PROSTATE DISEASE

Surgery for high-risk prostate cancer

CHRISTOPHER EDEN

Although most men with high-risk prostate cancer are offered radiotherapy with hormone treatment as a primary treatment option, there is no evidence to suggest that this has any advantages over surgery.

Prostate cancer is the commonest malignancy occurring in men in the UK, with 35,000 new cases being diagnosed per year and 10,000 deaths each year, which roughly equates to one death every hour. High-risk prostate cancer (HRPC) is associated with the highest rates of treatment failure, need for secondary intervention, metastasis and death among patients diagnosed with prostate cancer.

Although various definitions of HRPC have been used in the past, the most commonly used is derived from d’Amico’s risk stratification of prostate cancer, ie a patient with a prostate-specific antigen (PSA) ≥20ng/ml ± a Gleason grade of ≥8 ± a clinical stage of ≥T2c (Table 1).1 Although widespread PSA testing has led to earlier diagnosis of prostate cancer in general (stage migration), HRPC still comprises 20–37 per cent of newly diagnosed prostate malignancies.2

In spite of a lack of randomised controlled trials, most men with prostate cancer associated with high PSA levels, Gleason grades and clinical stage disease receive radiotherapy (RT). This use of RT + HT is based on the assumption that at the time of diagnosis most patients with HRPC will have at least microscopic spread of their tumour and that it is these micrometastases that will be the main determinant of the subsequent clinical course of their disease. However, as the guidelines of both the American Urological Association (AUA)4 and European Association of Urology (EAU)5 confirm, there is no evidence that demonstrates that this path constitutes the best treatment.

The increased detection of prostate cancer at all stages and grades in the PSA era, improved staging technologies, improved surgical techniques that allow wide excision of periprostatic tissues in cases of suspected T3 disease (Figure 1), increased interest in extended pelvic lymphadenectomy (Figure 2), the inevitability of the development of castrate-resistant prostate cancer (CRPC) in patients on HT and the limited life expectancy associated with these patients have all generated increased interest in

---

Table 1. d’Amico’s risk stratification of prostate cancer1

<table>
<thead>
<tr>
<th>Risk</th>
<th>PSA (ng/ml)</th>
<th>Gleason grade</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤10</td>
<td>≤6</td>
<td>T1–2a</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10–20</td>
<td>7</td>
<td>T2b</td>
</tr>
<tr>
<td>High</td>
<td>≥20</td>
<td>≥8</td>
<td>≥T2c</td>
</tr>
</tbody>
</table>

---

Figure 1. Radical prostatectomy specimen in a patient with T3 prostate cancer: the right neurovascular bundle has been preserved and the left neurovascular bundle has been widely excised to achieve a negative surgical resection margin

---

Christopher Eden, MB BS, FRCS(Urol), MS, Consultant Urologist, Royal Surrey County Hospital, Guildford, Surrey; The Prostate Clinic, Old Basing, Hampshire

---

www.trendsinurology.com
surgery as the primary intervention for patients with HRPC.

THE EVIDENCE

Several studies have demonstrated good and durable results in patients with HRPC for both RT + HT \(10^{-11}\) and for surgery,\(12,13\) but the limited number of comparative studies of RT + HT versus surgery performed have all been retrospective and are confounded by varying RT protocols, the ease of detection of treatment failure after surgery on the one hand (a PSA \(\geq 0.2\) ng/ml) and the difficulty in diagnosing radiation failure on the other (either three consecutive rises of PSA [ASTRO definition] or a rise in the post-treatment PSA to the nadir + 2 ng/ml [Phoenix definition]). This inevitably leads to results biased in favour of RT.

These retrospective studies have also suffered from the additional problems of the potential for selection bias, inconsistent definitions, incomplete data and different endpoints. However, two studies stand out in terms of their size and methodology and probably represent the best answer that currently exists to the question of how RT + HT and surgery perform relative to each other for men with HRPC.

Studies comparing surgery with radiotherapy

Zelefsky and colleagues from Baylor College of Medicine and Memorial Sloan-Kettering Cancer Center compared the results of open surgery performed by two experienced, high-volume surgeons versus intensity-modulated radiation therapy (≥81 Gy) + short-term HT (until completion of RT) in 2380 men with cT1c–T3b prostate cancer.\(14\) Endpoints were cancer-specific survival (CSS) and metastasis-free survival (MFS). The median length of follow-up was 5.0 years for RT + HT and 5.1 years for surgery. They found a 2.5 times greater (96.2 versus 91.5 per cent) CSS and a 7.8 per cent lower risk of metastasis in the surgical group at eight years. However, they cautioned that their results might not be applicable to centres with less experienced surgeons. Critics of the study pointed to the discrepancy in the time taken to institute salvage therapy after RT failure (69 months) compared with after surgery (13 months), which confounds the interpretation of MFS, but this is inevitable because of the problems in diagnosing treatment failure after RT.

In a study of 1847 patients with HRPC, Boorjian and colleagues compared the results of surgery (n=1238) with RT (n=609; 344 received HT and 265 did not).\(15\) Patients were treated contemporaneously in one of two high-volume centres and standardised definitions were used to describe the groups. Endpoints were distant metastasis, CSS and all-cause mortality. The study demonstrated an identical 10-year CSS for RT + HT and surgery at 92 per cent. However, the risk of all-cause mortality was greater in patients having RT + HT than in operated patients, reflecting the fact that although both treatment modalities appear equally effective, the excess cardiovascular mortality associated with HT makes this an inferior option overall.

Need for secondary intervention

The greater risk of treatment failure in patients with HRPC increases the likelihood of the need for secondary intervention, either as adjuvant therapy (before evidence of treatment failure) or as salvage treatment (after evidence of treatment failure).

The principal disadvantage of using RT + HT as the first line of treatment in patients with HRPC is the lack of effective salvage options in the form of cryotherapy, high-intensity focused ultrasound and surgery, which usually mandates the use of long-term HT in these patients, many of whom will eventually succumb from CRPC. Conversely, salvage RT is much more effective\(16\) and is better tolerated by patients in terms of its adverse effects than is salvage surgery,\(17\) and given the fact that the best opportunity for curing many patients with HRPC lies in multimodal treatment, ie a combination of surgery, RT and HT,\(18,19\) it makes intuitive sense to offer surgery as the primary intervention to most fit patients with HRPC.
Further trials are necessary to determine the relative performance of surgery for prostate cancer. Surgery allows the determination of a final grade and stage of the tumour, a critical factor in treatment decision making. Pelvic radiotherapy is well tolerated in patients who have recurrent or locally advanced prostate cancer, although recruitment to these trials is likely to remain problematic because of the very different nature of their treatments and the entrenched views of the clinicians who practise them.

KEY POINTS

- The available evidence suggests that surgery and radiotherapy with hormone treatment are equally effective in treating high-risk prostate cancer, but that the excess cardiovascular mortality from hormone treatment may make this a less effective option overall.
- Surgery allows the determination of a final grade and stage of the tumour, a target prostate-specific antigen of zero and the easy and prompt identification of tumour recurrence.
- Multimodal therapy (surgery, radiotherapy and hormone treatment) may represent the best chance of cure for many patients with high-risk prostate cancer.
- Pelvic radiotherapy is well tolerated in patients who have recurrent or residual disease after surgery, whereas salvage surgery after failed radiotherapy has a high complication and failure rate.
- Surgery for high-risk prostate cancer should be performed by experienced surgeons and should include an extended pelvic lymphadenectomy. Patients should be aware of the probability of future adjuvant or salvage treatment.
- Further trials are necessary to determine the relative performance of surgery and radiotherapy as primary treatment options in the management of patients with high-risk prostate cancer, although recruitment to these trials is likely to remain problematic because of the very different nature of their treatments and the entrenched views of the clinicians who practise them.

DECLARATION OF INTERESTS: None declared.

REFERENCES


