Study of Serum Tumor Marker Requisition Pattern in Tertiary Hospital of Nepal

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ABSTRACT

Introduction: Tumor markers are substances that may be present in higher than normal levels in the body fluids, tissue, serum, or urine of individuals with cancer. Requesting of multiple markers is rarely of use. The aim of the present study is to know the pattern of tumor marker prescription in our tertiary hospital.

Methods: The medical record of common tumor marker prescription viz. Total PSA, AFP, CEA, CA-125, CA 19-9 and CA 15-3 was reviewed over a period of one year (January 2021 to December 2021).

Results: A total of 1157 markers were requested from 535 patients. The most frequently prescribed marker was CA-125 and the least prescribed marker was CA 15-3. It was found that 219 (18.9%) markers were above the reference range, while 938 (81.07%) were within the reference range. Out of 535 patients, single tumor marker was prescribed for 261 (48.7%), dual markers for 49 (9.1%), triple markers for 117 (21.8%), quadruple markers for 93 (17.4%), and five or more markers for 15 (2.8%) patients. PSA was most commonly (98.47%) prescribed as a single marker, while other tumor markers were commonly prescribed in multiple pattern. The most common combination was that of CA 19.9, CA 125, and CEA in a triple prescription pattern, and AFP was added to these three markers in a quadruple combination.

Conclusion: Multiple tumor marker prescription is common in our setting. This might be due to unavailability of local guidelines and regular audit. Tumor markers should be used appropriately otherwise it may have many ill consequences.

Keywords: Guidelines; Pattern; Tumor markers.

INTRODUCTION

Cancer is a prevalent health concern worldwide. The World Health Organization (WHO) reported that in 2018, there were 18.1 million cancer diagnoses and 9.6 million deaths attributed to the disease. Projections indicate that these numbers are expected to almost double by 2040, primarily in low and middle-income nations.[1] Notably, cancer ranks as the primary or secondary cause of premature mortality in 134 out of 183 countries.[2] The approach to managing cancer includes primary prevention, early detection and diagnosis, comprehensive treatment, and palliative care.[1] Cancer diagnosis and staging typically require laboratory tests, imaging, histopathology, and immunohistochemistry. Histopathology remains the gold standard for the final diagnosis of many cancers, and tumor marker testing plays a significant role in screening, diagnosis, and monitoring of various cancers.[3] Tumor markers are substances that can be potentially found at elevated levels in body fluids, tissues, serum, or urine of individuals diagnosed with cancer.[4] When correctly requested and interpreted, tumor markers can aid in the clinical management of cancer patients.[5] Improperly requested tumor marker measurements can result in unnecessary and additional investigations. It is crucial to be aware of the limitations of tumor markers, not only due to the economic implications but also because incorrectly interpreted tumor marker results can cause patients heightened anxiety and distress. Moreover, unnecessary investigations can lead to delays in accurate diagnosis and treatment.[6] Similarly, the simultaneous request for multiple markers, such as CEA and the CA series of antigens, in an attempt to identify metastases from an unknown primary source, is seldom beneficial.[7] The aim of the present study is to know the pattern of tumor marker prescription in our tertiary hospital.

METHODS

This study conducted at the department of clinical biochemistry of Dhulikhel hospital is a quantitative, retrospective chart review study (secondary data analysis). Medical records of the patients who had undergone tumor marker testing from January 2021 to December 2021 were reviewed. The commonly prescribed tumor markers such as Total PSA, AFP, CEA, CA-125, CA 19-9 and CA 15-3 were included in the analysis. All the tumor markers were analyzed using chemiluminescence assay (i1000SR Abbott, USA).

The data was entered in MS Excel 2013 and analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, USA) version 21.0. The prevalence was presented through frequency and percentage. Continuous biochemical indicators was expressed as mean ± standard deviation or medians with interquartile ranges.

RESULTS

During a one-year period, tumor markers were prescribed for 535 patients, with a total of 1157 markers requested. Of these patients, 195 (36.4%) were male and 340 (63.6%) were female. The average age of the patients was 47.8±17.8 years, with 207 (38.7%) being less than 40 years, 190 (35.5%) between 40 and 60 years, and 138 (25.8%) being above 60 years. The most frequently prescribed marker was CA-125 and the least prescribed marker was CA 15-3. The specifics of the studied tumor markers is shown in Table 1.

Table 1: Frequency and median value of prescribed tumor markers

Tumor marker	Prescription frequency	Median value
AFP	136 (11.75%)	1.9 (1.3, 2.7)
CA 15-3	45 (3.88%)	7.9 (5.9, 11.7)
CA 19-9	260 (22.4%)	6.8 (2.0, 23.46)
CA 125	316 (27.3%)	20.04 (13.1, 44.0)
CEA	262 (22.6%)	1.5 (1.1, 2.5)
PSA	138 (11.9%)	1.6 (0.6, 6.0)

Upon analyzing the reports of the prescribed markers, it was found that 219 (18.9%) were above the reference range, while 938 (81.07%) were within the reference range. The positive rate of tumor markers was 29.09% among males and 16.54% among females. The distribution of different tumor markers within and above the reference range is shown in Table 2.

Table 2: Distribution of different tumor markers within and above reference range

Tumor marker (Total number of prescription)	Within Reference range (Normal)	Above reference range (Positive)
AFP (136)	129 (99.26%)	7 (0.73%)
CA 15-3 (45)	45 (100%)	0
CA 19-9 (260)	213 (81.9%)	47 (18.07%)
CA 125 (316)	222 (70.25%)	94 (29.74%)
CEA (262)	235 (89.7%)	27 (10.3%)
PSA (138)	94 (68.1%)	44 (31.98%)

Out of 535 patients, single tumor marker was prescribed for 261 (48.7%), dual markers for 49 (9.1%), triple markers for 117 (21.8%), quadruple markers for 93 (17.4%), and five or more markers for 15 (2.8%) patients. Table 3 shows the prescription pattern of the different tumor markers.

PSA was most commonly (98.47%) prescribed as a single marker, while other tumor markers were commonly prescribed in multiple pattern. The most common combination was that of CA 19-9, CA 125, and CEA in a triple prescription pattern, and AFP was added to these three markers in a quadruple combination. Table 4 shows the positive and negative rate of single and multiple prescribed tumor markers. The most common combination of dual marker positive was that of CA 19-9 and CA-125 (>90% cases) whereas CEA and or AFP was added in case of triple positive markers.

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Table 3: Prescription pattern of different tumor markers

Prescription Pattern (n)	AFP (136)	CA 15-3 (45)	CA 19-9 (260)	CA 125 (316)	CEA (262)	PSA (138)
Single (261)	25	1	20	55	31	129
Dual (49)	2	0	26	38	30	2
Triple (117)	13	15	107	115	98	3
Quadruple (93)	81	17	92	93	88	1
5 or more (15)	15	12	15	15	15	3

Table 4: Positive and negative rate of tumor markers according to prescription pattern

Prescription pattern	Negative rate	Single marker Positive	Dual marker positive	Triple Marker positive	Quadruple Marker positive
Single (261)	185 (70.9%)	76 (29.1%)	-	-	-
Dual (98)	83 (84.7%)	13 (13.2%)	2 (2.04%)	-	-
Triple (117)	71 (60.7%)	31 (26.5%)	14 (12%)	1 (0.85%)	-
Quadruple (93)	53 (57%)	26 (28%)	10 (11.7%)	3 (3.2%)	1 (1.07%)
5 or more (15)	8 (53.3%)	5 (33.3%)	1 (6.6%)	1 (6.6%)	-

DISCUSSION

The present study aimed to evaluate the pattern of tumor marker prescription in a tertiary hospital of Nepal. The study found that tumor marker prescription was higher in females compared to males, with no significant difference among the age groups. Though the total number of prescription was higher in females, the positive rate was higher in males. This may be due to the high rate of PSA positivity among males. Our study also depicted that the positive rate was higher for single marker in comparison to multiple markers. Furthermore, our study showed many instances of multiple marker prescriptions. The most common combination was that of CA 19-9, CA 125, and CEA in triple requisition, and AFP being added to these in the quadruple pattern.

The findings of this study are in line with other studies that have highlighted the prescription of multiple tumor markers.[8-13] Though various guidelines have discouraged the use of multiple markers in an attempt to identify metastases of unknown primary origin, it is commonly practiced.[14, 15] In the Northern Ireland audit, it was found that more than two markers were requested in 5% of the patients.[9] This rate is very low in comparison to our study which may be in large part due to implementation of local guidelines and regular audit over there. The emphasis of inter departmental collaboration and implementation of guidelines in tumor marker request can be seen in a study conducted at university hospital of Wales. Before the implementation of guidelines, 38% of all requests were for panels containing four or more tumor markers. Similarly, more than half (53%) of the requests from the surgery ward used to be for such panels. However after the implementation of guidelines, the total number of tumor marker requests decreased by 32% and requests for single marker increased while that of multiple markers in panel decreased significantly (78% reduction).[13] Similar to that of Northern Irish audit, we also found that most requests for three tumor markers were for CEA, CA-125, and CA 19-9, which may have been used to investigate suspected gastrointestinal tumors decreased significantly (78% reduction).[13] Similar to that of Northern Irish audit, we also found that most requests for three tumor markers were for CEA, CA-125, and CA 19-9, which may have been used to investigate suspected gastrointestinal tumors. Despite the utilization of multiple markers, there is no substantial enhancement in the sensitivity or specificity of individual markers when it comes to detecting gastrointestinal tumors. Furthermore, even when the appropriate individual marker is employed correctly for the suspected GI site of malignancy, the diagnostic capability of these markers is limited due to their lack of sensitivity and specificity.

Inappropriate laboratory utilization is often defined as "any test order in violation of a guideline produced by a government or professional society".[16] In our study, we have not taken account of the detailed history and final diagnosis but there are instances where tumor markers have been used inappropriately. The audit in Northern Ireland found that clinicians used tumor markers to screen malignancy with a low index of suspicion. Similarly, the audit in a UK hospital found that 26% of CA 15-3 requests were for men, even though none of these men had breast biopsies in the year of the study or in the two years prior.[11] In a retrospectively reviewed Greek study, 26% of CA-125 requests were for men.[10] Though we did not find any sort of inappropriateness regarding the gender specific tumor marker prescription, the Northern Irish audit found out that 17% of CA-125 and 26% of CA 15-3 requests were made for men.[9] Similarly, in a study done in tertiary hospital of eastern Nepal, 65 prescription for CA-125 was made for male and 49 prescription of PSA was made for female.[17] In another study, it was found that out of 3636 CA-125 requests, 612 were on men, and out of 374 CA 15-3 requests, 98 were on men.[11] Another laboratory audit found that up to 84% of multiple tumor marker requests in primary care were inappropriate when compared against National Academy of Clinical Biochemists guidance.[18] The economic consequences of improperly utilizing tumor markers can be substantial, as demonstrated by a retrospective assessment carried out at a university hospital in western Saudi Arabia.

This review estimated that the total expenses resulting from inappropriate requests for tumor markers amounted to $2,785,493 within a span of three years. Moreover, the study revealed that 71.5% of patients who underwent tumor marker testing lacked the clinical indications that typically prompt such requests.[19]

Improving the appropriate use of laboratory tests has become an increasingly challenging task for clinical laboratories. One of the primary responsibilities of laboratory professionals is to provide guidance on the most effective utilization of laboratory tests, aiming to enhance clinical effectiveness and improve patient outcomes.[20] This can be achieved by implementation of guidelines, audit and regular feedback. Though we do not have our own guidelines regarding the appropriate use of tumor markers, there are widely accepted guidelines published by various international committees and federations.[6, 14, 15, 21] These guidelines can serve as a useful framework for promoting best practices and reducing unnecessary testing. Divergence can be observed in the recommendations regarding which markers should be measured in specific malignancies, as outlined in guidelines issued by different organizations. However, it is important to note that when there is a moderate to high level of suspicion for malignancy, it is advisable not to discourage the measurement of the relevant tumor marker.[22]

CONCLUSION

In conclusion, the present study highlights the inappropriate use of tumor markers and the need for guidelines to promote best practice. Recognizing the limitations of tumor markers is of utmost importance, not only due to the economic consequences but, more significantly, because improperly interpreted tumor marker results can result in heightened anxiety and distress for patients. Therefore, the implementation of guidelines and interdepartmental collaboration between clinicians and laboratory professionals are necessary to increase the clinical efficacy of laboratory testing.

REFERENCES

1. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: World Health Organization. 2020.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. Lyon: International Agency for Research on Cancer; 2020.
3. Kleinert S, Horton R. Pathology and laboratory medicine: the Cinderella of health systems. Lancet (London, England). 2018;391(10133):1872-3.
4. Lai L, Cheong S, Goh K, Leong C, Loh C, Lopez J, et al. Clinical usefulness of tumour markers. The Malaysian journal of pathology. 2003;25(2):83-105.
5. Duffy MJ. Evidence for the clinical use of tumour markers. Annals of clinical biochemistry. 2004;41(5):370-7.
6. Sturgeon C, Lai L, Duffy M. Serum tumour markers: How to order and interpret them. BMJ.2009;339:b3527.
7. Duffy M. Clinical uses of tumor markers: a critical review. Critical reviews in clinical laboratory sciences. 2001;38(3):225-62.
8. Kilpatrick ES, Lind MJ. Appropriate requesting of serum tumour markers. BMJ. 2009 Sep 22;339:b3111.
9. McDonnell M. An audit of tumour marker requests in Northern Ireland. Annals of clinical biochemistry. 2004;41(5):378-84.
10. Ntaios G, Hatzitolios A, Chatzinikolaou A, Karalazou P, Savopoulos C, Karamouzis M, et al. An audit of tumour marker utilization in Greece. European Journal of Internal Medicine. 2009;20(3):e66-e9.
11. McGinley PJ, Kilpatrick ES. Tumour markers: their use and misuse by clinicians. Annals of clinical biochemistry. 2003;40(6):643-7.
12. Gravey F, Davy J, Grandhomme F, Allouche S. Serum Tumor Markers: Comparison Guidelines and the Clinical Practice in a University Hospital Center. J Clin Exp Pathol. 2015;5(5):246.
13. Schulenburg-Brand D, Kumar N, Zouwail S. The impact of local guidelines on the tumour marker requesting patterns of a general surgery department. Annals of Clinical Biochemistry. 2013;50(5):438-42.
14. Duy M, McGing P. Guidelines for the use of tumour markers. Association of Clinical Biochemists in Ireland. 2018
15. Duffy M, McGing P, McSweeney J. Guidelines for the use of tumour markers. Association of Clinical Biochemists in Ireland. 2000.
16. Hauser RG, Shirts BH. Do we now know what inappropriate laboratory utilization is? An expanded systematic review of laboratory clinical audits. American journal of clinical pathology. 2014;141(6):774-83.
17. Niraula A, Gelal B, Chaudhari R, Das B, Lamsal M. Tumour Marker Requisition Pattern in a Tertiary Care Centre of Eastern Nepal. Kathmandu Univ Med J. 2022;80(4):422-6.
18. Walker PL, Crook M. Tumour marker requesting in primary care and the role of the laboratory. Journal of clinical pathology. 2011;64(5):443-6.
19. Al-Mughales JA, Alahwal MS. Inappropriate practice in tumor marker requests at a university hospital in Western Saudi Arabia: A 3-year retrospective study. The International Journal of Biological Markers. 2020;35(4):35-43.

20. Ferraro S, Braga F, Panteghini M. Laboratory medicine in the new healthcare environment. Clinical Chemistry and Laboratory Medicine (CCLM). 2016;54(4):523-33.

21. Duffy MJ. Clinical Utility of Tumor Markers: What the Guidelines Recommend. diagnostyka. 2010;46(3):281-91.

22. Sturgeon C. Practice guidelines for tumor marker use in the clinic. Clinical chemistry. 2002;48(8):1151-9.