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Timing of Curative Treatment for Prostate Cancer: A Systematic Review

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Abstract

Context—Delaying definitive therapy unfavourably affects outcomes in many malignancies. Diagnostic, psychological, and logistical reasons but also active surveillance (AS) strategies can lead to treatment delay, an increase in the interval between the diagnosis and treatment of prostate cancer (PCa).

Objective—To review and summarise the current literature on the impact of treatment delay on PCa oncologic outcomes.

Evidence acquisition—A comprehensive search of PubMed and Embase databases until 30 September 2012 was performed. Studies comparing pathologic, biochemical recurrence (BCR), and mortality outcomes between patients receiving direct and delayed curative treatment were included. Studies presenting single-arm results following AS were excluded.

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Evidence synthesis—Seventeen studies were included: 13 on radical prostatectomy, 3 on radiation therapy, and 1 combined both. A total of 34 517 PCa patients receiving radical local therapy between 1981 and 2009 were described. Some studies included low-risk PCa only; others included a wider spectrum of disease. Four studies found a significant effect of treatment delay on outcomes in multivariate analysis. Two included low-risk patients only, but it was unknown whether AS was applied or repeat biopsy triggered active therapy during AS. The two other studies found a negative effect on BCR rates of 2.5–9 mo delay in higher risk patients (respectively defined as any with T 2b, prostate-specific antigen >10, Gleason score >6, >34–50% positive cores; or D’Amico intermediate risk-group). All studies were retrospective and nonrandomised. Reasons for delay were not always clear, and time-to-event analyses may be subject to bias.

Conclusions—Treatment delay of several months or even years does not appear to affect outcomes of men with low-risk PCa. Limited data suggest treatment delay may have an impact on men with non-low-risk PCa. Most AS protocols suggest a confirmatory biopsy to avoid delaying treatment in those who harbour higher risk disease that was initially misclassified.

Keywords

Active surveillance; Delay; Expectant management; Outcomes; Prostate cancer; Radiation therapy; Radical prostatectomy

1. Introduction

Delay of definitive therapy has an unfavourable impact on outcomes in different malignancies [1–3]. Because most malignant cells appear to grow exponentially with related systemic spread, we can reasonably assume that treatment delay of some tumours may risk missing the window of curability.

Prostate cancer (PCa) is generally considered a relatively slow-growing malignancy, with screening adding a considerable lead time [4,5]. Delay between diagnosis and active therapy of PCa is often common. Unintended causes for this delay may include the need for pretreatment diagnostics or psychological and logistical reasons. Active surveillance (AS), as opposed to immediate definitive therapy, has garnered considerable support for several reasons in the treatment of low-risk disease. This strategy has introduced a new intended reason for delay in treatment [6,7]. AS is designed to avoid unnecessary therapy in low-risk PCa, but identification of these tumours can be difficult and may miss the presence of occult higher risk disease. We review the current medical literature to identify evidence whether treatment delay in PCa results in worse oncologic outcomes. Effects on functional outcome are not addressed.

2. Evidence acquisition

2.1. Study selection

We conducted a systematic review of the electronic databases PubMed and Embase according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement guidelines [8]. Predefined search terms were used to identify articles describing the impact of a delay in treatment or extending the time interval between diagnosis and active curative therapy of PCa on pathologic, biochemical, and mortality outcomes. The literature search included papers published until 30 September 2012. Figure 1 presents the search strategy flowchart. Table 1 lists the terms used in the literature search. References of all retrieved articles were checked for additional cross-references.

2.2. Inclusion and exclusion criteria

We limited our search to full-text original articles published in English and available for review. Articles were independently assessed for eligibility using the following predefined criteria:

- Study population: Patients diagnosed with PCa
- Intervention: Surgery: open, laparoscopic, or robot-assisted radical prostatectomy; radiation therapy (RT): external-beam RT or brachytherapy
- Study outcomes: Pathologic characteristics, biochemical recurrence rates (BCRs), or longer term outcomes such as distant metastasis (DM) rates or overall survival (OS) and cancer-specific survival (CSS).

The following studies were excluded: single-arm studies reporting outcomes without direct comparison group (eg, single-arm AS studies) or without subanalysis of the effect of delay, articles only assessing the effect of short intervals (days to weeks) between biopsies and surgery on perioperative outcomes (eg, blood loss, length of surgery, hospital stay), articles presenting overviews of wait times for curative therapy without any of the relevant outcome parameters, and articles presenting the effect of treatment delay on quality of life (QoL) only. Finally, papers outdated by more recent studies using overlapping data sets were excluded.

2.3. Data extraction

The following data were extracted from full-text articles by the first author: treatment modality, study design, selection and inclusion criteria, study details (delay definition, patient numbers, differences between groups, and time-to-event analysis details), specific reasons for treatment delay and switch of treatment, and relevant outcomes. Potential biases were analysed and recorded.

3. Evidence synthesis

3.1. Search results

Our literature search identified 17 original articles that were included in the qualitative analysis [9–25]. Differences in study design, inclusion criteria, and outcome parameters between studies and the lack of study population details prevented combining data for quantitative analysis. Table 2 presents an overview of the 17 included studies. Four relevant studies were outdated by more recent publications using the same patient study group [26–29].

3.2. Study analysis

Thirteen studies presented outcomes after RP, 3 after RT, and 1 study combined RP and RT; none were found on brachytherapy. The reports include 34 517 patients with PCa diagnosed from 1981 to 2009. All studies excluded patients with adjuvant therapy. All were retrospectively designed. Summary data occasionally hindered detailed data extraction.

3.3. Patient population

Some of these studies focused on patients with low-risk PCa only; others had wider criteria for eligibility (clinical stage T3–4 disease, prostate-specific antigen [PSA] >20, Gleason scores 8–10). Treatment delay was often associated with older patient age or more favourable tumour characteristics (lower D'Amico risk groups, lower PSA, Gleason scores, clinical stage, less positive biopsies). In one study the delayed treatment group actually showed higher Gleason scores but explicitly stated it was due to the effect of repeat biopsies

during AS [11]. In general, the number of men receiving immediate treatment was much higher than the number of men undergoing delayed interventions. If described, the staging work-up such as the total number of biopsies differed between studies but not between the direct and delayed treatment groups within one study. Comorbidity status was presented in two studies [13,22], with significant differences between groups found in one [13].

3.4. Definition of interval and delay

Treatment delay was defined according to the following definitions: time interval shorter and longer than the median delay time ($n = 4$; range: 56 d to 3.7 mo), less than or more than a delay of 3 mo ($n = 3$), analysis per extra month delay ($n = 3$), <6 mo or >6 mo ($n = 2$), <60 d or >60 d ($n = 2$), or comparison of different 3-mo intervals ($n = 2$). Three studies considered men in the treatment delay category if they were labelled so in the study database; this mainly involved AS-like strategies [13,23,25]. One study used treatment delay as a continuous variable for the main analysis (other studies used this variable in subanalyses).

It was unclear whether delay was intended or unintended in 11 studies. Two studies reported that the delay group was followed with a fixed AS protocol [11,25], two reported on expectant management without fixed criteria [13,23], and one stated that AS was frequently applied [16]. Korets et al *excluded* men on AS [15].

3.5. Definition of outcome/end point

The selected studies used one or more of the following end points as the main outcome variables: PSA BCR rates after radical prostatectomy (RP) or RT ($n = 15$), pathologic characteristics after RP ($n = 8$), OS and/or CSS ($n = 3$), and lymph node or DM rates ($n = 2$). One study used a previously constructed nomogram predicting the chance of incurable cancer (<75% chance of remaining BCR free 10 yr postsurgery) as the outcome [25]. This was also the only study that did not include any form of a time-to-event analysis. Fourteen studies presented a time-to-event analysis with BCR as the outcome. Of these, seven studies used the time between RP and BCR as the outcome time parameter, four studies used the time between diagnosis and BCR, and one included both. The potential effect on outcomes of this important difference in time-to-event analyses is discussed later. The remaining two studies used other analyses: a landmark analysis in which analysis started at 1 yr after diagnosis for both direct and delayed treatment or binary end point BCR yes or no at a fixed period after treatment for direct or delayed treatment.

3.6. Observations of outcome

Seven studies found no significant impact of treatment delay on oncologic outcomes [10,11,15,17,21,23,24]. Two included only men with low-risk disease [11,23]; the other five included some men with higher risk PCa [10,15,17,21,24]. The longest treatment delay interval was 2.1 yr [23]. Four studies initially suggested an association between treatment delay and outcomes following univariate analysis but not multivariate analysis [14,16,18,25]. Two studies found *lower* rates of upstaging in the group with delayed therapy [12,22].

Four studies found that treatment delay had an unfavourable impact; however, none found a relationship of delay with DM, OS, or CSS. Abern et al noted that if RP was delayed >9 mo, BCR rates and positive surgical margins rates were higher among men with intermediate-risk disease but not among men with low-risk PCa (D'Amico risk classification) [9]. Specific reasons for delay or triggers to switch to active therapy were not presented. Holmström et al found that patients labelled initially as “expectant management” in the Swedish National Prostate Cancer Registry had higher Gleason scores in their surgical

specimens when compared with men who had undergone surgery at the time of diagnosis (delay of 19.2 mo vs 3.5 mo) [13]. All patients had stage T₂ disease, PSA <20 ng/ml, and Gleason score ≤6 at diagnosis. Treatment delay resulted from AS in these patients, but the reasons that triggered deferred radical surgery were known (eg, repeat biopsies). Nguyen et al found that treatment delay >2.5 mo independently predicted time to PSA failure after RT in patients labelled high risk (defined as any of the following criteria: T_{2b}, PSA >10, Gleason score >6, >34–50% positive biopsy cores) [19]. The authors did not provide reasons for delay or triggers to switch to active therapy. Finally, O'Brien et al found that in a cohort of men with low-risk disease, a delay in performing RP >6 mo after diagnosis was associated with a higher frequency of disease upgrading (47% vs 27% upstaging to Gleason score 7–10) and lower PSA progression-free survival rates [20]. Again, no specific reasons for treatment delay or triggers to undergo active therapy were provided.

Besides the effect of treatment delay, most studies included information on the known risk factors for worse pathologic and BCR outcomes after RP or RT.

3.7. Study evaluation

This review included studies monitoring the effect of PCa treatment delay on oncologic outcome. Most did not find any differences in outcomes between patients who received immediate or delayed RP or RT according to different definitions of delay. All are limited in varying degrees by suboptimal study design including unaccounted potential biases in the time-to-event analysis. Four studies did find a significant relation in multivariate analysis [9,13,19,20], of which two included intermediate- to high-risk PCa. One study found an unfavourable effect of delay of RP >9 mo in intermediate-risk disease groups, and one found worse outcomes in non-low-risk disease of RT >2.5 mo after diagnosis [9,19]. These two studies suggest that in men with non-low-risk disease, oncologic outcomes may be compromised if treatment is delayed. This finding is balanced, however, by five studies that also included intermediate- to high-risk men that did not show an unfavourable impact of treatment delay on outcomes [10,15,17,21,24].

The two other studies that showed a significantly unfavourable outcome associated with treatment delay included low-risk patients only [13,20]. Selection bias in these two studies very likely accounts for this contrary conclusion. In the article by Holmström et al, patients in the delayed treatment group (19.2 mo vs 3.5 mo) are labelled as “expectant management” [13]. The reasons why patients switched to active therapy were unclear. We hypothesise that men who initially chose expectant management may have subsequently developed unfavourable disease characteristics on repeat biopsies that resulted in their selection for RP. A similar selection bias might explain the large differences in Gleason upgrading between men undergoing direct RP and delayed RP (27% vs 47% for <6 mo vs ≥6 mo delay) in the study presented by O'Brien et al [20]. No reasons for delaying treatment were provided in this study that included recently treated patients with low-risk disease. Again, men may have been included who underwent repeat prostate biopsies as part of an AS-like protocol resulting in pathologic risk reclassification and deferred treatment. Dall'Era et al specifically cite this potential bias when analysing outcomes [11]. They used the most recent prostate biopsies when comparing outcomes between men undergoing immediate or delayed therapy. Treatment delay did not affect men with low-risk tumours in this study. This selection bias, as hypothesised earlier, probably does not explain the negative effect of treatment delay on non-low-risk disease because these patients are generally considered unsuitable for AS.

The contradictory protective effect of treatment delay as presented in two studies is also likely to be caused by selection bias [12,22]. Tumours with more favourable characteristics are often treated later and show more favourable outcomes.

Differences in comorbidity may also introduce potential biases between patients receiving direct versus delayed treatment. Patients with more comorbidity may be more likely to be selected for initial expectant management. This may artificially favour BCR or mortality outcomes after deferred treatment because these patients will succumb to non-PCa causes earlier than healthy men. This bias was noted in both studies presenting comorbidity scores.

Most studies used pathologic characteristics and BCR as the surrogate end points rather than DM, CSS, or OS. However, these surrogate end points have been found to show a significant correlation with metastatic and mortality rates [30].

Unfortunately, the quality of the evidence in these studies is low. The retrospective design and lack of randomisation cause these studies to be rated level 3. Furthermore, only a few of these studies included patients with unfavourable (intermediate- or high-risk) disease. Most studies show evidence of a selection bias in which patients with more unfavourable risk disease and who are younger are treated earlier than older men and those men with comorbidities. Most studies failed to provide information why patients were treated later or what triggers were used to initiate delayed therapy. It is therefore not possible to generalise findings from single studies or to draw definitive conclusions on the timing of curative treatment for PCa.

Although most included studies failed to reject the null hypothesis that there is no difference in outcomes between immediate and delayed treatment, this does not necessarily imply that we should accept the hypothesis. The power of most studies to reject the null hypothesis may have been too low.

3.8. Time-to-event analyses

Fourteen studies presented a time-to-event analysis with BCR as the outcome. Different starting points ($t = 0$ at the moment of diagnosis versus $t = 0$ at the moment of treatment) in these analyses may lead to considerable bias. Only 4 of 14 studies identified this potential bias in choosing a specific time-to-event analysis [9,18,23,24].

For example, consider two patients with occult metastases at diagnosis that will grow to clinically detectable BCR, independent of the specific local treatment. The first receives RP at 3 mo after diagnosis, and the second patient at 9 mo after diagnosis.

If the moment of RP is used as the starting point of the time-to-event analysis and BCR occurs at 12 mo after diagnosis, BCR will occur at 9 mo and 3 mo after RP, respectively. This artificially increased time to recurrence may lead to a bias with more favourable results in the early treatment group.

If the moment of diagnosis is used as the starting point of the time-to-event analysis and PSA would start to rise at 6 mo in both patients, the problem is that the first patient shows BCR at 3 mo after diagnosis, whereas the second is not even at risk for BCR. Such an analysis may be biased in favour of delayed surgery.

An alternative approach is to use a landmark analysis, as applied in one of the included studies [18]. Time to BCR is measured from a fixed starting point, such as 12 mo, after diagnosis. Patients are excluded if they are treated after the landmark time but also if they develop BCR before the landmark. This method may bias results in favour of early surgery because patients who develop disease recurrence rapidly would be excluded if they underwent early surgery but not if surgery was delayed.

BCR may also be used as a binary end point (yes vs no) at different time points after treatment [24]. This method may introduce the same bias in which early treatment leads to

more favourable results due to an artificial longer time until BCR. If the patients were treated at 3 and 9 mo after diagnosis and had a BCR at 18 mo after diagnosis but were analysed at 12 mo after treatment, the patient treated early would not show BCR, whereas the patient treated later would show BCR at this point. In analyses at 2 yr, however, this bias would be drastically reduced. Therefore the bias introduced in this last analysis may be the smallest.

3.9. Selection for treatment

The spectrum of clinical progression among men with PCa is very wide and depends on both disease-specific and patient-specific characteristics. Patients with high-grade PCa show an aggressive disease course with rapid spread and higher disease-specific mortality. These malignancies deserve prompt diagnosis and treatment. Vickers et al used data from the Scandinavian Prostate Cancer Group-4 trial and found that radical treatment is most justified in high-risk patients (Gleason 8 or Gleason 7 with clinical stage IIPC a) [31].

PCa with favourable disease features at the time of diagnosis, however, has been shown to have a relatively benign course in most cases, even when diagnosed clinically [32]. Screening for PCa results has advanced the date of diagnosis up to 10–15 yr for men with low-risk tumours [5]. Radical treatment for men with these malignancies may not lead to lower rates of metastases or lower PCa mortality, especially in older men or men with comorbidities. The results of the Prostate Cancer Intervention versus Observation Trial support this concept [33]. In this trial 731 men with localised PCa were randomised to either observation or RP. No differences were found regarding OS or CSS through 12 yr of follow-up. Patients in the intervention group received RP a median of 35 d after randomisation. A subanalysis of the Prostate Cancer Intervention versus Observation Trial study showed that in men with intermediate- and high-risk disease, OS was improved with RP compared with observation. For the reasons cited earlier, many clinicians have advocated initial AS strategies instead of radical treatment [34].

3.10. Clinical implications

A delay of several months or even years from diagnosis to definitive therapy in men with low-risk PCa is very unlikely to have any unfavourable impact on morbidity or PCa mortality. This is not surprising considering the favourable natural history of low-risk PCa with long lead times. Most of the studies included in this review are in line with this hypothesis. On the other side of the disease spectrum, however, as also found in this review, the risk of missing the window of curability due to treatment delay is a realistic concern. In patients with high-risk or even intermediate-risk disease, a delay of 2.5–9 mo might unfavourably affect outcomes after radical treatment, although the data on this point were mixed. Due to the limitations of the studies included in this review, it is not possible to reach any conclusions on more specific risk subgroups such as men with intermediate- and high-risk disease.

Figure 2 presents schematically the effect of a delay between diagnosis and treatment in men with low-risk and higher risk disease. Treatment delay may risk missing a window of curability in men with higher risk disease but may not have an impact on results among men with lower risk tumours.

For men with intermediate- or high-risk disease, 3 mo appears to be an acceptable period in which treatment choices should be made and additional diagnostic studies and treatment performed. Waiting lists for these patients should ideally not exceed this period.

Some of the included studies specifically mention AS. Others do not present specific reasons for delay, but they can be considered to have unintended reasons for delay instead of AS.

Although a similar delay would biologically have the same effect independent of the specific (intended or unintended) reason for delay, findings from this review may not be directly applicable to an AS situation.

The number of men on AS who will experience a pathologic upgrading following repeat biopsies may be as high as 28% [6]. Men thought to have low-risk disease at diagnosis may actually harbour higher risk PC. This upgrading is most likely the result of initial undersampling and is described as *risk reclassification* rather than disease progression [35]. A tumour initially assumed to be low risk but was reclassified as a higher risk tumour later may have a worse prognosis if treatment is delayed >1 yr [36]. Based on this information, clinicians adopting AS protocols may wish to perform confirmatory studies earlier rather than later [37,38]. This may especially hold true for patients on AS with more positive biopsy cores and higher PSA density at diagnosis [39]. Most AS protocols recommend repeat biopsies within 1 yr of the initial diagnosis [6].

3.11. Additional considerations

In the United Kingdom the Prostate Testing for Cancer and Treatment study is being conducted [40]. Patients are randomised for treatment including AS. This study may also provide answers on the effect of delay due to AS. Simulation models of differences in outcomes between direct and delayed treatment may provide an alternative to randomised studies. For example, Xia et al modelled PCa mortality after direct RP versus RP after initial AS [41]. It was found that AS may result in a small decline in CSS but large benefits in QoL in men with low-risk PCa.

We did not consider the potentially unfavourable effect of delayed treatment on QoL. Sun et al noted more postoperative urinary incontinence and erectile dysfunction and associated procedures among men undergoing delayed treatment [22]. Radomski et al found that the treatment delay due to AS did not increase the risk of urinary incontinence [42], but Fujita et al noted an unfavourable effect on erectile function possibly because of repeat biopsies [43]. Waiting for radical treatment may also cause distress, although many patients included in an AS protocol did not show high levels of anxiety [44,45]. Finally, other potentially negative effects of delaying therapy on physical or psychological domain outcomes are unknown. For example, delaying surgery may miss the opportunity to perform nerve-sparing surgery. Disease upgrading or upstaging after treatment following initial AS may lead to a greater need for secondary treatments, which may have a further unfavourable effect on QoL. The European and American guidelines do not specifically mention the timing of curative therapy for PCa [46,47].

4. Conclusions

Among men with low-risk PCa, a treatment delay of several months or even years does not appear to compromise long-term oncologic results following definitive treatment. Limited data suggest that treatment delay may compromise oncologic outcomes in men with non-low-risk PCa. The overall quality of evidence of included studies was <2b.

Curative treatment for low-risk PCa, if indicated at all, is not an urgent matter. This creates a window for additional risk stratification including initial AS. Patients deciding whether to commit to an AS protocol should consider a confirmatory biopsy to decrease the possibility that they may harbour occult higher risk disease.

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Take-home message

Delaying treatment for several months or even years for men with low-risk prostate cancer (PCa) does not appear to compromise long-term oncologic outcomes. Limited data suggest that treatment delay may compromise outcomes among men with intermediate- or high-risk PCa.

Fig. 1.
Literature search and selection of studies for analysis flowchart.

Fig. 2. Schematic presentation of the disease course of low-, intermediate-, and high-risk disease against life expectancy and the effect of treatment delay (dashed arrows). A similar delay may result in missing the window of curability for higher risk disease.

Table 1

Search terms used in PubMed and Embase databases

PubMed						
Delay [Title/Abstract]	AND	Prostate [Title/Abstract]	AND	Treatment [Title/Abstract]	AND	Outcomes [Title/Abstract]
OR				OR		OR
Deferral [Title/Abstract]				Expectant management [Title/Abstract]		Recurrence [Title/Abstract]
OR				OR		OR
Deferred [Title/Abstract]				Radiotherapy [Title/Abstract])		Survival [Title/Abstract]
OR				OR		OR
Interval [Title/Abstract]				Watchful waiting [Title/Abstract]		Biochemical [Title/Abstract]
				OR		OR
				Radiation [Title/Abstract]		Mortality [Title/Abstract]
				OR		OR
				Prostatectomy [Title/Abstract]		Pathology [Title/Abstract]
				OR		OR
				Brachytherapy [Title/Abstract]		Results [Title/Abstract]
				OR		
				Surgery [Title/Abstract]		
				OR		
				Active surveillance [Title/Abstract])		

Embase

The same search strategy was used in Embase ("[Title/Abstract]" was replaced by "ti,ab").

Table 2
Overview of included studies comparing the outcomes after direct versus delayed radical treatment

Study	Therapy	Study design	Period	Selection/inclusion criteria	Study details; delay definition, patient numbers, differences between groups, time-to-event analysis details	Specific reasons for treatment delay and switched treatment	Outcomes
Abern et al [9]	RP	Retrospective cohort. SEARCH database	1988–2011	D'Amico low- (52%) and intermediate- risk (48%) groups	Delay definition: <3 mo vs 3–6 mo vs 6–9 mo vs >9 mo Patient numbers: Total 1561. Low risk: 510, 225, 45, 33. Intermediate risk: 427, 250, 46, 25 Differences groups: Low- and intermediate-risk groups: Longer delay associated with surgery in later year and shorter follow-up. Intermediate group: Longer delay associated with lower rate in white race Time-to-event analysis details: Outcome: Time between RP and BCR	Not described	Low risk: Delay not related to BCR, ECE, PSM, pathologic upgrade Intermediate risk: Delay >9 mo significantly related to BCR ($p = 0.01$) and PSM ($p < 0.01$) Delay >9 mo associated with BCR also in subsets of men with biopsy Gleason 3 + 4 (HR: 2.51; $p < 0.01$), PSA 6.0 (HR: 2.82; $p = 0.06$), and low tumour volume (HR: 2.59; $p = 0.06$) Crude BCR-free survival at 5 yr in intermediate-risk groups and subgroups was worse for >9 mo delay (37% vs 70%)
Andrews et al [10]	RT	Retrospective cohort	1981–2001	T stage 1–4 (12 patients stage 3 or 4) PSA <10 to >20 (26 patients PSA <10 to >20) Gleason 2–10 (7 patients Gleason 8–10) Low risk 555; intermediate risk 515; high risk 252	Delay definition: <3 mo vs 3–6 mo vs 6–9 mo vs >9 mo less vs more median delay of 3.1 mo Patient numbers: Total 1322 Differences groups: Not described Time-to-event analysis details: Outcome 5-yr rates of OS, CSS, DM, freedom from BCR from diagnosis and from median delay of 3.1 mo. Kaplan-Meier analyses also included	Not described	No statistical differences in OS, CSS, DM; freedom from BCR No difference freedom from BCR or DM between less or more median delay in low-, intermediate-, or high-risk groups. Time to treatment did not predict worse OS, CSS, DM, freedom from BCR
Dall'era et al [11]	RP	Retrospective cohort	1996–2008	T1–2 PSA <10.0 Gleason 6 Positive biopsy cores 33% Single cores 50% involved Some other patients also on AS	Delay definition: <6 mo vs after AS Patient numbers: Total 1408. Low risk: 311; high risk: 1097. Direct group (median delay: 3 mo): 278 low risk, 1067 high risk. Delayed group (median delay: 18 mo, on AS): 33 low risk, 30 high risk Differences groups: Delay group: Higher free PSA, more biopsy cores taken, higher presurgical Gleason score due to repeat biopsies during AS Time-to-event analysis details: Outcome: Time between RP and BCR. Analysis in subgroup only	AS protocol: DRE, PSA, TRUS, repeat biopsy Not all patients underwent repeat biopsy (intervention based on biopsy in 23 of 63 patients)	Rates Gleason 7 (compared with most recent biopsy), T3, PSM did not differ significantly from the immediate RP group Multivariate: Treatment group not associated with Gleason upgrading, non-organ- confined disease or PSM AS >18 mo vs <18 mo no significantly different outcomes

Study	Therapy	Study design	Period	Selection/inclusion criteria	Study details; delay definition, patient numbers, differences between groups, time-to-event analysis details	Specific reasons for treatment delay and switched treatment	Outcomes
							Low-risk direct comparable to low-risk delay; similar results for high risk
Graefen et al [12]	RP	Retrospective cohort	1992–2000	T1–T3a (4.3% T3) PSA: 9.8% 0–4.0; 47.6% 4.1–10.0; 26.7% 10.1–20.0; 14.8% >20 Gleason 5–10 (3.7% 8–10)	Delay definition: Time between diagnosis and treatment analysed as continuous variable. Mean delay: 62 d; median 54; range 5–518. Kaplan-Meier analysis between <31 d and >70 d Patient numbers: Total 795 Differences groups: Not described Time-to-event analysis details: Outcome: time between RP and BCR; not specified	Not described	Time between biopsy and treatment not significantly related to BCR rate Subgroup analysis <1 mo vs >4 mo even showed protective effect of delay Even in high-grade disease subgroup no difference
Holmström et al [13]	RP	Retrospective cohort. NPCR Sweden	1997–2002	T1–2 PSA <20 Gleason 6 70 yr of age N0/x M0/x	Delay definition: Initial treatment labelled “expectant management” in database Patient numbers: Total 2566. 2344 direct (median delay: 3.5 mo), 222 delayed (median delay: 19.2 mo) Differences groups: Delay group: Older, lower PSA, lower clinical stage Time-to-event analysis details: Only OS and CSS analysed; from moment of diagnosis	Expectant management; no fixed protocol, no fixed triggers for switch treatment. Switch due to PSA in 50%; other signs progression in 9%; other causes in 39%	Upgrading Gleason lower after primary vs deferred RP (25% vs 38%; $p < 0.001$). No difference in PSM or ECE No differences in any one or more adverse characteristics
Khan et al [14]	RP	Retrospective cohort	1989–1994	T1c–T3a (35 patients T3a) PSA 0.4–41.8 (55 patients >20) Gleason 2–10 (43 patients 8–10))	Delay definition: <60 d vs > 60 d. Also comparison between 61 and 90, 91 and 120, 121 and 150, >151 d Patient numbers: Total 926; <60 d: 162, 61–90: 268, 91–120: 247, 121–150: 130, >151: 119 Differences groups: Longer delay: Lower stage (<60 d: 35% T1, 121–150 d: 48%, >151 d: 57%), lower Gleason (>151 d: 86% 2–6, <151 d: 65% 2–6), lower PSA Time-to-event analysis details: Outcome: Time between RP and BCR	Not described	Delay group: Higher BCR-free survival (>151 d group), lower rates positive LN, SVI (both 61–90 d and 91–120 d group) No differences when stratified according to preoperative characteristics
Korets et al [15]	RP	Retrospective cohort	1990–2009	T1c–T3 (0.8% T3) Gleason 7 to >7 (10.8% >7) D’Amico low, intermediate, high risk (12.1% high risk)	Delay definition: 60 d vs 61–90 d vs >90 d Patient numbers: Total 1568; 1098 d, 303 61–90 d, 167 >90 d Differences groups: Longer delay: Lower Gleason, lower D’Amico risk group Time-to-event analysis details: Outcome: Time between RP and BCR; not specified	Not described, but AS patients were excluded	Delay >60 d not associated with adverse pathologic findings at RP, not with BCR 5-yr survival rates similar Higher age, risk group, PSA, stage, Gleason and African American did give higher risk BCR

Study	Therapy	Study design	Period	Selection/inclusion criteria	Study details; delay definition, patient numbers, differences between groups, time-to-event analysis details	Specific reasons for treatment delay and switched treatment	Outcomes
					Men with > 180-d delay were individually reviewed to ensure that none had been placed on AS with delayed curative intervention protocols		
Kwan et al [16]	RT	Retrospective cohort	1993–2001	T1c–T3a Low PSA: >20 Gleason <6–10 261 patients low risk; 481 intermediate risk; 274 high risk	Delay definition: Less than vs more than median delay of 3.7 mo Patient numbers: Total 1024 Differences groups: Longer delay: Lower PSAs, lower Gleason scores, higher radiation dose (no <i>p</i> values) Time-to-event analysis details: Outcome: Time between diagnosis and BCR	Not described, but AS is mentioned as frequently applied strategy	No evidence that a longer time interval between diagnosis and radiation therapy was associated with poorer PSA control Intermediate- and high-risk patients with longer intervals better biochemical control, but not in multivariate analysis
Lee et al [17]	RP	Retrospective cohort	2001–2004	PSA mean 7.2 Mean Gleason 6.3 Mean age 59 yr	Delay definition: less or more than median delay of 36 d Patient numbers: Total 169 Differences groups: Not described Time-to-event analysis details: Outcome: Time between RP and BCR; not specified	Not described	No significant differences in operative duration, intraoperative blood loss, nerve-sparing rate, transfusion, hospital time, PSM, postoperative complications, continence Biopsy/treatment interval did not predict outcomes
Nam et al [18]	RP	Retrospective cohort	1987–1997	T1–2 PSA <4 to >20.0 (10.3% >20) Gleason 2–10 (10.2% 8–10)	Delay definition: <3 mo vs 3 mo. Median delay: 68 d Patient numbers: Total 645; 456 <3 mo; 189 3 mo Differences groups: Delay patients: Higher PSA Time-to-event analysis details: “Landmark analysis”; analysis starts at 1 yr after diagnosis for both direct and delayed group Only patients without evidence of residual tumour following surgery were included. BCRs 0–1 yr after diagnosis were not included	Not described.	Delay group had lower 10-yr BCR-free survival (61.3% vs 74.6%; <i>p</i> = 0.05) Crude HR for developing BCR 1.58 (<i>p</i> = 0.04), adjusted (for grade, stage, PSA) HR 1.46 (<i>p</i> = 0.09) of delay compared with direct treatment; so after adjusting no longer significant
Nguyen et al [19]	RT	Retrospective cohort	1992–2001	T1c–T2 PSA <4 to >20 (9.6% >20) Gleason <6–10 (9.6% 8–10)	Delay definition: Less than vs more than median delay of 2.5 mo Patient numbers: Total 460 Differences groups: In high-risk groups (defined as any of the following criteria: T 2b, PSA >10, Gleason >6, >34–50% positive biopsy cores) no differences between direct or delay. No analysis of other groups	Not described	Treatment delay independently predicted time to PSA failure following diagnosis for high-risk (<i>p</i> = 0.029) but not for low-risk (<i>p</i> = 0.31) patients High risk: Delay <2.5 mo 55% 5-yr PSA-free survival, delay >2.5 mo 39% (<i>p</i> = 0.014).

Study	Therapy	Study design	Period	Selection/inclusion criteria	Study details; delay definition, patient numbers, differences between groups, time-to-event analysis details	Specific reasons for treatment delay and switched treatment	Outcomes
O'Brien et al [20]	RP	Retrospective cohort	1989–2009	D'Amico low risk PCa (T1c/T2a, PSA<10.0, Gleason 6)	Time-to-event analysis details: Outcome: Time between diagnosis and BCR Delay definition: < 6 mo vs 6 mo Patient numbers: Total 1111; 1052 <6 mo; 59 6 mo Differences groups: Longer delay: Older, more African Americans, less T2a vs T1c Time-to-event analysis details: Outcome: Time between RP and BCR; not specified	Not described	Adjusted HR 1.08 per month delay Delay group: More high-grade (Gleason 7–10) disease (27% vs 47% upgrade), lower BCR-free survival (5% vs 12%) PSA, clinical stage, and delay >6 mo significant predictors of BCR No difference organ-confined disease, ECE, PSM, SVI, LN metastasis
Phillips et al [21]	RP/RT	Retrospective cohort. RP: 62%. RT: 38%	1991–2004	Stage T1 to T2b (9% T2b) PSA <10 to >20 (3% >20) Gleason 2–10 (3% 8–10) 59% low risk; 6% high risk	Delay definition: 3 mo vs >3 mo Patient numbers: Total 245; RP: 210 3 mo; 35>3 mo. RT: 100 3 mo; 48 >3 mo Differences groups: Delay group: Lower Gleason, more RT Time-to-event analysis details: Outcome: Time between diagnosis and BCR	Not described	BCR-free survival not associated with time to diagnosis/treatment Outcomes for RP/RT not separately presented
Sun et al [22]	RP	Retrospective cohort. SEER database	1995–2005	T1–2 Gleason <7 66 yr of age	Delay definition: 3 mo vs >3 mo (>75th percentile delay) Patient numbers: Total 17–153; 14–577 direct (median delay: 1.6 mo); 2576 delayed (median delay: 11.5 mo) Differences groups: Delay group: Lower age, fewer whites, higher socioeconomic status, fewer married, more metropolitan area, more ADT. Multivariate analyses: Higher age and higher comorbidity less likely to have treatment delay. Patients of black race and unmarried more likely to undergo delayed RP. Patients with baseline erectile dysfunction less likely to have delayed RP. Delayed RP more frequently applied in more recent years Time-to-event analysis details: Only OS and CSS analysed; t = 0 not described	Not described	Delay not associated with pathologic upstaging or survival Delay was associated with more postoperative urinary incontinence and erectile dysfunction and procedures
van den Bergh et al [23]	RP	Retrospective cohort. ERSPC section Sweden	1995–2009	T 2 PSA 10.0 PSA density<0.2 Gleason 3 + 3= 6 1–2 positive biopsies	Delay definition: Registered in database as WW or AS as initial treatment	AS but without standardised follow-up; no fixed thresholds; regular PSA,	No statistically significant differences between direct or delayed group ORs for delayed vs direct RP: Gleason score >6–1.54

Study	Therapy	Study design	Period	Selection/inclusion criteria	Study details; delay definition, patient numbers, differences between groups, time-to-event analysis details	Specific reasons for treatment delay and switched treatment	Outcomes
Vickers et al [24]	RP	Retrospective cohort	1987–2002	T1c–T3 (3% T3) PSA median 6.3 Gleason 6–10 (5% 8–10) Age median 61 yr	Patient numbers: Total 227; 158 direct (median delay: 0.5 yr), 69 delayed (median delay: 2.6 yr) Differences groups: Delay RP: Higher prostate volume, lower PSA density, lower positive biopsies, lower mm PCa tissue, higher percentage T1c, higher age, higher PSA at time of surgery Time-to-event analysis details: Kaplan-Meier curves with both diagnosis as t = 0 and treatment as t = 0	repeat biopsies, mainly in men with rising PSA	($p = 0.221$), capsular penetration 2.45 ($p = 0.091$), tumour volume 0.099 ml ($p = 0.155$), BCR (0.185, $p = 0.689$)
Warlick et al [25]	RP	Retrospective matched case-control study	1995–2005	PSA 2.0–12.0 PSA density 0.03–0.30 1–2 positive cores 1–50% of core involved	Delay definition: Outcomes presented per month extra delay after diagnosis Patient numbers: Total 3149; 29% >3 mo delay, 4% >6 mo, 1% >9 mo Differences groups: Not analysed Time-to-event analysis details: BCR as binary end point at 3, 5, 8, and 10 yr after diagnosis Patients treated >12 mo after diagnosis were excluded from study analysis ($n = 36$)	Not described	No clear evidence of significant effect of delay to diagnosis on BCR at 3-, 5-, 8-, 10-yr follow-up
					Delay definition: Delayed group were patients included in AS program Patient numbers: Total 188; 150 direct (median delay: 3.0 mo), 38 delayed (median delay: 26.5 mo) Differences groups: Delay group: Higher PSA density, lower maximal core involved with PCa Time-to-event analysis details: No BCR-free survival as outcome	AS program, switch if upgrading annual surveillance biopsies, 23% switched due to other reasons (PSA no trigger)	After adjusting for age and PSA density, the risk for incurable cancer did not differ significantly between direct and delayed treatment

ADT = androgen-deprivation therapy; AS = active surveillance; BCR = biochemical recurrence; CSS = cancer/cause-specific survival; DM = distance metastasis; DRE = digital rectal examination; ECE = extracapsular extension; ERSPC = European Randomised Study of Screening for Prostate Cancer; HR = hazard ratio; LN = lymph node; NPCR = National Prostate Cancer Registry; OR = odds ratio; OS = overall survival; PCa = prostate cancer; PSA = prostate-specific antigen; PSM = positive surgical margin; RP = radical prostatectomy; RT = radiation therapy; SEER = Surveillance, Epidemiology and End Results; SVI = seminal vesical invasion; TRUS = transrectal ultrasound; WW = watchful waiting.