The use of tumor markers in an Internal Medical Service – a baseline and post-intervention study

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Abstract

Background: Tumor markers (TM) are potentially useful in clinical practice, but have a limited role in diagnosis due to their poor sensitivity and specificity. Several international guidelines have been developed on the use of TM, but recent publications indicate that this procedure is frequently overused. The aim of this study was to assess the impact of informative and "self-auditing" activities in the correct use of TM in an internal medicine department.

Results: In the baseline study, TMs were requested for 19.6% of patients admitted. After the post-intervention (PI), there was a 42.6% reduction in the number of requests, down to 10.2%. In the baseline study, the main reason for the request for TM was diagnosis, while in the post-intervention study, the main reason was for screening purposes. In both studies, the appropriate situations were mainly in the area of screening, while the inappropriate situations were in the area of diagnosis. In the baseline study, 17.5% of the requests for TM were considered appropriate, a value which increased to 46% after intervention. Overall, there was a decrease in total costs, which was largely due to the decrease in the number of inappropriate requests.

Discussion: The present study shows that training/information and actions of "self-auditing" on the correct use of TM can have a positive impact on the modification and improvement of clinical practice, and a reduction in associated costs.

Key words: tumor markers, self-auditing, training/informative activities.

INTRODUCTION

Tumor markers (TM) play an important role in clinical practice, particularly in the monitoring of neoplasias. However their role in diagnosis is limited, due to their low sensitivity and specificity in this context.[1]

The appropriate use of a TM should result in a more favorable clinical performance, leading to better overall survival and disease-free time and better quality of life for patients, as well as a decrease in the cost of care.

In the last thirty years, various TMs have become available for clinical practice. Its introduction was not initially accompanied by appropriate guidelines, leading to a use that lacked clarification in terms of its potential and limitations.[2] Gradually, multiple studies emerged on TMs and their applicability, leading to the development of international guidelines.[3-5] Despite the existence of these guidelines, recent international publications have shown that TMs are used excessively by clinics.[1,3-5]

One way of promoting the rational use of healthcare resources, namely TM, is to carry out activities of training/information on the guidelines and recommendations that exist in this area, but experience with various groups indicates that these teaching actions have had limited effectiveness.[6-10]

To study the impact of training/information actions on the use of TM in the hospital context, we carried out a prospective intervention study with doctors. The aim is to characterize the profile of TM and the challenges relating to the guidelines. It also evaluates the impact of the training/information actions with doctors and the "self-auditing" clinic on the use of TM in an Internal Medicine Service, as well as the associated costs of the use of TM and the economic impacts of this intervention.

MATERIAL AND METHODS

Trial design

A prospective intervention trial was carried out with doctors of an Internal Medicine Service of a Central University Hospital, which included all patients for whom TM was requested.

In an initial (baseline) evaluation, the requests for TM over a three-month period were analyzed. Subsequently, training/information activities were carried out on the correct use of TM, and a post-intervention

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evaluation lasting three months. The aim of this second phase was to evaluate the impact of training and self-auditing actions on the performance of clinics.

The patients for whom TM was requested were identified, based on data from the Clinical Pathology Service of the Hospital. The clinical data were gathered through a review of the respective clinical processes.

The TM evaluated were: alpha-fetoprotein (αFP), carcinoembryonary antigen (CEA), CA19-9, CA125, CA15.3, CA72.4, CYFRA 21, neuron-specific enolase (NSE), total and free prostate-specific antigen (PSA), and squamous cell carcinoma antigen (SCC).

The main information elements gathered were:

- Type of TM requested;
- Reasons for the requests: Screening (request to detect cancer in asymptomatic patients), diagnosis (request to diagnose cancer before a definitive histopathological diagnoses), monitoring (request to identify response to therapy) and follow up (request to detect recurrence of the tumor);
- Grounds for a request (a request was considered valid when there was a written record explaining the reason for its use);
- The appropriateness or inappropriateness of the TM request (evaluated according to the international guidelines), determined by two of the investigators;
- The inherent costs of the TMs; costs of TMs were defined based on the prices stipulated by the National Health Service.

Description of the Intervention

The intervention consisted of presenting the results of the baseline evaluation to the doctors who work for the service, with special emphasis on explaining the inappropriate requests recorded. The guidelines for the correct use of TM were also reviewed with the doctors. The inappropriateness of the requests was discussed with the professionals.

The post-intervention analysis was carried out one year after the training/information actions, with the same characteristics as the initial evaluation, also covering a three-month period.

Statistical analysis

Statistical analysis was carried out using the program SPSS (SPSS Inc.) version 16. Bivariate analysis was carried out by the Chi^2 test for categorical variables, and the Student's T test (or its non-parametric Mann-Whitney) for the continuous variables. A level of significance of 5% was adopted.

RESULTS

Population

In the baseline study, for a population of 1,035 patients admitted during the period January to March 2005, TM was requested for 203 patients, corresponding to 19.6% of the patients admitted. In the PI study, for a population of 1233 patients admitted, TM was requested for 126 (10.2% of the patients admitted). The populations of the two studies were similar in terms of age ((mean± DP, years) baseline study: 73.1±13.3; PI study: 73.35±14.0)) and hospitalization time ((mean± DP, days) baseline study: 9.6± 8.3; PI study: 9.62± 9.0)). However, there was a higher proportion of males in the PI study (81% vs 65%).

Number of TMs requested

In the baseline study, TM was requested in 203 patients, with a total of 560 TMs (average 2.8 MT per patient, DP: 2,2). In the PI study, TM was requested in 126 patients, with a total of 239 requests (average 1.9 MTs per patient, DP: 1.3), which represents a 42.6% reduction in total requests ($p<0.001$).

Table I shows that in the baseline study in 59.6% of the patients, 1 or 2 TMs were requested simultaneously, and in 40.4% of the patients, 3 or more TMs were requested; in the PI study, 1 or 2 TM were requested, and in 12% 3 or more TM were requested ($p<0.001$).

Type of TM requested

The most commonly requested TM was the total PSA in both studies, followed by CEA. In the baseline study, the most commonly requested were CA 19-9 and AFP. In the PI study, the third most commonly requested TM was free PSA, followed by CA 19.9 *(Table II)*. It should be noted that the number of requests for all TMs decreased in the PI study.

Reasons for MT request

In the majority of cases (97.6%, n=197) in the baseline study and in the PI study (95.2%, n=120) there was no written basis for the TM request in the clinical process, although in many cases, it was possible to deduce the reason for the TM request. The main reason for the TM request in the baseline study was for diagnostic purposes (67.3% of requests), while in the

TABLE I

Total number of TM requests per patient

Number of requests/ patient (n)	Baseline study (n=203) Patients (n,%)		PI study (n=126) Patients (n,%)	
1	67 (33,0%)	59,6%	54 (42,8%)	88,0%
2	54 (26,6%)	(p<0,001)	57 (45,2%)	(p<0,001)
3	24 (11,8%)		5 (4,0%)	
4	31 (15,3%)		3 (2,4%)	
5	4 (2%)		2 (1,6%)	
6	11 (5,4%)		3 (2,4%)	
7	4 (2,0%)		1 (0,8%)	
8	4 (2,0%)		0 (0%)	
9	3 (1,5%)		1 (0,8%)	
10	2 (1,0%)		0 (0,0%)	
11	1 (0,5%)		0 (0,0%)	
12	1 (0,5%)		0 (0,0%)	

TABLE II

TM requests

TM	Basaline study n=560 % (n)	PI study n=239 % (n)
Total PSA	19,5% (109)	33,9% (81)
CEA	18,0% (101)	27,2% (65)
CA19.9	13,5% (76)	8,4% (20)
A FP	9,8% (55)	4,2% (10)
CA 125	9,2% (52)	9,2% (22)
Free PSA	8,0% (45)	5,0% (12)
CA 15.3	6,2% (35)	1,3% (3)
Cyfra 21	5,2% (29)	3,3% (8)
NSE	4,6% (26)	3,8% (9)
CA 72.4	3,6% (20)	0,4% (1)
SCC	2,1% (12)	3,3% (8)

IP study the main reason was for screening purposes (48.1% of requests).

Appropriateness

In the baseline study, only 17.5% of the TMs were considered appropriate, but there was a significant increase in TMs considered appropriate in the PI study for 46% (p<0.001). A reduction in inappropriate TMs, from 82.5% to 54%, was observed (p<0.001) *(Table III)*.

a) Appropriate TMs

Analyzing the appropriate requests, it is seen that in both studies, the main reason for the appropriate requests was screening, which corresponded to the requests for PSA. In the baseline study, 89.8% of the appropriate requests were for PSA (total PSA n=67; free PSA n=21). In the IP study, 83.6% of the appropriate requests were for PSA (total PSA n= 70, free PSA n= 22). In the IP study, an increase was also seen in the number of appropriate requests for diagnostic purposes, the majority of which corresponded to requests for PSA *(Table IV)*.

b) Inappropriate TMs

In the baseline study, the rate of inappropriate requests was 82.5 %, a value which decreased to 54% in the IP study (p<0.001) *(Table III)*. In both studies, the main inappropriate reason was diagnosis *(Table V)*.

In the baseline study, the main clinical contexts in which TM requests were made for diagnostic purposes were analyzed. The majority of these cases were for the purpose of investigating alterations in the chest x-ray, laboratory alterations (e.g.: Investigation of anemia or alterations in the hepatic tests), fever, investigation of tumors of the genitourinary system, the presence of metastases (cerebral, bone, hepatic) or the presence of pleural effusion and adenopathies *(Fig. 1)*.

Various TMs (non-PSA) requested for diagnostic reasons presented high values, corresponding to the following situations: 11 cases of Pneumonia, four cases of Congestive Cardiac Insufficiency (CCI), one case of Chronic Hepatic Disease (CHD), one case of acute Renal insufficiency (RI) coexisting with CCI and CHD, one case of renal lithiasis, one case of chronic obstructive RI, three cases of ischemic cerebral vascular accident, and one case of adenopathies with non-clarified diagnosis. The subsequent evaluation did not lead, in any of these cases, to the diagnosis

TABLE III

Appropriateness of the TM requests

Appropriateness	Basaline n (%)	Post-Intervention n (%)	P
Appropriate	98 (17,5%)	110 (46,0%)	<0,001
Inappropriate	462 (82,5%)	129 (54,0%)	<0,001

TABLE IV

Appropriate TM requests

Appropriate TM	Baseline Study (n=98) % (n)	PI study (n=110) % (n)
Screening	80,6% (79)	69,1% (76)
Diagnosis	9,2%(9)	22,7 % (25)
Monitoring	0 (0%)	1,8% (2)
Follow-up	10,2% (10)	6,4% (7)

TABLE V

Inappropriate TM requests: Inappropriate reasons

Inappropriate reason	Baseline Study (n=462) % (n)	PI study (n=129) % (n)
Screening	9,5% (44)	30,2% (39)
Diagnosis	71,2% (329)	41,9% (54)
Monitoring	0% (0)	2,3% (3)
Follow-up	5,6% (26)	14,7% (19)
Inappropriate for this type of tumor	7,8% (36)	0,8% (1)
Followed-up in oncology clinic	5,8% (27)	10,1% (13)

of any neoplastic disease. These data exemplify the limitations of specificity and sensitivity of TM.

Analyzing the inappropriate requests for TM, an increase was observed, in the IP study, in inappropriate TM requests for screening purposes, which did not meet the criteria given in the international guidelines for this purpose. In the majority of cases, this fact was related to requests for PSA for patients whose survival rate was clearly less than ten years. There was also a significant volume of requests for TM for patients followed up in oncology consultations who had been admitted for acute complications, where no reason for the TM was given, and in which the procedure is considered useless.

Requests for TM on hospital admission before any diagnostic investigation

It was seen that in the baseline study, 247 TMs were requested at the time of admission, before any diagnostic investigation (44.1% of all requests for TM), of which 26.3% were for PSA and 11.3 % were for AFP (62.3% were requests for other types of TM). After implementing the informative measures, 127 TM were requested on admission (53.1% of the TMs requested), of which 70.9% were for PSA and 4.7% were for AFP, with just 24.5% requests for other types of TM.

Analysis of requests for TM by the medical team

In the analysis of the requests for TM by the medical team, it was observed that in the baseline study, 58% of the requests were made by four of the sixteen medical teams, and 34.8% of the requests were made by just one team. In a linear regression model, when analyzed by sex and period of analysis (basal or PI), the medical team emerged as a significant independent variable ($p<0.001$) in the number of tumor markers requested.

After the training activities, a significant decrease was observed in the number of requests by the medical teams, who had previously clearly made excessive volumes of requests for TM.

Overall, a decrease was also observed in the percentage of inappropriate requests by the team, with the exception of one.

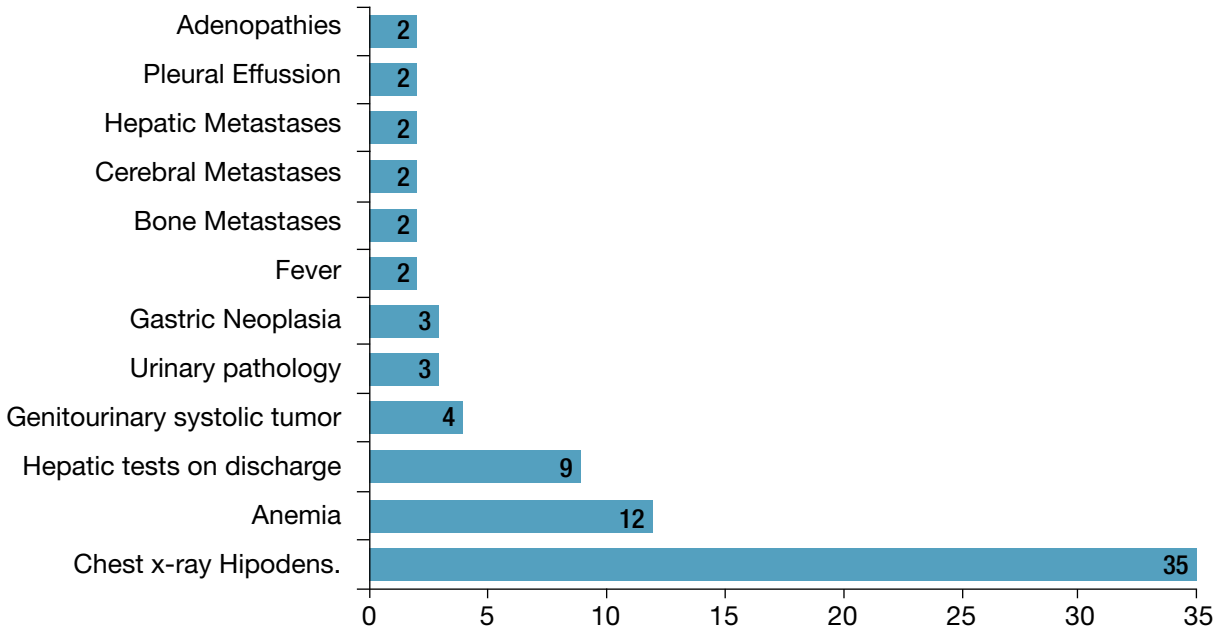
Repeat Requests

In the baseline study, there were 45 repeat requests for TM (85%), and a reduction in the PI study to 15 TM (6.3%) ($p=0.140$).

Evaluation of costs

Analyzing the costs of TM, in the baseline study it was seen that the total cost of TM was 4.765€, of which 4.194€ involved inappropriate requests. Extrapolating this for a period of one year would mean a cost of 16,778€ in inappropriate TMs.

In the PI study, it was observed that the total cost of TM was 1.748€, of which 1.094€ was spent on



Clinical contexts in which TM was requested for diagnostic purposes in the Baseline study.

FIG. 1

inappropriate requests, which translates as a decrease in costs of around 3,100 €, which extrapolated for a period of one year, would be 12,064€.

DISCUSSION

TMs are important tools in the day-to-day clinical practice, with a fundamental role in the follow-up of neoplasias, but limited to the area of diagnosis. The international literature indicates that there is a high percentage of requests for TM, which is clearly disproportional to the potential benefits of this procedure in clinical practice.[1,3-5] This study shows that in our reality, there is a high percentage of inappropriate requests. This inadequacy of TM use may be related to the fact that the introduction of TM to the clinical practice was not initially accompanied by appropriate guidelines, which probably led to the institution of inadequate standards of use of TM.[2] Clear guidelines are now available that can be incorporated into the clinical practice.

It is interesting to note a previous study,[1] carried out at a tertiary hospital in Austria, in which requests for TM were evaluated retrospectively over a period of three months, by the various hospital departments, including oncology requests for PSA were not included in this study. Overall, 476 TMs were requested for 373 patients. Of these, 69% were considered appropriate and 39% inappropriate. The two main reasons cited for the request for TM were screening and diagnosis. However, when the oncology units and non-oncology units were evaluated separately, it was seen that in the oncology units, which accounted for 27% of the requests, 86% of the TMs were appropriate and 14% inappropriate, while that in the non-oncology units, 35% of the TMs were appropriate and 64% inappropriate. These latter values are the ones that are of interest to us if we want to establish a comparison with our results, as it can be said that in terms of percentage of appropriate requests, the PI study shows comparable values.

The present study demonstrated, on the other hand, that presenting and confronting the health professionals with their inappropriate requests for TM in clinical practice ("self-auditing"), and reviewing the main guidelines on the use of TM, can have a very positive impact on altering clinical performances.

A marked decrease is also seen in the total number of requests for TMs, together with an alteration in the

profile of requests. In the baseline study, the main reason for the request for TM was diagnosis, while in the post-intervention study, the main reason was screening. The appropriateness of the requests increased from 17.5% to 46%. which represents a relative increase of around 162.9%, with a 37% decrease in inappropriate requests.

The decrease in inappropriate requests was attributed to a decrease in requests for diagnostic purposes, while the increase in appropriate requests was attributed to requests for the purpose of screening, notably the request for PSA.

This alteration in the profile of requests is directly related to the intervention carried out, and it can be concluded that the clinics take on board the idea that it may be appropriate to request some TM for screening purposes, whereas the request for TM for diagnostic purposes is more likely to be inappropriate.

Analyzing the appropriate requests, the question of the real appropriateness of the requests for screening purposes should be taken into account, particularly screening for cancer of the prostate with PSA in a context of admission to a hospital for acute cases. It is not clear how far acute pathologies can interfere in the volume of TM, and often this is done without any subsequent actions, such as reporting in the discharge note sent to the assistant doctor that this procedure has been carried out. If we reflect on the appropriateness of requests for screening purposes during hospitalization in a context of acute complications, we can conjecture as to whether it will be appropriate to request mammographies for hospitalized women, a procedure that is rarely done, and is probably considered inappropriate.

Thus, although for the purposes of this study, we have considered requests for PSA in this context as appropriate, we believe the screening should be carried out by the patient's assistant physician.

It is interesting to note that unlike our study, the international studies published on the appropriateness of TM requests fail to include PSA among the TMs analyzed, due to a lack of knowledge of its true value.[1,4]

In fact the value of PSA has recently been questioned in the screening of prostate cancer, because this is a neoplasia with slow evolution and progression, and its real impact on the survival of patients is not known. The results of the European Randomized Study of Screening for Prostate Cancer[11] reveal that death by prostate cancer at the age of 50-74 years can be reduced by 20% with PSA screening, but with a high risk of over diagnosis; on the other hand, the results of the Prostate, Lung, Colo-rectal and Ovarian Cancer Screening trial[12] regarding mortality by prostate cancer show that after 7-10 years of follow-up, the mortality rate of carcinoma of the prostate was very low, and was not significantly different from the control group. The current evidence is insufficient to determine the benefit/risk ratio of screening for prostate cancer in men aged under 75 years, and screening is not advised in patients over the age of 75.[13] In the present study, we decided to include this marker, owing to the fact that it is the most commonly requested TM in our hospital.

The low percentage of TM for monitoring and follow-up in the present study is due to the fact that it was carried out in a population of an Internal Medicine Service where unlike the oncology clinic, the existence of TM would not be expected for these purposes.

Analyzing the inappropriate request, it is curious to note that a high percentage of requests (58% in the baseline study) came from four teams, and 34.8% from a single team. It is also interesting to note that the intervention carried out led to a better performance of these teams. Contrary to what is often reported in the literature on the ineffectiveness of training measures[6-10] our intervention, based on a comparison with the practice of professionals analyzed during this study, effectively led to very satisfactory results in this regard, with a positive impact on the quality and appropriateness of the use of TM.

An interesting prospective trial was carried out in 2003 in a French University Hospital, by the Medical School of Broussais Hotel Dieu[14] which evaluated requests for TM before and after the implementation of computerized measures for restricting the number of requests. Local guidelines were developed, which were implemented through a new computerized form, with reminders to restrict the TM request. Evaluations (audits) were carried out before and after (one month and two years after) the implementation of this measure. There was a marked decrease in the number of TM requests (25% in the Internal Medicine department and 55% for the hospital as a whole) one month afterwards, and an increase in appropriate TM requests, from 54.6% to 73.6%, which then decreased to 54.6% in the evaluation carried out two years

afterwards. This aspect indicates a need for frequent repetition of the training/information actions, in order to maintain the good performance achieved, in the clinical practice of the professionals.

Another aspect, also reported in the literature, is the request for TM at the time of admission, before any complementary diagnostic evaluation. In the baseline study, it was seen that the majority of the requests (62.3%) on admission were not for screening purposes, but were probably for diagnostic purposes. In the PI study this situation was reversed, with 75.6% of TMs requested on entry being for PSA or αFP, suggesting that international guidelines had been assimilated as a result of the training actions.

The reference to the presence of repeated requests is a constant factor in studies on the appropriateness of requests for TM. The most frequent cause indicated was lack of knowledge that the TM had already been requested, or to confirm the high values. In the present study, the number of repeat requests was not significant, while in the baseline and PI studies, these represented less than 10%.

Associated with the marked decrease in requests for TM, a major decrease was also seen in the direct associated costs of their use.

The excessive volume of requests for these exams has the inconvenience that it not only increases costs, but can also lead to unnecessary investigations and increased anxiety for the patient, aspects that have not been quantified in this study.

CONCLUSION

We can therefore conclude that training/information actions, and encouraging reflection and "self-auditing" on the correct use of TM, may be a determining factor in the modification and improvement of the clinical practice, with impacts on the reduction of associated costs. ■

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