False Elevations of Carcinoembryonic Antigen Levels Are Common in Patients Under Surveillance for Colorectal Cancer Recurrence

A recent study found that false-positive elevations of carcinoembryonic antigen (CEA) in the range of 5 to 15 ng/mL were commonly found in patients under surveillance for disease recurrence after primary treatment for stages I to III colorectal cancer (CRC) (J Natl Compr Canc Netw. 2014;12:907-913).

The National Comprehensive Cancer Network guidelines recommend that CEA levels be routinely monitored every 3 to 6 months after the treatment of CRC with curative intent. A CEA level greater than 5 ng/mL will usually trigger a workup to look for possible disease recurrence. Although it has been established that false-positive CEA elevations occur, the study authors believed these elevations had not been well characterized within the context of currently available high-quality imaging, and set out to establish the frequency and range of false-positive CEA levels in patients previously treated for nonmetastatic CRC.

Anya Litvak, MD, medical fellow at the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, and colleagues identified patients from MSKCC electronic medical records who underwent resection for locoregional CRC between January 2003 and December 2012 and who had a perioperative CEA level of less than 5 ng/mL and developed an elevated CEA level during follow-up. These records were then manually reviewed to extract data regarding the disease, CEA levels at different time points, and imaging studies. Test results were considered to be false-positive if a CEA level exceeded 5 ng/mL in a patient with no evidence of disease recurrence on imaging or other diagnostic procedures with a follow-up of at least 1 year, or if the CEA elevation was followed by a spontaneous normalization, with at least 2 consecutive subsequent normal CEA measurements.

The researchers identified a total of 728 eligible patients. Of these, 358 patients (49%) were found to have a false elevation of CEA not related to any malignancy, 335 patients (46%) had a true-positive elevation of CEA that was associated with a CRC recurrence, and 35 patients (5%) had an elevation of CEA that was indicative of a new cancer that was not CRC. Approximately one-third of the patients who developed a new malignancy were found to have lung cancer, with breast, prostate, and non-CRC gastrointestinal malignancies comprising the majority of the rest. The median peak CEA level in these patients was 9.5 ng/mL, and the median time to diagnosis after treatment for CRC was 2.5 years.

Among the 358 patients with false-positive CEA elevations, the median lowest perioperative serum CEA level was 3.8 ng/mL, and the median peak CEA level during surveillance was 6.3 ng/mL. Of this group, 111 patients had only
1 elevated CEA level that subsequently normalized. Of these 111 patients, the peak CEA level was between 5.1 and 10.0 ng/mL in 104 patients (93%), 10.1 and 15.0 ng/mL in 3 patients (3%), 5.1 and 20.1 ng/mL in 1 patient (1%), 25.1 and 30.0 ng/mL in 1 patient (1%), and 40.1 and 50.0 ng/mL in 2 patients (2%).

The remaining 247 patients with false-positive CEA elevations experienced them at least twice. Among these 247 patients, the peak CEA level was between 5.1 and 10.0 ng/mL in 224 patients (91%), 10.1 and 15.0 ng/mL in 18 patients (7%), 15.1 and 20.0 ng/mL in 2 patients (1%), 20.1 and 30.0 ng/mL in 1 patient (0.4%), and 30.1 and 35.0 ng/mL in 1 patient (0.4%). No confirmed CEA elevation of greater than 35.0 ng/mL was found to be a false-positive result.

“CEA elevations between 5 and 10 ng/mL are just as likely to be a false-positive as a true-positive, so a single bump in CEA to this range should not necessarily prompt additional scanning and should instead be repeated and then reconsidered,” says Leonard Saltz, MD, corresponding author and chief of gastrointestinal oncology at MSKCC. “The other take-home message is that in every patient with a confirmed CEA over 35, cancer was present. We hardly ever saw a false-positive elevation over 20, and never saw a confirmed false-positive elevation over 35,” Dr. Saltz says.

**Clinical Implications**

The standard of care for follow-up after treatment of locoregional CRC is to check CEA levels every 3 to 6 months with routine computed tomography (CT) scans performed once a year. However, an elevated CEA level triggers CT to evaluate for disease recurrence, regardless of the timing of prior scans until the source of the elevated CEA is discovered. Therefore, false-positive results can result in unnecessary radiation exposure, costs, and anxiety.

“While we know that CEA levels can help identify patients with potentially resectable disease, this study should help make clinicians aware of the fact that the likelihood of a recurrence depends on the level of CEA elevation and whether or not the elevated level can be confirmed by a second [CEA] test,” says Axel Grothey, MD, professor of oncology at the Mayo Clinic in Rochester, Minnesota, who was not involved in the study. “This is important, as I have seen it over and over again that CEA elevations in the gray zone lead to extensive workups including PET [positron emission tomography]/CT imaging, which are not indicated.”

The current study identified 2 distinct groups of patients with falsely positive CEA levels: those with 1-time elevations (111 patients) and those with confirmed repeated elevations (247 patients). Approximately 93% of patients with the isolated elevations had a CEA level between 5.1 and 10 ng/mL. Litvak and colleagues noted that based on their study, these patients should have the level repeated and confirmed before any further workup is performed.

“In my opinion, the best interval for rechecking the CEA level is around 6 to 8 weeks,” says Dr. Saltz. “CEA has a half-life of up to 14 days, so it is preferable to give some time to allow for changes to happen. I do not believe that amount of time would be clinically relevant in an asymptomatic patient.”

In the patients with false-positive findings whose levels remained elevated in repeat testing, results demonstrated that the confirmed false-positive rate of an elevated, sustained CEA level was 40% when the standard CEA cutoff of 5 ng/mL was used. Raising the cutoff to 10 ng/mL would lower the false-positive rate to 8%. However, the authors found that 27% of patients with true-positive CEA elevations had a CEA level between 5 and 10 ng/mL, and therefore increasing the upper limit of normal to 10 ng/mL would lower the sensitivity too much.

The data do not include the causes of falsely elevated CEA levels, but false-positive results have been observed in smokers and patients with various conditions, including nonmalignant gastrointestinal disorders, lung disease, and hypothyroidism. The authors state that these elevations are usually less than 10 ng/mL, and chronic conditions such as smoking are unlikely to have caused the elevations noted in the current study because all patients were required to have normal perioperative CEA levels.

In summary, the results of the study demonstrate that the most false-positive CEA elevations were in the range of 5 to 10 ng/mL, false-positive CEA levels greater than 15 ng/mL were rare, and all sustained CEA elevations greater than 35 ng/mL were indicative of a true cancer recurrence. However, the authors were careful to point out that they do not recommend treating a patient with an elevated CEA level without imaging or pathological confirmation of disease recurrence.

Dr. Grothey says he considers CEA to be a valuable surveillance test, but that research into better tests is ongoing. “The future of ‘tumor markers’ lies in the determination of circulating tumor DNA, preferably based on a mutational analysis of the resected primary tumor to follow patients with this highly sensitive technology to see if they have evidence of minimal residual disease,” he says.