Treatment and prognosis of leptomeningeal disease secondary to metastatic breast cancer: A single-centre experience

Belinda Kingston, Hamzeh Kayhanian, Chloe Brooks, Nicola Cox, Narda Chaabouni, Stefania Redana, Eleftheria Kalaitzaki, Ian Smith, Mary O'Brien, Stephen Johnston, Marina Parton, Jill Noble, Susie Stanway, Alistair Ring, Nicholas Turner and Alicia Okines
The Royal Marsden NHS Foundation Trust, London and Surrey

Corresponding author:

Dr Alicia Okines
The Royal Marsden NHS Foundation Trust
Fulham Road,
London.
SW3 6JJ
Tel: 0207 8118100
Fax 0207 8118197
Email: Alicia.Okines@rmh.nhs.uk

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Abstract

Purpose

Leptomeningeal disease (LMD) is an uncommon complication of advanced breast cancer. The prognosis is poor, and although radiotherapy (RT), systemic and intra-thecal (IT) chemotherapy are accepted treatment modalities, efficacy data are limited. This study was designed to evaluate potential predictors of survival in this patient group.

Methods

Breast cancer patients with LMD diagnosed by MRI in a 10-year period (2004-2014) were identified from electronic patient records. PFS and OS estimates were calculated using Kaplan-Meier method, with planned sub-group analysis by treatment modality. Cox regression was employed to identify significant prognostic variables.

Results

We identified 182 eligible patients; all female, median age at LMD diagnosis 52.5 years (range 23-80). Ninety patients (49.5%) were ER positive/HER2 negative; 48 (26.4%) were HER2 positive, and 27 (14.8%) were triple negative. HER2 status was unknown in 17 (9.3%). Initial management of LMD was most commonly whole or partial brain RT in 62 (34.1%), systemic therapy in 45 (24.7%) or supportive care alone in 37 (20.3%). Fourteen patients (7.7%) underwent IT chemotherapy, of whom two also received IT trastuzumab.

From diagnosis of LMD, the median PFS was 3.9 months (95%CI 3.2-5.0) and median OS was 5.4 months (95%CI 4.2-6.6). Patients treated with systemic therapy had the longest OS (median 8.8 months, 95%CI 5.5-11.1), compared to RT; 6.1 months (95%CI 4.2-7.9 months), IT therapy; 2.9 months (95%CI 1.2-5.8) and supportive care; 1.7 months (95%CI 0.9-3.0). On multivariable analysis, triple negative histology, concomitant brain metastases, and LMD involving both the brain and spinal cord were associated with poor OS.

Conclusions

Breast cancer patients with triple negative LMD, concomitant brain metastases or LMD affecting both the spine and brain have the poorest prognosis. Clinical trials to identify more effective treatments for these patients are urgently needed.

Keywords

Breast cancer, leptomeningeal disease, presentation, survival, prognostic factors

Introduction

Metastatic cancer affecting the meninges, or leptomeningeal disease (LMD), is an uncommon complication of advanced breast cancer (ABC). Previously estimated to occur in 5% of ABC patients[1], the prevalence is thought to be increasing due to increased diagnostic accuracy and longer survival in breast cancer. Usually this is a late complication of ABC, but rarely it can be a presenting feature[2,3]. Symptoms of LMD vary according to the affected site, for example motor or sensory symptoms may occur from LMD affecting the meninges around the spinal cord or cauda equina, and headache, nausea and seizures can occur secondary to raised intracranial pressure from obstructive hydrocephalus. Diagnosis is normally made by MRI scan with gadolinium contrast, sometimes confirmed by cytological evaluation of cerebro-spinal fluid (CSF). As the sensitivity of CSF cytology is low[4], CSF examination for other biochemical markers such as CA15-3 have been investigated[5], but have not reached routine clinical practice. The mechanism of LMD development is not well understood, but it appears to occur via direct extension through the dura from spinal or skull bony metastases in most patients[6], and via haematogenous spread, sometimes in association with parenchymal brain metastases in others. The optimal management strategy for LMD remains unclear, and may differ according to the affected site, extent of disease and resulting symptoms.

Triple negative disease and HER2 positive disease are associated with a higher risk of developing parenchymal brain metastases than luminal breast cancer[7], but the risk factors for developing LMD are less clearly defined. An Italian cohort study identified both ER negative and HER2 positive as risk factors for developing LMD, as well as grade 3 tumours, young age, primary tumours >15mm and the involvement of 3 or more lymph nodes at breast cancer diagnosis [8]. Other retrospective studies have noted over representation of triple negative breast cancer and lobular histology [9–11].

Our study aimed to determine whether clinical outcomes from LMD varied with differing management strategies and to detect prognostic factors by studying the demographics and survival of all patients diagnosed with LMD within one UK breast oncology unit over a 10-year period. Identifying those at higher risk of developing the disease may then highlight areas for further research and direct future clinical trials.

Methods

Study Population

The study population included patients with a diagnosis of breast cancer and LMD treated at The Royal Marsden Hospital. Eligible patients were identified by searching reports from all MRI scans performed on breast cancer patients between January 2004 and January 2014 for the term “meningeal”. All MRI reports were verified by a Consultant Radiologist. MRI reports were manually checked for positive findings which were subsequently crosschecked against the notes for a clinical diagnosis. Those with suggestive radiological imaging and a clinical diagnosis of LMD were the included in the study. Due to the low sensitivity of CSF examination[12], this was not required to

make the diagnosis. The results were cross-checked with pharmacy records of breast cancer patients treated with intrathecal (IT) chemotherapy or trastuzumab.
Hormone receptor positive was defined as an oestrogen and/or progesterone receptor Allred score of 3/8 or greater. HER2 positive was defined as HER2 3+ positive by IHC, or an in situ hybridisation (ISH) ratio >2.0, or an absolute HER2 copy number of ≥ 6 also defined HER2 positivity regardless of ratio, as per ASCO/CAP guidelines[13].

Data Collection

The electronic patient record (EPR) was scrutinised for patient demographics; dates of diagnosis of early breast cancer, metastatic cancer, and LMD; grade of initial breast cancer, hormone and HER2 receptor status; sites of metastatic disease; sites of LMD (brain, spinal or both); symptoms at presentation of LMD; presence or absence of concomitant brain metastases, presence of skull bone or spinal metastasis; CSF cytology, protein and glucose findings; initial and subsequent management (palliative, systemic therapy, intrathecal (IT) chemotherapy, radiotherapy) of the LMD; outcome of treatment; date of death or last follow up.

Statistical Analysis

The primary endpoint of the study was the overall survival (OS) from date of diagnosis of LMD, to date of death from any cause, according to treatment received (radiotherapy, intrathecal treatment, systemic treatment versus supportive care only).

Secondary endpoints comprised of progression-free survival (PFS) from LMD diagnosis (date of diagnosis of LMD to date of imaging, clinical or CSF progression or death) by treatment modality; the frequency of different sub-types of breast cancer in patients with LMD; the proportion of patients who have prior or synchronous parenchymal brain metastasis at time of diagnosis of LMD; the proportion of patients who had skull bone or spinal bony disease prior to diagnosis of LMD; Response rate to treatment received as determined by change from CSF positive to negative cytology and/or resolution of leptomeningeal enhancement on MRI and/or resolution of neurological signs; and to determine whether any demographics or tumour characteristics predict survival from LMD.

Data were analysed using means and percentages for demographic data, clinico-pathological features, disease sites, symptoms, management, and response rate. PFS and OS estimates were calculated using Kaplan-Meier method, with planned sub-group analysis by treatment modality. Cox regression was employed to identify significant prognostic variables. P values of less than 0.05 were considered significant.

Results

Patients

We identified 182 eligible patients over the 10-year period: baseline characteristics are summarised in Table 1. The mean age at diagnosis of breast cancer was 47.7 years (range 19-75); younger than the average age of breast cancer diagnosis in the UK of 64 years[14]. Hormone receptor positive (HR+) and HER2 negative tumours were the largest sub-group (49.5%). Triple negative disease accounted for 14.8% of cases. HER2 positive disease was marginally more common in our LMD cohort (26%) than expected in the overall breast cancer population, estimated at around 10-15% [15] and HER2 status was unknown in a further 9.3%. Over half of patients (55.0%) had grade 3 primary tumours.

A third of the patients presented with multiple symptoms (59 patients, 32.4%). The most frequent solitary presenting symptoms were headache (40 patients, 22%) and cranial nerve palsy (17 patients, 9.2%).

At diagnosis of LMD, the majority of patients (73.6%) had concomitant skull bone or spinal bone disease, and 50% had pre-existing or concomitant intra-parenchymal brain disease. Interestingly, 13% had neither bone nor parenchymal brain metastases. Of this subgroup of patients, 35% had triple negative breast cancer, and 70% had grade 3 breast cancer at the time of diagnosis.

Few patients (n=19) underwent lumbar puncture for cytological confirmation, of whom 10 (52.6%) had positive cytology.

Treatment of LMD

The initial management strategy varied across this cohort of patients (summarised in Table 2). Treatment strategy was dependent on the patient's symptoms, performance status, systemic disease control, and patient and physician choice. The most frequent initial treatment for LMD was whole or partial brain radiotherapy (62 patients, 34.1%). One third of the patients who received RT as treatment for LMD also continued to receive their prior systemic therapy with chemotherapy (25), trastuzumab (3), or endocrine therapy (2).

Systemic chemotherapy was given as the initial treatment for LMD in 45 patients (24.7%), with a median of 4 cycles. The commonest therapy was capecitabine (21 patients, 46.7% of all patients receiving systemic therapy). Other systemic therapies included platinum salts (15.6%), taxanes (13.3%) anthracyclines (6.7%), T-DM1 (2.2%), eribulin (2.2%), vinorelbine (2.2%), and hormonal agents (6.7%). Six of the 21 patients receiving capecitabine additionally received targeted anti-HER2 therapy with lapatinib (5) or trastuzumab (1).

A supportive (palliative) care strategy was adopted in 44 patients (20.3%) for the LMD. Of these patients, 6 patients (13.6%) continued capecitabine (3) or hormonal therapy (3) for clinical benefit at other disease sites. Eight patients later underwent subsequent active treatment with chemotherapy (3 patients, 6.8%), or radiotherapy (5 patients, 9.1%).

Of the 14 patients receiving intrathecal chemotherapy as their first line treatment after diagnosis of LMD, 7 received IT methotrexate monotherapy (12.5mg weekly), 2 received methotrexate (12.5mg) plus hydrocortisone (12.5mg), 3 received IT methotrexate (12.5mg) combined with cytarabine (50mg) and hydrocortisone (12.5mg) and 2 patients received intrathecal methotrexate (12.5mg) with trastuzumab (test dose 40mg, then 105mg weekly). Four of the 14 patients (28.6%) received concomitant systemic chemotherapy (1 with trastuzumab, 1 with trastuzumab and pertuzumab, 2

with endocrine therapy) and 1 patient received spinal RT (8Gy) whilst awaiting IT treatment. Clinical symptoms improved in 4 of the 14 patients (28.6%) who received intrathecal treatment. Two of these patients showed a concomitant cytological and imaging response in addition to the clinical response.

Survival

The median PFS in all patients was 3.9 months (95% CI 3.2-5.0), median OS 5.4 months (95% CI 4.2-6.6). The longest median PFS and OS were observed in patients selected to receive initial systemic chemotherapy (5.3 and 8.8 months respectively; table 3). Amongst the fourteen patients who received first line IT chemotherapy the median PFS and OS were similar to that for supportive care alone: 2.4 and 2.9 months respectively compared to 1.3 and 1.7 months respectively for supportive care. However, one of the two patients who received IT trastuzumab with methotrexate is still alive and receiving on-going treatment with 3-weekly trastuzumab (21mg) via an Omaya reservoir plus sub-cutaneous trastuzumab more than 2 years after diagnosis of LMD. The second patient who received IT trastuzumab progressed at 4 weeks and died at 8 weeks. Amongst the 12 patients who received IT chemotherapy alone, 4 had symptomatic benefit. Two of these patients survived for 18 and 26 months, respectively. Figure 1 illustrates the PFS and OS by treatment groups.

Prognostic factors

On multivariate analysis, older age at diagnosis of LMD, triple negative sub-type, prior or concomitant brain metastases, presence of brain *and* spinal LMD, and low albumin level at LMD diagnosis were predictive of poorer prognosis (Table 4).

Discussion

We report the treatment and outcomes of 182 breast cancer patients diagnosed with leptomeningeal disease over a 10-year period in one single centre in the United Kingdom. Our study confirms that patients presenting with LMD have a poor prognosis, with a median OS of just 5.4 months (95% C.I 4.3 – 6.6). Our survival results are similar to two large cohort studies reported from centres in the USA, with median OS of 3.5 months and 3.1 months, respectively[16,17]. Intrathecal treatment was uncommon in our study (7.7% of patients), compared to 50% of patients reported in the study from the MD Anderson[17] and 14% of patients in the Memorial Sloan Kettering Cancer Centre study[16], demonstrating the lack of a standard approach for this disease site. Amongst the 14 patients in our study treated with IT therapy, the outcome was poor, with a median OS of just 2.9 months (95% C.I. 1.2-5.8), similar to that with palliative care alone (1.7 months (95% CI 0.9-3.0)). There are few randomised studies of IT treatment in LMD in any cancer type[18], and the single randomised trial in breast cancer assessed IT methotrexate monotherapy[19], with systemic chemotherapy and radiotherapy permitted in both arms. No benefit was reported from the addition of IT methotrexate to standard treatment in 35 randomised patients; median OS was numerically shorter in patients randomised to IT chemotherapy (median 18.3 compared to 30.3 weeks), but the

study was underpowered to detect a difference (p=0.32). It is notable that we had one HER2 positive patient who received IT methotrexate with trastuzumab who is still alive and has been free of symptoms for more than 2 years post LMD diagnosis[20]. The use of intrathecal trastuzumab has been reported in case studies, summarised in a pooled analysis published in 2013[21]. In this series, clinically significant improvement was seen in 68.8% of the 17 patients included, with no reports of serious events in 88.2% of the patients[21]. A prospective trial of IT trastuzumab for carcinomatous meningitis is underway in France (NCT01373710). The study plans to recruit 37 patients and the primary endpoint is to establish the maximum tolerated dose (MTD) of weekly IT trastuzumab. Interestingly, a USA study of IT anti-HER2 monoclonal antibodies will investigate the combination of pertuzumab and trastuzumab, but in patients with asymptomatic/minimally symptomatic brain metastases (NCT 02598427), with the primary endpoints of safety and MTD.

Radiotherapy was the most commonly used treatment, both in our study (43%) and the two USA cohort studies (75% and 64% respectively). We did not compare the survival outcome of the different treatment groups due to the inherent bias in choice of treatment modality, related to disease factors such as the site and bulk of the LMD and other sites of disease requiring treatment (for example patient factors such as patient wishes, symptom severity, co-morbidities, and performance status). There are no clinical trials of radiotherapy for LMD secondary to breast cancer, most likely as this treatment is delivered to symptomatic patients with palliative intent, therefore it would seem unethical to randomise patient to not receive this palliative treatment. A single arm study combining involved-field radiotherapy with intrathecal chemotherapy in patients with LMD from any solid tumour (n=59, of whom 11 had breast cancer) reported an 86.4% response rate and median OS of 6.5 months, but significant toxicity (grade 3-5 in 12 of 59 patients)[22].

Systemic therapy in our study comprised standard breast cancer cytotoxic agents, most commonly capecitabine. Other cytotoxics such as Temozolamide have been investigated for LMD due to known CNS penetration and efficacy in primary brain malignancies[23]; a phase II study of patients with LMD from any solid tumour, which was breast cancer in 53% reported that although the treatment was well-tolerated, clinical benefit was only reported in 3/19 patients (15.8%)[24].The results of small studies of pemetrexed[25] and patupilone[26] have been similarly disappointing. Perhaps more promising, a triplet regimen of cisplatin, etoposide and bevacizumab was investigated in 8 patients with breast cancer LMD and reported objective response in 3 of 5 evaluable patients, median PFS 4.7 months (95% CI 0.3-9 months). However, haematological toxicity and hyponatraemia were common [27]. As such, there is no current indication to deviate from standard breast cancer regimens when treating this site of metastatic disease. Current studies of systemic therapies for breast cancer LMD include a phase II study of high dose ($8g/m^2$) systemic methotrexate (NCT 02422641), a phase I study of intermittent high dose lapatinib with capecitabine (NCT02650752) and a phase II study of the CDK4/6 inhibitor abemaciclib (NCT02308020).

Concordant with previous studies[11,16,17,28], we report that LMD with triple negative histology was associated with poorer prognosis. We have also confirmed previous reports that older age[17], or having both cranial and spinal involvement[16] were independently associated with a poorer prognosis. We have additionally demonstrated that prior or concomitantly diagnosed brain metastases, and low albumin level at LMD diagnosis were also independently associated with poorer prognosis. Good performance status has been previously reported as a positive predictor of

outcome in LMD[4,9,28–30],but we were unable to assess the impact of this parameter in our study due to missing documentation. The use of systemic therapy was also associated with improved outcome in some retrospective studies[9,17,29,30], with independent benefit from IT chemo or RT also reported in one[31].

In conclusion, our study confirms previous reports that LMD carries a poor prognosis in ABC. Triple negative disease, older age, extent of LMD, presence of brain metastases and low albumin were predictors of shorter survival. Patients who received systemic chemotherapy or radiotherapy had a numerically longer median survival than those who received IT chemotherapy or palliative care alone, but the retrospective nature of this study limits the interpretation of these results. Prospective clinical trials, especially in the poor prognosis groups, are urgently needed in order to establish the optimal treatment and improve the outcome for these patients.

Table 1: Patient Characteristics

		Value (%)
Mean age at Breast cancer diagnosis/years (range)		46.7 years (19-75)
Histological subtype	IDC	153 (84.1)
	ILC	18 (9.9)
	Other	3 (1.6)
	Unknown	8 (4.4)
Immunohistochemistry	HR+HER2-	90 (49.5)
	HER2+	48 (26.4)
	Triple Negative	27 (14.8)
	HER2 Unknown	17 (9.3)
Tumour grade of primary breast tumour at diagnosis of early breast cancer	1	1 (0.55)
	2	61 (33.5)
	3	100 (55.0)
	Unknown	20 (11.0)
Skull bone or spinal disease prior or simultaneous to LMD diagnosis?	Yes	134 (73.6)
	No	47 (25.8)
	Unknown	1 (0.5)
Parenchymal brain metastases prior to/at time of LMD diagnosis?	Yes	91 (50.0)
	No	87 (47.8)
	Unknown	4 (2.2)
CSF Cytology	Positive	10 (5.49)
	Negative	9 (4.94)
	Not performed	163 (89.56)
Sites of LMD involvement	Brain	123 (67.6)
	Spine	36 (19.8)
	Brain and Spine	23 (12.6)
Symptoms at diagnosis of LMD	Multiple symptoms	59 (32.4)
	Headache	40 (22.0)
	Cranial Nerve palsy	17 (9.3)
	Pure motor symptoms	14 (7.7)
	Visual Changes	12 (6.6)
	Pure sensory symptoms	11 (6.0)
	Asymptomatic	10 (5.5)
	Nausea	5 (2.8)
	Seizure	5 (2.8)
	Pain	5 (2.8)
	Confusion	2 (1.1)
	Cerebellar Symptoms	1 (0.6)
	Diabetes Insipidus	1 (0.6)

IDC: Invasive ductal cancer; ILD: Invasive lobular cancer; HR+: Hormone receptor positive; HER2+: HER2 receptor positive; HER2-: HER2 receptor negative

Table 2. Initial management of leptomeningeal disease.

Management	**Number (%)**
Whole or partial brain RT	62 (34.1)
Systemic therapy	45 (24.7)
Supportive care	44 (24.2)*
RT to skull base or spine	16 (8.8)
IT chemotherapy	14 (7.7)
Surgery and stereotactic RT	1 (0.55)

*8 of the 44 patients initially receiving supportive care only later received active treatment; RT in 5, systemic chemotherapy in 3.

Table 3. Survival outcomes (median PFS and OS) in all patients and by treatment group.

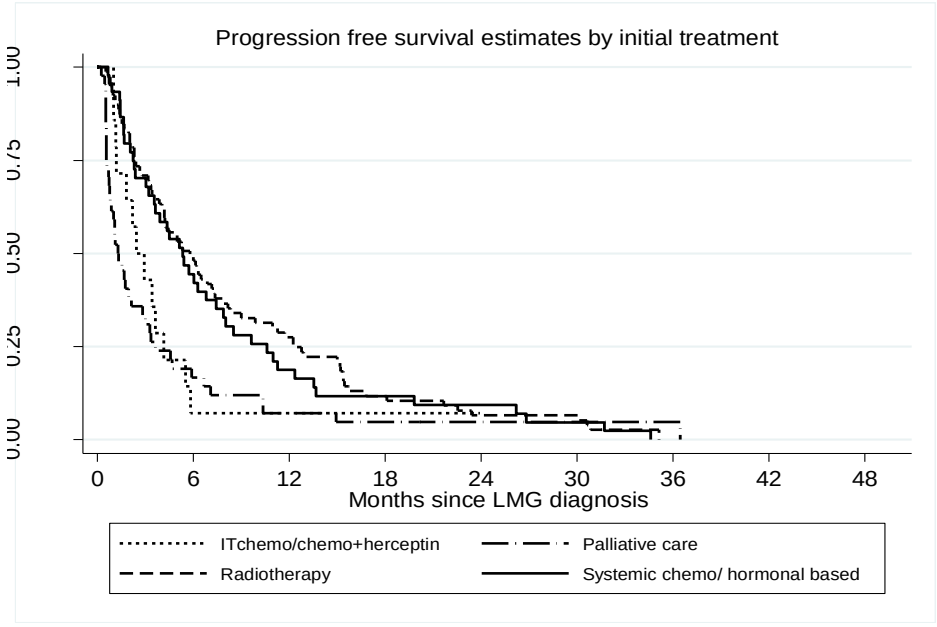
LMD Treatment	**PFS (months) (95% C.I.)**	**OS (months) (95% C.I.)**
Any	3.9 (3.2-5.0)	5.4 (4.2-6.6)
IT chemotherapy	2.4 (1.1-4.1)	2.9 (1.2-5.8)
Supportive Care	1.3 (0.8-2.1)	1.7 (0.9-3.0)
Radiotherapy*	5.8 (4.2-7.3)	6.1 (4.2-7.9)
Systemic therapy	5.3 (3.2-7.4)	8.8 (5.5-11.1)

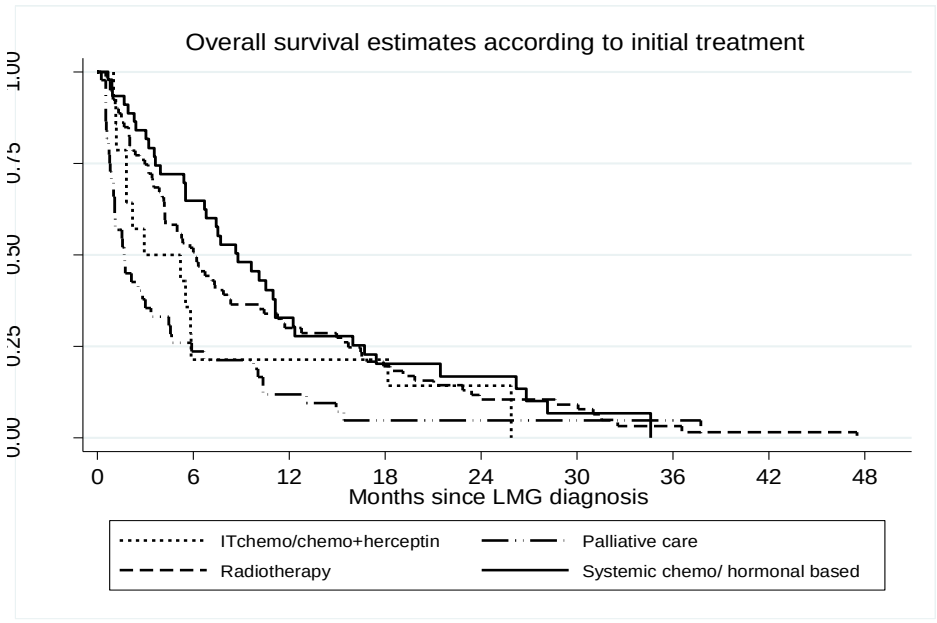
*Whole brain radiotherapy, partial brain radiotherapy, spinal radiotherapy and stereotactic radiotherapy have been combined.

Table 4 Multivariable analysis

Characteristic		Hazard Ratio (95% C.I)	P value
Age at diagnosis	Continuous	1.02 (1.00-1.03)	0.029
Histological Subtype	ER+ HER2-	Reference category	
	ER+ +/- PR+ HER2+	0.82 (0.51-1.33)	
	ER- HER2+	1.61 (0.85-3.04)	
	Triple negative	2.08 (1.24-3.46)	0.007
Concomitant or prior skull bone or spinal metastases	No (reference category)	Reference category	
	Yes	0.85 (0.60-1.20)	0.356
Concomitant or prior brain metastases	No (reference category)	Reference category	
	Yes	1.74 (1.17-2.57)	0.006
Location of LMD	Brain Only	Reference category	
	Both	2.81 (1.65-4.80)	
	Spine only	1.27 (0.81-1.99)	<0.001
Albumin at LMD diagnosis	Continuous	0.97 (0.93-1.0)	0.049

Figure 1.A . Progression-free and B. Overall survival by treatment type





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