# LA GESTIONE DELLA RECIDIVA BIOCHIMICA


## *Paolo Verze*

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***EAU Guidelines Sexual and Reproductive Health Panel - Member***
***EAU-YAU Men's health group – Chairman***
***European Society for Sexual Medicine (ESSM) - Member***


# Question Time 1

*How do we define the BCR?*

# Definition of Biochemical recurrence (BCR)

## AFTER RP

- 2 consecutive values of PSA 0.2 > ng/ml or greater;

The American Urological Association Prostate Guidelines for Localized Prostate Cancer. J Urol. 2007;
European Association of Urology. EAU guidelines on prostate cancer. Eur Urol. 2014;

- Best predicts further metastases is a PSA > 0.4 ng/mL and rising

## AFTER RT

- PSA increase ≥ 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir

After HIFU or cryotherapy no endpoints have been validated against clinical progression or survival.

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# Follow-up

| Recommendations | Strength rating |
|---|---|
| Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at three, six and twelve months after treatment, then every six months until three years, and then annually. | Strong |
| During follow up, perform a systematic DRE after surgery if unfavourable pathology (> pT3, pN1, Gleason ≥ 8). | Weak |
| During follow up, perform a systematic DRE after radiotherapy. | Strong |
| At recurrence, only image to detect local recurrence if it affects treatment planning. | Strong |
| Do not routinely offer bone scans and other imaging modalities to asymptomatic patients if there are no signs of biochemical relapse. In case patients have bone pain or other symptoms of possible progression, restaging should be considered irrespective of serum PSA level. | Strong |

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# Epidemiology

- Between 27% and 53% of all patients undergoing RP (20-40%) or RT (30-53%) develop PSA recurrence.

Freedland SJ, et al,JAMA 2005
Roehl KA et al. J Urol 2004
Kupelian PA et al.Urology 2006

- Not all patients with BCR after RP will develop clinical recurrences. In two studies of 1,997 and 2,400 men treated by RP, only 23-34% of those with BCR developed a clinical recurrence and 6% subsequently died of PCa.

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# Risk factors for relapse

- **Gleason score ≥ 7 or patients classified as pT3 pN0** after RP due to positive margins (highest impact), capsule rupture and/or invasion of the seminal vesicles are at high risk of relapse which can be as high as 50% after five years.

- Irrespective of the pT stage, **the number of removed nodes, tumour volume within the LN and capsular perforation of the nodal metastases** are predictors of early recurrence after RP for pN1 disease.
- **A LN density** (defined as the percentage of positive LNs in relation to the total number of analysed/removed LNs) **over 20%** was found to be associated with poor prognosis.
- Finally **the number of involved nodes** seems to be a major factor for predicting relapse, the threshold being considered to be less than **three positive nodes from an ePLND.**

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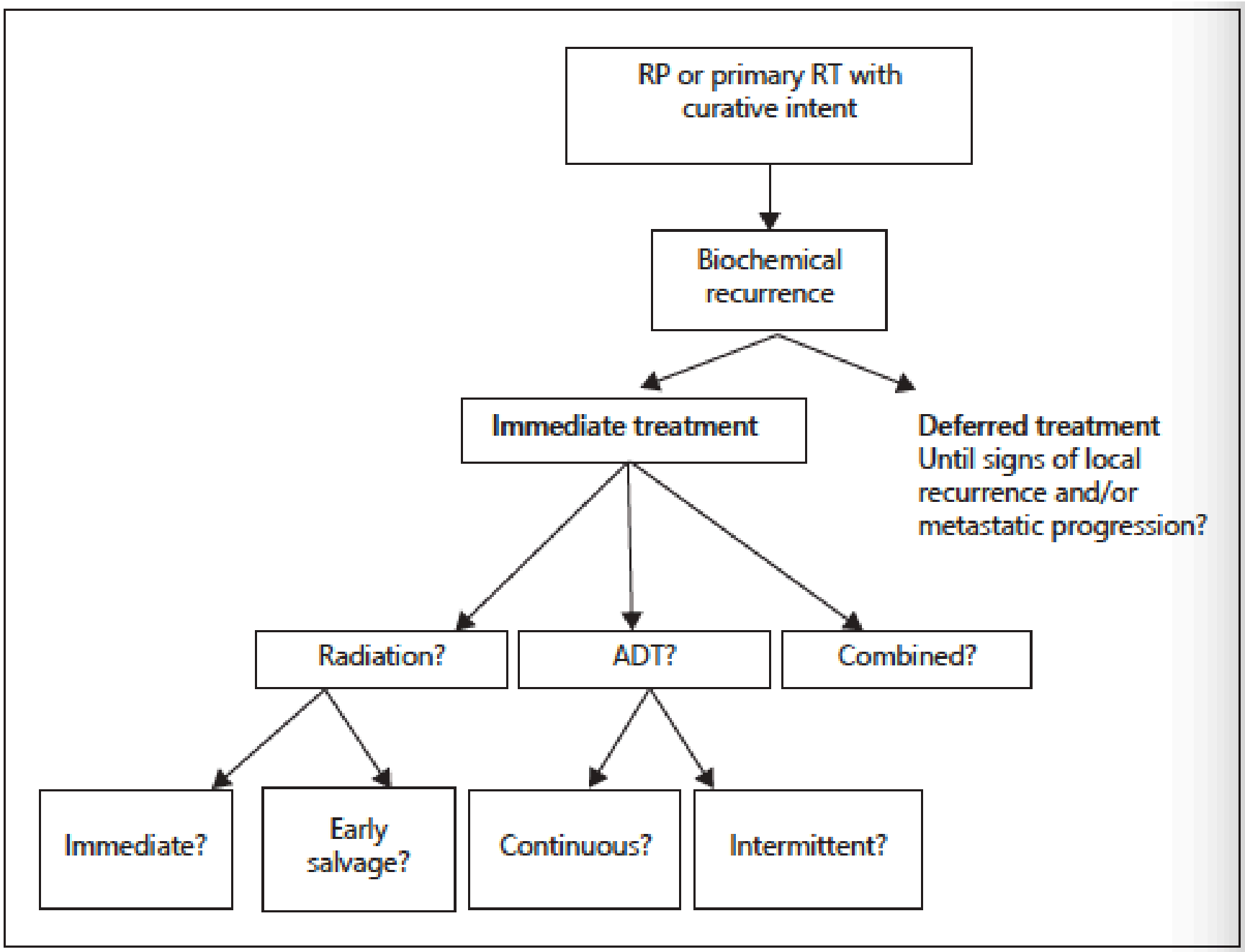
# Question Time 2

*Is it a unique (simple) clinical scenario?*




**Artibani et al.** Urol Int **Review 2017**

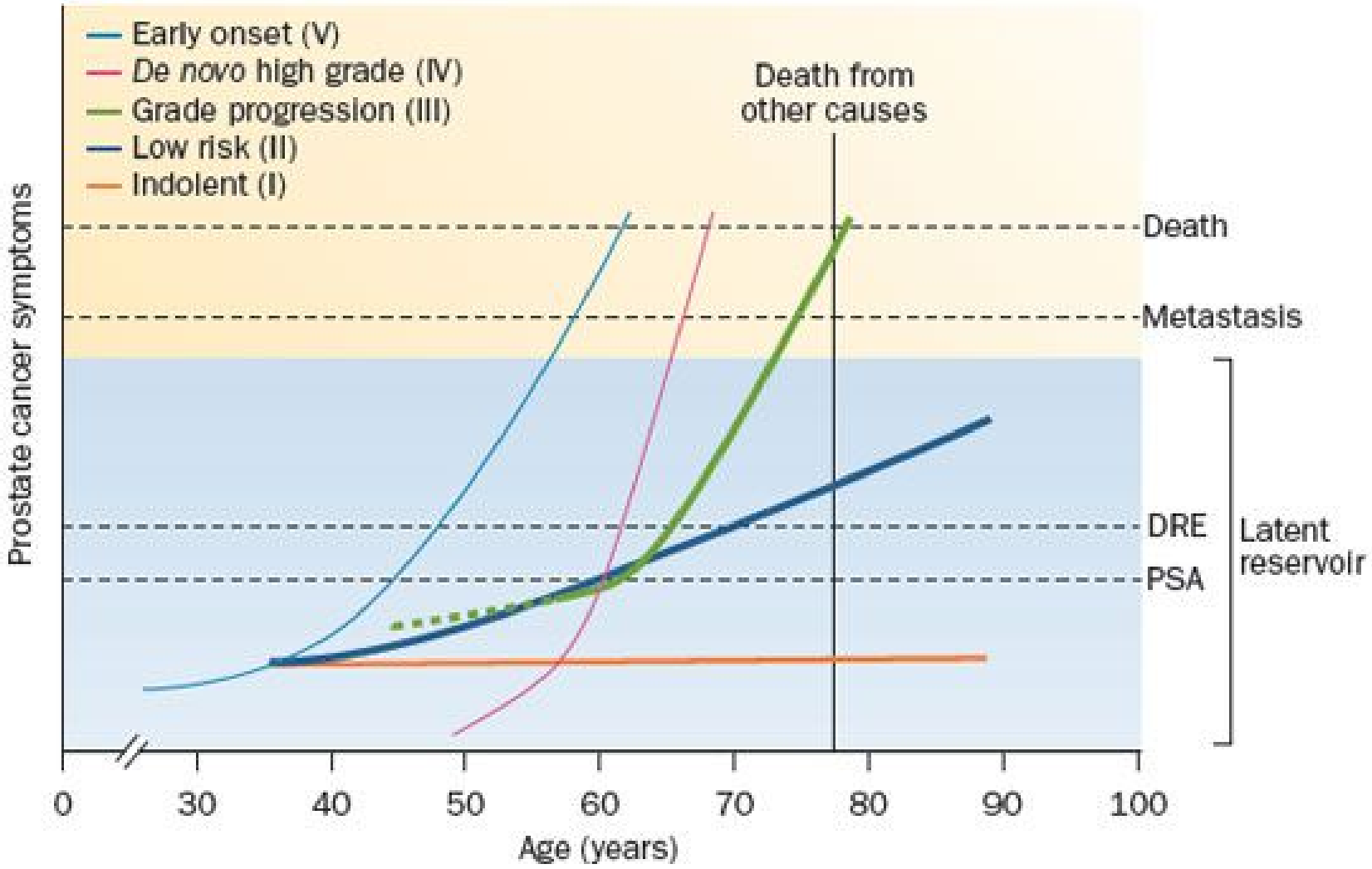
# CLINICAL CHALLENGES

- To prevent or delay the onset of metastatic disease and the resulting morbidity and mortality

  *1/3 develops metastatic disease within 15 yrs*

  *2-6% may die from PCa*

- To take into account the patients' QoL
- To avoid over-treatment in pts with low risk of clinical progression




Van der Kwast, T. HNat. Rev. Urol, 2013

Adjuvant treatment is by definition added to the primary or initial therapy to decrease the risk of relapse.


Regarding RP, the key factor is that the PSA must be below 0.1 ng/mL to be considered undetectable.

A post-operative PSA of above 0.1 ng/mL is an indication of persistent PCa cells. In such a case, further treatment will be salvage treatment

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# Risk factors

**Table 1.** Pre- and post-treatment prognostic factors in PSA-recurrent prostate cancer [21, 28, 33, 99]

| | Pre-treatment (factors relating to initial tumour) | Post-treatment |
|---|---|---|
| Biochemical features | Baseline PSA<br>Tumour stage (T-stage)* | PSA kinetics<br>– PSA-DT<br>– PSA velocity<br>Time to biochemical recurrence**<br>Absolute PSA value at time of testing |
| Pathologic features | Gleason score | Gleason score<br>Surgical margin status<br>Extracapsular extension<br>Seminal vesicle involvement<br>Lymph node status score |

* Based on both biochemical and biopsy findings.
** Studies report conflicting results as to whether time to biochemical recurrence is a prognostic indicator.
PSA, prostate-specific antigen; PSA-DT, PSA doubling time.

Review

**Artibani et al. Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review 2017**

- BCR within first 6 months from RP → local metastasis
- Short PSA-DT → early clinical recurrence

- Short PSA-DT (<3 mo)
- Seminal vesicle invasion
- BCR within 3 yrs
- pGleason score 8-10

} PCa-specific mortality

# Question Time 3

*Are we based only on PSA or is an in-depth imaging study necessary?*

### 6.3.4.4 *Guidelines for imaging in patients with biochemical recurrence*

| **Prostate-specific antigen (PSA) recurrence after radical prostatectomy** | **LE** | **Strength rating** |
|---|---|---|
| Perform imaging only if the outcome will influence subsequent treatment decisions. | | Strong |
| If the PSA level is ≥ 1 ng/mL, perform a prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT), if available, or a choline PET/CT imaging otherwise. | 2b | Weak |
| **PSA recurrence after radiotherapy** | | |
| Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients who are considered candidates for local salvage therapy. | 3 | Strong |
| Perform PSMA PET/CT (if available) or choline PET/CT imaging to rule out positive lymph nodes or distant metastases in patients fit for curative salvage treatment. | 2b | Strong |

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## LOCAL RECURRENCE

| After radical prostatectomy | After definitive radiotherapy |
|---|---|
| TRUS is not effective<br>Biopsy is unnecessary<br>Choline PET is promising<br>–But sensitivity is not optimum when PSA <0.5 ng/mL<br>The threshold often used for salvage radiotherapy | Ultrasonography not reliable enough<br>Biopsy is a major predictor of outcome<br>– When performed 18–24 months after treatment<br>mp-MRI can be useful in directing core sampling |

mp-MRI, multiparametric-magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

## SYSTEMIC RECURRENCE

- **Bone scan**
- **CT**

Low sensitivity for detecting local recurrence or lymph node metastases after RP

- **PET scans using agents such as choline, acetate or prostate-specific membrane antigen (PSMA)**

Better sensitivity and specificity for detecting bone metastases but with high cost

- **Whole body diffusion-weighted (MRI)**
- **Spinal MRI**
- **Lymph node MRI**

MRI Improve detection of bone metastases in patients with highrisk PCa but little is known about this technique in the context of BCR after RP or RT

**Artibani et al.** Urol Int **A Review 2017**

In men with PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL.

Only 11-14% of patients with BCR after RP have a positive CT. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively.

# PSMA PET -TC

- PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL.

- In a prospective multicentre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging.

- PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to prostate) and poor response (positive nodes or distant disease) to salvage RT.

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# Whole-body and axial MRI

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

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# Question Time 4

*How is the BCR managed?*

6.2.4.5.4 Guidelines for adjuvant treatment options after radical prostatectomy

| Recommendations | Strength rating |
|---|---|
| Only discuss adjuvant treatment in men with a post-operative prostate-specific antigen (PSA) < 0.1 ng/mL. | Strong |
| Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients. | Strong |
| Offer adjuvant external-beam radiation therapy to the surgical field to patients at increased risk of local relapse: pT3 pN0 with positive margins (highest impact), and/or invasion of the seminal vesicles. | Strong |
| Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics:<br>1. Offer adjuvant ADT for node-positive (pN+).<br>2. Offer adjuvant ADT with additional radiotherapy.<br>3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension. | Weak |

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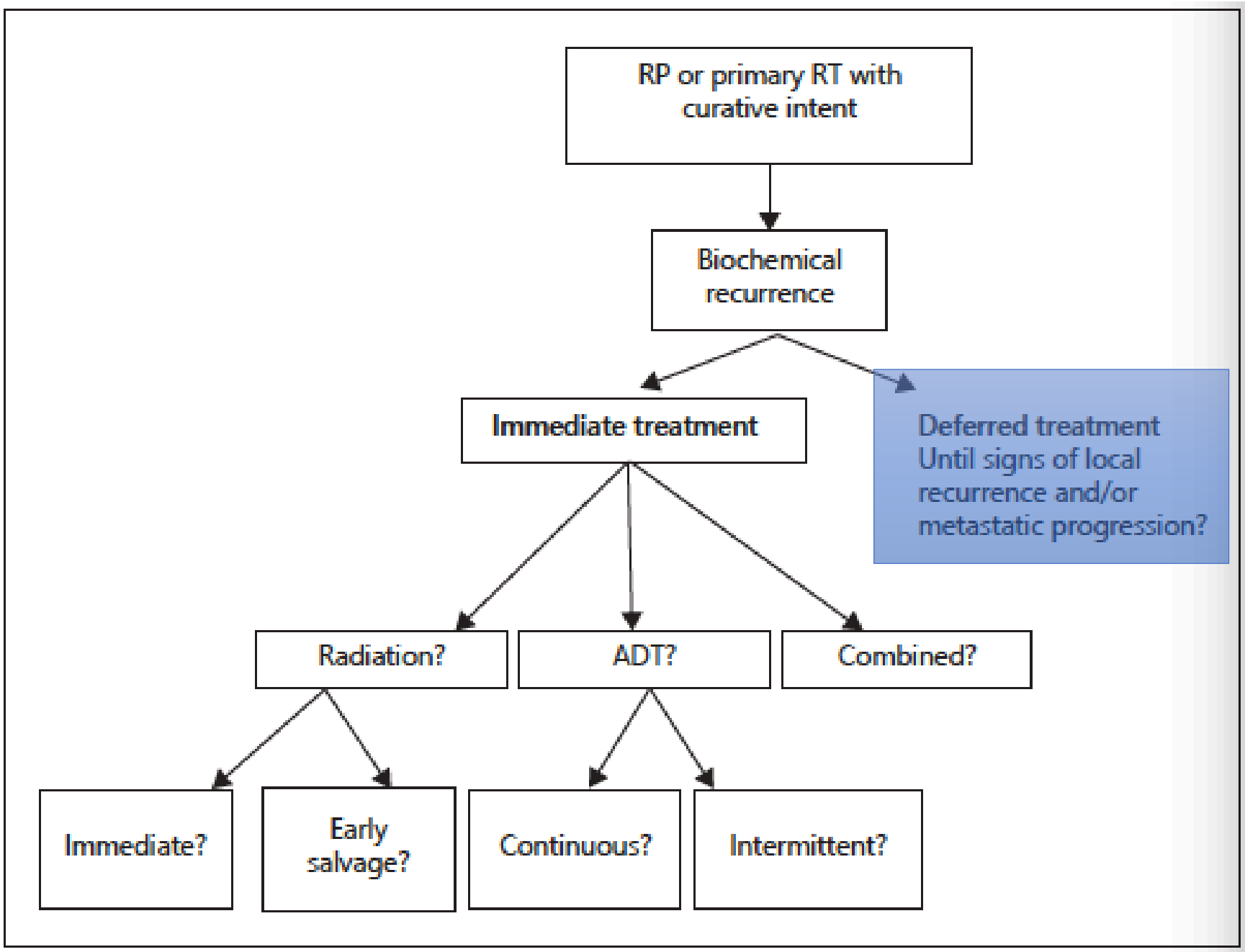



**Artibani et al.** Urol Int **Review 2017**

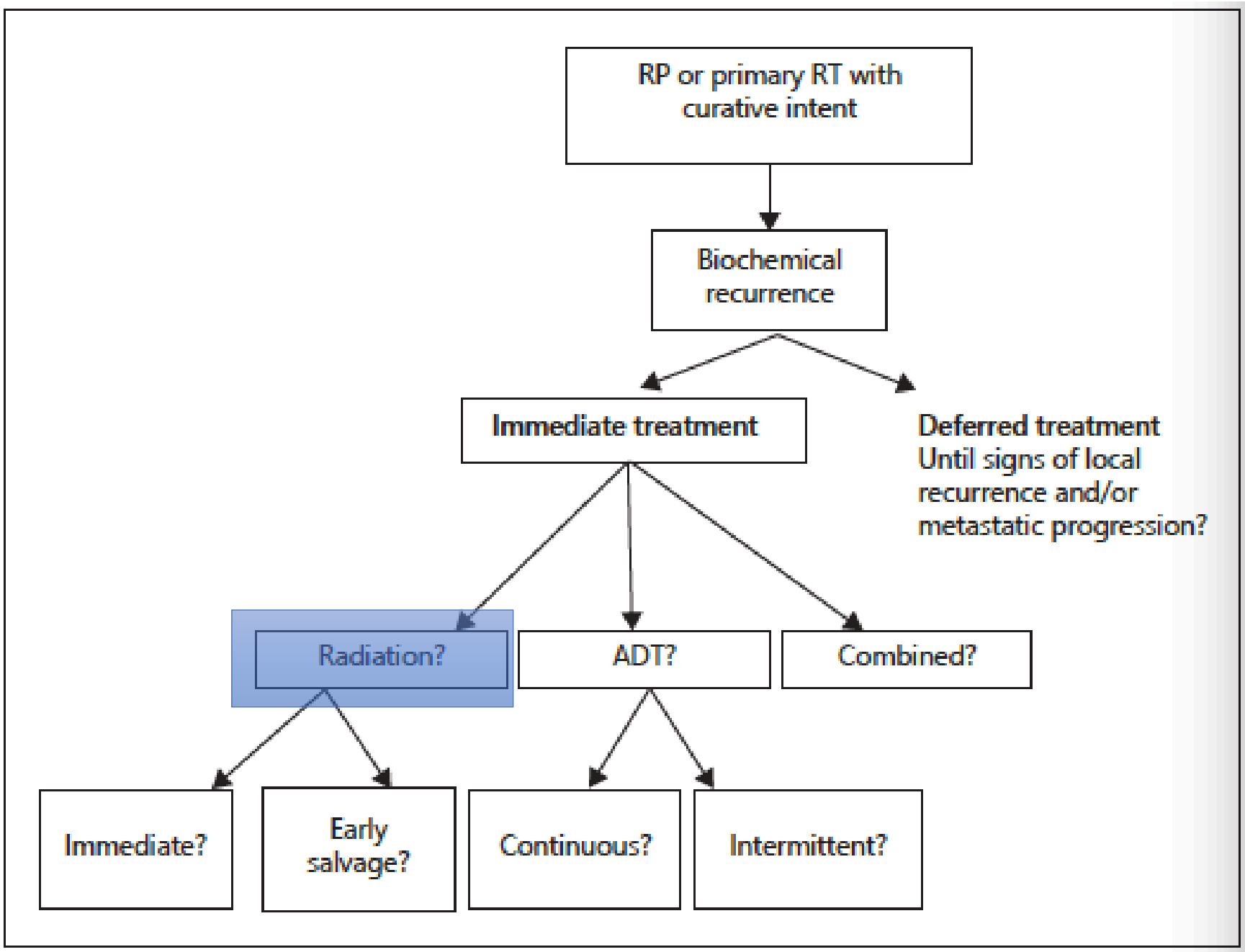
# Observation

## AFTER- RP

Observation until the development of clinically evident metastatic disease may represent a viable option for patients with low-risk features (PSA-DT > 12 months, time to BCR > 3 years, GS ≤ 7 and stage ≤ T3a) or unfit patients with a life expectancy less than ten years and/or are unwilling to undergo salvage treatment.

## AFTER – RT

For patients experiencing BCR post-RP, observation is appropriate for those with signs of only local recurrence (e.g., late BCR and a slow PSA rise) who do not wish to undergo second-line curative options.




**Artibani et al.** Urol Int **Review 2017**

| | |
|---|---|
| Offer adjuvant external-beam radiation therapy to the surgical field to patients at increased risk of local relapse: pT3 pN0 with positive margins (highest impact), and/or invasion of the seminal vesicles. | Strong |

| **Local salvage treatment** | **Strength rating** |
|---|---|
| **Recommendations for biochemical recurrence after radical prostatectomy** | |
| Offer active surveillance and possibly delayed salvage radiotherapy (SRT) to patients with biochemical recurrence and favourable prognostic factors (≤ pT3a, time to biochemical recurrence > three year, prostate-specific antigen doubling-time (PSA-DT) > twelve months, Gleason score ≤ 7), who may not benefit from intervention. | Strong |
| Treat patients with a PSA rise from the undetectable range with SRT.<br>The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL). | Strong |

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# SRT AFTER RP vs ART

EAU - ESTRO - ESUR - SIOG Guidelines on **Prostate Cancer**

The largest retrospective case-matching study to evaluate ART vs. early SRT included pT3N0 R0/R1 patients only (ADT was excluded)

Two and five years after surgery, biochemically no evidence of disease (bNED) rates were 91% and 78% for ART vs. 93% and 82% after salvage RT, respectively.

Subgroup analyses did not yield significant differences for the two approaches.

The results were confirmed for metastasis-free and OS.

It was concluded that early salvage RT does not impair PCa control, but clearly helps to reduce over-treatment, which is a major issue in both ART and in SRT

Briganti, A., *et al.*. Eur Urol, 2012.

JAMA Oncology | Original Investigation

# Comparison Between Adjuvant and Early-Salvage Postprostatectomy Radiotherapy for Prostate Cancer With Adverse Pathological Features

William L. Hwang, MD, PhD; Rahul D. Tendulkar, MD; Andrzej Niemierko, PhD; Shree Agrawal, BS; Kevin L. Stephans, MD; Daniel E. Spratt, MD; Jason W. Hearn, MD; Bridget F. Koontz, MD; W. Robert Lee, MD, MEd, MS; Jeff M. Michalski, MD; Thomas M. Pisansky, MD; Stanley L. Liauw, MD; Matthew C. Abramowitz, MD; Alan Pollack, MD, PhD; Drew Moghanaki, MD, MPH; Mitchell S. Anscher, MD; Robert B. Den, MD; Anthony L. Zietman, MD; Andrew J. Stephenson, MD; Jason A. Efstathiou, MD, DPhil

Pooled data from 1.566 pts with pT2N0M0/R1 or pT3N0M0/R0-1

Post-RP ART or ESRT at 10 academic medical centers

January 1987 – December 2013

JAMA Oncology, 2018

JAMA Oncology | Original Investigation

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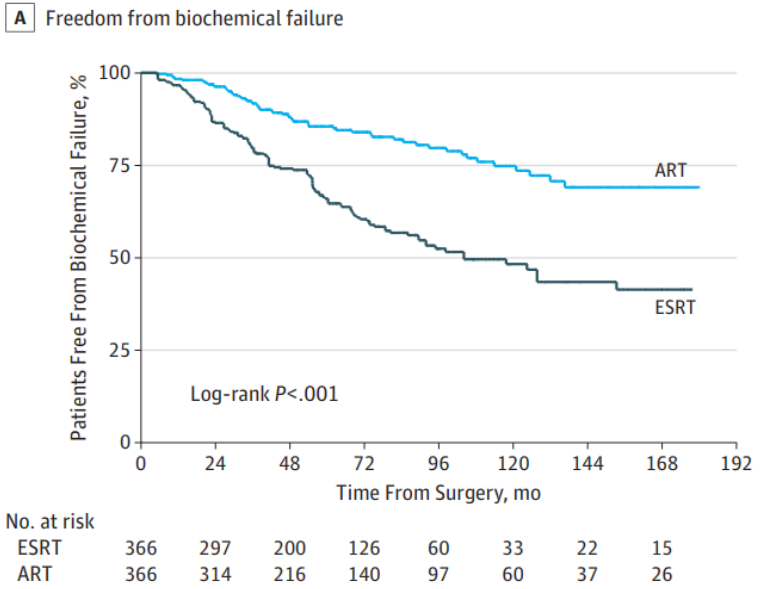
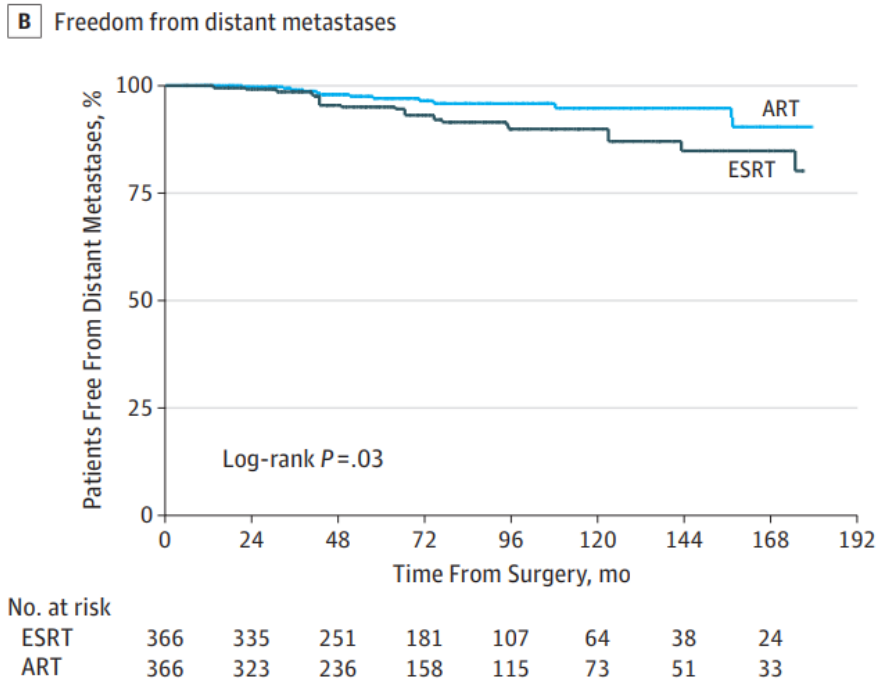
**Figure. Kaplan-Meier Curves After Adjuvant Radiotherapy (ART) vs After Early-Salvage Radiotherapy (ESRT) in a Propensity Score–Matched Cohort of Patients With pT2N0M0/R1 or pT3N0M0/R0-1 Prostate Adenocarcinoma**




JAMA Oncology, 2018

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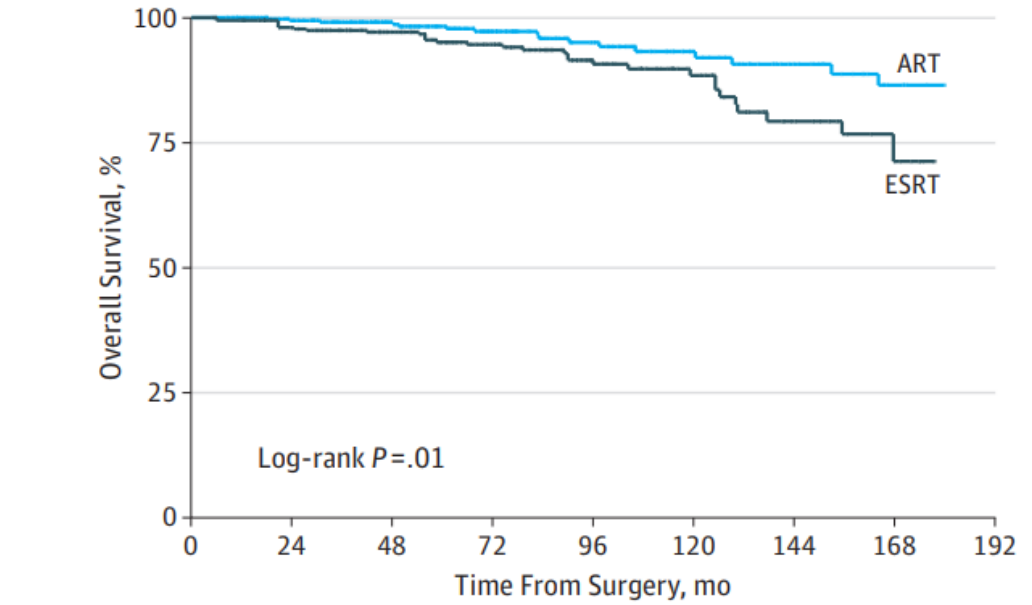
C Overall survival




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ESRT | 366 | 338 | 265 | 188 | 112 | 68 | 40 | 25 |
| ART | 366 | 324 | 240 | 162 | 116 | 75 | 53 | 36 |

JAMA Oncology, 2018

JAMA Oncology | Original Investigation

# Comparison Between Adjuvant and Early-Salvage Postprostatectomy Radiotherapy for Prostate Cancer With Adverse Pathological Features

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- ART compared with ESRT was associated with reduced biochemical recurrence, DM, and death for patients with prostate cancer with adverse pathological features (T3 disease and/or positive margins).

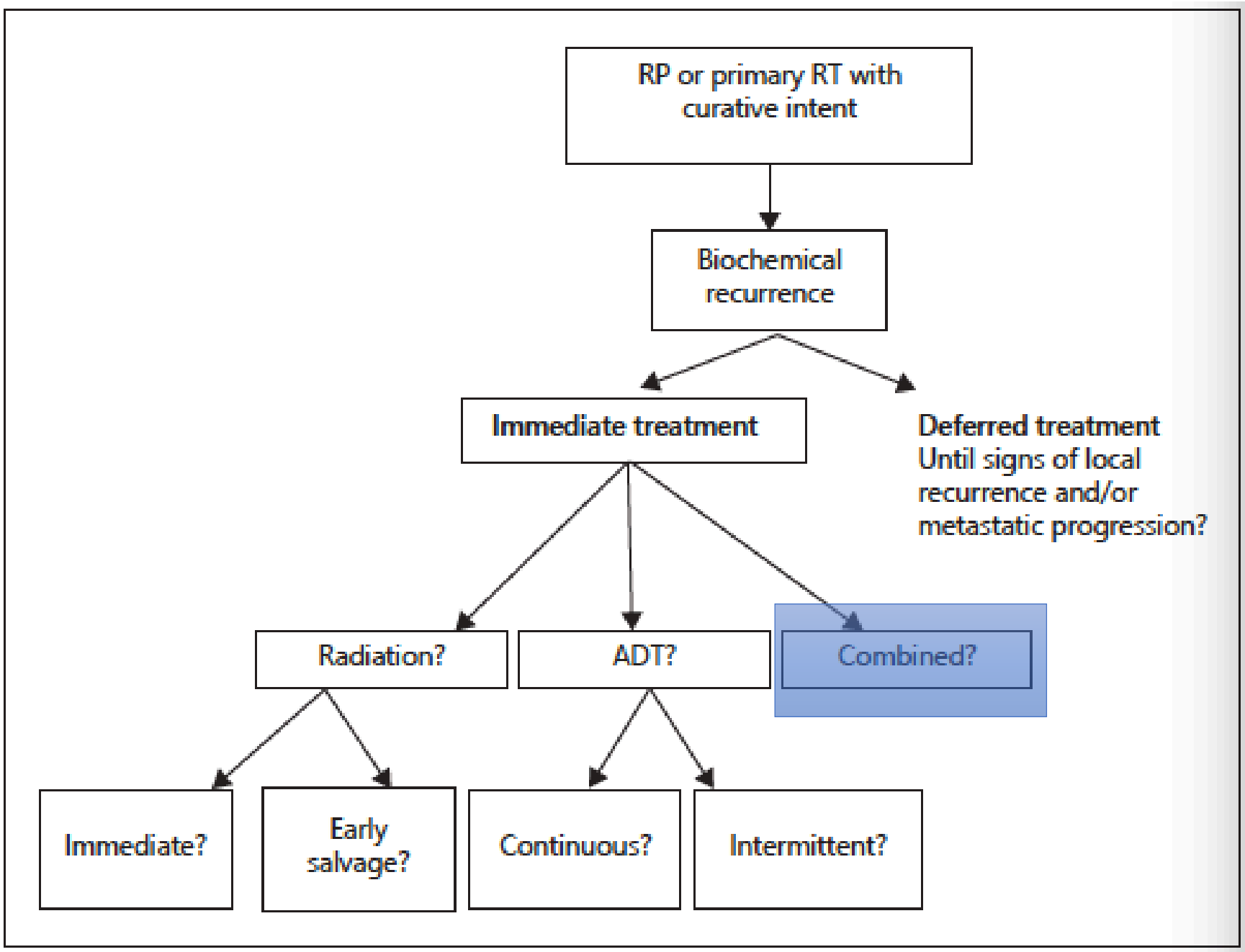
- The current use of ART in high-risk patients is less than 10%. Our findings suggest that a greater proportion of such men may benefit from ART, especially those for whom the estimated risk of post prostatectomy recurrence is greater than 50%.

# EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer

- The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa
- USA Guideline Panel regarded 64-65 Gy as the minimum dose that should be delivered post RP

However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at three to five years

*Relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level*




**Artibani et al.** Urol Int **Review 2017**

| | |
|---|---|
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# Concomitant administration of ADT to postoperative RT

**Table 6.3.3: RCTs comparing salvage radiotherapy alone and salvage radiotherapy combined with androgen deprivation therapy**

| Reference | Year | n | Risk groups | Median FU (mo) | Regimen | Outcome |
|---|---|---|---|---|---|---|
| GETUG-AFU 16<br>Carrie, *et al.*<br>[642] | 2016 | 369 RT + ADT<br>374 RT | GS ≤ 7 89%,<br>GS ≥ 8 11%<br>cN0 | 63 | 66 Gy + GnRH analogue<br>6 mo<br>66 Gy | 5 yr PFS 80%<br>p < 0.0001<br>5 yr PFS 62% |
| RTOG 9601<br>Shipley, *et al.*<br>[641] | 2017 | 384<br>RT + ADT<br>376 RT | pT2 R1, pT3<br>cN0 | 156 | 64.8 Gy + bicalutamide<br>24 mo<br>64.8 Gy + placebo | 12 yr DM 14%<br>p = 0.005<br>12 yr DM 23%<br>12 yr OS 76%<br>p = 0.04<br>12 yr OS 71%<br>12 yr DSM 5.8%<br>p < 0.001<br>12 yr DSM 13.4% |

*ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; GS = Gleason score; PFS = progression free survival; FU = follow-up; GnRH = gonadotropin-releasing hormone; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = Radiotherapy; yr = years.*

also six months treatment with GnRH analogue can improve five-year PFS significantly

CSS and OS benefits for adding two years of bicalutamide to SRT.

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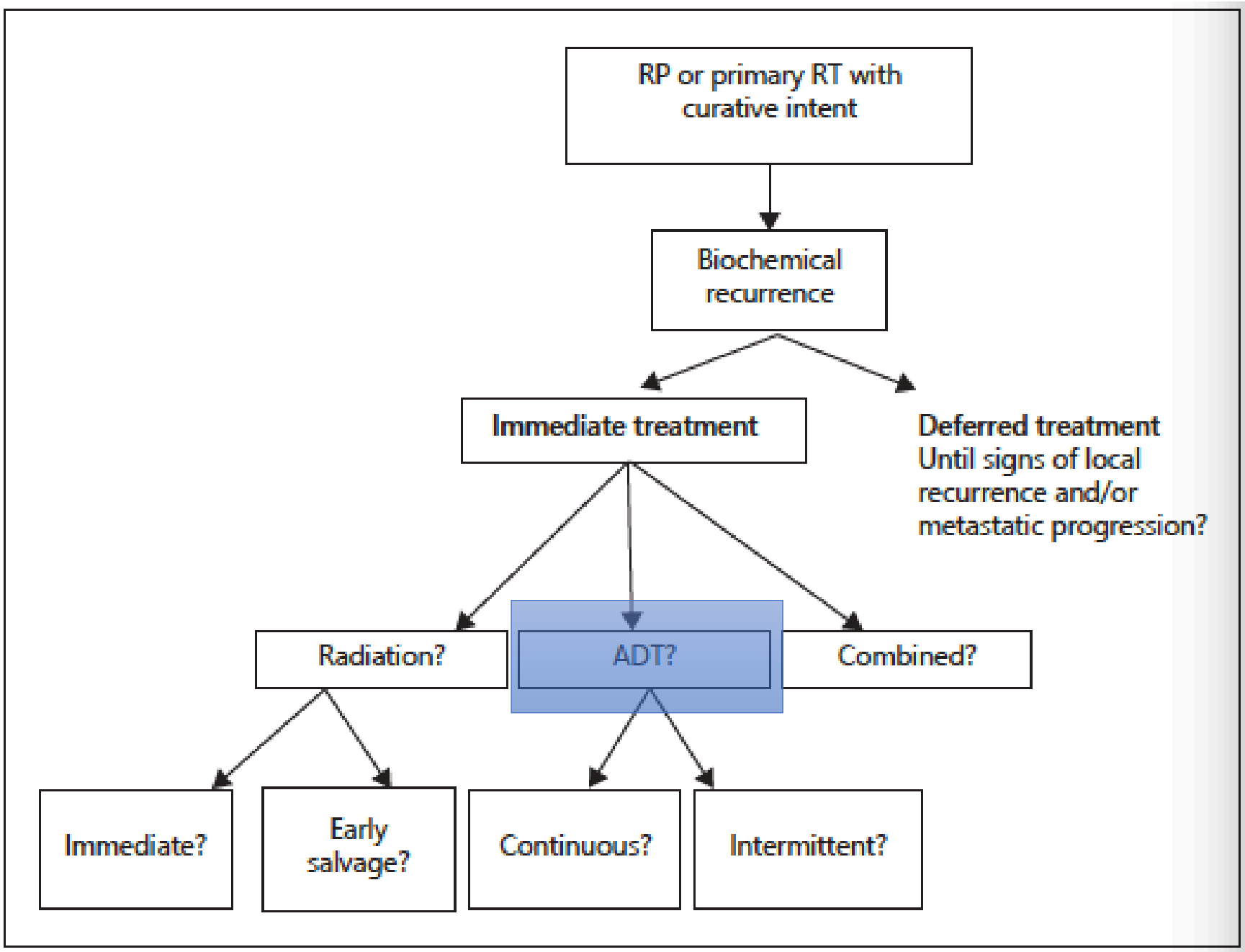


**Artibani et al.** Urol Int **Review 2017**

6.2.4.5.4 Guidelines for adjuvant treatment options after radical prostatectomy

| Recommendations | Strength rating |
|---|---|
| Only discuss adjuvant treatment in men with a post-operative prostate-specific antigen (PSA) < 0.1 ng/mL. | Strong |
| Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients. | Strong |

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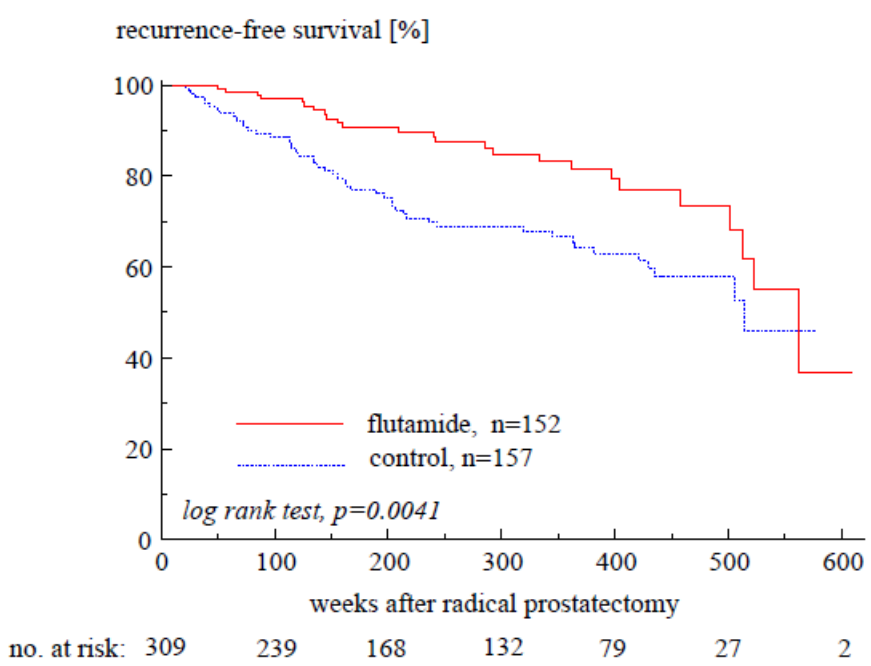
# ADT

European Urology

European Urology 45 (2004) 267–270

## Prospective Randomized Trial Comparing Flutamide as Adjuvant Treatment versus Observation after Radical Prostatectomy for Locally Advanced, Lymph Node-Negative Prostate Cancer

Manfred P. Wirth[a,*], Lothar Weissbach[b], Franz-Josef Marx[c], Wilhelm Heckl[d], Wilfried Jellinghaus[e], Hubertus Riedmiller[f], Birgit Noack[a], Axel Hinke[g], Michael Froehner[a]



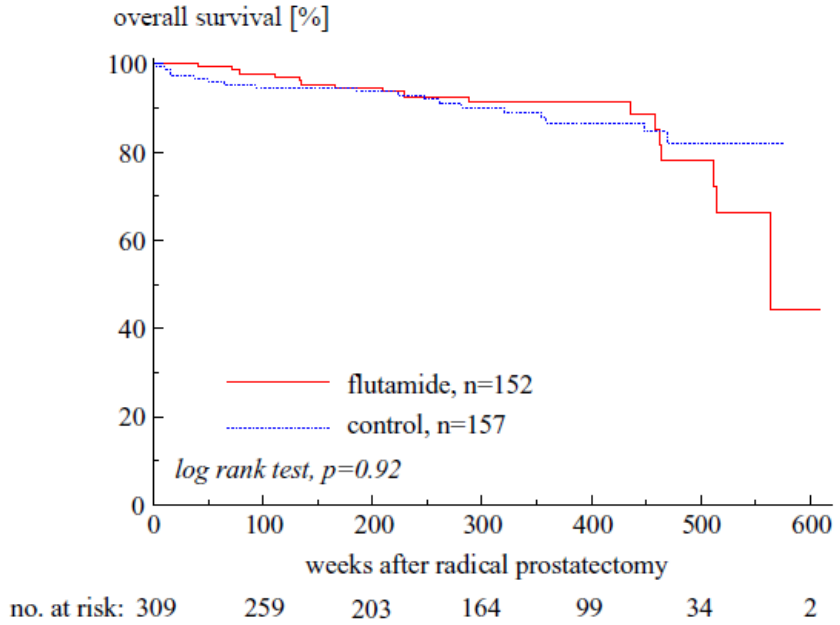




Fig. 2. Overall survival: flutamide versus control.

pN0

In conclusion, in this study, the application of flutamide as adjuvant treatment to patients with locally advanced, lymph node-negative prostate cancer after radical prostatectomy only influenced tumor progression but not survival.

# Salvage Androgen Deprivation

Factors that may favour ADT after RP include:

- a very high risk of clinical recurrence
- good recovery of continence
- long life expectancy
- the patient being anxious about the future or not being ready to accept the idea of sRT.

EAU Guidelines, 2018

The New England
Journal of Medicine

pN+

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VOLUME 341 DECEMBER 9, 1999 NUMBER 24

# IMMEDIATE HORMONAL THERAPY COMPARED WITH OBSERVATION AFTER RADICAL PROSTATECTOMY AND PELVIC LYMPHADENECTOMY IN MEN WITH NODE-POSITIVE PROSTATE CANCER

EDWARD M. MESSING, M.D., JUDITH MANOLA, M.S., MICHAEL SAROSDY, M.D., GEORGE WILDING, M.D., E. DAVID CRAWFORD, M.D., AND DONALD TRUMP, M.D.

- 98 pts who underwent RP + ePLND
- N+
- Randomized to ADT (LHRH agonist) vs Bilateral orchiectomy vs Observation

The New England
Journal of Medicine

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VOLUME 341 DECEMBER 9, 1999 NUMBER 24

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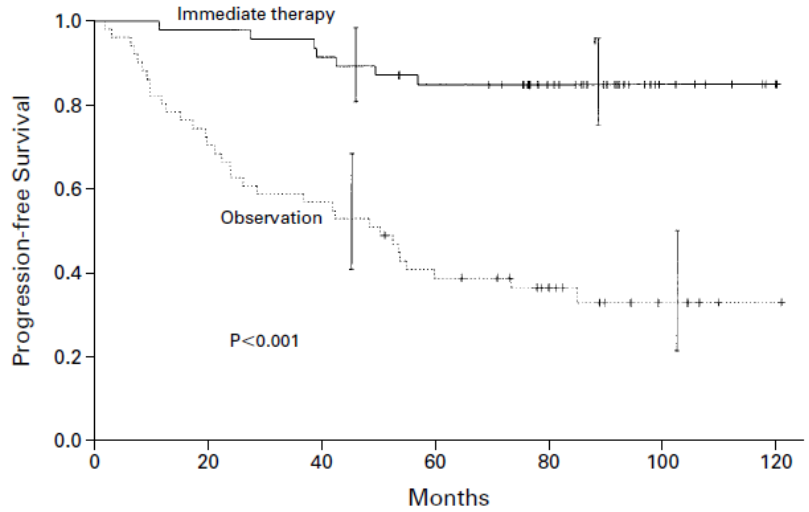


NO. AT RISK

| | | | | |
|---|---|---|---|---|
| Immediate therapy | 47 | 46 | 38 | 8 |
| Observation | 51 | 36 | 19 | 5 |

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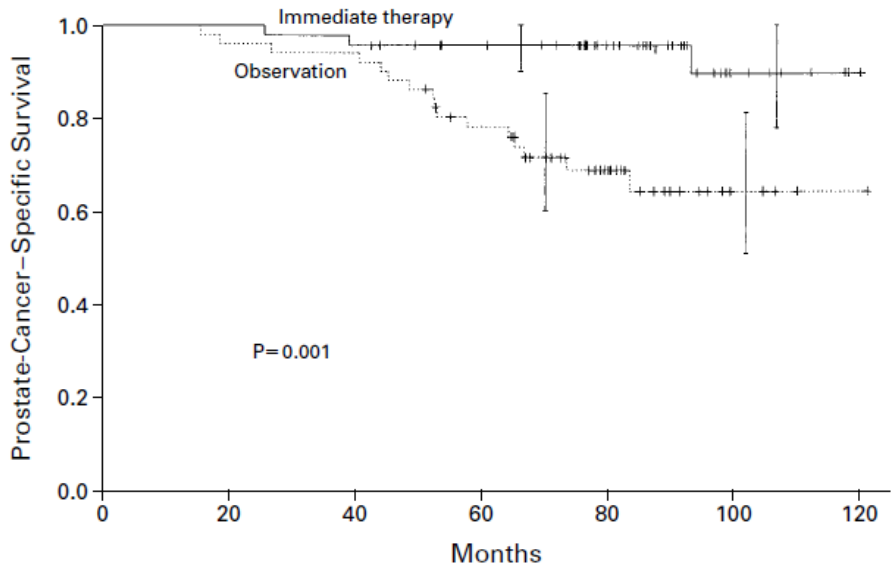
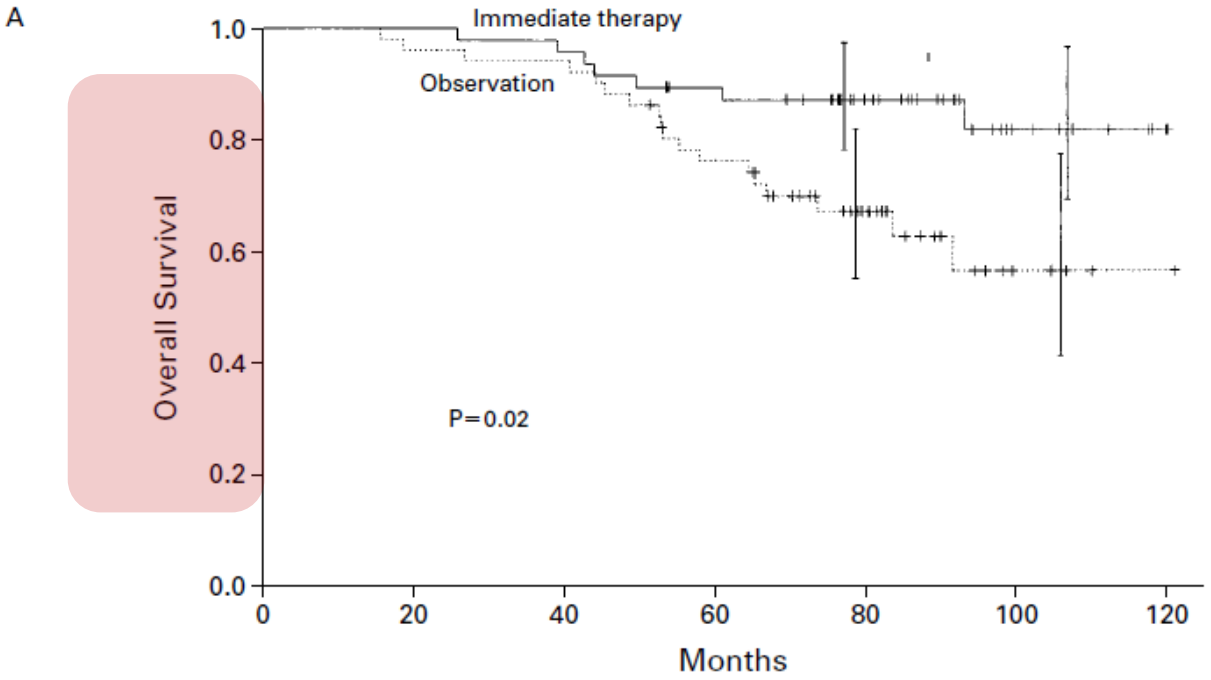



NO. AT RISK

| | | | | |
|---|---|---|---|---|
| Immediate therapy | 47 | 47 | 40 | 8 |
| Observation | 51 | 49 | 37 | 5 |




NO. AT RISK

| | | | | |
|---|---|---|---|---|
| Immediate therapy | 47 | 47 | 40 | 8 |
| Observation | 51 | 49 | 37 | 5 |

**Figure 1.** Kaplan–Meier Estimates of Overall Survival (Panel A), Prostate-Cancer–Specific Survival (Panel B), and Progression-free Survival (Panel C).

I bars are 95 percent confidence intervals. The log-rank test was used to calculate P values.

Immediate antiandrogen therapy after RP + ePLND improves survival and reduces the risk of recurrence in patients with node-positive prostate cancer.

Edward M. The New England Journal of Medicine, 1999

| **Intermittent treatment** | |
|---|---|
| In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major prostate-specific antigen (PSA) response after the induction period. | Strong |
| • In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment.<br>• Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment.<br>• Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL). | Weak |
| Do not use castration combined with any local treatment (radiotherapy/surgery) outside an investigational setting except for symptom control. | Strong |

EAU Guidelines, 2018

EUROPEAN UROLOGY 64 (2013) 722–730

available at www.sciencedirect.com
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European Association of Urology


Platinum Priority – Collaborative Review – Prostate Cancer
*Editorial by Laurence Klotz on pp. 731–733 of this issue*

# Intermittent Androgen-deprivation Therapy in Prostate Cancer: A Critical Review Focused on Phase 3 Trials

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- IAD, mainly in metastatic cases, can produce oncologic results similar (not inferior, as defined by some trials) to those of continuous ADT

- The frequency of early side effects such as hot flushes or sexual dysfunction significantly decreases in the IAD group when compared with the continuous-treatment group

- Independent of international recommendations, IAD is a treatment option used worldwide by urologists in particular and less by oncologists in clinical practice

# Question Time 5

*Is there a role for "adjuvant surgery"?*

# Salvage radical prostatectomy

Review

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Review

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Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review

RP provides the greatest likelihood of local control, but is associated with worse functional outcomes and an increased risk of Aes (e.g., urinary retention, urinary fistula, and fistula) compared with primary RP

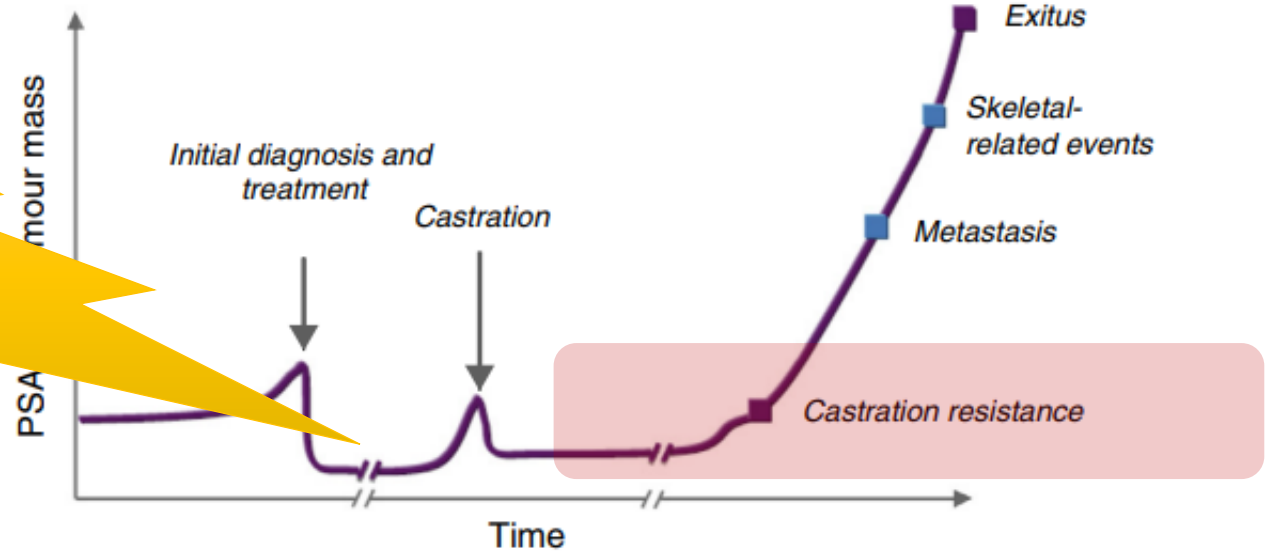
Only for patients with:

- Low comorbidity,
- Life expectancy of at least ten years
- Pre-SRP PSA < 10 ng/mL
- Biopsy GS ≤ 7,
- No LN involvement or evidence of distant metastatic disease pre-SRP
- Who's initial clinical staging was T1 or T2

# Question Time 6

*What are the future prospects?*

# APALUTAMIDE




| | |
|---|---|
| Localized | Disseminated |
| Asymptomatic | Symptomatic |
| Castration sensitive | Castration resistant |
| Hormone-sensitive | Hormone-refractory |

**Fig. 1.** Natural history of localized prostate cancer.

Prostate cancer progression is a continuous process despite discrete clinical states having been defined to subclassify the disease for therapeutic interventions