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Serum Tumor Marker Use in Patients With Advanced Solid Tumors

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QUESTION ASKED: The objective of this study is to evaluate the frequency of tumor marker use in patients with advanced solid tumors.

SUMMARY ANSWER: Over a 1-year period, the mean number of any individual test per patient was seven tests, and the maximum number was 35 tests; the mean number of total tests per patient was 12 tests, and the maximum number was 70 tests. In a 1-year time frame, 16.3% of patients had more than 12 individual tests, and 34.3% had more than one individual test in a 1-month span.

METHODS: For each patient with a diagnosis of advanced solid tumor who had outpatient visits between July 1, 2013, and June 30, 2014, at Columbia University Medical Center, we recorded the dates of the following tumor marker tests: α -fetoprotein, CA-125, CA 15-3, CA 19-9, CA 27-29, and carcinoembryonic antigen (CEA).

BIAS, CONFOUNDING FACTOR(S), DRAWBACKS: This was a 1-year evaluation of tumor marker use at a single institution. As a result, our findings may be skewed by the practice patterns of a few individual providers. Our cancer center is an urban academic tertiary care center; as a result, our experience may not be applicable to the general population.

REAL-LIFE IMPLICATIONS: We found a high rate of serum tumor marker testing overuse in patients with advanced solid tumors. There is currently a lack of evidence

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FIG 2. Percentage of patients (N = 928) with solid tumors who had excessive tumor marker testing in 1 month (> one test in 1 month). (*) Maximum number of tests over 1-month period. AFP, α -fetoprotein; CEA, carcinoembryonic antigen.

supporting the effectiveness of frequent tumor marker testing, and additional studies are needed to inform practice. Interventions to reduce overuse could help reduce the financial burden of cancer care. Future research should define the minimal frequency of testing. In the meantime, efforts should be made to limit use of tumor marker testing in patients with advanced solid tumors. **JOP**

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Abstract

Purpose

There is substantial variability in the frequency of serum tumor marker testing in patients with advanced solid tumors. We performed a retrospective analysis to evaluate the frequency of serum tumor marker use.

Methods

Patients with a diagnosis of advanced cancer with outpatient visits between July 1, 2013, and June 30, 2014, at a single center were included. Tumor and stage were determined by International Classification of Diseases, Ninth Revision codes and confirmed with tumor registry and medical record review. For each patient, we recorded the dates of each of the following tumor markers: α -fetoprotein, CA-125, CA 15-3, CA 19-9, CA 27-29, and carcinoembryonic antigen. We evaluated the number of tests per patient over 12 months and the maximum number of tests per patient per month.

Results

We included 928 patients in the analysis. The mean number of any individual test per patient was seven tests, and the maximum number was 35 tests; the mean number of total tests per patient was 12 tests, and the maximum number was 70 tests; 16.3% of patients had more than 12 individual tests per year. In a 1-month span, 34.3% of patients had more than one individual test. CA 19-9 and carcinoembryonic antigen were the most commonly overused tests.

Conclusion

We found a high rate of serum tumor marker testing use in patients with advanced solid tumors. Given the increasing costs of cancer care, efforts should be made to determine the benefit of serum tumor markers in the follow-up care of patients with advanced solid tumors.

ASSOCIATED CONTENT

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INTRODUCTION

At least 106,239 patients are newly diagnosed with metastatic solid tumors per year in the United States.¹ Current clinical guidelines suggest that patients with metastatic solid tumors should be monitored while undergoing systemic therapy.^{2,3} The overarching goal is to continue treatments

that are controlling disease and avoid toxicities from therapies that are not efficacious. Clinical trials precisely and reproducibly evaluate response to treatment by using the Response Evaluation Criteria in Solid Tumors to determine tumor response, stability, and progression from imaging studies.^{3,4} In clinical trials that are designed

to obtain drug approval, imaging studies are typically performed every 2 to 3 months. The optimal interval between imaging studies has not been prospectively assessed, but National Comprehensive Cancer Network guidelines recommend imaging studies every 2 to 4 months for solid tumors.^{2,3}

In addition to imaging studies, metastatic disease can be monitored by serum tumor markers. Serum tumor markers are biochemical indicators (tumor antigens) in the peripheral blood that can be produced directly by tumor or nontumor cells as a response to the presence of malignancy.⁵ Many limitations exist with regard to the use of tumor markers for screening and early detection, including lack of sensitivity (50% to 90%) and/or specificity (46% to 90%).⁶⁻¹³ In patients with metastatic cancer, however, elevated serum markers can be used as an optional measure of surveillance for disease progression. No recommendation is given regarding the frequency of measurement.^{2,5,14} However, two studies have suggested that changing treatment based on a change in serum biomarker does not change outcome.^{15,16}

The increasing cost of cancer care has resulted in recommendations to curb the use of expensive tests and procedures for which there is little or no evidence of benefit.^{17,18} It is estimated that between \$158 billion and \$226 billion are wasted annually on procedures, treatments, and diagnostics that are unnecessary.¹⁹ The objective of this study is to evaluate the frequency of tumor marker use in patients with metastatic solid tumors.

METHODS

Setting and Study Design

A retrospective study was conducted among outpatients treated at the Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center between July 1, 2013, and June 30, 2014. The study was approved by the Columbia University Institutional Review Board.

Patient Cohort

The cohort consisted of all patients who had the following serum tests done during the study period: α -fetoprotein, CA-125, CA 15-3, CA 19-9, CA 27-29, and carcinoembryonic antigen (CEA). Prostate-specific antigen was not included in this analysis to ensure we were not capturing patients who were being screened for prostate cancer. The data set was restricted to patients with multiple results for any individual test because patients without elevated tumor markers are often not observed serially. Our objective was to evaluate frequency

of testing among patients who were observed with serial serum tumor markers. Patients with cancers other than advanced breast, colorectal, ovarian, lung (both small-cell and non-small-cell lung cancers), pancreatic, and hepatobiliary cancers were excluded from the study sample. Advanced stage was defined as metastatic and/or unresectable disease. Cancer type was identified by International Classification of Diseases, Ninth Revision codes (153.0 to 154.1, 155.0 to 156.9, 157.0 to 157.9, 162.3 to 164.9, 174.1 to 175.9, and 183.0 to 183.9). Tumor stage was determined using site tumor registry data and electronic medical record review. In patients who had more than one cancer diagnosis, review of the medical record determined how the patient was classified based on which primary tumor was advanced and/or metastatic.

Measures and Data Analysis

The analyses were performed using descriptive statistics. The date of each order for the serum tumor marker tests was recorded. Each individual tumor marker was categorized by the number of tests performed per patient over 12 months, the number of tests per month the patient was alive, and the maximum number of tests per patient in any given month. In addition, the total number of any test per patient over the study period was calculated. Individual tumor markers were classified as disease specific or not (breast cancer: CA 15-3, CA 27-29, and/or CEA; colorectal cancer: CEA; ovarian cancer: CA-125; lung cancer: CEA; pancreatic cancer: CA 19-9 and/or CEA; and hepatobiliary cancer: α -fetoprotein, CA 19-9, and/or CEA).^{2,8,13,20-23} The proportion of patients who had disease-specific tumor markers was compared to the proportion of patients who had tumor markers not associated with their individual cancer to assess discordant use of tumor markers.

We categorized overuse as the percentage of patients who had more than 12 of any individual test during the year and the percentage of patients who had more than one of any individual test per month. Extreme overuse was defined as three or more orders for an individual test per month at any time. To determine the process and rationale for tumor marker evaluation in each practice, the medical records of patients in the top 10% of CEA and CA 19-9 testing were reviewed. In addition, the oncologists who ordered the serum tumor markers completed a survey to assess their practice patterns for tumor marker assessment.

RESULTS

We identified 2,223 patients with breast, colorectal, ovarian, lung, pancreatic, or hepatobiliary cancer treated as outpatients

at the Herbert Irving Cancer Center at Columbia University between July 1, 2013, and June 30, 2014. One thousand three hundred ninety-seven patients had more than one individual serum tumor marker test ordered during the study period. Of these, 928 patients had advanced disease. The most common cancer types were hepatobiliary (34.8%), pancreatic (24.1%), and breast (15.7%; Appendix Table A1, online only).

The mean number of any individual test per patient was seven, with a maximum number of 35. The mean number of any serum tumor marker tests per patient per year was 12, and the maximum number was 70. The most common individual markers were CEA (37.6% of ordered serum tests) and CA 19-9 (22.3% of ordered serum tests; Figure 1).

Of the 1,573 total number of serum tumor marker tests performed over the study period, 1,441 (91.6%) were disease specific and 132 (8.4%) were not. Patients with advanced breast cancer had the highest proportion of disease-specific tumor markers (98.0%), whereas patients with colorectal cancer had the highest proportion of discordant tumor markers (22.7%), and the majority of discordant tests (19.9%) were CA 19-9.

Overuse, defined as the number of patients with more than 12 of any individual test per year, occurred in 151 patients (16.3%). Because some patients died during the study period, we also evaluated monthly use. Overuse, defined as any patient with more than one individual test per month, occurred in 318 patients (34.3%). The most commonly overused tests (> one test per month) were CA 19-9 (45.9%), CEA (40.9%), and CA-125 (25.8%). Extreme overuse ($\geq$ three individual tests per month) occurred in 215 patients (23.2%). The most common markers with extreme overuse were CA 19-9 (38.2%) and CEA (27.9%; Figure 2). The distribution of testing for CA 19-9 and CEA is shown in Figure 3.

FIG 1. Percentage of patients (N = 928) with solid tumors who had excessive tumor marker testing (> 12 tests over 12 months). (*) Maximum number of tests over 12-month period. AFP, α -fetoprotein; CEA, carcinoembryonic antigen.

FIG 2. Percentage of patients (N = 928) with solid tumors who had excessive tumor marker testing in 1 month (> one test in 1 month). (*) Maximum number of tests over 1-month period. AFP, α -fetoprotein; CEA, carcinoembryonic antigen.

For all patients who had reviewed charts, CEA and CA 19-9 were ordered at every visit and not as a result of new signs or symptoms concerning for disease progression. Radiographic imaging studies performed as a result of increasing tumor markers occurred in 7.0% of patients within the CEA group and 10.5% of patients within the CA 19-9 group. Of this group, only 2% had a change in treatment. The majority of ordering oncologists (92.3%) reported that tumor markers were ordered by the administrative staff at every visit by copying the previous order.

DISCUSSION

Overuse of serum tumor marker testing in patients with advanced solid tumors was frequent. We found that 13.6% of patients had more than 12 individual tests over 1 year, and 23% of patients had more than two tests in a single month. CA 19-9 and CEA were the serum tumor markers that were most commonly overtested.

FIG 3. Distribution of CA 19-9 and carcinoembryonic antigen (CEA) testing frequency over the 12-month time frame.

The only evidence-based guidelines for tumor marker testing are for patients with metastatic colorectal cancer, where early detection of isolated metastases followed by metastasectomy improves outcome.²⁴⁻²⁹ ASCO recommends CEA surveillance in patients with metastatic colorectal every 2 to 3 months, along with abdominal imaging during active therapy³⁰; however, the National Comprehensive Cancer Network does not recommend routine monitoring of CEA in these patients.^{21,22} Currently, there are no guidelines regarding the use of serum tumor markers in patients with metastatic lung cancer.^{31,32} There are no guidelines for optimal tumor marker frequency in patients with metastatic breast, advanced liver, hepatobiliary, or pancreatic cancer.^{2,8,13} Physicians often follow multiple measures in cancers where multiple tumor markers are elevated at baseline.

Scant data exist regarding tumor marker use for monitoring disease status in patients after developing advanced disease; most studies have focused on surveillance of patients who have no evidence of disease to identify patients who have experienced progression. Merimsky et al³³ randomly assigned 61 patients with early breast cancer with increasing serum tumor markers to early treatment with tamoxifen or observation until radiographic evidence of metastatic disease. The 5-year event-free survival was similar in both groups. Similarly, in a study of 1,442 women with ovarian cancer who completed first-line chemotherapy, early initiation of second-line chemotherapy in asymptomatic patients at the time of increasing CA-125 levels was not associated with improved survival compared with routine care.¹⁵ Finally, in a recent randomized trial of 123 women with metastatic breast cancer who had persistent elevated levels of circulating tumor cells after first-line chemotherapy, early commencement of second-line therapy based on elevation of circulating tumor cells was not associated with improved progression-free or overall survival benefit compared with change in therapy based on clinical or imaging determination of progression of disease.¹⁶ No studies have evaluated the utility of tumor marker testing in patients with other tumors.

The 60% Medicare reimbursement rate for the individual serum tumor marker tests we evaluated was between \$31 and \$38.³⁴ Most analyses evaluating the cost and value of tumor marker testing have focused on use of biomarker testing for routine surveillance in patients without evidence of disease.³⁵⁻⁴⁰ A recent population-based evaluation of women with early-stage breast cancer found a significant and sustained increase of total costs of care in patients who had inappropriate serum tumor marker evaluation, suggesting

that tumor marker testing is done in individuals who also receive other expensive tests or procedures.⁴¹ To our knowledge, no studies have evaluated the cost-effectiveness of serum tumor marker surveillance in the metastatic setting.

Limited data exist regarding the prevalence of patients with metastatic cancer in the United States. According to the National Cancer Data Base, a national hospital-based cancer registry jointly sponsored by the American College of Surgeons and the American Cancer Society representative of approximately 70% of newly diagnosed patients with cancer, in 2011, 106,239 patients were diagnosed with de novo metastatic disease representing 15.6% of patients with newly diagnosed solid tumors.⁴² A recent analysis from the National Cancer Institute's Surveillance, Epidemiology, and End Results Colorectal Cancer Registry found a significantly increased median 5-year relative survival rate in patients with metastatic disease, from 8.6% in 1988 to 17.8% in 2009.⁴³ An increase in 5- and 10-year survival has also been noted in metastatic breast cancer.⁴⁴⁻⁴⁶ As treatment for cancer continues to improve and patients are living longer with metastatic disease, we can assume the prevalence of patients with metastatic disease will continue to increase, furthering the need for high-value modalities to monitor treatment response. Serum tumor markers are approved by the US Food and Drug Administration primarily on the basis of their sensitivity and specificity, whereas the effect on mortality and morbidity is not generally considered for their approval.⁴⁷

Our work has several limitations. This was a 1-year evaluation of tumor marker use at a single institution. As a result, our findings can be greatly skewed by the practice patterns of a few providers. Our center is an urban academic tertiary care center; as a result, our patient population may be different from other institutions and practices, which may limit the generalizability of the findings. We were also unable to capture patients who had tumor marker analysis at outside labs. Furthermore, we included patients who had more than one cancer diagnosis; this represented only a small proportion of our population, and it is unlikely that these patients were undergoing screening for other cancers because of the advanced nature of their metastatic disease. Finally, we do not know how, if at all, these results impacted clinical decision making.

In summary, we found a high rate of serum tumor marker testing overuse and extreme overuse in patients with advanced solid tumors. Given that our cohort represents less than 1% of patients with metastatic solid tumors, the results suggest that interventions could reduce the financial burden of cancer care.

The lack of evidence supporting the effectiveness of frequent tumor marker testing suggests that additional studies are needed to inform practice. Future research should define the minimal frequency of testing and determine whether response can help reduce more expensive radiologic tumor imaging. In the meantime, efforts should be made to limit use of tumor marker testing in patients with unresectable and/or metastatic solid tumors. **JOP**

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Characteristics of the Study Population

Cancer Type	No. of Patients (%)		
	Whole Cohort	Male	Female
All	928 (100)	417 (45.0)	511 (55.0)
Hepatobiliary	323 (34.8)	220 (52.8)	103 (20.2)
Pancreatic	224 (24.1)	120 (28.8)	104 (20.4)
Breast	146 (15.7)	1 (0.2)	145 (28.4)
Colorectal	111 (12.0)	53 (12.7)	58 (11.4)
Ovarian	70 (7.5)	0 (0)	70 (13.7)
Lung	54 (5.8)	23 (5.5)	31 (6.1)