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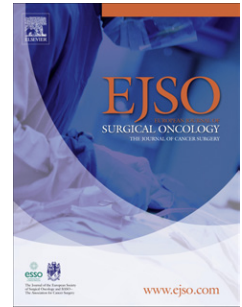
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Meta-analysis of predictive factors for non-sentinel lymph node metastases in breast cancer patients with a positive SLN.

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Abstract

Aims: A meta-analysis was performed to identify the clinicopathological variables most predictive of non-sentinel node (NSN) metastases when the sentinel node is positive.

Methods: A Medline search was conducted that ultimately identified 56 candidate studies. Original data were abstracted from each study and used to calculate odds ratios. The random-effects model was used to combine odds ratios to determine the strength of the associations.

Findings: The 8 individual characteristics found to be significantly associated with the highest likelihood (odds ratio > 2) of NSN metastases are SLN metastases > 2 mm in size, extracapsular extension in the SLN, > 1 positive SLN, ≤ 1 negative SLN, tumour size > 2 cm, ratio of positive sentinel nodes > 50% and lymphovascular invasion in the primary tumour. The histological method of detection, which is associated with the size of metastases, had a correspondingly high odds ratio.

Conclusions: We identified 8 factors predictive of NSN metastases that should be recorded and evaluated routinely in SLN databases. These factors should be included in a predictive model that is generally applicable among different populations.

Introduction

Axillary lymph node status remains a powerful prognostic factor in breast cancer.

Sentinel lymph node (SLN) biopsy is an accepted alternative to axillary lymph node dissection (ALND). Data from 7 randomized controlled trials have conclusively demonstrated that SLN biopsy is associated with less arm/shoulder morbidity and better quality of life than ALND [1-7].

SLN biopsy allows more accurate staging and identifies patients most likely to benefit from ALND. The high negative predictive value allows ALND and the associated morbidity to be safely avoided in SLN negative patients [8].

Due to its prognostic and therapeutic implications (better locoregional disease control) ALND remains the standard of care for SLN-positive patients. However, from the literature it is clear that axillary metastases are limited to the sentinel node in about 40- 60% of cases [9-40]. These patients are thus undergoing ALND without therapeutic benefit.

Over the past years multiple studies have been conducted to identify clinicopathological variables that are predictive of non-sentinel node (NSN) metastases in an attempt to select those patients who would benefit most from ALND. These studies demonstrated that different pathologic characteristics of the primary tumour and the sentinel node were associated with an increased likelihood of additional positive NSNs. The aim of the present study was to present an overview of the identified predictors of NSN positivity in cases of a positive SLN and to perform a meta-analysis to yield a pooled association.

Methods

Medline search

Two different MEDLINE search strategies were conducted to identify relevant articles published up to July 2009:

1. MeSH Database: ' "Breast Neoplasms"[Majr] AND "Sentinel Lymph Node Biopsy"[Majr] AND "Lymphatic Metastasis"[Majr] AND "Predictive" .
2. Clinical Queries, category 'clinical prediction guides,' sensitive search: positive non-sentinel lymph nodes in breast cancer.

Our first search yielded 13 (out of 60) candidate articles, and our second search yielded 45 (out of 180). Articles from the searches with titles pertinent to the topic were further evaluated.

Inclusion and exclusion criteria

The following criteria were used for inclusion in this review:

1. Studies identifying the population of patients with a positive sentinel lymph node who underwent completion ALND,
2. Original data (or odds ratios) reporting on the number of SLN positive patients who had positive NSNs stratified by various patient/tumour characteristics,
3. Studies including patients with both micro- and macrometastatic disease in the SLNs.

References cited in the identified articles were searched for additional relevant studies and these studies were also subject to the same inclusion criteria.

Studies that appeared to represent overlapping patient populations were evaluated for extent of data. If studies tested the same variables, the study with lesser relevance was excluded. The most updated data of each predictor was used.

Non-overlapping variables were included separately.

If a study reported clinicopathological variables of two subpopulations, these populations were included separately.

The following exclusion criteria were applied:

- Studies identifying predictors of positive axillary nodes in general (without the explicit condition of SLN positivity),
- Studies validating different nomograms to predict the risk of non-sentinel node metastases without presenting original data of their study population regarding the association between various patient/ tumour characteristics and the likelihood of positive non-sentinel nodes.
- Studies exclusively evaluating patients with SLN micrometastases.

Statistical methods

The number of patients with positive and negative NSNs for the different patient and tumour characteristics were abstracted and analysed from each study. As some studies did not present the data for characteristics that were not statistically significant, a complete dataset was not always obtainable for every characteristic evaluated in each study. For each characteristic, the pooled unadjusted odds ratio on positive NSNs was calculated according to the random-effects model of DerSimonian and Laird for meta-analyses along with the corresponding 95% confidence interval [41]. These ratios are graphically displayed. Pooled absolute risks on positive NSNs were also calculated. Studies with zero counts (no positive NSNs) were given a small count of 0.5 to avoid computational problems.

Findings and review

Candidate studies

Our MEDLINE searches identified 50 candidate studies. After reviewing the references cited in the selected articles we identified a total of 112 studies.

Excluded studies

After careful assessment, 56 studies were excluded (**Figure 1**).

Ten studies were excluded because they only validated a nomogram and did not test for predictive factors [42-51]. Two studies were excluded because the full text was not available [52;53]. Seventeen studies only presented predictive factors for positive axillary lymph nodes (SLN biopsy was not performed) [54-69].

Six studies only focused on predictive factors for having at least 4 positive axillary nodes [70-75]. Seven studies only evaluated patients with SLN micrometastases [8;76-81]. Furthermore, 4 studies were excluded for not presenting raw data on the association between patient/tumour characteristics and positive non-sentinel nodes [16;24;82;83]. Two studies only included patients with positive sentinel lymph nodes identified with cytokeratin-immunohistochemistry [84;85]. In 1 study, predictive factors in special tumour types were evaluated [86]. One study included patients with a tumour size less than 15 mm exclusively [87]. One study was excluded because it was also a meta-analysis of predictive factors [88]. Five studies were excluded because of the presumed overlap of the dataset with another study [14;26;27;89;90].

Included studies

Thus, 56 studies, published between January 1999 and June 2009 were included in this meta-analysis (**Table 1**) [9-13;15;17-23;25;28-40;91-118]. The study sample sizes ranged from 23 to 1253 patients (median 139 patients). The proportion of patients with positive non-sentinel nodes ranged from 24 to 65.7% (median 38%).

Clinicopathological variables

Point estimates and 95% c.i. of the pooled odds ratios for specified characteristics across studies using the random-effects model are shown in **Figure 2**. An odds ratio of at least 2.0 was considered to be clinically most relevant. The factors that were not clinically relevant (odds ratio < 2.0) included the following: age, oestrogen and progesterone receptor status, number of SLNs removed, multifocality, tumour grade, HER-2 status, palpability of the tumour, nuclear grade, tumour histology and tumour location. The characteristics found to be clinically most relevant (odds ratio > 2.0) were the following: method of detection, size of metastasis, extracapsular extension, number of negative sentinel nodes, number of positive sentinel nodes, ratio of positive sentinel nodes, tumour size and the presence of lymphovascular invasion. **Table 2** shows the absolute risks and 95% c.i. for all characteristics. For example, if the metastases size was ≤ 2 mm, the risk of having positive NSN was only 17%. This risk increased to 51% if the metastases size was > 2 mm.

Discussion and Conclusion

Prevalence of NSN metastases

The reported incidence of NSN tumour involvement varies from about 40% to 60% [9-40]. Small study populations, the size of the tumours investigated and differences in the extent of histological work-up of SLN and NSN partly explain the range in prevalence of NSN involvement [14].

However, it is clear that the sentinel lymph node is the only focus of axillary metastases in a significant proportion of patients. Thus, these patients are exposed to the morbidity of axillary clearance without therapeutic benefit.

Risk factors for NSN metastases

As we try to extend the limits of minimally invasive procedures, efforts must be made to identify the subset of patients with a positive SLN who would benefit from further ALND.

During the past years several, clinicopathological variables in 56 well-described studies have been identified in an attempt to select those patients most likely to benefit from ALND when the SLN is positive. The aim of this study was to present a conclusive meta-analysis of the identified predictors for NSN metastases. Factors identified in our study were method of detection (HE), SLN metastases > 2 mm in size, extracapsular extension in the SLN, > 1 positive SLN, ≤ 1 negative SLN, ratio of positive sentinel nodes > 50%, tumour size > 2 cm, and lymphovascular invasion in the primary tumour. In a previous study, we concluded that the *method of detection* was a surrogate for size of metastasis [51]. Thus, in general, macrometastases are detected by routine HE, micrometastases by serial HE and isolated tumour cells by

immunohistochemistry (IHC), which explains the corresponding high odds ratio of the method of detection.

In 2003, Degnim et al. performed a meta-analysis based on 11 studies [88]. In their study the same predictors were identified with the exception of number of negative sentinel nodes and the method of detection. A greater number of predictive factors were included in our study. The large number of studies included in this study contributed to the identification of significant predictors with smaller confidence intervals. To identify the most relevant predictors, an odds ratio > 2.0 was chosen as the reference. In general, patients with more “advanced” findings in the sentinel node were at greater risk for positive NSN nodes in the axilla.

Predictive models

Over the past years, several mathematical models based on the identified predictive variables have been developed to select those patients believed to be overtreated with completion ALND (Table3) [12;17;23;91;95;97;105;110;112;116;119]. Van Zee et al. was the first to develop a nomogram based on 8 different clinicopathological variables [116]. The models developed so far included one or more predicted variables found in this meta-analysis. They performed reasonably well, but to date no model predicts nodal involvement with optimal accuracy.

We suggest the development of a new model based on these 8 predictors that is generally applicable among different populations. Patients with a predicted low risk of further node involvement could then be spared an ALND even if the SLN is metastatic. However, it is unclear how minimal residual disease left in the axilla would affect the local recurrence rate and ultimate prognosis in patients predicted to have only SLN metastases if the SLNs are involved.

Trials evaluating regional disease control

Three prospective, randomized trials are assessing whether differences in survival and regional disease control exist between patients who have an SLN biopsy compared with ALND: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial [120], the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [121] and the International Breast Cancer Study Group (IBCSG)-23-01 trial [122].

The NSABP- B32 trial randomizes patients who are SLN negative, whereas the ACOSOG Z0011 trial compares patients who are SLN positive. The IBCSG-23-01 trial randomizes patients with micrometastases in the SLN. In the AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery?) trial, patients with positive SLNs are randomized to either ALND or nodal irradiation [123].

Giuliano et al. demonstrated in the ACOSOG Z0011 trial, which was closed early due to slow accrual, that SLN biopsy without ALND in SLN positive patients can offer excellent regional control for selected patients with early stage breast cancer treated with breast conserving therapy and adjuvant systemic therapy [124]. At a median follow up of 6.3 years, there were no statistically significant differences in local recurrence (1.8% in the SLN biopsy alone group, n= 446 vs 3.6% in the ALND arm, n= 445) or regional recurrence (0.9% in the SLN biopsy alone group vs 2.5% in the ALND arm) between the SLN positive patients who underwent ALND and those who did not. These results suggest that no further axillary surgery is needed in clinically lymph node negative patients with a positive SLN biopsy.

Some studies did not present the data for characteristics that were not statistically significant. Thus, a complete dataset was not always obtainable for every

characteristic evaluated in each study, which could lead to publication bias.

Therefore, further research is warranted to assess the definitive role of ALND particularly in patients with a moderate or high risk of positive NSNs.

Conclusion

We identified 8 factors predictive of non-sentinel node metastases that should be recorded and evaluated routinely in sentinel lymph node databases and included in a predictive model for NSN positivity that is generally applicable among different populations.

Conflict of interest

There were no conflicts of interest for any of the authors.

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Figure legends**Figure 1**

Flow chart of papers assessed for analysis. Search strategy applied July 2nd 2009.

Figure 2

Pooled odds ratios with 95% confidence interval for the specified characteristics. ER: oestrogen receptor; PR: progesterone receptor; UOQ: upper outer quadrant; SN: sentinel node; LVI: lymphovascular invasion; ECE: extracapsular extension; IHC: immunohistochemistry.

Tables

Table 1 Baseline information of the 56 included studies

Author	Year	No varia tested	No pat	Pos SNB + ALND	Median Age (yrs)	Median tumor size (mm)	method of SNB	median no of SN's harvested	median no of NSN's harvested	method of histopath evaluation of SN	Tumour size of pos SNs	Tumour size of pos SNs	Tumour size of pos SNs	pos SNB	pos SNB	pos SNB	positive NSN according to size SN meta	positive NSN according to size SN meta	positive NSN according to size SN meta	Positive NSN (%)	
											T1	T2	T3	ITC	microm	macro	SN ITC	SN micromet	SN macromet		
Coufal	2009	7		330	57	17														30	
Fougo	2009	15	476	143	54	22	both	1.94*	13.9*	IC, HE	21	45			20	123				46	
Mustac	2009	4		259	59*	14*														44.6	
Cho	2008	15	759	184	48.2*	26*	RV BD	3.67		HE	24	46	10							44.7	
van Deurzen	2008	10		357	53	24*	both	1.6*	14*	HE ± IHC	187	150	90	24	112	221	3	26	107	38	
Jinno	2008	8	239	131	52	25.3*	both	2.8*	23.9*	HE + IHC				8	123			0	46	35.1	
Kohrt	2008	10	784	285	53*	29.7*	RVBD/ both	1.91*		HE ± IHC	156	109	20	23%	70%	7%	4.7%	42%	71%	35.4	
Pal	2008	7		118		19	both	2.4*	14	HE ± IHC										33.9	
Zhang	2008	7		180	46.9*	32*														60.2	
Fink	2007	10	117	36	63*		both	2.4*	9.5*	HE + IHC	15	18	3	2	12	22	0	2	13	41.7	
Kapur	2007	3		58		21*				HE ± IHC	32	24	2		15					32.7	
Klar	2007	7	545	118		21*	RV BD			HE + IHC				16	28	60		5	24	46.6	
Ponzzone	2007	10	726	186			RI			IC, HE ± IHC											
Bolster	2006	6	541	186						HE ± IHC				54	53	96	14.6%	28.6%	38%	30.1	
Chappgar	2006	5	4131	1253	57	20		2	13		677	499	55							36.9	
Cripe	2006	8		1144	92	56*	33.8*	BD ± RI		FS, IC, HE + IHC	40	40	10							48.9	
Carcoforo	2006	1		690	296	63*	13*	RI (+BD in first 50 cases)		HE (+ IHC)										48.6	
Lambert	2006	9		200			BD ± RI			TIC/HE/IHC					58	238				32	
Motomura	2006	7	47	43	52*	18*	RI + IG	2.4*	13.7*	HE ± IHC	35	8			10	33		4	12	37.2	
Ozmen	2006	12	384	148	46	20*	BD ± RI	1.6*		HE ± IHC	130	83		2	18	130		2	73	51	
Wada	2006	10	726	185	52.6*	25*	RI + BD	2.1*		HE	69	116			34	151		9	72	43.8	
Barranger	2005	9	337	71	57*	14.4*	RI + BD	2.03*	9*	HE ± IHC	294	40	3		36	35		5	14	26.8	
Callejo	2005	10	80	23	56	22	RI + BD	1.3	16	HE ± IHC	12	11			9	14		0	9	39	
Degnim	2005	12					BD/ RV both													44 / 33	
Fan	2005	1		390	76		RI (+BD in first cases)	3.01*		HE ± IHC	40	54	19								
Hung	2005	9	139	55			RI + BD			HE ± IHC	26				45	68		3	23	34.2	
Menes	2005	8		124	52*	20*	RI ± BD	2*	9*	HE ± IHC					61	63	6	6	29	33	
Schrenk	2005	2		966	359		BD ± RI	2*	16.5*	HE ± IHC	179	202	T2/T3								
Soni	2005	9	749	149	54*	24*								44	122	237	4	22	121	18	
Tan	2005		644	86	53.5	21.9*	RI ± BD	2	14	HE ± IHC	54	32			15	71		3	30	38	
Viale	2005	5		4207	1228	53*	17*		1.58*	21.8*	HE ± IHC	901	290		116	318	794	17	68	399	39.4
Yu	2005	10	814	286	44.3*		BD	2.5*	20.3*	HE + IHC	105	181			70	216		5	183	65.7	
Changsi	2004	9	329	131	53	26*	BD ± RI	1	7	HE ± IHC	57	63	10	22	25	84	6	4	44	41.2	
Cserni	2004	8		150	57.2*	24*	BD ± RI	1	13	HE ± IHC	60	86	4	10	32	108	0	8	52	40	
Dabbs	2004	1	445	224						HE + IHC	146	78			41	71	112	4	6	47	25.9
Farshid	2004	7		82	54.9*	25.6*	RI + BD	2.2*	11.8*	HE + IHC					25	57		6	32	46.3	
Fleming	2004	8	180	54	53	26	RI + BD	2	23	HE ± IHC	16	33	5		16	38		3	23	48	
Fournier	2004	8	194	42	53	21	RI + BD	2		HE + IHC	28	14	T2/T3		21	27		1	14	35.7	
Goyal	2004	7	618	201/64	54		RI + BD	2.2*	15*	HE	92	99	6		14	45		7	145	48	
Joseph	2004	5	407	70	54.9*	18*	RI + BD	2.35*		HE + IHC	49	18	2		34	36		5	12	24	
Saidi	2004	10	116	34	58.7*	22*	RI + BD	2.2*	15*	HE + IHC	21	11	2		20	14		4	6	32.3	
van der Loo	2004	7		100	53	25*	RI + BD		13	HE + IHC										39	
Zavagno	2004	4	660	167	54	17.8*	RI			HE + IHC	122	45			77	79		12	38	34.1	
Hwang	2003	12	660	131	53	19	BD ± RI	2	15	HE + IHC	72	41	13		30	92		5	44	40.5	
van Iterson	2003	4	375	135	55	20.3*	BD ± RI	3	14	HE ± IHC	82	50	2		54	81		6	40	34	
Nos	2003	11	800	263	57*	15*	BD ± RI	2.2*	11.5*	HE ± IHC	143	80		83	40	140	5	3	55	24	
Stitzenberg	2003	6	260	70	56*	18.5*	RI + BD	2*		HE ± IHC										41.4	
Van Zee	2003	9	4790	1075			RI + BD			HE ± IHC	695	353	27	81	118	88	10	15	19		
Mignotte	2002	2	277	129			RI + BD			HE ± IHC	102	27			48	28	53	7	8	41	43.4
Abdessalam	2001	9	442	100	53.4	23.4*	RI + BD	2.4*	22.1*	HE + IHC	49	45	6	30	57	8	6	27	6	40	
Canavese	2001	2	212	72	61*																
Rahusen	2001	7	255	93			RI + BD	1.7*		HE ± IHC	53	40								49	
Turner	2000	6	514	194	52	20	BD ± RI	2.0	17	HE ± IHC	105	73	15	49	44	101	10	14	64	45.4	
Weiser	2001	8	1000	206	52	15	RI + BD			HE + IHC	152	54			93	107		17	48	32	
Chu 2	1999	11	421	157	52.5	20															
Reynolds	1999	8	222	182	55.5		BD ± RI			HE + IHC	36	24			27	33		6	22	46.7	

BD: blue dye; RI: radioisotope; HE: haematoxylin and eosin; IHC: immunohistochemistry; TIC: touch imprint cytology; ITC: isolated tumour cells; FS: frozen section; IG: indocyanin green
*mean

Table 2 absolute risks on positive NSNs and 95% CI for all predictors					
		Positive NSN			
		Pooled proportion	95% CI	Pooled OR	95% CI
Method of detection	IHC-only	0.11	0.06 – 0.16	4.37	2.78 – 6.86
	Other	0.40	0.36 – 0.44		
Size of metastasis	≤ 2 mm	0.17	0.15 – 0.20	4.22	3.51 – 5.07
	> 2 mm	0.51	0.47 – 0.55		
ECE	No	0.30	0.26 – 0.33	4.10	3.16 – 5.34
	Yes	0.64	0.56 – 0.72		
No negative SNs	>1	0.24	0.18 – 0.30	2.66	2.05 – 3.46
	≤ 1	0.48	0.44 – 0.53		
No positive SNs	1	0.33	0.30 – 0.36	2.60	2.03 – 3.34
	>1	0.56	0.47 – 0.66		
Tumour size	≤ 2 cm	0.30	0.28 – 0.33	2.41	2.00 – 2.91
	> 2 cm	0.52	0.46 – 0.57		
Ratio positive SNs	≤ 50 %	0.24	0.19 – 0.29	2.25	1.63 – 3.10
	>50 %	0.44	0.34 – 0.54		
LVI	Absent	0.31	0.27 – 0.35	2.24	1.93 – 2.59
	Present	0.52	0.48 – 0.56		
Nuclear grade	≤ 2	0.41	0.35 – 0.46	1.51	1.27 – 1.81
	>2	0.47	0.43 – 0.50		
Multifocality	Absent	0.37	0.33 – 0.40	1.40	1.23 – 1.60
	Present	0.46	0.40 – 0.52		
No SNs removed	>1	0.37	0.34 – 0.40	1.34	1.07 – 1.68
	1	0.44	0.38 – 0.49		
Palpable tumour	No	0.31	0.22 – 0.40	1.31	0.71 – 2.42
	Yes	0.36	0.30 – 0.42		
Tumour grade	≤ I + II	0.38	0.33 – 0.43	1.29	1.11 – 1.50
	> III	0.47	0.42 – 0.52		
HER-2	Negative	0.41	0.34 – 0.49	1.24	0.94 – 1.63
	Positive	0.48	0.38 – 0.57		
Histology	Ductal	0.40	0.37 – 0.43		

	Other	0.43	0.38 – 0.47	1.22	1.03 – 1.44
Tumour location	Other	0.42	0.35 – 0.49	1.13	0.78 – 1.65
	UOQ	0.45	0.39 – 0.51		
Age	≥ 50 yrs	0.40	0.35 – 0.45	1.07	0.91 – 1.25
	< 50 yrs	0.41	0.34 – 0.48		
PR	Negative	0.48	0.41 – 0.55	0.77	0.63 – 0.94
	Positive	0.40	0.35 – 0.46		
ER	Negative	0.47	0.40 – 0.54	0.74	0.62 – 0.89
	Positive	0.38	0.35 – 0.41		

LVI: lymphovascular invasion; ER: oestrogen receptor; PR: progesterone receptor; ECE: extracapsular extension; SNs: sentinel nodes; IHC: immunohistochemistry; UOQ: upper outer quadrant.

Table 3 Factors included in mathematical models to predict the risk of NSN positivity

Predictive factors	MSKCC nomogram [116]	MDA score [23]	Axilla score [112]	Mayo nomogram [17]	Tenon score [91]	Clinical Prediction Rule [95]	Cambridge model [110]	Stanford calculator [105]	SNUH score [12]	Mou model [97]	Ljubljana model [119]
Detection mode	•										
SN met size		•		•	•		•	•		•	•
ECE			•							•	
No.neg SNs	•			•					•	•	•
No.pos SNs	•			•		•			•	•	•
Tumour size	•	•	•	•		•	•	•	•	•	•
% pos SNs					•	•	•				
LVI	•	•	•					•	•	•	•
Nuclear grade	•										
Multifocal	•									•	
No. of SLNs removed		•									
Palp mass			•								
Tumour type	•									•	
Age				•							
ER positive	•										
US axilla									•		•

SN: sentinel node; met: metastasis; ECE: extracapsular extension; neg: negative; pos: positive; %: proportion; palp: palpable; US: ultrasound finding axilla

Figure 1

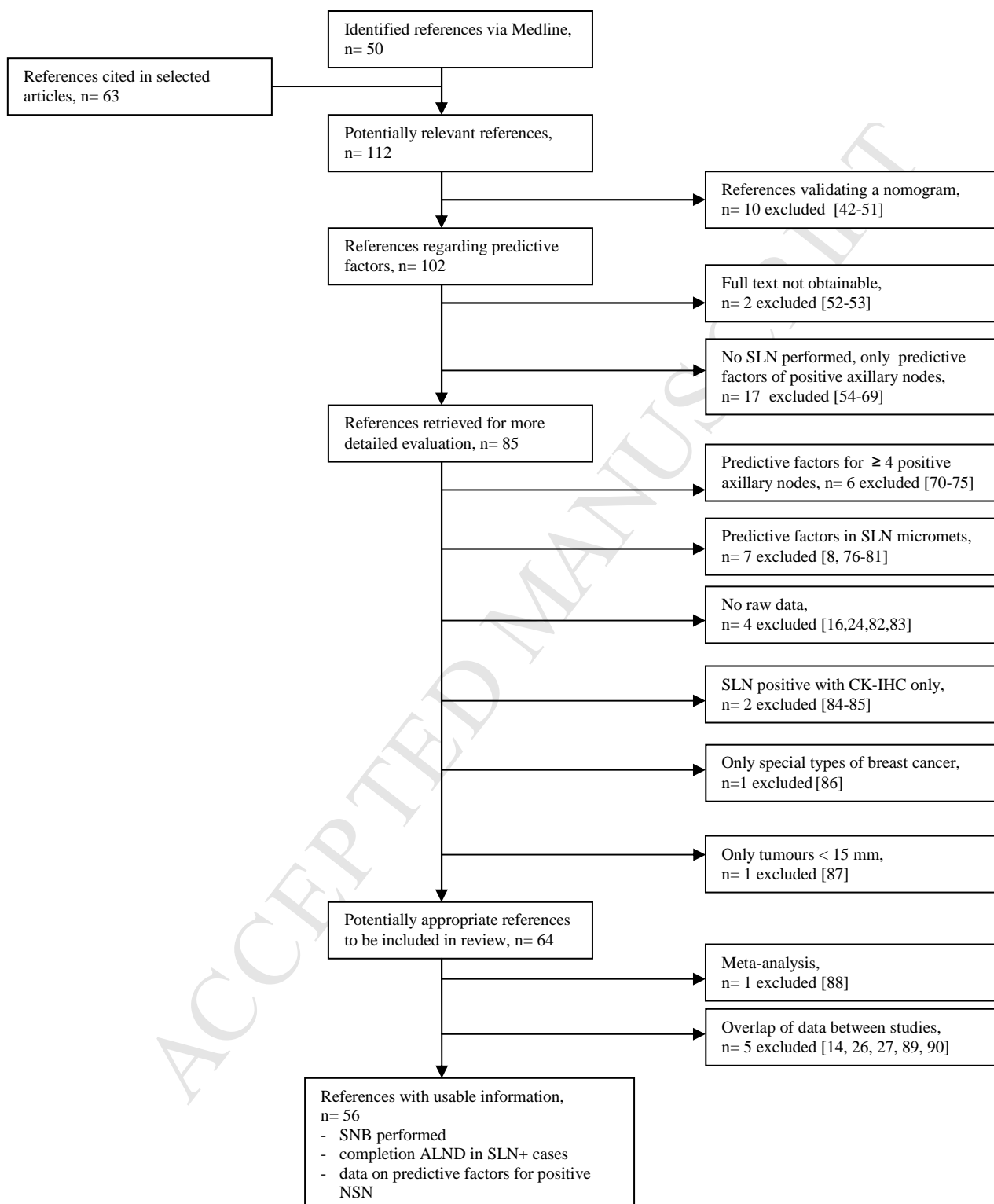
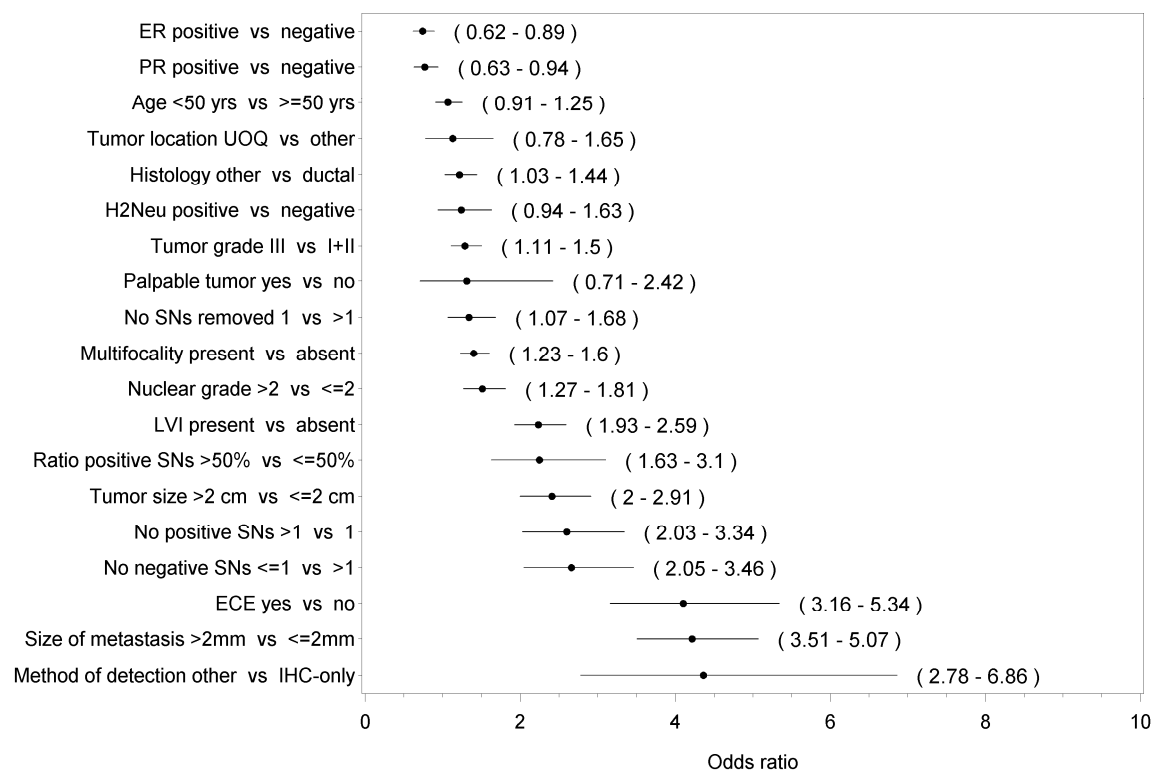


Figure 2



Author	Year	No varia tested	No pat	Pos SNB + ALND	Median Age (yrs)	Median tumor size (mm)	method of SNB	median no of SN's harvested	median no of NSI's harvested	method of histopath evaluation of SI	Tumour size of pos SNs	Tumour size of pos SNs	Tumour size of pos SNs	pos SNB	pos SNB	pos SNB	positive NSI according to size SI meta	positive NSI according to size SI meta	positive NSI according to size SI meta	Positive NSI (%)	
											T1	T2	T3	ITC microm	macro	SN ITC	SN micromet	SN macromet			
Coufal	2009	7		330	57	17														30	
Fuogo	2009	15	476	143	54	22	both	1.94*	13.9*	IC, HE	21	45			20	123				46	
Mustac	2009	4		259	59*	14*														44.6	
Cho	2008	15	759	184	48.2*	26*	RV BD	3.67		HE	24	46	10							44.7	
van Deurzen	2008	10		357	53	24*	both	1.6*	14*	HE ± IHC	187	150	90	24	112	221	3	26	107	38	
Jinno	2008	8	239	131	52	25.3*	both	2.8*	23.9*	HE ± IHC					8	123		0	46	35.1	
Kohrt	2008	10	784	285	53*	29.7*	RVBD/ both	1.91*		HE ± IHC	156	109	20	23%	70%	7%	4.7%	42%	71%	35.4	
Pal	2008	7		118		19	both	2.4*	14	HE ± IHC										33.9	
Zhang	2008	7		180	46.9*	32*														60.2	
Fink	2007	10	117	36	63*		both	2.4*	9.5*	HE ± IHC	15	18	3	2	12	22	0	2	13	41.7	
Kapur	2007	3		58		21*				HE ± IHC	32	24	2		15					32.7	
Klar	2007	7	545	118		21*	RV BD			HE ± IHC				16	28	60		5	24	46.6	
Ponzone	2007	10	726	186			RI			IC, HE ± IHC											
Bolster	2006	6	541	186						HE ± IHC					54	53	96	14.6%	28.6%	38%	30.1
Chapparg	2006	5	4131	1253	57	20			2	13	677	499	55							36.9	
Cripe	2006	8		1144	92	56*	33.8*	BD ± RI		FS, IC, HE ± IHC	40	40	10							48.9	
Carcoforo	2006	1		690	296	63*	13*	RI (+BD in first 50 cases)		HE (+ IHC)					58	238				48.6	
Lambert	2006	9		200			BD ± RI			TIC/HE/IC										32	
Motomura	2006	7	47	43	52*	18*	RI + IG	2.4*	13.7*	HE ± IHC	35	8		10	33		4	12	37.2		
Ozmen	2006	12	384	148	46	20*	BD ± RI	1.6*		HE ± IHC	130	83		2	18	130		2	73	51	
Wada	2006	10	726	185	52.6*	25*	RI + BD	2.1*		HE	69	116		34	151		9	72	43.8		
Barranger	2005	9	337	71	57*	14.4*	RI + BD	2.03*	9*	HE ± IHC	294	40	3	36	35		5	14	26.8		
Callejo	2005	10	80	23	56	22	RI + BD	1.3	16	HE ± IHC	12	11		9	14		0	9	39		
Degnim	2005	12		574	57/53*		BD/ RV/ both													44 / 33	
Fan	2005	1		390	76		RI (+BD in first cases)	3.01*		HE ± IHC	40	54	19								
Hung	2005	9	139	55			RI + BD			HE ± IHC	28			45	68		3	23	34.2		
Menes	2005	8		124	52*	20*	RI ± BD	2*	9*	HE ± IHC				24	31		4	13	31		
Schrenk	2005	2		968	359		BD ± RI	2*	16.5*	HE ± IHC	179	202			61	63	6	6	29	33	
Soni	2005	9	749	149	54*	24*								44	122	237	4	22	121	18	
Tan	2005	5	644	86	53.5	21.9*	RI ± BD	2	14	HE ± IHC	54	32		15	71		3	30	38		
Viale	2005	5	4207	1228	53*	17*		1.58*	21.8*	HE ± IHC	901	290		116	318	794	17	68	399	39.4	
Yu	2005	10	814	288	44.3*		BD	2.5*	20.3*	HE ± IHC	105	181		70	216		5	183	85.7		
Changstri	2004	9	329	131	53	26*	BD ± RI	1	7	HE ± IHC	57	63	10	22	25	84	6	4	44	41.2	
Cserni	2004	8		150	57.2*	24*	BD ± RI	1	13	HE ± IHC	60	86	4	10	32	108	0	8	52	40	
Dabbs	2004	1	445	224						HE ± IHC	146	78		41	71	112	4	6	47	25.9	
Farshid	2004	7		82	54.9*	25.6*	RI + BD	2.2*	11.8*	HE ± IHC				25	57		6	32	46.3		
Fleming	2004	8	180	54	53	26	RI + BD	2	23	HE ± IHC	16	33	5	16	38		3	23	48		
Fournier	2004	8	194	42	53	21	RI + BD	2		HE ± IHC	28	14 T2/T3		21	27		1	14	35.7		
Goyal	2004	7	618	201/64	54		RI + BD	2.2*	15*	HE	92	99	6	14	45		7	145	48		
Joseph	2004	5	407	70	54.9*	18*	RI + BD	2.35*		HE ± IHC	49	18	2	34	36		5	12	24		
Saidi	2004	10	116	34	58.7*	22*	RI + BD	2.2*	15*	HE ± IHC	21	11	2	20	14		4	6	32.3		
van der Loo	2004	7		100	53	25*	RI + BD		13	HE ± IHC										39	
Zavagno	2004	4	660	167	54	17.8*	RI			HE ± IHC	122	45		77	79		12	38	34.1		
Hwang	2003	12	660	131	53	19	BD ± RI	2	15	HE ± IHC	72	41	13	30	92		5	44	40.5		
van Nerson	2003	4	375	135	55	20.3*	BD ± RI	3	14	HE ± IHC	82	50	2	54	81		6	40	34		
Nos	2003	11	800	263	57*	15*	BD ± RI	2.2*	11.5*	HE ± IHC	143	80		83	40	140	5	3	55	24	
Stitzenberg	2003	6	260	70	56*	18.5*	RI + BD	2*		HE ± IHC										41.4	
Van Zee	2003	9	4790	1075			RI + BD			HE ± IHC	695	353	27	81	118	88	10	15	19		
Mignotte	2002	2	277	129			RI + BD			HE ± IHC	102	27		48	28	53	7	8	41	43.4	
Abdessalam	2001	9	442	100	53.4	23.4*	RI + BD	2.4*	22.1*	HE ± IHC	49	45	6	30	57	8	6	27	6	40	
Canavese	2001	2	212	72	61*																
Rahusen	2001	7	255	93			RI + BD	1.7*		HE ± IHC	53	40								49	
Turner	2000	6	514	194	52	20	BD ± RI	2.0	17	HE ± IHC	105	73	15	49	44	101	10	14	64	45.4	
Weiser	2001	8	1000	206	52	15	RI + BD			HE ± IHC	152	54		93	107		17	48	32		
Chu 2	1999	11	421	157	52.5	20															
Reynolds	1999	8	222	182	55.5		BD ± RI			HE ± IHC	36	24		27	33		6	22	46.7		

Table 2 absolute risks on positive NSNs and 95% CI for all predictors

		Positive NSN			
		Pooled proportion	95% CI	Pooled OR	95% CI
Method of detection	IHC-only	0.11	0.06 – 0.16	4.37	2.78 – 6.86
	Other	0.40	0.36 – 0.44		
Size of metastasis	≤ 2 mm	0.17	0.15 – 0.20	4.22	3.51 – 5.07
	> 2 mm	0.51	0.47 – 0.55		
ECE	No	0.30	0.26 – 0.33	4.10	3.16 – 5.34
	Yes	0.64	0.56 – 0.72		
No negative SNs	>1	0.24	0.18 – 0.30	2.66	2.05 – 3.46
	≤ 1	0.48	0.44 – 0.53		
No positive SNs	1	0.33	0.30 – 0.36	2.60	2.03 – 3.34
	>1	0.56	0.47 – 0.66		
Tumour size	≤ 2 cm	0.30	0.28 – 0.33	2.41	2.00 – 2.91
	> 2 cm	0.52	0.46 – 0.57		
Ratio positive SNs	≤ 50 %	0.24	0.19 – 0.29	2.25	1.63 – 3.10
	>50 %	0.44	0.34 – 0.54		
LVI	Absent	0.31	0.27 – 0.35	2.24	1.93 – 2.59
	Present	0.52	0.48 – 0.56		
Nuclear grade	≤ 2	0.41	0.35 – 0.46	1.51	1.27 – 1.81
	>2	0.47	0.43 – 0.50		
Multifocality	Absent	0.37	0.33 – 0.40	1.40	1.23 – 1.60
	Present	0.46	0.40 – 0.52		
No SNs removed	>1	0.37	0.34 – 0.40	1.34	1.07 – 1.68
	1	0.44	0.38 – 0.49		
Palpable tumour	No	0.31	0.22 – 0.40	1.31	0.71 – 2.42
	Yes	0.36	0.30 – 0.42		
Tumour grade	≤ I + II	0.38	0.33 – 0.43	1.29	1.11 – 1.50
	> III	0.47	0.42 – 0.52		
HER-2	Negative	0.41	0.34 – 0.49	1.24	0.94 – 1.63
	Positive	0.48	0.38 – 0.57		
Histology	Ductal	0.40	0.37 – 0.43	1.22	1.03 – 1.44
	Other	0.43	0.38 – 0.47		

Tumour location	Other	0.42	0.35 – 0.49	1.13	0.78 – 1.65
	UOQ	0.45	0.39 – 0.51		
Age	≥ 50 yrs	0.40	0.35 – 0.45	1.07	0.91 – 1.25
	< 50 yrs	0.41	0.34 – 0.48		
PR	Negative	0.48	0.41 – 0.55	0.77	0.63 – 0.94
	Positive	0.40	0.35 – 0.46		
ER	Negative	0.47	0.40 – 0.54	0.74	0.62 – 0.89
	Positive	0.38	0.35 – 0.41		

LVI: lymphovascular invasion; ER: oestrogen receptor; PR: progesterone receptor; ECE: extracapsular extension; SNs: sentinel nodes; IHC: immunohistochemistry; UOQ: upper outer quadrant.

Table 3 Factors included in mathematical models to predict the risk of NSN positivity

Predictive factors	MSKCC nomogram [116]	MDA score [23]	Axilla score [112]	Mayo nomogram [17]	Tenon score [91]	Clinical Prediction Rule [95]	Cambridge model [110]	Stanford calculator [105]	SNUH score [12]	Mou model [97]	Ljubljana model [119]
Detection mode	•										
SN met size		•		•	•		•	•		•	•
ECE			•							•	
No.neg SNs	•			•					•	•	•
No.pos SNs	•			•		•			•	•	•
Tumour size	•	•	•	•	•	•	•	•	•	•	•
% pos SNs					•	•	•				
LVI	•	•	•					•	•	•	•
Nuclear grade	•										
Multifocal	•									•	
No. of SLNs removed		•									
Palp mass			•								
Tumour type	•									•	
Age				•							
ER positive	•										
US axilla									•		•

SN: sentinel node; met: metastasis; ECE: extracapsular extension; neg: negative; pos: positive; %: proportion; palp: palpable; US: ultrasound finding axilla

