



Surveillance of breast cancer patients: time for an update?

Mara A. Piltin, Tina J. Hieken

Section of Breast and Melanoma Surgical Oncology, Department of Surgery, Mayo Clinic, Rochester, MN, USA

Correspondence to: Tina J. Hieken, MD. Professor of Surgery, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA. Email: hieken.tina@mayo.edu.

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Guidelines for surveillance after diagnosis and treatment of breast cancer are well defined and include clinical evaluation and annual mammography (1-3). Despite advancements in breast cancer care over the years, disease recurrence after successful initial treatment of breast cancer remains a substantial personal and public health issue. The standard surveillance recommendation for clinical evaluation with annual mammography was studied in randomized prospective trials performed almost thirty years ago and deemed efficacious, although compliance is likely sub-optimal (4-6). Follow-up care for breast cancer survivors can be a challenge and the number of clinical visits to a primary care provider, oncologist or surgeon decrease over time in the years following surgery (7). The authors of the interesting article “Serum tumor markers and positron emission tomography-computed tomography scan as post-breast cancer treatment surveillance” focus on the potential clinical utility of serum tumor markers as part of post treatment surveillance of breast cancer patients in the current era of sophisticated imaging and major advances in cancer treatment (8).

Many clinical societies have described guidelines for surveillance of breast cancer patients following treatment (Table 1). In 2006, the American Society of Clinical Oncology (ASCO) endorsed that in the absence of specific clinical exam findings, testing serum biomarkers, including carcinoembryonic antigen (CEA), cancer antigen (CA) 15-3 and CA 27-29, is not recommended. Routine use of panel or hepatic function panel blood testing, body imaging modalities, functional breast imaging including fluorodeoxyglucose (FDG)-positron emission tomography (PET) and breast magnetic resonance imaging studies also were not recommended (12,13). These guidelines were

reevaluated and maintained in a 2015 update (2).

Recommendations against using serum tumor markers for routine surveillance are rooted in a lack of adequate evidence showing a benefit to this approach. Efforts to evaluate the role of serum tumor markers in the management of breast cancer patients are ongoing. Retrospective data have suggested that preoperative elevation of serum tumor markers is an independent prognostic marker associated with worse disease-free and overall survival in breast cancer patients (14). However, more information is required to understand the role of these markers in surveillance for recurrence and new primary breast cancers. Several groups are working to identify the value of serum biomarkers in this setting. Assessing the combination of CA15-3 and CEA for detection of distant disease recurrence and early metastases has a reported specificity between 86.3–99% and sensitivity of 64–70.6% (15-17). When tissue polypeptide antigen (TPA) is monitored in addition to CA 15-3 and CEA, a specificity of 97.6% and sensitivity of 93% has been reported (15,18). As with the development of other cancer biomarkers, adopting serum CA 15-3 and CEA for routine post-treatment surveillance will require substantial work. Inconsistencies across studies regarding cut-off values for normal and change (increase) over time that heralds’ significance need to be resolved. In addition, endpoints must be defined clearly, e.g., detection of ipsilateral or contralateral breast cancer or distant recurrence.

We commend Co and colleagues for closely evaluating their institutional practice and sharing their data. They investigated the efficacy of routine CEA and CA 15-3 measurements for detecting recurrent breast cancer. Their protocol for patients following treatment of breast cancer

Table 1 Breast Cancer Surveillance Guidelines

Association	History & physical	Mammogram	Tumor markers	Additional imaging	Year updated
NCCN	1–4 times per year for 5 years then annually	Every 12 months	Can be considered when clinical evidence of recurrent disease	Can be considered when clinical evidence of recurrent disease	2020
ASCO	Every 3–6 months for 3 years, then every 6–12 months for 2 years, then annually	Every 12 months	Can be considered when clinical evidence of recurrent disease	Can be considered when clinical evidence of recurrent disease and MRI only if high risk	2015
ESMO	Every 3–4 months for 2 years, then every 6 months for years 3–5, then annually	Every 12 months with ultrasound	Can be considered when clinical evidence of recurrent disease	Can be considered when clinical evidence of recurrent disease and can consider ultrasound in invasive lobular carcinomas	2019
EGTM	X	X	Recommends serial CA 15.3 and CEA for early detection of recurrence in patients with no evidence of disease if the detection of recurrent or metastatic disease would alter clinical management, although the impact of this lead time information on patient outcome is not clear	X	2005

NCCN, National Comprehensive Cancer Network (9); ASCO, American Society of Clinical oncology (2); ESMO, European Society for Medical Oncology (10); EGTM, European Group on Tumor Markers (11).

with curative intent included a yearly mammogram and ultrasound with serologic CEA and CA 15-3 biomarkers on every outpatient visit. Their standard visit follow-up regimen included clinical evaluation every 3 months for 2 years after completion of treatment, every 6 months for the subsequent 2 years and yearly from 5 years. In their protocol, two consecutive elevations in biomarker levels triggered a PET-CT scan. They report on 250 patients with both regularly drawn tumor markers and PET-CT scans. After a median follow-up of 8 years, 93 patients experienced breast cancer related mortality. Approximately half of patients dying of breast cancer had elevated tumor markers at follow-up. This suggests that the tumor markers in this study have little clinical utility in predicting survival, contrary to much of what has been reported previously (14). The study of Co *et al.* looked at CEA and CA 15-3 separately. While helpful in identifying the efficacy of each biomarker independently, the clinical utility of this approach may be limiting, as previous studies have shown improved performance characteristics when CEA and CA 15-3 are measured together. It is not clear which patients in the present study had elevation of one versus both biomarkers and how this might affect their analyses.

Laboratory cutoff values in Co study were set at a CEA ≥ 5 ng/mL and CA 15-3 ≥ 23 U/mL, which correlated significantly with abnormal PET-CT findings. Based on their data, the calculated sensitivity of CEA for a corresponding abnormal PET-CT was 83.1% and specificity was 32.4%. For CA15-3, sensitivity was 57.2% and specificity was 47%. They report the positive predictive values of CEA and CA 15-3 to be 61.8% and 64.1% respectively.⁸ Unfortunately, despite statistical significance, the sensitivity and specificities of each individual biomarker when evaluated separately do not seem to be sufficient to drive a change in current clinical practice. The study does astutely ask the important question of whether early detection confers an overall survival benefit, which has yet been answered and raises several interesting questions for future research. One scenario that may warrant further commentary or investigation is the management and counseling of patients with an elevated serum tumor marker and a negative PET-CT scan.

Both biomarkers have the potential to be elevated in presentations other than breast cancer, making this a feasible clinical scenario to encounter. CEA has been shown to be elevated in the setting of benign liver disease,

inflammatory gastrointestinal disorders, infections, trauma, smoking, renal impairment, infarction and collagen vascular diseases (19). Similarly, CA 15-3 may be falsely elevated in patients with other forms of malignant adenocarcinomas such as ovarian, pancreatic, gastric or lung, as well benign conditions including hepatitis, sarcoidosis, hypothyroidism, liver cirrhosis, and megaloblastic anemia (20). In patients with biomarker elevation and negative imaging we would recommend close clinical follow-up including physical examination and, if biomarker elevation persists or increases, short-term repeat imaging.

It would be interesting to know more details on the type of recurrences the investigators identified and how they were treated. Future research could evaluate the utility of tumor biomarkers in each subset of metachronous disease including ipsilateral breast tumor recurrence, contralateral breast cancer, nodal relapse and distant relapse. Data to suggest that serum tumor markers may have higher detection rates in patients with bone and liver metastases exists, supporting that these subpopulations may in fact differ (12).

As the established post-operative surveillance recommendations for cancer survivors were studied prior to the development of the advanced breast imaging techniques and systemic therapies that are now available, it may be valuable to reassess the role of surveillance with serum tumor markers in this new decade. We commend the authors both for establishing a structured breast cancer surveillance program at their influential institution as well as collecting and reporting on their experience. We look forward to future discovery and investigations of relevant blood biomarkers to improve long-term outcomes for early breast cancer patients.

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