Use of ^{18}F -FDG PET/CT as an Initial Staging Procedure for Stage II–III Breast Cancer: A Multicenter Value Analysis

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ABSTRACT

Background: Metastatic staging imaging is not recommended for asymptomatic patients with stage I–II breast cancer. Greater distant metastatic disease risk may warrant baseline imaging in patients with stage II–III with high-risk biologic subtypes. NCCN Guidelines recommend considering CT of the chest, abdomen, and pelvis (CT CAP) and bone scan in appropriate patients. CT CAP and bone scan are considered standard of care (SoC), although PET/CT is a patient-centered alternative. **Methods:** Data were available for 799 high-risk patients with clinical stage II–III disease who initiated screening for the I-SPY2 trial at 4 institutions. A total of 564 complete records were reviewed to compare PET/CT versus SoC. Costs were determined from the payer perspective using the national 2018 Medicare Physician Fee Schedule and representative reimbursements to the University of California, San Francisco (UCSF). Incremental cost-effectiveness ratio (ICER) measured cost of using PET/CT per percent of patients who avoided a false-positive (FP). **Results:** The de novo metastatic disease rate was 4.6%. Imaging varied across the 4 institutions ($P < .0001$). The FP rate was higher using SoC versus PET/CT (22.1% vs 11.1%; $P = .0009$). Mean time between incidental finding on baseline imaging to FP determination was 10.8 days. Mean time from diagnosis to chemotherapy initiation was 44.3 days with SoC versus 37.5 days with PET/CT ($P = .0001$). Mean cost per patient was \$1,132 (SoC) versus \$1,477 (PET/CT) using the Medicare Physician Fee Schedule, with an ICER of \$31. Using representative reimbursements to UCSF, mean cost per patient was \$1,236 (SoC) versus \$1,073 (PET/CT) for Medicare, and \$3,083 (SoC) versus \$1,656 (PET/CT) for a private payer, with ICERs of $-\$15$ and $-\$130$, respectively. **Conclusions:** Considerable variation exists in metastatic staging practices. PET/CT reduced FP risk by half and decreased workup of incidental findings, allowing for earlier treatment start. PET/CT may be cost-effective, and at one institution was shown to be cost-saving. Better alignment is needed between hospital pricing strategies and payer coverage policies to deliver high-value care.

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Background

Breast cancer accounts for 30% of new cancer diagnoses in women, with approximately 276,480 new invasive breast cancers expected in the United States in 2020.¹ The likelihood of metastatic disease at presentation is stage-dependent. Some studies have shown de novo metastatic disease rates of 15% in patients with stage II disease² and $>40\%$ in patients with stage III disease.^{3,4} Greater metastatic disease risk in clinical stage II–III breast cancer may warrant baseline staging imaging, because treatment approaches for patients with distant metastatic disease are different for those with early-stage or locally advanced disease. Detection of distant metastases at diagnosis is also critical for identifying the correct patient population for clinical trials in adjuvant and neoadjuvant settings.⁵

^{18}F -FDG PET/CT (PET/CT) is effective in detecting regional and distant metastases^{4–8} and has outperformed standard imaging techniques in the detection of bone, lymph node, and liver metastases.^{9,10} PET/CT has shown little value in staging of low-risk breast cancer,^{11,12} but may be appropriate for clinical stage II–III disease, because PET/CT requires only a single test and is more sensitive and specific than standard imaging.^{13–17}

Guidelines, including those of NCCN, suggest when PET/CT for clinical stage II or operable stage III breast cancer is not indicated and conversely when it may be helpful. PET/CT is recommended as a supplement to standard imaging studies, such as CT of the thorax and/or abdomen-pelvis and whole-body bone scans.¹⁸

The value of PET/CT for staging in non-small cell lung cancer is well established and considered cost-effective.^{19–22} Similar analyses in breast cancer are less clear, especially in the United States.^{21,23} In silico analysis suggests that PET/CT is cost-effective for staging of clinical stage II–III breast cancer,²⁴ but is not uniformly

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accepted.⁵ Lack of endorsement of PET/CT in guidelines and inadequate insurance coverage remain barriers to the use of PET/CT.

This study explored staging practices at 4 geographically different US cancer centers participating in the I-SPY2 trial, a neoadjuvant trial for patients with molecularly high-risk stage II–III breast cancer. We sought to determine the clinical value and cost-effectiveness of PET/CT as an initial staging procedure compared with standard imaging.

Methods

Study Design and Population

This study was approved by the University of California, San Francisco (UCSF) Institutional Review Board and Quantum Leap Healthcare Collaborative. I-SPY2 is a multicenter, prospective, randomized phase II trial that enrolls patients with clinical stage II–III invasive breast cancer, tumors ≥ 2.5 cm, and high-risk molecular features. I-SPY2 has been described previously in detail.^{25,26} Patients consenting to screening undergo baseline staging imaging to rule out metastatic disease before randomization using either PET/CT or CT of the chest, abdomen, and pelvis (CT CAP) and full-body bone scan (standard of care [SoC] imaging).

We retrospectively reviewed records of patients who consented to screening at 1 of 4 clinical sites—UCSF, University of Minnesota (UMinn), University of Alabama at Birmingham (UAB), and Georgetown University (GU)—from March 2010 through December 2017. Only participants whose records contained complete screening workup and follow-up assessments were included in the primary analysis.

False-Positive Rates

The primary outcome of interest was false-positive (FP) identification of metastatic disease, defined as incidental findings on PET/CT or SoC imaging that were investigated and proved benign via subsequent workup. Patients with FPs were defined as having at least one FP finding on baseline imaging. The determination of whether an incidental finding required workup to rule out metastatic disease was made by the treating clinician with guidance from the local institution's radiologists as to how suspicious the lesion appeared. Examples of incidental findings included hypermetabolic bone lesions (possibly representing bone islands or Schmorl nodes), liver lesions (possible complex cysts, hemangiomas, or focal nodular hyperplasia), thyroid nodules, calcified and noncalcified “too small to characterize” pulmonary nodules, and enlarged and/or hypermetabolic lymph nodes (not including the axilla or internal mammary chains).

Time to initiation of neoadjuvant chemotherapy was the number of days between the date of core biopsy–proved cancer diagnosis and the date that neoadjuvant

chemotherapy began. Time for determination of FP was the number of days between initial staging and completion of the corresponding workup.

Differences in de novo metastatic rates, procedures used between sites, and associations between patient characteristics and procedure type were evaluated by chi-square test. A z test was used to test for differences in FP rates between the PET/CT and standard imaging group. In addition, a Cochran-Mantel-Haenszel (CMH) test was used to compare the FP rates between imaging groups, controlling for site (or other clinical covariates) with the Breslow-Day test to assess the homogeneity of the association. Where significant heterogeneity in odds ratio was observed between classes, FP rates within each stratum were evaluated separately using the z test. For all other comparisons, a 2-tailed t test was applied. ANOVA was also used to compare time to treatment initiation between SoC and PET/CT groups, with site as a covariate.

Economic Evaluation

To evaluate the relative healthcare value of PET/CT, incremental cost-effectiveness ratio (ICER) was assessed, with health outcome defined as percent of patients who avoided an FP, calculated by subtracting $100 - \%FP$ for SoC from $100 - \%FP$ for PET/CT. The cost difference using PET/CT was determined by subtracting the mean cost of SoC imaging (baseline scan + FP workup costs) from the mean cost of PET/CT (baseline scan + FP workup costs). The ICER was calculated as cost difference using PET/CT divided by the percent of patients who avoided an FP using PET/CT.

An aggregate cost analysis of all 4 sites was performed by estimating costs of ^{18}F -FDG PET/CT, SoC, and all workup procedures using the mean national 2018 Medicare Physician Fee Schedule (MPFS).²⁷ Payments were derived through the Outpatient Prospective Payment System (OPPS). As section 5102(b) of the Deficit Reduction Act of 2005 obligates a payment cap on the technical component of certain diagnostic imaging procedures,²⁸ the MPFS amount was compared with the OPPS payment amount. The lesser quantity, rounded to the nearest dollar, was used as the cost. HCPCS/CPT codes were used to derive outpatient and physician fees. No adjustments were made using the Consumer Price Index and no discounts were incorporated into calculating the costs. HCPCS/CPT codes used are shown in supplemental eTable 1 (available with this article at JNCCN.org).

Because UCSF has priced PET/CT lower than SoC within the past 3 years, a separate cost analysis of the UCSF cohort alone was also conducted. PET/CT, SoC, and workup procedure costs were estimated from reimbursements to the UCSF billing department. Representative reimbursement estimates for each procedure

were calculated by averaging reimbursements for CPT codes of 20667 reimbursements from Medicare and 88185 reimbursements from a large commercial private payer from January 2017 through April 2018. Patients with FP workup that included CPT codes for which there was no reimbursement data available were excluded from this part of the analysis.

Results

Of the 812 patients consenting to screening from March 2010 through December 2017, 799 were assessed for de novo metastatic disease status (Figure 1). The de novo

Figure 1. CONSORT diagram for 812 patients screened for I-SPY2 from March 2010 through December 2017.

Abbreviations: GU, Georgetown University; SoC, standard of care; UAB, University of Alabama at Birmingham; UCSF, University of California, San Francisco; UMin, University of Minnesota.

metastatic disease rate was 4.6% (37/799) and did not vary significantly across sites ($P=.583$) (Table 1).

Initial staging and subsequent workup of incidental findings, if applicable, were available for 564 patients (69.5%). Staging procedure varied between sites ($P<.0001$), with SoC imaging the principal technique used at UAB (92.8%) and GU (85.7%), and PET/CT most commonly used at UCSF (86.6%) and UMin (63.6%). Chest radiograph was used for 29.5% of patients at UMin. A small proportion of staging involved other techniques, such as bone scan with liver enzyme monitoring or CT CAP alone (Figure 2).

Characteristics of the 529 patients who underwent SoC ($n=231$) or PET/CT ($n=298$) imaging and were included in the primary analysis are shown in Table 2. Mean age of both groups was 49 years (range, 25–81 years). A greater proportion of Asian women received PET/CT, whereas Black women tended to receive SoC ($P<.0001$). Tumor receptors and lymph node status or invasive cancer type were similar between the 2 groups, although there was a trend for hormone receptor (HR)–negative/HER2–negative patients to receive SoC rather than PET/CT (32% vs 23.5%).

Significantly more patients with FP results were identified in the group undergoing SoC (22.1%; 51/231) versus PET/CT imaging (11.1%; 33/298) ($P=.0009$). Within the SoC group, rates of FP were similar at UCSF, UAB, and GU (only 1 SoC imaging procedure was performed at UMin), and rates of FP by PET/CT were similar across all sites (Table 3). FP rates for each imaging technique were similar across sites and the common odds ratio of FP stratified by site between the SoC and PET/CT groups was 2.4 (CMH $P=.035$).

In contrast, significant heterogeneity in association was observed when patients were stratified by age group. A significant difference in FP rate between the SoC and PET/CT groups was observed among women aged <45 years ($P=.0006$), but not among those aged ≥ 45 years ($P=.1302$). No significant heterogeneity in associations were observed when patients were stratified by race or other tumor characteristics (Table 3).

Table 1. Detection of De Novo Metastatic Disease by Cancer Center

Site	Rate of De Novo Metastatic Disease	P Value
UCSF	4.3% (17/392)	.5827
UMinn	3.7% (4/107)	
UAB	6.0% (13/218)	
GU	3.7% (3/82)	
Total	4.6% (37/799)	

Abbreviations: GU, Georgetown University; UAB, University of Alabama at Birmingham; UCSF, University of California, San Francisco; UMin, University of Minnesota.

Figure 2. Variation in initial staging procedures among 4 comprehensive cancer center sites. The types of procedures used for initial staging of patients with clinical stage II–III breast cancer were significantly different when comparing 4 geographically diverse US comprehensive cancer centers ($P < .0001$).

Abbreviations: GU, Georgetown University; SoC, standard of care; UAB, University of Alabama at Birmingham; UCSF, University of California, San Francisco; UMinn, University of Minnesota.

^aIncludes bone scan alone, CT of the chest, abdomen, and pelvis alone, and liver function test monitoring with or without imaging.

Mean time from diagnosis to initiation of neoadjuvant chemotherapy was 44.3 days in the SoC group versus 37.5 days in the PET/CT group ($P < .0001$). As study sites also have significant differences in time to treatment initiation (1-way ANOVA $P < .0001$), we used 2-way ANOVA with imaging modality and study site as independent variables and observed significant main effects for both factors (site: $P < .0001$; imaging modality: $P = .04$). Mean time between incidental findings on staging imaging to determination of FP was 10.8 days. There was no significant difference in the time from initial staging procedure to determination of FP between the 2 groups (11.3 days for SoC vs 8.1 days for PET/CT) (Table 4).

Table 5 lists costs of initial staging procedures and additional FP workup tests across sites. Mean cost per patient was \$1,132 for SoC and \$1,476 for PET/CT. Mean price increase over baseline imaging cost due to FP workup was 23.6% (\$216) for SoC and 4.6% (\$65) for PET/CT. Notably, 26 patients who underwent SoC (11.3%) were subsequently evaluated with PET/CT as part of their workup. The ICER was \$31 for each percent of patients who avoided an FP.

Using actual reimbursement estimates from Medicare at UCSF, mean cost per patient was \$1,236 for SoC and \$1,073 for PET/CT. The mean price increase over baseline imaging cost because of FP workup was 28.3% (\$273) for SoC and 5.4% (\$55) for PET/CT. In this cohort, the ICER was −\$15 for each percent of patients who avoided an FP. When using estimates from a private payer, the mean cost per patient was \$3,083 for SoC and

Table 2. Patient Demographics

	SoC (n=231)	PET/CT (n=298)	P Value
Age at diagnosis, y			
Mean (range)	49.1 (25–81)	48.8 (25–73)	.7951
Median	48	48	
<45	84 (36.4%)	108 (36.2%)	1.000
≥45	147 (63.6%)	190 (63.8%)	
Race/Ethnicity			
			<.0001
White	168 (72.7%)	230 (77.2%)	
Black	50 (21.6%)	14 (4.7%)	
Asian	10 (4.3%)	37 (12.4%)	
Hispanic/Latino	3 (1.3%)	12 (4.0%)	
Other	0 (0.0%)	5 (1.7%)	
Tumor characteristics			
Receptors ^a			.0542
HR+/HER2−	111 (48.1%)	152 (51.0%)	
HR+ or HR−/HER2+	42 (18.2%)	74 (24.8%)	
HR−/HER2−	74 (32.0%)	70 (23.5%)	
Missing	4 (1.7%)	2 (0.7%)	
Lymph node ^b			.8212
Positive	96 (41.6%)	117 (39.3%)	
Negative	134 (58.0%)	179 (60.1%)	
Missing	1 (0.4%)	2 (0.7%)	
Invasive cancer type ^c			.4675
Ductal	207 (89.6%)	276 (92.6%)	
Lobular	17 (7.4%)	15 (5.0%)	
Other	7 (3.0%)	7 (2.3%)	

Abbreviations: HR, hormone receptor; SoC, standard of care.

^aNo data available for 4 SoC patients and 2 PET/CT patients.

^bNo data available for 1 SoC patient 2 PET/CT patients.

^cDuctal includes patients with mixed ductal/lobular disease. Lobular includes patients with pleomorphic lobular. Other includes metaplastic, spindle cell, or unknown

\$1,656 for PET/CT. The mean increase in price over baseline imaging cost because of FP workup was 15.1% (\$404) for SoC and 8.7% (\$132) for PET/CT. In this cohort, the ICER was −\$130 for each percent of patients who avoided an FP (Table 5).

Discussion

PET/CT has become increasingly prevalent for cancer staging,²⁰ offering shorter scan duration⁹ and better diagnostic accuracy^{4,6–8,13} compared with SoC, with similar radiation doses.²⁹ Yet, the dearth of cost-effectiveness studies and lack of endorsement of PET/CT in guidelines have posed barriers to coverage. This is exacerbated by the practice of hospitals pricing PET/CT higher than SoC, reducing the incentive for payers to cover PET/CT despite previous studies showing that it may be more

Table 3. Characteristics of Patients With FP Results

	SoC (n=231)	PET/CT (n=298)	FP SoC/ FP PET/CT	Common OR (CMH P Value)	Breslow Day P Value	z Test P Value
Total	22.1% (51/231)	11.1% (33/298)	2.0	a	a	.0009
Site						
UCSF	25.7% (9/35)	11.1% (25/226)	2.3	2.4 (P=.035)	.8705	a
UMinn	0% (0/1)	10.7% (6/56)	0.0			a
UAB	22.0% (31/141)	10.0% (1/10)	2.2			a
GU	20.4% (11/54)	16.7% (1/6)	1.2			a
Age at diagnosis, y						
<45	23.8% (20/84)	5.6% (6/108)	4.3	a	.0337	.0006
≥45	21.1% (31/147)	14.2% (27/190)	1.5			.1302
Race						
White	24.4% (41/168)	12.6% (29/230)	1.9	2.3 (P=.001)	.8277	a
Black	16.0% (8/50)	7.1% (1/14)	2.2			a
Asian	20.0% (2/10)	5.4% (2/37)	3.7			a
Tumor characteristics						
Receptors						
HR+/HER2–	16.2% (18/111)	11.2% (17/152)	1.4	2.4 (P=.0004)	.1433	a
HR+ or HR–/HER2+	33.3% (14/42)	16.2% (12/74)	2.1			a
HR–/HER2–	25.7% (19/74)	5.7% (4/70)	4.5			a
Lymph node						
Positive	27.1% (26/96)	16.2% (19/117)	1.7	2.3 (P=.001)	.4839	a
Negative	18.7% (25/134)	7.8% (14/179)	2.4			a
Invasive cancer type						
Ductal	22.2% (46/207)	12.0% (33/276)	1.8	2.3 (P=.0008)	.2824	a
Lobular	23.5% (4/17)	0% (0/15)	—			a
Other	14.3% (1/7)	0% (0/7)	—			a

Abbreviations: CMH, Cochran-Mantel-Haenszel; FP, false-positive; GU, Georgetown University; HR, hormone receptor; OR, odds ratio; SoC, standard of care; UAB, University of Alabama at Birmingham; UCSF, University of California, San Francisco; UMinn, University of Minnesota.

*Tests were not performed (ie, z test in individual stratum when Breslow Day test >.05, or CHM test when Breslow Day test <.05).

sensitive and specific in detecting metastatic disease. With the ever-increasing cost of healthcare, there is opportunity for improvement in patient outcomes and reduction of costs if diagnostic procedures are optimized.^{30,31}

Given differences in imaging pricing and reimbursement patterns across the United States, we expected varied staging practices between institutions. Although practice variation has been shown previously in stage 0–II breast cancer,³² our study confirmed the variability of imaging used in the population with stage II–III disease. The difference in use of PET/CT versus SoC observed in Black and Asian patients was likely driven by the predominant use of one imaging modality over another at sites where one race is more prominently represented in the trial.

FPs were more commonly noted in patients aged <45 years. Whereas rates of FPs were higher with SoC than PET/CT in all biologic subsets, the ratios of FPs were

highest in triple-negative and HER2+ disease (4.5 and 2.1, respectively). Because these subtypes are more common in younger women, biologic differences likely drive the higher FP rate in younger patients, and greater consideration for routine use of PET/CT may be warranted.

Although the focus of this investigation was on differences between PET/CT and SoC in terms of cost-effectiveness and FP, the importance of diagnosing de novo stage IV disease in patients with locally advanced disease, as it relates to tailoring appropriate treatment and providing more accurate prognostic estimates to patients, cannot be underestimated. The de novo metastatic disease rate of 4.6% underscores the importance of staging imaging, especially within the setting of a neoadjuvant chemotherapy trial. The rate in I-SPY2 is lower than previously reported rates of 15% to 40% in patients with stage II–III disease,^{2–4,6–8,13} which may be

Table 4. Time From Diagnosis to Initiation of Neoadjuvant Chemotherapy and Initial Staging Procedure to Determination of FP

	n ^a	Days From Diagnosis to Initiation of Neoadjuvant Chemotherapy		P Value
		Mean (Range)	Median	
Imaging modality				<.0001
PET/CT	227	37.5 (12–100)	35	
SoC	194	44.3 (14–112)	42.5	
Site ^b				<.0001
GU	42	41 (19–73)	38.5	
UAB	127	45.6 (14–112)	44	
UMinn	40	36.8 (20–97)	35	
UCSF	212	38.4 (12–100)	36	
FP				.01174
Yes	75	44.6 (21–97)	45	
No	346	39.8 (12–112)	37	
	n ^c	Days From Initial Staging Procedure to Determination of FP		P Value
		Mean (Range)	Median	
Imaging modality				>.05
PET/CT	32	8.1 (1–33)	8.5	
SoC	56	11.3 (0–40)	9.0	

Abbreviations: FP, false-positive; GU, Georgetown University; SoC, standard of care; UAB, University of Alabama at Birmingham; UCSF, University of California, San Francisco; UMinn, University of Minnesota.

^aData were available for 421 patients from the primary analysis who had started treatment on the clinical trial.

^bP value from 1-way ANOVA.

^cData were available for 88 FP results.

due to selection bias for patients deemed fit for an intensive clinical trial, those without clinical suspicion of metastases, and those who may have had imaging performed at an outside institution to rule out distant metastases before referral to the trial.

Reducing FPs is of great value to patients, because FPs cause significant anxiety.^{33–35} Our study corroborated the superior specificity of PET/CT shown previously,^{5,13,36} with an FP incidence rate half that of SoC. We showed

further that FPs were resolved after approximately 11 days. This wait time creates significant anxiety for patients, who must cope with the possibility of having distant metastatic disease. FPs also may contribute to delays in starting chemotherapy, which can be detrimental to patients at high risk of recurrence,³⁷ such as those enrolled in I-SPY2. Patients who underwent PET/CT started chemotherapy 6.8 days sooner than those who underwent SoC, after controlling for study site. This likely was due, at least in

Table 5. Comparison of Total Costs by SoC Versus PET/CT Nationally and at UCSF

	Aggregate Cost Analysis of the 4 Cancer Centers		Cost Analysis at UCSF Using Medicare Reimbursements		Cost Analysis at UCSF Using Commercial Private Payer Reimbursements	
	SoC (n=231)	PET/CT (n=298)	SoC (n=35)	PET/CT (n=222) ^a	SoC (n=35)	PET/CT (n=223) ^b
Mean cost per patient	\$1,132	\$1,476	\$1,236	\$1,073	\$3,083	\$1,656
Mean increase over baseline cost because of FP workup	\$216 (23.6%)	\$65 (4.6%)	\$273 (28.3%)	\$55 (5.4%)	\$404 (15.1%)	\$132 (8.7%)
ICER	\$31		–\$15		–\$130	

Abbreviations: FP, false-positive; ICER, incremental cost-effectiveness ratio; SoC, standard of care; UCSF, University of California, San Francisco.

^aFour patients were excluded from the cost analysis because they had FP workup corresponding to CPT codes for which there was no available reimbursement data.

^bThree patients were excluded from the cost analysis because they had FP workup corresponding to CPT codes for which there was no available reimbursement data.

part, to the relative reduction in FPs for patients who underwent PET/CT, leading to fewer follow-up studies or confirmatory biopsies required. Furthermore, SoC can require scheduling of up to 3 separate appointments, which may have contributed to delays in baseline imaging for some patients. Given the authorization process that is currently often required before scheduling PET/CT, patients undergoing PET/CT might start treatment even sooner if this imaging was endorsed by guidelines and uniformly covered by insurance. However, the impact of institutional difference on timing in our study should not be understated. Future studies with larger numbers comparing imaging type within a single institution may be helpful.

Our study also highlighted financial toxicity associated with FP workup. Using national Medicare estimates, FP workup after SoC resulted in a greater percentage increase over baseline imaging cost than did FP workup after PET/CT. In addition, 11.3% of patients who received SoC subsequently underwent PET/CT as part of FP workup. Although the mean cost per patient after taking into account FP workup costs was still greater for patients who received PET/CT imaging (using national Medicare averages), the ICER of \$31 for each percent patient who avoided an FP likely supports PET/CT as cost-effective in this setting.

Hospitals can price imaging studies to make PET/CT more competitive with SoC. If the price of PET/CT were the same as SoC in our aggregate cost analysis using national Medicare averages, the ICER would be $-\$14$ and result in cost savings. Were this pricing policy instated, insurers might be more likely to reimburse PET/CT. SoC has been shown in multiple settings to be less sensitive and specific, yet remains mandated by insurance coverage, resulting in more appointments, FPs, patient anxiety, and possible delays to treatment.

When PET/CT was originally introduced, it was priced higher than SoC, but for at least the past 3 years, PET/CT has been priced lower at UCSF. Investigators worked with hospital administrators to ensure that pricing policy would not prohibit the use of more the patient-centered PET/CT approach. When using real estimates from Medicare and a large commercial private payer at UCSF where these pricing changes have been instituted, there were cost savings of \$15 and \$130 for each percent of patients who avoided an FP, respectively.

Our study had limitations. First, we could not determine FP rates between PET/CT and SoC given the retrospective nature of this study and incomplete data from follow-up scans. A prospective, randomized study in which patients undergo both imaging tests at baseline might be informative. Second, the aggregate cost analysis

was based on national Medicare averages, which may overestimate or underestimate costs given local and regional reimbursement differences. Third, patients were screened for an intensive clinical trial at academic centers, where patients and procedures are carefully coordinated and monitored, affecting the generalizability of our results. Fourth, 4 patients excluded from the Medicare cost analysis and 3 patients excluded from the private payer cost analysis at UCSF due to unavailable reimbursement data were all among the PET/CT group. Although this was likely negligible given the relatively lower FP workup cost compared with baseline imaging cost, this may have overestimated the savings of using PET/CT. Fifth, although resolution of FPs is mandated before patients are randomized in I-SPY2, review of imaging results and decisions to workup incidental findings were likely variable at different sites. Nonetheless, these data provided insight into real-time practice variation and its consequences.

Conclusions

Greater awareness is needed regarding the impact of staging on patients, variation in cost, and ability to set price at the institutional level to keep PET/CT competitive with SoC. These data support reassessment of guidelines so that patients with stage II–III breast cancer, especially those with molecularly high-risk disease, can access PET/CT for staging. We suggest that institutions set PET/CT prices to be equivalent to or lower than those of SoC to encourage the use of PET/CT. We also suggest that Medicare and private payer reimbursement policies be reevaluated with this consideration in mind.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2. Lebon V, Alberini JL, Pierga JY, et al. Rate of distant metastases on 18F-FDG PET/CT at initial staging of breast cancer: comparison of women younger and older than 40 years. *J Nucl Med* 2017;58:252–257.
3. Groheux D, Hindié E, Delord M, et al. Prognostic impact of (18)F-FDG-PET-CT findings in clinical stage III and IIB breast cancer. *J Natl Cancer Inst* 2012;104:1879–1887.
4. Riedl CC, Slobod E, Jochelson M, et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. *J Nucl Med* 2014;55:1578–1583.
5. Groheux D, Cochet A, Humbert O, et al. ¹⁸F-FDG PET/CT for staging and restaging of breast cancer. *J Nucl Med* 2016;57(Suppl 1):17S–26S.
6. Aliyev A, Yilmaz Aksoy S, Özhan M, et al. The role of FDG PET/CT in detection of distant metastasis in the initial staging of breast cancer. *Turk J Med Sci* 2016;46:349–360.
7. Nursal GN, Nursal TZ, Aytac HO, et al. Is PET/CT necessary in the management of early breast cancer? *Clin Nucl Med* 2016;41:362–365.
8. Ulaner GA, Castillo R, Goldman DA, et al. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. *Eur J Nucl Med Mol Imaging* 2016;43:1937–1944.
9. Lei L, Wang X, Chen Z. PET/CT imaging for monitoring recurrence and evaluating response to treatment in breast cancer. *Adv Clin Exp Med* 2016;25:377–382.
10. Groheux D, Giachetti S, Delord M, et al. 18F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. *J Nucl Med* 2013;54:5–11.
11. Jeong YJ, Kang DY, Yoon HJ, et al. Additional value of F-18 FDG PET/CT for initial staging in breast cancer with clinically negative axillary nodes. *Breast Cancer Res Treat* 2014;145:137–142.
12. Cooper KL, Harman S, Meng Y, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 2011;37:187–198.
13. Groheux D, Moretti JL, Baillet G, et al. Effect of (18)F-FDG PET/CT imaging in patients with clinical stage II and III breast cancer. *Int J Radiat Oncol Biol Phys* 2008;71:695–704.
14. Fuster D, Duch J, Paredes P, et al. Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. *J Clin Oncol* 2008;26:4746–4751.
15. Segar I, Mottaghy F, Ceyssens S, et al. Additional value of PET-CT in staging of clinical stage IIB and III breast cancer. *Breast J* 2010;16:617–624.
16. Koolen BB, Vrancken Peeters MJ, Aukema TS, et al. 18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. *Breast Cancer Res Treat* 2012;131:117–126.
17. Cochet A, Dygai-Cochet I, Riedinger JM, et al. ¹⁸F-FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. *Eur J Nucl Med Mol Imaging* 2014;41:428–437.
18. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2017. Accessed August 31, 2020. To view the most recent version, visit NCCN.org
19. Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. *Ann Thorac Surg* 1998;66:1876–1883, discussion 1883–1885.
20. Buck AK, Herrmann K, Stargardt T, et al. Economic evaluation of PET and PET/CT in oncology: evidence and methodologic approaches. *J Nucl Med Technol* 2010;38:6–17.
21. Langer A. A systematic review of PET and PET/CT in oncology: a way to personalize cancer treatment in a cost-effective manner? *BMC Health Serv Res* 2010;10:283.
22. Schreyögg J, Weller J, Stargardt T, et al. Cost-effectiveness of hybrid PET/CT for staging of non-small cell lung cancer. *J Nucl Med* 2010;51:1668–1675.
23. Annunziata S, Caldarella C, Treglia G. Cost-effectiveness of fluorine-18-fluorodeoxyglucose positron emission tomography in tumours other than lung cancer: a systematic review. *World J Radiol* 2014;6:48–55.
24. Miquel-Cases A, Teixeira S, Retèl V, et al. Cost-effectiveness of 18f-FDG PET/CT for screening distant metastasis in stage II/III breast cancer patients of the UK, the United States and the Netherlands [abstract]. *Value Health* 2015;18:Abstract MD4.
25. Rugo HS, Olopade OL, DeMichele A, et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. *N Engl J Med* 2016;375:23–34.
26. Park JW, Liu MC, Yee D, et al. Adaptive randomization of neratinib in early breast cancer. *N Engl J Med* 2016;375:11–22.
27. Centers for Medicare & Medicaid Services. Physician fee schedule search. Updated October 2, 2020. Accessed November 1, 2018. Available at: <https://www.cms.gov/apps/physician-fee-schedule>
28. Deficit Reduction Act of 2005. Pub L No. 109-171, 120 Stat 4.
29. American College of Radiology. Radiation dose to adults from common imaging examinations. Accessed August 31, 2020. Available at: <https://www.acr.org/-/media/ACR/Files/Radiology-Safety/Radiation-Safety/Dose-Reference-Card.pdf>
30. Salvatori M, Oradei M. Economic evaluation of nuclear medicine procedures. *Eur J Nucl Med Mol Imaging* 2010;37:1786–1792.
31. Graham MM. Cost-effectiveness of medical imaging. *Lancet Oncol* 2009;10:744–745.
32. Henry NL, Braun TM, Breslin TM, et al. Variation in the use of advanced imaging at the time of breast cancer diagnosis in a statewide registry. *Cancer* 2017;123:2975–2983.
33. Spiegel TN, Esplen MJ, Hill KA, et al. Psychological impact of recall on women with BRCA mutations undergoing MRI surveillance. *Breast* 2011;20:424–430.
34. Nelson HD, Pappas M, Cantor A, et al. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive Services Task Force Recommendation. *Ann Intern Med* 2016;164:256–267.
35. Wardle FJ, Collins W, Pernet AL, et al. Psychological impact of screening for familial ovarian cancer. *J Natl Cancer Inst* 1993;85:653–657.
36. Niikura N, Costelloe CM, Madewell JE, et al. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. *Oncologist* 2011;16:1111–1119.
37. de Melo Gagliato D, Gonzalez-Angulo AM, Lei X, et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *J Clin Oncol* 2014;32:735–744.

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Use of ^{18}F -FDG PET/CT as an Initial Staging Procedure for Stage II–III Breast Cancer: A Multicenter Value Analysis

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eTable 1: HCPCS/CPT Codes Used to Derive Costs for Baseline Staging Studies and False-Positive Workup Studies

eTable 1. HCPCS/CPT Codes Used to Derive Costs for Baseline Staging Studies and FP Workup Studies

Procedure	Code
Baseline staging studies	
Bone scan	78306
CT chest	71270
CT abdomen/pelvis	74178
PET/CT	78815
FP workup studies	
Ultrasound, thyroid	76536
FNA, thyroid	10022
Biopsy, thyroid	60100
Ultrasound, groin	77882
MRI, thorax	72157
MRI, lumbar	72158
Ultrasound, pelvic/transvaginal	76856, 76830
MRI, pelvis	72197
MRI, brain	70553
MRI, abdomen	74183
MRI, chest	71552
MRI, humerus	73218
Biopsy, endometrium	58100
Colonoscopy/Polypectomy	45384, 45378
Upper endoscopy	43239
Ultrasound-guided biopsy, parotid gland	42400, 76942
CT-guided biopsy, lung	32405, 77012
CT-guided biopsy, liver	77012, 47000
Ultrasound, abdomen	76700, 76705
Ultrasound-guided biopsy, liver	76942, 47000
CT-guided biopsy, kidney	77012, 50200
Ultrasound, kidney	76770
Hysteroscopy with dilation and curettage	00952, 58558
Ultrasound-guided dilation and curettage	76856
Biopsy, cervix	57500
Biopsy, transthoracic	32405
Ultrasound, transbronchial	31628
Biopsy, lymph node	38505
Radiograph, L-spine	72100
Radiograph, T-spine	72072
Radiograph, pelvis	72170
Radiograph, sternoclavicular region	71130
Radiograph, shoulders	73030
Moderate sedation	99156, 99157
Pathology evaluation	88173, 88305, 88307
PET/CT	78815

Abbreviations: FNA, fine-needle aspiration; FP, false-positive.