Evidence-Based Medicine: 15-Year Outcomes of Prostate Cancer Managed with Monitoring, Surgery or Radiotherapy

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CUSOM

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Our patient . . .

A 62-year-old man sees his primary physician for a health maintenance visit. He describes mild nocturia but no other symptoms. On examination, he has a mildly enlarged prostate with a 5 mm palpable nodule. A PSA is checked and measures 4.8.

He is referred to urology and undergoes a transrectal biopsy which confirms a Gleason score 6 adenocarcinoma of the prostate.

He returns to see his primary care physician and asks to review his options for managing his prostate cancer.

What we know about prostate cancer

What we know about prostate cancer

- In the US, 11% of men are diagnosed with prostate cancer
- In the US, 248,490 patients diagnosed with prostate cancer per year
- In the US, 34,500 patients die from prostate cancer per year
- In the US, overall five-year survival rate is > 98%

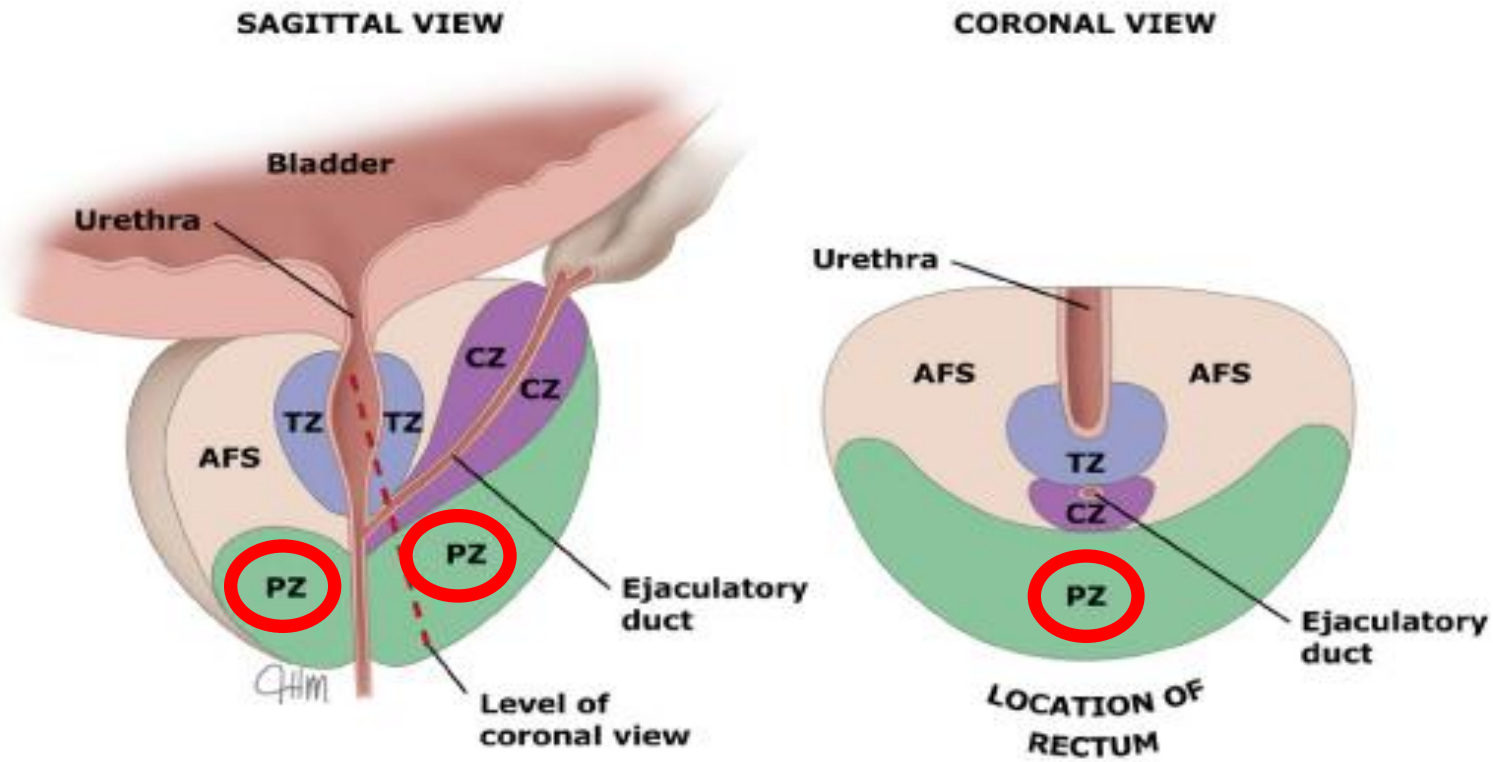
Taplin ME, UpToDate 2023

What we don’t know about prostate cancer

What we don’t know about prostate cancer

- The best approach to screening:
  - PSA: Age-specific reference ranges are:
    - 40 to 49 years – 0 to 2.5 ng/mL
    - 50 to 59 years – 0 to 3.5 ng/mL
    - 60 to 69 years – 0 to 4.5 ng/mL
    - 70 to 79 years – 0 to 6.5 ng/mL
  - Digital rectal exam
  - No screening
- Optimal treat of prostate cancer
  - Avoiding overtreatment with complications including urinary incontinence, erectile dysfunction
  - Avoiding undertreatment of aggressive cancers

Zones of the prostate gland



Most prostate cancers derive from the peripheral zone—palpable on rectal exam, but about 30% are NOT

CZ Central zone
TZ Transition zone
PZ Peripheral zone
AFS Anterior fibromuscular stroma

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Once prostate cancer is suspected, a transrectal prostate biopsy is done and the specimen is graded . . .

Gleason Grading System

- Based on architecture of prostate cancer cells
- Grading is 1 through 5
- The higher the score, the more likely, the prostate cancer will spread beyond the prostate.

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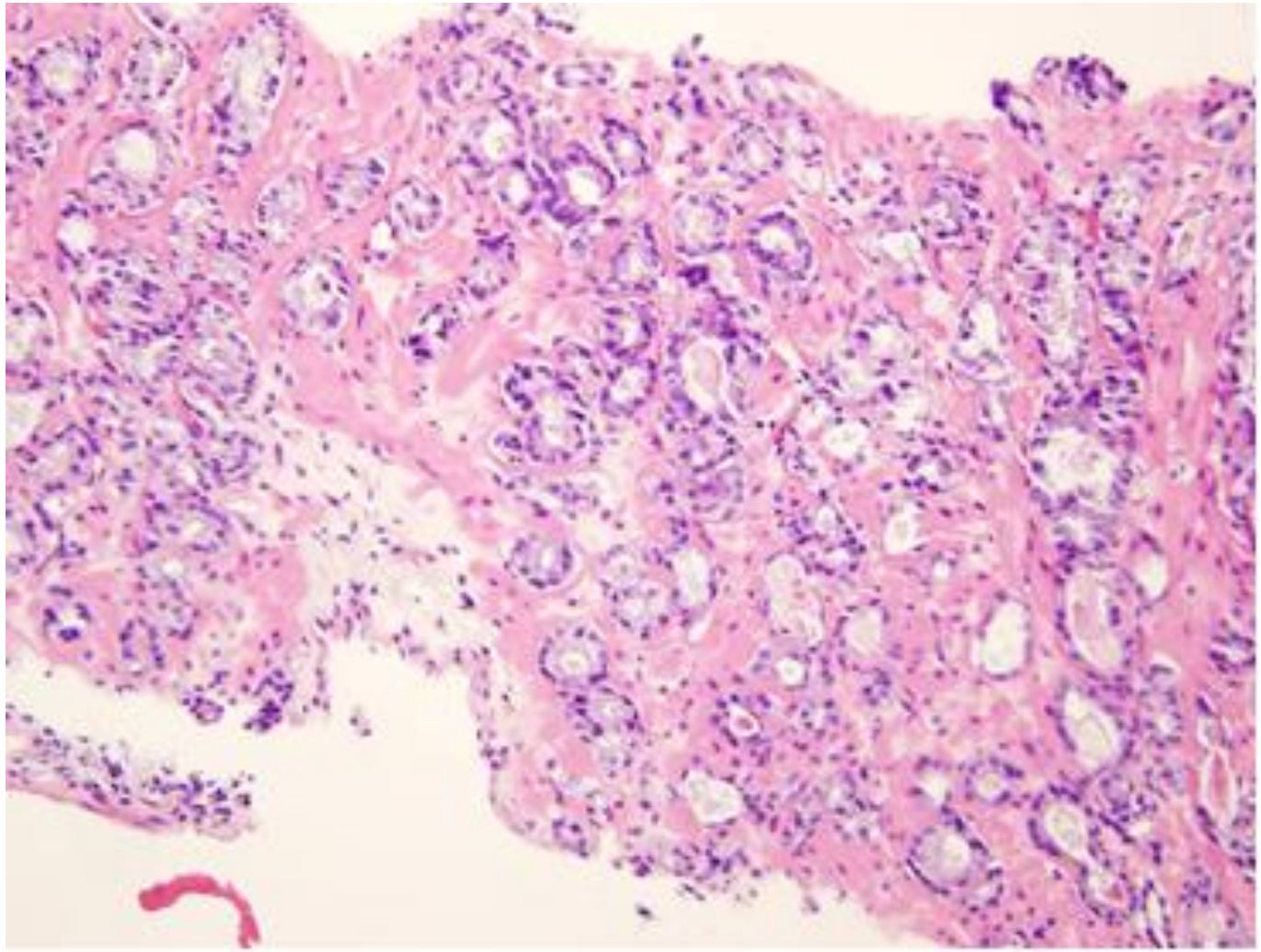
Gleason grade 3 Prostate Adenocarcinoma

Haphazardly infiltrating, well-formed malignant glands



Xang, XJ UpToDate 2023

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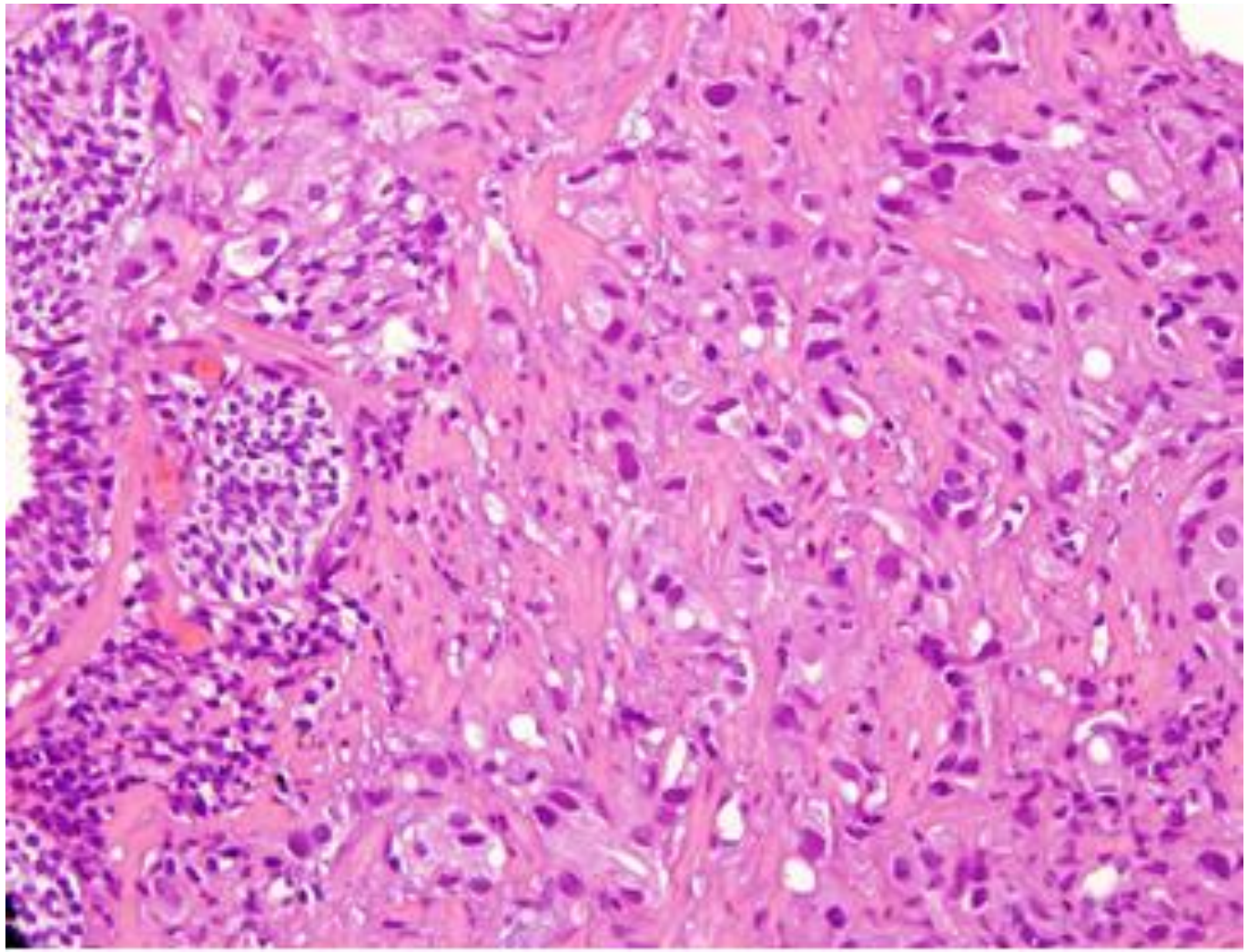

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Gleason Score

- The two most prevalence Gleason grades from a biopsy are added to give the Gleason score
- For example, if a prostate biopsy has prostate cancer cells which are predominantly Gleason grade 3 or 4, the Gleason score is 3+4 = 7
- Generally, the Gleason scores made for prostate cancer on biopsies range from 6 to 10.

Xang, XJ UpToDate 2023

Clinical Question:
Among patients with prostate cancer, what is the impact on prostate cancer-specific mortality with monitoring, surgery or radiotherapy?

Source:
Hamdy, FC et al. Fifteen-Year Outcomes after Monitoring, Surgery or Radiotherapy for Prostate Cancer. **N Engl J Med** 2023; 388(17): 1547-1558.

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Was the assignment of patients to treatment randomized? And was the randomization list concealed?

2. Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Were the patients and clinicians kept “blind” to which treatment was being received?

2. Aside from the experimental treatment, were the groups treated equally?

3. Were the groups similar at the start of the trial?

If the study satisfies these criteria, then it has *internal validity.*

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

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Do these results apply to your patient?

(ie. Do the results have *external validity*?)

- Is the patient so different from those in the trial that its results cannot help you?
- How great would the potential benefit of therapy actually be for your individual patient?

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

- Are your patient's values and preferences satisfied by the regimen and its consequences?
  - Do your patient and you have a clear assessment of their values and preferences?
  - Are they met by this regimen and its consequences?

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy

Design: Randomized, non-blinded, multicenter trial

Setting: Nine clinical centers in the United Kingdom

Was the assignment of patients treatment randomized?
And was the randomization list concealed?

X

Were the patients and clinicians kept “blind” to which treatment was being received?

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Patients included

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Trial Design

Between 1999 and 2009, 82, 429 men between 50 to 69 years received a PSA

2,644 men were diagnosed with localized prostate cancer

1643 agreed to randomization

Active monitoring	Prostatectomy	Radiotherapy
N= 545	N= 553	N= 545
545 men included in 15-year analysis	553 men included in 15-year analysis	545 men included in 15-year analysis

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Interventions

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy : Interventions

- Intention-to-treat analysis: every subject included in data analysis once randomization has occurred.

Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Interventions—Active monitoring

- PSA measured every three months for the first year, then every six to 12 months
- Increase in PSA of at least 50% triggered a review.
  - Further tests

  OR
  - Radical or palliative treatment as required

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Intervention--Radiotherapy

- Androgen-deprivation therapy

AND

- Radiation therapy

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Interventions--Surgery

- Prostatectomy then
  - PSA every three months for the first year, then every six months for two years, then yearly
  - Adjuvant or salvage radiotherapy offered for patients with:
    - Positive surgical margins
    - Extracapsular disease
    - Post op PSA $\geq$ 0.2 ng/ml

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Interventions—All patients

- Androgen deprivation therapy offered when PSA > 20 ng/ml
- Imaging of the skeleton (ie. bone scan) recommended if PSA > 10 ng/dl

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Interventions : Outcomes

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Outcomes

- Primary: death from prostate cancer

- Secondary:
  - Death from any cause
  - Metastases confirmed by imaging or PSA > 100 ng/ml
  - Clinical progression

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Interventions : Death from prostate cancer measured for prespecified subgroups

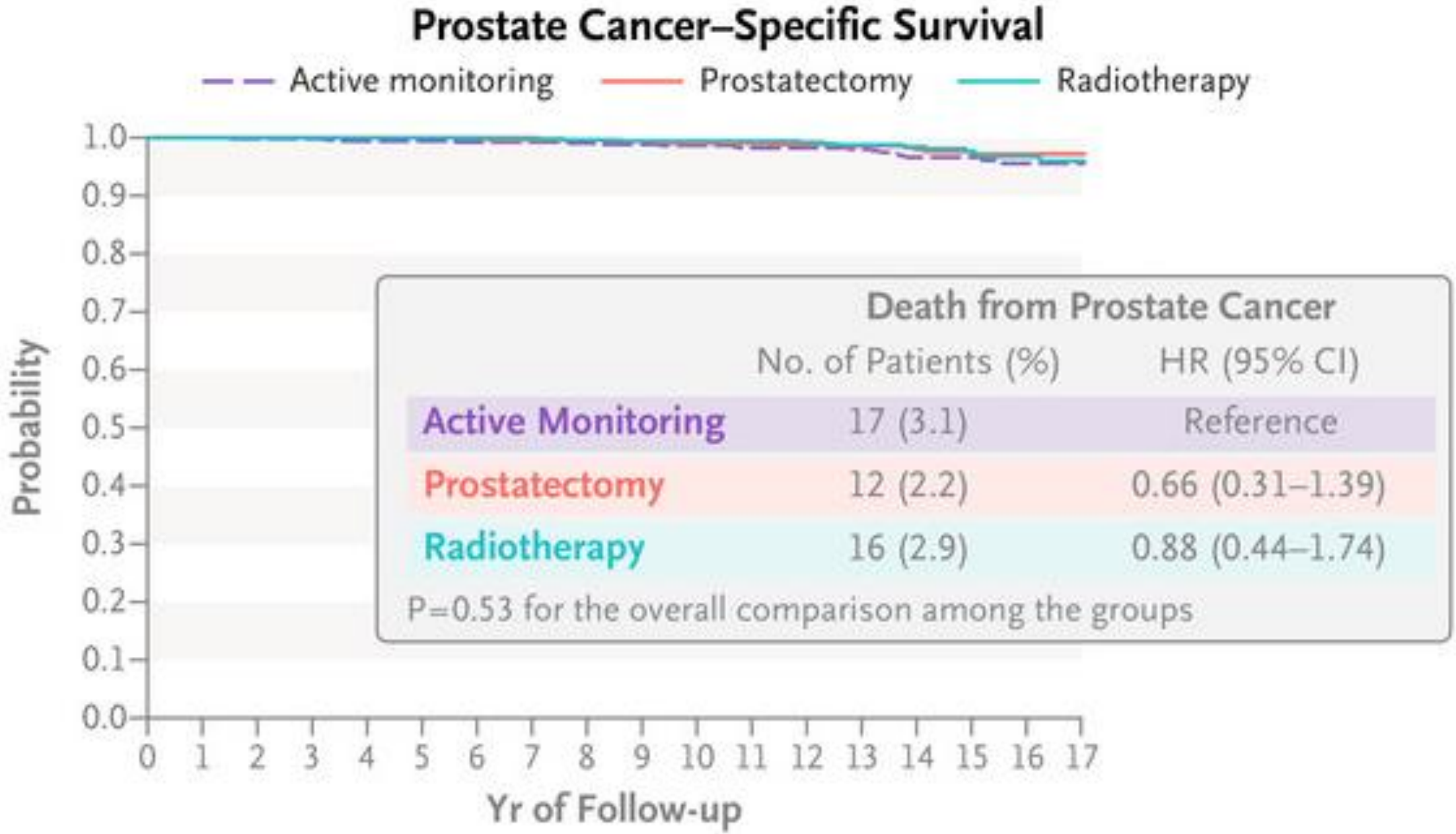
- Age < 65 years or ≥ 65 years
- Gleason grade 1 or 2 or ≥ 3
- PSA < 10 or 10 to 19.9 ng/ml
- Stage T1 or T2
- Aggregate tumor length in biopsies < 4 mm or ≥ 4 mm
- Maximum tumor length in a single biopsy < 2 mm or ≥ 2 mm

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Statistical Analysis

- Intention-to-treat analysis
- Data adjusted for:
  - Trial center
  - Patient's age
  - Gleason score
  - Baseline PSA
- Statistical significance was set at < 0.05 (ie. risk of type 1 error of < 5%)

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Main Results

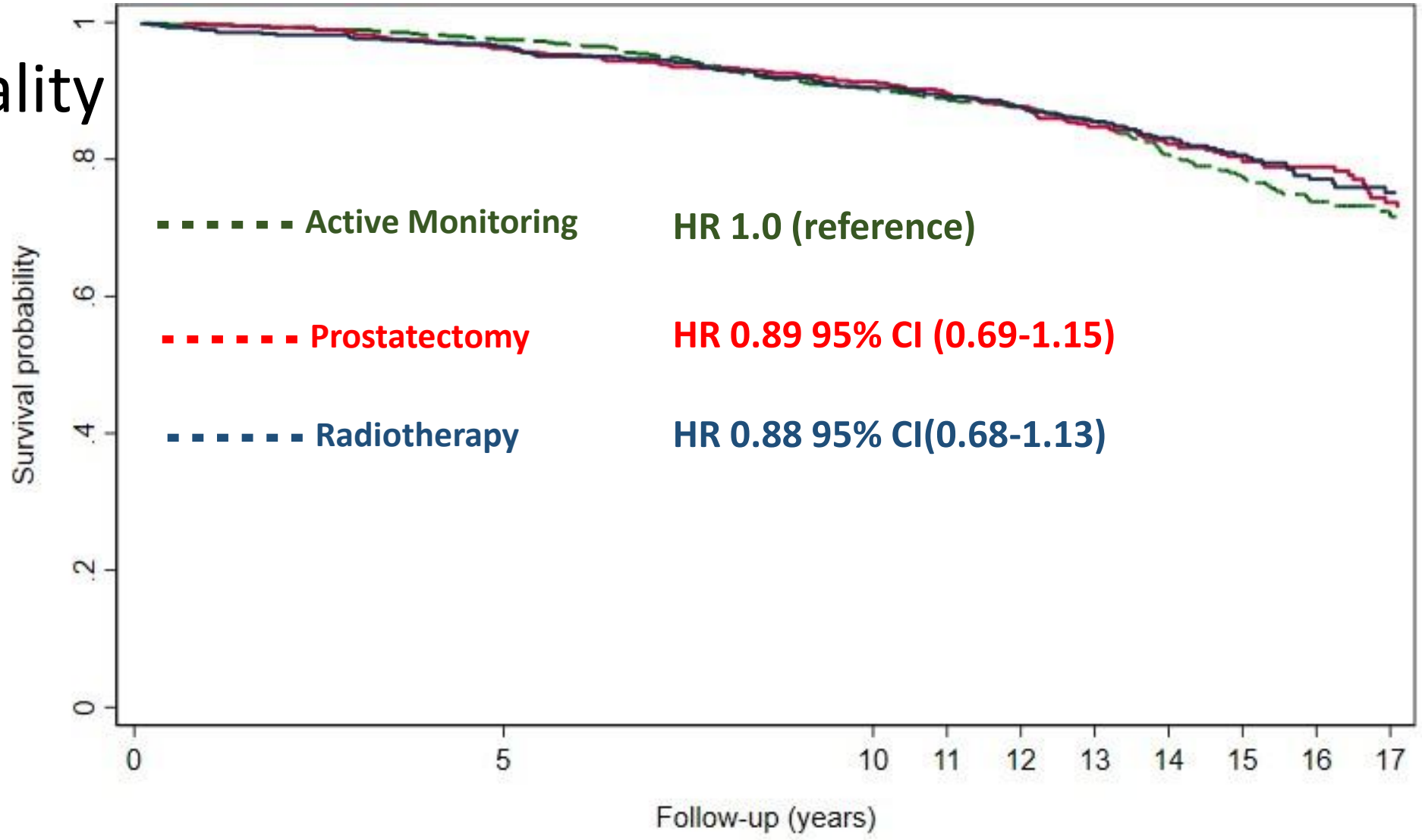
Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Primary Outcome


Prostate Cancer–Specific Survival
Active monitoring
Prostatectomy
Radiotherapy
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Yr of Follow-up
Death from Prostate Cancer
No. of Patients (%)
HR (95% CI)
Active Monitoring
17 (3.1)
Reference
Prostatectomy
12 (2.2)
0.66 (0.31–1.39)
Radiotherapy
16 (2.9)
0.88 (0.44–1.74)
P=0.53 for the overall comparison among the groups

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Secondary Outcomes

NOTE: Confidence intervals (CIs) for secondary outcomes have NOT been adjusted for multiple comparisons (ie. multiplicity) which increases the risk of a type 1 error (difference between groups is due to chance alone). Therefore CI cannot be used to determine significance.

All-cause mortality



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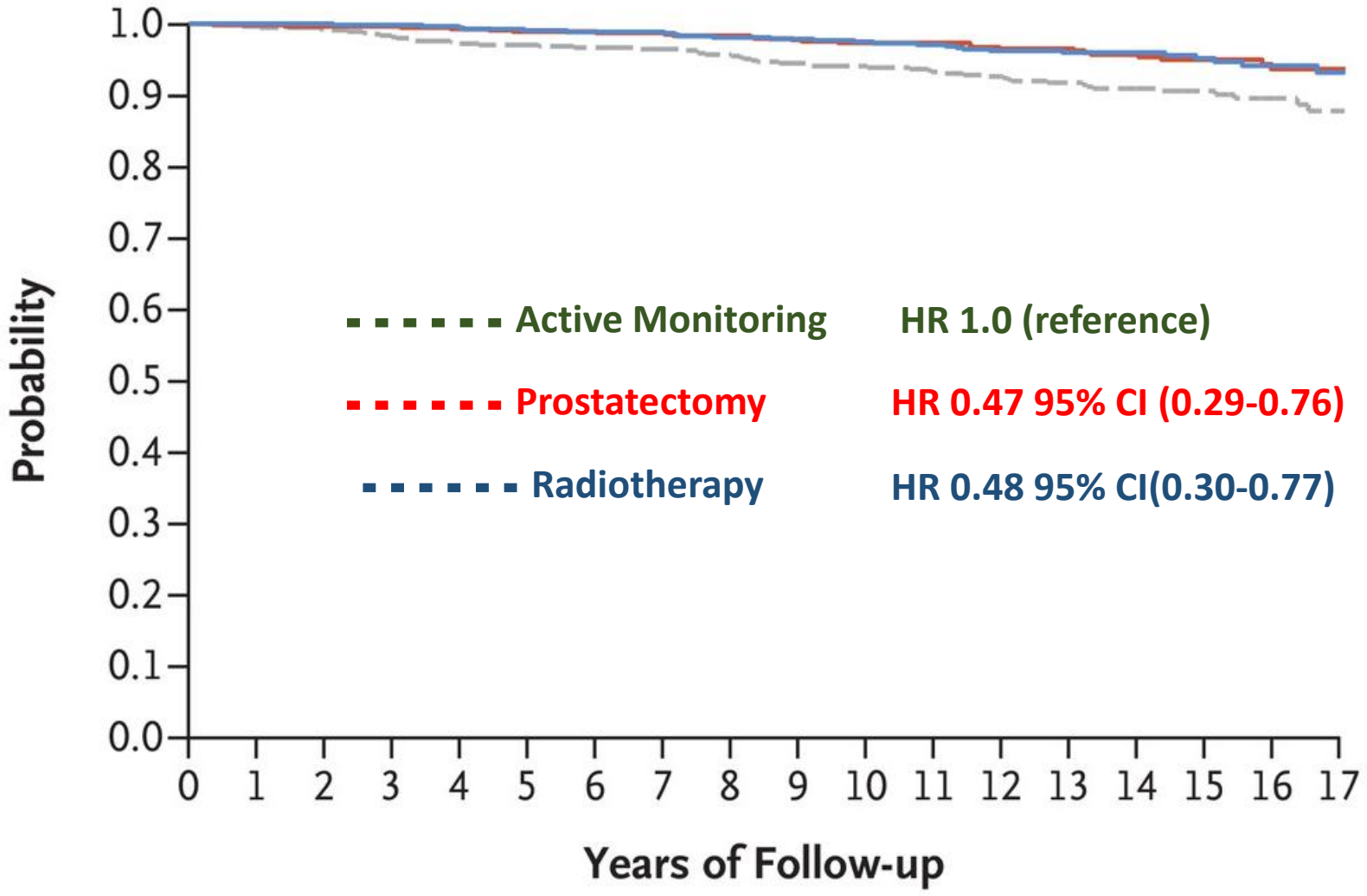
Metastasis-Free Survival



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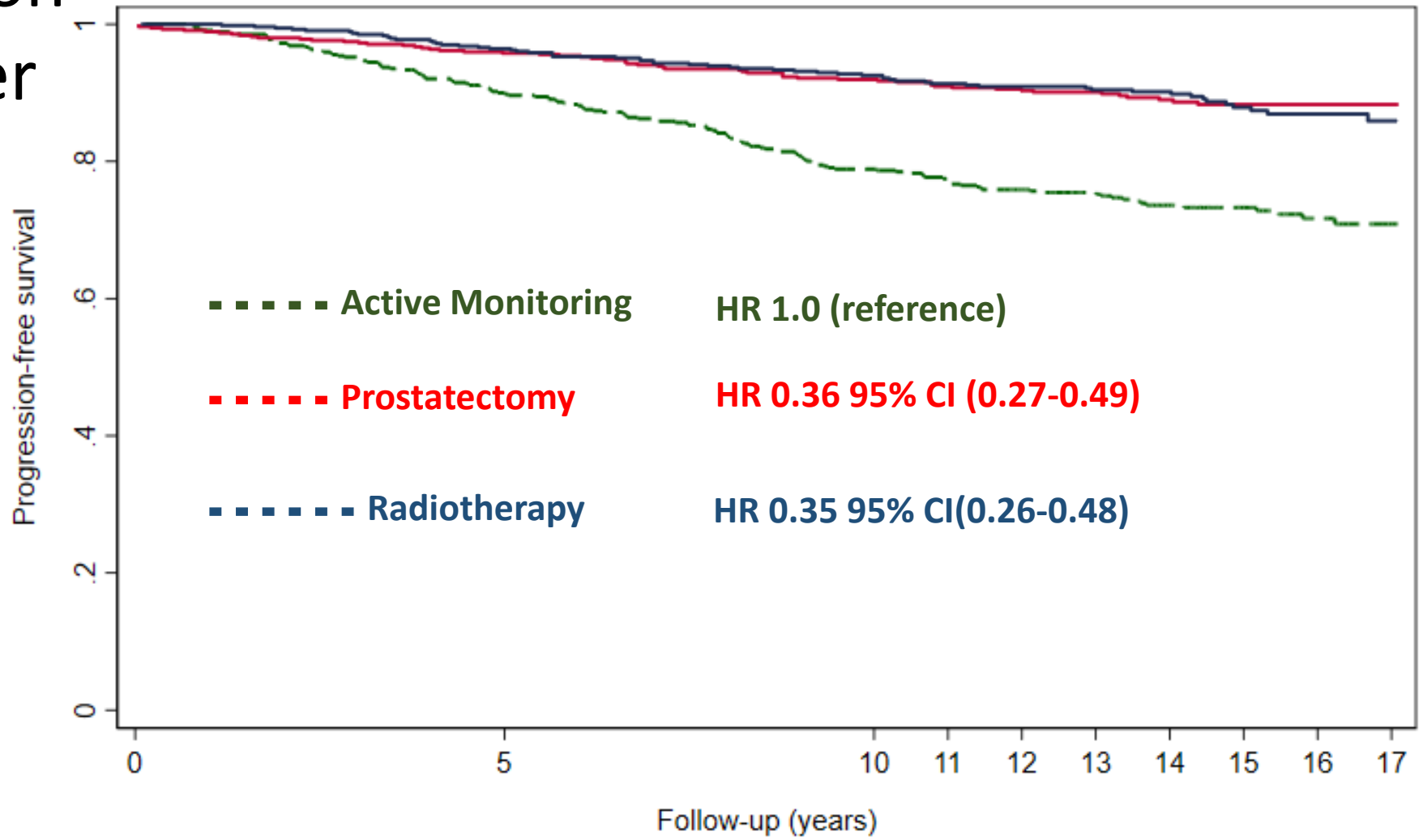
Clinical Progression of Prostate Cancer



Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Prespecified subgroup analysis

Prostate Cancer Mortality: Prespecified subgroup analysis

Age	**HR (95% CI) Prostatectomy vs Active Monitoring**	**HR (95% CI) Radiotherapy vs Active Monitoring**
< 65 years	1.15 (0.35-3.78)	2.06 (0.70-6.03)
≥ 65 years	0.47 (0.17-1.24)	0.43 (0.16-1.15)

Prostate Cancer Mortality: Prespecified subgroup analysis

Gleason Grade Group	**HR (95% CI) Prostatectomy vs Active Monitoring**	**HR (95% CI) Radiotherapy vs Active Monitoring**
1	0.43 (0.15-1.24)	0.78(0.32-1.89)
2	1.18 (0.32-4.39)	1.15(0.29-4.62)
≥ 3	1.04 (0.15-7.41)	1.18(0.20-7.08)

Prostate Cancer Mortality: Prespecified subgroup analysis

PSA Level	HR (95% CI) Prostatectomy vs Active Monitoring	HR (95% CI) Radiotherapy vs Active Monitoring
3.0-5.9 ng/ml	0.50(0.20-1.26)	0.71 (0.31-1.61)
6.0-9.9 ng/ml	1.03(0.26-4.12)	1.71(0.48-6.07)

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Main Conclusions

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Main Conclusions

- Among patients with localized prostate cancer, regardless of management with active monitoring, prostatectomy or radiotherapy, outcomes at 15 years of follow up included:
  - 97% survival from prostate cancer-specific death
  - 78% survival from death from any cause

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Main Conclusions

- Among patients with localized prostate cancer, regardless of management with active monitoring, prostatectomy or radiotherapy, there was also no difference in the risk of prostate cancer-specific death in the following prespecified subgroups:
  - Baseline PSA level
  - Tumor grade or stage

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Main Conclusions

- Among patients with localized prostate cancer, prostatectomy of radiotherapy reduced the incidence of metastases, local progression and need for long-term androgen deprivation therapy by about 50% BUT there was no significant impact on the risk of death from prostate cancer or on the risk of death from any cause.

Prostate Cancer 15-Year Outcomes with Monitoring, Surgery or Radiotherapy: Main Conclusions

- Study authors recommend that men be advised that early aggressive treatment of localized prostate cancer may do more harm than good.
  - Chronic urinary incontinence
  - Chronic bowel incontinence
  - Erectile dysfunction

Back to our patient. . .

Is the patient so different from those in the trial that its results cannot help you?

No—the patient is similar enough to those in the trial such that the trial results can help you with your decision-making.

A 62-year-old man sees his primary physician for a health maintenance visit. He describes mild nocturia but no other symptoms. On examination, he has a mildly enlarged prostate with a 5 mm palpable nodule. A PSA is checked and measures 4.8.

He is referred to urology and undergoes a transrectal biopsy which confirms a Gleason score 6 adenocarcinoma of the prostate.

He returns to see his primary care physician and asks to review his options for managing his prostate cancer.

You discuss with your patient that is prostate cancer can be managed with active monitoring, with prostatectomy or radiotherapy.

Active monitoring:

- PSA measured every three months for the first year, then every six to 12 months
- Increase in PSA of at least 50% triggered a review.
  - Further tests
  - OR
  - Radical (prostatectomy or radiotherapy) or palliative treatment as required

Radiotherapy:

- Androgen-deprivation therapy

AND

- Radiation therapy

Surgery:

- Prostatectomy
- THEN
- PSA every three months for the first year, then every six months for two years, then yearly
- Adjuvant or salvage radiotherapy offered for patients with:
  - Positive surgical margins
  - Extracapsular disease
  - Post op PSA $\geq$ 0.2 ng/ml

You discuss with your patient that the overall risk of death from prostate cancer is about 3% over 15 years of follow up with any of these three options.

However, prostatectomy and radiotherapy do reduce the risk of progression of the cancer and metastatic disease.

BUT, these treatments do have risks including chronic urinary or bowel incontinence or erectile dysfunction.

He tells you he will discuss these options carefully with his family and return to the office in one week.

Questions?

Thank you!

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