Evidence Summary PET 14

The Utility of PET/CT in Breast Cancer (Stages II-IV): An Evidence Summary

S. Kellett, U. Metser and D. Langer

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: January 14, 2014

QUESTIONS

In patients with breast cancer (stages II-IV), does the addition of positron emission tomography/computed tomography (PET/CT) impact clinical management at initial staging when compared to conventional practices?

Target Population

Patients with breast cancer (stages II-IV) including inflammatory breast cancer.

Target Users

This evidence summary is intended to guide the Ontario PET Steering Committee in their decision making concerning indications for the use of PET imaging.

This evidence summary may also be useful in informing clinical decision making regarding the appropriate role of PET imaging and in guiding priorities for future PET imaging research.

INTRODUCTION

At the request of the Ontario PET Steering Committee, literature pertaining to the utility of PET/CT in the clinical management of patients with breast cancer (stages II-IV) including inflammatory breast cancer was summarized.

METHODS

This evidence-based report was developed by the Ontario PET Steering Committee in collaboration with the PEBC. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed independently by one methodologist (SK).

Search Strategy

A literature search was performed using MEDLINE (1946 to present) and EMBASE (1988 to 2013 Week 10) through OVID. The search strategies are reported in Appendices 1 and 2.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review if they met all the following criteria:

1. Were published in full text from January 1, 1990 to March 18, 2013.
2. Study type was any of the following:
    a. Randomized controlled trials,
    b. Meta-analyses of RCTs,
    c. Prospective studies (patient population >12), or
    d. Retrospective studies (patient population >50).
3. Specifically evaluated breast cancer (stages II-IV) and inflammatory breast cancer.
4. Outcomes of interest were:
    a. Detection of unsuspected distant metastasis,
    b. Impact on initial staging,
    c. Impact on clinical management.

Exclusion Criteria

Articles were excluded if they met any of the following criteria:

1. Did not include relevant patient outcome data.
2. PET only (no CT)
3. Published in a language other than English.
4. Non-systematic reviews, letters, editorials, case studies, historical articles, or commentaries.

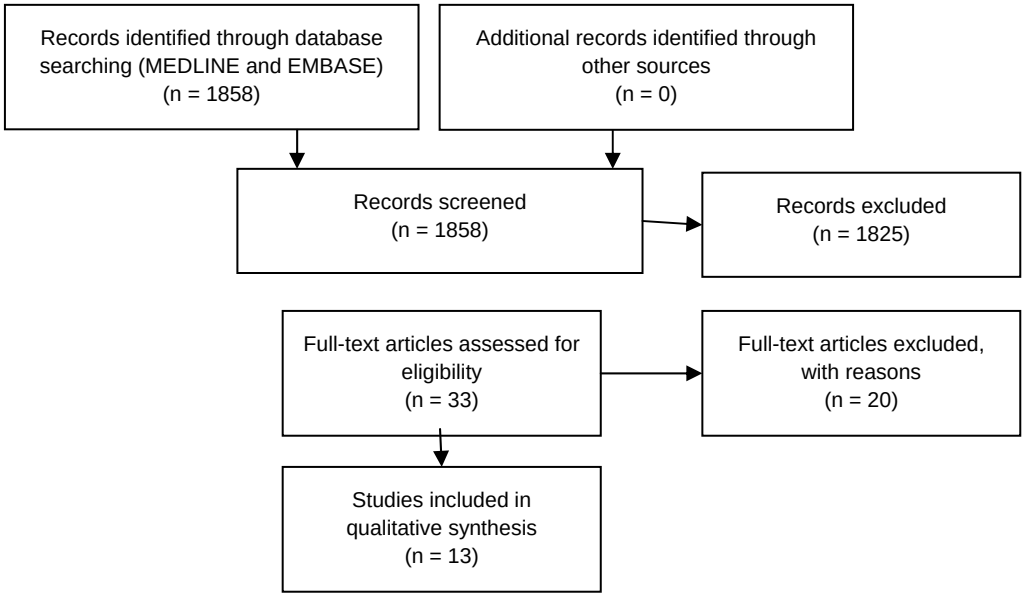
Data Abstraction

One reviewer went through the retrieved citation titles and abstracts from MEDLINE and EMBASE to identify potentially relevant articles, which were obtained for full texts, and then checked all the related references from these full texts. For each eligible study, one reviewer would extract all study data (such as design features, patient population, PET/CT modality, comparison tests, reference standards and clinical management impact data).

RESULTS

No existing systematic reviews or practice guidelines specifically addressed how PET/CT affected the clinical management of patients with late-stage breast cancer. Through MEDLINE and EMBASE, 1858 records were identified from the electronic searches; 1825 primary studies were excluded after reviewing the titles and abstracts. Thirty-three studies were potentially relevant, but upon full-text review, 20 did not meet the inclusion criteria. Therefore, 13 primary studies were subsequently included in this systematic review (Fig. 1). Details of the individual studies can be found in Appendix 3.

Figure 1. Literature Flow Diagram



All studies evaluated the use of FDG PET/CT in inflammatory or late-stage breast cancer. PET/CT detected additional sites of metastasis in 4.9% to 37% of cases across studies that were not demonstrated on conventional imaging techniques (1-9,11-13). In most cases the detection of metastasis was in the axillary lymph nodes and extra-axillary lymph nodes, followed by distant sites of metastasis and synchronous malignancies.

Additional information provided by PET/CT changed the initial staging of patients in 6.7% to 52% of cases, when reported (1,6-10,12,13). In the majority of cases, patients were upstaged due to the discovery of unsuspected metastasis.

Information provided by PET/CT modified the treatment plan of 5.6% to 56% of cases across the studies, when reported (2,4,5,7,8,10,12,13). Changes to the treatment regimens included: modification of the radiotherapy treatment plan (field boarders, target volumes and/or dose prescriptions) (2,4,5,8,10,12); modification of the systemic therapy treatment plan (dose prescriptions, intent changes from curative to palliative and vice versa) (4,5,7,8); and, surgical treatment plan (determination of surgical suitability or inoperability) (4,5,8,13).

DISCUSSION

Based on the literature described above, the addition of PET to the staging regimen in patients with clinical stage II and III breast cancer provided valuable additional information that led to relevant treatment changes in 6% to 56% of cases. Specifically, PET/CT can show involvement in locoregional lymph nodes, mediastinal lymph nodes and distant metastasis that were not observed on conventional imaging modalities. Accurate detection of distant metastasis is important for several reasons. In some cases, surgical removal of primary breast tumour may be futile, and in other cases, the discovery of metastasis may modify systemic therapy or combined-modality therapy. In several studies, most commonly the retrospective studies, results for distant metastasis on PET/CT were unable to be verified by the gold standard (biopsy, histopathology or follow-up scans) as to its true or false nature. In these studies, true positive findings were straightforward to confirm; however, true negative findings only meant that it was not possible to acquire positive findings during the follow-up period, making it uncertain whether the findings were truly negative. While the current evidence is compelling, there is a need for randomized controlled trials to evaluate this further.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated
as described in the PEBC Document Assessment and Review Protocol.

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Groheux D, Giacchetti S, Delord M, Hindie E, Vercellino L, Cuvier C, 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(1):5-11.
2. Walker GV, Niikura N, Yang W, Rohren E, Valero V, Woodward WA, et al. Pretreatment staging positron emission tomography/computed tomography in patients with inflammatory breast cancer influences radiation treatment field designs. Int J Radiat Oncol Biol Phys. 2012;83(5):1381-6.
3. Riegger C, Koeninger A, Hartung V, Otterbach F, Kimmig R, Forsting M, et al. Comparison of the diagnostic value of FDG-PET/CT and axillary ultrasound for the detection of lymph node metastases in breast cancer patients. Acta Radiol. 2012;53(10):1092-8.
4. Riegger C, Herrmann J, Nagarajah J, Hecktor J, Kuemmel S, Otterbach F, et al. Whole-body FDG PET/CT is more accurate than conventional imaging for staging primary breast cancer patients. Eur J Nucl Med Mol Imaging. 2012;39(5):852-63.
5. Koolen BB, Vrancken Peeters M-JTFD, Aukema TS, Vogel WV, Oldenburg HSA, van der Hage JA, 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(1):117-26.
6. Groheux D, Hindie E, Delord M, Giacchetti S, Hamy A-s, de Bazelaire C, et al. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. J Natl Cancer Inst. 2012;104(24):1879-87.
7. Niikura N, Costelloe CM, Madewell JE, Hayashi N, Yu T-K, Liu J, et al. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. Oncologist. 2011;16(8):1111-9.
8. Groheux D, Giacchetti S, Espie M, Vercellino L, Hamy A-S, Delord M, et al. The yield of 18F-FDG PET/CT in patients with clinical stage IIA, IIB, or IIIA breast cancer: a prospective study. J Nucl Med. 2011;52(10):1526-34.
9. Segaert I, Mottaghy F, Ceyssens S, De Wever W, Stroobants S, Van Ongeval C, et al. Additional value of PET-CT in staging of clinical stage IIB and III breast cancer. Breast J. 2010;16(6):617-24.
10. Aukema TS, Straver ME, Peeters M-JTFDV, Russell NS, Gilhuijs KGA, Vogel WV, et al. Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer. 2010;46(18):3205-10.
11. Alberini J-L, Lerebours F, Wartski M, Fourme E, Le Stanc E, Gontier E, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. Cancer. 2009;115(21):5038-47.
12. Groheux D, Moretti J-L, Baillet G, Espie M, Giacchetti S, Hindie E, 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(3):695-704.
13. Fuster D, Duch J, Paredes P, Velasco M, Munoz M, Santamaria G, 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(29):4746-51.

Appendix 1: Searching Strategies from MEDLINE OVID (March 18, 2013)

(N=516)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or Fluorodeoxyglucose F18/ or 18f fluorodeoxyglucose.ti,ab. or 18f fluorodeoxyglucose.ti,ab. or 18fdg.ti,ab. or 2-fluoro-2-deoxy-d-glucose.ti,ab. or 2-fluoro-2-deoxyglucose.ti,ab. or 18f-fdg.ti,ab. or fluorine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluorodeoxyglucose.ti,ab. or flourine-18-fluorodeoxyglucose.ti,ab. or flourine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluordeoxyglucose.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.	72726
2	deoxyglucose/ or deoxyglucose.ti,ab. or desoxyglucose.ti,ab. or desoxy-glucose.ti,ab. or desoxy-d-glucose.ti,ab. or deoxy-d-glucose.ti,ab. or 2deoxyglucose.ti,ab. or 2deoxy-d-glucose.ti,ab. or fluorodeoxyglucose.ti,ab. or fluorodesoxyglucose.ti,ab. or fludeoxyglucose.ti,ab. or fluordeoxyglucose.ti,ab. or fluodeoxyglucose.ti,ab. or fluordesoxyglucose.ti,ab. or 18fluorodeoxyglucose.ti,ab. or 18fluorodesoxyglucose.ti,ab. or fdg$.ti,ab. or 18fdg$.ti,ab. or 18f-dg$.ti,ab.	32697
3	(fluor or 2fluor$ or fluoro or flouro or fluorodeoxy or fludeoxy or flourodeoxy or fluorine or 18f or 18flu$ or 18fluo$).ti,ab.	32878
4	glucose.ti,ab.	305770
5	(pet or petscan$ or pet ct).ti,ab.	48392
6	Tomography, Emission-Computed/	24217
7	emission.ti,ab.	104014
8	(tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.	34279
9	7 and 8	3301
10	5 or 6 or 9	61637
11	3 and 4	5615
12	2 or 11	33255
13	10 and 12	17729
14	breast.ti,ab.	263783
15	(late stage or advanced or inflammatory or IBC or stage II or stage III or stage IV or metasta$).ti,ab.	890098
16	14 and 15	55267
17	1 and 16	892
18	13 and 16	491
19	17 or 18	892
20	limit 19 to English language	797
21	(comment or editorial or letter or case reports).pt.	2670730
22	20 not 21	659

#	Searches	Results
23	(integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/	101474
24	(review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.	1767230
25	(peto$ or der simonian or dersimonian or fixed effect$).ti,ab.	6473
26	23 or 24	1815183
27	22 and 26	135
28	22 not 26	524
29	(conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.	212643
30	27 not 29	132
31	28 not 29	519
32	limit 31 to abstracts	516

Appendix 2: Searching Strategies from EMBASE OVID (March 18, 2010)

(N=1342)

#	Searches	Results
1	Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or Fluorodeoxyglucose F18/ or 18f fluorodeoxyglucose.ti,ab. or 18f fluorodeoxyglucose.ti,ab. or 18fdg.ti,ab. or 2-fluoro-2-deoxy-d-glucose.ti,ab. or 2-fluoro-2-deoxyglucose.ti,ab. or 18f-fdg.ti,ab. or fluorine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluorodeoxyglucose.ti,ab. or flourine-18-fluorodeoxyglucose.ti,ab. or flourine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluordeoxyglucose.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.	113872
2	deoxyglucose/ or deoxyglucose.ti,ab. or desoxyglucose.ti,ab. or desoxy-glucose.ti,ab. or desoxy-d-glucose.ti,ab. or deoxy-d-glucose.ti,ab. or 2deoxyglucose.ti,ab. or 2deoxy-d-glucose.ti,ab. or fluorodeoxyglucose.ti,ab. or fluorodesoxyglucose.ti,ab. or fludeoxyglucose.ti,ab. or fluordeoxyglucose.ti,ab. or fluodeoxyglucose.ti,ab. or fluordesoxyglucose.ti,ab. or 18fluorodeoxyglucose.ti,ab. or 18fluorodesoxyglucose.ti,ab. or fdg$.ti,ab. or 18fdg$.ti,ab. or 18f-dg$.ti,ab.	38399
3	(fluor or 2fluor$ or fluoro or flouro or fluorodeoxy or fludeoxy or flourodeoxy or fluorine or 18f or 18flu$ or 18fluo$).ti,ab.	43021
4	glucose.ti,ab.	302187
5	(pet or petscan$ or pet ct).ti,ab.	71936
6	Tomography, Emission-Computed/	13156
7	emission.ti,ab.	111321
8	(tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.	31598
9	7 and 8	3339
10	5 or 6 or 9	79680
11	3 and 4	7708
12	2 or 11	39120
13	10 and 12	26693
14	breast.ti,ab.	290817
15	(late stage or advanced or inflammatory or IBC or stage II or stage III or stage IV or metasta$).ti,ab.	1043204
16	14 and 15	67398
17	1 and 16	1886
18	13 and 16	949
19	17 or 18	1886
20	limit 19 to English language	1692
21	(comment or editorial or letter or case reports).pt.	1085428
22	20 not 21	1670
23	(integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$)	142478

#	Searches	Results
	or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/	
24	(review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.	1765896
25	(peto$ or der simonian or dersimonian or fixed effect$).ti,ab.	7802
26	23 or 24	1843791
27	22 and 26	229
28	22 not 26	1441
29	(conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.	263031
30	27 not 29	222
31	28 not 29	1392
32	limit 31 to abstracts	1342

Appendix 3: Details of Primary Studies

Study								Impact of PET/CT (%)		
Reference	**Year**	**Type**	**Setting**	**# of pts**	**PET/CT Modality**	**CI performed**	**Reference Standard**	**Detection of unsuspected mets**	**Modification in initial staging**	**Modification of treatment plan**
Groheux et al (1)	2013	Prospective	Stage II-III or IBC	117	WB PET/CT	BS, chest radiography, CT, US	Pathology	37 (43/117)	52 (61/117)	NA
Walker et al (2)	2012	Retrospective	IBC	62	PET/CT	Physical examination, staging mammography, US of the breast and draining lymphatics, chest radiography, or BS, liver imaging, abdominal CT, MRI, chest CT	Pathology, clinical follow-up	44 (27/62)	NA	17.7 (11/62) (11-changes to radiotherapy treatment plans)
**Riegger et al (3)	2012	Retrospective	Not specified	90	WB PET/CT	Axillary US	Histology, imaging, clinical follow-up	8 (7/90)	NA	NA
**Riegger et al (4)	2012	Retrospective	Stages I-IV (65 pts stage II-III)	106	WB PET/CT	X-ray, mammography, MR mammography, chest plain radiography, BS, breast, liver, axillary US	Histology, imaging, clinical follow-up	13 (14/106)	NA	14 (15/106) (2- FP changes) (3- ALND with no SLNB; 5 – surgical management; 1-additional radiation therapy; 2- systemic therapy changes; 3-surgical resection
Koolen et al (5)	2012	Prospective	Stage II and III	154	WB PET/CT	BS, US of the liver, chest radiograph	Pathology	13 (20/154)	NA	8 (13/154) (7- palliative treatment instead of curative; 3- radiation field changed; 4-additional intervention performed; 3-palliative radiotherapy for

Study								Impact of PET/CT (%)		
Reference	**Year**	**Type**	**Setting**	**# of pts**	**PET/CT Modality**	**CI performed**	**Reference Standard**	**Detection of unsuspected mets**	**Modification in initial staging**	**Modification of treatment plan**
										bone mets; 4-palliative systemic therapy
*Groheux et al (6)	2012	Prospective	Stage II or III	254	WB PET/CT	BS, chest x-ray, CT, liver US, abdominal pelvic CT	Pathology	24.9 (47/189)	30.3 (77/254)	NA
Niikura et al (7)	2011	Retrospective	Stage II or III	225	PET/CT	Chest x-ray, skeletal scintigraphy, CT, US	Histology, imaging, clinical follow-up	4.9 (11/225)	6.7 (15/225)	6.6 (15/225) (distant metastasis confirmed in 11 pts) (15- administration of systemic therapy for stage IV disease)
*Groheux et al (8)	2011	Prospective	Stage IIA-IIIA	131	WB PET/CT	Breast MRI, breast US, chest radiography, CT, abdomen US, BS	Pathology	IIA: 2.8 (1/36) IIB: 8.3 (4/48) IIIA: 21 (10/47)	IIA: 5.6 (2/36) IIB: 14.6 (7/48) IIIA: 27.6 (13/47)	IIA: 5.6 (2/36) – treatment adapted to metastatic disease, not specified IIB: 13 (10/77) – treatment changes not specified IIIA: 56 (10/18) – systemic therapy was adapted to metastatic diseases, and radiation therapy for some bone lesions
Sageart et al (9)	2010	Retrospective	Stage IIB and III breast cancer	70	WB PET/CT	Chest radiography, liver US, BS, and breast and axilla US	Histopathology, imaging, clinical follow-up	10 (7/70)	10 (7/70)	NA
Aukema et al (10)	2010	Prospective	Stage II and III	60	WB PET/CT	Mammography, Breast US, breast MRI	Pathology	NA	17 (10/60)	12 (7/60) – radiotherapy plan was changed based on extra-axillary LN involvement)
Alberini et al (11)	2009	Prospective	IBC	59	WB PET/CT	Chest radiography,	Pathology	31 (18/59)	NA	NA

Study								Impact of PET/CT (%)		
Reference	**Year**	**Type**	**Setting**	**# of pts**	**PET/CT Modality**	**CI performed**	**Reference Standard**	**Detection of unsuspected mets**	**Modification in initial staging**	**Modification of treatment plan**
						abdominal US, BS; additional CT Investigations if necessary				
*Groheux et al (12)	2008	Prospective	Stage II or III	39	WB PET/CT	Breast MRI, breast US, chest radiography, CT, abdomen US, BS	Pathology	10 (4/39)	18 (7/39)	13 (5/39) – changes to radiotherapy treatment plans
Fuster et al (13)	2008	Prospective	LABC (TNM stage T3 or greater)	60	WB PET/CT	Breast MRI, chest CE-CT, liver, US, BS	Pathology	8.3 (5/60)	42	42 (25/60) – 7 avoid invasive procedures; 10 – taxanes; 3-– additional surgery; 5-– inoperability

CI = conventional imaging; LABC = locally advanced breast cancer; IBC = inflammatory breast cancer; Pts = patients; PET/CT = Positron emission tomography/computed tomography; mets = metastasis; CE-CT = contrast-enhanced computed tomography; US = ultrasonography; BS = bone scan. NA = not stated; WB = whole-body; MRI = magnetic resonance imaging; FP = false positive; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy

*** Patient population is part of an ongoing series. Current version of this study is Groheux et al (1)**

**** Patient population overlaps in these studies.**