High-risk prostate cancer—classification and therapy

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Abstract | Approximately 15% of patients with prostate cancer are diagnosed with high-risk disease. However, the current definitions of high-risk prostate cancer include a heterogeneous group of patients with a range of prognoses. Some have the potential to progress to a lethal phenotype that can be fatal, while others can be cured with treatment of the primary tumour alone. The optimal management of this patient subgroup is evolving. A refined classification scheme is needed to enable the early and accurate identification of high-risk disease so that more-effective treatment paradigms can be developed. We discuss several principles established from clinical trials, and highlight other questions that remain unanswered. This Review critically evaluates the existing literature focused on defining the high-risk population, the management of patients with high-risk prostate cancer, and future directions to optimize care.


Introduction

The diagnosis and treatment of prostate cancer is based on a series of clinical states. These states begin with localized disease, followed by the non-castrate rising prostate-specific antigen (PSA) state and the non-castrate metastatic state. Finally, the castration-resistant states are lethal for most men (Figure 1). For all states, clinical management decisions and the design of clinical research are often based on a determination of risk. Localized tumours can range from those with a low malignant potential (which, if left untreated, are still unlikely to result in morbidity or reduce life expectancy), to those that are curable with a single modality directed exclusively to the gland itself or those destined to recur locally or systemically despite optimal local therapy. It is the last category that encompasses tumours that are broadly classified as ‘high-risk’ or alternatively ‘locally advanced’.

Although the literature on ‘high-risk’ prostate cancer is extensive and is increasing, no classification scheme exists that enables outcomes for patients with high-risk prostate cancer to be determined reliably and consistently to optimize patient management. The situation is further hindered by the wide range of diagnostic methods used to classify patients, and by variations in the treatment itself from studies based primarily on a surgical or radiotherapy approach. The specific outcomes vary between studies, and few of these outcomes adequately represent how a patient functions, feels or how long he will survive. The fact that most reports are retrospective further limits the ability to formulate meaningful standards, and thus ultimately compromises counselling.

We present a critical review of the published literature, and highlight key areas on which to focus, to enable more-reliable treatment recommendations by physicians and better-informed decisions by patients.

Defining high-risk disease

In the USA, approximately 238,590 men were diagnosed with prostate cancer in 2013, and 29,720 patients with prostate cancer were anticipated to die of their disease. Many patients who die of prostate cancer initially present with tumours seemingly confined to the gland that represent true ‘high-risk’ disease for which new approaches are needed. By current estimates, high-risk disease accounts for 15% of all prostate cancer diagnoses. The limitations of determining risk on the basis of TNM classification—which does not include Gleason score or prostate-specific antigen (PSA) levels—have long been recognized (Box 1). An important first step toward a more-reliable schema was first proposed by D’Amico et al., who used an end point of PSA failure and defining high-risk as a clinical T stage ≥cT2c, a Gleason score ≥8, or a PSA >20 ng/ml; this definition has been adopted by the American Urological Association (AUA). The Radiation Therapy Oncology Group (RTOG) developed the first classification that associated specific baseline factors with overall survival and cause-specific survival, arguably more relevant measures. High risk in the RTOG classification includes Gleason score ≥8 or Gleason score 7 plus either ≥cT3 or node-positive disease; PSA adds little to this model for the prediction of cause-specific survival or overall survival. When combining the RTOG model with the original Kattan nomogram that predicts for PSA relapse-free survival and includes pre-treatment PSA, clinical stage, and biopsy Gleason sum, the ability to predict prostate cancer-specific survival improves.
Recent risk classifications for localized prostate cancer include a measure of the overall extent of tumour in biopsy specimens, based on the percentage of core involvement being associated with prostate cancer-specific mortality. One would assume, for example, that the prognosis of a patient with cT3b, Gleason 9 (4+5) tumour in 14 of 16 pretreatment biopsy cores, and a baseline PSA of 65 ng/ml would have a worse outcome than a patient with cT3a, Gleason 8 (4+4) disease in 3 of 16 biopsy cores and the same PSA. The Cancer of the Prostate Risk Assessment (CAPRA) score was developed to better classify risk by considering disease extent within the gland. CAPRA includes the percentage of positive biopsy cores (>33% of positive cores) and age—in addition to stage, PSA, and Gleason score—and was shown to predict prostate cancer-specific mortality, independent of treatment, in a validation set of 10,627 men. The National Comprehensive Cancer Network (NCCN) defines ‘high-risk’ as T3a, Gleason ≥8, or PSA ≥20 ng/ml, and ‘very high risk’ as T3b or T4 disease, the prognostication of which was improved by recording the proportion of biopsies with ≤50% versus >50% tumour involvement. Nonetheless, because of the difficulty in reliably and reproducibly determining the percentage of cores involved by the tumour, many physicians continue to use more traditional nomograms (such as the Kattan nomogram) based on T-stage, PSA, and Gleason score, to categorize their patients.

Significant heterogeneity in prognosis has been observed using the risk stratification schemes mentioned above. The range of outcomes was highlighted in an analysis showing 5-year relapse-free survival probabilities ranging from 49% to 80% for the same patient population using different published schemas. The Kattan nomogram, for example, considers Gleason score and PSA as a continuous variable and reports the probability of a disease-specific outcome in a continuous fashion; consequently, what actually constitutes high-risk can vary considerably.

An additional problem with all of these schemes is the inherent inaccuracy in determining T stage. Assessing disease by digital rectal examination (DRE) has significant inter-observer variability and while understaging is more common, there is also a problem with overstaging. In one series, 23.5% of clinical T3a tumours defined by DRE were found to be pathological T2 disease at radical prostatectomy. The American Joint Committee on Cancer staging system allows the use of imaging to refine the determination of T stage. The use of imaging is highly variable. One study showed that the addition of multiparametric MRI improved staging accuracy and provided a quantitative volumetric assessment of the extent of tumour in the gland that could be compared to DRE assessment. The MRI was performed with an endorectal coil and used diffusion-weighted imaging and dynamic contrast enhancement, detecting extracapsular extension with an accuracy of 91% and specificity of 99%, using pathological staging at prostatectomy as the gold standard. However, this single-centre study did not report clinical stage for comparison. Quantitative MRI has also been shown to improve performance in detecting clinically significant prostate cancer. In a series of patients who underwent both extended systematic biopsy and MRI-targeted biopsy, 12 of 51 patients (24%) had Gleason score upgraded after biopsy. MR spectroscopy is another potential biomarker that provides metabolic information and is being studied to determine whether it can more reliably assess pathological tumour grade and overall disease aggressiveness.

A number of groups are studying specific biological determinants measured in tumours from the diagnostic biopsy samples to further refine risk. These include markers of tumour proliferation such as Ki-67, alterations in specific pathways such as the PI3K/PTEN signalling axis, and copy-number alterations at the DNA level. A four-gene signature assessing PTEN, SMAD4, cyclin D1 (CCND1), and secreted phosphoprotein 1 (SPP1) that was derived from a mouse model was prognostic of biochemical recurrence and metastasis in human samples. P16, Ki-67, MDM2, Cox-2, and PKA were identified by RTOG

**Key points**
- Patients with high-risk prostate cancer have a significant chance of developing systemic or local recurrence, and are at higher risk for symptoms and/or death from the disease.
- Definitions vary for what constitutes high-risk disease in localized prostate cancer, but are historically based on clinicopathological findings including clinical stage, Gleason score, and PSA.
- The literature is limited as a consequence of variations in definition, lack of prospective randomized trials, limitations in statistical plan (underpowered studies), the need for long-term follow-up, and suboptimal end points.
- Several key principles for radiotherapy have been established, including the importance of dose, and the addition of androgen-deprivation therapy.
- Optimal surgical management requires completely removing the gland itself, confirming negative margins intraoperatively, and discussing the potential need for post-operative radiotherapy.
- Treatment of potential lymph-node involvement, either surgically or with extended pelvic radiation, is favoured in high-risk disease, but lacks level I evidence.

**Figure 1** | Clinical states of prostate cancer. Adapted with permission from Scher & Heller, Urology 55, 323–327 (2000). *Approved by the FDA to treat cancer that has spread to bones but not to other organs. Shown to improve survival in a phase III trial, and under Priority Review by the FDA. Abbreviation: PSA, prostate-specific antigen.
Whereas the optimal duration of long-term ADT is still an open question, a number of trials have now established the importance of radiation dose in achieving better biochemical relapse-free survival.30–33 On the basis of these trials, there has been a presumption that trials conducted before the establishment of high-dose radiotherapy (≥75 Gy) should be interpreted cautiously because the doses used were suboptimal by contemporary standards. However, given that none of these studies has demonstrated an improvement in overall survival, one might argue that the evidence for the appropriate use of ADT might be more important than dose escalation, most likely related to the effect of ADT on micrometastatic disease.34

There is an increasing trend of undertreating high-risk prostate cancer, with many high-risk patients receiving ADT alone rather than curative treatment consisting of radiotherapy or radical prostatectomy.3 A Scandinavian randomized phase III trial, SPCG-7/SFUO-3 (ISRCTN01534787), showed that the addition of radiotherapy with total androgen blockade improved rates of overall survival and disease-free survival for high-risk patients (Table 1).35 The National Cancer Institute of Canada and the UK Medical Research Council randomly assigned 1,201 patients with high-risk prostate cancer to lifelong ADT alone or with pelvic radiotherapy. The addition of radiotherapy significantly improved overall survival (74% versus 66%, P = 0.033) and disease-specific survival (90% versus 79%, P = 0.0001) at 7 years.36 The benefits observed in these end points meant that the number of patients needed to be treated to prevent one prostate cancer-specific death was very low (approximately 6.25–9.0 patients).

No age threshold applies to the first principle, which states that treating the primary tumour is essential. A recent study demonstrated that although elderly men are more likely to have high-risk disease, they are less likely to receive definitive therapy,37 even though they have a substantial risk of dying from prostate cancer and would benefit from curative therapy.37,38 Although ADT alone is inferior to radiotherapy in high-risk disease, the combination of both treatments is firmly established in high-risk disease.39,40

Regarding the second principle, the study RTOG 8531, conducted between 1987–1992, was the first trial to randomly assign patients with locally advanced disease (n = 977) with cT3 or lymph node-positive disease to radiation alone (60–70 Gy) versus radiation combined with life-long ADT. Approximately 15% of these patients had undergone radical prostatectomy, but had evidence studies to be promising biomarkers that might determine which high-risk patients could benefit from long-term androgen-deprivation therapy (ADT).32 PCA3 is a prostate-specific noncoding mRNA that can be measured in the urine and is overexpressed in prostate cancer relative to benign prostatic tissue; it has been studied mostly in the active surveillance setting. PCA3 levels in urine have been correlated with Gleason score and tumour volume in radical prostatectomy specimens, although its use in identifying high-risk disease that would otherwise be undetected is uncertain.33

Two genetic signature-based biomarkers have become available. The Prolaris® (Myriad Genetics, Salt Lake City, Utah) test is a 46-gene panel associated with tumour proliferation.25 This biomarker is designed to determine which tumours categorized as ‘low-risk’ might be more aggressive and thus not appropriate for an active surveillance approach. The role of the test in the management of high-risk tumours is unclear. The Oncotype DX® (Genomic Health, Redwood City, CA) test reports the expression of 17 genes to determine probability of adverse pathology at surgery and overall disease aggressiveness,26 to inform whether an active surveillance approach is appropriate; it is not targeted to tumours determined to be high-risk by NCCN standard clinicopathological criteria. These tests are among a myriad of biomarkers in various stages of analytical and clinical validation to improve standard biomarkers by accounting for tumour genetics and biology.22

### Box 1 | Common definitions of high-risk prostate cancer

**American Urological Association**
- Preoperative PSA >20 ng/ml, and/or preoperative Gleason score of 8–10, and/or clinical stage ≥T2c4,5

**European Association of Urology**
- Preoperative PSA >20 ng/ml, and/or preoperative Gleason score of 8–10, and/or clinical stage ≥T3a4,11

**Radiation Therapy Oncology Group**
- High risk: T1–2 and Gleason 8–10, or T3 or N1 with Gleason 7
- Very high risk: T3 or N1 with Gleason 8–106

**National Comprehensive Cancer Network**
- High risk: Preoperative PSA >20 ng/ml, preoperative Gleason score of 8–10, or clinical stage T3a
- Very high risk: T3b–T4

**Cancer of the Prostate Risk Assessment (CAPRA)**
- Includes age, PSA, clinical stage, Gleason score, and percentage of positive biopsy cores9,14,2

Abbreviation: PSA, prostate-specific antigen.

### Box 2 | Key principles for radiotherapy of localized, high-risk disease

- Multiple trials have been conducted that have established the key principles of management for radiotherapy of clinically localized prostate cancer
- Principle 1: Definitive treatment of the primary tumour is essential; ADT alone is inadequate
- Principle 2: ADT in addition to radiotherapy is associated with superior outcomes compared with radiotherapy alone
- Principle 3: The importance of radiation dose using intermediate end points (such as PSA) to assess treatment effects

Abbreviations: ADT, androgen-deprivation therapy; PSA, prostate-specific antigen.

### Treatment of high-risk disease

Treatment of high-risk localized prostate cancer has evolved based on evidence from clinical trials that have established important principles (Box 2). The first of these principles is that treatment of the primary tumour is paramount: not only for local control, but also to prevent subsequent spreading to distant metastatic sites. The second principle has established that combining androgen-deprivation therapy (ADT) with external-beam radiotherapy (EBRT) is superior to either of these approaches alone.28,29 Whereas the optimal duration of long-term ADT is still an open question, a number of trials have now established the importance of radiation dose in achieving better biochemical relapse-free survival.30–33
of positive margins and/or seminal vesicle invasion (Table 2). Patients who received ADT with radiation had superior outcomes than those who received radiotherapy without ADT. At 10 years, the rates of local failure (23% versus 38%, \( P < 0.0001 \)), distant metastasis (24% versus 39%, \( P < 0.001 \)), disease-specific mortality (16% versus 22%, \( P = 0.0052 \)), and overall survival (49% versus 39%, \( P = 0.002 \)) favoured the combination arm.\(^{29}\) The European Organisation for Research and Treatment of Cancer (EORTC) 22863 trial randomly assigned 415 men to radiotherapy alone (70 Gy) or to radiotherapy plus concurrent and adjuvant goserelin for 3 years. Approximately 90% of the patients had T3/4 disease. At 5-year follow-up, benefits were observed for the patients receiving both radiotherapy and hormone therapy, in terms of local failure (1.7% versus 16.4%, \( P < 0.0001 \)), distant metastases (9.8% versus 29.2%, \( P < 0.0001 \)), disease-specific survival (74% versus 40%, \( P < 0.0001 \)), and overall survival (78% versus 62%, \( P = 0.0002 \)).\(^{30}\)

Together, these two trials confirm a significant benefit in clinical outcome with the addition of long-term ADT to EBRT doses up to 70 Gy. The challenge arises when trying to extrapolate the use of long-term ADT with dose-escalated EBRT to high-risk patients in the absence of level I evidence. The ongoing RTOG 0815\(^{40}\) study will address the role of ADT in dose-escalated disease in intermediate-risk populations, while the RTOG 0924 trial\(^{41}\) might clarify the issue of the benefit of adding pelvic lymph-node radiation to prostatic irradiation in patients with intermediate-risk to high-risk disease receiving dose-escalated radiation with ADT.\(^{34,42}\)

### Long-term versus short-term hormone therapy

Recognizing the long-term toxic effects associated with continuous ADT, several trials have studied different durations of exposure to hormones in combination with radiotherapy in patients with high-risk disease (Table 2). In the EORTC 22961 trial, 970 men with locally advanced-stage prostate cancer (defined as T1c–T2a, N1–N2, or T2c–T4, N0–N2) were randomly assigned to 6 months or 3 years of complete androgen blockade using a non-inferiority trial design. The short-term and long-term ADT arms received the same treatment for the first 6 months, triptorelin plus flutamide/bicalutamide, with patients in the long-term arm continuing triptorelin for another 2.5 years. Short-term androgen suppression provided inferior overall survival (81% versus 85%, HR 1.42, \( P = 0.65 \) for inferiority) and higher prostate cancer-specific mortality relative to 3 years of ADT (4.7% versus 3.2%, HR 1.71, \( P = 0.002 \)).\(^{43}\) In the RTOG 9202 trial, 1,554 men receiving radiotherapy were randomly assigned to receive 4 months or 28 months of ADT. The 10-year outcomes showed improvements for the 28-month ADT group in disease-free survival (22.5% versus 13.2%, \( P < 0.0001 \)), disease-specific survival (88.7% versus 83.9%, \( P = 0.0042 \)), and local recurrence (12.3% versus 22.2%, \( P < 0.0001 \)). Across the study, no difference in overall survival was observed, but for the subset of patients with Gleason 8–10 disease, rates of overall survival at 5 years were 45% versus 32% (\( P = 0.0061 \)), for the 28-month relative to 4-month exposure groups.\(^{44}\)

A more recent phase III trial that included 630 men with node-negative high-risk prostate cancer receiving pelvic radiotherapy (70 Gy) randomly assigned them to 18 months versus 36 months of androgen blockade.\(^{45,46}\) The median follow-up was 78 months, and 5-year overall survival was 86.1% versus 91.1% (\( P = 0.06 \)) in the 18-month and 36-month groups, with a hazard ratio of 1.15 (95% CI 0.85–1.56). Non-inferiority of the shorter-duration ADT cannot be assumed with this design. In addition, cT1c–T2a/b represented 75% of patients, while cT3/4 represented only 25% of the cohort.

The evidence of overall trends and subset analysis favours long-term use of ADT over short-term ADT in high-risk disease. We acknowledge that this is not definitive owing to the previously described limitations and uncertainties regarding the generalizability of study populations and definitions of high-risk disease. Some physicians and investigators interpret the lack of significance between short-term and long-term ADT regimens as showing equivalence, implying that the observed 4% or 6% differences are not meaningful and that ADT beyond 6 months provides no additional benefit. Others believe that 3 years of ADT should remain the standard, based on results of the EORTC 22961 trial that compared short-term versus long-term ADT with a non-inferiority design; note, this trial was stopped for futility at interim analysis.\(^{48}\) As the definitive benefit of short-term versus long-term ADT is unlikely to be resolved soon, it is essential that patients receive counselling on the trade-offs for long-term ADT so that they are in a position to make an informed decision on how they wish to be managed.

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**Table 1 | Improved outcomes with addition of radiotherapy to long-term ADT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Outcomes</th>
<th>ADT alone (%)</th>
<th>ADT plus radiotherapy (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPCG-7/SFUO-3(^{5*})</td>
<td>cT1b–T2 and grade 2–3, or cT3 40% with PSA ≥20 ng/ml 19% with grade 3 78% with T3</td>
<td>7-year DFS</td>
<td>79</td>
<td>90</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-year OS</td>
<td>66</td>
<td>74</td>
<td>0.033</td>
</tr>
<tr>
<td>NCIC CTG PR.3/ MRC UK PRO7(^{2*})</td>
<td>cT3–T4, cT2 with PSA &gt;40, cT2 with PSA &gt;30 and Gleason &gt;8</td>
<td>7-year DFS</td>
<td>79</td>
<td>90</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*For ADT alone \( n = 439 \); ADT plus radiotherapy \( n = 436 \). \(^{*}\)For ADT alone \( n = 602 \); ADT plus radiotherapy \( n = 603 \).

Abbreviations: ADT, androgen-deprivation therapy; BFS, biochemical failure; DFS, disease-free survival; DSS, disease-specific survival; EORTC, European Organisation for Research and Treatment of Cancer; OS, overall survival; PSA, prostate-specific antigen; SPCG, Scandinavian Prostate Cancer Group; NCIC, National Cancer Institute of Canada; OS, overall survival; PSA, prostate-specific antigen; SFUO, Swedish Association for Urological Oncology; SPCG, Scandinavian Prostate Cancer Group.
An important consideration of short-term versus long-term ADT is the toxic effects associated with ADT. Principal differences in patient-reported outcomes (PRO) assessed after 1 year of enrolment in the EORTC 22961 (short-term versus long-term ADT) trial included increased hot flushes, insomnia, and decreased sexual interest and sexual activity in the long-term ADT group. No difference in overall quality of life was found.43 RTOG 9202 found late radiotherapy-related toxicity grade ≥3 (bowel, bladder) in 10% of patients receiving long-term ADT compared with 7% in patients who received short-term ADT. Rates of grade ≥3 hormone-related toxic effects (such as hot flushes) were comparable between arms (approximately 5%), although it should be noted that this is a clinician-rating scale, rather than a PRO outcome.44 Metabolic and endocrine effects with ADT, such as bone loss, are not insignificant and are reviewed elsewhere.45–50

### Improving radiotherapy outcomes

A third principle of prostate cancer management is assessment of radiation delivery (dose and accuracy) using intermediate end points to assess treatment effects (Box 2). Intermediate end points are crucial because trials that focus on long-term end points—such as time to metastatic disease or prolongation of life—cannot yield results quickly enough to steer management of an individual patient or guide the choice of radiation dose to be used in phase III trials. Survival results can also be confounded by use of new post-relapse or progression systemic therapies that are now approved by the FDA and other regulatory bodies.51–55 These therapies have been reported to improve survival in phase III trials of advanced-stage prostate cancer, thus it is expected that their use in late-stage disease will skew the long-term follow-up survival data collected for trials of earlier-stage prostate cancer.

As there are several ways to improve radiation dose delivery to the tumour, it becomes essential to ensure that only those most likely to succeed in definitive phase III trials are brought forward. One early end point is a post-treatment biopsy of the prostate, typically performed at 2 years.56 This end point was the one used to show the impact of radiotherapy dose in high-risk disease relative to low-risk tumours.57

The observation that dose escalation in patients with high-risk disease conveyed significant benefit in terms of biochemical recurrence-free survival has been confirmed across five randomized trials (Table 3).52,53,58–61 In one trial, patients were randomly assigned to receive radiotherapy doses of 70 or 78 Gy.52 In the high-risk cohort of patients (32–35% of the overall population) with median follow-up of 9 years, patients receiving the higher dose had improved biochemical recurrence-free survival: 79% for 78 Gy compared with 57% for 70 Gy (P = 0.0188). Similarly, distant failure rates were 4% for 78 Gy and 19% for 70 Gy (P < 0.05), with all distant failures in the high-risk group occurring before 2.5 years. With 10-year follow-up, death from prostate cancer was 4% for the 78 Gy arm versus 16% for 70 Gy (P = 0.05).52 Other data indicate that improvements in local control with higher doses of radiation (>75.6 Gy) are associated with a reduced rate of distant metastases and improved disease-specific survival.62

### Improving local control with brachytherapy

Addition of a brachytherapy boost can also improve the outcome of high-risk patients receiving EBRT and androgen blockade. Brachytherapy enables high-precision delivery of extreme radiation doses to the prostate. The tight conformity minimizes dose to the bladder, rectum, and urethra, resulting in an increase of the therapeutic ratio. Brachytherapy is more convenient for the patient as the treatment course can be truncated from 9 weeks to 5 weeks.

Multiple institutional series have demonstrated a PSA relapse-free survival rate ranging from 70–98% at 7–8 years of follow-up.53,63 One large series included 560 patients, each with one-to-three risk factors, treated with high-dose rate brachytherapy and EBRT with...
Radical prostatectomy

Radical prostatectomy is a second option for patients with high-risk prostate cancer. Studies from a number of institutions show 5-year PSA relapse-free survival rates ranged from 55% to 71% and 10-year prostate cancer-specific survival rates from 72% to 92%. The rates vary as a function of disease extent, and according to the criteria used to define 'high-risk'. Optimal surgical management also requires adherence to several principles. The radical prostatectomy procedure requires complete removal of the gland itself, confirming intraoperatively that the surgical margins are negative on frozen section and, for this high-risk population in particular, performing an extended pelvic lymph-node dissection (ePLND). The procedure is best performed by experienced high-volume surgeons who, as a group, have been shown to have better outcomes. Prior to surgery, patients should also be informed about the possible need for post-operative radiation, as noted in the AUA and American Society for Radiation Oncology (ASTRO) consensus statements.

The first principle in Box 3 acknowledges that the survival benefit of radical prostatectomy will vary by patient, as a function of the patient’s risk of death from prostate cancer and risk of death from other causes such as cardiovascular events, other comorbidities, or old age. Several large retrospective studies that focused on high-risk disease have demonstrated favourable long-term prostate cancer-specific survival rates with radical prostatectomy and node dissection (Table 4). In these large studies, 10-year prostate cancer-specific survival rates were generally over 90%, and were remarkably consistent across all the studies reported. Such consistency and high survival rates might reflect definitions of high-risk disease, which in most studies were based on the D’Amico classification and captured more favourable ‘high-risk’ disease. In a study of 712 patients with PSA >20 ng/ml at diagnosis, patients with one high-risk feature (PSA >20 ng/ml) were more likely to have favourable histopathology (pT3a or lower, Gleason ≤7, R0, pN0) than patients with more than one preoperative high-risk factor, such as Gleason ≥8 and/or cT3 disease. In this report, 27% of patients with a PSA >20 ng/ml as the only adverse feature had a favourable histology at radical prostatectomy in comparison to 0% of patients with three risk factors (PSA >20 ng/ml, cT3–4, and Gleason score 8). Prostate cancer-specific survival also varied by the number of high-risk features: at 10 years it was 91% for those patients with only a PSA >20 ng/ml and 65% in those patients with a PSA >20 ng/ml and Gleason ≥8.

This highlights the importance of the definitions and risk profiles used for patient groups reported in retrospective series, and has important implications for clinical trials purported to evaluate ‘new approaches’ in patients broadly classified as ‘high-risk’.

Another theme that has emerged from retrospective surgical series that dovetails with the concept of more favourable versus less favourable ‘high-risk’ disease, is which patients are most likely to benefit from adjuvant therapy. The use of adjuvant radiotherapy and/or ADT

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Improved outcomes with dose-escalated radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Design</td>
</tr>
<tr>
<td>Sathya et al. (2005)</td>
<td>66 Gy EBRT vs 40 Gy+35 Gy Ir-192 implant</td>
</tr>
<tr>
<td>Peeters et al. (2006)</td>
<td>68 vs 78 Gy EBRT</td>
</tr>
<tr>
<td>Dearmaley et al. (2007)</td>
<td>64 vs 74 Gy EBRT (ADT on each arm)</td>
</tr>
<tr>
<td>Zietman et al. (2010)</td>
<td>70.2 Gy EBRT vs 79.2 Gy with protons</td>
</tr>
<tr>
<td>Kuban et al. (2011)</td>
<td>70 vs 78 Gy EBRT</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen-deprivation therapy; DMFS, distant metastasis-free survival; EBRT, external beam radiotherapy; Ir-192, iridium-192; PSA, prostate-specific antigen; vs, versus.

Box 3 | Key principles for surgical management

- Principle 1: The survival benefit of radical prostatectomy is a function of the patient’s risk
- Principle 2: The importance of an extended pelvic lymph node dissection
- Principle 3: Assessing the need for post-operative radiotherapy

or without neoadjuvant ADT (≤6 months versus no ADT). This study demonstrated a biochemical relapse-free survival rate ranging from 81–85%. Interestingly, the development of metastasis at 5 years was actually higher in those patients receiving neoadjuvant ADT (10% versus 5%, P = 0.04)—a trend consistent across risk groups. The fact that the addition of androgen blockade did not improve outcomes, in contrast to other studies, led to the apparent benefit of neoadjuvant ADT being questioned in the setting of high-dose radiation brachytherapy.

Another retrospective study of 174 patients with Gleason 8–10 prostate cancer and PSA <15 ng/ml who underwent permanent interstitial brachytherapy, 91% of whom also received EBRT, demonstrated biochemical recurrence-free survival rates of 92.6% and 86.5% in patients treated with and without androgen blockade, respectively. This difference was not statistically significant and suggested that the use of ADT may not affect brachytherapy outcome. However, such post-hoc analysis must be viewed with caution, because potential selection biases could explain the findings. In addition, biochemical outcomes are not established as surrogates for more meaningful end points, such as cause-specific survival and overall survival in patients with high-risk disease. As none of the dose-escalation studies to date has demonstrated an improvement in overall survival, one might argue that the evidence for the appropriate use of ADT is more robust than the evidence for dose escalation, because definitive trials addressing the dose escalation question have not been completed.
is variable across retrospective surgical studies (Table 4). Use of adjuvant radiation, for example, varied between 8.2–51% depending on the study. Because these were retrospective studies, the use of adjuvant therapy likely varied by physician, patient, and institutional practice. For instance, one study found that patients with more than one adverse risk feature were more likely to receive adjuvant therapy than those patients with an isolated adverse or high-risk feature.

There are no large prospective randomized phase III trials assessing the value of radical prostatectomy exclusively in men with high-risk disease. However, two recent prospective randomized phase III trials (which included a few high-risk patients) concluded that radical prostatectomy did not confer a survival benefit to men with localized disease, or that the benefit was modest at best. The implication was that a significant proportion of men were undergoing an operation from which they would not benefit, but which could cause harm through the loss of erectile function and urinary control. However sobering the reality of overtreatment for some cancers may be, these trials also provide insight into outcomes for high-risk disease.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT) study randomly assigned 731 men with newly diagnosed prostate cancer to watchful waiting or radical prostatectomy. The study did not reach the originally planned accrual target (>2,000), and no overall survival benefit was seen, although bone metastasis-free survival rates favoured radical prostatectomy (10.6% versus 4.7% for watchful waiting; *P* <0.001). Radical prostatectomy did, however, prolong prostate cancer-specific survival in the 251 patients with PSA >10 ng/ml (HR 0.36, 95% CI 15–89%), with a trend for the 157 patients aged ≤8 ≤60 years, 87% ≤60 years, 85% immediate vs deferred ADT 2/275 adjuvant RT (<1%).

### Table 4 | Large retrospective series of radical prostatectomy in high-risk patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Definition of high-risk</th>
<th>PCSS by age:</th>
<th>Comments on population</th>
<th>Adjuvant therapy</th>
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<tbody>
<tr>
<td>Briganti et al. (2012)*</td>
<td>1,366</td>
<td>PSA &gt;20 ng/ml or cT3 or biopsy Gleason ≥8</td>
<td>10-year PCSS 81%</td>
<td>57% with cT3 75% with pT3–4 Adjuvant RT 66.4% of organ-confined vs 16.8% of non-organ confined disease</td>
<td>48% received therapy (ADT and/or RT) 8.2% adjuvant RT 29.7% adjuvant ADT 10.2% adjuvant RT + ADT</td>
</tr>
<tr>
<td>Boorjian et al. (2011)*</td>
<td>1,238</td>
<td>PSA &gt;20 ng/ml or cT3 or biopsy Gleason ≥8</td>
<td>10-year PCSS 92%</td>
<td>33% with cT3-4 40% received therapy (6.9% adjuvant RT; 29.5% adjuvant ADT; 4.1% both RT and ADT)</td>
<td></td>
</tr>
<tr>
<td>Stephenson et al. (2009)*</td>
<td>1,962</td>
<td>PSA &gt;20 ng/ml or cT3 or biopsy Gleason ≥8</td>
<td>10-year PCSS 92%</td>
<td>Large study, high-risk represented 17% of overall population Not reported</td>
<td></td>
</tr>
<tr>
<td>Ward et al. (2005)*†</td>
<td>841</td>
<td>cT3</td>
<td>10-year PCSS 89%</td>
<td>18% with Gleason ≥8 Mean PSA 10.2 (4.7–23.7) ng/ml 51% received adjuvant RT; 16% received adjuvant ADT</td>
<td></td>
</tr>
<tr>
<td>Yossepowitch et al. (2008)*</td>
<td>1,359*</td>
<td>8 high-risk definitions compared</td>
<td>10-year PCSS 93% per D’Amico 10-year PCSS 92% per NCCN</td>
<td>10-year cumulative incidence varied by definition (3–11%) 30–39% received ADT and/or RT within 5 years, but almost all at BCR or salvage; no adjuvant ADT and only 31 cases of adjuvant RT</td>
<td></td>
</tr>
<tr>
<td>Eggener et al. (2011)*</td>
<td>631</td>
<td>modelling; 726 validation cohort</td>
<td>High-risk per se not defined, but reports on subset of patients with Gleason ≥8</td>
<td>PCSS by age: 70–79 years: 82% 60–69 years: 87% &lt;60 years: 85% Not reported</td>
<td></td>
</tr>
<tr>
<td>Spahn et al. (2010)*†</td>
<td>712</td>
<td>PSA &gt;20 ng/ml</td>
<td>10-year estimated PCSS 89.8%</td>
<td>44% with cT3-4 20% with Gleason ≥8 Adjuvant RT varied by number of additional risk factors (11.9–21.6%); adjuvant ADT similarly varied based on additional risk factors (35.4–84.1%)</td>
<td></td>
</tr>
<tr>
<td>Zwergel et al. (2007)*</td>
<td>275</td>
<td>PSA &gt;20 ng/ml</td>
<td>10-year PCSS 83%</td>
<td>75% also pT3 49% with Gleason ≥8 129/275 (47%) immediate ADT (almost all before 2000, when practice patterns changed at this institution) Survival did not differ between immediate vs deferred ADT 2/275 adjuvant RT (&lt;1%)</td>
<td></td>
</tr>
</tbody>
</table>

*Based on D’Amico definition. †Based on NCCN definition. Abbreviations: ADT, androgen-deprivation therapy; BCR, biochemical recurrence; NCCN, National Comprehensive Cancer Network; PCSS, prostate cancer-specific survival; PSA, prostate-specific antigen; RT, radiotherapy; vs, versus.
prostatectomy will not be sufficient. Or stated differently, to determine at what point it is necessary to plan a combined modality approach that includes additional local therapy (radiation to primary site and/or pelvic lymph nodes), and systemic therapies to address micrometastatic disease that was undetected at the time of diagnosis or at prostatectomy.

**Extended pelvic lymph-node dissection**

The second principle for surgical management of localized prostate cancer emphasizes the importance of an ePLND (Box 3). The morbidity of extended nodal procedures that remove nodal chains that spread to the pelvic side wall and/or the pelvic brim (sacral promontory), and perhaps also stage migration of cT1c disease of low risk, led to modifications in the procedure, such that fewer lymph nodes were removed. Nonetheless, some surgeons still hesitate to perform an ePLND because of potential complications, which vary widely from 2% to 51%. In two studies, complications were more frequent for an ePLND than for a limited PLND: 35.9% versus 2% (P < 0.001)82 and 19.8% versus 8.2% (P < 0.001).83 although others have reported rates below 5%. Lymphocele formation is perhaps among the most common complication, which was seen in 10.3% and 4.3% of patients treated with an ePLND and PLND respectively (P < 0.01). No increased deep vein thrombosis, blood loss, or pelvic haematomas were found in one study.85 Although lymphocele is among the more commonly reported complications, this can be as low as <5% with ePLND, perhaps owing to different definitions of lymphocele and post-prostatectomy imaging practices across series, because more routine post-operative imaging will detect more sub-clinical lymphoceles. A prospective phase III German multi-institutional study comparing ePLND with limited PLND will attempt to address the role of ePLND.86 The proportion of men with low-risk disease, in whom nodal spread is rare, led many surgeons to abandon PLND entirely or to remove one or two nodes from each side. Unfortunately, there have also been reported trends of less-extensive PLND with robotic prostatectomy than with open prostatectomy, despite the evidence that nodal dissection can be competently performed with either procedure.89–91

A variety of pre-operative nomograms and risk assessment algorithms can estimate the frequency of nodal spread at prostatectomy. At the Memorial Sloan–Kettering Cancer Center (MSKCC), the policy is to perform a lymph-node dissection when the predicted probability of spread is 2% or more, with a plan to remove 20 or more nodes. Some may argue that this probability is too low to justify the procedure, but for patients with high-risk disease, for whom the frequency of nodal spread can vary from 30% to 40%, the dissection is essential for three reasons: the therapeutic benefit, the more accurate staging to estimate prognosis and therapy, and to inform the need for subsequent therapy. Two systematic reviews suggested that ePLND increased the detection of positive nodes, with an associated improvement in survival, attributed to the elimination of micrometastatic disease.81,94 A retrospective single-centre analysis of men with lymph node–positive disease treated with radical prostatectomy and lymph-node dissection found that 28% of these men remained free from biochemical recurrence at 10 years. This observation, along with other retrospective studies, favours completion of radical prostatectomy when node-positive disease is found on intra-operative node dissection. Additionally, a prospective randomized trial of standard versus ePLND in open prostatectomy cases demonstrated improved 10-year biochemical relapse-free survival rates when the more-extensive procedure was used (51.1% versus 71.4%; P = 0.036).77

**Post-operative radiotherapy**

***Adjuvant radiotherapy***

The third principle is to assess the need for post-operative radiotherapy in patients with clinically localized prostate cancer treated with radical prostatectomy (Box 3). Adjuvant radiotherapy is administered to men with a high risk of local recurrence when the PSA is undetectable (<0.2 ng/ml) and based on pathological features from prostatectomy. It is typically started 3–6 months post-operatively when incontinence has stabilized or resolved. Support for its use is based on three prospective randomized trials that showed a clinical benefit or survival benefit in patients with pT3 disease or positive margins, with the highest level of evidence for the latter.89–101

SWOG 8794 assigned 425 men with pT3 disease or positive margins to either observation or to receive 60–64 Gy adjuvant radiotherapy. With long-term follow-up (median approximately 12.5 years), both overall survival (HR 0.72, 95% CI 0.55–0.96; P = 0.023) and metastasis-free survival (HR 0.71, 95% CI 0.54–0.94; P = 0.016) favoured adjuvant radiotherapy over observation.100 The absolute 10-year metastasis-free survival rates were 71% and 61%, and overall survival rates were 74% and 66%, respectively. The initial trial results (median 10.6 year follow-up) did not reach statistical significance for these end points, although they did find differences in PSA relapse-free survival favouring adjuvant radiotherapy (10.3 years for radiotherapy versus 3.1 years for observation; HR 0.43, 95% CI 0.31–0.58; P < 0.001).102

EORTC 22911 enrolled 1,005 patients who were randomly assigned to receive post-prostatectomy radiotherapy or no postsurgical treatment, during a median follow-up of 10.6 years. This study demonstrated an improvement in biochemical relapse-free survival (74.0% versus 52.6%; P < 0.0001) and local failure (7.0% versus 16.5%; P < 0.0001) in patients receiving adjuvant radiotherapy, but failed to demonstrate an improvement in overall survival (80.7% versus 76.9%; P = 0.20) or metastasis-free survival (11.3% versus 11.0%; P = 0.94). Salvage radiotherapy was administered in 56% of patients with biochemical recurrence on the observation arm, although the trigger to treat in the salvage setting was variable. Examining the observation arm retrospectively, using an intent-to-treat approach, demonstrated that 83.7% of patients did not develop a local recurrence.89
The question is whether it is worth treating 100% of patients to lower the relapse rate by 9.7% (83.7% to 74.0%).\textsuperscript{99,100} It is for this reason that many groups prefer a salvage radiotherapy approach. The German Cancer Society enrolled 388 patients on the trial ARO 96-02, which compared post-prostatectomy radiotherapy with no post-surgical treatment, and demonstrated an improvement in 5-year biochemical progression-free survival (PFS) in the post-surgical radiotherapy arm.\textsuperscript{101} Unlike SWOG 8794, no differences in rates of distant metastases or overall survival were seen in the EORTC 22911 or ARO 96-02 studies.\textsuperscript{98,99,101} This finding might be related to differences in patient characteristics at baseline between trials. The SWOG 8794 trial was powered for survival, whereas EORTC 22911 was only powered to detect biochemical PFS.

Adjuvant radiotherapy can cause toxicity. In the SWOG 8794 study, men received adjuvant radiotherapy versus observation post-prostatectomy, and this trial reported rectal complications (proctitis or rectal bleeding) in 3.3% versus 0% ($P = 0.02$), total urinary incontinence in 6.5% versus 2.8% ($P = 0.11$), and urethral stricture in 17.8% versus 9.5% ($P = 0.02$), respectively, although the time points of these occurrences were not reported.\textsuperscript{103} Toxic effects can impair quality of life; hence, the patient's tolerance for such risk is considered in decision making. In general, quality-of-life assessments may be 'front loaded', as events that occur early may improve with time, which is an important aspect of the discussion of treatment options with patients. In the SWOG 8794 trial, initially acute gastrointestinal and genitourinary effects were worse with adjuvant radiotherapy when compared with observation, but at 2 years, no differences were observed.\textsuperscript{104} The EORTC 22911 trial demonstrated only a 3% rate of grade 3 late toxicity, and no grade 4 late effects.\textsuperscript{99} Moreover, self-reported toxic effects improved because the bowel symptoms that occurred in the first 2 years resolved. Global 5-year quality-of-life measures were improved with adjuvant radiotherapy compared with observation, with the exception of the symptoms related to urinary function.\textsuperscript{103}

**Salvage radiotherapy**

In patients with a rising or detectable PSA after radical prostatectomy, salvage EBRT is often considered. Rising PSA values indicate continued cancer growth, but do not necessarily mean that a patient will develop symptoms or metastasis or succumb to his disease if left untreated. In these cases, the question is whether the source of the PSA is from only the prostate bed itself (which could potentially be treated with salvage EBRT); nodal disease (which could be treated with surgery, radiation or a systemic approach); or a systemic failure (distant metastasis, which would require systemic therapy). PSA levels can also come from a combination of these locations in which case a local approach such as salvage EBRT would not have curative intent.

Radiation therapy that is given when a previously undetectable PSA becomes detectable is considered ‘salvage radiotherapy’. Proponents of salvage radiotherapy over adjuvant radiotherapy argue that the use of PSA testing to detect recurrent disease may still allow effective radiation to be delivered when disease is localized to the prostatic bed.\textsuperscript{105} The salvage radiation approach avoids overtreatment of men who are not destined to recur and restricts to a smaller cohort the potential complications of radiotherapy. An important consideration is that, even when a recurrence is documented, the risk of death from competing comorbidities may exceed the risk of developing prostate cancer-related symptoms or dying from prostate cancer. Additional radiation to the prostate bed may come with the potential risk of secondary malignancies.\textsuperscript{105–108} Although no randomized trials have demonstrated a survival benefit for salvage radiotherapy, evidence from retrospective and observational studies indicate that it might be effective for controlling local recurrence, decreasing distant metastasis, and lowering prostate cancer mortality. For such reasons, the AUA/ASTRO guidelines\textsuperscript{11} consider that the strength of evidence for recommending salvage radiation is grade C (defined as observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). If a patient is to consider salvage radiotherapy, the effectiveness is maximized if radiation is administered when PSA levels are low (<0.5 ng/ml), which requires close monitoring of patients when a recurrence is documented. In one study, PFS varied from approximately 20% to 50% depending on the PSA level at which salvage radiotherapy was offered. The 6-year PFS was 48% in patients with a PSA <0.5 ng/ml and 18% if the PSA level was >1.5 ng/ml.\textsuperscript{109}

An important question to be addressed in trials is to formally compare the strategy of adjuvant radiotherapy relative to early salvage radiotherapy when a low PSA is the trigger to administer treatment. Some have argued that in most trials that reported a so-called benefit for the adjuvant approach, salvage therapy was not administered until it was less likely to be effective, on the premise that identifying patients who were likely to develop local recurrence based on the pathological findings would allow for adjuvant treatment to be given early to those who need it. However, because many of the patients included in the major trials actually had detectable PSA levels and their outcomes were better if irradiated early—given that so-called salvage EBRT is only modestly effective—caution is recommended in advising patients with adverse pathological features to delay adjuvant EBRT.

In randomized trials of adjuvant radiotherapy, adverse pathology at prostatectomy was associated with biochemical recurrence rates around 60%.\textsuperscript{74,99,100} Two phase III randomized trials are being conducted by the UK Medical Research Council (RADICALS, Radiotherapy and Androgen Deprivation in Combination after Local Surgery)\textsuperscript{110,111} and the Trans-Tasman Radiation Oncology Group (RAGES, Radiotherapy Adjuvant versus Early Salvage following Radical Prostatectomy)\textsuperscript{112} that will address whether adjuvant versus salvage radiotherapy is associated with improvements in prostate cancer-specific mortality or biochemical PFS, respectively. The AUA/ASTRO guidelines provide the best summary and recommendations for patients in the postoperative setting.\textsuperscript{74}
Radiation therapy or radical prostatectomy

A frequently asked question is whether surgical approaches are superior to radiotherapy-based approaches or vice versa. Although no prospective randomized trials assessing this question have ever been completed, several studies have compared retrospectively radical prostatectomy with radiotherapy. A combined analysis involving patients from the Mayo Clinic and Fox Chase Cancer Center included 1,238 patients who underwent radical prostatectomy and 690 patients who underwent EBRT.\(^7\)

In total, 344 of the patients receiving radiotherapy also received ADT. All patients had high-risk prostate cancer classified as PSA ≥20 ng/ml, Gleason score 8–10, or ≥T3 disease. The respective 10-year cancer-specific survival rates were 92%, 92%, and 88% for patients receiving radical prostatectomy, EBRT and ADT, and EBRT alone \((P = 0.06)\). After multivariable risk adjustment, there was no significant difference in distant metastasis or cause-specific survival. However, the risk of all-cause mortality was greater after EBRT with ADT when compared with radical prostatectomy. Reasons for the increased all-cause mortality could include selection bias for patients with greater medical comorbidities to be treated with radiation rather than surgery. All retrospective studies suffer this potential inherent bias, and in the absence of comorbidity scores for all patients, this is difficult to prove or disprove. This study did, however, attempt to control for comorbidities (when available) using the Charlson comorbidity index and did not find comorbidities to influence outcomes.\(^7\)

Alternatively, the potential adverse cardiovascular effects of ADT might have contributed to more cardiovascular deaths and all-cause mortality, a controversial topic in the literature.\(^4,5,7,13-15\)

Several additional limitations should be mentioned about the Mayo and Fox Chase study.\(^7\) The median radiation dose of 72 Gy used is suboptimal as indicated by the multiple randomized trials demonstrating a clinical benefit with higher doses of radiation. In addition, the radiation target volume included the prostate and seminal vesicles with omission of the pelvic lymph nodes. The pelvic lymph nodes are often included in the radiation treatment volume for patients with high-risk disease. With escalated doses of radiation and incorporation of pelvic lymph nodes in the radiotherapy field, further improvements in clinical outcome might have been observed for the radiation treatment arms.

A smaller retrospective study from Italy enrolled 288 patients with high-risk prostate cancer; 162 of whom underwent EBRT in combination with 9 months of ADT and 122 patients underwent radical prostatectomy with PLND. Patients treated with radiotherapy received 80 Gy in standard fractions of 2 Gy each or a hypofractionated course to 62 Gy in 20 fractions of 3.1 Gy. The target was the prostate and seminal vesicles, with no pelvic lymph-node treatment. The median follow-up was approximately 3 years for each group. This study demonstrated an improvement in 3-year biochemical failure-free survival favouring radiation (86.8% versus 69.8%; \(P = 0.001\)).\(^11\) A significant limitation of this study was the use of biochemical failure as a primary end point. Different definitions of biochemical failure were used for radiotherapy and surgery, causing difficulty in comparing outcome across modalities. Additionally, the 9-month duration of ADT may not have been optimal, as multiple trials have demonstrated a survival benefit for longer-term hormone therapy for 2–3 years. Lastly, because biochemical failures often occur after 4 years, especially in patients receiving ADT, many failures may have been missed with the relatively short follow-up.

The largest retrospective study evaluated patients with cT1c–T3b prostate cancer who underwent either radical prostatectomy with pelvic lymphadenectomy or radiotherapy at MSKCC. Radiation was delivered to the prostate with omission of the pelvic lymph nodes to a total dose of 81–86.4 Gy. ADT for 3–6 months was given in combination with radiation treatment. The 8-year distant metastasis-free survival rate was similar (97% versus 93%) for radical prostatectomy and radiotherapy, respectively, with overlapping confidence intervals. In the high-risk cohort of patients, an absolute benefit of 7.8% in distant metastasis-free survival favoured radical prostatectomy.\(^117\)

Several aspects of the MSKCC study limit comparisons to other studies. Firstly, long-term ADT was not routinely used. The addition of long-term ADT to radiotherapy decreases metastases by 40–50% and improves survival compared with the addition of short-term ADT. Secondly, pelvic lymph-node irradiation was not routinely performed. Patients with high-risk prostate cancer are at increased risk of harbouring microscopic lymph-node involvement, and pelvic lymph-node irradiation is part of treatment for all prospective randomized trials, establishing the role of hormone therapy and radiation in this patient population.\(^42,9,39,44\) Contemporary radiation delivery is now routinely performed using image guidance, which was not available for all patients included in the series when they were treated. Image guidance radiotherapy improves biochemical tumour control in patients with high-risk prostate cancer and is associated with lower rates of urinary toxicity.\(^118\) In addition, the pre-treatment risk profile was worse in the radiation group relative to the radical prostatectomy group with respect to PSA, clinical stage, and Gleason score. Also, patients receiving radiation were less likely to remain disease-free based on the preoperative Kattan nomogram, which predicts for disease recurrence after radical prostatectomy. Future studies should consider using pretreatment nomograms to predict for the 5-year and 10-year probability of distant metastasis\(^119\) rather than biochemical recurrence. An additional consideration was that patients undergoing radical prostatectomy were more likely to undergo early salvage treatment after treatment failure than the radiation cohort. Salvage radiation was offered after failure at 13 months in patients undergoing surgery and after 69 months in patients who underwent radiotherapy.\(^117\) Data demonstrate that the earlier salvage treatment is offered, the greater chance of success. Earlier salvage treatment is associated with improved PFS compared with delayed treatment.\(^119\) The efficacy of salvage brachytherapy in patients with biochemical failures after EBRT (both in terms of disease control and reduced morbidity)
is likely to make physicians more likely to refer, and patients more likely to accept treatment should biochemical failure develop owing to incomplete control of the primary tumour.\textsuperscript{109,123} Salvage radical prostatectomy in this setting is associated with a high rate of incontinence and as such, may be less acceptable to patients.

Retrospective comparisons of survival after radical prostatectomy and radiotherapy are inherently difficult because of selection bias in the general health of men with high-risk disease selected for surgery when compared with those selected for radiation treatment. For example, one study showed that patients with prostate cancer treated with radical prostatectomy had better overall survival than men in the general population who did not have cancer.\textsuperscript{122} A second study showed that death from non-prostate cancer causes was lower in 11,000 men who underwent a radical prostatectomy compared with men in the general population.\textsuperscript{123} Also, patients receiving radiotherapy are more likely to have more advanced T stage disease, Gleason score, and higher PSA.\textsuperscript{75,117,122}

Differences in the definition of biochemical failure in radiation and radical prostatectomy also limit the ability to place results in a more global context. The preferred outcome measures should be distant metastasis-free survival and cause-specific survival. Many studies attempt to account for this selection bias with multivariate regression models and competing risk-regression analysis. The retrospective nature of the studies and the inability to completely account for differences in baseline characteristics between the patient cohorts make meaningful comparisons virtually impossible.

Randomized trials focusing not only on survival but also on quality of life are essential. Currently, the Prostate Testing for Cancer and Treatment (ProtecT) trial is ongoing and hopes to address both survival and quality-of-life questions.\textsuperscript{124} This trial includes patients diagnosed with prostate cancer of all risk categories. However, it is unclear if the trial will successfully address the relative effectiveness of each modality in the high-risk cohort after accrual.

Ultimately, prostate cancer treatment will be individualized for each patient. Current risk stratification tools are inadequate for tailoring therapy, as they only consider tumour characteristics and not patient characteristics, such as comorbidities. Biomarker-driven decision analyses are being developed to predict disease aggressiveness, response to treatment, and toxicity from treatment. Biomarkers might allow better assessment of the benefit versus the toxicity of each treatment, alone or in combination, to guide decisions. Rather than choosing only surgery or radiation treatment, patients with highly aggressive tumours may benefit from surgery, radiation, and ADT, similar to that in other disease sites such as rectal or breast cancer. Furthermore, by accounting for patient comorbidities in addition to tumour characteristics, biomarkers could improve treatment decisions by accounting for the relative risk of death from cancer versus other causes. A multidisciplinary effort between urologists, radiation oncologists, and medical oncologists is critical to improve treatment outcomes. In practice the modality used to treat localized prostate cancer is heavily influenced by the type of treating physician and referral patterns, with <5% of patients seeing all three specialties.\textsuperscript{125,126} For the high-risk patient multidisciplinary consultations and collaborations might not only improve patient satisfaction, but potentially outcomes.\textsuperscript{127–129}

Future directions
Technical advances and refinements in surgical and radiotherapy techniques have enabled the outcomes for patients with ‘high-risk’ prostate cancer to be improved in terms of both cancer control and the reduction of the morbidity associated with treatment.\textsuperscript{32,39,130–132} These improvements have been shown through well-designed and executed clinical trials. Owing to the advances in our understanding of the biology of the disease, in surgical technique, radiation biology, technical advances in radiation delivery, and in systemic therapy, the field is uniquely poised to shift the paradigm even further and to begin to extend the limits of curability beyond what can be achieved with any single or dual-modality approach.

Unfortunately, as the various definitions of high-risk include patients with a wide range of prognoses, published reports reflect a wide range of quality, limiting our ability to establish practice standards based on hard evidence. Clinical trials are experiments with an objective and defined eligibility criteria, intervention, outcomes, statistical methods, and conclusions designed to determine whether that objective has been met. Many reports are retrospective analyses of a particular modality or treatment approach, and these reports differ in the cases treated, determining disease extent, the intervention (radiation portal, dose and dose rate, whether nodal radiation or node dissection was performed), the specifics and the timing of the assessments used to monitor disease following the intervention, the specific outcomes reported, the follow-up period, and the interpretation of the data. Few reports include a clearly defined statistical design, and those that do rarely define a level of improvement that would justify the development of a large-scale definitive trial to generate the evidence required to change practice standards. Care must be taken not to overinterpret results. For example, demonstrating benefit in an analysis of a subset of patients enrolled on a trial is not level I evidence, it is a ‘hypothesis-generating conclusion’ to be studied in future trials.

Optimizing future studies
Redefining high-risk
High-risk disease must ultimately be defined and placed in a clinically meaningful context. For most men, this is represented by control of the primary tumour and treatment of the metastatic disease that is ultimately the major cause of morbidity and mortality from prostate cancer. These outcomes, and the need for treatment, must be balanced against the competing causes of death in this population. Arguably, preventing morbidity by controlling the disease to the point where a patient dies ‘with it’ rather than ‘of it’ can be considered a therapeutic success.
Clinical benefit from a therapeutic intervention is defined in regulatory terms as an improvement in the way a patient feels, functions or how long he survives. The benefit might result from an improvement in disease control or by reducing the toxic effects and morbidities associated with a treatment. Patient-reported outcomes, which are essential for a patient to consider the risk/benefit ratio and to determine the net clinical benefit of an intervention, are rarely included, yet this ratio is of particular importance when considering whether to pursue or to continue a treatment that might have a modest gain in overall survival at the expense of a reduced quality of life. This heterogeneity in both definitions and end points limits the ability to place outcomes in context, determine utility, or to provide clinicians, patients, regulators, and payers with meaningful data.

These difficulties are highlighted in one large retrospective study that compared radical prostatectomy and EBRT. The investigators reported a 10-year prostate cancer-free survival rate of 92% both for patients who underwent radical prostatectomy or EBRT with ADT.\(^7\) High survival rate might underscore the effectiveness of the therapy, but it might also reflect a high-risk definition that is not truly high-risk disease. Traditional clinicopathological variables such as T stage are hindered by inter-clinician judgement, limiting its validity and utility as a biomarker. Gleason score is subject to inter-observer variability, and sampling error, and PSA lacks sensitivity and specificity; these risk factors might simply not be adequate, even in combination. Assessing tumour burden by quantifying the percentage of core involvement, such as with the CAPRA score, has shown enhanced performance for the determination of risk, but is not a paradigm shift. Clinically validated biomarkers to assess risk more reliably based on biological determinants in the tumour itself and that establish an association with an aggressive disease phenotype are needed. Much of the development in this area is being applied to the decision of active surveillance versus treatment for low-risk disease, but the same sensitivity is required to distinguish those patients with high-risk disease so that clinical trials can also address this population of patients (Box 4).

Although few practitioners would disagree that a man with Gleason 10 T3b disease has a significant risk of mortality from his prostate cancer, there are few measures to help identifying a patient with, for example, Gleason 7, T1–T2 disease that may also actually have a similar risk of death from prostate cancer. The pathway to biomarker development is treacherous and under-appreciated. After the biomarker itself is identified comes the analytical validation of the assay, including issues around sample acquisition and processing, and the range of conditions under which the assay provides reproducible and consistent results. Clinical validation requires a series of prospective trials from phase I to phase III focused specifically on the biomarker question. Finally, there is clinical utility, the demonstration that the results of the biomarker test guide the choice of treatment relative to other tests that are currently available and which may be obtained at a significantly reduced cost.

**Box 4 | Principles for trial design and treatment of localized high-risk disease**

**Improving trial design**
- Principle 1: Trials dedicated to the ‘very high-risk’ patient, that is, those with multiple adverse risk features (such as seminal vesicle invasion, Gleason 8–10)
- Principle 2: The identification and incorporation of biomarkers and inclusion of imaging, serum and tissue acquisition into all therapeutic trials, including early-phase studies
- Principle 3: Exploration of intermediate end points given the long natural history of prostate cancer, the duration required to measure overall survival and cancer-specific survival, and the evolving therapeutic landscape in metastatic disease that may affect long-term outcomes

**High-priority prospective comparisons**
- Principle 1: Establish the role of ADT in contemporary dose escalation: ADT plus brachytherapy plus EBRT versus brachytherapy plus EBRT without ADT
- Principle 2: Optimal timing of radiation to prevent and/or treat local recurrence: adjuvant versus salvage RT
- Principle 3: Management of node-positive disease after RP: adjuvant ADT ± other systemic therapy (such as AR-targeted agents) versus adjuvant RT plus ADT versus observation
- Principle 4: Optimal management of locally advanced disease: ADT plus EBRT versus ADT plus other systemic therapy (such as AR-targeted agents) plus EBRT versus surgically based bi-modality therapy (for example, neoadjuvant ADT ± other systemic therapy plus RP)

Abbreviations: ADT, androgen-deprivation therapy; AR, androgen receptor; EBRT, external-beam radiotherapy; RP, radical prostatectomy; RT, radiotherapy.

**Meaningful clinical end points for validation**
Comparing biochemical recurrence rates or PSA relapse-free survival times between surgery and radiation is inherently flawed, because PSA nadirs are achieved at different time points, and patterns of biochemical relapse cannot be reliably compared. PSA relapse-free survival can be considered as a screening end point for a phase II intervention, but does not in itself represent a clinical benefit. The rise in PSA could represent recurrent local disease, locoregional disease, systemic disease or all three. Furthermore, for men who relapse after primary treatment and enter the rising PSA state, only a small proportion require immediate intervention based on their probability of developing metastasis or symptoms or dying of their cancers. More important is the risk of developing metastatic disease, at which point the risk of dying of prostate cancer exceeds that from other causes. It is important that new biomarkers be clinically validated using measures, such as metastasis-free, overall, or prostate cancer-specific survival that more clearly reflect patient benefit. It is important to show that the ‘new’ marker adds predictive accuracy to the currently available risk classification criteria currently in use.\(^4\)\(^6\)\(^7\)

**Therapeutic strategies**
Markers to define high-risk populations need to be standardized and validated to advance the field. Of particular importance is what level of risk would lead a patient or physician to consider an experimental approach relative to the current standard. Once this is estimated, trials can be designed to assess the impact of different therapeutic interventions more reliably, and more-promising approaches can be considered for the phase III
setting. Narrowing the definition of high-risk disease by increasing specificity may lead to a smaller proportion or subset of high-risk patients, but is the only way to generate the evidence needed to establish standards and change practice.

Interventions to improve outcomes for high-risk populations can be given either alone or in combination. Improving on existing modalities is another common approach in clinical trials assessing high-risk disease. For example, investigating the benefit of ePLND with prostatectomy, whole pelvic radiotherapy, use of hypofractionated versus conventional radiotherapy, or lengthening the duration of ADT with radiation have all been evaluated. Use of multi-modality therapy is yet another common approach, such as radical prostatectomy with adjuvant radiation or ADT with EBRT; if the boundary of high-risk disease is pushed to micrometastatic disease, then systemic therapies will likely be a critical aspect to multi-modality therapy.

The development of multi-modality approaches often pursues therapies already proven to be effective in metastatic populations and applies to earlier disease states. The phase II trial of abiraterone with ADT in a neoadjuvant setting before radical prostatectomy is one such example; this trial demonstrated a 30% pathological complete response rate and holds potential to eliminate early castration-resistant clones.135,136 A phase II trial of ADT with the anti-CTLA-4 agent ipilimumab in patients with locally advanced disease found that a higher proportion achieved an undetectable PSA (54% versus 38%) with the addition of ipilimumab.137 In the ongoing CALGB 90203 trial, high-risk patients will be randomly assigned to neoadjuvant ADT with docetaxel or immediate radical prostatectomy, to inform on this potential neoadjuvant strategy.138 Similarly, a series of trials will assess the benefit of adding other systemic therapies to standard ADT and radiation, such as enzalutamide,137 TAK700,138 or taxane chemotherapy.139,140 It will be years before the data have matured to determine if an advantage in overall survival or metastasis-free survival is demonstrated. However, if the population selected is more accurately defined, more homogenous, and shares a higher likelihood of developing prostate cancer-related morbidity or mortality, these end points may be reached sooner. Overall survival and metastasis-free survival are arguably the most clinically relevant end points and the best comparisons for surgery versus radiotherapy, which serve as the backbone for localized disease therapy.

Conclusions
The future of clinical trials in the high-risk population anticipates a paradigm shift, away from the standard risk definitions and design challenges that have limited the existing literature. There are multiple open questions for the field, some of which await follow-up from existing trials and others that will require new trials with new designs. Importantly, however, there is consensus across disciplines that risk stratification is in need of refinement and standardization, and that innovative strategies to optimize care are needed for the truly high-risk patient.

Review criteria
The PubMed database was searched for articles with the following search terms with no limitation on publication date: “prostate cancer” with “high-risk”, “high-risk diagnosis”, or “high-risk treatment”. Data from randomized clinical trials were included whenever possible. The authors used their own judgement about which papers to include from the literature search based on the relevance of the article to the clinical scenario. This Review includes a summary of the authors’ knowledge based on reading the oncology literature as well as guidelines from the American Urological Association, European Association of Urology, American Society of Radiation Oncology, and National Comprehensive Cancer Network.

Advances in robotic (“trifecta”).


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Author contributions

All authors researched the data for the article, contributed substantially to discussion of content, wrote and reviewed and edited the manuscript before submission.