Programma Mirrors of Medicine

- 00.00 uur: Ontvangst
- 00.00 uur: **<u>Module 4</u> Biochemical recurrence**
  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

- *"Translating scientific evidence into everyday practice"*

- Developed 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

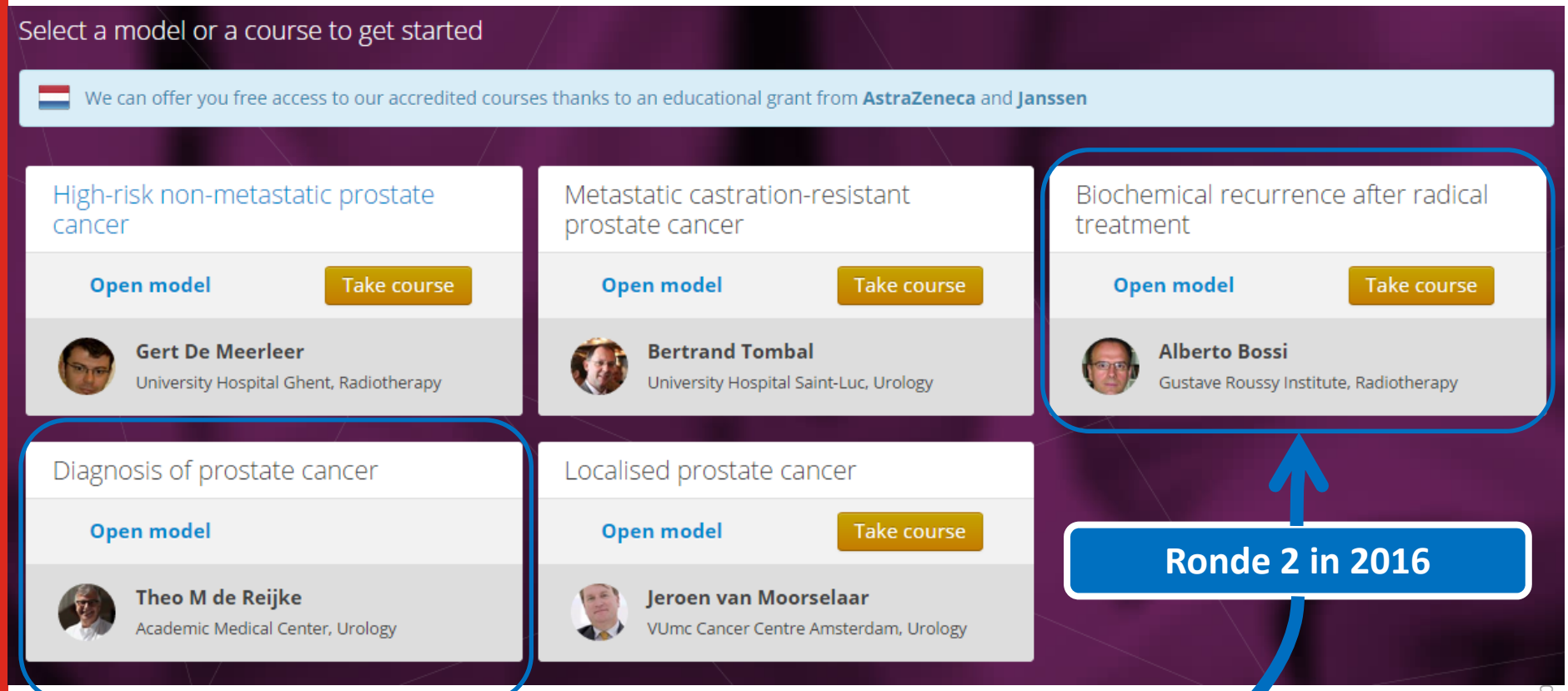
- Focus on education and research in uro-oncology (starting PCa)
  - Urologists
  - Oncologists
  - Radiation oncologists

Mirrors of Medicine models

- **Five prostate cancer modules**
  - **High risk M0, mCRPC, Localised, Biochemical recurrence, Diagnosis**
- Treatment recommendations for hundreds of different profiles
  - Updated every 6 months with evidence and guidelines
- 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]

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.

Mirrors of Medicine



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

PHNL/ZYT/0115/0002b

PHNL/ZYT/0

Mirrors of medicine is..

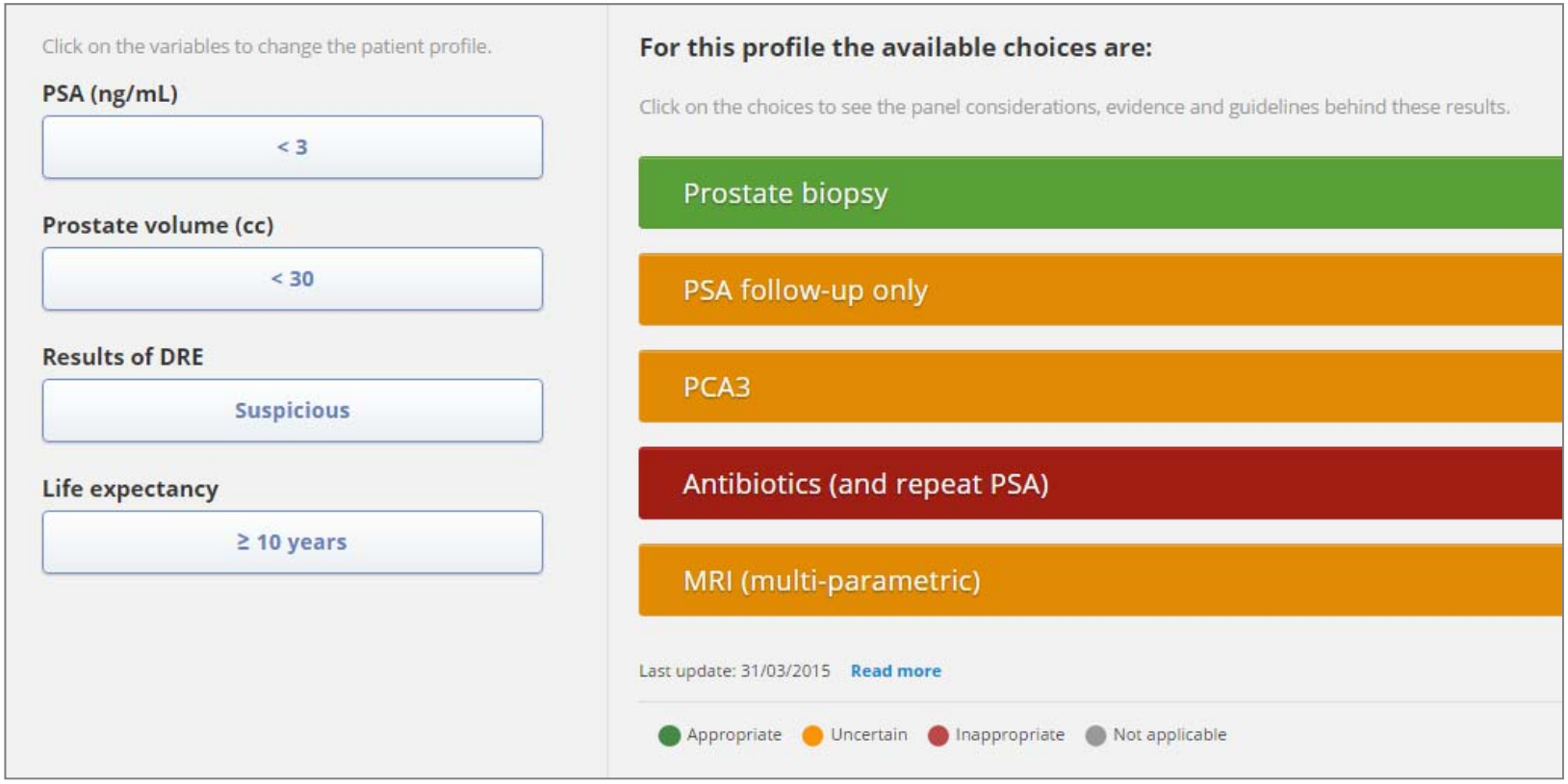
selecting a patient profile…..

see panel recommendations…..

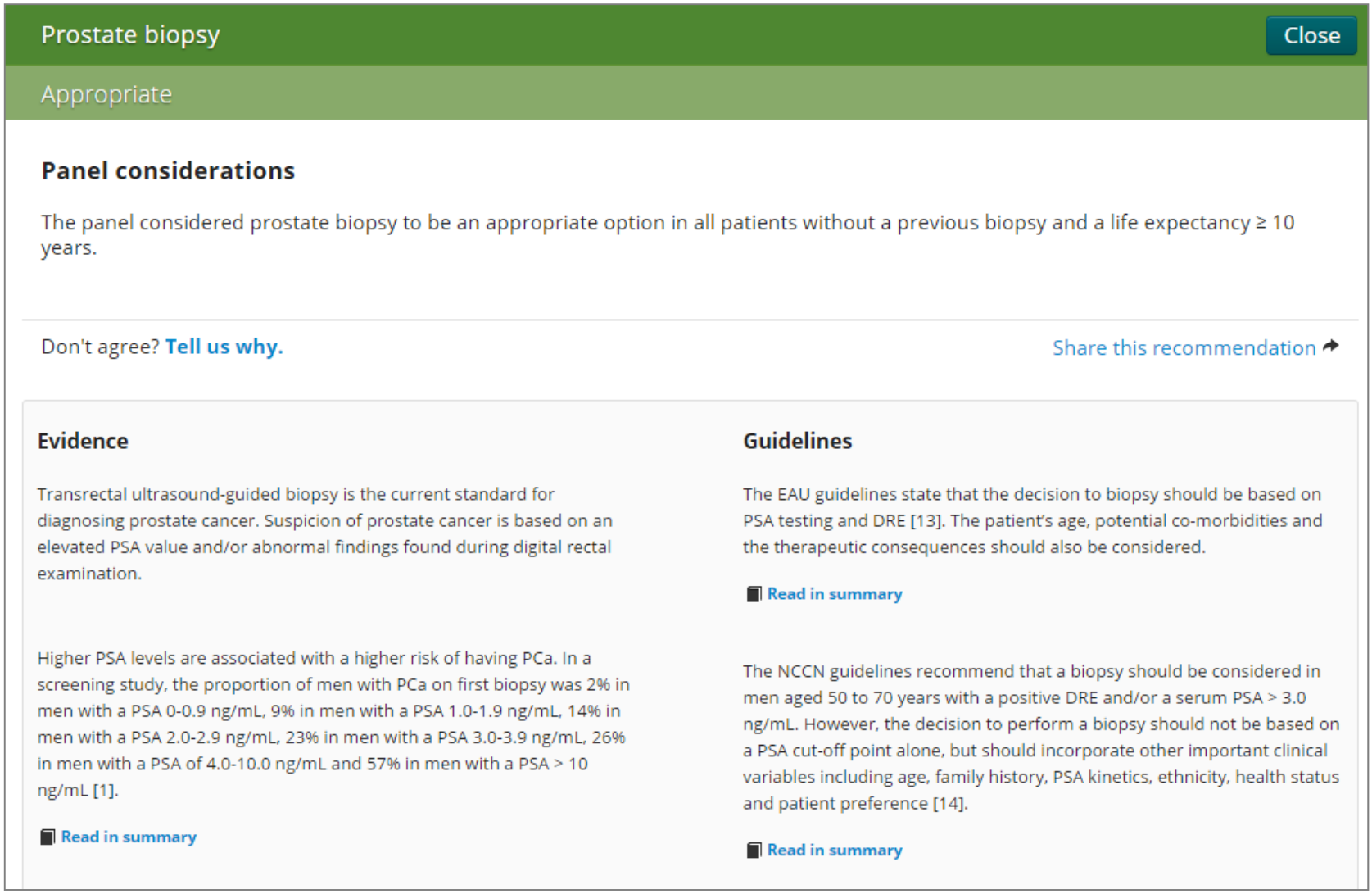
and an overview of underlying evidence + guidelines

Selecting a profile

see panel recommendations……



… with underlying evidence and guidelines



Prostate biopsy

Close

Appropriate

Panel considerations

The panel considered prostate biopsy to be an appropriate option in all patients without a previous biopsy and a life expectancy ≥ 10 years.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

Transrectal ultrasound-guided biopsy is the current standard for diagnosing prostate cancer. Suspicion of prostate cancer is based on an elevated PSA value and/or abnormal findings found during digital rectal examination.

Higher PSA levels are associated with a higher risk of having PCa. In a screening study, the proportion of men with PCa on first biopsy was 2% in men with a PSA 0-0.9 ng/mL, 9% in men with a PSA 1.0-1.9 ng/mL, 14% in men with a PSA 2.0-2.9 ng/mL, 23% in men with a PSA 3.0-3.9 ng/mL, 26% in men with a PSA of 4.0-10.0 ng/mL and 57% in men with a PSA > 10 ng/mL [1].

Read in summary

Guidelines

The EAU guidelines state that the decision to biopsy should be based on PSA testing and DRE [13]. The patient's age, potential co-morbidities and the therapeutic consequences should also be considered.

Read in summary

The NCCN guidelines recommend that a biopsy should be considered in men aged 50 to 70 years with a positive DRE and/or a serum PSA > 3.0 ng/mL. However, the decision to perform a biopsy should not be based on a PSA cut-off point alone, but should incorporate other important clinical variables including age, family history, PSA kinetics, ethnicity, health status and patient preference [14].

Read in summary

PHNL/ZYT/0115/0002h(1)

… and all references

References

1. Postma R, Schröder FH. Screening for prostate cancer. Eur J Cancer 2005;41:825-33.
2. Harvey P, Basuita A, Endersby D, et al. A systematic review of the diagnostic accuracy of prostate specific antigen. MBC Urology 2009;9:14.
3. Partin AW, Yoo J, Carter HB, et al. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol 1993;150:110-4.
4. Partin AW, Carter HB, Chan DW, et al. Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. J Urol 1990;143:747-52.
5. Sajadi KP, Kim T, Terris MK, et al. High yield of saturation prostate biopsy for patients with previous negative biopsies and small prostates. Urology 2007;70:691-5.
6. Briganti A, Chun FKH, Suardi N, et al. Prostate volume and adverse prostate cancer features: fact not artifact. Eur J Cancer 2007;43:2669-77.
7. Okotie OT, Roehl KA, Han M, et al. Characteristics of prostate cancer detected by digital rectal examination only. Urology 2007;70:1117-20.
8. Richie JP, Catalona WJ, Ahmann FR, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology 1993;42:365-74.
9. Schröder FH, van der Maas P, Beemsterboer P, et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 1998;90:1817-23.
10. Smith DS, Catalona WJ. Interexaminer variability of digital rectal examination in detecting prostate cancer. Urology 1995;45:70-4.

… and NVU guideline for Dutch participants

NVU richtlijn prostaatcarcinoom 2014

De NVU richtlijn geeft aan dat klinische factoren zoals leeftijd (comorbiditeit), het rectaal toucher en in het bijzonder de aanwezigheid van BPH moeten worden meegenomen in de beslissing over het nemen van prostaatbiopten bij mannen met een PSA ≥ 3.0 ng/mL.
Het is aannemelijk dat risicowijzers en nomogrammen de efficiëntie van de besluitvorming tot het nemen van prostaatbiopten op basis van de PSA test verbeteren. Een voorwaarde is dat het model informatie bevat over het prostaatvolume en het model met acceptabel resultaat is gevalideerd.

Bekijk de volledige richtlijn

All European MoM 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
- Bertrand Tombal
- **Bradley Pieters**
- Christophe Massard
- Dominik Berthold
- Filip Ameye
- François Cornud
- Frédéric Lecouvet
- Geert Villeirs
- Gert De Meerleer
- Hein Van Poppel
- **Inge van Oort**
- **Jack Schalken**
- Jacques Irani
- James Eastham
- **Jelle Barentsz**
- **Jeroen van Moorselaar**
- Joaquim Bellmunt
- Jochen Walz
- Johan Braeckman
- Jonas Hugosson
- **Jorg Oddens**
- Jörg Schröder
- Karim Fizazi
- Karin Haustermans
- Malcolm Mason
- **Marco van Vulpen**
- Maria De Santis
- Mark Speakman
- Markus Graefen
- Martin Spahn
- Mesut Remzi
- **Monique Roobol**
- Nicholas Van As
- Nicolas Mottet
- Noel Clarke
- Paolo Gontero
- **Paul Kil**
- Paul Perrin
- Piet Ost
- Scott Eggener
- Sergio Villa
- Srinivas Samavedi
- Steven Joniau
- **Theo de Reijke**
- Thomas Wiegel
- Vincent Khoo
- Vip Patel
- Xavier Maldonado

Panel - BCR

Chair

Alberto Bossi
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View biography

Model

Panel

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Registration

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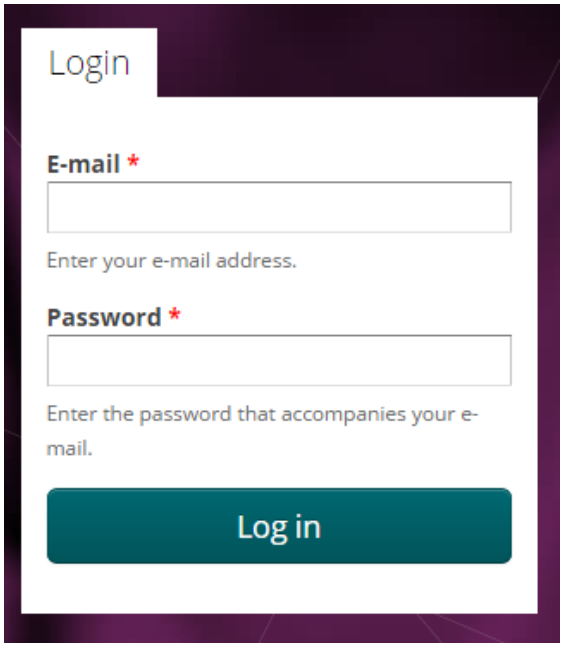
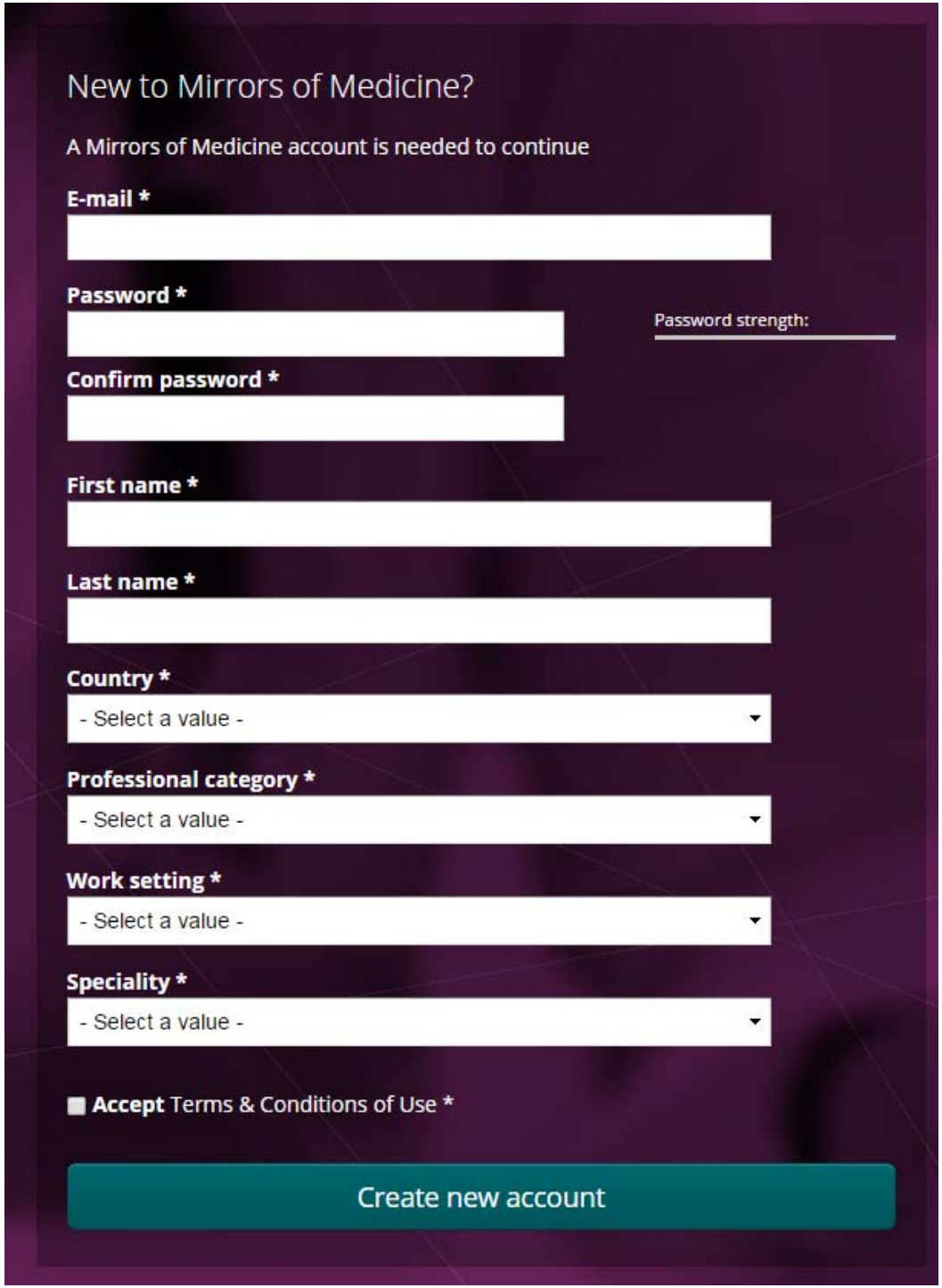




Stemronde geopend

Wie zijn er aanwezig?

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

CME accredited educational module

Biochemical recurrence after radical treatment

PHNL/ZYT/0115/0002h(1)

Mirrors of medicine

April 2016

Select a module and compose a patient profile

- Diagnosis of prostate cancer
- Localised prostate cancer
- High-risk non-metastatic prostate cancer
- Biochemical recurrence after radical treatment
- Metastatic castration-resistant prostate cancer

Please select a model

Biochemical recurrence after radical prostatectomy → patient case 1

Biochemical recurrence after radiation therapy → patient case 2

Biochemical recurrence (BCR) definitions

- **BCR after radical prostatectomy (BCR/RP):**
  - Rising PSA ≥ 0.2 ng/mL[1] (confirmed by 2 tests with an interval of ≥ 1 month)
  - BCR/RP model: all patients considered as pN0 and M0
- **BCR after radiation therapy (BCR/RT):**
  - Men having previous RT
    - External beam radiotherapy (EBRT)
    - Brachytherapy (BT)
  - PSA increase ≥ 2 ng/mL higher than the PSA nadir[2]
    - Regardless of the nadir value
    - Confirmed by 2 tests with an interval of ≥ 1 month
  - BCR/RT model: all patients considered as N0 and M0 (no metastases found after extensive work-up)

[1]EAU guidelines 2016; [2]Roach M et al. IJROBP 2006;65:965-74

Therapeutic options: BCR/RP model

After radical prostatectomy	After radiation therapy
Observation	Observation
Salvage EBRT alone	Salvage radical prostatectomy
Salvage EBRT + ADT	Salvage EBRT
Salvage ADT alone	Salvage brachytherapy
	Cryotherapy or HIFU
	ADT

How to translate evidence from clinical studies to individual patients?

Clinical variables: BCR/RP model

Time to relapse

≥ 3 years	< 3 years

PSA doubling time

≥ 6 months	< 6 months

PSA (ng/mL) at time of relapse

0.2 – 0.9	1.0 - 3.9	≥ 4.0

Pathological Gleason sum

≤ 6 or 3+4	4+3 or ≥ 8

pT3 and/or positive margins

No	Yes

Life expectancy

≥ 5 years	< 5 years

BCR/RP model:
Patient case 1

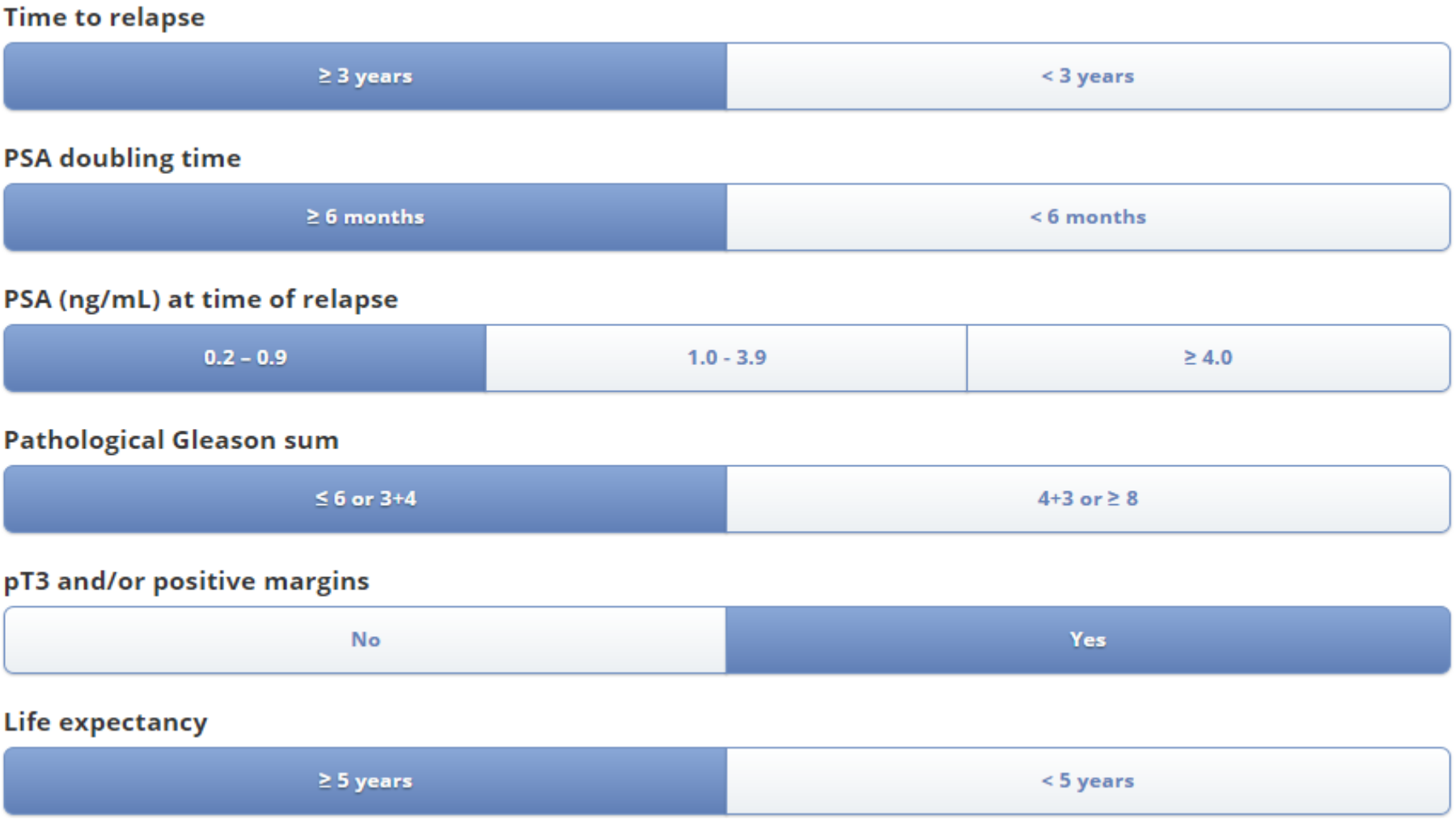
Mirrors of medicine

BCR after RP: Patient case 1

- 71 yr old, retired police officer
- Treated with RP for localised PCa in June 2013:
  - GS: 3+4
  - pT3b N0 M0
  - PSA nadir (June 2013): 0.3 ng/mL
- Elevated PSA in March 2016: 0.6 ng/mL
  - PSA-DT: 9 months
  - Imaging: no evidence of metastatic disease
- No comorbidities (life expectancy ≥ 5 yr)

What would be the most appropriate treatment for this patient?

Clinical variables: patient case 1



What would be the most appropri treatment for this patient?

Stemronde geopend

1. Observation

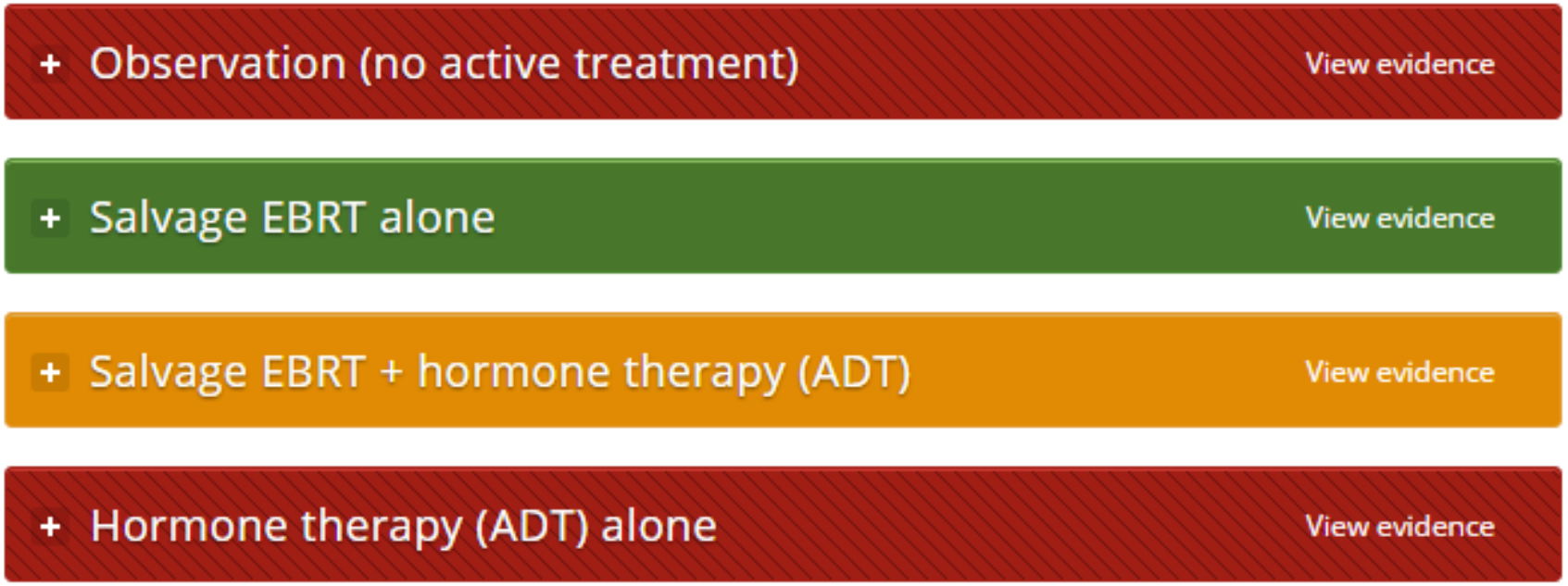
2. Radiation therapy alone

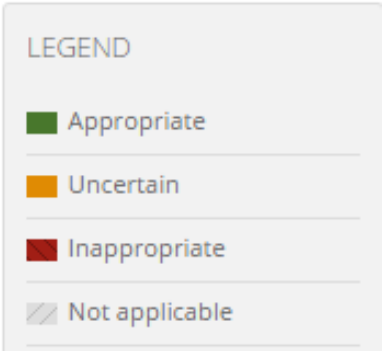
3. Radiation therapy + hormone therapy (ADT)

4. Hormone treatment (ADT) alone

What do the MoM experts recommend?

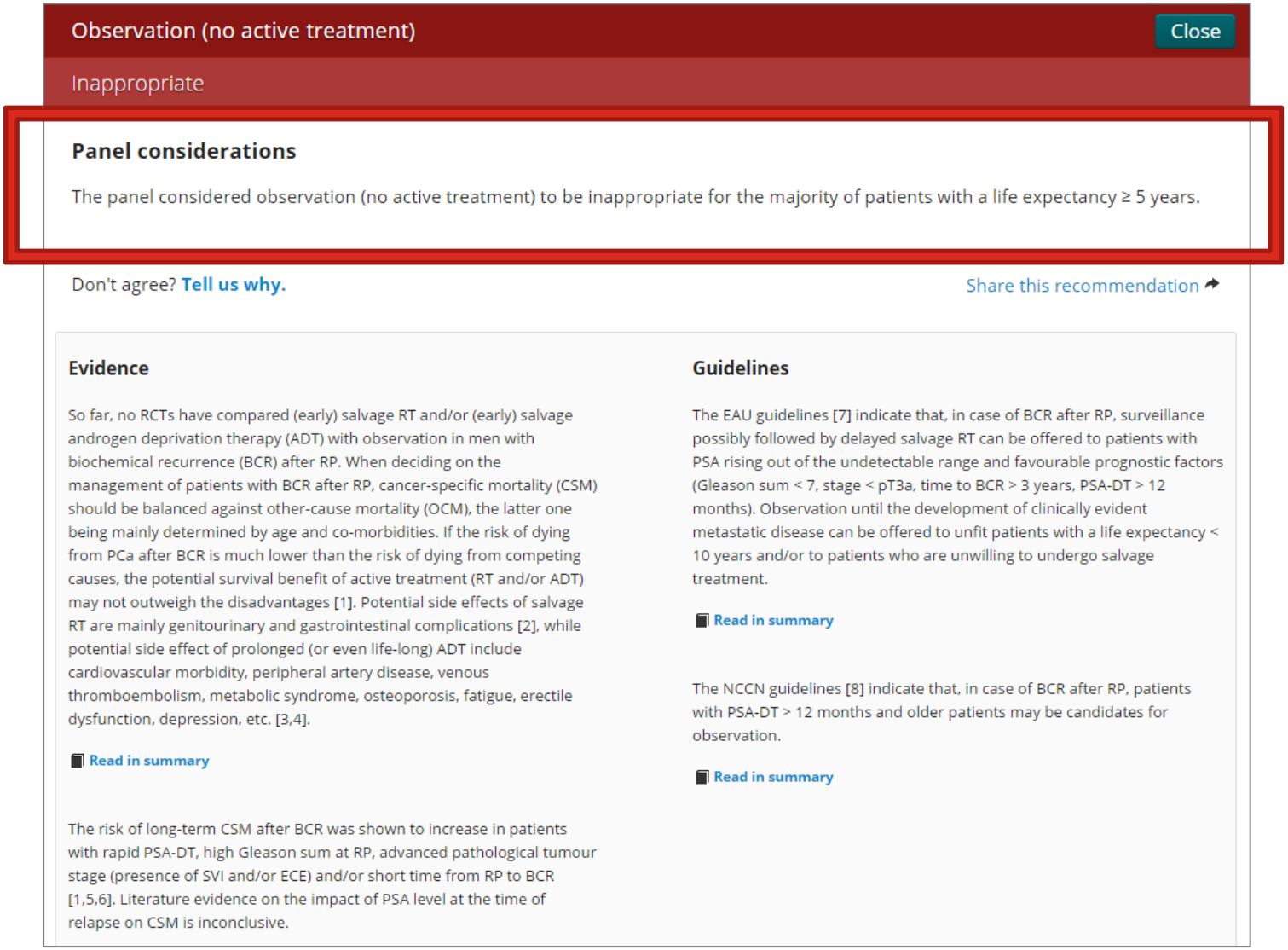
For this profile the available choices are:





Observation

Is observation an option?



Observation (no active treatment) Close

Inappropriate

Panel considerations

The panel considered observation (no active treatment) to be inappropriate for the majority of patients with a life expectancy ≥ 5 years.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

So far, no RCTs have compared (early) salvage RT and/or (early) salvage androgen deprivation therapy (ADT) with observation in men with biochemical recurrence (BCR) after RP. When deciding on the management of patients with BCR after RP, cancer-specific mortality (CSM) should be balanced against other-cause mortality (OCM), the latter one being mainly determined by age and co-morbidities. If the risk of dying from PCa after BCR is much lower than the risk of dying from competing causes, the potential survival benefit of active treatment (RT and/or ADT) may not outweigh the disadvantages [1]. Potential side effects of salvage RT are mainly genitourinary and gastrointestinal complications [2], while potential side effect of prolonged (or even life-long) ADT include cardiovascular morbidity, peripheral artery disease, venous thromboembolism, metabolic syndrome, osteoporosis, fatigue, erectile dysfunction, depression, etc. [3,4].

Read in summary

The risk of long-term CSM after BCR was shown to increase in patients with rapid PSA-DT, high Gleason sum at RP, advanced pathological tumour stage (presence of SVI and/or ECE) and/or short time from RP to BCR [1,5,6]. Literature evidence on the impact of PSA level at the time of relapse on CSM is inconclusive.

Guidelines

The EAU guidelines [7] indicate that, in case of BCR after RP, surveillance possibly followed by delayed salvage RT can be offered to patients with PSA rising out of the undetectable range and favourable prognostic factors (Gleason sum < 7, stage < pT3a, time to BCR > 3 years, PSA-DT > 12 months). Observation until the development of clinically evident metastatic disease can be offered to unfit patients with a life expectancy < 10 years and/or to patients who are unwilling to undergo salvage treatment.

Read in summary

The NCCN guidelines [8] indicate that, in case of BCR after RP, patients with PSA-DT > 12 months and older patients may be candidates for observation.

Read in summary

Stemronde geopend

Is observation an option if..

PSA after RP would have been undetectable?

1. 1 Yes
2. 2 No, still not an option

Observation: evidence

NO RCTs comparing salvage RT and/or salvage ADT with observation

Oncological efficacy of active treatment

- *Cancer-specific mortality*
- *Other-cause mortality*

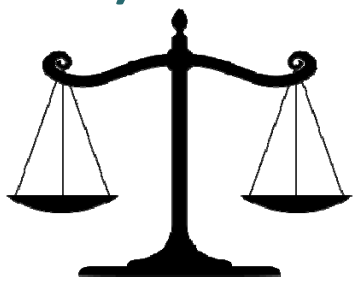
Morbidity and cost of active treatment

- **RT[1]:** genitourinary/ gastrointestinal complications
- **ADT[2,3]:** cardiovascular morbidity, peripheral artery disease, venous thromboembolism, metabolic syndrome, osteoporosis, fatigue, erectile dysfunction, depression, etc.

[1]Cremers RGHM et al. Radiother Oncol 2010;97:467-73;
[2]Schulman CC et al. Eur Urol Suppl 2010;9:675-91; [3]Hu JC et al. Eur Urol 2012;61:1119-28

Which patients are the best candidates for observation?

Cancer-specific mortality (CSM) ⟷ Other-cause mortality (OCM)



Long-term CSM ↑with:

- Rapid PSA-DT[1,2]
- High GS at RP[1,2]
- Short TTR[1,2]
- ≥ pT3[2]

OCM ↑ with:

- Age
- Co-morbidities

Observation may be considered in pts with a high risk of OCM (high age, co-morbidities) and a low progression risk (low risk of CSM)

[1]Freedland SJ et al. JAMA 2005;294:433-9; [2]Boorjian SA et al. Eur Urol 2011;59:893-9

What do the guidelines say? (1)

- EAU guidelines (2016): In case of BCR after RP,

  surveillance and possibly delayed salvage RT may be offered to:

  – Patients with a PSA rise from the undetectable range and favourable prognostic factors **(Gleason sum < 7, stage < pT3a, time to BCR >3 year, PSA-DT > 12 months)** observation until the development of clinically evident metastatic disease can be offered to:

  – **Unfit** patients with a **life expectancy < 10 yr**

  – Patients who are **unwilling** to undergo salvage treatment

What do the guidelines say? (2)

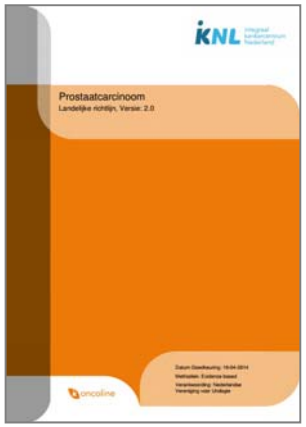
- NCCN guidelines (2015):

  Candidates for observation in case of BCR after RP:

  - Patients with **PSA-DT > 12 months**
  - **Older** patients

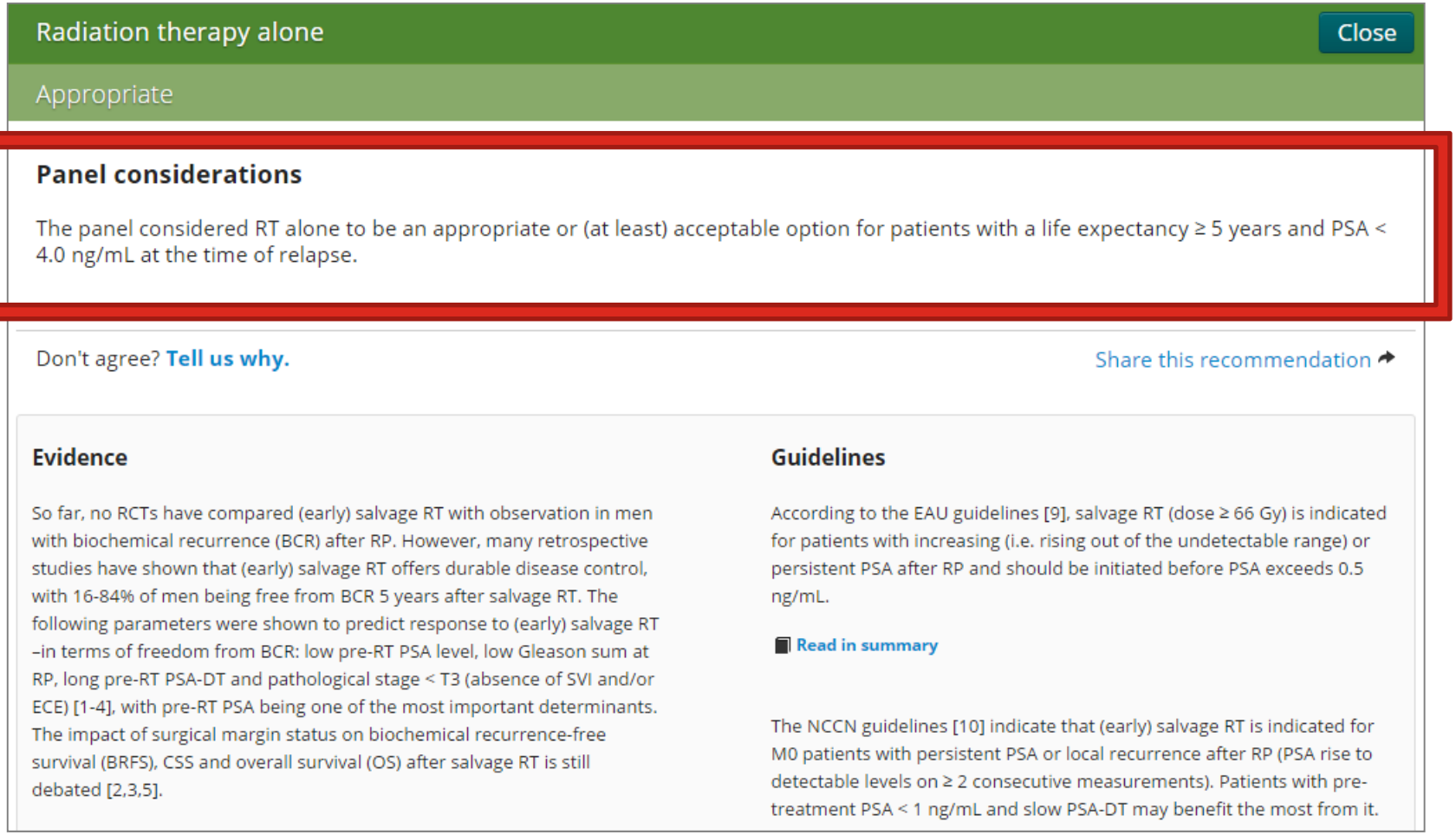
Wat zegt de NVU richtlijn over observatie?

- Geen specifieke aanbevelingen over observatie bij patiënten met PSA-recidief na radicale prostatectomie.



Salvage RT

Is salvage RT an appropriate treatment option?



Radiation therapy alone

Close

Appropriate

Panel considerations

The panel considered RT alone to be an appropriate or (at least) acceptable option for patients with a life expectancy ≥ 5 years and PSA < 4.0 ng/mL at the time of relapse.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

So far, no RCTs have compared (early) salvage RT with observation in men with biochemical recurrence (BCR) after RP. However, many retrospective studies have shown that (early) salvage RT offers durable disease control, with 16-84% of men being free from BCR 5 years after salvage RT. The following parameters were shown to predict response to (early) salvage RT –in terms of freedom from BCR: low pre-RT PSA level, low Gleason sum at RP, long pre-RT PSA-DT and pathological stage < T3 (absence of SVI and/or ECE) [1-4], with pre-RT PSA being one of the most important determinants. The impact of surgical margin status on biochemical recurrence-free survival (BRFS), CSS and overall survival (OS) after salvage RT is still debated [2,3,5].

Guidelines

According to the EAU guidelines [9], salvage RT (dose ≥ 66 Gy) is indicated for patients with increasing (i.e. rising out of the undetectable range) or persistent PSA after RP and should be initiated before PSA exceeds 0.5 ng/mL.

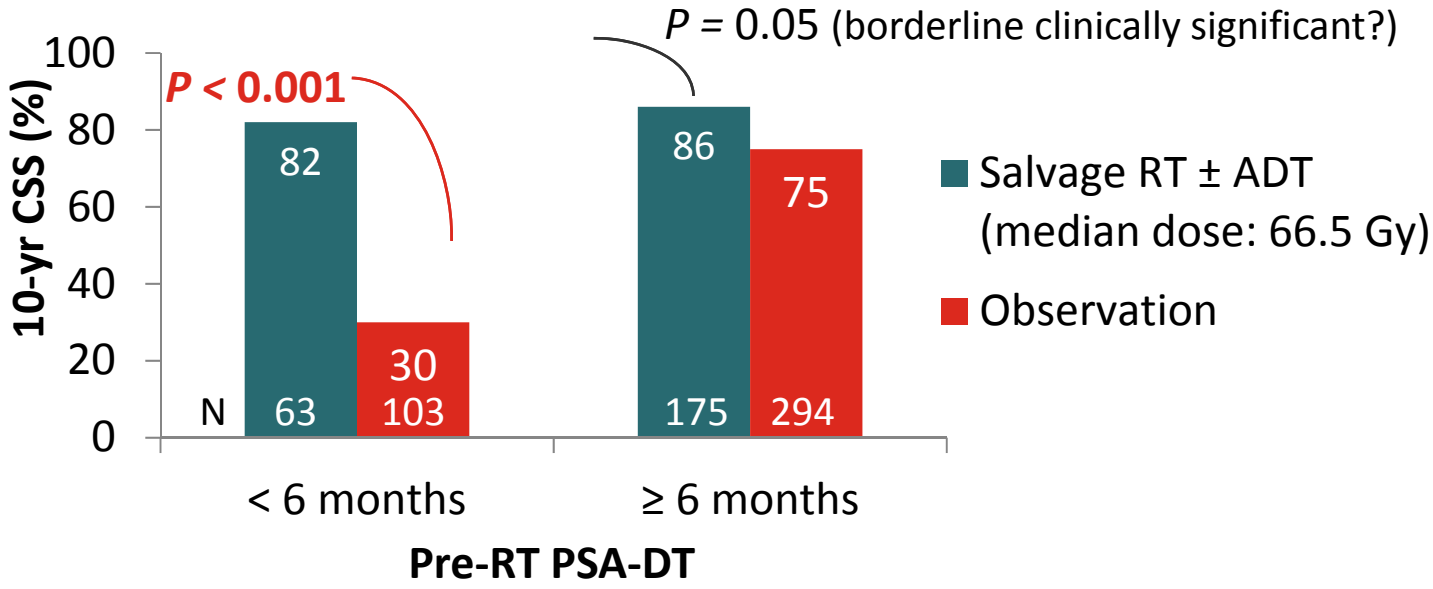
Read in summary

The NCCN guidelines [10] indicate that (early) salvage RT is indicated for M0 patients with persistent PSA or local recurrence after RP (PSA rise to detectable levels on ≥ 2 consecutive measurements). Patients with pre-treatment PSA < 1 ng/mL and slow PSA-DT may benefit the most from it.

Salvage RT: evidence

NO RCTs comparing (early) salvage RT with observation

- Retrospective cohort study[1]: N = 635 men with BCR after RP



Salvage RT (± ADT) significantly improved CSS vs observation, but only in men with PSA-DT < 6 mo who underwent salvage RT within 2 yr of BCR and whose PSA became undetectable after salvage RT

Salvage RT: benefits versus risks

Oncological efficacy

- *Cancer-specific mortality*
- *Other-cause mortality*

Morbidity and cost

- Genitourinary/ gastrointestinal complications[1]

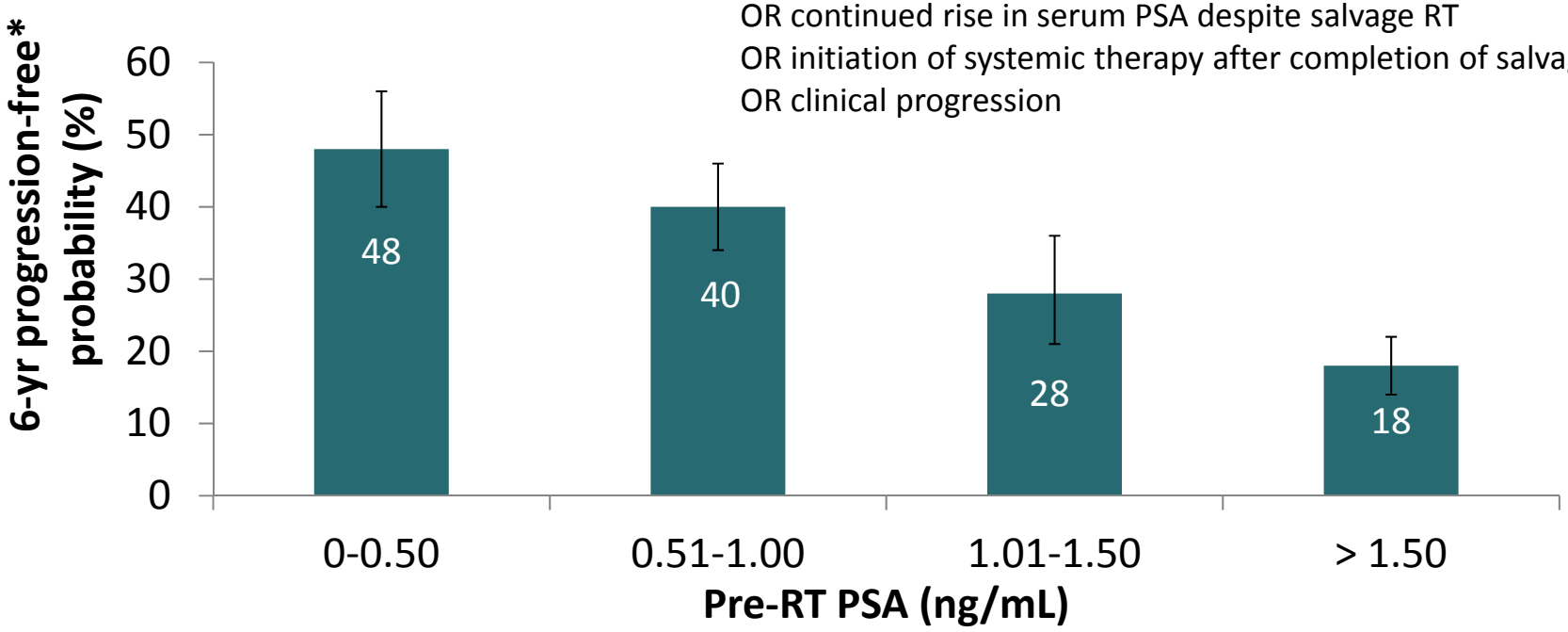
Life expectancy should be long enough to benefit from salvage RT

[1]Cremers RGHM et al. Radiother Oncol 2010;97:467-73

Which patients benefit most from salvage RT?

- Retrospective, multi-institutional cohort study: N = 1,540 men undergoing salvage RT for BCR after RP

*Serum PSA ≥ 0.2 ng/mL above post-RT nadir, followed by another higher value
OR continued rise in serum PSA despite salvage RT
OR initiation of systemic therapy after completion of salvage RT
OR clinical progression



As high pre-RT PSA levels strongly predict recurrence after salvage RT, salvage RT should be initiated at the earliest signs of PSA recurrence

Stephenson AJ et al. J Clin Oncol 2007;25:2035-41

Salvage RT: predictors of response

Predictors of response to (early) salvage RT (in terms of freedom from BCR)
Low pre-RT PSA
Low GS at RP
Long pre-RT PSA-DT
< pT3 (no SVI, no ECE)
Undetectable PSA after RP
High salvage RT dose
Addition of ADT before/during salvage RT
SM+ or SM-?: conflicting data

Stephenson AJ et al. J Clin Oncol 2007;25:2035-41; King CR. IJROBP 2012;84:104-11; Briganti A et al. Eur Urol 2013; doi:10.1016/j.eururo.2013.11.045; Mauermann J et al. Eur Urol 2013;64:19-25

What do the guidelines say?

EAU guidelines (2016)

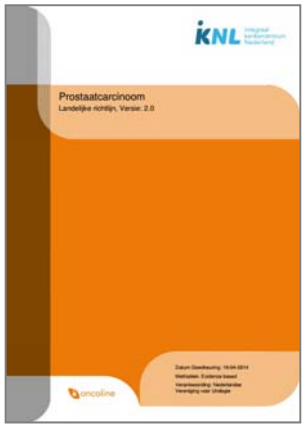
- **Indications for salvage RT after RP:**
  - Pts with increasing (i.e. rising out of the undetectable range) or persistent PSA after RP; salvage RT (dose ≥66 Gy) should be initiated before PSA exceeds 0.5 ng/mL

NCCN guidelines (2016)

- **Indications for salvage RT after RP:**
  - M0 patients with persistent PSA or an undetectable PSA after RP (with a subsequent detectable PSA that increases on ≥ 2 consecutive measurements)
  - Optimal candidates: Pts with pre-treatment PSA < 0.5 ng/mL and slow PSA-DT

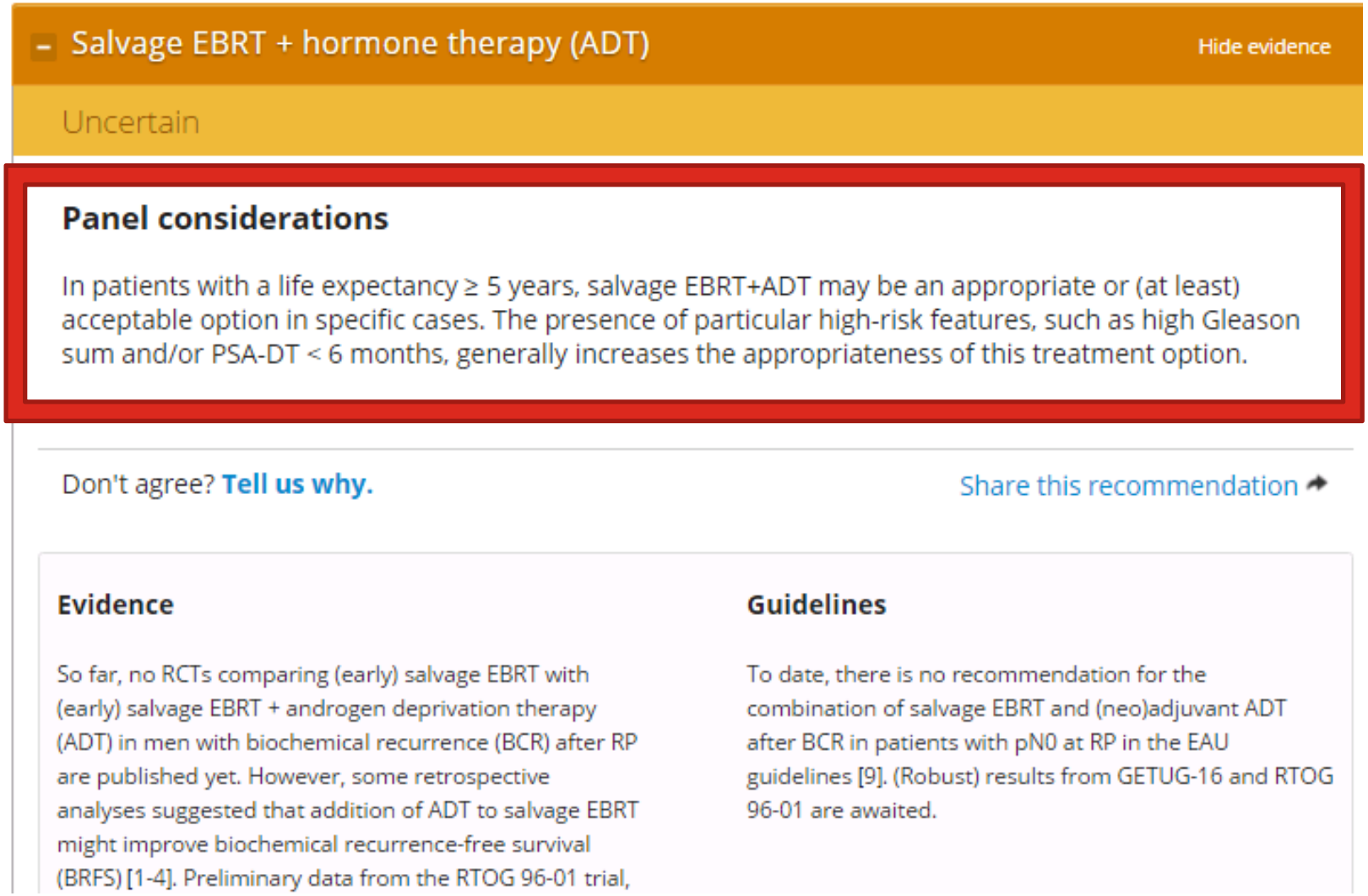
Wat zegt de NVU richtlijn over salvage RT?

- Indien een behandeling met salvage radiotherapie wordt overwogen, dient het PSA zo laag mogelijk te zijn, bij voorkeur ≤ 0,5 ng/mL.



Salvage RT + ADT

Salvage RT + ADT: an appropriate option?



Salvage EBRT + hormone therapy (ADT) Hide evidence

Uncertain

Panel considerations

In patients with a life expectancy ≥ 5 years, salvage EBRT+ADT may be an appropriate or (at least) acceptable option in specific cases. The presence of particular high-risk features, such as high Gleason sum and/or PSA-DT < 6 months, generally increases the appropriateness of this treatment option.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

So far, no RCTs comparing (early) salvage EBRT with (early) salvage EBRT + androgen deprivation therapy (ADT) in men with biochemical recurrence (BCR) after RP are published yet. However, some retrospective analyses suggested that addition of ADT to salvage EBRT might improve biochemical recurrence-free survival (BRFS) [1-4]. Preliminary data from the RTOG 96-01 trial,

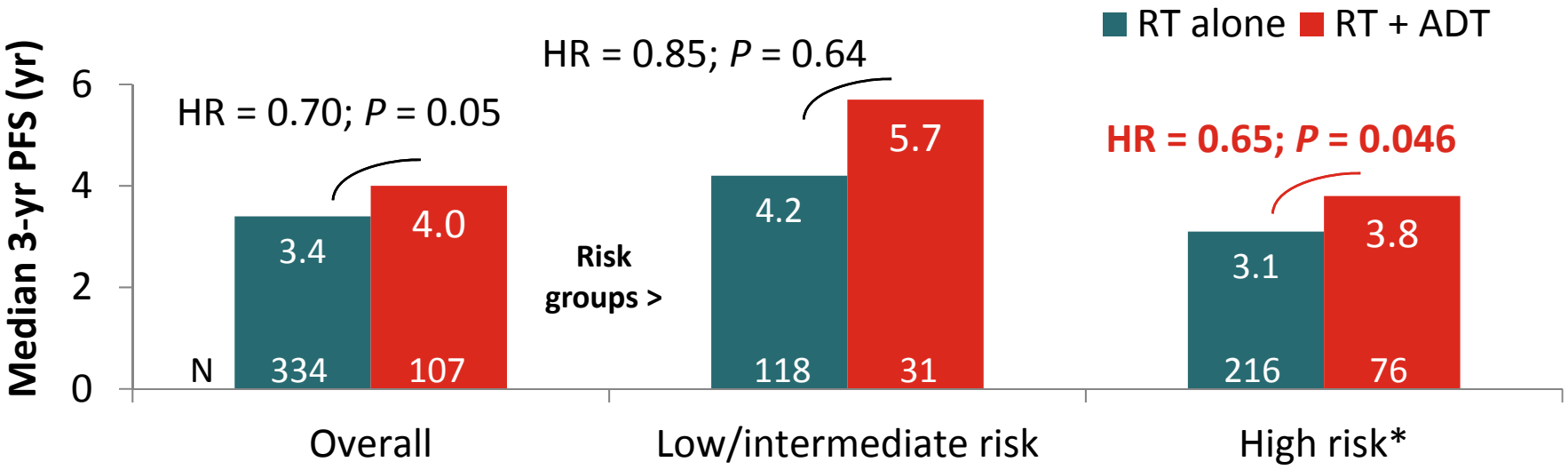
Guidelines

To date, there is no recommendation for the combination of salvage EBRT and (neo)adjuvant ADT after BCR in patients with pN0 at RP in the EAU guidelines [9]. (Robust) results from GETUG-16 and RTOG 96-01 are awaited.

Salvage RT + ADT: evidence

No RCTs comparing (early) salvage RT with (early) salvage RT + ADT

- Retrospective study[1]: N = 441 men receiving salvage RT (mean dose: 68 Gy) for BCR after RP



*≥ pT3, GS ≥ 8 or PSA ≥ 20 ng/mL; *P*-values: multivariable Cox proportional hazards model

Addition of ADT to salvage RT is correlated to improved BRFS, but the benefit may be limited to pts with high-risk features

Soto DE et al. IJROBP 2012;82:1227-32

Salvage RT + ADT: benefits versus risks

Oncological efficacy

- *Cancer-specific mortality*
- *Other-cause mortality*

Morbidity and cost

- **RT[1]:** genitourinary/ gastrointestinal complications
- **ADT[2,3]:** cardiovascular morbidity, peripheral artery disease, venous thromboembolism, metabolic syndrome, osteoporosis, fatigue, erectile dysfunction, depression, etc.

Life expectancy should be long enough to benefit from salvage RT + ADT

[1]Cremers RGHM et al. Radiother Oncol 2010;97:467-73;
[2]Schulman CC et al. Eur Urol Suppl 2010;9:675-91; [3]Hu JC et al. Eur Urol 2012;61:1119-28

Which patients benefit most from salvage RT + ADT?

Patient groups suggested to benefit from addition of ADT to salvage RT (in terms of BRFS[1,2] or CSS[3])
SM- and pre-RT PSA > 0.5 ng/mL[1]
≥ pT3, GS ≥ 8 and/or pre-RP PSA ≥ 20 ng/mL[2]
Short TTR, short PSA-DT and/or high pre-RT PSA[3]

[1]Cheung R et al. IJROBP 2005;63:134-40; [2]Soto DE et al. IJROBP 2012;82:1227-32; [3]Trock BJ et al. JAMA 2008;299:2760-9

What do the guidelines say?

- EAU/NCCN guidelines (2016):

  NO recommendation for the combination of salvage RT and (neo)adjuvant ADT after BCR in patients with **pN0** at RP

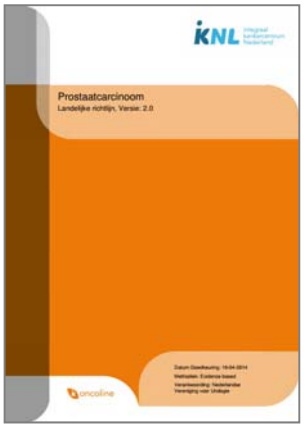
  (Robust) results from GETUG-16 and RTOG 96-01 are awaited

- NCCN guidelines (2016):

  Use of (neo)adjuvant ADT in combination with post-operative RT is mentioned as an **option (M0, persistent PSA, after RP)**, without specifying exact indications

Wat zegt de NVU richtlijn over RT+ADT?

- Geen specifieke aanbevelingen over combinatietherapie met radiotherapie en hormoonbehandeling bij PSA-recidief na radicale prostatectomie.
- Geen goede data voorhanden over de waarde van adjuvante hormonale therapie naast adjuvante of salvage radiotherapie
- Twee grote multicentrische studies moeten deze vraag beantwoorden: de Britse RADICALS en de EORTC 22043-30041 studie.



Salvage ADT

ADT alone: an appropriate option?

Radiation therapy + hormone therapy (ADT) — Open

Hormone treatment (ADT) alone — Close

Inappropriate

Panel considerations

ADT alone was considered inappropriate for the majority of patients with biochemical recurrence following RP.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

So far, no RCTs nor retrospective studies have shown a survival benefit of (early) salvage androgen deprivation therapy (ADT) compared with observation in men with biochemical recurrence (BCR) after RP. Only adjuvant ADT was shown to delay progression – but not to improve OS– compared with observation in N0 patients with ≥ pT3 at RP [1,2,3].

Read in summary

The potential benefit of (early) salvage ADT –if any– should be outweighed against the side effects of prolonged (or even life-long) ADT, such as

Guidelines

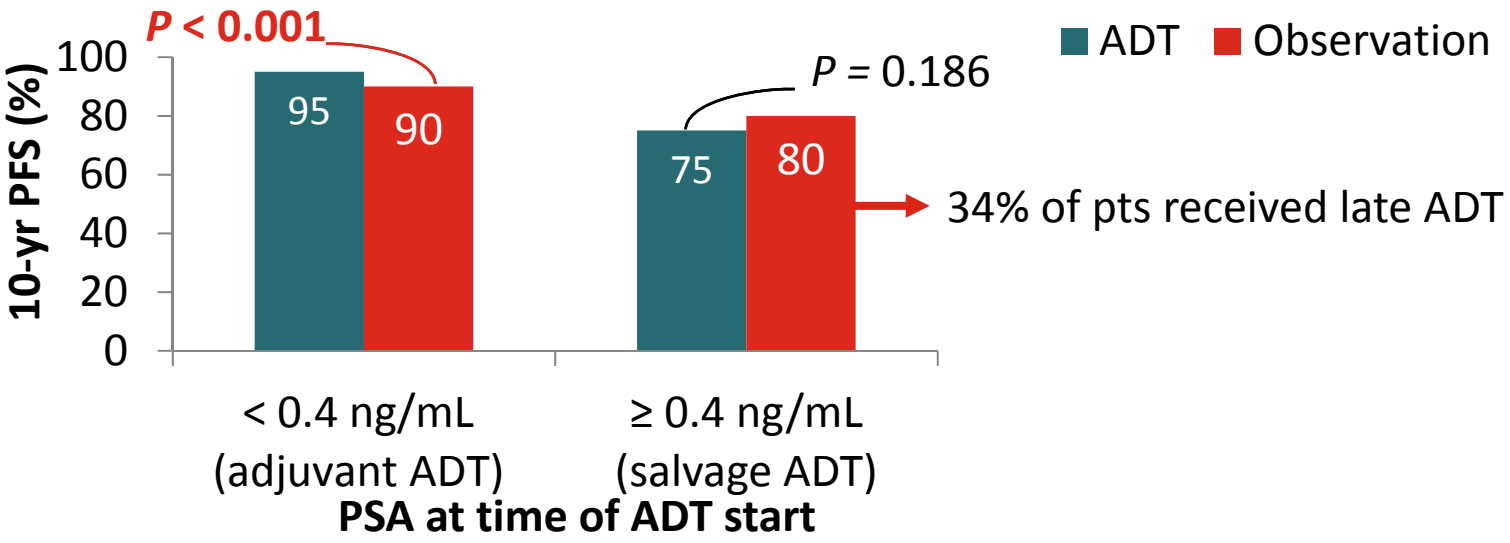
The EAU guidelines [8] state that although salvage ADT is often used, **not** all patients with relapse after primary curative treatment benefit from it. A favourable effect is observed in a high-risk group, which may be defined by short PSA-DT and/or tumour characteristics.
Intermittent ADT seems non-inferior to continuous hormones.
In asymptomatic men with BCR, ADT should not be given routinely.
Patients with a PSA-DT >12 months should not receive ADT.

Read in summary

ADT alone: evidence

NO **RCTs** comparing (early) salvage ADT with observation
NO **retrospective studies** showing survival benefit of (early) salvage ADT compared with observation

- Retrospective matched comparison[1]: N =6,401 men who underwent RP



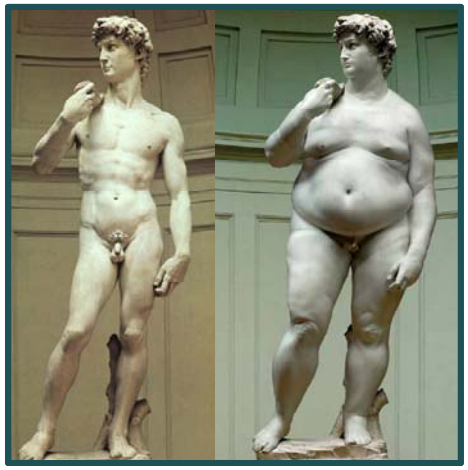
- **Adjuvant ADT: - Modest delay of progression, but only in ≥ pT3 N0 pts[2,3]**
  - No OS benefit[1,2,3]

[1]Siddiqui SA et al. J Urol 2008;179:1830-7; [2]Wirth MP et al. Eur Urol 2004;45:267-70; [3]McLeod DG et al. BJU Int 2006;97:247-54

ADT alone: side effects

- Short-term side effects
  - Loss of libido and sexual interest, erectile dysfunction, impotence
  - Hot flushes
  - Decline in intellectual capacity, emotional liability, depression
  - Decline in physical activity and general vitality (fatigue)

- Long-term side effects
  - Sarcopenic obesity
  - Osteoporosis
  - Increased risk of cardiovascular events
  - Metabolic syndrome



Payne H et al. World J Urol 2013;31:1333-8;
Schulman CC et al. Eur Urol Suppl 2010;9:675-91; Hu JC et al. Eur Urol 2012;61:1119-28

ADT alone: benefits versus risks

Oncological efficacy

Morbidity and cost

- Cancer-specific mortality
- Other-cause mortality

The potential benefit of salvage ADT –if any– should be outweighed against the side effects of prolonged (or even life-long) ADT

When should salvage ADT be initiated?

Early salvage ADT (initiated within 3 months of PSA relapse)

?

=

Deferred salvage ADT (initiated ≥ 2 yr after PSA relapse or at clinical progression)

≠ ⟷ **=**

Retrospective study[1]: N = 1,352:

Early salvage ADT may delay onset of clinical metastases in high-risk pts (GS > 7 and/or PSA-DT ≤ 12 months) compared with deferred salvage ADT

Retrospective study[2]: N = 2,022:

No sign. differences in OS or CSS between early salvage ADT and deferred ADT

PHNL/ZYT/0115/0002h(1)

[1]Moul JW et al. J Urol 2004;171:1141-7;
[2]Garcia-Albeniz X et al. J Clin Oncol 2014;32(5 Suppl):323s (abs.5003)

What do the guidelines say? (1)

EAU guidelines (2016):

- ADT should not be routinely offered to asymptomatic men with biochemical recurrence.
- T should not be offered to patients with a PSA-DT > 12 months
- A favourable effect is observed in a high-risk group, which may be defined by short PSA-DT at relapse or a high initial Gleason score (>7), and a long life expectancy

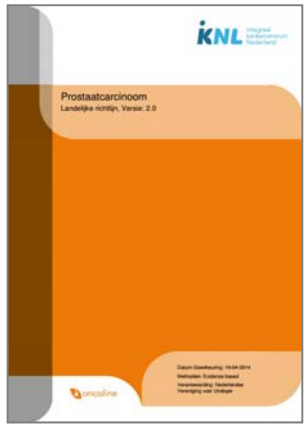
- In all other situations: the potential benefits of salvage HT should balanced against its potential harms.
-

What do the guidelines say? (2)

- NCCN guidelines (2016):
  - Since the benefit of early ADT is not clear in pts with BCR after RP, **treatment should be individualised** until definitive studies are completed
  - The timing of ADT may be influenced by PSA velocity, patient anxiety, short- and long-term side effects of ADT, and comorbidities
  - Earlier ADT may be better than delayed ADT, although definitions (level of PSA) are controversial
  - Patients with a shorter PSA-DT (or rapid PSA velocity) and otherwise long life expectancy should be encouraged to consider ADT earlier

Wat zegt de NVU richtlijn over (uitsluitend) HT?

- Hormonale therapie voor PSA-recidief wordt niet aanbevolen.

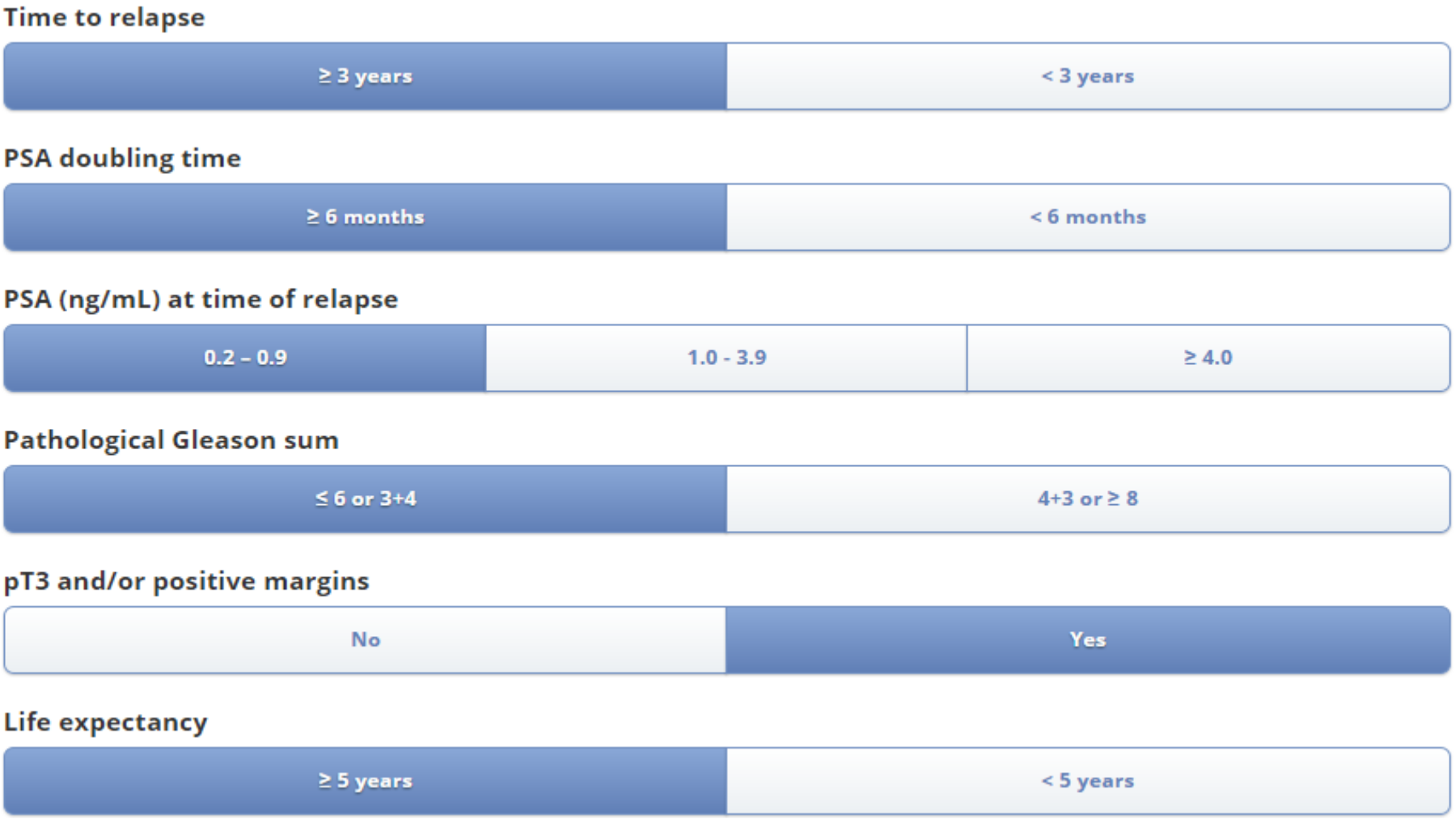


BCR after RP: Patient case 1

- 71 yr old, retired police officer
- Treated with RP for localised PCa in June 2014:
  - GS: 3+4
  - pT3b N0 M0
  - PSA nadir (September 2014): 0.3 ng/mL
- Elevated PSA in March 2016: 0.6 ng/mL
  - PSA-DT: 9 months
  - Imaging: no evidence of metastatic disease
- No comorbidities (life expectancy ≥ 5 yr)

What would be the most appropriate treatment for this patient?

Clinical variables: patient case 1



What would be the most appropri treatment for this patient?

Stemronde geopend

1. Observation

2. Radiation therapy alone

3. Radiation therapy + hormone therapy (ADT)

4. Hormone treatment (ADT) alone

Compare voting before - after

1st voting

2nd voting

1. Observation

2. Radiation therapy alone

3. Radiation therapy + hormone therapy (ADT)

4. Hormone treatment (ADT) alone

Stemronde geopend

Next: PSA rises after radiation

Within six months after radiation treatment, PSA rises to 3.1 ng/mL. Would you decide to wait and see:

1. Yes
2. No

Next: PSA rises after radiation

Stemronde geopend

After another six months, PSA rises to 5.0 ng/mL and the patient is worried. What would you do:

1. No further action
2. Start with hormonal treatment
3. Other: imaging

BCR/RP model:

Case change

What if the previous patient would have...

- 71 yr old, retired police officer
- Treated with RP for localised PCa in June 2012:
  - GS: 4+3
  - pT3b N0 M0
  - PSA nadir (September 2012): 0.3 ng/mL
- Elevated PSA in March 2014: 0.6 ng/mL
  - PSA-DT: 5 months
  - Imaging: no evidence of metastatic disease
- No comorbidities (life expectancy ≥ 5 yr)

What would be the most appropriate treatment for this patient?

Clinical variables: patient 1 case change

Time to relapse

≥ 3 years	< 3 years

PSA doubling time

≥ 6 months	< 6 months

PSA (ng/mL) at time of relapse

0.2 – 0.9	1.0 - 3.9	≥ 4.0

Pathological Gleason sum

≤ 6 or 3+4	4+3 or ≥ 8

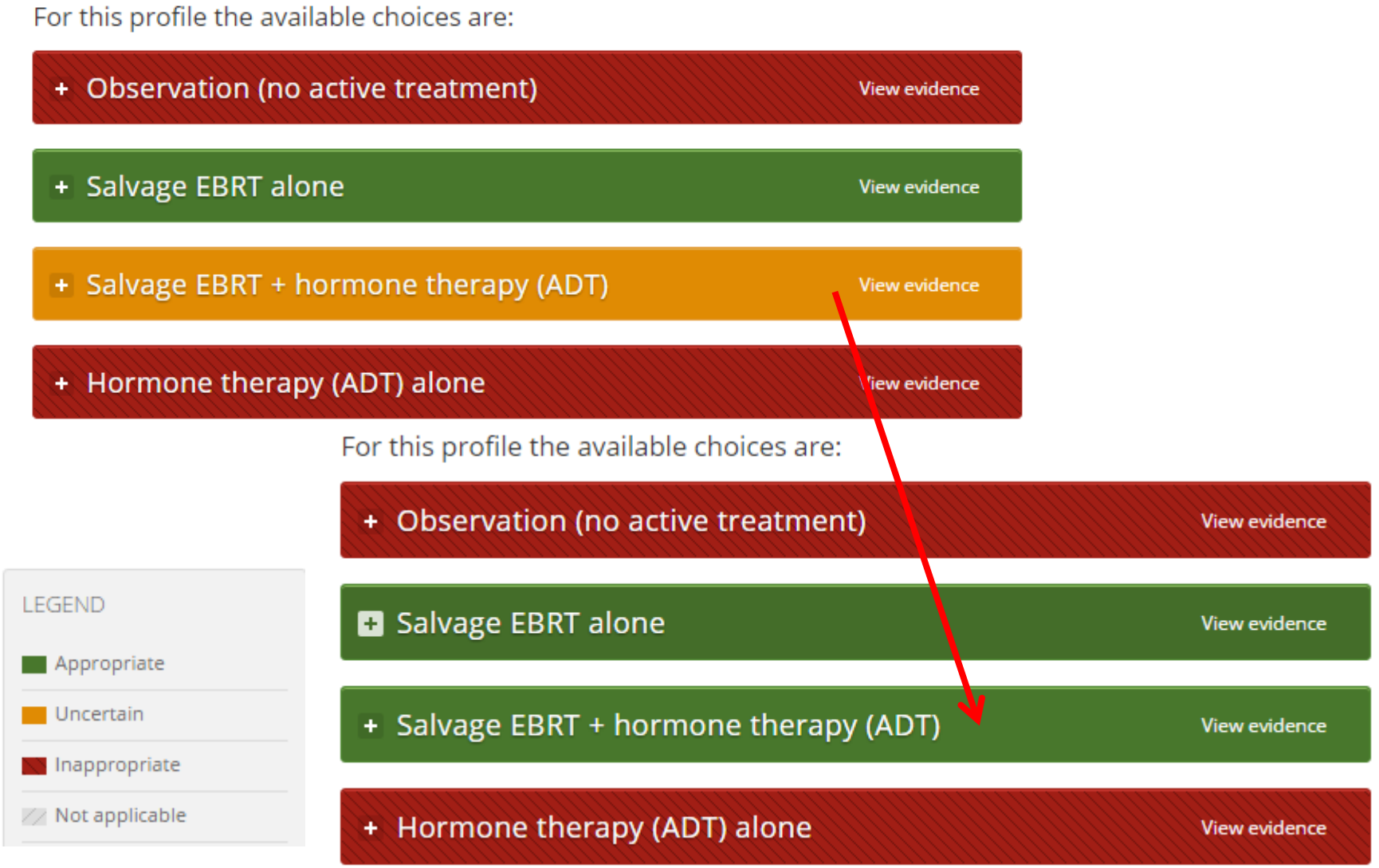
pT3 and/or positive margins

No	Yes

Life expectancy

≥ 5 years	< 5 years

What have we learned from this case?

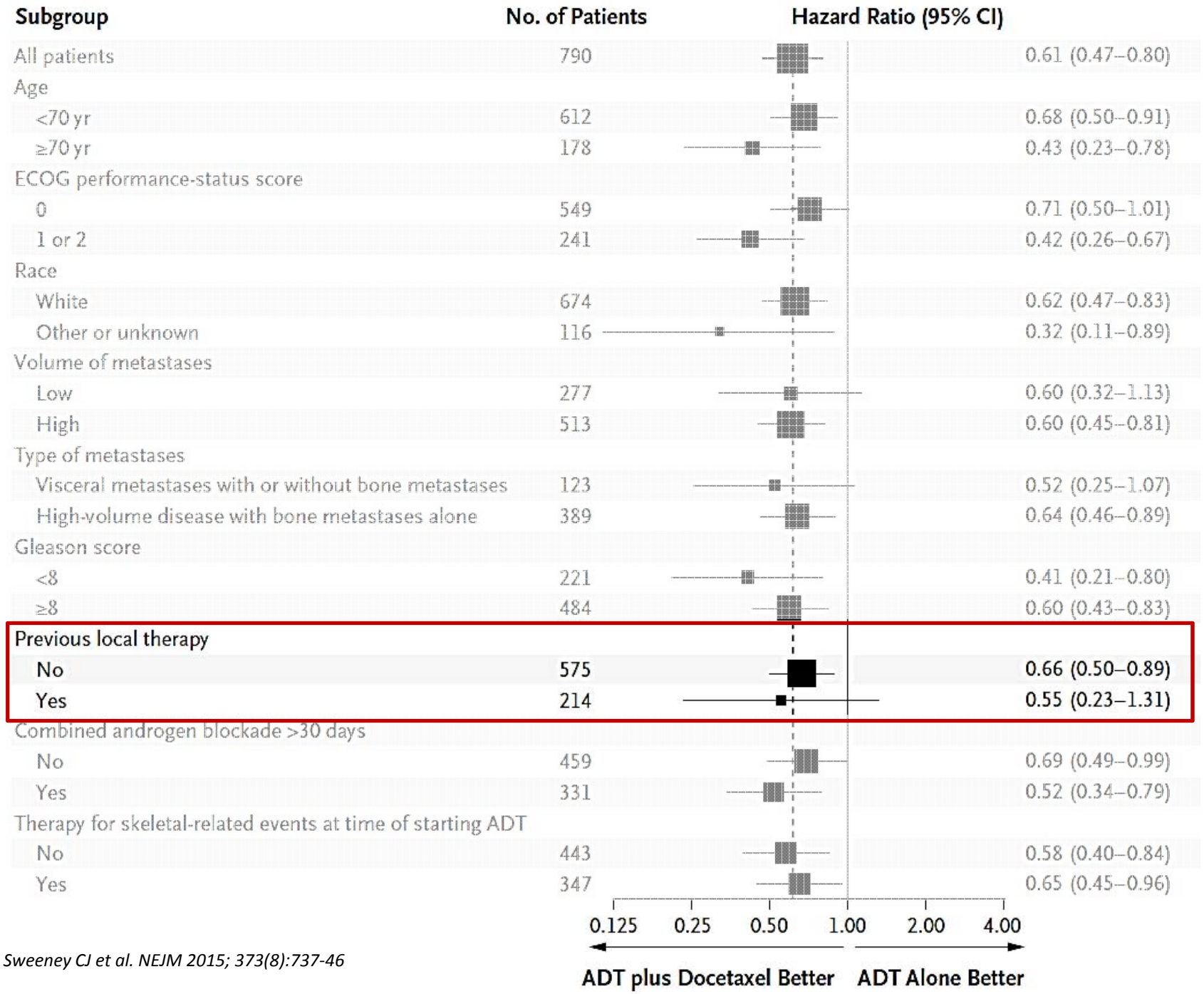


Stemronde geopend

Is there evidence for benefit of treatment with ADT + docetaxel for this patient with a pT3b N0 M0 and Gleason 4+3?

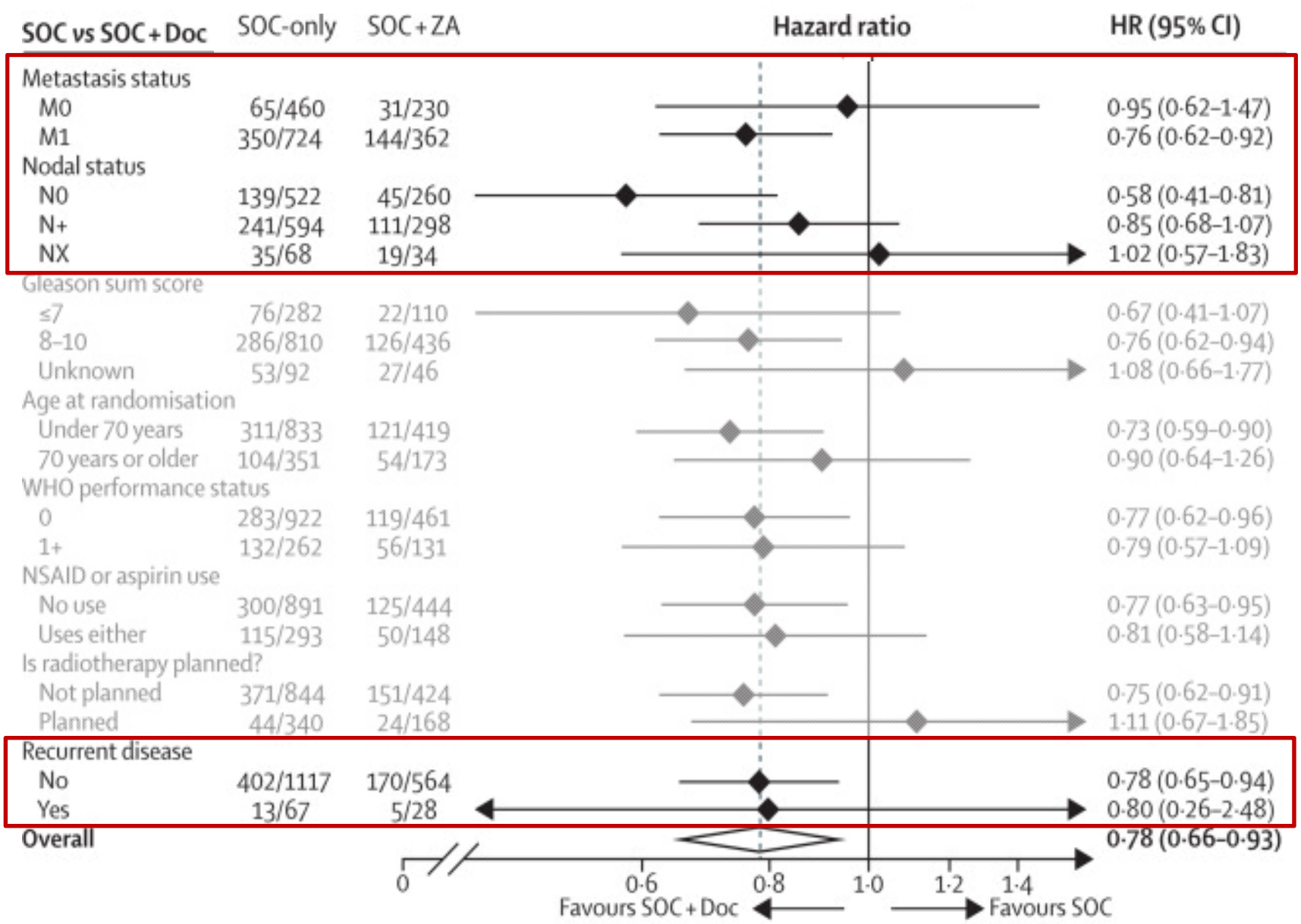
1. Yes
2. No

CHAARTED



Sweeney CJ et al. NEJM 2015; 373(8):737-46

STAMPEDE



James ND et al. Lancet 2015;S0140-6736(15)01037-5

BCR/RT model:

Patient case 2

Therapeutic options

After radical prostatectomy	After radiation therapy
Observation	Observation
Salvage EBRT alone	Salvage radical prostatectomy
Salvage EBRT + ADT	Salvage EBRT
Salvage ADT alone	Salvage brachytherapy
	Cryotherapy or HIFU[1]
	ADT[2]

[1]Salvage cryosurgical ablation of the prostate (CSAP) or salvage high-intensity ultrasound (HIFU)

[2]Salvage ADT (continous or intermittent)

BCR after RT: Patient case 2

- 67 yr old, retired engineer
- Initial PSA 8 ng/mL
- Treated with EBRT for localised T2 PCa in 20012
- PSA nadir (2015): 2 ng/mL
- Elevated PSA in October 2016: 7 ng/mL
- PSA-DT: 10 months
- Biopsy in November 2016:
  - GS: 3+3
  - Imaging: no evidence of metastatic disease
- No comorbidities (life expectancy ≥ 5 yr)

What would be the most appropriate treatment for this patient?

Stemronde geopend

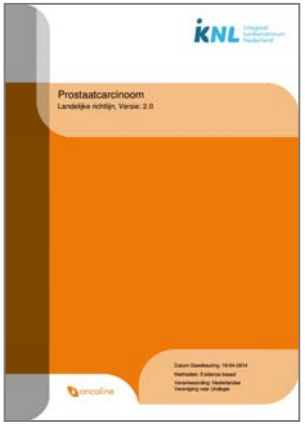
Stijging van het PSA boven de nadir na externe radiotherapie of brachytherapie is..

1. Bewijs voor een recidief
2. Bewijs voor een recidief, mits tweemaal een stijging
3. Bewijs voor een recidief, mits de waarde van PSA ≥ 2 ng/mL boven nadir
4. “PSA-bounce”, mits < 2,0 ng/mL boven de nadir

PHNL/ZYT/0115/0002h(1)

Wat zegt de NVU richtlijn?

- Het PSA beloop na uitwendige radiotherapie en brachytherapie moet vanwege het bestaan van de “PSA-bounce” voorzichtig worden geïnterpreteerd.
- Indien er sprake is van een PSA stijging van 2 ng/mL boven de nadir wordt van een recidief gesproken.



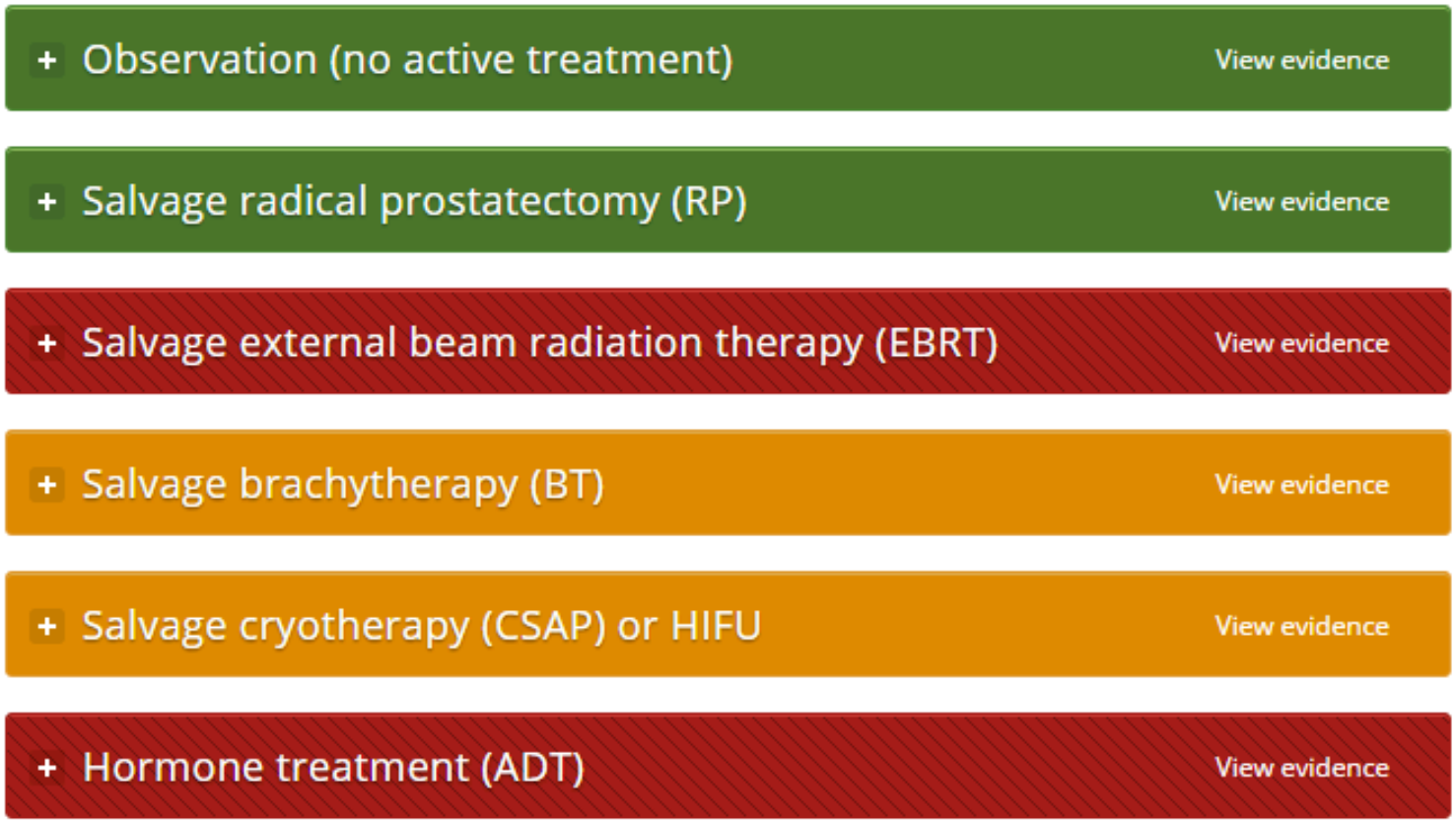
Clinical variables: patient case 2

What would be the most appropri treatment for this patient?

Stemronde geopend

1. Observation (no active treatment)
2. Salvage radical prostatectomy
3. Salvage external beam radiation
4. Salvage brachytherapy
5. Cryotherapy or HIFU
6. Hormone treatment (ADT)

What do the MoM experts recommend?



Observation

Is observation an appropriate option?

Observation (no active treatment) Close

Appropriate

Panel considerations

The panel considered observation (no active treatment) to be less appropriate for most patients with a life expectancy ≥ 5 years. In this specific case, the outcome was appropriate because the patient has no compromising disease-specific conditions.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

The evidence regarding observation for men with biochemical recurrence (BCR) after RT, but no evidence of metastatic disease, is scarce.

A retrospective cohort analysis in 248 men with BCR after RT showed no difference in freedom from distant metastases between androgen deprivation therapy (ADT) and watchful waiting in the subgroup of men with a PSA-DT of ≥ 12 months after RT [1]. In the group of men with PSA-DT < 12 months, the median time to distant failure was significantly shorter in men who received watchful waiting vs. those receiving ADT.

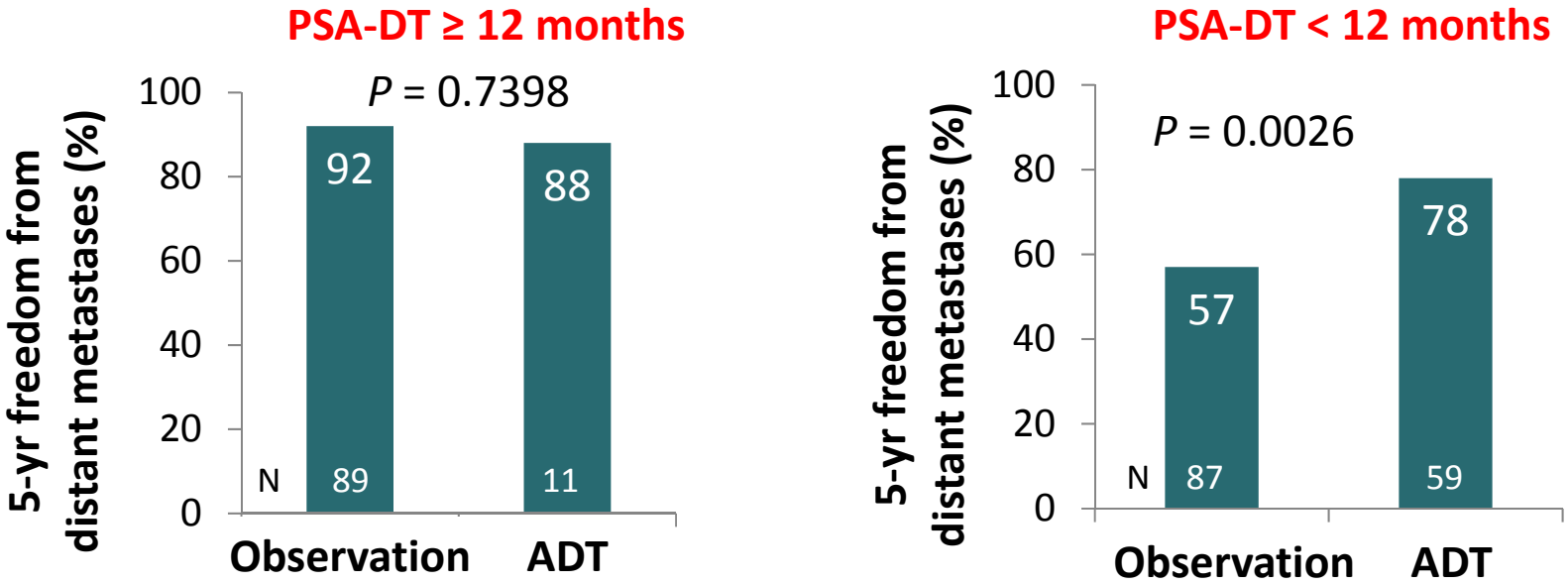
Guidelines

The EAU guidelines indicate that in patients with BCR after RT who have signs of only local recurrence (i.e. low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone [4].

The NCCN guidelines indicate that observation is an option for selected men with BCR after RT and low suspicion of metastases to distant organs [5]. Men with prolonged PSA-DT (>12 months) and who are older are candidates for observation. In addition, observation is an option for men who are not candidate for local therapy.

Observation: evidence

- Evidence is scarce
- Retrospective cohort analysis of men with BCR after RT[1]



- Shorter PSA-DT and higher GS were independent predictors of distant metastases[2]

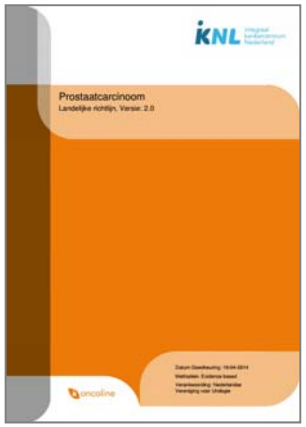
[1]Pinover WH et al. Cancer 2003;97:1127-33; [2]Zelefsky MJ et al. J Clin Oncol 2005;23:826-31

What do the guidelines say?

- EAU guidelines (2016):
  - Patients who have signs of only local recurrence (i.e. low-risk patients with **late recurrence and a slow PSA rise**) who do not wish to undergo second-line curative options are best managed by observation alone
- NCCN guidelines (2016):
  - Observation is an option for
    - Men who are not candidate for local therapy
    - Selected men with BCR after RT and low suspicion of metastases to distant organs
    - Men with prolonged PSA-DT (>12 months) and who are older are candidates for observation

Wat zegt de NVU richtlijn over observatie?

- Geen specifieke aanbevelingen over observatie bij patiënten met PSA-recidief na radiotherapie.



Salvage RP

Is salvage RP an appropriate option?

Salvage radical prostatectomy

Close

Appropriate

Panel considerations

Salvage RP may be an appropriate option in very specific cases. In this patient, the most important factors favouring salvage RP choice are life expectancy ≥ 5 years, PSA ≤ 10 ng/mL and PSA-DT ≥ 6 months.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

Salvage radical prostatectomy (RP) in men with biochemical recurrence (BCR) after RT has mainly been evaluated in cohort studies. A systematic review showed that salvage RP resulted in 5- and 10-year biochemical recurrence-free survival (BRFS) from 47-82% and from 28-53%, respectively [1]. The 10-year CSS and OS ranged from 70-83% and from 54-89%, respectively.

Read in summary

Guidelines

The EAU guidelines state that selected patients with localised cancer at primary treatment and histologically proven recurrence without evidence of metastatic disease should be treated with salvage RP [5]. Salvage RP should be considered only for lymph node negative patients with a low co-morbidity, a life-expectancy of at least 10 years, organ-confined cancer (stage ≤ T2b), Gleason sum ≤ 7 and a pre-operative PSA < 10 ng/mL. Due to the increased rate of treatment-related complications and side effects salvage RP should only be performed in experienced centres.

PHNL/ZYT/0115/0002h(1)

Salvage RP: evidence (1)

- Evaluated in mostly retrospective, single-centre cohort studies
- Systematic review including 40 papers:

Range across studies	BRFS	CSS	OS
5 yr	47-82%	73-95%	-
10 yr	28-53%	70-83%	54-89%

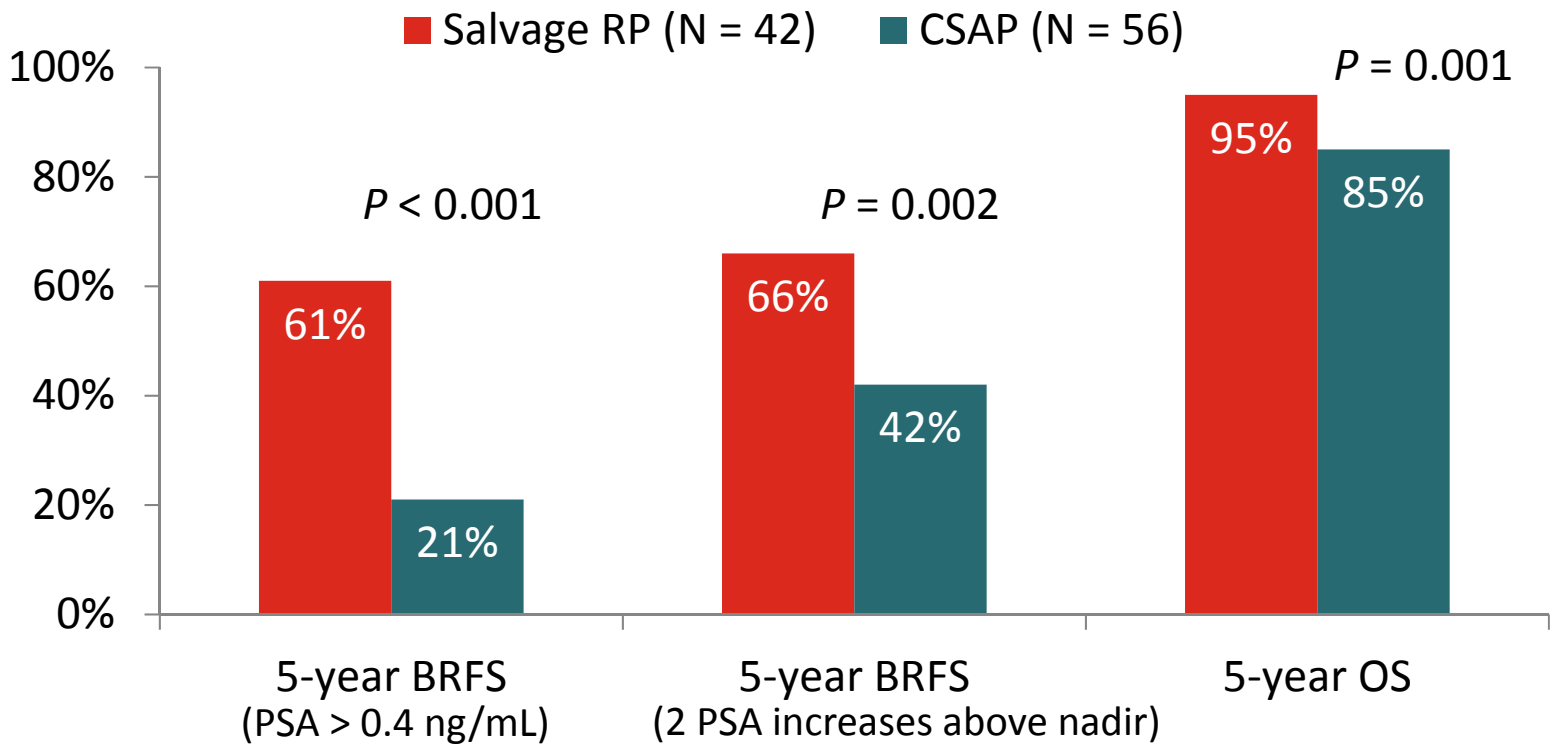
BRFS: biochemical recurrence-free survival; CSS: cancer-specific survival; OS: overall survival

Common complications	Range across studies (% of pts)
Erectile dysfunction	80-100
Urinary incontinence	10-79
Anastomotic stricture	7-41
Rectal injury	0-28

Chade DC et al. Eur Urol 2012;61:961-71

Salvage RP: evidence (2)

- Retrospective case-matched control study



CSAP: salvage cryosurgical ablation of the prostate

Pisters LL et al. J Urol 2009;182:517-25

What do the guidelines say? (1)

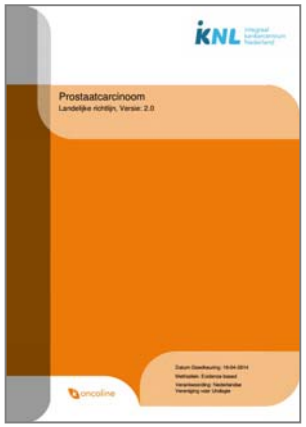
- EAU guidelines (2016):
  - Selected patients with localised cancer at primary treatment and histologically proven recurrence without evidence of metastatic disease should be treated with salvage RP
  - Salvage RP should be considered only for **N0** patients with:
    - Low co-morbidity
    - Life expectancy ≥ 10 yr
    - Organ-confined cancer (≤ T2b)
    - GS ≤ 7
    - Pre-operative PSA < 10 ng/mL
  - Due to increased rate of treatment-related complications and side effects, salvage RP should **only** be performed in **experienced centres**

What do the guidelines say? (2)

- NCCN guidelines (2016):
  - In case of BCR after EBRT or brachytherapy, salvage RP is an option for highly selected men with a positive biopsy but in absence of metastases to distant organs (original clinical stage T1-T2, Nx or N0, life expectancy > 10 years, pre-RP PSA <10 ng/mL)
  - Since the morbidity is high (i.e. incontinence, loss of erection, anastomotic stricture), the operation should be performed by surgeons who are experienced in sRP
  - Treatment needs to be **individualised** based upon the patient's risk of progression, the likelihood of success and the risks involved with salvage therapy

Wat zegt de NVU richtlijn over salvage RP?

- Bij een histologisch bewezen lokaal recidief zonder lymfeklier- of afstandsmetastasen en een gering risico op occulte micrometastasen kan een in opzet curatieve behandeling overwogen worden, mits de levensverwachting meer dan 10 jaar is.
- De keuze voor een salvage behandeling wordt individueel bepaald op basis van de levensverwachting, comorbiditeit en initiële tumorkarakteristieken alsmede op basis van een afweging van de patiënt betreffende de voor- en nadelen van deze ingreep.
- Salvage behandeling van de gehele prostaat heeft een groot risico op ernstige toxiciteit en moet daarom terughoudend worden aangeboden; centralisatie van deze behandeling wordt aanbevolen



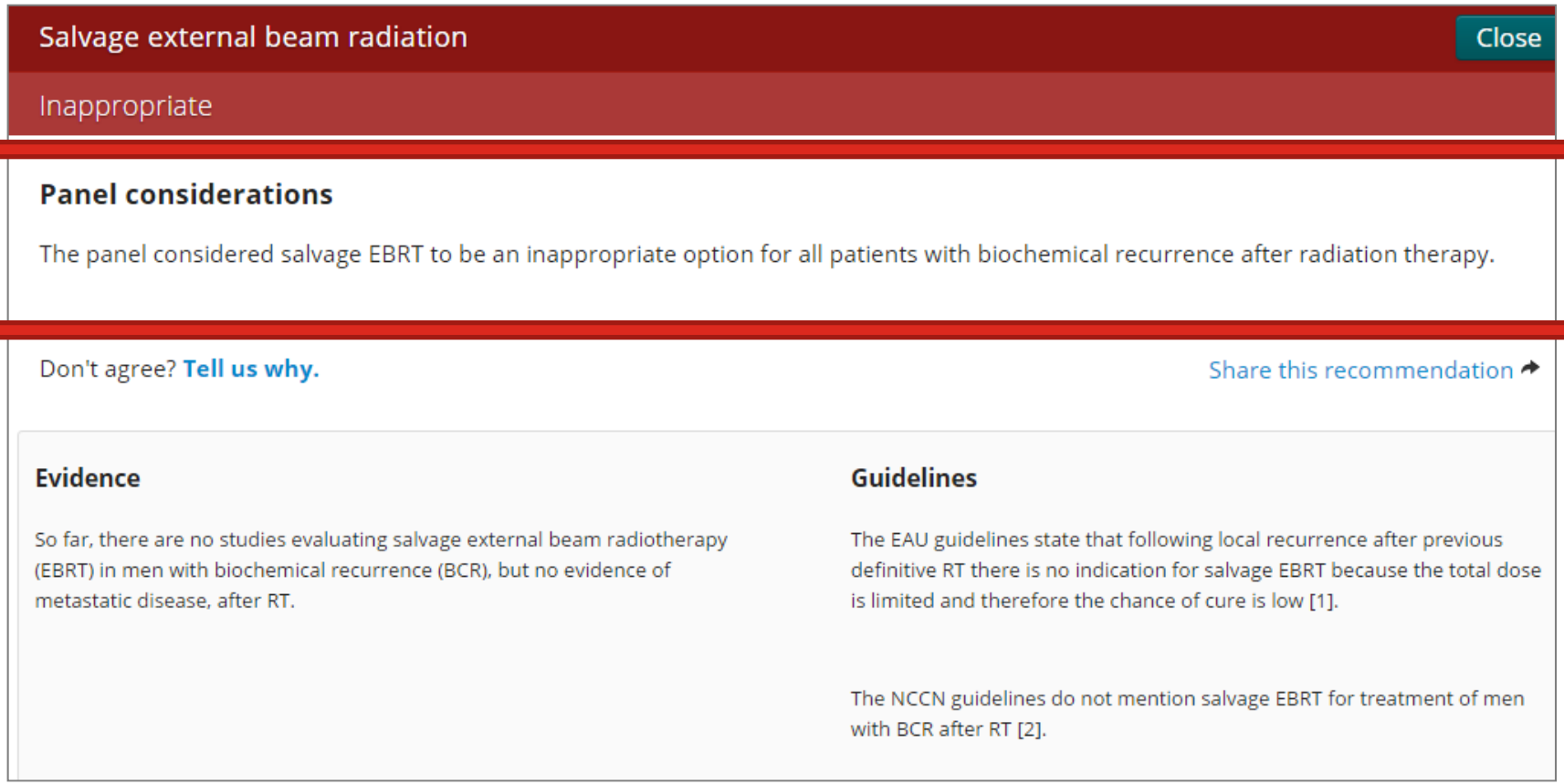
Stemronde geopend

Waardoor wordt de keuze voor een salvage behandeling volgens de NVU richtlijn prostaatcarcinoom bepaald?

1. Comorbiditeit
2. Eerdere hormonale behandeling
3. Initiële tumorkarakteristieken
4. Levensverwachting
5. 1&2
6. 1&3
7. 3&4
8. 1,3&4

Salvage EBRT

Is salvage EBRT an appropriate option?



Salvage external beam radiation

Close

Inappropriate

Panel considerations

The panel considered salvage EBRT to be an inappropriate option for all patients with biochemical recurrence after radiation therapy.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

So far, there are no studies evaluating salvage external beam radiotherapy (EBRT) in men with biochemical recurrence (BCR), but no evidence of metastatic disease, after RT.

Guidelines

The EAU guidelines state that following local recurrence after previous definitive RT there is no indication for salvage EBRT because the total dose is limited and therefore the chance of cure is low [1].

The NCCN guidelines do not mention salvage EBRT for treatment of men with BCR after RT [2].

Salvage EBRT: evidence

- There are **no studies** evaluating salvage EBRT in men with BCR after RT and no evidence of metastatic disease

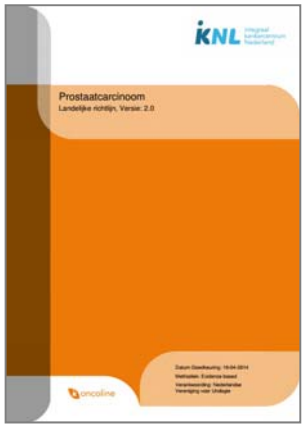
What do the guidelines say?

- EAU guidelines (2016):
  - There is **no indication** for salvage EBRT following local recurrence after previous definitive RT because the total dose is limited and therefore the chance of cure is low

- NCCN guidelines (2016):
  - Salvage EBRT is **not mentioned**

Wat zegt de NVU richtlijn over salvage RT?

- Geen specifieke aanbevelingen over salvage radiotherapie bij patiënten met PSA-recidief na radiotherapie.



Salvage brachytherapy (BT)

Is salvage BT an appropriate option?

Salvage brachytherapy

Close

Uncertain

Panel considerations

The panel considered salvage BT generally to be a less appropriate option for patients with biochemical recurrence after radiation therapy. It may be considered in certain patients with a life expectancy ≥ 5 years and time to relapse ≥ 3 years.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

There are currently no comparative studies between salvage brachytherapy (BT) and other salvage therapies for men with biochemical recurrence (BCR) after RT. The experience with salvage BT is limited to small-sized cohort studies with mostly short follow-up data.

The reported 5-year biochemical recurrence-free survival (BRFS) rates after salvage BT range from 20-77% [1-6].

A systematic review of salvage BT reported grade 3-4 genitourinary events in 13% of patients, urinary incontinence in 6% of patients, grade 3-4 rectal injury in 5% of patients, recto-urinary fistula in 3% of patients and strictures in 8% of patients [7]. There was a wide variability in complication rates across studies.

Guidelines

The EAU guidelines mention that the freedom from BCR after salvage BT is promising and the rate of severe side effects in experienced centres seems to be acceptable [9]. Therefore, it remains a treatment option for selected M0 patients with histologically proven local recurrence after RT. Due to the increased rate of treatment-related complications and side effects, salvage BT should only be performed in experienced centres. Patients must be informed about the experimental nature of this approach.

Read in summary

Salvage BT: evidence

- Evidence limited to small-sized cohort studies with mostly short follow-up data
- 5-yr BRFS: range 20-77%[1-6]
- Systematic review of 13 studies[7]:

Common complications	% of pts
Grade 3-4 genitourinary events	13
Strictures	8
Urinary incontinence	6
Grade 3-4 rectal injury	5
Recto-urinary fistula	3

[1]Moman MR et al. Brachytherapy 2010;9:119-25; [2]Lee HK et al. Brachytherapy 2008;7:17-21; [3]Burri RJ et al. IJROBP 2010;77:1338-44; [4]Chen CP et al. IJROBP 2013;86:324-9; [5]Yamada Y et al. Brachytherapy 2014;13:111-6; [6]Henriquez I et al. Radiat Oncol 2014;9:102; [7]Parekh A et al. Semin Radiat Oncol 2013;23:222-34

What do the guidelines say? (1)

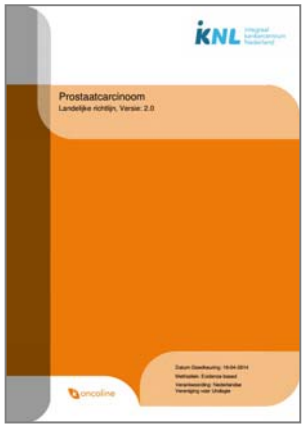
- EAU guidelines (2016):
  - The freedom from BCR after salvage BT (HDR and LDR) is promising and the rate of severe side effects in experienced centres seems to be acceptable
  - Salvage BT is a treatment **option for selected M0 patients** with histologically proven local recurrence after RT
  - Due to the increased rate of treatment-related complications and side effects salvage BT should **only** be performed **in experienced centres**
  - Patients must be informed about the experimental nature of this approach

What do the guidelines say? (2)

- NCCN guidelines (2016):
  - Salvage BT (LDR, dose 100-110 Gy) can be an option for men with BCR after RT who have a positive biopsy but **low suspicion of metastases** to distant organs, if they are candidates for local therapy (original clinical stage T1-T2, Nx or N0, life expectancy > 10 years, current PSA <10 ng/mL)
  - Treatment needs to be **individualised** based upon the patient's risk of progression, the likelihood of success and the risks involved with salvage therapy

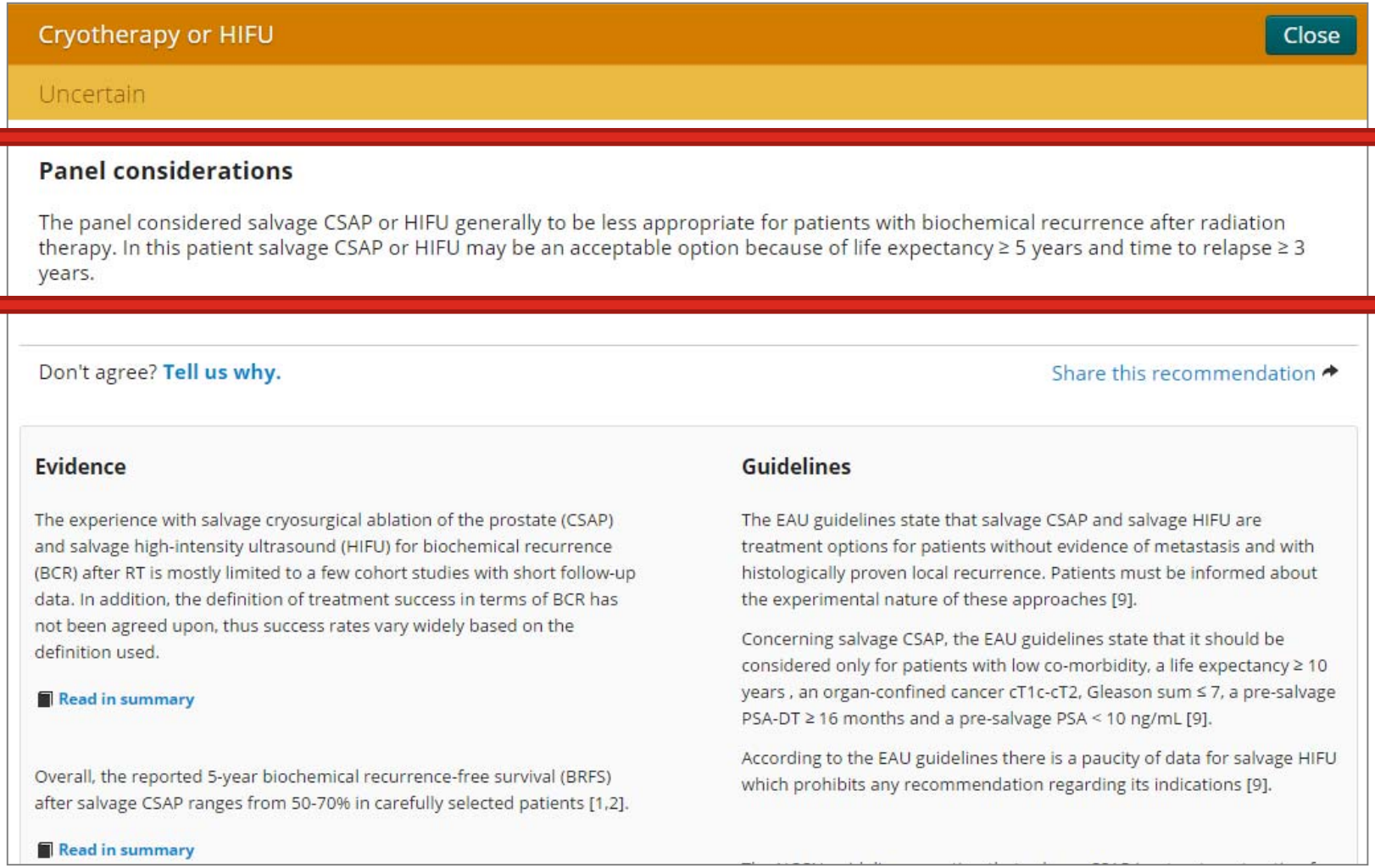
Wat zegt de NVU richtlijn over salvage BT?

- Bij een histologisch bewezen lokaal recidief zonder lymfeklier- of afstandsmetastasen en een gering risico op occulte micrometastasen kan een in opzet curatieve behandeling overwogen worden, mits de levensverwachting meer dan 10 jaar is.
- De keuze voor een salvage behandeling wordt individueel bepaald op basis van de levensverwachting, comorbiditeit en initiële tumorkarakteristieken alsmede op basis van een afweging van de patiënt betreffende de voor- en nadelen van deze ingreep.
- De ervaring met brachytherapie is nog onvoldoende om hierover in een richtlijn voor de standaard patiëntenzorg aanbevelingen te kunnen formuleren.



Salvage CSAP or HIFU

Are salvage CSAP and HIFU appropriate options?



Cryotherapy or HIFU

Close

Uncertain

Panel considerations

The panel considered salvage CSAP or HIFU generally to be less appropriate for patients with biochemical recurrence after radiation therapy. In this patient salvage CSAP or HIFU may be an acceptable option because of life expectancy ≥ 5 years and time to relapse ≥ 3 years.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

The experience with salvage cryosurgical ablation of the prostate (CSAP) and salvage high-intensity ultrasound (HIFU) for biochemical recurrence (BCR) after RT is mostly limited to a few cohort studies with short follow-up data. In addition, the definition of treatment success in terms of BCR has not been agreed upon, thus success rates vary widely based on the definition used.

Read in summary

Overall, the reported 5-year biochemical recurrence-free survival (BRFS) after salvage CSAP ranges from 50-70% in carefully selected patients [1,2].

Read in summary

Guidelines

The EAU guidelines state that salvage CSAP and salvage HIFU are treatment options for patients without evidence of metastasis and with histologically proven local recurrence. Patients must be informed about the experimental nature of these approaches [9].

Concerning salvage CSAP, the EAU guidelines state that it should be considered only for patients with low co-morbidity, a life expectancy ≥ 10 years , an organ-confined cancer cT1c-cT2, Gleason sum ≤ 7, a pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL [9].

According to the EAU guidelines there is a paucity of data for salvage HIFU which prohibits any recommendation regarding its indications [9].

Salvage CSAP and HIFU: evidence (1)

- Evidence is scarce:
  - Mostly limited to small-sized cohort studies with short follow-up
  - Definition of BCR differs between studies
- Salvage CSAP: 5-yr BRFS: 50-70% in selected pts[1,2]
- Salvage HIFU: 5-yr BRFS: 45% low-risk* pts, 21% high-risk (according to D'Amico criteria) pts[3]
- Retrospective case-matched control study[4]:

5-yr oncological outcome	Salvage RP (N = 42)	Salvage CSAP (N = 56)	*P*
BRFS (PSA > 0.4 ng/mL	61%	21%	< 0.001
BRFS (2 PSA increases above nadir)	66%	42%	0.002
OS	95%	85%	0.001

[1]Ismail M et al. BJU Int 2007;100:760-4; [2]Pisters LL et al. J Urol 2008;180:559-63; [3]Crouzet S et al. Radiother Oncol 2012;105:198-202; [4]Pisters LL et al. J Urol 2009;182:517-25

Salvage CSAP and HIFU: evidence (2)

- Systematic review (salvage CSAP: 16 studies; salvage HIFU: 7 studies):

Common complications

CSAP	% of pts
Incontinence	16
Perineal pain	16
Bladder neck stricture/retention	12
Tissue sloughing	8

HIFU	% of pts
Incontinence	37
Bladder neck stricture	15
Urinary retention	8
Fistula	4
Rectal injury	2

Parekh A et al. Semin Radiat Oncol 2013;23:222-34

What do the guidelines say? (1)

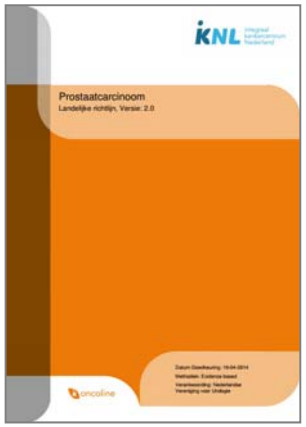
- EAU guidelines (2016):
  - Salvage CSAP and salvage HIFU are treatment options for patients without evidence of metastasis and with histologically proven local recurrence. Patients must be informed about the experimental nature of these approaches
    - Salvage CSAP should be considered only for patients with low comorbidity, a life expectancy ≥10 years, initial organ-confined PCa cT1c - cT2, initial GS ≤ 7, pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL
    - For salvage HIFU there is a paucity of data which **prohibits any recommendations** regarding its indications

What do the guidelines say? (2)

- NCCN guidelines (2016):
  - Salvage CSAP is a treatment option for men with BCR after RT who have a positive biopsy but **low suspicion of metastases** to distant organs, if they are candidates for local therapy (original clinical stage T1-T2, Nx or N0, life expectancy > 10 years and current PSA <10 ng/mL)
  - Treatment needs to be **individualised** based upon the patient's risk of progression, the likelihood of success and the risks involved with salvage therapy
  - Salvage HIFU is **not mentioned**

Wat zegt de NVU richtlijn over cryo/HIFU?

- Bij een histologisch bewezen lokaal recidief zonder lymfeklier- of afstandsmetastasen en een gering risico op occulte micrometastasen kan een in opzet curatieve behandeling overwogen worden, mits de levensverwachting meer dan 10 jaar is.
- De keuze voor een salvage behandeling wordt individueel bepaald op basis van de levensverwachting, comorbiditeit en initiële tumorkarakteristieken alsmede op basis van een afweging van de patiënt betreffende de voor- en nadelen van deze ingreep.
- De ervaring met HIFU en cryotherapie is nog onvoldoende om hierover in een richtlijn voor de standaard patiëntenzorg aanbevelingen te kunnen formuleren.



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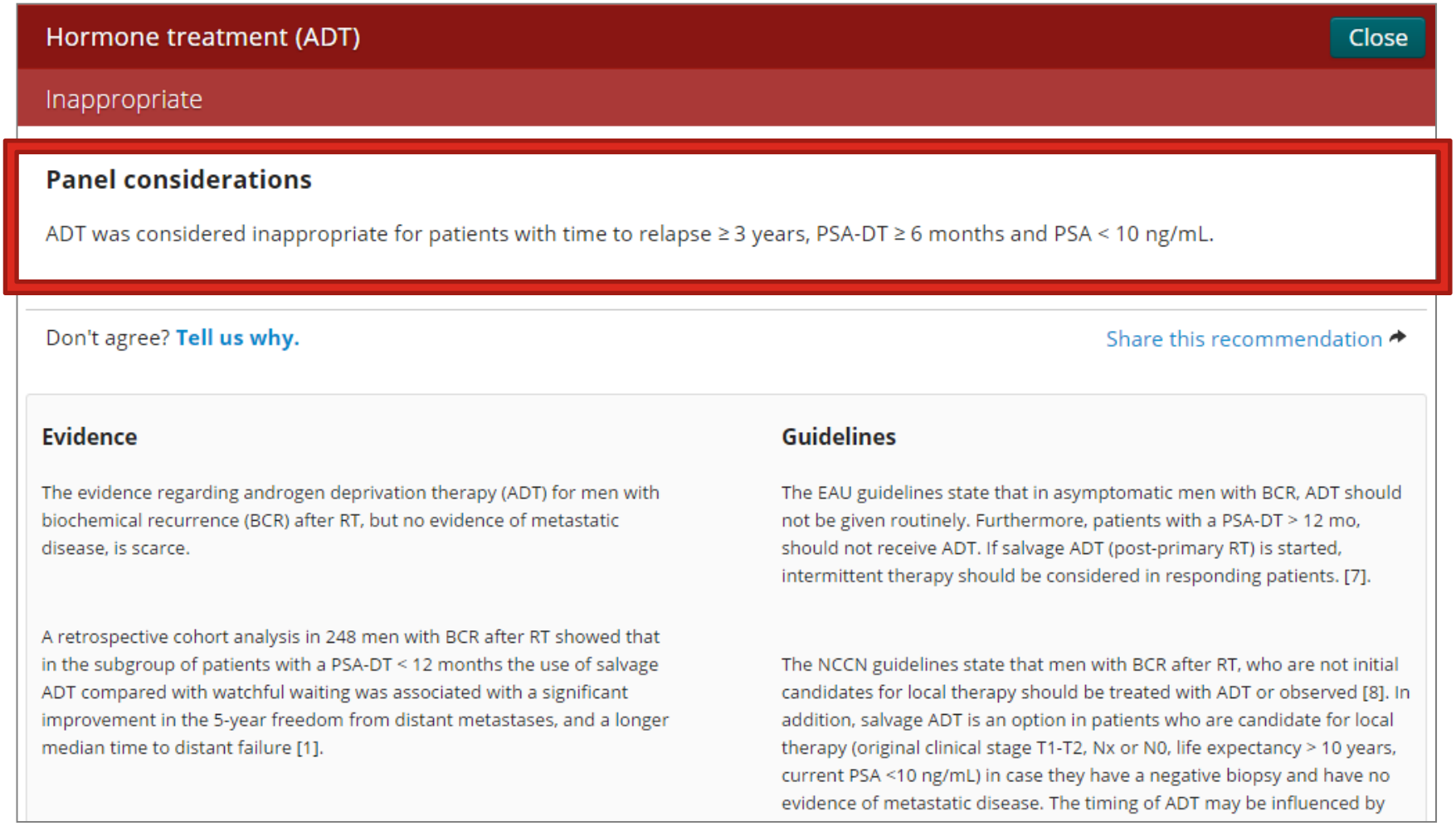
Salvage hormone therapy (ADT)

Is ADT an appropriate option?



Hormone treatment (ADT) Close

Inappropriate

Panel considerations

ADT was considered inappropriate for patients with time to relapse ≥ 3 years, PSA-DT ≥ 6 months and PSA < 10 ng/mL.

Don't agree? **Tell us why.**

Share this recommendation

Evidence

The evidence regarding androgen deprivation therapy (ADT) for men with biochemical recurrence (BCR) after RT, but no evidence of metastatic disease, is scarce.

A retrospective cohort analysis in 248 men with BCR after RT showed that in the subgroup of patients with a PSA-DT < 12 months the use of salvage ADT compared with watchful waiting was associated with a significant improvement in the 5-year freedom from distant metastases, and a longer median time to distant failure [1].

Guidelines

The EAU guidelines state that in asymptomatic men with BCR, ADT should not be given routinely. Furthermore, patients with a PSA-DT > 12 mo, should not receive ADT. If salvage ADT (post-primary RT) is started, intermittent therapy should be considered in responding patients. [7].

The NCCN guidelines state that men with BCR after RT, who are not initial candidates for local therapy should be treated with ADT or observed [8]. In addition, salvage ADT is an option in patients who are candidate for local therapy (original clinical stage T1-T2, Nx or N0, life expectancy > 10 years, current PSA <10 ng/mL) in case they have a negative biopsy and have no evidence of metastatic disease. The timing of ADT may be influenced by

ADT: evidence (1)

- Evidence is scarce
- Retrospective cohort analysis of men with BCR after RT[1]:

5-yr freedom from distant metastases

PSA-DT ≥ 12 months			PSA-DT < 12 months		
Observation (N = 89)	**ADT (N = 11)**	***P***	**Observation (N = 89)**	**ADT (N = 59)**	***P***
92%	88%	0.7398	57%	78%	0.0026

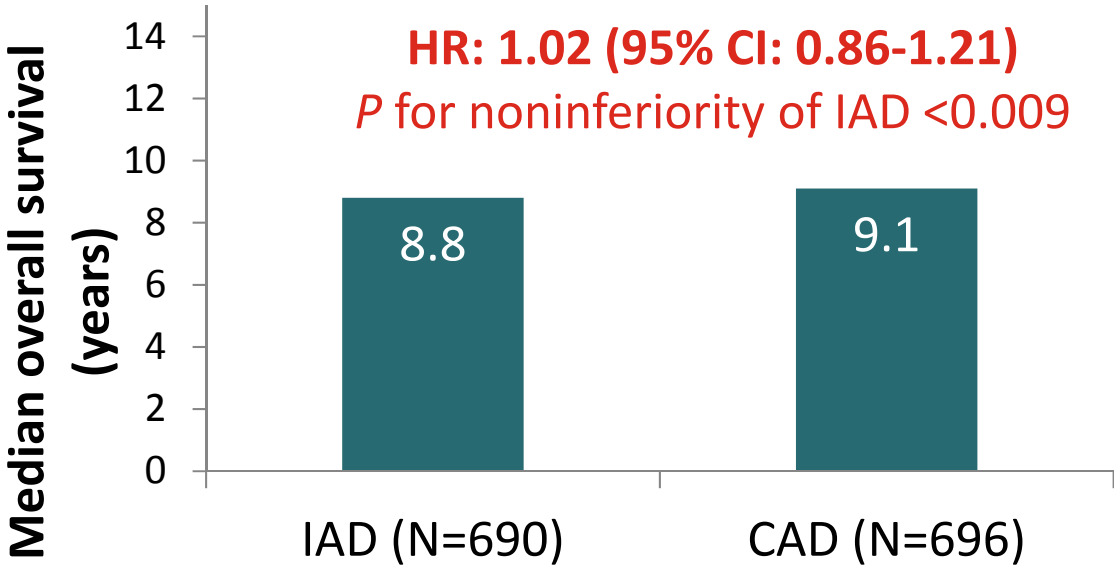
- Retrospective cohort analysis of 178 men with BCR after RT and no metastatic disease[2]:
  - Men with low PSA and long PSA-DT: observation
  - Men with higher PSA and shorter PSA-DT: ADT

Similar CSS at 7 yr follow-up

PHNL/ZYT/0115/0002h(1)

ADT: evidence (2)

- Phase 3 RCT: intermittent ADT (IAD) vs continuous ADT (CAD) in men with BCR after RT and no distant metastases; median follow-up: 6.9 yrs



- IAD: potential benefits in physical function, fatigue, urinary problems, hot flushes, libido, and erectile function

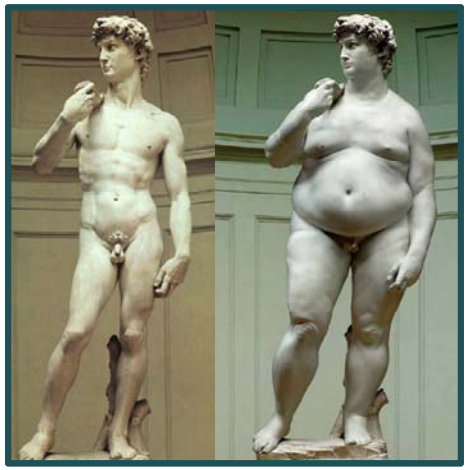
IAD was noninferior to CAD regarding overall survival and may improve quality of life

Crook JM et al. N Engl J Med 2012;367:895-903

ADT: side effects

- Short-term side effects
  - Loss of libido and sexual interest, erectile dysfunction, impotence
  - Hot flushes
  - Decline in intellectual capacity, emotional liability, depression
  - Decline in physical activity and general vitality

- Long-term side effects
  - Sarcopenic obesity
  - Osteoporosis
  - Increased risk of cardiovascular events



Payne H et al. World J Urol 2013;31:1333-8

What do the guidelines say? (1)

- EAU guidelines (2016):
  - In asymptomatic men with BCR, ADT should not be given routinely
  - Patients with a PSA-DT > 12 mo, should not receive ADT
  - If salvage ADT (post-primary RT) is started, intermittent therapy should be offered to responding patients

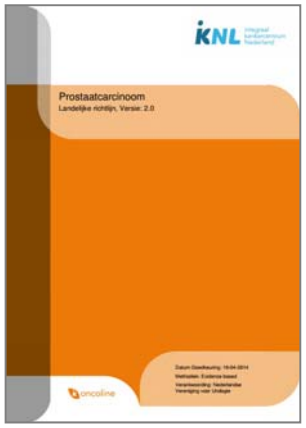
What do the guidelines say? (2)

- NCCN guidelines (2016):
  - Men with biochemical failure after RT who are **not initial candidates for local therapy** should be treated with ADT or observed
  - Salvage ADT is also an option in pts who are candidate for local therapy* in case of negative biopsy and no evidence of metastatic disease
  - Timing ADT: influenced by PSA velocity, patient anxiety, short- and long-term side effects of ADT and comorbidities
    - shorter PSA-DT (or rapid PSA velocity) and otherwise long life expectancy: consider ADT earlier
  - Men who choose ADT should consider intermittent ADT
  - Treatment needs to be **individualised** based upon pt's risk of progression, likelihood of success and risks involved with salvage therapy

* original clinical stage T1-T2, Nx or N0, life expectancy > 10 years, current PSA <10 ng/mL

Wat zegt de NVU richtlijn over ADT?

- Hormonale therapie voor alleen een PSA-recidief zonder aantoonbare afstands- of lymfekliermetastasen wordt niet aanbevolen, tenzij in studieverband.



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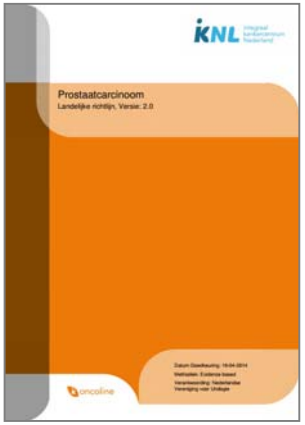
Wat zegt de NVU richtlijn?

- Het PSA beloop na uitwendige radiotherapie en brachytherapie moet vanwege het bestaan van de “PSA-bounce” voorzichtig worden geïnterpreteerd.
- Indien er sprake is van een PSA stijging van 2 ng/mL boven de nadir wordt van een recidief gesproken.



Clinical variables: patient case 2

What would be the most appropri treatment for this patient?

Stemronde geopend

1. Observation (no active treatment)
2. Salvage radical prostatectomy
3. Salvage external beam radiation
4. Salvage brachytherapy
5. Cryotherapy or HIFU
6. Hormone treatment (ADT)

Compare voting before - after

1st voting

2nd voting

1. Observation (no active treatment)
2. Salvage radical prostatectomy
3. Salvage external beam radiation
4. Salvage brachytherapy
5. Cryotherapy or HIFU
6. Hormone treatment (ADT)

BCR/RT model:

Case change

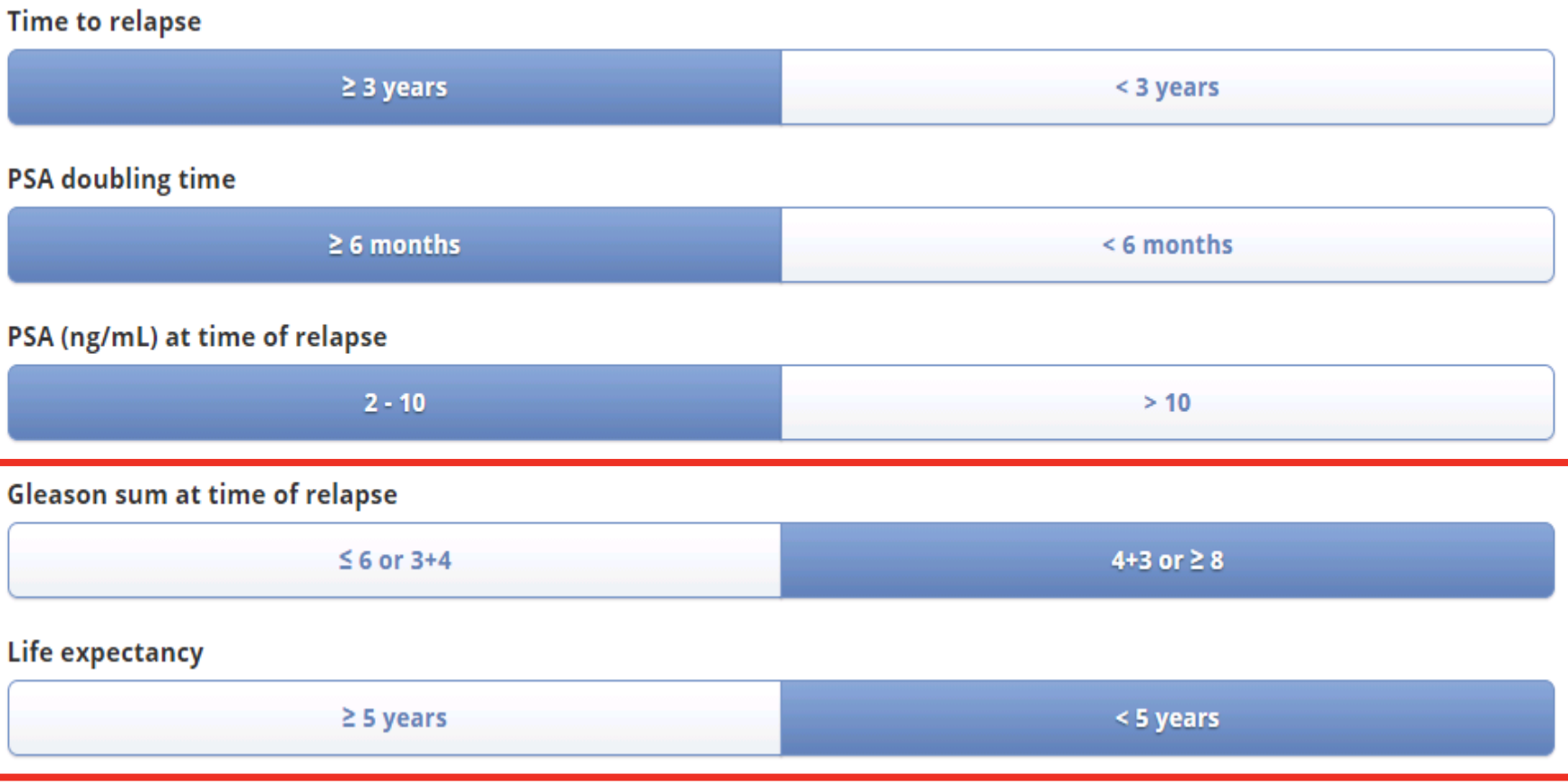
What if the previous patient would have....

- 67 yr old, retired engineer
- Initial PSA 8 ng/mL
- Treated with EBRT for localised T2 PCa in 2009
- PSA nadir (2012): 2 ng/mL
- Elevated PSA in October 2013: 7 ng/mL
- PSA-DT: 10 months
- Biopsy in November 2013:
  - GS: 4+3
  - Imaging: no evidence of metastatic disease
- Comorbidities:
  - Non-controlled diabetes mellitus
  - Recent CVA
  - History of 2 acute myocardial infarctions
  - Smoker

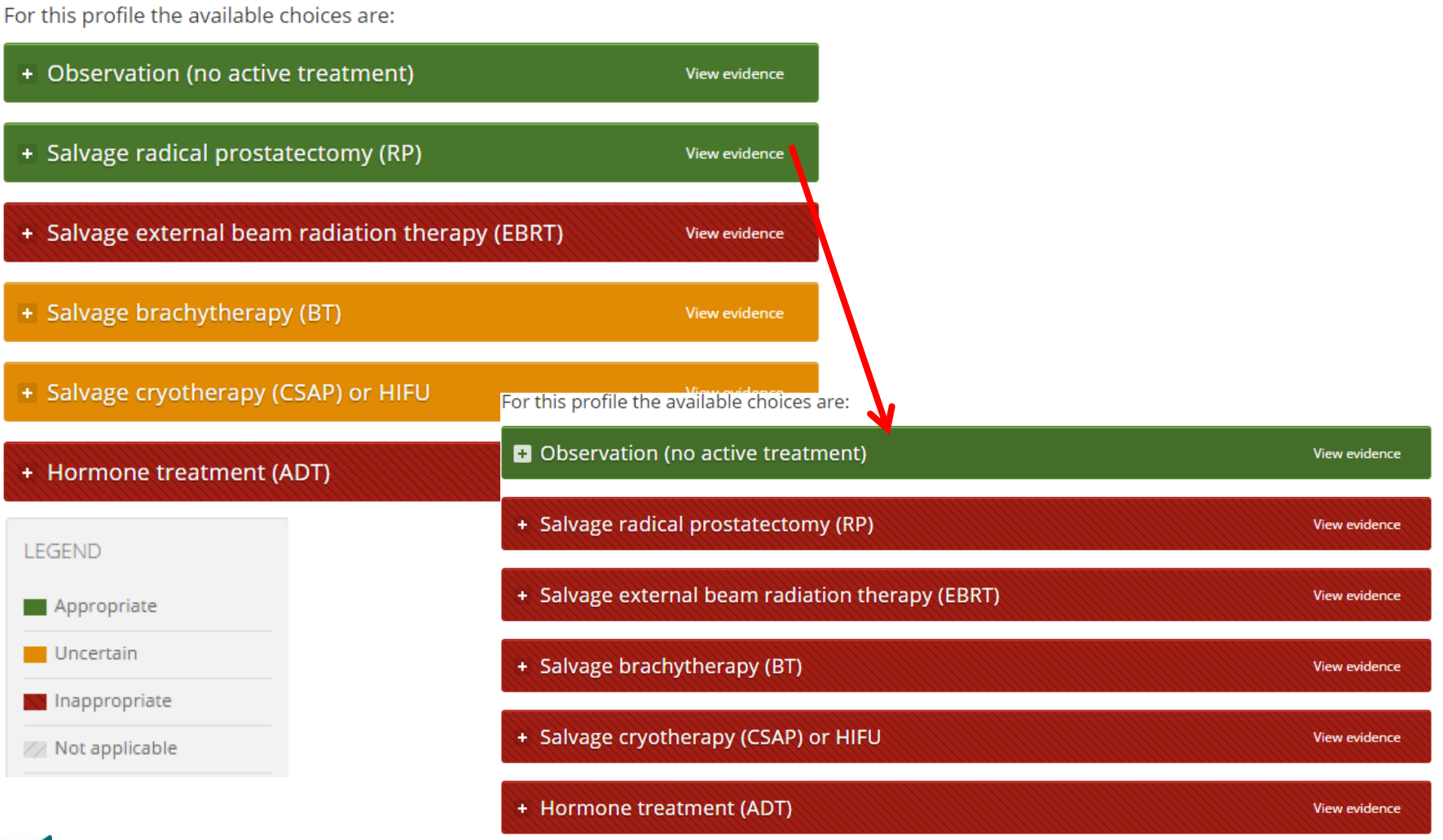
Life expectancy: 2 yr

What would be the most appropriate treatment for this patient?

Clinical variables: patient 2 case change



What have we learned from this patient case?



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Key messages:
Which salvage therapy to choose? (1)

Direct comparison of different salvage therapies is difficult:

- Lack of RCTs and comparative studies
- No standardised definition of BCR
- No standardised definitions of outcome measures
- Wide variability in follow-up times
- Lack of standardised reporting of tolerability

Key messages: which patients would benefit most from salvage therapy?

- Generally, a worse outcome of salvage therapy is associated with:
  - Short time to PSA relapse
  - Rapid PSA-DT
  - High PSA level at time of relapse
  - High GS at time of relapse
- Life expectancy should be long enough to benefit from treatment

Treatment needs to be individualised

Nguyen PL et al. Cancer 2007;110:1417-28; Parekh A. Semin Radiat Oncol 2013;23:222-34; Chade DC et al. Eur Urol 2012;61:961-71

Key messages: BCR after RP

- Salvage RT:
  - Offers durable disease control: 16-84% of pts free from BCR 5 yr after salvage RT
  - Significantly improves CSS vs observation, but only in men with PSA-DT < 6 mo, who underwent salvage RT within 2 yr of BCR and whose PSA became undetectable after RT
  - As high pre-RT PSA levels strongly predict recurrence after salvage RT, salvage RT should be initiated **at the earliest signs of PSA recurrence**
- Salvage RT + ADT:
  - Addition of ADT to salvage RT may improve BRFS, but the benefit may be limited to patients with **high-risk features**
- Salvage ADT:
  - The potential benefit of salvage ADT –if any– should be outweighed against the **side effects** of prolonged (or even life-long) ADT

Key messages: BCR after RT

- Salvage RP: scientific evidence best documented
  - Mostly cohort studies
  - Comparative study showed better outcomes for salvage RP vs CSAP
  - 5-yr BRFS: 47-82%
  - However, high rate of incontinence and anastomotic strictures
- Salvage EBRT: not indicated
- Salvage BT, CSAP:
  - Mostly small-sized cohort studies with limited follow-up
  - 5-yr BRFS rates are comparable (about 50%)
  - Morbidity rates vary highly amongst studies
- Salvage HIFU, ADT:
  - Limited evidence

Nguyen PL et al. Cancer 2007;110:1417-28; Parekh A. Semin Radiat Oncol 2013;23:222-34;
Chade DC et al. Eur Urol 2012;61:961-71

Thank you

Mirrors of medicine

Evaluatie

1. Hoe waardeert u de inhoud? **1 2 3 4 5**
2. Module 3: Diagnosis of prostate cancer **1 2 3 4 5**
3. Module 4: Biochemical recurrence after radical treatment **1 2 3 4 5**
4. Door de nascholing heb ik meer inzicht gekregen in de behandeling van prostaatkanker en mijn kennis ervan vergroot **1 2 3 4 5**
5. Ik wil graag een persoonlijk account aanmaken **1 2 3 4 5**
6. Hoe waardeert u de locatie? **1 2 3 4 5**
7. Sluit de gevolgde nascholing Mirrors of Medicine voldoende aan bij de klinische praktijk? **1 2 3 4 5**
8. Vond u dat er voldoende tijd was voor het stellen van vragen? **1 2 3 4 5**
9. Zou u op basis van deze nascholing Mirrors of Medicine aanbevelen bij uw collega's? **1 2 3 4 5**
10. Vond u de rol van Janssen en AstraZeneca passend tijdens de nascholing Mirrors of Medicine? **1=Ja 2=Nee**