Sentinel node micrometastases in breast cancer do not affect prognosis: a population-based study

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Running title: Prognosis of sentinel node micrometastases in breast cancer

Adriana J Maaskant-Braat, M.D.,[2] Lonneke V van de Poll-Franse, Ph.D.,[1,4] Adri C Voogd, Ph.D.,[1,3] Jan Willem W Coebergh, M.D., Ph.D.,[1] Rudi M Roumen, M.D., Ph.D.,[5] M Cathelijne Tutein Nolthenius-Puylaert, M.D.[6], Grard A Nieuwenhuijzen, M.D., Ph.D.[2]

[1]Eindhoven Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, The Netherlands

[2]Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands

[3]Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

[4]Center of Research on Psychology in Somatic Diseases (CoRPS), Tilburg University, Tilburg, The Netherlands

[5]Department of Surgery, Máxima Medical Centre, Veldhoven, The Netherlands

[6]Department of Pathology, Elkerliek Hospital, Helmond, The Netherlands

Address for correspondence

AJG Maaskant-Braat, M.D., Department of Surgery, Catharina Hospital

PO Box 1350, 5602 ZA Eindhoven, The Netherlands

Tel.: +31 40 2399111; Fax: +31 40 2443370

E-mail: sabrinamaaskant@gmail.com

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Abstract

Sentinel node biopsy (SNB) for axillary staging in breast cancer allows the application of more extensive pathologic examination techniques. Micrometastases are being detected more often however coinciding with stage migration. Besides assessing the prognostic relevance of micrometastases and the need for administering adjuvant systemic and regional therapies, there still seems to be room for improvement. In a population based analysis we compared survival of patients with sentinel node micrometastases with those with node-negative and node-positive disease in the era after introduction of SNB. Data from the population based Eindhoven Cancer Registry were used on all (n=6803) women who underwent SNB for invasive breast cancer in the South-East Region of The Netherlands in the period 1996-2006. In 451 patients (6.6%) a sentinel node micrometastasis (pN1mi) was detected and in 126 patients (1.9%) isolated tumor cells (pN0(i+)). Micrometastases or isolated tumor cells in the SNB did not convey any significant survival difference compared with node-negative disease. After adjustment for age, pT and grade, still no survival difference emerged (pN1mi: HR 0.9 (95% CI, 0.6-1.3) and pN0(i+): (HR 0.4 (95% CI, 0.14-1.3)) and neither was the case after additional adjustment for adjuvant systemic therapy. Our practice based study showed that the presence of sentinel node micrometastases in breast cancer patients has hardly any impact on breast cancer overall survival during the first years after diagnosis.

Keywords: breast carcinoma, sentinel node biopsy, micrometastasis, prognosis

Introduction

During the last decades an increase in breast cancer incidence has occurred [1]. Combined with improving survival rates this implies that the number of prevalent breast cancer cases will continue to rise as well as the health care burden of breast cancer. Sentinel node biopsy (SNB) as an axillary staging procedure in primary breast cancer was introduced about ten years ago to avoid axillary lymph node dissection (ALND) in patients with tumor negative lymph nodes. The main advantage of performing SNB is a markedly lower morbidity [2,3] whereas axillary staging capacities are similar to ALND [4,5]. A randomized trial showed the 8-year survival of patients with primary breast cancer to be equal in the SNB-group and the ALND-group [6]. Furthermore, in observational research with cancer registry data, survival of patients with negative SNB without completion ALND has been shown to be at least equivalent to the survival of node-negative patients with extensive ALND [7]. These findings support the validity and safety of SNB as a staging procedure and thus the removal of clinically negative axillary lymph nodes by ALND seems no longer justifiable.

Since only a few nodes are being removed, the introduction of the SNB led to application of more extensive time-consuming and costly pathologic examination techniques like serial sectioning and immunohistochemistry. Occult metastases or micrometastases were detected in 9-23% of originally Hematoxylin & Eosin node-negative cases [8]. Recent studies showed a 4.3-10% increase among patients diagnosed with micrometastatic disease in the sentinel node as well [9,10]. This increase led to stage migration after adjustment for the simultaneous, favorable trend in tumor size [9]. A discussion followed on prognostic significance and possible need for additional systemic and regional treatment. Some studies on the prognostic significance of micrometastases in ALND before introduction of the sentinel node biopsy showed that patients with axillary micrometastases had higher recurrence rates and lower overall survival [11-14], others however demonstrated no such difference [15,16]. Although most studies with larger sample sizes

and longer follow-up tend to show a negative effect of micrometastatic disease on overall and disease free survival [17,18], comparison between these retrospective studies and extrapolation to patients with SNB is hampered by different inclusion criteria and large technical variances in the assessment of micrometastases.

The purpose of our study was to perform a population based analysis to determine survival of patients with sentinel node micrometastases as compared to patients with sentinel node-negative and sentinel node-positive disease and thus comment on the prognostic value of these micrometastases in the era after introduction of SNB.

Patients and methods

Methodology, results and discussion of this study were reported according to the REMARK criteria on reporting of tumor marker studies [19]. Patient data were retrieved from the population based Eindhoven Cancer Registry, which records data on all patients newly diagnosed with cancer in the Southeast region of The Netherlands, an area with approximately 2.4 million inhabitants. Collected data were derived from 10 hospitals, consisting of large non-university teaching hospitals and community hospitals, and two radiotherapy departments. Data on patient and tumor characteristics and local and systemic treatment were collected by the Cancer Registry based on the pathology reports and medical records. The patients were staged according to the Tumor-Node-Metastasis (TNM) system of the International Union Against Cancer (UICC) [20].

Sentinel node biopsy followed by axillary lymph node dissection was introduced in the Southeast Netherlands in 1995. In 1997, surgeons gradually started to perform SNB procedures as a routine staging procedure and since 2000 indications for SNB were described in national guidelines [21]. We included all women who underwent SNB for primary invasive breast cancer in the Southeast Netherlands in the period 1996-2006 and we used characteristics and data of the entire group in the analyses.

In The Netherlands the pathology protocol advocated by the EORTC Breast Cancer Group has been adopted by the pathologists since 2000 and included in the Dutch evidence-based guideline for the treatment of breast cancer. According to this guideline, sentinel nodes should be investigated at three levels at 0.25mm intervals and from each section at least two slides should be made: one for H&E staining and one for IHC [21]. For this study, data were categorized according to axillary lymph node status. Node-negative patients were categorized as pN0. Patients with metastases smaller than 0.2 mm were categorized as pN0(i+) (isolated tumor cells) and as pN1mi (micrometastases) in case of metastases between 0.2 mm and 2.0. Node-positive patients were categorized as pN1a if 1 to 3 axillary lymph nodes were positive and >pN1a if more than 3 axillary lymph nodes were positive or if metastases were present in supraclavicular or internal mammary lymph nodes. The discrimination between micrometastases and isolated tumor cells in the Cancer Registration data has only been made since 2003, after introduction of the revised TNM system in 2002.

Follow-up was completed until January 2008 and endpoint of the study was question whether or not the patient was still alive. This information was obtained from the municipal registries in the area of the Eindhoven Cancer Registry and the Central Bureau for Genealogy. The latter institution collects data on all deceased Dutch citizens via the municipal registries. In this way, information on patients who moved outside the registry area was also obtained. The few patients (<0.3%) who died outside The Netherlands might be wrongly considered as “being alive”.

Statistical analyses were carried out using SAS (version 9.1 for Windows, SAS institute Inc., Cary, NC). Survival analyses were carried out using the Kaplan-Meier life-table analysis. Survival time was defined as the period between the diagnosis of breast cancer and death or date of last available follow-up. Patients were stratified according to sentinel lymph node status and survival comparison between these groups was performed by means of the log-rank test. We censored the data if the effective sample size was smaller

than 10 in the overall survival analyses. Multivariate analyses were carried out using Cox proportional hazards analyses. Variables that showed a significant influence on survival in univariate analyses were entered in the multivariate model. We adjusted for the possible confounding influences of age at diagnosis, tumor size (defined as T-stage) and grade. We additionally adjusted for the effects of administrating adjuvant systemic therapy. P-values <0.05 were considered statistically significant.

Results

Between 1996 and 2006 a total of 6803 patients underwent SNB for primary invasive breast cancer in the Southeast region of The Netherlands. Their characteristics stratified according to lymph node status are demonstrated in Table 1. Micrometastatic lymph node involvement was observed in 6.6% of the patients. Age at diagnosis, pT-stage, grade and histology all differed significantly according to nodal status (P<0.0001). Patients without metastases or with micrometastatic disease underwent breast conserving surgery significantly more frequent than those with macrometastases (P<0.0001). Administration of adjuvant systemic therapy significantly increased with lymph node involvement. 28% of the patients with a negative sentinel node received adjuvant systemic therapy (chemo- and/or hormonal therapy) versus 74% in the pN1mi-group and 93% in the pN1a-group.

Median follow-up was 50 months for patients with pN0- and pN1mi-disease, 53 months for patients with pN1a-disease, 47 months for patients with >pN1a-disease and 36 months for patients with pN0(i+)-disease. Overall (unadjusted) survival was significantly worse for patients with pN1a- and >pN1a-disease compared to pN0-disease (P<0.0001). Survival of patients with pN0(i+) and pN1mi did not differ significantly from pN0-disease (P=0.19 and P=0.52) (Figure 1). In multivariate analysis adjusted for age, pT and grade, no significant survival difference was shown between isolated tumor cells and node-negative disease (HR 0.4 (95% CI, 0.14-1.3)) or between micrometastatic disease and node-negative disease (HR 0.9 (95% CI, 0.6-1.3)) (Table 2). Patients with pN1a-disease had an

increased risk of overall mortality with a hazard ratio of 1.4 (95% CI, 1.2-1.7) compared to pN0. Patients with >pN1a-disease had a hazard ratio of 2.2 (95% CI, 1.7-3.0) compared to pN0.

After additional adjustment for adjuvant systemic therapy still no significant survival difference was observed for isolated tumor cells (P=0.15) and micrometastatic disease (p=0.97) compared to node-negative patients. Patients with pN1a-disease and >pN1a-disease still had an increased risk of overall mortality (Table 2). We performed additional analyses excluding grade as a covariate considering the relatively high percentage of missing values for this variable, but this did not change the result of our analyses in any way. Neither did the additional analyses we performed adjusting for the execution of completion ALND. Separate unadjusted analyses of prognosis by N-stage according to whether patients received no adjuvant systemic therapy, adjuvant chemo- or hormonal therapy or both did also not change the result of our analyses (Figure 2, 3, 4 and 5).

Discussion

Based on studies conducted before the introduction of the sentinel node procedure, administration of adjuvant systemic therapy to patients with micrometastatic disease in the sentinel node seems justifiable under the assumption that these micrometastases are prognostic indicators of worse survival and outcome. Our study however, which is based exclusively on patients who underwent SNB, showed no overall survival difference between patients with micrometastatic disease and those without axillary lymph node metastasis. Even after adjustment for age, pT, grade and administration of adjuvant systemic therapy no significant survival differences could be detected.

By using data of the Eindhoven Cancer Registry, we were able to present results based on a large, unselected population-based patient population. The patients were treated in both teaching and community hospitals and data are thought to reflect the usual care in The Netherlands. This report is one of the first on the prognosis of patients with

micrometastases in the sentinel node. Despite a fairly short follow-up time and a small number of events, the 95% confidence intervals of the estimated Hazard Ratio's are small enough to rule out a large difference in survival between node-negative patients and patients with micrometastases.

Apparently, the biological behavior of sentinel node micrometastases is of limited prognostic significance, at least during the first five years after diagnosis. In order for tumor cells to metastasize, a number of sequential processes have to take place, such as tumor cell invasion, adhesion and angiogenesis. This is a rather inefficient process and not all circulating tumor cells are viable and capable of forming regional and distant metastasis [22]. Furthermore, expansion of metastasized tumor masses beyond 1-2 mm in diameter depends on the development of a new blood supply by angiogenesis, which again raises the question whether these very small metastases have biologic implications at all [23]. The observation that occult axillary and distant involvement might never become clinically overt [6,24] led to the emergence of the stem cell hypothesis, which postulates that a population of cancer cells consists of a limited number of cancer stem cells that cause cancer progression and a larger number of non-stem cancer cells being dormant [25]. Presence of cancer stem cells in a metastatic focus is hypothesized to be important or possibly crucial for development and growth of these foci. Without these stem cells the metastatic focus would be destined to disappear by apoptosis or have a very long dormancy.

As stated before, studies on the significance of micrometastases that used data from patients before the introduction of the sentinel node biopsy showed contradicting results. In one of the larger studies with long follow-up, which was also based on data from the Eindhoven Cancer Registry, 10111 patients were included, of whom 179 had micrometastases. They were diagnosed with invasive breast cancer between 1975 and 1997 and had complete follow-up until April 2002. Remarkably, the results of this study showed that patients with axillary nodal micrometastasis in ALND had a significantly worse

survival rate than node-negative patients independent of age or tumor size [14]. Since these data were derived from the same database, covering the same hospitals and pathology laboratories, we must conclude that ALND nodal micrometastases do not have the same prognostic implication as sentinel node micrometastases. We might have studied two different breast cancer patient populations with different tumor-characteristics and metastatic tumor burden. This seems quite unlikely however, since we adjusted for tumor stage and completion ALND and other studies showed no change in prognosis during this period. Treatment plans have altered and have included the use of systemic adjuvant therapy far more often, but we adjusted for the possible effect of adjuvant systemic therapy in our study. Detection of metastases might be directly dependent on the methods used to investigate them. By using serial sectioning and immunohistochemistry in routine daily practice, more and smaller metastases are being detected which may not be a harbinger of undetected macrometastases as may have been the case in older studies.

In an American publication the SEER database was used to determine prognostic significance of micrometastases in pre- as well as post-SN era [26]. This relatively large study demonstrated only a minimal detrimental impact in tumors less than 2.0 cm in diameter and a more significant detrimental impact in larger tumors (1 vs. 4-6% decrease in 5-year survival). The authors, however, were not able to track the use of adjuvant therapies and therefore they could not adjust for the possible confounding effects of administration of adjuvant systemic therapy. Another Dutch publication based on a much smaller population sample showed that despite a higher risk of distant metastases in the micrometastatic group there was no significant difference in overall or disease-free survival between pN0- and pN1mi-disease [27]. In a recently published study by Hansen et al [28] patients with isolated tumor cells or micrometastases did not have a worse disease-free and overall survival compared to SN-negative patients. Also consistent with our results was their finding that patients with macrometastases have a worse prognosis than the SN-negative patients and patients with isolated tumor cells or micrometastases.

The MIRROR study (Micrometasases and Isolated tumor cells: Relevant and Robust or Rubbish?) showed that patients with isolated tumor cells or micrometastases as final N-stage after SNB had a significantly lower 5-year disease-free survival than patients without nodal involvement [29]. This study, which is also a retrospective cohort study, only included patients with favorable tumor characteristics for whom adjuvant systemic treatment was not indicated according to the Dutch treatment guidelines. In contrast, we also included patients who had been receiving systemic treatment according to those guidelines, as well as patients with macrometastases to see how their prognosis compares to the prognosis of patients with micrometastastic disease or isolated tumor cells. In the MIRROR study pathology of removed axillary lymph nodes was reviewed. Reviewing of the pathology seems to have led to a detection of more isolated tumor cells as compared to micrometastases and node-negative patients. We chose to base our analyses on the information that was retrieved from the pathology report and thus to present results based on usual care in The Netherlands. Finally, no data on overall survival were available in the MIRROR trial.

In conclusion, our population-based study showed that the presence of sentinel node micrometastases in breast cancer patients did not have significant impact on breast cancer overall survival during the first 5 years after diagnosis. We therefore postulate that micrometastatic disease itself should not be an indication for adjuvant systemic therapy.

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Figure legends

Figure 1 Kaplan-Meier life table analysis of overall survival by lymph node status of 6803 patients who underwent SNB for primary breast cancer in the Southeast Netherlands, 1996-2006.

Figure 2 Kaplan-Meier life table analysis of survival by lymph node status of patients who underwent SNB for primary breast cancer and received no systemic therapy, 1996-2006.

Figure 3 Kaplan-Meier life table analysis of survival by lymph node status of patients who underwent SNB for primary breast cancer and received both hormonal therapy and chemotherapy, 1996-2006.

Figure 4 Kaplan-Meier life table analysis of survival by lymph node status of patients who underwent SNB for primary breast cancer and received hormonal therapy, 1996-2006.

Figure 5 Kaplan-Meier life table analysis of survival by lymph node status of patients who underwent SNB for primary breast cancer and received chemotherapy, 1996-2006.

Table 1 Patient characteristics by lymph node status of 6803 patients who underwent SNB for primary invasive breast cancer in the Southeast Netherlands, 1996-2006.

Lymph node status	pN0	pN0(i+)	pN1mi	pN1a	>pN1a	P-value
Number of patients (%)	4562 (67.1)	126 (1.9)	451 (6.6)	1347 (19.8)	317 (4.7)	
Accrued months of follow-up	228100	4536	22550	71391	14899	
Age at diagnosis						
≤35	107 (2.4)	2 (1.6)	14 (3.1)	47 (3.5)	17 (5.4)	<0.0001
36-49	993 (21.8)	29 (23.0)	119 (26.4)	409 (30.4)	98 (10.9)	
50-69	2483 (54.4)	67 (53.2)	238 (52.8)	682 (50.6)	155 (48.9)	
≥70	979 (21.5)	28 (22.2)	80 (17.7)	209 (15.5)	47 (14.8)	
pT-stage						<0.0001
1	3408 (74.7)	84 (66.7)	294 (65.2)	710 (52.7)	114 (36.0)	
2	1037 (22.7)	39 (31.0)	141 (31.3)	564 (41.9)	168 (53.0)	
3	17 (0.4)	0 (0.0)	8 (1.8)	17 (1.3)	15 (4.7)	
4	25 (0.6)	2 (1.6)	3 (0.7)	28 (2.1)	9 (2.8)	
Unknown	75 (1.6)	1 (0.8)	5 (1.1)	28 (2.1)	11 (3.8)	
Grade						
I	1077 (23.6)	29 (23.0)	91 (20.2)	236 (17.5)	40 (12.6)	<0.0001
II	1590 (43.9)	49 (38.9)	174 (38.6)	488 (36.2)	118 (37.2)	
III	940 (20.6)	30 (23.8)	97 (21.5)	335 (24.9)	91 (28.7)	
Unknown	955 (20.9)	18 (14.3)	89 (19.7)	288 (21.4)	68 (21.5)	
Histology						
Ductal	3618 (79.3)	101 (80.2)	361 (80.0)	1100 (81.7)	241 (76.0)	<0.0001
Lobular/mixed	635 (13.9)	18 (14.3)	75 (16.6)	216 (16.0)	68 (21.5)	
Mucinous/tubular/medullary	236 (5.2)	3 (2.4)	8 (1.8)	24 (1.8)	5 (1.6)	
Other	73 (1.6)	4 (3.2)	7 (1.6)	7 (0.5)	3 (1.0)	
Type of definitive surgery						
Breast-conserving surgery	3520 (77.2)	84 (66.7)	307 (68.1)	817 (60.7)	149 (47.0)	<0.0001
Mastectomy	1029 (22.6)	42 (33.3)	144 (31.9)	528 (39.2)	167 (52.7)	
None/unknown	13 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.3)	
Type of axillary surgery						
SNB alone	4097 (89.8)	49 (38.9)	126 (27.9)	133 (9.9)	8 (2.5)	<0.0001
SNB+ALND	465 (10.2)	77 (61.1)	325 (72.1)	1214 (90.1)	309 (97.5)	
Radiotherapy						
Yes	3460 (75.8)	81 (64.3)	296 (65.6)	875 (65.0)	259 (81.7)	<0.0001
No	1102 (24.2)	45 (35.7)	155 (34.4)	472 (35.0)	58 (18.3)	
Adjuvant systemic therapy						
Chemotherapy	447 (9.8)	16 (12.7)	71 (15.7)	368 (27.3)	109 (34.4)	<0.0001
Hormonal therapy	526 (11.5)	35 (27.8)	180 (39.9)	539 (40.0)	81 (25.6)	
Chemo- and hormonal therapy	301 (6.6)	12 (9.5)	81 (18.0)	342 (25.4)	98 (30.9)	
None	3288 (72.1)	63 (50.0)	119 (26.4)	98 (7.3)	29 (9.2)	

SNB: Sentinel Node Biopsy; ALND: Axillary Lymph Node Dissection

Table 2 Hazard ratio of overall mortality by lymph node status of 6803 patients who underwent SNB for primary breast cancer in the Southeast Netherlands, 1996-2006.

				Univariate model		Multivariate model I *		Multivariate model II **	
	No. of patients	Follow-up (months)	No. of events	crude HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
pN0	4562	50 ± 27	347	1.00		1.00		1.00	
pN0(i+)	126	36 ± 14	3	0.46 (0.15-1.45)	0.19	0.42 (0.14-1.32)	0.14	0.44 (0.14-1.36)	0.15
pN1mi	451	50 ± 25	31	0.89 (0.61-1.28)	0.52	0.88 (0.61-1.27)	0.48	0.99 (0.68-1.45)	0.97
pN1a	1347	53 ± 29	167	1.50 (1.25-1.81)	<0.0001	1.43 (1.18-1.73)	0.0002	1.62 (1.30-2.01)	<0.0001
>pN1a	217	47 ± 25	57	2.50 (1.89-3.31)	<0.0001	2.23 (1.67-2.98)	<0.0001	2.51 (1.84-3.42)	<0.0001

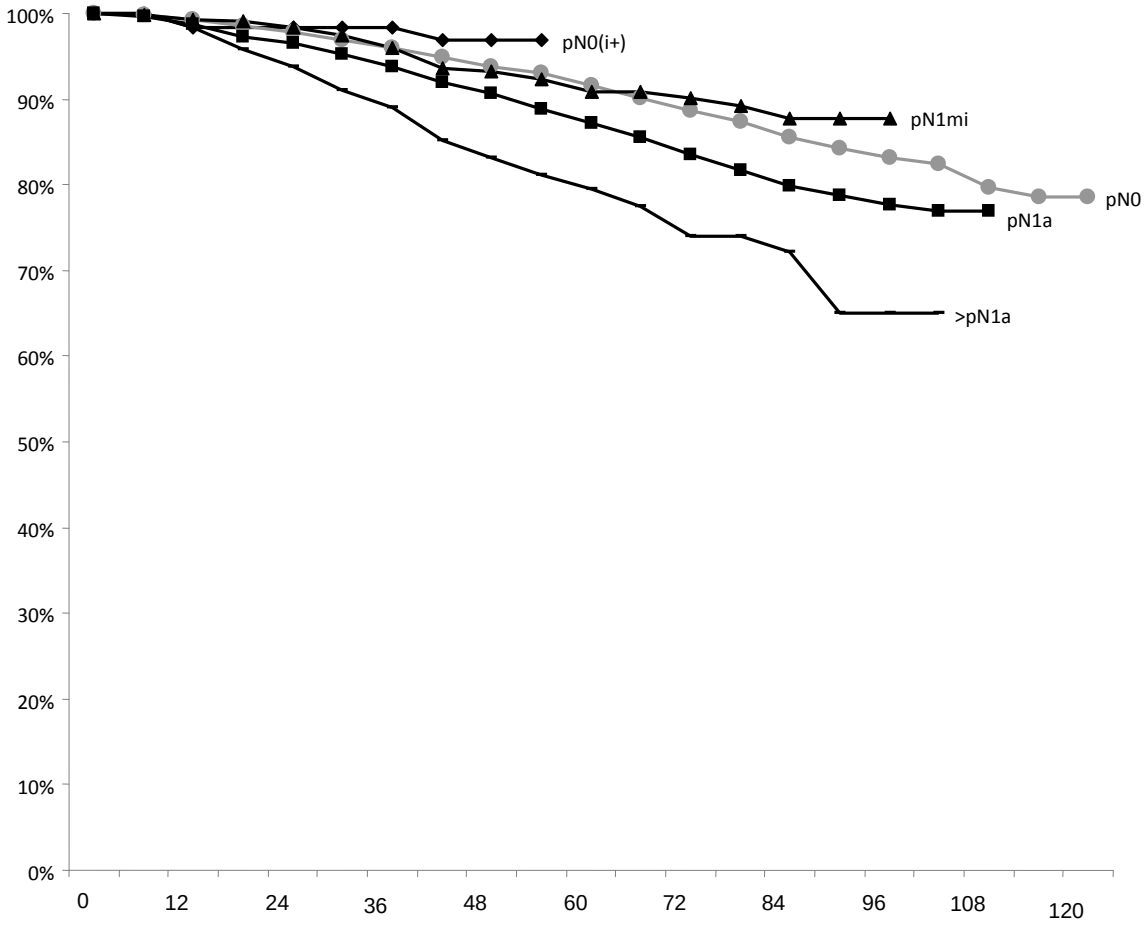
HR: Hazard Ratio

95%CI: 95% Confidence Interval

* Model I: Adjusted for age, pT and grade

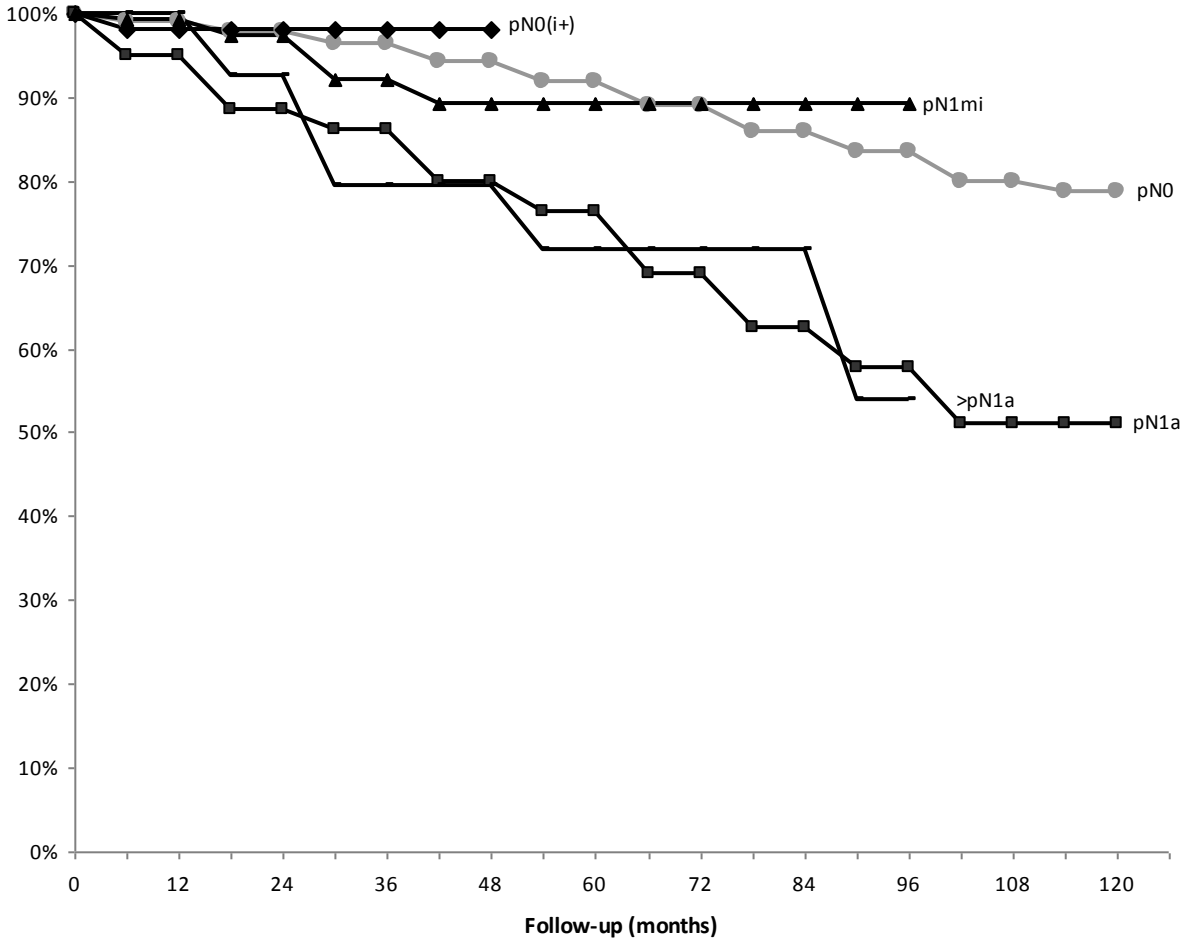
** Model II: Additionally adjusted for adjuvant systemic therapy

Overall survival according to pN-status



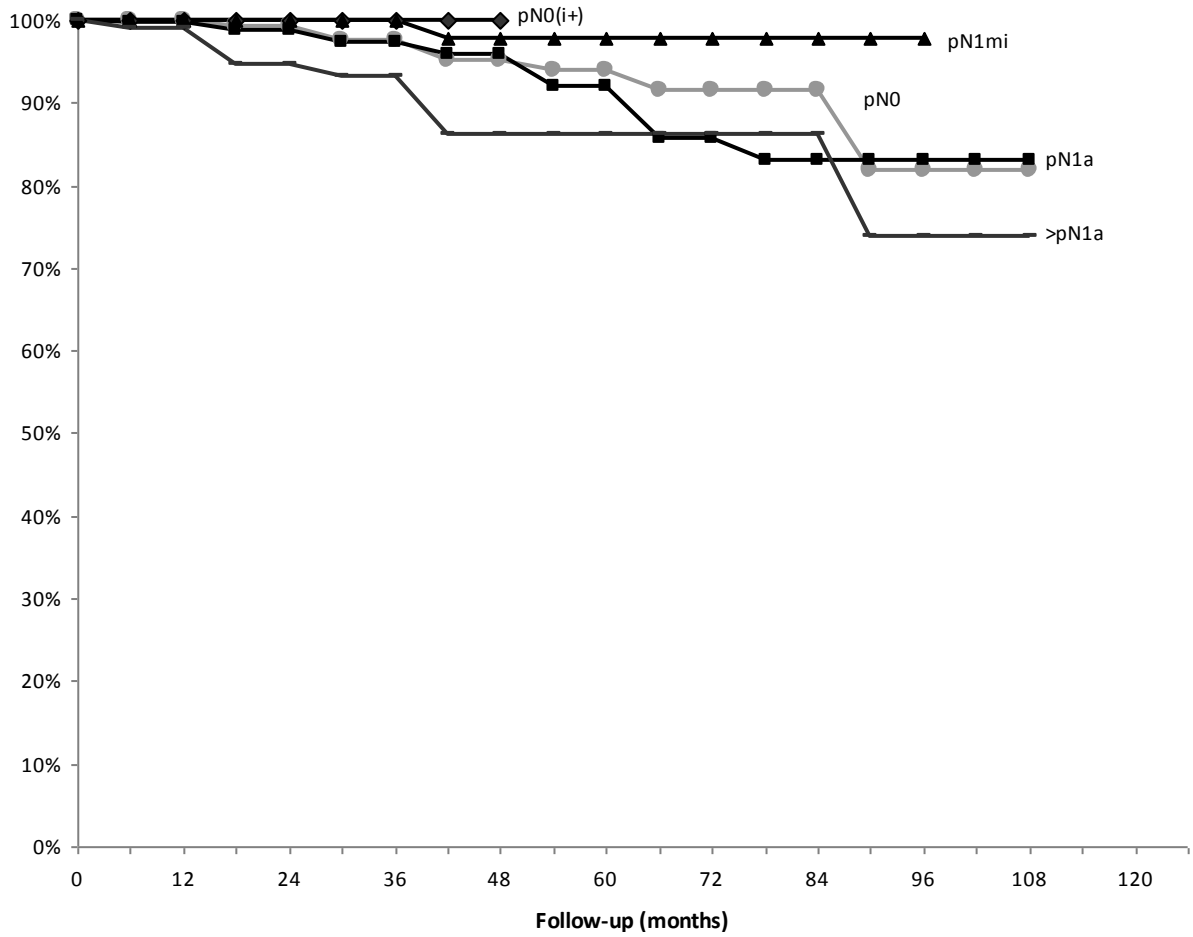
Patients at risk											
pN0(i+)	126	116	91	61	25						
pN0	4562	4328	3522	2754	2026	1378	894	523	245	79	29
pN1mi	451	427	352	285	214	152	91	43	12		
pN1a	1347	1285	1065	861	675	513	331	207	104	44	12
>pN1a	317	302	247	191	129	80	51	29	12		

Survival according to pN-status, no systemic therapy



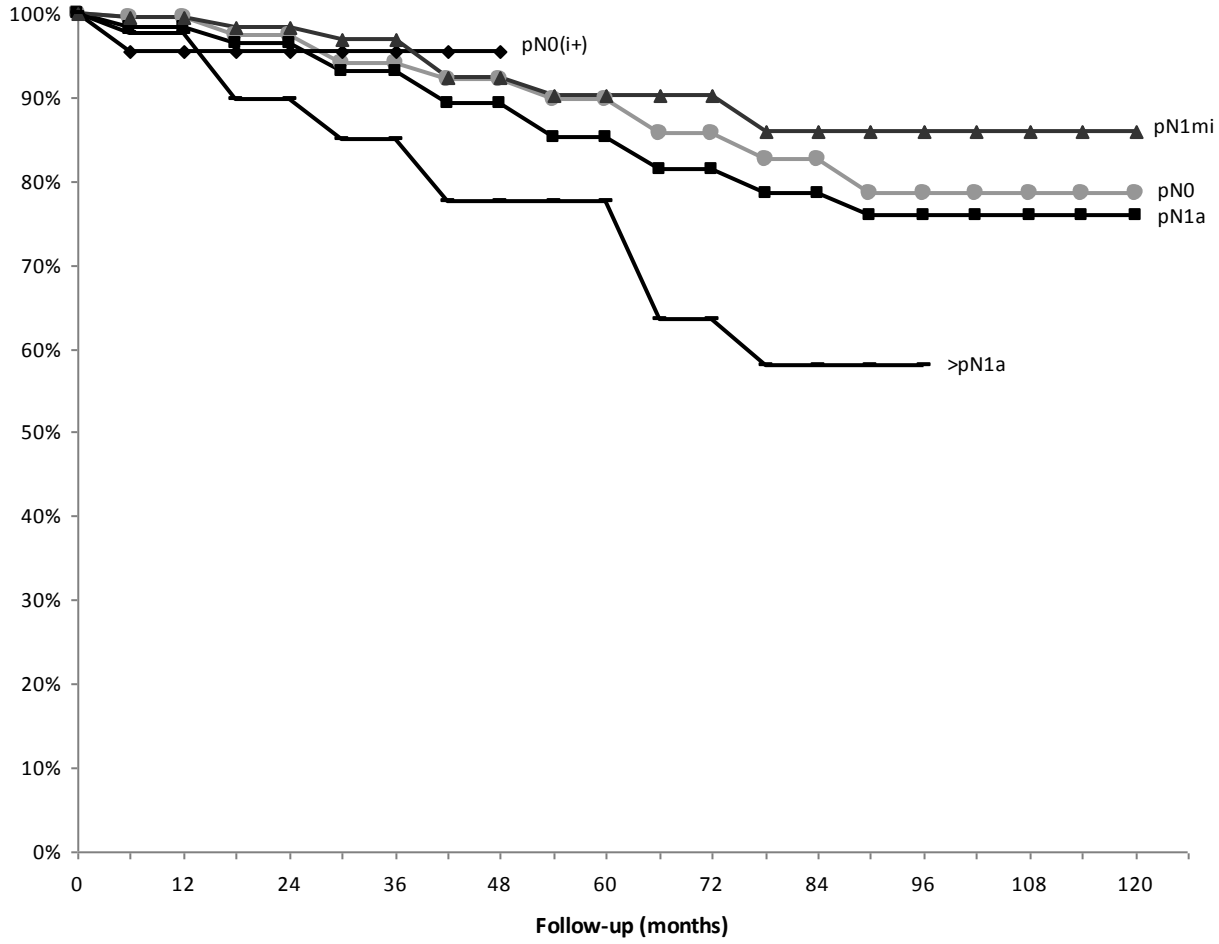
Patients at risk											
pN0	3285	2991	2442	1906	1381	938	597	339	161	62	18
pN0(i+)	53	43	30	21	8						
pN1mi	128	114	92	65	41	28	16	8	2		
pN1a	98	91	74	56	42	32	21	14	9	4	1
>pN1a	29	27	21	15	11	7	5	4	2		

Survival according to pN-status, hormonal- and chemotherapy



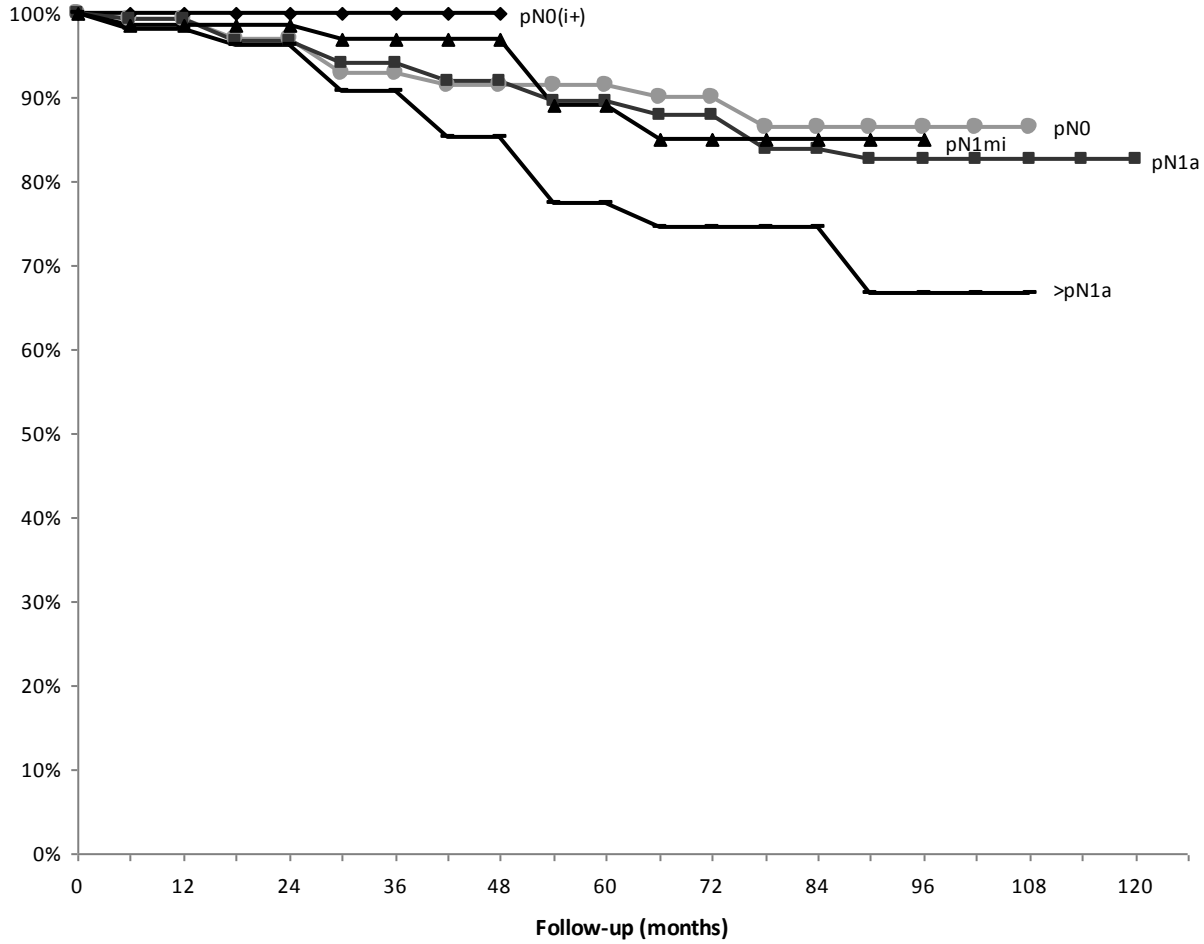
Patients at risk										
pN0	301	257	184	125	72	38	20	10	2	1
pN0(i+)	8	7	5	4	2					
pN1mi	86	79	64	46	27	17	12	7		
pN1a	350	302	212	142	96	59	31	15	6	1
>pN1a	101	91	70	53	30	17	12	7	3	1

Survival according to pN-status, hormonal therapy



Patients at risk											
pN0	527	475	377	297	229	162	107	62	24	6	2
pN0(i+)	22	17	10	6	3						
pN1mi	183	171	148	124	96	69	42	18	7	2	1
pN1a	548	512	446	365	286	211	142	85	41	15	4
>pN1a	81	74	59	46	31	22	12	7	3		

Survival according to pN-status, chemotherapy



Patients at risk											
pN0	444	410	338	264	194	128	77	41	15		
pN0(i+)	11	10	7	4							
pN1mi		64	54	47	37	23	11	4			
pN1a	36	345	307	269	221	165	111	64	34	16	4
>pN1a	106	99	87	67	44	28	18	10	4	1	