

Clinical Article

Incidence and Risk Factors for Leptomeningeal Carcinomatosis in Breast Cancer Patients with Parenchymal Brain Metastases

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Objective : The objective of study is to evaluate the incidence of leptomeningeal carcinomatosis (LMC) in breast cancer patients with parenchymal brain metastases (PBM) and clinical risk factors for the development of LMC.

Methods : We retrospectively analyzed 27 patients who had undergone surgical resection (SR) and 156 patients with whole brain radiation therapy (WBRT) as an initial treatment for their PBM from breast cancer in our institution and compared the difference of incidence of LMC according to clinical factors. The diagnosis of LMC was made by cerebrospinal fluid cytology and/or magnetic resonance imaging.

Results : A total of 27 patients (14%) in the study population developed LMC at a median of 6.0 months (range, 1.0-50). Ten of 27 patients (37%) developed LMC after SR, whereas 17 of 156 (11%) patients who received WBRT were diagnosed with LMC after the index procedure. The incidence of LMC was significantly higher in the SR group compared with the WBRT group and the hazard ratio was 2.95 (95% confidence interval; 1.33-6.54, $p < 0.01$). Three additional factors were identified in the multivariable analysis : the younger age group (<40 years old), the progressing systemic disease showed significantly increased incidence of LMC, whereas the adjuvant chemotherapy reduce the incidence.

Conclusion : There is an increased risk of LMC after SR for PBM from breast cancer compared with WBRT. The young age (<40) and systemic burden of cancer in terms of progressing systemic disease without adjuvant chemotherapy could be additional risk factors for the development of LMC.

Key Words : Brain metastasis · Breast cancer · Leptomeningeal carcinomatosis · Surgery · Whole brain radiation therapy.

INTRODUCTION

The incidence of parenchymal brain metastasis (PBM) from primary systemic cancer has been increasing along with prolonged survival of the patients with cancer. Recent report showed that up to 30% of cancer patients can be expected to develop PBM according to the types of primary cancer^{6,12}. A population-based estimate of the incidence proportion of PBM was highest for lung cancer followed by melanoma, renal-, and breast cancer³.

However, leptomeningeal carcinomatosis (LMC), which is one of terminal manifestations of central nervous system (CNS) metastasis from systemic malignancy, remains incurable without a discernible advance in treatment over the past decades. LMC

also has been diagnosed more frequently with the advancement of neuroimaging and prolonged survival of cancer patients^{8,13,29}. Among the pathogenesis of LMC, spread of cancer cells followed by surgical resection (SR) has been suggested from several clinical observations of solid tumors including malignant brain tumors^{2,11,16,22,23,34}. Although the overall incidence of LMC is difficult to estimate according to PBM status, it is apparent that the primary cancer showing a high incidence of PBM, such as lung cancer, breast cancer or melanoma, develops into a high proportion of LMC among those cancer patients^{5,35}.

Several reports suggested that the risk for development of LMC may increase in patients with PBM who underwent SR compared with non-surgical treatment, and at the same time, the risk may also be affected by factors such as location of the tu-

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mor, treatment modality and the histology of primary cancer^{21,23,24,30-33}). However, to our knowledge, neither a controlled-prospective study nor any study which attempted to adjust these variables to evaluate the significant risk factors for LMC has been reported.

Breast cancer is known to be the second most common cancer associated with PBM and is also, one of the most common primary cancers that causes LMC^{5,6,38}). Thus, we retrospectively collected data on patients with PBM from one primary histology of breast cancer. The primary objective of the study was to estimate the incidence of LMC after SR or whole brain radiation therapy (WBRT) as the initial treatment in a cohort of breast cancer patients with PBM. Further, we examined if SR confers a higher risk for the development of LMC than WBRT in these patients, and also, analyzed the influence of the above mentioned clinical factors on the development of LMC.

MATERIALS AND METHODS

Study population

From our institutional medical record database, we identified 274 cases of SR or WBRT as the initial treatment for PBM from breast cancer between August, 2001 and December, 2010. Eleven breast cancer patients, who received radiosurgery as the initial treatment for their PBM, were not included in this cohort.

Patients were excluded if they were diagnosed with LMC before the index procedure (12 patients), did not have a MRI follow-up at our institution after the index procedure (76 patients), or had incomplete data (3 patients) on entities under study. A total 183 patients met the eligibility criteria and are included in this analysis. Twenty-seven patients (15%) underwent SR of their tumors, and the remaining 156 patients (85%) received WBRT. Among 27 SR group, 11 patients underwent WBRT within one month after SR as an adjuvant treatment, 10 patients received WBRT after local or distant recurrence of their brain metastasis, and the remaining 6 patients were observed without WBRT. Patients were followed up with MRI every 3 to 6 months, until the patients died or no longer returned to our hospital.

Evaluation of clinical factors

We reviewed the following factors from medical records and conventionally categorized them for the analysis : type of index procedure (SR or WBRT), age, time from diagnosis to brain metastasis, volume of tumor, number of brain metastatic lesions (single or multiple), location (supratentorial or infratentorial) of the brain metastatic lesion, adjuvant chemotherapy, Karnofsky Performance Status (KPS) scale and systemic disease status (no evidence of disease, stable, or progressing).

Outcome evaluation

The primary outcome was the incidence of LMC, as diagnosed by cytological CSF analysis or neuroimaging findings such as "clear leptomeningeal enhancement extending into the

cerebral sulci or into the folia of the cerebellum, spinal cord, cauda equina or subependyma"¹³). All patients were evaluated by brain MRI at least once for monitoring local or cerebral recurrence. Spinal MRI and CSF cytology was examined only if the patient had symptoms of LMC. Time to event (LMC) was defined as the time from the index procedure to the diagnosis of LMC or the last follow-up image. WBRT group patients were censored when they received SR for the management of recurrent tumor to avoid overlapped exposure to higher risk.

Statistics

The differences in the distributions of categorical variables for SR and WBRT groups as well as the incidence of LMC were analyzed using the chi-square test or Fisher exact test, as appropriate. Continuous variables were tested using Student's t-test or Wilcoxon test. A *p*-value of 0.05 or less was considered statistically significant. For the analysis of the cumulative incidences of LMC, patients were censored at the end of observation or lost to follow-up. In the univariable analysis, the Cox proportional hazard model was used to estimate the hazard and corresponding 95% confidence interval (CI) of developing LMC for each of the risk factors. Factors that showed at least marginal significance from the univariable analysis (*p*-value <0.2) were included in the multivariable analysis to account interrelationships among the variables.

RESULTS

Characteristics of the patients

Characteristics of patients who underwent SR or WBRT for their PBM are presented in Table 1. The median follow-up (of image) after index procedure was 6.0 months (range, 1-51 months), and the follow-up periods were not different according to the treatment modality with a median of 5.8 months for the WBRT group and 8.0 months for the SR group. The median survival of SR group was 14.5 months (95% CI; 10.5-28.7) and that of WBRT only was 9.4 months (95% CI; 7.4-11.9). However, this apparent difference of median survival between SR group and WBRT group was not statistically significant (*p*>0.05).

The median age of the patients at the time of the index procedure was 52 years (range, 28-80 years), and the median time from diagnosis of the primary cancer to brain metastasis was 41 months (range, 1-271 months). The median tumor volume was 4.0 cm³ (range, 0.01-105.0 cm³), and it was significantly different between two modes of treatment : the median tumor volume of the SR group was 10.9 cm³ while that of the WBRT group was 3.1 cm³ (*p*<0.001). Fifty-eight patients (32%) had a single lesion at the time of index procedure while the remaining 125 patients (68%) had multiple metastases. Patients with a single lesion were more frequently treated by SR than those with multiple lesions (*p*<0.001). Supratentorial lesions constituted 28% of the patients, and an infratentorial lesion occurred in 72% of the patient. Infratentorial lesion includes the case with

both supratentorial and infratentorial brain metastases. Adjuvant chemotherapy after the index procedure was performed in 103 patients (56%) KPS was equal or greater than 70 in 90% of the patients. At the time of the index procedure, 118 patients (64%) had 'progressive' systemic disease and 65 patients had 'stable' disease or 'no evidence of disease (NED)'.

Analysis of factors affecting the incidence of LMC

LMC occurred in 27 out of 183 patients (14%) with the median time to LMC of 8.0 months (range, 2-26 months) (Fig. 1). LMC was diagnosed only by typical MRI findings for ten patients, only by cytology for two patients, and by both CSF cytology and MRI for the remaining 15 patients. After diagnosed with LMC, 15 patients received intra-CSF chemotherapy. Four patients received WBRT only with or without spinal radiation and the remaining 8 patients deferred any further treatment.

The distributions of the incidence of LMC according to various patients' characteristics and the hazard ratios of these factors based on cumulative LMC incidences are presented in Table 2.

The incidence of LMC was significantly higher in the SR group than the WBRT group, as 10 of 27 (37%) patients were diagnosed with LMC. The hazard ratio (HR) for development of LMC in the SR group compared to WBRT was 2.95 (95% CI, 1.33-6.54; $p=0.008$) (Fig. 2). The incidence of LMC was higher in the younger age group (<40 years old) compared with that in patients aged 40 years or older as 8 out of 24 younger age patients developed LMC after the index procedure. However, the difference was not statistically significant at 0.05 (HR=2.36, 95% CI, 0.98-5.65, $p=0.055$). The time from diagnosis to brain metastasis (<12 versus ≥ 12 months), tumor volume (≤ 4.0 versus >4.0 mL³), number of lesions (single versus multiple), location of tumor (supratentorial versus infratentorial), adjuvant chemotherapy, KPS (≥ 70 versus <70) and systemic disease status (NED or stable versus progressing) were not significantly associated with the incidence of LMC in univariable analysis.

Multivariable analysis of factors affecting the incidence of LMC

Among the factors analyzed univariately for the cumulative incidence of LMC, variables with a p -value less than 0.2 were included in the multivariable Cox proportional hazards model (Table 3).

Table 1. Characteristics of patients with who underwent surgical resection or whole brain radiation therapy for brain metastases of breast cancer

Characteristics	All patients (n=183)	Surgical resection (n=27)	WBRT (n=156)	p -value
Age (range)	52.0 (28-80)	50 (33-77)	52.0 (28-80)	0.392
Follow-up (range)	6.3 months (1-51)	8.0 (1-36)	5.8 (1-51)	0.081
Time from diagnosis to brain metastasis (range)	41 months (1-271)	35 months (6-120)	44 months (1-271)	0.312
Tumor volume (range)	4.0 cm ³ (0.01-105.00)	10.9 cm ³ (1.00-105.00)	3.1 cm ³ (0.01-72.20)	<0.001
No. of lesions				
Single	58 (32)	21 (78)	37 (24)	<0.001
Multiple	125 (68)	6 (22)	119 (76)	
Location				
Supratentorial	52 (28)	22 (81)	30 (19)	<0.001
Infratentorial*	131 (72)	5 (19)	126 (81)	
Adjuvant chemotherapy				
No	80 (44)	10 (37)	70 (45)	0.449
Yes	103 (56)	17 (63)	86 (55)	
KPS				
≥ 70	164 (90)	24 (89)	140 (90)	0.893
<70	19 (10)	3 (11)	16 (10)	
Systemic disease status				
NED & stable	65 (36)	16 (60)	49 (31)	0.005
Progressing	118 (64)	11 (41)	107 (69)	

Numbers in parenthesis, not specified elsewhere, represents column percentage. *Multiple lesions distributing both supra- and infratentorial area are classified into "Infratentorial". WBRT : wholebrain radiation therapy, KPS : Karnofsky Performance Status, NED : no evidence of disease

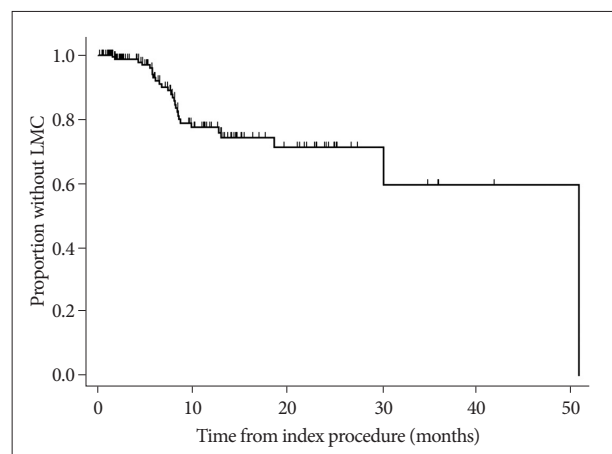


Fig. 1. Kaplan-Meier curve for time to development of LMC after treatment of the parenchymal brain metastases plotted for 183 patients in our study. Y-axis represents the proportion of patients without LMC at each follow-up time at the X-axis. 27 patients developed LMC (14%) during the follow-up. LMC : leptomeningeal carcinomatosis.

Among the preoperative characteristics, the index procedure was still significant and the younger age group gained statistical significance in this multivariable analysis. The administration of adjuvant chemotherapy and NED/stable systemic disease status significantly reduced the cumulative incidence of LMC in multivariable analysis even though these variables were not significant at the p -value 0.05 in the univariable analysis. Com-

Table 2. Univariable analysis of factors possibly affecting the cumulative incidence of leptomeningeal seeding after surgical resection or whole brain radiotherapy for brain metastases

Variables	No. of patients (%)*		p value	Cumulative incidence		
	No LMC (n=156)	LMC (n=27)		Hazard ratio	95% CI	p value
Index procedure			<0.001			
Surgical resection	17 (11)	10 (37)		2.95		
WBRT	139 (89)	17 (63)		1.0	1.33-6.54	0.008
Age			0.006			
<40	16 (10)	8 (30)		2.36		
≥40	140 (90)	19 (70)		1.0	0.98-5.65	0.055
Time from diagnosis to brain metastasis			0.893			
<12 months	16 (10)	3 (11)		1.18		
≥12 months	140 (90)	24 (89)		1.0	0.35-3.95	0.787
Tumor volume			0.057			
≤4.3 mL ³	83 (53)	9 (33)		1.0		
>4.3 mL ³	73 (47)	18 (67)		1.63	0.72-3.66	0.241
No. of lesions			0.015			
Single	44 (28)	14 (52)		1.0		
Multiple	112 (72)	13 (48)		0.53	0.24-1.15	0.108
Location			0.045			
Supratentorial	40 (25)	12 (44)		1.0		
Infratentorial	116 (75)	15 (56)		0.66	0.30-1.42	0.285
Adjuvant chemotherapy			0.449			
No	70 (45)	10 (37)		1.0		
Yes	86 (55)	17 (63)		0.51	0.23-1.15	0.104
KPS			0.218			
≥70	138 (88)	26 (96)		1.0		
<70	18 (12)	1 (4)		0.31	0.04-2.28	0.249
Systemic disease status			0.489			
NED & stable	57 (37)	8 (30)		1.0		
Progressing	99 (63)	19 (70)		2.08	0.87-4.95	0.099

*Numbers in parenthesis represents column percentage. LMC : leptomeningeal carcinomatosis, WBRT : wholebrain radiation therapy, KPS : Karnofsky Performance Status, NED : no evidence of disease, CI : confidence interval

pared to the WBRT group, the HR of the SR group was 4.03 (95% CI, 1.51-10.73; $p=0.005$). The HR of the younger age (<40) group was 2.89 (95% CI, 1.16-7.19; $p=0.022$), adjuvant chemotherapy group decreased the risk for development of LMC at a HR of 0.43 (95% CI, 0.19-0.99; $p=0.048$), whereas patients with progressing systemic disease showed increased risk of LMC at a HR of 3.53 compared with NED or stable systemic disease (95% CI, 1.35-9.23; $p=0.010$).

Differential effects of the index procedure on the incidence of LMS according to the age group

To evaluate the differential effect of treatment modality on the development of LMC according to the age group, we performed the subgroup analysis presented in Table 4. For the different modes of treatment, WBRT group showed lower incidence of LMC in the old age (≥40) group (Fisher's exact test, $p=0.005$), whereas the difference according to the index procedure became not significant in the young age (<40) group due to high incidence of LMC regardless of the index procedures.

DISCUSSION

Brain metastases increase the risk of LMC in breast cancer?

LMC most often presents in patients with progressive systemic cancer. However, occasionally it occurs in the absence of systemic disease, and it can even be the first manifestation of cancer⁵. Thus, LMC can develop independently from systemic malignancy without PBM, but some studies reported that patients who underwent SR for their PBM had a higher incidence of LMC compared with that of patients received non surgical treatments³¹⁻³³. It is unclear how PBM spreads and causes LMC, but we could observe the surgical spillage or the drop-metastasis of malignant brain tumors^{2,25,35}. The incidence of LMC in patients with PBM compared with that in patients without PBM are yet to be studied, and even reports investigating the incidence of LMC in patients with PBM are rare^{17,18,30}. Kim et al.¹⁷ reported that in 400 patients with CNS metastases of breast cancer, 318 patients (79.5%) had PBM only, 52 patients (13%) had both PBM and

LMC, and 30 patients (7.5%) had LMC only. The number of breast cancer patients diagnosed with histologic confirmation during the same period was 10172 in that study, and based on this, we inferred the incidence of LMC in patients with PBM as 52/370 (14%), which was much higher than that in patients without PBM (30/9, 802, 0.3%). Lee et al.¹⁸ reported that the incidence of LMC among CNS metastases of breast cancer was 25% (68 of 272 patients), which was apparently higher than the known incidence proportion of LMC in breast cancer patients which is about to 1-5%⁵. However, this simple comparison should be understood with caution because many clinical factors including systemic disease status may affect the incidence.

The hematogenous pathway can be a route for both PBM and LMC as tumor cells overcome blood-brain and blood-CSF barrier²⁸. Although it is not clear whether systemic chemotherapy can prevent either PBM or LMC, several studies indicated that systemic chemotherapy could prolong patients' survival with PBM from breast cancer and intra-CSF chemotherapy is currently considered the best treatment option for LMC^{14,17,26,28,36}. It is noteworthy that systemic disease status and chemotherapy were significant factors affecting the incidence of LMC in our study.

Diagnosis of LMC

In view of the poor prognosis of patients with LMC, early diagnosis of LMC with prompt initiation of treatment is important to prolong survival, especially in patients with good performance status and neurological function⁸. Physicians should be alerted to a differential risk of the condition depending on certain characteristics, and the method of treatment; early appropriate actions to prevent or treat LMC in higher-risk patients should be taken. Recent trends in diagnosing LMC with MRI are highly sensitive although it is not definitive¹³. A strong adherence of malignant cells to the leptomeninges or the presence of a focal rather than widespread leptomeningeal tumor, can contribute to false-negative cytological results^{15,37}. Although the neuroimaging-based diagnosis of LMC without CSF cytology is not generally accepted as a definitive diagnosis, a consensus is reached to allow for the treatment of LMC diagnosed by radiographic evidence only in known cancer patients. In our study, 10 patients were diagnosed with LMC based only on an MRI. Four of them revealed a negative CSF finding and in the remaining 6 pa-

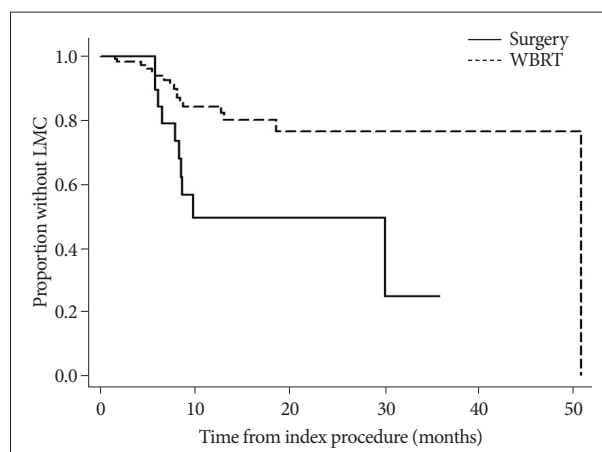


Fig. 2. Kaplan-Meier curves for time to development of LMC after treatment of the parenchymal brain metastases according to index procedure. Y-axis represents the proportion of patients without LMC at each follow-up time at the X-axis. Patients in the surgical resection (n=27) conferred greater risk for developing LMC compared to those in the WBRT (n=156) (HR estimated by the Cox proportional hazard model=2.95, 95% confidence interval, 1.33-6.54, p=0.008). LMC : leptomeningeal carcinomatosis, WBRT : whole brain radiation therapy, HR : hazard ratio.

Table 3. Multivariable analysis of factors potentially affecting the cumulative incidence of leptomeningeal carcinomatosis after surgical resection or wholebrain radiation therapy

Variables*	Cumulative incidence		
	Hazard ratio	95% CI	p value
Index procedure			
Surgical Resection	4.03	1.51-10.73	0.005
WBRT	1.0		
Age			
<40	2.89	1.16-7.19	0.022
≥40	1.0		
No. of lesions			
Single	1.0	0.33-2.00	0.657
Multiple	0.82		
Adjuvant chemotherapy			
No	1.0	0.19-0.99	0.048
Yes	0.43		
Systemic disease status			
NED & stable	1.0	1.35-9.23	0.010
Progressing	3.53		

*Factors with marginal significance (p-value <0.2) from the univariable analysis were included in the model. NED : no evidence of disease, WBRT : wholebrain radiation therapy, CI : confidence interval

Table 4. Differential effects of the index procedure on the incidence of LMC according to the age group

Age		Index procedure		p value
		Surgical resection (%)	WBRT (%)	
<40	No LMC	3 (50)	13 (72)	0.362
	LMC	3 (50)	5 (28)	
≥40	No LMC	14 (67)	126 (91)	0.005
	LMC	7 (33)	12 (9)	

Fisher's exact test. Numbers in parenthesis represents column percentage. LMC : leptomeningeal carcinomatosis, WBRT : whole brain radiation therapy

tients, CSF testing was not performed.

Risk factors for the development of LMC

It is known that certain biological features of breast cancer affect clinical finding including LMC. Several reports have suggested a higher risk for brain metastasis in HER-2 positive and triple negative (TN) breast subtypes than in hormone receptor (HR) positive subtypes^{6,19,20}. Lee et al.¹⁸ reported a different distribution of subtypes of breast cancer between PBM with LMC and PBM without LMC, and a worse prognosis of patients with TN. However, the direct comparison of incidence of LMC according to the subtypes of breast cancer was not made.

Several studies suggested that mechanical spread of tumor cells to the CSF space could contribute to the development of LMC. Some studies reported an increased incidence of LMC after posterior fossa tumor surgery compared with supratentorial lesions^{25,35}. Other studies observed a higher incidence of LMC after SR compared with non-surgical treatment³¹⁻³³. Norris et al.²⁵ suggested that the more chance of CSF exposure in patients receiving posterior fossa tumor removal was responsible for the increased development of LMC. Suki et al.³³ reported increased incidence of LMC in patients with PBM, whose tumor was removed in a piecemeal manner than en-bloc excision. Thus, authors investigated the incidence of LMC after SR of PBM according to the proximity to CSF pathway and suggested the PBM not entirely surrounded by brain parenchyma should be removed in caution not to spill the tumor by piecemeal removal or using Cavitron ultrasonographic aspirator¹. In our study, the SR group showed a significantly higher incidence of LMC than the WBRT group, which is in accordance with previous finding. However, the PBM location whether or not the lesions involved posterior fossa, did not affect the risk of development of LMC. This result may reflect not tumor location itself but a chance for CSF exposure to be responsible for development of LMC.

Known prognostic factors for the survival of breast cancer patients include axillary nodal status, tumor size/type/grade, lymphatic/vascular invasion, proliferation markers, ethnicity and patient age at diagnosis. Many studies, which evaluated the influence of age on outcome in breast cancer have been small and had conflicting results. Two relatively large trials have, however, demonstrated a worse prognosis for patients younger than 35 years of age, even after adjustment for other prognostic factors^{4,39}. Studies suggested different and aggressive biological behaviors of younger age breast cancer. A different distribution of molecular phenotypes in the population of young women with breast cancer compared to the general population of women with breast cancer was reported⁷. Young age appears to be an independent risk factor and the median age of patients with brain metastases is about 5 years younger than those without brain metastases⁹. In our study, an age of younger than 40 years was an independent risk factor for development of LMC in patients with PBM from breast cancer. This propensity is in accor-

dance with the observation of Lee et al.¹⁸, where the age of PBM from breast cancer patients with LMC was significantly younger than those without LMC although the variables were not adjusted.

The role of systemic chemotherapy to prevent CNS metastasis has not yet been proven. However, a recent study reported a favorable outcome showing significantly prolonged survival in patients with PBM from breast cancer who received chemotherapy, compared with the patients without chemotherapy¹⁶. These finding leave a possibility that the chemotherapy directly reduce PBM from breast cancer or LMC, in addition to prolonging patient's survival by decreasing the systemic cancer burden. In our study, the patients in a direction of reduced systemic cancer burden (i.e. patients with stable or NED of systemic cancer and patients with systemic chemotherapy) showed a decreased risk for the development of LMC after treatment for their PBM from breast cancer.

The role of WBRT for preventing CNS recurrence after SR of PBM was proven in a randomized controlled clinical trial²⁷. However, it is unclear whether or not this "CNS recurrence" included LMC, and we could not find any study that compared not the local recurrence rate, but the risk of LMC after SR in patients with or without WBRT^{9,10}. An 11% incidence of LMC in the WBRT only group in our study is the first presented figure indicating the natural risk for the development of LMC without SR. But in this cohort, we did not have a group of patients, who had PBM from breast cancer without WBRT. Thus, to evaluate the role of WBRT for preventing the development of LMC, a further well controlled cohort study is needed.

CONCLUSION

This retrospective analysis revealed an increased risk for the development of LMC after SR of PBM from breast cancer compared with WBRT. The young age (<40) and systemic cancer burden in terms of progressing systemic could be additional risk factors for LMC, whereas continued systemic chemotherapy after the index procedure may reduce the incidence of LMC in patients with PBM from breast cancer.

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