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Are We Ordering Tumor Markers Appropriately?

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Abstract **Background:** Serum Tumor Markers (TM) have limited role in screening, diagnosis and management of malignancy and there are international guidelines on the use of TMs. However, increasing TM orders are made in clinical practice with evidence to suggest misuse of TMs for indications not supported by guidelines. The inappropriate use of TMs not only results in waste of resources but can also generate anxiety and distress in patients. We audited the appropriateness of commonly used serum TM requests in a large acute teaching hospital and analyzed the cost implications of inappropriate use of TMs. **Methods:** We audited serum TM orders from the 1st to 31st of January 2010 in our hospital. Data was extracted from the clinical notes on the type of TMs requested and the reason/indication for the request and final diagnosis. Requests were judged appropriate or inappropriate based on the published guidelines on indication for the TMs. Using the tariff for individual TMs during the audit period, we analyzed the cost implication of inappropriate requests. **Results:** 131 TM orders were audited and 104 (79%) of these orders were judged inappropriate. Furthermore, 12 patients with the inappropriate orders who had abnormal TM result went on to have additional tests including 4 endoscopies and 5 CT scans. Based on the tariff for the TMs in the audit period, we estimated that £1107 was wasted due to the inappropriate orders of TMs alone during the audit period. **Conclusion:** Rationalizing the use of TMs in clinical practice can deliver substantial savings. Education and training for the clinicians is needed to raise awareness of the guidelines on appropriate use of TMs and change clinical practice.

Keywords Tumor markers, Malignancy, Guidelines

1. Introduction

The tumor marker (TM) can be defined as any molecule or substance produced by the tumor or the host tissue in response to the tumor that can be detected by an assay in body fluids or tissues. [1] TMs, if used appropriately could be valuable in the management of malignant diseases. Serum TMs such as AFP and HCG and PSA are extremely useful in the management of germ cell tumors and prostate cancer, respectively. Similarly, the tissue markers such Estrogen receptor and human epidermal growth factor receptor (HER)-2 have contributed enormously to tailoring treatment of breast cancer. The audit and the discussion here is restricted to commonly used serum TMs.

The major limitation of the commonly used TMs is the lack of high specificity and sensitivity. Most of these TMs are not specific for one malignancy and are elevated in many non-malignant conditions. Therefore, the utility of TMs in screening, diagnosis and treatment is limited. Given these limitations, when is a TM request considered appropriate? The American Society of Clinical Oncology, [2] The National Academy of Clinical Biochemistry [3] and the European Group on Tumor Markers [4] have published guidelines on the use of TMs. Several conclusions can be drawn from these guidelines. Firstly, TMs should not be used for routine population-based screening for cancer. Secondly, some TMs could be used as an aid in diagnosis of selected cancers in conjunction with clinical examination and imaging. Thirdly, the main role of TMs is in surveillance and monitoring and finally, requesting a panel or panels of TMs, PSA in women and CA125 and C153 in men are inappropriate. Based on these guidelines on which there is a broad agreement on TM use, the indications for the common TMs are summarized in appendix 1.

We audited the appropriateness of TM orders and the financial impact of inappropriate use of the TM orders in our hospital.

2. Aims of the Audit

1. To assess the appropriateness of TM requests
2. To assess the financial impact of inappropriate use of TMs

3. Methods

List of TM orders from 1st January 2010 to 31st January

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2010 was extracted from the biochemistry laboratory data base in our hospital. We excluded requests from primary care, orders for HCG from emergency rooms and obstetrics in assessment of women with pregnancy related presentations, duplicate requests and cases where no data could be retrieved. We compiled a list of approved indications for each TM based on the international guidelines on TMs. We judged each order as appropriate or inappropriate based on the approved indications for TMs as per the guidelines.

Patient notes were reviewed and data was collected on a) reason/indication for the orders b) pattern of TM orders c) additional investigations as result of abnormal TM result and d) final diagnosis. Finally, appropriateness of the TM order was judged after review of the data for each patient.

Following the completion of our audit data we assessed the financial implications of the inappropriate TM orders. We used the tariff (see appendix 2) for each TM during the audit period to estimate the financial impact.

4. Results

During the audit period, 482 TM requests were made, of which 131 TM orders that met the audit criteria were audited.

a) **Reason for TM request (Fig1)**

The reason for the request was either not clear or not specified in 57% of orders and TMs were ordered for a wide range of conditions and presentations. In around a fifth of the cases, it was for diagnosis of suspected malignancy and 7% and 2% for surveillance and monitoring of known cancers respectively. TM requests were for screening of malignancy in 10% of the cases.

The five most common final diagnoses were as follows: non-malignant hepato- biliary disease (23), benign prostatic hypertrophy (9), and gastro-esophageal reflex disease (8), 'no malignancy' (8). Only 18 out of the 131 patients had a confirmed cancer diagnosis.

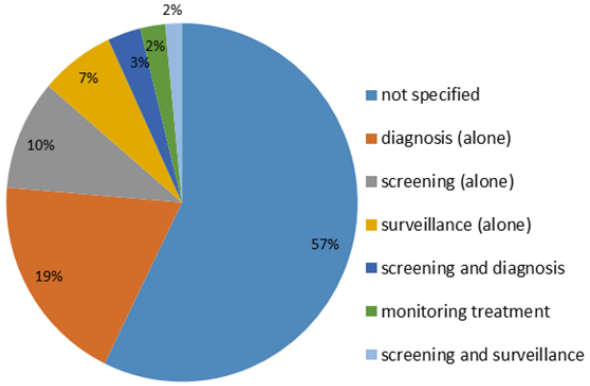

Figure 1. Reason for TM order

b) **Pattern of TM orders: Which TM and how many?**

The pattern of TM orders is shown in fig 2. In more than half of the cases two or more different TMs were ordered. As evident from the graph shown, variety of combination of TMs were ordered and in many instances a whole panel of TM ordered, a practice not supported by any of the guidelines.

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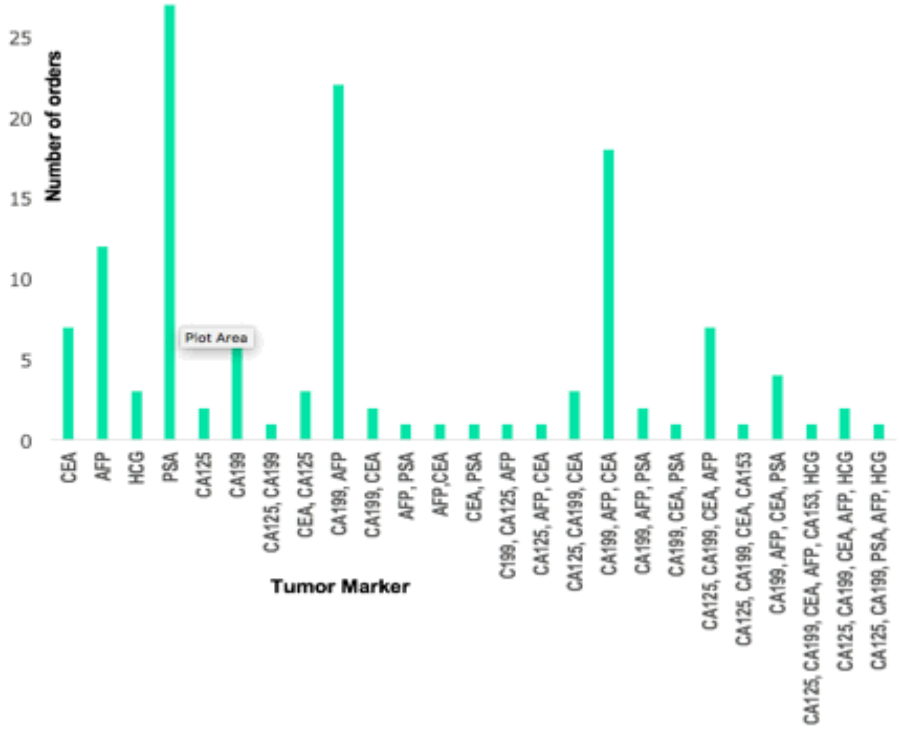

Figure 2. Pattern of TM orders

***c)* Additional Investigations because of abnormal TM**

We analyzed the cases of inappropriate TM orders where abnormal TM results led to further investigations. In 12 cases, additional investigations were carried out to investigate the abnormal TM result which included CT scan (4 cases), US scan (4 cases), endoscopies (3) and flexible sigmoidoscopy (1 case). In none of these cases the additional investigations helped to explain the abnormal TM result.

***d)* Appropriateness of TM requests**

We assessed the appropriateness of each TM order based on the approved indications for each TM as specified in the guidelines. As shown in fig 3, majority of TM orders were inappropriate with no justification for the order for the given clinical problem.

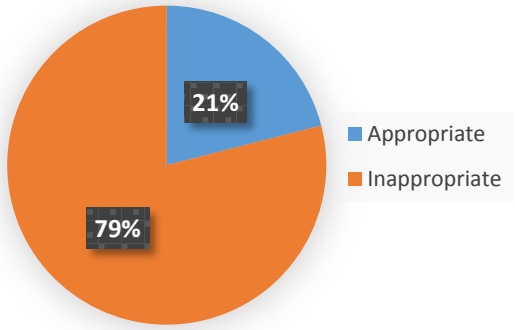

Figure 3. Appropriateness of TM orders

***e)* Financial impact of inappropriate use of TMs**

We analyzed the financial impact of the inappropriate TM orders using the tariff for each TM during the audit period. We calculated the total cost of individual TM order and estimated the amount of money lost from inappropriate use of TM. Given that 79% of these orders were inappropriate we estimated that a total of £1107 was wasted from inappropriate use of TM during the audit period.

5. Discussion

There are limited and specific indications for TM use in screening, diagnosis and surveillance of malignancy as per the published guidelines. Despite the limitation of TMs, increasing TM requests are made both in general practice as well as in teaching hospitals. Our audit showed that 79% of the orders were inappropriate, a practice that seems to be widely prevalent as shown by numerous audits and retrospective studies. In an audit on the use of TMs in general practice, a staggering 84% TM requests were deemed inappropriate [5]. Our audit also showed multiple TM orders in more than half of the cases and in several cases a panel of TMs were ordered, a practice not supported by any guidelines. The extreme case of inappropriate requests was highlighted in an audit from a teaching hospital in Turkey where 23% of CA 125 (marker used for ovarian cancer) and 26.6% of CA 15-3 (maker used for breast cancer) requests were made in men. [6] The reason for TM orders in more than half of the cases in our audit is unclear from the notes and it appears that in many instances these were used in investigation of symptoms or presentations of suspected cancer. There is no evidence for routine use of TMs in the work up of suspected malignancy and TMs are generally not useful in identifying the primary in patients presenting with metastatic carcinoma of unknown primary. National Institute for Health and Clinical Excellence (NICE) guidance on carcinoma of unknown primary sets out the specific indications for TMs in presentations of metastatic disease with unknown primary [7]. In majority of cases in our audit, neither the presentation nor the final diagnosis justified the TM order and importantly we could not see any role for TMs in the diagnosis or the management of the patient.

The inappropriate use of any test such as TM comes with consequences that could be harmful. For the patient, the abnormal results could bring unnecessary anxiety and distress. The raised TMs might prompt clinician to order imaging and investigations, many of which could be invasive with the attendant risks and this could result in further anxiety and stress for the patients. Furthermore, it can initiate inappropriate referrals. In our audit, additional investigations were performed in 12 cases as result of abnormal TMs. In a retrospective study on the utility of imaging carried out because of elevated common TMs, McMahan et el found that imaging was futile in diagnosing the malignancy or providing an explanation for the cause of raised TMs. A mean of 1.2 imaging studies were carried out per patient because of elevated TM, which is significant waste of resources as well as money. [8]

The financial implication of inappropriate orders cannot be underestimated particularly in the current financial crisis, which is putting strain on the health services across the world. Extrapolating the data for the one-month audit, we estimate that over £ 12000 could be lost per year from the inappropriate orders. If we were to assume that a modest 30% of the estimated 15 million TM request made per year in the United Kingdom, [9] are inappropriate, this could result in a loss of 18 million pounds a year (an average cost of £4-5 per TM request). The financial impact could be much higher if we add other overheads such as cost of phlebotomy, transport of samples, doctors and laboratory technicians' time and the cost of additional investigations.

One of the reasons for the widespread use TMs appear to be the lack of understanding of the limitation of TMs and awareness of guidelines on the use of TMs among clinicians. Several measures have been suggested that might change clinicians' behavior and help in curtailing the inappropriate TM requests in clinical practice. Education on the guidelines and auditing of TM's requests is vital to change practice. Use of technology could help reduce inappropriate TM requests. Majority of hospitals now use electronic ordering system for laboratory investigations. It is possible to use flags or alerts when a TM is ordered, that will guide the clinicians on specific indications as well as the frequency of the testing of TMs. In addition to these measures, it also calls for a strong

leadership from clinical biochemistry department, empowering the department to reject orders that are not in line with the guidelines. We plan to implement these measures to bring a change in the current practice of TM orders. It is imperative that we as clinicians take lead in cutting costs of unnecessary investigations including TMs.

6. Conclusions

Routine use of TMs is unjustified and clinicians should restrict TM requests complying with the published guidelines on the use of TMs. Education and training of clinicians and strict implementation of TM guidelines could deliver substantial cost savings for the health services.

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Appendix 1: Appropriate TM Requests

PSA

☐ Diagnostic work-up and staging in men with symptoms and signs of prostate cancer

☐ Surveillance after treatment of prostate cancer

☐ Monitoring treatment of Advanced Prostate cancer

☐ CUP- Men with presentations compatible with prostate cancer

CEA

☐ Pre-op/ staging of bowel cancer

☐ Surveillance after treatment of bowel cancer

☐ Monitoring treatment of advanced bowel cancer

CA19-9

☐ Monitoring treatment of advanced pancreatic carcinoma

CA125

☐ Assessment of suspicious pelvic masses in postmenopausal women

☐ Monitoring treatment of advanced ovarian cancer

☐ CUP- Women with presentations compatible with ovarian cancer (Including inguinal nodes, chest, pleural, peritoneal and retroperitoneal presentations)

AFP

☐ Screening for HCC in high risk groups along with Ultrasound liver

☐ CUP- Presentations compatible with hepatocellular cancer

☐ Monitoring after treatment of HCC

hCG

☐ Diagnosis, surveillance and monitoring of treatment of gestational trophoblastic neoplasia

hCG and AFP

☐ Staging and prognosis of Germ cell tumors

☐ Surveillance after treatment of Germ cell tumors

☐ Monitoring treatment of Germ cell tumors

☐ CUP- Ppresentations consistent with germ cell tumours (Midline nodal / retroperitoneal disease in young men)

CA 15-3

☐ Monitoring treatment of advanced breast cancer

(CUP- Carcinoma unknown primary, HCC- hepatocellular cancer)

Appendix 2: Tariff for Tumour Markers (2010)

Tumour Marker	£
CA-125	£6.61
CA-153	£12.10
CA-199	£7.02
CEA	£4.02
AFP	£4.22
HCG	£4.07
PSA	£3.61

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