COMMENTARY

PROSTATE CANCER

Prostate cancer is the most common non-skin cancer in men in the western world and the second leading cause of cancer mortality in men. In a study in Ghana, a sub- Saharan African country, it was the second cause of cancer mortality after hepatocellular carcinoma[1]

The established risk factors for developing prostate cancer include advancing age, race (high in men of African ancestry) and a positive family history. Androgens, dietary factors such as high saturated fat intake, physical inactivity, sexual factors with associated inflammation and obesity are also acknowledge risk factors[2]

Genetic factors are considered important and said to account for about 42% of the risk of developing prostate cancer. A high penetrant gene inherited as autosomal dominant is implicated in 10% of all cases of prostate cancer. Of the many loci investigated, only HPC1 has been found to have positive results[2]. This suggests interactions between multiple low penetrant genes and environmental factors in the causation of hereditary prostate cancer. Migrant studies reveal that ethnic factors, life style, or environmental factors may explain the difference between high risk and low-risk populations.

Surgical treatment of localized disease by open radical prostatectomy has been shown to decrease disease-specific mortality in patients with prostate cancer. The introduction of robotic radical prostatectomy with its technical innovation of binocular three-dimensional visualization, a times 10 magnification, tremor filtration, motion scaling and wristed instruments allow for ease of working in the male pelvis[3]. With reduction in the occurrence of side effects such as erectile dysfunction and urinary incontinence, no or minimal blood transfusions and same day discharge from hospital, more patients are opting for these procedures. While the robotic technology is being used in increasing proportions of men with prostate cancer opting for surgery, it is yet to be available in most developing/ low-resource countries.

The use of external beam radiotherapy (>74 Gy) has been noted to have a prostate cancer specific mortality higher than that of radical prostatectomy[4]. However, with use of computer based treatment planning such as 3-dimensional conformal radiotherapy (3D-CRT), intensity- modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), it has led to a more precise radiation delivery and the ability to escalate the tumor dose to the prostate, seminal vesicles and adjacent adventitia with reduction of toxicity to normal tissues. Current reports indicate that the use of brachytherapy alone for prostate cancer with low risk of extra capsular extension offers satisfactory survival rate comparable to radical prostatectomy[4]. With its relatively minimal side effects it is likely to increase in importance in the management of localized prostate cancer. (T1/T2, PSA<10ng/ml, and Gleason score ≤ 6). However if there is a significant risk of extra capsular extension then brachytherapy and a supplementing external beam radiotherapy has a better survival advantage[5]. Post-operative supplemental external beam radiation therapy has also been found to lead to significant PSA remission rate in patients with a rising PSA after radical prostatectomy[6].

For locally advanced disease (T3/T4), the use of adjuvant androgen ablation in addition to external beam radiation therapy offers an improved survival advantage.

The management of metastatic prostate cancer with androgen deprivation continues to be practiced. The challenge is the management of castrate resistant prostate cancer (rising PSA or development of symptoms of metastatic disease despite androgen deprivation therapy) with disease progression within a median of 18-24 months. Initial institution of maximum androgen blockade using androgen receptor blockers such as bicalutamide leads to an observed PSA responses in 30% -35% of the patients. Should there be evidence of disease progressing, withdrawing of the anti- androgen leads to a response rate in the range of 20% -30% of patients. It has been suggested that other anti- androgens such as nilutamide, flutamide or ketoconazole if instituted are associated with a transient PSA reductions in about 30%[7]. The use of diethylstilboesterol with aspirin (to counteract the feared thrombo-embolism) is practiced in low resource countries. As the androgen receptors remain active, androgen deprivation therapy is recommended to be continued even in the presence of perceived castrate resistant state. While newer treatments such as enzalutamide (androgen receptor blocler) and abiraterone (irreversible inhibitor of CYP17) with prednisone is of clinical benefit, the order in which to use them to achieve the greatest survival advantage is under investigation. The availability and cost makes it largely in accessible to those in low income regions.

Systemic chemotherapy using docetaxel (75mg/ m^2 every three weeks) with oral prednisone (5mg twice a day) is recommended in men with clinical or biochemical progression and with detectable macroscopic metastatic disease. This is observed to

lead to improve over all survival, disease control, symptom palliation and quality of life.

Immunotherapy using sipuleucel-T has been found to lead to improvement in mortality risk. Palliative radiation is used for pain associated with bone metastasis. Radioisotopes such as Strontium and samarium are useful in the presence of wide spread bony metastasis. Their use results in an improvement in the quality of life due to reduction in metastatic bone pain. The use of bisphosphonates such as zoledronic acid (4mg every 3-4 weeks) prevents prostate cancer related skeletal complications such as bone pain and pathological fractures. Denosumab (inhibitor of receptor activator for nuclear factor κB ligand) prevents bone loss resulting from androgen deprivation therapy.

Screening for prostate cancer has been an area of debate in recent times. There is however an agreement on the fact that early detection of a localized prostate cancer can be cured with an improved survival rate or quality of life. Two approaches have been described; early detection and systematic screening. Early detection is based on evaluation from a patient's request or as part of a medical examination. Systematic screening is that of a planned examination of the at risk population. The evaluation involves the use of digital rectal examination and serum PSA. The overall benefit of population based screening (systematic) as relates to reducing deaths due to prostate cancer has been called into question. In some countries however, screening using the serum PSA with digital rectal examination is a policy in men above 50 years with life expectancy more than 10 years[8].

The areas that need research has to do with disparity in the incidence, presentation, clinical and survival between those of African ancestry and the rest of the world. Genome wide studies/ research have identified some association between high risk prostate cancers with abnormalities of specific chromosomes. The clinical significance of these findings are yet to be integrated into clinical practice. It is expected that these studies will contribute to understanding some of the genetic associations. Of interest also is the effective management of castrate resistant prostate cancer to achieve a longer survival more so after failure of docetaxel based chemotherapy.

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