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A Quantitative review of the use of FDG-PET in the axillary staging of breast cancer

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Summary

Breast cancer is the most frequent type of cancer in women and is the second leading cause of cancer death in Canadian women. It is an important source of morbidity and mortality in today's society and confers risk to the patient both in terms of the disease itself and the treatment of the disease. Axillary lymph node status is the most important prognostic factor for determining breast cancer survival and it guides the treatment of the disease based on the disease stage. The aim of this study is to assess the diagnostic value of positron emission tomography (PET) utilizing [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) in the axillary staging of breast cancer. A systematic literature search was carried out in the Medline, Embase and Cochrane databases. Seventy one original studies were identified, 20 of which evaluated the axillary status of women. The studies were graded based on recommended procedures from similar studies. Aggregate sensitivities and specificities were calculated for various levels of quality for all included studies. Recommendations for future studies were made based on patient positioning, acquisition time, attenuation correction, fasting state, and image interpretation. A large variation in the sensitivity and specificity of large diagnostic trials of similar quality was noted. We concluded that PET has promise for the axillary staging of breast cancer once the variability of sensitivity and specificity in these large trials is addressed.

key words: **Positron Emission Tomography • axillary staging • breast cancer**

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BACKGROUND

Breast cancer is the most frequent type of cancer in Canadian women (21 400 new cases in the year 2004), and is the second leading cause of cancer death in women (5200 deaths in 2004) [1]. Axillary lymph node status is the most important prognostic factor for determining breast cancer survival [2,3] and knowledge of axillary lymph node status is used for the planning of appropriate systemic adjuvant therapy, especially in postmenopausal women [3,4]. Currently, the clinical standard for determining the status of the axillary lymph nodes, and thus the stage of the disease, is through surgical removal (axillary lymph node dissection [ALND]) and subsequent histological examination [3]. In Canada, virtually all Stage I and II [5] breast cancer patients undergo axillary lymph node dissection (ALND) in order to evaluate these nodes pathologically [6].

Although ALND provides valuable information on the stage of the disease, there is an ongoing debate whether ALND is cost effective for certain types of breast cancer [7]. It has been suggested that ALND may be postponed until the clinical appearance of nodal metastases without altering the prognosis for the patient [3,8]. There may be no survival advantage to the routine removal of axillary lymph nodes [4,9,10], and the only advantage of ALND may be a substantial reduction of regional axillary reoccurrence [8,11] – ALND may also only be necessary for patients with palpable or detectable adenopathy [12]. Complications of ALND include arm lymphedema and brachial plexopathy [3]. ALND is also somewhat inaccurate as a staging tool, with some studies describing a 39% false negative rate [13]. In order to avoid the morbidity associated with ALND, several studies have suggested that ALND may be minimized in subgroups of patients who are unlikely to have lymph node metastases (i.e. those with small primary tumors or noninvasive disease) [4,14,15]. However, avoidance of ALND in patients with small tumours may still result in residual metastases [16].

The British Columbia Cancer Agency recommends that patients with stage I or stage II breast cancer receive either breast conserving surgery (BCS) plus ALND or modified radical mastectomy, along with a referral to a radiation oncologist. BCS can be performed on an outpatient basis if the ALND is not included [15]. Therefore, a noninvasive technique for detecting breast cancer metastases to axillary lymph nodes would reduce the need for hospitalization in the majority of patients with early stage breast cancer, reducing both morbidity and costs [15]. A significant proportion of women with primary breast cancer may benefit from the pre-staging of axillary lymph nodes [17], especially as more than 80% of these women are lymph node negative [18].

Positron Emission Tomography (PET) utilizing [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) has been evaluated in several studies for clinical use in staging breast cancer and axillary nodes[4,14,19–33]. FDG-PET is a noninvasive imaging modality that provides information that is useful for tumour imaging [34,35]. Increased glucose utilization by malignant cells results in increased FDG accumulation and this can be used to tomographically identify metastatic sites. Some studies have shown that PET imaging is more sensitive and specific than mammography, especially in young women with dense breasts [31] and in patients with post augmentation mammoplasty [29,36]. Other radiopharmaceuticals are currently being investigated.

Recently, PET has been shown to be cost effective in Canada for both lung cancer [37] and recurrent colorectal cancer [38]. In order to evaluate the evidence of PET for the staging of axillary lymph nodes, a literature search was conducted with the intent of performing a meta-analysis of all available studies [38,39].

MATERIAL AND METHODS

Search strategy

A literature search was completed in December 2005 as a comprehensive search through MEDLINE, Current Contents and EMBASE and was restricted to English, Spanish and French language articles. The search strategy was based on recommendations for a comprehensive, unbiased search strategy for identifying literature on FDG-PET [40–42]. The abstracts were then analyzed for studies that evaluated FDG-PET in breast cancer. The bibliographies of these studies were then searched for further referenced studies that were subsequently added to the studies from the literature search.

Several forms of bias are expected in a literature search [43] including publication, language, database and multiple publication bias. Unpublished work was not included because it is likely that most studies of reasonable quality would be published, irrespective of the results [44]. One German language article was found that may have met the inclusion criteria of this analysis but was not included due to the inability of the authors to read German, thus introducing a small language bias to our search results. MEDLINE, Current Contents and EMBASE were searched for all available years in order to reduce database bias. Multiple publication bias was avoided by not including abstracts or preliminary results that were superceded by final reports. Inclusion and exclusion criteria are listed in Table 1.

Selection did not exclude studies that did not blind their results between PET and other modalities (i.e. unblended studies were included) [45]. In these cases, many patients are selected for PET imaging because of positive findings in other staging modalities, thus introducing a case-selection bias resulting in an over-representation of positive findings in these other staging modalities (both false and true), with a resulting overestimation of sensitivity and underestimation of specificity. Therefore, the PET studies are not conditionally independent from the other modalities and some results may depend on diagnostic sequence.

Analysis of studies

Studies were analyzed using guidelines from the literature [47]. Using the method of Flynn and Adams [46] as well as input from Oxman [42] and Harbour [47], the studies were graded on methodological quality as in Table 2 [46].

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Full reports All articles in the published literature Both retrospective and prospective studies Only studies that confirmed the diagnosis with biopsy or ALND Studies published in English, Spanish or French Only studies that present all data (true/false positives/negatives)
Exclusion Criteria	No abstracts No articles that report results based solely on lesion No preliminary reports No studies that include patients published elsewhere

Table 2. Template used for grading methodological quality of PET studies [46]. This template was used to initially categorize the studies. Studies were then downgraded using observations on the study design, and study data acquisition and analysis procedures.

Grade	Criteria
A	*Studies with broad generalizability to a variety of patients and no significant flaws in research methods*
	>35 patients with disease and >35 patients without disease
	Patients drawn from a clinically relevant sample (not selected to include only severe disease) with clinical symptoms fully described
	Diagnoses defined by an appropriate reference standard
	PET studies technically of high quality and assessed independently of the reference diagnosis
	Prospective study
B	*Studies with a narrower range of generalizability, and with only a few flaws that are well described (and effect on conclusions can be assessed)*
	>35 cases with and without disease
	Smaller range of patients, typically reflecting referral bias of university centers
	Free of other methodological flaws that promote interaction between test results and disease determination
	Prospective study
C	*Studies with several methodological flaws*
	Small sample size
	Incomplete reporting
	Retrospective study
D	*Studies with multiple flaws in methods*
	No credible reference standard for diagnosis
	Test result and determination of final diagnosis not independent
	Source of patients' cohort could not be determined or was obviously influenced by the test result

Results

Search results

The initial search in MEDLINE resulted in 56 studies of FDG-PET for breast cancer. A search through Current Contents resulted in 4 more with EMBASE contributing an additional 2 studies. A search through the bibliographies of these studies resulted in an additional 8 potentially relevant studies for a total of 71 studies. 1 of these was an abstract [48], 2 were case reports [49,50], 2 of these dealt with the special case of augmented breasts [36,51], 7 of these were for the monitoring of various chemotherapies [52–58], 4 of these were for recurrent breast cancer surveillance [59,62], 10 of these were for primary breast cancer diagnosis [19,20,22,24,27,31,63–66] and 20 studies were for the

Table 3. Study design parameters recorded from 19 studies for staging axillary lymph nodes. Studies are ordered by publication year.

First Author	Study date	Study type	Patients	Prevalence of disease	Average age	Age range	Recruitment	Gold standard
Tse	1992	Prospective	11	7/11		Not stated	PE/Mammo	Histo
Hoh	1993	Prospective	17	12/17		Not stated	N.S.	Histo
Adler	1993	Prospective	18	9/18	55	35–79	Breast mass >1cm	Histo and ALND
Nieweg	1993	Retrospective	14	5/14	49	30–64	N.S.	Histo
Utech	1996	Retrospective	124	44/124	59	32–94	Dx'd Br CA via histo	Histo
Scheidhauer	1996	Prospective	18	9/18	57	35–79	PE/Mammo/US	Histo
Avril	1996	Prospective	51	24/51	50	18–74	Dx'd Br lesion via histo	Histo via ALND
Adler	1997	Prospective	50	20/50		36–79	Dx'd Br CA via histo	Histo via ALND
Palmedo	1997	Prospective	17	5/17	58	28–84	PE/Mammo	Histo
Smith	1998	Prospective	49	20/49		Not stated	Dx'd Br CA via histo	Histo
Noh	1998	Retrospective	27	15/27		Not stated	Dx'd Br lesion via histo	Histo
Yutani	1999	Prospective	30	26/30		32–78	PE/Mammo	Histo
Rostom	1999	Retrospective	74	49/74	40	14–67	Primary/Recurrent/Metastatic	Histo
Greco	2001	Prospective	167	72/167	54	28–84	Dx'd Br lesion via histo	Histo via ALND
Guller	2002	Prospective	31	14/31	65	47–88	Dx'd Br lesion via histo/non-palpable ALN	SNB
van der Hoeven	2002	Prospective	70	32/70	58	Not stated	Dx'd Br CA via histo	Histo + SNB
Barranger	2003	Prospective	32	14/32	58	29–77	Clinically negative nodes	SNB + Histo/ALND
Wahl	2004	Prospective	308	109/308	52	27–82	Dx'd Br CA via histo	Histo via ALND
Zornoza	2004	Prospective	200	100/200	52	25–74	Dx'd Br CA via histo	SNB + Histo/ALND
Fehr	2004	Prospective	24	10/24	56	+/–11	Breast mass <3cm, clinically negative nodes	SNB + Histo/ALND

PE – physical exam; N.S. – not stated; Dx'd – diagnosed; Br CA – breast cancer; mammo – mammography; Histo – histology; ALN – axillary lymph node; ALND – axillary lymph node dissection; SNB – sentinel node biopsy.

staging of axillary lymph nodes[4,14,19–27,29–33,67–70]. Tables 3 and 4 list the study design and study acquisition and analysis parameters.

Initially, all studies were categorized to Grade A, B, or C [46] based on study type and patient number alone. Reasons for downgrading the study were based on information in Tables 3 and 4, and are listed in Table 5. These reasons are alluded to in Table 2 with respect to methodological flaws and incomplete reporting. When only 1 minor reason (usually incomplete reporting of a data acquisition parameter) for downgrading a study is given, the study was not downgraded. Incomplete reporting of age statistics, data analysis, and recruitment strategies were sufficient to downgrade a study one grade. The aggregate sensitivities, specificities, positive and negative predictive values were calculated separately for each grade, for grades B and C combined, and for grades B, C and D combined (Table 6). It should be noted that all studies in Group A are newer studies from more accurate, newer scanners.

Discussion

Whole body PET has been used successfully to detect axillary lymph node involvement [20] and has drawn attention given the limits of other modalities to accurately stage a patient's breast cancer [71]. Many studies have demonstrated accuracies of 95% or more for the detection of the primary tumour and axillary lymph node involvement in both natu-

Table 4. Study data acquisition and analysis parameters recorded from 19 studies for staging axillary lymph nodes. Studies are ordered by publication year.

First author	Study date	Algorithm	Resolution	Acquisition	Analysis	Device type
Tse	1992	FBP	Not stated	Not stated	V	Siemens ECAT 931
Hoh	1993	FBP	Not stated	Not stated	V	Siemens CTI 931/08-12
Adler	1993	FBP	5 mm	Not stated	V/DUR	Scanditronix SP3000
Nieweg	1993	FBP	5.5 mm FWHM	Not stated	V/TNT	Posicam 6.5
Utech	1996	FBP	10.2 mm FWHM	Not stated	V	Siemens ECAT 951-031
Scheidhauer	1996	FBP	6.0 mm FWHM	Not stated	V	Siemens Exact
Avril	1996	Not Stated	8 mm FWHM	Not stated	SUV	Siemens CTI 951R/31
Adler	1997	FBP	11.5 mm	2D	V	Siemens Exact
Palmedo	1997	Not stated	5.4 mm FWHM	Not stated	SUV	Siemens CTI 921
Smith	1998	FBP	6 mm FWHM	Not stated	V	Siemens Exact 31
Noh	1998	FBP	4.6 mm FWHM	Not stated	SUV	Siemens Exact 47
Yutani	1999	FBP	4.5 mm FWHM	Not stated	V/SUV/TNT	Shimadzu Headtom V
Rostom	1999	Not stated	Not stated	Not stated	V	Siemens Exact 47
Greco	2001	FBP	Not Stated	Not stated	V	GE 4096 WB Plus
Guller	2002	Not Stated	Not Stated	Not stated	N.S.	Siemens Exact 922/47
van der Hoeven	2002	FBP	7 mm FWHM	2D	V	Siemens Exact
Barranger	2003	ML-EM	Not Stated	Not stated	V	Irix hybrid
Wahl	2004	FBP	5 mm	Not stated	V/SUV	Several
Zornoza	2004	Not stated	4.5 mm FWHM	2D	V/SUV	ECAT Exact HR+
Fehr	2004	FBP and Iterative	Not Stated	2D	V	GE PET Trace 2000

V – visual analysis; TNT – tumor to normal tissue ratio; SUV – standardized uptake value; DUR – dose uptake ratio; N.S. – not stated; FBP – filtered backprojection.

ral and augmented breasts [19,22,29,36]. Some studies have claimed a very high sensitivity of FDG-PET in the staging of axillary lymph nodes [4,14,21,23] while others have described much lower sensitivities. Recently, three large studies have shown high negative predictive values (95-96%) for the staging of axillary lymph nodes [4,14,26].

This meta analysis has shown that there is great variability in both the results of studies to detect axillary lymph node involvement and great variability in the design of the studies themselves (Tables 3, 4). Several study design issues have made it difficult to compare the reported studies to one another. The variability between studies is, in part, due to the different clinical demographics of the patients in each study, the different imaging protocols used (eg 2D vs 3D and FBP vs iterative reconstruction techniques), the variation in the resolution of each PET camera, the types of PET camera and the clinical condition of each patient (eg diabetic comorbidity [72]). As well, all are single site studies. Because meta analysis requires a largely consistent study design when aggregating studies, it may be that the meta analysis contained herein is not ultimately valid due to these inconsistencies. This section addresses some of these inconsistencies between the study designs and makes recommendations for future studies.

General

In terms of clinical and pathological findings, FDG uptake into breast tumours has been found to be independent of age, menopausal status, race, tumor size, laterality, histologic differentiation, ploidy, DNA index, estrogen or progesterone receptor value, pathologic stage and serum glucose [73]. PET scan accuracy is the same irrespective of the N stage comparing N0 with N2 patients [28]. Therefore, these factors do not contribute to errors in aggregation.

Study design

The study design affects the quality of results [46], with prospective studies being preferred over retrospective studies. The more patients in a study, the more confident one may

Table 5. Initial grading of studies and reasons for downgrading studies based on study design and iniquities in study data acquisition and analysis.

Author	Year	Study type	Patients	Inital grade	Downgrade reason	Final grade
Wahl	2004	Prospective	308	A	Acquisition resolution not stated	A
Zornoza	2004	Prospective	200	A	Reconstruction algorithm not stated	A
Greco	2001	Prospective	167	A	Acquisition resolution not stated	A
van der Hoeven	2002	Prospective	70	B		B
Avril	1996	Prospective	51	B	Reconstruction algorithm not stated	B
Adler	1997	Prospective	50	B	Relatively large FWHM resolution	B
Smith	1998	Prospective	49	B		B
Fehr	2004	Prospective	24	C	Resolution not stated, multiple resconstruction algorithms used	D
Barranger	2003	Prospective	32	C	Resolution not stated, use of a hybrid device instead of dedicated PET	D
Guller	2002	Prospective	31	C	Reconstruction algorithm and acquisition resolution not stated, method for analysis of data not stated	D
Yutani	1999	Prospective	30	C		C
Adler	1993	Prospective	18	C		C
Scheidhauer	1996	Prospective	18	C	Relatively large FWHM resolution	C
Hoh	1993	Prospective	17	C	Age statistics not stated, small study, recruitment strategy not stated, resolution not stated	D
Palmedo	1997	Prospective	17	C	Reconstruction algorithm not stated	C
Tse	1992	Prospective	11	C	Age statistics not stated, small study, resolution not stated	D
Utech	1996	Retrospective	124	C		C
Rostom	1999	Retrospective	74	C	Reconstruction algorithm and acquisition resolution not stated	D
Noh	1998	Retrospective	27	C	Age statistics not stated, small study	D
Nieweg	1993	Retrospective	14	C	Small study, recruitment strategy not stated	D

be of the results [46]. The prevalence of the disease in the population sample directly affects both the negative and positive predictive values [31] and should be consistent when comparing studies. The population demographics (age) are important parameters because they affect the sensitivity of some modalities (such as mammography) [31] and they subsequently affect the decision of whether to use a certain test for a given patient [42]. Consistent selection of these parameters is preferred.

Position

Patient positioning and the use of supporting brassieres may change the effectiveness of FDG-PET to detect breast lesions. One study has shown that prone positioning with the use of scintomammography positioning pads is more effective at separating deep breast structures of the left breast from the myocardium and it reduces motion artifacts [74]. The SUV and tumour to normal tissue ratio were significantly higher with the patient prone than with the patient supine. Arm positioning is also an especially important consideration in the staging of axillary lymph nodes since the level I lymph nodes may not be easily differentiated from primary tumours in the upper outer quadrant [4]. The studies found by literature search demonstrated great variability in patient positioning – some studies had the patients wear brassieres, some patients were supine, some were prone, some had arms above their heads, and some had the breast and axilla centered in the field of view. A more consistent approach to patient positioning is preferable.

Fasting

Fasting prior to administration of FDG is important in the use of PET in oncology. Some studies have demonstrated that fasting prior to FDG improves the SUV [75,76]. We found no studies that tested uptake of breast neoplasms of any description in relation to fasting, and so we would recommend that such a study be implemented prior to initiating any large study investigating the diagnostic use of PET for the detection of breast cancer. Such a study should account for the various types of breast neoplasms. Again, the

Table 6. Aggregate sensitivities (sens), specificities (spec), positive predictive values (PPV) and negative predictive values (NPV) for each grade of study, including aggregates for grades B and C combined and grades B, C and D combined. Some values for true/false positives/negatives were calculated from given sens, spec, PPV and NPV using 4 equations with 4 unknowns.

Final grade	Author	Year	TP	TN	FP	FN	Patients	Sens	Spec	PPV	NPV
A	Greco	2001	68	82	15	4	167	94%	85%	82%	95%
	Wahl	2004	65	161	40	42	308	61%	80%	62%	79%
	Zornoza	2004	90	91	2	17	200	84%	98%	98%	84%
Aggregate A			223	334	57	63	675	78%	85%	80%	84%
B	Avril	1996	19	26	1	5	51	79%	96%	95%	84%
	Adler	1997	19	21	11	1	52	95%	66%	63%	95%
	Smith	1998	18	28	1	2	49	90%	97%	95%	93%
	van der Hoeven	2002	8	37	1	24	70	25%	97%	89%	61%
Aggregate B			64	112	14	32	222	67%	89%	82%	78%
C	Adler	1993	7	10	0	1	18	88%	100%	100%	91%
	Scheidhauer	1996	9	8	1	0	18	100%	89%	90%	100%
	Utech	1996	44	60	20	0	124	100%	75%	69%	100%
	Palmedo	1997	5	12	0	0	17	100%	100%	100%	100%
	Yutani	1999	8	20	0	2	30	80%	100%	100%	91%
Aggregate C			73	110	21	3	207	96%	84%	78%	97%
D	Tse	1992	4	4	0	3	11	57%	100%	100%	57%
	Hoh	1993	9	5	0	3	17	75%	100%	100%	63%
	Nieweg	1993	5	9	0	0	14	100%	100%	100%	100%
	Noh	1998	14	12	0	1	27	93%	100%	100%	92%
	Rostom	1999	42	25	0	7	74	86%	100%	100%	78%
	Fehr	2004	2	13	1	8	24	20%	93%	67%	62%
Aggregate D			76	68	1	22	167	78%	99%	99%	76%

studies found by literature search demonstrated great variability in fasting specifications.

Attenuation correction

Attenuation correction (AC) uses a transmission image for the correction of emission images. The advantage of AC over non-AC images is that an improved anatomic orientation may be gained, thus allowing the images to be evaluated semi-quantitatively (is standardized uptake values [SUV] can be calculated) which may also be useful for therapy monitoring [77]. However, the use of AC in visually-interpreted images has been shown to be less accurate than the use of non-AC images [78,79]. The pros and cons of AC methods have been debated [77], but their use may ultimately depend on whether a visual or quantitative method is used for interpretation. Most of the reported studies have used AC in their methods.

Tumour size

In a small breast cancer, there is only a low probability (7–15%) of axillary lymph node involvement [80] and these most likely consist of micrometastases. FDG-PET may not yet have the spatial resolution to pick up micrometastases [25]. The current expectation for the lower limit of spatial resolution for a PET scanner is 2 mm [81] and the sensitivity of PET rapidly declines below 5 mm [32,82,83]. Even though the spatial resolution of PET is a technical limitation [84], the interpretation of PET images also relies on the differential of FDG uptake; the mean uptake of carcinomas that metastasize to the axilla is considerably higher than that of carcinomas that do not metastasize [28].

The detection of uninvolved axillary lymph nodes would be of great clinical benefit. However, there is great variability in the sensitivity and specificity shown in clinical studies for the detection of clinical T1N0 tumours, ranging from a sensitivity of 33% in pathologic stage T1 tumours [25,28] and higher [14] to 100% [4]. A meta-analysis of this subgroup is needed before a conclusion can be made regarding the use of PET as an alternative to ALND.

Imaging patients with larger or locally advanced breast cancer may increase the sensitivity and specificity since the sen-

sitivity of PET is limited by the resolution of the PET camera [4]. Therefore, the recruitment criteria of the study directly affects the sensitivity and specificity of PET. Some studies are limited by preselection and high prevalences of advanced breast cancer [21]. Some studies may only recruit patients with tumors of a given size [21] and some studies may only recruit patients with nonpalpable lymph nodes [32]. These are limits that both increase or decrease the sensitivity of PET (respectively) and therefore affect the outcome of the study.

Acquisition

The procedures and algorithms used to acquire and analyze the data also greatly affect the test interpretation. Variability may be introduced by the type of PET camera itself since this dictates the image resolution and available field of view, especially with different detector configurations [84]. Dual-head coincidence gamma camera imaging of FDG are not as accurate as FDG-PET with a dedicated camera for the staging of axillary lymph node metastasis [30].

Scan time

Inflammatory lesions accumulate FDG earlier and more intensely than malignancies [85]. The sensitivity of FDG-PET for the detection of malignant lesions has been shown to increase when the delay between the administration of FDG and the acquisition phase is increased from a usual 1–1.5 hours to 3 hours, thus increasing the tumour to background ratio [86]. Again, great variability in scan time and delay was noted for the various studies found via literature search.

Reconstruction algorithm

The algorithm by which the acquisition data is reconstructed to image representation has both quantitative and qualitative implications for the interpretation of the data [87]. Signal to noise ratios may be reduced with the use of iterative techniques over analytic (eg filtered back-projection [FBP]) techniques, however lesion detection may not be improved [88]. Iterative reconstruction techniques may be superior for the detection of axillary lymph nodes over filtered backprojection reconstruction [89,90]. Quantitatively, iterative techniques reduce the image noise [90], which may be better for quantitative image analysis methods such as SUV. It may be, however, that iterative reconstruction of attenuation corrected images does not improve on lesion detectibility when using a visual interpretation protocol [78].

Image Interpretation

Quantitative methods of image analysis have been used to interpret FDG-PET images by using various ratios of signal to background. The standardized uptake value (SUV) is a relative measure of radiolabelled tracer uptake in tissue used in FDG-PET [91]. Studies have shown that such techniques complement the visual interpretation of images and have been recommended to reduce interobserver variability [91]. As well, it might be possible to correct for artifacts introduced by the patient's weight [92]. There was a great deal of variation in the use of visual vs quantitative techniques in the reported studies.

Diabetes

In diabetic patients, the rate of FDG accumulation in lung tumors is impaired [93]. Diabetes may reduce the sensitivity of FDG-PET for lung cancer detection, however no studies have been found to show this to be true for breast cancer. We recommend that such a study be implemented to determine the effect of diabetes on the sensitivity of FDG-PET for breast cancer.

CONCLUSIONS

FDG-PET has been shown to successfully detect axillary lymph node involvement [20] and has gained considerable attention given the limits of other modalities to accurately stage a patient's breast cancer [94]. However, the variability between study designs has made it difficult to compare and aggregate the results of these studies. As well, the variability in the sensitivity and specificity of the better quality studies needs to be explained in order to maximize the potential of PET. FDG-PET may, in fact, be more than 85% sensitive and specific for the diagnostic evaluation of axillary lymph node involvement in some patient populations if contributory variables are maximized. However, without addressing issues such as scan times, reconstruction algorithms, patient position, fasting, diabetes, and others, it may well be difficult to draw conclusions from the literature regarding the applicability of PET for the staging of breast cancer. A recent large multi-center study has addressed some of these issues [68]. However, we recommend that further studies be performed that control for contributory variables (patient position, etc) in order to explain the variability of study results. As well, caution must be exercised when analyzing results from older studies because of the increased accuracy of the newer scanners.

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