Histopathologic profile of mastectomy specimens of operable breast cancer cases

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Abstrak

Informasi yang adekuat mengenai profil histopatologik dari sediaan mastektomi memberikan ramalan yang lebih baik tentang prognosis tiap penderita kanker payudara. Sejauh ini, belum pernah dilaporkan data dari kasus-kasus di Indonesia, yang antara lain disebabkan karena pada umumnya kasus-kasus yang datang sudah pada stadium lanjut yang inoperabel. Pada makalah ini akan dilaporkan profil histopatologik dari sediaan mastektomi kasus kanker payudara yang operabel yang tercakup dalam penelitian bersama Indonesia – Jepang, tentang Etiologi dan Klinikopatologi pada Kanker Payudara. Dari tiap kasus, diperiksa masing-masing 4-6 sediaan HE untuk dinilai jenis histopatologinya, sebukan limfosit, invasi pembuluh darah dan limfe, invasi jaringan lemak, otot dan kulit serta penyebaran ke kelenjar getah bening. Juga dikumpulkan data-data ketahanan hidup 5 tahun. Sebanyak 70 dari 107 kasus yang operabel dapat dinilai secara lengkap sediaannya dan pada 20 di antaranya dianalisa untuk ketahanan hidup 5 tahun. Mayoritas kasus adalah jenis duktal invasif (79,9%), 2,8% duktal in situ dan sisanya adalah tipe khusus. Jenis skirus merupakan yang terbanyak di antara jenis duktal invasif (43%). Limapuluh kasus menunjukkan sebukan limfosit, namun separuhnya adalah derajat ringan. Invasi vaskuler hanya ditemukan pada 4 kasus, invasi pempuluh limfe pada 16 kasus. Invasi lemak pada 36 kasus, otot pada 3 kasus dan kulit pada 1 kasus. Di antara 48 kasus dengan sediaan kelenjar getah bening, 28 kasus menunjukkan metastasis. Usia penderita dan sebukan limfosit merupakan gambaran yang cukup menonjol dalam kaitannya dengan ketahanan hidup 5 tahun. Terlihat kecenderungan penurunan usia dari kelompok hidup tanpa penyakit, kelompok hidup dengan penyakit dan yang meninggal. Pada kelompok yang hidup tanpa penyakit sebukan limfosit derajat sedang sampai keras terdapat pada sebagian besar kasus, sedangkan pada kelompok hidup dengan penyakit, sebukan limfosit umumnya berderajat ringan. Pada satu kasus yang meninggal tidak ditemukan sebukan limfosit. Disarankan untuk melakukan studi serupa lebih lanjut dengan menggunakan teknik-teknik mutakhir agar didapatkan informasi yang lebih akurat mengenai profil histopatologik yang adekuat.

Abstract

Adequate description of histopathologic profile of mastectomy specimens offers a better prognostic prediction of individual breast cancer patient. Such a data hasn't been reported so far from Indonesian breast cancer cases, due to the fact that the majority of admitted cases were already in unoperable late stage. In this report, we present the extensive histopathologic profile of mastectomy specimen from cancer cases included in Indonesia - Japan Joint Study on Etiology and Clinicopathology of Breast Cancer. Four to 6 H & E slides were reviewed from each cases; all data about histopathological type, lymphocytic infiltration, blood and lymph vessels invasion, fat , muscle and skin invasion and lymph node involvement were recorded. Five years survival data were collected. Only 70 out of 107 operable cases were available for a complete histopathological review and 20 cases were evaluated for their 5 years survival data. Most of the patients were of ductal invasive type (79.9%); 2.8% ductal in situ and the rest were of the special types. Scirrhous subtype predominated the ductal invasive type (43.3%). Fifty cases showed lymphocytic infiltration. Vascular invasion were found only in 4 cases, lymph vessel invasion in 16 cases. More than half cases showed fat invasion (36 cases), muscle invasion in 3 cases and skin invasion in 1 case. Among 48 cases with dissected lymph node, 28 showed metastasis. Age of patients and lymphocytic infiltration were significant encountered in the evaluation of survival data. There was a tendency for a decreasing age among group alive without disease, alive with disease and deceased. Almost all of cases who were alive without disease showed lymphocytic infiltration which were mostly moderate to severe; while 6 cases who were alive with disease mostly showed mild infiltration. One case who was deceased has no lymphocytic infiltration. It is recommended to study further with the help of ancillary techniques to get more accurate information about the histopathologic profile.

Keywords : *Histopathologic, breast cancer, mastectomy specimen.*

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INTRODUCTION

Breast cancer is the second most frequent malignancy among women in Indonesia.[1] Previous report on our study revealed that most breast cancer patients, namely 87%, came in their late stage (2). So, only few of them were subjected to surgical treatment and no information about extensive histopathologic profile was reported so far in our country.

There are many factors known to influence the prognosis or clinical outcome of breast cancer patient. An extensive histopathologic profile of mastectomy specimen provides more accurate information about the prognosis of the individual breast cancer case than the small biopsy specimens.

In this study, various histopathological finding on mastectomy specimen will be reported and correlated to the clinical outcome whenever possible.

MATERIALS AND METHODS

The samples of this study were part of the total samples of 300 cases including in the Indonesia-Japan Joint Research Project on Breast Cancer: an epidemiological study. Only 107 out of 300 cases were operable.

The mastectomy specimens, consisting 4 to 6 routine H&E slides section taken from the tumor and surrounding tissue, were reviewed histopathologically for their histopathologically types, lymphocitic infiltration, blood and lymph vessels invasion, fat and muscle tissue invasion. Lymph nodes section were also reviewed and counted for the presence of metastatic tumor cell. Clinical data about their survival were recorded.

Histological typing was done according to the Japanese classification for breast cancer (3); lymphocitic infiltration was graded according the severity as mild, moderate and severe. Tumor emboli in the blood and lymph vessels were search and also the destruction of the vessel's wall by the tumor cells.

Fat infiltration was recorded either within interlobular fat or submammary fat tissue. Same observation was done for muscle tissue.

RESULTS

Seventy cases were available for a complete review. The histological type is presented in Table 1. Lymphocyte infiltration were present in 50 cases (71.4%). Most of them were of mild infiltration (50%). Most of the scirrhous types were not or only mildly infiltrated by lymphocyte compare to papilo-tubular and solid-tubular which have more dense lymphocyte infiltration. (Table 3).

Table 1. Histopathological type of mastectomy specimens

Histological type	Total cases	
Ductal carcinoma in situ	2	(2.8 %)
Papilo-tubular carcinoma	9	(12.8 %)
Solid-tubular carcinoma	16	(22.8 %)
Scirrhous carcinoma	31	(44.3 %)
Mucinous carcinoma	3	(4.3 %)
Medullary carcinoma	4	(5.7 %)
Lobular carcinoma	3	(4.3 %)
Adenoid cystic carcinoma	1	(1.4 %)
Paget's disease	1	(1.4 %)
Total	70	(100.0 %)

Table 2. The histopathologic profile of the mastectomy specimens

Histopathologic profile	Positive	Negative	Total
Lymphocytic infiltration	50 (25mild, 19 mod, 6 sev)	20	70
Vascular invasion	4	66	70
Lymph vessel invasion	16	54	70
Fat invasion	36	33	70
Muscle invasion	3	67	70
Skin invasion	1	69	70
Lymph node involvement	28	20	48*

** No lymph node was found in 22 cases.*

Table 3. Correlation between histological type and lymphocytic infiltration

Histological type	No filtration	Mild	Moderate	Severe	Total
Ductal in situ	1	1	0	0	2
Papilo-tubular	2	2	4	1	9
Solid-tubular	2	4	8	2	16
Scirrhous	13	12	5	1	31
Mucinous	1	2	0	0	3
Medullary	0	2	1	1	4
Lobular	0	2	1	0	3
Adenoid cystic	1	0	0	0	1
Paget's disease	0	0	0	1	1
Total	20	25	19	6	70

Table 4. Correlation between Histological type and various structure invasion

Histological Type	Vasc	Lymph.	Fat	Muscle	Skin	Lymph node
Ductal in situ	0	0	0	0	0	0
Papilo-tubular	1/9 (11%)	4/9 (44%)	5/9 (55%)	1/9 (11%)	1/9 (11%)	3/9 (30%)
Solid-tubular	2/16 (12%)	3/16 (18%)	10/16 (62%)	0	0	8/16 (50%)
Scirrhous	1/31 (3%)	9/31 (29%)	18/31 (58%)	2/31 (6%)	0	14/31 (45%)
Mucinous	0	0	1/3 (33%)	0	0	0
Medullary	0	0	0	0	0	2/4 (50%)
Lobular	0	0	2/3 (66%)	0	0	1/3 (33%)
Ad.cystic	0	0	0	0	0	0
Paget's	0	0	0	0	0	0
Total	4	16	36	3	1	28

Table 5. Histopathologic profile of cases alive without disease

Nr.	Age	Type	Lymphocyte infiltration	Vasc. Inv.	Lymph Inv.	Fat Inv.	Muscle Inv.	Lymph node
8902303	50	Scirr	-	-	+	-	-	-
8900292	42	Scirr	mod	-	-	+	-	+
8910090	47	Scirr	sev	-	+	+	-	+
8910224	62	Scirr	mild	-	-	+	-	-
8911250	46	Sol-tub	sev	-	-	-	-	-
9000785	50	Sol-tub	mild	-	-	-	-	-
9006042	40	Scirr	mod	-	-	+	-	+
9109241	44	Scirr	mod	-	-	+	-	+
9104354	61	Lob	mod	-	-	-	-	-
9102082	41	Lob	mild	-	-	+	-	-
9104800	61	Sol-tub	mod	-	+	+	-	+
9105836	34	Pap-tub	mod	-	+	-	-	+
9107011	37	Scirr	mild	-	-	-	-	-

Vascular invasion was found only in 4 out of 70 cases. The 4 cases were all of ductal invasive type, with the solid-tubular has the most frequent invasion. Lymphatic vessels invasion were present in 16 cases out of 70 cases, and more than half were of scirrhous type. Invasions of fat tissue were present in 36 out of 70 cases in which most of them were found in the scirrhous type. Muscle invasion and skin invasion were found only in 3 and 1 cases respectively. Two cases who has muscle invasion were of scirrhous type and 1 of papilo-tubular type; while the only 1 case with skin invasion was of papilo-tubular type (Table 4).

Nineteen cases showed involvement of 1-3 lymph nodes removed and 9 cases showed involvement of 5 to 21 nodes.

Five years follow up data with complete histopathological data which were available in 20 cases showed: 13 out of 20 were alive without disease, 6 cases were alive with disease and 1 patient died.

Among 13 cases that still alive without disease, 7 cases were of scirrhous type, 3 of solid-tubular type, 2 of lobular type and 1 of papilo-tubular type. Almost all cases showed lymphocytic infiltration, 4 cases with lymph vessel invasion, 7 showed fat invasion and 6 cases showed lymph node involvement (Table 5).

Table 6. Histopathologic profile of cases alive with disease

Nr.	Age	Type	Lymphocyte infiltration	Vasc. Inv.	Lymph Inv.	Fat Inv.	Muscle Inv.	Lymph node
9008071	37	Scirr	mild	-	-	-	+	-
9109331	42	Scirr		-	-	-	-	-
9105609	30	Scirr	mod	-	-	+	-	+
9107232	53	Scirr	mild	-	-	+	-	+
9107430	39	Pap-tub	mild	-	-	-	-	-
9111031	33	Sol-tub	-	-	-	-	-	+

Six cases alive with disease had scirrhous type in 4 cases, 1 has papilo-tubular and 1 has solid-tubular type. Their age was relatively younger than the group who lived without disease (mean age 39 vs. 47.3 years). Almost all of them showed lymphocyte infiltration, 2 had fat invasion, 1 had muscle invasion and 3 had lymph node involvement. The only 1 case who died was of 33 years old with scirrhous type, and had lymph vessel and fat tissue invasion.

DISCUSSION

The most frequent histological type found is ductal type, comprising more than half of the total cases. Most of the tumors had lymphocyte infiltration. The prognosis significance of lymphocyte was a subject of controversy. Some investigators found it related to the favorable prognosis,[4] while other group did not[5]. Looking at our series, the scirrhous type was the less infiltrated by lymphocyte, and this type has the worse prognosis compare to the ductal invasive subtypes like papilo-tubular and solid-tubular. The discordant results might need to be clarified by further identification of the lymphocyte sub-population. If the lymphocyte population is B cell, they have no meaning in the tumor surveillance, while if the population is T lymphocyte it has the property of tumor control. The presence of B lymphocyte could be result of secondary infection. In breast cancer, the presence of infection is possible if ulceration occur; which are commonly complicating the advance inoperable cases. In operable cases, which is of earlier stage it is uncommon to find this complication. So, the T lymphocyte is most likely to be the main population in this condition, and consequently it can be expected as an indicator of better outcome.

We found lymphatic invasion more common than vascular invasion. These results were similar to Fisher's finding.[6] Structurally, vascular vessels are more resistant to invasion due to its thicker layer than the lymphatic vessels, which are composed only by a single layer of endothelial cell. Lymphatic emboli have an unfavorable prognosis in node negative patients treated by mastectomy[7] and give rise to a higher local recurrence rate in node negative patients who underwent breast conserving treatment.[8]

Blood vessel invasion is also still a subject of controversy, but it was recorded that visceral metastasis occurred in 67% of cases with blood vessel invasion, compared to only 35% visceral metastasis in the absence of blood vessel invasion in stage I cases.[9] Death, due to metastasis breast cancer was significantly greater in frequency in women with blood vessel invasion irrespective of their total lymph node involvement in stage II cases.[10]

Weigand et al[11] in their study revealed a strong correlation between blood vessel invasion and early recurrence. The presence of blood vessel invasion in their series was much higher than our study and Fisher's large series.[6] Several investigators claimed the high interobserver variation in assessing vessels invasion, either lymph or blood. The most possible source of this variation is the difficulty in differentiating between vessels and tissue artifact affecting carcinomatus duct. The use of special staining is then highly recommended to overcome this problem, either histochemically using elastic staining or immunohistochemically using endothelial antibodies.[12-13] Fat tissue invasion has never been regarded as a prognostic factor. Our series revealed more than half cases with fat invasion, and the significance of which couldn't be stated yet. Recently, several studies has done to correlate the presence of proteolytic enzymes, like collagenase and cathepsins bear by the tumor cells, with their ability to degrade the basement membrane and extracellular matrix as their initial steps to metastasis.[14-16] It is reasonable then to speculate that the tumor cells might have an ability to

produce a lipolytic enzyme besides proteolytic enzymes; and if it is proced to be the case, it might serve as an additional bad prognostic factor.

Cases who are alive without disease are of older age compare to cases that are alive with disease. The most prevalence type in all groups (alive with/without disease and died) were ductal type, mostly of scirrhous subtype. Among the group alive with disease, lymphocytic infiltration was mostly mild, while in the group without disease, the infiltration were mostly moderate to severe. The occurrence of lymph node metastasis was found comparably in the group with disease and the group without disease. A higher yield of lymph node positivity can be obtained actually by performing special staining using antibodies against epithelial cells. This procedure had been done by some investigators.[17-19] They had proved around 30% positive finding in negatively stated lymph nodes by routine H&E staining. This staining is able to find the micromestastases, which is usually overlooked by routine staining. By performing this staining, it will probably change the clinical or pathological staging in certain cases and consequently the management and prognosis prediction.

It seems that breast cancer affecting younger age group is more aggressive. The mean age of cases were decreasing from group of cases alive without disease, alive with disease and deceased case. If we assume that menopausal status is related to age, then this finding was differed from American breast cancer cases, in which, post menopausal group which were generally of older age, showed poorer survival compare to the premenopausal group.[20] However, several studies showed that higher hormon receptor positivity, another indicator of better clinical outcome, were found in post menopausal women[12-21] and these are in keeping with our findings. This finding may indicate the difference of cancer biology between Asian and non-Asian, which might be due to genetic and geographic properties.

Lymphocyte infiltration seems also play a role for a better outcome among invasive ductal carcinoma. The presence and severity of lymphocyte infiltration was decreasing from the group alive without disease, alive with disease and the died case. Of interest to note is the finding that none of the cases in the group alive with disease showed lymph and blood vessels invasion, unlike the other two groups, especially the group alive without disease. The explanation of this phenomenon might be the multisteps process of metastasis. After being able to invade the vessels, the tumor cells must be able to survive the defense mechanism encountered in the circulation, and also is the new environment of tissue or organ where they are entrapped. Then, the cell must be able also to proliferate and grow in distant organ.[22]

It will be very interesting to design a further study on a larger series of cases with the help of an additional ancillary techniques in order to get a more accurate information about the nature of lymphocyte infiltrates, blood and lymph vessels invasion and the presence of an occult or micrometastasis.

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