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INCIDENCES, SCREENING AND MANAGEMENT OF PROSTATE CANCER

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ABSTRACT

Retrospective study in different ethnic groups determines the burden and patterns of prostate cancer during the last eight years reported in Oncology wards of hospitals of Karachi, Pakistan. Compares the management pharmacotherapy/chemotherapy/surgery with international guidelines, develops strategies for screening and evidence based pharmacotherapy/chemotherapy/surgery of cases. Every single one male case with histologically and cytologically established prostate cancer was enrolled from January 2003 to December 2010. Data for all patients were collected retrospectively by patient's file & charts, which represents the population of Karachi, Interior Sindh & Balochistan. 72 male patients investigated for their diagnosis of cancer type, ethnicity, age & gender. The statistical analysis was performed for mean, standard error & proportions. Screening, Pharmacotherapy/Chemotherapy/Surgery employed by the hospitals was compared with international guidelines and evidences. Proportionately major ethnic groups male diagnosed with prostate cancer in total male cases of prostate cancer was Sindhi (43%), Urdu Speaking/Immigrants (24%), Baloch (10%), Pukhtoon (8%), Punjabi (7%), Minorities & others (8%). Mean age at the time of diagnosis was 65.44±10.89 years, SE± 0.227 and RSD 34%. Screening strategies are implemented in <10% targeted population, however pharmacotherapy/chemotherapy/surgery was comparable with international guidelines. The study reveals that prostate cancer incidences are highest among Sindhi Speaking and then Urdu Speakings. Rests of the ethnic groups are in the range of 7-10%. There is a need to implement the screening strategies more extensively to the small/basic/rural health care centers for early diagnosis of the disease and new treatments strategies especially in surgical management like application of cryosurgery, high intensity ultrasound and proton beam radiation therapy are making revolution in the management of prostate cancer.

Key words: Ethnic group, prostate cancer, incidences.

INTRODUCTION

Prostate cancer is a type of cancer which develops in the gland of a male reproductive system termed as prostate gland. Usually they are slow growing,[1] but some cases may progress aggressively.[2] Sometimes metastasis may occur to bones and lymph nodes, however the main issues associated with prostate cancers are difficulty in urination, painful urination, problems during sexual intercourse and erectile dysfunctions. The detection rate vary in different geographic regions like less reported in south and east Asia than in Europe and specially in United States of America.[3] Prostate cancer tends to develop in men over the age of fifty years.[4] Internationally it is 6th main cause of death among men.[5] Many cases of prostate cancer never develop any symptoms so never go for treatment and die because of other

complications. Diet and genetic factors have been implicated in development of prostate cancer.

Diagnosis of prostate cancer can be done by symptoms, physical examination, PSA (prostate specific antigen) and biopsy. PSA detection is essential however it does not reduce mortality.[6] The United States of America preventive task force recommendation is against the PSA test as this test benefit is lower than the potential harm because of over diagnosis and over treatment in asymptomatic patients.[7]

Disease state management is usually depends upon the severity of cancer. Low risk tumors are followed with active surveillance. Treatment for cure generally includes surgery, radiation therapy, cryosurgery, hormonal therapy and for advanced cases chemotherapy. Masturbation may reduces the risk of prostate cancer.[8,9,10]

Age-adjusted incidence rate in Pakistan is 5.3 per 100,000 person-years,[11] which is slightly lower than India (6.8 per 100,000 person-years), but higher than rates in China (3.1 per 100,000 person-years).[12,13] Pattern of prostate cancer incidence and mortality suggests that both environmental and lifestyle factors, especially trend of urbanisation and change in socioeconomic status may have accrued the prostate cancer risk in developing countries.[14] In Pakistan, population drift towards cities and rising poorly regulated industrialization for the last two to three decades is likely to add new risk factors or modifying the existing deleterious exposures in the community, which in turn may have contributed in growing number of reported prostate cancer cases in Pakistan. Despite high morbidity and mortality, etiology of prostate cancer remains largely unknown. Advancing age, race and family history are the only established risk factors.[15,16] Other risk factors like raised androgen levels, high saturated fat in diet, use of red meat, reduced physical activity and obesity have also been reported,[17-20] but their role in disease causation remains to be explained. Epidemiological studies are consistently documenting that farmers have around 10% excess risk of developing prostate cancer. This may be due to exposure to insecticides and pesticides.[21] Long term physical activity has been found to be protective against prostate cancer because of its role in lowering levels of free and total testosterone, reducing obesity, and enhancing immune system, all of which contribute in protecting individuals from prostate cancer.[22-24] It is hypothesized that in high socioeconomic status, sedentary lifestyle, obesity and consumption of high saturated fats in diet, after adjusting for age and family history of disease, have increased the risk of developing prostate cancer in Pakistani men.

MATERIAL AND METHODS

This retrospective study conducted in Karachi, Pakistan, where material is collected from six different state of the art government and private hospitals located in Karachi and more than 2424 male patients histopathologically diagnosed with any type of cancer and among which 72 cases of prostate cancer included in analysis for the period of 2003 to 2010. 31 patients were excluded because of preliminary diagnosis, lack of patient's objective findings; diagnosis is not confirmed for any cancer, availability of incomplete data of patient like ethnic community, age, gender & belonging to geographic location and children ≤ 12 years. Majority of cases were received from state owned hospital at Karachi. The information is obtained from case sheets and patient's file available in medical record room of the hospital. The data collected include age, gender, ethnic group, occupation, cancer type, date of diagnosis and the pharmacotherapy/chemotherapy/surgery received. SPSS software applied to collected data to calculate occurrence of cancer in each ethnic group and mean age, standard deviation and standard error. The pharmacotherapy/chemotherapy/surgery was compared with the guidelines internationally recommended to treat prostate cancer.

OBSERVATION AND RESULTS

Incidences: The findings of present study include Sindhis, Urdu Speaking, Balochs, Pukhtoons, Punjabis & Other Minorities male from January 2003 to December 2010 suffering from prostate cancer, 2424 male patients attended the oncology wards out of which 72 were analysed & 31 (3%) were excluded from analysis due to incomplete information or loss of follow-up, among which 31 (43%) Sindhi male, 17 (24%) Urdu Speaking/Immigrants male, 7 (10%) Baloch male, 6 (8%) Pukhtoon male, 5 (7%) Punjabi male, 6 (~8%) Minorities male (Pie Chart-I). Mean age of all males at the time of diagnosis were 65.44±10.89 years, SE± 0.227 and RSD 34% (Sindhi; 63.38±15.25, SE± 0.473 and RSD 35%, Urdu Speaking; 64.42±14.66, SE± 0.459 and RSD 31%, Baloch; 66.80±15.64, SE± 1.024 and RSD 33%, Pukhtoon; 64.50±16.71, SE± 1.349 and RSD 37%, Punjabi; 66.51±14.72, SE± 1.042 and RSD 30%, Minorities; 67.74±16.37, SE± 1.490 and RSD 37%). The incidence rate among Sindhis and Urdu Speaking female is greater compares to Punjabis, Balochs, Pukhtoons and Minorities male.

Screening of Prostate Cancer: The 2005 estimates in United States of America mentioned that in forthcoming period the estimated death rate with prostate cancer is 10% while estimated new cases are 33%,[25] therefore guidelines and recommendation of American cancer society for early detection of cancers, prostate cancer screening should be done in men at the age of 50+ by digital rectal examination and prostate specific antigen (PSA).[26] Digital rectal exam (DRE) is an exam of the rectum. Physician or paramedical staff inserts a lubricated, gloved finger into the rectum and feels the prostate through the rectal wall for lumps or abnormal areas. In PSA test, measures the level of antigens in the blood. PSA is a substance made by the prostate that may be found in an increased amount in the blood of men who have prostate cancer. PSA levels may also be high in men who have any inflammation or infection of the prostate or Benign Prostatic Hyperplasia (BPH) where an enlarged, but noncancerous, prostate. Another approach is transdermal ultrasound, which is a procedure in which a probe that is about the size of a finger is inserted into the rectum to check the prostate. The probe is used to bounce high-energy sound waves off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. Biopsy is another option to confirm the diagnosis where removal of cells or tissues can be viewed by microscope by pathologist. The pathologist will check the tissue sample to see if there are cancer cells and also determine Gleason score ranges from 2-10 and describes how likely it is that a cancer will spread. The lower the number, the less likely the tumor is to spread. There are two types of biopsy procedures used to diagnose prostate cancer: one is trans-rectal biopsy, where removal of tissue from the prostate by inserting a thin needle through the rectum and into the prostate. This procedure is usually done using transrectal ultrasound to help guide where samples of tissue are taken from. A pathologist views the tissue under a microscope to look for cancer cells. Where second is trans-perineal biopsy in which removal of tissue from the prostate by inserting a thin needle through the skin between the scrotum and rectum and into the prostate. This procedure is usually done using transrectal ultrasound to help guide where samples of tissue are taken from. A pathologist views the tissue under a microscope to look for cancer cells.

Stages of Prostate Cancer as per NCI (National Cancer Institute of USA):

Stage I: cancer is confined in the prostate only and the cancer:

- is found by needle biopsy for a high level of PSA or in a small amount of tissue during surgery for other reasons like BPH. The PSA level is lower than 10 and Gleason score is 6 or lower.[27]
- is found in one-half or less of one lobe. The PSA level is lower than 10 and the Gleason score is 6 or lower or
- cannot be identified during digital rectal exam and cannot be seen by imaging. Cancer is in ½ or less of one lobe. The PSA level and Gleason scores are not known.[27]

Stage II: Cancer is more advanced, but did not spread outside the prostate so far. Stage II is sub-divided into IIA and IIB.[27]

IIA cancer is:

- found by needle biopsy for a high level of PSA or in a small amount of tissue during surgery for other reasons like BPH. The PSA level is lower than 20 and Gleason score is 7 or
- found by needle biopsy for a high level of PSA or in a small amount of tissue during surgery for other reasons like BPH. The level of PSA level is at least 10 but lower than 20 and Gleason score is 6 or lower or
- found in ½ or less of one lobe. The level of PSA is at least 10 but lower than 20 and Gleason score is 6 or lower or
- found in ½ or less of one lobe. The level of PSA is lower than 20 and Gleason score is 7 or
- found in more than ½ of one lobe.[27]

IIB Cancer:

- is found in opposite sides of prostate. The level of PSA can be any level and Gleason score can be 2-10 or
- can not be identified during digital rectal exam and can not be seen in imaging studies. The level of PSA is 20 or higher and Gleason score is 2-10 or
- can not be identified during digital rectal exam and cannot be seen in imaging studies. The level of PSA can be any and Gleason score is 8 or more.[27]

Stage III: Cancer has spread beyond the outer layer of the tissues of prostate and may have spread to the seminal vesicles. The level of PSA can be any and Gleason score is 2-10.[27]

Stage IV: PSA can be any level and Gleason score is 2-10 and cancer:

- has spread beyond the seminal vesicles to nearby tissue/organ like rectum, bladder or pelvic wall or
- may have spread to the seminal vesicles or to nearby tissue or organs, such as the rectum, bladder, or pelvic wall. Cancer has spread to lymph nodes as well or

- has spread to distant parts of the body, which may include lymph nodes or bones.[27]

NCI Standard Treatment of Prostate Cancer: Eight types of treatments recommended by NCI of USA.[27]

1. Surgery: If health of the patients is good and tumor is located only in prostate gland then surgery is preferred option. There are different types of surgery:
   - Radical prostectomy: Removal of prostate, surrounding tissue and seminal vesicle, it is further divided in to two types:-
     - ✓ Retropubic prostectomy: removal of prostate through incision in abdominal wall and may also remove nearby lymph nodes.
     - ✓ Perineal prostectomy: removal of prostate through incision in perineum and nearby lymph nodes may also be removed at the same time.
   - Pelvic lymphadenectomy: Removal of lymph nodes, if pathologist find cancerous cells then followed by removal of prostate and subsequent treatment.
   - Transurethral resection of prostate: Removal of tissue from prostate gland by resectoscope, a thin lighted tube with cutting tools, inserted through urethra. Usually this method is use to treat BPH, however sometimes also used with the cases of cancer.
2. Radiation therapy: High energy X-rays are used for radiation therapy. They are also further categorized in to two:
   - External radiation therapy, where radiation is sent to the targeted tumor via computer.
   - Internal radiation therapy, where radioactive substance sealed in needles, seeds, wires or catheters are placed directly near to the cancer. Strontium89 can be used through skin between scrotum and rectum.
3. Hormone therapy: In hormone therapy, blocking or inhibition of hormones occur which are causing cancer. High levels of Testosterone observed in the cases of prostate cancer. Their action can be blocked or inhibited by:-
   - LHRH (Luteinizing Hormone Releasing Hormone): Leuprolide, goserelin, buserelin are agonist of LHRH and inhibits production of testosterone.
   - Antiandrogens: Flutamide, bicalutamide, enzalutamide and nilutamide blocks the action of testosterone.
   - Drugs: Ketoconazole and aminoglutethimide are the drugs which prevents adrenal glands to make androgens.
   - Orchiectomy: Surgical removal of testosterone source which is testis.
   - Estrogens: This hormone also reduces the production of testosterone by testis, however because of serious adverse effects potential, its use is limited.
4. Chemotherapy: It is a type of treatment where drugs are employed to stop the growth of cancerous cells, however its use depends upon the stage of cancer. Chemotherapy is sometimes use when cancer spread away from prostate gland and where hormone therapy are failed. For prostate cancer, chemo drugs are typically use one at a time, some drugs include: Docetaxel, Cabazitaxel, Mitozantrone, Estramustine, Doxorubicin, Etoposide, Paclitaxel, Carboplatin, Vinblastine, Vinorelbine. In most cases, first choice of drug is Docetaxel with prednisolone, in case of failure second choice is Cabazitaxel.
5. Biological therapy: Biologic therapy enhances the activity of immune system to fight against cancer cells. Sipuleucell-T is a type of biological substance use in the cases of prostatic cancer with metastasis.
6. Bispohosphonate therapy: Clodronate is a type of drug use in prostate cancer in order to reduce bone pain, if cancer spread to bone.
7. Targeted therapy: Monoclonal antibody (mAb) are used as targeted therapy. The main objective of mAb therapy to kill cancer cells without affecting normal cells. mAb attach to the substances and kill the cancer cells, block their growth, or keep them from spreading. mAbs are given by infusion. They may be used alone or to carry drugs, toxins, or radioactive material directly to cancer cells.Denosumab is a monoclonal antibody that slows damage to the bone from cancer and lessens bone problems such as weak bones and bone pain.
8. News treatments in clinical trials:
   - i. Cryosurgery: Freezing and destroying of prostatic cancer cells. Ultrasounds are used to find exact location for cryosurgery.
   - ii. High intensity focused ultrasound: High energy sound waves destroy the cancer

cells, endorectal probe is use to make sound waves.

iii. Proton beam radiation therapy: It is a type of high energy external radiation that target cancer cells with protons (positively charged small particles).

NCI Treatment Options by Stage:

Stage-I:

- Watchful waiting in the beginning.
- If cancer begins it grow then hormone therapy.
- Radical prostectomy, with pelvic lymphadenectomy. After surgery, radiation therapy.
- External beam radiation therapy. Hormone therapy may be after radiation therapy.
- Internal radiation therapy with radioactive seeds.
- High intensity focused ultrasounds.
- Cryosurgery.

Stage-II:

- Watchful waiting in the beginning.
- If cancer begins it grow then hormone therapy.
- Radical prostectomy, with pelvic lymphadenectomy. After surgery, radiation therapy.
- External beam radiation therapy. Hormone therapy may be after radiation therapy.
- Internal radiation therapy with radioactive seeds.
- Cryosurgery.
- High intensity focused ultrasounds.
- Proton beam radiation therapy.
- Hormone therapy followed by radical prostectomy.

Stage-III:

- External beam radiation therapy. Hormone therapy may be after radiation therapy.
- Hormone therapy
- Radical prostectomy, after surgery, radiation therapy.
- Watchful waiting.
- If cancer begins it grow then hormone therapy.
- External beam radiation therapy.
- Internal radiation therapy with radioactive seeds.
- Transurethral resection of the prostate.
- New type of radiation therapy.
- Cryosurgery

Stage-IV:

- Hormone therapy.
- Bisphosphonates therapy.
- External beam radiation therapy. Hormone therapy may be after radiation therapy.
- Watchful waiting.
- If cancer begins it grow then hormone therapy.
- Radical prostectomy with orchiectomy.
- Transurethral resection of the prostate (In lessen urinary symptoms).
- Radiation therapy.
- Pain medicine (For bone pains)
- External radiation therapy.
- Internal radiation therapy with strontium89.
- Monoclonal antibody (mAb).

Adverse/Side Effects of Chemotherapy: Hair loss, mouth sores, loss of appetite, nausea, vomiting, diarrhea, lower resistance to infection, easy bruising and bleeding, fatigue.

DISCUSSION

Prostate cancer is most common in North America, Australia and Western Europe. Its incidences are relatively low in South East Asian countries, however, increasing number of cases are reported perhaps because of implementation of screening tools in certain parts. Most of the studies suggest that, prevalence is high among elderly people aged 65 years and in 70 years and probability of its occurrence is two folds above the age of 70s.[28] The most alarming situation is the shift of mean age of diagnosis of prostate cancer from 69.77±4.9 years,[29] 71±09 years[30] to 65.44±10.89 years. The shift of mean age is perhaps because of lack of screening facilities in different urban and rural health care centers as early diagnosis by screening may prevent progression of early signs and symptoms to established cancer. Mortality with prostate cancer is mostly in elderly patients because of the diagnosis at late stage.[31] Other than family history of prostate cancer, oxidative stresses, environmental carcinogens and natural aging process may have contributing role in the development of cancerous changes in individuals.

Screening techniques are not well applied in Pakistan except few hospitals of big cities. Guidelines and recommendation of American cancer society for early detection of prostate cancer screening should be done in men at the age of 50+ by digital rectal examination and prostate specific antigen (PSA).[26] However, PSA is tissue specific rather than cancer specific, because it may be increased in benign,

normal and malignant prostates.[32] Some may have BPH and some may have prostate cancer. The distinguishing between prostatic cancer and BPH is difficult task. Being agricultural country, most of population of Pakistan is living in rural area and villages, where health care facilities are limited and lacks screening of cancers and other preventable diseases. Farmers may have higher odd ratio of prostate cancer compare to other profession probably because of high degree of exposure of pesticides and herbicides.[29] Similar findings were reported by Sharma-Wagner et al[33] in Sweden (7–12% higher risk among farmers) and Nelsen et al[19] in a cohort of 22,895 Norwegian men. Several studies reported that increase in physically activity not only reduces the free and total testosterone but also reduces the obesity and improve the immune activity of body, thus results in prevention of cancer cells development. The positive effect in the prevention of prostate cancer is reported for men who exercise regularly at least once weekly by representing lower odds of prostate cancer compares to those who have sedentary life style.[29] This inverse relationship was also reported by studies in Turkey,[34] Canada,[35] China[36] and Sweden.[37,38] Height may be another risk factor for the development of prostate cancer. Weak association has been reported by Andersson et al[39] for height and prostate cancer, however another researcher found strong association and mentioned that two fold increased risk in 165 cm height and may lead up to six fold increased risk in 180 cm height for the development of prostate cancer.[29] These finding s are also supported by Norrish et al.[40]

In our study, most of the cases of prostate cancers are treated by transurethral resection (TUR). Majority of cases from smaller cities and villages and cases were suspected because of weak urine stream. PSA has been done only in few cases. TUR was done if carcinoma was present, however radiotherapy and chemotherapy was comparable with the international guidelines mentioned above.[27]

Pakistan, being a developing country, scarce resources, needed to develop strategies to reduce the burden of cancer in terms of financial and other losses. National Cancer Control Program (NCCP) should be implemented strictly and WHO, government and other health authorities including private sector NGOs should provide necessary resources to develop strategies for screening, prevention, diagnosis and treatment of prostate cancer. Pharmaceutical companies should invest in cancer research to come up with new cost effective medications which are not only safe but having compelling evidences of efficacy. The possible strategy for prevention and early diagnosis of prostate cancer is screening of men at the age of 50+ by digital rectal examination and prostate specific antigen (PSA).[26] The government, NGOs and private sector should design and implement effective awareness campaigns for general public for the age specific symptoms and screening and to emphasize that early diagnosis, which may not only reduce economic burden but also families emotions and painful treatment.

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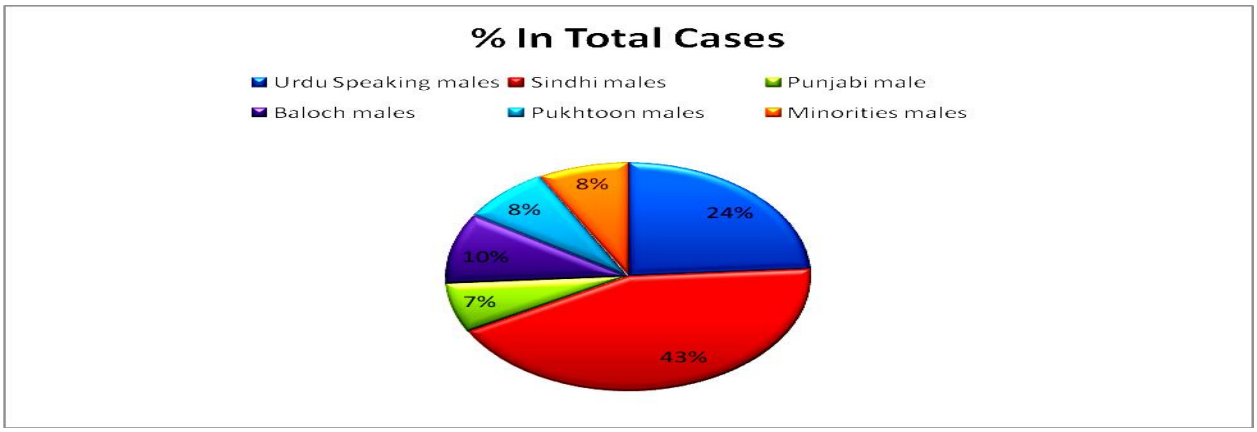
CONCLUSION

Incidences of prostate cancer are increasing in Pakistan and alarming situation is shift of mean age of diagnosis to lower side. Villages and small cities and towns should be targeted for screening of prostate cancer by digital rectal exam and PSA, as recommended by international guidelines for early diagnosis and screening. Healthy life style should be promoted which includes physical activities and exercises, avoidance from exposure to pollutants and discourage the sedentary life styles. Pakistan, being a developing country, scarce resources, needed to develop strategies to reduce the burden of cancer in terms of financial and other losses. The government, NGOs and private sector should design and implement effective awareness campaigns for general public for the age specific symptoms and screening and to emphasize that early diagnosis, which may not only reduce economic burden but also families emotions and painful treatment.

Pie Chart. 1



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