Improving the surgical treatment of high-risk localised or locally advanced prostate cancer

ROGER KIRBY, HEATHER PAYNE, VINCENT KHOO, NOEL CLARKE, MARK BERESFORD, CAROLINE MOORE, PHILIPPA ASLETT, AMIT BAHL, RUPESH BHATT, GREG BOUSTEAD AND SIMON BREWSTER

Radiologists, oncologists, urologists and clinical nurse specialists met to evaluate how patients with high-risk localised or locally advanced prostate cancer might be better diagnosed and managed. In the first article in this series, the authors reviewed diagnosis and hormonal and radiotherapy. In this second paper, they evaluate findings from the meeting relating to the surgical management of the disease and how this might be optimised.

The management of patients with high-risk localised or locally advanced disease (stage T3-T4, Nx–N0, M0) is considered one of the most perplexing areas of prostate cancer. Issues relate to the classification of the disease and the optimal treatment decisions for these patients. Current guidelines do not provide a treatment strategy, which is clearly needed.

RADICAL PROSTATECTOMY

There is no consensus on the optimal treatment of men with high-risk prostate cancer; radical prostatectomy is an option provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter (Figure 1). The use of neoadjuvant hormones in this setting is uncertain: the majority of studies have shown a reduction in positive margins but no survival advantage, and research is ongoing in this area.

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Ghavamian et al. reported the combined approach of orchiectomy (within 3 months of radical prostatectomy) plus or minus radical prostatectomy/pelvic lymphadenectomy in a series of patients with pT3N+ treated between 1966 and 1995. This matched-pair study reported an overall survival advantage at 10 years for the combined treatment approach (66% versus 28%; p<0.001) as well as for cause-specific survival (79% versus 39%). However, it is important to be cautious in interpreting non-randomised case series data of this type.

Radical prostatectomy has been compared to observation in a randomised study of men with early prostate cancer (predominantly T2) and shown to reduce disease-specific mortality, overall mortality and the risk of metastases and local progression for up to 10 years. This contrasts with the lack of benefit at 12 years reported by Wilt et al., where a reduction in all-cause mortality was reported only for men with a PSA >10ng/ml and possibly for those with low- or high-risk prostate cancer. Additional support for the use of radical prostatectomy in high-risk prostate cancer patients comes from the Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) registry of 7538 men. Results from the study indicated that radical prostatectomy was associated with a significant and substantial reduction in mortality relative to radiation therapy and to androgen deprivation therapy as monotherapy. The absolute differences between prostatectomy and radiation therapy were small for men at low risk but increased substantially for men at intermediate and high risk.

Table 1. Cumulative incidence of death in men treated with radical prostatectomy. Reproduced with permission from Rader et al. BJU Int 2014;113:541–7

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>5 years</th>
<th>10 years</th>
<th>15 years</th>
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<tr>
<td>Death from any cause</td>
<td>4.9 (4.2–5.7)</td>
<td>15.4 (13.2–17.7)</td>
<td>33 (17.3–48.8)</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.8 (1.6–4)</td>
<td>8.4 (4.9–11.9)</td>
<td>19 (4.2–33.7)</td>
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<td>Intermediate risk</td>
<td>5.4 (4.3–6.5)</td>
<td>12.6 (9.9–15.3)</td>
<td>18.1 (12.4–23.7)</td>
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<td>High risk</td>
<td>6 (4.5–7.5)</td>
<td>21.6 (16.2–27.1)</td>
<td>41.9 (21.2–62.6)</td>
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<td>Death from prostate cancer</td>
<td>1.3 (0.9–1.9)</td>
<td>6.6 (4.9–8.2)</td>
<td>20 (4.5–35.4)</td>
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There have been no randomised studies of the relative effectiveness of radiotherapy and surgery in this setting but there are an increasing number of case series reports suggesting that surgery can be advantageous. Interpretation of these must be with caution because of the inevitable problems of case selection and stage/grade migration. An example of such series is the report of the effect of radical prostatectomy compared with external beam radiotherapy (EBRT) on the rate of distant metastases in 2380 men with localised disease, in a single-centre study by Zelefsky et al. The 8-year probability of freedom from metastatic progression was 97% for radical prostatectomy patients and 93% for EBRT patients. The Kaplan-Meier probability of prostate cancer death at 8 years for low-, intermediate- and high-risk patients was 0, 4.5 and 9.5%, respectively, for radiotherapy patients, and 0, 1.9 and 3.8%, respectively, for surgery patients. Multivariate Cox regression analysis showed that the most significant variable associated with metastatic progression was risk group (high versus lower risk group; p<0.0005) followed by treatment (surgery versus radiotherapy; p<0.001).

Spahn et al. examined pre-treatment outcome predictors in men with PSA >20ng/ml treated with radical prostatectomy in a European multi-institute study of 712 men. The strongest predictor of progression and mortality was biopsy Gleason score; a Gleason score ≤7 resulted in a 10-year prostate-cancer-specific mortality rate of 5% compared with 35% in men with a Gleason score ≥8. Lymph node positivity in patients with a Gleason score >7 was high at around 30%.

Adjuvant treatment: lymphadenectomy

Extended lymphadenectomy is being advocated more widely on the basis of increased node-positive detection, although the effect in relation to curative benefit remains to be determined. A limited pelvic lymph node dissection (PLND) has a lower positive node detection rate than extended lymphadenectomy (eLND). A number of studies have reported the lymph node invasion (LNI) according to the type

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of dissection conducted. Large-scale studies on limited LND report LNI rates of 2–3.7%,15–17 which compares with the rate of 11–26% in ePLND studies.18–20 It is generally accepted that the eLND provides important staging information, but there is no consensus regarding the absolute indications for eLND.2

The European Association of Urology guidelines recommend that eLND is not necessary in low-risk localised prostate cancer, where the risk of lymph node involvement does not exceed 5%.2 However, for intermediate- and high-risk prostate cancer, they state that eLND should be conducted, as the relative risk of lymph node involvement is 5% and 15–40%, respectively. It has been estimated that the removal of ≤10 nodes provides a <10% ability to detect LNI, while removing 28 nodes increases the ability to 90%;21 although, once again, there is no clear evidence to support the notion that this affects long-term outcome.

Nomograms to assist decision making based on preoperative biochemical markers and biopsies are available.17 These suggest that patients with PSA <10ng/ml and biopsy Gleason score <7 have a low risk of lymph node metastasis. A caveat is that the majority of nomograms are based on a limited eLND and consequently they underestimate the incidence of patients with positive nodes.22 In patients with PSA <10ng/ml and Gleason score ≥7, the incidence of nodal involvement has been reported as 25%.23

eLND increases the morbidity associated with prostate cancer treatment: a number of studies have reported a higher rate of complications compared with limited LND,24–26 while others have reported no increase.18,27 Complications include lymphocele, lymphoedema, deep venous thrombosis and a higher rate of pulmonary embolism.

The debate as to whether LND should be conducted routinely at the time of radical prostatectomy was addressed in a population-based cohort study that examined the benefits of LND in 281 patients and matched these against 41 case controls who died of their prostate cancer within 10 years.28 A therapeutic benefit of LND was reported in node-negative patients. However, this study exemplifies the problem of interpreting data of this type because of selection bias and the inevitable ‘Will Rogers’ effect, which may have been responsible itself for the difference in outcome in the two cohorts.

**Postoperative radiotherapy**

Ten-year biochemical recurrence rates of 49–57% after radical prostatectomy in patients with clinical T3 prostate cancer have been reported.7,8,29 Multivariate analysis shows that higher preoperative PSA, clinical stage, estimated tumour volume and pathological Gleason score were factors associated with an increased risk of biochemical recurrence.29 Postoperative radiotherapy may be beneficial in the situation when there are residual prostate cancer cells limited to the prostate bed, although current imaging techniques are unable to identify these patients.

A number of retrospective studies show improved biochemical progression-free survival, but there is less convincing evidence for a benefit in overall survival, metastasis-free or prostate-cancer-specific survival.30–32 As expected, there were more side-effects in the adjuvant radiotherapy groups, including rectal complications, urethral strictures and incontinence, although quality-of-life assessments were similar or better after 2 years. There are not yet any large published comparisons of immediate adjuvant versus early salvage radiotherapy to the prostate bed on biochemical recurrence, but the UK RADICALS trial will address this issue.

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**REFERENCES**


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