This report contains the first eight web pages of the web site

www.prostate-cancer-radiotherapy.org.uk

in an Adobe Acrobat pdf format. These are the pages that contain the ‘meat’ of the web site.

I have not converted them from the web page structure so that there are links that will obviously not work in the document and there are references to web pages that you can only access from the web site. However, it will certainly be easier to print and browse through this single document rather than read the contents on a computer screen.

As far as references are concerned, there are thousands of papers on the treatment of prostate cancer by external beam radiotherapy and I have only included those papers that are directly relevant to the web page contents.

L.J.S.Bradbury

Updated 9th November 2005
1. Summary and website contents.

*Patients deserve and need access to accurate, timely and understandable information on their health service.*
*(Patient empowerment and public participation - UK General Practitioners Committee Report 2001)*

**SUMMARY.**
This website is for men with prostate cancer and their families who want to know more about its treatment with external beam radiotherapy (EBRT). Although there is an increasing number of treatment options for prostate cancer, external beam radiotherapy is and will remain a mainstay therapy for sometime to come and this website is intended to give patients information about possible improvements to this method of treatment so that when they discuss their case with their consultant, they can actively engage in a dialogue about the options open to them. The site is biased towards the UK NHS service but the discussion has general applicability. It is recommended that a visitor to this site be reasonably familiar with the general terminology of prostate cancer and there is a web page of links which lists books and websites where this can be obtained. However, important terms are defined either as they are introduced or in a series of pop-up windows that can be accessed by a left click of the mouse button.

Prostate cancer is one of the biggest killers of men today and, in a recent submission to the UK House of Commons Public Accounts Committee (April 2005), Sir Nigel Crisp (NHS CEO) and Professor Michael Richards (National Cancer Director) acknowledged that progress with treating the disease was lagging behind that of other forms of cancer. Changing this situation requires action mainly from the medical profession but patients can and should play a part in this too. The "NHS Expert Patient Programme" is an NHS initiative concerned with empowering patients. Empowerment arises from patients educating themselves to become sufficiently expert in their disease so that they may actively participate in a dialogue with their medical carers about their treatment and also to enable them to apply pressure in whatever ways are appropriate to improve the quality of the service that they receive.

This website arises out of my own experience as a prostate cancer patient and it focuses on the primary treatment of prostate cancer by external beam radiotherapy (EBRT). Of the 30,000 or so men diagnosed in the UK each year with prostate cancer, about 6,000 are treated with EBRT and a similar number undergo surgery. For those treated by EBRT, the overall probability of remaining disease free over a ten year period is only around 50% and this website focuses on possible improvements that could be made to this form of treatment to improve this situation.

Although there is no 'standard' treatment for prostate cancer with EBRT, a common treatment regime has emerged over time that is based on giving a total dose of radiation of 70 Gray delivered in daily 2 Gray doses or fractions. There is good evidence that significant improvements on this treatment can be made: by combining EBRT with hormone therapies; by increasing the total dose above the 'standard' 70 Gray; and, more radically, by increasing the daily dose fraction above the 'standard' 2 Gray - this is called hypofractionation. These issues are discussed on separate web pages and are primarily...
aimed at patients. Medical practitioners and researchers may find the content of value too. There are new review papers that cover the content in more detail - web pages 10, 11 and 12.

The website pages are accessed from the navigation menu on the left hand side of each web page. The web pages are numbered so that they can be referenced from one another.

Before discussing possible improvements in treatment, there is a discussion in web page 2 on what constitutes 'standard' radiotherapy treatment and the patient parameters that make external beam radiotherapy a suitable option.

The issues that are discussed are

(1) the interaction between hormone therapies and radiotherapy - web page 3.
(2) escalating the overall dose above the 'standard' 70Gy level - web page 4.
(3) increasing the daily fraction above the 'standard' 2Gy level - web page 5.
(4) the side-effects from external beam radiotherapy - web page 6
(5) the behaviour of PSA measurements after radiotherapy including PSA bounce - web page 7.

There is also a checklist (web page 8) that is intended as a guide to the sort of questions that a patient might ask of his consultant. In my experience, most consultants are quite prepared to discuss these questions and, indeed, will modify details of the treatment if they think the changes are clinically reasonable. If you don't ask, you may not 'get!' The primary treatment you receive for prostate cancer is the best chance you have of overcoming the disease and so it is vital that you make sure that this is as effective as possible. There is no room for reticence here.

On web page 9, there is a Microsoft Excel spreadsheet that can be run or downloaded to estimate the long-term disease free survival probability for a range of radiotherapy scenarios including EBRT, permanent seed brachytherapy and combinations of the two. This 'calculator' is based on work described in the REVIEW 2 (web page 11).

It should be noted that it is not the aim of this website to provide general information on prostate cancer. There are thousands of internet sites and books on prostate cancer and it is assumed that anyone using this site will be familiar with the general terminology of prostate cancer and its treatment. A list of books and links to websites that can provide this general information is given in web page 13.

On web page 14, I include some details of my own prostate cancer history which is still an ongoing story.

Also, the relative merits of external beam radiotherapy as compared to, say, low dose rate brachytherapy and surgery are not discussed. It is assumed that a patient has already opted - for whatever reason - to accept external beam radiotherapy. I am not even necessarily advocating EBRT because there is no clear winner in choosing a treatment therapy for prostate cancer. They all have their pros and cons and the reasons to choose one rather than another is a difficult decision that may have many factors in it including personal preferences. On the other hand, EBRT is a mainstay form of therapy and, at its best, it offers treatment outcomes that are comparable with other forms of treatment. The prospects are that EBRT can be improved significantly with developments such as: intensity modulated radiotherapy (IMRT); hypofractionation; tracking and targeting of the prostate gland during treatment; and synergy with drug therapies.
Finally, I should stress that the opinions in this site are my own. I am a patient rather than a medical practitioner but I have spent a lifetime in multi-disciplinary research and many of the types of problems associated with EBRT occur in other fields with which I am familiar.

L.J.S.Bradbury
(12th October 2005)
2. The basics of external beam radiotherapy and the 'standard' prostate cancer treatment.

They sought it with thimbles, they sought it with care; They pursued it with forks and hope; They threatened its life with a railway share; They charmed it with smiles and soap.

(The Hunting of the Snark - Lewis Carroll)

SUMMARY.
This web page describes the general principles of external beam radiotherapy and, in particular, the forms of EBRT most commonly in use - namely three-dimensional conformal radiotherapy (3-D CRT) and, increasingly, intensity modulated radiotherapy (IMRT). Conventional EBRT uses high energy photons as the form of radiation. There are other forms of radiation therapy using protons and neutrons but these are not routinely available in the UK and so 'conventional' EBRT will remain an important mainstay therapy for some time to come.

SUITABILITY FOR EXTERNAL BEAM RADIOTHERAPY.
The essential requirement to be a suitable candidate for radiotherapy of the prostate is that the disease has not spread from the prostate or the area immediately around it to sites remote from the prostate - i.e. the disease has not metastasized. This is established from a bone and CT scan carried out soon after a biopsy confirming the presence of prostate cancer.

The earlier prostate cancer is diagnosed, the better the chances of successfully treating the disease. From the diagnostic parameters, a level of risk can be defined. A patient at 'low' risk would have the following parameters; PSA less than 10, Gleason score less than 7 and a T-staging less than T2a. If any one of these was exceeded, the patient would be described as being at an 'intermediate' stage of risk and, if two parameters were exceeded, the risk would be assessed as 'high'. Using the Partin tables for a 'low' risk patient, there would only be a small probability (less than 5%) of the cancer having spread outside of the prostate to the seminal vesicles or the lymph nodes. This is referred to as 'locally confined' prostate cancer although this is a sort of statistical definition. For an 'intermediate' risk patient, the probability of seminal vesicle or lymph node involvement is higher at around the 15% to 20% level and for a 'high' risk patient, say, with a PSA of 20, Gleason 4+3 and a t-staging of T2b, the probability rises to around the 40% level. The disease is then referred to as 'locally advanced'. For low risk patients, external beam radiotherapy would be one of several treatment options that were available - others being surgery, brachytherapy on its own, cryosurgery and, more recently, high intensity focused ultrasound (HIFU). However, for patients at an 'intermediate' or 'high' level of risk, the options are fewer and EBRT along with brachytherapy (either low dose rate permanent seeds or high dose rate temporary seeds) combined with EBRT become almost the only options because, with EBRT, it is possible to extend the field of radiation to treat the region beyond the prostate in ways that are not possible with some of the other therapies. Of course, as will be shown in web page 4 on dose escalation, the probability of remaining disease free is diminished as the level of risk rises.

UNITS OF RADIATION AND THE 'STANDARD' RADIATION DOSE.
The unit in which radiation dose is most commonly measured is the Gray (abbreviated to Gy) after the British radiation physicist Louis Harold Gray. Its precise definition is not particularly important for present purposes but, for completeness, one Gray is the absorption of one joule of radiation energy by one kilogram of matter. In the case of prostate cancer, the most common dose given in external beam radiotherapy is 70 Gy delivered in short duration doses of 2 Gy per day. These short doses are given over a period of tens of seconds only and are
called acute fractions. Treatment lasts 35 days but because no treatment is given at the weekends, the overall period of treatment is 7 weeks. Prostate cancer is generally a slowly developing cancer where the number of cancer cells doubles only over a period of months possibly even years. As a result, missing treatment at the weekends is not of any great importance. For other cancers where the doubling time can be measured in days, this is more problematic.

The choice of 70 Gy given in 2 Gy fractions seems to have emerged over time as a reasonable compromise between achieving good tumour control (i.e. destroying the cancerous tissue) and avoiding serious short or long term side effects. However, the technology of the era from which it emerged has been superseded by better technologies and this 'standard' treatment now needs to be carefully re-evaluated. One of the aims of this website is to draw patients attention to these changes so that they can discuss their treatment with their consultant more knowledgeably.

THE BASIC PROBLEM.
The sketch below shows a simplified but roughly to scale diagram of the prostate in relation to the bladder and the rectum. One sketch shows a side view and the other is a transverse slice through the body. The basic problem in external beam radiotherapy is to be able to subject the prostate to beams of radiation consisting of streams of high energy particles (photons) so that the prostate receives a sufficiently high dose of radiation to destroy the cancerous tissue without serious damage being inflicted on the surrounding organs - the rectum being the most sensitive to damage. It is clear that this cannot be achieved with a single beam because the organs in front of and behind the prostate would receive more or less the same level of radiation as the prostate.

3-D CONFORMAL RADIOTHERAPY.
To avoid this problem, beams are directed at the prostate from several angles and the second sketch shows a simple 3-beam arrangement with a frontal beam and two lateral beams. Where the beams intersect is the region of highest radiation intensity and this is centred on the prostate.
To improve the concentration of radiation further, the beam cross-sectional shapes are conformed to the outline of the prostate (with some margin around it typically of about 10mm) by passing the beam through a multileaf collimator. Below is shown a sketch of such a device which consists of 20 to 40 pairs of Tungsten leaves that can be individually positioned to the outline shape of the prostate seen from the direction of the beam. Information about the three-dimensional shape of the prostate is obtained from a CT scan taken just prior to the radiation treatment.

The photograph below shows a linear accelerator (linac) used to deliver a beam of radiation. The patient lies on the couch and the beam of radiation is directed at the prostate gland from the head of the linac which also contains the multileaf collimator. The whole head unit can be rotated so that beams can be directed at the prostate from different angles.

The process of optimising and calculating the radiation that is delivered by the linac is a complex one and is carried out by specialised computer software. In the example above, only three beam angles were used but five beam angles is also a common geometry. The final output from the whole process is a so-called planning chart which shows the contours of equal strength radiation that occur in and around the prostate and the aim is to maximise the radiation level directed at the prostate gland whilst minimising the radiation to which the surrounding organs are subjected. The figure below is an example of a planning chart showing the target area for the highest levels of radiation and the contours of radiation at lower levels. The position of the rectum is also shown. Even with 3-D conformal radiotherapy,
it is impossible to avoid some part of the rectum being subjected to high levels of radiation and this is the source of rectal bleeding that sometimes occurs after treatment. However, at radiation levels between 70 and 80 Gy, it is quite rare and only affects about one or two percent of patients. By the same token, serious urinary problems are equally rare although around 40% of men will experience temporary urinary urgency or stinging either during or soon after treatment.

INTENSITY MODULATED RADIOTHERAPY (IMRT)
One of the weaknesses of 3-D conformal radiotherapy is that it is not possible to have three dimensional indentations in the surfaces of equal radiation dose. This is because the intensity of the radiation across the beam is constant. A refinement in technique that allows these three dimensional concave surfaces to be developed is intensity modulated radiotherapy - IMRT. In IMRT, there is an additional freedom to control the intensity distribution across the beam. This is achieved by dynamically adjusting the collimator during the exposure time and this is equivalent to producing a variable intensity beam. The addition of this extra freedom allows the radiation contours to be fitted more closely around the prostate and, in particular, to curve them inwards around the rectum thus reducing the extraneous radiation to which the rectum would otherwise be subjected. As a result, for a given radiation dose, the damage to adjacent organs will be lower or, more importantly, higher radiation doses can be delivered to the prostate without adversely affecting the damage to the rectum and bladder.

The sketch below is an illustration of the sort of intensity profiles that would produce a closer fitting of the radiation contours to the prostate. Intuitively, it is clear that beams of constant intensity could not achieve the same sort of 'fit' as beams of variable intensity.
Although IMRT can be thought of as an incremental improvement on 3-D conformal radiotherapy, it involves substantially more computing to produce the optimum beam angles and intensity profiles. As a result, the number of beam angles tends to be greater than is the case with 3-D conformal radiotherapy and as many as 7 beam angles are used with IMRT. The linear accelerator also has to be capable of dynamically controlling the positions of the Tungsten leaves in the collimator. Nevertheless, an increasing number of NHS Trusts are being equipped with both the hardware and the software for undertaking intensity modulated radiotherapy.

MONITORING THE MOVEMENT OF THE PROSTATE.
There have been a number of studies of the movement of the prostate over the period of radiotherapy treatment. Generally, this movement is just a few millimetres but occasionally it can be larger than this with movements of around 10mm or more being reported. Generally, a margin in the targeted field of 10mm around the prostate is sufficient to ensure that the prostate remains within the high intensity radiation pattern. However, with the increasing accuracy of dose delivery that can be achieved with techniques like IMRT, it begins to be important to monitor the movement of the prostate during the treatment period. There are a variety of techniques for doing this and some are already commercially available like the ultrasonic technique referred to as the BAT system. With this system, ultrasonic images of the prostate are obtained prior to each treatment session and movements of the prostate are compensated for on every daily radiation treatment.
3. The interaction between external beam radiotherapy and hormone therapies.

The whole is greater than the sum of the parts.

SUMMARY
The outcome of external beam radiotherapy is significantly enhanced if the radiotherapy is given in conjunction with hormone therapy. The addition of hormone therapy benefits both disease free survival and overall survival. These drugs are usually given for a period of two or three months before the start of radiation therapy and continued during and after the radiation treatment. Drugs given before the radiotherapy seem to have little impact on disease free survival but those taken during and after radiotherapy have a significant effect. The period of drug treatment after the end of radiotherapy may only need to be a few months for men at a low or intermediate level of risk but a conservative approach would be to continue them for, say, six months to a year. For high risk patients, the period may need to be longer. Most of the data on hormone therapies relate to the use of LHRH agonists like Zoladex and although the less toxic anti-androgen Casodex seems to have a similar effect on disease free survival, it doesn't appear from data published so far to confer any overall survival benefit. This is not the case with Zoladex. At the end of this web page, there are some conjectural comments on the use of Casodex.

The use of hormone therapy in conjunction with external beam radiotherapy is emerging as an important contributor to improving the overall efficacy of radiation treatment. The two principal types of hormone therapy in use are goserelin (trade name of Zoladex) and bicalutamide (trade name of Casodex). However, the action of the two drugs and their side-effects are quite different. Goserelin is known as an LHRH agonist and its action is effectively to chemically castrate the patient and cause the testosterone level in the blood to fall to a low value. Bicalutamide is known as an anti-androgen and is a drug that has similarities to testosterone and it locks into the receptors on those cells that require testosterone and thus prevents testosterone reaching the cells. The effect of both drugs is similar in that they slow the rate of replication of prostate cells that are sensitive to testosterone and they also reduce the size of the prostate gland.

Before discussing the interaction between hormones and radiotherapy, three common terms need to be defined. Neo-adjuvant hormone use means taking the hormones before the start of radiotherapy. Concurrent hormone use is taking the hormones during radiotherapy and adjuvant hormone use is taking the hormones following radiotherapy. Most of the detailed results on the interaction of hormones with radiotherapy have been using goserelin (Zoladex) and the comments below apply to that hormone only. The effect of concurrent and adjuvant use of hormones will be discussed first because their effects seem to be the most significant.

CONCURRENT AND ADJUVANT HORMONE USE FOR MEN AT A LOW OR INTERMEDIATE LEVEL OF RISK.
Contrary to earlier ideas, neo-adjuvant hormones seem to have little impact on treatment efficacy and it is concurrent and adjuvant use that seems to have a major effect both on disease free survival and overall survival. It is difficult often to compare the results of trials on hormones and radiotherapy because they are carried out on dissimilar patient groups but work by Bolla and colleagues (2002) and D'Amico and colleagues (2004) are sufficiently similar in this respect that the results can be compared. In the case of the D'Amico trial, the average pre-treatment PSA was 11 ng/ml with the majority of the patients having a Gleason score of 7 and a t-staging of T1c to T2a. This is similar to the group defined by Bolla as being at an intermediate stage of risk. In both cases, the trial consisted of several hundred patients split into two groups. One of the groups received just external beam radiotherapy with a total dose of 70 Gy delivered in daily
fractions either equal to or close to 2 Gy per day. The other group received the same radiotherapy dose but were also treated with hormones in the form of LHRH agonists (mainly Zoladex). However, whereas Bolla’s group continued the hormone therapy for three years after the radiation treatment, D’Amico continued hormone therapy for only two months after the end of the radiotherapy. The table below summarises the differences in the hormone treatments.

<table>
<thead>
<tr>
<th>Trial size</th>
<th>Neo-adjuvant. (Before ebrt)</th>
<th>Concurrent (During ebrt)</th>
<th>Adjuvant (After ebrt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolla et al (2002)</td>
<td>195</td>
<td>No</td>
<td>Yes - 2 months</td>
</tr>
</tbody>
</table>

The graph below shows the effects of hormones combined with radiotherapy on disease free survival as compared with radiotherapy alone. Failure of treatment was defined slightly differently in the two trials. In Bolla’s case, it was taken as a PSA greater than 1.5 ng/ml and two consecutive increases in PSA. In D’Amico’s case, it was taken to be a PSA of greater than 1.0 ng/ml and two consecutive increases of more than 0.2 ng/ml. However, these differences in definition of failure will not alter significantly the general conclusions that can be drawn from the results shown in the figure. The first and most important point is that the probability of disease free survival is very significantly improved by the use of concurrent and adjuvant hormones. The second and even more surprising result is that there does not seem to be too much difference between the results when adjuvant hormones were taken for three years after treatment and just two months after treatment. Since Zoladex leads to a significant loss of quality of life, this is a significant finding. If Zoladex had only to be taken for even, say, six months after the end of ebrt, many would be able to accept this more stoically than taking it for three years.

Whilst there are different definitions of treatment failure, there are no uncertainties about death in overall survival data. The figure below shows the D’Amico trial data for overall survival and it again demonstrates the favourable influence of combining concurrent and adjuvant hormones with external beam radiotherapy. The actual survival figures are interesting too. There were 103 men in the radiotherapy only group. In the six year period, 6 died from prostate cancer whilst 17 died from other causes (heart disease being the most common). In the radiotherapy with hormones group, there were 98 men and
none of these died from prostate cancer in the six year period but there were 12 deaths from other causes (heart disease again being the most common).

The figure below shows the overall survival data from the Bolla trial. It is important to note that whereas Bolla gave disease free survival data for intermediate risk patients, his overall survival data contained all patient groups including those at a high risk. This is almost certainly why the survival data are more unfavourable than the result from the D'Amico trial. Nevertheless, it once again shows that concurrent and adjuvant hormones combine with radiotherapy to produce better treatment outcome than radiotherapy alone.

REFERENCES.
*Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial.*

*6-month androgen suppression plus radiation therapy versus radiation therapy alone for*
patients with clinically localised prostate cancer.

CONCURRENT AND ADJUVANT HORMONE USE FOR MEN AT A HIGHER LEVEL OF RISK.
A trial of 945 men has also been carried out in the US on patients at a higher level of risk with palpable tumours at a T3 stage and/or evidence of spread to the lymph nodes. This trial was conducted by the Radiation Therapy Oncology Group and was called trial 85-31 (Pilepich and colleagues(2005)). The men received typically 65 Gy of radiation in 1.8 to 2 Gy fractions. About half the group were given adjuvant Zoladex started during the last week of radiotherapy and continued indefinitely thereafter. The other half only received hormone therapy when they showed signs of disease relapse. The figure below shows a clear survival benefit for those receiving hormone therapy as an immediate adjuvant to the radiotherapy. It is important to emphasise that the majority of the deaths in both arms of the trial were from causes other than prostate cancer. From the data in the original paper, 477 men were in the group who had Zoladex immediately after the radiotherapy and, of these, 269 had died at ten years but only 82 from prostate cancer. The figures for the other group are 468 men of whom 306 had died at ten years with 113 dying from prostate cancer.

In view of the result of D'Amico and Bolla, it is possible that the same benefit might have arisen even if the adjuvant hormones were given for a period of just a year or two. Evidence in support of this can be found in an analysis of about 300 patients treated in Canada with radiotherapy with a dose ranging from 66 to 72 Gys. The average pre-treatment PSA for the whole group was about 33 ng/ml so that these men were within a high risk group. About half the men had hormone therapies whose average duration was about 6 months (i.e. the less than 12 months group) whereas the other half had hormone therapies extending for an average of about 33 months. Precise details of the hormone therapies are given in the paper (Berthelet and colleagues(2005)) but, in the short period group, the hormones were mainly either neo-adjuvant or neo-adjuvant and concurrent. In the longer period group, it was neo-adjuvant, concurrent and adjuvant use. The figure below shows the overall survival data for the two groups and shows a survival benefit from the longer period of hormone therapy.
It seems clear that it is the adjuvant use of hormone therapy that brings the main benefits and there seems to be some synergy between the hormone therapies and the radiation treatment. As to the optimum length of adjuvant use, it may be that this is a function of the patient pre-treatment parameters and that low risk patients may get most of the benefit from just a few months of adjuvant therapy whereas longer periods may be appropriate for men at a higher level of risk.

REFERENCES.

Long-term androgen deprivation therapy improves survival in prostate cancer patients presenting with prostate-specific antigen levels > 20ng/ml.

NEO-ADJUVANT HORMONE USE.
In terms of a long term improvement in either the probability of overall survival or the probability of disease recurrence, the influence of neo-adjuvant hormones seems at best to be weak. In fact, in the case of permanent seed brachytherapy, there is even a suggestion that it diminishes long term survival - Beyer and colleagues (2005). However, in the case of EBRT, there is still probably an advantage in using neo-adjuvant hormones because they shrink the prostate and so make it a more compact target which, in turn, may reduce the degree to which the rectum is subject to a high dose of radiation. From Canadian work (Crook and colleagues (2004)), it seems that three months of neo-adjuvant Zoladex reduces the prostate volume to about 70% of its original volume. The linear dimensions of the prostate will be reduced by about 10%. The sketch shows a cross-section through the body with the prostate and rectum roughly to scale. The effect of reducing the volume to around 70% is shown. Whilst this reduction may seem small, it will affect the extent of the rectum that is exposed to high levels of radiation although by what percentage is difficult to estimate until the beam angles and beam geometries are specified.
The same Canadian work also included results from 8 months of neo-adjuvant hormones and although this resulted in a greater prostate volume reduction to about 50%, no long term benefit over 3 months use was found in disease free survival.

REFERENCES.
Beyer D.C., McKeough T., Thomas T (2005)
Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy.
Int.J.Radiation Oncology Biol. Phys., Vol.61, No.5, pp.1299-1305

Report of a multicenter Canadian phase III randomized trial of 3 months versus 8 months neoadjuvant androgen deprivation before standard-dose radiotherapy for clinically localized prostate cancer.

THE USE OF CASODEX RATHER THAN ZOLADEX AS THE PRIMARY ADJUVANT HORMONE.
The side effects from the anti-androgen Casodex are not as unpleasant as those of LHRH agonists like Zoladex so it is an attractive alternative hormone therapy. However, detailed data on its use with external beam radiotherapy have not yet been published although a very large trial (See et al(2002)) on the general use of Casodex has been carried out which contained 1370 patient who received Casodex at 150mg per day as the primary adjuvant hormone used in conjunction with external beam radiotherapy. A later report (Wirth et al (2005)) on one of the trial groups with an initial average PSA of 11.7 ng/ml (trial 24) showed that whereas the use of Casodex improved disease free survival, it did not increase overall survival. Although fewer died of prostate cancer in the Casodex group compared with the placebo control group, there was an increase of non-prostate cancer deaths in the Casodex group so that the overall mortality was statistically the same. The problem with the trial is that most of the patients were treated either by radical prostatectomy or watchful waiting and the results for those treated by radiotherapy were not reported separately. It is just possible that the effect of Casodex on overall survival might be treatment specific but until the data for radiotherapy is reported separately, a question mark must hang over the effect of Casodex on overall survival. This does not seem to be the case with Zoladex where there seems to be a clear survival benefit.

It should also be noted that Casodex was taken for a period of five years in the trial. In view of the results of the Zoladex trials shown earlier, it is possible that the beneficial effects of Casodex on disease free survival might have been achieved with a shorter period of use and, with this shorter period, the increase in non-prostate cancer deaths
might have been reduced. The use of Casodex clearly requires further study in order to optimise its potential benefits.

One final point should be made. Whereas Casodex taken over five years led to an increase in non-prostate cancer deaths in trial 24 in the Worth et al (2005) paper, there is a hint in the results shown earlier on the adjuvant use of Zoladex that this drug might not only reduce prostate cancer deaths but reduce also the non-prostate cancer deaths. This can be seen in both the D'Amico trial results and the RTOG 85-31 trial results. A proper statistical analysis would be necessary to check on the significance of the actual numbers. With Zoladex, blood testosterone levels are reduced to castration levels whereas, with Casodex, blood testosterone levels apparently increase slightly. It is impossible not to conjecture on whether or not it is this most obvious of differences that causes the differences in non-prostate cancer deaths behaviour.

REFERENCES.
Bicalutamide as immediate therapy either alone or as an adjuvant to standard care of patients with localised or locally advanced prostate cancer: first analysis of the early prostate cancer program.

Bicalutamide (‘Casodex’) 150mg in addition to standard care in patients with non-metastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme.
Prostate Cancer and Prostatic Disease, Vol.8, No.2, pp.194-200.
4. The effect of escalating the overall dose level.

*Moderation is a fatal thing. . . . Nothing succeeds like excess.*
*(Oscar Wilde)*

**SUMMARY.**
The 'standard' dose in external beam radiotherapy is 70 Gy but, with 3-D conformal or intensity modulated radiotherapy, it is possible to deliver higher doses than this whilst maintaining acceptable side-effect levels. There is a significant gain in the probability of disease free survival by increasing the dose to somewhere between 76 and 80 Gy; the beneficial effect is significant for patients at all levels of risk although it is most marked for high risk patients.

With this increase in dose level coupled with concurrent and adjuvant use of hormone therapies, there should be a very significant improvement in both disease free survival and overall survival compared with external beam radiotherapy of 70Gy and neo-adjuvant hormones only.

The dilemma in using radiation as a treatment for cancer is that of walking the line between having a high enough dose to achieve good tumour control and yet not so high as to cause unacceptable adverse side effects. Additionally, there is some variability in an individual's tolerance to radiation, which further complicates the matter. In the case of prostate cancer, general practice over the last decade or so seems to have settled on a figure of about 70 Gy delivered at around 2Gy per day. However, progress in recent years with beam collimation in linear accelerators coupled with the development of mathematical techniques to optimise radiation dose profiles has enabled dose levels to be increased without increasing adverse side effects. The technique of three-dimensional conformal radiotherapy has now been further incrementally improved by beam intensity modulated techniques and dose levels as high as 86.4 Gy have been tested at the Memorial Sloan-Kettering Cancer Center (Zelefsky et al (2002)) without significant changes to acute or long-term side effects. This group has also developed nomograms for predicting the outcome of various forms of treatment for prostate cancer and these have been collated into a single Microsoft Access database that can be download from the Memorial Sloan- Kettering website ([www.mskcc.org/mskcc/html/10088.cfm](http://www.mskcc.org/mskcc/html/10088.cfm)). For present purposes, the nomogram for predicting the outcome of external beam radiotherapy is the one that is of interest - see Kattan et al (2000). This nomogram was based on data from 1042 patients at Memorial Sloan-Kettering and then compared with a second independent set of patient data from the Cleveland Clinic, Ohio. The real value of this nomogram is not its absolute accuracy but in its prediction of trends. Although there has been a number of publications on dose escalation, this nomogram provides a compact means of looking at the influence of a variety of factors on treatment outcome. The figure below shows predictions for 5 year disease free survival as a function both of total dose with and without neoadjuvant hormones and also as a function of initial patient risk factors. Adjuvant hormones were not used in the data from which this nomogram was compiled. Failure is based on the ASTRO definition of three successive rises in PSA. The confidence intervals have not been shown to avoid cluttering up the graph.
This figure shows a number of interesting trends. The first is the very strong influence of the initial risk factors on disease free survival probability. The prospects for low and intermediate risk patients are comparatively good with conventional 70Gy treatment but the outlook when PSA rises above 10 coupled with a palpable tumour and high Gleason score diminishes rapidly. The second point is that the improvement in outlook by increasing the dose from 70Gy to around 76 to 80Gy is significant and there have been a number recent reports in addition to the Zelefsky work that indicate that this increase in dose can be achieved without a significant impact on side effects provided that advanced three dimensional conformal or intensity modulated techniques are used. The third point to note is that whereas the nomogram predicts an improvement in disease free survival from the use of neo-adjuvant hormones (Sloan Kettering used goserelin), the effect is not large particularly for low and intermediate risk patients - particularly when compared to adjuvant use. This has already been discussed on the web page 3 concerned with hormone therapies used in conjunction with radiotherapy.

Recent confirmation of the value of dose escalation even for patients at a low level of risk has been provided by Zietman and colleagues (2005). They carried out a trial of 393 patients with a median PSA of 6.3 ng/ml, a predominant Gleason score of 6 or less and T-staging mainly of T1c. About half were given 70 Gy of radiation without any hormones and the other half were given 79 Gy without hormones. The five year disease free percentage was 61% and 80% for the two respective groups. Precise details of the radiation treatment are given in their paper and was a mixture of photon and proton radiation. No significant differences in early or late side-effects were noted. It should be noted that these disease free survival figures are lower than those predicted by the MSKCC nomogram which suggests that the nomogram may be rather too optimistic in its predictions.

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High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients.

Comparison of Conventional-dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate.
5. Increasing the daily dose fraction above 2 Gray. The dose rate effect and hypofractionation.

* A win/win situation?

**SUMMARY.**

Cells are sensitive not only to the overall dose of radiation but also to the rate at which it is given. There is evidence that prostate cells are more sensitive to this rate effect than the rectum and bladder and there is therefore a potential advantage in delivering the dose at a greater rate than 2 Gray per day. This is still the subject of controversy but a conservative approach would be to replace the existing 70 Gray in 2 Gray fractions with 63 Gray in 3 Gray fractions. Such a change potentially would improve the treatment effectiveness without increasing side effects and it would save both the patient and the hospital money because of the reduction in treatment days from 35 to 21 days.

The effect of radiation on cells is not dependent just on the overall dose of radiation but it also depends on the rate at which the radiation is delivered - the so-called dose-rate effect. Some cells are more sensitive to dose rate than others. In particular, work started by by Brenner and Hall (1999) suggests that prostate cells are more sensitive to the rate at which radiation is delivered than the surrounding organs like the rectum and bladder. The evidence about this is still the subject of discussion in the literature but, if it is correct, the effectiveness of external beam radiation therapy can be further improved by replacing the current daily fraction of 2 Gray by a larger daily fraction like 3 or 4 Gray. Moreover, by increasing the daily fraction, the overall dose necessary to have the same effect as 70 Gy given in 2 Gy fractions is reduced. It is unfortunately not possible to describe easily how these equivalent doses are calculated so that, for present purposes, only the results will be presented. A second review paper (web page 11) can be downloaded from this site as an Adobe Acrobat document and this gives more complete information and references on this subject.

Calculations about the equivalence of different radiation doses depend on theoretical models of how radiation interacts with cells and there are a number of such theories. However, they are not substantially different from one another and one of the simplest theoretical models is called the linear-quadratic model - abbreviated to the LQ model. For external beam radiotherapy delivered in acute fractions, there is one important parameter in this model called the alpha-beta ratio and it is this parameter that determines the equivalence of doses delivered at different rates. The units of this parameter are Grays and the lower the value of this parameter, the more sensitive the cells are to the dose rate effect. According to Brenner and Hall, the value of this parameter for prostate cells is about 1.5 Gy whereas the value for rectal tissue that causes long term side effects is thought to be nearer 6 Gy. The graph below shows the ratio of the overall dose at different daily fractions compared to the overall dose with a 2Gy per day fraction. The equivalent doses have been calculated for both an alpha-beta ratio of 1.5 Gy and for an alpha-beta ratio of 6 Gy.
As an example of the potential advantage of increasing the daily dose fraction, consider the red curve with an alpha-beta ratio of 6.0 that is representative of rectal tissue. Suppose that the daily fraction is increased from 2 Gy per day to 4 Gy per day. The iso-effect dose ratio is 0.8 which means that if we wished to have the same effect on the rectal tissue as 70 Gy dose delivered at 2 Gy per day, we would now only need a dose of 0.8 x 70 = 56 Gy. Since this dose is delivered now in 4 Gy fractions, the number of treatment days would only be 14. However, the really important point now arises when we consider what this dose means in terms of the prostate cells having an alpha-beta ratio of 1.5. The iso-effect dose ratio for these cells at 4 Gy per day is 0.64 and this means that the 56 Gy dose in 4 Gy fractions would be equivalent to 56/0.64 = 87.5 Gy delivered in 2 Gy fractions. By reference to the graph shown in web page 4, this would increase the probability of being disease free for, say, an intermediate risk patient, from around 75% for radiation treatment alone up to nearer 90% but without increasing the extent of damage to the rectum. This is a very significant improvement in the effectiveness of the treatment and it seems like an unusually propitious win/win situation. The patient only has to attend for 14 treatment days rather than the present 35 days and this will save money for both the patient and the hospital; additionally, treatment outcome will be improved!

At this point, it would be reasonable to ask why there hasn't been a rush towards changing the 'standard' protocol to this new type of regime - which is called hypofractionation on the basis that the number of treatment days is reduced (hypo meaning below normal). At least part of the answer is that the precise values of the alpha-beta ratio for the prostate and the rectum are the subject of controversy and uncertainty so that this necessitates some caution in making what is a comparatively radical change in treatment procedure. However, it is possible to adopt a cautious approach that carries very little risk to it by considering a more modest change in the daily fraction from 2 Gy to 3 Gy. In this case, the iso-effect dose ratio for an alpha-beta ratio of 6 is 0.89 and for an alpha-beta ratio of 1.5, it is 0.78. Keeping the effect on the rectum the same as 70 Gy in 2 Gy fractions now leads to an overall dose of 0.89 x 70 = 62 Gy. Delivered in 3 Gy fractions, this rounds up to 21 days of treatment (i.e. 63 Gy). For the prostate, this dose would be the equivalent of 63/0.78 = 81 Gy in 2 Gy fractions. This would still result in a significant improvement in the probability of disease free progression and carries very little risk of worsening side effects.
It is worth noting that a trial was carried out at the Christie Hospital NHS trust between 1995 and 1998 in which 705 men were treated with daily fractions of 3.13 Gy over 16 days amounting to a total dose of 50 Gy. From the above graph for an alpha-beta ratio of 1.5, this would have amounted to a dose of 65 Gy delivered in 2 Gy fractions. They reported similar tumour control and side effects to a 2 Gy per day protocol and they then reported that they were now treating patients with 60 Gy in 3 Gy fractions over 20 days - Livesey and colleagues (2003). This is just one day less than than the 63 Gy in 3 Gy fractions referred to as a reasonably conservative protocol in the previous paragraph.

In recent times, more trials with hypofractionation are being carried out both in the UK and in the US and whilst it is unlikely that a consultant would change his treatment routine to a hypofractionated one for an individual patient, it would be worth asking about such trials and whether or not one was eligible to take part in them.

REFERENCES.
Brenner, D.J., Hall E.J.(1999)
Fractionation and protraction for radiotherapy of prostate carcinoma.

How low is the alpha-beta ratio for prostate cancer.

Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis.
6. Side effects from external beam radiotherapy.

*Everything is funny as long as it is happening to somebody else.*

(Will Rogers)

**SUMMARY.**
This web page describes the type of side effects that can arise from external beam radiotherapy. They primarily affect the rectum, bladder and urethra and they also affect sexual function. Some of the side effects occur during or shortly after radiotherapy but generally these are not too severe and clear up after a few weeks. Longer term side effects may not emerge for months or even years after treatment but it is only in a small minority of a few percent that the effects are sufficiently serious to need significant medical treatment.

Side effects (referred to as toxicity) that occur during or shortly after the radiotherapy treatment are known somewhat misleadingly as 'acute' side effects. Side effects that develop due to the radiation damage over a longer time scale (typically six months to a year) are known as 'late' side effects.

The US Radiation Therapy Oncology Group (RTOG) have devised a grading scheme for side effects but, for simplicity, we will simply divide them into mild and moderate to severe and these will be discussed below.

There have been numerous papers published on side effects and these all show that side effects are reduced by using 3-D CRT or IMRT compared with earlier radiotherapy techniques. There is a good deal of variation between the results of the different trials and, for the moderate to severe side effects, this is partly due to statistical uncertainty because the actual numbers experiencing the more serious side effects are small. The figures below are an amalgam of figures from several reports and should be treated as a guide rather than as an accurate statistical analysis.

**URINARY SIDE-EFFECTS.**
The mild early (acute) side effects are simply an increased urgency to urinate and/or a stinging sensation when urinating. With 3-D conformal radiotherapy or IMRT at doses between 70 and 80 Gray, these mild effects occur in about 40% of men. About 30% experience nothing at all. Of the remainder, the urinary side effects may be a little more severe in terms of the urinary urgency, stinging or very weak flow. However, even these moderate side effects are generally temporary and can be alleviated by medication. Only very rarely (less than about 0.5%) do more serious problems like urinary retention occur which might necessitate the temporary use of a catheter.

Late urinary side effects are also quite rare. About 75% of men will not experience any late side effects and about 15% will experience only mild problems in terms of continuing urinary urgency (i.e. having to go to the toilet more than twice as often as previously). Most of the remainder will experience a frequent need to urinate (every hour or so) and they may experience pain or stinging when urinating. Medication is needed to deal with these problems. A very small minority (under 1%) will experience more serious problems like urinary retention, blood in the urine and so on. This unlucky small minority may require major medical intervention to deal with their problems.

**RECTAL SIDE EFFECTS**
About 75% of men experience no early rectal side effects. About 20% experience either some rectal discomfort or a tendency to diarrhoea. The remainder may suffer from more
severe diarrhoea or abdominal pains and will need some medication to deal with the problems. Rectal bleeding at an early stage is extremely unlikely.

About 90% of men will experience no late rectal side. Of the remainder, most will experience a continuing problem of diarrhoea but an unfortunate small minority of between 1% and 2% will experience more serious problems like rectal bleeding. These few may need more serious medical treatment like surgery to deal with or alleviate the problems. The occurrence of rectal bleeding is certainly a function of the dose and treatment at 80 Gy or thereabouts is likely to lead to about a doubling of rectal bleeding cases compared to 70 Gy treatments but the incidence is still reasonably low. Nevertheless, it does emphasise the increasing importance of more accurate targeting methods like IMRT at higher doses. It has also been shown that a history of diabetes has a significant impact on the likelihood of rectal bleeding - Akimoto et al (2004). It is also likely that other factors - like a large prostate - that make it difficult to avoid subjecting the rectum to high doses of radiation will also influence the occurrence of rectal bleeding.

SEXUAL FUNCTION.
Since radiotherapy is usually given in conjunction with hormone therapies, the side effects from the two therapies become entangled. The comments below apply to EBRT alone or to the period after hormone therapy ceases.

The impact of radiotherapy on sexual function seems less well documented than urinary and rectal side effects. The most immediate effect that develops over a few months to a year is that orgasms become largely 'dry'. A small amount of ejaculatory fluid may continue to be produced probably by the Cowper glands that are not irradiated. These glands are normally responsible for the production of a small amount of pre-ejaculatory fluid. From postings in internet newsgroups, opinions about the 'quality' of dry orgasms are variable but most seem to feel that they do not diminish sexual pleasure too much.

In the longer term, the radiation is thought to damage the nerves that control erections. These run down either side of the prostate. However, because prostate cancer affects mainly older men, it is difficult to distinguish between effects due to general ageing and those due to the radiation. However, for men in their sixties who were potent at the start of their treatment, about half will retain their potency at three years after treatment. For younger men, the figure is probably higher. Because the radiation damages rather than destroys the nerves responsible for erections, drugs like Viagra and Cialis can help to mitigate against 'creeping' impotence.

The likelihood of developing side effects may well be linked to other things like overall health and diet. Keeping fit and eating well are worthwhile in their own right but they assume even greater importance in responding to medical illnesses and their treatment.

REFERENCES.
Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding.
7. PSA behaviour after radiotherapy.
PSA bounce.

What goes up, must come down - hopefully!

SUMMARY.
In the absence of hormone therapy, PSA levels decline slowly after radiotherapy and can take several years to reach a nadir. During this period, about a third of men experience a 'bounce' in the PSA levels which may last from a few months to about a year. With adjuvant hormone therapy, the PSA behaviour is more complex but upward excursions in the PSA level should not necessarily be taken as a sign of treatment failure.

The measurement of PSA levels after treatment is an important indicator of the outcome of treatment. In the case of surgical removal of the prostate (prostatectomy) in which all the prostate tissue is removed and where no prostate cells have metastasised to remote sites, the PSA should fall to an undetectable level in two or three months after the operation.

For radiotherapy, the behaviour is more complex even without any hormone use. The radiation does not of itself kill cells. Radiation works by damaging the DNA molecule in a cell. Generally, this is repairable but sometimes it produces fatal damage so that when the cell comes to divide into two cells (mitosis), these off-spring cells have fatally flawed genetic information and so they are not viable cells. They either die at mitosis or peter out after a few generations. The time scale for prostate cells to reproduce is significant and may range from a few months up to periods of the order of a year or so - as evidenced by PSA doubling times. Now, the cells with fatally damaged DNA still continue to produce PSA and this only ceases when they die. As a result, PSA declines quite slowly after radiotherapy. However, even in the case of successful treatment, this decline is not always smooth but it may rise again for a period of a few months before declining towards its final minimum value - the nadir. This 'bounce' in PSA has been studied mainly in connection with brachytherapy but some data is available for external beam radiotherapy too - Zietman et al (2005). The sketch below shows a rather idealised version of PSA bounce after external beam radiotherapy without any hormone use.
The reason for the bounce is not known for sure but somewhere between a third and a half of patients experience bounce and it may occur anywhere between about 1 to 3 years after treatment. The magnitude of the bounce lies in the range from about 0.5 ng/ml to 2 ng/ml and may last from a few months to around a year.

It should be stressed that PSA variation after treatment varies significantly from patient to patient and the above figures are only a guide. However, one should not jump too rapidly to the conclusion that treatment has failed because of upward variations in PSA values. Monitoring of PSA at three monthly intervals over a period of three years is probably necessary before any definite conclusions can be drawn about the effectiveness of the treatment - unless, of course, the PSA values rise in a sustained and significant way. It should also be noted that an analysis of PSA records of 4,839 patients from nine institutions in the US showed that there was no difference in long term survival or cure between patients with bounce and those without - Horwitz (2004).

With hormone treatment, the PSA behaviour after the radiation treatment is even more uncertain. With neo-adjuvant, concurrent and adjuvant hormone use, the PSA may fall to low or even undetectable levels a few months after radiation. If, then, a patient stops taking the hormones, the PSA level will recover but it may take some months to do so and it may not do so smoothly. Even second 'bounces' occur in a number of cases. However, if the treatment has been effective, the PSA should finally level off at somewhere in the region of 0.5 to 1.0 ng/ml although this will depend on many things including the total radiation dose. Once again, these are guideline figures only.

With radiotherapy, the PSA nadir will not fall to 'zero' because the prostate is not entirely destroyed by the radiation. However, if the treatment has been successful, all the cancerous tissue will have been destroyed but 'healthy' prostate cells are more resistant to radiation damage and some of these will remain. The prostate gland will be significantly reduced in volume but will still produce residual PSA. Clearly, the more of the prostate that remains, the greater the chance of a recurrence of the disease either through cancer re-developing in the remaining tissue or through the fact that not all the original cancerous tissue was destroyed. It certainly seems to be the case that the lower the final PSA nadir, the better the chances of remaining disease free. There seems to be a consensus that external beam radiotherapy should aim to achieve a PSA nadir of 0.5 ng/ml or less. However, there are many cases where a stable but higher nadir of, say, between 1 and 2 ng/ml is achieved.

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8. Patient checklist for external beam radiotherapy.

*He who asks a question is a fool for five minutes; he who does not ask a question remains a fool forever.*

*(Chinese proverb)*

Consultants are busy people and often under some pressure. Nevertheless, it is important as a patient to know the why's and wherefore's of your treatment and, if you are prepared, this need not necessarily take up very much time in a consultation. Below are listed some questions I would ask of a consultant. Most of them can be briefly answered but some may need elaboration.

1. What type of radiotherapy treatment am I going to receive? Conformal beam or IMRT?
(I would not accept conventional ebrt and would go elsewhere if either of the above was not available)

2. What overall dose am I to receive and in what fractions?
(Normal is 70Gy in 2Gy fractions - i.e. 35 days of treatment excluding weekends but see follow-up actions below.)

3. Is anything done to allow for prostate movement during the course of treatment?
(The prostate gland can move around during the course of treatment. Generally, the movement is small but there are techniques for tracking the movement and adjusting the beam profiles. However, the probable answer in the UK is that nothing is done except to allow a margin around the prostate which it is hoped will ensure that the prostate gland is always within the high dose target region).

4. What is the targeted field?
(You could ask to see your planning chart so that the consultant can explain just what is to receive high doses of radiation and how much of the rectum is to be within this high intensity field.

5. What hormone treatment is to be given?
(The probability is that you will be recommended to have three months of hormone therapy before the external beam radiotherapy treatment (neo-adjuvant use) and that the hormones will be continued both during treatment (concurrent use) and after treatment (adjuvant use). The main questions are what type of hormones are to be used and why - either LHRH agonists like Zoladex or anti-androgens like Casodex - and how long after the end of the radiation treatment will you continue to use them? - see follow-up actions and the comments about Casodex in web page 3.

5. How many prostate cancer patients have you treated in the last year and what do you think the outcome of my treatment will be?
(This is always worth asking to establish the general level of expertise of the clinic or hospital. The response to the second half of the question can also be revealing about the general awareness and competence of the consultant. Not all consultants and hospitals have a high level of experience and success in treating prostate cancer.)
Follow-up actions during and after radiotherapy.

1. If you show no signs of significant side-effects towards the end of your treatment, ask if the overall dose can be increased. 75 to 80 Grays would be better than the usual 70 Grays (see web page 4) but you should be conscious that you will be increasing the risk of developing late side effects - particularly rectal bleeding. However, you should be able to discuss the balance of risk with a good consultant using some of the results given in this web site. If you are diabetic, this fact should be included in the discussion - see web page 6.

2. After treatment, measure PSA every three months and be aware of the possibility of PSA bounce at around two years after treatment - see web page 7. The PSA behaviour after the radiation will be strongly affected by hormone use.

3. If the first couple of post-radiotherapy PSA measurements seem satisfactory, the possibility of shortening the period of adjuvant therapy should be discussed. The trial data shown in web page 3 suggests that the main benefits of adjuvant hormone therapy can be achieved in as short a period as two months. A more conservative period might be between six months and a year - see web page 3.