Things We Do for No Reason: Tumor Markers CA125, CA19-9, and CEA in the Initial Diagnosis of Malignancy

Sigal Israilov, MD[1,2]*, Hyung J Cho, MD[1,3], Mona Krouss, MD[1,2]

[1]*New York City Health and Hospitals, New York, New York;* [2]*Icahn School of Medicine at Mount Sinai, New York, New York;* [3]*New York University School of Medicine, New York, New York.*

Inspired by the ABIM Foundation's *Choosing Wisely*® campaign, the "Things We Do for No Reason™" (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent clear-cut conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

A 56-year-old woman presents to the emergency department with a 2-week history of abdominal pain associated with nausea and an episode of nonbilious, nonbloody emesis. Her last bowel movement was 2 days prior to her presentation. The patient has tachycardia to 105 beats per minute but otherwise normal vital signs. Findings on her physical examination include dry mucous membranes and increased bowel sounds. A review of systems reveals an unintentional weight loss of 15 kg over the past 4 months and increased fatigue. Computed tomography scan of the abdomen and pelvis with contrast reveals multiple areas of attenuation in the liver and small bowel obstruction. The hospitalist admits the patient to the medicine service for supportive treatment and workup for underlying malignancy. Her admitting team orders serum tumor biomarkers on admission to expedite the diagnosis.

BACKGROUND

When patients present with unexplained weight loss or with metastasis from an unknown primary location, the initial workup often includes imaging and a tumor biomarker panel (eg, cancer antigen 125 [CA125], carbohydrate antigen 19-9 [CA19-9], carcinoembryonic antigen [CEA]). The CA125, CA19-9, and CEA biomarkers are traditionally associated with ovarian, pancreatic, and colorectal cancer, respectively.[1] While clinicians initially used these serum biomarkers to monitor for cancer recurrence or treatment response, they have since become widely used in multiple clinical stages of oncological evaluation.

***Corresponding Author:** Sigal Israilov, MD; Email: sigal.israilov@icahn.mssm.edu; Telephone: 646-620-8200.

Received: January 29, 2021; **Revised:** April 16, 2021; **Accepted:** May 4, 2021

 DOI 10.12788/jhm.3645

WHY YOU MIGHT THINK CA125, CA19-9, AND CEA ARE HELPFUL IN THE DIAGNOSIS OF CANCER

Hospitalists routinely order biomarkers as part of the malignancy workup. More than a dozen oncology biomarkers are used in the clinical setting to risk stratify, plan treatment, and monitor for recurrence. For example, studies associate elevated preoperative levels of CEA and CA19-9 with metastatic invasion of colorectal[2] and gastric[3] cancers and with poor prognosis of intrahepatic cholangiocarcinoma. Similarly, CA125 has demonstrated utility in monitoring response to ovarian cancer treatment.[4] Specific biomarkers, such as alpha-fetoprotein, improve diagnosis of liver and nonseminomatous testicular tumors.[5] Clinicians often apply the same paradigm to other biomarkers due to their widespread availability, noninvasiveness, reproducibility, and ease of use, particularly in acute settings wherein any new information is perceived to be potentially helpful.

WHY YOU SHOULD NOT USE CA125, CA19-9, AND CEA TO DIAGNOSE CANCER

Utilizing these serum biomarkers to diagnose cancer has the potential for diagnostic error and can result in unnecessary patient anxiety and follow-up testing. Since tissue sampling is necessary and remains the gold standard in most cancer diagnoses, obtaining these tumor biomarkers in the early diagnostic stage does not change management and may even lead to harm. Furthermore, due to their poor sensitivity and specificity, these biomarkers cannot rule in or rule out cancer. Elevated CA125, CA19-9, and CEA biomarkers occur in a variety of malignancies, including gastric, gallbladder, hepatocellular, bladder, and breast cancers.[1,3,6] In addition, these biomarkers have a very limited role in the workup of cancer of unknown primary origin.[7]

Even in the setting of a known pelvic mass, the use of CA125 alone has poor sensitivity at a cut-off level of 35 U/mL as a biomarker for the diagnosis of early ovarian cancer.[8]

Serum CA19-9 is not a useful diagnostic biomarker as elevated CA19-9 can occur in benign conditions, including cirrhosis, chronic pancreatitis, and cholangitis. In a systematic review of patients with histologic confirmation of pancreatic malignancy, the median positive predictive value of CA19-9 was 72% (interquartile range, 41%-95%).[9] Additionally, patients with Lewis-null blood type, which is present in 5% to 10% of the Caucasian population, do not produce CA19-9.[10] Therefore, CA19-9 will be 0% specific for tumors in this population.

The use of CEA in the diagnosis of colorectal cancer is also questionable. In stage I colorectal cancer, CEA was only 38.1%

sensitive at a cut-off level of 2.41 ng/mL; it was 78.3% sensitive in stage IV disease.[11] The specificity of CEA is limited since elevated CEA occurs in benign conditions, such as inflammatory bowel disease, smoking, hypothyroidism, pancreatitis, biliary obstruction, peptic ulcers, and cirrhosis—though CEA levels in these conditions are rarely >10 ng/mL.[11] Regardless of the results of biomarker testing, definitive diagnosis requires tissue biopsy; therefore, biomarker findings are of little utility in the initial workup.

In addition to variable diagnostic utility, overreliance on these biomarkers has the potential for serious patient harm. In a study examining patients with established rectal cancer, combination CEA and CA19-9 testing alone was insufficient to predict the pathologic stage of disease correctly.[2] A cancer misdiagnosis not only traumatizes patients but also erodes their trust in clinicians and creates anxiety during future clinical encounters. Overutilization of these tumor biomarkers is also costly and contributes to waste in the US healthcare system.

WHEN YOU SHOULD USE CA125, CA19-9, AND CEA

There is a role for tumor biomarker testing in specific cancers after the primary source of malignancy has been determined. When evaluating a known pelvic mass, CA125 testing is performed in conjunction with transvaginal ultrasound and assessment of menopausal status in the risk of ovarian malignancy algorithm for prognostication of disease prior to surgery.[12] This algorithm takes into account levels of CA125 in addition to levels of human epididymis protein 4 and patient age, yielding an area under the curve as high as 0.93 for ovarian cancer risk classification.[8] Beyond the prognostication process, oncologists follow CA125 to monitor response to first-line ovarian cancer treatment. However, CA125 has a less defined role in surveillance for ovarian cancer recurrence.

CA19-9 has demonstrated utility for pancreatic cancer and cholangiocarcinoma survival estimates. A national cohort analysis of patients with established intrahepatic cholangiocarcinoma found that CA19-9 independently predicted increased mortality. Patients with elevated CA19-9 also had significantly more nodal metastases and positive-margin resections.[6] A study of 353 patients with pancreatic ductal adenocarcinoma undergoing radical resection further demonstrated the utility of CA19-9. In this study, patients with postoperative CA19-9 normalization had improved survival by almost 12 months when compared to those with consistently elevated CA19-9.[13]

Last, the literature describes CEA biomarker testing in the surveillance of patients after curative treatment of colon and rectal cancer. The American Society of Colon and Rectal Surgeons recommends regularly tracking this biomarker following curative resection, in conjunction with colonoscopy and chest and liver imaging studies.[14] A prospective randomized controlled study that followed this monitoring protocol in cured asymptomatic patients on a bimonthly basis found that early diagnosis of recurrent colorectal cancer improved survival.[15] The use of CEA testing as a monitoring tool should therefore be a point of discussion between providers and patients, as its utility varies based on patient comorbidities, their ability to tolerate surgery or chemotherapy, risk factors for recurrence, performance status, compliance, age, and preference.[14]

WHAT YOU SHOULD DO INSTEAD

The use of CA125, CA19-9, and CEA testing alone as initial diagnostic tools for malignancy are problematic due to their poor sensitivities and/or positive predictive value. Multiple studies have demonstrated their utility as markers of metastasis or malignancy progression rather than as clinically useful markers for the detection of any one type of cancer.[1,3,6] In an undiagnosed symptomatic patient with unexplained weight loss or symptoms of a tumor mass, elevated CA125, CA19-9, and CEA add no new information as metastatic pancreatic, colorectal, ovarian, gastric, gallbladder, hepatocellular, bladder, ovarian, and breast cancers all remain in the differential diagnosis. Clinicians should approach the initial diagnosis of cancer in such patients with appropriate imaging studies, a thorough physical examination, and prompt biopsy of abnormal findings, as long as these are consistent with the patient's goals of care. After establishing a tissue diagnosis, some tumor biomarkers have valid prognostic, staging, and monitoring roles.[6,13,14]

RECOMMENDATIONS

- Do not routinely order CA125, CA19-9, and CEA tests for the initial diagnostic workup of visceral malignancy of unknown origin regardless of whether imaging studies have been obtained.
- Use appropriate imaging, perform a thorough physical examination, and obtain tissue biopsy in the initial diagnostic workup of a visceral malignancy of unknown origin.

CONCLUSION

Clinicians should use serum biomarkers, like any other diagnostic test, to maximize benefit while preventing patient harm. In general, CA125, CA19-9, and CEA do not have a role in cancer diagnosis. The patient described in our clinical scenario would not benefit from a serum tumor biomarker panel at the time of admission. Regardless of findings from these tests, a tissue sample is required to make a definitive diagnosis of underlying malignancy in this patient.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason™"? Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason™" topics by emailing TWDFNR@hospitalmedicine.org

Disclosure: The authors have no conflicts of interest to disclose.

References

1. Yotsukura S, Mamitsuka H. Evaluation of serum-based cancer biomarkers: a brief review from a clinical and computational viewpoint. *Crit Rev Oncol Hematol*. 2015;93(2):103-115. https://doi.org/10.1016/j.critrevonc.2014.10.002
2. Zhang B, Sun Z, Song M, et al. Ultrasound/CT combined with serum

CEA/CA19.9 in the diagnosis and prognosis of rectal cancer. *J Buon*. 2018;23(3):592-597.
3. Zhou YC, Zhao HJ, Shen LZ. Preoperative serum CEA and CA19-9 in gastric cancer--a single tertiary hospital study of 1,075 cases. *Asian Pac J Cancer Prev*. 2015;16(7):2685-2691. https://doi.org/10.7314/apjcp.2015.16.7.2685
4. Karam AK, Karlan BY. Ovarian cancer: the duplicity of CA125 measurement. *Nat Rev Clin Oncol*. 2010;7(6):335-339. https://doi.org/10.1038/nrclinonc.2010.44
5. Gilligan TD, Seidenfeld J, Basch EM, et al; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol*. 2010;28(20):3388-3404. https://doi.org/10.1200/jco.2009.26.4481
6. Bergquist JR, Ivanics T, Storlie CB, et al. Implications of CA19-9 elevation for survival, staging, and treatment sequencing in intrahepatic cholangiocarcinoma: a national cohort analysis. *J Surg Oncol*. 2016;114(4):475-482. https://doi.org/10.1002/jso.24381
7. Milovic M, Popov I, Jelic S. Tumor markers in metastatic disease from cancer of unknown primary origin. *Med Sci Monit*. 2002;8(2):MT25-MT30.
8. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res*. 2019;12(1):28. https://doi.org/10.1186/s13048-019-0503-7
9. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol*. 2007;33(3):266-270. https://doi.org/10.1016/j.ejso.2006.10.004
10. Loosen SH, Neumann UP, Trautwein C, Roderburg C, Luedde T. Current and future biomarkers for pancreatic adenocarcinoma. *Tumour Biol*. 2017;39(6):1010428317692231. https://doi.org/10.1177/1010428317692231
11. Polat E, Duman U, Duman M, et al. Diagnostic value of preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 in colorectal cancer. *Curr Oncol*. 2014;21(1):e1-e7. https://doi.org/10.3747/co.21.1711
12. Sölétormos G, Duffy MJ, Othman Abu Hassan S, et al. Clinical use of cancer biomarkers in epithelial ovarian cancer: updated guidelines from the European Group on Tumor Markers. *Int J Gynecol Cancer*. 2016;26(1):43-51. https://doi.org/10.1097/igc.0000000000000586
13. Xu HX, Liu L, Xiang JF, et al. Postoperative serum CEA and CA125 levels are supplementary to perioperative CA19-9 levels in predicting operative outcomes of pancreatic ductal adenocarcinoma. *Surgery*. 2017;161(2):373-384. https://doi.org/10.1016/j.surg.2016.08.005
14. Steele SR, Chang GJ, Hendren S, et al. Practice guideline for the surveillance of patients after curative treatment of colon and rectal cancer. *Dis Colon Rectum*. 2015;58(8):713-725. https://doi.org/10.1097/dcr.0000000000000410
15. Verberne CJ, Zhan Z, van den Heuvel E, et al. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: results of the randomized "CEAwatch" trial. *Eur J Surg Oncol*. 2015;41(9):1188-1196. https://doi.org/10.1016/j.ejso.2015.06.008