Programma Mirrors of Medicine

- 00.00 uur: Ontvangst
- 00.00 uur: **Module 1** High-risk non-metastatic Pca
  Presentatie en interactieve discussie
- 00.00 uur: Pauze
- 00.00 uur: **Module 2** Metastatic castration-resistant PCa
  Presentatie en interactieve discussie
- 00.00 uur: Afsluiting

Mirrors of medicine

An online program that helps discover the best available evidence at the patient-specific level

Combining the best of two worlds....

Mirrors of Medicine

Select a model or a course to get started

We can offer you free access to our accredited courses thanks to an educational grant from **AstraZeneca** and **Janssen**

Ronde 1 in 2015/2016

High-risk non-metastatic prostate cancer

Open model | Take course

Gert De Meerleer
University Hospital Ghent, Radiotherapy

Metastatic castration-resistant prostate cancer

Open model | Take course

Bertrand Tombal
University Hospital Saint-Luc, Urology

Biochemical recurrence after radical treatment

Open model | Take course

Alberto Bossi
Gustave Roussy Institute, Radiotherapy

Diagnosis of prostate cancer

Open model

Theo M de Reijke
Academic Medical Center, Urology

Localised prostate cancer

Open model | Take course

Jeroen van Moorselaar
VUmc Cancer Centre Amsterdam, Urology

Interactive session: 1 CME point/module
E-course: 1 CME point/module

Mirrors of Medicine

- "translating scientific evidence into everyday practice"
- Accredited CME programme
- Adopted by scientific society ISSECAM
  - **I**nternational **S**ociety for the **s**tudy and **e**xchange of evidence from **c**linical research **a**nd **m**edical experience
- Focus on education and research in uro-oncology (starting PCa)
  - Urologists
  - Oncologists
  - Radiation oncologists

PHNL/ZYT/0115/0002b(1)

Mirrors of medicine is..

selecting a profile…..

see panel recommendations…..

and the underlying evidence.

Mirrors of Medicine models

- **Five prostate cancer modules**
  - **High risk M0, mCRPC, localised, biochemical recurrence, diagnosis**

- Developed using the RAND/UCLA appropriateness method[1]
  - Systemic approach to develop patient-specific recommendations by combining evidence from RCT with the collective judgement of experts
  - Produces reliable, internally consistent and clinically valid results[2]

- Treatment recommendations for a variety of patient profiles
  - Updated every 6 months with data and regulations

1 Brook RH, Chassin MR, Fink A, et al. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care 1986;2:53-63.
2 Lawson EH, Gibbons MM, Ko CY, Shekelle PG. The appropriateness method has acceptable reliability and validity for assessing overuse and underuse of surgical procedures. J Clin Epidemiol 2012;65:1133-43.

Panel members

- Alberto Bossi
- Alberto Briganti
- Alessandro Volpe
- Alex Mottrie
- Alexander Govorov
- Alexander Haese
- Alexandre de la Taille
- Amit Bahl
- Andreas Blana
- Andrew Stephenson
- Antonio Alcaraz
- Arnoud Templeton
- Ash Tewari
- Aurelius Omlin
- Bertrand Tombal
- **Bradley Pieters**
- Camilla Thellenberg Karlson
- Christophe Massard
- David Dearnaly
- Dominik Berthold
- Filip Ameye
- François Cornud
- Frédéric Lecouvet
- Geert Villeirs
- Gert De Meerleer
- Guillaume Ploussard
- Hein Van Poppel
- **Inge van Oort**
- **Jack Schalken**
- Jacques Irani
- James Eastham
- **Jelle Barentsz**
- **Jeroen van Moorselaar**
- Joaquim Bellmunt
- Jochen Walz
- Johan Braeckman
- Johan Stranne
- Jonas Hugosson
- **Jorg Oddens**
- Jörg Schröder
- Karim Fizazi
- Karin Haustermans
- Levent Turkerei
- Malcolm Mason
- **Marco van Vulpen**
- Mark Speakman
- Markus Graefen
- Martin Spahn
- Mesut Remzi
- **Monique Roobol**
- Nicholas Van As
- Nicolas Mottet
- Noel Clarke
- Paolo Gontero
- **Paul Kil**
- Piet Ost
- Scott Eggener
- Srinivas Samavedi
- Steven Joniau
- **Theo de Reijke**
- Thomas Wiegel
- Vincent Khoo
- Vip Patel
- Xavier Maldonado

Registration

pca.mirrorsmed.org

Login

E-mail *

Enter your e-mail address.

Password *

Enter the password that accompanies your e-mail.

Log in

New to Mirrors of Medicine?

A Mirrors of Medicine account is needed to continue

E-mail *

Password *

Password strength:

Confirm password *

First name *

Last name *

Country *

- Select a value -

Professional category *

- Select a value -

Work setting *

- Select a value -

Speciality *

- Select a value -

Accept Terms & Conditions of Use *

Create new account

CME accredited educational module

High-risk non-metastatic prostate cancer (PCa)

Last update: 01/12/2016

Mirrors of medicine

PHNL/ZYT/0115/0002b(1)

Stemronde geopend

Even weten wie er aanwezig zijn

1. uroloog
2. aios urologie
3. radiotherapeut
4. aios radiotherapie
5. medisch oncoloog
6. oncologie verpleegkundige/ verpleegkundig specialist

10

What is the minimal definition of high-risk non metastatic PCa?

- Initial PSA ≥ 20 ng/mL **and/or**
- Gleason sum ≥ 8 **and/or**
- Clinical stage ≥ T2c
- Clinical N0

The exact definition of high-risk non-metastatic PCa is a matter of debate

	Risk category	Clinical stage		Pre-treatment tPSA		Biopsy Gleason sum
D'Amico risk criteria[1]	High	≥T2c	OR	>20 ng/mL	OR	8-10
AUA (2007; validated 2011)	High	T2c	OR	>20 ng/mL	OR	8-10
EAU (2013)	High	T3a	OR	>20 ng/mL	OR	8-10
	Very high	T3b-4 N0 OR any T, N+		Any		Any
NCCN (2013)	High	T3a	OR	>20 ng/mL	OR	8-10
	Very high	T3b-4		Any		Any
ESMO (2013)	High	T3-4	OR	>20 ng/mL	OR	8-10

PHNL/ZYT/0115/0002b(1)

[1]D'Amico AV et al. JAMA 1998;280:969-74

Definition of low-, intermediate- and high-risk prostate cancer (PCa) according to the EAU guidelines

2013

Risk category	Clinical stage		Pre-treatment tPSA		Biopsy Gleason sum
Low-risk PCa	T1-2a	AND	< 10 ng/mL	AND	≤ 6
Intermediate-risk PCa	T2b-2c	OR	10-20 ng/mL	OR	7
High-risk PCa	≥ T3a	OR	> 20 ng/mL	OR	8-10

2015

Risk category	Clinical stage		Pre-treatment tPSA		Biopsy Gleason sum
Low-risk PCa	T1-2a	AND	< 10 ng/mL	AND	≤ 6
Intermediate-risk PCa	T2b	OR	10-20 ng/mL	OR	7
High-risk PCa	T2c	OR	> 20 ng/mL	OR	8-10
High-risk PCa Locally Advanced	cT3-4 or N+		any		any

PHNL/ZYT/0115/0002b(1)

Initial management options for high-risk non-metastatic PCa

- Watchful waiting/active surveillance
- Surgery/radical prostatectomy (RP)
- Radiation therapy (RT):
  - External beam radiation therapy (EBRT)
  - Brachytherapy (BT)
- Hormone therapy (HT)/androgen-deprivation therapy (ADT)
- Combination therapy: RT + short-/long-term HT

How to translate evidence from clinical studies to individual patients?

Clinical variables

Gleason sum

< 8	≥ 8

Clinical stage ≥ T2c

No	Yes

Seminal vesicle invasion

No	Yes

PSA (ng/mL)

< 20	≥ 20

Life expectancy

≥ 5 years	< 5 years

PHNL/ZYT/0115/0002b(1)

Patient case 1

PHNL/ZYT/0115/0002b(1)

Patient profile:

- Thomas, 64 yr old, retired teacher
- Yearly check-up, including PSA screening
- Elevated PSA in October 2014: 14 ng/mL
- PCa diagnosed in November 2014:
  - PSA: 16 ng/mL
  - Gleason sum: 4 + 3 (7/10 pos. cores, bilateral)
  - Imaging MRI: T3a N0 M0; bone scan negative
- No comorbidities (life expectancy ≥5 yr)

What would be the most appropriate treatment for this patient?

Clinical variables

Gleason sum

< 8	≥ 8

Clinical stage ≥ T2c

No	Yes

Seminal vesicle invasion

No	Yes

PSA (ng/mL)

< 20	≥ 20

Life expectancy

≥ 5 years	< 5 years

PHNL/ZYT/0115/0002b(1)

Multidisciplinary discussion

- Which data drives your treatment choice?
- Which data are you missing for your treatment choice?

Take 2 minutes for multidisciplinary discussion to decide on a treatment

Stemronde geopend

Treatment options?

1. Surgery
2. EBRT + short-term hormone therapy
3. EBRT + long-term hormone therapy
4. Hormone therapy alone

What do the MoM experts recommend?

+ Surgery — View evidence

+ EBRT + short-term hormone therapy — View evidence

+ EBRT + long-term hormone therapy — View evidence

+ Hormone therapy alone — View evidence

Appropriate · Uncertain · Inappropriate · Not approved

The MoM model was last updated in Dec 2016 (www.mirrorsmed.org)

Surgery

Would surgery be a valid treatment option?

Surgery Hide evidence

Appropriate

Panel considerations

The panel considered RP to be an appropriate option for all patients with a life expectancy ≥ 5 years.

What can be potential advantages of surgery for high-risk PCa?

Monotherapy or 1st step in multimodal approach:

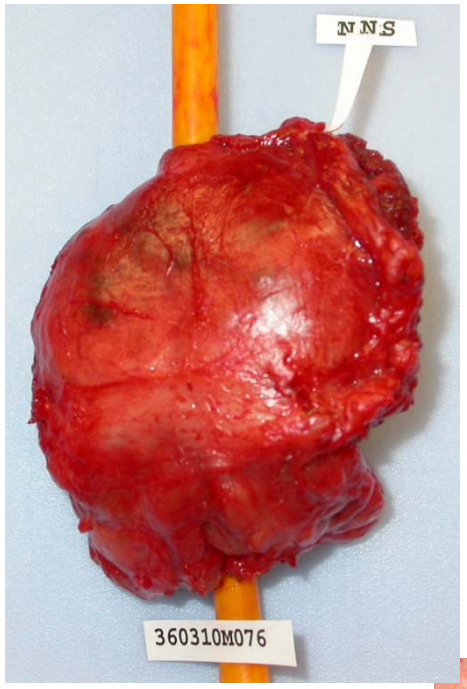
- Tumour volume reduction + optimal local control (?)
- Pathological staging (examine RP specimen + resected LNs) → better selection of pts needing adjuvant Tx

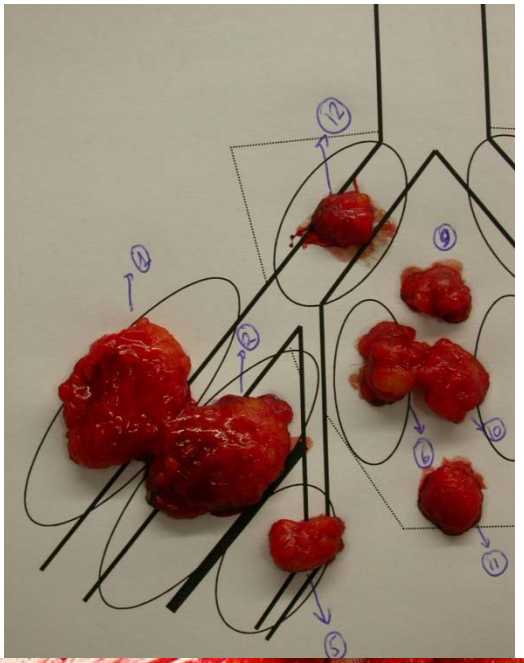
Is the surgical procedure the same as for patients with low- or intermediate-risk PCa?

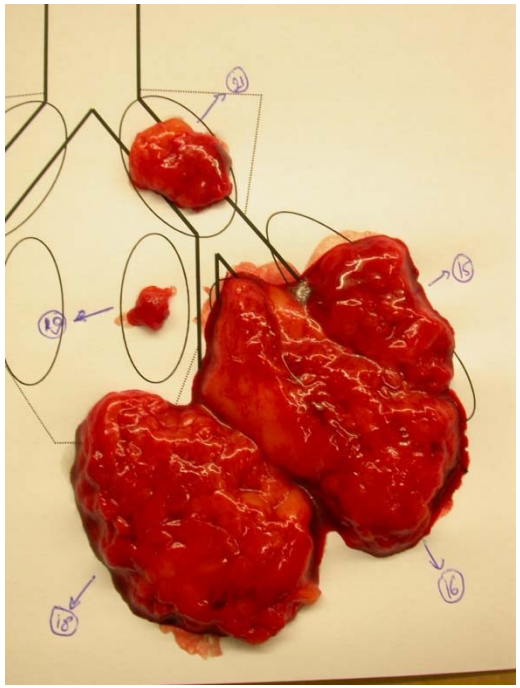
- Radical extirpation (RP), including[1]:
  - Extended pelvic lymph node dissection (ePLND)
  - Clean apical dissection
  - Neurovascular bundle resection at the tumour-bearing side
  - Complete resection of the SV
  - Resection of the bladder neck when the tumour is located at the base

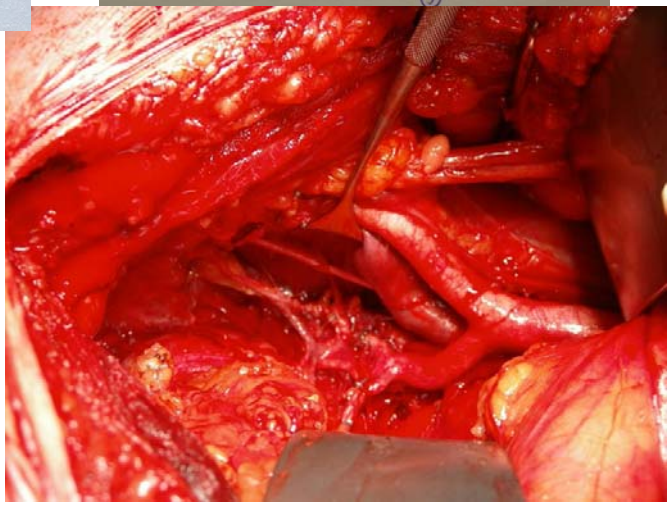
[1]Van Poppel H et al. Eur Urol 2008;53:253-9

Is the surgical procedure the same as for patients with low- or intermediate-risk PCa? (2)









PHNL/ZYT/0115/0002b(1)

Courtesy: Joniau S.

Is surgery an option for patients with (very) high-risk PCa? (1)

No RCTs, only large retrospective studies

High-risk PCa

Study	Time span	Pts (N)	Pathological outcomes (% of pts)						OS (% of pts)			CSS (% of pts)			Adjuvant/salvage treatment (%)
(i)			pT2	pT3a	pT3b	pN1	SM+	GS 8-10	5 yr	10 yr	15 yr	5 yr	10 yr	15 yr	
cT3a															
Ward 2005 [51]	1987-1997	841	27	-	-	27	56	18	90	76	53	95	90	79	78
Carver 2006 [52]	1983-2003	176	30	-	-	19	27	15	-	-	-	94	85	76	47
Hsu 2007 [53]	1987-2004	200	24	57	16	9	34	41	96	77	-	99	92	-	56
Freedland 2007 [54]	1987-2003	58	9	-	-	31	22	41	-	-	-	98	91	84	26
Yossepowitch 2007 [55]	1985-2004	144	22	-	-	23	26	28	-	-	-	-	-	-	-
Yossepowitch 2008 [56]	1985-2005	243	-	-	-	-	-	-	-	-	-	96	89	-	-
Xylinas 2009 [57]	1995-2005	100	21	53	26	17	61	9	-	-	-	90	-	-	31
Stephenson 2009 [58]	1987-2005	254	-	-	-	-	-	-	-	-	-	-	85	62	-
Walz 2010 [59]	1987-2005	293	-	-	-	12	37	30	-	-	-	-	-	-	-

Is surgery an option for patients with (very) high-risk PCa? (2)

Study	Time span	Pts (N)	Pathological outcomes (% of pts)						OS (% of pts)			CSS (% of pts)			Adjuvant/salvage treatment (%)
(i)			pT2	pT3a	pT3b	pN1	SM+	GS 8-10	5 yr	10 yr	15 yr	5 yr	10 yr	15 yr	
GS 8-10 at biopsy															
Donohue 2006 [60]	1983-2004	238	34	-	-	18	32	55	-	-	-	-	-	-	-
Bastian 2006 [61]	1982-2004	220	-	-	-	17	29	66	-	-	-	-	-	-	-
Yossepowitch 2007 [55]	1985-2004	274	35	-	-	19	30	52	-	-	-	-	-	-	-
Yossepowitch 2008 [56]	1985-2005	401	-	-	-	-	-	-	-	-	-	96	88	-	-
Stephenson 2009 [58]	1987-2005	702	-	-	-	-	-	-	-	-	-	-	84	66	-
Walz 2010 [59]	1987-2005	269	-	-	-	14	38	45	-	-	-	-	-	-	-
PSA > 20 ng/mL															
Zwergel 2007 [62]	1986-2005	275	21	42	33	28	-	49	87	70	58	93	83	71	≥ 47
Magheli 2007 [63]	1984-2005	265	-	-	-	24	41	30	-	-	-	-	-	-	-
Yossepowitch 2007 [55]	1984-2004	275	33	-	-	15	46	16	-	-	-	-	-	-	-
Yossepowitch 2008 [56]	1985-2005	441	-	-	-	-	-	-	-	-	-	97	91	-	-
Stephenson 2009 [58]	1987-2005	726	-	-	-	-	-	-	-	-	-	-	90	78	-
Walz 2010 [59]	1987-2005	370	-	-	-	16	46	11	-	-	-	-	-	-	-
Gontero 2011 [64]	1987-2005	712	21	28	38	24	55	26	90	73	-	95	89	-	≥ 50

Is surgery an option for patients with (very) high-risk PCa? (3)

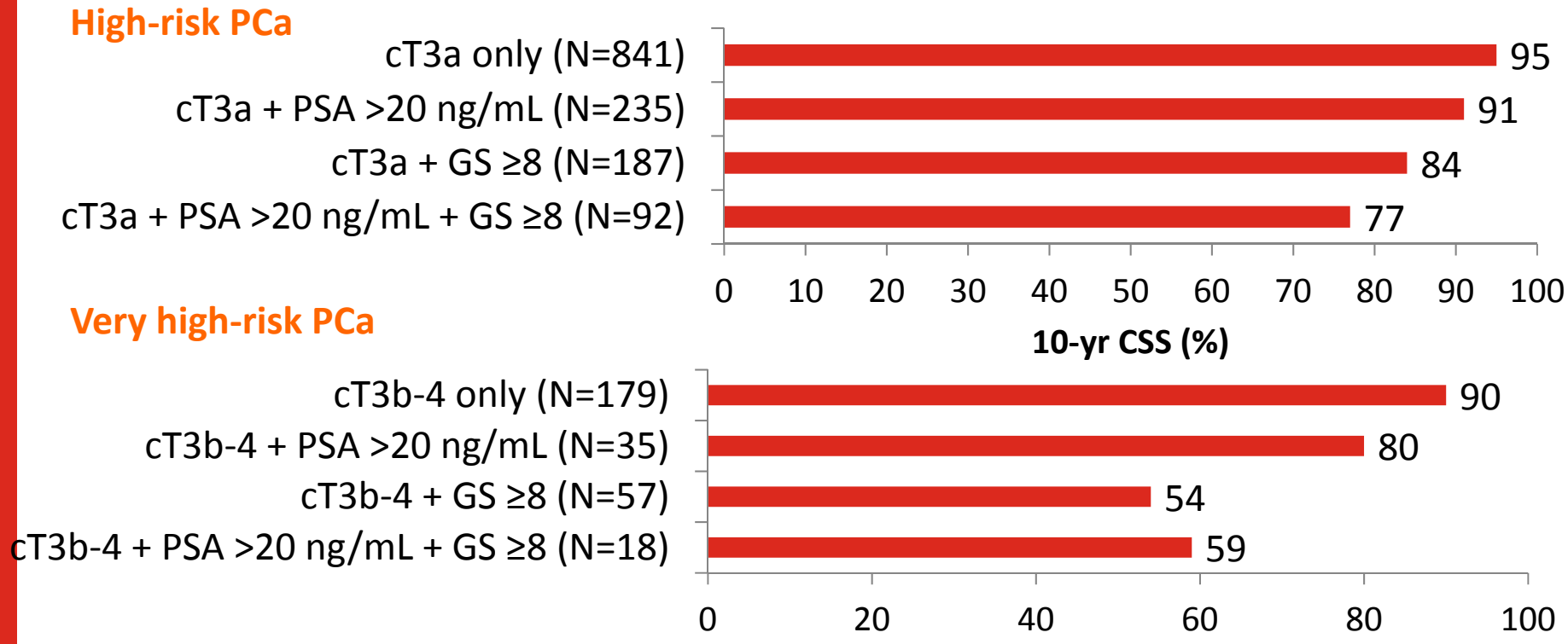
Very high-risk PCa

Study	Time span	Pts (N)	Pathological outcomes (% of pts)							OS (% of pts)			CSS (% of pts)			Adjuvant treatment (%)
(ii)			pT2	pT3a	pT3b	pT4	pN1	SM+	GS 8-10	5 yr	10 yr	15 yr	5 yr	10 yr	15 yr	
cT3b-T4																
Johnstone 2006 [65]	1995-2001	72	33*			43	-	-	-	73	-	-	88	-	-	31
Joniau 2012 [66]	1989-2004	51	8	29	45	18	22	63	-	88	71	-	92	92	-	65
Any T and N1																
Schumacher 2008 [67]	1989-2007	122	24	26	40	10	100	-	-	83	52	42	85	60	45	50
Da Pozzo 2009 [68]	1988-2002	250	8	15	61	16	100	62	33	-	-	-	89	80	-	100
Engel 2010 [69]	1988-2007	688	-	-	-	-	100	-	-	84	64	-	95	86	-	≥ 72
Steuber 2010 [70]	1992-2004	108	5	19	61	16	100	-	-	79	69	-	84	76	-	≥ 90
Briganti 2011 [71]	1988-2003	364	2	9	83	7	100	71	34	85	60	-	90	75	-	100

Large retrospective studies have shown good long-term oncological outcomes for RP in patients with (very) high-risk non-metastatic PCa

Do all patients with high-risk PCa equally benefit from RP + ePLND?

- Retrospective, multi-centre cohort study (Europe, USA; 1987-2011): N=1,644 cT3a or cT3b-4 pts who underwent RP + PLND (median FU: 75 mo)



Long-term CSS after RP decreases with # primary risk factors at diagnosis, with SVI and/or GS ≥8 being the most adverse factors

Joniau S et al. Eur Urol 2013;12(1):e688 (abs.688)

What do the guidelines say?

RP + ePLND

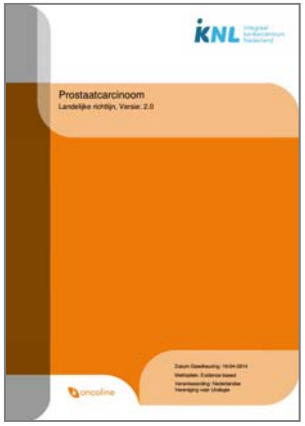
- **= reasonable treatment option for selected patients with high-risk PCa**

  if tumour is not fixed to the pelvic wall/adjacent organs and if no fixation of the urethral sphincer

- **= 1st step of multimodality approach in selected patients with very high-risk PCa**

- Given potential perioperative morbidity, minimal life expectancy:
  - EAU guidelines (2016): ≥10 yr
  - NCCN guidelines (2016): ≥10 yr
  - ESMO guidelines (2015): ≥5 yr

Wat zegt de NVU richtlijn?



- **RP = optie bij cT3 patiënten met:**
  - **Een lange levensverwachting EN**
  - **Een lage PSA EN**
  - **Een lage Gleason score EN**
  - **Zonder uitgebreide lokale tumor EN**
  - **Een negatief disseminatie onderzoek (cT3 M0)**
- Gebruik nomogrammen om de **kans** in te schatten op het vinden van **positieve lymfeklieren**:
  - Meestal grote kans bij patiënten met hoog-risico prostaatcarcinoom
  - Indien grote kans: **uitgebreide lymfeklierdissectie** is aangewezen
- RP: bij voorkeur uitgevoerd door een vast team in instellingen en met ≥ 20 procedures/jaar

PHNL/ZYT/0115/0002b(1)

Radiation therapy + short term hormone therapy

Patient profile:

- 64 yr old
  - PSA: 16 ng/mL
  - Prostate cancer Gleason sum: 4 + 3=7 (7/10 pos. cores, bilateral)
  - Imaging: MRI: T3a N0 M0; bone scan negative
- No comorbidities (life expectancy ≥5 yr)

Stemronde geopend

Radiotherapie: hoeveel gray tenminste volgens NVU richtlijn?

- 66 Gy
- 70 Gy
- 74 Gy
- 78 Gy

Is RT alone a valid treatment option for patients with high-risk PCa? (1)

– EBRT + short-term hormone therapy Hide evidence

Uncertain

Panel considerations

The panel considered the appropriateness of EBRT + short-term ADT (6 months) to be uncertain for most patients with high-risk PCa. The smaller survival benefit compared with long-term EBRT should be outweighed against the lower toxicity.

NVU richtlijn prostaatcarcinoom 2014

Volgens de NVU richtlijn is hoge dosis uitwendige radiotherapie (≥ 74 Gy) in combinatie met **langdurige** (≥ 2 jaar) gelijktijdige en adjuvante hormonale therapie de standaard behandeling voor patiënten met hoog-risico prostaatcarcinoom (cT2c-4 N0-1 M0). De richtlijn geeft ook aan dat RT bij voorkeur wordt gegeven in centra met minstens 20 behandelingen per jaar en dat het volume bestraald gezond weefsel zo laag mogelijk gehouden moet worden om het risico op late toxiciteit te beperken.

Bekijk de volledige richtlijn

Is RT alone a valid treatment option for patients with high-risk PCa? (2)

- EBRT monotherapy: disappointing success rate:
  - RTOG 86-10[1] (EBRT-alone arm): 5-yr BRFS: 10%
  - RTOG 85-31[2] (EBRT-alone arm): 5-yr BRFS: 21%

- But:
  Suboptimal radiation doses and techniques:
  65-70 Gy to prostate + 44-46 Gy to pelvic LNs

[1]Pilepich MV et al. Int J Radiat Oncol Biol Phys 2001;50:1243-52;
[2]Lawton CA et al. Int J Radiat Oncol Biol Phys 2001;49:937-46

Is RT alone a valid treatment option for patients with high-risk PCa? (2)

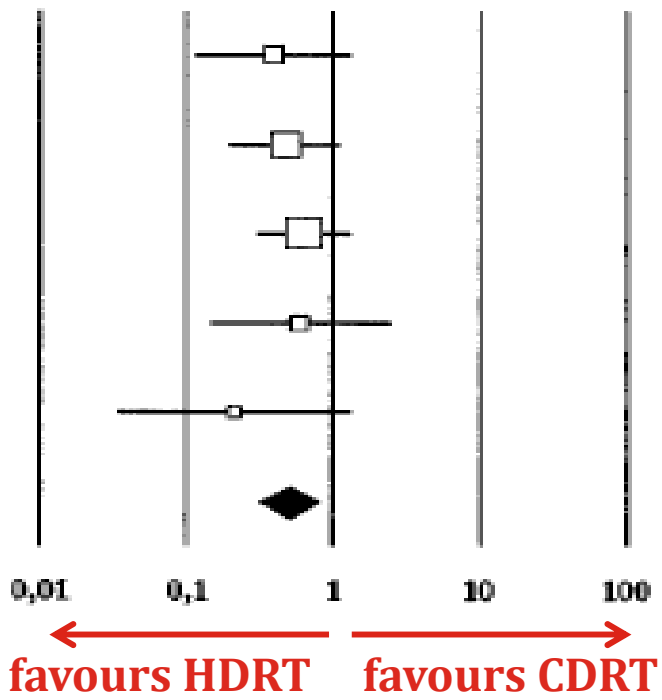
- Meta-analysis: 7 RCTs comparing conventional-dose RT (CDRT) with high-dose RT (HDRT) for localised PCa: N=2,812

High-risk PCa

	CDRT	HDRT
Zietman 2005 JAMA	70.2 Gy	79.2 Gy
Peeters STH 2006 JCO (Dutch)	68 Gy	78 Gy
Dearnaley DP 2007 Lancet Oncol (MRC RT01)	64 Gy	74 Gy
Kuban DA 2008 IJROBP (MD Anderson)	70 Gy	78 Gy
Sathya JR 2005 JCO	66 Gy	75 Gy

Overall: OR=0.603; P<0.001

OR (95% CI) for risk of biochemical failure



High RT doses to the prostate are key to achieve local control

Viani GA et al. Int J Radiat Oncol Biol Phys 2009;74:1405-18

Is there any benefit of adding (neo)adjuvant ADT to RT?

Stemronde geopend

1. Ja
2. Nee
3. Alleen neo-adjuvant
4. Alleen adjuvant

10

Is there any benefit of adding (neo)adjuvant ADT to RT? (1)

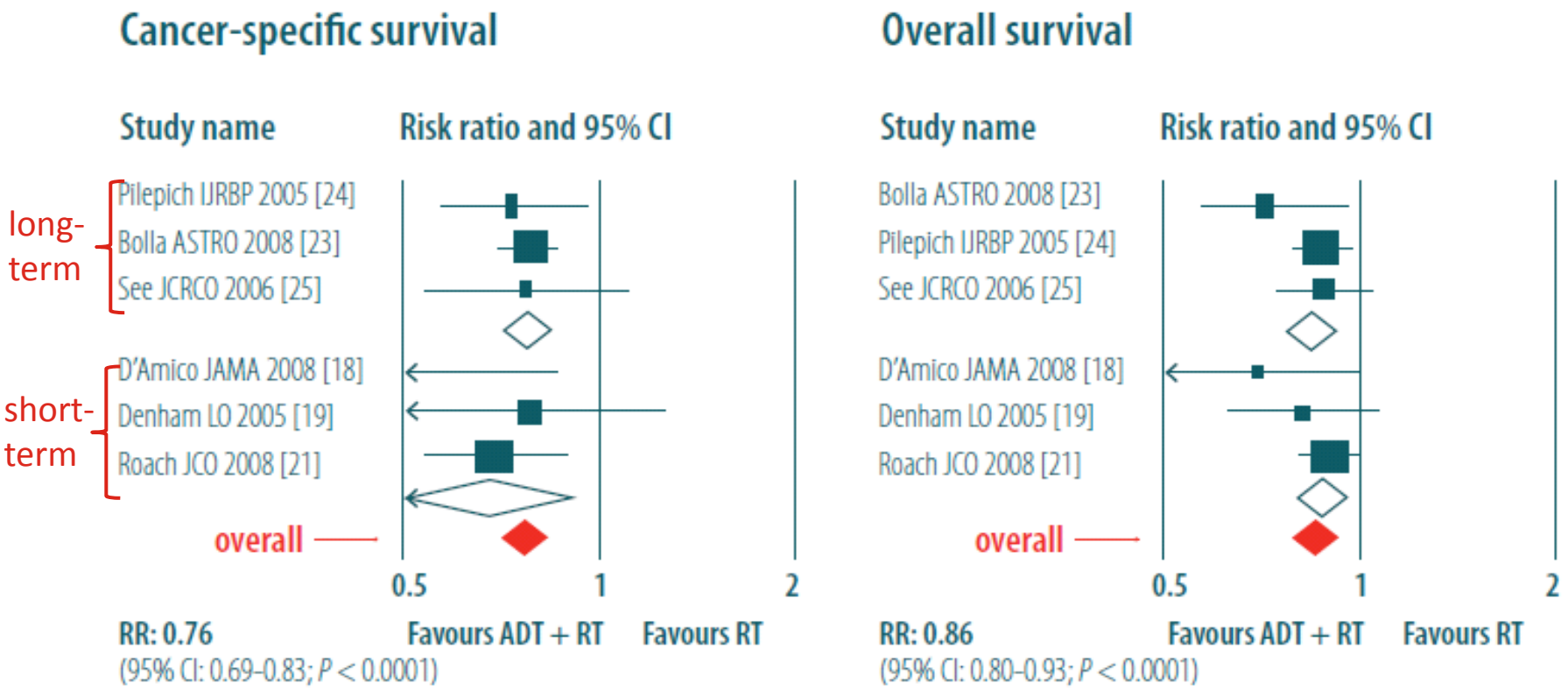
- **Meta-analysis:** 7 RCTs (N=4,387)

Suboptimal RT doses

Study	Population	N	RT dose	Median FU (yr)
Long-term adjuvant ADT				
RTOG 85-31 [24]	cT1-2 N1 Mo or cT3-4 N0-1 M0 or pT3 after RP	977	44-46 Gy to WP + 21-24 Gy boost to prostate	7.6
EORTC 22863 [23]	T1-2 grade 3 M0 or T3-4 N0-1 M0	415	50 Gy to WP + 20 Gy boost to prostate and SV	9.1
EPCP [25]	T1-4 Nx-1 M0	1,370	64 Gy	7.2
Short-term (neo)adjuvant/concomitant ADT				
[18]	cT1b-2b N0 M0 and PSA >10 ng/mL, GS 7-10 or radiographic evidence of extraprostatic disease	206	3D-CRT	7.6
TTROG 96-01 [19]	T2b-4 N0 M0	818	66 Gy to prostate and SV	5.9
RTOG 86-10 [21]	T2-4 N0-x M0	456	44-46 Gy to WP + 21-24 Gy boost to prostate	12.6

Bria E et al. Cancer 2009;115:3446-56

Is there any benefit of adding (neo)adjuvant ADT to RT? (2)



Compared with RT alone, RT + (neo)adjuvant ADT decreases risk of death from PCa by 24% and risk of death by any cause by 14%

Bria E et al. Cancer 2009;115:3446-56

PHNL/

Radiation therapy + long term hormone therapy

Is there any benefit of adding (neo)adjuvant ADT to RT? (3)

- Compared with RT, RT + ADT decreases risk of:
  - Biochemical failure by 24%
  - Clinical progression by 19%
  - Local relapse by 36%
  - Distant metastases by 28%

Compared with RT alone, RT + (neo)adjuvant ADT improves oncological outcomes, while not significantly affecting grade 3/4 toxicity or cardiac death

Bria E et al. Cancer 2009;115:3446-56

Are these results still valid in contemporary RT settings?

High RT doses to the prostate are key to achieve local control

Recommended doses for high-risk patients:

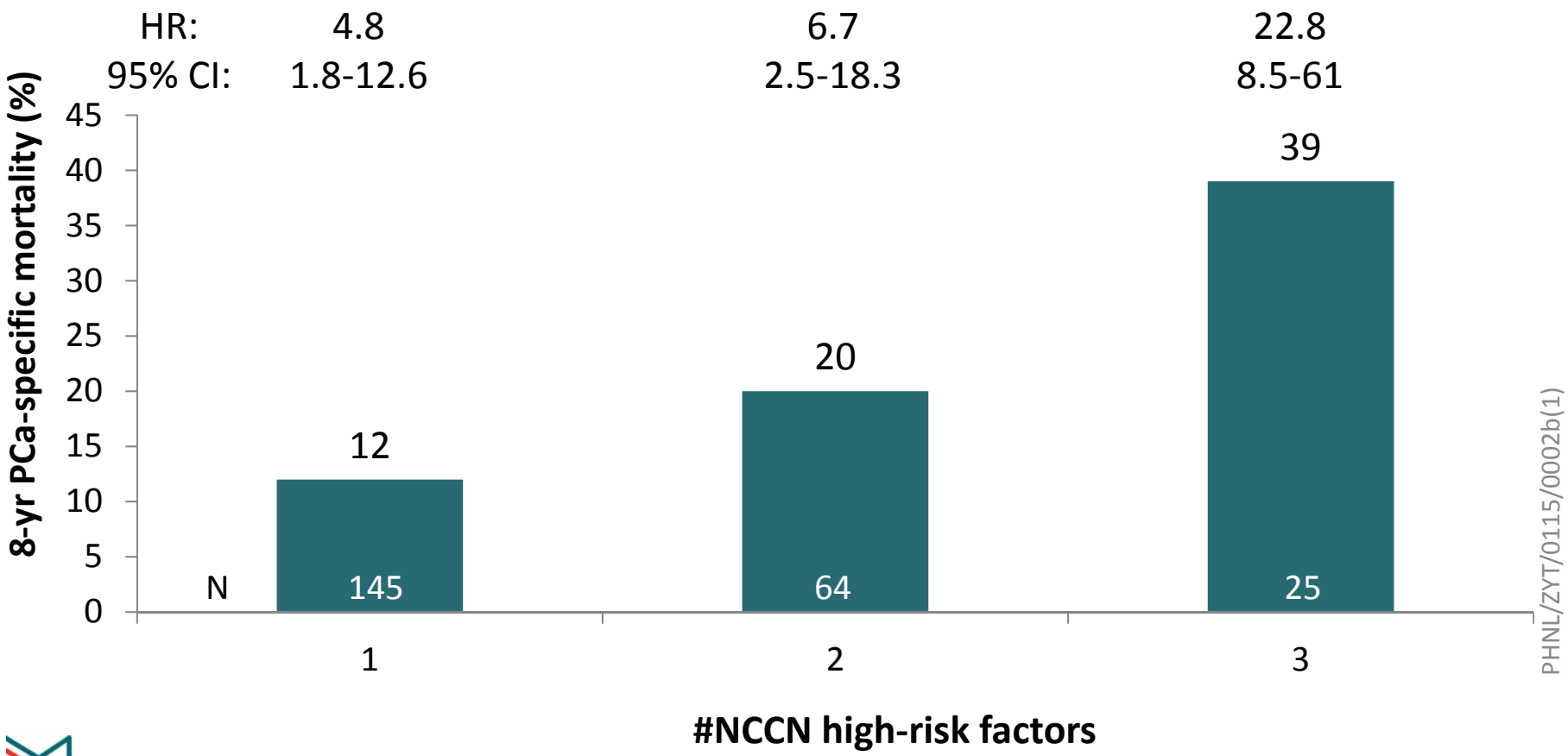
- **EAU guidelines (2016)/ESMO guidelines (2015): ≥74 Gy**
- **NCCN guidelines (2016): doses up to 81.0 Gy**

⇒ New RCTs needed to reinvestigate benefit of RT ± (neo)adjuvant ADT in contemporary RT settings (IMRT/IGRT, stereotactic body RT, dose-escalated 3D-CRT, HDR-BT, etc.) using adequate doses for patients with high-risk PCa

[1]Pilepich MV et al. Int J Radiat Oncol Biol Phys 2001;50:1243-52;
[2]Lawton CA et al. Int J Radiat Oncol Biol Phys 2001;49:937-46

Do all patients with high-risk PCa equally benefit from RT ± ADT? (1)

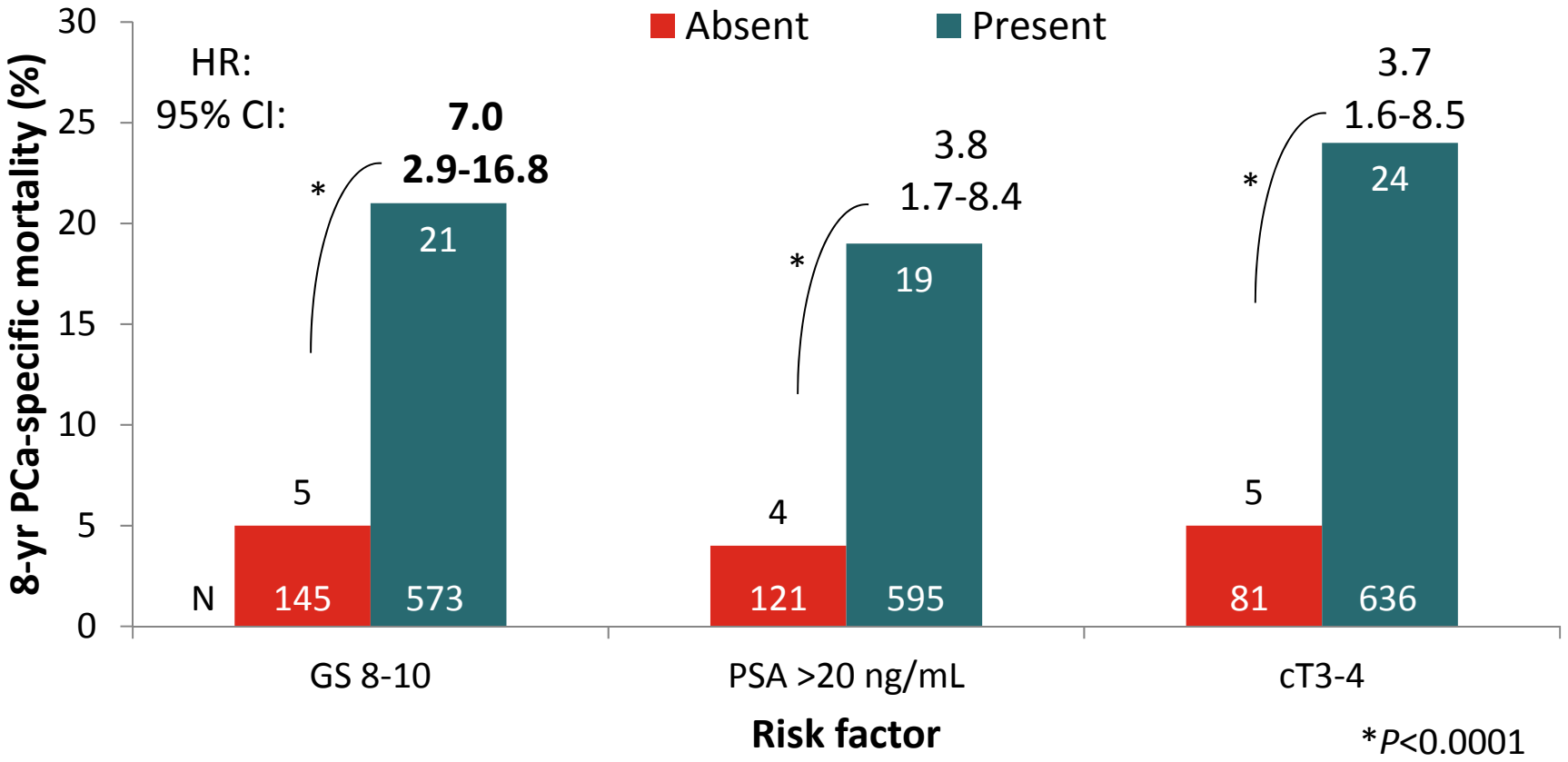
- Retrospective analysis (USA, 1998-2008):
  718 PCa patients treated with EBRT (≥75 Gy) ± ADT; median FU: 69 months



PHNL/ZYT/0115/0002b(1)

Stenmark MH et al. Int J Radiat Oncol Biol Phys 2011;81:e335-44

Do all patients with high-risk PCa equally benefit from RT ± ADT?



Long-term CSS after EBRT ± ADT decreases with # primary risk factors at diagnosis, with GS ≥8 being the most adverse factor

Stenmark MH et al. Int J Radiat Oncol Biol Phys 2011;81:e335-44

What is the optimal duration of adjuvant ADT to RT?

Stemronde geopend

1. 6 maanden
2. 12 maanden
3. 18 maanden
4. 24 maanden
5. 36 maanden

10

What is the optimal duration of adjuvant ADT to RT? (1)

– EBRT + short-term hormone therapy Hide evidence

Uncertain

Panel considerations

The panel considered the appropriateness of EBRT + short-term ADT (6 months) to be uncertain for most patients with high-risk PCa. The smaller survival benefit compared with long-term EBRT should be outweighed against the lower toxicity.

– EBRT + long-term hormone therapy Hide evidence

Appropriate

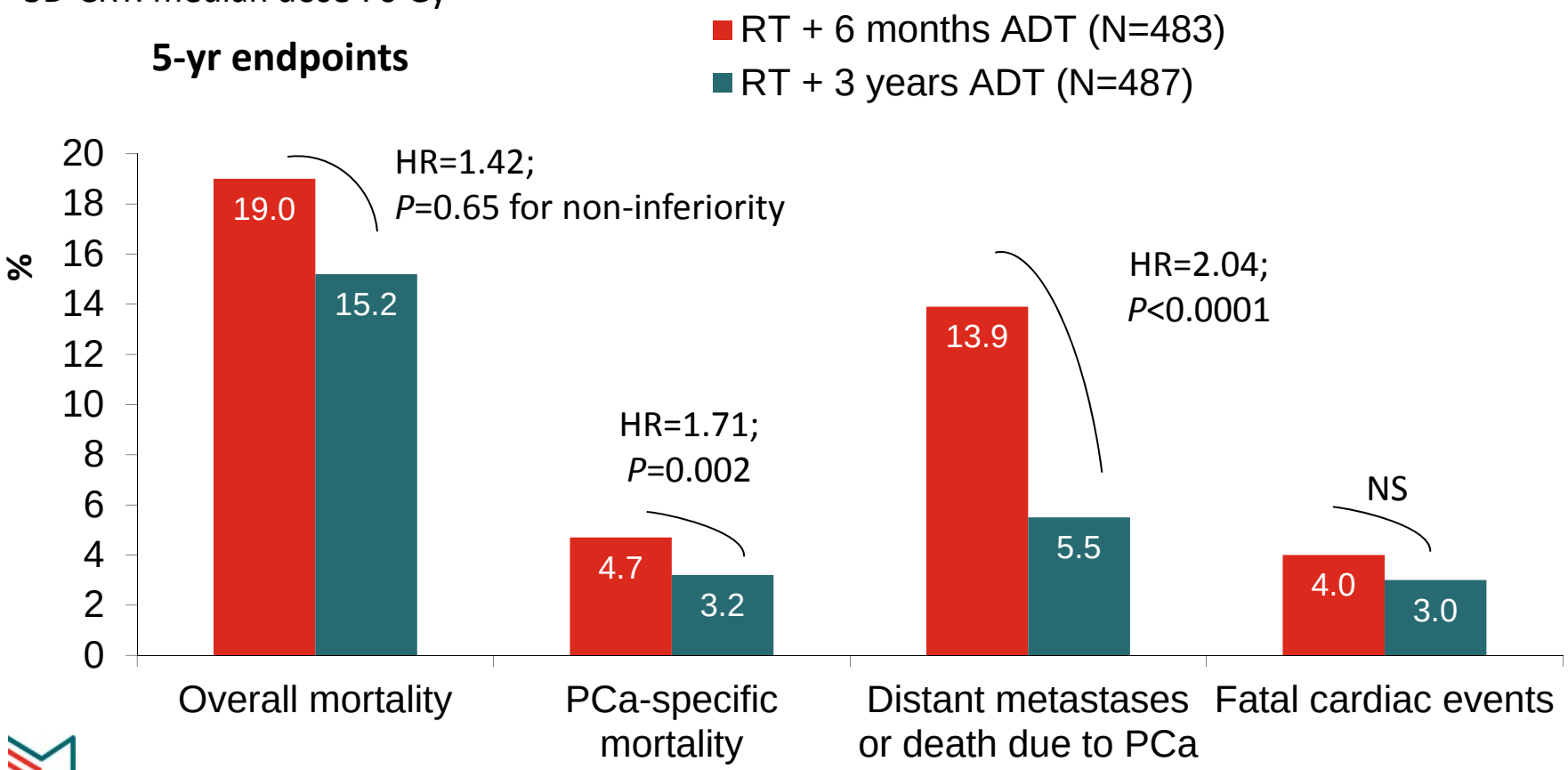
Panel considerations

The panel considered EBRT + long-term ADT (2-3 years) to be an appropriate option for all patients with a life expectancy ≥ 5 years.

What is the optimal duration of adjuvant ADT to RT? (2)

EORTC 22961 non-inferiority trial: N=970 men with locally advanced PCa (T1c-T2b N1-2 or pN1-2 M0 or T2c-T4 cN0-2 M0 with PSA <150 ng/mL); median FU: 6.4 yr; 3D-CRT: median dose 70 Gy

5-yr endpoints

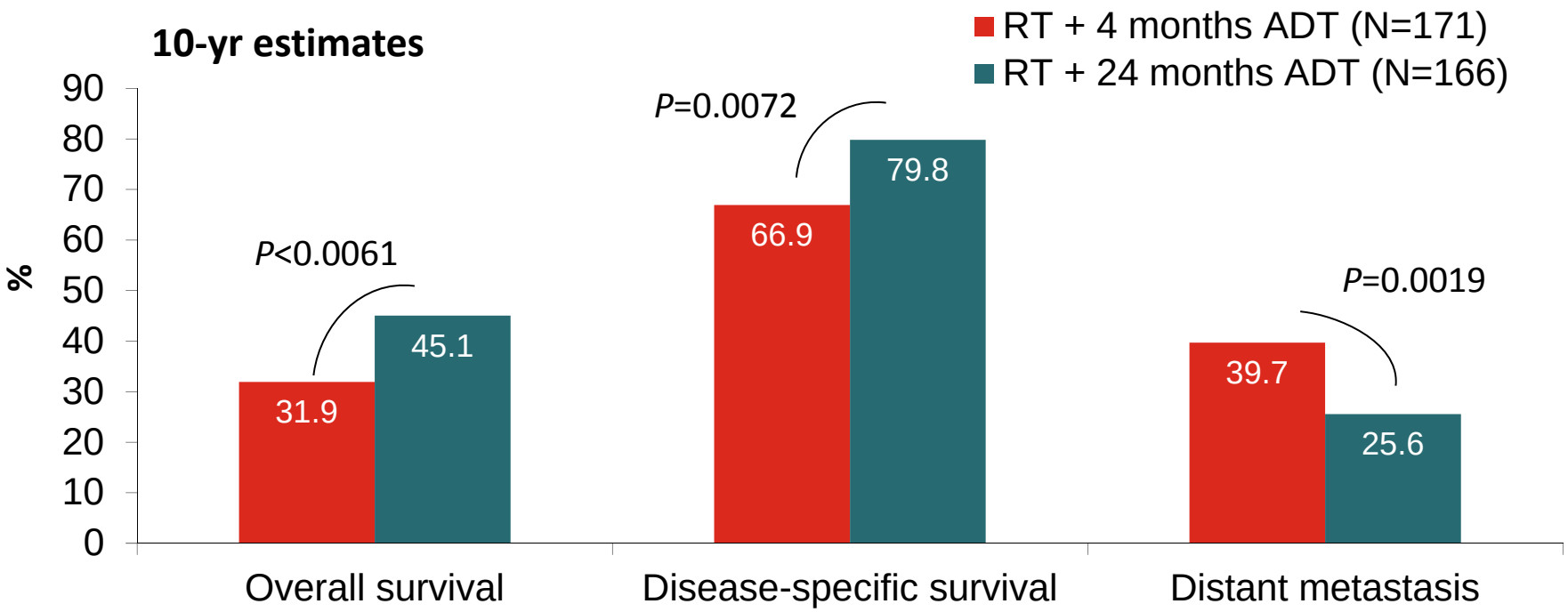


PHNL/ZYT/0115/0002b(1)

Bolla M et al. NEJM 2009;360:2516-27

What is the optimal duration of adjuvant ADT to RT? (2)

RTOG 92-02 trial: N=1,554 patients with T2c-T4 N0/Nx PCa, Gleason 8-10 and PSA <150 ng/mL; median FU: 11.3 yr; 46 Gy to pelvic nodes / 65-70 Gy to prostate



Long-term adjuvant ADT (2-3 yr) to RT significantly improves survival compared with short-term ADT (4 months)

Horwitz EM et al. J Clin Oncol 2008;26:2497-504

What is the optimal duration of adjuvant ADT to RT?

Stemronde geopend

1. 6 maanden
2. 12 maanden
3. 18 maanden
4. 24 maanden
5. 36 maanden

10

What do the guidelines say?

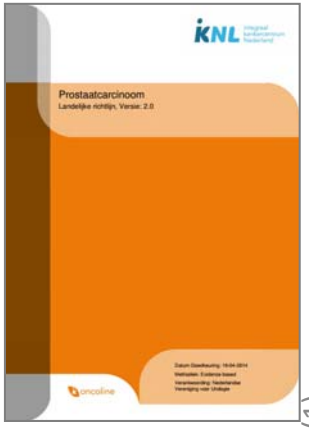
RT + long-term ADT
= standard treatment option
for all patients with high-risk PCa

- Recommended duration of ADT:
  - EAU guidelines (2016): 2-3 yr
  - NCCN guidelines (2016): 2-3 yr
  - ESMO guidelines (2015): ≥2 yr

- Restrictions: Minimal life expectancy:
  - EAU guidelines (2016): >5-10 yr
  - NCCN guidelines (2016): >5 yr / only if bulky T3-4 or GS ≥8 and complications (e.g. hydronephrosis, metastatis) may be expected within 5 yr: ≤5 yr
  - ESMO guidelines (2015): >5 yr

Wat zegt de NVU richtlijn?

RT + langdurige gelijktijdige en adjuvante ADT = standaard behandeling voor patiënten met hoog-risico prostaatcarcinoom



- Aanbevolen dosering van RT: ≥74 Gy
- Aanbevolen duur van ADT: ≥ 2 yr
- Opmerkingen:
  - Bij voorkeur gegeven in centra met ≥ 20 behandelingen/jaar
  - Volume bestraald gezond weefsel moet zo laag mogelijk gehouden om het risico op late toxiciteit te beperken

Hormone therapy

Is ADT alone a valid treatment option for patients with high-risk PCa?

Hormone therapy alone

Hide evidence

Inappropriate

Panel considerations

Hormone therapy (ADT) alone was considered inappropriate for all patients with high-risk PCa in this study population.

What do the guidelines say?

- **EAU (2016), NCCN(2016) and ESMO (2015) guidelines:**

In patients with high-risk PCa who are fit enough to receive local treatment, ADT alone is inappropriate

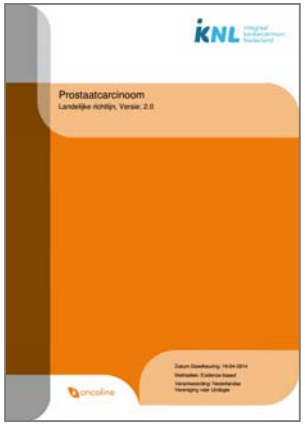
Primary ADT is only recommended as monotherapy for selected patients with (very) high-risk PCa who are unfit for or unwilling to undergo local treatment

- EORTC 30891 subanalysis[1] (pts unsuitable for local curative Tx): Timing of ADT initiation guided by baseline PSA and/or PSA-DT:

If baseline PSA >50 ng/mL and/or PSA-DT <12 months:
Increased risk of cancer-specific mortality
→ potential benefit from immediate ADT

[1]Studer UE et al. Eur Urol 2007;53:941-9

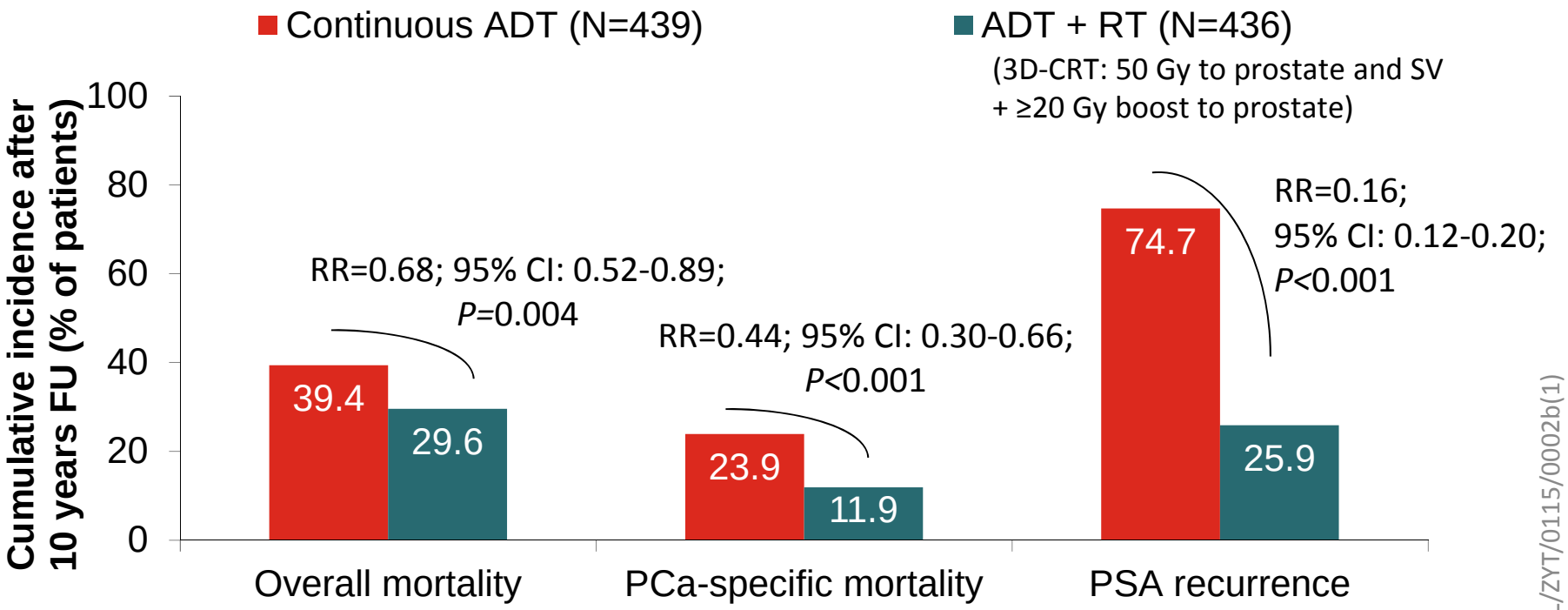
Wat zegt de NVU richtlijn?



- **ADT is niet aan te raden als primaire therapie voor cT3 patiënten, behalve voor:**
  - **Patiënten die geen curatieve behandeling willen ondergaan**
  - **Patiënten met contra-indicaties voor curatieve behandeling**
  - **Patiënten met een korte levensverwachting en lage Gleason score**
- Informeer de patiënt over de bijwerkingen van langdurige ADT
- Wanneer ADT opstarten?
  - Bij voorkeur initieel afwachtend beleid: start ADT enkel in geval van symptomatische progressie (klachten, botmetastasen, enz.)
  - Uitzondering: patiënten met een initiële PSA > 50 ng/mL + PSA-DT < 12 maanden: onmiddellijke start van ADT

Is there any benefit of adding (neo)adjuvant RT to ADT? (1)

SPCG-7/SFUO-3 (Scandinavia; 1996-2002): N=875 patients with T1b-2G2-3 or T3 N0 M0 (78%); median FU: 7.6 yr

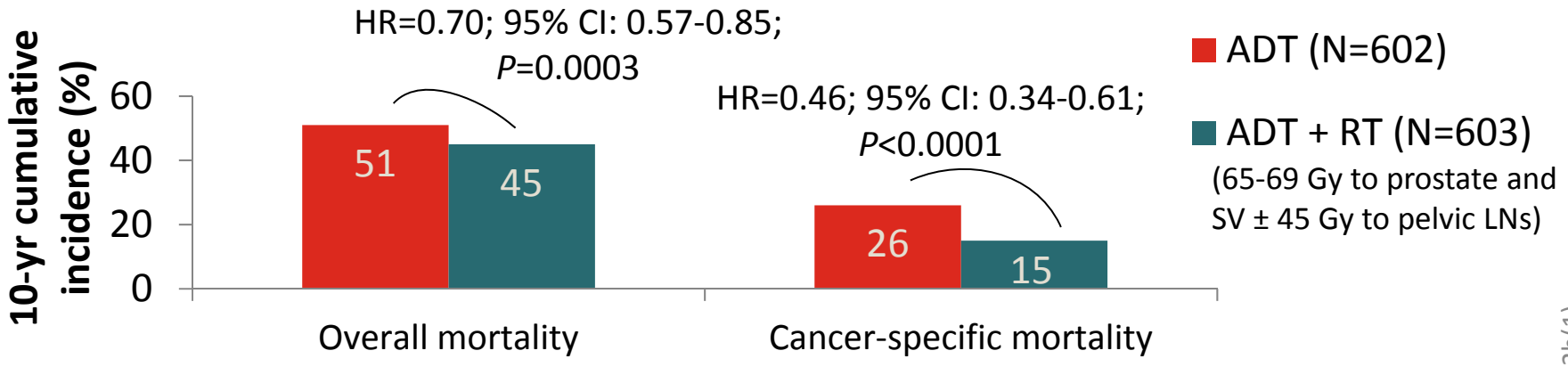


- 5-yr FU: significantly more patients with urinary incontinence, urgency, urethral stricture or erectile dysfunction in ADT + RT group than in ADT alone group

Widmark A et al. Lancet 2009;373:301-8

Is there any benefit of adding (neo)adjuvant RT to ADT? (2)

PR3/PR07: Multi-centre RCT; N=1,205 pts with locally advanced (N=1,057; T3-4 N0-x) or organ-confined PCa (N=144; T2 N0-x with either PSA >40 ng/mL or PSA >20 ng/mL + GS ≥8); median FU: 8.0 yr



Late gastrointestinal toxicity	ADT	ADT + RT	*P*
>grade II proctitis	0.3%	1.0%	0.54
EORTC rectal symptoms (mean change)	-0.3	1.7	0.54

Addition of RT to ADT improves CSS and OS compared with ADT alone in patients with high-risk PCa, with only a minimal increase in late toxicity

Warde P et al. Lancet 2011;378:2104-11; Mason MD et al. J Clin Oncol 2012;30(Suppl 15):279s (abs.4509s)

Patient profile:

- 64 yr old
  - PSA: 16 ng/mL
  - Prostate cancer Gleason sum: 4 + 3=7 (7/10 pos. cores, bilateral)
  - Imaging: MRI: T3a N0 M0; bone scan negative
- No comorbidities (life expectancy ≥5 yr)

Multidisciplinary discussion

- You have 2 minutes time to reconsider your decision

Stemronde geopend

Treatment options?

1. Surgery
2. EBRT + short-term hormone therapy
3. EBRT + long-term hormone therapy
4. Hormone therapy alone

Patient case 1 (continued)

PHNL/ZYT/0115/0002b(1)

Patient case 1 (continued)

- 64 yr old, retired teacher
- Yearly check-up, including PSA screening
- Elevated PSA in October 2014: 14 ng/mL
- PCa diagnosed in November 2014:
  - PSA: 16 ng/mL
  - Gleason sum: 4 + 3 (7/10 pos. cores, bilateral)
  - Imaging: MRI: T3a N0 M0; bone scan negative
- No comorbidities (life expectancy ≥5 yr)
- **After MDT consult: RP + ePLND is chosen**
- **Positive LNs found during ePLND**

Should RP be continued or stopped?

Stemronde geopend

Should RP be continued or stopped?

1. Continued
2. Stopped

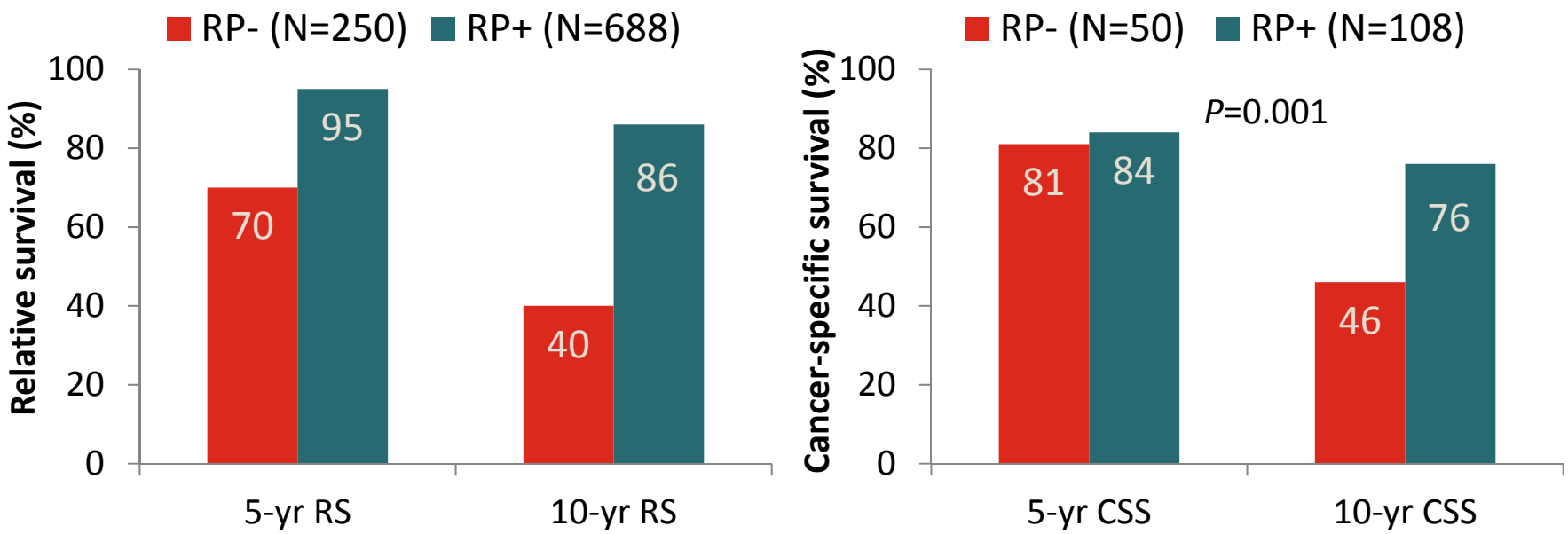
10

If positive LNs would be found during ePLND, should RP be continued or stopped?

- 2 retrospective analyses in men with N+ PCa:

Munich Cancer Registry (1988-2007)[1]
Median FU: 5.6 yr

Single-institution study (1992-2004)[2]
Median FU: 8.2 yr



If positive LNs are found during ePLND, RP should not be abandoned, since patients still benefit from removal of the primary tumour

[1]Engel J et al. Eur Urol 2010;57:754-61; [2]Steuber T et al. BJU Int 2010;107:1755-61

Patient case 1 (continued)

- 64 yr old, retired teacher
- Yearly check-up, including PSA screening
- Elevated PSA in October 2014: 14 ng/mL
- PCa diagnosed in November 2014:
  - PSA: 16 ng/mL
  - Gleason sum: 4 + 3 (7/10 pos. cores, bilateral)
  - Imaging: MRI: T3a N0 M0; bone scan negative
- No comorbidities (life expectancy ≥5 yr)
- **After MDT consult: RP + ePLND is chosen**
- **Pos. LNs found during ePLND**

Would this patient benefit from (neo)adjuvant ADT?

Would this patient benefit from (neo)adjuvant ADT?

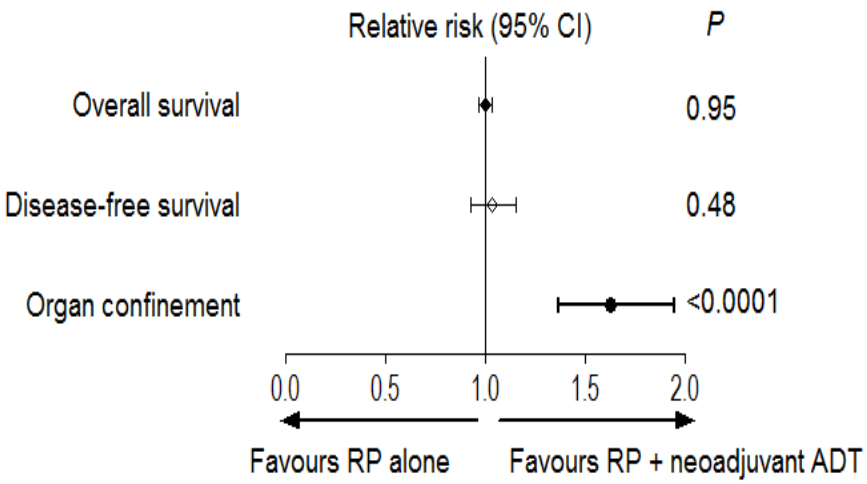
Stemronde geopend

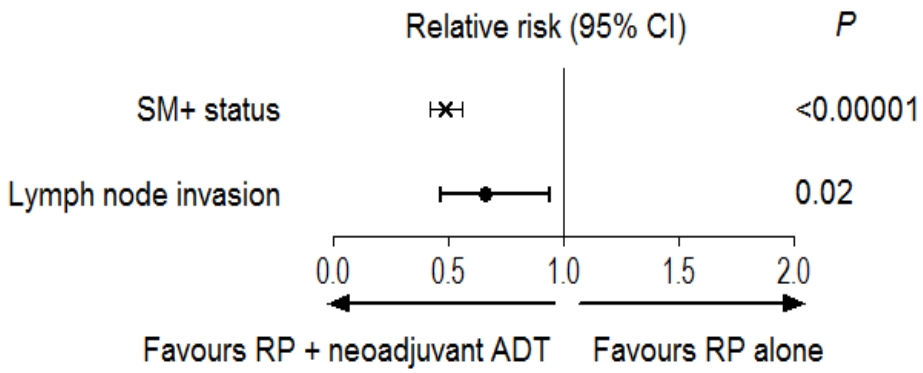
1. Ja
2. Nee

10

Would this patient benefit from addition of neoadjuvant ADT to RP?

- Systematic review and meta-analysis:
  10 RCTs of neoadjuvant ADT prior to RP in pts with T1-3 N0-1 M0 PCa





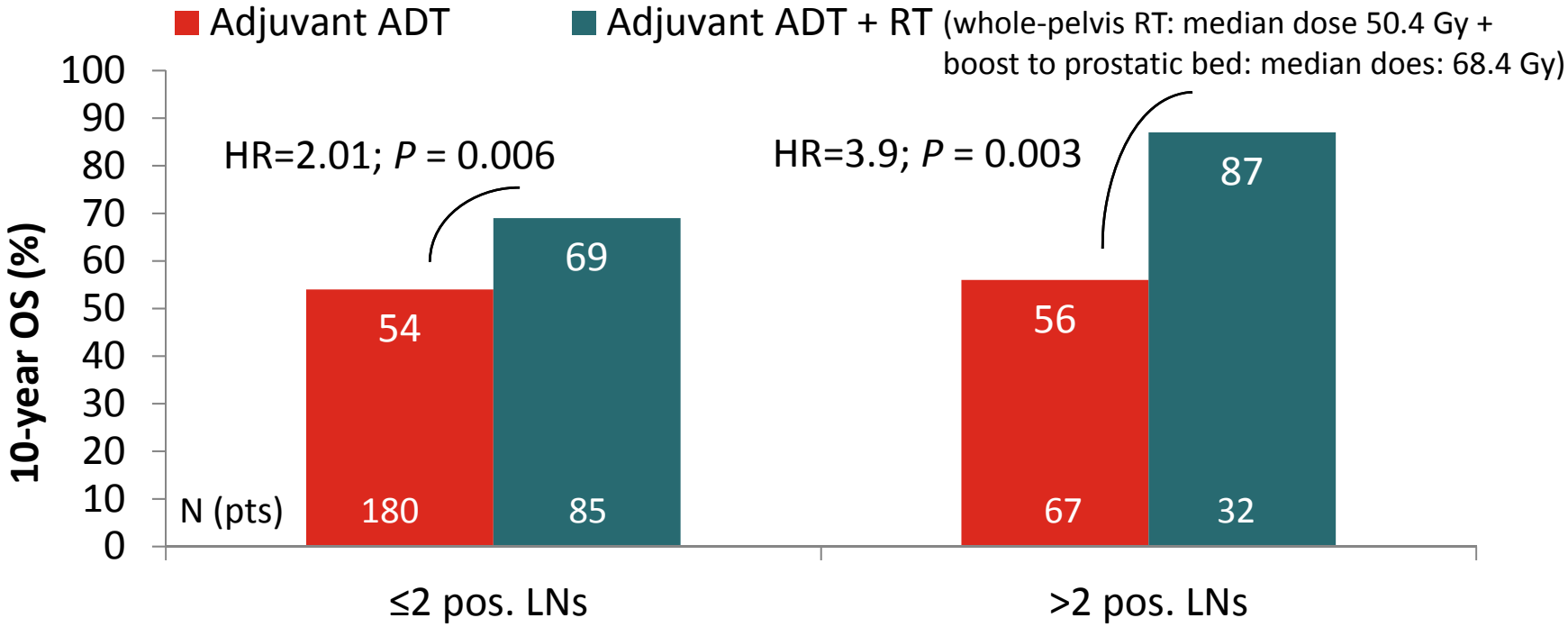
- Additional studies needed to investigate impact of new hormonal agents (e.g. abiraterone acetate) on OS and CSS when added as neoadjuvant therapy before RP

Neoadjuvant ADT before RP does not significantly improve OS or CSS

Shelley MD et al. Cancer Treat Rev 2009;35:9-17

Would this patient benefit from addition of adjuvant ADT ± RT to RP?

- Retrospective, match-controlled study (1986-2002): N=703 pT2-4 pN1 patients who underwent RP + PLND; mean FU: 8.4 yr



Adjuvant ADT + RT seems to improve survival in pT2-4 pN1 pts, regardless the extent of nodal invasion, but confirmation from RCTs is needed

Briganti A et al. Eur Urol 2011;59:832-40

What do the guidelines say?

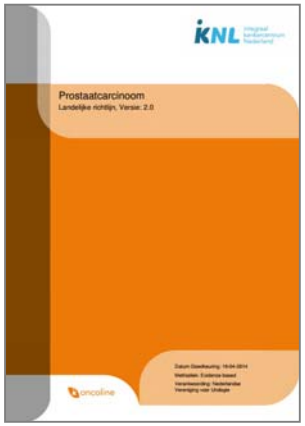
- Addition of ADT to RP has only been shown to improve OS in N+ patients in 1 RCT (i.e. ECOG 3886 trial[1];USA 1988-1993), but "the results may not apply to current patients" (ESMO 2015)

- **Recommendations for N+ patients at RP:**
  - **EAU guidelines (2016): Adjuvant ADT ± RT is optional;**
    Observation + delayed start of ADT in pts with rising PSA is acceptable in selected cases
  - **NCCN guidelines (2016):**
    Adjuvant ADT ± pelvic RT or observation until detectable PSA
  - **ESMO guidelines (2015):**
    If high risk of progression: immediate adjuvant ADT;
    RT added to ADT is not standard treatment but may be considered in selected cases

[1]Messing EM et al. Lancet Oncol 2006;7:472-9

Wat zegt de NVU richtlijn?

- **N+ patiënten na RP:**
  - **ADT + RP dient overwogen te worden per casus in multidisciplinair team**
  - ADT + RP is geen optie als er grote kans is dat patiënt al verder gemetastaseerd is



Key messages (1/3): Surgery

- Retrospective studies have shown good long-term outcomes for RP in patients with (very) high-risk non-metastatic PCa
- Therefore, RP is considered as a reasonable treatment option in selected patients with high-risk PCa, and as a first step of a multimodal approach in selected patients with very high-risk PCa
- If RP is performed, it must be combined with ePLND
- Since removal of the primary tumour was shown to provide survival benefit in N+ patients, RP should not be abandoned if positive LNs are found at RP

PHNL/ZYT/0115/0002b(1)

Key messages (2/3): Radiation therapy

- High radiation doses to the prostate are key to achieve local control. Several techniques are now available to achieve this goal (EBRT + HDR-BT, IMRT/IGRT, dose-escalated 3D-CRT, etc.)
- Addition of ADT to RT significantly improves OS and CSS compared with RT alone in patients with high-risk PCa, without significantly increasing toxicity
- Long-term adjuvant ADT (2-3 yr) to RT significantly improves survival compared with short-term ADT (6 months)
- Therefore, RT combined with long-term ADT is considered as a standard treatment option for all patients with high-risk PCa and a life expectancy >5-10 yr

Key messages (3/3) : Hormone therapy

- ADT is only recommended as a monotherapy in selected patients with (very) high-risk PCa who are unfit for local treatment

Thank you!