Prostate cancer management - helping your patient choose what is best for him

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Abstract

The biggest problems in prostate cancer management are how to identify patients with potentially life-threatening cancer, and how to choose the best form of management from among the large array of treatment options. Although prostate cancer is the second or third most common cause of cancer death in males, most men with this diagnosis will die of other causes.

The most important prognostic factors are the patient's life expectancy, the grade and stage of the tumour and the serum prostate specific antigen (PSA) at diagnosis. The most important management options are (1) active surveillance (watchful waiting), (2) androgen deprivation therapy (ADT), (3) radical prostatectomy and (4) radiotherapy.

Patients with a limited life expectancy or non-aggressive cancer can be managed with active surveillance and be treated only if and when it becomes necessary. ADT (hormone therapy) provides excellent palliation in men with locally advanced or metastatic cancer, but the side-effects decrease quality of life.

Radical prostatectomy and radiotherapy are potentially curative if the cancer is localised to the prostate. The use of laparoscopic radical prostatectomy is increasing in affluent countries, although (apart from reduced blood loss) there are no significant advantages compared to retropubic or perineal radical prostatectomy. The main complications are erectile dysfunction and urinary incontinence. The use of brachytherapy is increasing, although there is no convincing evidence that it is more effective or has fewer complications than external beam radiotherapy.

Although a vast amount of information on prostate cancer is available on the internet, some of the websites are driven by financial incentives to promote their products or procedures, and patients may emerge with unrealistic expectations based on misinformation. There are certain websites, based on the Partin tables or the Kattan nomogram, which can be used by the doctor to calculate the patient's statistical probability of being cured with radical prostatectomy or radiotherapy.

The probability of cure has to be weighed up against the risk of complications or side-effects that impair quality of life. There are very few randomised clinical trials comparing treatment options, so there is no real answer to the question which form of management is "best".

Patients and their families should be given comprehensive and unbiased information and sufficient time to make decisions. Because there are no absolutely right or wrong choices, and because patients all have different expectations, it is best for the patient himself to decide what form of management would be best for him.

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Introduction

The first problem in prostate cancer management is how to identify patients with potentially life-threatening cancer. The second problem is how to choose the best form of management from among the large array of treatment options. There is a vast amount of information on the internet (entering the words "prostate cancer" on Pubmed produces more than 63,000 titles) but much of it is conflicting and controversial, so there is a lot of confusion and very little consensus.

Even worse, entering "prostate cancer" on the internet search engine Google produces more than 12,6 million results. Although many of these websites provide excellent and unbiased information, some of them are driven by financial incentives to "hard-sell" their products and procedures.[1]

Patients already bewildered by a diagnosis of cancer in an obscure organ they know very little about, may embark on an internet odyssey seeking information, but eventually end up feeling totally lost in a maze

of contradictory opinions, or emerge with unrealistic expectations based on misinformation.

The aim of this article is to provide some information and guidelines on how a patient with prostate cancer can be helped to choose the management option which is best for him.

Tigers and pussycats

In the USA and Europe prostate cancer is the second or third most common cause of cancer death in men. However, there is a discrepancy between the number of men diagnosed with prostate cancer and the number dying of it. In the USA the incidence-to-mortality ratio is almost 9:1. In the UK and Africa, where PSA screening is less widespread, the ratio is about 3:1. This discrepancy is largely due to non-aggressive cancers being diagnosed in elderly men who will die of some condition other than prostate cancer.[2]

Increasing use of prostate specific antigen (PSA) testing of asymptomatic men has led to increasing numbers being diagnosed with early stage cancer that will not cause symptomatic disease or death. The risk of overdiagnosis and overtreatment has become a matter of great concern.[3,4]

As yet, there is no simple and reliable way of distinguishing between the tigers and the pussycats. The most important prognostic indicators in prostate cancer are the patient's age, the grade and stage of the tumour and the PSA at presentation.

Age

Much more important than the patient's chronological age is his physiological age, i.e. estimated life expectancy. This depends on many factors, e.g. concomitant diseases, obesity, smoking, physical activity and family history (at what age and of what conditions did his parents or siblings die?). It is notoriously difficult, but nonetheless important to "guesstimate" the patient's probable life expectancy.

In someone with 10–15 years' life expectancy it is important to cure prostate cancer, even if there is a loss in quality of life. In someone with less than 5–10 years' life expectancy, it is more important to palliate symptoms and maintain quality of life.

Grade

The Gleason grading system is based on the glandular architecture seen at relatively low magnification. There are 5 Gleason grades, 1 being most differentiated and 5 being least differentiated. Both the primary (most prevalent) and secondary (second most prevalent) patterns are graded. The Gleason score is the sum of the Gleason grades for the primary and secondary patterns, so the Gleason score ranges from 2 (well differentiated) to 10 (poorly differentiated).

There is a strong correlation between histological grade and prognosis. Well differentiated cancer (Gleason score 2–4) has a good prognosis, while high grade cancer (Gleason 8–10) has a poor prognosis. Unfortunately, most patients fall into the intermediate range (Gleason 5– 7) where it is more difficult to predict the prognosis.

A problem inherent in prostate needle biopsy is the risk of sampling error, because only a part of the prostate is obtained for histology. The Gleason score of cancer found on biopsy may be lower than the Gleason found if the whole prostate is histologically examined. Under-grading may give a false sense of security.

Stage

Prostate cancer is staged according to the TNM system. Clinical tumour stage (cT) is determined on digital rectal examination (DRE) whereas pathological T-staging (pT) is determined by histopathological examination of a radical prostatectomy specimen.

There is a strong correlation between stage and prognosis, regardless of treatment. Early stage cancer localised to the prostate (T1-2) is potentially curable, whereas locally advanced (T3-4) or metastatic cancer (N1 or M1) can not be cured, although very good palliative treatment is available.

There is quite often a difference between clinical and pathological staging, with understaging being much more common than overstaging. Therefore, cancer that appears on clinical staging to be localised to the prostate (potentially curable) may on histological examination prove to be extracapsular (usually not curable).

The percentage of biopsy cores which are positive for cancer correlates with the volume of tumour in the prostate, and this correlates with the outcome after treatment.[5-8]

PSA at diagnosis

There is a correlation between grade, stage and PSA (high-grade tumours are more often locally advanced or metastatic and have a higher PSA at diagnosis). However, these correlations are not linear or absolute, and exceptions to the rule are common. On multivariate analysis pretreatment PSA is a strong prognostic indicator, independent of grade and stage, and regardless of the treatment given.[9,10]

For selecting treatment and predicting the probable outcome of therapy it is essential to consider not only the grade and stage of the tumour, but also the PSA at presentation. Other important considerations are the patient's life expectancy and his expectations from life, e.g. is he sexually and socially very active and wants to remain so? In short, is he more worried about losing years of life than losing quality of life, or vice versa?

Management Options

The management options for prostate cancer are shown in Table I, and the most common side-effects and complications are summarised in Table II.

The four most important management options are:

1. Active surveillance (watchful waiting)
2. Androgen deprivation therapy ("hormone treatment")
3. Radical prostatectomy
4. Radiotherapy

Studies have shown that delays of up to 6 months from prostate cancer diagnosis to radical prostatectomy do not compromise the probability of cure. Therefore, patients can be reassured that there is no urgency for immediate treatment and they should be given sufficient time to discuss and consider all treatment options.[11-13]

Active surveillance or watchful waiting

Studies on the natural history of untreated prostate cancer show that men with well-differentiated, locally confined cancer have a minimal risk of dying from their cancer during 20 years of follow-up, whereas men with high-grade cancer have a high probability of dying from it within 10 years.[14-16]

Traditionally, watchful waiting was recommended for men with a life expectancy of less than 5–10 years, low grade (Gleason 5–6 or less) low stage (T1) cancer with a PSA 10 ng/ml or less. However, active surveillance is now being studied in younger patients with low grade,

Table I: Management options in prostate cancer

Active surveillance/Watchful waiting
Palliative treatment
Androgen deprivation therapy ("hormone therapy")
○ Bilateral orchidectomy
○ Oestrogens
○ LHRH agonists
○ Anti-androgens
Chemotherapy
Curative treatment
Radical prostatectomy
○ Retropubic
○ Perineal
○ Laparoscopic (± robot-assistance)
Radiotherapy
○ External beam (EBRT)
○ 3-dimensional conformal
○ Brachytherapy
Thermotherapy
○ Cryotherapy
○ High-intensity focused ultrasound (HIFU)
Photodynamic therapy

Table II: Most common side-effects and complications of prostate cancer treatment

Active surveillance/Watchful waiting
○ Anxiety/depression
○ Risk of cancer progression
Androgen deprivation therapy ("hormone therapy")
○ Loss of libido
○ Erectile dysfunction (ED)
○ Hot flushes
○ Gynaecomastia, mastodynia
○ Thrombo-embolic complications
Radical prostatectomy
○ Haemorrhage, blood transfusion
○ ED
○ Incontinence
○ Bladder neck stenosis
Radiotherapy
○ Cystitis (hematuria, incontinence)
○ Proctitis (diarrhoea, haematochezia)
○ ED
○ Fistula (prostato-rectal)
Thermotherapy
○ ED
Incontinence

early stage tumours. The rationale is that treatment and adverse effects may be deferred for several years, yet may be instituted at a stage where the cancer is still curable.[17]

Patients who choose active surveillance should be followed up with DRE and PSA every 3–6 months and prostate biopsy every 12–24 months. If the PSA doubling time is less than 12–24 months, or the DRE shows local progression, or rebiopsy shows an increase in the Gleason score or the percentage of biopsies involved by cancer, treatment can be instituted.

There is no evidence that cancer grade worsens significantly during an 18–24 month period after prostate biopsy. Therefore men undergoing active surveillance can be reassured that waiting 18–24 months before re-biopsy is a relatively safe option.[18]

The advantage of active surveillance is that patients avoid the costs and complications of treatment that is unlikely to prolong survival. The disadvantage is that patients may suffer anxiety associated with uncertainty regarding if and when to initiate treatment, and the risk of progression from a curable to an incurable stage.

Androgen deprivation therapy (ADT) – hormone treatment

The forms of androgen deprivation therapy (ADT) and their complications are shown in Tables III and IV.

ADT provides excellent palliation for patients with metastatic (N1, M1) or locally advanced (T3–4) cancer. ADT is also used for biochemical failure (increasing PSA) after radical prostatectomy or radiotherapy, although the most appropriate PSA level at which to initiate ADT in such patients is unknown.

The response to ADT is better in men with higher testosterone levels before treatment. The reason is that cancers which have progressed in a low testosterone environment are not really dependent on androgens, therefore ADT does not have much effect on their growth.

The PSA response to ADT is a very good prognostic indicator. Longer survival correlates with a lower PSA nadir (the lowest PSA level before it starts to increase again), a shorter time to reach the PSA nadir, and a longer PSA doubling time.[19]

Table III: Types of androgen deprivation therapy (ADT)

Ablation of androgen sources
Bilateral orchidectomy (BO)
Inhibition of LH and testosterone secretion
Oestrogens
○ Diethylstilbestrol (DES)
○ Oestradiol (Estrofem®)
LHRH agonists
○ Goserelin (Zoladex®)
○ Buserelin (Suprefact®)
○ Leuprorelin (Lucrin®)
○ Triptorelin (Decapeptyl®)
Blocking of androgen receptors with anti-androgens
Steroidal anti-androgen
○ Cyproterone acetate (Androcur®)
Nonsteroidal anti-androgens
○ Flutamide (Eulexin®)
○ Bicalutamide (Casodex®)
Inhibition of androgen synthesis
○ Ketoconazole (Nizoral®)

Table IV: Complications of androgen deprivation therapy

BO, LHRH and non-steroidal anti-androgens:
○ Hot flushes
○ Loss of libido
○ Erectile dysfunction (ED)
○ Decreased cognitive function
○ Increased depression and anxiety
○ Decreased muscle mass
○ Increased body fat
○ Anaemia
○ Osteoporosis
Oestrogens and steroidal anti-androgens
○ Loss of libido
○ ED
○ Mastodynia (breast tenderness)
○ Gynaecomastia (breast enlargement)
○ Thrombo-embolic phenomena
▪ Deep vein thrombosis
▪ Pulmonary embolism
▪ Myocardial infarction
▪ Cerebro-vascular incident
○ Salt and water retention
Hypertension
Cardiac failure

Bilateral orchidectomy (BO)

Bilateral orchidectomy (BO) reduces serum testosterone by more than 90% (to castration levels) within 24 hours. The observation that BO leads to a marked clinical improvement in men with locally advanced

or metastatic prostate cancer was first reported in 1941 by Charles Huggins, who received the Nobel prize for his work on the endocrine control of the prostate in 1966.[20]

Oestrogens

Oestrogens such as oestradiol and diethylstilbestrol (DES®) suppress the secretion of LH and FSH by the pituitary. The decreased LH leads to decreased secretion of testosterone by the Leydig cells in the testis. DES® is as effective as BO in the treatment of prostate cancer.

LHRH

Luteinising hormone releasing hormone (LHRH) is a decapeptide (consisting of 10 amino acids) secreted by the hypothalamus. It is released intermittently (phasic secretion) in small amounts which stimulate the pituitary gland to secrete LH and FSH, and LH stimulates the secretion of testosterone. LHRH was identified and isolated by Andrew Schally and colleagues in 1971 and this achievement won the Nobel prize in 1977.

Synthetic LHRH agonists are administered as 1-, 3- or even 12-month depot formulations and cause an immediate increase in LH, FSH and testosterone. After about 2 weeks the continuous release of large (supraphysiological) doses of LHRH and the loss of phasic stimulation lead to a decrease in LH and FSH levels, with a decrease of testosterone.

The initial increase in testosterone lasts 10–20 days and may cause a severe, life-threatening exacerbation of symptoms ("flare phenomenon"). Co-administration of an anti-androgen to block the androgen receptors can prevent this symptom flare.

LHRH agonists are as effective as BO and DES in terms of subjective and objective response in men with prostate cancer.

Anti-androgens

All anti-androgens inhibit androgen action by competitive blocking of the androgen receptor. Steroidal anti-androgens have the additional effect of suppressing LH secretion, which leads to a decrease in testosterone levels. Non-steroidal anti-androgens do not suppress LH, and by blocking the inhibiting feedback of testosterone on the pituitary they produce an increase in LH and testosterone. This can preserve potency, but the peripheral conversion of the excessive testosterone to oestrogen can cause painful gynaecomastia.

Using an anti-androgen alone is not as effective as treatment with BO, LHRH or DES. However, monotherapy with a high dose of bicalutamide (Casodex®) appears to be as effective as BO or LHRH in men with locally advanced or metastatic cancer, with a lower risk of ED, but a high incidence (around 66%) of mastodynia and gynaecomastia.

Androgen synthesis inhibitors

Ketoconazole is an anti-fungal agent which inhibits steroid synthesis in the testes as well as adrenals, thereby decreasing testosterone. Because it also inhibits the synthesis of other steroids in the adrenals, it should be combined with steroid supplementation if used long-term.

Timing of ADT

There is no dispute about the fact that immediate ADT compared to deferred ADT delays biochemical and clinical progression, but there is no clear evidence that it prolongs overall survival. The costs and side-effects of long-term ADT are important issues.

In men with clinically localised prostate cancer the overall survival was worse in those treated with immediate bicalutamide versus placebo.[21] This suggests that in men with low-risk, localised cancer, the adverse effects of immediate and long-term ADT may be worse than delaying treatment until clinical progression has occurred.

With regard to locally advanced or metastatic cancer, if the patient is asymptomatic and wants to remain sexually active, then ADT can be deferred until there is symptomatic progression, provided the patients are carefully followed up clinically and with 3- to 6-monthly PSA measurement.[17,22]

Combined ADT

In an attempt to eliminate androgens from the testes as well as the adrenals, anti-androgens have been used in combination with an LHRH agonist or BO. Initially there was great enthusiasm, because a randomised clinical trial showed a median survival of 36 versus 28 months for patients with advanced cancer treated with LHRH plus an anti-androgen versus LHRH alone.[23]

However, when BO plus an anti-androgen was compared to BO alone, there was no survival advantage.[24] A possible explanation for this is that in some men treated with an LHRH agonist the serum testosterone does not reach castration levels, and in such patients the addition of an anti-androgen may provide a survival benefit. However, after BO the testosterone always reaches castration levels, and in this situation there is no benefit in using an anti-androgen.

A meta-analysis of clinical trials using an anti-androgen with an LHRH agonist or BO showed that there was no clinically significant survival advantage in so-called combined androgen blockade (CAB). The costs and side-effects of CAB are greater, without any real survival advantage.[25]

Androgen refractory (hormone resistant) prostate cancer

ADT is one of the most effective therapies against any solid tumour, but eventually almost all prostate cancers become androgen refractory. A rise in PSA level in a patient on ADT indicates the emergence of androgen refractory prostate cancer (ARPC). Most of these cancers remain sensitive to androgens; therefore ADT should continue in ARPC.

Numerous chemotherapeutic drugs have been tested in men with ARPC, without significant benefit. Mitoxantrone plus hydrocortisone leads to a significant improvement in quality of life parameters (including pain) but there is no survival advantage. Recently docetaxel versus mitroxantrone showed a median survival of 18.9 versus 16.4 months, decreased PSA and relief of pain in men with metastatic ARPC.[26]

Intermittent versus continuous ADT

Laboratory animal studies have suggested that intermittent versus continuous ADT delays the development of ARPC and prolongs survival. Early results of ongoing clinical trials with intermittent versus continuous ADT indicate that there is no survival difference, but because the costs and side-effects are less, intermittent therapy is an attractive option. However, long-term results should be awaited before intermittent rather than continuous ADT is routinely recommended.

Radical prostatectomy

Radical prostatectomy was the first treatment used for prostate cancer and remains the gold standard for curative treatment. There are three different surgical approaches: retropubic, perineal and laparoscopic.

Retropubic radical prostatectomy is the most commonly used technique worldwide. It is done through a lower abdominal incision and extraperitoneal approach, sometimes with pelvic lymph node dissection.

Perineal radical prostatecomy is done through an incision between the scrotum and anus, with the patient lying in hyperflexed lithotomy position. In the USA only about 10% of radical prostatectomies are done perineally.

Laparoscopic radical prostatectomy is done with 3 to 5 ports of 5 to 10 mm each, placed through the abdominal wall for the insertion of a camera and instruments which are used to perform the procedure. The prostate is removed by enlarging one of the port sites sufficiently to extract the organ.

The advantages of laparoscopic prostatectomy are reduced blood loss, less pain, shorter hospitalisation, quicker return to work and smaller surgical scars. However, some studies have failed to show quantifiably less pain or significantly shorter hospitalisation with laparoscopic compared to open prostatectomy, but the operation time is longer and instrument costs are higher.

Robot-assisted laparoscopic prostatectomy makes use of a master-slave robotic system, where the camera and instruments are inserted through the abdominal wall and connected to the arms of the robot, which is controlled by the surgeon sitting in a console some distance away. The robotic system makes the procedure easier for the surgeon (better visualisation, less fatigue) but it is much more expensive. The use of robotic prostatectomy is rapidly increasing in affluent countries, probably due to aggressive internet marketing and because patients are attracted by the latest technology.

There are no significant differences between retropubic, perineal and laparoscopic prostatectomy with regard to positive surgical margins or complication rates. The only significant difference is blood loss, which is lower in laparoscopic than perineal, and lower in perineal than retropubic prostatectomy.

The most common complication of radical prostatectomy is erectile dysfunction (ED).[27] This is because the neurovascular bundles mediating erection pass very close to the lateral borders and apex of the prostate. Nerve-sparing prostatectomy can preserve the neurovascular bundles, but runs the risk of positive surgical margins.

The incidence of ED varies from around 20% to 80%. It is less common in younger men, those with greater sexual activity pre-operatively, and those with smaller tumours who underwent nerve-sparing surgery. ED after radical prostatectomy can be treated with oral phosphodiesterase-5 inhibitors (e.g. sildenafil) or intracavernosal prostaglandin injections or implantation of a penile prosthesis.

The second most common complication is urinary incontinence. The reported incidence varies considerably, depending on the definition and the time since the operation. A large percentage of patients who are incontinent immediately after removal of their catheter will regain continence in the following 6 to 12 months. The risk of severe long-term incontinence is around 5%, and is lower in younger men and those with a smaller prostate.[27] Minor degrees of incontinence can be managed with pads. Severe incontinence requires surgery, usually the implantation of a sling or artificial sphincter.
Other complications of radical prostatectomy include bladder neck contracture, lymphocele, incisional or inguinal hernia and, rarely, rectal injury. Mortality is less than 1%.[27,28]

Radiotherapy

Conventional external beam radiotherapy (EBRT) is usually delivered in daily fractions of around 2 Gray (Gy) to a total cumulative dose of 70 Gy.[29]

External beam radiotherapy (EBRT)

Three-dimensional conformal radiotherapy (3D-CRT) is performed with CT planning which enables delivery of radiation to the prostate while limiting irradiation of the bladder and rectum.

Intensity-modulated radiation therapy (IMRT) can provide even greater localisation of the radiation dose while limiting toxicity to adjacent organs.[30]

Conventional doses of EBRT (65 to 70 Gy) are unable to sterilise large cancers, so dose escalation to 75 Gy or more is necessary, but this leads to increased treatment morbidity.[9,31-33]

The most common complications are radiation proctitis and cystitis, which occur in about 30% of patients, but are usually transient. After 1 year about 5% to 10% of patients have persistent problems with diarrhoea, rectal bleeding, urinary incontinence or gross haematuria.[34] Urinary incontinence after radiation is usually due to detrusor dysfunction, so an artificial sphincter will not solve the problem.

The reported rates of ED vary greatly, but 1–2 years after radiotherapy ED is present in about 50% to 80% of patients. ED is more common in older men with less sexual activity before treatment, and the rate increases with the duration of followup.[34]

Brachytherapy

Brachytherapy involves implantation of radioactive pellets or "seeds" into the prostate to deliver a high dose of radation (up to 160 Gy) while sparing the bladder and rectum. The word comes from the Greek *brachus*, short, referring to the high dose of radiation delivered at short distance from the seeds.

Implantation of radio-active iodine-125 needles into the prostate via open retropubic surgery was used in the 1960s to 1980s and was then known as interstitial therapy. The long-term results at 15 years were poor, but this is ascribed to technical limitations of the procedure with suboptimal distribution of the isotope within the prostate.[35,36]

The current resurgence of interest in brachytherapy is due to the development of new technology. The procedure is performed under general or regional anaesthesia. It uses transrectal ultrasound (TRUS) to visualise and measure the prostate, sophisticated computer software to plan treatment, and needles which are inserted through the perineum to place the radio-active pellets inside the prostate. The most commonly used implants are iodine-125 or palladium-103.[8]

Brachytherapy is relatively easy to perform and has become increasingly popular due to perceptions that it is high-technology, minimally invasive, more effective than EBRT and has lower morbidity. However, there is no convincing evidence that brachytherapy is more effective than EBRT, although it is considerably more expensive. The increasing use of brachytherapy may be due to patient demand, but there have also been allegations of "kickbacks" from the pellet manufacturers and perverse incentives, in that the doctors' fees for brachytherapy are higher than for radical prostatectomy or EBRT.

Initially, certain conditions were regarded as contra-indications for brachytherapy (very large prostate, severe urinary symptoms, previous transurethral resection of the prostate [TURP], high-risk cancer) but nowadays virtually all patients are considered suitable.[8] There has been a reluctance to recommend brachytherapy for younger patients, because age was shown to be an independent risk factor for biochemical failure after radiotherapy.[37]

One has to keep in mind that the prostate is not totally destroyed by radiotherapy, as evidenced by the fact that PSA almost always remains detectable. Even if the original cancer is destroyed, if the patient survives long enough the prostate, which has already shown a predisposition to malignancy, may produce other foci of cancer. This may explain why the long-term failure rate at 15 years appears to be significantly higher after EBRT compared with radical prostatectomy.

Most patients have some lower urinary tract symptoms after brachytherapy, and the reported incidence of urinary retention varies from 2% to around 20% To avoid these problems, alpha-blockers and ADT are often administered before and after treatment. Proctitis and rectal injury are reported to be less common with brachytherapy than with EBRT. Urethral strictures occur in about 5% to 12%, and rectal bleeding in approximately the same percentage of cases, although it usually resolves spontaneously.[8]

ED has been reported in 6% to 90% of patients after brachytherapy, and appears to be more common after brachytherapy than EBRT, despite some claims to the contrary. Haematospermia, orgasmalgia and alteration in the intensity of orgasm have been reported in 15% to 40% of patients, but in most cases these side-effects were transitory. A rare but devastating complication of brachytherapy is prostato-rectal fistula.[8]

Combination of radical prostatectomy and radiotherapy with ADT

Clinical trials have shown that ADT for 3 months before radical prostatectomy reduced the rate of positive surgical margins – from about 50% to 15%. However, with long-term follow-up there was no difference in PSA progression or survival between the groups with and without ADT before radical prostatectomy.

Some clinical trials have shown that in men with high-risk or locally advanced prostate cancer, radiotherapy combined with ADT (for periods varying from 3 months to 3 years) compared to radiotherapy alone led to longer survival.[31,38] Unfortunately, there are as yet no randomised clinical trials comparing ADT plus radiotherapy to ADT alone, therefore it is difficult to know what the contribution of radiotherapy is towards increased survival.

It is difficult to understand why ADT in combination with radical prostatectomy makes no difference to disease-free survival, whereas ADT in combination with radiotherapy does lead to longer survival. This raises the question whether the increased survival observed with radiotherapy plus ADT is not due mainly to the effect of ADT.

Because of this increased survival, patients with high-risk prostate cancer who undergo brachytherapy often receive ADT, although there are no randomised trials proving greater efficacy of ADT with brachytherapy.[8]

Salvage after failed radical prostatectomy or radiotherapy

Patients who have positive surgical margins or PSA recurrence after radical prostatectomy can be treated with radiotherapy with the aim of eradicating residual or recurrent cancer. However, patients with PSA recurrence within the first 6–12 months after surgery rarely benefit from radiotherapy, probably because the majority of such patients have metastatic disease outside the pelvis.

Patients with PSA recurrence 12 months or more after radical prostatectomy and with a PSA doubling time of more than 12 months are more likely to benefit, provided salvage radiotherapy is administered before the PSA is over 2 ng/ml.[38,39]

Patients with persistence or local recurrence of cancer after radiotherapy can be treated with salvage radical prostatectomy. If performed before the PSA increases to more than 10–20 ng/ml it provides 5-year biochemical relapse-free rates of around 60%. However, the risk of complications is much higher than with primary radical prostatectomy: rectal injury in about 15%, bladder neck contracture in 15% and urinary incontinence in about 60%.[40]

Thermotherapy

Extreme cold or heat can be used to destroy the prostate, theoretically without damaging the surrounding structures. There are 3 treatment modalities currently available: cryotherapy, high-intensity focused ultrasound (HIFU) and photodynamic therapy (PDT).[2]

Cryotherapy

Cryotherapy of the prostate delivered via a transurethral probe is a relatively old technique, but the initial results were poor. Renewed interest was generated by the availability of third-generation cryoprobes using gas (helium or argon) rather than liquid nitrogen, allowing smaller diameter probes which are inserted via the perineum under transrectal ultrasonography (TRUS) guidance. Cryotherapy causes disruption of cell membranes, leading to vascular thrombosis and necrosis. It is reasonably effective, producing intermediate term biochemical control in a reasonable proportion of patients.[2]

The most common complication is ED in around 90% of previously potent men, urinary incontinence in about 10% and urethral sloughing in about 5%. A serious but rare complication is prostato-rectal fistula.[2,34]

High-intensity focused ultrasound (HIFU)

Tightly focused ultrasound energy is absorbed by the tissues, creating temperatures greater than 60°C which cause protein denaturation and coagulative necrosis. HIFU is performed under general or regional anaesthesia, using a TRUS probe equipped with a cooling device and real-time visualisation to monitor the treatment effect.

Complications include urethral strictures in about 20% and urinary incontinence in around 10%. Since the overall experience is limited and followup is immature, widespread use of HIFU can not be recommended at this stage.[2]

Photodynamic therapy (PDT)

PDT works on the basis of systemic administration of a photosensitiser which accumulates in the prostate where it can be activated by light (laser), generating active radicals which are tissue-toxic. Clinical studies using a photosensitizer derived from chlorophyll are being conducted in men with prostate cancer, but the technique remains experimental.[2]

Which treatment is best?

Both radical prostatectomy and radiotherapy are potentially curative, provided the cancer is confined to the prostate, but there are no large, randomised clinical trials directly comparing them with each other, or with active surveillance.[41,42] There are numerous studies of patient groups selected for either type of treatment, but because the reasons for selection may affect the outcome of treatment it is not possible to make direct comparisons, so there is no valid answer to the question which form of treatment is "best".

It is extremely important to inform patients and their families about all the management options with all their potential advantages and disadvantages. The information should be unbiased, and patients should be encouraged to seek a second opinion if they have any doubts.

Because there are no absolutely right or wrong choices, and because no two men are exactly the same, each patient should be given sufficient information and time to decide which management option would be best for him, in terms of his own fears and expectations.

The doctor should resist the temptation of influencing or coercing the patient or, even worse, making a decision on his behalf, because if anything goes wrong, the patient will hold the doctor responsible. It is best for the patient himself to decide what is best for him.

Nomograms available on the internet

Based on the data from large groups of patients, nomograms have been developed using various pre- and post-treatment parameters to predict the probability of cure after radical prostatectomy or radiotherapy.[43-47] These nomograms are available on the internet and can be used by the doctor to calculate the patient's probability of cure, given his disease parameters.

The Partin nomogram uses the biopsy grade, clinical T-stage and PSA at diagnosis to predict the probability of organ confined (curable) cancer. The Partin tables can be accessed on the internet by simply entering "Partin" into a search engine, e.g. Google. The web address is: http://urology.jhu.edu/prostate/partintables.php

The Kattan nomogram of the Memorial Sloan Kettering Cancer Centre uses the patient's age, biopsy grade, clinical T-stage, pre-operative PSA and number of positive biopsy cores to predict the probabilities of the patient having indolent cancer (not requiring treatment) or organ confined disease (potentially curable) and of remaining progression-free after radical prostatectomy or radiotherapy. It can be accessed by entering "Kattan nomogram" into Google. The web address is: http://www.mskcc.org/mskcc/html/10088.cfm

Words of wisdom

When considering the management options for prostate cancer, it is good to remember the words of wisdom attributed to Dr Willett F Whitmore of the Memorial Sloan Kettering Cancer Centre, New York:

- When cure is possible, is it necessary? When cure is necessary, is it possible?
- Patient selection is the often silent partner in treatment success.
- More people have made a living from prostate cancer than have died from it.

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