Radiotherapy for treating locally-advanced prostate cancer

Prostate cancer in the UK

Prostate cancer is the most common cancer in men in the UK. Around 37,000 men are diagnosed with prostate cancer each year, and 250,000 men are living with the disease. Many men with prostate cancer have a good prognosis, but because of the large number of men with the disease it is an important cause of mortality. 12% of cancer deaths in men are from prostate cancer.

Widespread PSA screening has meant that cases are being diagnosed earlier. However locally advanced prostate cancer remains a common problem. There is controversy about how locally advanced disease should be managed. A recent systematic review found that there is not enough evidence on outcomes from the main treatment options. The different approaches to treatment also have differing side effects. This means that there is uncertainty around how best to treat locally advanced prostate cancer.

Treatment approaches for locally advanced prostate cancer

Several different approaches can be used for treating locally advanced prostate cancer. These include:

- Hormone therapy (Androgen Deprivation Therapy) to control the cancer
- External beam radiotherapy to destroy the cancer cells
- Radical prostatectomy to remove the cancerous cells

These approaches are discussed in more detail below.

The Radiotherapy Dataset Annual Report 2009/2010 highlights considerable inconsistencies in the approach used to treat prostate cancer within England. For example, the percentage of new prostate cancer patients receiving radical radiotherapy ranged from less than 25% in the North of England and Yorkshire cancer networks, to more than 50% in the Surrey, West Sussex and Hampshire cancer network. Some of this variation may be explained by differences in patient characteristics and the case mix between cancer networks. However there may be other factors that influence what treatment patients are offered or take up. This variation is present in other nations: research in the US has also found considerable variation in the treatment approach used for prostate cancer, which is not substantially explained by the disease characteristics.

This variation in treatment approaches may lead to concerns regarding equity. An audit of prostate cancer treatment is planned in the UK. This will provide comparable data on which treatments are being offered and accepted by men, which will help to identify if all men are being given the most effective treatment available.

Key points

- Prostate cancer is the most common cancer in men and causes 12% of male cancer deaths in the UK
- There is inconsistency in how it is treated
- Radiotherapy given in addition to hormone therapy improves the survival of men with locally advanced prostate cancer in randomised controlled trials. Radiotherapy together with hormone therapy should be the standard of care
- More can still be done to determine the optimal treatment strategy for prostate cancer patients. Clinical trials are essential to answering important questions about how to treat prostate cancer

Locally advanced prostate cancer is cancer that has spread to the area just outside the prostate gland, but has not spread to other parts of the body.
Hormone therapy

There is good evidence that hormone therapy in addition to radiotherapy improves both overall and disease-specific survival. Hormone therapy may also improve survival in selected groups of patients if used following prostatectomy. Long-term hormonal therapy is regarded as the mainstay of treatment for locally advanced prostate cancer. The use of hormone therapy alone has risen in the last 20 years. Hormone therapy does increase the risk of diabetes and myocardial infarction, but does not increase the risk of cardiovascular death. Other side effects associated with hormone therapy include erection problems; hot flushes and sweating; breast tenderness; pain; weight gain; mood swings and depression and bone thinning. The optimal duration of hormone therapy is not known. It is likely that life-long treatment may not be needed, but more research into this is required.

External beam radiotherapy

External beam radiotherapy has been used to treat locally advanced prostate cancer for many years. There has been some uncertainty about the contribution of radiotherapy to treatment with a combination of hormone therapy and radiotherapy. Consequently, hormone therapy alone has become a standard of care in many places. A trial carried out in the 1980s attempted to compare radiotherapy alone with orchectomy (irreversible hormone therapy) alone, with orchectomy and radiotherapy together. However this trial was small and did not find any evidence of differences in local disease control or overall survival between the three arms. Two randomised controlled trials have now published results testing the addition of radiotherapy to hormone therapy alone, both showing that the addition of radiotherapy significantly improves overall and disease-specific survival. Evidence of effectiveness: The SPCG-7/SFUO-3 trial

The SPCG-7/SFUO-3 trial randomised 875 patients with locally advanced prostate cancer to hormone treatment alone or hormone treatment combined with radiotherapy. The study found that the addition of local radiotherapy to hormone treatment halved the 10-year prostate-cancer-specific mortality and decreased overall mortality by 32% in relative terms. The hormone therapy used in the trial was unconventional by UK standards (three months of total androgen blockade followed by flutamide), but it is likely that the benefits seen for radiotherapy would also be seen for standard hormone therapy. Evidence of effectiveness: The PR.3/PR07 trial

The PR.3/PR07 trial randomised 1,205 patients to receive hormone therapy alone or hormone therapy and radiotherapy. Interim results from this study found that the addition of radiotherapy to hormone therapy reduced the risk of death after seven years by 23%. It reduced the risk of death from prostate cancer by 46%, and reduced disease progression by 70%. Figure 1 shows the number of men alive or dead after 7 years for those treated with hormone therapy alone compared to those who also received radiotherapy. Patients entering the PR.3/PR07 trial had more advanced disease than those entering the SPCG-7/SFUO-3 trial. The hormone therapy used in PR.3/PR07 was standard hormone therapy with LHRH analogues. Despite these differences, both trials show that the addition of radiotherapy to hormone therapy significantly improves the survival of men with locally advanced prostate cancer. Recent changes in radiotherapy techniques

Radiotherapy treatment techniques have improved dramatically since the protocols for the SPCG-7/SFUO-3 and PR.3/PR07 trials were developed. Advances in the ability to shape beams to match the tumour and modulate the intensity of the dose, mean that higher doses can now be delivered to the target volume than were used in these two trials. This increases the probability of controlling the tumour. It is possible that the improvements in survival with the addition of radiotherapy that were seen in these two trials could be greater with the use of modern radiotherapy techniques.

Side effects

Both SPCG-7/SFUO-3 and PR.3/PR07 found that there was an increase in non-severe gastrointestinal side-effects for those men who had radiotherapy. Severe side-effects were uncommon. PR.3/PR07 found that the negative impact of radiotherapy on bowel function disappeared by 36 months to match that of the men who received hormone therapy alone. These results suggest that concern about side-effects do not justify withholding treatment. Feasibility

Using radiotherapy in addition to hormone therapy to treat locally advanced prostate cancer is feasible. The facilities and equipment needed to deliver the treatment already exist, and the radiotherapy techniques involved are not new. The National Audit Office found that the average number of patients being treated per linear accelerator was 6,670 fractions per year, (varying from 4,100 to 9,700) which is considerably lower than the target of 8,700 fractions per year, indicating that there is under-used equipment capacity in some places.

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Potential Impact

If all men with locally advanced prostate cancer who are currently treated with hormone therapy alone were to receive radiotherapy in addition to hormone therapy, this could reduce the risk of death from any cause by almost a quarter. For every 13 men treated with radiotherapy in addition to hormone therapy, an extra life is saved compared to if they had received hormone therapy alone.

A combination of radiotherapy and hormone therapy should be offered to all patients suitable for a curative treatment approach.

Radical prostatectomy

Surgical techniques have improved in the last two decades, making surgery more effective than it used to be for treating locally-advanced prostate cancer, and reducing the side-effects (such as urinary incontinence) associated with prostatectomy. There is evidence that the addition of external beam radiotherapy may improve overall survival and disease-free survival of men treated with radical prostatectomy, compared with prostatectomy alone. However there are no good data comparing radiotherapy with radical prostatectomy for locally advanced disease. Several trials have attempted to look at this, but have been closed due to problems recruiting patients. The ProtecT trial will provide some answers in the future, but only for patients with earlier-stage disease. In the meantime, treatment decisions must be made based on the evidence that is currently available.

Determining the optimal treatment strategy

The SPCG-7/SFUO-3 and PR.3/PR07 trials provide strong, clear evidence that using a combination of radiotherapy and hormone therapy can considerably improve the survival of men with locally advanced prostate cancer, compared to hormone therapy alone. However there are still many questions that remain about what the optimal treatment strategies are for prostate cancer. Clinical trials are essential to answering these questions. Examples of prostate cancer trials that are currently ongoing include:

- **STAMPEDE**: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: this trial is examining the effectiveness of docetaxel, zoledronic acid, celecoxib and abiraterone at increasing survival.

- **RADICALS**: Radiotherapy and Androgen Deprivation In Combination After Local Surgery. This trial aims to decide whether it’s best to give men radiotherapy straight after surgery, or wait until there are signs that the cancer may be growing again. The trial also aims to decide whether a man having radiotherapy at any time after surgery should also have hormone therapy and if so, for how long.

- **PATCH (MRC PR09)**: A randomised controlled trial of transcutaneous oestrogen patches versus LHRH analogues in prostate cancer. This study is examining whether oestrogen patches can effectively shrink tumours while not having the bone-thinning effects of other hormone therapies for prostate cancer.

Trials like these are fundamental to improving prostate cancer treatment. Clear results will only emerge if men with prostate cancer volunteer to take part in trials. All men with prostate cancer should be given information about trials they are eligible for, the potential benefits and risks, and encouraged to consider enrolling.
RECOMMENDATIONS

• A combination of radiotherapy and hormone therapy should be offered to all patients with locally advanced prostate cancer suitable for a curative treatment approach. This approach uses a currently available, non-experimental treatment method.

• The advice given to men on which treatments they should have should be determined by the best available evidence on what works for the specific tumour and patient characteristics.

• Clinical trials are essential for determining the optimal treatment strategy for prostate cancer, and patients should be encouraged to enrol if eligible.

Recommended reading


http://ncat.nhs.uk/sites/default/files/RTDS%20Annual%20Report%202009%202010_0.pdf


Wikibooks Radiation Oncology/Prostate/Localized Prostate Cancer webpage accessed 7th September 2011

http://en.wikibooks.org/wiki/Radiation_Oncology/Prostate/Localized_Prostate_Cancer#Surgery_vs_RT

Credits

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