Active Surveillance in Intermediate-Risk Prostate Cancer

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Active surveillance (AS) is a monitoring strategy to avoid or defer curative treatment, minimizing the side effects of radiotherapy and prostatectomy without compromising survival. AS in intermediate-risk prostate cancer (PC) has increasingly become used. There is heterogeneity in intermediate-risk PC patients. Some of them have an aggressive clinical course and require active treatment, while others have indolent disease and may benefit from AS. However, intermediate-risk patients have an increased risk of metastasis, and the proper way to select the best candidates for AS is unknown. In addition, there are several differences between AS protocols in inclusion criteria, monitoring follow-up, and triggers for active treatment. A few large series and randomized trials are under investigation.

Keywords: active surveillance ; conservative management ; intermediate-risk ; prostate cancer

1. Introduction

Worldwide, prostate cancer (PC) is the second most commonly diagnosed cancer after lung cancer and the fifth cause of death by cancer in men [1]. In 2020, there were an estimated 1.4 million new cases diagnosed with PC and 375,000 deaths worldwide. With the growth of the aging population, the number of PC cases is expected to increase by 3.5 times by 2040 worldwide [2].

Active surveillance (AS) is a monitoring strategy to avoid or defer curative treatment, minimizing treatment-related toxicity without compromising survival. AS consists of long-term follow-up with evaluation of prostate-specific antigen (PSA), imaging, and prostate biopsy. AS allows appropriate risk reclassification and patient selection for intervention. In the last decades, AS has become a standard of care for men with low-risk PC (≤cT2a, Gleason score [GS] ≤ 6, and PSA < 10 ng/mL) [3][4][5]. Moreover, a trend toward the increased use of AS has been observed in patients with low and intermediate-risk PC. For example, in the United States (US), low- and intermediate-risk patients choosing AS increased from 14.5% in 2010 to 42.1% in 2015, and from 5.8% to 9.6%, respectively [6]. In a study from Sweden that included 98% of newly diagnosed PC from 2009 to 2014, the AS use increased from 57% to 91% for very low-risk PC, from 40% to 74% for low-risk, but remained at approximately 19% for intermediate-risk PC [7].

2. Evidence on Non-Active Treatment in Intermediate-Risk PC

2.1. Prognosis in Intermediate-Risk PC by Observation vs. Active Treatment

To date, the Prostate Cancer Intervention versus Observation Trial (PIVOT [8]) and the Scandinavian Prostate Cancer Group 4 Study (SPCG-4 [9]) have investigated immediate treatment (radical prostatectomy [RP] or radiation therapy [RT]) versus observation (AS or watchful waiting) in localized PC. In addition, the three-arm Prostate Testing for Cancer and Treatment (ProtecT [10]) compared RP versus RT versus observation in this setting. Additionally, other non-randomized studies compared AS versus intervention [11][12]. **Table 1** shows a summary of the studies.

Table 1. Active surveillance versus other active treatment in localized PC.

Authors	Study Name	Number of Patients Intermediate Risk/Total, *n* (%)	Type	Initiation	Comparator	Gleason 4	Median Follow-Up	PC Mortality	Non-PC Mortality	Refer Numb
Hamdy et al.	ProtecT	490/1634 (31%)	Prospective RCT	2001–2009	AS vs. PR vs. RT	NA	10 years	Similar deaths per 1000 person year of 1.5, 0.9 and 0.7 for AS, RP, and RT, respectively	Similar all cause mortality per 1000 person year AS = 10.9; RP = 10.1; and RT = 10.3	[1(
Wilt et al.	PIVOT	Observation = 120/348 (34.5%) RP = 129/383 (33.6%)	Prospective RCT	1994–2002	RP vs. observation (WW)	NA	12.7 years	Slightly higher 10-year PC mortality in RP (9.0% vs. 8.6%)	Higher 10 year mortality in AS (71.2% vs. 62.6%)	[8
Bill-Axelson et al.	The Scandinavian Prostate Cancer Group 4 Study	Observation = 133/348 (38.2%) RP = 148/347 (42.7%)	Prospective RCT	1989–1999	RP vs. observation (WW)	54/116 (46.5%)	13.4 years	Higher number of deaths by PC during follow-up in WW (99 vs. 63)	Higher number of deaths by any cause during follow-up in WW (247 vs. 200)	[9
Thomsen et al.	Active surveillance versus radical prostatectomy in favorable-risk localized prostate cancer	AS = 271/647 (42%) RP = 276/647 (43%)	Retrospective	2002–2012 for AS 1995–2011 for RP	RP vs. AS	NA	8.6 years	Slightly higher 10-year PC mortality in RP (1.5% vs. 0.4%)	Slightly higher 10-year non-PC mortality in RP (12.0% vs. 10.7%)	[1:
Stattin et al.	Outcomes in localized PC: National PC Register of Sweden follow-up study	AS/WW = 936/2021 (42%) RP = 2172/3399 (52.5%)	Retrospective	1997–2002	RP vs. AS/WW	NA	8.2 years	Higher 10-year PC mortality in AS/WW (5.2% vs. 3.4%)	Higher 10-year non-PC mortality in AS (23.4% vs. 11.3%) *	[1:

AS, active surveillance; NA, not available; PC, prostate cancer; RCT, randomized control trial; RP, radical prostatectomy; RT, radiotherapy; WW, watchful waiting. * Include low- and intermediate-risk cohorts.

In men with intermediate-risk of the PIVOT, the 10-year overall survival (OS) was higher (71% vs. 62%) undergoing RP than observation. Similarly, in men with intermediate-risk PC in the SPCG-4 study, RP was associated with an absolute reduction in overall mortality (15.5 percentage points), PC death rate (24.2 percentage points), and risk of metastases (19.9 percentage points) [9]. Meanwhile, in the ProtecT study, patients in observation presented a higher rate of metastases than RP and RT, probably due to intermediate and high-risk PC included in the observation group. However, there was no significant difference in 10-year survival outcomes. Thus, previous studies showed inferior results in intermediate-risk PC when non-active treatment was chosen.

However, some limitations of these three randomized controlled trials (RCT) include watchful waiting or monitoring less close than current AS, without confirmatory and serial biopsies. In addition, there was no opportunity for active treatment or use of magnetic resonance imaging (MRI). Additionally, the PIVOT trial was initiated before the PSA era. Thus, the findings from these studies cannot be applied to the current AS strategy.

2.2. Oncological Outcomes by AS in Intermediate-Risk versus Low-Risk PC

Many series have compared the outcomes among intermediate- and low-risk patients [13]. Musunuru et al. demonstrated that 15-year metastasis-free survival (MFS), OS, cancer-specific survival (CSS), and treatment-free survival were inferior in the intermediate-risk group than the low-risk, with more than three times increased risk of metastasis at 15-year follow-up (hazard risk [HR] 3.14, 95% confidence interval [CI] 1.51, 6.53; p = 0.001) [14]. Similarly, a study from the Veterans

Health Administration included 9733 men initially managed under AS (*n* = 1003, 10.3% with intermediate-risk disease, of whom 76.8% had favorable- and 23.2% unfavorable-risk disease) [15]. With a median follow-up of 7.6 years, the 10-year cumulative incidence of metastasis and PC-specific mortality were higher for patients with intermediate-risk (favorable- and unfavorable-risk) than in low-risk disease.

A systematic review and meta-analysis comparing results of 17 AS series in low- and intermediate-risk showed worse CSS in the intermediate-risk group after 10 years (odds ratio [OR] 0.47; 95% CI, 0.31–0.69) and 15 years (OR 0.34; 95% CI, 0.2–0.58) [16]. There was no statistical difference in 5-year OS (OR 0.84; 95% CI, 0.45–1.57), but 10-year OS was worse in the intermediate-risk group (OR 0.43; 95% CI, 0.35–0.53). Similarly, there was no statistical difference in 5-year MFS (OR 0.55; 95% CI, 0.2–1.53), but MFS was worse in the intermediate-risk group after 10 years (OR 0.46; 95% CI, 0.28–0.77). Thus, this evidence suggests that AS outcomes for intermediate-risk and low-risk are comparable in short-term and medium-term follow-up, but poorer in the long term.

2.3. Patients-Reported Outcomes in AS

Living with untreated PC causes anxiety and uncertainty. Men with intermediate-risk PC likely have a higher anxiety rate than low-risk patients. A study showed that 29% of men in AS presented mild PC-specific anxiety during the first year, and the rate decreased significantly with time [17]. However, only 22 of 413 (5%) patients had GS 7, and a separate analysis was not performed. A systematic review including 34 studies suggested no differences in anxiety and depression rates for up to five years between men on AS and active treatment (RP or RT) [18].

A systematic review of 13 qualitative studies on factors that influence the decision-making between AS and active treatment showed that the decision of AS was an ongoing behavior (not a punctual choice) and included their assessment of risk, the influence of family and friends, beliefs about treatment, and doctor and system factors [19]. A scoping review in men undergoing AS identified interventions that affect the psychosocial burden, such as lifestyle, education, information, coping, and psychosocial support [20]. Interventions that appear to decrease psychosocial burden include psychosocial support involving the family and spouse in the decision-making, education, and tailored information on treatment options [20]. In addition, they recommend the assessment and promotion of effective coping and self-management strategies.

3. Risk Stratification of Intermediate-Risk PC in AS

A systematic review including men with intermediate-risk PC found high variability in outcomes, with adverse surgical pathology ranging from 15 to 64% and 5-year disease progression of 21–91%, showing that outcomes in intermediate-risk PC are heterogeneous [21]. The distinction between favorable and unfavorable intermediate-risk is based on a study that analyzed 1024 men with National Comprehensive Cancer Network (NCCN) intermediate-risk PC who were treated with radiation therapy (RT) alone or in addition to androgen deprivation therapy [22]. Primary Gleason pattern 4, ≥50% rate of positive cores number, and two or more than among clinical-stage T2b–2c, PSA 10–20 ng/mL, and GS 7, were predictors of increased distant metastasis [22]. Thus, NCCN guidelines categorize intermediate-risk as favorable if present all the followings: <50% biopsy cores positive, GS ≤ 3+4, only one between (PSA 10–20 ng/mL, cT2b–cT2c, and GS 3+4).

Favorable intermediate-risk PC is also a heterogeneous group. For example, a patient with one positive core of GS 6 and a PSA of 12 ng/mL (due to an enlarged prostate) and a patient with two cores of GS 3+4 with 40% of Gleason pattern 4 and a PSA below 10 ng/mL, are both categorized as favorable intermediate-risk PC. However, both have different risks of adverse pathological findings at surgery. Studies have shown no difference in 15-year MFS between men with GS 6 and PSA between 10 and 20 ng/mL and men with low-risk PC (GS 6 and PSA < 10 ng/mL) [14]. On the other hand, men categorized as intermediate-risk men due to a GS 3+4 have a higher risk of adverse pathology [14]. Another study compared adverse pathology (upgrading or upstaging to ≥pT3a) on RP specimens in intermediate-risk PC men under AS. A total of 382 of 1731 (22.1%) men who had intermediate-risk due to PSA 10–20 ng/mL (and a GS 6) and 2340 of 8367 (28%) men who were categorized as intermediate-risk due to GS 3+4 (and a PSA < 10 ng/mL) presented adverse pathology at RP [23]. On the multivariable analysis, a PSA level of 10–20 ng/mL had lower odds of harboring an adverse pathology (versus PSA < 10 ng/mL, OR 1.87, 95% CI 1.71–2.05, $p < 0.001$) than GS 3+4 men (versus GS 6, OR 2.56, 95% CI 2.40–2.73; $p < 0.001$) [23]. Thus, the presence of Gleason pattern 4 increased the metastatic rate, but not a PSA level between 10 and 20 ng/mL [13].

Therefore, risk stratification is essential to implement AS for patients with intermediated-risk PC by utilizing the risk factors described below.

3.1. High-Volume GS 6

A study including 6775 (*n* = 1288 with intermediate-risk) men on AS evaluated the factors related to conversion to active treatment [24]. With a median follow-up of 6.7 years, 2260 (33.4%) patients converted to active treatment. Interestingly, conversion rates for high-volume GS 6 (defined as ≥4 biopsy cores involved) men were higher than the intermediate-risk disease (63.6% versus 38.3%, with a 5-year conversion-free probability of 35.8% and 64.1%, respectively) and similar to

other high-risk men. In addition, a study including 561 men (25% intermediate-risk) under AS showed that an increasing percentage of positive core involvement was an independent predictor of progression (HR, 1.03) [25].

3.2. Percentage of Gleason 4 Pattern

Another main factor is the percentage of Gleason 4 pattern. A study showed that men with GS 3+4 with less than 5% of pattern 4 on prostate biopsy presented similar GS, pathologic stages, total tumor volume, and insignificant tumor rate at RP to those men who had GS 3+3 [26]. In addition, patients with GS 3+4 with less than 5% of pattern 4 presented a high rate of downgrade at the RP specimen. Additionally, several studies have shown that the percentage of pattern 4 in biopsy samples is a predictor of pathological T3 on RP specimens and biochemical recurrence disease [27]. On the other hand, a study that evaluated 608 men with low-volume intermediate-risk PC (1 or 2 cores of GS 3+4 and PSA < 20 ng/mL) undergoing RP showed that approximately 25% presented GS ≥ 4+3, seminal vesicle invasion, or lymph-node involvement [28]. Moreover, they could not identify any presurgical clinical or pathological criteria that could identify a subgroup of the low-volume intermediate-risk PC with similar rates of adverse pathologic findings with those of low- and very-low risk cohorts. Based on these findings, Klotz et al. suggested that men with GS 3+4 with <10–20% of Gleason pattern 4 may be considered for AS while patients with GS 3+4 with >20% Gleason pattern 4 or GS 4+3 disease should be treated [13].

Moreover, patients with PC with intraductal carcinoma or cribriform pattern histology have more aggressive behavior and an increased risk of metastasis and PC-specific mortality [29][30]. European Association of Urology (EAU) guidelines discourage AS for patients with these findings [3].

3.3. PSA Density

Some protocols include PSA density (the ratio between PSA and prostate size). A systematic review and meta-analysis performed on low-risk men under AS showed that higher PSA density was associated with an increased risk of upgrade [31]. In addition, a study in intermediate-risk men showed that an increased PSA density predicted adverse pathologic findings at RP [28]. While a high PSA density is not specific enough to exclude a patient from AS, men with a higher PSA density should be evaluated with MRI, targeted, and systematic biopsies [13].

3.4. Race/Ethnicity

African Americans with low-risk PC on AS have a higher risk of grade or volume progression than Caucasian Americans [32][33][34][35]. In a study from the Surveillance, Epidemiology, and End Results (SEER) Prostate AS/Watchful Waiting database, only black men with GS 6 presented increased cancer-specific mortality compared to nonblack men [36]. Treatment disparities and access to health care may play an important role in these clinical racial disparities [37]. On the other hand, other studies have shown similar rates of upstaging or upgrading [38]. A recent study from the SEARCH database involving 355 African American and 540 Caucasian men with low-risk treated with RP showed no significant difference in upgrading, upstaging, or biochemical recurrence [39]. Thus, there is controversial evidence on upstaging or upgrading in African Americans. Therefore, guidelines recommend AS in African America men, advising of a possible higher risk of significant cancer.

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