Positive sentinel lymph node (SLN): Model(s) predicting non-SLN status in early breast cancer

Are models general applicable?

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5th International Congress of Breast Disease Centers

UZ LEUVEN

Presentation overview

- **Introduction**
  - ALND→SLN → (pos) ALND→no ALND
  - Models (predictors) for a pos N-SLN
- **Improving models for pos N-SLN**
  - Own data
  - Validation set
- **Why not general applicable**
- **Conclusion & take home message**

*__ALN-status: ! prognostic factor__ ~ patient-, tumor -related
*__SLN is safe for LN-staging cN0__
→5-10% false negative: & 5-10% upstaging

ALMANAC/ NSABP B32/Veronesi
ASCO 2004 : cALND if pSLN

Pos SLN→ Frequency Non-SLNs pos varies?

EJSO
the Journal of Cancer Surgery
M. Noguchi / EJSO 34 (2008) 129–134

SLN = MacroM (> 2 mm):
46% - 87%

SLN = MicroM (0,2 – 2 mm):
0% - 80%

SLN = ITC (< 0,2 mm):
15% & 19%

Size of SLN metastases	Tumor size	No. of patients	Incidence of non-SLN metastases (%)
Macrometastasis			
Chu et al.[21]	T1	40	48
	T2-3	49	59
Reynolds et al.[22]	T1	18	50
	T2	15	87
Viale et al.[23]	T1-2	794	50 ←
Menes et al.[24]	T1-3	63	46
Micrometastasis			
Chu et al.[21]	T1	46	4
	T2-3	23	13
Reynolds et al.[22]	T1	18	0
	T2	9	67
Viale et al.[33]	T1	93	22 ←
	T2	17	24
den Bakker et al.[34]	T1	22	14
	T2-3	10	80
Viale et al.[23]	T1-2	318	21
Menes et al.[24]	T1-3	30	20
Isolated tumor cells			
Viale et al.[23]	T1-2	116	15 ←
Menes et al.[24]	T1-3	31	19

Pos SLN→ cALND→ no cALND

***A positive SLN→ Omit ALND?**

ACOSOG Z0011/ IBCSG 23-01
AMAROS

→cT1-2; low n° & load in SLN; BCS + TF-WBI

→RT if criteria differ from ACOSOG/IBCSG but most cT1, CT, age 48-65

ASCO 2014: no cALND [pN1(sn)] <3 pSLN & BCS and TF-WBI

→Not included: Mastectomy, large tumors, > 2 pos LN**, young age, …

*Mastectomy : only in IBCSG (9%) and AMAROS (17%)

Underpowered trials, low risk disease, early follow-up, cT1, CT, ME, …

→Previous Models differ Future Models←

Introduction: Predictors positive SLN in EBC

Prior to current guidelines…

Models predict n-SLN better than random chance

How perform 6 predictive models in different studies?

Characteristics of 6 predictive models for NSLNmetastasis

	Cambridge	Tenon	MSKCC	Mayo	MDA	Stanford
General information						
Age				√		
Method for SLN assessment			√			
Characteristics of the primary tumor						
Tumor size (pT-stage)		√	√	√	√	√
Multifocality			√			
ER status			√	√		
Lymphovascular invasion			√		√	√
Grade	√		√			
Pathology subtype			√			
Characteristics of the SLNs						
Number of SLNs					√	
Number of positive SLNs			√	√		
Number of negative SLNs			√	√		
Proportion of positive SLNs	√	√				
Metastasis size in the involved SLNs	√	√		√	√	√
Extracapsular extension				√		

Breast Cancer Res Treat (2013) 137:783–795

Which nomogram is best for predicting non-sentinel lymph node metastasis in breast cancer patients? A meta-analysis

Meta-analysis using 6 nomograms
Pooled AUC

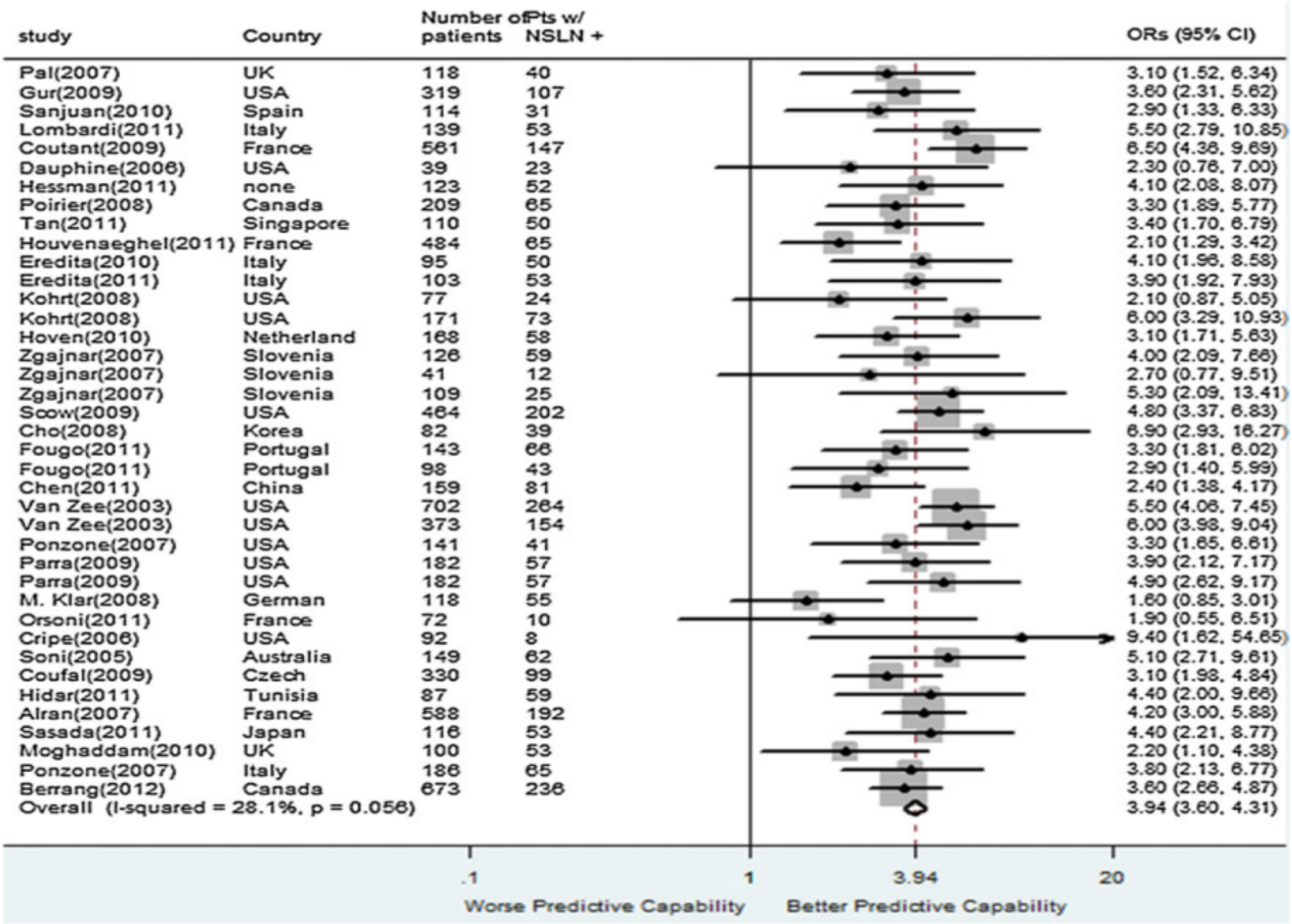
- Cambridge n=2156 0.721
- Mayo n=2431 0.728
- MDA n=843 0.706
- MSKCC n=8143 0.715
- Stanford n=3700 0.688
- Tenon n=3648 0.720

Performance ~ Proportion mi(SN)

The discriminative capabilities ~ different populations
So, we do need improved models!

Forest plots of MSKCC model validated in 39 studies→

Liling Zhu | Breast Cancer Res Treat (2013) 137:783–795



Forest plots of the MSKCC model validated in 39 studies

Breast Cancer Res Treat (2013) 137:783–795

EACH PREDICTIVE TOOL USED IN CLINICAL PRACTICE FOR PATIENT AND PHYSICIAN DECISION ON FURTHER AXILLARY TREATMENT OF SLN-POSITIVE PATIENTS REQUIRES INDIVIDUAL INSTITUTIONAL VALIDATION

SUCH VALIDATION MAY REVEAL DIFFERENT TOOLS TO BE THE BEST IN DIFFERENT INSTITUTIONS

Presentation overview

- **Introduction**
  - SLN positive → ALND
  - Predictors for a positive N-SLN
- **Improving existing models for pos N-SLN**
  - **Own data (single hospital large study population)**
  - **Validation set**
- **Why not generally applicable**
- **Conclusion & take home message**
- Aknowledgements

OBJECTIVE:
UHL model PREDICTING non-SLN
Less factors than MSKCC Nomogram

Patient selection and data collection for UZL series (07-2003 & 12-2010)

At the UHL the SLN was identified using subdermal injection of Technetium-99m-nanocolloid and subareolar patent blue dye.

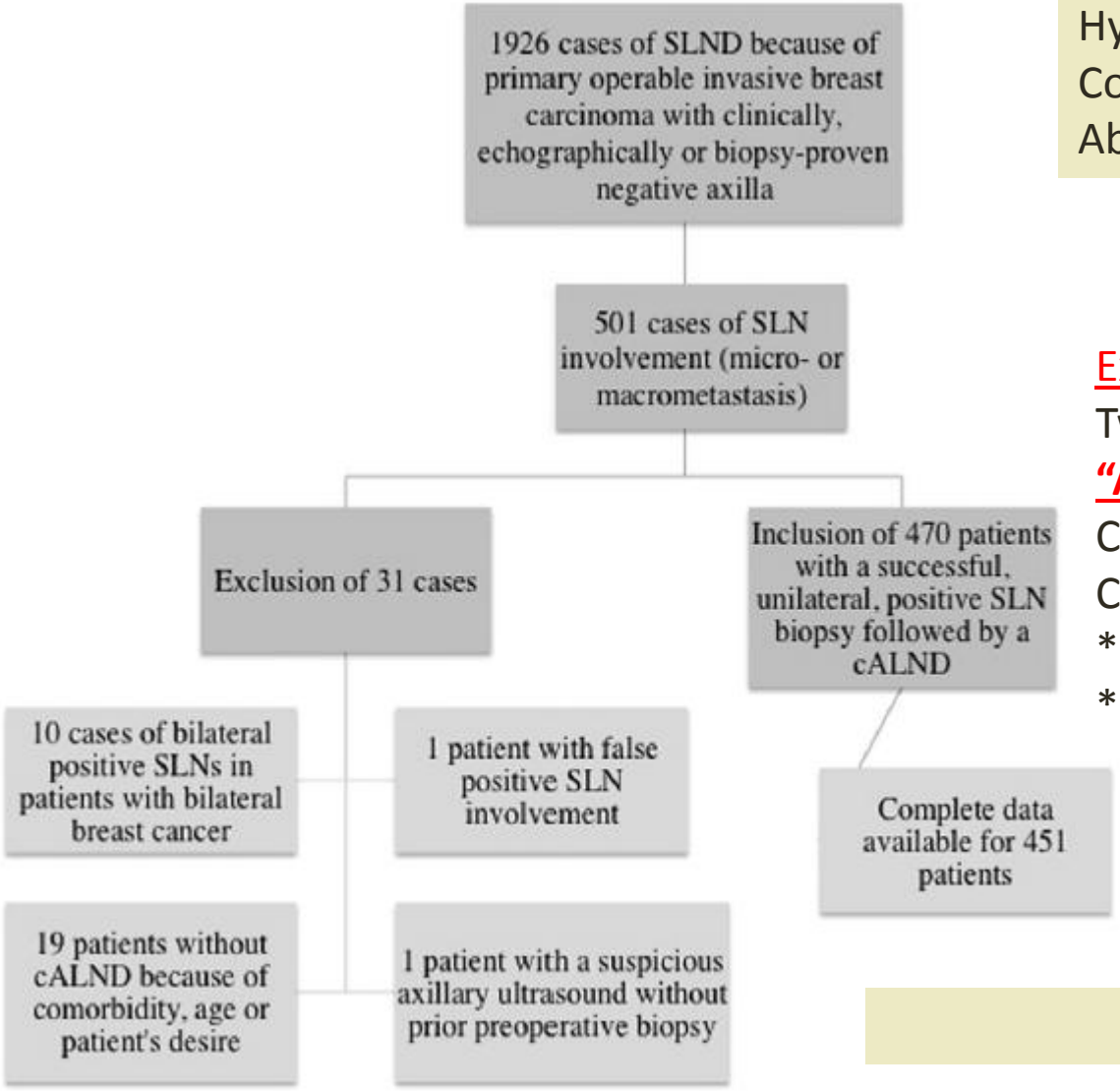


Fig. 1. Patient selection and collection of data for UHL patient series.

Increased short axis
Hypoechogenic hilus
Cortical thickness > 2mm
Abnormal contour

External Validation

Two independent Belgian centers

"Almost similar" inclusion criteria

Center A: 149 (2003-2012)*

Center B: 119 (2006-2011)**

* No Patent blue

** Patent Blue if Mapping neg

SLN-assessment→

SLN-assessment

Intra-Operative evaluation:

- Touch Imprint Cytology/ Frozen Section/ Both
- Every SLN sectioned in thin slices of 2mm
- Frozen slices cut with cryostat microtome 5um thick sections
- H&E light microscope

Postoperative evaluation:

SLN:

- Enhanced path examination after FFPE:
- H&E and Cytokeratin IHC on paired sections taken at 0.3mm interval entire block

cALND:

- H&E (epithelial markers only if ILA)

There were between-center differences

Centre A – B: touch imprint cytology only

Centre B did not use Cytokeratin path evaluation

Tumor Characteristics & NSLN-Status

Tumor and lymph node characteristics of the UHL patient series.

Characteristics	Total $n = 470$		Incidence NSLN+	
	n	%	Proportion	%
Tumor type				
Ductal	431	91.7	91/431	21.1
Lobular	39	8.3	12/39	30.8
Tumor grade				
1	90	19.2	8/90	8.9
2	220	46.8	51/220	23.2
3	160	34.0	44/160	27.5
LVI				
Yes	154	32.8	51/154	33.1
No	300	63.8	51/300	17.0
Unknown	16	3.4	1/16	6.3
Multifocality				
No	420	89.4	90/420	21.4
Yes	50	10.6	13/50	26.0
ER status				
Negative	38	8.1	11/38	28.9
Positive	432	91.9	92/432	21.3
PR status				
Negative	80	17.0	22/80	27.5
Positive	390	83.0	81/390	20.8
Her2 status				
Negative	433	92.1	93/433	21.5
Positive	36	7.7	10/36	27.8
Unknown	1	0.2	0/1	0.0

Tumor Characteristics & NSLN-Status

			Incidence NSLN+	
			Proportion %	
Tumor location				
Upper inner	59	12.6	11/59	18.6
Upper outer	281	59.8	60/281	21.4
Lower inner	43	9.1	8/43	18.6
Lower outer	62	13.2	18/62	29.0
Retro-areolar	25	5.3	6/25	24.0
No. of SLNs assessed				
1	103	21.9	30/103	29.1
2	160	34.0	31/160	19.4
3	113	24.0	19/113	16.8
4	51	10.9	14/51	27.5
5	19	4.0	3/19	15.8
6	13	2.8	4/13	30.8
≥7	11	2.3	2/11	18.2
No. of +SLNs				
1	359	76.4	66/359	18.4
2	87	18.5	24/87	27.6
3	15	3.2	8/15	53.3
≥4	9	1.9	5/9	55.6
No. of − SLNs				
0	153	32.6	50/153	32.7
1	160	34.0	30/160	18.8
2	83	17.7	11/83	13.3
3	44	9.4	8/44	18.2
4	14	3.0	2/14	14.3
5	8	1.7	1/8	12.5
≥6	8	1.7	1/8	12.5
Size of SLN M+				
Macro	276	58.7	87/276	31.5
Micro	194	41.3	16/194	8.2
Intraoperative pathological evaluation				
Positive	204	43.4	78/204	38.2
Negative	263	56.0	25/263	9.5
Not performed	3	0.6	0/3	0.0

How variables were choosen/validated?

***Logistic regression models with +/- NSLN -mets as a binary response variable**

- **Non-linear relationship for size & age was dealt with using restricted cubic splines**
- **A bivariate model for 'size of SLN met' (macro/micro) & 'IOA' (+/-) was considered**

***UV-model for all plausible predictors→If significant build MV-model**

***A test was statistically significant is *p*-value <0.05**

Internal validation: → bootstrap-corrected area under the ROC (AUC)

SAS software version 9.2 of the SAS system for Windows

Resultaten – Univariaat

Parameter	P-waarde
Age	0.5627
Tumor size (mm)	0.0007
Tumor type (IDA vs ILA)	0.1664
Tumor grade **Overall effect** **1 vs 2** **1 vs 3**	 0.0010 0.0051 0.0009
2 vs 3	0.3376
LVI (yes vs no)	0.0001
Multifocal (yes vs no)	0.4610
Receptor status	0.6640
Tumor localisation	0.4954
N° + SLN	<.0001
N° - SLN	0.0031
Size SLN-met (macro vs micro)	<.0001
APO perop (pos vs neg)	<.0001

Resultaten – Multivariaat

Parameter	*P*-value
Tumor size (mm)	0.2095
Tumor grade	0.1623
N°+ SLN	0.1444
N° - SLN	**0.0111**
APO per-op (pos vs neg)	**<.0001**
LVI (yes vs no)	**0.0251**
Size M* (macro vs micro)	**0.0099**

Resultaten – Model

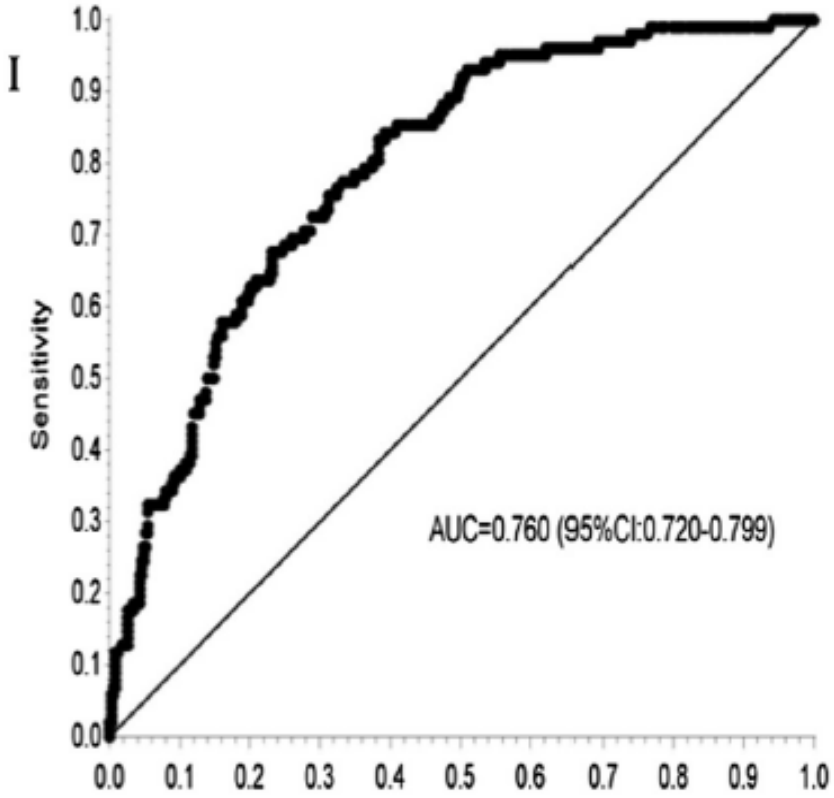
Predicted chance to get pos non-SLN = exp(mu)/(1+exp(mu))

mu = -1.6489 + 0.0114x(T size) - 0.8093x(Grade 1) - 0.1510x(Grade 2) + 0.2374 x(#pos SLN) – 0.2427x(#neg SLN) – 1.2496x(APO per-op neg) + 0.5942x(LVI) + 0.8661x (macromet)

- **T size** — **in millimeter**
- **Grade 1** — **yes = 1, no = 0**
- **Grade 2** — **yes = 1, no = 0**
- **# pos SLN** — **= N° pos SLN**
- **# neg SLN** — **= N° neg SLN**
- **APO per-op neg** — **yes = 1, no = 0**
- **LVI** — **yes = 1, no = 0**
- **Macrometa** — **yes = 1, no = 0**

Bootstrap-corrected C-index = 0.75970

Receiving Operating Characteristics UHL



If subgroup analysis for
-macrometastatic SLN only: bootstrap-corrected AUC= 0.69
-mastectomy: bootstrap-corrected AUC = 0.72

} ACOSOG/IBCSG inclusions

Results of Model

Patient 1

Predicted chance = 1.7%

Size:	10mm
Grade:	1
# pos SLN:	1
# neg SLN:	3
APO perop:	neg
LVI:	no
Size M+:	micro

Patiënt 2

Predicted chances = 79.1%

T size:	50mm
Grade:	3
# pos SLN:	4
# neg SLN:	0
APO perop:	pos
LVI:	ja
Size M+:	macro

Comparison of tumor and lymph node characteristics between institutions.

Characteristics	UHL patient series ($n = 470$)		Center A ($n = 149$)		Center B ($n = 127$)	
	n	%	*n*	%	*n*	%
Mean age	57 (range 27–86)		58 (range 34–85)		57 (range 30–89)	
Median tumor size in mm	22.6 (range 1–119)		17.1 (range 4–45)		21.3 (range 6–70)	
Tumor grade						
1	90	19.2	36	24.2	18	14.2
2	220	46.8	87	58.4	61	48.0
3	160	34.0	26	17.4	46	36.2
Unknown	0	0	0	0	2	1.2
LVI						
Yes	154	32.8	105	70.5	56	44.1
No	300	63.8	44	29.5	64	50.4
Unknown	16	3.4	0	0	7	5.5
No. of SLNs assessed						
Median	2 (range 1–10)		1 (range 1–5)		2 (range 1–8)	
1	103	21.9	97	65.1	60	47.2
2	160	34.0	42	28.2	37	29.1
3	113	24.0	7	4.7	21	16.5
4	51	10.9	2	1.3	6	4.7
5	19	4.0	1	0.2	0	0
6	13	2.8	0	0	0	0
≥7	11	2.3	0	0	3	2.4

Comparison of tumor and lymph node characteristics between institutions.

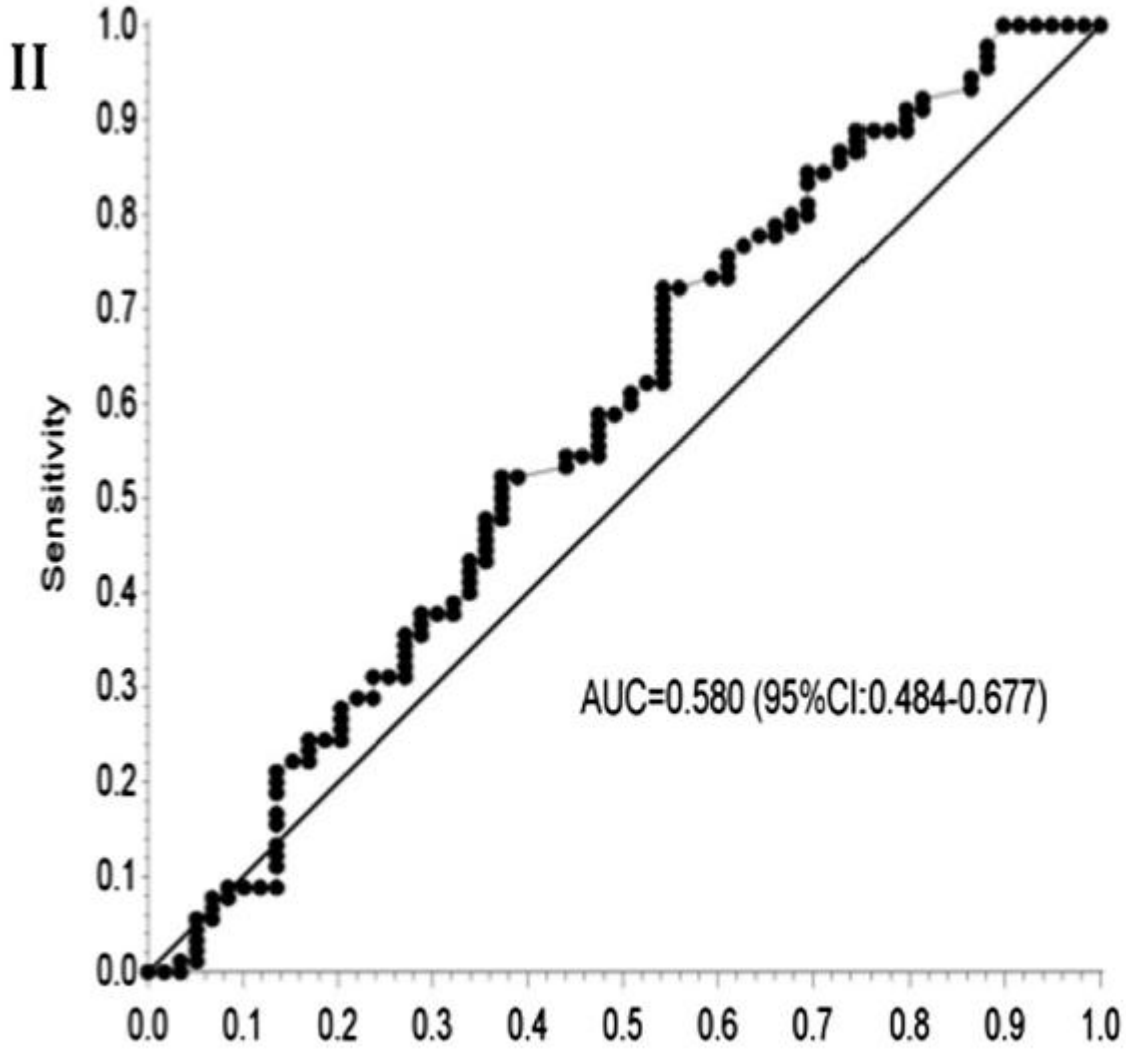
Characteristics	UHL patient series ($n = 470$)		Center A ($n = 149$)		Center B ($n = 127$)	
	n	%	*n*	%	*n*	%
No. of +SLNs						
1	359	76.4	134	89.9	111	87.4
2	87	18.5	14	9.4	10	7.9
3	15	3.2	1	0.7	5	3.9
≥4	9	1.9	0	0	1	0.8
No. of −SLNs						
0	153	32.6	110	73.8	71	55.9
1	160	34.0	31	20.8	32	25.2
2	83	17.7	6	4.0	16	12.6
3	44	9.4	1	0.7	5	3.9
4	14	3.0	1	0.7	2	1.6
5	8	1.7	0	0	0	0
≥6	8	1.7	0	0	1	0.8
Size of SLN M+						
Macro	276	58.7	101	67.8	99	78.0
Micro	194	41.3	48	32.2	28	22.0
Intraoperative pathological evaluation						
Positive	204	43.4	89	59.7	83	65.4
Negative	263	56.0	60	40.3	44	34.6
Not performed	3	0.6	0	0	0	0
Positive NSLN	103	21.9	59	39.6	43	33.9

External validation of UHL model: ROC was constructed and AUC with 95% CI was estimated

Each patient information from the external validation patient series was introduced into the predictive model to perform the external validation

AUC values with CI were calculated for each center separately and ROC curves were plotted

Receiving Operating Characteristics Center A



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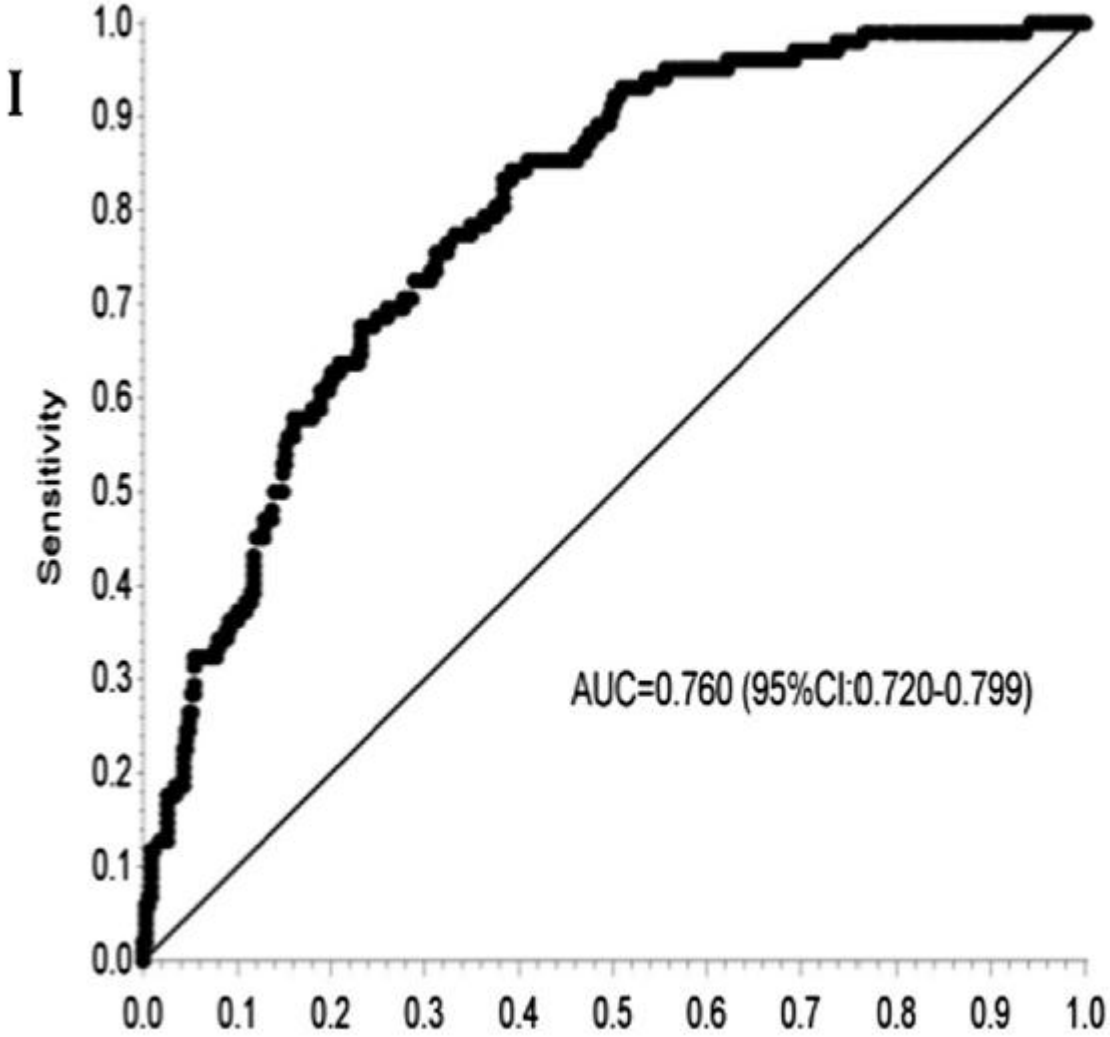
Receiving Operating Characteristics Center B



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ARTICLE

J Natl Cancer Inst 2012;104:1888–1896

So, models not general applicable!

International Multicenter Tool to Predict the Risk of Nonsentinel Node Metastases in Breast Cancer

Table 4. Performance of the predictive model in internal and external validation*

Patient series	No.	Nonsentinel metastases	AUC (95% CI)	Bonferroni corrected CI (99.4%) for AUC	Sensitivity	Specificity
Original patient series	1000	327 (32.7%)	0.756 (0.725 to 0.787)	0.713 to 0.800	38.5%	89.2%
Internal validation series	500	155 (31.0%)	0.714 (0.665 to 0.763)	0.646 to 0.783	36.8%	90.1%
Center A	100	36 (36.0%)	0.692 (0.586 to 0.797)	0.545 to 0.841	41.7%	85.9%
Center B	134	43 (32.1%)	0.760 (0.675 to 0.844)	0.642 to 0.880	39.5%	89.0%
Center C	42	15 (35.7%)	0.841 (0.706 to 0.976)	0.650 to 1.000	46.7%	92.6%
Center D	200	56 (28.0%)	0.686 (0.600 to 0.771)	0.565 to 0.805	32.1%	91.7%
→ Center E	24	5 (20.8%)	0.458 (0.176 to 0.740)	0.069 to 0.868	0	94.7%
External validation series	1068	451 (42.2%)	0.719 (0.689 to 0.750)	0.676 to 0.762	51.4%	79.4%
Center F	100	53 (53.0%)	0.762 (0.669 to 0.856)	0.629 to 0.892	62.3%	85.1%
Center G	137	51 (37.2%)	0.747 (0.663 to 0.831)	0.625 to 0.861	62.7%	75.6%
Center H	67	30 (44.8%)	0.577 (0.440 to 0.715)	0.389 to 0.775	23.3%	83.8%
Center I	153	64 (41.8%)	0.715 (0.635 to 0.795)	0.603 to 0.827	51.6%	71.9%
→ Center J	43	13 (30.2%)	0.949 (0.886 to 1.000)	0.866 to 1.000	84.6%	93.3%
Center K	100	47 (47.0%)	0.702 (0.598 to 0.805)	0.557 to 0.847	48.9%	83.0%
Center L	200	64 (32.0%)	0.673 (0.591 to 0.756)	0.556 to 0.789	56.2%	72.1%
Center M	268	129 (48.1%)	0.731 (0.672 to 0.792)	0.648 to 0.817	44.2%	86.3%

* Sensitivity and specificity calculated for a cutoff value of greater than 50% risk estimate score. AUC = area under the receiver operating characteristics curve; CI = confidence interval.

→ Low numbers ~ poor / excellent validation

ALN-status in EBC ~ a lot

Population studied: ALND versus SLN

Tumor characteristics: LVI, size, focality, location areolar/lateral, morphology, …

Age interferes with size (U-curve)

Mode of detection: Screen < Palpable

Subtype: ER-PR-HER-2 (triple positive)

Our model: how to explain differences?

- **Different between-center procedures**
  - SLN ident & path evaluation not standard
  - Different radiologists, surgeons, pathologists (also within)
- **Important differences comparing A with UHL & B (both comparable)**
  - A: larger size/ more LVI/lower grade/less N° SLN assessed (~N° involved N-SLNs)
  - **Involved- NSLN (25%-60%) [UHL: 21.9% /A: 39.6% /B: 33.9%]**
- **Time of SLN-Assessment**
  - UHL: more post than per-op versus A/B more per than postop
    - Important variable : 9.5% (postop) versus 38.2% (perop)
      - Independent of lobular subtype

And many more….

Conclusion:

- **Predictive models perform differently in external validation**
  - Chance calculation = no exact science
  - Don’t apply a certain model; adjust for own data/ own model
- **UHL MV:**
  - Less parameters than MSKCC Nomogram but as good
  - IOA / Applicable after Mastectomy/ Large size T/ any age
    - Value when judging postoperatively (LVI; SLN-size)

BUT

    - Overtreatment
    - Importance might decrease over time

Aknowledgement

UZ Leuven

AZ Groeninge - Kortrijk

St Augustinus: Antwerp

Statistician: Annouschka Laenen

Radiologists
Breast surgeons
Nuclear Physicians
Pathologists
....

UV & MV analysis

UNIVARIATE: Size, grade, LVI, n° +SLN, n° -SLN, SLN-size, IOA
→Confounding factor?:SLN-size with IOA: (constructed bivariate model): NO

MULTIVARIATE: LVI, N° -SLN, SLN-size, IOA

The parameter estimates for 4 variables in MV model could be used to predict NSLN
The bootstrap-corrected AUC for MV model = 0.76

Multivariate logistic-regression analysis testing the relationship between clinico-pathological tumor and sentinel lymph node characteristics and the incidence of non-sentinel lymph node involvement in the UHL patient series.

Variable	*p*-Value	OR	Lower C.I.	Upper C.I.
Tumor size	0.2095	1.011	0.994	1.030
Tumor grade	0.1623	–	–	–
Grade 1 vs grade 2	0.1268	0.518	0.222	1.205
Grade 1 vs grade 3	0.0698	0.445	0.186	1.068
Grade 2 vs grade 3	0.5825	0.860	0.502	1.473
LVI (yes vs no)	0.0251	1.812	1.079	3.041
No. +SLNs	0.1444	1.268	0.922	1.743
No. –SLNs	0.0111	0.784	0.644	0.956
Size SLN M+ (macro vs micro)	0.0099	2.378	1.212	4.664
Intraoperative pathological evaluation (positive vs negative)	<0.0001	0.287	0.160	0.512

Parameter estimates for the calculation of the predicted probability of non-sentinel lymph node involvement in the UHL patient series.

Variable	Level	Estimate
Intercept		–16.489
Tumor size (mm)		0.0114
Tumor grade	1	–0.8093
Tumor grade	2	–0.1510
LVI	Yes	0.5942
No. +SLNs		0.2374
No. –SLNs		–0.2427
Size of SLN M+	Macro	0.8661
Intraoperative pathological evaluation	Neg	–12.496

Table 4 Multivariable logistic regression predicting ALN involvement for all patients and for the SLN patients separately

Variable	All patients n = 4292			SLN subgroup n = 1506		
	Coefficient	OR (95% CI)	*P*	Coefficient	OR (95% CI)	*P*
ILC	−0.421	0.66 (0.53–0.82)	<0.001	−0.722	0.49 (0.30–0.78)	0.003
Grade						
1	Reference level			Reference level		
2	0.314	1.37 (1.10–1.71)	<0.001	0.091	1.10 (0.80–1.51)	0.714
3	0.550	1.72 (1.38–2.18)		0.151	1.16 (0.81–1.67)	
ER, PR, HER-2						
ER−, PR−, Her-2−	Reference level		0.005	Reference level		0.183
ER−, PR−, Her-2+	0.436	1.55 (1.06–2.25)		0.516	1.68 (0.67–3.98)	
ER+, PR−, Her-2−	0.350	1.42 (1.04–1.94)		0.557	1.75 (0.95–3.23)	
ER+, PR−, Her-2+	0.219	1.25 (0.76–2.03)		−0.313	0.73 (0.20–2.15)	
ER+, PR+, Her-2−	0.415	1.51 (1.19–1.93)		0.571	1.77 (1.10–2.92)	
ER+, PR+, Her-2+	0.669	1.95 (1.37–2.79)		0.609	1.84 (0.91–3.69)	
Multifocality	0.466	1.60 (1.30–1.96)	<0.001	0.372	1.45 (0.93–2.24)	0.097
Age	−0.003	0.97 per 10 year (0.92–1.02)	0.206	0.003	1.03 per 10 year (0.93–1.14)	0.604
Tumor size (cm)	0.422	1.53 per cm (1.46–1.60)	<0.001	0.433	1.54 per cm (1.37–1.73)	<0.001

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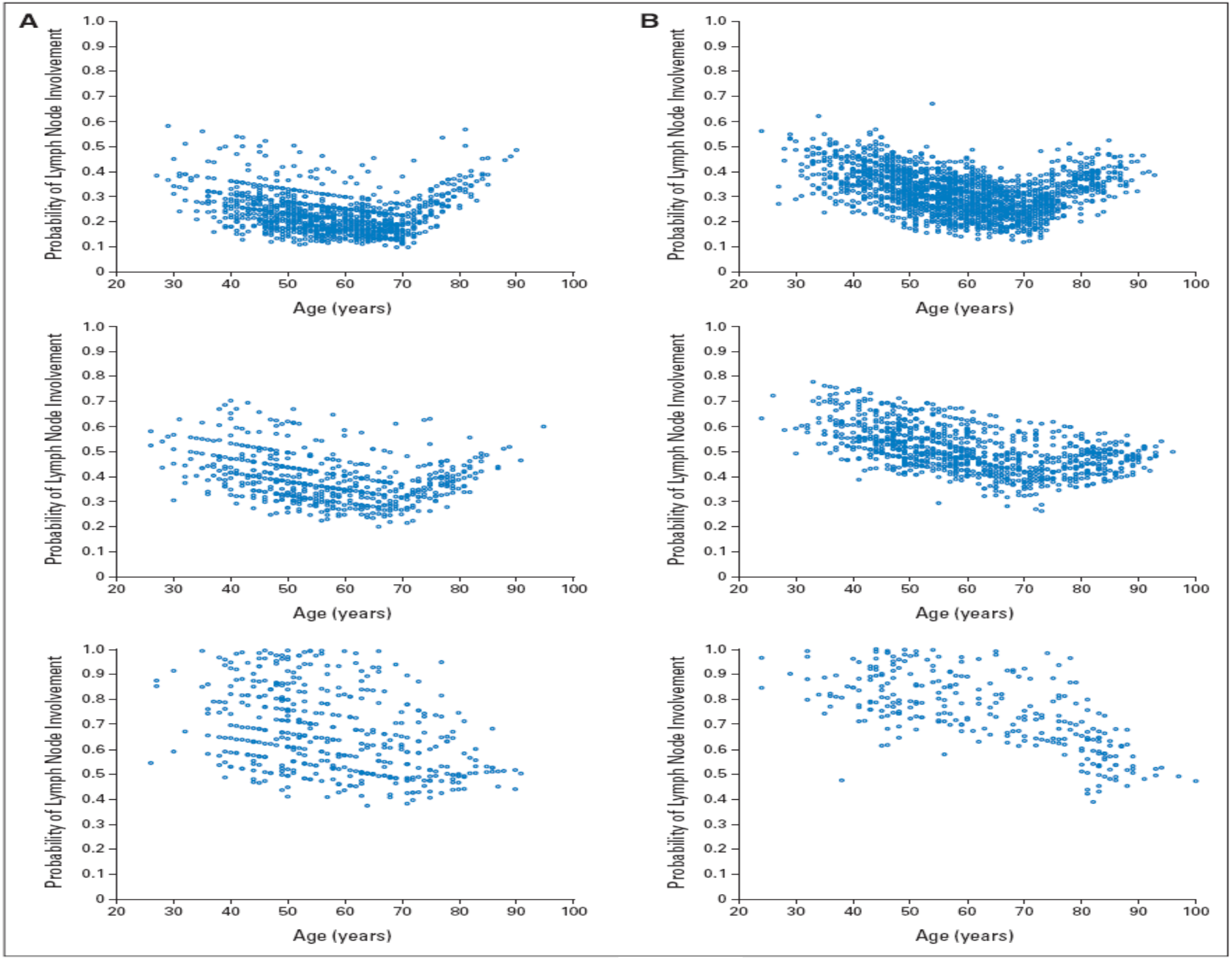
A
B
Probability of Lymph Node Involvement
Age (years)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
20
30
40
50
60
70
80
90
100

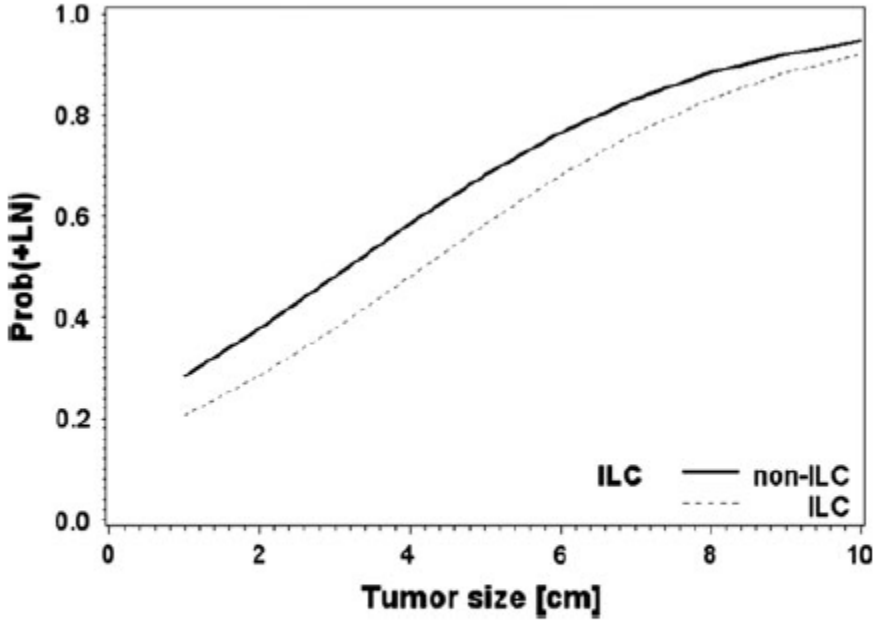

Fig. 1 Multivariable logistic regression: probability of ALN involvement versus tumor size. *Full* and *dashed* plot lines are model predictions for, respectively, non-ILC and ILC tumors with the following fixed characteristics: grade II, unifocal, ER+, PR+, and HER-2− for age 58