Chapter 2
Patient Selection for Active Surveillance

John B. Eifler and H. Ballentine Carter

Introduction

Prostate cancer is both the most common cancer in men and the second leading cause of cancer death in men. However, the majority of patients diagnosed with prostate cancer will never die of disease, with a ratio of new cases to mortality of 6.8:1 in 2010 [1]. Autopsy series have demonstrated the high prevalence of incidental prostate cancer, with as many as 87% of men over 80 years old found to have disease at autopsy [2, 3]. In comparison, the lifetime risk of dying from prostate cancer is roughly 2.5% [1]. Unfortunately, a potentially lethal tumor cannot be reliably distinguished from one that is insignificant with certainty. Faced with this management dilemma, physicians are tempted to treat low-risk prostate cancer aggressively, as evidence from large cancer registries has demonstrated [4, 5]. Ironically, these data also suggest that many men with high-risk disease are undertreated, particularly those that are elderly [4, 6].

In the era of PSA screening, prostate cancer is identified at an earlier stage, when it is more likely to be localized to the prostate. The European Randomized Screening Study of Prostate Cancer (ERSPC) demonstrated that PSA screening every 4 years conferred a 20% decrease in prostate cancer-specific mortality (PCSM) after 9 years of median follow-up [7]. In the Göteborg screening trial, PSA screening reduced PCSM by 40% after a median follow-up of 14 years [8]. Unfortunately, many additional patients undergo treatment as a result of PSA screening to achieve this survival benefit [9, 10]. In the ERSPC, the number needed to treat (NNT) to prevent one prostate cancer death was 48 men at a median of 9 years [7] and 18 men at a median of 12 years for men aged 50–69 years [11]. However, if the treatment were limited to older men with low-volume Gleason 6 disease, the NNT would undoubtedly be higher (and potentially as high as 100) [12]. Nonetheless, in the United States, many older men with such low-risk cancers will receive definitive treatment. An analysis of the SEER database found that 2 in 3 men between 65 and 74 years old with low-risk cancer and PSA below 4 ng/mL undergo radiation or surgery [13]. Thus, clearly many men are treated for prostate cancer that would never have been harmed if left untreated.

Strategies to reduce the overtreatment of prostate cancer are an active area of research. Novel biomarkers are under development to distinguish indolent tumors from lethal disease, including PCA3 [14, 15], GSTP-1 hypermethylation [16], a kallikrein panel [17], and PSMA [18]. Molecular and genetic profiling has led to promising approaches to better predict prognosis, such as BRCA [19], TMPRRSS2-ERG fusion protein [20], and tumor expression signatures [21, 22]. Despite the promise of these and other diagnostic tests, prospective clinical trials are needed to determine their efficacy. In the absence
of a proven diagnostic test, urologists have investigated methods of monitoring carefully selected men with favorable risk prostate cancer, with curative intervention in the event of disease progression: active surveillance.

To reduce overtreatment, most active surveillance (AS) programs use enrollment criteria to choose men at low risk of dying from prostate cancer and then monitor for disease progression at regular intervals. If higher-risk features are detected during surveillance (i.e., reclassification), these men are encouraged to undergo definitive therapy. By delaying intervention until reclassification is evident, care is individualized to address the phenotype of each patient’s disease. However, clinical parameters do not determine patient risk with perfect accuracy (e.g., some patients with high-grade disease may be misclassified as low risk due to undersampling error inherent in prostate biopsy), and a legitimate concern is that some men will lose the window of curability during monitoring. Thus, the ideal selection criteria would include all men with a nonlethal phenotype while excluding all who harbor the lethal phenotype. Not surprisingly, there is a lack of general agreement on patient selection and triggers for intervention. The subsequent discussion will focus on current strategies for patient selection based on what is known about the natural history of favorable risk prostate cancer, the corresponding oncologic outcomes of surveillance by risk categories, and limitations of the current paradigms for selection of patients for active surveillance.

Natural History of Prostate Cancer

Determining the risk of prostate cancer-specific mortality (PCSM) relies on understanding the natural history of prostate cancer. Much of our knowledge is based on data from the pre-PSA era. Albertsen et al. determined that cancer-specific survival of untreated older men in an unscreened population was 78% for men with Gleason scores of 5 or 6, after a median follow-up of 24 years [23]. These findings may not be applicable to contemporary experience, however, since men screened with PSA are diagnosed with prostate cancer a mean of 11.6 years earlier than men who did not undergo screening, according to data from the ERSPC trial [10]. Furthermore, changes in the interpretation of the Gleason scoring system would likely upgrade approximately 37% of the men in the Albertsen study with Gleason score 6 disease (the “Will Rogers effect”) [24]. If 37% of “Gleason 6” tumors in Albertsen’s series behaved like Gleason score 7 cancers (with a 45% PCSM rate at 20 years), they would account for 16.6% of deaths in the Gleason score 6 group. With these considerations, the long-term PCSM for Gleason score 6 or less disease in PSA-screened men would be approximately 6.4%. This interpretation would be consistent with an analysis of conservatively managed men that found a 2.8% risk of prostate cancer mortality at 10 years for men with Gleason score 5 to 7 disease diagnosed by PSA screening [25]. Contemporary data from cancer registries and large cohort studies support the long natural history of untreated favorable risk disease.

Stattin et al. evaluated the outcomes of men with low-risk prostate cancers who underwent surveillance and curative intervention in a large national cancer registry. The overall 10-year prostate cancer-specific mortality was below 3% for men with low-risk disease managed initially with surveillance. Among men with an average age of 61–65 years depending on management group, the absolute difference in prostate cancer-specific mortality at 10 years for those managed with surveillance compared to surgery was 2% [26]. This could be compared to a 5% absolute difference in the SPGS-4 [27]. The authors concluded that surveillance may be a suitable option for many men with low-risk prostate cancer – a stance that is consistent with recent guidelines (NCCN) [28].

An evaluation of over 3,000 men in the Health Professionals Follow-up Study with a mean age of 68 years demonstrated that 10% of men overall deferred treatment, and that at 8 years, 51% remained untreated [29]. Of those treated, on average, 4 years elapsed prior to treatment. At a median follow-up of 8–9 years, there were no
Patient Selection for Active Surveillance

Differences in the rates of metastatic disease or prostate cancer deaths when comparing those who deferred treatment with those who were treated initially. The prognostic risk category (low, intermediate, high) was strongly predictive of the lethal phenotype. When compared to those with low-risk disease, those with intermediate- and high-risk disease were three- and six-fold more likely to die of prostate cancer, respectively. When comparing deferred and immediate treatment, there were no differences in prostate-specific outcomes for men with low- or intermediate-risk disease. Among men with low-risk prostate cancer, prostate cancer metastases occurred in 7 of 139 (5%) and 33 of 1,252 (3%) of the men in the deferred and treatment groups, respectively; death from prostate cancer occurred in 3 of 139 (2%) and 9 of 1,252 (1%) of the men in the deferred and treatment groups, respectively [29]. Taken together, these data suggest that for many men, active surveillance could be a preferred strategy.

Risk Stratification

Favorable Risk Prostate Cancer

An optimal active surveillance program would identify patients at low risk of dying from prostate cancer and develop tools and techniques to discover the more aggressive tumors that develop during surveillance. To determine which men harbor cancers that are low risk, Epstein et al. examined men with pathological stage T2, Gleason sum 6 prostate cancer with tumor volume <0.2 cm$^3$ who underwent radical prostatectomy (RP), finding that no man developed biochemical recurrence in 5 years [30, 31]. The authors deemed these tumors “insignificant” and subsequently defined preoperative factors predictive of insignificant disease for men with clinical T1c, Gleason sum 6 prostate cancer: low PSA density with few positive biopsy cores and low maximum percentage in any one core [32]. A prospective analysis utilized these criteria to predict insignificant T1c disease using readily available clinical features (now defined as “very low risk”) [28]: Gleason score <7, PSA density <0.15, number of positive cores <3, and less than 50% involvement in any one core [33]. Of patients meeting these criteria, 75% had insignificant disease and 25% moderate disease at radical prostatectomy (RP), defined as a tumor 2–5 cm$^3$ in volume [33]. Two contemporary studies found that greater than 90% of men who met the Epstein criteria had organ-confined disease at surgery [34, 35].

Strategies other than the original Epstein criteria [32] have been used to determine patients at low risk of prostate cancer mortality. Partin et al. developed tables to predict pathological outcome at surgery based on serum PSA, clinical stage, and biopsy Gleason score [36]. Using the same clinical parameters, D’Amico defined low-, intermediate-, and high-risk categories to predict biochemical recurrence following treatment [37]. The D’Amico risk classification is the most widely used stratification scheme today and has been adopted in the National Comprehensive Cancer Network Guidelines for Prostate Cancer (Table 2.1) [28]. Other risk stratification schemes to identify men with favorable risk cancer using pretreatment variables have been reported and appear to have accuracies comparable to the Epstein criteria [38–41].

Active Surveillance Experience by Risk Profile

Multiple studies evaluating the safety and efficacy of active surveillance using different enrollment criteria have been reported (Table 2.2) [42–46]. In aggregate, the 10-year disease-specific survival in active surveillance is 99.7% for over 200 patients enrolled in active surveillance followed for over 10 years [42]. These data can be used to inform patients considering active surveillance of the 10-year risk for developing lethal prostate cancer based on an individual’s age, life expectancy, and risk profile.
### Table 2.1 Risk stratification for clinically localized prostate cancer

<table>
<thead>
<tr>
<th>Risk</th>
<th>Gleason score</th>
<th>Serum PSA (ng/mL)</th>
<th>Clinical stage</th>
<th>Positive cores (n)</th>
<th>Max core involvement</th>
<th>PSA density (ng/mL/g)</th>
<th>NCCN recs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤6</td>
<td>&lt;10</td>
<td>T1c</td>
<td>≤2</td>
<td>50%</td>
<td>≤0.15</td>
<td>AS rec’d if LE &lt;20 years</td>
</tr>
<tr>
<td>Low&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≤6</td>
<td>&lt;10</td>
<td>T1 or T2a</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>AS rec’d if LE &lt;10 years</td>
</tr>
<tr>
<td>Intermediate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7</td>
<td>or 10–20</td>
<td>or T2b or T2c</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>AS optional if LE &lt;10 years</td>
</tr>
<tr>
<td>High&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8–10</td>
<td>or &gt;20</td>
<td>or T3a</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>AS not recommended</td>
</tr>
</tbody>
</table>

*AS* active surveillance, *rec’d* recommended, *LE* life expectancy, *NCCN* National Comprehensive Cancer Network  
<sup>a</sup>Based on the Epstein criteria [32]  
<sup>b</sup>Based on the D’Amico criteria [37]

### Table 2.2 Inclusion criteria for active surveillance and oncologic outcome

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Inclusion criteria</th>
<th>NCCN risk category</th>
<th>Treatment-free survival</th>
<th>DSS</th>
<th>Overall survival</th>
</tr>
</thead>
</table>
| Tosoian (JHH)<sup>a</sup> | 1. Clinical stage T1c  
2. Gleason sum ≤6  
3. ≤2 positive biopsy cores  
4. ≤50% max percentage positive  
5. PSA density ≤0.15 | Very low             | 41% (10 years)     | 100% (10 years)         | NR       |
| van den Bergh (PRIAS) | 1. T1c/T2  
2. PSA ≤10.0 ng/mL  
3. PSA density ≤0.2 ng/mL  
4. Gleason sum ≤6  
5. ≤2 positive cores | Very low/low         | 43% (10 years)     | 100% (10 years)         | 77% (10 years) |
| Soloway (Miami)      | 1. Gleason sum ≤6  
2. PSA ≤15 ng/mL  
3. Stage ≤T2  
4. ≤50% max percentage positive  
5. ≤2 positive cores | Low/intermediate     | 85% (5 years)      | 100% (10 years)         | NR       |
| van As (Royal Marsden)| 1. Clinical stage T1/T2a  
2. Gleason sum ≤7 (3+4)  
3. PSA ≤15 ng/mL  
4. ≤50% positive cores | Low/intermediate     | NA                 | 100% (5 years)          | NR       |
| Klotz (Toronto)      | <70 years of age  
1. PSA ≤10 ng/mL  
2. Gleason ≤6  
≥70 years of age  
1. PSA ≤15 ng/mL  
2. Gleason sum ≤7 (3+4) | Low/intermediate     | 62% (10 years)     | 97.2% (10 years)        | 68% (10 years) |
| Roemeling (Erasmus)  | 1. T1c or T2  
2. PSA ≤15  
3. Gleason <8 | Low/intermediate     | 70.8% (5 years)    | 100% (8 years)          | 89% (8 years) |

<sup>a</sup>80% of patients were very low risk and 20% were low risk
Very Low-Risk Prostate Cancer

The category of very low-risk prostate cancer is now recognized as defining a risk group that differs from the low-risk category in terms of pathological outcomes at surgery, progression risk without treatment, and recommendations for management (NCCN). The criteria for defining very low-risk disease are based on the classification scheme of Epstein et al. (with the exception of PSA <10 ng/mL) and include PSA density which has been confirmed to be a predictor of reclassification to a higher-risk category, including high-grade disease [46–49]. These criteria have been used by some investigators to define a subset of men for whom surveillance may be safest.

The Johns Hopkins Active Surveillance Program has primarily used the criteria for very low-risk disease for enrollment (80% of subjects) but also followed carefully selected men with low-risk disease. Tosoian et al. [46] reported that men with very low-risk disease were less likely to develop biopsy progression (27.4% vs 42.2%, \( p = 0.0002 \)), undergo curative intervention (31.2% vs 40.4%, \( p = 0.026 \)), and develop upgrading (12.6% vs 18.1%, \( p = 0.07 \)) compared to men with low-risk disease electing active surveillance at a median follow-up of 2.7 years (range 0.1–15.0). The majority of men that underwent treatment were free from biochemical recurrence after at least 1 year of follow-up (95.8% after RP, 85.4% after RT). No men followed with surveillance have developed metastatic disease or died of prostate cancer (10-year prostate cancer-specific survival 100%), though three men with low-risk prostate cancer who underwent RP had positive lymph nodes [46]. Very low-risk prostate cancer was reclassified to a higher-risk classification in nearly a third of men, but with careful follow-up, these patients seem unlikely to lose the “window of curability” [50]. In addition, the PSA-free outcomes of patients enrolled in the Johns Hopkins Active Surveillance Program who underwent delayed intervention, 80% of whom had very low-risk disease at diagnosis, appear more favorable when compared to biochemical free outcomes of men meeting low-risk criteria only, who undergo immediate intervention [51]. However, other uncontrolled factors could explain these intermediate results.

Clinical factors have been used to predict men in active surveillance likely to progress to less favorable disease. Tseng et al. evaluated patients with very low-risk disease who were reclassified during AS (defined as Gleason score >6, more than two positive biopsy cores, or >50% involvement of any one core). At the time of cancer diagnosis, percent-free PSA \(<15\%\) and maximum percent core involvement \(\geq35\%\) were associated with decreased time to reclassification in a Cox proportional hazards analysis. At the initial surveillance prostate biopsy 1 year after diagnosis, both PSA density \(\geq0.08\) and a biopsy showing cancer (among men not reclassified on the first surveillance biopsy) were associated with decreased time to reclassification 3 years later or 4 years after diagnosis [47]. The value of PSA density in defining a very low-risk profile has been demonstrated by others [48, 49]. These and other risk factors may assist the clinician in distinguishing those suitable for AS from those better served with immediate treatment.

Low-to Intermediate-Risk Prostate Cancer

Because of the uncertainty regarding the long-term risk of a prostate cancer that is low to intermediate risk, these men must weigh the risks of harm from disease without treatment, against the risks of treatment side effects. Both radiation therapy [52] and surgery [27] reduce prostate cancer mortality by about 50% a decade after diagnosis for men with non-screen-detected prostate cancers that are low to intermediate risk. Accounting for the lead time with PSA testing, results from the SPGS-4 would suggest that there is minimum risk of death from prostate cancer in 10–15 years without treatment for a man with low- to intermediate-risk disease [53]. However, given the absence of longer term data
from randomized trials to demonstrate the safety of a surveillance approach, men with more than an estimated 10–15 year life expectancy should be told that active surveillance is an experimental approach that may result in a lost opportunity for disease control. For those men who are older with associated comorbidity that limits the remaining years of life, active surveillance could be considered the optimum management (NCCN). The greatest experience with active surveillance has been among men with low- to intermediate-risk disease.

The reported series of men with low-risk disease electing active surveillance demonstrate excellent oncologic outcomes, though many men will ultimately undergo curative intervention and some may harbor aggressive disease. In the ERSPC, 57% of the 616 patients on AS who met PRIAS criteria ultimately underwent treatment by 10 years [54]. The prostate cancer-specific survival was 100% at 10 years while 23% died of other causes. However, one patient died of prostate cancer 11.2 years after diagnosis (though he refused treatment despite a concerning rise in PSA), and one patient had metastatic disease at the time of the report. Similar oncologic outcomes have been observed in other cohorts [48, 55].

A subset of men meeting the criteria for intermediate-risk disease may also have favorable prognosis. Van den Bergh et al. retrospectively evaluated 50 patients in the screening arm of the ERSPC diagnosed with Gleason 3+4 disease who otherwise met the PRIAS criteria for AS (see Table 2.2) and elected surveillance [56]. With a median follow-up of 2.6 years, the authors noted a 100% cancer-specific survival and a treatment-free survival of 66%.

In the longest prospective contemporary study of active surveillance for low- to intermediate-risk disease, Klotz followed 450 men (median age 70 years) with low- and intermediate-risk prostate cancer for a median of 7 years [57]. Seventeen percent of the subjects had a Gleason score of 3+4, 83% were Gleason 6 or less, and 71% were considered low risk by D’Amico criteria. Thus, one in three men had intermediate-risk disease. The 10-year actuarial prostate cancer-specific survival was 97%. Five deaths have occurred in this cohort between 4 and 10 years after diagnosis, and all deaths occurred in men who were initially diagnosed with sextant biopsy and reclassified as higher-risk disease during follow-up. It could be argued that deaths in the Klotz et al. study occurred in men who had advanced disease to begin with and that surveillance did not compromise length of life. Alternatively, it could be argued that deaths occurred in men who were not favorable candidates for surveillance, and that earlier intervention would have prolonged life.

In the National Prostate Cancer Register Follow-up Study, pretreatment data and treatment modality were assessed in men diagnosed with prostate cancer from 1997 to 2002 in Sweden. Mean age at diagnosis was 64.7, 61.2, and 63.4 in men undergoing surveillance, radical prostatectomy, or radiation therapy (RT), respectively. Curative intervention was undertaken in 34% of men who initially elected surveillance, similar to other AS cohorts. In men with low-risk prostate cancer, the PCSM was 2.4% and 0.7% at 10 years in men electing surveillance and curative intervention, respectively. PCSM for intermediate-risk prostate cancer was 5.2% at 10 years in the surveillance group versus 3.4% and 3.8% in the RP and radiation therapy groups, respectively [26]. These results are similar to the Toronto experience [42]. Data from the SPSG-4 suggest that in older men, the benefits of curative intervention are less clear. Untreated men over age 65 years had a 12-year prostate cancer-specific survival of approximately 88% that did not differ from those that underwent surgical treatment [27]. Nonetheless, there is a definite, long-term risk to men who choose surveillance as a management option for low- to intermediate-risk disease, regardless of how indolent the disease appears on a prostate biopsy. These men must be carefully monitored to avoid missing the window of curability.

In summary, men with very low-risk disease represent a unique cohort that appears to be particularly safe for surveillance. Many men with low- or intermediate-risk disease may also be appropriate candidates for AS depending upon
Patient Selection for Active Surveillance

Age and comorbidity status, although 2–5% may die of prostate cancer with longer follow-up [26]. The National Comprehensive Cancer Network (NCCN) recommends that men with very low-risk prostate cancer and life expectancy <20 years undergo AS rather than definitive therapy (Fig. 2.1). Men with low-risk disease and life expectancy less than 10 years are also recommended to undergo AS. For men with low-risk disease with 10–20 years of life expectancy or intermediate-risk disease with <10 year life expectancy, AS should be considered (Fig. 2.1). It is not recommended that any patient with high-risk disease be offered AS [28].

Limitations of Current Paradigms

Current limitations of identifying the “ideal” candidate for active surveillance involve difficulty classifying risk based on pretreatment parameters, estimating life expectancy, and determining a man’s preferences for living with cancer and side effects of treatment.

Misclassification

A limitation of all risk stratification schemes is misclassification of risk due to underestimation of grade. If aggressive disease lurks beyond the biopsy needle, its presence could remain undetected for years with the potential loss of the opportunity for cure. Not surprisingly, some patients with aggressive characteristics are misclassified as having low-risk disease. Several retrospective analyses have characterized the risk of misclassification.

Suardi et al. evaluated patients treated with RP between 2002 and 2008 at a single institution with a low-risk profile to determine the percentage who harbored aggressive disease. More than 26% of patients meeting the criteria of Epstein et al. for very low-risk disease (JHH) (see Table 2.2) and 28.2% of patients meeting the van den Bergh criteria (PRIAS) had Gleason ≥7 disease on RP [58]. In other studies, the risk of upgrading varied by inclusion criteria for AS and ranged from 23% in men with very low-risk prostate cancer to 35% in those with low-risk disease [48, 59, 60]. Development of preoperative criteria that predict upgrading with accuracy has not been successful, including PSA density cutoffs [61] and preoperative nomograms [62]. Furthermore, the utility of PSA kinetic data in predicting high-grade disease has been called into question. Khatami et al. found that men undergoing active surveillance who developed low PSA doubling times were more likely to have biochemical recurrence after definitive therapy [63]. However, in men with very low-risk disease in an active surveillance program,
Ross et al. demonstrated that neither PSA velocity nor PSA doubling time was significantly associated with progression to higher Gleason score on subsequent biopsy or at surgery [64]. As a result, even men considered to have favorable risk prostate cancer based on clinical criteria may harbor aggressive disease and must be monitored closely for progression.

Changing the number or location of biopsies in potential AS candidates may improve risk stratification. Five men in a large AS cohort who died of prostate cancer were initially staged with 6-core biopsies and later reclassified with aggressive disease during surveillance, raising the possibility that a greater number of cores during diagnostic biopsy may have identified aggressive disease within the window of curability [57]. To analyze the impact of increasing biopsy number, Ploussard et al. performed a 6-core biopsy, then added the six lateral peripheral biopsies, and finally added three midline cores and six transition zone cores for a total of 21 biopsy cores. Increasing the number or cores decreased the number of patients who met AS enrollment criteria and decreased the rate of unfavorable disease at RP (Gleason ≥8 and/or pT3/4 disease) by approximately 50% [65]. Some AS cohorts now require 20-core biopsy for AS enrollment and surveillance [49], and some authors recommend performing 14–18 cores for men with gland size >50 [66].

Dufﬁeld et al. [67] reviewed the pathological ﬁndings of patients on AS with very low-risk disease that underwent RP for biopsy reclassiﬁcation. The authors found that all tumors with a dominant nodule greater than 1 cm³ were located anteriorly. As a result of this work, two transition zone biopsies are now routinely performed during surveillance biopsies at this institution, as well as others [68]. In the Johns Hopkins Active Surveillance Program, 23% of the transition zone biopsies have harbored cancer. These data suggest that sampling of this region in men on surveillance is important for reducing misclassiﬁcation [46].

Another strategy frequently utilized is a repeat biopsy prior to enrollment in AS to identify and exclude patients with higher grade disease. Berglund et al. [69] reviewed 104 patients referred to a tertiary center from 2002 to 2007 with a diagnosis of prostate cancer who underwent repeat biopsy prior to enrollment. All men had T2a disease or less, PSA less than 10 ng/mL, three or fewer positive cores, and no core greater than 50% involved. The authors performed 14-core biopsies on each patient, who had a median of 10 biopsy cores on the diagnostic biopsy. Of these men, 27% were reclassiﬁed or upgraded at repeat biopsy. The majority of these patients subsequently underwent RP where pathology revealed Gleason 7 or greater disease in 91% and pT3 or greater disease in 48% [69]. These results have been veriﬁed in other series [55, 68].

While increasing the number of cores or repeating a biopsy prior to enrollment may reduce misclassiﬁcation, it would also decrease the number of patients eligible for surveillance. Recent evidence from the CaPSURE registry suggests that few men are candidates for active surveillance using the most stringent criteria (16% meet the Epstein criteria). Of note, it is likely that the percentage of patients meeting the Epstein criteria would be higher in a representative population, since approximately two of every three patients in the CaPSURE registry with low-risk disease were missing PSA density data, and these patients had lower average PSA, Gleason score, and number of positive cores. Nonetheless, few patients, with or without complete data, elected active surveillance (5% and 6%, respectively) [70]. Increasing the number of biopsy cores without modifying enrollment criteria would likely reduce this number further [69]. Regardless of biopsy technique, some men enrolled in AS will harbor aggressive disease.

Will these patients miss the opportunity for cure? Warlick et al. compared the pathological ﬁndings of 38 men with low-risk disease in AS who underwent delayed treatment with similar patients who had immediate RP. There was no statistically signiﬁcant increase in the rate of non-cur-able disease (based on pathological ﬁndings at RP and the Han tables [71]) in men who elected AS [50]. These ﬁndings were supported by Van den Bergh et al., who performed a similar analysis.
on low-risk patients in the ERSPC trial with one to two positive biopsy cores. With a mean follow-up of 5.7 years, no significant difference was observed in pathological Gleason score >6, tumor volume, or biochemical recurrence when comparing men who underwent immediate versus delayed surgical intervention [43]. Finally, the aggregate data from AS cohorts demonstrate an excellent 10-year DSS exceeding 99%, reinforcing the safety of AS despite misclassification error. However, the possibility that a rare patient may progress to incurable disease while on AS cannot be excluded with certainty and remains a limitation of this strategy.

**Determining Life Expectancy**

Critical to determining which men are appropriate candidates for active surveillance is an accurate determination of life expectancy, which remains quite difficult [72–75]. Tables such as the Social Security Administration Life Insurance Tables allow an estimation of the average life expectancy for men by age [76], though they are subject to the limitations of predicting life expectancy (with ~60% accuracy) [74]. Comorbidities and overall health have significant impact on life expectancy, and it is recommended that 50% be added to the life expectancy for men judged to be in the top quartile of overall health and that 50% be subtracted for men in the lowest quartile of overall health [28, 77]. Based on these estimations and the SSA Life Insurance Tables, surveillance might be the preferred strategy for a 55-year-old man in the lowest quartile of health with very low-risk disease. Alternatively, a very healthy 70-year-old man with very low-risk disease might benefit from curative intervention.

**Patient Preferences**

Men choosing active surveillance should be comfortable living with untreated prostate cancer without significant anxiety. Several studies using validated questionnaires have demonstrated that men in AS cohorts face more anxiety than men who undergo curative intervention and are free of disease [78, 79]. In the SPCG-4, a lower percentage of men reported worry, anxiety, or depression in the RP cohort than the watchful waiting cohort, though these differences failed to reach statistical significance [80]. Furthermore, changes in clinical parameters during follow-up may contribute to anxiety in AS, as opposed to watchful waiting. In a Dutch active surveillance cohort, men with a neurotic personality were more likely to have heightened anxiety, as were men with high PSA [63, 81]. Developing high anxiety levels are understandable with rising PSA and perhaps unavoidable. However, there is also a population of men who develop anxiety independent of clinical parameters of worsening disease. Latini et al. found that men whose anxiety increased during AS were more likely to receive treatment independent of PSA kinetics [82]. A substantial minority of men in AS cohorts elect curative intervention without clinical evidence of progression (range 7.7–26.3%) (see Table 2.2). Thus, identifying those patients likely to have substantial anxiety in the absence of clinical progression is important while counseling patients about active surveillance.

Men considering AS must weigh the anxiety of living with untreated disease against the potential for side effects with curative intervention. Johansson et al. evaluated self-assessments of quality of life in men who participated in the SPCG-4, at least 12 months after surgery in the RP cohort. Watchful waiting decreased the incidence of ED (80% in RP patients vs 45% in watchful waiting) and urinary incontinence (49% in RP patients vs 21% in watchful waiting) [78, 81]. Similar results would likely be seen in men undergoing brachytherapy or external beam radiation therapy [83]. Men who value continence and erectile function to a great extent are likely to benefit most from electing active surveillance and should be counseled accordingly.

Recently, computer models of prostate cancer have been used to model quality of life after curative intervention or AS. Liu et al. performed
a decision analysis of surveillance and surgery for low-risk disease, assessing the ratio of side effects per additional year of life gained with surgery. As age increases and health status worsens at diagnosis, the benefits of surgery decrease while AS becomes more attractive. Surveillance resulted in a higher quality adjusted life expectancy in low-risk men aged above 54, 67, and 74 years with 50%, 100%, and 150% of average life expectancy, respectively [84]. Hayes et al. modeled the comparative effectiveness of curative intervention (RP, external beam radiation therapy, or brachytherapy) versus AS in 65-year-old men of average health, also finding that surveillance is an appropriate and underutilized management option [4, 70, 85]. Strategies to identify and decrease anxiety among men may improve patient selection and retention in AS programs. Psychological support during AS [86], support groups [87], and patient education regarding selection criteria and appropriate triggers for intervention [88] may have a role in future management. Ultimately, not everyone who qualifies by NCCN criteria (see Fig. 2.1) should undergo AS. Patients must carefully consider whether they are capable of living with untreated prostate cancer. Those who cannot are better served with immediate curative intervention.

**Conclusion**

Active surveillance is an excellent option for carefully selected men with favorable risk prostate cancer that avoids the potential side effects of curative intervention for a disease that often would not be clinically relevant. However, some patients who harbor the lethal phenotype may be misclassified as favorable risk and could miss the opportunity for cure. In the future, improved markers and imaging strategies may assist in predicting the lethal phenotype to guide management.

Who is the ideal candidate for active surveillance? Men with a risk profile and estimated life expectancy that are consistent with a low probability of harm during the remaining years of life (see Fig. 2.1), who understand the potential risk of a missed opportunity for cure and can live with an untreated cancer, and who wish to avoid the potential side effects of curative intervention. For carefully selected men who agree to close follow-up, active surveillance preserves quality of life with an apparent minimal risk of harm from cancer.

**References**

11. Loeb S, Vonesh EF, Metter EJ, Carter HB, Gann PH, Catalona WJ. What is the true number needed to screen...


32. Epstein JI, Walsh DC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994 Feb 2;271(5):368–74.


67. Duffield AS, Lee TK, Miyamoto H, Carter HB, Epstein JJ. Radical prostatectomy findings in patients


Active Surveillance for Localized Prostate Cancer
A New Paradigm for Clinical Management
Klotz, L. (Ed.)
2012, XI, 208 p. 33 illus., 22 illus. in color., Hardcover
A product of Humana Press