The New Ropanasuri Journal of Surgery

Volume 3 | Number 2 Article 8

10-20-2018

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Recommended Citation

Yulian, Erwin D. and Salim, Adrian (2018) "Survival Analysis in Young–Age Breast Cancer and Related Clinicopathologic Factors at dr. Cipto Mangunkusumo General Hospital 2008–2015," *The New Ropanasuri Journal of Surgery*: Vol. 3 : No. 2 , Article 8.
DOI: 10.7454/nrjs.v3i2.57
Available at: https://scholarhub.ui.ac.id/nrjs/vol3/iss2/8

New Ropanasuri Journal of Surgery 2018 Volume 3 No.2:48–53.

The New Ropanasuri Journal of Surgery
OPEN ACCESS
Published by Department of Surgery
Faculty of Medicine, Universitas Indonesia

Survival Analysis in Young–Age Breast Cancer and Related Clinicopathologic Factors at dr. Cipto Mangunkusumo General Hospital 2008–2015

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Email: erwinjln@yahoo.com Received: 9/Aug/2018 Accepted: 28/Sep/2018 Published: 20/Oct/2018
http://www.nrjs.ui.ac.id DOI: 10.7454/nrjs.v3i2.57

Abstract

Introduction. Various cancer registrations and reports had confirmed the higher proportion of young women with breast cancer in Asian countries. This mandates special attention for clinician since this group of patients need different management approach, especially regarding the more aggressive biological behavior, worse prognosis and the escalating psychosocial burden that young women endure. We conducted a study to describe the clinicopathological characteristics of young–aged breast cancer in Indonesia and its relationship with overall survival.
Method. This study is a survival analysis using samples all young–aged women with histologically–proven cancer diagnosis that underwent treatment (surgery and/or chemotherapy and/or irradiation and/or hormonal therapy) since January 2008 to August 2015. Data were collected from both medical records and interview. Data were analyzed using SPSS
Results. Young–age women comprise 35% of total breast cancer patients, with most cases were in the locally advanced stage, histologic type NST, grade 2, no lymphovascular invasion, positive hormone receptors, negative HER2 status, high Ki–67 and Luminal B subtype. The 5–year overall survival rates were 64%; variables that showed statistically significant correlation was tumor size, nodal status, metastasis status and clinical stage. Histologic type NST, grade 2, positive lymphovascular invasion, high Ki–67 and positive HER2 were related to survival, but this correlation was not statistically significant.
Conclusion. Overall 5–year survival rates of young–aged breast cancer at dr. Cipto Mangunkusumo General Hospital was 64%, much lower that reported figures from literatures and other countries' reports. Clinical stage was the only variable with statistically significant correlation. Luminal B subtype was observed the most, but the worst survival was found in the HER2 subtype group.

Keywords: *survival, young–aged breast cancer*

Introduction

Age is an established risk factors for breast cancer, the most prevalent cancer globally for women. Various cancer registrations have shown that almost a decade earlier Asian breast cancer patient have a younger age of onset than those in the Western population. Consequently, higher proportions of young–age breast cancer patients were observed in Asian countries,[1,2] including in Indonesia. Reports from Dharmais Cancer Centre showed that breast cancer of <35 years reach up to 11%,[1] while as reports from dr. Cipto Mangunkusumo General Hospital (RSCM) showed even a higher proportion where as 31.7% of breast cancer were in age group of <40 years.[3] Young–age patients in Asian and Western countries also showed differences in clinicopathologies as well as molecular subtypes, as reported by many studies,[4,5] including those from Indonesia.[6]

Young–aged patients need special attention since breast cancer in this group shows the features that are different to the older groups. This young age breast cancer group is associated with a poor prognosis that cannot be explained by the application of high–risk phenotypic proportions in the older group, such as higher or triple–negative subtypes. Young–aged population also shows a more advanced stage. On the other side, young–aged population lives in a period dealing with sexual life and reproduction, child–bearing, self–actualization and body image; all of those are significantly affected the course of breast cancer. Since young–aged population have a relatively longer life–expectancy, any adverse reaction of the treatment may lead to sexual dysfunction, earlier menopause, osteoporosis, weight–gain and increasing risk to have second primary cancer which is a significant issue.[7]
Considering these potential issues, more information is needed; particularly the prevalence and the course of young–aged breast cancer. Therefore, we conducted a study to find out prevalence and survival rate of the young–aged breast cancer, along with the related clinicopathologies in RSCM.

Method

This study was a survival analysis using data in medical record and cancer registration in Division of Surgical Oncology, RSCM, aimed to find out association between survival and the clinicopathologies of young–aged breast cancer. The sample size calculated based on proportion and hazard ratio in accordance with study of Fredholm (2009);[8] a total sampling method was used. All young–aged females with histologically–proven cancer underwent treatment (surgery and/or chemotherapy and/or irradiation and/or hormonal therapy) in period of January 2008 to August 2015 were included in the study. Mortality due to any etiology was the outcome of a study. Univariate

analysis carried out to find out the frequency of distribution in each variable. Survival analysis carried out using Kaplan–Meier method. Bivariate and multivariate analysis carried out using Cox regression to find the association between survival rate and variables. Data analysis proceeded using SPSS 20.0 for Windows. The committee of ethic Faculty of Medicine, Universitas Indonesia approved the study No 9610/UN2.F1/ETIK/2016 and research bureau of RSCM No LB.02.01/X2./033/2016.

Results

There were a total of 1360 subjects underwent treatments in Division of Surgical Oncology, RSCM, during 2008–2015. The young–aged group comprised of 477 out of total subjects (35%). Most of the subjects were in the categorized as T4, N0, M0, locally advanced stage, pathologic type of NST, grade 2, no lymphovascular invasion, positive hormone receptors, negative HER2 amplification, high Ki–67 proliferation rate and molecular subtype Luminal B. Subjects characteristics presented in table 1.

Survival rate

Survival analysis of Kaplan–Meier showed an overall survival rate in 12, 24, 36 and 60 months were 91%, 79%, 70% and 64%, respectively. Median survival was 79 months (59–98 months), while as median follow–up period was 21 months (18–23 months). The overall survival curve of Kaplan–Meier is shown in Figure 1. Bivariate analysis of Cox regression found that variables of T status, N status, M status and clinical stage were statistically showed a significant hazard ratio (table 2).

Table 1. Subjects characteristics on the study

Variables	Frequency	%
Size and extension (T)		
– 1	8	2.0%
– 2	29	7.4%
– 3	35	8.9%
– 4	172	43.9%
– X	148	37.8%
Lymph node involvement (N)		
– 0	149	38%
– 1	134	34.2%
– 2	39	9.9%
– 3	42	10.7%
– X	28	7.1%
Distant metastasis (M)		
– 0	270	68.9%
– 1	122	31.1%
Clinical stage		
– Early	62	15.8%
– Locally advanced	118	30.1%
– Metastatic	117	29.8%
– X	95	24.2%
Pathology	321	82%
– NST		
– Lobular	20	5%
– Others	51	13%
Grade		
– 1	37	9.4%
– 2	212	54.1%
– 3	121	30.9%
Lymphovascular invasion		
– Positive	88	22.4%
– Negative	122	31.1%
Estrogen receptors		
– Positive	216	55.1%
– Negative	176	44.9%
Progesterone receptors		
– Positive	217	55.4%
– Negative	175	44.6%
HER2		
– Positive	143	36.5%
– Negative	238	60.7%
Ki–67		
– High	228	58.2%
– Low	133	33.9%
Molecular subtype		
– Luminal A	67	17.1%
– Luminal B	198	50.5%
– HER2	55	14%
– Triple negative	72	18.4%

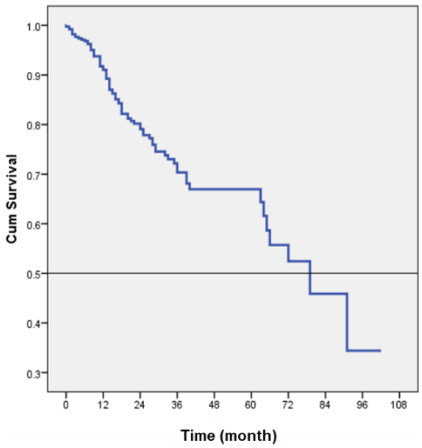

Figure 1. Overall survival curve of Kaplan–Meier

Table 2. Bivariate analysis of clinicopathologies and overall survival

Variables	Censored n (%)	Death n (%)	p	HR	95% CI	p
Size and extension (T)						
– T1	7 (87.5)	1 (12.5)	0.035	1		0.000*
– T2	26 (89.7)	3 (10.3)		1.438	0.148–13.924	0.754
– T3	30 (85.7)	5 (14.3)		2.573	0.300–22.096	0.389
– T4	124 (72.1)	48 (27.9)		7.168	0.980–52.455	0.052
– TX	124 (83.8)	24 (16.2)		2.600	0.349–19.399	0.351
Lymph node Involvement (N)						
– N0	130 (87.2)	19 (12.8)	0.000*	1		0.000*
– N1	109 (81.3)	25 (18.7)		1.768	0.972–3.215	0.062
– N2	25 (64,1)	14 (35,9)		3,830	1,915–7,661	0.000*
– N3	23 (54.8)	19 (45.2)		4.842	2.548–9.199	0.000*
– Nx	24 (85.7)	4 (14.3)		1.231	0.418–3.621	0.706
Distant metastasis (M)						
– M0	228 (84.4)	42 (15.6)	0.000*	1		
– M1	83 (68)	39 (32)		2.399	1.545–3.726	0.000*
Clinical Stage						
– Early	56 (90.3)	6 (9.7)	0.000*	1		0.000*
– Locally advanced	90 (76.3)	28 (23.7)		4.497	1.843–10.973	0.001*
– Metastatic	78 (66.7)	39 (33.3)		5.348	2.235–12.801	0.000*
– X	87 (91.6)	8 (8.4)		0.973	0.334–2.832	0.960
Pathology						
– NST	255 (79.7)	65 (20.3)	0.855	1		0.867
– Lobular	17 (81)	4 (19)		0.727	0.227–2.333	0.593
– Others	39 (76.5)	12 (23.5)		0.984	0.518–1.870	0.961
Grade						
– 1	31 (83.8)	6 (16.2)	0.437	1		0.466
– 2	172 (81.1)	40 (18.9)		1.381	0.584–3.263	0.462
– 3	92 (76)	29 (24)		1.676	0.695–4.041	0.250
Lymphovascular invasion						
– Positive	99 (81)	23 (18.9)	0.492	1		
– Negative	68 (77.3)	20 (22.7)		1.055	0.572–1.946	0.864
Estrogen receptors						
– Negative	144 (81.8)	32 (18.2)	0.273	1		
– Positive	167 (77.3)	49 (22.7)		1.034	0.662–1.616	0.884
Progesterone receptors						
– Negative	139 (79.4)	36 (20.6)	0.968	1		
– Positive	172 (79.3)	45 (20.7)		0.907	0.584–1.409	0.665
HER2						
– Negative	191 (80.3)	47 (19.7)	0.772	1		
– Positive	113 (79)	30 (21)		1.262	0.795–2.003	0.324
Ki–67*						
– Low	114 (85.7)	19 (14.3)	0.026*	1		
– High	173 (75.9)	55 (24.1)		1.585	0.939–2.676	0.085

Table 2. Bivariate analysis of clinicopathologies and overall survival (cont.)

Molecular Subtype							
–	Luminal A	56 (83.6)	11 (16.4)	0.692	1		0.776
–	Luminal B	153 (77.3)	45 (22.7)		1.372	.0708–2.659	0.348
–	HER2	45 (81.8)	10 (18.2)		1.516	0.641–3.589	0.344
–	Triple Negative	57 (79.2)	15 (20.8)		1.288	0.591–2.810	0.525

Table 3. Multivariate analysis

			p	HR	95% CI
Step 1	–	T	0.486	0.826	0.482–1.415
	–	N	0.026	1.397	1.042–1.873
	–	M	0.611	1.246	0.534–2.905
	–	Stage	0.432	1.280	0.692–2.368
	–	Pathology	0.412	0.797	0.463–1.370
	–	Lymphovascular invasion	0.875	0.947	0.480–1.868
	–	Ki–67	0.543	1.268	0.590–2.726
	–	Molecular subtype	0.454	0.850	0.555–1.301
Step 2	–	T	0.476	0.823	0.481–1.407
	–	N	0.026	1.397	1.041–1.874
	–	M	0.606	1.250	0.536–2.914
	–	Stage	0.432	1.280	0.692–2.370
	–	Pathology	0.416	0.798	0.464–1.373
	–	Ki–67	0.546	1.265	0.589–2.718
	–	Molecular subtype	0.435	0.845	0.554–1.289
Step 3	–	T	0.429	0.806	0.472–1.376
	–	N	0.004	1.454	1.130–1.870
	–	Stage	0.324	1.342	0.748–2.409
	–	Pathology	0.345	0.775	0.457–1.315
	–	Ki–67	0.457	1.326	0.630–2.788
	–	Molecular subtype	0.365	0.827	0.548–1.248
Step 4	–	T	0.395	0.791	0.461–1.358
	–	N	0.003	1.454	1.132–1.868
	–	Stage	0.308	1.359	0.754–2.449
	–	Pathology	0.338	0.771	0.452–1.313
	–	Molecular subtype	0.472	0.872	0.601–1.266
Step 5	–	T	0.386	0.787	0.457–1.353
	–	N	0.003	1.453	1.135–1.861
	–	Stage	0.287	1.377	0.764–2.480
	–	Pathology	0.363	0.782	0.460–1.329
Step 6	–	N	0.004	1.394	1.111–1.749
	–	Stage	0.529	1.112	0.799–1.549
	–	Pathology	0.393	0.794	0.467–1.349
Step 7	–	N	0.002	1.414	1.130–1.769
	–	Pathology	0.381	0.789	0.464–1.341
Step 8	–	N	0.003	1.414	1.128–1.771
Step 9	–	N0	0.004	Ref	
	–	N1	0.336	1.559	0.630–3.857
	–	N2	0.001*	3.951	1.447–10.791
	–	N3	0.007*	5.212	2.028–13.399
	–	Nx	0.168	2.525	0.678–9.410

The significant factors ($p < 0.25$) and known factors that strongly influencing the survival were included in the multivariate analysis. The factors analyzed were: tumor size and extension, lymph node involvement, distant metastasis, pathology, grade, lymphovascular invasion, Ki–67 proliferation rate and molecular subtype. The only variable associated with overall survival was lymph node involvement. Group N2 and N3 had the highest hazard ratio, both were statistically (table 3).

Discussion

Our subjects in this study showed major differences from reported studies particularly the clinicopathologies. The prevalence of young–aged population in RSCM (35%) is similar to those reported by Dhityo (2004),[3] which is much higher than those reported in Western countries (~5%) and Asia (Korea 13.2%,[9] Malaysia–Singapore 15%).[10] In lined with reports from other developing countries, the majority (60%) of Indonesian admitted to the hospital in a more

advanced stage, of which is not only a locally advanced (30.1%), but also with distant metastasis (29.8%); in contrast to those reported in United States and Korea, which is both showing only a total of 3–4% young–aged with advanced stage.[11]

Our data also showed a distinct characteristic at RSCM as a national top referral hospital, where as the total of postoperative patients reached up to 37.8%. For most of this population, there were no data of preoperative staging available. Hence, this was notated as Tx, Nx and Stage X. The practice referred to uncommon in any oncology literature,[12] but it was necessary in our study seeing that stage X comprises 24% of the total subjects.

The pathology type NST is the most common type and found to be similar with a previous study.[13] As in the study of Lin (2014),4 we found the most prevalent grade was grade 2, although in other study the grade 3 is reported to be the most prevalent one.[14] Molecular characteristics showed positive hormone receptors, negative HER2 and high Ki–67 proliferation rate; these were depicted by Luminal B as the most prevalent molecular subtype. These results were found in contrast with traditional literatures denoting younger patients shows a more prevalent negative hormone receptors and molecular subtypes with poor prognosis, e.g. HER2 and triple–negative.[15] However, there were recent studies reported similar results; the one is by Tang.[16] This shows that our understanding about molecular characteristics of young–aged breast cancer, particularly in different populations remains evolving.

The overall 5–year survival rate in this study reach up to 64%, which is much lower than those reported.[15,16] The logic explanation to these findings is the high proportions of advanced stage population presented at RSCM. Almost 60% of population presented in a locally advanced and metastatic stage; both were associated with poor survival rate (85% and 38%, respectively) compared to those of the earlier stage (96%).[17] Statistical analysis confirmed a significant association between each component of staging (i.e. T, N, M) and overall clinical stage with overall survival rate.

Pathology type NST (invasive ductal carcinoma) confers the worse prognosis for invasive breast cancer, while lobular carcinoma shows similar or slightly better prognosis. These two types represented by the most subjects in this study (87%) and consequently responsible to the overall prognosis. Young–aged subjects are known to have higher pathologic grade, though studies are split to grade 2 or 3. Our findings showed the majority cases were of grade 2, and the higher grade was found to confer the worse prognosis, but somehow shows no statistical significance. Data of lymphovascular invasion were notably lacking, our finding in this study is lymphovascular invasion is associated with worse survival. The finding is consistent to those reported although it showed no statistical significance.

There were reviews suggested that the worse prognosis in young–aged breast cancer may be attributed to the higher proportion of high-risk characteristics, such as negative hormone receptors, overexpressed HER2 or triple–negative subtypes.[18] Our findings showed that HER2 subtype did confer the worse hazard ratio, however no statistical significance is shown. Luminal B was the subtype that was remarkably represented and had higher hazard ratio than the Luminal A and triple–negative subtypes; conforming with other studies.[16] It might just show how the biology behavior of breast cancer were differently in different age groups.

Ki–67 is a cellular marker which is expressed in most phases of cell cycle, except the G0 phase. It is the most widely used marker in the assessment of tumor proliferation. Most of the subjects in this study showed a high Ki–67 proliferation rate, which is consistent to other studies in young–aged breast cancer who showed inverse correlation between Ki–67 level and age. High Ki–67 proliferation rate also showed higher hazard ratio although in the study shows no statistical significance. The underlying mechanism of a higher proliferation index in young–aged females may be related to the status of HER2 expression, but this has not been conclusively determined.[19]

The bivariate and multivariate analysis using Cox regression showed no statistical significance in most variables in this study, but the pattern of hazard ratio showing a consistency with those in the literatures. The bivariate analysis showed the variables with statistically significant hazard ratios were the lymph node involvement N2 (HR 3.830; 95% CI 1.915–7.661), N3 (HR 4.842; 95% CI 2.548–9.199), distant metastasis M1 (HR 2.399; 95% CI 1.545–3.726), locally advanced stage (HR 4.497; 95% CI 1.843–10.973), and metastasis stage (HR 5.348; 95% CI 2.235–12.801).

Further analysis using multivariate method found only the lymph node involvement showing a significant correlation to overall survival with HR of N2 3.951 (95% CI 1.447–10.791) and N3 5.212 (95% CI 2.028–13.399). The exclusion of clinical stage might be partially explained by the high proportion of the Tx and, to a lesser degree, the Nx group. The X status let the analysis to be complicated because it contributes the subjects supposed to be included in the early or locally advanced groups to a distinct one (stadium X). This might potentially blur the correlation of stage and survival, especially for Tx cases since the proportion is found larger than the Nx group. The exclusion of the pathology type and molecular subtypes from multivariate models were much difficult to be explained, aside from the high proportion of our l lost–to–follow–up cases.

Our data had substantial lost–to–follow–up cases, accounting for as much as 56% of censored cases. While proven to be a limitation in this study, this finding reflecting the obstacles found in the management of cancer in RSCM and, in a larger scale, Indonesia. Geographical distribution of health care, insufficient data of subject residence, even for those who lives in Jakarta. Patient's compliance is another issue found let a poor surveillance of those who completed the treatments. The median of follow–up period of 21 months is just showing a poor surveillance. However, it contributes the poor overall survival of young–aged breast cancer patients in RSCM.

Another important issue to be consider is inadequacy of treatment both in the previous care center and RSCM. We do not have a specific data about such an issue, but the common scenario found was incomplete management. These patients underwent surgical excision for therapeutic or merely diagnostic purpose in previous hospital (in this case, adequacy of surgery could not be concluded accurately) and referred to RSCM for completion. The completion certainly consists of surgical intervention or an adjuvant therapy (chemotherapy, irradiation, hormonal therapy). At least 37.8% of subjects were in such a scenario, which is the Tx group. Another inadequacy of treatment that may influence a low survival rate including delay to provide initial therapy (surgical intervention, chemotherapy, irradiation, hormonal therapy), incomplete systemic therapy, or prolonged chemotherapy interval; but there is no solution may solve this problem to date.

Conclusion

Young–aged breast cancer in RSCM showed overall 5–year survival rate of 64%. Majority of cases were of locally advanced stage, histologic type NST, grade 2, no lymphovascular invasion, positive hormone receptors, negative HER2 status, high Ki–67 and Luminal B subtype. Tumor size, nodal status, metastatic status and clinical stage showed significant correlation. Histologic type NST, grade 2, positive lymphovascular invasion, high Ki–67 proliferation rate and positive HER2 were inversely correlated to survival, but not significant. The substantial number of lost–to–follow–up subject might partially explain these results, reflecting the obstacles in the management of breast cancer in RSCM.

Conflict of interest

Author disclose there was no conflict of interest.

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