High-Risk Prostate Cancer: From Definition to Contemporary Management


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Abstract

Context: High-risk prostate cancer (PCa) is a potentially lethal disease. It is clinically important to identify patients with high-risk PCa early on because they stand to benefit the most from curative therapy. Because of recent advances in PCa management, a multimodal approach may be advantageous.

Objective: Define high-risk PCa, and identify the best diagnostic and treatment patterns for patients with clinically localized and locally advanced disease. A critical analysis of published results following monomodal and/or multimodal therapy for high-risk PCa patients was also performed.

Evidence acquisition: A review of the literature was performed using the Medline, Embase, Scopus, and Web of Science databases as well as the Cochrane Database of Systematic Reviews.

Evidence synthesis: High-risk PCa accounts for <15% of all new diagnoses. Compared with patients with low- and intermediate-risk PCa, patients with high-risk PCa are at increased risk of treatment failure. Unfortunately, no contemporary randomized controlled trials comparing different treatment modalities exist. Evaluation of the results published to date shows that no single treatment can be universally recommended. Most often, a multimodal approach is warranted to optimize patient outcomes.

Conclusions: A significant minority of patients continue to present with high-risk PCa, which remains lethal in some cases. Outcomes following treatment of men with high-risk tumors have not substantially improved over time. However, not all high-risk patients are at the same risk of PCa progression and death. At present, a multimodal approach seems the best way to achieve acceptable outcomes for high-risk PCa patients.

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1. Introduction

In Europe, prostate cancer (PCa) is the most common solid neoplasm, with an incidence rate of 214 cases per 100,000 men. PCa cases outnumber lung and colorectal cancer cases [1,2]. In 1989, Stamey and colleagues first showed that pretreatment prostate-specific antigen (PSA) levels correlated with the extent of disease in untreated patients and with biochemical and clinical outcomes after irradiation and radical prostatectomy (RP) [3–5]. Several years later, Zagars et al. showed the independent impacts of T stage, Gleason score (GS), and PSA on outcome in men managed with definitive radiation therapy (RT) [6,7]. It was not until nearly 10 yr later that preoperative PSA value, clinical stage, and biopsy GS were combined to define risk groups for PCa [8,9].

To better understand and classify the biologic behavior of PCa, different models to define subclasses of this disease were formulated. The well-established risk stratification by D’Amico et al. includes low-, intermediate-, and high-risk PCa. These criteria define high-risk PCa using any of the following three parameters: PSA value >20 ng/ml, biopsy GS 8–10, or clinical stage ≥T2c [8]. According to the guidelines of the European Association of Urology (EAU) and the American Urological Association (AUA), patients with high-risk PCa are at an increased risk of disease recurrence following primary treatment [1,10]. The advantage of PCa screening is the possibility of detecting high-risk PCa earlier (ie, when still in clinically localized stages) [11–14]. However, even in screened populations, high-risk PCa accounts for ≤15% of newly diagnosed cases [15].

From a clinical perspective, the best treatment of high-risk PCa remains unclear, although it is of note that these patients are at increased risk of undertreatment [16,17], perhaps resulting from a sense of therapeutic nihilism on the part of the treating physicians. Treatment options include various forms of primary treatments used alone or in combination: RP, external-beam radiation therapy (EBRT), brachytherapy, androgen-deprivation therapy (ADT), and chemotherapy. However, neoadjuvant or adjuvant chemotherapy should be used only in clinical trial settings.

The aim of this review was to define high-risk PCa and to identify the diagnostic and treatment patterns for men with localized and locally advanced high-risk disease. Critical analysis of the published results in localized and locally advanced high-risk PCa patients undergoing monomodal and/or multimodal therapy was also performed.

2. Evidence acquisition

A critical review of the literature was performed using the Medline, Embase, Scopus, and Web of Science databases, as well as the Cochrane Database of Systematic Reviews, between January 2000 and July 2011. The search included free-text protocols with the following search terms: prostate, prostate cancer, carcinoma of the prostate, high-risk prostate cancer, high-grade prostate cancer, radical prostatectomy, radiation therapy, adjuvant therapy, biomarker, and androgen-deprivation therapy. The search was limited to publications in the English language. No manual search of meeting abstracts was performed.

3. Evidence synthesis

3.1. Definition of high-risk prostate cancer

At present, the exact definition of high-risk PCa remains controversial (Table 1). This lack of consensus on a definition of high-risk disease represents a critical barrier for patient counseling, the comparative assessment of treatment outcomes, and the design of randomized trials. The combination of preoperative PSA value, clinical stage, and biopsy GS was first used in 1998 to define distinct risk groups of PCa [8]. D’Amico et al. defined high-risk PCa as a PSA value >20 ng/ml, biopsy GS 8–10, or clinical stage ≥T2c. However, the estimation of patients’ risk of progression with this definition is far from perfect, because these criteria encompass a heterogeneous group of patients. Nevertheless, the AUA adopted the D’Amico et al. criteria to define high-risk PCa [10]. Interestingly, the role of clinical stage remains controversial, as it does not necessarily add information and displays a interobserver variability [1]. The definition of high-risk disease supported by the EAU, as well as the National Comprehensive Cancer Network [18], is a PSA value >20 ng/ml, biopsy GS 8–10, or clinical stage ≥T3a [1].

The Radiation Therapy Oncology Group (RTOG) also described a classification system to predict overall and cause-specific survival [19]. Interestingly, however, a
Kattan-based nomogram for predicting the risk of metastatic disease was shown to be better at predicting survival than the RTOG risk groups [20]. An alternative risk stratification scheme has since been proposed by investigators from the RTOG and consists of (1) PSA 20–100 ng/ml, biopsy GS ≥7, and any clinical T stage or (2) PSA <100 ng/ml, GS 8–10, and clinical stage 2c [21,22].

Another definition of high-risk PCa was reported by Cooperberg et al. using the Cancer of the Prostate Risk Assessment (CAPRA) score [23]. The CAPRA score combines age, PSA value, clinical stage, biopsy GS, and percentage of positive biopsy cores (>33% of biopsy cores positive for PCa); a score of 6–10 represents high-risk disease. A recent report revealed that 26% of men ≥75 yr of age presented with high-risk disease according to the CAPRA score [24].

Adding secondary parameters such as the extent of cancer in needle biopsy, prediagnosis PSA velocity >2 ng/ml per year, PSA doubling time, or the presence of a tertiary Gleason pattern was proposed to enhance risk stratification [2–5]. Unfortunately, some of these parameters are not routinely collected during clinical practice, and thus the additional clinical value remains uncertain.

While one study investigating high-risk PCa patients who were identified using multiple definitions and who were treated with RP with or without adjuvant treatment revealed that the biochemical relapse–free survival did not substantially differ [25], separate investigations showed substantial heterogeneity in the outcomes of patients with high-risk PCa after RP depending on the definition of high-risk disease used [29,44].

The CAPRA-S score was recently presented as a postsurgical model to predict outcome following RP [26]. Ultimately, novel biomarkers are needed to identify high-risk patients who may benefit from different treatment modalities and to allow better prediction of the cancer’s metastatic potential [2–5].

### 3.2. Treatment of high-risk prostate cancer

#### 3.2.1. Radical prostatectomy

Traditionally, RP was not considered a viable treatment option for high-risk PCa cases. Because of recent advances, however, this approach has changed. Today, according to the EAU and AUA guidelines, RP is a reasonable treatment option for selected PCa patients with cT3a disease, GS 8–10, or PSA >20. However, when performing an RP, following wider lines of excision of the prostate with an extended pelvic lymphadenectomy may be needed, because lymph node (LN) involvement is frequently found in these patients. In addition, patients must be informed about the possible need for a multimodal approach to accomplish the best possible result. In other words, patients with adverse tumor characteristics may benefit from adjuvant RT alone or in combination with ADT following surgery [1,10,18].

Table 2 lists series investigating RP in men with high-risk PCa. Of note, in 1994, Partin et al. reported a 5-yr postoperative PSA-free survival rate of 43% for patients with GS 8–10 cancers undergoing RP [32]. Interestingly, several recent series demonstrated that the outcomes for patients with high GSs have not significantly changed over the course of the PSA era. For example, data from the Shared Equal Access Regional Cancer Hospital (SEARCH) database (community-based data) demonstrated that the outcomes following RP for high-risk cases diagnosed on the basis of PSA or biopsy GS did not change over time, categorized as intervals from 1988 to 1991, 1992 to 1995, 1996 to 1999, and 2000 to 2003 [33].

Likewise, Boorjian et al. in a series of 584 men treated with RP for GS 8–10 tumors, noted no significant difference in 7-yr biochemical recurrence–free survival (37% and 45%; p = 0.09) or cancer-specific survival (89% and 91%; p = 0.73) for men treated in early PSA eras (1988–1993) versus late PSA eras (1998–2001), respectively [34].

Table 2 – Series investigating radical prostatectomy in men with high-risk prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases, no.</th>
<th>Median follow-up</th>
<th>BCR-free survival at 5 yr, %</th>
<th>BCR-free survival at 10 yr, %</th>
<th>PCa-specific survival at 5 yr, %</th>
<th>PCa-specific survival at 10 yr, %</th>
<th>Overall survival at 5 yr, %</th>
<th>Overall survival at 10 yr, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephenson et al. [36]</td>
<td>1962</td>
<td>48 mo</td>
<td>–</td>
<td>–</td>
<td>92</td>
<td>81</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eggener et al. [38]</td>
<td>1326</td>
<td>56.1 and 96.2 mo</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nguyen et al. [25]</td>
<td>1104</td>
<td>44 mo</td>
<td>45.4 and 52.5</td>
<td>35.4 and 52.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yossepowitch et al. [40]</td>
<td>957</td>
<td>4.3 yr</td>
<td>68</td>
<td>99</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Spahn et al. [42]</td>
<td>712</td>
<td>77 mo</td>
<td>64.8</td>
<td>51.9</td>
<td>89.8</td>
<td>84.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ward et al. [49]</td>
<td>1179</td>
<td>2.4 yr</td>
<td>47.4</td>
<td>35.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mattei et al. [51]</td>
<td>188</td>
<td>60 mo</td>
<td>71</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zwerger et al. [41]</td>
<td>275</td>
<td>42 mo</td>
<td>–</td>
<td>–</td>
<td>93</td>
<td>83</td>
<td>71</td>
<td>87</td>
</tr>
</tbody>
</table>

n/a = not available; BCR = biochemical recurrence; PCa = prostate cancer; PSA = prostate-specific antigen.
1 High-risk prostate cancer is defined according to D’Amico et al. [8].
2 Modeling cohort.
3 Validation cohort.
4 Defined as PSA >20 ng/ml.
Bastian et al. compared data from a tertiary referral center (Johns Hopkins Hospital [JHH]) and the SEARCH database [35]. In their study, a favorable pathologic finding (organ-confined PCa and negative surgical margins) was observed in 21% of men in the JHH cohort and in 41% of the men in the SEARCH cohort. On multivariate analysis, higher PSA was the only variable that significantly predicted an unfavorable pathologic finding in both the JHH cohort \((p = 0.047)\) and the SEARCH cohort \((p = 0.002)\). Importantly, the overall 5- and 10-yr estimated biochemical-free survival rates were nearly identical in the two cohorts. In the JHH cohort they were 40% (95% confidence interval [CI], 33–48) and 27% (95% CI, 18–36), respectively, and in the SEARCH cohort they were 32% (95% CI, 22–42) and 28% (95% CI, 18–38), respectively. Among men with favorable pathologic findings, the 5- and 10-yr estimated biochemical-free survival rates in the JHH cohort were 79% (95% CI, 62–89) and 50% (95% CI, 25–71), respectively, and in the SEARCH cohort were 49% (95% CI, 32–65) and 49% (95% CI, 32–65), respectively [35]. Thus, even among men with organ-confined disease and negative surgical margins or pathologic GS < 8, at least half experienced a PSA recurrence. Interestingly, no single preoperative variable significantly predicted the risk of biochemical progression in either the SEARCH or JHH cohorts. It is noteworthy that of 25% of cases with favorable pathologic findings or pathologic GS < 8, almost 25% developed disease progression within the first 24 mo following RP, suggesting micrometastatic disease at the time of RP. Those patients could be good candidates for early systemic therapy [35].

However, keeping the data of Stephenson et al. in mind, only 34% of contemporary patients with GS 8–10 die of PCa after 15 yr [36]. In contrast, >50% of PSA recurrences occurred later than 2 yr following RP, suggesting local recurrence; salvage RT may be able to improve the outcome among this group. Patients who fail to achieve an undetectable PSA level after undergoing RP are appropriate candidates for adjuvant treatment [37]. Predictors such as the slope of PSA change, RP GS, seminal vesicle status, surgical margin status, and LN status may be helpful to identify these patients [37]. From these data one may get the impression that a postoperative definition of high-risk PCa is warranted to identify the best candidate for adjuvant treatment planning. These findings are substantiated by the work of Eggener et al., revealing that a Gleason pattern 4–5 or seminal vesicle invasion is an independent predictor for PCa-specific mortality [38].

Nguyen et al. investigated high-risk patients following RP with or without adjuvant treatment using six different definitions and showed that the biochemical relapse-free survival did not substantially differ when different definitions were used [25]. Within each era the variation in biochemical relapse-free survival among various high-risk definitions was not substantial [25].

Yossepowitch et al. performed a similar study defining eight different criteria to identify high-risk PCa patients and subsequently evaluating the oncologic outcome and the risk of metastatic progression [39,40]. In the first study, which included 4708 men treated with RP alone, patients at high risk included 3–38% of the study population, depending on the definition used. The proportion of patients with extracapsular extension, seminal vesicle invasion, and LN metastases among men with high-risk cancer ranged from 35% to 71%, from 10% to 33%, and from 7% to 23%, respectively. Of the high-risk PCa patients, 22–63% proved to be organ-confined, whereas high-risk patients overall had a 1.8- to 4.8-fold increased risk of PSA relapse. In addition, their 5-yr relapse-free probability after RP alone ranged from 49% (95% CI, 39–58) to 80% (95% CI, 77–83).

In the second study of 5960 men undergoing RP, the proportion of high-risk patients was comparable to that of the earlier study [39]. As a result, the authors reported that each individual high-risk criterion was associated with an increased risk of secondary cancer therapy (hazard ratio [HR]: 1.3–5.2; \(p < 0.05\)) and metastatic progression (HR: 2.1–6.9; \(p < 0.05\)). However, depending on the definition, the probability of freedom from additional therapy 10 yr after surgery ranged from 35% to 76%. The 10-yr cumulative incidence of PCa-specific mortality in high-risk patients ranged from 3% to 11% (HR: 3.2–10.4; \(p < 0.0005\)) [39].

Other retrospective series have looked at the outcome of patients undergoing RP for clinical stage T3a PCa or PSA values >20 ng/ml [41–49]. Table 2 lists the results of selected series.

### 3.2.2. Pelvic lymph node dissection during radical prostatectomy

As stated in the various guidelines, if RP is performed in high-risk PCa cases, an extended pelvic LN dissection (ePLND) should be performed. For a urologic surgeon, it is of great interest to identify the primary landing sites of lymphatic spread in patients undergoing pelvic LN dissection (PLND) during RP. It would be an easy surgical task just to remove more LNs and neglect the morbidity of this extended surgery. It was shown that even in experienced hands, however, the complication rate of ePLND (ie, >10 LNs removed) is increased, which has to be considered when planning the treatment strategy [50].

Mattei et al. studied the primary lymphatic landing sites in patients undergoing RP and ePLND [51]. In this study the authors described a multimodality technique using single-photon emission computed tomography combined with computed tomography or magnetic resonance imaging and compared the results with patients undergoing limited or extended PLND [51]. From their data the authors concluded that PLND for PCa should include not only the external and obturator regions and the areas lateral and medial to the internal iliac vessels but also the common iliac LNs up to the ureteric crossing; this technique may lead to the removal of approximately 75% of all nodes potentially harboring metastatic spread [51].

The true value of ePLND is based on a well-defined field of resection, which means that more LNs will be removed and the primary landing sites of potential metastasis should be included.

Supporting the idea of extending the field of resection, Heidenreich et al. emphasized the value of extended compared with standard PLND during RP [52]. They found that ePLND is associated with a high rate of LN metastases
outside the fields of standard lymphadenectomy in cases of clinically localized PCa [52]. Bader et al. observed that meticulous PLND reveals a high rate of metastases (25%) [53]. In patients with positive nodes, time to progression is significantly correlated with the number of diseased nodes. The authors suggest that meticulous PLND in patients with micrometastasis not only may be a staging procedure but also may have a positive impact on disease progression and long-term disease-free survival [53]. More recently, the pathologic extent of nodal metastases was investigated, and it was found that both the diameter of any individual LN metastasis and its extranodal extension have a significant prognostic impact [54,55]. Also, it has been shown that the number of positive nodes and the LN density are of significant importance [56–59].

A prospective multi-institutional German trial, investigating the role of extended compared with limited PLND in high-risk PCa patients, is under way and may answer questions concerning this important topic.

One additional point about locally advanced PCa warrants discussion: the value of treating the primary tumor (prostate) in the setting of LN-positive disease. Two studies compared the oncologic outcome in pathologic LN-positive patients with or without completed RP following PLND. Using the Munich cancer registry, including abandoned RP in 456 LN-positive patients and completed RP in 957 patients who were noted to have positive LNs during PLND, Engel et al. found an overall survival at 5 and 10 yr of 84% and 64%, respectively, with completed RP compared with 60% and 28%, respectively, after aborted RP. These results suggest that RP may have a survival benefit and that the abandoning of RP in node-positive cases may not be justified [58]. However, because of the nature of the data and the data’s inherent selection bias (ie, cases perhaps were abandoned because they were deemed unresectable and thus had worse disease), this study must be interpreted with caution [60]. Further evidence that patients with positive LN status may benefit from removal of the primary tumor was provided by Steuber et al. [61]. They observed a beneficial impact of RP in patients with completed RP compared with abandoned RP, resulting in the superior survival of patients with LN-positive PCa after controlling for LN tumor burden [61].

### 3.2.3. Radical prostatectomy: the role of adjuvant treatment with androgen-deprivation therapy

As previously mentioned, despite surgery, many patients with high-risk PCa progress [42]. A major limitation of studies to date has been focusing on a single form of primary treatment while not considering the potential value of a multimodal approach. As Gerber et al. stated, the urologic community has moved from wondering whether surgery is an option for high-risk PCa to whether it might be the preferred therapeutic option [13]. According to the recent EAU guidelines, patients must be informed about the possible need for a multimodal approach [62]. A recent Cochrane meta-analysis of adjuvant and neoadjuvant ADT concluded that neoadjuvant ADT does significantly reduce the rate of adverse pathologic parameters, including tumor stage and margin status, but does not improve overall survival [63]. Accordingly, neoadjuvant ADT in the RP setting is not recommended in either the EAU or AUA guidelines [10,62–64].

In contrast, when ADT is considered in the adjuvant setting following RP, an increase in biochemical- and progression-free survival has been reported [65,66]. However, the effect of adjuvant ADT on overall survival remains unclear, and it appears to be influenced by the individual risk profile [64]. The landmark trial by Messing et al. reported a survival advantage for immediate ADT in patients with LN-positive disease at RP [67,68]. In this trial, 98 patients with LN metastases were randomized to immediate ADT or ADT at the time of distant metastases or of symptomatic recurrences. Patients receiving immediate ADT had a significantly improved overall survival (HR: 1.84; \( p = 0.04 \)) at a median follow-up of 11.9 yr [67,68]. However, because the trial was initiated in the pre-PSA era, delayed ADT was not given at PSA recurrence, but only at clinical disease progression. Two-thirds of the patients also had seminal vesicle invasion and/or positive margins, and as such they were at a very high risk of recurrence regardless of LN status. Consequently, these findings cannot necessarily be transferred to contemporary patients [64].

More recently, several, albeit retrospective, studies evaluating the value of adjuvant ADT in LN-positive patients met with conflicting results [64,69,70]. In one study, Boorjian et al. analyzed the data for 507 patients with node-positive PCa following RP [69]. Patients with immediate ADT had a statistically significantly decreased risk of biochemical and local recurrence. There was no statistically significant difference, however, in the rate of systemic progression or of cancer-specific survival between the two groups [64,69]. The side effects of continuous ADT must be weighed against the potential benefits of treatment [64].

#### 3.2.4. Radical prostatectomy: neoadjuvant and adjuvant treatment with chemotherapy

Other novel approaches to the multimodal treatment of high-risk patients have included using adjuvant chemotherapy with agents such as docetaxel [71]. A prospective randomized trial was closed, however, because of insufficient patient accrual.

A phase 2 trial investigated the use of docetaxel and estramustine prior to RP or RT in high-risk localized PCa [72]. Patients with locally advanced and high-risk localized PCa \((n = 24)\) were treated with neoadjuvant intravenously administered docetaxel at a dosage of 36 mg/m² weekly for 3 wk and orally administered estramustine at a dosage of 140 mg 3 times daily for 3 consecutive days every 28 d prior to definitive treatment with RP or RT. All except one patient completed the neoadjuvant chemotherapy with minimal dose reductions or delays. Following local treatment, the 2-yr progression-free survival was 45% (median follow-up: 24 mo). Thus, the authors concluded that this approach was safe, well tolerated, and effective in patients with high-risk locally advanced prostate adenocarcinoma. The relative
contributions of ADT compared with docetaxel could not be determined, which suggests that a large phase 3 clinical trial would be required [72].

3.2.5. Radiation therapy with and without androgen-deprivation therapy

RT represents a valid approach to treat high-risk localized PCa. However, it has been found that as with surgery, RT, when administered as monotherapy for high-risk PCa patients, is associated with modest success. Initial results from RTOG 86–10 and 85–31 revealed a 5-yr biochemical recurrence–free survival rate of only 10–20% in the radiation-only arms in locally advanced cancers (44–46 Gy to the pelvic LNs and 65–72 Gy to the prostate) [73,74]. Dose escalation studies combined with improved RT techniques increased the 5-yr biochemical recurrence–free survival rate ≤38% in a monotherapy setting [75]. To address this issue, it would appear that RT in combination with long-term ADT may be necessary to address high-risk PCa in the most optimal way. Several randomized trials for high-risk PCa have evaluated the combination of RT plus ADT. According to a Cochrane Review, neoadjuvant ADT improved both biochemical and clinical progression–free survival [63]. Adjuvant ADT improved disease-specific survival at 5 yr and overall survival at 5 and 10 yr [63].

In a subset analysis of a phase 3 trial from Canada that randomized high-risk patients to 3 or 8 mo of neoadjuvant ADT, patients receiving 8 mo of treatment were reported to have an improvement in 5-yr disease–free survival from 42% to 71% (p < 0.01); no advantage was noted in overall survival [76]. This observation may be explained by the size of this study, however. The Trans-Tasman Radiation Oncology Group reported that 3 mo of ADT was insufficient to improve overall survival compared with 6 mo of treatment [77]. Other trials also support the benefit of combined treatment [78–82]. The preponderance of evidence supports the use of long-term ADT over short-term ADT in the patients with the highest risk disease.

In the landmark European Organization for Research and Treatment of Cancer 22961 trial by Bolla et al. [83], 970 men were randomized to short-term ADT (n = 483, 6 mo) or long-term ADT (n = 487, 3 yr) combined with EBRT. The authors reported a 5-yr overall mortality for short- and long-term ADT of 19.0% and 15.2%, respectively, and they concluded that 6 mo of ADT was associated with inferior survival [83]. However, most patients had ≥CT2c disease (ie, large tumor volume), and thus the results may not apply to patients with small tumors or high-grade disease alone [83]. In contrast, the RTOG trial 92–02 reported an improved 10-yr disease-specific survival among patients with GS 8–10 disease treated with RT and long-term ADT (24 mo) compared with short-term ADT (4 mo) [79]. These findings were highlighted by a meta-analysis of five RTOG trials incorporating 2743 patients [84]. Roach et al. identified four prognostic risk groups and showed that men with GS 8–10 or T3 disease had a greater survival chance when treated with ADT [84]. In another phase 3 trial in patients with PCa and high metastatic risk, immediate ADT for 3 yr after external RT was associated with improved 10-yr disease-free and overall survival without increasing late cardiovascular toxicity compared with RT alone [85]. It would therefore appear that the most optimal nonsurgical treatment approach using EBRT for high-risk disease may be the administration of high radiation dose levels in conjunction with long-course ADT.

3.2.6. Radiation therapy: combination with brachytherapy

Another option to improve the PCa-specific outcome of high-risk patients includes the addition of brachytherapy to external RT and ADT [86]. A total of 1342 PCa patients with PSA < 20 ng/ml, ≥T3, or biopsy GS 8–10 were studied retrospectively. Patients were treated with brachytherapy alone or with supplemental ADT, RT, or both; the analysis was adjusted for age, year of treatment, and other known PCa prognostic factors. After a median follow-up of 5.1 yr, there was a significant reduction in the risk of PCa-specific mortality in men treated with brachytherapy and both ADT and RT [86].

A small study enrolled 174 patients with GS 8–10 and PSA < 15 ng/ml undergoing permanent interstitial brachytherapy with or without ADT [87]. A total of 159 patients (91%) received supplemental EBRT, and 113 patients (64.9%) received ADT. The 10-yr outcomes for patients treated without and with ADT included cancer-specific survival rates of 95.2% and 92.5%, respectively; biochemical recurrence–free survival rates of 86.5% and 92.6%, respectively; and overall survival rates of 75.2% and 66.0%, respectively. The use of ADT did not have a significant impact on any end point [87].

These findings were also supported by the study by Dattoli et al. investigating 164 high-risk patients with the combination of RT, brachytherapy, and ADT [88]. For the high-risk group, the authors observed a likelihood of biochemical recurrence–free survival of 74% at 16 yr.

According to the data of Nanda et al, the administration of complete androgen blockade in high-risk disease may further improve disease-specific mortality [89]. In men >65 yr of age with high-risk PCa, the combination of brachytherapy, RT, and ADT significantly improved PCa-specific mortality relative to brachytherapy alone (median follow-up: 4.9 yr) [90].

Another approach involves the combination of long-term ADT, RT, brachytherapy boost, and adjuvant docetaxel [91]. The phase 2 trial by Dibiase et al. investigated 42 patients with a median follow-up of 5.6 yr. The treatment consisted of RT (45 Gy to the pelvis) followed by a brachytherapy boost 1 mo later (either iodine 125 or palladium103). A month later, patients received three cycles of docetaxel chemotherapy (35 mg/m² weekly). ADT was administered for 2 yr. Of the patients, 85.7% were able to complete the planned multimodality treatment. Notably, grade 2 and 3 acute genitourinary and gastrointestinal toxicities occurred in 50% and 14.2%, respectively, with no grade 4 toxicities noted. Also, grade 3 and 4 acute hematologic toxicities were observed in 19% and 2.4%, respectively. The 5- and 7-yr actuarial biochemical recurrence–free survival rates were 89.6% and 86.5%, respectively, and corresponding rates for disease-free survival were 76.2% and 70.4%, respectively.
The 5- and 7-yr actuarial overall survival rates were 83.3% and 80.1%, respectively. Taken together, the group implies that a validation in a large phase 3 multi-institutional setting is required [91].

3.2.7. Proton beam therapy

The use of proton beams has been a tempting innovation in the treatment of PCa because almost the entire dose is delivered to the prostate, which does not leave a potentially harmful tissue path, as is the case with photon therapy [1]. Critical tissue beyond the target may be spared because of an effective fall-off for protons beyond their deposition depth, thus sparing sensitive organs such as the bladder and rectum and thereby limiting side effects. To date, only one randomized trial (Proton Radiation Oncology Group 9509 trial), which randomized men to either RT (70.2 Gy) or a combination of proton and photon irradiation (79.2 Gy), has been published [92]. The estimated 10-yr PSA progression probability was 32% and 17% for standard and combination therapy, respectively (median follow-up: 9.4 yr) (p < 0.001). Surprisingly, no difference in urinary, sexual, or rectal functions was reported [92]. It should be noted that this trial was a dose escalation trial but should not be considered a study testing the efficacy of proton beam therapy compared with conventional photon therapy. To compare the oncologic efficacy of protons compared with photons, a randomized trial using equivalent doses and comparing proton beam therapy with intensity-modulated RT (IMRT) must be performed. According to two recent planning studies comparing conformal proton therapy with IMRT, this is a challenging task, each describing equivalence in sparing the rectum [93,94]. However, one study reported IMRT to be superior in terms of bladder sparing [93]; the other study favored protons [94]. However, based on the doses delivered, PSA responses (nadirs), and the degree of metabolic atrophy noted on magnetic resonance spectroscopy, there is no reason to assume better cancer control outcomes with protons compared with brachytherapy [95–97].

3.2.8. Comparison of radical prostatectomy and radiation therapy

The comparison of surgical therapy and RT is extremely difficult, since different nadirs are defined and cannot be compared [6]. A large retrospective series compared cT1–T3b PCa patients undergoing either RP or RT [98]. Importantly, all patients were treated by very experienced, high-volume physicians. RP consisted of standard open RP, including bilateral PLND. RT was carried out as IMRT, applying doses of 81–86.4 Gy to the prostate but leaving out the pelvic nodes. RT was combined with short-term ADT and stopped at the completion of RT; long-term ADT was not used even for the high-risk cases in this cohort [98]. The results showed an 8-yr probability of freedom from metastatic progression of 97% for RP patients and 93% for RT patients. The rates of metastatic progression were similar for favorable-risk disease (1.9% difference in 8-yr metastasis-free survival), somewhat reduced after RT for intermediate-risk disease (3.3%), and more substantially reduced after RT for unfavorable-risk disease (7.8% in 8-yr metastatic progression) [98]. As the authors pointed out, a limitation of the comparison of these two cohorts is the time to offering salvage therapies after treatment failure. Salvage RT was offered after surgical failure within an average of 13 mo, but only after 69 mo after IMRT failure. This point is particularly relevant given the encouraging recent data suggesting that brachytherapy salvage may be successful in patients failing EBRT [111]. In addition, as the authors also pointed out in this study, one of the limitations for the RT cohort in the treatment of high-risk patients was that long courses of ADT and the use of elective pelvic LN irradiation were not routinely used. With a longer course of ADT and the use of brachytherapy boosts to achieve a greater degree of dose escalation, it is likely that the RT results would have been further improved and not significantly different from surgery outcomes. The comparison data are also supported by a Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study [112]. The paper reveals that higher-risk patients have better cancer-specific survival following surgery [112]. A particular strength of both the Memorial Sloan-Kettering Cancer Center and CaPSURE studies is their use of very rigorous multivariable risk adjustment, which increases confidence in the outcomes.

A separate small retrospective study compared RT plus ADT (n = 162) with RP (n = 122) [99]. Patients with adverse pathologic factors underwent adjuvant EBRT with or without ADT. The two groups of high-risk patients were homogeneous in terms of freedom from biochemical failure on the basis of the clinical T stage, biopsy GS, and initial PSA level. The median follow-up was 38.6 and 33.8 mo in the RT and RP groups, respectively. At 3 yr, the biochemical recurrence–free survival rates were 86.8% and 69.8% in the RT and RP groups, respectively [99].

In contrast, Boorjian et al. compared patients with high-risk PCa undergoing RP (n = 1238) or RT with ADT (n = 344) or without ADT (n = 265) from 1988 until 2004 [100]. The median follow-up was 10.2, 6.0, and 7.2 yr after RP, RT plus ADT, and RT monotherapy, respectively. Surprisingly, the 10-yr cancer-specific survival rates were 92%, 92%, and 88% after RP, RT plus ADT, and RT monotherapy, respectively (p = 0.06). The risk of all-cause mortality, however, was greater after RT plus ADT than after RP (HR: 1.60; 95% CI, 1.25–2.05; p = 0.0002). The authors concluded that whereas RP alone and RT plus ADT may provide similar long-term cancer control for patients with high-risk PCa, the impact of treatment on noncancer mortality (ie, the potential for increased cardiovascular deaths with ADT) and on quality of life must be considered as well [100,101].

One problem of the studies is the relatively long treatment period, acknowledging that both RP and RT have been optimized over the years and cannot be compared with what was done some 15 or 20 yr ago. All series are retrospective and do reflect a selection bias in choosing the optimal treatment modality for each individual patient. For example, there is clear selection bias shown in the report by Giordano et al, in which men with PCa treated by RP had a higher survival than a matched control group of men.
without cancer [102]. Thus, the ideal comparison of RP and RT for high-risk patients would be in a prospective randomized trial setting.

4. Conclusions

The ultimate goal of the search for the best treatment of high-risk PCa is to match treatment intensity to the level of disease aggressiveness. By achieving this goal, we may offer customized treatment plans while minimizing side effects from overtreatment and overcoming potential undertreatment.

It is imperative to identify the group of high-risk patients who will benefit the most from an aggressive therapeutic approach. Promising biomarkers in development, including the use of circulating tumor cells, have been reported to be potential predictors of response to therapy [103,104]. Other markers include various forms of genetic or epigenetic alterations, such as CpG island hypermethylation and histone modifications [31,105–110]. These markers may be integrated with the many novel agents becoming available for advanced PCa to create new adjuvant treatment strategies for these patients.

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