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Recent Advances in Management of Prostate Cancer

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Abstract

Prostate cancer is the second most common cancer in males worldwide and the incidence is increasing due to ageing population, screening facilities and rising awareness. This is a disease of the elderly and is biologically less aggressive as compared to some other malignancies. Most of the patients present with organ-confined disease, thus the age adjusted death rates are declining due to early detection and timely intervention. The various treatment options include external radiotherapy, brachytherapy or radical prostatectomy for low-risk early stage disease; hormonal therapy and external radiotherapy for advanced high-risk cases; and hormonal therapy, palliative radiotherapy with or without chemotherapy for metastatic disease. The main aim of this article is to sensitize the readers with the recent advances in management of cancer prostate.

Prostate cancer is the second most common cancer in men worldwide with about 75% of the cases occurring in developed countries. More than 1.1 million cases of prostate cancer were recorded in 2012, accounting for around 8% of all new cancer cases and 15% in men. With an estimated 307,000 deaths in 2012, it is the fifth leading cause of death from cancer in men. The worldwide Ca prostate burden is expected to grow to 1.7 million new cases and 499,000 new deaths by 2030 simply due to the growth and aging of the global population; thus making it a major public health problem [1-4]. Standard options for the initial treatment of men with clinically localized prostate cancer (without distant metastases) include radiation therapy (RT in the form of brachytherapy and/or external beam), radical prostatectomy, or in carefully selected patients, active surveillance. The treatment options for locally advanced high-risk cases include external RT and androgen deprivation therapy (ADT). The choice of treatment is determined by a variety of factors including patient preference, clinician judgment, and resource availability. The ^{68}Ga-prostate-specific membrane antigen (^{68}Ga-PSMA) has been recently developed to be used, as a ligand, in positron emission tomography/computed tomography (PET/CT) prostate cancer imaging, to detect prostate disease. ^{68}Ga-PSMA PET/C is more effective in detecting metastases, lymph nodes, and recurrent prostate cancer when compared to ^{18}F-choline-based PET/CT and CT [5].

The surgical option for early Ca prostate includes open or robotic radical prostatectomy along with extended pelvic lymph node dissection. Radical prostatectomy is indicated in patients with localized Ca prostate with more than 10 years of life expectancy and with no coexisting medical morbidities. In high volume centers with good expertise, the results of robotic and laparoscopic assisted prostatectomy are similar to open prostatectomy. Robot-assisted surgery has been rapidly adopted in the developed countries for prostate cancer. Robot-assisted radical prostatectomy has comparable intermediate cancer control as evidenced by less use of additional postoperative cancer therapies and equivalent cancer specific and overall survival [6-9]. Longer term follow-up is needed to assess for differences in prostate cancer specific survival, which was similar during intermediate follow-up. Salvage prostatectomy is an option in highly selected patients who suffer local recurrence without metastasis and were previously treated by external RT or brachytherapy.

Patients with early stage prostate cancer have a variety of curative radiotherapy options, including brachytherapy, conventionally-fractionated external beam radiotherapy (CF-EBRT) and hypofractionated stereotactic body radiotherapy (SBRT) [10,11]. The dose of RT by conventional fractionation is 75.6 to 79.2 Gy; and up to 81 Gy for intermediate and high risk cases for optimum local control. Over the past several decades, there has been a rapid technologic advancement in the treatment of prostate cancer with external beam radiation. The previous standard was 3-dimensional (3D) conformal radiation therapy (CRT), in which multiple shaped radiation beams were used to limit dose to structures other than the prostate. This technique slowly paved the way for intensity modulated radiation therapy (IMRT) and later by image-guided radiotherapy (IGRT). Moderately hypofractionated image-guided IMRT plan using a fraction size of 2.4-4 Gy over 4-6 weeks has got similar efficacy and toxicity and is an alternative to conventional fractionation schedules. The potential advantage of IMRT compared with conformal radiation therapy is its ability to deliver high radiation doses to the prostate while minimizing doses to surrounding organs, including dose to bowel and femoral heads [12]. Patients with high-risk and very-high risk cancers should receive ADT of 2-3 years in neoadjuvant, concurrent and adjuvant setting along with RT.

Extremely hypofractionated image-guided stereotactic body radiotherapy (SBRT) using a fraction size of 6.5 Gy and more is an upcoming and promising technique [13,14]. Although results of CF-EBRT are well known, the use of SBRT for prostate cancer is a more recent development, and long-term follow-up is not yet available. The delivery of a simultaneous integrated boost with hypofractionated SBRT, by Rapid Arc or Multiplan and other such tools, to the intra-prostatic tumor nodule may improve local control [15]. In one recent study, patients treated with SBRT experienced a lower PSA nadir and greater rate of decline in PSA 2 and 3 years following completion of RT

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than with CF-EBRT, consistent with delivery of a higher bioequivalent dose [16]. In another such study, stereotactic body radiation therapy (SBRT) for patients with oligometastatic prostate cancer provided optimal metastasis control and acceptable toxicity with doses ≥18 Gy [13].

SBRT should also be considered in patients with castration-refractory, oligometastatic prostate cancer who have limited options for systemic therapy. SBRT could minimize rectal toxicity by reducing the volume of rectum receiving high radiation doses and offers the potential radio biologic benefits of hypofractionation. The rate and severity of dysuria and hematuria following SBRT is comparable to patients treated with other radiation modalities [12].

Proton therapy is a relatively new, high-profile, high-cost prostate cancer treatment. Protons differ from the high-intensity X-rays typically used in radiation treatments in how they interact with tissue to deposit radiation dose. Although they are no more effective biologically than the X-rays used in typical external beam radiation, the physical properties of protons result in the ability to regulate the range they penetrate within the body. The resulting sparing of damage to tissue before and beyond the target is unattainable with traditional X-ray-based approaches and makes proton beam radiation appealing dosimetrically. Proton therapy through the use of the Bragg peak affords clinicians a tool with which highly conformal dose can be delivered to the target while minimizing integral dose to surrounding healthy tissue. To gain maximum benefit from proton therapy adequate patient immobilization must be maintained to ensure accurate dose delivery. PBT has significant theoretical dosimetric advantages over photon EBRT. However, proton therapy has the disadvantage of being too costly and is available only in very limited Oncology centers [17-20].

Patients with a high probability of organ-confined disease with low-risk factors can be appropriately treated with low dose rate (LDR) brachytherapy alone [21]. Most practitioners include patients with stage T1-T2a cancer, a prostate-specific antigen (PSA) level of 10 ng/mL or less, and a Gleason score of 6 or lower in this category. Selected patients with intermediate and high-risk factors can be offered LDR brachytherapy and external RT, with or without ADT [22-24]. The recommended prescription doses for monotherapy are 145 Gy for I-125 and 125 Gy for Pd-103; while doses after 40-50 Gy of external RT are 110 Gy and 90-100 Gy respectively. Relative contraindications to brachytherapy include previous transurethral resection of the prostate (TURP), pubic arch interference, obstructive symptoms and morbid obesity. Glands between 50 and 60 g should be downsized. Hormone ablation has been reported to downsize the prostate gland by 25-40% and is used to facilitate brachytherapy in patients with large glands. The toxicity profile of ADT should always be considered before prescribing it. The patients who underwent radical prostatectomy can be offered adjuvant external radiotherapy if pathological stage pT3, positive margins, Gleasons score 8-10 or seminal vesicle involvement is noted [25,26]. Radiopharmaceutical therapy with Radium-223 is beneficial for patients with castration-resistant prostate cancer (CRPC) with painful bony metastases and no visceral spread [27].

Androgen deprivation therapy (ADT) has been the mainstay for management of advanced/metastatic Ca prostate [28,29]. ADT is also recommended in combination with radiotherapy in the management of intermediate and high-risk localized disease [30,31]. Surgical castration, the seminal 'gold standard' ADT, is irreversible and can have negative psychological effects on patients. Surgical castration has generally been replaced by medical castration induced by gonadotrophin-releasing hormone (GnRH) agonists. However, GnRH agonists may be associated with mechanism-of-action drawbacks, for example, promoting a counterintuitive initial testosterone surge that might delay the onset of initial testosterone suppression and may also result in potentially detrimental exacerbation of clinical symptoms (clinical flare) in advanced disease. Hence anti-androgens should be administered prior to and along with GnRH agonists for initial 7 days of therapy. The GnRH antagonists offer an alternative ADT that avoids the testosterone surge and micro surges associated with agonists, and thus more closely resembles the original goal of surgical castration. LHRH agonists or antagonists are as effective as surgical castration [32].

Degarelix is a gonadotrophin-releasing hormone (GnRH) antagonist for the first line treatment of androgen-dependent advanced prostate cancer. It has a direct mechanism of action that blocks the action of GnRH on the pituitary with no initial surge in gonadotrophin or testosterone levels. Degarelix is the most extensively studied and widely available GnRH antagonist worldwide. Clinical studies have demonstrated similar efficacy to the GnRH agonist leuprolide in achieving testosterone suppression in patients with prostate cancer. However, degarelix produces a faster suppression of testosterone and prostate-specific antigen (PSA), with no testosterone surge or micro surges, thus preventing the risk of clinical flare in advanced disease and is likely to delay progression to castration-resistant disease), and a more significant impact on bone serum alkaline phosphatase and follicle-stimulating hormone. Degarelix is generally well tolerated, with no reports of systemic allergic reactions in any clinical studies [33,34].

Eventually, almost all patients with metastatic disease become resistant to androgen ablation. In patients with castrate serum testosterone levels (less than 50 ng/dL), castrate-resistant prostate cancer is defined as 2-3 consecutive rises in PSA levels obtained at intervals of greater than 2 weeks and/or documented disease progression based on findings from computed tomography (CT) scan and/or bone scan, bone pain, or obstructive voiding symptoms. Once the prostate cancer becomes resistant to ADT and becomes CRPC, several options of secondary hormonal manipulation exist. Patients who never received docetaxel and have minimal symptoms are likely to benefit by different anti-androgen like flutamide, bicalutamide, nilutamide and enzalutamide. Since androgen receptor activation and autocrine/paracrine androgen synthesis are likely mechanisms of CRPC, addition of adrenal/paracrine androgen synthesis inhibitors like ketoconazole (with or without hydrocortisone) or abiraterone with prednisolone can be tried [35-38]. In the patients of CRPC who received prior doectaxel based therapy, administration of enzalutamide and abiraterone plus prednisolone provide survival benefit [39-41]. Immunotherapy with Sipuleucel-T can be offered to patients with metastatic CRPC who are well-preserved, have minimal symptoms, have life expectancy of more than 6 months and don't have liver metastases [42]. Palliative chemotherapy with docetaxel with or without prednisolone may provide symptomatic relief in

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patients of metastatic CRPC [43].

Patients who have completed their definitive management should be followed up with serial PSA monitoring at 6-12 months duration for initial 5 years, and then annually, along with digital rectal examination. Patient must be evaluated for therapy-induced acute and delayed toxicities like erectile dysfunction, dysuria, hematuria, radiation proctitis and colitis etc and rehabilitated accordingly [44-47]. To conclude, cancer prostate has got various therapeutic options and each patient needs to be managed multimodally with close collaboration of urologists, radiation oncologists and medical oncologists.

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