

BEST VERSUS AFFORDABLE TREATMENT OPTIONS IN PROSTATE CANCER

Adenocarcinoma of the prostate is a complex disease to treat. Management is multidisciplinary and is influenced by patient's factors, disease stage, extent, logistics and economic factors. It is also changing rapidly with the development of new agents and trials that demonstrate their efficacy.

Several trials provide strong arguments against population-based screening with prostate-specific antigen (PSA). An American trial showed no difference in prostate-specific mortality but was confounded because a high proportion of men in the control arm had PSA tests.^[1] The European trial showed a small benefit for prostate-specific mortality, but the number needed to treat to save a prostate-specific death was large, and there was no difference in overall mortality.^[2] If screening has been undertaken and shown high PSA, the knee-jerk reaction is to do a transrectal ultrasound biopsy and the difficult question arises, as to whether the disease should be treated. There is reinforcement of active monitoring from results of the excellent ProtecT trial, which randomised 1643 men with screen-detected prostate cancer three ways, between active treatment (radical prostatectomy [RP] or external radiation therapy) and active monitoring.^[3] After 10 years of follow-up, the cancer-specific survival was the same between those actively treated and those on active monitoring (99% and 98.8%, respectively), as was overall survival. Only metastatic progression differed (6% in the active monitoring group as compared to 2.6% in the treated group).^[3] Screening has resulted in overdiagnosis and overtreatment and the ProtecT trial provides strong evidence against population-based screening since there is negligible benefit from subsequent treatment. We strongly discourage the use of population-based screening with PSA; it should be limited to men at high risk of disease.

Although population-based screening does not appear to impact on survival, there is evidence that local treatment can improve survival for clinically diagnosed localised

prostate cancer. Improvements in overall survival due to surgery or radiotherapy, as compared to active monitoring or hormonal therapy alone, are, however, relatively small^[4-6] and radical treatment should be limited to younger men whose life expectancy in the absence of prostate cancer is at least 10 years. Due to lack of primary health care services in Pakistan, cancers are usually diagnosed at a late stage and relatively few patients are candidates for surgical options with open or laparoscopic RP that is available only in few centres. Robotic surgery is not performed in Pakistan, but this is appropriate since there has been no difference in outcome with robotic prostatectomy as compared to RP.^[7] Pelvic nodal dissection is not performed routinely as surgeons are not trained to do this procedure.

Due to recent advances in radiotherapy techniques such as intensity-modulated radiotherapy and volumetric arc therapy with or without image-guided radiation therapy, higher doses of radiotherapy can be delivered safely to the prostate gland without causing local damage. Radiotherapy dose of >74 Gray with hormonal treatment as per risk stratification is the standard of treatment in prostate cancer. 6 months of hormonal therapy (see below) are considered standard in patients with intermediate risk prostate cancer and durations of 2–3 years are supported by clinical trials in patients with high-risk disease since outcomes are superior to those with radiation alone.^[8] Dose escalation trials have shown improved biochemical control (i.e., without rise in PSA) with higher doses; however, there was no effect on overall mortality or disease-related mortality.^[9]

Androgen deprivation therapy (ADT) to achieve castration (serum testosterone <20 ng/dl) enhances the effects of radiotherapy for locoregional disease^[8] but has not provided consistent benefit when given before or after RP. ADT is the mainstay of treatment for advanced incurable disease. Orchiectomy was used historically and is effective and cheap, but ADT is now most often achieved using a luteinising hormone-releasing hormone agonist (LHRH), which is injected usually every 3 months in a long-acting depot form. Since LHRH agonists lead initially to a rise in serum testosterone before a subsequent fall, a peripheral

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antiandrogen such as bicalutamide is given for about 10 days before and after the initial injection to prevent a flare. An LHRH antagonist (degarelix) is also available that does not cause a flare, but it is more expensive and requires a larger and more frequent volume of injection.

The most common sites for distant metastases are lymph nodes and bone, but visceral metastases may also occur and are associated with poor prognosis. ADT is the backbone of treatment for metastatic prostate cancer and can be given continuously or using an intermittent schedule guided by changes in PSA.^[10] The initial response (both symptomatic and biochemical - i.e., a fall in serum PSA) is observed in about 90% of men; the median duration of response is 1.5–2 years, although prolonged responses are observed, especially in men with well-differentiated (low Gleason score) tumours. Antiandrogens such as flutamide or bicalutamide, which block the androgen receptor, have been used to achieve maximal androgen blockade (MAB). However, multiple trials have not shown consistent benefit from initial use of MAB,^[11] and the preferred strategy is to add bicalutamide after progression of disease following initial response to orchiectomy or an LHRH agonist when about a third of men will have a further, usually shorter, response to treatment. There is no evidence to support the dose escalation of antiandrogens. However, hormonal therapy is changing with the development of androgen synthesis inhibitors (abiraterone acetate) and more potent antiandrogens (enzalutamide) - see below. If these agents are not available, a small proportion of men can respond to further hormonal treatment with ketoconazole (which inhibits androgen synthesis) given with hydrocortisone to dexamethasone or low-dose (1 mg/day) diethylstilbestrol (DES). Higher doses of DES (3–5 mg/day) have also been used in the past as primary ADT with high response rates, but cardiovascular toxicity occurred in 10–30% of patients, with events including deep vein thrombosis, myocardial infarction, transient ischemic attack, oedema and gynaecomastia. Side effects are reduced with lower dose of DES and prophylactic aspirin.

When metastatic prostate cancer progresses after ADT (with or without further hormonal treatments), the usual treatment in men fit enough to receive it has been chemotherapy with docetaxel and prednisone. About 50% of men with respond to treatment and the median survival in the pivotal TAX 327 trial was about 19 months^[12]

although shorter when given to less selective patients in everyday practice.^[13]

Recent advances have changed the flow and sequence of metastatic prostate cancer. Phase III evidence of improved survival in metastatic prostate cancer with abiraterone or enzalutamide in both pre- and post-chemotherapy patients^[14-17] changed the canvas of prostate cancer treatment. The recent CHAARTED and STAMPEDE trials showed that giving docetaxel to men with hormone-sensitive prostate cancer together with ADT improved survival^[18,19] and upfront docetaxel for 6 cycles became a standard approach in treating men with a heavy burden of disease, or those presenting initially with metastases. Recent strong evidence has emerged for giving abiraterone in castration naïve metastatic prostate cancer. In two large randomised controlled trials (STAMPEDE and LATITUDE),^[20,21] ADT plus abiraterone and prednisolone showed significantly higher rates of overall and failure-free survival than ADT alone. The unanswered question is sequencing: Whether abiraterone is better than docetaxel in the upfront setting. Abiraterone is better tolerated; however, the high cost means that the majority of men in developing countries are unable to afford it. However, abiraterone is produced more cheaply in India than in the west, and there is good evidence that abiraterone can be given at 250 mg/day after a meal with similar pharmacokinetics and efficacy as the approved dose of 1000 mg/day fasting, thereby reducing the cost of treatment substantially.^[22] Docetaxel is still cheaper but considerably more toxic.

Other newer agents include cabazitaxel, which has shown improved survival compared to the older mitoxantrone as the second-line chemotherapy for patients after docetaxel.^[23] The alpha-particle-emitting radioisotope alpharadin was also shown to improve survival in men with bone-dominant metastatic prostate cancer.^[24]

Like all other cancers, quality of life is most important. Unfortunately, quality of life data is not well reported. Supportive care including palliative radiotherapy and analgesics is important in controlling disease-related symptoms. Zoledronic acid and denosumab are used regularly to reduce skeletal-related events. They have similar efficacy but are overused since they have not influenced survival or delayed progression of disease,

and all other types of effective therapy decrease skeletal-related events.

Advances in the treatment of prostate cancer will continue, but it is not great progress if new and effective agents are so expensive that they cannot be given to men who need them. Cheaper options such as ketoconazole and DES will remain important in developing countries.

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Received: 26 March 2018 / Accepted: 29 March 2018

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