Evidence report

Active surveillance and active therapies for (low risk) localized prostate cancer

(active surveillance vs. radical/active therapy; radical prostatectomy vs. external beam radiotherapy vs. LDR brachytherapy)

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List of abbreviations

AM	Active monitoring/active surveillance
DA	Decision aid
LDR	Low-Dose-Rate brachytherapy
PCa	Prostate cancer
RP	Radical prostatectomy
RT	(external beam) Radiotherapy
RCT	Randomized controlled trial

1. PROJECT OBJECTIVES

A key aim of the research project “Bayern goes SDM” is to inform patients as part of shared-decision making (SDM).

Methodologists (MA/FS/KW) have prepared an evidence report with a synthesis of the evidence of the relevant treatment options.

The topic of this evidence report is treatment of localized prostate cancer (active surveillance vs. active treatment; radical prostatectomy vs. external beam radiotherapy vs. LDR brachytherapy).

2. BACKGROUND

Most prostate cancers diagnosed with PSA-based screening are low-risk. That means they are small, confined to the prostate, and not considered to be aggressive according to a common grading system known as the Gleason score.

Nevertheless, throughout the last decades, many men diagnosed with low-risk prostate cancer had immediate treatment with surgery or radiotherapy. Although both are cures for low-risk prostate cancer, they can also have serious and lifelong side effects, including urinary problems and erectile dysfunction. Furthermore, studies concluded that many screen-detected cancers would likely never grow to the point where they would even cause symptoms, let alone become life-threatening.

Therefore, protocols for active surveillance were first proposed in the mid-1990s and have since been studied and implemented in various forms. Patients must work with their doctors to carefully monitor the cancer via a process known as active surveillance, holding off on treatment until there are signs of progression.

Each respective treatment option aims to reduce the risk of prostate cancer-specific mortality, whilst minimizing treatment-related morbidity and maintaining a good quality of life.

Patients should be prepared by the decision aid (DA) to participate in decision-making which treatment suits best for them.
The planned decision support should be used after diagnosis and/or in different treatment stages. The available treatment options are compared with each other.

3. METHODS

3.1 INCLUSION CRITERIA

The research questions underpinning the literature searches for this topic were developed in conjunction with the department of radiology and the department of urology at the University medical centers of Munich (Großhadern) and Augsburg. The two questions were framed in terms of participants, intervention, comparators, outcomes and study design (PICOS), see Table 1 +2.

Randomized controlled trials (RCTs) or systematic reviews (SRs) of RCTs evaluated herein will aim to inform patients, clinicians, researchers, and health policy makers on relevant evidence relating to the treatment options for low risk localized prostate cancer.

Table 1: Inclusion and exclusion criteria PICO 1

	Included	Excluded
Population	Men diagnosed with a low-risk PCa (PSA < 10 ng/mL, Gleason ≤ 6 (in exceptional cases 7), stage ≤ T2a)	other than the specified
Intervention	Active surveillance	other than the specified
Comparators	Active therapy: • radical prostatectomy • external beam radiotherapy • LDR brachytherapy	other than the specified
Outcomes	• Prostate-cancer mortality • All-cause mortality • (Prostate-cancer related) Quality of life • Psychological aspects (e.g., depression, anxiety) • Disease progression • Metastases • Risks of prostate biopsies (incl. bleeding and infection) • Risks of active treatment incl. surgery risks like bleeding, infection or radiation risks • Sexual function /erectile dysfunction • Urinary and bowel function/ incontinence (urine, fecal)	other than the specified
Study design	Guidelines, systematic reviews, health technology assessments (and RCTs*)	Literature reviews, expert opinions
*RCTs were only searched to identify additional publications with long-term data.		

3.2 PICO 1 WITH FREQUENTLY ASKED QUESTIONS

Should I choose active surveillance or active therapy for (low risk) localized prostate cancer?

The following research questions were identified (by needs assessment) as frequently asked questions (FAQs):

- FAQ 1: What does the treatment for localized prostate cancer involve? (What is the procedure?)

- FAQ 2: How will it affect survival? What are the benefits?
    - Prostate-cancer mortality

- All-cause mortality

- FAQ 3: Will it impact my quality of life and psychological well-being?
  - (Prostate-cancer related) Quality of life
  - Psychological aspects (depression, anxiety, stress, fatigue, …)

- FAQ 4: What are the long-term implications regarding disease progression (incl. metastases)

- FAQ 5: What are the risks, side effects and long-term implications for the patient?
  - Sexual function /erectile dysfunction
  - Urinary function/ bowel function/ incontinence (urine, stool)
  - Complications of prostate biopsies (as part of active surveillance approach) and active treatment approaches
- FAQ 6: Additional aspects of interest

3.3 PICO 2 WITH FREQUENTLY ASKED QUESTIONS

Table 2: Inclusion and exclusion criteria PICO 2

	Included	Excluded
Population	Men diagnosed with a low-risk PCa (PSA < 10 ng/mL, Gleason ≤ 6 (in exceptional cases 7), stage ≤ T2a)	other than the specified
Intervention	Any active therapy: • radical prostatectomy • external beam radiotherapy • LDR brachytherapy	other than the specified
Comparators	Any other active treatment option: • radical prostatectomy • external beam radiotherapy • LDR brachytherapy	other than the specified
Outcomes	• Prostate-cancer mortality • All-cause mortality • (Prostate-cancer related) Quality of life • Psychological aspects (e.g., depression, anxiety) • Disease progression • Metastases • Risks of prostate biopsies (incl. bleeding and infection) • Risks of active treatment incl. surgery risks like bleeding, infection or radiation risks	other than the specified

	• Sexual function /erectile dysfunction • Urinary and bowel function/ incontinence (urine, fecal)	
Study design	Guidelines, systematic reviews, health technology assessments (and RCTs*)	Literature reviews, expert opinions
*RCTs were only searched to identify additional publications with long-term data.		

Should I choose radical prostatectomy or external beam radiotherapy or LDR brachytherapy for (low risk) localized prostate cancer?

The following research questions were identified (by needs assessment) as frequently asked questions (FAQs):

- FAQ 1: What does the (active/radical) treatment for localized prostate cancer involve? (What is the procedure?)

- FAQ 2: How will it affect survival? What are the benefits?
  - Prostate-cancer mortality
  - All-cause mortality
- FAQ 3: Will it impact my quality of life and psychological well-being?
  - (Prostate-cancer related) Quality of life
  - Psychological aspects (e.g., depression, anxiety)

- FAQ 4: What are the long-term implications regarding disease progression (incl. metastases)

- FAQ 5: What are the risks, side effects and long-term implications for the patient?
  - Sexual function /erectile dysfunction
  - Urinary problems and bowel function
  - Complications of active treatment approaches

3.4 LITERATURE SEARCHES

Starting point to answer the predefined research questions was the current version of the German S3-guideline (including all former versions and related evidence reports) [1].

We assumed that there were not any further RCTs than included in the German S3-guideline. Therefore, we only conducted literature searches to identify recently published systematic reviews, health technology assessments (HTAs) and publications with follow-up data of relevant RCTs about local treatments of localized prostate cancer in men.

In addition, searches were carried out to answer specific aspects e.g., complications of different biopsy approaches as these aspects were not addressed in the main sources. These

additional publications are not included in tables 3 & 10 but referenced in the specific FAQ sections.

4. RESULTS PICO 1

4.1 OVERVIEW OF INCLUDED STUDIES PICO 1

We identified a Cochrane review [2], three IQWiG-reports on LDR brachytherapy [3-5] and a Health Technology Assessment (HTA) of the National Institute for Health and Clinical Excellence [6].

None of the identified SR compared all predefined treatment options. Therefore, we used the S3-guideline [1] to identify primary studies (RCTs). In addition, we added a German RCT comparing all predefined treatment options (PREFERE) [7] which was not included in the S3-guideline. However, the trial was prematurely closed due to poor recruitment. Therefore, we identified ProtecT [6, 8-15] as the most suitable and best available evidence (with long-term data up to 15 years) to answer the predefined PICOs. The RCT ProtecT compared active monitoring, external beam radiotherapy, and radical prostatectomy [10]. In addition, we used the IQWiG reports on LDR brachytherapy [3-5], Cochrane reviews [2, 16] and evidence reports of the S3-guideline [1].

Table 3 summaries the sources of evidence used to answer the FAQs of PICO 1.

Table 3: Sources of evidence PICO 1

Study/year reference	Evidence source	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will it prolong my life?	FAQ3: Will it impact my quality of life?	FAQ4: What are the long-term implications regarding disease progression (incl. metastases)	FAQ5: What are the risks or side effects?	FAQ6: Additional facts
ProtecT [6, 8, 10-12]	RCT	active surveillance vs. External beam radiotherapy vs. radical prostatectomy	✓	✓	✓	✓	✓	✓
IQWIG [3-5]	Benefit assessment / rapid report	LDR brachytherapy vs. (active surveillance vs. external beam radiotherapy vs. radical prostatectomy)		✓	✓	✓	✓	

Vernooij [2]	MA	active surveillance vs. radical prostatectomy	✓	✓		✓		
PREFERE [7]	RCT	active surveillance vs. external beam radiotherapy vs. LDR brachytherapy vs. radical prostatectomy		✓				✓
MA = meta-analysis; RCT = randomized controlled trial								

4.2 FAQ 1: What does the treatment for localized prostate-cancer involve?

This section covers the four main treatment options for low risk localized prostate cancer: active surveillance and the three active treatment options radical prostatectomy, external beam radiotherapy, and LDR brachytherapy. All four treatment options are described below.

Active surveillance

Active surveillance or active monitoring is defined as close follow-up that involves periodic clinical examination, assessment of symptoms, and PSA testing and repeat biopsy [2]. 'Active monitoring', which was an intervention of ProtecT [10], represents an early form of active surveillance in which monitoring was mostly PSA-based (but did not include follow-up biopsies). Recently, magnetic resonance imaging (MRI) has been added to the follow-up routine of active surveillance. The purpose of active surveillance is to postpone curative treatment as long as possible, typically when evidence of relevant disease progression is found [1].

Surgery / Radical prostatectomy

Radical prostatectomy involves removal of the entire prostate gland along with sufficient surrounding tissue with the aim of obtaining negative margins. The goal of radical prostatectomy is to completely remove the tumor and avoid surgical morbidity [2]. For radical prostatectomy different approaches are available: open radical prostatectomy, laparoscopic approach, and robotic-assisted radical prostatectomy approach [16].

External beam radiotherapy

External radiotherapy is the most common form of radiation therapy. It is called “external” because the radiation is beamed from a source outside of the body through the skin into the body and right through to the tumor tissue. The kind of radiation used in external radiotherapy is high-energy (ionizing) radiation. It has the ability to damage the structure of cells and the genome.

In most cases the side effects are only temporary (appear a few days after treatment and some might last for a few weeks): Most common general side effect is tiredness. Its exact

cause is not known. It is suspected that it may come from the body breaking down the cancer cells that die during the therapy.

Skin irritations occur directly within the scope of the applied radiation. The skin can become sensitive and slightly reddened. After some weeks the skin may become dry and start to peel, which is sometimes combined with itching.

It also can cause nausea, vomiting or diarrhea. Most of these side effects can effectively be treated by using medication.

LDR brachytherapy

In LDR brachytherapy the radioactive source is either placed very close to the tumor or directly into the tumor. The aim of using radiotherapy in prostate cancer is to destroy the cancer cells, while at the same time trying to limit the damage to the surrounding healthy tissue. Unlike external radiotherapy, radiation can reach the tumor directly, thereby minimizing the damage done to healthy tissue [1].

In interstitial LDR brachytherapy the source of radiation is placed directly into the tissue (prostate gland). There are two options: The radioactive material is placed in the tissue and left there permanently (implanted) in small containers – capsules about the size of a grain of rice (seeds). It remains there, and the radiation decreases over the course of several months. Or the source of radiation is repeatedly inserted and removed over shorter time periods.

4.3 FAQ 2: How will it affect survival?

4.3.1 Prostate-cancer survival/mortality

One RCT (PREFERE) aiming to assess noninferiority of active surveillance, external beam radiotherapy, or LDR brachytherapy versus radical prostatectomy was identified [7]. However, the trial started in 2012 and was prematurely closed due to poor recruitment (median follow-up until February 2018 was 19.7 months).

One three-armed trial comparing radical prostatectomy versus active monitoring versus external radiotherapy (ProtecT) was included. Several publications of this trial at different follow-up periods are available. The latest published paper by Hamdy et al. (2023) reported at a median follow-up of 15 years (range, 11 to 21 years) [11]. In the UK between 1999 and 2009, men between the ages of 50 and 69 years at nine centers were enrolled in the Prostate Testing for Cancer and Treatment (ProtecT) trial to evaluate the effectiveness of conventional treatments in clinically localized prostate cancer that was detected on prostate specific antigen (PSA) testing. Localized prostate cancer was diagnosed in 2664 men, who were eligible for treatment, and 1643 underwent randomization to receive active monitoring (545 men), prostatectomy (553 men), or external radiotherapy (545 men). The median age at diagnosis was 62 years (range, 50 to 69), and the median PSA level was 4.6 ng per milliliter (range, 3.0 to 18.9). No material clinicopathological differences were seen among the randomized groups or among the men who accepted or declined to undergo randomization.

IQWiG report on LDR brachytherapy for men with localized prostate cancer concludes that the evidence base is (still) inadequate as a large German study (PREFERE [7]) failed due to lack of interest. Due to a lack of conclusive data, it still remains an unresolved issue as to whether this procedure has advantages compared with other treatments [5].

Table 4: Evidence synthesis PICO 1 – FAQ 2 Prostate-cancer survival

Author	Type of study	Follow-up time	Active surveillance	Radical prostatectomy	External -beam radiotherapy	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event intervention/ control groups event rate n/N (%)					
Prostate-cancer survival								
ProtecT (follow-up: 10y)	RCT	10 years	537/545 (98.8)	548/553 (99.0)		HR 0.63 (95% CI, 0.21 to 1.93)	Moderate (imprecision: low event rate + wide CI)	No difference
ProtecT (follow-up: 10y)	RCT	10 years	537/545 (98.8)		541/545 (99.6)	HR 0.51 (95% CI, 0.15 to 1.69)	Moderate (imprecision: low event rate + wide CI)	No difference
ProtecT (follow-up: 15y)	RCT	15 years	528/545 (96.9)	541/553 (97.8)		HR 0.66 (0.31–1.39)	Moderate (imprecision: low event rate + wide CI)	No difference
ProtecT (follow-up: 15y)	RCT	15 years	528/545 (96.9)		529/545 (97.1)	HR 0.88 (0.44–1.74)	Moderate (imprecision: low event rate + wide CI)	No difference

According to the results of the IQWiG reports, prostate-cancer-specific survival data on LDR brachytherapy compared to the treatment alternatives are missing [3-5]. This does not mean equivalence to the other interventions. Risk of bias is high for the included studies. The quality of the evidence (outcome-specific) is rated moderate to low.

The uncertainty regarding the benefit of LDR brachytherapy is also reflected in the S3-guideline. However, LDR brachytherapy is being seen there as a possible alternative based on observational studies [1]. According to the guideline, these indicates that LDR brachytherapy achieved recurrence-free survival rates comparable to other curative therapies.

Conclusion for DA: Prostate-cancer-specific survival at ten years follow-up was at least 98.8% in all groups with no significant difference among the three groups (p= 0.48). Prostate-cancer-specific survival at 15 years follow-up was at least 96.9% in all groups with no significant difference among the three groups (p= 0.53).

Certainty of the evidence was moderate (due to imprecision). We would recommend to present quantitative numbers on prostate-cancer-specific mortality.

Data on LDR brachytherapy is missing. However, the German guideline recommends LDR brachytherapy as an alternative treatment strategy.

PICO 1: We would state, that “About 1 out of 100 men will die of prostate cancer in the ten years after diagnosis (irrespective of the chosen treatment strategy).”

We would state, that “About 3 out of 100 men will die of prostate cancer in the fifteen years after diagnosis (irrespective of the chosen treatment strategy).”

4.3.2 ALL-CAUSE MORTALITY

Table 5: Evidence synthesis PICO 1 – FAQ 2 all-cause mortality

Author	Type of study	Follow-up time	Active surveillance	Radical prostatectomy	External beam radiotherapy	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event intervention/ control groups event rate n/N (%)					
All-cause mortality								
ProtecT (follow-up: 10y)	RCT	10years	59/545 (10.8)	55/553 (9.9)		HR 0.93 (95% CI, 0.65 to 1.35)	Moderate (imprecision: low event rate + wide CI)	No difference
ProtecT (follow-up: 10y)	RCT	10 years	59/545 (10.8)		55/545 (10.1)	HR 0.94 (95% CI, 0.65 to 1.36)	Moderate (imprecision: low event rate + wide CI)	No difference
ProtecT (follow-up: 15y)	RCT	15 years	124/545 (22.8)	117/553 (21.2)		HR 0.89 (95% CI, 0.69 to 1.15)	Moderate (imprecision: low event rate + wide CI)	No difference
ProtecT (follow-up: 15y)	RCT	15 years	124/545 (22.8)		115/545 (21.1)	HR 0.88 (95% CI, 0.68 to 1.13)	Moderate (imprecision: low event rate + wide CI)	No difference

At 15 years follow-up approximately 78% of men were still alive, irrespectively of received treatment. The cause of death is available for 318 of 356 men who died. Main causes were from cardiovascular or respiratory disease (n= 101; 31.8%) and from other cancers (n=164; 51.6%) (Hamdy 2023).

According to the results of the IQWiG reports, overall survival data on LDR brachytherapy compared to the treatment alternatives is missing [5]. Risk of bias is high is for the included studies (one RCT = e.g., missing information on allocation concealment, blinding; two cohort studies). The quality of the evidence (outcome-specific) is rated moderate to low.

The uncertainty regarding the benefit of LDR brachytherapy is also reflected in the German guideline [1]. However, LDR brachytherapy is being seen there as a possible alternative based on observational studies [1]. According to the guideline, LDR brachytherapy achieved recurrence-free survival rates comparable to other curative therapies.

Conclusion for DA: All-cause mortality was at approximately 10% in all groups at ten years with no significant difference among the three groups. Certainty of the evidence was moderate. Due to moderate quality of evidence (downgraded due to imprecision) we would give quantitative numbers on all-cause mortality.

All-cause mortality was at approximately 22% in all groups after 15 years with no significant difference among the groups.

Data on LDR brachytherapy is missing. However, the German guideline recommends LDR brachytherapy as an alternative treatment strategy.

PICO 1: We would state, that "10 out of 100 men will die of any cause in the ten years after diagnosis (irrespective of the chosen prostate cancer treatment strategy)."

We would state, that "About 22 out of 100 men will die of any cause cancer in the fifteen years after diagnosis (irrespective of the chosen radical treatment strategy)."

4.4 FAQ 3: How will it affect health-related quality of life/psychological issues?

The comparisons of health-related quality of life revealed no significant differences among the treatment groups in the physical and mental health subscores of the SF-12 general health measure, in scores on the HADS, or in any of the symptom or function scale scores of the EORTC QLQ-C30 up to year 5 [8].

Donovan et al. (2023) reported similar levels of mental health, anxiety, depression, and cancer-related quality of life at 5 and 10 years. A gradual decline over time was not seen for mental health. Although anxiety and depression fluctuated, they remained at similar levels throughout.

It is likely that there are no differences in overall quality of life between patients who underwent active monitoring compared to active (radical) treatment. Certainty of evidence is moderate due to risk of bias (lack of blinding).

IQWiG benefit assessment and update rapid report on LDR brachytherapy concludes that no statement can be made on differences in the LDR brachytherapy compared with the other treatment options (low quality of evidence) [4, 5].

Conclusion for DA: Quality of life as well as other psychological aspects seem to be equal in all treatment groups over the follow-up period (with low to moderate certainty of evidence).

PICO 1: We would state, that “quality of life is similar in all treatment groups (at any follow-up assessments).”

4.5 FAQ 4: What are the long-term implications regarding disease progression (inkl. Metastases)?

Table 6: Evidence synthesis PICO 1 – FAQ 4 Disease progression & metastases

Author	Type of study	Follow-up time	Active surveillance	Radical prostatectomy	External beam radiotherapy	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event intervention/ control groups event rate n/N (%)					
Disease progression								
ProtecT (follow-up: 10 y)	RCT	10 years	112/545 (20.6)	46/553 (8.3)		HR 0.39 (95% CI, 0.27 to 0.54)	moderate	Difference in favor of RP
ProtecT (follow-up: 10y)	RCT	10 years	112/545 (20.6)		46/545 (8.4)	HR 0.39 (95% CI, 0.27 to 0.55)	moderate	Difference in favor of RT
ProtecT (follow-up: 15 y	RCT	15 years	141/545 (25.9)	58/553 (10.5)		HR 0.36 (95% CI, 0.27 to 0.49)	moderate	Difference in favor of RP
ProtecT (follow-up: 15 y	RCT	15 years	141/545 (25.9)		60/545 (10.8)	HR 0.35 (95% CI, 0.26 to 0.48)	moderate	Difference in favor of RP
Metastases								
ProtecT (follow-up: 10 y)	RCT	10 years	33/545 (6.1)	13/553 (2.4)		HR 0.39 (95% CI, 0.21 to 0.73)	moderate	Difference in favor of RP
ProtecT (follow-up: 10 y)	RCT	10 years	33/545 (6.1)		16/545 (2.9)	HR not reported	moderate	Difference in favor of RT
ProtecT (follow-up: 15 y	RCT	15 years	51/545 (9.4)	26/553 (4.7)		HR 0.47 (95% CI, 0.29 to 0.76)	moderate	Difference in favor of RP
ProtecT (follow-up: 15 y)	RCT	15 years	51/545 (9.4)		27/545 (5.0)	HR 0.48 (95% CI, 0.30 to 0.77)	moderate	Difference in favor of RT

The IQWiG report noticed that there is still no substantial data available for disease-free survival and the results for the surrogate PSA-based recurrence-free survival still does not allow a reliable statement [5].

Conclusion for DA: Radical prostatectomy or external radiotherapy likely reduce disease progression and incidence of metastases (compared to active surveillance). Certainty the evidence is moderate. Therefore, communication of quantitative numbers would be possible/adequate.

PICO 1: We would state, that "About 8 out of 100 men with active treatment (radical prostatectomy or external radiotherapy), and 21 out of 100 men with active surveillance will have disease progression" (in the next ten years).

11 out of 100 men with active treatment (radical prostatectomy or external radiotherapy), and 26 out of 100 men with active surveillance will have disease progression (in the next fifteen years).

We would state, that "About 2-3 out of 100 men with active treatment (radical prostatectomy or external radiotherapy), and 6 out of 100 men with active surveillance will develop metastases in the next ten years.

About 5 out of 100 men active treatment (radical prostatectomy or external radiotherapy) and 9 out of 100 men with active surveillance will develop metastases in the next fifteen years."

4.6 FAQ 5: What are the risks, side effects and long-term implications for the patient?

4.6.1 Sexual function

Table 7: Evidence synthesis PICO 1 – FAQ 5 Sexual function

Sexual function - Erections firm enough for intercourse

	AM		RP		RT		
	n / N	(%)	n / N	(%)	n / N	(%)	p-value
EPIC: Erections firm enough for intercourse							
Baseline	164/243	(67.5)	161/245	(65.7)	169/247	(68.4)	
6 months	173/375	(51.6)	43/359	(12.0)	75/338	(22.2)	
12 months	167/340	(49.1)	52/356	(14.6)	132/351	(37.6)	
24 months	178/378	(47.1)	74/391	(18.9)	132/388	(34.0)	
36 months	173/421	(41.1)	89/427	(20.8)	143/420	(34.0)	
48 months	163/442	(36.9)	90/447	(20.1)	142/447	(31.8)	
60 months	157/449	(35.0)	94/464	(20.3)	125/462	(27.1)	
72 months	134/452	(29.6)	76/461	(16.5)	125/456	(27.4)	<0.001

Erectile function was reduced from baseline to 6 months in all the men, with clear differences among the treatment groups ($p<0.001$) [8, 12].

In ProtecT erectile function (= erection firm enough for intercourse) was reported at baseline by (approx.) 67% of included men. By six months this rate fell to 52% in the active-monitoring

group, to 22% in the external radiotherapy group, and to 12% in the prostatectomy group. The risk difference between men under active surveillance and men with prostatectomy is 40%, and to men with external beam radiation is 30% at this point. Erectile function remained worse in the prostatectomy group at all time points. Further long-term data on sexual function up to twelve years is reported by Donovan et al. 2023 [17]. Continuing functional declines and differences between the groups could be seen in all prespecified sexual function measures from 7 to 12 years. Although all groups converged to a similarly low level of potency by year 12 (13 to 17%), each group exhibited a different profile of decline. Sexual/erectile function was retained most and for the longest in the active monitoring group. Levels of sexual/erectile function were lower in the radiotherapy group and lowest in the prostatectomy group [17].

The data available on LDR brachytherapy in the IQWiG reports did not meet the requirements for synthesis and the individual studies have a high risk of bias. Considering the available evidence there is no stat. significant difference between external beam radiotherapy and LDR brachytherapy (two cohort studies). Results of one RCT and two cohort studies showed a statistically significant, but clinical non relevant difference in favor of LDR brachytherapy compared to radical prostatectomy [5]. Quantitative information on the endpoint sexual function (in comparison to the treatment alternatives) is therefore not possible.

Conclusion for DA: Sexual function declined due to radical treatment (external radiotherapy or radical prostatectomy). Certainty of the evidence is moderate. Therefore, communication of quantitative numbers (at six months) would be possible/adequate for active surveillance, radical prostatectomy and external beam radiotherapy. Quantitative information on the endpoint sexual function for LDR brachytherapy (in comparison to the treatment alternatives) is not possible.

PICO 1:

Erection problems increase with age. Approximately more than one third of the average male population report erection problems at this age.

Men with active monitoring have no risk to develop erection problems (except due to usual aging). However, they may develop erection problems if they switch to a radical treatment like prostatectomy or external radiotherapy.

Both radical treatments (external radiotherapy and prostatectomy) cause erection problems. 30-40% of men with radical treatment have erection problems due to the treatment (in the first six months). Erection problems are more often in radical treatments up to six years. Continuing functional declines and differences between the groups could be seen from 7 to 12 years with a similarly low level of potency by year 12 (13 to 17%). Erectile function was retained most and for the longest in the active monitoring group. Erectile function was lower in the radiotherapy group and lowest in the prostatectomy group.

4.6.2 URINARY AND BOWEL FUNCTION

Table 8: Evidence synthesis PICO 1 – FAQ 5 Urinary function

Urinary problems: EPIC urinary incontinence sub-score (ProtecT; Donovan et al. 2016) [8]

	AM		RP		RT		
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	p-value
EPIC urinary incontinence sub-score							
Baseline	93.5 (11.3)	244	92.8 (11.6)	255	92.8 (11.0)	246	
6 months	89.1 (16.0)	345	67.4 (29.1)	361	88.7 (16.8)	338	
12 months	89.1 (15.3)	353	76.5 (23.7)	354	90.5 (13.5)	354	
24 months	88.9 (15.0)	389	80.3 (21.4)	393	89.0 (14.1)	387	
36 months	87.3 (16.7)	426	79.3 (21.8)	425	89.8 (13.5)	417	
48 months	86.8 (17.4)	446	80.2 (20.3)	445	89.2 (14.4)	449	
60 months	87.2 (16.8)	455	80.6 (20.2)	455	89.4 (14.4)	455	
72 months	85.8 (18.5)	446	80.9 (20.2)	449	89.4 (14.0)	443	<0.001

Urinary incontinence was assessed with different measurement tools, e.g., International Consultation on Incontinence Questionnaire (ICIQ), Expanded Prostate Index Composite (EPIC). We decided to use the EPIC (scores range from 0 [most affected] to 100 [least affected] as that measure is suggested by the German guideline.

Baseline-scores for the urinary-incontinence sub-score is approximately 93/100 in all three groups (see tab. 8). After six months the score did not drop noticeably for men with active surveillance or radiotherapy (89/100). Men with prostatectomy showed a strong decrease 67/100 (defined minimally important differences (MID) for urinary incontinence: 6-9 points). The score slightly increased to 76/100 after twelve months and was stabile for men with active surveillance or radiotherapy.

Long-term follow-up data showed a gradual increase in incontinence for men in the active surveillance and external radiotherapy groups. Risk increased with treatment strategy switch (= radical prostatectomy).

In the external radiotherapy group scores for voiding symptoms were a little worse than in the other treatment groups at 6 months but then returned close to baseline levels and were like the scores in the prostatectomy group and the active-surveillance group.

The rate of use of absorbent pads (one or more pads per day in past 4 weeks) increased from approximately 1% at baseline to 46% at 6 months (26% after twelve month) in the prostatectomy group, as compared with 4% at 6 months in the active-monitoring group and 5% at 6 months (4% after twelve months) in the radiotherapy group [8].

Certainty of evidence is moderate due to risk of bias (lack of blinding).

Overall, there might be advantage of LDR brachytherapy in terms of impairment due to urinary tract dysfunction (urinary incontinence) compared to radical prostatectomy [5]. A statement on a difference between LDR brachytherapy and RP regarding urinary tract problems is not possible due to the usage of different survey instruments and are

consistently based on studies with a high risk of bias (low certainty of evidence) [4, 5]. The same applies to the comparisons to all other treatment options.

Table 9: Evidence synthesis PICO 1 – FAQ 5 Bowel function/fecal incontinence

Bowel function: Fecal incontinence more than once per week (EPIC) [8]

	AM		RP		RT		
	n / N	(%)	n / N	(%)	n / N	(%)	p-value
EPIC: Fecal incontinence more than once per week							
Baseline	5/249	(2.0)	7/255	(2.8)	1/250	(0.4)	
6 months	6/348	(1.7)	4/367	(1.1)	18/346	(5.2)	
12 months	4/356	(1.1)	3/363	(0.8)	14/358	(3.9)	
24 months	10/395	(2.5)	8/406	(2.0)	17/393	(4.3)	
36 months	10/436	(2.3)	8/437	(1.8)	11/433	(2.5)	
48 months	12/460	(2.6)	8/459	(1.7)	11/458	(2.4)	
60 months	11/463	(2.4)	6/472	(1.3)	11/476	(2.3)	
72 months	12/462	(2.6)	9/468	(1.9)	19/465	(4.1)	0.027

In the group of men with external radiotherapy, the risk of having fecal incontinence at least once a week is comparable high just after treatment. Risk difference to the group of men under active surveillance is at 6 months about 4% and after 24 months about 2%.
There was no relevant difference for fecal incontinence between men who were actively monitored and men undergoing a prostatectomy [8].

In addition, proportion of men with “loose stools about half the time or more frequently” as well as “bloody stool” are higher in the external radiotherapy group compared to both other groups [8].

About 16% (of all men) reported loose stool at baseline. The risk of loose stool is increased in the long term for men with external radiotherapy. The risk difference is approximately 6% at six, twelve and 24 months between men with external radiotherapy compared to active surveillance. After 60 months the risk difference is about 4%. There was no relevant difference in the occurrence of liquid stool between men who were actively monitored and men who had a prostatectomy.
Bloody stools, on the other hand, are very rare at the start of the study (1-2%) and only become apparent during the study in the group of men receiving external beam radiotherapy [8].

According to available research (low quality of evidence) bowel problems seem to be less common following LDR brachytherapy than after external beam radiotherapy [5]. No quantitative results usable.

Further long-term data on urinary problems as well as bowel function up to twelve years are reported by Lane et al. 2022 [12], and Donovan et al. 2023.

Conclusion for DA:

Prostatectomy had the greatest negative effect on urinary continence at 6 months, and although there was some recovery, urinary incontinence remained worse in the prostatectomy group than in the other groups at all time points. Men with external radiation

therapy have a higher risk of fecal incontinence just after treatment. Risk difference to the group of men under active surveillance is at 6 months about 4% (and after 24 months about 2%). Certainty of the evidence is moderate. Therefore, communication of quantitative numbers (at six/twelve months) would be possible/adequate for active surveillance, radical prostatectomy and external beam radiotherapy. Quantitative information on this outcome for LDR brachytherapy (in comparison to the treatment alternatives) is not possible.

PICO 1:

We would state, that “Men with active monitoring have no risk to develop problems with urinary or stool incontinence. However, they may develop urinary incontinence (urinary problems) if they switch to prostatectomy or problems with bowel function if they switch to radiotherapy.

Prostatectomy can cause urinary incontinence. The problems with unwanted urine leakage increase significantly within the first few months after the operation. After 1 year they are slightly improved.

In the first months after the operation, the score drops by about 25 points to 67 out of 100. Another 6 months later, the value improves to 76 out of 100. This means that unintentional leakage of urine affects at least a little bit daily living. About 46 out of 100 men will need one or more pads a day 6 months after surgery. After 12 months, it's still about 26 out of 100 men.

Active surveillance as well as radiotherapy are unlikely to increase the incidence of urinary incontinence. Men with active surveillance (or radiotherapy) have a consistent score of about 90 on a 100 scale within the first year. This means that unintentional urine leakage does not affect daily living.

Additional information: The influence of urinary incontinence on quality of life can be recorded on a scale from 0 to 100. The higher the value, the fewer problems with unwanted urine leakage. A value of 100 means completely continence. Changes in continence are considered noticeable if they are more than 6 to 9 points.

Men with external radiation therapy have a higher risk of fecal incontinence just after treatment. Risk difference to the group of men under active surveillance is at 6 months about 4% (and after 24 months about 2%). (Bowel problems seem to be less common following LDR brachytherapy than after external beam radiotherapy. No difference for fecal incontinence between men who were actively monitored and men undergoing a prostatectomy.)”

4.6.3 Complications of prostate biopsies and active treatment approaches

Additional searches were run to identify information (and quantitative data) on complications as those were not assessed/reported or did not occur in the ProtecT study.

Prostate biopsy (as part of active surveillance approach): The most frequently reported complication after prostate biopsy is minor and self-limiting bleeding (blood in urine or

semen for several days), irrespective of the biopsy approach or technique. Reviews report wide ranges of occurrences. Secondary bleeding (usually stops by itself), leaking blood from the anus or bruising on the perineum, and pain also occur. A non-negligible proportion of men undergoing biopsy experience temporary erection problems for 1 to 6 months after the procedure. It is unclear whether these changes are due to the procedure itself or to the psychological impact of the event [18, 19].

Following complications can occur with transrectal prostate biopsy:
• Lower urinary tract symptoms (LUTS) in up to 25 out of 100 men [18]
• Temporary urinary retention in 0.4-6 out of 100 men [18]; acute urinary retention <2% [19]
• Infections in about 5-6 out of 100 men (antibiotics and rectal disinfection can reduce the incidence of infections <3%) [20]
• sepsis requiring hospitalization 0.8% [19, 20]
Less quantitative data were available for transperineal prostate biopsy. Following complications can occur with trans perineal prostate biopsy:
• Lower urinary tract symptoms (LUTS): no specific data available; based on different levels of evidence, there is some evidence that LUTS occur with similar frequency compared to transrectal biopsy [21]
• temporary urinary retention in 1.7-11 out of 100 men [18]
• Infections in about 1 out of 100 men [22]
• sepsis requiring hospitalization 0.1% [19, 20]
Optimal pain control, either by topical or infiltrative anesthesia, reduces discomfort and improves biopsy acceptance [18].

Radical prostatectomy:

As with any major surgery, complications can occur with radical prostatectomy. The surgical method has little effect on the type, frequency and severity, but the surgeon's experience and improved surgical techniques may have a positive effect. Perioperative complications are (major) bleeds (with need for blood transfusions), infections, thrombosis, postoperative pain, urinary problems (urinary retention with the need to use a urinary catheter) and wound healing problems. Late complications occur in the connection (anastomosis) of the urethra (leakage or narrowing = stricture of the bladder neck or urethra due to scars) or the lymph vessels (e.g. formation of a lymphocele = local accumulation of tissue fluid after lymph node removal) [1]. In addition, general risk associated with general anesthesia may occur.

External beam radiotherapy: Adverse effects may occur some weeks after the start of radiotherapy. In addition to urinary and bowel problems, skin irritations and fatigue are common**.** Late complications (years later) may occur due to the delayed effect of the radiation, for example inflammation of the bladder (cystitis), blood in the urine (hematuria), urinary incontinence (usually urge incontinence due to irritation of the bladder), scarring narrowing (stricture) of the urethra, proctitis. Radiation may also increase the risk of getting a different type of cancer. Radiotherapy for prostate cancer can increase the risk for patients of developing secondary cancer within the next 5 to 10 years - for example bladder cancer or

rectal cancer [23-25].
The risk of secondary cancer also depends on the radiation technique used. According to studies, modern radiation techniques such as LDR brachytherapy or intensity-modulated radiotherapy (IMRT) probably do not increase the risk of a secondary cancer (compared with men without radiotherapy for prostate cancer or the general population).

Results from a qualitative interview study (embedded in ProtecT) showed that men experienced bowel, sexual, and urinary side effects, mostly in the short term but some persisted and were bothersome [14]. Most men downplayed the impacts, voicing expectations of age-related decline, and normalizing these changes. There was some reticence to seek help, with men prioritizing their relationships and overall health and well-being over returning to pretreatment levels of function. Some unmet needs with regard to information about treatment schedules and side effects were reported, particularly among men with continuing functional symptoms [14].

LDR brachytherapy: Various bowel and urinary problems are common. Seed-migration may occur.

The results of a former IQWiG Rapid Report (N10-01) showed statistically significant differences in advance of LDR brachytherapy compared to external beam radiation therapy on duration and necessity of catheterization [4]. The update found no new evidence and there was still no data available for comparison to other treatment options. No reliable results on the frequency of necessary follow-up examinations regarding bladder, urethral, sexual and rectal function was available [5].

The risk of a second tumor (after radiotherapy) depends on the radiation technique used. According to studies, modern radiation techniques such as LDR brachytherapy or intensity-modulated radiotherapy (IMRT) probably do not increase the risk of a second tumor.

Treatment complications in the ProtecT trial [10]
The following treatment complications were reported for men who were randomized to surgery (n=553; 71% received surgery within 9 months): no deaths related to surgery; 9 men had thromboembolic or cardiovascular events, 14 required transfusions of more than 3 units of blood, 1 had a rectal injury, and 9 required intervention for anastomotic problems.
For men who were randomized to radiotherapy (n=545; 74% received radiotherapy within 9 months) were reported that there were 3 deaths unrelated to prostate cancer within 90 days after the completion of radiotherapy.

Conclusion for DA: All (invasive) procedures are associated with general risks (e.g., bleeding, infection) and/or specific complication risks like e.g., secondary cancer due to radiation. However, the incidence of complications depends on several factors like patient characteristics (age, multimorbidity), procedures used (e.g., surgical approach) or doctors' experience. Therefore, we suggest communicating a list of specific risks/complications without a quantitative value.

PICO 1: Suggestion for prostate biopsy complications in a category called "What else is important?

A prostate biopsy can have side effects or complications which vary in the frequencies depending on route of tissue sampling (transperineal/transrectal). Fewer infections (+ sepsis) occur when tissue is removed via the perineum, but more urinary retention with hospital admissions.

The following applies to tissue sampling through rectum:

- Infections affect about 5 to 6 men in 100. Antibiotics and skin disinfection can significantly reduce the number of infections.
- temporary retention of urine in up to 6 out of 100 men

The following applies to tissue sampling through the dam:

- Infections affect about 1 in 100 men
- temporary retention of urine in up to 11 out of 100 men

Other complications, regardless of biopsy approach, can be:

- feeling of incomplete emptying of the bladder, frequent urge to urinate, weak stream of urine and dribbling urine in up to 25 out of 100 men
- postoperative bleeding, which usually stops by itself
- bleeding from the anus or bruising on the perineum
- blood in the urine or semen for several days
- temporary erection problems for 1 to 6 months. In addition to the biopsy, psychological stress can also have an effect

PICO 1: Suggestion for radical prostatectomy complications in a category called "What else is important?": The procedure can have complications like bleeding, infections, wound-healing problems, postoperative pain and thrombosis. You may need a urinary catheter after the surgery for some days. The use of anesthesia is associated with risks."

PICO 1: Suggestion for external beam radiotherapy complications in a category called "What else is important?" Skin irritation and fatigue may occur. Radiation may also increase the risk of getting a different type of cancer. However, the risk is very low.

PICO 1: Suggestion for LDR brachytherapy complications in a category called "What else is important?" General risks of surgical procedures may occur, e.g., infections, or anesthetic-related problems. The seeds may migrate to other organs or excreted via the urinary tract."

4.7 FAQ 6: Additional aspects of interest – change of management (switch to active/radical treatment)

In ProtecT within nine months after randomization the men received the assigned treatment: active monitoring (88%), radical prostatectomy (71%), and external radiotherapy (74%). The majority of men who were randomly assigned to active monitoring (88%)

accepted their treatment assignment, but a quarter of them received radical treatment within 3 years after their initial assignment [10].

In the prematurely terminated PREFERE study after randomization, 12% of the patients decided to change from their assigned treatment [7]. Immediate change within one month occurred in 5% of men randomized to active surveillance, in 19% of radical prostatectomy, 19% of external beam radiotherapy, and 11% of LDR brachytherapy patients, respectively. Of 141 “as treated” AS patients, 56 experienced biopsy confirmed progression and 48 received active treatment (2-years rate for GS 6: 35%, GS 7a: 66%, overall: 44%) [7].

In PREFERE the rate of men who switched from active surveillance to radical treatment (44% at 2 years) was twice as high as in the ProtecT trial [10].

In ProtecT, by the end of the median 15-year follow-up, radical treatment (defined as prostatectomy or radiotherapy) had been performed in 92.5% of men in the external radiotherapy group, in 90.4% of men in the prostatectomy group, and 61.1% of men in the active-monitoring group. The increase of radical treatment in the active-monitoring groups from year 10 to year 15 was 6.3 percentage points (54.8% at 10 years) [11].

The authors of a qualitative interview study (embedded in ProtecT) conclude that trust in the clinical team was critical for men in balancing anxiety and facilitating successful management change/continued monitoring [15].

PICO 1: “Half of the man who decided to follow the active surveillance strategy decide to have surgery or radiotherapy later on. Switches of treatment strategy were made for various reasons: some were worried about the thought of having growing cancer, others were stressed by the regular examinations, and some needed a radical treatment due to growing cancer. Doctors (clinical team) play an important role in the treatment process (to go on with the monitoring approach.”

5. RESULTS PICO 2

5.1 OVERVIEW OF EVIDENCE PICO 2

Table 10 summarizes the sources of evidence used to answer the FAQs of PICO 2.

Table 10: Sources of evidence PICO 2

Study/year reference	Evidence source	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will it prolong my life?	FAQ3: Will it impact my quality of life?	FAQ4: What are the long-term implications regarding disease progression (incl. metastases)	FAQ5: What are the risks or side effects?	FAQ6: Additional facts
ProtecT [6, 8, 10-12]	RCT	active surveillance vs. External beam radiotherapy vs. radical prostatectomy	✓	✓	✓	✓	✓	✓
IQWIG [3-5]		LDR brachytherapy vs. (active surveillance vs. external beam radiotherapy vs. radical prostatectomy)		✓	✓	✓	✓	
Vernooij [2]	MA	active surveillance vs. radical prostatectomy	✓	✓		✓		
PREFERE [7]	RCT	active surveillance vs. external beam radiotherapy vs. LDR brachytherapy vs. radical prostatectomy		✓				✓

HTA = health technology assessment; MA = meta-analysis; RCT = randomized controlled trial

5.2 FAQ 1: WHAT DOES THE TREATMENT FOR LOCALIZED PROSTATE-CANCER INVOLVE?

For information on the three active treatment options radical prostatectomy, external beam radiotherapy, and LDR brachytherapy see section “3.2. FAQ1: What does the treatment for localized prostate cancer involved? (What is the procedure?)”.

5.3 FAQ 2: How will it affect survival?

5.3.1 Prostate-cancer survival/mortality

Table 11: Evidence synthesis PICO 2 – FAQ 2 Prostate-cancer survival

Author	Type of study	Follow-up time	Active surveillance	Radical prostatectomy	External -beam radiotherapy	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event intervention/ control groups event rate n/N (%)					
Prostate-cancer survival								
ProtecT (follow-up: 10y)	RCT	10 years	537/545 (98.8)	548/553 (99.0)		HR 0.63 (95% CI, 0.21 to 1.93)	Moderate (imprecision: low event rate + wide CI)	No differences
ProtecT (follow-up: 10y)	RCT	10 years	537/545 (98.8)		541/545 (99.6)	HR 0.51 (95% CI, 0.15 to 1.69)	Moderate (imprecision: low event rate + wide CI)	No differences
ProtecT (follow-up: 15y)	RCT	15 years	528/545 (96.9)	541/553 (97.8)		HR 0.66 (0.31–1.39)	Moderate (imprecision: low event rate + wide CI)	No differences
ProtecT (follow-up: 15y)	RCT	15 years	528/545 (96.9)		529/545 (97.1)	HR 0.88 (0.44–1.74)	Moderate (imprecision: low event rate + wide CI)	No differences

According to the results of the IQWiG reports, overall survival data on LDR brachytherapy compared to the treatment alternatives are missing [3-5]. Risk of bias is high for the included studies (one RCT = e.g., missing information on allocation concealment, blinding; two cohort studies). The quality of the evidence (outcome-specific) is rated moderate to low.

The uncertainty regarding the benefit of LDR brachytherapy is also reflected in the German guideline [1]. However, LDR brachytherapy is being used there on the basis of results from observational studies are seen as a possible alternative [1]. According to the guideline, these indicates that PSA-based LDR brachytherapy achieved recurrence-free survival rates comparable to other curative therapies.

Conclusion for DA: Prostate-cancer-specific survival at 15 years follow-up was at least 96.9% in all groups with no significant difference among the three groups (p= 0.53). Certainty of the evidence was moderate. Due to moderate quality of evidence (imprecision) we would give quantitative numbers on prostate-cancer-specific mortality.

Data on LDR brachytherapy is missing. However, German guideline recommends LDR brachytherapy as an alternative treatment strategy.

PICO 2: To be in accordance with numerical data of decision aid 1 (PICO 1) we would state, that “About 3 out of 100 men will die of prostate cancer in the fifteen years after diagnosis (irrespective of the chosen treatment strategy).

Additional to LDR brachytherapy: There is no reliable scientific data on brachytherapy. Experts/Guideline authors think that number of deaths is similar in men with brachytherapy compared to those with external radiotherapy.”

5.3.2 ALL-CAUSE MORTALITY

Table 12: Evidence synthesis PICO 2 – FAQ 2 all-cause mortality

Author	Type of study	Follow-up time	Active surveillance	Radical prostatectomy	External beam radiotherapy	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event intervention/ control groups event rate n/N (%)					
All-cause mortality								
ProtecT (follow-up: 10 y)	RCT	10 years	59/545 (10.8)	55/553 (9.9)		HR 0.93. (95% CI, 0.65 to 1.35)	Moderate (imprecision: low event rate + wide CI)	No differences
ProtecT (follow-up: 10y)	RCT	10 years	59/545 (10.8)		55/545 (10.1)	HR 0.94 (95% CI, 0.65 to 1.36)	Moderate (imprecision: low event rate + wide CI)	No differences
ProtecT (follow-up: 15 y)	RCT	15 years	124/545 (22.8)	117/553 (21.2)		HR 0.89 (95% CI, 0.69 to 1.15)	Moderate (imprecision: wide CI)	No differences
ProtecT (follow-up: 15 y)	RCT	15 years	124/545 (22.8)		115/545 (21.1)	HR 0.88 (95% CI, 0.68 to 1.13)	Moderate (imprecision: wide CI)	No differences

According to the results of the IQWiG reports, overall survival data on LDR brachytherapy compared to the treatment alternatives are missing [3]. Risk of bias is high for the studies included (one RCT = e.g., missing information on allocation concealment, blinding; two cohort studies). The quality of the evidence (outcome-specific) is rated moderate to low.

The uncertainty regarding the benefit of LDR brachytherapy is also reflected in the S3-guideline. However, LDR brachytherapy is being used there on the basis of results from observational studies and is seen as a possible alternative [3]. The guideline indicates that PSA-based LDR brachytherapy achieved recurrence-free survival rates comparable to other curative therapies.

Conclusion for DA: All-cause mortality was at approximately 22% in all groups after 15 years with no significant difference among the groups. Certainty of the evidence was moderate. Due to moderate quality of evidence (downgraded due to imprecision) we would give quantitative numbers on all-cause mortality.

PICO 2: We would state, that "10 out of 100 men will die of any cause in the ten years after diagnosis (irrespective of the chosen prostate cancer treatment strategy)."

We would state, that "About 22 out of 100 men will die of prostate cancer in the fifteen years after diagnosis (irrespective of the chosen radical treatment strategy)."

Additional to LDR brachytherapy: There is no reliable scientific data on brachytherapy. Experts/Guideline authors think that number of deaths is similar in men with brachytherapy compared to those with external radiotherapy."

5.4 FAQ 3: How will it affect health-related quality of life/psychological issues?

The comparisons of health-related quality of life revealed no significant differences among the treatment groups in the physical and mental health subscores of the SF-12 general health measure, in scores on the HADS, or in any of the symptom or function scale scores of the EORTC QLQ-C30 up to year 5. The effect of urinary incontinence on quality of life was worse in the prostatectomy group for 2 years, but then became somewhat like that reported in the other groups [8].

Donovan et al. (2023) reported similar levels of mental health, anxiety, depression, and cancer-related quality of life at 5 and 10 years. A gradual decline over time was not seen for mental health. Although anxiety and depression fluctuated, they remained at similar levels throughout.

It is likely that there are no differences in overall quality of life between patients who underwent both active (radical) treatments. Certainty of evidence is moderate due to risk of bias (lack of blinding).

Rapid review on LDR brachytherapy concludes that no statement can be made on differences in the LDR brachytherapy compared with the other treatment options (low quality of evidence) [5].

Conclusion for DA: Quality of life as well as other psychological aspects seems to be equal in all treatment groups over the follow-up period.

PICO 2: We would state, that “quality of life is similar in all treatment groups (at any follow-up assessments).”

5.5 FAQ 4: What are the long-term implications regarding disease progression (inkl. metastases)?

Table 13: Evidence synthesis PICO 2 – FAQ 4 Disease progression & metastases

Author	Type of study	Follow-up time	Active surveillance	Radical prostatectomy	External beam radiotherapy	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event intervention/ control groups event rate n/N (%)					
Disease progression								
ProtecT (follow-up: 10 y)	RCT	10 years	112/545 (20.6)	46/553 (8.3)		HR 0.39 (95% CI, 0.27 to 0.54)	moderate	Difference in favor of RP
ProtecT (follow-up: 10 y)	RCT	10 years	112/545		46/545 (8.4)	HR 0.39 (95% CI, 0.27 to 0.55)	moderate	Difference in favor of RT
ProtecT (follow-up: 15 y	RCT	15 years	141/545 (25.9)	58/553 (10.5)		HR 0.36 (95% CI, 0.27 to 0.49)	moderate	Difference in favor of RP
ProtecT (follow-up: 15y)	RCT	15 years	141/545 (25.9)		60/545 (10.8)	HR 0.35 (95% CI, 0.26 to 0.48)	moderate	Difference in favor of RT
Metastases								
ProtecT (follow-up: 10 y)	RCT	10 years	33/545	13/553 (2.4)		HR 0.39 (95% CI, 0.21 to 0.73)	moderate	Difference in favor of RP
ProtecT (follow-up: 10 y)	RCT	10 years	33/545		16/545 (2.9)	HR	moderate	Difference in favor of RT
ProtecT (follow-up: 15 y	RCT	15 years	51/545 (9.4)	26/553 (4.7)		HR 0.47 (95% CI, 0.29 to 0.76)	moderate	Difference in favor of RP
ProtecT (follow-up: 15 y)	RCT	15 years	51/545 (9.4)		27/545 (5.0)	HR 0.48 (95% CI, 0.30 to 0.77)	moderate	Difference in favor of RT

Radical prostatectomy or external radiotherapy likely reduces disease progression and incidence of metastases (compared to active surveillance). No differences were seen between radiotherapy compared to radical prostatectomy.

IQWiG report noticed that there is still no usable data for disease-free survival and the results for the surrogate PSA-based recurrence-free survival still do not allow a reliable statement [5].

Conclusion for DA: Radical prostatectomy or external radiotherapy likely reduces disease progression and incidence of metastases (compared to active surveillance). Certainty of the evidence is moderate. Therefore, communication of quantitative numbers would be possible/adequate.

We would state, that "(Approx.) 5 out of 100 men with radical prostatectomy or with radiotherapy will develop metastases (fifteen years follow-up).

(Approx.) 11 out of 100 men with radical prostatectomy or with external radiotherapy will have disease progression" (fifteen years follow-up).

Additional to LDR brachytherapy: There is no reliable scientific data on brachytherapy."

5.6 FAQ 5: What are the risks, side effects and long-term implications for the patient?

5.6.1 Sexual function

Table 14: Evidence synthesis PICO 2 – FAQ 5 Sexual function

Sexual function - Erections firm enough for intercourse

	AM		RP		RT		
	n / N	(%)	n / N	(%)	n / N	(%)	p-value
EPIC: Erections firm enough for intercourse							
Baseline	164/243	(67.5)	161/245	(65.7)	169/247	(68.4)	
6 months	173/375	(51.6)	43/359	(12.0)	75/338	(22.2)	
12 months	167/340	(49.1)	52/356	(14.6)	132/351	(37.6)	
24 months	178/378	(47.1)	74/391	(18.9)	132/388	(34.0)	
36 months	173/421	(41.1)	89/427	(20.8)	143/420	(34.0)	
48 months	163/442	(36.9)	90/447	(20.1)	142/447	(31.8)	
60 months	157/449	(35.0)	94/464	(20.3)	125/462	(27.1)	
72 months	134/452	(29.6)	76/461	(16.5)	125/456	(27.4)	<0.001

Erectile function was reduced from baseline to 6 months in all the men, with clear differences among the treatment groups (p<0.001) [8].

In ProtecT erectile function (= erection firm enough for intercourse) was reported at baseline by (approx.) 67% of included men. By six months this rate fell to 52% in the active-monitoring group, to 22% in the external radiotherapy group, and to 12% in the prostatectomy group. The risk difference between men with prostatectomy and men with external beam radiotherapy is 10% at this point. Erectile function remained worse in the prostatectomy group at all time points [8].

External radiotherapy causes erection problems (=lack of firmness) in the first few months (from 38% baseline to 69% one year after external radiotherapy; 74% after six years). The portion of men reporting (moderate/big) impact of sexual dysfunction on quality of life increased from 17% to 42 (after one year; and 37% after six years) [8].

Prostatectomy causes erection problems (=lack of firmness) in the first few months (from 35% baseline to 95% one year after external radiotherapy; 85% after six years). The portion of men reporting (moderate/big) impact of sexual dysfunction on quality of life increased from 16% to 64% (after one year; and 43% after six years) [8].

Further long-term data on sexual function up to twelve years are reported by Lane et al. 2022 [12], and Donovan et al. 2023.

The data available on LDR brachytherapy in the IQWiG reports did not meet the requirements for synthesis and the individual studies have a high risk of bias [5]. Considering the available evidence there is no stat. significant difference between external beam radiotherapy and brachytherapy (two cohort studies). Results of one RCT and two cohort studies showed statistically significant, but clinical non relevant difference in favor of LDR brachytherapy compared to radical prostatectomy [5]. Quantitative information on the endpoint sexual function (in comparison to the treatment alternatives) is therefore not possible.

Conclusion

Sexual function declined due to radical treatment (external radiotherapy or radical prostatectomy). Certainty of evidence is moderate. Therefore, communication of quantitative numbers (at six months) would be possible/adequate for radical prostatectomy and external beam radiotherapy. Quantitative information on the endpoint sexual function for LDR brachytherapy (in comparison to the treatment alternatives) is not possible.

PICO 2: We would state, that "Radical treatment (radiotherapy or prostatectomy) causes erection problems. Only 22% of men with external radiotherapy have an erection that allows sexual intercourse (after six months/in the first few months). In men with radical prostatectomy the proportion is even lower (12%) (in the first few month).

(In addition to LDR brachytherapy: Erection problems are similarly common in men with external radiotherapy and brachytherapy. They are less common after brachytherapy than after radical prostatectomy.)

5.6.2 URINARY AND BOWEL FUNCTION

Table 15: Evidence synthesis PICO 2 – FAQ 5 Urinary problems

Urinary problems: EPIC urinary incontinence sub-score (ProtecT; Donovan et al. 2016 [8])

	AM		RP		RT		
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	p-value
EPIC urinary incontinence sub-score							
Baseline	93.5 (11.3)	244	92.8 (11.6)	255	92.8 (11.0)	246	
6 months	89.1 (16.0)	345	67.4 (29.1)	361	88.7 (16.8)	338	
12 months	89.1 (15.3)	353	76.5 (23.7)	354	90.5 (13.5)	354	
24 months	88.9 (15.0)	389	80.3 (21.4)	393	89.0 (14.1)	387	
36 months	87.3 (16.7)	426	79.3 (21.8)	425	89.8 (13.5)	417	
48 months	86.8 (17.4)	446	80.2 (20.3)	445	89.2 (14.4)	449	
60 months	87.2 (16.8)	455	80.6 (20.2)	455	89.4 (14.4)	455	
72 months	85.8 (18.5)	446	80.9 (20.2)	449	89.4 (14.0)	443	<0.001

Urinary incontinence was assessed with different measure tools, e.g., International Consultation on Incontinence Questionnaire (ICIQ), Expanded Prostate Index Composite (EPIC). We decided to use the EPIC (scores range from 0 [most affected] to 100 [least affected] as that measure is suggested by the German guideline.

Baseline-scores for the urinary-incontinence sub-score is approximately 93/100 in both groups (see tab. 15). After six months the score did not drop noticeably for men with radiotherapy (89/100). Men with prostatectomy showed a strong decrease 67/100 (defined minimally important differences (MID) for urinary incontinence: 6-9 points). The score slightly increased to 76/100 after twelve months and was stabile for men with external radiotherapy [8].

Long-term follow-up data showed a gradual increase in incontinence for men in the external radiotherapy groups. Risk increased with treatment strategy switch (= radical prostatectomy).

The rate of use of absorbent pads (one or more pads per day in past 4 weeks) increased from approximately 1% at baseline to 46% at 6 months (26% after twelve month) in the prostatectomy group, as compared with 5% at 6 months (4% after twelve months) in the radiotherapy group [8].

Certainty of evidence is moderate due to risk of bias (lack of blinding).

Overall, there might be an advantage of LDR brachytherapy in terms of impairment due to urinary tract dysfunction (urinary incontinence) compared to radical prostatectomy [5].

The results of a former IQWiG Rapid Report showed statistically significant difference in advance of LDR brachytherapy compared to external beam radiotherapy on duration and necessity of catheterization [4].

Table 16: Evidence synthesis PICO 2 – FAQ 5 Bowel function/fecal incontinence

Bowel function: Fecal incontinence more than once per week (EPIC) [8]

	AM		RP		RT		
	n / N	(%)	n / N	(%)	n / N	(%)	p-value
EPIC: Fecal incontinence more than once per week							
Baseline	5/249	(2.0)	7/255	(2.8)	1/250	(0.4)	
6 months	6/348	(1.7)	4/367	(1.1)	18/346	(5.2)	
12 months	4/356	(1.1)	3/363	(0.8)	14/358	(3.9)	
24 months	10/395	(2.5)	8/406	(2.0)	17/393	(4.3)	
36 months	10/436	(2.3)	8/437	(1.8)	11/433	(2.5)	
48 months	12/460	(2.6)	8/459	(1.7)	11/458	(2.4)	
60 months	11/463	(2.4)	6/472	(1.3)	11/476	(2.3)	
72 months	12/462	(2.6)	9/468	(1.9)	19/465	(4.1)	0.027

In the group of men with external radiotherapy, the risk of have fecal incontinence at least once a week is comparatively high just after treatment. Risk difference to the group of men with prostatectomy is at 6 months about 4% and after 24 months about 2% [8].
In addition, proportion of men with “loose stools about half the time or more frequently” as well as “bloody stool” are higher in the external radiotherapy group compared to both other groups.

About 16% (of all men) reported loose stool at baseline. The risk of loose stool is increased in the long term for men with radiotherapy.

Bloody stools, on the other hand, are very rare at the start of the study (1-2%) and only become apparent during the study in the group of men receiving external beam radiotherapy.

According to available research (low quality of evidence) bowel problems seem to be less common following LDR brachytherapy than after external beam radiotherapy [5]. No quantitative results usable.

Further long-term data on urinary problems as well as bowel function up to twelve years are reported by Lane et al. 2022 [12], and Donovan et al. 2023.

Conclusion for DA: Prostatectomy had the greatest negative effect on urinary continence at 6 months, and although there was some recovery, urinary incontinence remained worse in the prostatectomy group than in the other groups at all time points.

Certainty of evidence is moderate. Therefore, communication of quantitative numbers would be possible/adequate for prostatectomy and external beam radiotherapy. Quantitative information on the endpoint urinary and fecal incontinence for LDR brachytherapy (in comparison to the treatment alternatives) are not possible.

PICO 2:

We would state, that “Radical prostatectomy causes urinary incontinence. The problems with unwanted urine leakage increase significantly within the first few months after the operation. After 1 year they are slightly improved.

In the first months after the operation, the score drops by about 25 points to 67 out of 100. Another 6 months later, the value improves to 76 out of 100. This means that unintentional leakage of urine affects at least a little bit daily living. About 46 out of 100 men will need one or more pads a day 6 months after surgery. After 12 months, it's still about 26 out of 100 men.

Radiotherapy is unlikely to increase the incidence of urinary incontinence. Men with radiotherapy have a consistent score of about 90 on a 100 scale within the first year. This means that unintentional urine leakage does not affect daily living.

Additional information: The influence of urinary incontinence on quality of life can be recorded on a scale from 0 to 100. The higher the value, the fewer problems with unwanted urine leakage. A value of 100 means completely continence. Changes in continence are considered noticeable if they are more than 6 to 9 points.

Implanting radiotherapy seeds may cause damage to the urinary system. A urinary catheter may be needed to urinate. This seems to be more often than with external radiotherapy.

Men with external radiotherapy have a higher risk of fecal incontinence just after treatment. (Approx.) 5 out of 100 men with external radiotherapy have (at least once a week) fecal incontinence. 1 out of 100 men with prostatectomy will have it.

The risk of loose stool is increased in the long term for men with external radiotherapy. Bloody stools, on the other hand, are very rare at the start of the study (1-2%) and only become apparent during the study in the group of men receiving external beam radiotherapy.

Bowel problems seem to be less common following brachytherapy than after external beam radiotherapy.”

5.6.3 Complications of active treatment approaches

For information on the three active treatment options radical prostatectomy, external beam radiotherapy, and LDR brachytherapy see section “3.*4.4 Complications of prostate biopsies (as part of active surveillance approach) and active treatment approaches”*

6. DISCUSSION

6.1 SUMMARY OF MAIN FINDINGS

After being diagnosed with low-risk prostate cancer, men face a serious decision. They have to choose between an observational treatment strategy (active monitoring) and various curative treatments (radical prostatectomy or radiotherapy).

Only one RCT comparing all the four treatment options (active surveillance, external beam radiotherapy, brachytherapy, radical prostatectomy) was identified, but the trial was prematurely closed. The ProtecT trial included no brachytherapy. It showed no difference between the three included treatment strategies after 15 years of follow-up for prostate-cancer mortality and overall mortality. Certainty of the evidence is moderate. Patients with active treatment (radiotherapy, prostatectomy) have a lower risk of disease progression and metastasis. However, ative treatment strategies increase the risk of getting problems with erection, urinary function, and bowel functions. High quality evidence on brachytherapy (one kind of radiotherapy) is still missing.

6.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

Since the PRFERE trial was prematurely closed, the main basis of this evidence report is one RCT (ProtecT trial). A RCT which evaluates the four treatment strategies for low risk localized prostate cancer is still missing.

However, strengths of the trial are the intention-to-treat analysis and the long-term follow-up (15 years and ongoing). A limitation of the ProtecT trial is that a PSA-based "active monitoring" strategy was examined, which differs from the described in the German S3 guideline. The German guideline for men with low risk localized prostate cancer recommends an active surveillance strategy, which includes in addition to regular PSA tests control biopsies. In addition, active monitoring according to the S3 guideline is only required for men with prostate cancer, which have a very low risk of progression. In this regard, the population in ProtecT differs somehow from the group of men which in Germany outlined the guideline for active surveillance. According to contemporary methods of risk stratifications up to 34% of the ProtecT cohort had intermediate or high-risk prostate cancer at the time of the diagnosis. Additionally, since its inception, treatments and diagnostic methods have evolved.

For men with low-risk prostate cancer LDR brachytherapy might be a treatment option. However, state of knowledge on the benefits and harms of LDR brachytherapy is insufficient, new findings after termination of the PREFERE study are not to be expected.

Watchful waiting is considered a palliative option and takes a special position/role [1]. It (= waiting observation/watchful waiting) is usually only an option for one subgroup: men with low-risk prostate cancer whose remaining life expectancy is less than 10 years. Then it is not to be expected that the cancer will grow significantly, and that treatment will have advantages. With wait-and-see observation, only the complaints are treated and not the tumor itself (palliative or palliative approach). Watchful waiting was not a predefined

treatment option (as well the target population) for the planned patient information.
Therefore, it should only briefly described/mentioned.
However, this option should always be discussed with patients for whom it is an option [1].

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