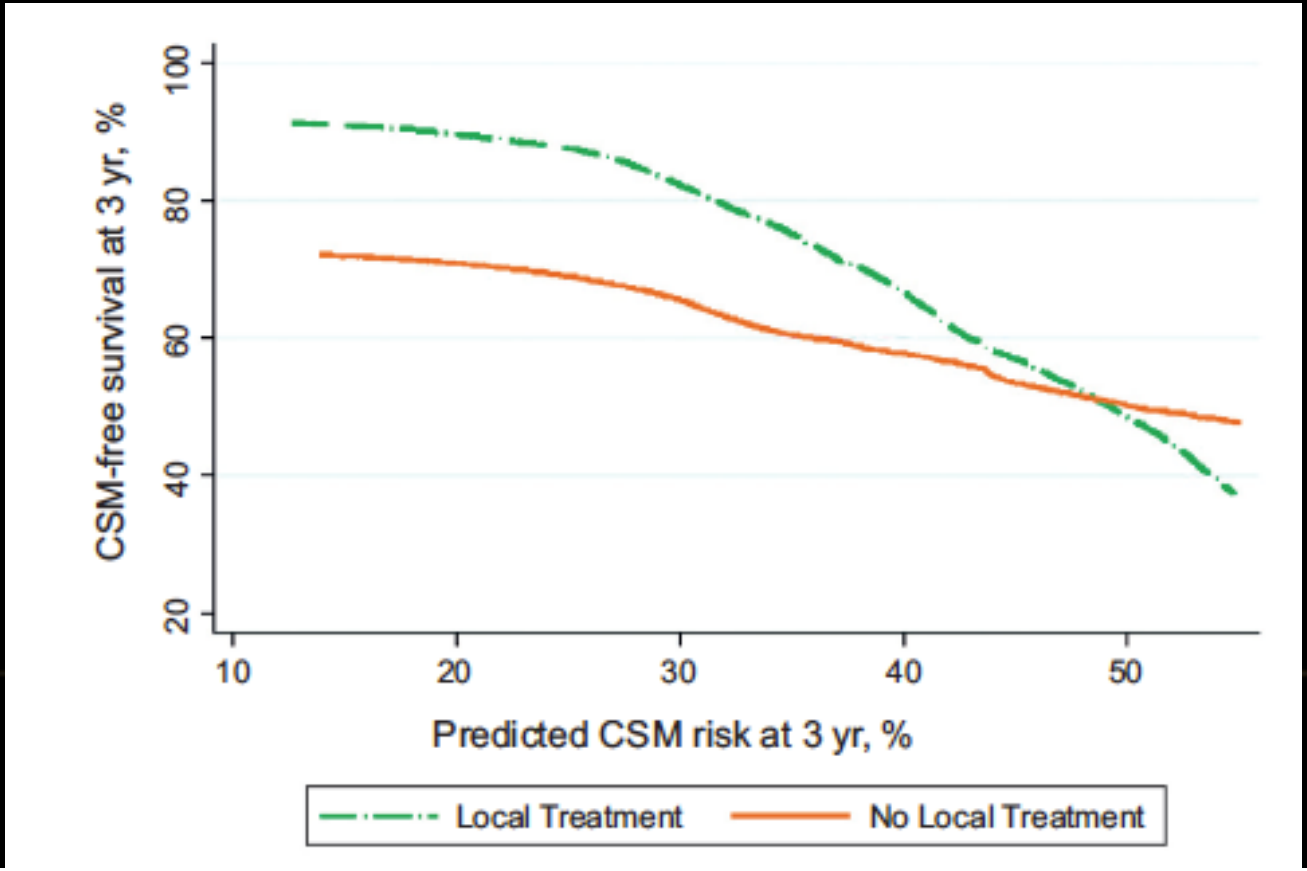


**Identifying Optimal Candidates for Local Treatment of the Primary Tumor Among Patients Diagnosed with Metastatic Prostate Cancer: A SEER-based Study**

*Nicola Fossati[a,b], Quoc-Dien Trinh[c], Jesse Sammon[d], Akshay Sood[d], Alessandro Larcher[b,e], Maxine Sun[e], Pierre Karakiewicz[e], Giorgio Guazzoni[b], Francesco Montorsi[b], Alberto Briganti[b], Mani Menon[d], Firas Abdollah[d,*]*

EUROPEAN UROLOGY 67 (2015) 3–6

- LT conferred a survival benefit at 3 yr after diagnosis only in patients with a CSM risk 40%
- the NNT remained substantially constant from 10% to 30%, whereas it exponentially increased for predicted CSM risk >40%



**Cancer-specific Survival After Metastasis Following Primary Radical Prostatectomy Compared with Radiation Therapy in Prostate Cancer Patients: Results of a Population-based, Propensity Score–Matched Analysis**

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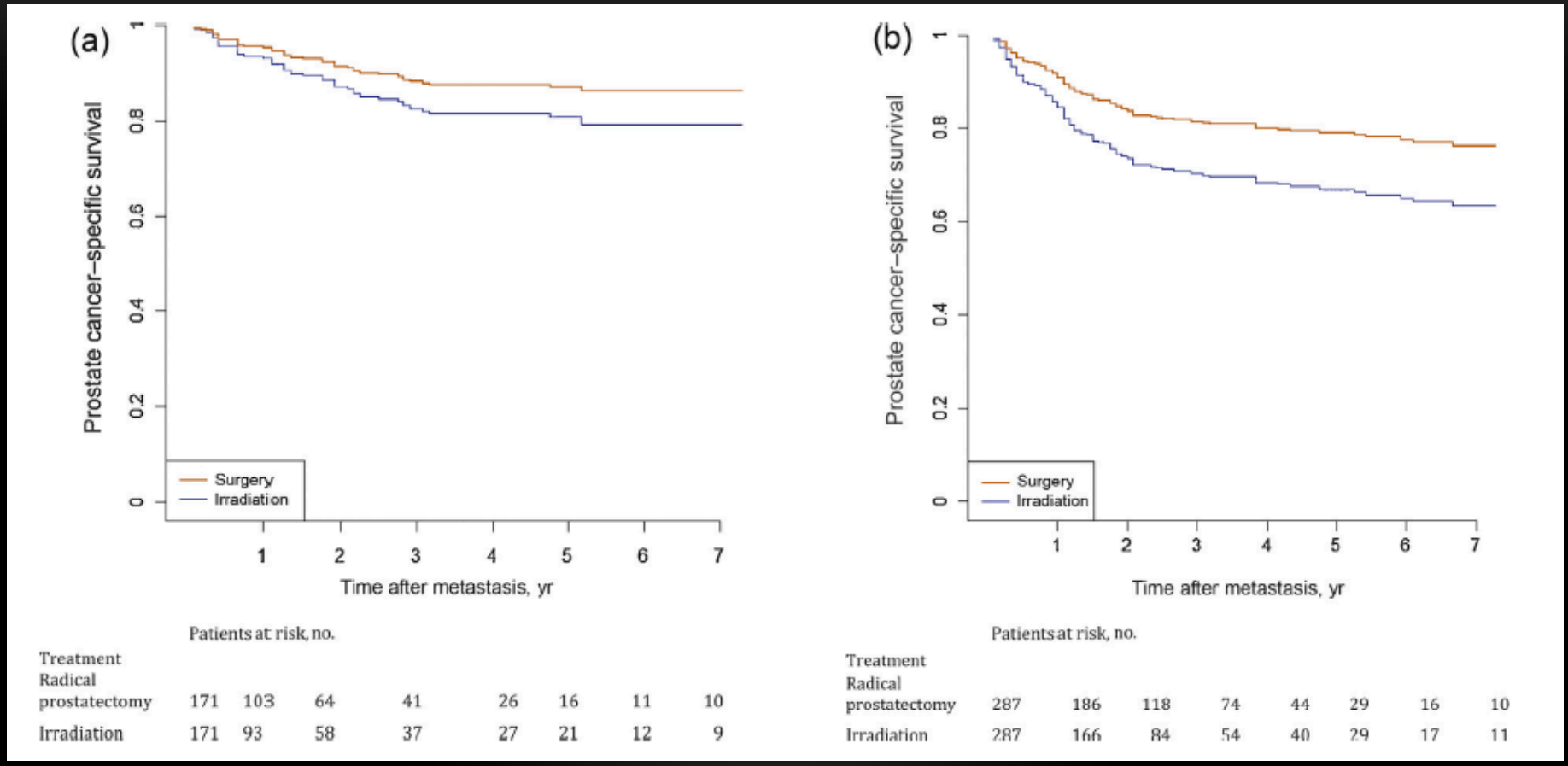
EUROPEAN UROLOGY 65 (2014) 693–700




**MEN WHO RECEIVED RP WERE LESS LIKELY TO DIE FROM PCA AFTER METASTASIS THAN MEN WHO RECEIVED RT**

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# ONE POSSIBLE EXPLANATION

- Residual tumor cells after aggressive treatment may contribute to tumor progression and predict cancer-specific survival

- self-seeding may be more likely to occur in irradiated patients

**Role of Radical Prostatectomy in Clinically Non-Organ-Confined Prostate Cancer**

Christian Gratzke · Jutta Engel · Christian G. Stief

Curr Urol Rep (2014) 15:455

- phase II, randomized trial of best systemic therapy or best systemic therapy plus definitive treatment of the primary tumor (radiation or surgery) in metastatic prostate cancer is enrolling in the US http://clinicaltrials.gov/show/

- multicenter European trial, 500 patients in 60 months with a follow-up of 60 months

# SYNCHRONOUS METASTATIC DISEASE

Local therapy

+

Lymph node dissection ( for N+)

+

androgen deprivation therapy

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# RADICAL PROSTATECTOMY IN THE MANAGEMENT OF N+ PROSTATE CANCER

| | Messing et al., ECOG 3886 | Bader et al., Bern | Messing et al., ECOG 3886 | Frohmüller et al., Würzburg | Engel et al., Munich | Boorjian et al., Mayo Clinic | Schiavina et al., Univ of Bologna | Briganti et al., Milan and Mayo Clinic | Briganti et al., Milan and Mayo Clinic | Steuber et al., Martinic Clinic Hamburg |
|---|---|---|---|---|---|---|---|---|---|---|
| Patients (n) | 51 | 87 | 47 | 52 | 688 | 507 | 98 | 247 | 117 | 108 |
| Treatment | RP alone | RP alone | RP with immediate ADT | RP plus immediate ADT | RP plus immediate ADT | RP plus immediate ADT | RP plus immediate ADT | RP plus immediate ADT | RP plus immediate ADT and RT | RP plus ADT |
| F/u (yr) | 11.9 | 3.7 | 11.9 | 4.3 | 6.7 | 10.3 | 5.7 | 8.6 | 8 | 98 months |
| 5 yr OS | 75 % | 74 % | 90 % | 74 % | 84 % | | 84 % | 82 % | 90 % | |
| 10 yr OS | 55 % | | 80 % | 51 % | 64 % | | 64 % | 55 % | 74 % | |
| 5 yr PCSS | 75 % | 74 % | 95 % | | | 94 % | 86 % | 88 % | 95 % | 84 % |
| 10 yr PCSS | 55 % | | 90 % | | | 86 % | 72 % | 70 % | 86 % | 76 % |
| 5 yr PFS | 28 % | | 82 % | 62 % | | | | | | 77 % |
| 10 yr PFS | 15 % | | 70 % | 36 % | | | | | | 61 % |

# SYNCHRONOUS METASTATIC DISEASE

Local therapy

+

Salvage stereotactic body radiotherapy (SBRT)

(oligometastatic )

+

androgen deprivation therapy

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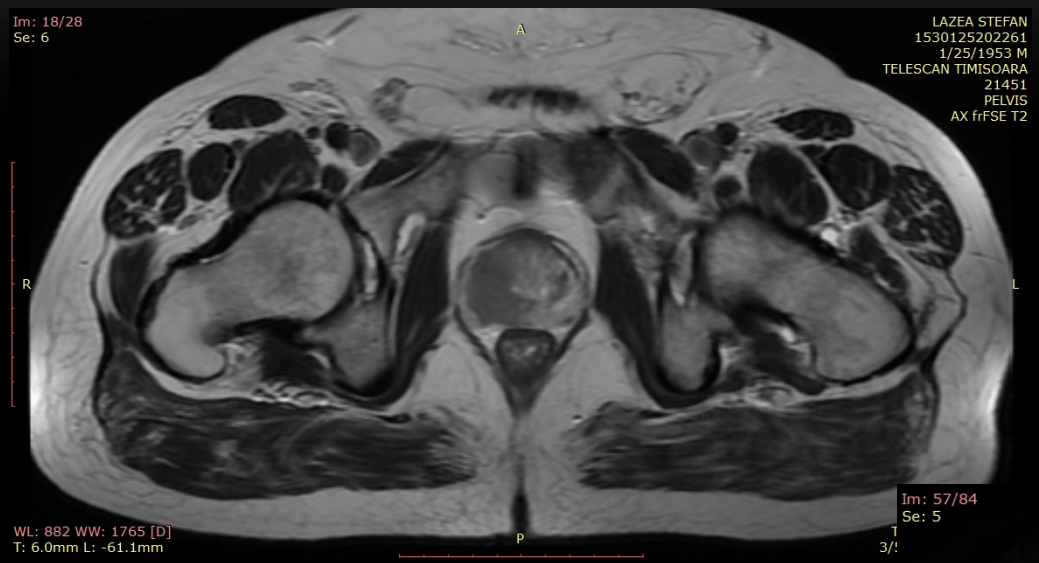
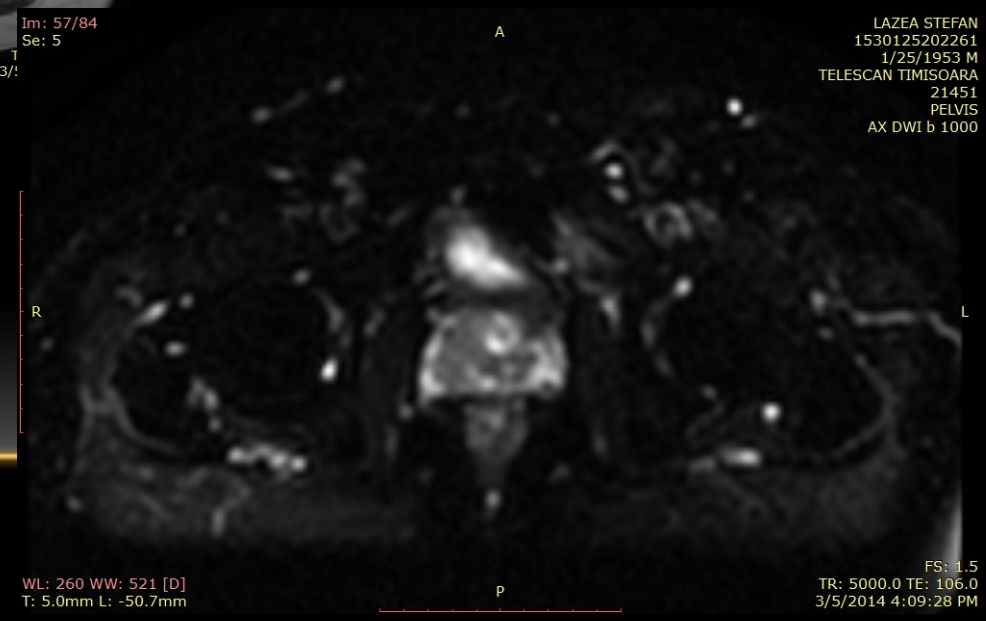
Table 1: Stereotactic body radiotherapy for oligometastatic prostate cancer.

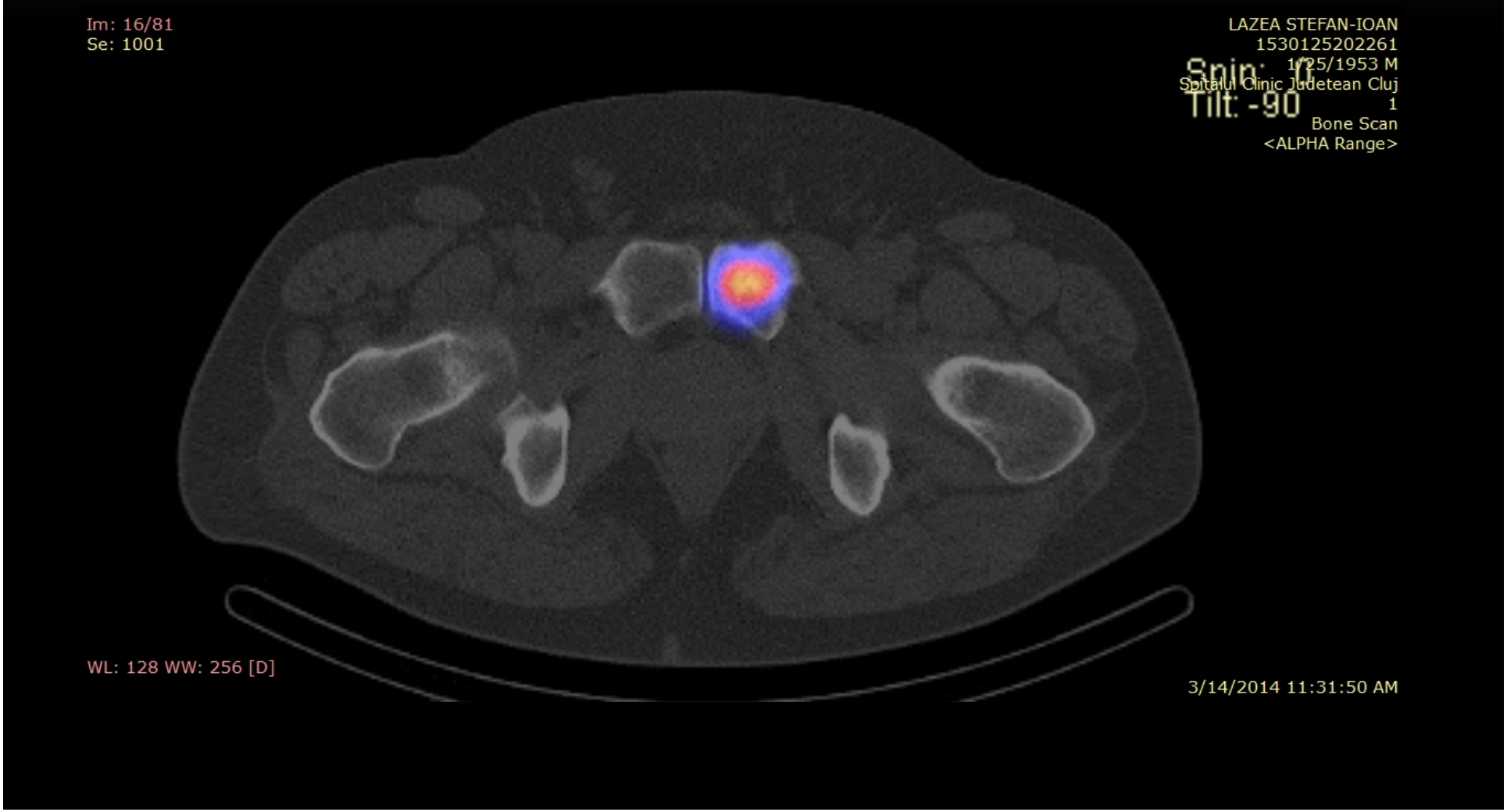
| Author | Year | Number of patients (number of lesions) | Dose | Primary site | Treated site (s) | Local control | Toxicity | Remarks |
|---|---|---|---|---|---|---|---|---|
| Greco et al. [70] | 2011 | 103 (126) | 18–24 Gy in 1 fraction (SBRT) | Prostate, renal, and colorectal | Bone, LN, and soft tissue | 64% (82% if >22 Gy, 25% for 18–20 Gy) at 2 years | <4% grade 3 (stricture, neuritis) | |
| Jereczek-Fossa et al. [71] | 2009 | 14 (14) | 30 Gy in 3 fractions (Linac-CyberKnife) | Prostate | Pelvic LN | 100% at 18.6 months | No grade 3 or higher | |
| Casamassima et al. [73] | 2011 | 25 (25) | 30 Gy in 3 fractions | Prostate | Prostate, Pelvic LN, para-aortic LN, and mediastinal LN | 90% at 3 years | No grade 2 or higher | DFS 17% at 3 years |
| Jereczek-Fossa et al. [72] | 2012 | 34 (38) | 30 Gy in 5 fractions to 36 Gy in 3 fractions (CyberKnife) | Prostate | LN and bone | 88% at 16.9 months | 6% grade 3 urinary and 3% grade 3 rectal | All toxicities seen in prostate recurrence patients |
| Muacevic et al. [74] | 2013 | 40 (64) | 20 Gy in 1 fraction (SBRT) | Prostate | Bone | 95.5% at 2 years | No grade 3 or higher | |
| Berkovic et al. [75] | 2013 | 24 (29) | 50 Gy in 10 fractions (repeated SBRT) | Prostate | Bone or LN | 100% at 2 years | No grade 3 or higher | DFS of 42% at 2 years |

# OUR EXPERIENCE + IEO MILAN



# OUR EXPERIENCE



# 1 YEAR FOLLOW UP

- PSA = 0
- Continent
- Impotent

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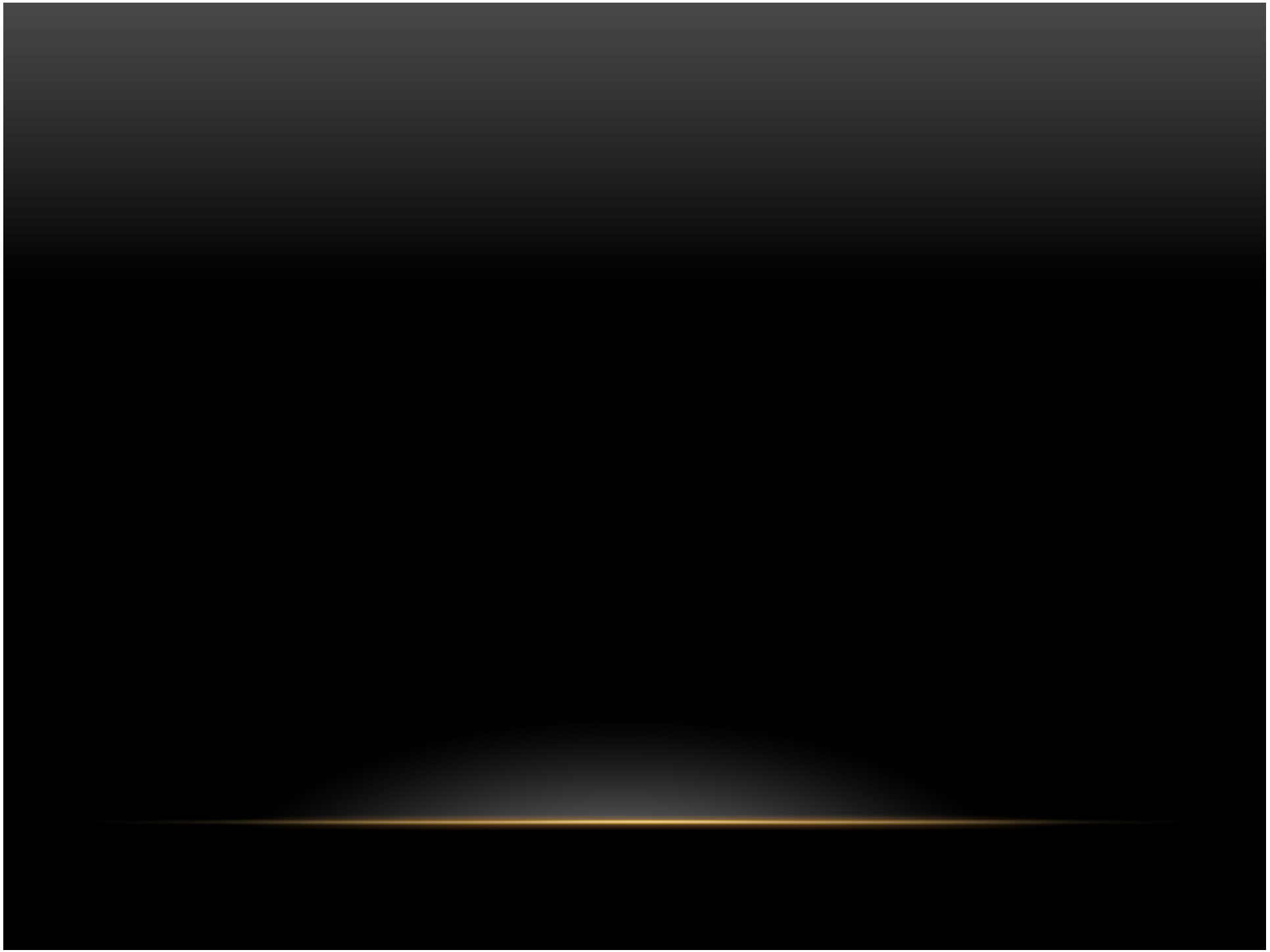
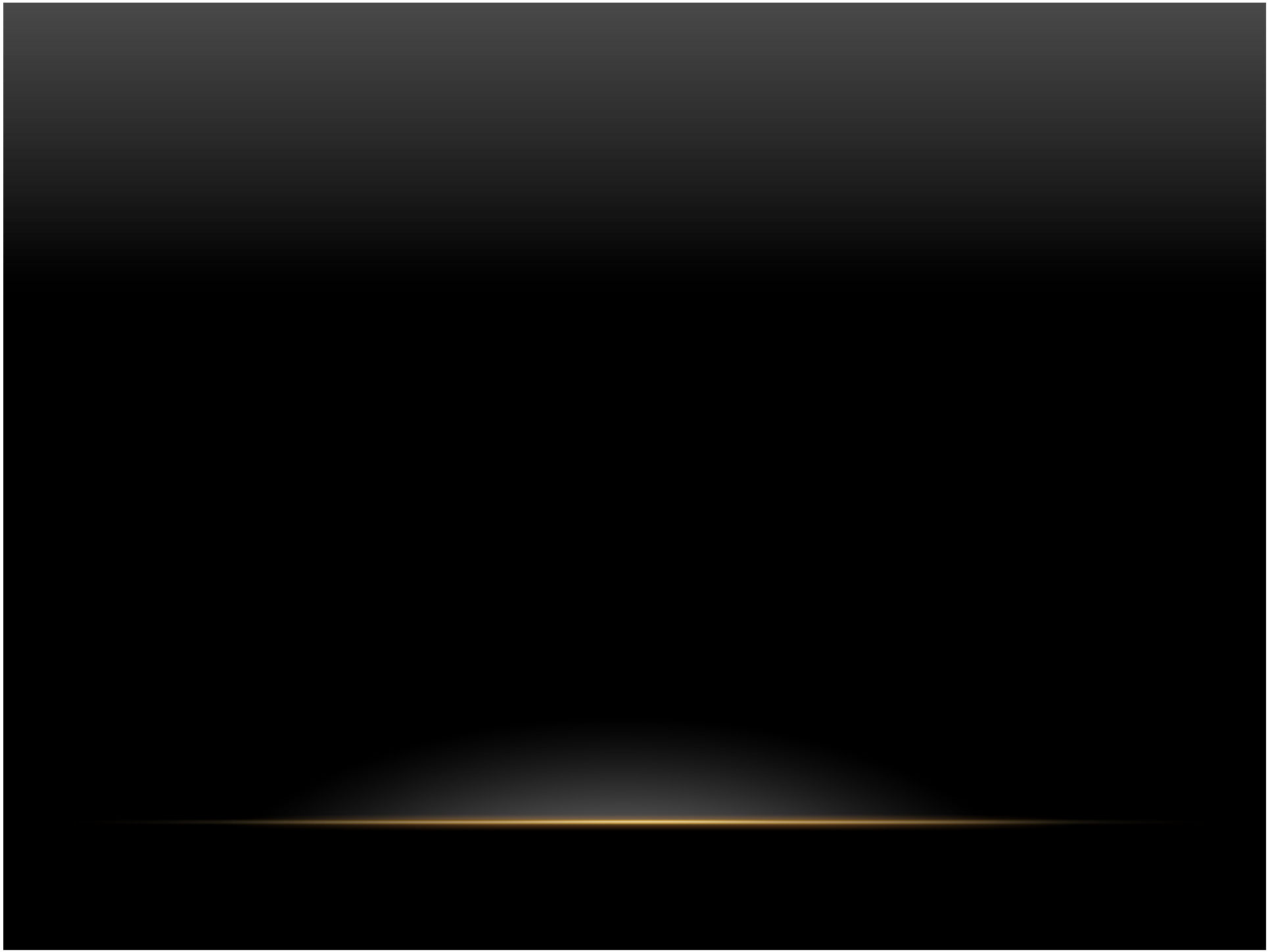
# CONCLUSION

- Definition of an oligometastatic state of cancer
- Local control of primary tumor in metastatic prostate cancer remains experimental
- SBRT has been demonstrated as a safe, well tolerated, and efficacious treatment for lymph node and bone lesions

# THANK YOU!



# CONCLUSIONS



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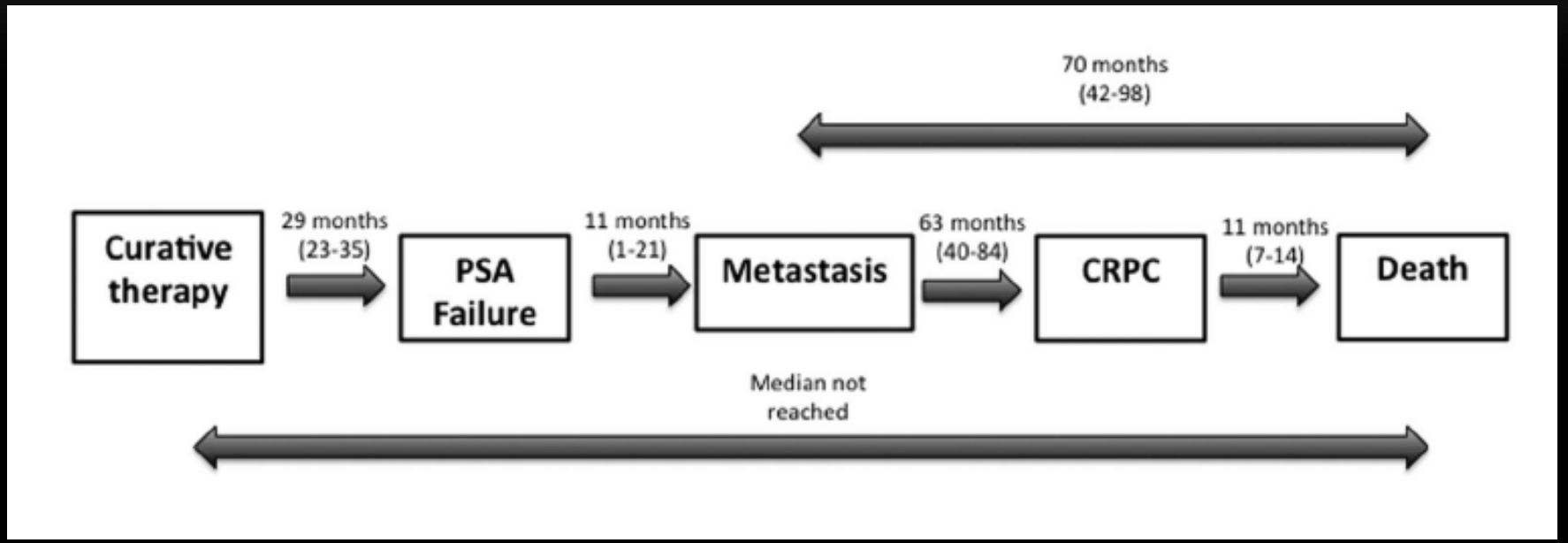


- interval between initial PCa treatment and diagnosis of metastases
  - 4.9 years for 5 lesions
  - 3.3 years > 5 lesions (P. 0.02)

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**TABLE III. Univariate and Multivariate Cox Proportional Hazards Analyses of Covariates Associated With Prostate Cancer-Specific Survival Measured From Time of Metastases in Noncastrate Patients**

| Covariate | Univariate analysis HR (95% CI) | *P*-value | Multivariate analysis HR (95% CI) | *P*-value |
|---|---|---|---|---|
| Prognostic group at diagnosis | | | | |
| Low | 1 | | | |
| Intermediate | 0.8 (0.7–9.1) | 0.87 | | |
| High | 1.3 (0.2–10.5) | 0.80 | | |
| Very high | 2.0 (0.2–17.0) | 0.54 | | |
| Interval from diagnosis to PSA relapse (year) | 0.98 (0.96–1.0) | 0.09 | | |
| Interval from diagnosis to metastases (year) | 0.98 (0.96–0.99) | **0.02** | | |
| PSA level at first documented metastases (ng/ml) | 0.99 (0.99–1.0) | 0.37 | | |
| PSA DT at first documented metastases (month) | 0.67 (0.50–0.89) | **0.006** | 0.73 (0.57–0.92) | **0.008** |
| Number of lesions at diagnosis of metastases | 1.01 (1.01–1.15) | **<0.001** | 1.07 (1.02–1.12) | **0.005** |
| Pattern of metastatic spread | | | | |
| Minimal | 1 | | 1 | **0.03** |
| Extensive | 2.82 (1.15–6.9) | **0.02** | 3.6 (1.14–11.9) | |
| Treatment at time of metastases | | | | |
| Androgen deprivation therapy | 1 | | | |
| Active clinical surveillance | 0.53 (0.07–4.14) | 0.55 | | |
| Metastases-directed therapy | 0.24 (0.09–0.59) | **0.002** | | |

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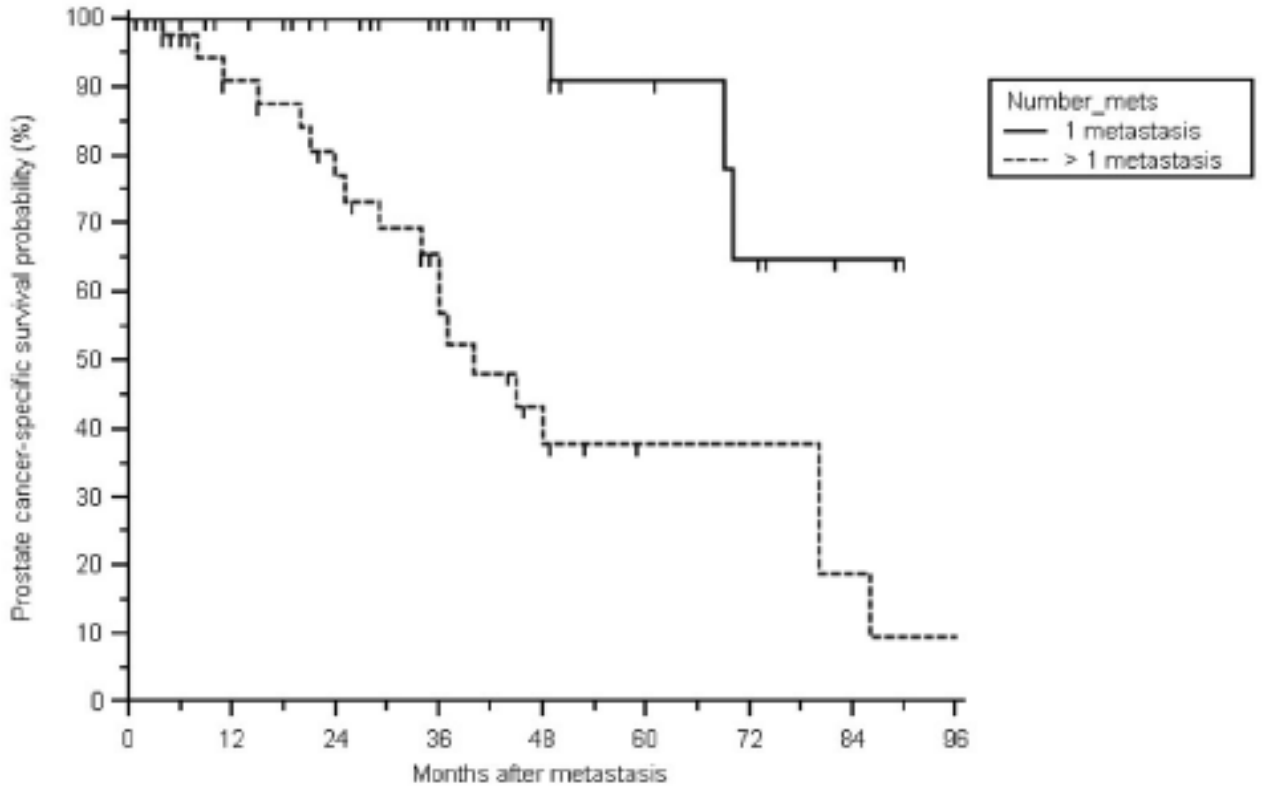

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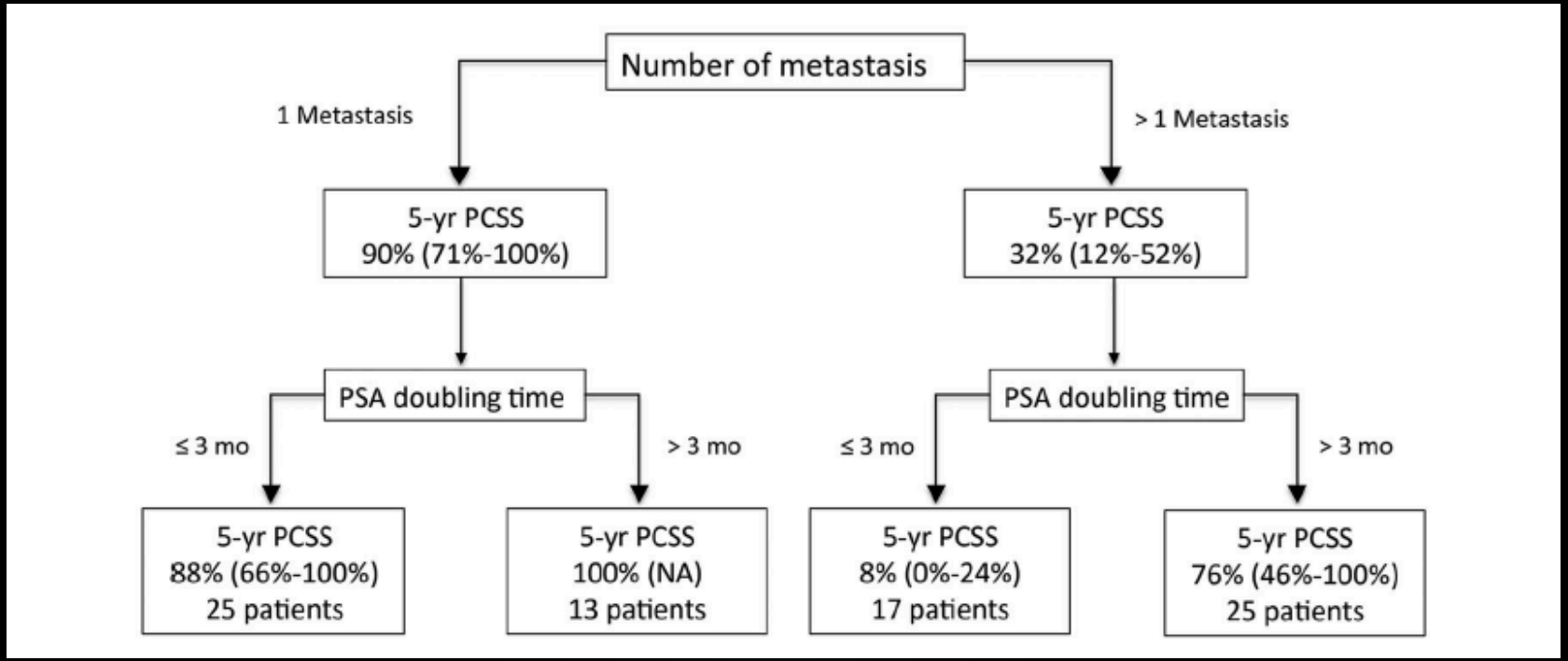

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# HOW?

- salvage lymph node dissection (SLND) for patients with clinical lymph node relapse

- salvage stereotactic body radiotherapy (SBRT) for patients with limited prostate cancer metastases (CyberKnife image-guided stereotactic radiotherapy)

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# SALVAGE LYMPH NODE DISSECTION

Table 2: Salvage lymph node dissection for biochemical recurrence following radical prostatectomy.

| Author | Year | Number of patients | Mean number of positive LNs (mean number of LNs removed) | Median follow-up, mo | Complete biologic response, % | Mean 5-yr BCR-free survival, % | 5-year progression-free survival, % | 5-year cancer-specific survival, % |
|---|---|---|---|---|---|---|---|---|
| Schilling et al. [94] | 2008 | 10 | 2.8 (7.1) | — | — | — | — | — |
| Rinnab et al. [93] | 2008 | 15 | — (13.9) | 13.7 | — | — | — | — |
| Winter et al. [96] | 2010 | 6 | 1 (10) | 24 | 50 | — | — | — |
| Rigatti et al. [99] | 2011 | 72 | 9.8 (30.6) | 39.4 | 56.9 | 19 | 34 | 75 |
| Jilg et al. [92] | 2012 | 52 | 9.7 (23.3) | 35.5 | 46 | 9 | 26 | 78 |
| Suardi et al. [101] | 2013 | 162 | 6.1 (24.6) | 29.2 | 40.7 | 40 | 47 | 86 |
| Suardi et al. [100] | 2014 | 59 | 8.9 (29.5) | 81.1 | 59.3 | 29.4 | 52.0 | 89.1 |
| Tilki et al. [98] | 2013 | 56 | 5.1 (21) | — | — | — | — | — |

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