Original Research

Patterns of Utilization of Imaging Studies and Serum Tumor Markers Among Patients With De Novo Metastatic Breast Cancer

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Abstract

Background: When monitoring patients with metastatic breast cancer (mBC), the optimal strategies for imaging and utilization of tumor markers (TM) are uncertain. **Patients and Methods:** We used a retrospective cohort of 302 patients with de novo mBC treated from 2000 to 2012 at Dana-Farber Cancer Institute to describe the type and timing of imaging and TM testing during the first line of treatment (baseline, first, and subsequent testing). **Results:** At baseline, all patients had staging scans, with increasing use of PET/PET-CT (17.5% from 2000–2002; 40.3% from 2009–2012). PET/PET-CT was used by itself in only 12.5% of cases. Overall, 30.1% of patients, of whom 80.2% had no neurologic symptoms, underwent central nervous system (CNS) screening; 78.2% of patients had baseline TM testing. Over the course of treatment, 23.5% of patients had TM retested once a month or more. Time-to-first reimaging varied by disease site (hazard ratios for shorter time-to-first reimaging [95% CI] vs bone: brain, 4.27 [1.46–12.50]; liver, 2.19 [1.39–3.46]; lung, 2.75 [1.66–4.57]), but was not associated with tumor subtype or baseline TM testing, regardless of test results. First reimaging was prompted by an elevation in TM in only 1.4% of cases. There was weak correlation between frequency of imaging and TM tests (r=0.33; R^2=0.11; P<.001). **Discussion:** Over time, we found an increased utilization of more sophisticated imaging staging techniques, such as PET/PET-CT scan, which was mostly requested in addition to other radiographic studies. CNS evaluations were frequently performed to screen asymptomatic patients. TM testing was often ordered, both at baseline and after treatment initiation. However, patterns of imaging utilization, although appropriately influenced by clinicopathologic factors such as disease site, did not appear to be impacted by TM testing. **Conclusions:** Studies focused on optimizing disease monitoring, including better integration of TM testing with imaging, are encouraged.

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Background

Metastatic breast cancer (mBC) is a heterogeneous disease, with a multitude of treatment options available.[1–3] Monitoring patients with mBC with a combination of clinical, laboratory, and imaging evaluations allows for assessment of response and toxicity of treatments.[4,5]

In clinical trials, imaging studies are ordered for work-up and periodic disease reevaluations after prespecified schedules. Outside of trials, guidelines unanimously acknowledge that the frequency of scans should be tailored to the individual patient, accounting for factors including disease biology, symptoms variation, and anticipated

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response to treatment.[5] Nevertheless, the suggested interval between follow-up imaging studies has a wide range, and the optimal monitoring frequency has not been yet prospectively assessed.[5–7]

Serum tumor markers (TM), such as carcinoembryonic antigen (CEA) and the MUC-1 cancer antigens (CA) 15-3 and CA 27.29, are frequently part of mBC monitoring.[8] Informal consensus among ASCO guidelines panel members discourages the use of these markers as a stand-alone tool to guide mBC treatment decision-making, but supports TM use as an adjunctive assessment for clinical decisions.[9,10] Indeed, declaring disease progression and changing treatment based on isolated increases in TM values has not been proven to affect breast cancer outcomes.[9,11]

Today, limited recommendations inform TM utilization, leaving use and frequency of testing to the treating physician's discretion,[5,9] and the best way to integrate TM with imaging remains uncertain. Moreover, previous studies showed a high rate of TM testing on patients with advanced solid tumors, including mBC, questioning their true utility and suggesting a substantial impact on the financial burden of cancer care.[12,13]

We sought to describe the patterns of imaging and TM utilization, and the integration of both among patients with mBC treated at Dana-Farber Cancer Institute (DFCI).

Patients and Methods

Data Source

We reviewed the electronic medical records (EMRs) of 456 consecutive outpatients diagnosed with de novo mBC and treated at DFCI from January 1, 2000, through December 31, 2012. The end date was chosen to ensure at least 2 years of follow-up.

This study was approved and performed according to the guidelines of the DFCI Institutional Review Board.

Patient Selection

Women with newly diagnosed stage IV breast cancer in the DFCI patient database were included. We defined stage using the AJCC Cancer Staging Manual[14] available at the time of diagnosis. We excluded EMRs with missing or incomplete data (n=15), patients with follow-up studies and/or treatment not directly scheduled by DFCI providers (n=70), patients with a second active concurrent malignancy (n=11), and patients who participated on clinical trials or screened for trial eligibility (n=58).

Outcomes of Interest

Baseline Staging: Baseline staging included imaging and TM tests ordered/performed before or on day 1 of first-line treatment. Specifically, we examined (1) imaging modality used (chest/abdomen/pelvis CT, bone scan, ^{18}F-fluorodeoxyglucose [FDG]-PET/PET-CT, abdominal MRI, abdominal ultrasound, chest radiograph, spine MRI, head CT, brain MRI); (2) TM tests used (CEA, CA 15-3, CA 27.29, CA 125, CA 19.9), and TM values (normal, elevated); and (3) time trends in imaging and TM use.

First Reevaluation of Disease: For each patient, we recorded the time from baseline to first reimaging (regardless of the type of imaging modality requested) and, when available, the reason for first reimaging (symptoms, TM alteration, prescheduled [if not otherwise specified in the EMR]), and the time from baseline to first TM test.

Subsequent Reevaluations of Disease: We calculated the frequency of imaging scans (ratio of treatment duration to number of scans, regardless of the type of imaging modality requested) and TM tests (ratio of treatment duration to number of tests).

We excluded imaging studies performed for purposes other than restaging (eg, to evaluate for other concomitant, nonmalignant conditions). We followed patients throughout the duration of first-line treatment for mBC (baseline to day 1 of second-line treatment or death date) for a maximum of 24 months, after which patients were censored. Treatment modifications not resulting from disease progression/unacceptable toxicity (eg, maintenance regimens) were not considered as treatment change.

Covariates

Covariates abstracted via chart review were categorized as per Table 1. Tumor subtypes were classified as hormone receptor (HR)+ (estrogen receptor [ER]+ and/or progesterone receptor [PR]+)/HER2–; HR+ (ER+ and/or PR+)/HER2+; HR– (ER– and PR–)/HER2+; and HR– (ER– and PR–)/HER2–. Patients with >1 disease site were assigned to the category of the first site listed, according to a prespecified ranking system defined by importance.

Table 1. Patient Demographics and Clinicopathologic Characteristics (n=302)

Characteristic	N	%
Total	302	100
Age at diagnosis, y		
<50	105	34.8
50–64	122	40.4
≥65	75	24.8
Marital status		
Married	198	65.6
Not married[a]	104	34.4
Education level		
High school or lower	62	20.5
Some college or higher	106	35.1
Other/unknown	134	44.4
Race/ethnicity		
Non-Hispanic white	258	85.4
Other[b]	44	14.6
Employment		
Employed[c]	135	44.7
Unemployed[d]	94	31.1
Retired	73	24.2
Charlson comorbidity score[33]		
0	256	84.8
≥1	46	15.2
Histology		
Ductal	180	59.6
Lobular	58	19.2
Other[e]	64	21.2
Tumor subtype		
HR+/HER2–	203	67.2
HR+/HER2+	32	10.6
HR–/HER2–	30	9.9
HR–/HER2+	37	12.3
Tumor grade		
I	30	9.9
II	115	38.1
III	128	42.4
Unknown	29	9.6
Number of sites involved		
1	164	54.3
2	74	24.5
≥3	64	21.2
Site of metastasis at first evaluation[f]		
Brain	11	3.6
Liver	83	27.5
Lung	40	13.2
Other[g]	28	9.3
Distant lymph nodes[h]	34	11.3
Bone	106	35.1
Year of diagnosis		
2000–2002	40	13.2
2003–2005	53	17.5
2006–2008	85	28.1
2009–2012	124	41.1
Systemic signs/symptoms/laboratory alterations[i]		
No	151	50.0
Yes	151	50.0
CNS-related signs/symptoms[j]		
No	281	93.1
Yes	21	6.9
Type of first-line treatment (± HER2-directed therapy)		
Chemotherapy	129	42.7
Endocrine therapy	173	57.3

Abbreviations: CNS, central nervous system; HR, hormone receptor.
[a]Includes divorced, separated, single, widowed, and unknown.
[b]Includes non-Hispanic black, Asian, other race, and unknown.
[c]Includes full-time, part-time, and self-employed.
[d]Includes unemployed, disabled, and unknown.
[e]Includes mixed ductal/lobular, carcinoma not otherwise specified, and unknown.
[f]± any other site in the list; when patients had >1 metastatic site, they were only assigned to the category of the site first listed, using a prespecified ranking system.
[g]Includes skin, pleural effusion, pericardial effusion, peritoneum, ovaries/other pelvic sites, adrenal glands, and visceral sites other than lung and liver.
[h]Includes lymph nodes other than ipsilateral axillary (level I–II), infraclavicular, supraclavicular, and internal mammary.
[i]Includes bone pain, weight loss, fatigue, and presence of alterations in routine labs (eg, CBC, serum biochemical profile with renal and liver functionality).
[j]Includes motor impairment, seizures, headaches, nausea/vomiting, and cognitive dysfunctions, assessed by neurological examination.

Central nervous system (CNS)–related signs or symptoms were defined as "present" or "absent" based on whether the evaluating physician noted signs or symptoms suspicious for CNS involvement at the first physical examination, and reported the symptom in the notes.

Statistical Analysis

We used descriptive statistics to characterize baseline mBC evaluation (type of imaging, CNS evaluation, type of TM) and time trends. Time-to-first reimaging and time-to-first TM test were evaluated based on baseline characteristics using the log-rank test. Multivariable Cox proportional hazard regression models were fit, adjusting for all our covariates and for baseline TM testing (not performed vs performed–TM elevated vs performed–TM normal).

We descriptively summarized the frequency of reimaging and TM retesting over the course of treatment. Pearson correlation tests were used to determine the relationship between the frequency of imaging and TM tests. All presented *P* values are 2-sided; $P<.05$ was considered statistically significant. All analyses were performed using R version 3.2.2 (RStudio, Boston, MA).

Results

Study Cohort

We included 302 patients treated at DFCI during 2000 through 2012 by 38 providers, who scheduled the workup and follow-up examinations. Median age at diagnosis was 54 years (range, 23–92 years). Of these patients, 67.2% had HR+/HER2–, 10.6% had HR+/HER2+, 9.9% had HR–/HER2–, and 12.3% had HR–/HER2+ breast cancer. Most patients (55.7%) had nonvisceral disease, 40.7% had visceral metastases (liver and/or lung), and 3.6% had CNS disease at initial diagnosis. Systemic signs/symptoms/laboratory alterations were present in 50.0% of patients and neurologic signs/symptoms were present in 6.9%. First-line treatment included chemotherapy (±HER2-directed) for 42.7% of patients, and endocrine therapy (±HER2-directed) for 57.3% (73.6% of those with HR+ disease) (Table 1). Median duration of first-line therapy was 10.6 months (first quartile [Q_1]–third quartile [Q_3], 4.6–19.2; range, 0.3–24.0 months). At the end of the 24-month study period, 80.1% of patients had switched to a second-line

regimen, 6.0% had died, and 13.9% were censored (first-line treatment still ongoing).

Baseline Staging

All patients underwent baseline imaging, most (51.3%) with ≥3 different techniques. The most requested combination was CT plus bone scan (± any other modality, except PET/PET-CT; 51.7% of patients). A PET/PET-CT was requested for 34.4% of patients. For most of these patients (87.5%), PET/PET-CT was added to other types of scans (for 38.5%, to CT + bone scan); but for 12.5%, PET/PET-CT was the only baseline scan performed. Approximately one-third of patients (30.1%), of whom 80.2% presented without neurologic symptoms, underwent baseline CNS evaluation (head CT and/or brain MRI). The CNS baseline evaluation was performed on 30.5% of patients with HR+/HER2–, 23.2% of patients with HER2+, and 43.3% of patients with HR–/HER2– disease. Only 11 patients (3.6%), most frequently with HR–/HER2+ or HR–/HER2–, and very uncommonly with HR+/HER2– breast cancer, had brain metastases on initial staging; of these, 6 were asymptomatic at the time of CNS screening: 5 of 6 and 1 of 6 patients had ≥5 and <5 brain metastases, respectively.

Baseline TM testing was ordered for 78.2% of patients. Among tested patients, the most requested TM types were CEA and/or CA 27.29 (86.0%), and 78.4% had elevated TM values.

The use of baseline PET/PET-CT increased from 17.5% to 40.3% from 2000–2002 to 2009–2012 (Figure 1A); no time trend was found for baseline CNS scans or TM orders (Figure 1B,C).

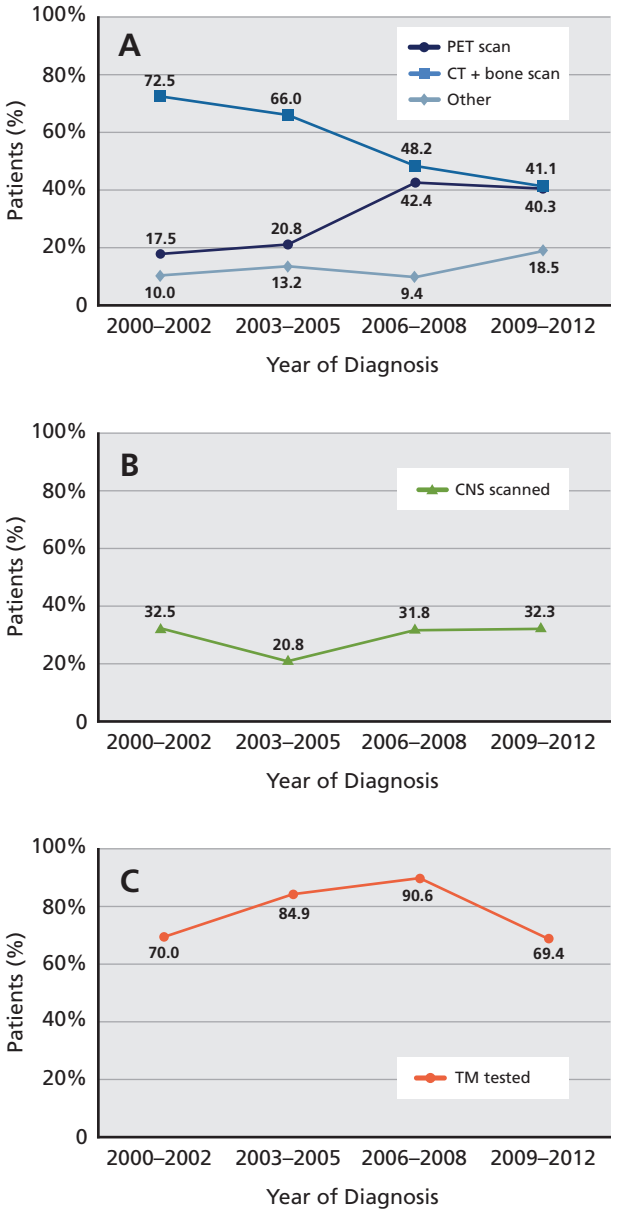

Figure 1. Time trends in baseline staging procedures. (A) Baseline imaging studies. (B) Baseline CNS screening. (C) Baseline TM orders. Abbreviations: CNS, central nervous system; TM, tumor marker.

First Reevaluation of Disease

After baseline, 93.7% of patients had ≥1 reimaging study, which was either prescheduled (83.0%) or prompted by variation in symptoms (15.6%) or by an alteration in TM values (1.4%). Overall, median time from baseline to first reimaging was 3.0 months (Q_1–Q_3, 2.1–4.3; range, 0.4–19.1 months).

Nineteen patients were never reimaged during first line of treatment: 16 had short first-line treatment, ranging from 2 to 5 months (9 patients died, 7 experienced disease progression on clinical examination or experienced early toxicities), and 3 patients were censored after 24 months (all with indolent disease, treated with endocrine therapy, and followed with clinical examinations).

Time-to-first reimaging was associated with disease site (adjusted hazard ratios of shorter time to reimaging versus bone: brain, 4.27 [95% CI, 1.46–12.50]; liver, 2.19 [95% CI, 1.39–3.46]; lung, 2.75 [95% CI, 1.66–4.57]; other, 2.57 [95% CI, 1.51–4.38]) and year of diagnosis (adjusted hazard ratios of shorter time to reimaging vs 2000–2002: 2006–2008, 1.67 [95% CI, 1.02–2.74]; 2009–2012, 1.39 [95% CI,

1.02–2.30]), but not with tumor subtype and baseline TM testing (regardless of TM values).

After baseline, 87.4% of patients had ≥1 TM test, including the 68.2% of patients who did not have any baseline TM test (n=45/66) and the 90.2% of those with normal baseline TM values (n=46/51). Overall, median time from baseline to first TM test was 1.0 month (Q_1–Q_3, 0.7–2.0; range, 0.2–15.7 months).

Presence of systemic signs/symptoms/laboratory alterations and baseline TM testing impacted time to first TM testing (adjusted hazard ratios of shorter time to first TM test: for systemic signs/symptoms/laboratory alterations present vs absent, 1.53 [95% CI, 1.14–2.05]; for TM tested–elevated vs not tested, 2.57 [95% CI, 1.75–3.78]). Complete data from these analyses are displayed in Table 2.

We found no correlation between time-to-first reimaging and TM test (r=0.08; R^2<.01; P=.187).

Subsequent Reevaluations of Disease

Overall, median time between reimaging studies was 3.6 months (Q_1–Q_3, 2.5–5.3; range, 0.8–24.0 months). For 47.7% of patients, the frequency of reimaging was 2 to 4 months; 11.7% of patients had ≥1 reimaging every 2 months (Figure 2A).

Overall, median time between TM tests was 1.4 months (Q_1–Q_3, 1.0–2.4; range, 0.4–12.0 months). For 45.8% of patients the frequency of retesting was 1 to 2 months; 23.5% of patients had ≥1 test per month (Figure 2B).

We found a weak, positive correlation between frequency of imaging and TM testing (r=0.33; R^2=0.11; P<.001).

Discussion

In this cohort of patients with de novo mBC treated at DFCI, outside of a clinical trial, more sophisticated staging techniques such as PET/PET-CT were increasingly used since 2000, with almost half of patients being evaluated by baseline PET/PET-CT in the most recent years. Additionally, we found that 30.1% of patients (of whom 80.2% had no neurologic symptoms) also had baseline CNS screening. The timing of reevaluations was consistent among providers and concordant with current guidelines[5]: most patients underwent reimaging and TM retesting every 2 to 4 months and every 1 to 2 months, respectively. However, nearly one-quarter (23.5%) of patients underwent ≥1 TM test per month. Although appropriately impacted by clinicopathologic factors, including disease site, imaging utilization appears not to be substantially influenced by TM testing.

The surveillance of patients with mBC has evolved over the past decade. Although different imaging and TM options now exist, no consensus exists on the best monitoring strategy. Data provided by this study highlight some of the areas of controversy that may deserve practice improvement and research interventions.

First, findings suggest that PET/PET-CT was gradually incorporated into practice during baseline evaluation of mBC, in most cases in association with other scans. This practice agrees with current guidelines, endorsing CT and bone scan as the backbone of mBC workup and considering PET/PET-CT as "optional,"[5,6] and with the recommendation of CMS, which routinely reimburses PET/PET-CT when standard diagnostic workup yields unclear results.[15,16] This is based on several studies that showed that PET/PET-CT added important functional and metabolic information to traditional anatomic imaging, resulting in modifications in initial N and M statuses in 18% to 37% of patients and in treatment modification in 8% to 18% of patients, respectively.[17–22] Nevertheless, because use of PET/PET-CT substantially increases costs, it is important to better understand which patients would really benefit from a PET/PET-CT scan and whether its upfront use as the only staging technique may represent a cost-effective alternative. Based on 2016 CMS data,[23] the payment rate is $1,285.17 for a whole-body PET/PET-CT imaging, which in addition to $1,375.81 of a torso-CT with contrast and bone scan leads to a total of approximately $2,661 per patient.

Second, although CNS screening is not routinely recommended, given the absence of data demonstrating a benefit from early detection and treatment of asymptomatic CNS lesions,[2,24–28] baseline CNS evaluations occurred frequently in the absence of neurologic symptoms (eg, among our patients with HR–/HER2– disease, 43.3% had baseline CNS screening). The overall incidence of detection of occult CNS metastases was low, particularly in patients with HR+/HER2– tumors. Even among patients with HR–/HER2– tumors, brain metastases were only identified in 2 of 13 screened asymptomatic patients. Furthermore, when CNS lesions were detected in asymptomatic patients, 5 of 6 patients had ≥5 lesions, whose early detection, before the onset

Table 2. Univariate and Multivariate Analyses of Time to First Reevaluation of Disease

	Time-to-First Reimaging (Number of Events=283)			Time-to-First TM Test (Number of Events=264)		
	Univariate Analysis		Multivariate Analysis	Univariate Analysis		Multivariate Analysis
Variable	Median Time (mo)	*P* Value[a]	Hazard Ratio[b] (95% CI)	Median Time (mo)	*P* Value[a]	Hazard Ratio[b] (95% CI)
Age at diagnosis, y		.432			.591	
<50	2.9		1.00	1.0		1.00
50–64	3.0		1.10 (0.80–1.51)	0.9		0.83 (0.60–1.16)
≥65	3.1		**1.75 (1.04–2.92)**	1.1		0.91 (0.52–1.59)
Marital status		.563			.211	
Married	3.0		1.00	1.0		1.00
Not married[c]	3.1		0.80 (0.60–1.08)	1.0		1.07 (0.80–1.44)
Education level		.593			.980	
High school or lower	2.8		1.00	1.1		1.00
Some college or higher	3.3		0.94 (0.66–1.33)	1.2		0.99 (0.68–1.44)
Other/unknown	2.8		0.89 (0.60–1.32)	1.0		0.83 (0.54–1.27)
Race/ethnicity		.204			.720	
Non-Hispanic white	3.0		1.00	1.0		1.00
Other[d]	2.9		1.26 (0.87–1.82)	1.0		1.05 (0.71–1.55)
Employment		**.014**			.586	
Employed[e]	**3.0**		1.00	1.1		1.00
Unemployed[f]	**2.7**		**1.52 (1.12–2.08)**	0.9		0.92 (0.68–1.27)
Retired	**3.5**		0.71 (0.45–1.12)	1.1		0.88 (0.55–1.43)
Charlson comorbidity score[33]		.724			.946	
0	3.0		1.00	1.1		1.00
≥1	3.0		0.95 (0.63–1.42)	1.0		0.95 (0.63–1.43)
Histology		.265			.086	
Ductal	3.0		1.00	1.2		1.00
Lobular	3.1		0.89 (0.58–1.37)	0.9		1.15 (0.74–1.80)
Other[g]	2.9		0.86 (0.58–1.27)	1.0		0.95 (0.65–1.40)
Tumor subtype		**.001**			.179	
HR+/HER2–	**3.3**		1.00	1.0		1.00
HR+/HER2+	**2.8**		1.08 (0.66–1.76)	1.4		1.21 (0.73–1.98)
HR–/HER2–	**2.3**		1.19 (0.68–2.10)	0.9		0.90 (0.48–1.67)
HR–/HER2+	**2.6**		0.98 (0.57–1.68)	1.3		1.10 (0.61–1.97)
Tumor grade		.313			.603	
I	3.3		1.00	0.9		1.00
II	3.0		0.89 (0.54–1.45)	1.0		0.78 (0.46–1.34)
III	2.8		0.91 (0.45–1.52)	1.1		0.85 (0.50–1.45)
Unknown	3.1		0.78 (0.43–1.43)	1.1		0.92 (0.50–1.73)
Number of sites involved		**.048**			**.019**	
1	**3.1**		1.00	**1.1**		1.00
2	**3.2**		**0.63 (0.44–0.90)**	**1.0**		1.00 (0.69–1.45)
≥3	**2.5**		0.86 (0.54–1.35)	**0.9**		0.96 (0.61–1.51)

(continued on next page)

Results in bold are statistically significant with a *P* value<.05.
Abbreviations: CNS, central nervous system; HR, hormone receptor; TM, tumor marker.
[a]Log-rank test *P* values.
[b]Hazard ratios are adjusted for all the covariates listed in the table.
[c]Includes divorced, separated, single, widowed, and unknown.
[d]Includes non-Hispanic black, Asian, other race, and unknown.
[e]Includes full-time, part-time, and self-employed.
[f]Includes unemployed, disabled, and unknown.
[g]Includes mixed ductal/lobular, carcinoma not otherwise specified, and unknown.
[h]Includes skin, pleural effusion, pericardial effusion, peritoneum, ovaries/other pelvic sites, adrenal glands, and visceral sites other than lung and liver.
[i]Includes lymph nodes other than ipsilateral axillary (level I–II), infraclavicular, supraclavicular, and internal mammary.
[j]includes bone pain, weight loss, fatigue, and presence of alterations in routine labs (eg, CBC, serum biochemical profile with renal and liver functionality).
[k]Includes motor impairment, seizures, headaches, nausea/vomiting, and cognitive dysfunctions, assessed by neurological examination.
[l]When multiple TM were tested, TM were considered elevated if ≥1 type was elevated.

Table 2. Univariate and Multivariate Analyses of Time to First Reevaluation of Disease (cont.)

	Time-to-First Reimaging (Number of Events=283)			Time-to-First TM Test (Number of Events=264)		
	Univariate Analysis		Multivariate Analysis	Univariate Analysis		Multivariate Analysis
Variable	Median Time (mo)	*P* Value[a]	Hazard Ratio[b] (95% CI)	Median Time (mo)	*P* Value[a]	Hazard Ratio[b] (95% CI)
Disease site		**<.001**			.006	
Bone	**3.5**		1.00	**1.1**		1.00
Brain	**1.8**		**4.27 (1.46–12.50)**	**0.7**		**3.17 (1.28–7.87)**
Liver	**2.5**		**2.19 (1.39–3.46)**	**1.1**		1.37 (0.86–2.18)
Lung	**2.8**		**2.75 (1.66–4.57)**	**1.1**		1.34 (0.79–2.27)
Other[h]	**2.5**		**2.57 (1.51–4.38)**	**0.9**		1.67 (0.94–2.95)
Distant lymph nodes[i]	**3.7**		1.01 (0.64–1.60)	**1.0**		1.12 (0.68–1.83)
Year of diagnosis		**.033**			.119	
2000–2002	**3.4**		1.00	1.1		1.00
2003–2005	**3.0**		1.05 (0.64–1.71)	1.0		1.27 (0.77–2.11)
2006–2008	**2.9**		**1.67 (1.02–2.74)**	1.2		0.97 (0.58–1.63)
2009–2012	**3.0**		**1.39 (1.02–2.30)**	1.0		0.91 (0.54–1.55)
Systemic signs/symptoms/laboratory alterations[j]		.441			**<.001**	
No	2.9		1.00	**0.9**		1.00
Yes	3.0		0.99 (0.73–1.33)	**1.4**		**1.58 (1.17–2.13)**
CNS-related signs/symptoms[k]		.069			.063	
No	2.5		1.00	0.9		1.00
Yes	3.0		1.12 (0.59–2.14)	1.0		1.32 (0.75–2.33)
Type of treatment		**<.001**			.089	
Chemotherapy	**2.6**		1.00	1.2		1.00
Endocrine therapy	**3.4**		0.76 (0.51–1.12)	1.0		1.32 (0.88–1.98)
Baseline TM testing		.432			<.001	
Not performed	3.0		1.00	**1.4**		1.00
Performed–TM elevated[l]	3.0		1.00 (0.71–1.40)	**1.0**		**2.57 (1.75–3.78)**
Performed–TM normal	2.8		1.40 (0.90–2.19)	**1.8**		1.51 (0.91–2.50)

Results in bold are statistically significant with a *P* value<.05.
Abbreviations: CNS, central nervous system; HR, hormone receptor; TM, tumor marker.
[a]Log-rank test *P* values.
[b]Hazard ratios are adjusted for all the covariates listed in the table.
[c]Includes divorced, separated, single, widowed, and unknown.
[d]Includes non-Hispanic black, Asian, other race, and unknown.
[e]Includes full-time, part-time, and self-employed.
[f]Includes unemployed, disabled, and unknown.
[g]Includes mixed ductal/lobular, carcinoma not otherwise specified, and unknown.
[h]Includes skin, pleural effusion, pericardial effusion, peritoneum, ovaries/other pelvic sites, adrenal glands, and visceral sites other than lung and liver.
[i]Includes lymph nodes other than ipsilateral axillary (level I–II), infraclavicular, supraclavicular, and internal mammary.
[j]ncludes bone pain, weight loss, fatigue, and presence of alterations in routine labs (eg, CBC, serum biochemical profile with renal and liver functionality).
[k]Includes motor impairment, seizures, headaches, nausea/vomiting, and cognitive dysfunctions, assessed by neurological examination.
[l]When multiple TM were tested, TM were considered elevated if ≥1 type was elevated.

of symptoms, would not have necessarily spared them whole-brain radiation therapy. As such, because of the lack of evidence showing an impact on treatment decisions and patient outcomes, CNS screening is still not advisable, regardless of tumor subtype.

Third, this study shows that our providers routinely order TM testing. We observed a 78.2% rate of baseline testing, and that, after baseline, TM tests were requested for 68.2% of patients without any baseline TM evaluation, and retested in 90.2% of those with normal baseline values. Moreover, 23.5% of patients underwent retesting ≥1 time per month. Consistent with our results, Accordino et al[12] recently reported that TM tests were requested more than once per month among 34.3% of patients with advanced solid tumors at their center. Additionally, an analysis of a Medicare-covered population of >2,400 elderly patients with mBC suggested that frequent monitoring (>12 TM tests/year and/or >4 radiographic imaging scans/year) occurred in more than a third of patients.[13] The most recent ASCO guidelines for TM use state that data are insufficient to recommend CEA, CA 27.29, or CA 15-3 for breast cancer staging,[10] nor is TM testing included in the NCCN-sug-

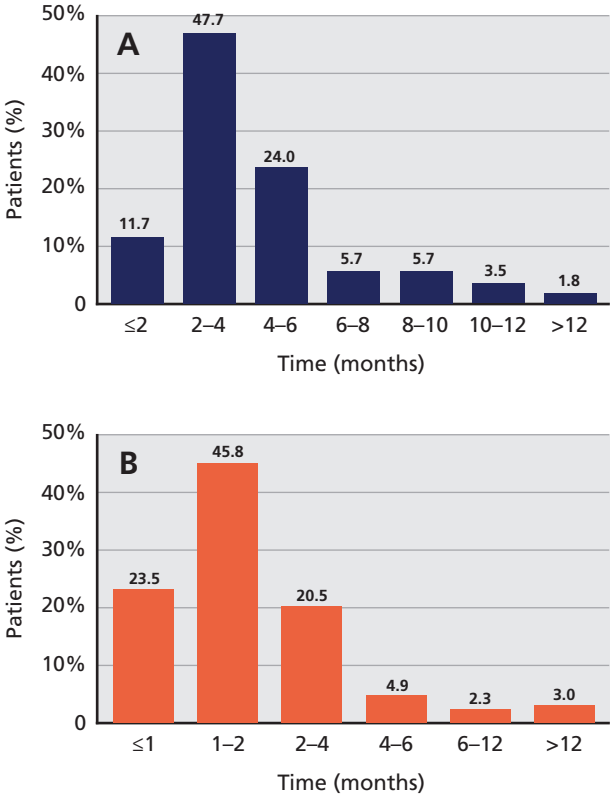

Figure 2. Distribution of mean frequency of disease reevaluations over the course of first-line treatment. (A) Imaging studies. (B) TM testing. Abbreviation: TM, tumor marker.

gested workup for metastatic disease.[5] Nevertheless, in both, TM testing is given as an option for monitoring mBC.[5,10] The kinetics of CEA and CA 15-3 have been retrospectively correlated with treatment response in patients with mBC undergoing chemotherapy,[29] but there is no standardized criteria for biochemical response or progression, because how to integrate TM with imaging was prospectively evaluated.

The overall assumption has been that clinicians use TM to help determine the appropriate timing of restaging scans and to aid in clinical decision-making, but interestingly, in our series the timing of imaging did not vary by TM use. We found that in very few patients (1.4%), the first reimaging was prompted by an elevation in TM; that the time-to-first reimaging was not impacted by baseline TM testing (adjusted hazard ratio for shorter time to reimaging: TM–elevated vs TM–not tested, 1.00; 95% CI, 0.71–1.40); and that frequencies of imaging and TM tests were not correlated or, at most, only weakly correlated (first reimaging and first TM test: r=0.08; P=.187; overall frequency of imaging and TM tests: r=0.33; P<.001). In line with these findings, Accordino et al[12] also found that 92.3% of providers declared that TM orders were placed by administrative staff copying orders from previous visits.

This practice is not devoid of consequences. The previously referenced Medicare study suggested that testing overuse is associated with increased use of other healthcare services (more frequent office visits, use of more expensive imaging tests, and more aggressive end of life care), and therefore with cost increases and no impact on survival.[13] Moreover, other studies highlighted a possible relationship between frequent monitoring and higher levels of patient anxiety and distress.[30]

Given the relatively low costs of TM testing,[31] substantial savings might be demonstrated by studies assessing whether the frequency of other requests, including more expensive imaging studies, may be reduced based on a stable or decreasing trend in TM values.

Although this study describes modern time trends in practice at a large comprehensive cancer center spanning >10 years, it has several limitations. As a single-institution experience, it may not reflect practice elsewhere. Also, although we excluded patients not directly treated by DFCI providers, part of the baseline examinations recorded may have been performed before the first DFCI appointment. Given the retrospective nature of the study, some important patient characteristics, such as performance status, could not be captured, even though exhaustive review of the charts allowed us to collect information on the presence of signs, symptoms, and laboratory alterations among this population. Moreover, data regarding frequency of office visits, specific treatment schedule/regimen administered, type of insurance coverage, changes in workflow and staffing, or software updates, which may have impacted our results, were not available in our database. We must acknowledge, though, that all of these components are important drivers of care decisions, and that there might be other unmeasured confounders for which we could not account. Next, in order to reduce referral bias, and because we focused on initial patterns of care, we limited our cohort to patients with de novo mBC. It is possible that more extensive baseline imaging/testing was performed in these patients as a result, and that the patterns of imaging utilization may be somewhat different among patients who experienced disease recur-

rence after an initial primary breast cancer diagnosis. Unfortunately, we did not collect detailed data in our dataset on the sequence of imaging orders (eg, whether PET/PET-CT orders were placed before or after other imaging), or on whether PET/PET-CT findings meaningfully altered clinical management. Finally, given the relatively small sample size, we could not perform associations and subgroup analyses, or explore the relationship between patterns of care and clinical outcomes.

Conclusions

In an era when cancer-related costs are increasing faster than those of other medical conditions,[32] available resources should be managed conscientiously to provide each patient with high-quality and high-value care. This study summarized the current practice patterns and identified areas suitable for additional study and quality improvement. In particular, the results support a more focused effort to integrate TM testing and frequency of imaging, as part of a comprehensive and rational disease management strategy.

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