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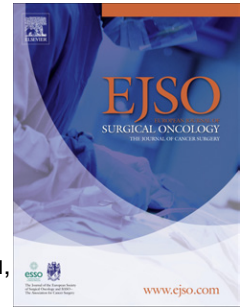
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Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis

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Abstract

Purpose: Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) are used to assess axillary nodal status in breast cancer, but are invasive procedures associated with morbidity, including lymphoedema. This systematic review evaluates the diagnostic accuracy of positron emission tomography (PET), with or without computed tomography (CT), for assessment of axillary nodes in early breast cancer.

Methods: Eleven databases including MEDLINE, EMBASE and the Cochrane Library, plus research registers and conference proceedings, were searched in April 2009. Study quality was assessed using the QUality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist. Sensitivity and specificity were meta-analysed using a bivariate random effects approach.

Results: Across 26 studies evaluating PET or PET/CT (n=2,591 patients), mean sensitivity was 63% (95% CI: 52-74%; range 20-100%) and mean specificity 94% (95% CI: 91-96%; range 75-100%). Across 7 studies of PET/CT (n=862), mean sensitivity was 56% (95% CI: 44-67%) and mean specificity 96% (90-99%). Across 19 studies of PET-only (n=1,729), mean sensitivity was 66% (50-79%) and mean specificity 93% (89-96%). Mean sensitivity was 11% (5-22%) for micrometastases (≤ 2 mm; five studies; n=63), and 57% (47-66%) for macrometastases (> 2 mm; four studies; n=111).

Conclusions: PET had lower sensitivity and specificity than SLNB. Therefore, replacing SLNB with PET would avoid the adverse effects of SLNB, but lead to more false negative patients at risk of recurrence and more false positive patients undergoing unnecessary ALND. The present evidence does not support the routine use of PET or PET-CT for the assessment of the clinically negative axilla.

Abbreviations

ALND	Axillary lymph node dissection
CT	Computed tomography
DCIS	Ductal carcinoma in situ
FDG	Fluorodeoxyglucose
FN	False negative
FNAC	Fine needle aspiration cytology
FP	False positive
LCIS	Lobular carcinoma in situ
NICE	National Institute for Health and Clinical Excellence (UK)
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SLNB	Sentinel lymph node biopsy
SUV	Standardised uptake value
TN	True negative
TNM stage	Tumour, node, metastases stage
TP	True positive

Introduction

Axillary metastases are present in approximately 40% of women with breast cancer and have great prognostic significance. Traditionally, all women with breast cancer would undergo complete surgical removal of all ipsilateral axillary lymph nodes (axillary lymph node dissection; ALND) which is associated with almost 100% diagnostic accuracy and local disease control but has a substantial complication rate including surgical complications [1-3] and lymphoedema of the arm; the latter occurs in around 20% of patients and can be long-term [2;4;5].

Over the past decades there has been a shift towards minimising the extent of axillary surgery via a combination of pre-operative axillary imaging and targeted sampling of axillary nodes rather than complete surgical excision. Pre-operative ultrasound and biopsy of any abnormal nodes detects approximately 45% of metastases [6]. For patients shown by needle biopsy to have metastases, standard management is ALND to remove all ipsilateral nodes. For those with negative ultrasounds, most Breast Units now undertake sentinel lymph node biopsy (SLNB) where a limited number of nodes are identified by either radioisotope uptake, blue dye uptake or a combination. Patients in whom metastases are identified via SLNB undergo ALND [7], traditionally as a separate procedure (two operations required) but increasingly during the same operation. In the latter case, intra-operative assessment of the dissected sentinel node(s) is undertaken via frozen section, touch imprint cytology [8;9] or polymerase chain reaction (PCR) [10;11]; if the sentinel node contains metastases then the procedure is converted to a full ALND [12].

SLNB has therefore replaced routine ALND in the clinically negative axilla in most units, but is not without problems. SLNB is associated with lower incidence of surgical complications and lymphoedema than ALND; however, these still occur in some patients [1-3;13;14]. SLNB requires specialist expertise, expensive equipment and facilities, and is not 100% accurate. In addition, the use of intra-operative diagnostic techniques add to the cost and complexity and make surgical scheduling more complex [15]. There is therefore a need for less invasive techniques to identify axillary metastases. One such technique may be positron emission tomography (PET).

PET uses a radioactive tracer to produce three-dimensional images of body processes, and is increasingly used for cancer diagnosis and staging. A commonly-used tracer comprises the glucose analogue fluorodeoxyglucose (FDG) attached to the radioactive isotope fluorine-18. This can be used to detect cancerous cells, which frequently have higher glucose uptake than normal cells [16;17]. Modern scanners often perform a computed tomography (CT) scan alongside the PET scan; the combined PET/CT scan allows concurrent visualisation of tissue anatomy and metabolic activity [16-18]. PET and CT scanning are non-invasive but involve exposure to a low level of ionizing radiation.

Whilst initial reports of PET sensitivity were promising, subsequent reports have shown wide variability between estimates of sensitivity from different studies [19-21]. This review aims to systematically evaluate the diagnostic accuracy of PET and PET/CT for assessment of axillary nodal status in patients with newly-diagnosed early-stage breast cancer. This was undertaken as part of a wider review on behalf of the UK NIHR Health Technology Assessment (HTA) Programme [22].

Methods

Search strategy

The systematic review followed the recommendations in the PRISMA statement [23;24]. The following databases were searched in April 2009: MEDLINE, Medline in Process, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, DARE, NHS EED, HTA database, Science Citation Index, and BIOSIS previews. The following research registers were searched: National Research Register archive (www.nrr.nhs.uk; to 2007); UK NIHR Clinical Research Network (www.ukcrn.org.uk; post-2007); ClinicalTrials.gov (www.clinicaltrials.gov); and Current Controlled Trials (www.controlled-trials.com). The following conference proceedings were also searched: American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO). The search strategy included terms for breast cancer, PET imaging, the axilla or lymph nodes, and diagnostic studies (the full search strategy is available in Appendix 1). The search was undertaken as part of a broader review on imaging technologies for assessment of the axilla. Additional methods included contact with experts and scrutiny of bibliographies of retrieved papers and reviews. No search restrictions were used for language or date of publication.

Inclusion and exclusion criteria

Studies were included if they assessed sensitivity and specificity of PET or PET/CT for assessment of axillary nodal status, in comparison to a reference standard test such as ALND or SLNB. Because several large studies were identified, studies with fewer than 20 analysable patients were excluded, since they were thought to add little to the overall estimates of accuracy. Non-English language papers were excluded. Many studies recruited patients prior to full staging investigations and therefore included a range of cancer stages. Where data allowed, only patients newly diagnosed with early-stage breast cancer (TNM stage I, II or IIIA) [25-27] were included in our analysis. Patients with carcinoma in situ (ductal or lobular; DCIS or LCIS) were excluded where possible as they rarely undergo diagnostic axillary surgery. Where separate data was not presented by cancer stage, studies were excluded if more than 20% of the population had breast cancer that was non-early-stage, non-newly

diagnosed, or carcinoma in situ. Cohort studies (prospective or retrospective) were included and case-control studies were excluded (however, no case-control studies were identified).

Data extraction and quality assessment

Data were extracted by one reviewer and checked by a second, and discrepancies resolved by discussion. Study quality was assessed using the QUality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [28]. Of the fourteen items in the checklist, eleven items relevant to this review were used.

Data synthesis

Patients were classified as true positive (TP) where both PET scan and reference standard (e.g. ALND or SLNB) detected axillary metastases; true negative (TN) where neither test detected metastases; false negative (FN) where the PET scan failed to detect metastases identified by the reference standard; and false positive (FP) where the PET scan incorrectly suggested metastases not detected by the reference standard. Sensitivity was defined as $TP/(TP+FN)$ and specificity as $TN/(TN+FP)$. Sensitivity and specificity were meta-analysed using a bivariate method within Stata (copyright StataCorp). This approach assumes a bivariate normal distribution for the logits of sensitivity and specificity, which accounts for the correlation between them in the meta-regression model [29;30]. Where significant heterogeneity was observed, the random effects method was used to account for variation within and between studies. Forest plots were generated within Review Manager (copyright Cochrane Collaboration).

Subgroup analyses

Subgroup analyses were undertaken according to whether PET or PET/CT was used; size and number of axillary metastases; clinical nodal status; T stage (size) of breast tumour; and reference standard test used. In addition, all study quality variables were added as covariates in univariate regression models to assess whether any had a significant effect ($p<0.10$) on sensitivity or specificity.

Results

Number and characteristics of included studies

The search identified 658 unique citations, of which 138 were examined as full texts (numbers refer to all results from a broader search undertaken within a wider review). In total, 26 PET studies (reported within 36 citations) were suitable for inclusion. Study characteristics are described in Table 1. There were 7 studies assessing PET/CT [31-37] and 19 studies assessing PET alone [38-56]. The number of analysed patients (relevant to this review) ranged from 24 to 308. The mean age of included patients ranged from 49 to 67 years (mean across studies 56 years), and the majority of patients were female. The prevalence of axillary metastases (measured via reference standard) ranged from 26% to 59%, the average being 41%. Eight studies consisted entirely of clinically node-negative patients, 13 studies included both node-negative and node-positive patients, and in 5 studies nodal status was not reported.

Quality of included studies

Figure 1 summarises the methodological quality of the 26 included studies. Some studies did not have a representative patient spectrum due to inclusion of up to 20% participants who were not early stage or newly diagnosed (11 studies), or because patients were not recruited prospectively and consecutively (3 studies; unclear in 12). The reference standard was adequate (ALND or SLNB) in nearly all studies; 8 used ALND for all patients, 12 used a combination of ALND and SLNB, 3 did not specify (just stating that histology was used), and 3 used other methods for some patients. The delay between reference standard and index test was considered acceptable (≤ 3 months) in 14 studies and not reported in 12. Where patients received a different reference standard depending on index test results (6 studies), this was either ALND or SLNB; since SLNB has slightly lower accuracy, differential verification bias may occur. Blind interpretation of reference standard results was under-reported with 20 studies scoring 'unclear'. The index test was interpreted blind to reference standard results in most studies. The index test was often interpreted blind to other clinical data, possibly to ensure a robust evaluation of PET; however, as this may differ from expected clinical practice, such studies scored negatively for 'relevant clinical information'. Uninterpretable results were dealt with appropriately in 8 studies, and not discussed in 16 studies. Most studies had no withdrawals to explain, so this item scored well. The reference standard was often only partially described, probably due to widespread routine use, whilst the index test was usually well described.

Sensitivity and specificity of PET and PET/CT

Across 26 studies evaluating PET or PET/CT (n=2,591 patients), the mean sensitivity was 63% (95% CI: 52-74%; range 20-100%) and mean specificity 94% (95% CI: 91-96%; range 75-100%). Of 7 studies evaluating PET/CT (n=862), the mean sensitivity was 56% (95% CI: 44-67%) and mean specificity 96% (95% CI: 90-99%). Of 19 studies evaluating PET-only (n=1,729), the mean sensitivity

was 66% (95% CI: 50-79%) and mean specificity 93% (95% CI: 89-96%). Some early studies of PET-only reported higher sensitivity estimates than later studies (discussed below), which may account for the slightly higher mean sensitivity for the PET-only studies compared with PET/CT. Results are presented in Table 2 and Figure 2.

Effect of publication date

Although the majority of studies do not show a clear trend in results according to publication date, the earliest six studies (1996 to 2001) [51-56] report higher sensitivities than later studies (Figure 2). This may reflect differences in methodology; for example, four of six early studies [52;53;55;56] did not report using ALND or SLNB for all patients, which may have overestimated sensitivity. Also, none of these early studies restricted inclusion by clinical nodal status, whereas some later studies included clinically node-negative patients only, which may have decreased the sensitivity estimate for later studies.

Effect of size and number of axillary metastases

A few studies analysed sensitivity according to size and number of axillary metastases (Table 3 and Figure 3). Although the number of patients in this analysis was small, there was a trend for lower sensitivities where metastatic lymph nodes were smaller or fewer in number. Axillary micrometastases ($\leq 2\text{mm}$) were associated with a mean sensitivity of 11% (95% CI: 5-22%) based on 5 studies (n=63) [37;38;44;46;47], while macrometastases ($> 2\text{mm}$) were associated with a mean sensitivity of 57% (95% CI: 47-66%) based on 4 studies (n=111) [31;38;46;47]. Some studies reported the mean size of axillary metastases in true positive and false negative cases. Results varied between studies; however, the smallest metastatic nodes detected by PET measured 3mm [46;47], while PET failed to detect some nodes measuring $>15\text{ mm}$ [42;44;53].

Effect of clinical nodal status

Studies in which all patients were clinically node-negative (generally defined as non-palpable) showed a trend towards lower sensitivity compared with studies that included both clinically node-negative and node-positive patients (Table 3). This may reflect the fact that clinically negative axillary metastases are likely to be smaller. This analysis was limited since, even in studies with a mixed population, the majority of patients were clinically node-negative (Table 3).

Effect of T stage (size) of the breast tumour

A subset of studies reported sensitivity and specificity according to T stage (size) of the primary breast tumour. The pooled sensitivity and specificity estimates did not show a clear pattern, possibly due to the wide variation in estimates between studies (Table 3). However, some individual studies suggested

a trend for lower sensitivity in patients with smaller breast tumours (e.g. when comparing T1 versus T2 [32;39;51] or T2 versus T3 [37;53]).

Effect of reference standard

In terms of reference standard, sensitivity and specificity were similar between studies using only ALND and studies using a combination of ALND and SLNB, while studies in which not all patients received ALND/SLNB or this information was not reported had a higher sensitivity (Table 3).

Effect of study quality

No study quality variables had a significant effect on specificity. Study quality variables with a significant effect ($p < 0.10$) on sensitivity were as follows. Studies with a representative patient spectrum had higher average sensitivity than those where this was unclear ($p = 0.001$). Studies using the same reference standard regardless of index test results had lower sensitivity than those where this was not done or unclear ($p < 0.001$). Studies in which the index test was interpreted blind to reference standard results had higher sensitivity than those where this was unclear ($p < 0.001$). Studies in which the reference standard was interpreted blind to index test results had lower sensitivity than those where this was unclear, but higher sensitivity than the single study where this was unblinded ($p < 0.001$). Studies in which uninterpretable test results did not occur, or occurred and were included in the analysis, had a lower sensitivity than studies where this was unclear ($p < 0.001$). Studies which score “unclear” on reporting of quality variables may be expected to be of poorer quality, but this could theoretically lead to either underestimates or overestimates of diagnostic accuracy.

Withdrawal rates, adverse events and contraindications

No adverse events were reported for any of the 26 studies. Many studies excluded patients who were pregnant or had diabetes mellitus. In 20 of 26 studies, no withdrawals were reported (however, studies that were not prospective and consecutive may have only included patients with complete data). The remaining 6 studies reported that between 4% and 22% of patients withdrew. Reasons for withdrawal included anxiety and inconvenience, unavailability of PET scanner, unusable PET scans, and patients not undergoing ALND.

Discussion

Across all 26 studies of PET or PET/CT, the pooled sensitivity was 63% and pooled specificity 94%. The sensitivity varied widely between individual studies (range 20% to 100%), while the specificity varied from 75 to 100%. Therefore, the pooled data should be interpreted with caution, since the sensitivity and specificity achieved in a particular clinical setting may be lower than the average values. Variations in sensitivity and specificity of PET across studies may reflect differences in clinical populations and methods of PET imaging and interpretation. Sloka et al. have compiled a set of technical aspects of PET which should be considered and optimised in future clinical studies; these include scan times, reconstruction algorithms, patient position, fasting and attenuation correction [21]. Sensitivity was lower for smaller metastases; for micrometastases ($\leq 2\text{mm}$), sensitivity was only 11%. Though this analysis included few patients, it is unlikely that PET would reliably detect small metastases, since current PET cameras are only thought to achieve spatial resolutions of around 4-5mm [57].

Imaging techniques such as PET could potentially be used in two ways in axillary assessment; to replace surgical methods such as SLNB, or as an additional test prior to SLNB. The sensitivity of SLNB has been estimated at 93% in a meta-analysis of 69 studies [58], while its specificity is likely to approach 100% due to use of histological methods. Our review indicates that PET has lower sensitivity and specificity than SLNB. Therefore, replacing SLNB with PET would lead to more false negative patients at risk of cancer recurrence and more false positive patients who would undergo unnecessary ALND, although all patients would avoid the adverse effects associated with SLNB.

Use of PET scanning prior to SLNB would allow patients with a positive PET scan to progress directly to ALND, thus preventing the need for two sequential operations (SLNB then ALND). However, since PET has lower specificity than SLNB, there would be more false positive patients who would undergo unnecessary ALND. Intra-operative assessment of nodal status [12] may also reduce the number of patients requiring two operations, irrespective of prior imaging. Use of PET prior to SLNB must be considered in the context of existing diagnostic methods such as clinical examination, ultrasound, and needle biopsy of suspicious nodes [19]. A systematic review estimated the average sensitivity of ultrasound as 69-71% and specificity as 75-86% [6]. As sensitivity of PET and ultrasound appear broadly similar, it is unclear whether PET would provide sufficient improvement in diagnostic accuracy to be of significant value.

PET is being evaluated for several aspects of breast cancer management in addition to axillary assessment. The National Comprehensive Cancer Network 2007 report concluded that PET was not indicated for detection or screening of primary breast cancer; post-treatment surveillance; or staging of

the primary tumour or metastatic disease in patients with clinically early-stage breast cancer (due to low yield and psychological distress associated with false-positive results) [19]. However, this report stated that there were some promising results relating to PET for locoregional staging in locally-advanced disease; assessing treatment response to neoadjuvant chemotherapy or metastatic disease therapy; and as an adjunct to other imaging techniques in evaluation of recurrent or metastatic disease.

Conclusions

Studies of PET for evaluation of axillary metastases in breast cancer have demonstrated wide variations in sensitivity and specificity. Current aggregated estimates of sensitivity suggest that PET is unlikely to be sufficiently sensitive to replace surgical methods such as SLNB. Sensitivity is low for small metastases and PET is unlikely to reliably detect micrometastases. Use of PET imaging prior to SLNB would allow PET-positive patients to progress directly to ALND, but would lead to more false positive patients who would undergo ALND unnecessarily. The average sensitivity of PET appears similar to that of ultrasound, which is already routinely used in axillary assessment. At present therefore, this review does not find evidence to recommend the use of PET or PET-CT for routine evaluation of axillary disease in women with early breast cancer.

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Table 1: Characteristics of included studies

Study	Country	Index test	Reference standard	Prospective/ retrospective? Consecutive?	N met criteria ^a N analysed	Age Gender	Cancer stage	Clinical nodal status	Prevalence of axillary metastases	Confirmation of breast cancer	Other inclusion and exclusion criteria
Studies of PET/CT											
Chae 2009 [31]	South Korea	PET/CT	100% ALND (plus SLNB)	Retrospective NR	108 108	49 (27 - 75) NR	T1=71%, T2=27%, T3=2% N0=69%, N1=17%, N2=9%, N3=5%	100% negative; micrometastases/ ITCs excluded	31%	CNB or FNAC	NR
Heusner 2009 [32]	Germany	PET/CT	ALND and/or SLNB	Retrospective Consecutive	54 54	56 (28 - 78) Female	T1=44%, T2=56% N0=59%, N1=26%, N2=7%, N3=7%	Positive and negative (% NR)	41%	Histopathology	NR
Kim 2009 [33]	South Korea	PET/CT	ALND and/or SLNB (plus non-SLNB)	Prospective Consecutive	137 137	51 (27-85) 99% female	T1/T2=100%, no DCIS	NR	26%	Biopsy	Exclusion: diabetes, neoadjuvant chemotherapy, excisional biopsy
Taira 2009 [34]	Japan	PET/CT	ALND (if PET or SLNB positive) and/or SLNB	Retrospective NR	92 axilla 92 axilla	55 ^b (21-82) Female	T1=68%, T2=29%, T3=2%, no DCIS	100% negative	29%	6 EB; remainder NR	Exclusion: prior chemotherapy, hormone therapy, radiotherapy
Fuster 2008 [35]	Spain	PET/CT	100% ALND	Prospective Consecutive	60 52	57 +/- 13 NR	T1=0%, T2=21%, T3=68%, T4=11% (all primary tumour >3cm)	97% negative 3% positive	38%	CNB	Exclusion: IBC, breast surgery, chemotherapy or radiotherapy, pregnant, diabetes, age <18 years
Ueda 2008 [36]	Japan	PET/CT	ALND and/or SLNB	Prospective Unclear (states "series")	183 183	57 (32-81) NR	Tis=5%, T1=50%, T2=37%, T3=8%	Positive and negative (% NR)	32%	CNB	Exclusion: distant metastases, systemic therapy, excisional biopsy, diabetes, pregnancy
Veronesi 2007 [37]	Italy	PET/CT	ALND (if PET or SLNB positive) and/or SLNB	Prospective Consecutive	236 236	49 ^b (24-79) 99.6% female	T1=58%, T2=37%, T3=6%, no DCIS. N0=56%, N1=32%, N2=8%, N3=4%	100% negative	44%	FNAC, CNB or EB	Exclusion: neoadjuvant chemotherapy
Studies of PET-only											
Cermik 2008 [38] Kumar 2006 [59]	USA	PET-only	ALND and/or SLNB	Prospective Consecutive	188 axilla 188 axilla	51 (24-80) Female (confirmed by author)	N0=61%, N1=31%, N2=8%	Positive and negative (% NR)	39%	CNB 67.5%, EB 32.5%	NR
Gil-Rendo 2006 [39] Zornoza 2004 [60]	Spain	PET-only	ALND (first n=150 and next n=125 if PET/SLNB +ve) and/or SLNB	Prospective Unclear (states "series")	275 275	51 (24-87) Female	Stage I-II=100%, T1=49%, extensive DCIS=4%, neoadjuvant chemo=2%	100% negative	52%	CNB	Exclusion: stage III/IV, biopsy or surgery to breast or axilla, uncontrolled diabetes
Weir 2005 [40]	Canada	PET-only	ALND and/or SLNB	Retrospective NR	40 40	52 ^b (30-88) Female	Stage not reported. Newly-diagnosed.	NR	45%	Histology (no further detail)	Exclusion: non-newly diagnosed, axillary surgery, chemotherapy
Agresti 2004 [41] Agresti 2001 [61]	Italy	PET-only	ALND (if PET or SLNB positive) and/or SLNB	NR NR	71 71	55 (24-78) NR	T1=86%, T2=14%	100% negative	44%	NR	Exclusion: primary tumour >2.5cm
Fehr 2004 [42]	Switzerland	PET-only	100% ALND (plus SLNB)	NR NR	24 24	56 +/- 10.8 NR	T1 = 14 (58%) T2 = 9 (38%) T3 = 1 (4%)	100% negative	42%	FNAC	Exclusion: tumour >3cm, IBC, multifocality, pregnancy, lactation, diabetes, radiotherapy, breast/axilla surgery

Study	Country	Index test	Reference standard	Prospective/ retrospective? Consecutive?	N met criteria ^a N analysed	Age Gender	Cancer stage	Clinical nodal status	Prevalence of axillary metastases	Confirmation of breast cancer	Other inclusion and exclusion criteria
Inoue 2004 [43] Yutani 2000 [62] Yutani 1999 [63]	Japan	PET-only	All confirmed by histology, "almost all" ALND (via author)	Retrospective (via author) NR	81 81	53 ^b (32-78) Female	T1=41%, T2=46%, T3=14% N0=23%, N1-N2=77%	23% negative 77% positive	43%	Histology after surgery (via author)	Exclusion: distant metastases
Lovrics 2004 [44] Lovrics 2002 [64]	Canada	PET-only	ALND and/or SLNB	Prospective Consecutive	115 90	56 (SD 11) Female	T1=81%, T2=18%, T3=1%	Positive and negative (% NR)	28%	Histology: 14 EB, NR for remainder	Exclusion: stage III/IV, multiple, multicentric, IBC, male, prior ALND, pregnancy, uncontrolled diabetes
Wahl 2004 [45]	USA	PET-only	100% ALND (some SLNB also)	Prospective Consecutive (via author)	330 axilla 308 axilla	52 (27-82) Female	T1=65%, T2=28%, T3=2%, Tx=1%, missing=4%	92% negative 8% positive	35%	NR	Exclusion: non-invasive, distant metastases, diabetes, infections, serious organ dysfunction, neoadjuvant chemotherapy, SLNB only
Barranger 2003 [46]	France	PET-only	100% ALND (plus SLNB)	Prospective Consecutive	32 32	58 (29-77) NR	T0=28%, T1=56%, T2=16%	100% negative	47%	FNAC or CNB	Exclusion: neoadjuvant chemotherapy, pregnancy, diabetes
Guller 2002 [47]	Switzer- land	PET-only	ALND and/or SLNB	Prospective Consecutive	31 31	65 (47-88) Female	T1=61%, T2=39%	100% negative	45%	Histopathology (no further detail)	Exclusion: pregnancy, diabetes, inability to lie still in PET scanner
Nakamoto 2002 [48]	USA	PET-only	100% ALND	Prospective NR	30 30	51 (28-78) 94% female	T1=67%, T2=37%, T3=7%	NR	43%	Histology (no further detail)	NR
Rieber 2002 [49]	Germany	PET-only	Histology (no further details)	NR NR	43 40	53 (27-84) NR	DCIS=3%, Tmic=3%, T1=21%, T2=49%, T3=10%, T4=15%	NR	50%	Histology (no further detail)	NR
van der Hoeven 2002 [50]	Nether- lands	PET-only	ALND and/or SLNB (depending on tumour size)	Prospective Unclear	70 70	58 yrs (SD 13) NR	T0=6%, T1=53%, T2=26%, T3=6%, T4=4%, unknown=6%	71% negative 29% positive	46%	EB 17%, FNAC 83%	Exclusion: diabetes
Greco 2001 [51] Crippa 1998 [65] Bombardieri 1998 [66] Crippa 1997 [67]	Italy	PET-only	100% ALND	Prospective Consecutive	167 167	54 (28-84) NR	T1=59%, T2=41%	77% negative 23% positive	43%	Histology (no further detail)	Exclusion: primary tumour >5cm, abnormal blood glucose
Noh 1998 [52]	South Korea	PET-only	Histology (no further details)	NR NR	31 axilla 27 axilla	NR NR	Stage not reported DCIS=12%; not clear if included in analysis	70% negative 30% positive	56%	Histology (no further detail), 1 FNAC	NR
Smith 1998 [53]	UK	PET-only	ALND 90%; FNAC 10% (large / locally advanced)	NR NR	38 38	67 (26-89) Female	T1=21%, T2=55%, T3=24%	70% negative 30% positive	42%	FNAC	Exclusion: age <18 years, pregnant, diabetes, unable to lie still on PET scanner
Adler 1997 [54] Adler 1996 [68]	USA	PET-only	100% ALND	Part of prospective study NR	54 axilla 52 axilla	36-79 NR	Benign=2%, T1=60%, T2=33%, T3=6%	NR	38%	NR	Exclusion: primary tumour <0.5cm, < level II ALND, <10 nodes dissected, age <30 years, prior ALND, neoadjuvant chemotherapy

Study	Country	Index test	Reference standard	Prospective/ retrospective? Consecutive?	N met criteria ^a N analysed	Age Gender	Cancer stage	Clinical nodal status	Prevalence of axillary metastases	Confirmation of breast cancer	Other inclusion and exclusion criteria
Avril 1996 [55]	Germany	PET-only	ALND 90%; clinical examination 10% (locally advanced)	NR NR	41 41	50 (18-74) Female	T1=44%, T2+ =56%, locally advanced=10%, distant or non-axillary metastases \geq 12%	Positive and negative (% NR)	59%	Histology (no further detail) after surgery	Exclusion: age <18 years, pregnancy, diabetes
Utech 1996 [56]	USA / Germany	PET-only	ALND 44%; modified radical mastectomy 56%	Prospective NR	124 124	59 (32-94) NR	T1=67%, T2=29%, T3=4% N0=64%, N1=35%, N2=2%	92% negative 8% positive	35%	CNB 42%, EB 54%, partial mastectomy 4%	NR

^aNumber meeting criteria for this review. Ages are mean (range) unless marked ^b which indicates median (range). ALND=axillary lymph node dissection; CNB=core needle biopsy; CT=computed tomography; EB=excisional biopsy; FNAC=fine needle aspiration cytology; IBC= inflammatory breast cancer; ITCs=isolated tumour cells; PET=positron emission tomography; NR=not reported; SLNB=sentinel lymph node biopsy.

Table 2: Pooled sensitivity and specificity for PET and PET/CT

Diagnostic test	N studies	N patients	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
All PET studies [31-56]	26	2591	63 (52 to 74)	94 (91 to 96)
PET/CT [31-37]	7	862	56 (44 to 67)	96 (90 to 99)
PET (no CT) [38-56]	19	1729	66 (50 to 79)	93 (89 to 96)

Table 3: Effect of clinical variables on sensitivity and specificity

Subgroup	N studies	N patients	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Size of axillary metastases				
≤ 2mm [37;38;44;46;47]	5	63	11 (5 to 22)	Not calculable ^a
< 5mm [36]	1	15	33 (15 to 59)	Not calculable ^a
> 2mm [31;38;46;47]	4	111	57 (47 to 66)	Not calculable ^a
> 5mm [37]	1	51	57 (43 to 70)	Not calculable ^a
> 10mm [36]	1	28	79 (60 to 90)	Not calculable ^a
Number of axillary metastases				
1 metastatic node [36;50;55]	3	52	27 (7 to 63)	Not calculable ^a
Multiple metastatic nodes [50]	1	12	50 (21 to 79)	Not calculable ^a
2-5 metastatic nodes [36;55]	2	23	61 (40 to 78)	Not calculable ^a
>5 metastatic nodes [36;55]	2	24	77 (53 to 91)	Not calculable ^a
Nodal stage				
pN1 [38;39]	2	147	63 (24 to 91)	Not calculable ^a
pN2 [38;39]	2	53	83 (51 to 96)	Not calculable ^a
pN3 [38;39]	2	21	88 (66 to 97)	Not calculable ^a
Clinical nodal status				
All clinically negative [31;34;37;39;41;42;46;47]	8	869	48 (32 to 64)	94 (90 to 97)
Mix of positive and negative [32;35;36;38;43-45;50-53;55;56]	13	1423	72 (54 to 85)	93 (88 to 96)
Nodal status not reported [33;40;48;49;54]	5	299	65 (44 to 81)	95 (82 to 99)
T stage (size) of breast tumour				
T1 (≤ 2cm) [32;37;39;42;47;48;51;53;55;56]	10	451	53 (34 to 72)	87 (82 to 91)
T2 (>2cm, ≤ 5cm) [32;35;37;39;42;47;48;51;53]	9	343	67 (40 to 86)	86 (78 to 92)
T2 or above (>2cm) [55;56]	2	82	96 (84 to 99)	82 (13 to 99)
T3 (>5cm) [32;35;37;42;48;53]	6	41	65 (44 to 82)	88 (58 to 98)
T4 (tumour spread/fixed to skin/chest wall, or IBC) [53]	1	10	100 (54 to 100)	100 (40 to 100)
Reference standard				
100% ALND [31;35;42;45;46;48;51;54]	8	773	59 (36 to 78)	90 (80 to 95)
ALND and/or SLNB [32-34;36- 41;44;47;50]	12	1467	52 (40 to 63)	95 (93 to 97)
Not all ALND/SLNB, or not reported [43;49;52;53;55;56]	6	351	88 (68 to 96)	94 (85 to 98)

^aSpecificity not calculable for these subgroups since by definition all patients had metastases

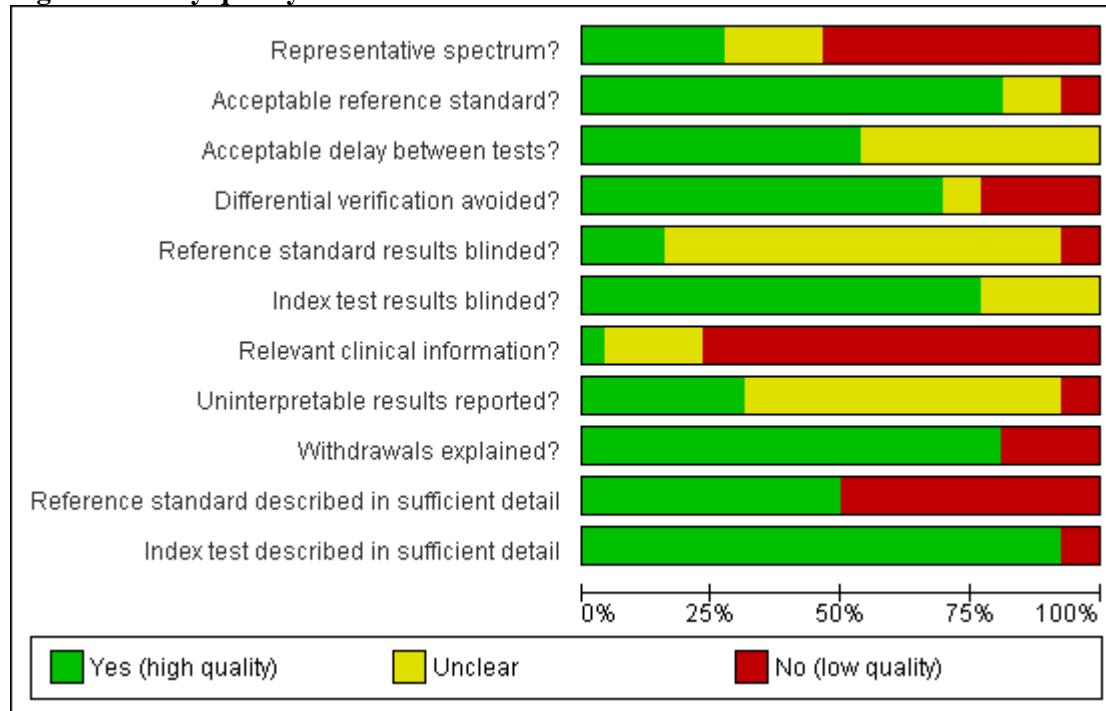
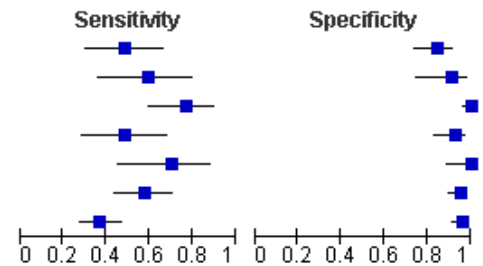
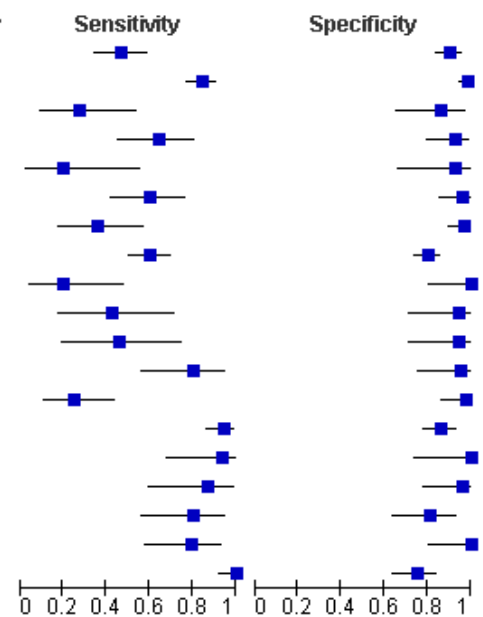
Figure 1: Study quality

Figure 2: Forest plot of sensitivity and specificity for all studies**PET/CT**

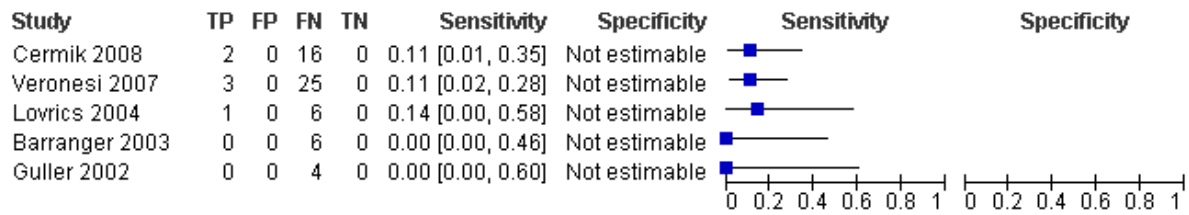
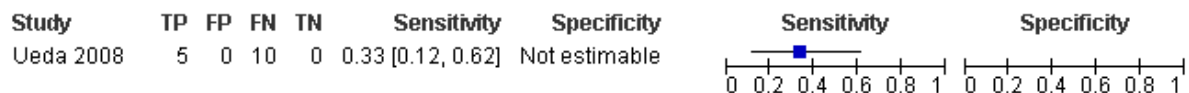
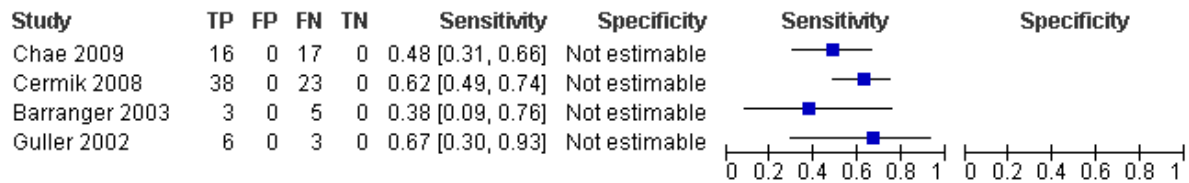
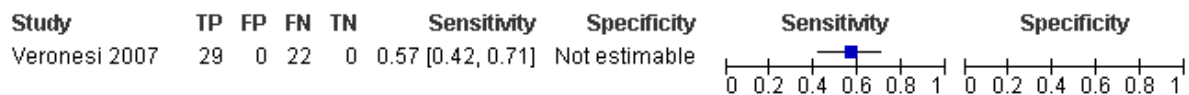
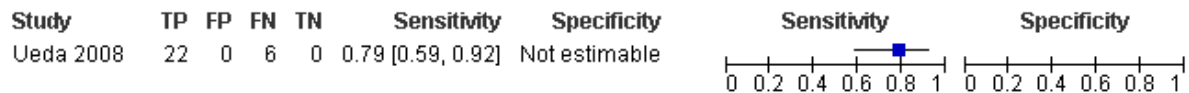
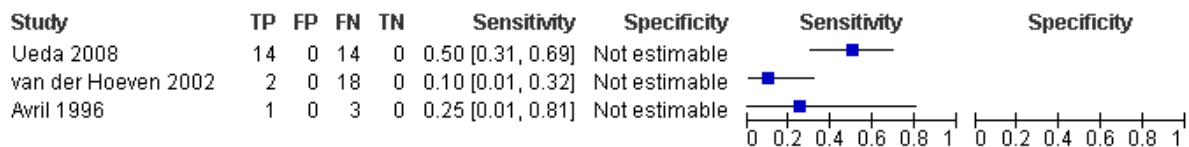
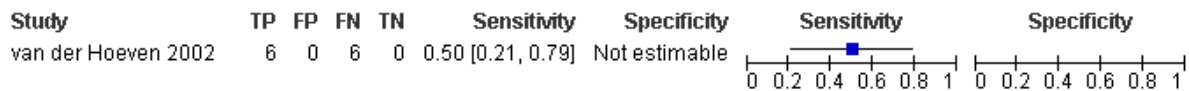
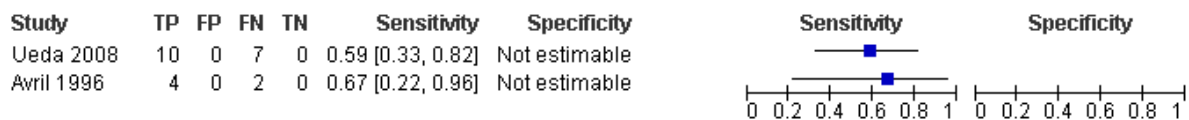
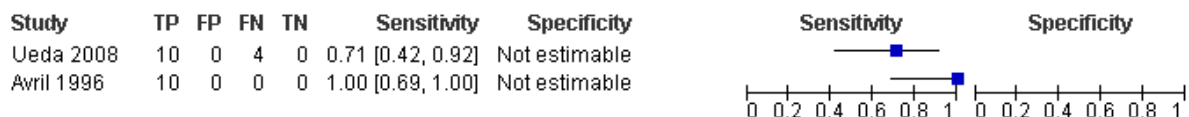
Study	TP	FP	FN	TN	Sensitivity	Specificity
Chae 2009	16	12	17	63	0.48 [0.31, 0.66]	0.84 [0.74, 0.91]
Heusner 2009	13	3	9	29	0.59 [0.36, 0.79]	0.91 [0.75, 0.98]
Kim 2009	27	0	8	102	0.77 [0.60, 0.90]	1.00 [0.96, 1.00]
Taira 2009	13	5	14	60	0.48 [0.29, 0.68]	0.92 [0.83, 0.97]
Fuster 2008	14	0	6	32	0.70 [0.46, 0.88]	1.00 [0.89, 1.00]
Ueda 2008	34	6	25	118	0.58 [0.44, 0.70]	0.95 [0.90, 0.98]
Veronesi 2007	38	5	65	128	0.37 [0.28, 0.47]	0.96 [0.91, 0.99]

**PET only**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cermik 2008	34	11	39	104	0.47 [0.35, 0.59]	0.90 [0.84, 0.95]
Gil-Rendo 2006	120	2	22	131	0.85 [0.77, 0.90]	0.98 [0.95, 1.00]
Weir 2005	5	3	13	19	0.28 [0.10, 0.53]	0.86 [0.65, 0.97]
Agresti 2004	20	3	11	37	0.65 [0.45, 0.81]	0.93 [0.80, 0.98]
Fehr 2004	2	1	8	13	0.20 [0.03, 0.56]	0.93 [0.66, 1.00]
Inoue 2004	21	2	14	44	0.60 [0.42, 0.76]	0.96 [0.85, 0.99]
Lovrics 2004	9	2	16	63	0.36 [0.18, 0.57]	0.97 [0.89, 1.00]
Wahl 2004	66	40	43	159	0.61 [0.51, 0.70]	0.80 [0.74, 0.85]
Barranger 2003	3	0	12	17	0.20 [0.04, 0.48]	1.00 [0.80, 1.00]
Guller 2002	6	1	8	16	0.43 [0.18, 0.71]	0.94 [0.71, 1.00]
Nakamoto 2002	6	1	7	16	0.46 [0.19, 0.75]	0.94 [0.71, 1.00]
Rieber 2002	16	1	4	19	0.80 [0.56, 0.94]	0.95 [0.75, 1.00]
van der Hoeven 2002	8	1	24	37	0.25 [0.11, 0.43]	0.97 [0.86, 1.00]
Greco 2001	68	13	4	82	0.94 [0.86, 0.98]	0.86 [0.78, 0.93]
Noh 1998	14	0	1	12	0.93 [0.68, 1.00]	1.00 [0.74, 1.00]
Smith 1998	13	1	2	22	0.87 [0.60, 0.98]	0.96 [0.78, 1.00]
Adler 1997	16	6	4	26	0.80 [0.56, 0.94]	0.81 [0.64, 0.93]
Avril 1996	19	0	5	17	0.79 [0.58, 0.93]	1.00 [0.80, 1.00]
Utech 1996	44	20	0	60	1.00 [0.92, 1.00]	0.75 [0.64, 0.84]



TP=true positive, FP=false positive, FN=false negative, TN=true negative. Brackets show 95% confidence intervals. The figure shows the sensitivity and specificity for each study (squares) and 95% confidence intervals (horizontal lines).

Figure 3: Forest plot of sensitivity of PET according to size and number of axillary metastases**3a) According to size of axillary metastases****Less than 2mm****Less than 5mm****More than 2mm****More than 5mm****More than 10mm****3b) According to number of axillary metastases****1 metastatic node****Multiple metastatic nodes****2-5 metastatic nodes****>5 metastatic nodes**

3c) According to nodal stage

Nodal stage pN1

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Cermik 2008	24	0	34	0	0.41 [0.29, 0.55]	Not estimable		
Gil-Rendo 2006	72	0	17	0	0.81 [0.71, 0.88]	Not estimable		

Nodal stage pN2

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Cermik 2008	10	0	5	0	0.67 [0.38, 0.88]	Not estimable		
Gil-Rendo 2006	35	0	3	0	0.92 [0.79, 0.98]	Not estimable		

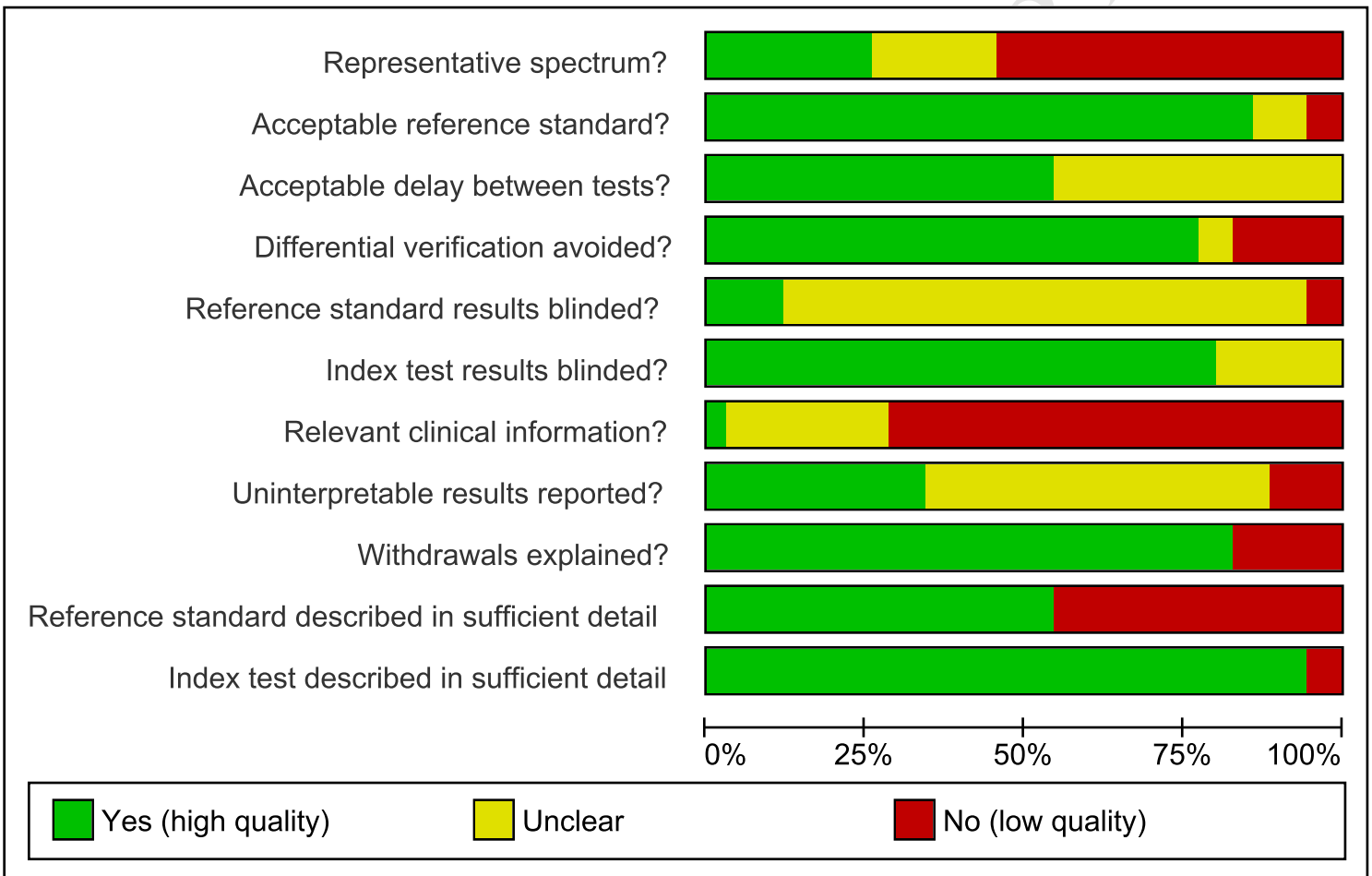
Nodal stage pN3

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Cermik 2008	6	0	0	0	1.00 [0.54, 1.00]	Not estimable		
Gil-Rendo 2006	13	0	2	0	0.87 [0.60, 0.98]	Not estimable		

TP=true positive, FP=false positive, FN=false negative, TN=true negative. Brackets show 95% confidence intervals. The figure shows the sensitivity and specificity for each study (squares) and 95% confidence intervals (horizontal lines).

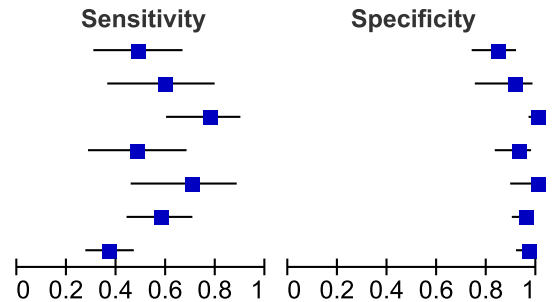
Appendix 1: MEDLINE search strategy

- 1 exp Breast Neoplasms/
- 2 exp Neoplasms/
- 3 exp Carcinoma/
- 4 exp Adenocarcinoma/
- 5 2 or 3 or 4
- 6 exp Breast/
- 7 5 and 6
- 8 ((breast\$ or mamma\$) adj5 (cancer\$ or carcin\$ or tumour\$ or tumor\$ or neoplasm\$ or malignan\$)).tw.
- 9 1 or 7 or 8
- 10 Positron-Emission Tomography/
- 11 positron emission tomography.tw.
- 12 PET.tw.
- 13 or/10-12
- 14 9 and 13
- 15 Axilla/
- 16 axilla\$.tw.
- 17 exp lymphatic system/ or exp lymph nodes/
- 18 Lymphatic Metastasis/
- 19 lymphatic system/ or exp lymphatic vessels/ or exp lymphoid tissue/
- 20 lymph\$.tw.
- 21 or/15-20
- 22 14 and 21
- 23 exp "Sensitivity and Specificity"/
- 24 sensitivity.tw.
- 25 specificity.tw.
- 26 ((pre-test or pretest) adj probability).tw.
- 27 post-test probability.tw.
- 28 predictive value\$.tw.
- 29 likelihood ratio\$.tw.
- 30 or/23-29
- 31 22 and 30



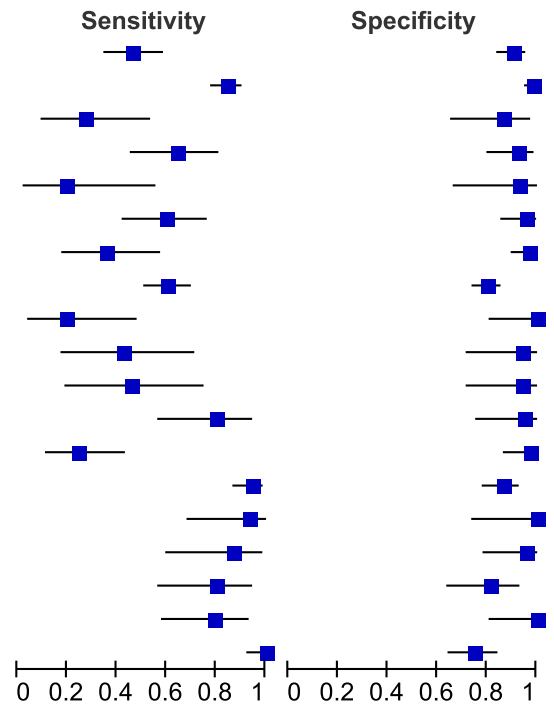
PET/CT

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chae 2009	16	12	17	63	0.48 [0.31, 0.66]	0.84 [0.74, 0.91]
Heusner 2009	13	3	9	29	0.59 [0.36, 0.79]	0.91 [0.75, 0.98]
Kim 2009	27	0	8	102	0.77 [0.60, 0.90]	1.00 [0.96, 1.00]
Taira 2009	13	5	14	60	0.48 [0.29, 0.68]	0.92 [0.83, 0.97]
Fuster 2008	14	0	6	32	0.70 [0.46, 0.88]	1.00 [0.89, 1.00]
Ueda 2008	34	6	25	118	0.58 [0.44, 0.70]	0.95 [0.90, 0.98]
Veronesi 2007	38	5	65	128	0.37 [0.28, 0.47]	0.96 [0.91, 0.99]

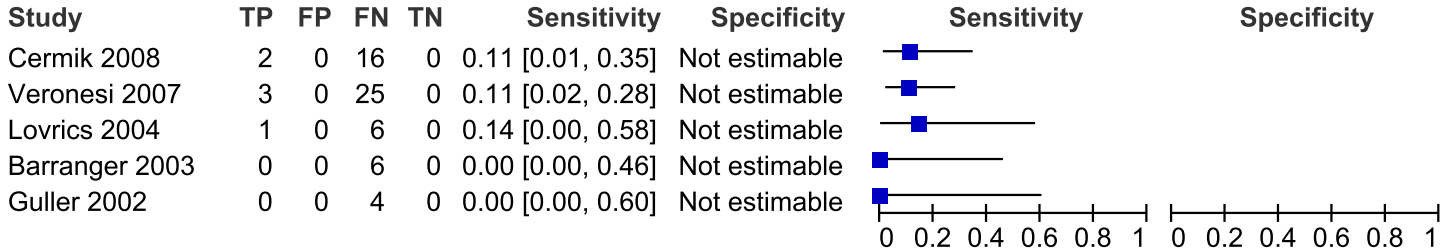


PET only

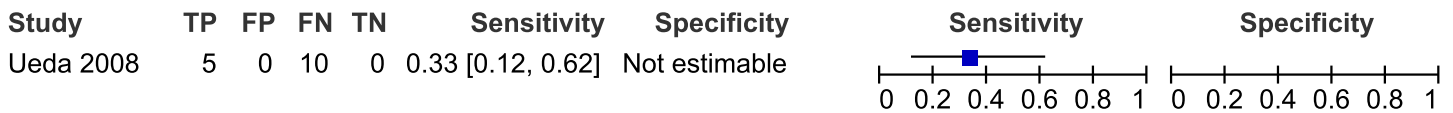
Study	TP	FP	FN	TN	Sensitivity	Specificity
Cermik 2008	34	11	39	104	0.47 [0.35, 0.59]	0.90 [0.84, 0.95]
Gil-Rendo 2006	120	2	22	131	0.85 [0.77, 0.90]	0.98 [0.95, 1.00]
Weir 2005	5	3	13	19	0.28 [0.10, 0.53]	0.86 [0.65, 0.97]
Agresti 2004	20	3	11	37	0.65 [0.45, 0.81]	0.93 [0.80, 0.98]
Fehr 2004	2	1	8	13	0.20 [0.03, 0.56]	0.93 [0.66, 1.00]
Inoue 2004	21	2	14	44	0.60 [0.42, 0.76]	0.96 [0.85, 0.99]
Lovrics 2004	9	2	16	63	0.36 [0.18, 0.57]	0.97 [0.89, 1.00]
Wahl 2004	66	40	43	159	0.61 [0.51, 0.70]	0.80 [0.74, 0.85]
Barranger 2003	3	0	12	17	0.20 [0.04, 0.48]	1.00 [0.80, 1.00]
Guller 2002	6	1	8	16	0.43 [0.18, 0.71]	0.94 [0.71, 1.00]
Nakamoto 2002	6	1	7	16	0.46 [0.19, 0.75]	0.94 [0.71, 1.00]
Rieber 2002	16	1	4	19	0.80 [0.56, 0.94]	0.95 [0.75, 1.00]
van der Hoeven 2002	8	1	24	37	0.25 [0.11, 0.43]	0.97 [0.86, 1.00]
Greco 2001	68	13	4	82	0.94 [0.86, 0.98]	0.86 [0.78, 0.93]
Noh 1998	14	0	1	12	0.93 [0.68, 1.00]	1.00 [0.74, 1.00]
Smith 1998	13	1	2	22	0.87 [0.60, 0.98]	0.96 [0.78, 1.00]
Adler 1997	16	6	4	26	0.80 [0.56, 0.94]	0.81 [0.64, 0.93]
Avril 1996	19	0	5	17	0.79 [0.58, 0.93]	1.00 [0.80, 1.00]
Utech 1996	44	20	0	60	1.00 [0.92, 1.00]	0.75 [0.64, 0.84]



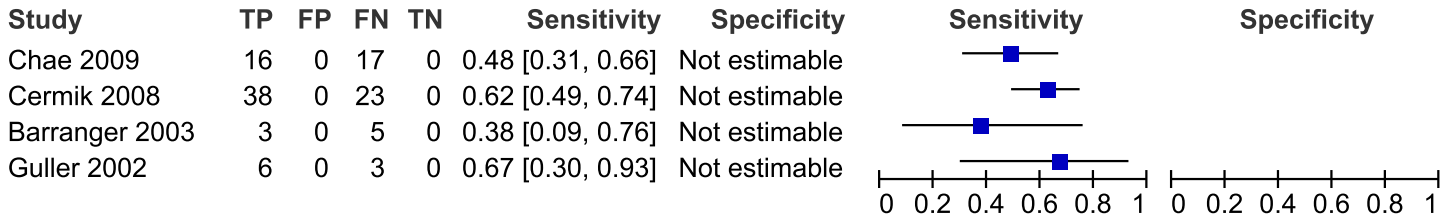
Less than 2mm



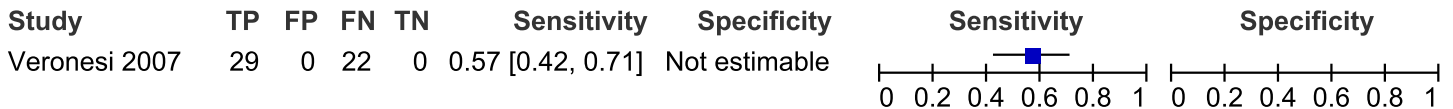
Less than 5mm



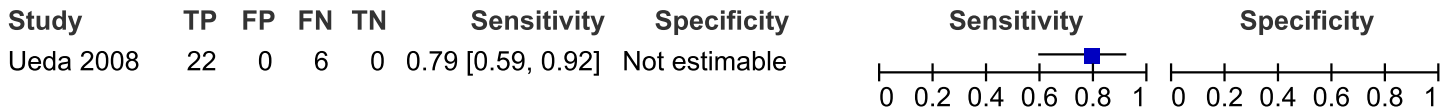
More than 2mm



More than 5mm



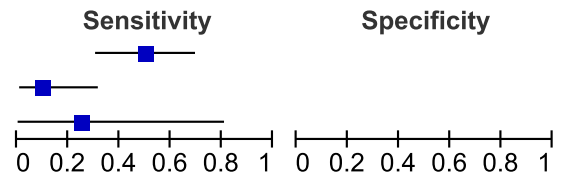
More than 10mm



RIPT

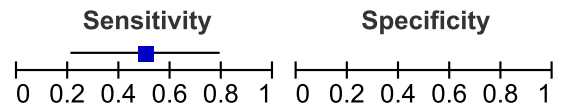
1 metastatic node

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ueda 2008	14	0	14	0	0.50 [0.31, 0.69]	Not estimable
van der Hoeven 2002	2	0	18	0	0.10 [0.01, 0.32]	Not estimable
Avril 1996	1	0	3	0	0.25 [0.01, 0.81]	Not estimable



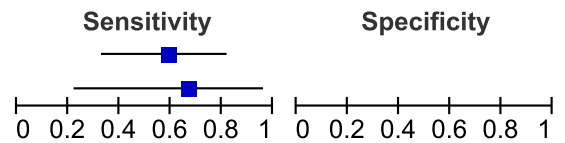
Multiple metastatic nodes

Study	TP	FP	FN	TN	Sensitivity	Specificity
van der Hoeven 2002	6	0	6	0	0.50 [0.21, 0.79]	Not estimable



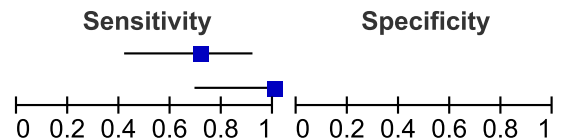
2-5 metastatic nodes

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ueda 2008	10	0	7	0	0.59 [0.33, 0.82]	Not estimable
Avril 1996	4	0	2	0	0.67 [0.22, 0.96]	Not estimable



>5 metastatic nodes

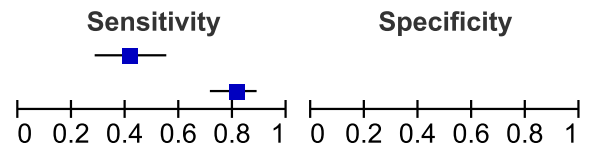
Study	TP	FP	FN	TN	Sensitivity	Specificity
Ueda 2008	10	0	4	0	0.71 [0.42, 0.92]	Not estimable
Avril 1996	10	0	0	0	1.00 [0.69, 1.00]	Not estimable



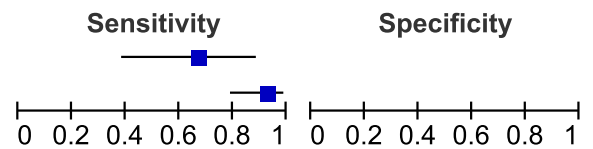
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Nodal stage pN1

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cermik 2008	24	0	34	0	0.41 [0.29, 0.55]	Not estimable
Gil-Rendo 2006	72	0	17	0	0.81 [0.71, 0.88]	Not estimable

**Nodal stage pN2**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cermik 2008	10	0	5	0	0.67 [0.38, 0.88]	Not estimable
Gil-Rendo 2006	35	0	3	0	0.92 [0.79, 0.98]	Not estimable

**Nodal stage pN3**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cermik 2008	6	0	0	0	1.00 [0.54, 1.00]	Not estimable
Gil-Rendo 2006	13	0	2	0	0.87 [0.60, 0.98]	Not estimable

