Original Study

Ventriculoperitoneal Shunt for CNS Metastasis in Breast Cancer: Clinical Outcomes Based on Intrinsic Subtype

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Abstract

We show the real-world outcomes of patients with metastatic breast cancer who received a ventriculoperitoneal shunt (VPS) owing to central nervous system metastasis. More than one-half of the patients received a VPS for uncontrolled intracranial pressure (57.1%) and headache (55.7%), and most (77.1%) of these patients improved after VPS. During 36 months of median follow-up, the median overall survival after central nervous system metastasis and after VPS was 7.6 and 2.3 months, respectively.

Background: Leptomeningeal metastasis (LM) is associated with a grave prognosis in breast cancer (BC) and can be controlled with a ventriculoperitoneal shunt (VPS). Information regarding LM and VPS based on intrinsic subtype is limited; thus, we investigated the clinical outcomes of BC treated with VPS. **Patients and Methods:** The present retrospective study comprised 70 patients diagnosed with LM who received a VPS. The patients were divided into 4 groups based on BC subtype: hormone receptor $(HR)^+$/human epidermal growth factor receptor 2 $(HER2)^-$, HR^+/$HER2^+$, HR^-/$HER2^+$, and triple negative BC (TNBC). **Results:** The most common indications for VPS were uncontrolled intracranial pressure (57.1%) and uncontrolled headache (55.7%), which improved in 54 (77.1%) of 70 patients after VPS. The median overall survival (OS) after brain or LM and overall survival after VPS were 7.6 and 2.3 months, respectively. Anti-HER2 treatment was a significant prognostic factor for better OS after brain or LM based on multivariate analysis (hazard ratio, 0.15; 95% confidence interval, 0.04-0.57; $P = .005$), whereas TNBC was correlated with shorter OS after central nervous system metastasis (hazard ratio, 2.82; 95% confidence interval, 1.46-5.48; $P = .002$). **Conclusions:** There were significant differences in clinical outcome based on the intrinsic subtype of patients with BC with LM who received a VPS. Anti-HER2 treatment in patients with $HER2^+$ BC was associated with better survival in patients with metastatic BC with VPS insertion compared with those without. Survival of metastatic BC with VPS remained poor, especially in the TNBC subgroup.

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Keywords: Breast cancer subtype, Leptomeningeal metastasis, Metastatic breast cancer, Overall survival, VP shunt

Introduction

Breast cancer (BC) is the second most common cancer associated with central nervous system (CNS) metastasis.[1,2] Approximately 10% to 16% of patients with metastatic BC (MBC) experience symptomatic brain metastases (BM),[3] and diagnosis of CNS metastasis has increased owing to advances in neuroimaging. Recent studies have reported a higher incidence of BM ranging from 25% to 46%.[4-6] According to historical studies, the median survival of

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Table 1 Patient Characteristics

Characteristics	No. Patients (%)				
	All Patients (n = 70)	HR$^+$/HER2$^-$ (n = 21)	HR$^+$/HER2$^+$ (n = 11)	HR$^-$/HER2$^+$ (n = 11)	TNBC (n = 27)
Median age, y (range)					
At diagnosis, primary BC	47 (27-66)	45 (28-64)	39 (27-47)	53 (29-59)	48 (29-66)
At the time of LM	49 (30-69)	49 (31-66)	41 (31-63)	55 (31-64)	50 (30-69)
ECOG PS					
0-1	26 (37)	12 (57)	3 (27)	7 (63)	4 (14)
≥2	44 (63)	9 (43)	8 (73)	4 (36)	23 (85)
Histology					
IDC	63 (90)	17 (81)	10 (91)	11 (100)	25 (93)
ILC	4 (5)	3 (14)	1 (9)	0	0
Others	3 (4)	1 (5)	0	0	2 (7)
Initial TNM stage					
1	1 (1)	0	0	0	1 (4)
2	19 (27)	3 (14)	1 (9)	5 (46)	10 (37)
3	31 (44)	10 (48)	8 (73)	2 (18)	11 (41)
4	19 (27)	8 (38)	2 (18)	4 (36)	5 (19)
Metastatic sites					
Bone	23 (33)	11 (52)	4 (36)	2 (18)	6 (22)
Lung	14 (20)	6 (29)	4 (36)	0	4 (15)
Liver	6 (9)	5 (24)	1 (9)	0	0
Distant lymph node	12 (17)	4 (19)	1 (9)	3 (27)	4 (15)
Isolated CNS metastasis	26 (37)	4 (19)	3 (27)	5 (46)	14 (52)
Ommaya reservoir insertion before VPS	41 (59)	13 (62)	4 (36)	8 (73)	16 (59)
≥3 prior chemotherapy cycles before VPS	22 (31)	12 (55)	4 (18)	1 (5)	5 (23)
Progression of extracranial disease (N = 58)	27 (47)	8/20 (40)	5/8 (63)	3/7 (43)	11/23 (48)
Whole brain RT					
Yes, before VPS	34 (49)	7 (33)	6 (55)	10 (91)	11 (41)
Yes, after VPS	13 (19)	6 (29)	3 (27)	0	4 (15)
No	23 (33)	8 (38)	2 (18)	1 (9)	12 (44)
Systemic chemotherapy after VPS	13 (19)	6 (29)	4 (36)	0	3 (11)

Abbreviations: BC = breast cancer; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LM = leptomeningeal metastasis; RT = radiotherapy; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt.

patients with BM is less than 6 months.[7] However, more patients are surviving BC owing to improvements in systemic therapy; in fact, a retrospective study of patients with MBC with BM showed a median survival of 14.4 months.[8]

CNS metastases are classified as either BM and/or leptomeningeal metastasis (LM).[9] In patients with symptomatic LM, various treatment approaches such as radiotherapy, chemotherapy including intrathecal chemotherapy, and surgery including ventriculoperitoneal shunt (VPS) insertion are used to relieve the symptoms and mitigate increased intracranial pressure (ICP). However, optimal treatment for LM remains to be defined, and there is no United States Food and Drug Association-approved systemic chemotherapy for BC with LM. A number of prospective studies with a combination of chemotherapeutic agents such as temozolomide, capecitabine, cisplatin, sagopilone, and patupilone has been conducted in patients with BC with LM; however, survival after LM usually did not exceed 4 months.[10-14] Furthermore, most patients with increased ICP with or without hydrocephalus could not be controlled with medical treatments, and they required implantation of an Ommaya reservoir or a VPS.

Intrathecal chemotherapy can be delivered through an Ommaya reservoir when ICP is controllable. When ICP increases beyond a tolerable range or hydrocephalus develops, VPS becomes an essential palliative treatment, after which intrathecal chemotherapy cannot be continued.[15] Although BC is the malignancy most commonly associated with LM, little information is available regarding patients with BC with LM who received VPS, and the clinical utility and value of VPS need to be defined. In the current

Table 2 Indications for VPS

	No. Patients (%)				
	All Patients (n = 70)	$HR^+/HER2^-$ (n = 21)	$HR^+/HER2^+$ (n = 11)	$HR^-/HER2^+$ (n = 11)	TNBC (n = 27)
Obstructive hydrocephalus	11 (15.7)	1 (4.8)	6 (54.5)	1 (9.1)	3 (11.1)
Increased ICP	40 (57.1)	13 (61.8)	5 (45.5)	6 (54.5)	16 (59.3)
Uncontrolled headache	39 (55.7)	17 (81.0)	5 (45.5)	6 (54.5)	11 (40.7)
Nausea/vomiting	22 (31.4)	7 (33.3)	3 (27.3)	3 (27.3)	9 (33.3)
Altered mental status (eg, confusion)	14 (20.0)	5 (23.8)	2 (18.2)	0	7 (25.9)
Seizure	10 (14.3)	3 (14.3)	0	2 (18.2)	5 (18.5)
Muscle weakness	6 (8.6)	2 (9.5)	2 (18.2)	0	2 (7.4)
Other neurologic symptoms	4 (5.6)	1 (4.8)	0	2 (18.2)	1 (3.7)
Clinical improvement, yes	54 (77.1)	16 (76.2)	11 (100)	11 (100)	18 (66.7)

Abbreviations: ICP = intracranial pressure; VPS = ventriculoperitoneal shunt.

study, we investigated the clinical features of patients with VPS based on intrinsic subtype.

Patients and Methods

The aim of the current study was to analyze the treatment outcomes of VPS in patients diagnosed with MBC with LM. We retrospectively analyzed patients who received a VPS owing to BC with LM between October 2001 and December 2017 at Samsung Medical Center. Patients with MBC were treated based on disease course. After diagnosis of CNS metastasis, a VPS and/or Ommaya reservoir were implanted by skilled neurosurgeons. Patients were divided into 4 groups based on BC subtype: hormone receptor $(HR)^+$/human epidermal growth factor receptor 2 $(HER2)^-$, $HR^+/HER2^+$, $HR^-/HER2^+$, and triple negative BC (TNBC). The subtypes were classified based on immunohistochemical (IHC) staining for estrogen receptor, progesterone receptor, and HER2. Grades 0 and 1 for HER2 based on IHC were defined as negative and grade 3 as positive. In patients who were HER2 2+ based on

Table 3 Summary of 15 Patients Who Survived More Than 4 Months After VPS

	Gender/Age	Subtype	Indications for VPS	Chemotherapy After VPS	Radiotherapy After VPS	Time to Death From VPS, mos
Patient 1	F/62	$HR^+/HER2^-$	Headache, nausea/vomiting, dizziness	3 cycles of capecitabine	WBRT	9.2
Patient 2	F/49	$HR^+/HER2^-$	IICP, headache	11 cycles of capecitabine	WBRT	22.0
Patient 3	F/40	$HR^+/HER2^-$	Headache, nausea/vomiting	—	RT to spine	12.5
Patient 4	F/37	$HR^+/HER2^-$	IICP, headache	—	WBRT	11.2
Patient 5	F/59	$HR^+/HER2^-$	Altered mental status, paraplegia	—	WBRT	21.1
Patient 6	F/35	$HR^+/HER2^-$	IICP, headache	8 cycles of docetaxel, 1 cycle of gemcitabine/ cisplatin	WBRT	11.4
Patient 7	F/32	$HR^+/HER2^-$	Right arm weakness, aphasia, hydrocephalus	—	—	5.3
Patient 8	F/54	$HR^+/HER2^-$	IICP, seizure	—	WBRT, RT to breast	5.8
Patient 9	F/36	$HR^+/HER2^-$	IICP, headache	—	—	5.8
Patient 10	F/67	$HR^+/HER2^-$	IICP, headache	10 cycles of capecitabine, letrozole	RT to bone, WBRT	11.4
Patient 11	F/41	$HR^+/HER2^+$	IICP, altered mental status, headache	—	—	13.5
Patient 12	F/40	$HR^+/HER2^+$	IICP, headache, dizziness	5 cycles of AC	RT to spinal cord	6.2
Patient 13	F/48	$HR^+/HER2^+$	IICP, headache, nausea/vomiting	8 cycles of gemcitabine/ cisplatin, 3 cycles of capecitabine	—	16.6
Patient 14	F/40	$HR^+/HER2^+$	Hydrocephalus	Letrozole	—	9.6
Patient 15	F/50	$HR^+/HER2^+$	Dizziness, hydrocephalus	—	RT to spine & spinal cord	4.2
Patient 16	F/54	TNBC	IICP, paraplegia	—	—	9.0
Patient 17	F/31	TNBC	IICP, headache altered mental status,	3 cycles of paclitaxel/ carboplatin	—	6.0

Abbreviations: AC = doxorubicin with cyclophosphamide; F = female; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IICP = increased intracranial pressure; RT = radiotherapy; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt; WBRT = whole-brain radiotherapy.

Table 4 Frequency of Palliative Chemotherapy After LM or BM

	All Patients (n = 70)	$HR^+/HER2^-$ (n = 21)	$HR^+/HER2^+$ (n = 11)	$HR^-/HER2^+$ (n = 11)	TNBC (n = 27)
Endocrine therapy only	4	4	0	–	–
Endocrine therapy with targeted therapy	1	1	0	–	–
Cytotoxic chemotherapy only	23	12	2	5	4
HER2-targeted therapy only	1	–	1	0	–
Chemotherapy with HER2-targeted therapy	8	–	4	4	–
Intrathecal chemotherapy	29	9	1	7	12

Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.

IHC, fluorescence in situ hybridization was performed to confirm HER2 amplification. TNBC was defined as absence of estrogen receptor, progesterone receptor, and HER2 expression. CNS metastasis was defined as BM, LM, or both. BM was diagnosed using brain magnetic resonance imaging and/or brain computed tomography, and LM was diagnosed using enhanced brain magnetic resonance imaging with T2-weighted and/or fluid-attenuated inversion recovery images[16,17] and/or cerebrospinal fluid cytology. We assigned cerebrospinal fluid cytology positivity as results of atypical, suspicious, or positive.[16,18,19]

Patient characteristics were compared based on BC subtype. Differences in characteristics were examined using the Pearson χ^2 test. OS_{CNS} was defined as the time from CNS metastasis to death or last follow-up, and OS_{VPS} was defined as the time from VPS surgery to death or last follow-up. Patients alive or lost to follow-up were censored. The Kaplan-Meier method was used to evaluate OS. Differences in survival were analyzed using the log-rank test, and a *P*-value less than .05 was considered statistically significant. A multivariable Cox proportional hazards regression model was used to assess the effect of each prognostic variable on OS. Data were analyzed using the statistical software IBM SPSS 23.0 software (SPSS Inc, Chicago, IL).

This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB No.2019-01-121).

Results

Patient Characteristics

After review of the electronic patient database, we identified 70 patients with BC and confirmed LM who received a VPS. Patient characteristics based on subtype are shown in Table 1. The proportions of $HR^+/HER2^-$, $HR^+/HER2^+$, $HR^-/HER2^+$, and TNBC in the study were 30%, 16%, 16%, and 39%, respectively. The median age at diagnosis was 47 years (range, 27-66 years), and the median age at the time of CNS metastasis was 49 years (range, 28-68 years). Approximately two-thirds (44/70; 63%) of patients showed Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$ 2. Fifty-one (73%) patients had recurrent disease after treatment with curative aim, and the remaining 19 (27%) patients had stage IV BC at diagnosis. The most common site of metastasis was bone (23/70; 33%), and isolated CNS metastasis was present in 37% (26/70) of patients. More than one-half (41/70; 59%) of the patients underwent Ommaya reservoir insertion before VPS insertion for the purpose of intrathecal chemotherapy. Approximately one-third (22/70; 31%) of patients received more than 3 lines of systemic chemotherapy before diagnosis of CNS metastasis. Whole brain radiotherapy (WBRT) was administered to 67% of patients, and systemic chemotherapy after VPS was administered to 19% of patients.

Indications for VPS and Characteristics of Patients Who Survived More Than 4 Months

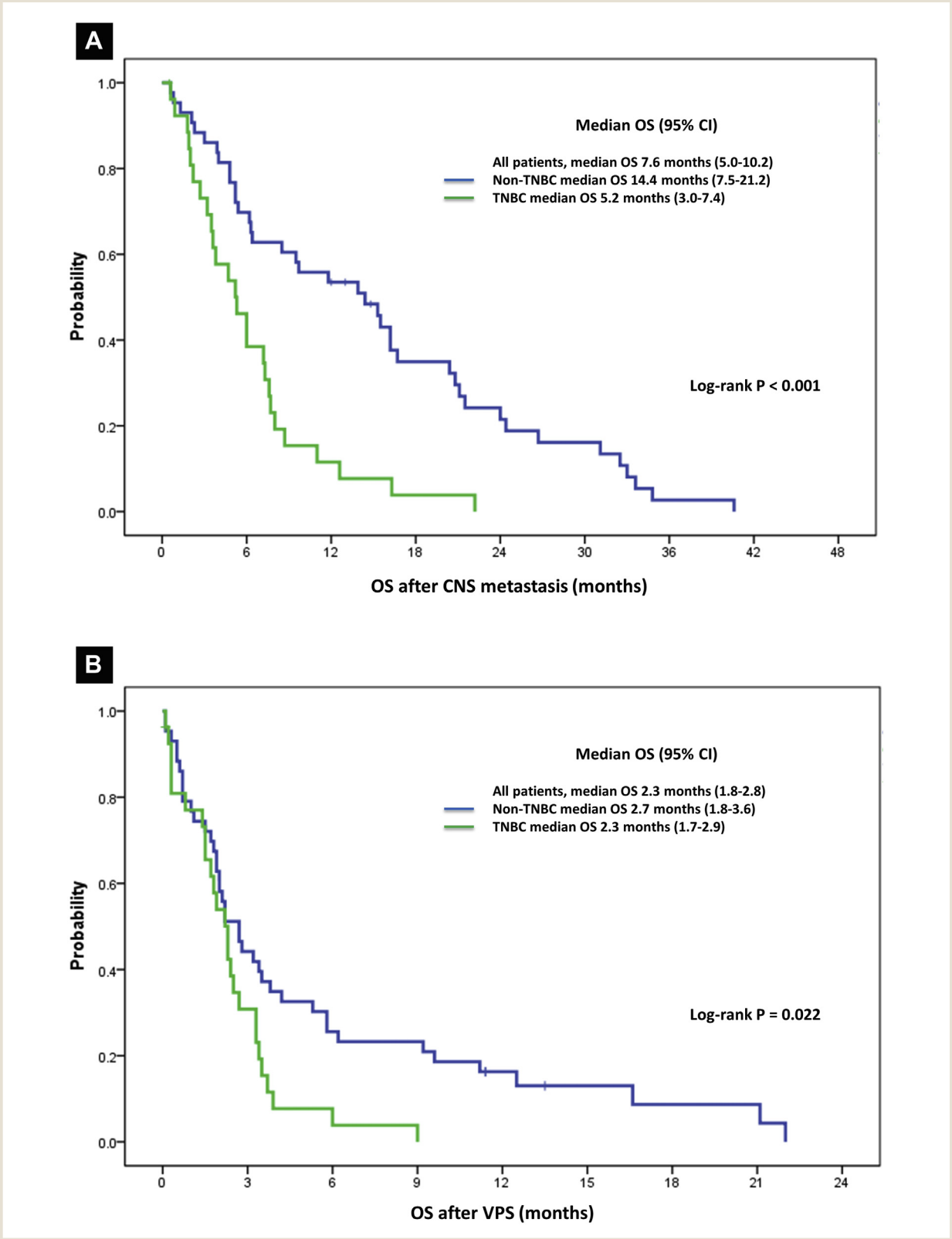
Table 2 demonstrates the indications for VPS based on subtype and noted whether patients showed improvement after VPS placement. The most common indications for VPS placement were documented increased ICP (57.1%) and uncontrolled headache (55.7%). Obstructive hydrocephalus, which was a typical indication for VPS, was the fifth most frequent reason for VPS surgery (15.7%). However, 16 (54.5%) patients in the $HR^+/HER2^+$ group received VPS owing to obstructive hydrocephalus, and it was the most common cause in that group. In addition, 77.1% of patients who received a VPS experienced clinical improvement in symptoms as well as neurologic signs, in addition to decreased steroid use. VPS ameliorated symptoms related to increased ICP in all patients with $HER2^+$ BC, though lesser improvement was shown in the TNBC group.

Table 3 shows 17 patients who survived more than 4 months after VPS, with a median age of 41 years (range, 31-67 years), of whom patients with HR^+ BC accounted for 88% (15/17). Eight (47.0%) of 17 patients received palliative chemotherapy after VPS, and the most common regimen was capecitabine. Seven (41.2%) of 17 patients received WBRT. The median time to death after VPS placement for these 17 patients was 9.6 months (Table 3).

Chemotherapy for Patients With BC With CNS Metastasis

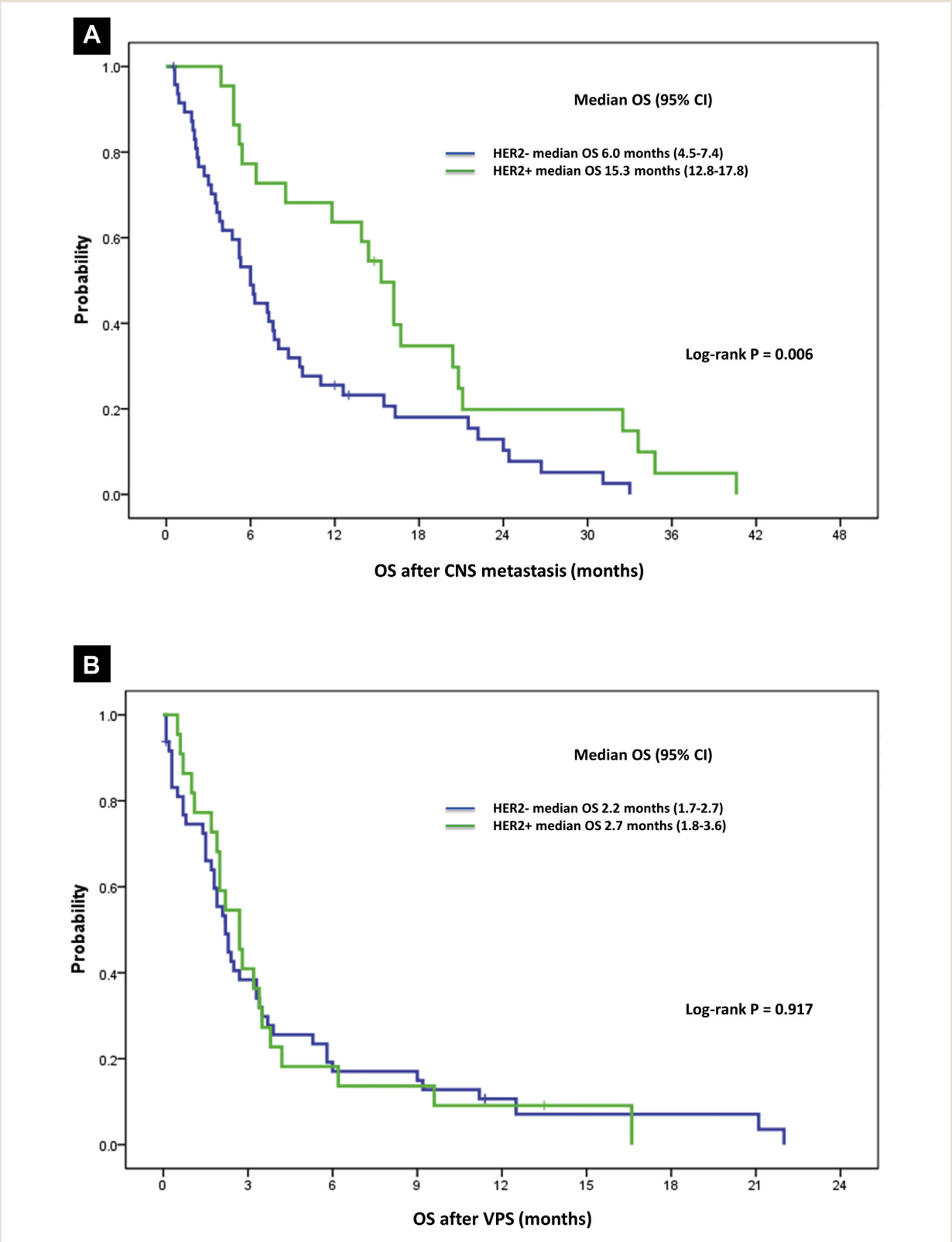
After CNS metastasis, 45 (64%) patients received palliative chemotherapy. Intrathecal chemotherapy via Ommaya reservoir was the most frequently administered treatment before VPS (29/70; 41%) (Table 4). The next most common regimens for BC with CNS metastasis were AC (cyclophosphamide with doxorubicin) and capecitabine monotherapy (see Supplemental Table 1 in the online version). In addition, 7 (32%) of 22 patients with $HER2^+$ BC received anti-HER2 treatment after CNS metastasis, and 41 (59%) patients received VPS insertion without administration of intrathecal therapy, including 15 (15/41; 37%) patients with TNBC (see Supplemental Table 2 in the online version). Patients did not receive intrathecal anti-HER2 treatment because this is not approved in Korea. A summary of 13 patients who received systemic chemotherapy after VPS is shown in Supplementary Table 3 (in the

Figure 1 Kaplan-Meier Curves of Overall Survival after Central Nervous System Metastasis (A) and OS after Ventriculoperitoneal Shunt Insertion (B) in Patients With TNBC and Non-TNBC



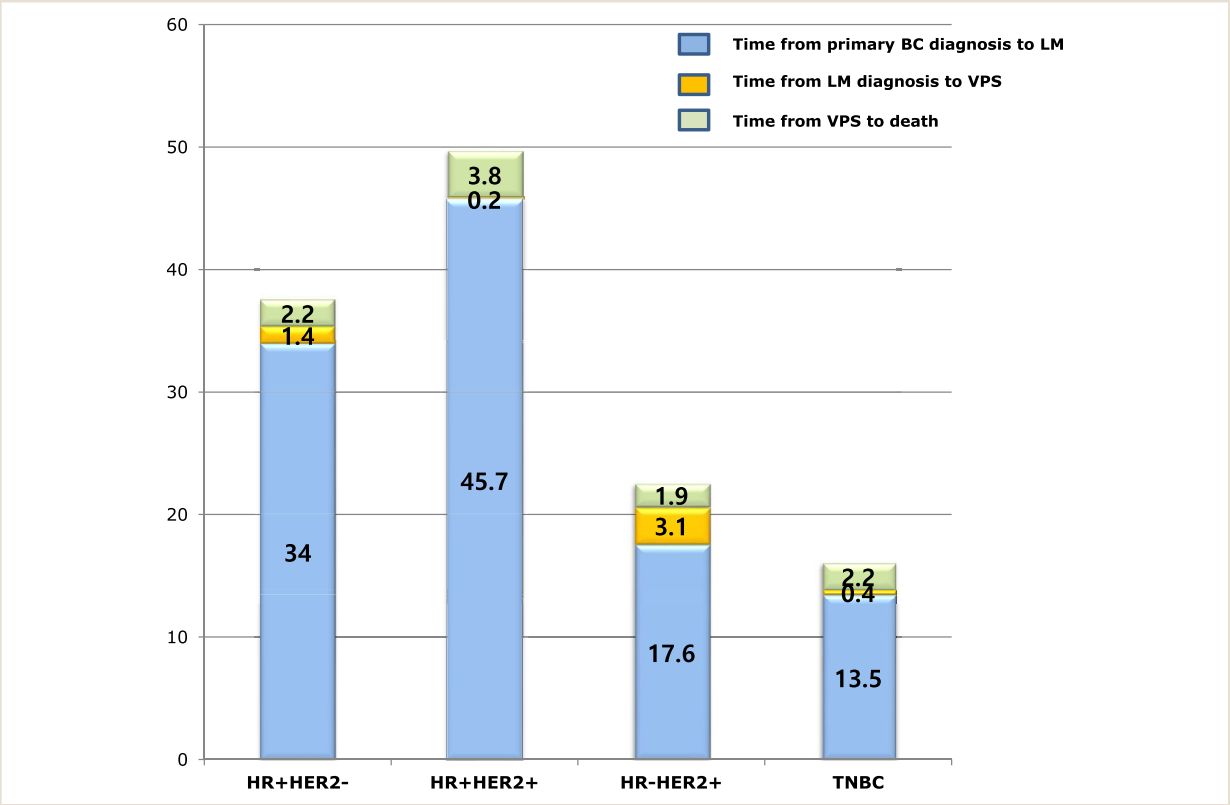
Abbreviations: CI = confidence interval; CNS = central nervous system; OS = overall survival; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt.

Figure 2 Kaplan-Meier Curves of Overall Survival after Central Nervous System Metastasis (A) and OS after Ventriculoperitoneal Shunt Insertion (B) in HER2^{+} and HER2^{-} Patients



Abbreviations: CI = confidence interval; CNS = central nervous system; HER2 = human epidermal growth factor receptor 2; OS = overall survival; VPS = ventriculoperitoneal shunt.

Figure 3 Median Time to Disease Progression according to Intrinsic Subtype



Abbreviations: BC = breast cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; LM = leptomeningeal metastasis; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt.

online version). The most common regimen for BC with LM after VPS was capecitabine.

Treatment Outcomes Based on BC Subtype

During 36.5 months of median follow-up, the median OS_{CNS} was 7.6 months (95% confidence interval [CI], 5.0-10.2 months) (Figure 1A), and the median OS_{VPS} was 2.3 months (95% CI, 1.8-2.7 months) (Figure 1B) in all patients. The median OS_{CNS} was 14.4 months (95% CI, 7.5-21.2 months) for the non-TNBC group and 5.2 months (95% CI, 3.0-7.4 months) for patients with TNBC (log-rank $P < .001$) (Figure 1A). The median OS_{VPS} was 2.7 months (95% CI, 1.8-3.6 months) for the non-TNBC group and 2.3 months (95% CI, 1.7-2.9 months) for patients with TNBC ($P = .022$) (Figure 1B). The median OS_{CNS} was 6.0 months (95% CI, 4.5-7.4 months) for $HER2^-$ groups and 15.3 months (95% CI, 12.8-17.8 months) for $HER2^+$ groups ($P = .006$) (Figure 2A). The

Table 5 Univariate and Multivariate Analyses

	$OS_{CNS\ metastasis}$			OS_{VPS}		
	Univariate	Multivariate		Univariate	Multivariate	
	P Value	*P* Value	HR (95% CI)	*P* Value	*P* Value	HR (95% CI)
Age ≥ 40 y[a]	.052	.971	1.01 (0.49-2.12)	**.008**[c]	.310	1.45 (0.71-2.95)
ECOG PS ≥ 2	**.013**[c]	.076	1.96 (0.93-4.00)	**<.001**[c]	**.003**[c]	2.91 (1.45-5.82)
Extracranial PD	.306	**.024**[c]	0.51 (0.28-0.91)	.261	.126	0.61 (0.33-1.15
TNBC	**<.001**[c]	**.003**[c]	2.98 (1.44-6.18)	**.026**[c]	.198	1.53 (0.79-2.94)
Isolated CNS	.977	**.048**[c]	1.85 (1.01-3.39)	.813	.539	1.23 (0.64-2.36)
Anti-HER2 (n = 22)[b]	**.006**[c]	**.005**[c]	0.15 (0.04-0.57)	.643	.661	0.80 (0.29-2.17)

Abbreviations: CI = confidence interval; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; OS = overall survival; PD = progressive disease; TNBC =triple negative breast cancer; VPS = ventriculoperitoneal shunt.
[a]Comparison of patients < 40 and ≥ 40 years.
[b]Anti-HER2 treatment after CNS metastasis.
[c]Bold *P* value indicates statistical significance at the $P < .05$ level.

median OS_{VPS} was 2.2 months (95% CI, 1.7-2.7 months) for $HER2^-$ groups and 2.7 months (95% CI, 1.8-3.6 months) for $HER2^+$ groups ($P = .917$) (Figure 2B).

The median time to disease progression from primary BC to death based on subtype was investigated in the study cohort (Figure 3). The time from primary BC to LM was significantly longer in patients with HR^+ BC. Kaplan-Meier survival curves from primary cancer to death and from metastatic cancer to death based on subtype are shown in Supplemental Figures 1 to 4 (in the online version).

In univariate analysis using a Cox proportional hazards regression model, patients with TNBC with ECOG PS ≥ 2 had worse OS_{CNS} and OS_{VPS}. In multivariate analysis, progression of extracranial disease, TNBC subtype, isolated CNS metastasis, and anti-HER2 therapy in patients with $HER2^+$ BC were identified as significant prognostic factors for OS_{CNS} (Table 5).

Discussion

We previously investigated the clinical features of breast cancer with LM based on subtype, and the median survival duration from LM to death was 4.5 months.[20] In the current study, OS_{CNS} was 7.6 months in patients with MBC with LM who underwent VPS placement. This finding is an encouraging clinical outcome with respect to VPS placement for patients with LM. We show that median OS_{CNS} was 16.2 months in patients with $HR^-/HER2^+$ BC and 5.2 months in patients with TNBC. In our previous report regarding patients with $HER2^+$ BC, a median survival of 14.9 months was observed with anti-HER2 treatment[4]; in several retrospective analyses, up to 23 months of survival after CNS metastasis in $HER2^+$ BC was reported.[8,21] A similarly poor prognosis was reported for patients with TNBC, with a median OS_{CNS} ranging from 2.9 to 4.9 months.[5,22-24]

Patients with TNBC have worse outcomes in both OS_{CNS} and OS_{VPS}, even though 44% of patients with TNBC received intrathecal chemotherapy (see Supplemental Table 1 in the online version). In sharp contrast to patients with TNBC, patients with $HER2^+$ BC had significantly longer survival after CNS metastasis (16.2 vs. 5.2 months) (see Supplemental Figure 3 in the online version). Specifically, patients in the $HR^-/HER2^+$ group showed early BM and substantial survival from BM to LM. In several studies, improvement of brain metastasis in patients with $HER2^+$ BC treated with trastuzumab was reported, although the drug does not cross the blood-brain barrier.[4,25,26] The combination of lapatinib with capecitabine showed a response in brain metastasis in patients with $HER2^+$ MBC.[27-29] In the current study, patients with $HER2^+$ BC were more likely to receive chemotherapy with anti-HER2 therapy than to receive anti-HER2 therapy alone. Active and intensive treatment should be provided to patients with $HER2^+$ BC with CNS metastasis even if the aggressive nature of $HER2^+$ BC results in a higher incidence of CNS metastasis.

Despite advances in survival after brain metastasis, the prognosis is grave for patients with BC with LM, with a median survival of less than 6 months.[20] In particular, patients in the TNBC group showed early LM, shorter survival, and notable isolated CNS metastasis in the current study. VPS treatment could prolong the survival of patients with BC with CNS metastasis; however, the OS_{VPS} was less than 3 months in the current study. Notably, the 6-month OS rate was 0% and 3.9% in the $HR^-/HER2^+$ and TNBC groups, respectively (see Supplemental Figure 4 in the online version). No patients in the $HR^-/HER2^+$ group received palliative treatment (chemotherapy or WBRT) after VPS, and less than 15% of patients in the TNBC group were treated with chemotherapy or WBRT after VPS. The worse survival and less treatment after VPS in the HR^- groups could have resulted from aggressive tumor behavior, patient selection, and timing of VPS placement, which remain unsolved problems regardless of subtype. Hence, further studies are necessary to determine whether VPS is appropriate only for patients with increased ICP, for patients with LM, or for certain subgroups such as TNBC.

Treatment effects of VPS insertion might be heterogeneous across intrinsic subtypes, because the patients received different palliative therapies before VPS insertion. However, the heterogeneity of treatments before VPS also is owing to the relatively rare presentation of LM. Research on LM with VPS is difficult owing to the limited availability of cases. In addition, selection bias could exist because only patients who could tolerate VPS surgery with general anesthesia were included in the current study. To the best of our knowledge, this is the first study to analyze the clinical outcomes of patients with BC who received a VPS. Our results show the real-world treatment patterns and outcomes of patients with BC who were diagnosed with LM and received a VPS.

Survival of patients with MBC who underwent VPS insertion differed based on intrinsic subtype; anti-HER2 treatment in $HER2^+$ tumors was significantly correlated with better survival, and TNBC had significantly worse outcomes. Based on the study results, the use of VPS in patients with MBC with LM remains debatable; thus, further studies are warranted and should include a case-control study to compare patients with LM with and without VPS in MBC.

Clinical Practice Points

- Although MBC is commonly associated with LM, little is known about the clinical utility and value of VPS in patients with MBC with LM.
- Our study aimed to investigate the real-world treatment patterns and outcomes of patients with BC who were diagnosed with LM and received a VPS.
- We found that most common indications for VPS were uncontrolled ICP (57.1%) and uncontrolled headache (55.7%), which were improved after VPS in 77.1% of the patients.
- The median OS after BM or LM (OS_{CNS}) was 7.6 months, and the median overall survival after VPS (OS_{VPS}) was 2.3 months.
- The prognosis of patients with MBC with VPS is worse in the TNBC subtype, and anti-HER2 treatment was identified as a significant prognostic factor for better OS after LM.
- Our results might support the use of VPS in symptomatic patients with MBC with LM.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures and tables this article can be found in the online version at https://doi.org/10.1016/j.clbc.2020.12.013.

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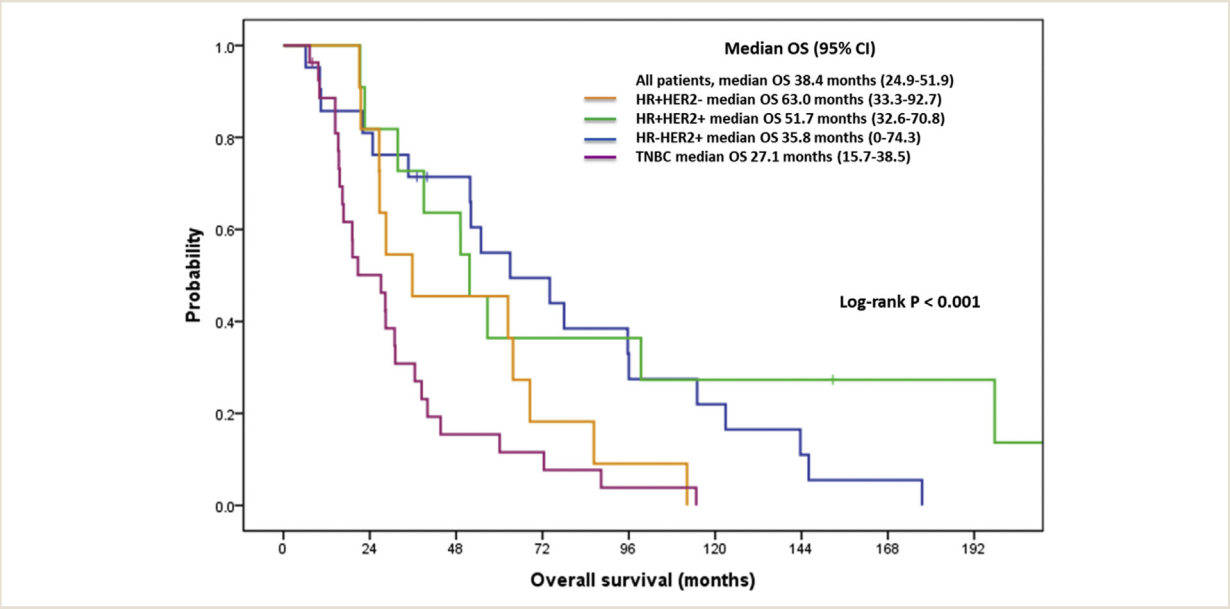
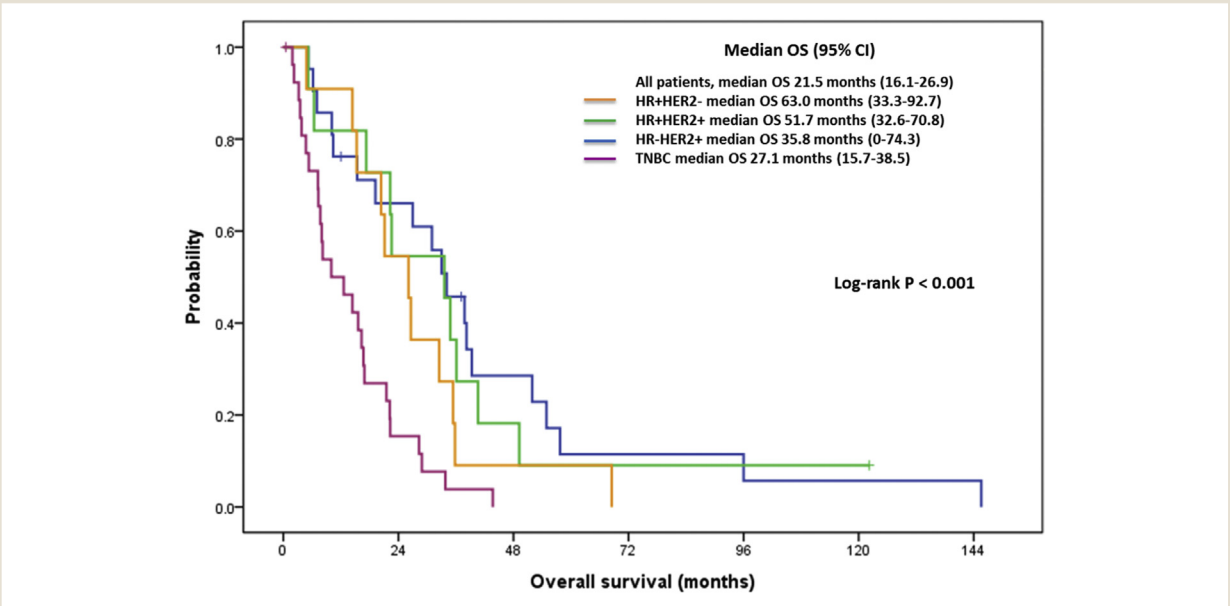
Supplemental Figure 1 Overall Survival Based on Subtype From Primary Cancer to Death



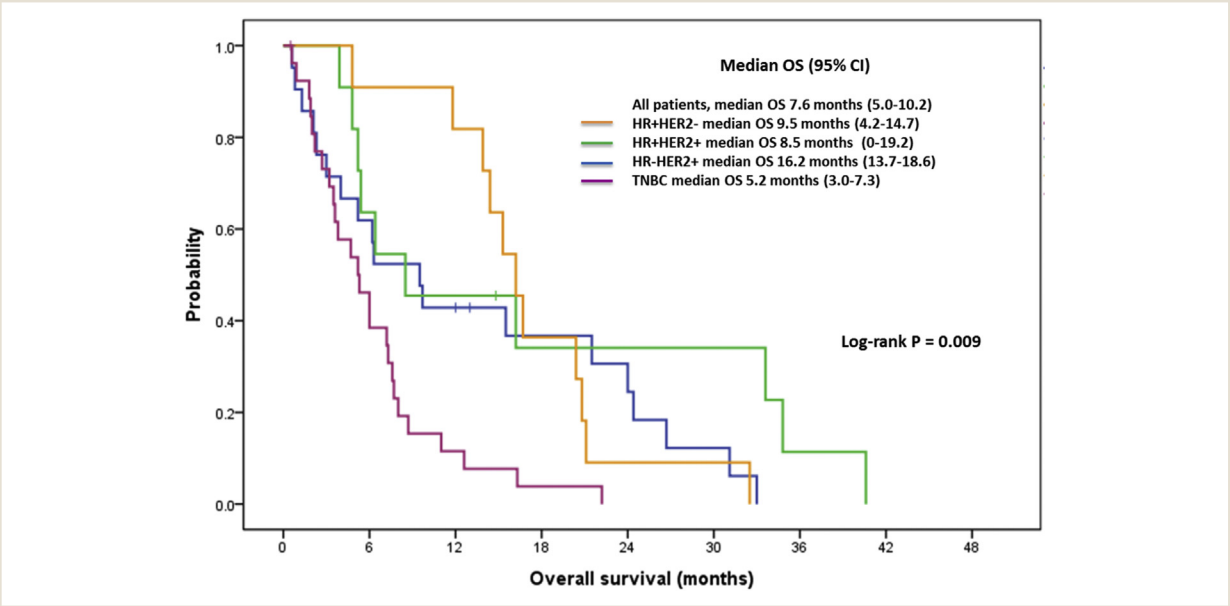
Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OS = overall survival; TNBC = triple negative breast cancer.

Supplemental Figure 2 Overall Survival Based on Subtype From Metastatic Breast Cancer to Death



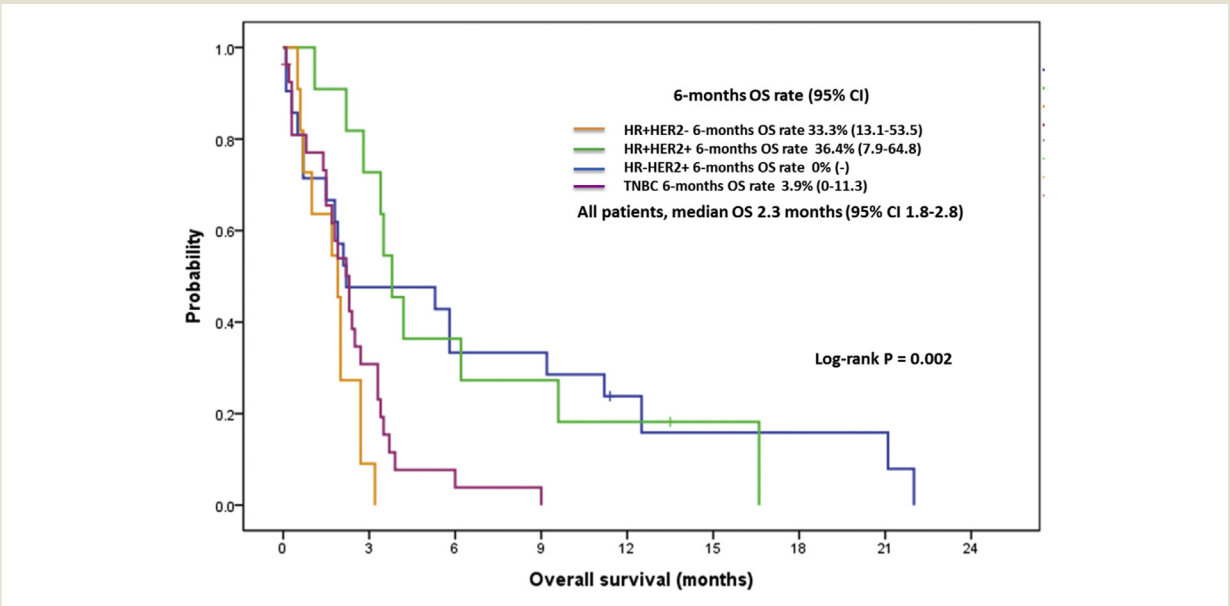
Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OS = overall survival; TNBC = triple negative breast cancer.

Supplemental Figure 3 Overall Survival Based on Subtype From CNS Metastasis to Death



Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OS = overall survival; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt.

Supplemental Figure 4 Overall Survival Based on Subtype From VPS to Death



Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OS = overall survival; TNBC = triple negative breast cancer.

Supplemental Table 1 The Regimens of Palliative Chemotherapy After CNS Metastasis

	All Patients (n = 70)	$HR^+/HER2^-$ (n = 21)	$HR^+/HER2^+$ (n = 11)	$HR^-/HER2^+$ (n = 11)	TNBC (n = 27)
Intrathecal methotrexate[a]	29	9	1	7	12
Intrathecal trastuzumab	0	–	0	0	–
Tamoxifen	2	2	0	–	–
Letrozole	1	1	0	–	–
Fulvestrant with gosereline	1	1	0	–	–
Exemestane with everolimus	1	1	0	–	–
AC	6	3	0	3	0
Gemcitabine with cisplatin	3	1	1	1	
Gemcitabine with vinorelbine	1	0	0	0	1
Paclitaxel with carboplatin	1	0	0	0	1
Paclitaxel monotherapy	3	2	0	1	0
Vinorelbine with cisplatin	1	1	0	0	0
Vinorelbine with 5-FU	1	0	1	0	0
Capecitabine monotherapy	6	4	0	0	2
Eribulin monotherapy	1	1	0	0	0
Trastuzumab with chemotherapy[b]	4	–	1	3	–
Trastuzumab monotherapy	1	–	1	0	–
Lapatinib with capecitabine	3	–	2	1	–
Lapatinib with vinorelbine	1	–	1	0	–

Abbreviations: AC = doxorubicin with cyclophosphamide; CNS = central nervous system; 5-FU = 5-fluorouracil; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer
[a]Intrathecal methotrexate was the only regimen used in this cohort.
[b]Combined chemotherapy with trastuzumab were 2 docetaxel, 1 vinorelbine, 1 paclitaxel.

Supplemental Table 2 The Frequency of Intrathecal Chemotherapy According to Intrinsic Subtypes

Subtype	IT-MTX(+) → VPS	IT-MTX(−) → VPS	*P* Value
$HR^+/HER2^-$	9 (31.0)	12 (29.3)	.069
$HR^+/HER2^+$	1 (3.4)	10 (24.4)	
$HR^-/HER2^+$	7 (24.1)	4 (9.8)	
TNBC	12 (41.4)	15 (36.6)	
Total	29	41	

Data presented as n (%).
Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IT-MTX = intrathecal methotrexate; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt.

Supplemental Table 3 Summary of 13 Patients Who Received Chemotherapy After VPS Insertion

	Gender/Age	Subtype	Chemotherapy After VPS	Time to Death From VPS, mos	Survival Status
Patient 1	F/61	$HR^+/HER2^-$	Capecitabine	9.2	Death
Patient 2	F/49	$HR^+/HER2^-$	Capecitabine	22.0	Death
Patient 3	F/40	$HR^+/HER2^-$	Capecitabine	12.5	Death
Patient 4	F/35	$HR^+/HER2^-$	Docetaxel → GP	11.4	Alive
Patient 5	F/54	$HR^+/HER2^-$	Letrozole	5.8	Death
Patient 6	F/66	$HR^+/HER2^-$	Capecitabine	11.4	Alive
Patient 7	F/41	$HR^+/HER2^+$	Docetaxel with herceptin	13.5	Alive
Patient 8	F/41	$HR^+/HER2^+$	AC	6.2	Death
Patient 9	F/46	$HR^+/HER2^+$	GP → capecitabine	16.6	Death
Patient 10	F/38	$HR^+/HER2^+$	Letrozole	9.6	Death
Patient 11	F/35	TNBC	Pactliaxel → GP	3.5	Death
Patient 12	F/47	TNBC	Capecitabine	2.3	Death
Patient 13	F/31	TNBC	AC → paclitaxel/carboplatin	6.0	Death

Abbreviations: AC = doxorubicin with cyclophosphamide; BC = breast cancer; F = female; GP = gemcitabine with cisplatin; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer; VPS = ventriculoperitoneal shunt.