Tumour Marker Requisition Pattern in a Tertiary Care Centre of Eastern Nepal

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Citation

Niraula A, Gelal B, Chaudhari RK, Das BKL, Lamsal M. Tumour Marker Requisition Pattern in a Tertiary Care Centre of Eastern Nepal. *Kathmandu Univ Med J.* 2022;80(4):422-6.

ABSTRACT

Background

Tumor markers have been a valuable tool for decades to aid in the diagnosis, treatment, and monitoring of oncological diseases.

Objective

To retrospectively analyze the requisition pattern of tumor marker requests at the largest tertiary care center in eastern Nepal.

Method

A retrospective hospital-based cross-sectional study was conducted to obtain the data for 5 common tumor markers i.e., Alpha-Fetoprotein (AFP), Cancer antigen-125 (CA-125), Carbohydrate antigen (CA) 19-9, Carcinoembryonic antigen (CEA), and Prostate-specific antigen (PSA) analyzed in the Department of Biochemistry at B.P. Koirala Institute of Health Sciences, Dharan, Nepal for 5 years.

Result

A total of 8716 tests for tumor marker was conducted over 5 years. The most common tumor marker requested at our hospital was Prostate-specific antigen (48.77%) followed by Cancer antigen-125 (39.02%), Carcinoembryonic antigen (9.30%), Alpha-Fetoprotein (2.29%), and Carbohydrate antigen 19-9 (0.63%) respectively. The majority of the tumor markers (Alpha-Fetoprotein, Cancer antigen-125, Carbohydrate antigen 19-9, and Carcinoembryonic antigen) were requested from in-patient wards while Prostate-specific antigen was majorly requisitioned from the out-patient department (OPD) [74%] respectively.

Conclusion

The finding from the present study suggest that though Nepal is one of the developing countries where the specialized health care services are limited only to cities and developed areas, the burden of oncological disease is high. Dharan is one of the small cities in the eastern part of Nepal and serves the majority of the population in the periphery. The number of tumor marker requisitions as per the laboratory data is significant (n=8716) over a period of 5 years where few tests like Alpha-Fetoprotein, Carcinoembryonic antigen, and Carbohydrate antigen 19-9 have just been initiated. Also, the findings delineate that the outpatient departments have requested more tumor markers which might/ might not be inconsistent with the preliminary diagnosis.

KEY WORDS

Alpha-Fetoprotein, Antigens, Neoplasm, Carcinoembryonic antigen, Neoplasms, Tumor markers

INTRODUCTION

Tumor markers (TM) are synthesized by malignant cells or certain benign conditions and released into the bloodstream; however, markers may be produced by host tissues in response to direct invasion or metabolic changes induced by the tumor.[1] They are used in the clinical detection (diagnosis, screening) and management (monitoring, prognosis) of cancer patients.[2,3]

In today's era, the requisition of TM in most tertiary care hospitals has augmented due to the advancement of technologies, availability of the assay for TM measurement in the automated system, and improved turnaround time.[4] B.P. Koirala Institute of Health Sciences (BPKIHS), being the largest tertiary care center of eastern Nepal serves the majority of the population with suspected oncological diseases. Hence, the tumor marker requisition is made on a large scale.

This retrospective hospital-based cross-sectional study was performed to conduct the audit of tumor markers commonly requested namely Alpha-Fetoprotein (AFP), Cancer antigen- 125 (CA-125), Carcinoembryonic antigen (CEA), Carbohydrate antigen (CA) 19-9, and Prostate-specific antigen (PSA) in the Department of Biochemistry at BPKIHS, Dharan, Nepal.

METHODS

This is a hospital-based retrospective cross-sectional study conducted in the Department of Biochemistry at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal. We retrospectively evaluated the common tumor markers i.e., AFP, CA-125, CA 19-9, CEA and PSA requested from the clinical departments in the Department of Biochemistry at BPKIHS for the period of 5 years i.e., from August 2015 to July 2020. This research was approved by the Institutional Review Committee (Code No: IRC 1815/020). Data were obtained and recorded from the hospital record system. A convenient sampling technique was used to include the patients for whom one or more serum tumor markers were requested from the BPKIHS in-patient or out-patient department. The sample size was calculated by the prevalence taken by a similar study done by Laine et al.[5] The most common tumor marker requested in their study was CEA with a prevalence of 50.6%. Hence the prevalence was taken to be 50.6%.

Using the formula,

$N= z^2pq/d^2$

Where,

z=1.96; p=0.506; q (1-p) = 0.494; d (Permissible error) = 0.05 (10% of p)

Hence, $n= z^2 pq/d^2$

$n=1.96X1.96X0.506X0.494/ (0.05)^2$

n=384

Thus, the estimated sample size was n= 384 was for 1 year. Since we vow to take the retrospective data of 5 years. Hence, an estimated sample size for the audit for 5 years was n= 2000. On the retrospective evaluation of the laboratory-based record we found that a total of 8716 tumor marker request was done during the 5 years study period and thus, all the data were included in the study.

Data from the hospital laboratory database, including their date of birth, gender, date of sample collection, and tumor marker result was recorded. Patients referred from outside for the test were excluded. The laboratory estimation was done using Chemiluminescence immunoassay (CLIA) in Maglumi, 2000, Snibe Diagnostics. We recorded the source for the laboratory requests i.e. (Inpatient or Outpatient), year, and analyzed the values.

Data were entered in Microsoft Excel and statistical analysis was done using SPSS version 22.0 (Chicago, Inc). Data were expressed as frequencies, percentages, mean values for parametric data, and median values for non-parametric data respectively.

RESULTS

A total of 253370 tests were conducted in the special biochemistry laboratory during the 5 years study period. Out of which, 8716 tests were requested for tumor markers. The mean age of the patient for the different tumor markers i.e., AFP, CA-125, CA 19-9, CEA, and PSA is depicted in table 1. The median values (25^{th} and 75^{th} Percentile) for the laboratory analyses are shown in table 1 respectively.

Table 1. Mean age and the obtained laboratory values for the different tumor markers (n=8716)

Variables	Age	Value
AFP	39.78 ± 7.85	2.96 (2.16, 4.04)
CA-125	62.66 ± 15.51	15.96 (8.93, 36.72)
CA 19-9	56.25 ± 20.30	12.85 (7.65, 105.98)
CEA	47.48 ± 17.34	2.51 (1.33, 5.40)
PSA	66.43 ± 12.01	1.62 (0.63, 5.11)

On dividing the source of tumor marker requests i.e., whether from in-patient/outpatient services, AFP, CA19-9, and CEA were mostly requested from wards while a majority of requisitions for CA 125 and PSA were from outpatient services as shown in table 2 respectively.

Tumor marker requests were further divided based on gender which depicted that majority of requests for AFP, CA 19-9, and PSA was for male patients and requisition for CA 125 and CEA were done for female patients as illustrated in table 3.

Table 2. Representation of tumor markers as per the source of request in Out-patient and In-Patient departments (n=8716)

Parameters	Total number of tests	Source for the tests	
		OPD	IN-PATIENT
AFP	200	44%	56%
CA 125	3400	52%	48%
CA 19-9	55	44%	56%
CEA	811	34%	66%
PSA	4250	74%	26%

Table 3. Differentiation of tumor markers request based on gender (n=8716)

Parameters	Male n(%)	Female n(%)	Total
AFP	112 (56)	88 (47)	200
CA 125	65 (1.91)	3335 (98.09)	3400
CA 19-9	46 (84)	9 (16)	55
CEA	603 (74)	208 (26)	811
PSA	4201 (99)	49 (1)	4250

The values of individual tumor marker at high cut-off values in the total population has been shown in table 4. The high number of the patients (39%) who underwent PSA had higher cutoff values compared to the other as depicted in table 4.

Table 4. Depiction of individual tumor markers at high cut-off values in the total population (n=8716)

Parameters	Limit value	Proportion of patients n (%)
AFP	> 6.05 IU/ml	35 (18)
CA 125	> 35.0 U/ml	1017 (30)
CA 19-9	> 37 U/ml	13 (23.6)
CEA	> 5.09 ng/ml	213 (26.26)
PSA	Male > 4.0 ng/ml	1643 (39)
	Female > 0.5 ng/ml	37 (0.9)

The distribution of tumor markers as per the test requested is represented in table 2. The highest proportion of tumor markers requested at our hospital was PSA (48.77%) followed by CA-125 (39.02%) respectively as depicted in figure 1.

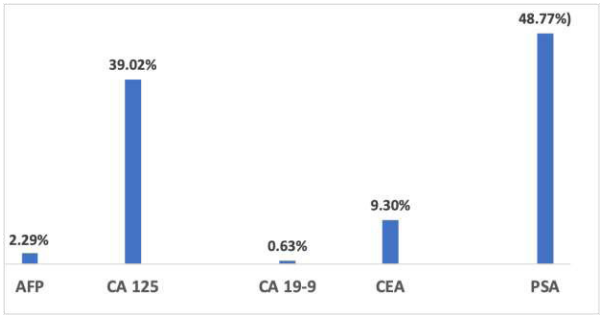

Figure 1. Distribution of tumor markers according to a number of tests requested in 5 years (n= 8716)

DISCUSSION

Tumor markers are commonly used as a screening tool for the possible tumor or tumor-like growth in patients with high risk or even in healthy individuals.[6-8] Though, the tumor markers are used as a potential screening tool, they lack a very high sensitivity or specificity for the determination of tumor.8 The most commonly requested tumor marker at our hospital are AFP, CA-125, CA 19-9, CEA, and PSA. We report the retrospective analysis of the requisition pattern of these 5 tumor markers at our hospital i.e., BPKIHS.

Alpha-fetoprotein (AFP) is the commonly requested fetal-specific glycoprotein.[9] It is produced primarily by the fetal liver. However, its concentration in serum declines rapidly after birth and its synthesis in adult life is repressed. More than 70% of HCC patients have a high serum concentration of AFP because of tumor excretion.[9,10] Serum AFP is still considered a most useful tumor marker in screening HCC patients even after four decades. Apart from HCC, increased levels of AFP are also seen in germ cell tumors arising from the ovaries and non-seminomatous germ cell tumors of the testes. Also, peritoneal fluid AFP measurement might help identify ascites due to HCC, particularly in cases where cytologic findings are inconclusive.[9,10] The present study depicts that a total of 200 tests for AFP were requested in 5 years duration with the mean age of the patient being 39.78 ± 7.85 years. The assay-dependent cut-off value was taken <6.05 IU/ml with the majority of the request being done from in-patient (wards) i.e., 56% and male patients (56%) respectively. This finding was similar to the study reported by Chaminda et al. where the median age of the patient was 64 (range 12-88) years and 88.5% were males.[11] Also, we report a total of 15% of the patients with a higher cut-off value of AFP with the minimum and maximum range of values being 0.5-1123 IU/ml.

CA-125 is a commonly requested tumor marker for ovarian cancer.[9,12] It is a high molecular weight glycoprotein expressed by a large proportion of epithelial ovarian cancers. It is a commonly employed test to aid in the workout for the benign/malignant differential diagnosis of pelvic masses in postmenopausal women.[12] Although it is the tumor marker for epithelial ovarian cancer it has many disadvantages. One of them is the inability to be characterized as a screening test, primarily due to the low incidence of ovarian cancer in the general population and also because of the possibility of false-positive results as approximately 1% healthy population has raised CA125 (> 35 U/mL).[13,14] Despite this, consecutive measurement of baseline CA-125 levels and increase in successive values has been shown to illustrate the risk for malignancy calculated using the algorithm (Risk of ovarian cancer algorithm, ROCA).[15] But, the expediency of CA-125 is not only limited to epithelial ovarian cancer but has been seen to be associated with malignancies of endometrium, cervix, lung, breast, liver, and in gastric, pancreatic, colorectal malignancies, cirrhosis of the liver, hepatic of

renal insufficiency and pancreatitis.[16-18] Our study findings depict that a total of 3400 tests for CA-125 was requested during 5 years which comprised 39.02% of total tumor markers processed in our laboratory. Among them, 3335 (98.09%) were from female patients and OPD i.e. 52%. The assay-dependent cut-off for CA-125 was taken as >35.0 U/ml which was seen in 30% of the total tests requisitioned. The finding was similar to the study reported from India by Ample et al. where 92.8% were female who underwent the CA-125 test.[19]

CA 19-9 is a tetrasaccharide carbohydrate-related antigen that is predominantly secreted by human epithelia of the pancreas, bile duct, colon, stomach, endometrium, and salivary glands.[9] It has been significantly associated with adenocarcinomas, particularly in the pancreas and in other organs, including the bile duct, colon, stomach, and endometrium. Thus, it is a well-known tumor marker for monitoring the treatment of patients with pancreatic cancer.[20,21] Also, evidence has insinuated that serum CA 19-19 has shown to be associated with nonmalignant conditions including type 2 diabetes, dyslipidemia, and metabolic syndrome.[22] The findings from our study reveals that the mean age of the patient undergoing for CA 19-9 test was 47.48 ± 17.34 years with the median values of 12.85 (7.65, 105.98). A total of 55 tests were requested in the study period which accounts for 0.63% of total tumor marker requisition, out of which 55% request was from in-patient department with the majority of the patient being males (84%) respectively. The assay-dependent cut-off was > 37 U/ml with 23.6% of the patients with increased levels of the CA 19-9 among the total tumor marker requisition. The finding was approximately similar to the study reported by Thomsen et al.[23]

CEA is a glycoprotein that belongs to the adhesion group of molecules and is produced in the epithelium of the large intestine and may be involved in malignancy.[24] The role of CEA is well known as a tumor biomarker in the diagnosis, treatment, and surveillance of colorectal carcinoma. Generally, the clinical significance of CEA lies in the assessment of the tumor pre-operatively and its prognosis and post-operative recurrence monitoring. Also, studies have shown that an elevated level of CEA is significantly associated with a poorer prognosis.[25] Our study findings depict that the mean age of the patient undergoing the CEA test was 47.48 ± 17.34 years with the majority of the patients being male (74%). In addition, the majority of the requisition for CEA were for in-patients (66%). This was similar to study reported by Thomsen et al.[23] The cut-off limit was 5.09 ng/ml, of which 26.26% had higher cut-off values (> 5.09 ng/ml) which were according to the study reported by Young et al. who reported 32% positivity of CEA in their study patients.[26]

Lastly, we assessed the pattern of requisition of PSA, one of the most commonly requested tumor markers by the clinicians. PSA is a glycoprotein released by prostate gland-specific cells. Elevated PSA could be associated with prostate cancer but can also be associated with benign prostatic hyperplasia (BPH), prostatitis, or prostatic trauma.[27] Increased age is one of the risk factors for disease related to the prostate gland. Normally, a very low concentration of PSA is present in apparently normal human beings (0.1 to 4.0 ng/ml). PSA is highly specific to the prostate gland, as it is the organ of origin, however, the values for PSA are not highly specific to prostate cancer.[27] Increased levels are seen in 20% to 50% of men with BPH and 10% of the male population can have PSA > 10 ng/ml but not necessarily due to cancer. A high level of PSA is also detected in females with breast cysts and fibroadenoma.[28] It is thought to be a prognostic marker in women with metastatic breast cancer.[28] It has been found that the levels of PSA increase in carcinoma of the female prostate (Skene's gland).[28] In our retrospective analysis, a total of 4250 tests for PSA were requested during 5 years which comprised 48.77% of total tumor marker requisition. Also, the mean age of the patient was 66.43 ± 12.01 years who underwent test with the majority of the patients being males [n=4201 (99%)] with the requisition from OPD (74%) respectively. These findings were similar to the study reported by Banerjee et al.[29] Also, the assay-dependent cut-off i.e., > 4.0 ng/ml in males was obtained in 39% of the male patients and 0.9% of females respectively.

Testing for PSA, if the value ranges from 3-4 ng/ml with subsequent biopsy is a commonly accepted method by both the American Urology Association (AUA) and the European Association of Urology (EAU) for screening of prostate cancer.[29,30] Nevertheless, PSA bestows few limitations as there is no universally accepted threshold value.[31] Also, numerous factors affect the serum PSA values like age, acute prostatitis, ejaculation, catheterization, and certain comorbidities like diabetes and certain medications.[9]

Our study could not illustrate the diagnostic and clinical findings of the patients undergoing the tumor marker investigations due to resource constraints. Also, the follow-up values could not be traced due to the unavailability of appropriate data. A large prospective study could be conducted by taking the baseline findings from the present study to explore the inappropriateness of tumor marker requests at a tertiary care setting.

CONCLUSION

The finding from the present study suggests that the burden of oncological disease is high despite the limited specialized health care services in Nepal. Our findings are similar to studies done in other comparable settings. The use of tumor markers must be meticulous and appropriate to prevent the unnecessary economic burden and stress to the patients.

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