Prostate cancer is reported to be the leading cancer diagnosis and the second most common cause of cancer related death in men in the United States. It is the fourth most common cancer in men worldwide, with incidence and mortality rates that vary markedly among and within different countries. The incidence of prostate cancer in black men as estimated by Bozeman et al is 30% - 50% higher than among age-matched white men, and black men have twofold higher mortality rate. In the study of Onuigbo amongst the Igbos of Nigeria, 13% of the total prostatic diseases were cancer of the prostate while in the study by Adigun amongst Ekiti people of South West Nigeria; the prevalence was 9.2% of prostatic diseases. In China, the incidence is less than 2 per 100,000. All these studies in Nigeria which may not be too different from other parts of Africa, point to the fact that the rate of disease is high amongst Africans as compared to China. However, a startling incidence of 304 per 100,000 men recorded in Jamaica, appears to be the highest in the world.

**Etiology**

Although the specific causes of prostate cancer initiation and progression are not yet known, considerable evidence suggests that both genetics and environment play a role in the evolution of this disease. However, the presence of testosterone is necessary for its development.

**Possible etiologies include:**

Hereditary studies have established that men with one first degree relative with prostate cancer had a twofold risk of developing prostate cancer, while men with two or three affected first degree relatives had a 5 to 11-fold risk respectively.

Racial predilection: In United States of America, the age adjusted rates in 1992 for black and white men were 249 and 182 per 100,000 men respectively showing that blacks are more prone to the disease.

High fat diet: foods rich in saturated fat may increase testosterone levels, which stimulates the growth of the prostate.

Other factors which have not been generally accepted include Selenium as a dietary supplement for protection against cancer of prostate, role of phyto-oestrogens and viral infection.

**Natural History**

Prostate cancer is primarily the disease of older men, uncommon in men under age 50. It usually begins at the peripheral zone of the prostate, although a small percentage of malignancies arise in the central (5 - 10%) and transition zones (20%).

In prostate cancer, unlike any cancers, it is often assured that most localized disease will have little or no effect on the quality or duration of life. This difference in perspective has arisen because of the high prevalence of undiagnosed prostate cancer in men older than 50 years.

Autopsy prevalence of prostatic carcinoma reaches:

- 30% in 7th decade
- 40% in 8th decade
- 50% in 9th decade

An estimated 1.05% of the total population reservoir of cancer were said to reach clinical diagnosis in any year and given the total prevalence of histologic cancer, the annual mortality rate is only 0.31%.

The prolonged natural history of prostate cancer in the absence of interventional therapy, especially in the early clinical stages, is evident in the following examples of data regarding progression:

More than two thirds of all clinical stage A & B (organ confined) take in excess of 4 years to double.
In patients younger than 70 years of age with clinical stage B disease, cumulative 5 and 10 year probability for:
Progression to stage C was 49% and 79%, respectively
Developing metastases, 8% and 23%, respectively.
Dying of prostate cancer, 2% and 8%, respectively
In a ten-year follow-up of 29 men with palpable clinical stage B tumors 20 of whom were “expectantly” treated, the followings were found:
Three had died of prostate cancer
Six had developed metastases.

Clinical Presentation
Prostate cancer does not usually cause symptoms until it has become locally invasive or metastatic.

Symptoms may include:
Urinary frequency and obstruction because of local tumor mass.
Leg edema due to metastases to pelvic lymph nodes.
Bone pain/ Back pain may be due to metastases.

Clinical findings may include:
Evidence of bladder fullness as a result of chronic retention.
Digital Rectal Examination (DRE) may reveal a firm, indurated, asymmetrical, stony (like the bridge of the nose) mass.

The differential diagnosis may include:
Very large benign prostate.
Prostatitis.
Prostatic calculi.
Focal infarction.
Prior biopsies or transurethral prostatectomy.

Investigations
1. PSA-Prostate Specific Antigen. Normal range is usually 0 -<4ng/ml in BPH, suspicious between 4 -10ng/ml and highly suggestive in >10ng/ml.
However, caution should be applied when interpreting PSA values in patients with the following conditions:
Large benign Prostatic Hyperplasia.
Prostatitis.
Prostatic Ischemia and Infarction.
Acute urinary retention.
Recent prostate Biopsy.
It is advisable to repeat serum PSA at least 2to3 weeks after the possible causes are stabilized.
To avoid the risk of unnecessary biopsy and treatment, a PSA level of > 10 20 is the arbitrary cut off level recommended for West Africa region.

2. Serum prostatic acid phosphatase which was used before the advent of PSA is only elevated in patients with metastatic disease.

3. Core tissue biopsy
a. TRUS guided biopsy now the gold standard.

Advantages
Less painful
It achieves direct sampling of prostatic tissue
It can examine periprostatic, seminal vesicles or bladder invasion by the tumour and any suspicious areas can be biopsied as well.

**Disadvantages**
Possible infection with rectal bacteria.
Excessive bleeding may be difficult to control.

**Complications that may arise include:**
Rectal injury.
Sepsis.
Urethral injury.
Haematuria.
Urinary retention.

b. Trucult needle biopsy This is still the most popular in most centres in Nigeria.
   It gives similar results as TRUS guided biopsy except that it is more difficult and a blind procedure.

4. Other investigations include:
   Abdomino-pelvic Ultrasound to assess other organs in the abdomen including the bladder.
   - CT Scan computerized tomography in case of metastases.
   - X-rays:
     - Lunbosacral x-ray/to check for metastases
     - CXR
     - X-ray of the limbs in case of pathological fractures.
   - Haematological investigations to check and manage haemoglobin level.
   - Urine microscopy, culture and sensitivity
   - Urinalysis To detect microhaematuria
   - Urea and creatinine level to rule out back pressure effect on the kidneys.

**Histological Grading**
This can be difficult because distinct architectural patterns are often found in different areas of the same tumour. The grading system most commonly used by pathologists, the Gleason sum system, handles this problem by assigning a “primary” grade to the cancer pattern occupying the greatest area of the specimen and a “secondary” grade to that in the second largest area.
The Gleason sum system is based on five patterns of prostate cancer that represent a continuum of dedifferentiation. As the newly formed malignant cells lose their ability to form normal glands, the cancer's grade of severity increases.

**Gleason scores can be divided into:**
Well differentiated: Gleason 2,3,4 (1+1, 1+2, 2+2)
Moderately differentiated: Gleason 5,6,7.
Poorly differentiated: Gleason 8, 9, 10.

Gleason 1: Sharply circumscribed aggregate of small, closely packed, uniform glands.
Gleason 2: Greater variation in glandular size.
Gleason 3: Further variation in glandular size glands more widely dispersed in stroma. Distinctly infiltrative margins, with loss of circumscription.
Gleason 4: “Fused gland” patterns; irregular masses of neoplastic glands coalescing and branching. There is Infiltration of prostatic stroma.
Gleason 5: Diffusely infiltrating tumor cells with only occasional gland formation. There are prominent nucleoli.
Staging

Once the diagnosis is made, the extent of spread must be evaluated. The two commonly used systems are TNM staging system and organ systems coordinating center classification for clinical staging of prostate cancer. We shall describe TNM here.

Table 1: TNM Staging Tumor, nodes and metastases

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Tumor in less than half of one lobe</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumor in both lobes</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor in more than half of one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor in less than half of one lobe</td>
</tr>
<tr>
<td>T3a</td>
<td>Unilateral extracapsular extension</td>
</tr>
<tr>
<td>T3b</td>
<td>Bilateral extracapsular extension</td>
</tr>
<tr>
<td>T3c</td>
<td>Seminal vesicle involvement</td>
</tr>
<tr>
<td>T4</td>
<td>Adjacent organ involvement</td>
</tr>
<tr>
<td>N</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in lymph node &gt; 2cm and &lt;5cm or multiple nodes more than &gt;5cm</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in lymph node &gt;5cm</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>Mx</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>Mo</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>Mi</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

Stage Grouping

Stage i or A  Ti  No Mo G1
Stage ii or B Ti  No Mo G2, 3 - 4
Tib, c  No Mo AnyG
Ti, T2  No Mo AnyG
Stage iii or C T3  No Mo AnyG
Stage iv or D T4  No Mo AnyG
AnyT Ni Mo AnyG
AnyT  AnyN Mi AnyG

Treatment of Prostate Cancer

Treatment depends on the stage of the disease, age of the patient, patients' preference, and the available treatment options.

A. Localized Prostate Cancer (early)
1. Radical Prostatectomy  Total removal of the prostate to achieve a “Cure” of the disease. Useful in patients who have no significant surgical risk factors, whose life expectancy is > 10 yrs & prefer surgery.
2. Radiotherapy The patient likely to benefit from external beam radiotherapy must have long life expectancy (>10yrs), moderately differentiated tumour and prefers it.

3. Interstitial radiotherapy (Brachytherapy) Placement of radioactive sources into or near tumours for therapeutic purpose.

4. Cryosurgery cellular damage during freezing. The mechanism of action is such that after reaching a tissue temperature of less than 00c, the extracellular fluid starts to crystallize. This increases the osmotic pressure of the unfrozen portion of the extracellular fluid compartment leading to water shifting from the intracellular space to the extracellular space. As a result, cells become dehydrated. Cellular PH also changes, leading to denaturing of cellular proteins. With further drop in temperature, crystallization of water in the intracellular space takes place. This mechanically breaks the cellular membrane. On thawing, extracellular fluid shifts back again into the intracellular space, leading to cellular bursting.

5. Watchful Waiting Patient most likely to benefit from this is one with well to moderately differentiated tumours with low volume, low PSA, has a life expectancy of less than ten years and prefers the option. Apart from watchful waiting (WW) which refers to the strategy of initial observation and later starting hormonal treatment when the patient develops symptoms and signs of metastasis; there are also concepts of Deferred Treatment (DT) and active surveillance (AS). All of these are aimed at avoiding unnecessary treatment and also to prevent metastasis. However, to be suitable for any of these, patient has to have an early stage disease of Gleason less than 7, life expectancy of at least 10 years and suitable for available radical curative treatments.

B. Advanced Prostate Cancer
1. Hormonal therapy: This can be achieved surgically or pharmacologically. The primary strategy of hormone therapy is to decrease the production of testosterone by the testicles, adrenal gland or prevention of binding of testosterone to target cells.

Table 1: Summary of agents of hormonal therapy and their site of action.
Androgen Ablation for Prostate Cancer
a. Surgical removal of testes (Orchidectomy) this is done bilaterally. It used to be a total orchidectomy in the past but to reduce the psychological trauma of not having a testicle, bilateral subcapsular orchidectomy or insertion of testicular implant is now the current practice.

b. Estrogen initially inhibits testosterone synthesis by inhibiting the release of LHRH and, in turn, of luteinizing hormone (LH), which acts at the Leydig cells in the testes to control testosterone production.

* Types - Diethylstibesterol (DES), 1-2 mg/day
  - Premarin, 1-10 mg/day
  - Ethinylestradiol, 0.5-1.0 mg/day

* Side Effects - refer to table1.

c. LHRH Analogue:

Short-term administration of these agents produces surges in follicle stimulating hormone (FSH) and LH levels and in turn, a “flare” in testosterone release. After 1-2 weeks, however, testosterone levels are reduced, presumably as a result of a decreased number of LHRH receptors in the pituitary, caused by over stimulation of LHRH down regulation. At this point, there is a concomitant fall in testosterone and dihydrotestosterone levels.

Currently available LHRH agonists:
- Leuprolide acetate, 7.5 mg IM monthly or 22.5 mg IM 3 monthly.
- Goserelin acetate (Zoladex) 3.6 mg SC monthly or 10.8 mg 3 monthly. 6 monthly injection is now available.

d. Antiandrogens The more effective and now commonly used nonsteroidal antiandrogens act solely as competitive inhibitors for DHT and testosterone receptors in the prostate.

Two commonly used formulations:
- Flutamide 250 mg tds
- Bicalutamide 50 mg daily
e. Aminoglutethimide 750–2000mg/day inhibits adrenocortical steroid synthesis by blocking conversion of cholesterol to progesterone, resulting in decreased production of adrenal glucocorticoids, mineralocorticoids, estrogens, and androgens.

f. Ketoconazole This antifungal drug (400mg q 8hrs) impairs the production of androgen by inhibiting the enzymes of gonadal and adrenal corticosteroid synthesis. Castration levels of androgens occur within 4–8hrs of 400mg oral dose.

h. Combined hormonal treatment the advantage of this over monotherapy has been demonstrated by some authors, even though, at a very minimal level. Usually surgical or pharmacologic castration is combined with antiandrogens.
Or Diethylstilbesterol 1mg OD + Asprin 75mg OD + hydrocortisone 20mg BD.

E. Management of Terminally Ill Patient
- Where all appropriate treatments have been tried, and PSA continues to rise, the patient should be considered as having unresponsive incurable cancer and therefore terminally ill. Initially, the patient may not appear unwell but in time they rapidly develop symptoms of metastases and deteriorate to renal failure and multiple organ dysfunction.
  * Commence counseling of patient and relatives
  * Control pain may invite pain specialist
  * Not reasonable to continue with expensive but ineffective drugs.
  * Continue to administer reasonable treatment until patient dies. Some authors advocate withholding treatment if patient not responding. I consider this as unethical and a lazy way out. Since, we are not the custodian of life; we have no moral right to take it either directly or indirectly.
  * Spiritual care of the patient is a welcome development at this stage.
  * The relatives should be encouraged to show love at this crucial period.

F. The Role of a General Practitioner in Management of Prostate Cancer
The general practitioners are usually the first to see most of these patients, it is important that they (GP) should carry out the following role whenever the patient present to them:
1. Educate their patients on the need to have PSA test whenever they are above the age of 50yrs.
2. Refer suspicious case to a Urologist for a definitive diagnosis.
3. Initiate hormonal management on patients presenting with advanced prostate cancer especially in our environment.
4. Educate their patients on various modalities of management, their benefits and adverse effects.
5. Be actively involved in the management of their patient presenting with terminal illness
6. Advise their patients to keep to follow-up plans.

References


