° PET/CT in breast cancer staging

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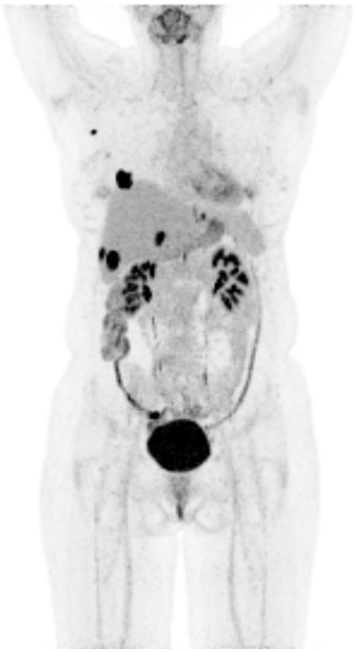
18F-FDG PET/CT for breast cancer staging

- Where is the clinical impact?
- To which women should 18F-FDG PET/CT be offered?



The population is large and increasing

Breast cancer is the most common cancer and the 2. leading cause of cancer death among women

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2016 Estimates

Estimated New Cases		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 180,890 (21%)	Breast 246,660 (29%)	Lung & bronchus 85,920 (27%)	Lung & bronchus 72,160 (26%)
Lung & bronchus 117,920 (14%)	Lung & bronchus 106,470 (13%)	Prostate 26,120 (8%)	Breast 40,450 (14%)
Colon & rectum 70,820 (8%)	Colon & rectum 63,670 (8%)	Colon & rectum 26,020 (8%)	Colon & rectum 23,170 (8%)
Urinary bladder 58,950 (7%)	Uterine corpus 60,050 (7%)	Pancreas 21,450 (7%)	Pancreas 20,330 (7%)
Melanoma of the skin 46,870 (6%)	Thyroid 49,350 (6%)	Liver & intrahepatic bile duct 18,280 (6%)	Ovary 14,240 (5%)
Non-Hodgkin lymphoma 40,170 (5%)	Non-Hodgkin lymphoma 32,410 (4%)	Leukemia 14,130 (4%)	Uterine corpus 10,470 (4%)
Kidney & renal pelvis 39,650 (5%)	Melanoma of the skin 29,510 (3%)	Esophagus 12,720 (4%)	Leukemia 10,270 (4%)
Oral cavity & pharynx 34,780 (4%)	Leukemia 26,050 (3%)	Urinary bladder 11,820 (4%)	Liver & intrahepatic bile duct 8,890 (3%)
Leukemia 34,090 (4%)	Pancreas 25,400 (3%)	Non-Hodgkin lymphoma 11,520 (4%)	Non-Hodgkin lymphoma 8,630 (3%)
Liver & intrahepatic bile duct 28,410 (3%)	Kidney & renal pelvis 23,050 (3%)	Brain & other nervous system 9,440 (3%)	Brain & other nervous system 6,610 (2%)
All sites 841,390 (100%)	All sites 843,820 (100%)	All sites 314,290 (100%)	All sites 281,400 (100%)

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Survival rate depends on stage and progression

Table 8. Five-year Relative Survival Rates* (%) by Stage at Diagnosis, US, 2005-2011

	All stages	Local	Regional	Distant		All stages	Local	Regional	Distant
Breast (female)	89	99	85	26	Ovary	46	92	73	28
Colon & rectum	65	90	71	13	Pancreas	7	27	11	2
Esophagus	18	40	22	4	Prostate	99	>99	>99	28
Kidney†	73	92	65	12	Stomach	29	65	30	5
Larynx	61	76	45	35	Testis	95	99	96	74
Liver‡	17	31	11	3	Thyroid	98	>99	98	54
Lung & bronchus	17	55	27	4	Urinary bladder§	77	70	34	5
Melanoma of the skin	92	98	63	17	Uterine cervix	68	92	57	17
Oral cavity & pharynx	63	83	62	38	Uterine corpus	82	95	68	17

*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER website April 2015.

American Cancer Society, Inc., Surveillance Research, 2016

Survival rate is decreased in young women

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Breast Cancer Before Age 40 Years

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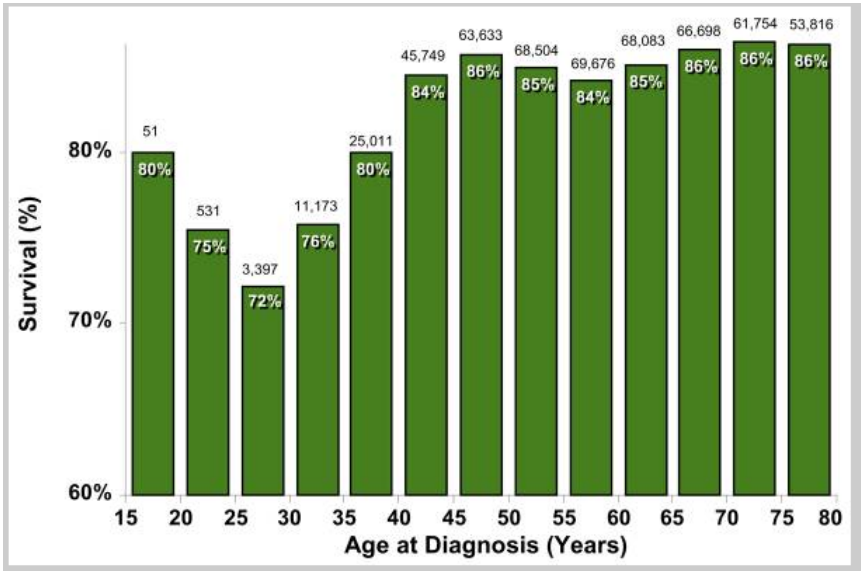
Abstract

Approximately 7% of women with breast cancer are diagnosed before the age of 40 years, and this disease accounts for more than 40% of all cancer in women in this age group. Survival rates are worse when compared to those in older women, and multivariate analysis has shown younger age to be an independent predictor of adverse outcome. Inherited syndromes, specifically *BRCA1* and *BRCA2*, must be considered when developing treatment algorithms for younger women. Chemotherapy, endocrine, and local therapies have the potential to significantly impact both the physiologic health —including future fertility, premature menopause, and bone health—and the psychological health of young women as they face a diagnosis of breast cancer.



The numbers above the bars designate the number of patients with breast cancer in the SEER17 registry for 2000-2005

Increasing request for PET/CT scans in routine clinical practice

FROM:
Imaging tests in staging and surveillance of non-metastatic breast cancer: changes in routine clinical practice and cost implications
S De Placido, C De Angelis, M Giuliano, C Pizzi, R Ruocco, V Perrone, D Bruzzese, G Tommasielli, M De Laurentiis, S Cammarota, G Arpino and G Arpino

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Table 2. Imaging test prescriptions per year

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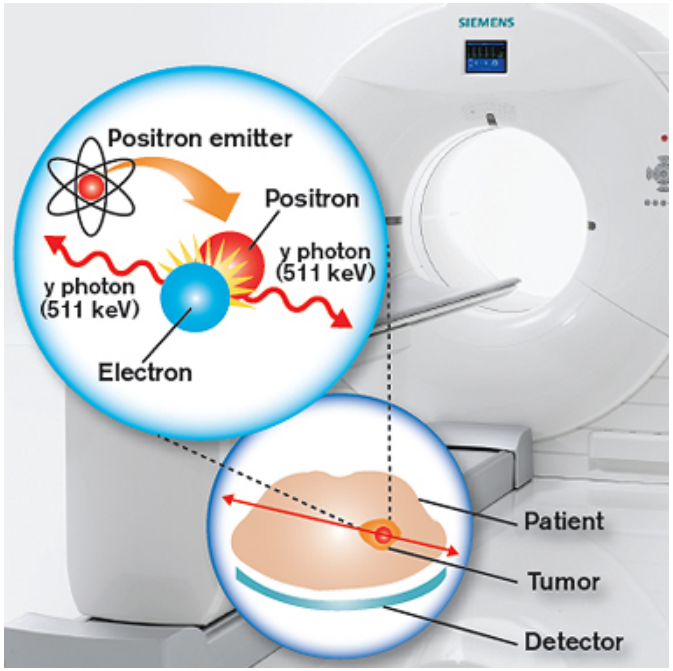
	Year of diagnosis (No of tests per 100 patients)										
Imaging test	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Annual increase % (95% CI)**
Routine											
Chest radiograph	100.5	112.2	122.0	114.1	110.4	110.2	94.6	107.4	117.2	95.2	−0.8 (−1.8 to 0.2)
Abdominal ultrasound	117.1	120.3	140.5	134.6	127.2	135.8	125.1	142.9	152.9	135.7	1.9 (1.0 to 2.9)
Bone scan	73.1	76.3	84.5	80.2	80.0	82.7	77.4	88.6	96.0	90.1	2.2 (1.0 to 3.4)
Mammograms	87.9	90.2	89.1	91.4	86.8	90.4	88.6	88.2	87.7	77.5	−0.6 (−1.8 to 0.5)
Total	378.6	399.0	436.1	420.3	404.3	419.1	385.7	427.1	453.7	398.5	0.1 (−0.1 to 0.3)
New											
CT	23.9	34.4	35.0	33.5	39.1	45.5	39.8	55.5	72.8	74.7	11.9 (10.0 to 13.8)
PET	0.7	2.4	4.6	7.0	9.3	7.9	11.4	17.4	22.3	22.2	29.8 (25.0 to 34.7)
MRI	5.9	4.1	7.2	6.1	9.5	6.9	9.5	12.6	7.4	14.1	9.0 (4.9 to 13.3)
Breast MRI	0.5	1.0	2.5	3.0	5.7	4.8	7.2	10.8	13.0	13.2	32.9 (26.3 to 39.9)
Total	32.3	43.5	49.8	50.4	65.0	68.2	69.6	101.4	120.0	128.9	15.7 (14.2 to 17.2)

Abbreviations: CT=computerised tomography; MRI=magnetic resonance imaging; PET=positron emission tomography.

Data from South Italy, published in *British Journal of Cancer* (2017) **116**, 821–827

PET/CT skanning



PET Radiopharmaceuticals

Nuclide	*Half-life*	*Tracer*	*Application*
O-15	2 mins	Water	Cerebral blood flow
C-11	20 mins	Methionine	Tumour protein synthesis
N-13	10 mins	Ammonia	Myocardial blood flow
F-18	110 mins	FDG	Glucose metabolism
Ga-68	68 min	DOTANOC	Neuroendocrine imaging
Rb-82	72 secs	Rb-82	Myocardial perfusion

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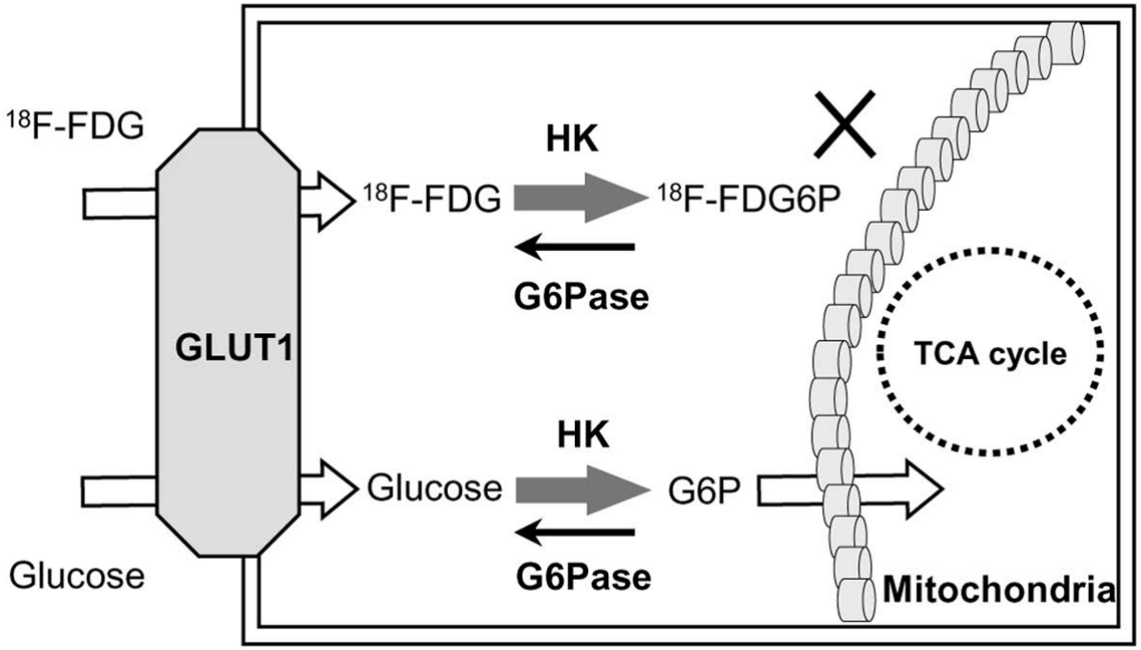
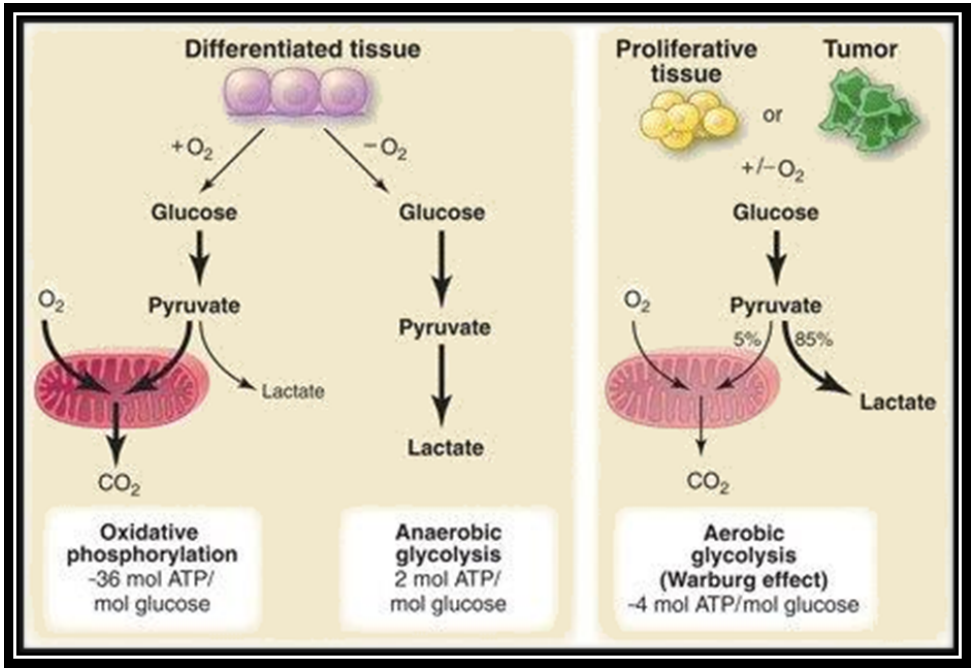
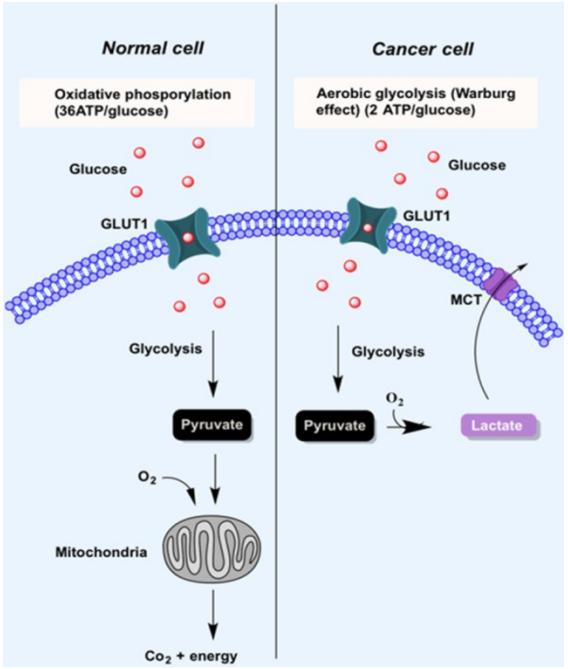
18F-FDG is a glucose-analog

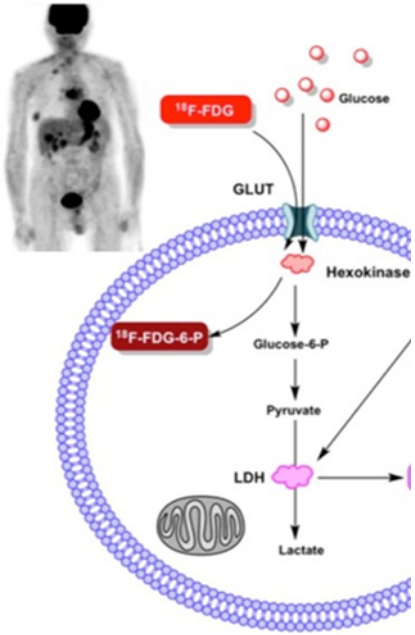


Glucose metabolism and Warburg effect

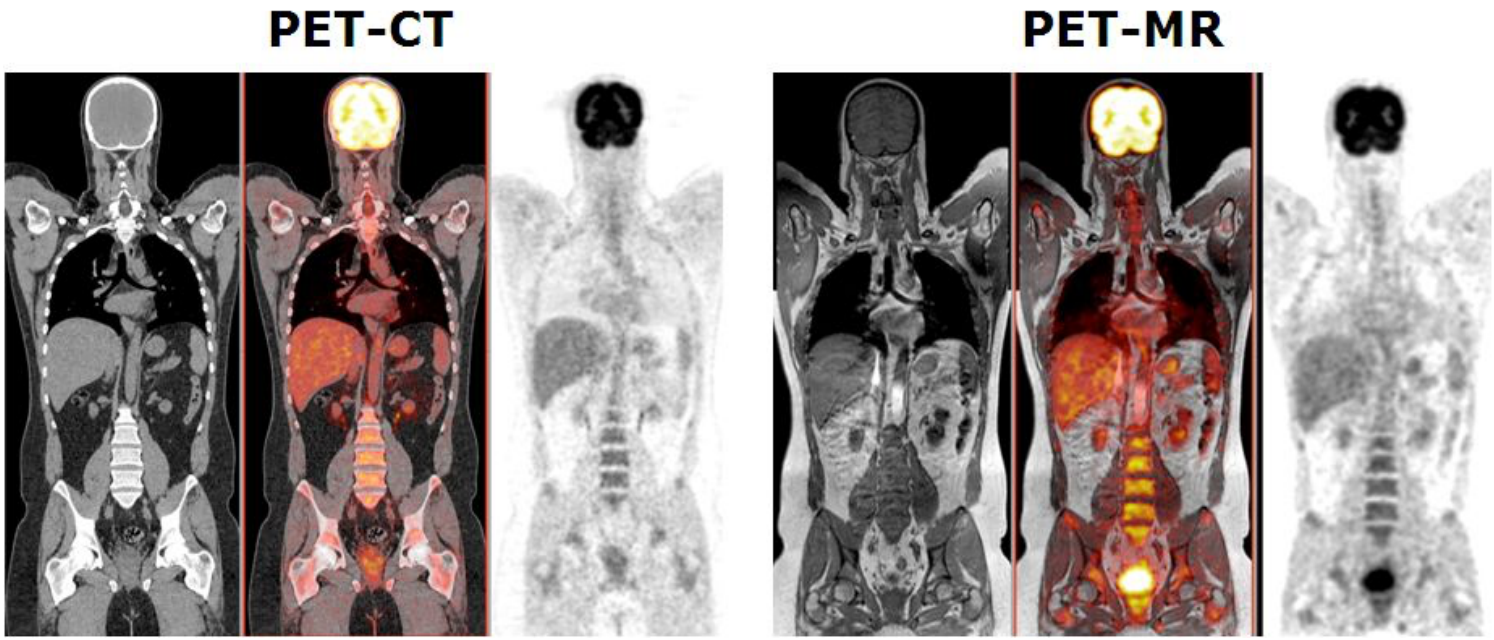


The Warburg effect and 18F-FDG



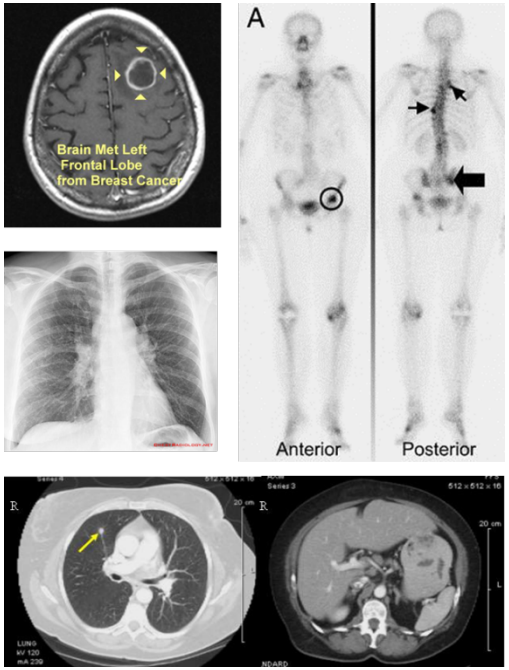


Hybrid imaging provide combined anatomical-metabolic image information

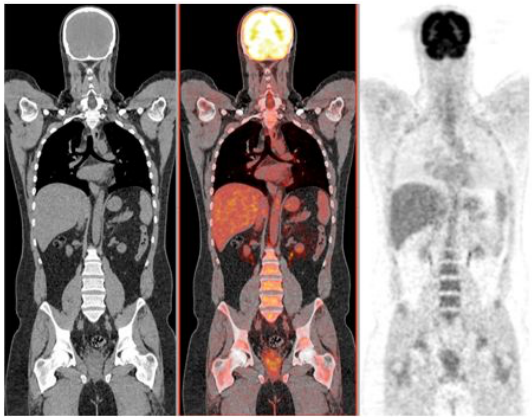


18F-FDG PET/CT allows the examination of extraaxillary nodes, chest, abdomen and bone in a single session

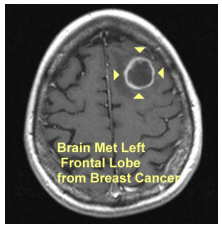
Conventional imaging



18F-FDG PET/CT



MRI brain



18F-FDG PET/CT for BC staging
Where is the clinical impact?

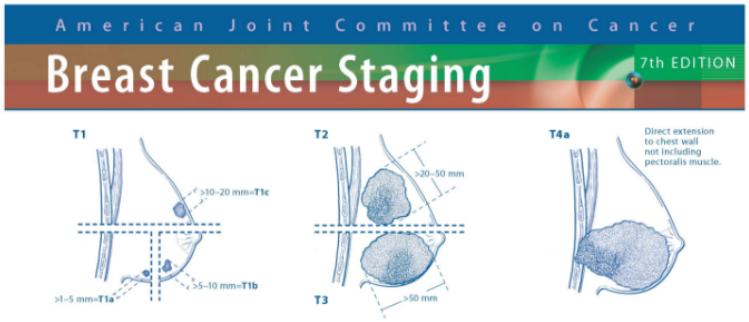


TABLE 1
TNM Clinical Stage Grouping for Breast Cancer*

AJCC	TNM			NCCN
Stage I	T1	N0	M0	Primary operable breast cancer
Stage IIA	T0	N1	M0	Primary operable breast cancer
	T1	N1	M0	Primary operable breast cancer
	T2	N0	M0	Primary operable breast cancer
Stage IIB	T2	N1	M0	Primary operable breast cancer
	T3	N0	M0	Primary operable breast cancer
Stage IIIA	T3	N1	M0	Primary operable breast cancer
	T0	N2	M0	Locally advanced breast cancer
	T1	N2	M0	Locally advanced breast cancer
	T2	N2	M0	Locally advanced breast cancer
	T3	N2	M0	Locally advanced breast cancer
Stage IIIB	T4	N0	M0	Locally advanced breast cancer
	T4	N1	M0	Locally advanced breast cancer
	T4	N2	M0	Locally advanced breast cancer
Stage IIIC	Any T	N3	M0	Locally advanced breast cancer
Stage IV	Any T	Any N	M1	Metastatic disease

*According to 7th edition of *AJCC Cancer Staging Manual* (6).

Groheux D et al. J Nucl Med 2016; 57: 17S-26S

18F-FDG PET/CT is not recommended for the initial assessment of patients with T1N0

- Sentinel node superior for assessing axillary lymph node involvement
- Risk of distant metastases in early stage cases is low

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Stage IIA	T0	N1	M0	Primary operable breast cancer
	T1	N1	M0	Primary operable breast cancer
	T2	N0	M0	Primary operable breast cancer
Stage IIB	T2	N1	M0	Primary operable breast cancer
	T3	N0	M0	Primary operable breast cancer
Stage IIIA	T3	N1	M0	Primary operable breast cancer
	T0	N2	M0	Locally advanced breast cancer
	T1	N2	M0	Locally advanced breast cancer
	T2	N2	M0	Locally advanced breast cancer
	T3	N2	M0	Locally advanced breast cancer
Stage IIIB	T4	N0	M0	Locally advanced breast cancer
	T4	N1	M0	Locally advanced breast cancer
	T4	N2	M0	Locally advanced breast cancer
Stage IIIC	Any T	N3	M0	Locally advanced breast cancer
Stage IV	Any T	Any N	M1	Metastatic disease

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18F-FDG PET/CT is useful for staging of LABC*

- Accurate staging is important for management decisions (neoadjuvant chemo+surgery+RT vs systemic chemotherapy)
- LABC is associated with high risk of metastases
- 18F-FDG PET/CT may advantageously replace conventional imaging methods
- Baseline for response evaluation
- *no clear definition of LABC (large tumors, skin involvement, multiple local LN, inflammatory)

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Stage IIIA	T3	N1	M0	Primary operable breast cancer
	T0	N2	M0	Locally advanced breast cancer
	T1	N2	M0	Locally advanced breast cancer
	T2	N2	M0	Locally advanced breast cancer
	T3	N2	M0	Locally advanced breast cancer
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18F-FDG PET/CT may advantageously replace conventional imaging methods for staging in LABC patients

Groheux D et al. J Nucl Med 2013;54: 5-11

Prospective study, 117 LABC patients

Conventional imaging (bone scintigraphy, x-ray/CT chest, CT/US abdomen) compared with 18F-FDG PET/CT

Distant metastases were found in 43 patienter with PET/CT and 28 patienter with conventional imaging

At which clinical stage should 18F-FDG PET/CT be initiated?

Increasing evidence for substantial yield in stage IIB and IIIA

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Groheux D et al. J Nucl Med 2016; 57: 17S-26S

Studies evaluating 18F-FDG PET/CT for baseline staging of clinical stage II or III

TABLE 2
Studies Evaluating ^{18}F-FDG PET/CT for Baseline Staging of Clinical Stage II or III Breast Cancer*

Study	Year	Type of study	Patient recruitment	No. of patients	Conventional imaging (CI)	Results of PET/CT examination (compared with those of CI)	Reference for diagnosis	Conclusion of study
Fuster et al. (14)	2008	P	Noninflammatory large BC (≥3 cm)	60	Breast MRI, chest CT, liver US, BS	Sensitivity and specificity to detect LN involvement were 70% and 100%, respectively	Histopathologic confirmation or ≥1 y of follow-up	PET/CT accurately detected unsuspected extraaxillary LN involvement and distant metastases
						Sensitivity and specificity to detect metastases were 100% and 98%, respectively (vs. 60% and 83%, respectively, for CI)		PET/CT accurately ruled out false-positive distant metastases on CI
						Change of BC staging in 42% of patients		
Segaert et al. (16)	2010	R	Clinical stage IIB or III BC	70	Chest radiography, liver US, BS	Sensitivity and specificity to detect axillary LN involvement were 62.5% and 100%, respectively (vs. 87.5% and 100%, respectively, for CI)	Histopathologic confirmation or clinical or imaging follow-up	For LABC, PET/CT was superior to CI for detecting internal mammary-chain nodes and metastatic disease but not for axillary staging
						Sensitivity to detect internal mammary LN involvement was 100%		
						7 patients were identified as having distant metastases despite normal CI results		
Koolen et al. (17)	2012	P	Clinical stage II or III BC	154	Chest radiography, liver US, BS	Correct stage IV upstaging in 13% of patients	Histopathologic confirmation or additional imaging or follow-up	PET/CT outperformed CI in detection of distant metastases
						Incorrect stage IV upstaging in 3% of patients		
						Change of BC therapeutic management in 8% of patients		
Groheux et al. (18)	2012	P	Clinical stage II or III BC	254	Mammography, breast + axilla US, breast MRI ± additional directed radiologic studies	Change of clinical stage in 30% of patients	Histologic confirmation or directed radiologic studies + patient follow-up	Yield of PET/CT in staging of BC was substantial in patients with clinical stage IIB BC or higher
						Upstaging to stage IV in 2% of stage IIA, 11% of stage IIB, 17% of stage IIIA, 36% of stage IIIB, and 47% of clinical stage IIIC BC patients		PET/CT provided powerful prognostic stratification of patients
						Status of M stage on PET/CT and TNBC phenotype were independent predictors of worst survival		

TABLE 2 (Continued)

Study	Year	Type of study	Patient recruitment	No. of patients	Conventional imaging (CI)	Results of PET/CT examination (compared with those of CI)	Reference for diagnosis	Conclusion of study
Cochet et al. (19)	2014	P	BC ≥ 2 cm	142	Mammography, breast + chest US ± breast MRI, chest radiography, abdominal US, BS ± abdominal or chest CT	Upstaging in 30% of patients (to stage IV in 8%)	Histopathologic confirmation or additional imaging + patient follow-up	BC staging with PET/CT more accurately stratified prognostic risk than did CI
						Downstaging in 16% of patients		
						Change of BC therapeutic management in 13% of patients		
						Stronger prognostic stratification than CI ($P < 0.0001$)		
Riedl et al. (20)	2014	R	≤40 y old with clinical stage I–IIIC BC	134	Mammography, breast US ± breast MRI	Unsuspected extraaxillary LN involvement in 11% of women	Histologic confirmation for patients with upstaging	PET/CT was valuable for baseline staging in young patients with asymptomatic stage IIB and III BC
						Unsuspected metastasis in 15% of women		
						Upstaging to stage IV in 5% of stage I + IIA, 17% of stage IIB, 31% of stage IIIA, and 50% of stage IIIB + IIIC BC patients		
Krammer et al. (21)	2015	P	T ≥ T2 or positive LN	101	Mammography, breast + chest US ± breast MRI, chest radiography, abdominal US, BS	Upgrading of N or M stage in 19% of patients	Histopathologic confirmation or additional imaging or follow-up	Compared with CI, PET/CT had relevant impact on baseline staging and therapeutic management of BC
						Change of BC therapeutic management in 11% of patients		

*In the case of several reports by the same team, study with largest number of patients was selected. Studies with only inflammatory breast cancer were not included.
P = prospective; BC = breast cancer; US = ultrasonography; BS = bone scintigraphy; LN = lymph node; R = retrospective.

Groheux D et al. J Nucl Med 2016; 57: 17S-26S

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						Downstaging in 16% of patients		
						Change of BC therapeutic management in 13% of patients		
						Stronger prognostic stratification than CI ($P < 0.0001$)		
Riedl et al. (20)	2014	R	≤40 y old with clinical stage I–IIIC BC	134	Mammography, breast US ± breast MRI	Unsuspected extraaxillary LN involvement in 11% of women	Histologic confirmation for patients with upstaging	PET/CT was valuable for baseline staging in young patients with asymptomatic stage IIB and III BC
						Unsuspected metastasis in 15% of women		
						Upstaging to stage IV in 5% of stage I + IIA, 17% of stage IIB, 31% of stage IIIA, and 50% of stage IIIB + IIIC BC patients		
Krammer et al. (21)	2015	P	T ≥ T2 or positive LN	101	Mammography, breast + chest US ± breast MRI, chest radiography, abdominal US, BS	Upgrading of N or M stage in 19% of patients	Histopathologic confirmation or additional imaging or follow-up	Compared with CI, PET/CT had relevant impact on baseline staging and therapeutic management of BC
						Change of BC therapeutic management in 11% of patients		

*In the case of several reports by the same team, study with largest number of patients was selected. Studies with only inflammatory breast cancer were not included.
P = prospective; BC = breast cancer; US = ultrasonography; BS = bone scintigraphy; LN = lymph node; R = retrospective.

Groheux D et al. J Nucl Med 2016; 57: 17S-26S

Stage IIB and IIIA

Prospective study of 254 patients with clinical stage II or III

Conventional imaging: mammography, US, breast MRI, ± additional directed radiological studies

18F-FDG PET/CT

Histologic confirmation or directed radiologic studies + patient follow up

PET/CT changed clinical stage in 77 patients (30%)

PET/CT identified unknown N3 lymph node metastases in 40 patients

PET/CT led to upstaging to stage IV in 2,3 % of stage IIA (1 of 44), 10,7 % of stage IIB (6 of 56), 17,5 % of stage IIIA (11 of 63), 36,5% of stage IIIB (27 of 74), and 47,1% of stage IIIC (8 of 17)

Groheux D et al, J Natl Cancer Inst. 2012;104: 1879–1887

PET-CT provided powerful prognostic stratification of patients

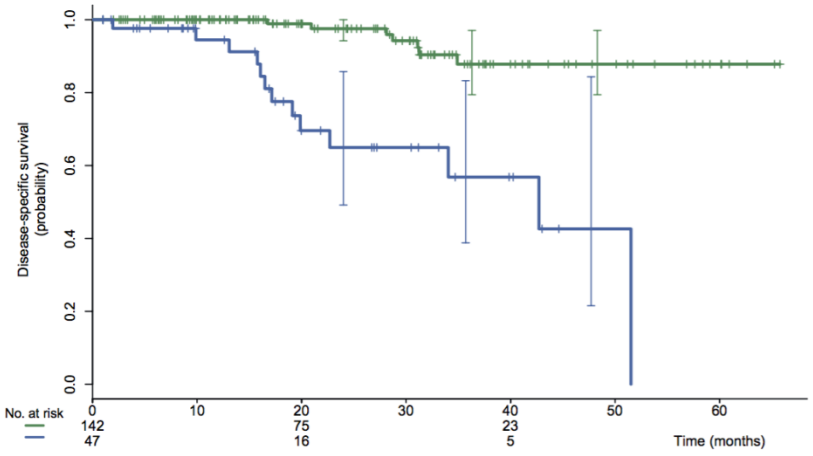


Figure 4. Kaplan–Meier disease-specific survival for 189 patients with clinical stages IIB, IIIA, IIIB, and IIIC disease and adequate follow-up. Comparison of patients with and without distant metastases on fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG-PET-CT). The upper curve (in green color online) shows patients without distant metastases (n = 142; events = 7). The lower curve (in blue color online) shows patients with distance metastases detected by PET-CT (n = 47; events = 13). Log-rank *P* less than .001.

Groheux D et al. J Natl Cancer Inst. 2012;104: 1879–1887

PET/CT and international guidelines

NCCN

- *Clinical stage IIIA; staging with chest CT, abdominopelvic CT or MRI, bone scan or sodium flouride PET. 18F-FDG PET/CT is optional.*
- *18F-FDG PET/CT may be helpful in identifying unsuspected regional node and/or distant metastasis in LABC*

NCCN Breast Cancer Version 2.2015 Clinical Practice Guidelines in Oncology; Gradishar WJ, Anderson BO et al. J Natl Compr Canc Netw 2015; 13(4): 448-474

ESMO

- 18F-FDG PET/CT may replace traditional imaging for initial staging in high-risk patients considered for neoadjuvant chemotherapy, LABC and/or inflammatory disease

Senkus E, Kyriakides S, et al on behalf of the ESMO Guidelines Committee, Annals of Oncology 26 (Suppl 5): v8-v30, 2015

Should tumor biology, histology and phenotype be considered for the use of 18F-FDG PET/CT for breast cancer staging?

- Invasive ductal carcinoma have higher FDG uptake than lobular
- SUVs are higher in tumors negative for hormone receptors
- High proportion of extra-skeletal metastases in TNBC and HER2-pos tumors (Groheux 2012)
- Positive correlation between FDG uptake and Ki-67 index
- Age may be independent prognostic factor

18F-FDG PET/CT for initial staging in patients < 40 years

Riedl C 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

Retrospective study of 134 patients < 40 years with newly diagnosed clinical stage I-IIIC BC

18F-FDG PET/CT for initial staging

PET/CT detected N3 lymph node metastases in 11% and distant metastases in 15%

8 of 34 patients with initial stage IIB were upstaged to stage IV (17%)

Rate of distant metastases on 18F-FDG PET/CT in young vs older patients

Lebon V et al. The rate of distant metastases on FDG-PET/CT at initial staging of breast cancer: Comparison between women younger and older than 40 Years. J Nucl Med 2017; 58: 252-257

Retrospective single-institution study of 107 patients < 40 years and 107 patients > 40 years with newly diagnosed clinical stage I-III BC and no clinical signs of metastatic disease

PET/CT detected distant metastases in 21% and 22% of patients <40 and ≥40 years, respectively

Demonstrating the high yield of 18F-FDG PET/CT for initial breast cancer staging , even in stage II, whatever their age

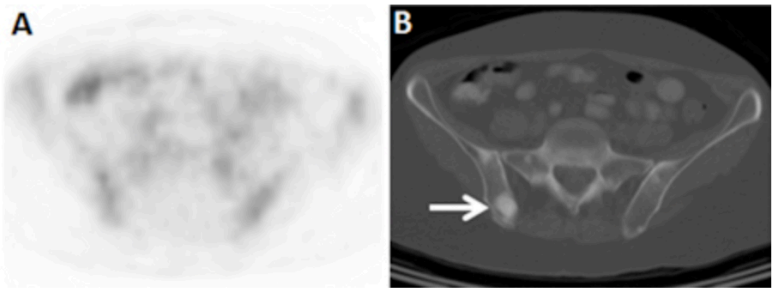
The utility of 18F-FDG PET/CT may not be as strong in lobular as in ductal carcinomas

Hogan MP et al. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med 2015; 56:1674–1680

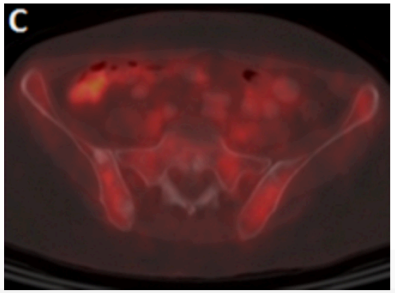
Retrospective study, 146 ILC and 146 IDC clinical stage III patients. Patient with IDC were more frequently upstaged to IV by PET/CT compared to patients with ILC

Dashevsky BZ et al. Appearance of untreated bone metastases from breast cancer on FDG PET/CT: importance of histologic subtype. EJNMMI 2015; 42:1666–1673

Retrospective study, 74 IDC, 13 ILC, 8 MDL. Bone metastases more often sclerotic and had lower SUVmax in ILC compared to IDC. Sclerotic bone metastases with no FDG uptake more frequent in ILC compared to IDC



A 56-year-old woman with initial stage III invasive lobular cancer is upstaged to stage IV based on the CT component of FDG-PET/CT. The axial FDG-PET image (A) does not demonstrate suspicious foci, but the axial CT component (B) shows multiple osseous sclerotic lesions, suspicious for metastases (solid arrow). Axial fused FDG-PET/CT (C) confirms that the osseous sclerotic lesions demonstrate background FDG-avidity. Biopsy confirmed an osseous metastasis. Images courtesy of Dr. Gary Ulaner and Dr. Molly Hogan.



Triple-negative BC

Ulaner GU et al, Castillo R, Goldman DA et al. 18F-FDG PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. EJNMMI 2016; 43:1937–1944

Retrospective study, 232 patients with TNBC, PET/CT for initial staging

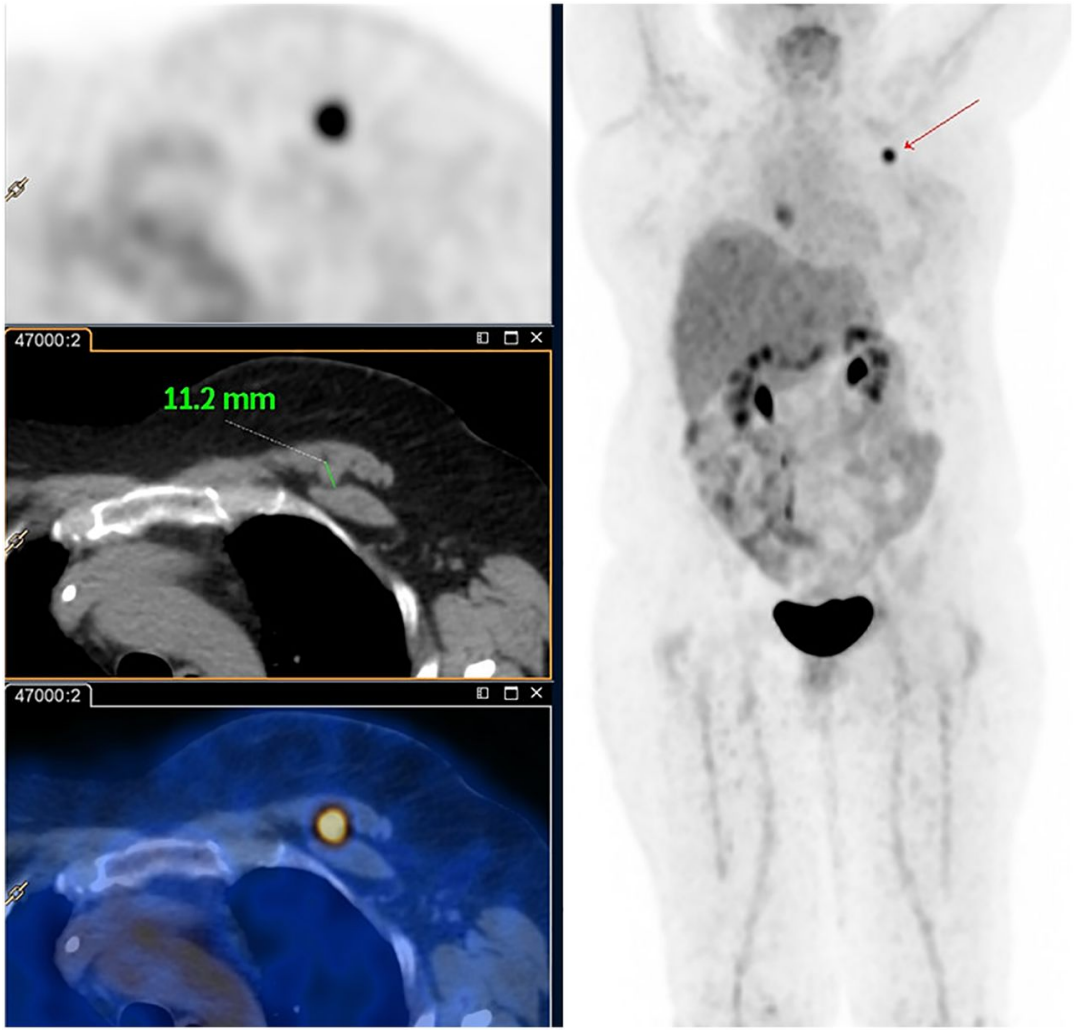
PET/CT identified unsuspected distant metastases in 15% of clinical stage IIB TNBC

PET/CT had prognostic value in clinical stage IIB (patients with metastases on PET/CT had significantly shorter survival compared to patients who were not upstaged by PET/CT)

PET/CT identified 7 unknown synchronous cancers in 6 patients

PET/CT for restaging of BC

- Allows for better discrimination between posttreatment scar/fibrosis and viable tumor tissue
- Discriminate patients with locoregional recurrence only from those with distant recurrence
- Helpful in down-staging suspected lesions in some situations



TNBC in left breast initially classified as T3N1M0 and treated with neoadjuvant chemotherapy, conservative surgery, and locoregional radiotherapy in 50-y-old woman. David Groheux et al. J Nucl Med 2016;57:17S-26S

JNM The Journal of NUCLEAR MEDICINE

Conclusion

- 18F-FDG PET/CT is useful for initial staging in LABC
- Growing evidence in support for using 18F-FDG PET/CT for initial staging of patients with clinical stage IIB or IIIA BC (stage migration)
- 18F-FDG PET/CT may advantageously replace conventional imaging methods for staging
- 18F-FDG PET/CT is useful for detecting recurrence and for restaging