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Identifying the potential long-term survivors among breast cancer patients with distant metastasis

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ABTRACT

Background: We aimed to develop a prediction model to identify long-term survivors after developing distant metastasis from breast cancer.

Patients and Methods: From the institution's database, we collected data of 547 patients who developed distant metastasis during their follow-ups. We developed a model that predicts the post-metastasis overall survival (PMOS) based on the clinicopathologic factors of the primary tumors and the characteristics of the distant metastasis. For validation, the survival data of 254 patients from four independent institutions were used.

Result: The median duration of the PMOS was 31.0 months. The characteristics of the initial primary tumor such as tumor stage, hormone receptor status, and Ki-67 expression level, and the characteristics of the distant metastasis presentation including the duration of disease-free interval, the site of metastasis, and the presence of metastasis-related symptoms, were independent prognostic factors determining the PMOS. The association of tumor stage and the PMOS was only seen in tumors with early relapses. The PMOS score, which was developed based on the above six factors, successfully identified patients with superior survival after metastasis. The median PMOS for patients with PMOS score less than 2 and for patients with PMOS score higher than 5 were 71.0 months and 12 months, respectively. The clinical significance of the PMOS score was further validated using independent multicenter datasets.

Conclusion: We have developed a novel prediction model that can classify breast cancer patients with distant metastasis according to their survival after

metastasis. Our model can be a valuable tool to identify long-term survivors who can be potential candidates for more intensive multi-disciplinary approaches. Furthermore, out model can provide a more reliable survival information for both physicians and patients during their informed decision making process.

KEY WORDS

Breast cancer, survival after metastasis, prediction model, stage IV

KEY MESSAGE

In breast cancer patients who develop metastases after initial treatments, the survival after metastasis can be predicted by using a model comprised of initial tumor characteristics and the mode of recurrence. The prediction model is helpful in giving prognostic information for both physicians and patients, and also valuable in selecting patients for more intensive multidisciplinary treatments.

INTRODUCTION

Most breast cancer-related deaths are caused by distant metastasis of cancer cells rather than local complications of the primary tumors and a significant number of breast cancer eventually experience distant relapse despite the recent improvement of breast cancer treatment.[1-3] In a prospective trial involving stage I and II early breast cancer patients, the cumulative rate of distant metastasis was 44.0% after 22 years follow-up.[4] The treatment options for patients who develop distant metastasis vary from traditional palliative therapies to more intensive multidisciplinary approaches aiming for potential long-term remissions.[5]

A reliable prediction of the expected survival in breast cancer patients with distant metastasis is a critical basis for appropriate treatment selection. Furthermore, for patients with stage IV disease, more than 90% of patients consider the information on survival as the most required information for informed decision making,[6] and sharing detailed information on the expected survival with the patients can help them planning their remaining time.[7] However, accurate prediction of survival in a newly diagnosed metastatic breast cancer patient is one of the most difficult challenges that physicians face.

Several studies have addressed the prognostic factors that determine the overall survival in metastatic breast cancer patients, and found some common clinical factors associated with improved survival such as hormone receptor status and burdens of metastasis.[8-14] However, at present, we do not have a valid model to identify a potential long-term survivor among the metastatic breast cancer patients.

In the present study, we aimed to develop a model that predicts the survival after distant metastasis in breast cancer patients.

PATIENTS AND METHODS

To develop a prediction model, the data of patients who underwent curative surgery in Seoul National University Hospital were obtained from the web-based database of Seoul National University Hospital Breast Care Center.[15] Written informed consents were taken prior to surgery in all patients to register their information in the database (IRB No 1405-088-580). The review and analysis of the collected information were separately approved (IRB No. 1308-051-512). All procedures were done in accordance with the Declaration of Helsinki.

We selected patients who were initially diagnosed between Jan 1997 and Dec 2010 and underwent for curative surgery. From the database, we obtained the baseline demographic and clinicopathologic information including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2) status, and Ki-67 expression levels. Initial breast cancer was pathologically staged according to 7th AJCC criteria. We reviewed the electric medical records of the patients to identify the occurrence of distant metastasis and the nature of the metastasis. Patients were excluded if they had suspicious radiologic findings of distant metastasis at the time of initial diagnosis. Distant metastasis did not include the cases with isolated ipsilateral or contralateral breast recurrence, isolated regional lymph node patients, or local chest wall recurrence. Patients who had metachronous carcinoma at other organs, male breast cancer patients, and patients who received prior systemic chemotherapy were excluded from the analysis.

The metastatic sites were classified as bone, brain, liver, lung/pleura, distant lymph nodes and multiple site metastases. In instances where patients developed another distant organ involvement within less than 3 months after initial metastasis, they were also considered as multiple site metastases. We investigated the presence of metastasis-related symptoms at the time of first metastasis development based on the each patient's medical record. Ambiguous symptoms such as general weakness or fatigue were not considered as metastasis-related symptoms.

Distant metastasis-free interval was defined as the time from the curative surgery of primary breast cancer to the date of the first distant metastases. Post-metastasis overall survival was measured from first metastasis to the date of death from any cause or to most recent follow-up date. The information of death date was obtained from the Korean National Statistical Office.

To validate the developed prediction model, we obtained pooled clinical data of 254 breast cancer patients from four teaching hospitals in Korea (175 patients from National Cancer Center, 31 patients from Gyeongsang National University Hospital, 24 patients from Dankook University Hospital, and 24 patients from Seoul National University Bundang Hospital). Same exclusion criteria were used for patient selection in the validation set. For Ki-67 expression, patients were classified according to the each institution's median Ki-67 value to adjust the inter-laboratory variations of Ki-67 staining.[16]

Survival outcome was estimated by the Kaplan-Meier method and compared across groups using the log-rank. For analyses in where the early events and late events showed different patterns, we added the Gehan-Breslow-Wilcoxon test to stress the importance of early events. For multivariate analysis, a Cox proportional hazards ratio model was used to estimate the adjusted hazard ratio for significance.

All analyses were carried out using SPSS (version 19.0; SPSS Inc). The statistical significance was assumed at $p < 0.05$.

RESULTS

Factors affecting survival after distant metastasis

To identify the prognostic factors affecting post-metastasis overall survival, we reviewed the data of 547 patients who developed distant metastasis during their follow-up after the initial treatment from the Seoul National University Hospital. The clinical and pathologic information at the time of the initial treatment and the characteristics of the first distant metastasis are listed in the Table 1. The median time between initial diagnosis and the development of the first distant metastasis was 29.0 months (3-176 months), and the median duration of the post-metastasis overall survival was 31.0 months (0-173 months) (Supplementary Fig. S1). The median survival after metastasis has been significantly improved during the last two decades (Supplementary Fig. S2).

The tumor stage, hormone receptor status, Ki-67 level, and histologic grade of the initial tumors were significantly associated with post-metastasis overall survival (Table 2). The observed importance of initial tumor stage in survival was further dissected by investigating the post-metastasis overall survival according to initial tumor size and nodal involvement. As shown in the Figure 1a-c, the tumor size and nodal status at initial diagnosis were both significantly associated with the post-metastasis overall survival. In addition to the initial tumor characteristics, the clinical characteristics of first distant metastasis were analyzed with regard to the post-

metastasis overall survival. The interval between the initial diagnosis and the development of first metastasis, the presence of metastasis-related symptoms, and the sites of metastasis were significantly associated with the post-metastasis overall survival (Figure 1e-g).

Interaction between the initial tumor stages and the duration of the distant metastasis-free intervals

We analyzed the effect of the initial tumor stages on the post-metastasis overall survival according to the duration of the distant metastasis-free intervals. In patients who developed distant metastasis within 3 years from the initial treatment, the initial tumor stages showed significant association with the post-metastasis overall survival (Figure 2a). However, in patients who developed distant metastasis after 3 years, the initial tumor stages showed no prognostic significance (Figure 2b). This observation was in contrast with other prognostic characteristics of the initial tumors such as hormone receptor status or Ki-67 levels, which showed consistent effect regardless of the distant metastasis-free intervals.

Prediction of long-term survivors with distant metastasis

Cox proportional regression model showed initial tumor characteristics such as advanced tumor stage, hormone receptor negativity, high Ki-67 level, and clinical features of metastasis presentation including short duration of disease-free interval, the site of metastasis, and the presence of symptom were independent predictors of shorter survival after distant metastasis (Supplementary Table 1). Based on the

hazard ratio, we constructed a scoring system, the post-metastasis overall survival score (PMOS Score), to estimate the likelihood of long-term survival in breast cancer patients who developed distant metastasis (Figure 3a). The PMOS score ranged from 0 to 8, and the patients were categorized into 4 groups according to their scores. The PMOS score in patients with distant metastasis clearly separated groups of different survival outcomes (p<0.0001). The patients with score 4-5 or score 6-8 showed substantially short post-metastasis survival. The median survival for Group I patients was 71 months while it was 12 months for the Group IV patients (Figure 3b).

Multicenter validation of the PMOS score

To validate the clinical usefulness of the PMOS score, we constructed an independent dataset of 254 breast cancer patients who developed distant metastasis after initial treatment from four teaching hospitals in Korea. As shown in the Figure 3c, the PMOS score successfully predicted the post-metastasis survival in the validation dataset. Although the survival difference between Group I and Group II was not significant in the validation dataset, the Group III and IV patients showed significantly worse post-metastasis survival (p<0.0001). The median survival for the Group III and IV in the validation dataset was highly reproducible with the value of 13.5 months and 28.2 months, respectively (12.0 and 23.0 in the development dataset).

DISCUSSION

In patients who develop distant metastasis during their post-treatment follow-up, deciding optimal therapeutic approach is often clinically challenging. Recent studies suggest that a small group of metastatic breast cancer patients can achieve clinical remission status for a sustained period of time.[5, 17] These small group of patients, who are mostly characterized by the presence of a solitary or a few metastatic lesions in a single organ (oligometastatic disease), are potential candidates of intensive multidisciplinary therapy aimed for the long-term clinical remission. However, in many patients, the appearance of the first metastasis is often followed by rapid progression in multiple organs making the intensive approach a futile one.[18] Therefore, a valid prediction tool to identify long-term survivors among the metastatic breast cancer patients can offer a reasonable basis of selecting patients for appropriate therapy without increasing unnecessary compromise in quality of life.

Our results show that both initial tumor characteristics and the clinical features of metastasis presentation are significantly associated with the post-metastasis overall survival. Some of the factors were also suggested to be prognostic in previous studies dealing with the outcomes of metastatic breast cancer patients.[8, 10, 11, 13, 19] Based on the findings, we constructed a prediction model to identify long-term survivors after distant metastasis, and validated the clinical usefulness of our prediction model in an independent validation dataset. In both dataset, the group of patients who were predicted to have relatively worse outcome (Group III and IV) showed median survival of less than 30 months. Based on our model, we propose that these patients are unlikely to benefit from intensive multidisciplinary therapy

aimed at clinical remission since their disease may progress rapidly. More importantly, the ability to predict the individual metastastic breast cancer patient's outcome is essential in choosing personal plans for the remaining lifetime in addition to the one's therapeutic options.

The association between the initial tumor stages and the survival after metastasis was also interesting. Previous studies have suggested the importance of initial nodal status in determining survival after relapse.[17, 20-26] Our data shows that both initial tumor size and the number of metastatic nodes are inversely associated with the post-metastasis overall survival. Furthermore, unlike the hormonal receptor and Ki-67 status, the association is only significant in patients who develop distant metastasis within three years. Advanced tumors with a higher burden of disseminated tumor cells often carry micro-metastastic foci in multiple organs.[27, 28] Therefore, distant metastasis in patients with initially advanced diseases may mimic the behavior of the tumors with multiple site metastasis. The risk of having occult metastases at multiple organs might be low in patients who develop metastasis many years after the initial treatment.

Our study carries several limitations. First, the retrospective nature of the study necessitates the prospective validation of the prediction model. Second, the classification of the Ki67 staining for the patients included in the multicenter validation dataset was not determined by the absolute value. Rather, we used each institution's median value to define the high Ki67 values due to the apparent inter-laboratory variation of the Ki67 staining[16]. Finally, we were not able to collect data on the molecular profiling of the metastastic lesions that may provide a mechanistic insight into the outcomes of the metastatic breast cancer patients [29].

In conclusion, we revealed important prognostic factors in breast cancer patients who developed distant metastasis and elucidated the dynamic interactions between the factors. Based on our observations, we have constructed a prediction model that can help patients to obtain more clear insights into their future outcomes and can also guide the physicians to select personalized treatment options for individual metastatic breast cancer patients.

FUNDINGS

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FIGURE LEGENDS

Figure 1. The effects of tumor stage and the characteristics of metastasis on the post-metastasis overall survival.

The Kaplan-Meier survival curves for post-metastasis overall survival in 547 patients according to the initial tumor stages (a), tumor size (b), and the numbers of lymph node involvement (c). The relationship between the survival and the characteristics of the metastasis including the presence of symptoms at the diagnosis of first metastasis (e), the distant metastasis-free interval (f), and the sites of first distant metastasis (g) is shown in the lower panel.

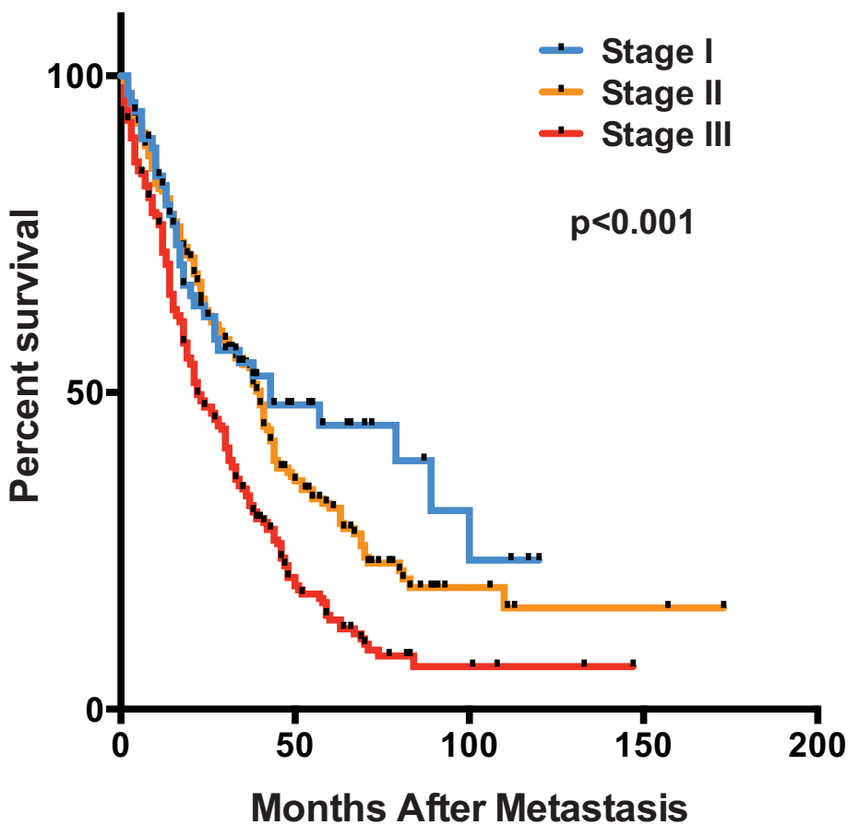
Figure 2. The prognostic effects of initial tumor characteristics on post-metastasis overall survival according to the distant metastasis-free intervals.

In patients who developed distant metastasis within 3 years of the initial treatment (upper panels), the stage, hormone receptor status, and the Ki-67 levels were significantly associated with the post-metastasis overall survivals. In patients who developed distant metastasis after 3 years, the initial tumor stage did not affect the post-metastasis overall survival while the hormone receptor status and the ki-67 level still had similar associations (lower panes). The p value derived from the Gehan-Breslow-Wilcoxon tests are shown in the parenthesis.

Figure 3. The post-metastasis overall survival (PMOS) prediction model.

The left panel (a) shows the components of the PMOS prediction model, and the performance of the prediction model in the 547 patients from the development cohort (b) and in 254 patients from the multicenter validation cohort (c).

a



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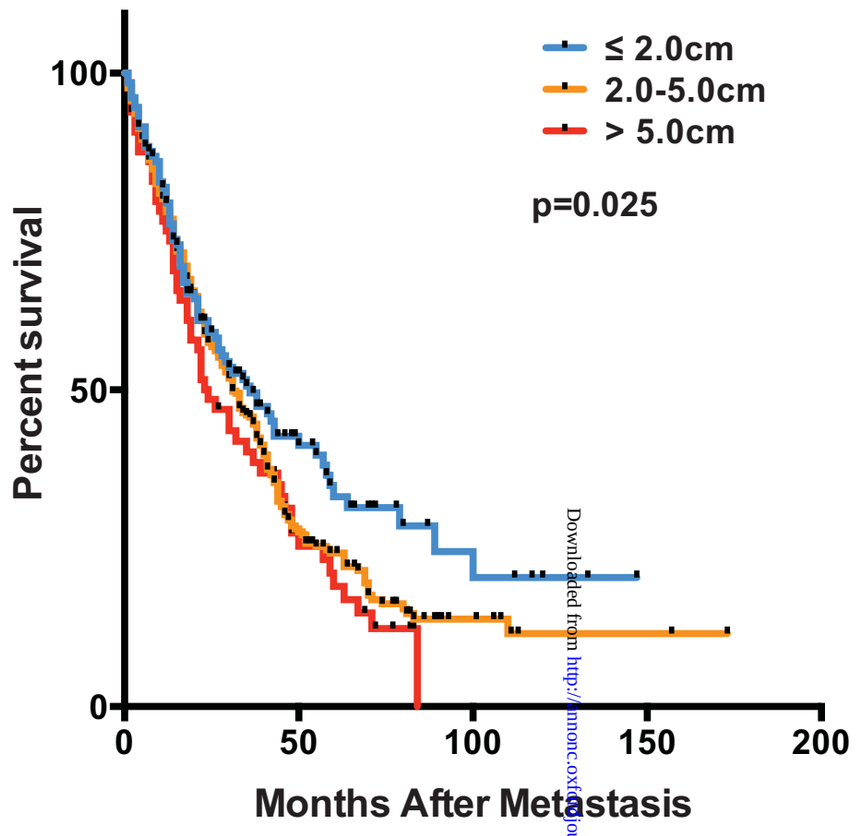

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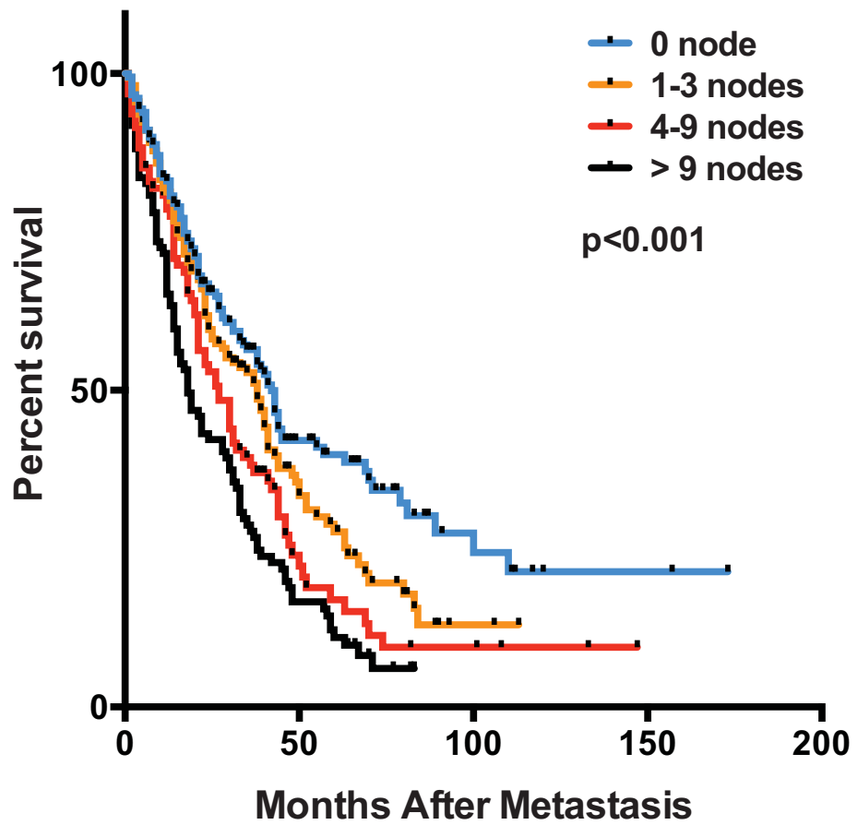

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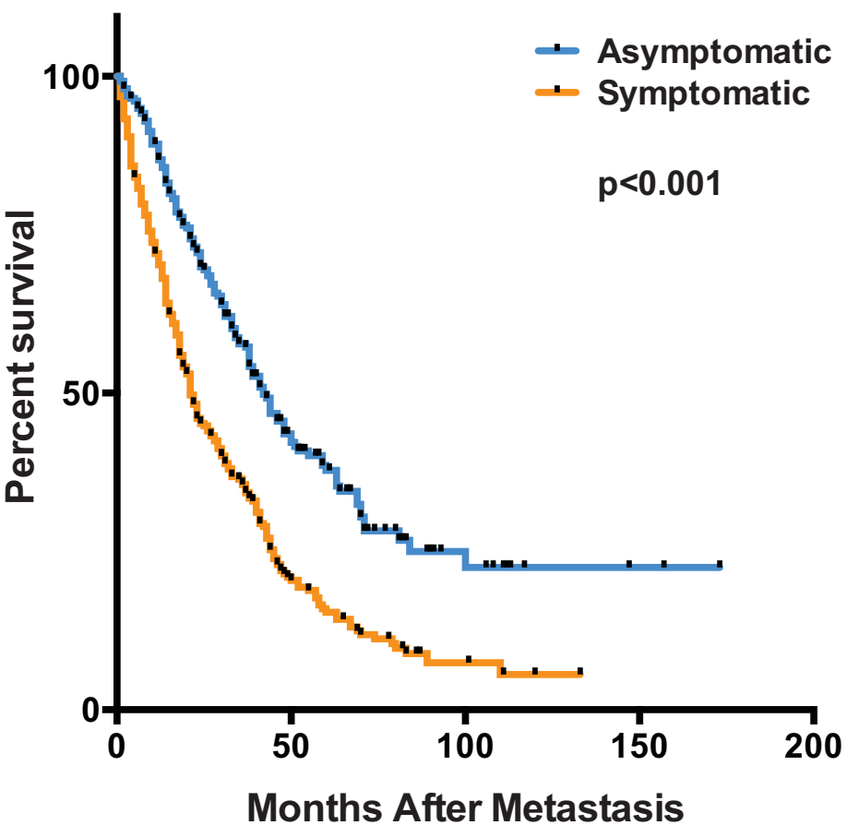

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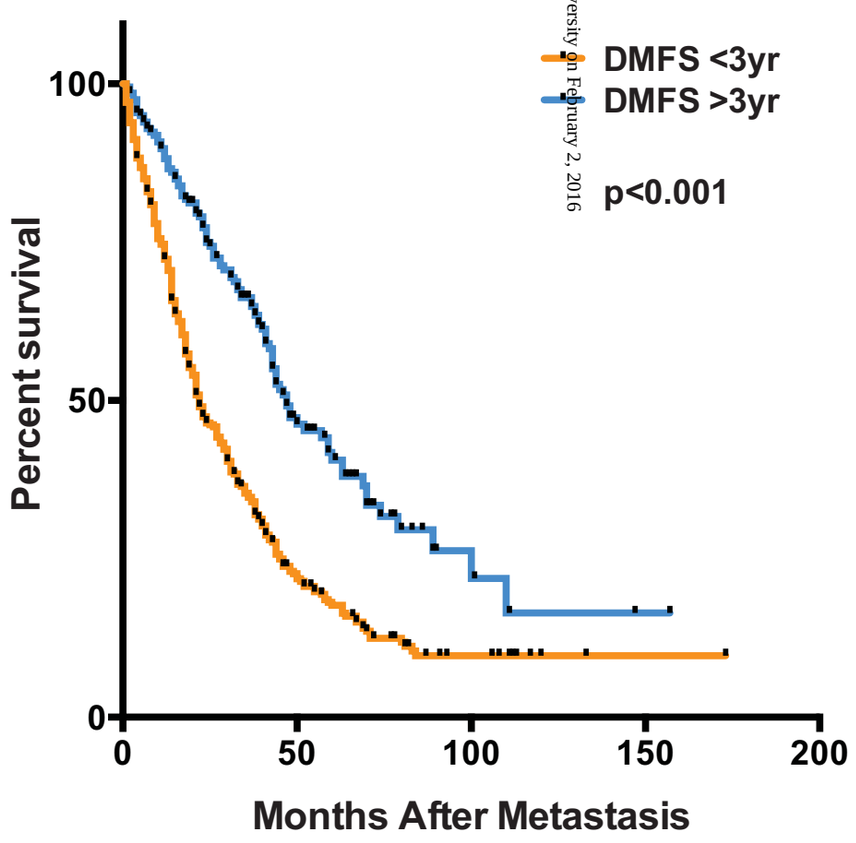

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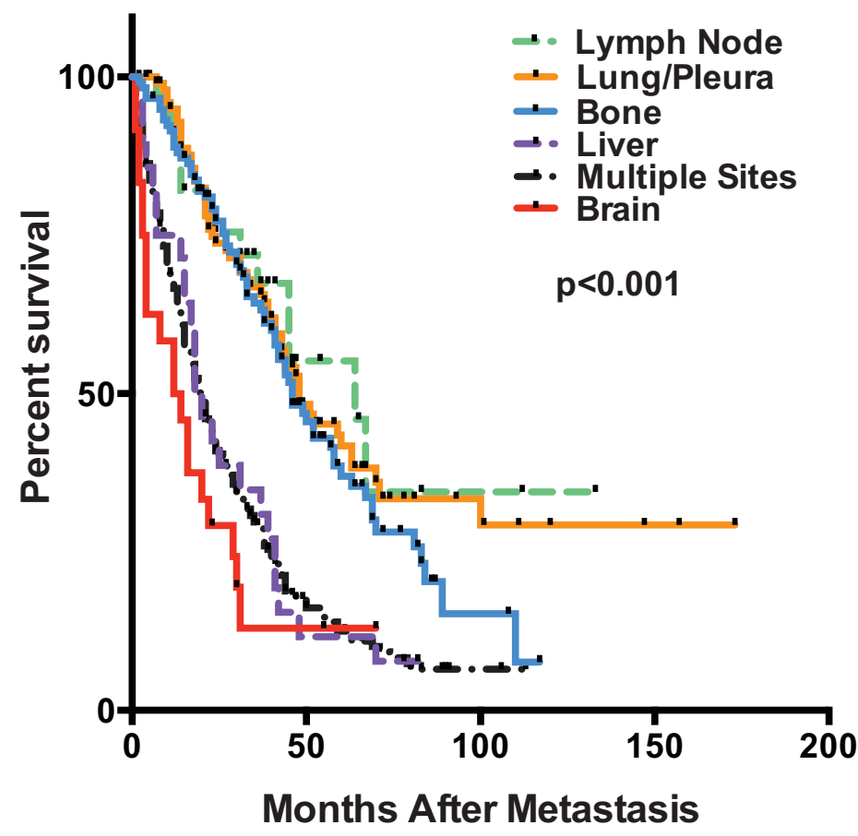

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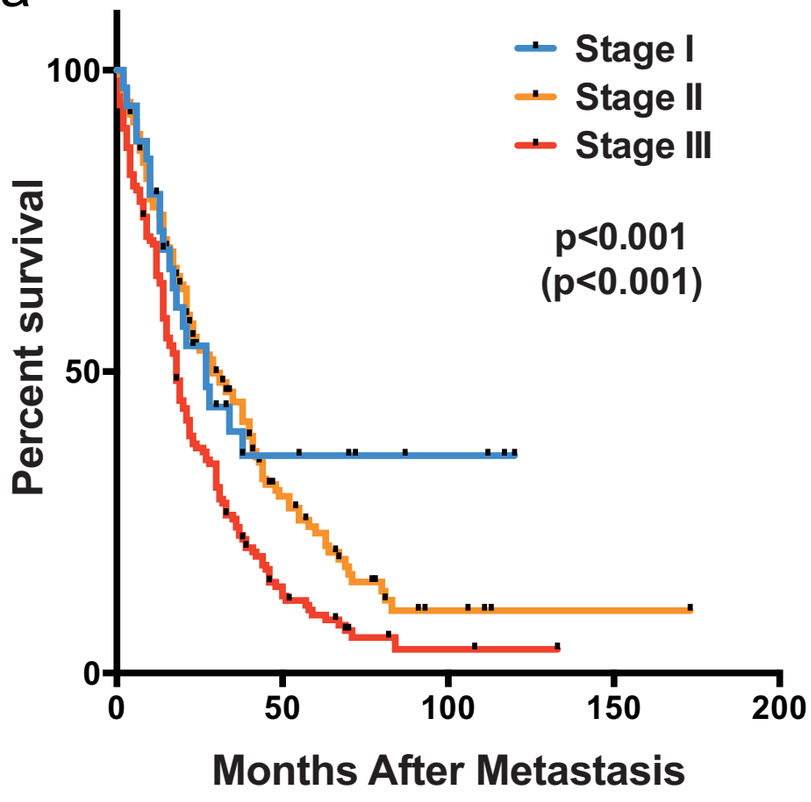

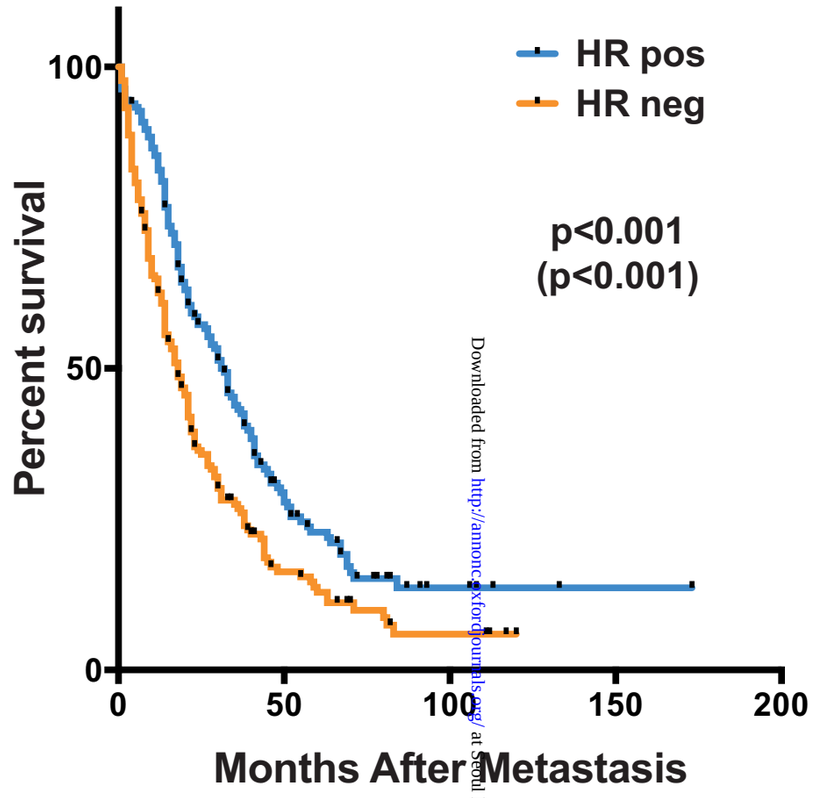

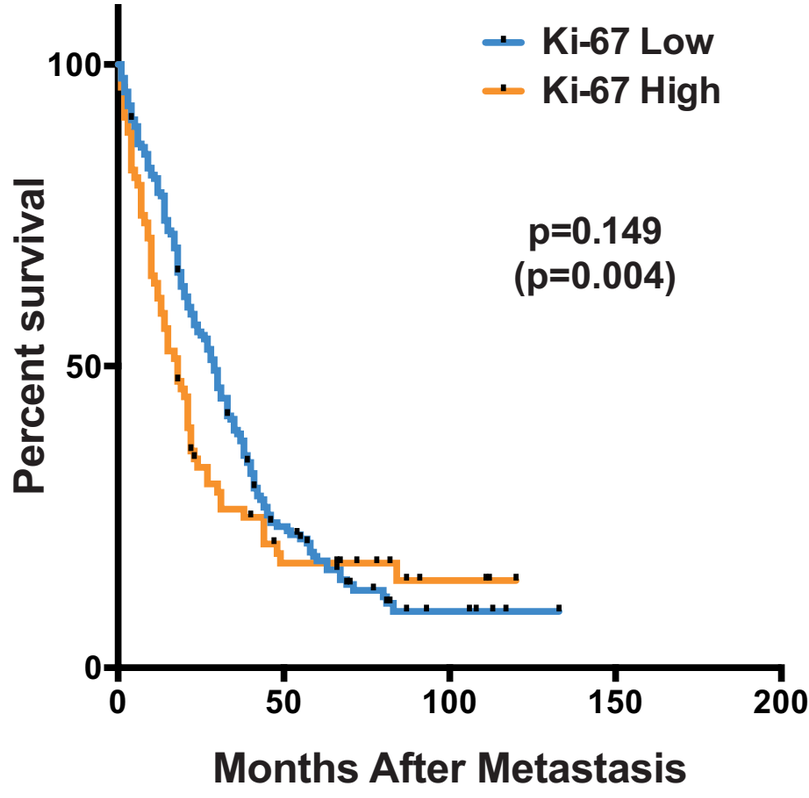

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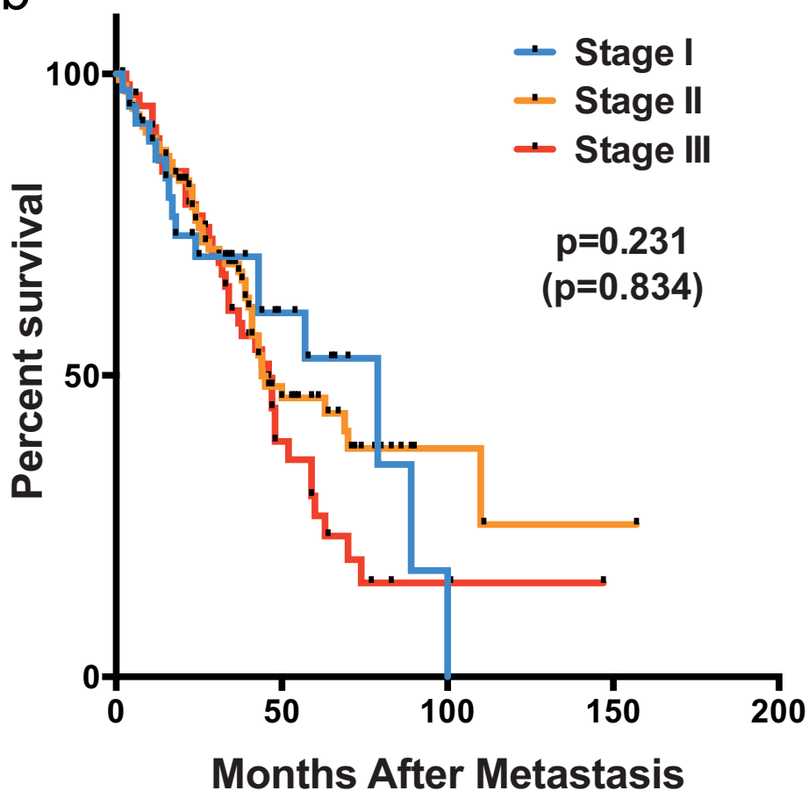

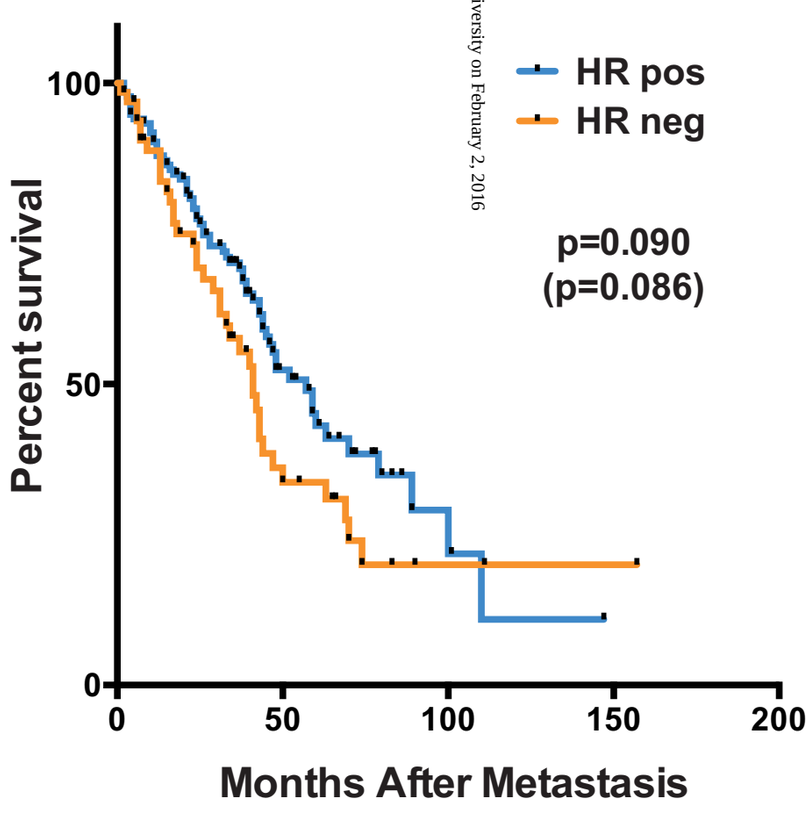

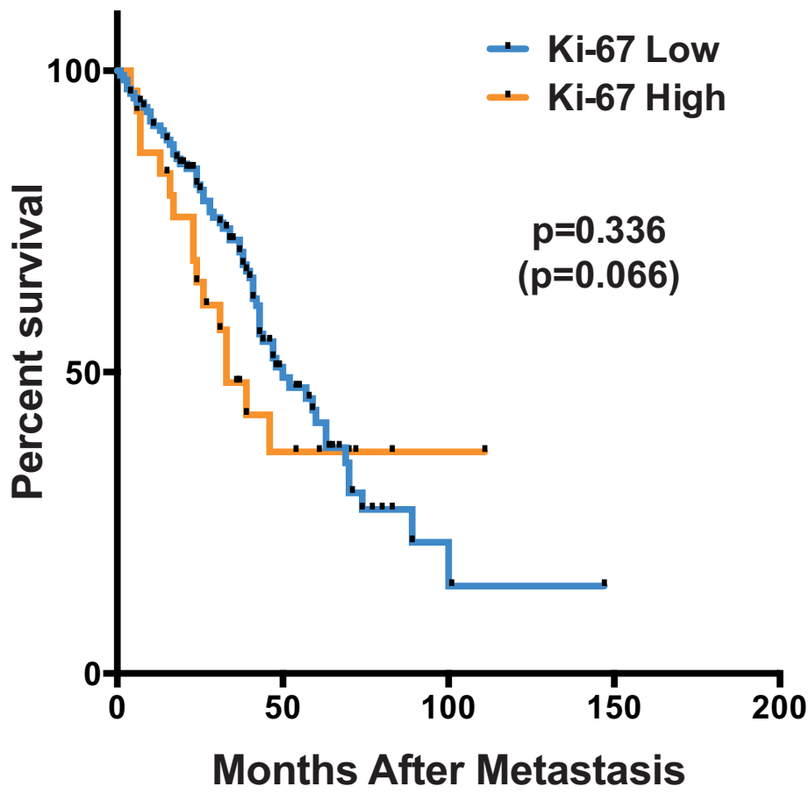

a

PMOS Scoring System

Parameters		Score
Stage	Stage 1	0
	Stage 2	1
	Stage 3	2
HR status	HR pos	0
	HR neg	1
Ki67	Ki-67 Low or Unknown	0
	Ki-67 High	1
DMFI	DMFI > 3yr	0
	DMFI ≤ 3yr	1
Symptom	Asymptomatic	0
	Symptomatic	1
Metastasis site	Bone, Lung/Pleura, Lymph Node	0
	Liver	1
	Brain, Multiple Sites	2

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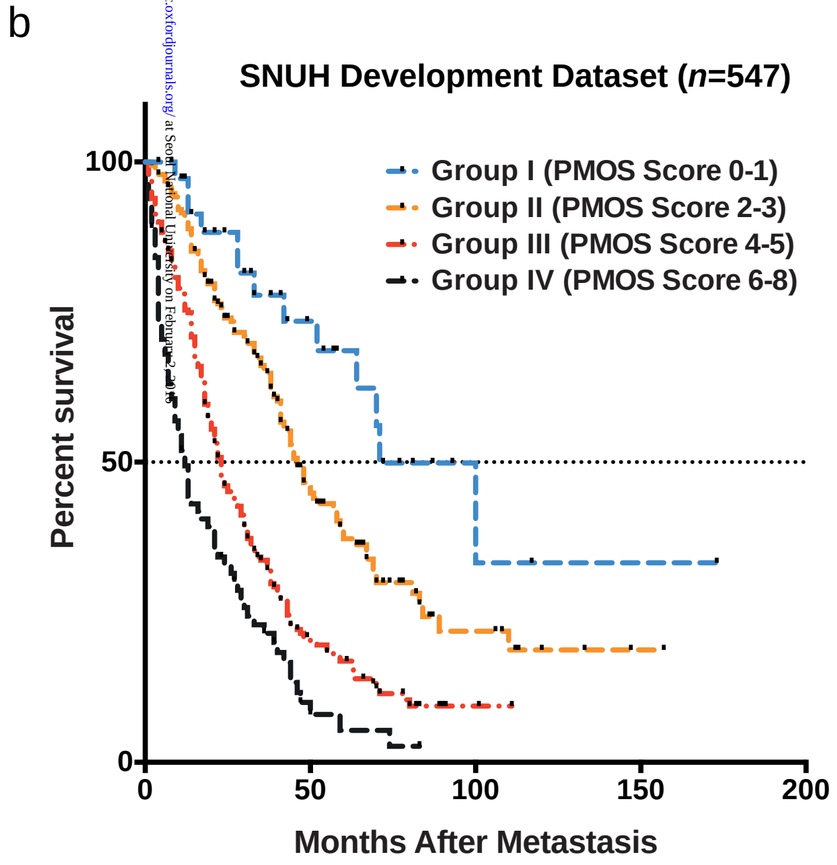

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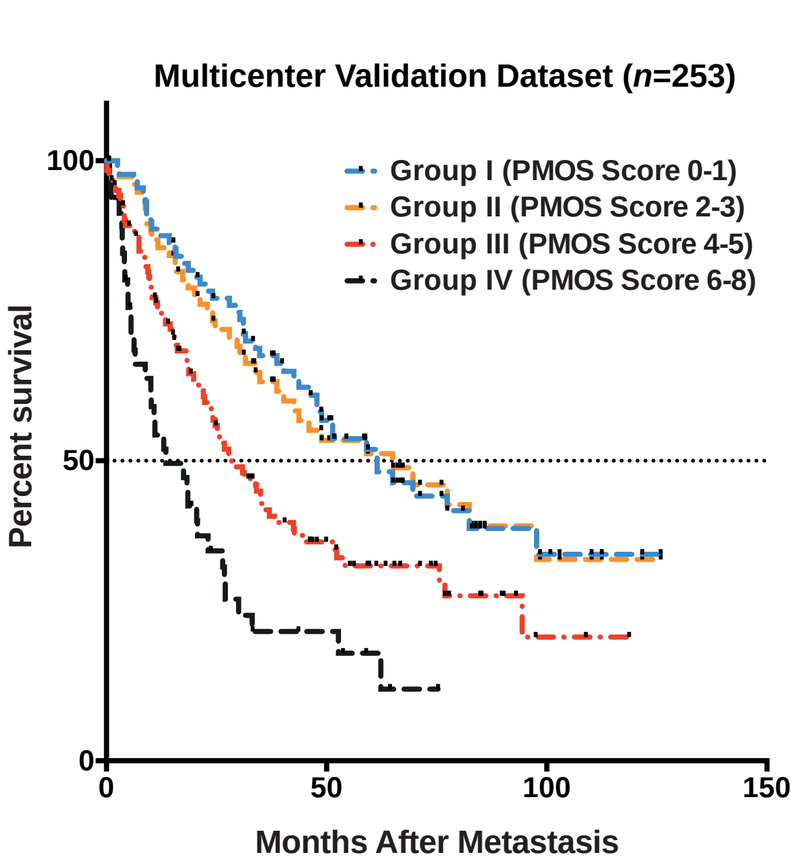

Table 1. Demographic and clinical information of the patients.

Characteristics		Number of patients (%)
Initial age (mean±SD, years)		46.8±10.9
Menopausal status	Premenopause	349 (63.8)
	Postmenopause	198 (36.2)
TNM stage	I	73 (13.3)
	II	258(47.2)
	III	216(39.5)
Hormone receptor	Positive	247(45.2)
	Negative	300(54.8)
HER2	Negative	312(57.3)
	Positive	109(19.9)
	Unknown	126(23.0)
Ki-67	<10%	310(56.7)
	≥ 10%	112(20.5)
	Unknown	125(22.9)
Grade	I-II	197(36.0)
	III	309(56.5)
	Unknown	41(7.5)
Lymphovascular invasion	Absent	271(49.5)
	Present	276(50.5)
Operation type	Mastectomy	380(69.5)
	Conservation	167(30.5)
Sites of first metastasis	Bone	120(21.9)
	Brain	24(4.4)
	Liver	28(5.1)
	Lung and pleura	104(19.0)
	LN metastasis	35(6.4)
	Multiple organs	236 (43.1)
Symptom at metastasis	Absent	258(47.2)
	Present	289(52.8)
Status at last follow up	Alive	168(30.7)
	Death	379(69.3)

Table 2. Initial tumor characteristics and the post-metastasis overall survival.

		Median survival	log rank p value	univariate HR (±95% CI)
Initial age, years	≤40	38.0	0.269	Ref
	>40	30.0		1.13 (0.91-1.40)
Menopause	Premenopause	35.0	0.511	Ref
	Postmenopause	30.0		1.07 (0.87-1.32)
TNM stage	I	43.0	<0.001	Ref
	II	40.0		1.24 (0.88-1.73)
	III	22.0		1.97 (1.34-2.44)
Hormone receptor	Positive	40.0	<0.001	Ref
	Negative	22.0		1.66 (1.40-2.13)
HER2	Negative	31.0	0.472	Ref
	Positive	36.0		0.91 (0.70-1.18)
	Unknown	28.0		1.08 (0.85-1.39)
Ki-67	< 10%	38.0	0.031	Ref
	≥ 10%	21.0		1.36 (1.07-1.86)
	Unknown	21.0		1.28 (1.00-1.72)
Histologic grade	I-II	41.0	0.021	Ref
	III	12.0		1.35 (1.09-1.67)
	Unknown	26.0		1.07 (0.69-1.67)
Lymphovascular invasion	Absent	30.0	0.09	Ref
	Present	38.0		0.84 (0.68-1.03)
Operation type	Mastectomy	30.0	0.185	Ref
	Conservation	35.0		0.86 (0.69-1.07)