Original Article

Multiple Primary Cancers: Simultaneously Occurring Prostate Cancer and Other Primary Tumors-Our Experience and Literature Search

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ABSTRACT

Introduction: Prostate cancer is a leading cause of death in men all over the world, and it is becoming an increasing public health burden in sub-Saharan Africa. In our practice, we identified that prostate cancer co-existed with other primary cancers even in noncontiguous regions of the body and this co-existence impacted on our management of these patients. **Materials and Methods:** We retrospectively studied a 2-year period (June 2012-July 2014), the records of patients in our hospital with prostate cancer, who in addition, had other primary cancers; and studied the management and outcomes of these patients. We also reviewed the existing literatures for possible biologic links between prostatic carcinoma and other primary tumors. **Results:** There were six patients with multiple primary cancers who had prostate cancers. The age range was 60-84 years and the mean age of 72.2 ± 0.4 years. The primary tumors co-existing with prostate cancer were colonic adenocarcinoma, rectal adenocarcinoma, urinary bladder transitional cell carcinoma, primary liver cell carcinoma, and thyroid follicular carcinoma in both synchronous and metachronous relationships. **Conclusions:** Prostate cancers often co-exist with other cancers. The precise mechanism by which prostate cancer co-exists with another primary cancer is yet to be clearly defined. With more study of the syndromic cancers involving the prostate, definite associations could be identified, and this may help in managing these patients better.

KEYWORDS: *Multiple primary cancers, primary tumors, prostate cancer*

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INTRODUCTION

Prostate cancer is a leading cause of death in men all over the world, and it is becoming an increasing public health burden in sub-Saharan Africa.[1] Credible data about the incidence of prostate cancer in sub-Saharan Africa have been scanty, but the trend is presently changing since the landmark publication by Osegbe in Lagos in 1997 when he described an incidence rate of 127/100,000.[2] Many of the other workers from the region have reported higher incidences. These workers include Ogunbiyi and Shittu in Ibadan in 1999[3] who reported higher incidence. Ikuerowo *et al*. in 2013 from Lagos State reported from a state wide community screening program a much higher incidence of about 1046/100,000.[4] In addition to this, increasing incidence is the high mortality rate as many of these patients presented at late stages of the disease. Osegbe in the paper referenced above reported that 64% of these patients died within 2 years of diagnosis, whereas Ikuerowo *et al*. reported that 35% of the patients had metastatic diseases at presentation and more than 74% had Gleason scores >7. This dismal picture of prostate cancer is similar across the West African sub region.[5,6]

In our practice, we identified that prostate cancer often co-existed with other primary cancers even in noncontiguous regions of the body and this co-existence impacted on our management of these patients. Although, prostate cancers have been reported to co-exist with other cancers either in synchronous or metachronous relationship;[7,8] to the best of the authors' knowledge, there has not been a report of definite relationship of these cancers like in some cancer complexes such as von Hippel-Lindau (VHL) syndrome.

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We report the multiple primary cancers (MPCs) involving prostate cancer in our practice; and sought to identify from existing literatures possible associated links in the occurrence of prostate cancer with other primary cancers.

Materials and Methods

We retrospectively studied, over a 2-year period (June 2012-July 2014), the records of patients with prostate cancer who in addition had other primary cancers in our hospital, a tertiary hospital in North-Central Nigeria; with emphasis on the management and outcome of these patients. We also reviewed the existing literatures through PubMed search engine with MeSH terms of "MPCs" and "prostate cancer" and Google Scholar on cancer complexes involving prostate cancer for possible documented biological links.

Results

There were six patients with MPCs who had prostate cancers. The age range was 60–84 years and the mean age was 72.2 ± 0.4 years. The primary tumors co-existing with prostate cancer were colonic adenocarcinoma, rectal adenocarcinoma, urinary bladder transitional cell carcinoma, primary liver cell carcinoma, and thyroid follicular carcinoma. The frequency of the co-existing cancers in the patients was depicted in Table 1.

In each of these patients, the diagnosis of prostate cancer preceded those of the other cancers in five out of six cases, whereas in the sixth case, the diagnosis of prostate cancer and rectal cancer was made about the same time. Three of the cancer complexes were in synchronous relationship, while the other half had metachronous relationships (the diagnosis intervals between the two cancers ranged between 12 and 24 months with a mean of 20 months). The serum prostate specific antigen at presentation ranged between 45 and 121 ng/mL with a mean of 83.7 ng/mL. The Gleason grades of the prostate cancers were 3 in half of the patients, 4 in two patients, and 5 in one and a mean grade of 3.7; the scores were 5 in 3 patients, 7 in 2 patients, and 9 in the remaining one, and the mean score was 6.3. Five patients had bilateral orchidectomy (BTO), whereas the patient with associated bladder cancer was commenced on cisplatin-based chemotherapy. One of the patients with colonic tumor had intestinal obstruction for which he had exploratory laparotomy with colostomy to decompress the bowel; subsequently, he had neo-adjuvant chemotherapy for the colonic tumor. The patient with co-existing rectal tumor posed a diagnostic dilemma which required immunohistochemistry to differentiate the rectal tumor as a primary tumor from possible direct extension of the prostate cancer. The patient with co-existing thyroid carcinoma had in addition to BTO external beam radiotherapy to the spine for spine metastasis from prostate cancer before the diagnosis of thyroid carcinoma; and he subsequently had total thyroidectomy

Table 1: Frequency of primary tumours co-existing with prostate cancer in the patients

Primary tumours	Frequency (*n*=6)	Percentage
Colonic adenocarcinoma	2	33.3
Rectal adenocarcinoma	1	16.7
Urinary bladder transitional cell carcinoma	1	16.7
Primary liver cell carcinoma	1	16.7
Thyroid follicular carcinoma	1	16.7

Table 2: The cases of prostate cancer, the Gleason's grades/scores, relationship with other primary tumours, treatment and outcome

Age (years)	PSA (ng/dL)	Gleason's scores/grades	Second tumours	Duration between first and second tumours	Treatment	Outcome
75	121.0	3+2=5	TCC of urinary bladder	Synchronous	BTO + chemotherapy	Death from urosepsis
72	50.0	5+4=9	Colonic ca	Metachronous (2 years)	BTO + colostomy + neo-adjuvant chemotherapy	Died of complication of intestinal obstruction
84	116.7	4+3=7	Colonic ca	Metachronous (1 year)	BTO	Lost to follow-up
60	110.0	3+2=5	Rectal ca	Synchronous	BTO	Lost to follow-up
72	45.0	3+2=5	Thyroid ca	Metachronous (2 years)	BTO + EBRT + thyroidectomy + chemotherapy	Death from progression of prostate cancer
70	60.0	4+3=7	PLCC	Synchronous	Supportive care	Death from hepatic failure

TCC=Transitional cell carcinoma; Colonic ca=Colonic adenocarcinoma; Rectal ca=Rectal adenocarcinoma; Thyroid ca=Thyroid follicular carcinoma; PLCC=Primacy liver cell cancer; BTO=Bilateral orchidectomy; EBRT=External beam radiotherapy; PSA=Prostate specific antigen

and chemotherapy for the thyroid cancer. Two of the patients died of complications of the other cancer - hepatic failure and intestinal obstruction with sepsis; one patient died from the progression of the prostate cancer. Moreover, one patient died from urosepsis attributable to both prostate cancer and bladder cancer, while the remaining two patients were lost to follow-up.

Summary of the above cases treatment and outcome are depicted in Table 2.

Discussion

In general terms, Multiple primary cancers (MPCs) can be categorized into synchronous (cancers occur almost at the same time) with Surveillance, Epidemiology, and End Results (SEER) definition of occurrence within 2 months; and metachronous (cancers occurring in sequence) with SEER definition of occurrence in more than 2 months apart.[9] MPCs involving prostate cancer either as synchronous or metachronous tumors are not common but deliberate search for these other primary tumors have yielded some results. Ozsoy *et al*.[10] in Switzerland in his deliberate search for secondary primary tumors in patients with prostate cancer yielded six out of 480 patients during staging pelvic computed tomography. The other primary tumors found included four cases of renal cell cancer and one case of rectal and pancreatic cancer each. However, there are other studies that showed higher incidences of second primary tumors occurring with prostate cancer, especially tumors involving the urinary bladder.[11,12] MPCs have been reported to be on the increase[13] and cancer survivors have also been reported to have a 10-30% increased risk of developing another cancer.[14]

Second tumors associated with prostate cancers that have been documented as components of MPCs include Urinary bladder cancers, colonic cancers, rectal cancers, thyroid cancers, pancreatic tumors, renal cancers, and melanoma.[15] These are quite similar to the second primary cancer diagnosed in our patients which were colonic, rectal, urinary bladder, thyroid, and primary liver cell cancers.

The precise mechanism by which a patient with prostate cancer develops a second primary cancer is yet to be clearly defined. There may be a link between the occurrences of the malignancies or it may occur randomly or a coincidence. Ray *et al*.[16] in their study to evaluate the relationship of prostate cancer with multiple primary malignant neoplasm syndrome found out that persons with malignant tumor appear not to be at more risk of developing prostate cancer than individual who have never had a tumor. However, recent studies have suggested some causal mechanisms in the occurrence of MPCs. Such causal mechanisms include shared mutagens/ genetic predispositions, environmental factors, treatment effect of the first diagnosed primary tumors.[17] An example of shared mutagens is BRCA1/BRCA 2 mutations. Studies have shown increased risk of prostate cancer among men with BRCA 1/BRCA 2 mutations in a family setting with hereditary breast/ovarian cancer or early onset of prostate cancer.[18-21] These mutagens have also been associated with cancers of stomach, pancreas, melanoma, and colon.[20,22] Thus, MPCs involving these tumors may arise from shared mutagens in the form of BRCA 1/BRCA mutations. Other genetic predisposition to MPCs involving prostate cancer include the risk of bladder cancer in patients with prostate cancer which is about 3.4%; this was related to an association between DNA repair and N-acetyl transferase polymorphism which suggest both cancers may share a common carcinogenic process or it may be due to the susceptibility of an individual to both cancers.[12] However, an individual with genetic predisposition usually develops cancer at an earlier age than a person who develops cancer sporadically.[23] In our case series, all the patients develop the MPCs much later in life; this might preclude a possible link of familial or shared mutagens/genetic predisposition in their occurrence.

Shared exposure to environmental factors/carcinogens has also been considered to be involved in the development of MPCs. Such factors include exposure to tobacco and alcohol; whereas tobacco and alcohol may be the contributing factors to the development of some malignancies such as bronchogenic cancer and primary liver cell cancers, respectively;[24] there is little evidence that alcohol consumption is associated with the risk of developing prostate cancer; however, data suggest that smoking increases the risk of fatal prostate cancer.[25-27] Moreover, in the SEER data, shared environmental etiology was reported to be unlikely for some of the combination of MPCs found;[26] an explanation of likely relationship was attributed to increased medical surveillance which allow for their diagnosis.[26,28]

Many more MPCs are expected to be seen in our practice with implications for surveillance, adoption of investigation methods, and treatment. The reasons for this include increase in the number of cancer survivors as awareness about disease become more in our society and such cancers would be picked up at early curable stages; more aggressive care of a tumor has been associated with the occurrence of another malignancy. A good example of this is a patient developing thyroid cancer after external beam radiotherapy for prostate cancer. This has also been documented in literature as due to scattering of radiation effect.[29]

Challenges with management of MPCs

With more studies of the syndromic cancers involving the prostate, definite associations could be identified and the second tumors would be anticipatorily detected at early stages, as in VHL syndrome. In VHL, once a cancer is picked up, the other cancers are anticipated and looked out for, for early intervention with the hope of cure.

Management of any single cancer is daunting for the patients and the care givers, because the diagnosis of any cancer is a challenge to life. This involves emotional turmoil for the patient and the family members. Effective management involves being able to administer appropriate treatment with their significant side effects or complications. Alongside all these is the distortion in lifestyle of the patients and possibly family members and the enormous cost of care, especially in many parts of sub-Saharan Africa, where most cost of cancer care are not covered by health insurance, even in the few instances where this was available.

Patients who have had abdomino-perineal resection for rectal cancer, diagnosis of prostate cancer will be challenging as the closed anus makes digital rectal examination and transrectal prostate biopsy difficult.

The outcome of the management of the patients with MPCs in resource poor settings is usually very poor for many reasons. Diagnosis of second cancers requires additional cost which is usually borne out of pockets by patients. This sometimes serves as the limitation to how well patients are investigated to stage the primary cancer and to make diagnosis of second cancers. In addition, investigation armamentarium is often lacking. In one of the patients, in our series, who presented with rectal bleeding and difficulty with passing urine and had rectal mass. It required immunohistochemistry to make the diagnosis of prostate cancer and then later rectal adenocarcinoma.

The incidence of MPCs involving prostate cancer may be difficult to determine in our region as many of the patients die at home, and there are inadequate post mortems being carried out, thus, many cases of MPCs are missed. Moreover, much co-existence with prostate cancer is probably missed because patients with bladder cancers like other cancers present late. Curative treatment such as cysto-prostatectomy is therefore rarely performed; hence, synchronous occurrences of early stages of bladder and prostate cancers are missed. The late presentations of one primary cancer may be so overwhelming that other possibly coexisting cancers are not looked out for.

Conclusions

Prostate cancers often co-exist with other cancers. The precise mechanism by which prostate cancer co-exists with another primary cancer is yet to be clearly defined. However, MPCs have been reported to be on the increase with increasing numbers of cancer survivors who are at risk of developing another cancers. These co-existing cancers impact on survival of patients. With more study of the syndromic cancers involving the prostate, definite associations could be identified, and this may help in managing these patients better. However, in the absence of established syndromic patterns, surveillance for possible co-existing tumors in patient with prostate cancer, and prompt management of the cancers may help to improve outcomes in these patients.

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Conflicts of interest

There are no conflicts of interest.

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