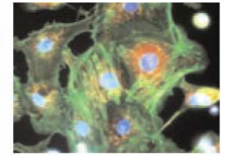


Therapie des Prostatacarcinoms

**Fortbildungskurs
Onkologie in Klinik und Praxis**

Wien 08.11.2011

OA Dr. Konrad Namberger
Universitätsklinik für Innere Medizin III
Salzburger Landeskliniken
Paracelsus Medizinische Privatuniversität



Prostatacarcinom

Cooperberg MR et.al,
J Natl Cancer Inst
2003

- Mittleres Erkrankungsalter bei Diagnosestellung 65 Jahre,

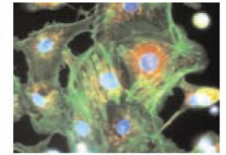
- 10% in Autopsiebefunden bei 50-Jährigen,
- 70 % in Autopsiebefunden bei 80-Jährigen !

Nelson et al.,
NEJM, 2003

- Ätiologie : Diätetische Faktoren, Lebensstil,
Sexualverhalten, hormonelle Einflüsse

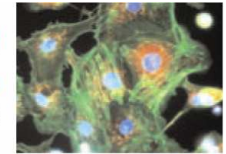
Visakorpi et al.,
Nat Genet 4,
1995

- Familiäre Häufung
- Ca. 10% autosomal-dominant vererbt



Prognose:

- TNM
- Malignitätsgrad (Grading, Gleason)
- PSA
- Erkrankungsalter, Komorbidität



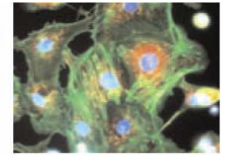
<u>Stadium I:</u>	T1a N0 M0 G1
<u>Stadium II:</u>	T1a N0 M0 G2-4 T1b / T1c / T2 / N0 Mo jedes G
<u>Stadium III:</u>	T3 N0 M0 jedes G
<u>Stadium IV:</u>	T4 N0 M0 oder jedes T/N1 oder jedes T/M1

T1	weder tastbar noch sichtbar
T1a	unter 5% (nach Resektion)
T1b	über 5%
T1c	Nadelbiopsie
T2	Begrenzt auf Prostata
T2a	ein Lappen
T2b	beide Lappen
T3	Kapseldurchbruch
T3a	unilateral, bilateral
T3b	Samenblase
T4	fixiert/andere Strukturen als Samenblasen
N1	regionär
M1a	nichtregionäre Lymphknoten
M1b	Knochen
M1c	andere

G 1 = Gleason 2 – 4

G 2 = Gleason 5 – 6

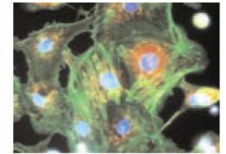
G 3 – 4 = Gleason 7 - 10



Risikokonstellationen:

	PSA	GS	Stadium	%Relapse*
Low Risk	<10	≤6	T1,2a	6-20%
Intermediate Risk	10-20	7	T2b,3a	34-60%
High Risk	>20	8-10	T3b	50-100%

* Lokale und Fernrezidive



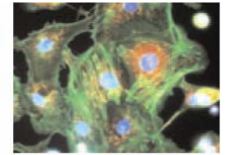
Verbleibende Lebenserwartung (In Jahren) in Abhängigkeit von Lebensalter und Komorbidität nach Diagnose Prostatacarcinom

Albertsen et al.:
J Urol 1996

Komorbiditäts- index	Diagnosealter 65 J	Diagnosealter 70 J	Diagnosealter 75 J
0	17,9	14,8	11,9
1	15,9	12,9	10,1
2	10,8	8,4	6,3
3	4,0	2,8	1,9
Gesamt	15,7	12,7	10,0

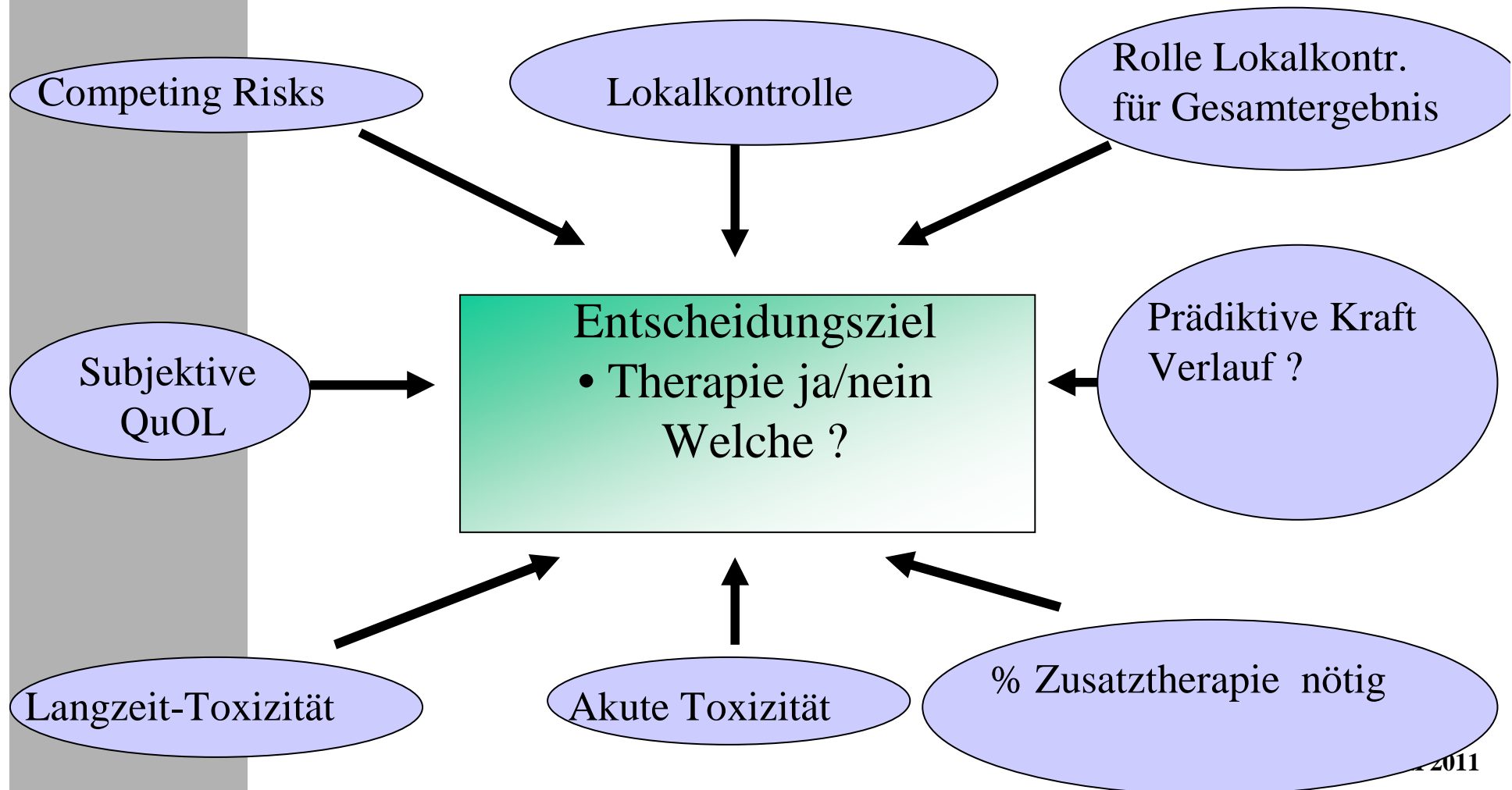
Index of coexistent Disease – Score

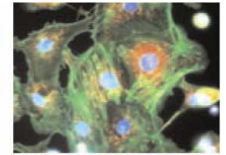
14 medizinische Konditionen, 12 Funktionszustände



Lokale Therapie des Prostatacarcinoms

Grundsatzüberlegungen





Indikationen für eine Radikale Lokal-Therapie

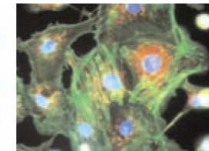
Aus, Eur Urol, 2005,48,
546-551

Middleton, CA Cancer J
Clin 1996,249-253

Scardino, J Natl Comprh
Cancer Center Netw
2005, 46, 249-253

**Standard Guideline (EAU guideline 2005, American urological
Association 1996, NCCN 2011)**

- **Radikale Lokaltherapie indiziert bei verbleibender Lebens-
Erwartung von > 10 Jahren**
- Extrem schlechte Voraussagbarkeit der individuellen versus
kollektiven Lebenserwartung



Prostate Cancer

To treat or not to treat?

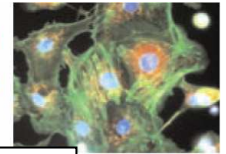
*Holmberg et al.,
 N Engl J Med, 2002
 Randomisiert*

**watchful waiting
 versus rPE**

- T1b, T1c, T2a,
- clinically detected,
- N=695
- 1989-1999

	Watchful waiting	rPE	Hazard
• Local progr (at 8a)	61.1%	9.3%	.31[.22-.44]
• Distant mets (at 8a)	27.3%	13.4%	.63[.41-.96]
• Cancer death	8.9%	4.6%	.50[.27-.91]
• Death other causes	8.9%	10.6%	
• Overall mortality	28.3%	22%	.83[.57-1.2]

Benefit first emerging after 5 years



Prostatacarcinom

To treat or not to treat?

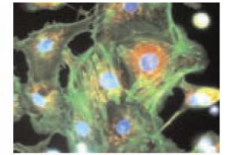
Steineck,
N Engl J Med, 2002

- **Randomized Study of watchful waiting versus rPE**
- N=696

	Watchful waiting	rPE
• erectile dysfunction	45%	80%
• urinary leakage 21%		49%
• urinary obstruction	44%	28%

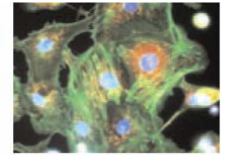
Equivalent:

Bowel function, prevalence of anxiety, depression, well-being, subjective quality of life



Lokale Therapiemodalitäten

- **Operation**
 - RRP (radikale retropubische Prostatektomie)
 - RPP (radikale perianale Prostatektomie)
 - Laparoskopische PE
 - Da Vinci Roboter
- **RT**
 - EBRT
 - Brachytherapie
 - Brachytherapie+EBRT
 - Protonen-Bestrahlung
- **Kryoablation**
- **Ultraschallablation**
- **Äthanol-Ablation**



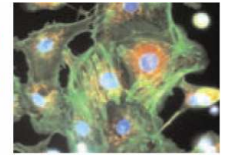
Prostatektomie – Einschätzung des Tumors

Tumorvolumen
Organüberschreitung
Aggressivität
Lymphknotenbefall

Verzicht auf pelvine LA nur bei
PSA < 10, Gleason < 6
Weniger als 10% des Patientenguts

Normogramme unzureichend validiert

Kattan et al,
Curr Opin Urol,
2003

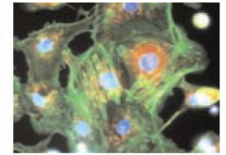


Bildgebung und Stadien *Entscheidungsrelevant?*

Partin et al., Urol Clin North Am, 1993, n=1,000

- Alle Patienten klinisch mit organbeschränktem Carcinom diagnostiziert
- Operativ/pathologisches Ergebnis:

Organbeschränkt	37%
Kapselpenetration	40%
Regionalaussaat	14%



Grundlagen der Diagnostik des Prostatacarcinoms

Digital-rektale Untersuchung

Transurethraler Ultraschall mit Biopsie

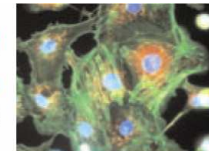
PSA

CT, Sono, MRI häufig keine zusätzliche Hilfe
Knochenszintigramm bei G3, PSA über 10 ng/ml.

Cholin-PET, PSA-Dichte, PSA-Velocity,
Quotient freies/gesamtes PSA etc. ,

Lymphoszintigraphie und sentinel node bez.

Extended lymphadenektomie brauchen weitere Studien !

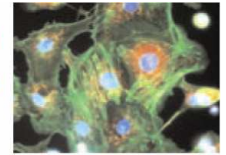


*Partin and Fenely,
ASCO, 2000,
Educational Book,
Update of Partin
Tables (n=4,300)*

Risikofaktoren und Prädiktion

SV und LN-Befall

GS	T1(a-c), T2(a-c) PSA				T3 PSA			
	0-4	4-10	10-20	>20	0-4	4-10	10-20	>20
2-6	6%	10%	19%	34%	12%	20%	32%	47%
7-10	12-31%	14-45%	26-59%	—73%	28%	59%	54-71%	68-82%

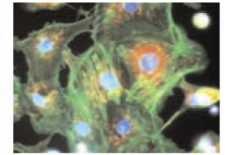


Radiotherapien

Wedding et al,
2003

Das Prostatacarcinom ist strahlensensibel
mit einer eindeutigen Dosis-Wirkung-Beziehung

Alternative zur radikalen Prostatektomie

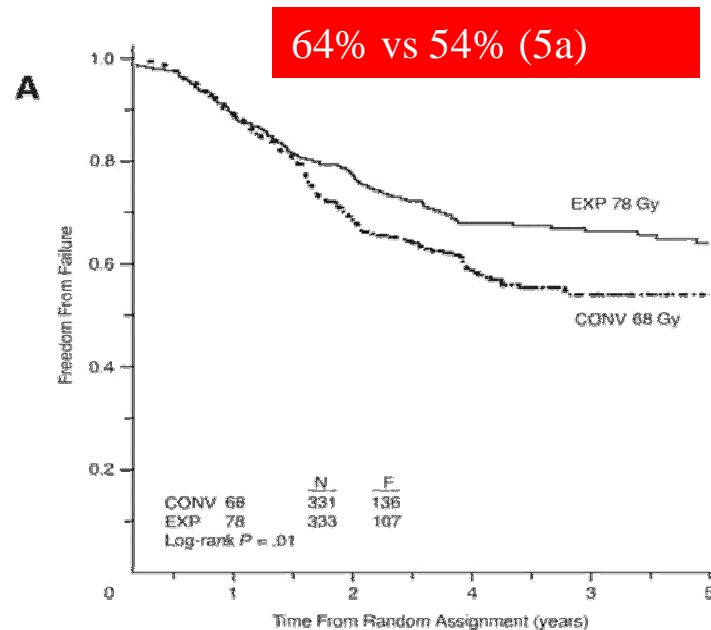


Bedeutung der Dosis der EBRT

FF Survival biochemical/clinical

Peeters, S. T.H.
et al. J Clin Oncol;
24:1990-1996 2006

- randomisiert
- 68 vs 78 Gy



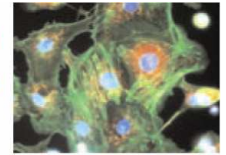
78 gy 3D conformal RT

68 gy conventional dose

Side effect prize:

Nonsignificant increase

In GI toxicity grade 2

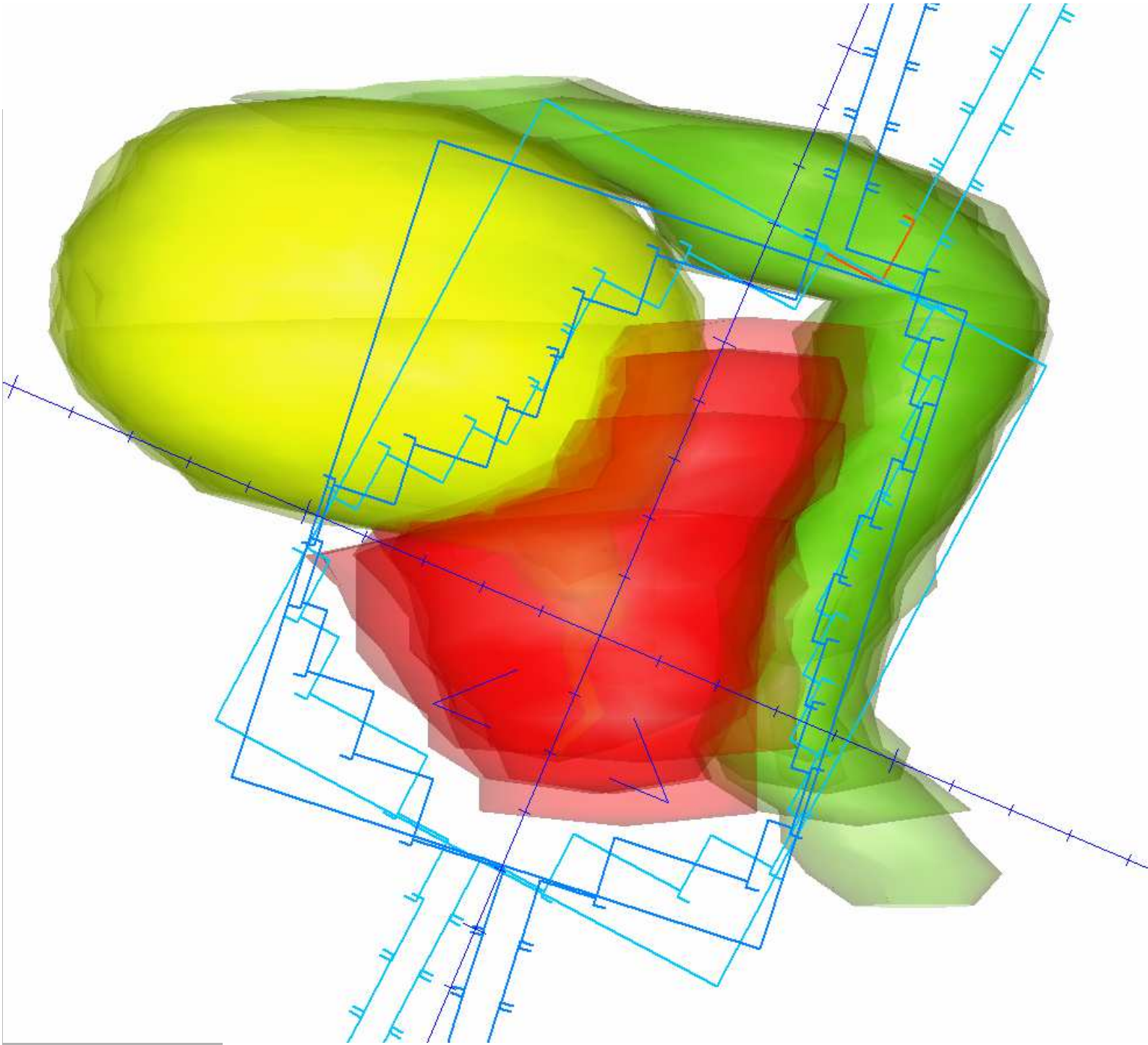


Zielvolumen der perkutanen Radiotherapie

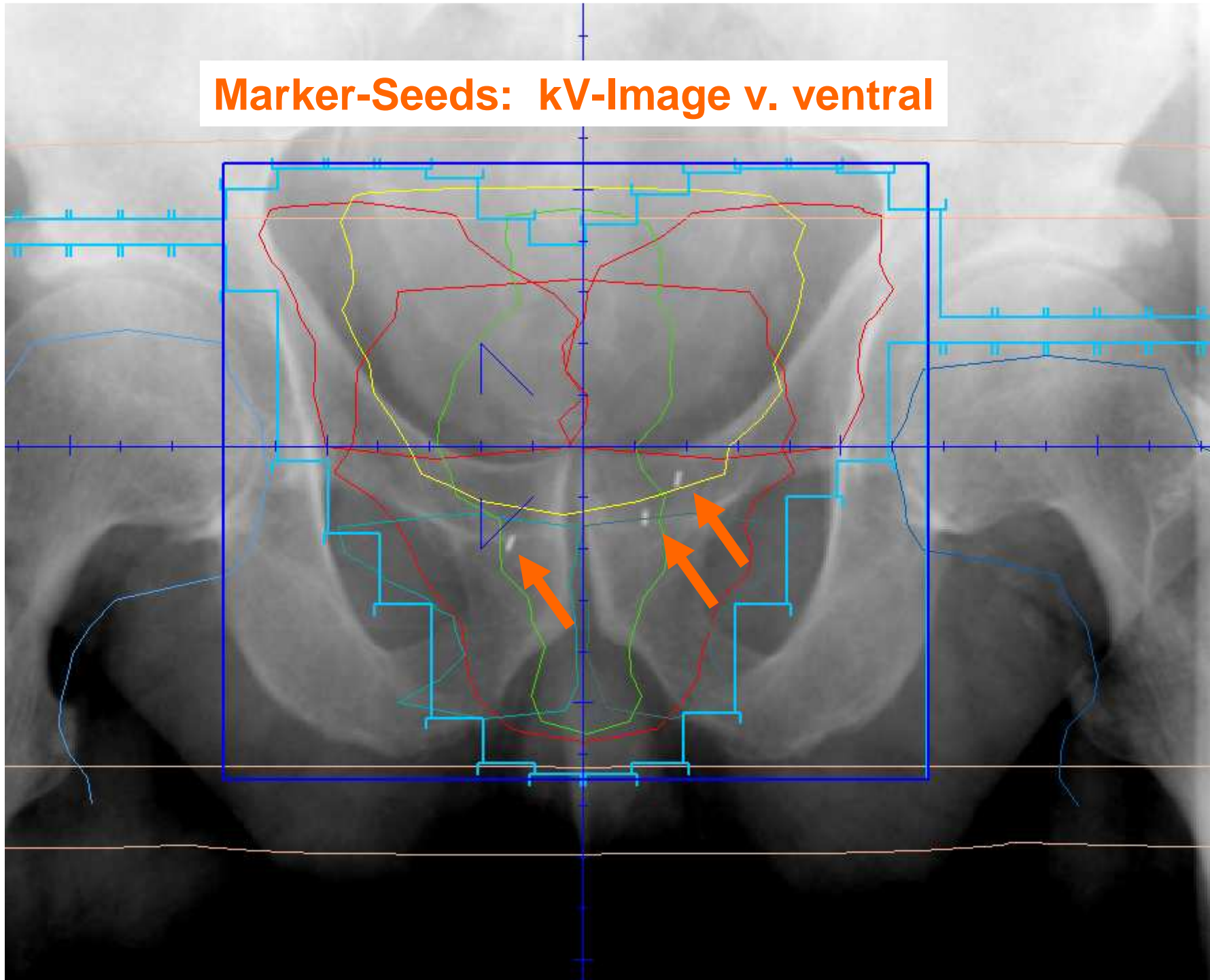
Gesamte Prostata

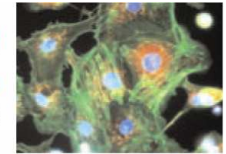
+ Samenblasen bei
V.a. Infiltration bzw.
>= T2b,
G3 oder
PSA > 10 ng/ml

Ev. Markierung der Prostata ?



Marker-Seeds: kV-Image v. ventral



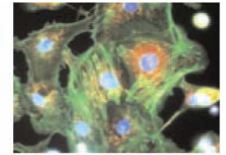


Ashesh B Ja,
[361,9362](#) ,
2003, 1045-1053

Nebenwirkungsvergleich der Lokalverfahren

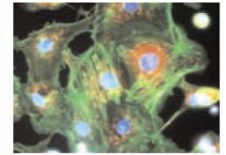
Site	Prosta- tectomy	External- beam radiotherapy	Brachy- therapy	External-beam radiotherapy and brachytherapy
Rectal	+	+++	+	++
Sexual (impotence)	+++	++	+	++
Urinary				
Incontinence	+++	+	+	+
Retention	+	+	+++	+++

Increasing number of +s indicates increasing complication rates.



Lokaltherapien Konklusionen

- mehr randomisierte Studien nötig
- RT hat vergleichbaren Nutzen mit rPE mit weniger Nebenwirkungen
- Profit von rPE könnten haben
 - > junge Männer mit sehr kleinem Tumor und geringer Wahrscheinlichkeit für Samenblasen- und extrakapsulären Befall
 - > Ohne Bedarf für zusätzliche RT
 - > Ohne Notwendigkeit zusätzlicher Hormontherapie
 - > an Orten mit exzellenter Erfahrung in Nervensparender Operation
 - > bei initial intakter Potenz



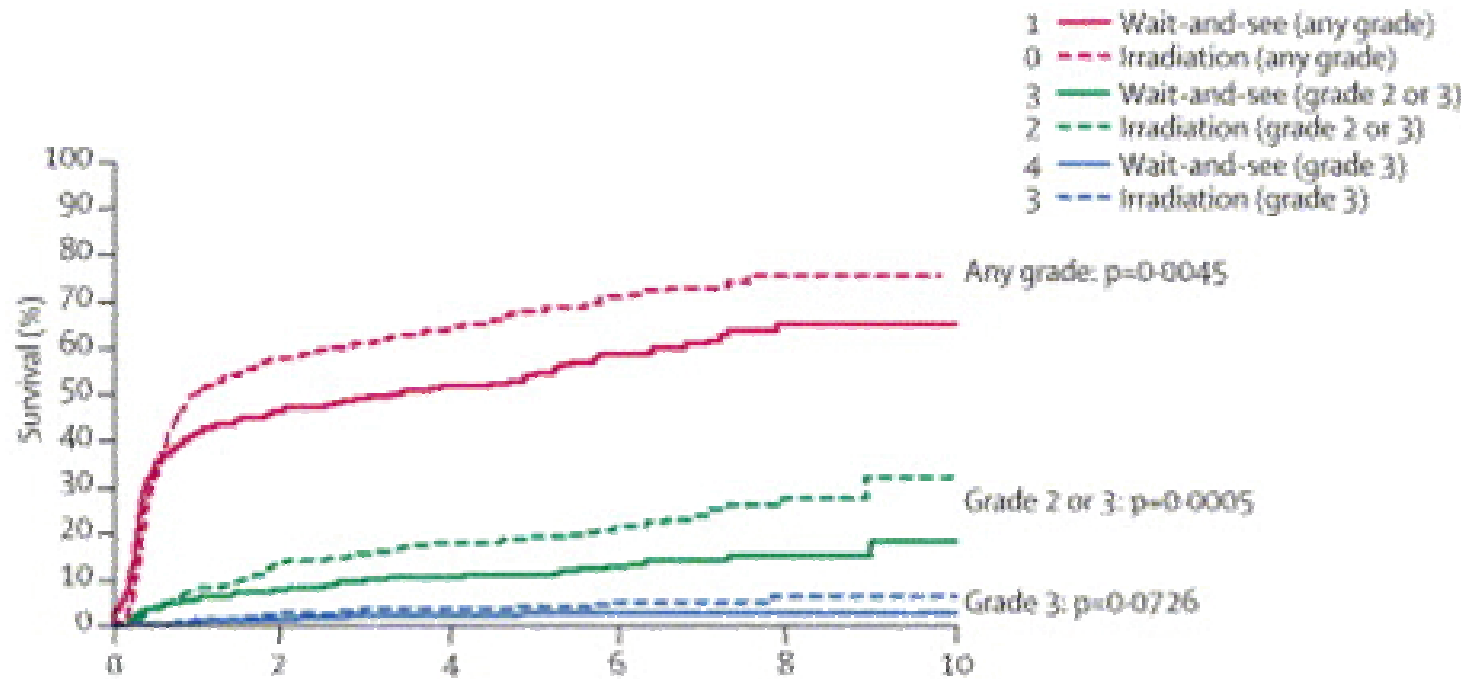
Michel Bolla
[The LANCET](#)
2005

N>1,000 Pt

one or more pathological
risk factors:

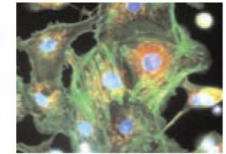
- capsule perforation,
- positive surgical margins,
- invasion of seminal vesicles

Postoperative Radiotherapy after Radical Prostatectomy



Overall Survival:

- Death by prostate cancer 2x increased for watchful waiting
- Net effective: No gain in OS



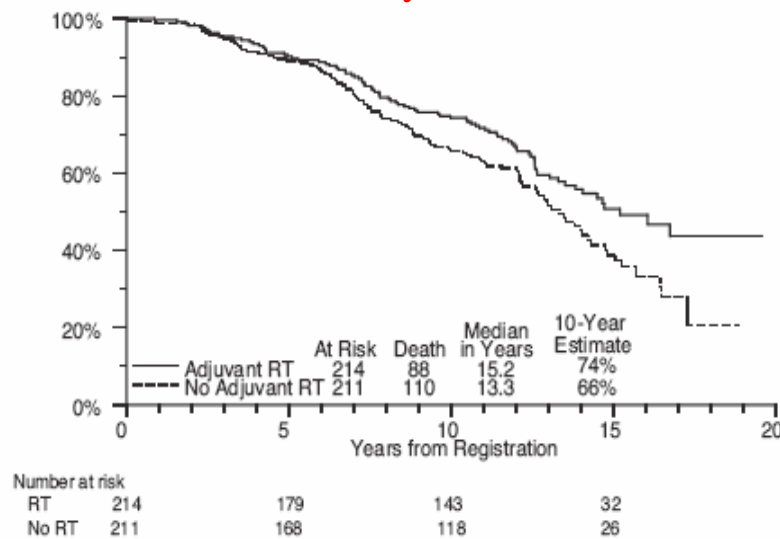
I. Thompson

Journal of
Urology
März 2009

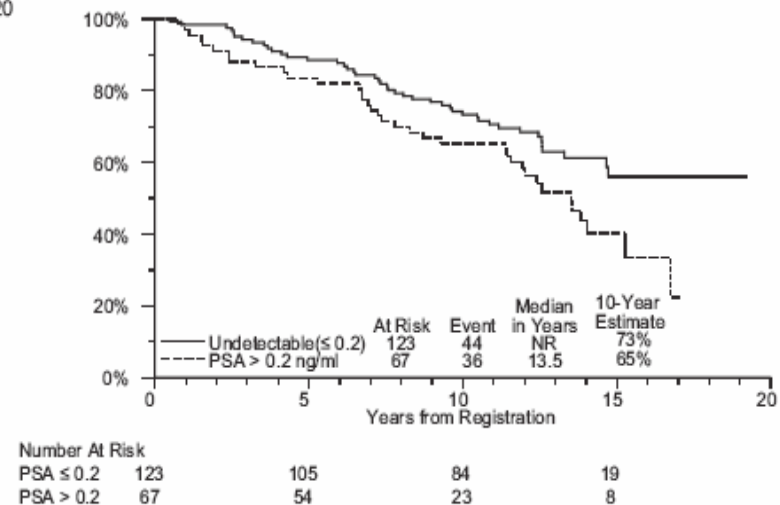
N = 431

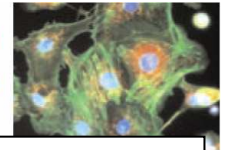
Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer after Radical Prostatectomy

Survival by Treatment Arm



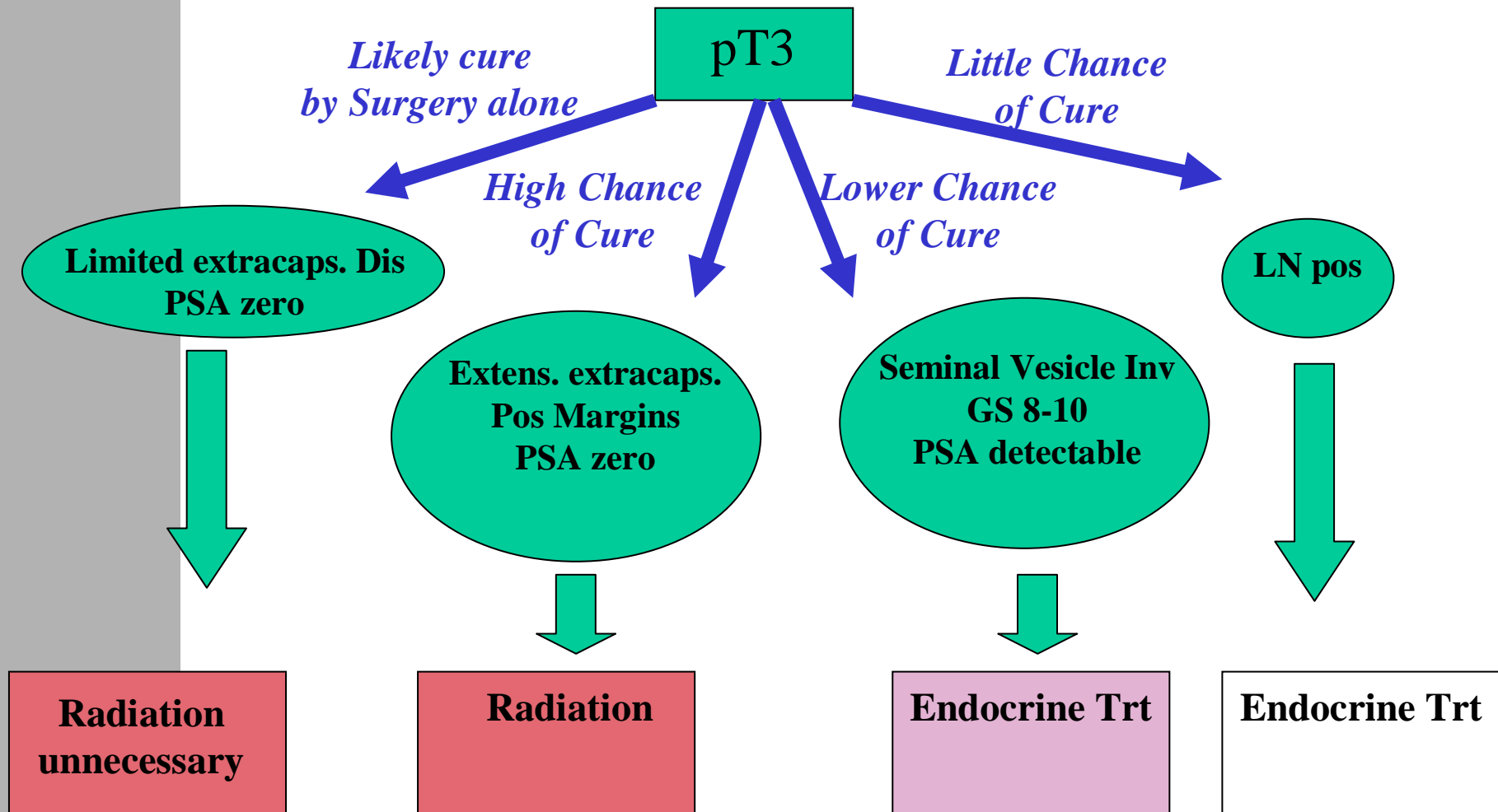
Metastasis-free Survival by Treatment Arm

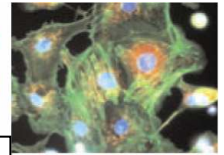




rPE und pT3

Adjuvante Therapie-Risikostratifikation



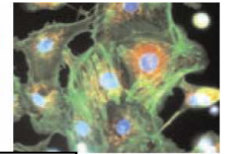


Neoadjuvante Hormontherapie vor RT ?

- **Kein Benefit bei low risk Patienten**
- **Kein Benefit bei Hochrisikopatienten**

RTOG 9202 und Subset-Analyse von RTOG 9413

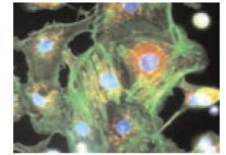
definiert als GS 7-10 und PSA >30



Neoadjuvante Hormontherapie vor Radiotherapie

- Hochrisikopatienten: neoadjuvante AHT ist zu kurz, die Patienten benötigen längere adjuvante Hormontherapie
- Keine Unterschiede zwischen 3m, 5m, 8m 12m AHT vor, während und nach der EBRT

- Klassische Population
 - GS 7
 - T1,2 klinisch
 - GS 6 und bulky 5x5 cm
 - PSA 7



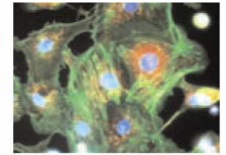
Relaps- adjuvante HAT nach Radiotherapie ?

Who is at risk for relapse after EBRT

Typically

→ T2 or T3, GS 7-10, PSA >20 (RTOG)

bulk 5X 5 cm



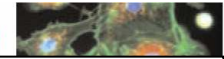
Stellenwert adjuvanter Hormontherapie nach EBRT

Metaanalyse
ESMO
2006
N=4,373
7 trials

RR relapse **0.74 [0.7-0.78]** **p<.0001**

Absolute benefit PFS **10%**

RR death **0.84 [0.78-0.91]**



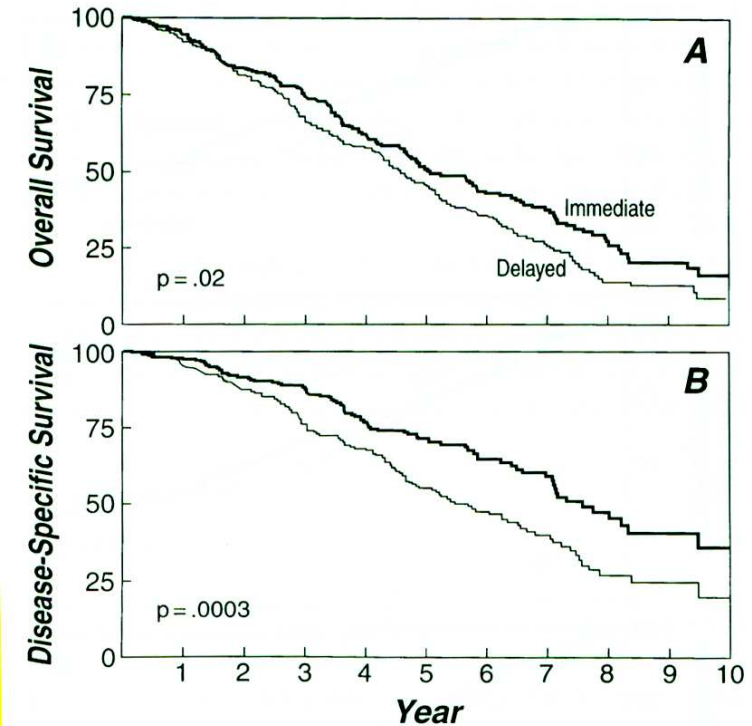
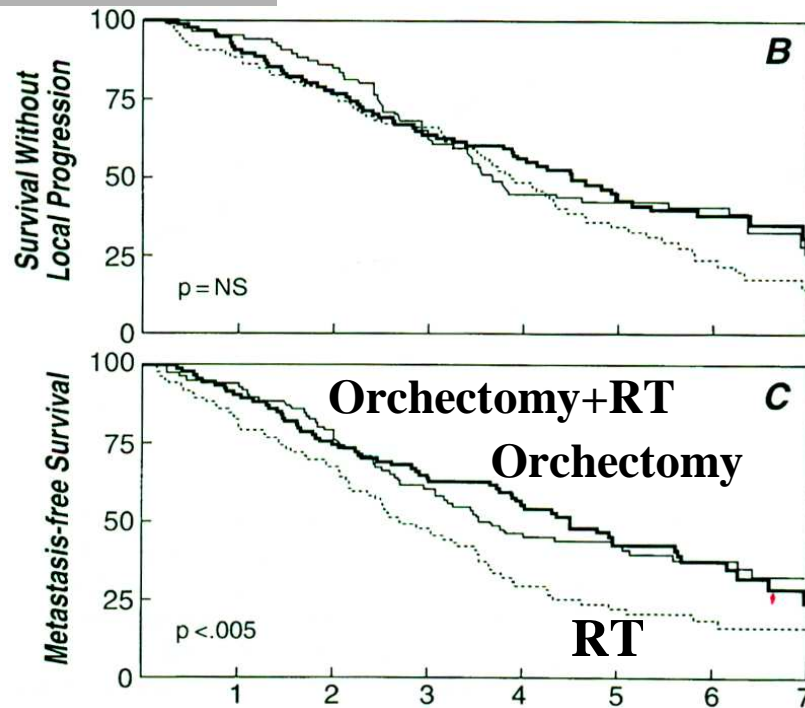
Genügt eine alleinige Hormontherapie bei T3/4?

Lokalkontrolle

Sofortige vs Verzögerte Trt

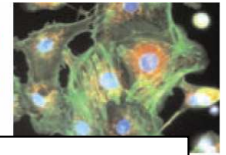
MRC Trial, T2-4, Nx, M0, n=277

MRC Trial, T2-4, Nx, M0, n=503



5a Lokalkontrolle 90% mit HT.

Frage: Stellenwert der RT für Lokalkontrolle und OS?



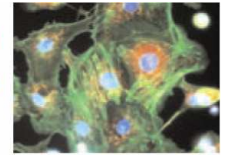
Persistierend postoperativ erhöhter PSA-Wert

- Normalerweise postoperative PSA-Werte in 6w undetektierbar

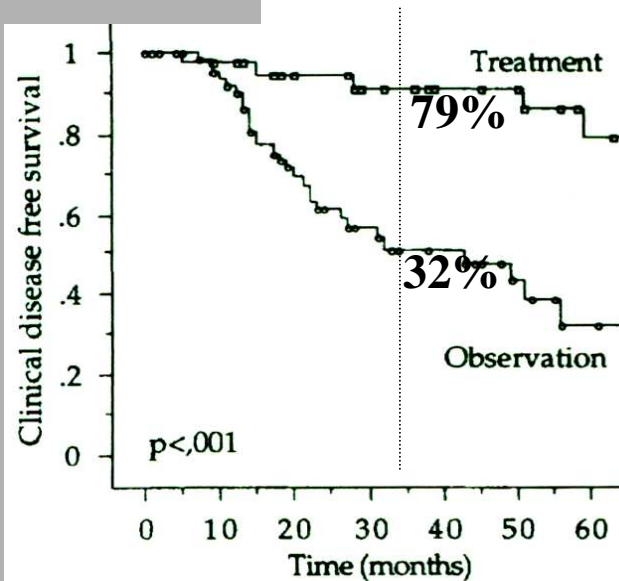
Effekte lokaler adjuvanter RT bei postoperativ persistierendem PSA

Biochemisches Relapsfreies Überleben nach 7a,
Hudson, J Clin Oncol, 1999: 18 %

Somit RT bei persistierend erhöhtem PSA fragwürdig!
Indirekte Daten (LN+ Pt, *Messing, ECOG, NEJM; 1999*) und MRC
Trial (*Br JUrol 1997*) sprechen für sofortige Hormon-Trt. (OS-Benefit)

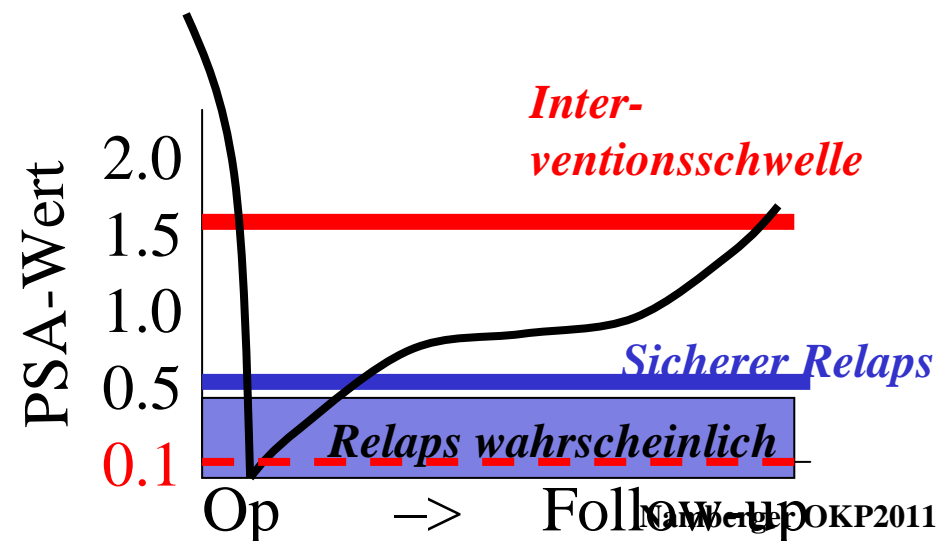


Später PSA-Anstieg Sofortige Therapie vs Warten ??

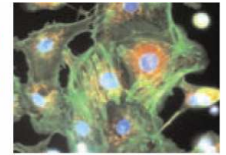


*Kupelian, Int J
Radiat Biol Oncol
Phys, 1997
bRel 0.2ng/ml*

*Am Soc Ther Rad Oncol Consensus
J Clin Oncol, 1999*



Pound et.al, N= 1997, WW
JAMA 1999 Metastasenachweis 8 a
nach PSA-Anstieg.

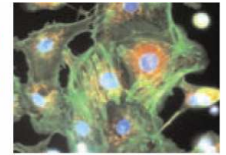


Vorgehen bei PSA-Anstieg:

LE unter 10 J : WW

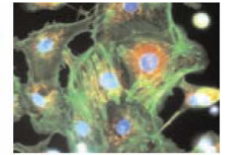
LE über 10 J

- + unvollständiger PSA-Abfall: HAT
- + PSA-Anstieg < 1 a, ungünstige RF: HAT
- + PSA-Anstieg > 1a, günstige RF: Salvage RT
+/- HAT



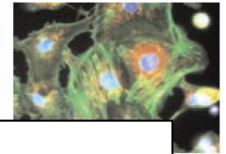
Metastatic prostate cancer

- **85% metastasize to bone**
- **otherwise liver, lymph nodes, lung and brain**
- **Overall survival is 3-4 years**



Metastatic Prostate Cancer Surgical vs Medical hormonal ablation

- **Orchectomy and LHRH analogs are similar effective !**
- **LHRH analogs treated patients have greater problems with their overall sexual functioning**



Timing of hormone therapy

Deferred vs immediate therapy

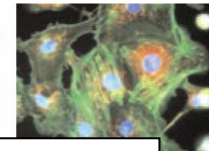
- Four trials involving 2,167 patients

	1	2	5	10 years
OS immediate trt	88%	73%	44%	18%*
OS deferred trt	86%	71%	37%	12%

OS favored early therapy but was significant only at 10 years

PFS was consistently better in the early intervention group at all time points.

Wilt Cochrane Review Group on 4 randomized trials, 2003

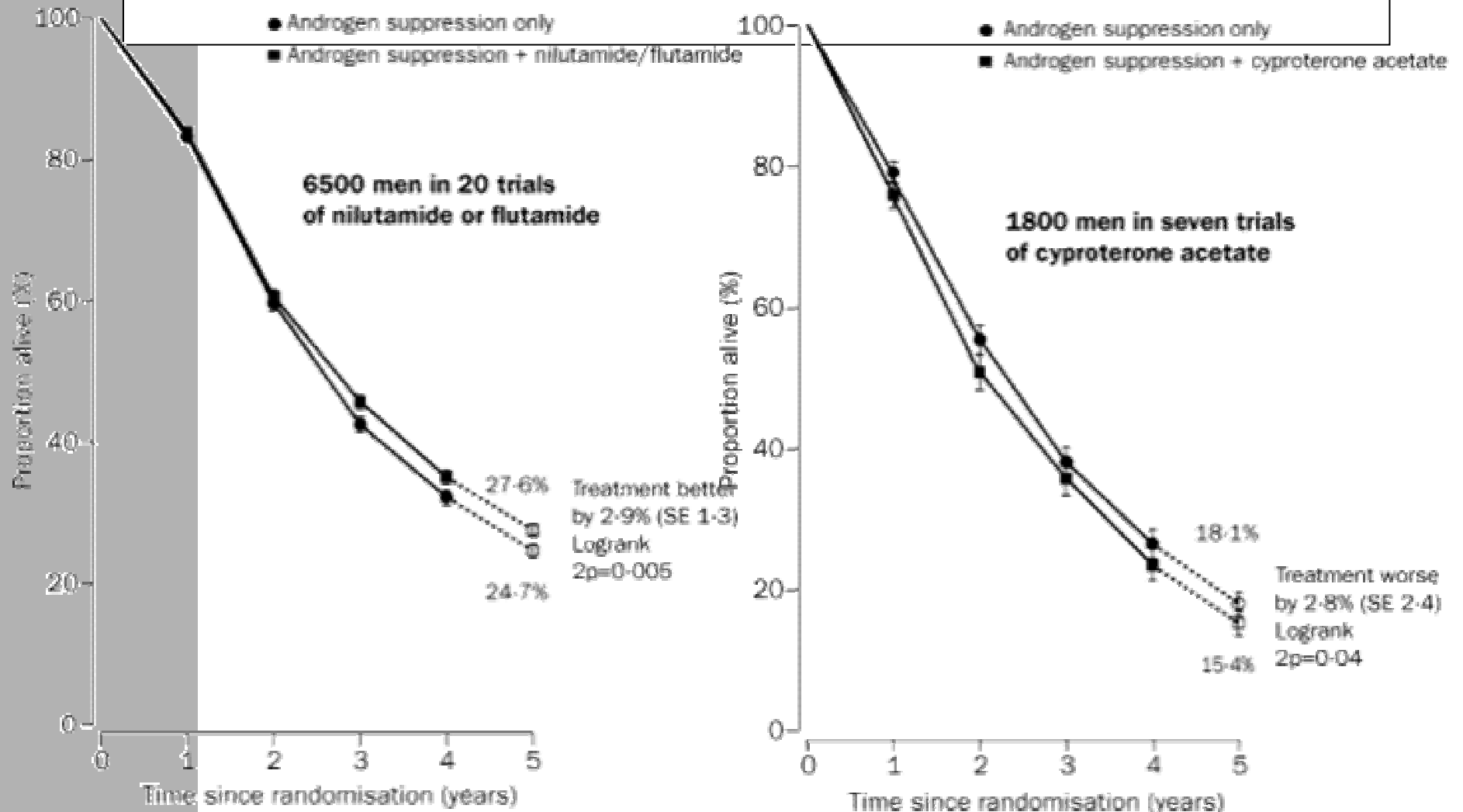


The side effect profile

	Leuprolide (n = 26)	Bicalutamide (n = 25)	P
Anemia, %	77	40	.007
Breast enlargement, %	54	100	< .001
Breast tenderness, %	8	100	< .001
Fatigue, %	77	40	.007
Loss of sexual interest, %	81	40	.003
Vasomotor flushing, %	96	8	<.001

*** Prophylactic irradiation of the breast indicated [two randomized trials]**

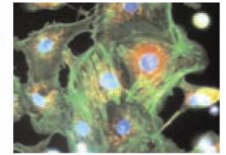
CAB vs Monotherapy Overview





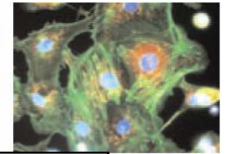
ASCO recommendation

- **1st approach→ LHRH agonist (or castration)**
- **Non-steroidal antiandrogen is an alternative, being considered where the preservation of sexual life is important**
- **CAB should be discussed with the patient because of the small survival benefit**



Androgen-Independence

- **Rise of PSA level within 4 weeks during treatment with any type of antihormonal therapy**
- **Progression of bone disease or visceral disease**



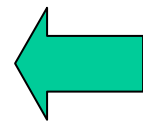
Prostatacarcinom

Versagen nach Hormontherapie

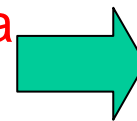
CAB→Progress

Antiandrogenentzug: 20% Response
PSA Response in 14d

Androgensensitiv
[Androgenspiegel+]
Antiandrogen



LHRH Analoga
Progress



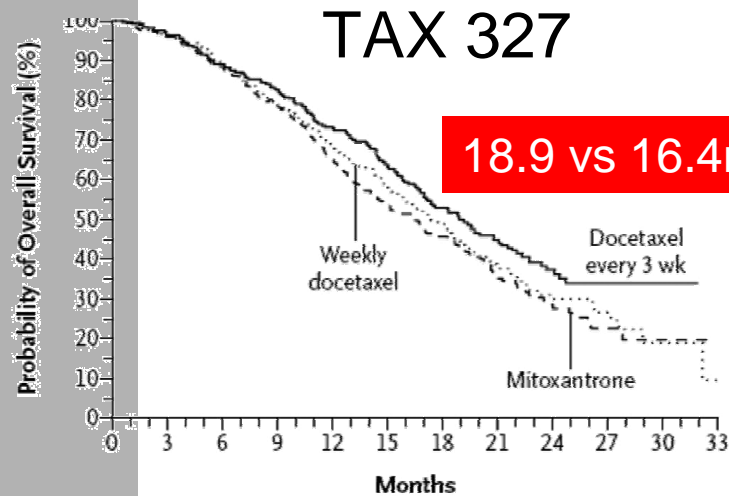
Hormonresistent
Chemotherapie



Hormonsensitiv
[Androgenspiegel-]
Cortison 4x5mg/d
RR 20%
OS 10-11m

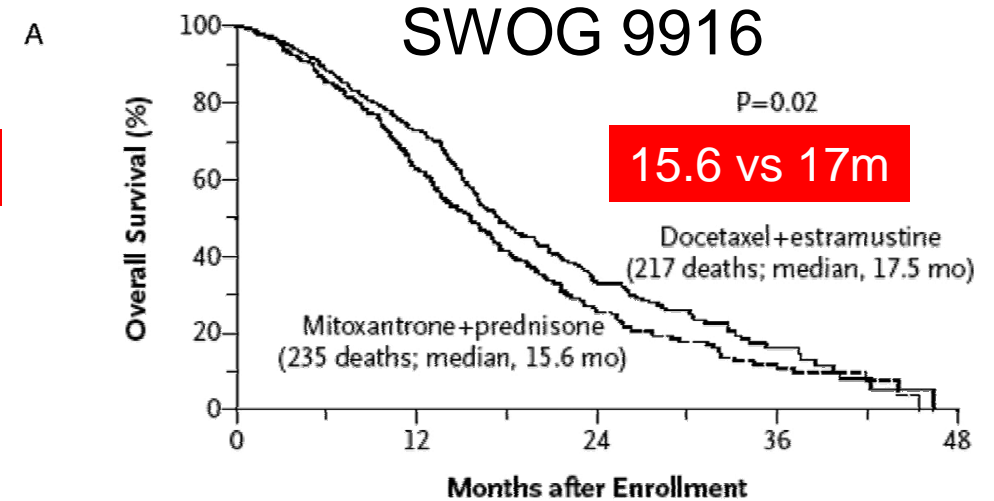


First Line : Docetaxel



No. at Risk						
Docetaxel every 3:wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

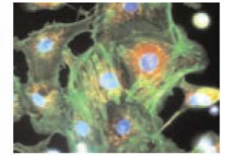
DOCETAXEL 60/m², d2



No. at Risk				
Docetaxel+estramustine	338	218	60	13
Mitoxantrone+prednisone	336	185	50	10

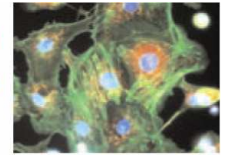
DOCETAXEL 60/m², d2

Estramustine 280/m²x3/d d1-5



Second Line: Mitoxantrone / Prednison or what ?

- Mitoxantrone and Prednison significantly improves symptom control and pain relief and anagetics consumption over prednison alone but does not increase survival, **Tannock, J Clin Oncol, 1996**
- Ketokonazol 200 mg 1-1-1
- Sipuleucel
- Sartaplatin
- Angiogenesis Inhibition
- TKI
- Vaccination
- else ?



Cabazitaxel – New Taxane

- **June 2010 FDA Approval .**
- **Nature Reviews 2010:**
- **Patients with castration-refractory prostate-cancer,**
- **previously treated with docetaxel**
- **Randomised, open-labeled trial, n=755,**
- **Prednisone/Cabazitaxel vs. Mitoxantrone/Prednisone :**
- **OS 15,1 vs. 12,7 months**
- **Tumor response rate 14,4 % vs. 4,4%**



Targeted agents

Attard et al.,
JCO 2008,
JCO 2009,
JCO 2010.

deBono et al.
The Lancet
2010.

Abiraterone

**Potent and selective irreversible inhibitor of cytochrome P-17,
High androgen-receptor expression in castration-refractory prostate-cancer.**

Phase I/II trial , pre-docetaxel, n=54 (UK)

Phase II trial, post-docetaxel , n=48 (UK)

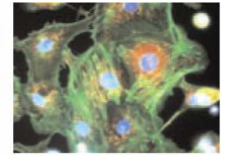
US trials confirm

Abiraterone :

45% PSA decline > 50% .

median time to PSA progression 169 d.

Reduction of circulating cancer cells

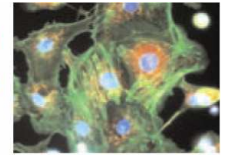


More Problems :

Spinal Cord Compression
Urinary Tract Obstructions
Intracranial Nerve Involvement
Hypercalcemia
Hematologic Complications
Inflammatory Complications

Intravascular Coagulopathy
(often without symptoms –
Docetaxel when symptomatic !)

Osteoporotic Fractures !



Bisphosphonate

5-fold risk of bone fracture in prostate cancer (castrated),
(Hatano et al. , J Urol 2000)

Reduction of bone loss, zoledronate vs. Placebo

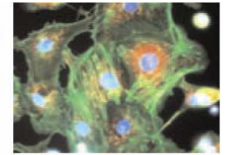
- Smith et al. , J Urol 2003
- Shahinon et al., NEJM 2005
- Greenspan et al., Ann Int Med 2007

Denosumab :

(Smith et al. , NEJM 2009)

Reduction of bone loss and fractures : 60 mg q 6 months

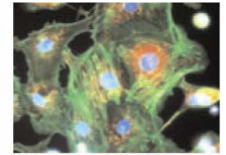
Therapy of bone metastases : 120 mg q 4 weeks



VORSORGE / NACHSORGE

ERSPC, N Engl J Med Juli 2009 :

- **PSA-screening reduced the death rate from prostate cancer by 20 %**
- **Associated with overdiagnosis**
- **? Overall survival - benefit**



WICHTIG:

Gute interdisziplinäre Zusammenarbeit von

**Urologen,
Strahlentherapeuten,
Onkologen.**

**Patientenorientierte individuelle
Entscheidung zu jedem Zeitpunkt !**