Optimizing decisions about treatment in locally advanced prostate cancer

The decision-making process for the management of locally advanced prostate cancer is very complex for both patients and health-care professionals. The Vitality Index can be used to help tailor therapy approaches to match the individual lifestyle needs of patients.

The management of men with all stages of prostate cancer is an increasingly complex process with a variety of available treatments and involvement of many different disciplines. Locally advanced disease is a common presentation in the UK, accounting for one third of all new cases. There is no clear consensus on optimal management as was highlighted by a survey of oncologists and urologists specializing in the treatment of this condition (Payne and Gillatt, 2007). This can be extremely confusing for patients, their families and their carers as they are faced with the dilemma of treatment options.

The majority of men want to be involved in management decisions after a diagnosis of cancer is made (Davison, 2004). However, it was identified that one fifth of all prostate cancer patients do not discuss or fully understand the potential discomfort and side effects associated with their treatment (*Table 1*) and the possible alternatives that are available (House of Commons Committee of Public Accounts, 2006). The Vitality Index is a tool that can be used in this situation by helping patients and health-care professionals to jointly review and agree on the most appropriate treatment by clarifying the patient's quality of life preferences. This structured approach to the management of locally advanced prostate cancer supports the Improving Outcomes Guidance (National Institute for Clinical Excellence, 2002) that advocates that the treatment selected for prostate cancer should be based on a combination of the multidisciplinary team's recommendations and the individual patient's values, attitudes and lifestyle preferences.

This article will review the current treatments available for locally advanced prostate cancer and discuss the practical ways that health-care professionals can involve patients in the decision-making process, using the Vitality Index.

Table 1. Some common side effects that may be experienced with treatment for prostate cancer

Bladder changes
Changes to bone health
Bowel changes
Breast changes
Changes to energy levels
Hot flushes
Mood changes
Changes to physical strength
Changes to your sex life
Weight changes

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Incidence and staging of prostate cancer

Prostate cancer has overtaken lung cancer to become the most commonly occurring cancer in men in the Western world. There are now over 30 000 new cases of prostate cancer diagnosed per year in the UK and it accounts for one in five of all new male cancers (Cancer Research UK, 2002). The mortality rate for prostate cancer stands at 10 000 men/year in the UK (Cancer Research UK, 2004) and it is the second most common cause of cancer-related death for men, accounting for 14% of male cancer deaths. Although the incidence of prostate cancer has risen in the last 20 years, the mortality has remained relatively stable. Increasing use of prostate-specific antigen (PSA) screening and advances in diagnostic techniques have led to prostate cancer being diagnosed at progressively earlier stages which have a lower risk of death in the majority of cases. The challenge is to identify and treat patients most at risk of dying from prostate cancer as opposed to those men who have less aggressive disease, who will die with their prostate cancer and not from it.

The investigations for the diagnosis and staging of prostate cancer are:

- Digital rectal examination to determine local involvement of the disease including any extracapsular spread or seminal vesicle involvement
- Measurement of PSA levels which is influenced by age, prostatitis, acute urinary retention and benign prostatic hypertrophy

- Transrectal ultrasound with needle biopsy, preferably to obtain octant biopsies which should be histologically analysed using the Gleason grading system (*Table 2*) (Gleason and The Veteran's Administration Cooperative Urologic Research Group, 1977).

Prostate cancer can be further staged with a bone scan and computed tomography or magnetic resonance imaging scan of the pelvis in order to determine any evidence of nodal or distant metastases.

The most widely used staging system for prostate cancer is the TNM (tumour, nodes, metastases) definition (*Table 3*). Using this staging system prostate cancer can be divided into three groups with different management approaches:

- Localized (confined to prostate, i.e. T1/T2 N0)
- Locally advanced (extracapsular spread or nodal disease, i.e. T1/T2/N+ or T3/T4N0/N+)
- Advanced (metastatic, i.e. any T/N with M1).

Locally advanced prostate cancer

Locally advanced, non-metastatic prostate cancer is common and accounts for approximately one third of all men with a prostate malignancy in the UK (British Association of Urological Surgeons, 2005).

There are a number of possible management options including watchful waiting, radiotherapy, prostatectomy and hormonal therapy either alone or in combination with radiotherapy or surgery. These therapies can be given with either palliative or radical intent. Men with locally advanced prostate cancer generally have a significant risk of disease progression and cancer-related death if left untreated. In principle, there are two major challenges involved in the management of this stage of disease:

1. The first is to treat the cancer in the prostate and surrounding tissues and this has traditionally involved external beam radiotherapy
2. The second takes into account the fact that the majority of men with locally advanced prostate cancer will already have microscopic metastases at distant sites that are too small to be detected on imaging.

This means that despite improvements in local treatment, many patients will ultimately progress to symptomatic metastatic disease which can cause debilitating morbidity including bone pain, fracture, spinal cord compression and urinary dysfunction. There is evidence that the addition of systemic treatment in the form of hormone therapy causing androgen suppression is superior to local treatment alone in patients with locally advanced disease (Zagars et al, 1997; Pilepich et al, 2001, 2005; Bolla et al, 2002, 2005; Al-Salihi et al, 2006; Messing et al, 2006). There is no consensus on the optimal treatment of locally advanced prostate cancer. Management decisions should be made after all treatments have been discussed by the multidisciplinary team (to include urologists, oncologists and nurse specialists) and the balance of benefits and side effects of each modality have been considered by the patient with regard to his own individual circumstances.

Treatment options for locally advanced prostate cancer

Watchful waiting

Watchful waiting is an approach in the management of prostate cancer which aims to avoid treatment or delay it for as long as possible, thereby avoiding any side effects from therapy. Patients who eventually develop symptoms of progressive prostate cancer receive palliative treatment, usually with hormone therapy. For the majority of men with locally advanced prostate cancer there is a risk of significant disease progression which can cause debili-

Table 2. Gleason grade scoring

Prostate cancer biopsy is analysed according to:	Degree of glandular differentiation
	Relationship of glands to stroma
	Graded 1–5 (1 = well differentiated; 5 = poorly differentiated)
	Two most commonly occurring grades are summed to give the total Gleason score (minimum 2; maximum 10)

From Gleason and Mellinger (1974)

Table 3. Tumour, nodes, metastases (TNM) definitions of prostate cancer

Primary tumour (T)	TX: Primary tumour cannot be assessed	
	T0: No evidence of primary tumour	
	T1: Clinically inapparent tumour not palpable nor visible by imaging	T1: Clinically inapparent tumour not palpable nor visible by imaging
		T1a: Tumour incidental histological finding in ≤5% of tissue resected
		T1b: Tumour incidental histological finding in >5% of tissue resected
		T1c: Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen)
	T2: Tumour confined within prostate	T2a: Tumour involves 50% of one lobe or less
		T2b: Tumour involves >50% of one lobe but not both lobes
		T2c: Tumour involves both lobes
	T3: Tumour extends through the prostate capsule	T3a: Extracapsular extension (unilateral or bilateral)
		T3b: Tumour invades seminal vesicle(s)
	T4: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	
Regional lymph nodes (N)	NX: Regional lymph nodes were not assessed	
	N0: No regional lymph node metastasis	
	N1: Metastasis in regional lymph node(s)	
Distant metastasis (M)	MX: Distant metastasis cannot be assessed (not evaluated by any modality)	
	M0: No distant metastasis	
	M1: Distant metastasis	

From American Joint Committee on Cancer (2002)

tating symptoms. This is especially so for those men who have other unfavourable disease characteristics at presentation that are associated with more rapid progression, such as a Gleason grade equal to or above eight or a PSA above 20 ng/ml.

The data for watchful waiting in locally advanced disease are sparse. The Medical Research Council prostate working party conducted a large trial in which men not suitable for treatment with curative intent were randomized to immediate *vs* deferred hormone therapy. The results suggested an advantage for immediate therapy in terms of symptomatic progression and survival for men with locally advanced prostate cancer (Nilsson et al, 1997).

Watchful waiting can be suitable for some older men with significant co-morbidities and slowly progressive disease which can be monitored with regular PSA measurements and careful clinical assessment and discussion.

Hormone therapy alone

Hormone therapy is often the mainstay of treatment for locally advanced prostate cancer as there is a high risk of microscopic metastases. It can be used alone or in combination with radiotherapy or surgery. As stated above, there can be advantages in terms of delaying cancer progression and preventing the complications of metastatic prostate cancer (e.g. spinal cord compression, fractures) when treatment is given early rather than waiting until symptoms develop. Patients with locally advanced prostate cancer can be treated with two different types of hormone therapy:

1. The lutenizing hormone-releasing hormone agonists (LHRHa), e.g. goserelin, act by suppressing testosterone production from the testes through positive feedback of LHRH at pituitary level. These drugs are administered either monthly or 3-monthly by subcutaneous injections. There can be an initial testosterone flare at the time of administration of the first implant and this associated tumour flare can be prevented by treating with an antiandrogen drug to block testosterone at a cellular level for 2 weeks before and 2 weeks after the first injection. The side effects of LHRHa include erectile dysfunction, loss of libido, hot flushes, osteopenia/osteoporosis and breast swelling.
2. The alternative use of antiandrogen therapy alone, e.g. bicalutamide 150 mg, has been investigated in the Early Prostate Cancer (EPC) programme which is the largest ever prostate cancer treatment study in the world. In this trial, over 8100 men with non-metastatic prostate cancer were randomized to bicalutamide 150 mg *vs* placebo in addition to standard care which could be either radical prostatectomy, radical radiotherapy or watchful waiting. Results from the third analysis of EPC at a median follow up of 7.4 years have shown that use of bicalutamide compared to watchful waiting significantly ($P<0.001$) increases disease progression-free survival in men with locally advanced prostate cancer (McLeod et al, 2006). In addition, this trial showed a trend towards increased overall survival for this subgroup of men. Bicalutamide 150 mg has some advantages over castration-based therapy in that it can maintain physical capacity and bone mineral density and reduces the risk of hot flushes and loss of sexual function. However, it can cause gynaecomastia and mastalgia. The different side-effect profiles of these two types of hormone therapy can allow clinicians and patients to choose the best approach to maintain quality of life for that individual.

Radical prostatectomy in combination with hormone and/or radiotherapy

Radical prostatectomy has traditionally been reserved for cases with low risk of significant extraprostatic spread. However, for men with pathological high-risk disease after surgery (pT3 or pN1), there is evidence that the addition of adjuvant treatment may increase control or survival.

Messing et al (2006) showed that 10-year survival in men with nodal spread undergoing radical prostatectomy is significantly increased by the addition of adjuvant castration-based therapy. The EORTC 22911 study (Bolla et al, 2005) showed a significant improvement in clinical progression-free survival for men with pT3 disease treated with adjuvant radiotherapy after prostatectomy. A survey of specialist oncologists and urologists in the UK indicated that there is a trend for radical prostatectomy to be included in the management of locally advanced prostate cancer as part of a combined modality approach for carefully selected patients and this needs further evaluation (Payne and Gillatt, 2007). The more traditional recommendations are that patients with locally advanced disease should be treated first line with external beam radiotherapy in combination with hormone therapy, or hormone therapy alone.

Radiotherapy in combination with hormone therapy

Radical therapy for locally advanced prostate cancer has traditionally included external beam radiotherapy. However, more than one third of patients can experience disease progression within 5 years with this treatment modality alone. The risk of progression or relapse increases with an initial PSA level ≥10 ng/ml and any single Gleason score equal to or above four on biopsy (Zagars et al, 1997). There is evidence that increased radiation dose is associated with increased cancer cell kill for men with prostate cancer. Clinical studies have shown that dose escalation to ≥70 Gy results in better disease control (Pollack et al, 2002). However, the traditional two-dimensional technique of treatment planning and delivery is limited by the normal tissue toxicity of the surrounding structures (bladder, rectum and bowel), such that the dose that can be safely delivered to the prostate by external beam radiotherapy is 65–70 Gy.

New technological advances have improved the precision of external beam radiotherapy and have permitted the delivery of higher doses. These include the use of the conformal radiotherapy (3D-CRT) approach, that is shaping the beam to the prostate gland in three dimensions, and intensity modulated radiotherapy (IMRT) which is an even more advanced form of 3D-CRT. A further method of dose escalation is with a high dose rate brachytherapy boost in combination with external beam radiotherapy (Al-Salihi et al, 2006). The treatment fields can include the prostate gland and seminal vesicles and pelvic lymph nodes. Acute toxicity of radiotherapy to the prostate includes diarrhoea, cystitis and tiredness, and long-term morbidity includes impotence (50%) and proctitis (<5%). Patients with significant bowel disease or bilateral hip replacements are not suitable for radiotherapy.

There is strong evidence that the addition of systemic treatment in the form of hormone therapy is superior to radiotherapy alone in patients with locally advanced disease. Hormones are often used in the neoadjuvant setting to reduce tumour bulk before radiotherapy and allow smaller fields of radiation to be applied with potentially less dose to the surrounding normal tissues. This has been shown to demonstrate a significant (P=0.004) improvement in disease-free survival (Pilepich et al, 2001).

Adjuvant androgen suppression immediately after radical radiotherapy has been shown to significantly increase overall survival and progression-free survival, and significantly reduce local progression, distant metastases and biochemical progression in several large randomized studies using goserelin (an LHRHa) (Bolla et al, 2002; Hanks et al, 2003). One such study randomized 977 men to radiotherapy alone or radiotherapy in combination with goserelin. At a median follow up of 7.6 years adjuvant goserelin significantly improved survival compared with radiotherapy alone (estimated 10-year survival rate 49 *vs* 39%; P=0.002). The largest benefits were seen in the subgroups with high Gleason grades (eight or above) (Pilepich et al, 2005). There is still some debate regarding the optimal timing and duration of hormone treatment which is usually between 2 and 3 years. The EPC study has also demonstrated a significant increase in overall survival with the addition of bicalutamide 150 mg to radical radiotherapy in men with locally advanced disease and this can be used as an alternative to LHRHa in this setting (McLeod et al, 2006). As previously discussed, the differences in side effects between these two types of hormone therapy allow patients to select the treatment that is best suited to their individual needs and lifestyle.

The use of combined modality treatment for locally advanced prostate cancer has been an exciting development and is now generally accepted as standard therapy for men with locally advanced prostate cancer who are to be treated with radical intent.

The Vitality Index

The Vitality Index was developed to support the physician or specialist nurse and patient in their discussions about the available treatments for locally advanced prostate cancer and to help determine the extent that the treatment's side effects may impact on the patient's quality of life. It is known that men who incorporate quality of life consideration when deciding on their treatment options feel better about their treatment choices and are less likely to experience regret (Barry et al, 2004). Men with prostate cancer generally report a worse experience than patients with other cancers. It has been reported that they were almost twice as likely not to have been informed about side effects of treatment and less likely to have understood what they have been told (National Audit Office, 2005).

The Vitality Index was developed to try and address some of these issues (*Figure 1*). It is designed to enable men to indicate their level of concern about the common side effects for the treatment of locally advanced prostate cancer (O'Connor and Fitzpatrick, 2006) on a visual analogue scale. Emphasis is given to the fact that treatment side effects affect men differently and may differ in how long they last and whether they disappear when a treatment is stopped. This facilitates discussion and enables the health-care professionals to agree on, or review with the patient, the most appropriate treatment by clarifying quality of life preferences for both therapies of palliative and radical intent.

Conclusions

In the last 10 years there have been major advances in the treatment of locally advanced prostate cancer. There is ongoing evidence for significant survival benefits of combined modality treatment with hormones and radiotherapy. This has been shown for both goserelin and bicalutamide 150 mg. Hence, the patient has a choice of hormonal agents in this setting depending on his individual needs and lifestyle. There have also been advances in radiotherapy and the benefits of dose escalation have been demonstrated. However, there is no optimal treatment for all men with locally advanced prostate cancer. A multidisciplinary team approach is required to maxi-

Figure 1. Using the Vitality Index with the patient.

The Vitality Index helps the health-care professional to explain, in simple terms, that there are different treatment options available for locally advanced prostate cancer and that each of these treatments has its own side effects and potential impact on quality of life. The most common side effects, as identified by a literature review and health-care professionals' feedback, are explained in a concise and patient-friendly format. Emphasis is given to the fact that treatment side effects affect men differently and may differ in how long they last and whether they stop with a change in treatment

Using the Vitality Index involves the patient being asked to indicate how concerned he would be, or are, about the listed side effects affecting his quality of life. This enables the patient and his health-care professional to discuss the benefits and side effects of the different treatment options and explore any concerns that he may have

mize clinical outcomes while taking men's preferences into consideration. In addition, using tools such as the Vitality Index in consultation can provide a structured approach for men diagnosed with this disease and their carers to participate in the decision-making process and ensures they are fully informed of both the efficacy and side effects of any proposed therapies, thereby tailoring their management according to their individual lifestyle and needs. **BJHM**

Conflict of interest: Dr H Payne has been an advisor to AstraZeneca who have developed the Vitality Index.

KEY POINTS

- In the UK, 30 000 new cases of prostate cancer are diagnosed each year with a mortality rate of 10 000 men/year.
- Locally advanced prostate cancer is a common presentation in the UK, accounting for one third of all new cases.
- There is no clear consensus as to the optimal management of locally advanced prostate cancer.
- Management options can include watchful waiting, radical radiotherapy, surgery and hormone therapy either alone or in combination.
- The use of a multidisciplinary team is required to maximize clinical outcomes.
- The majority of men want to be involved in management decisions after a diagnosis of cancer is made.
- Decision-making tools can be used to tailor management according to the individual patient's lifestyle and needs.

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