



Survival outcomes of surgical resection of metastasis to the breast from extra-mammary malignancies: an individual patient data analysis

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Background: It remains unclear whether surgical resection of in-breast metastasis from extramammary malignancies would improve survival.

Methods: There were 29 cases including 25 cases reported by 24 studies and 4 unreported cases from PUMC Hospital in this individual patient data (IPD) meta-analysis. The clinicopathological characteristics and overall survival (OS) were compared. The subgroup of patients who might potentially benefit from surgical resection of the metastatic lesion to the breast was identified.

Results: The breast symptoms were 22 lumps (75.9%), 4 huge mass (13.8%), 3 inflammatory changes (10.3%), 1 ulceration (3.4%) and 1 non-palpable lesion (3.4%). There were 2 male patients (6.9%) with breast metastasis and 3 female patients (10.3%) with bilateral breast metastasis. The primary malignancy sites included 10 gastrointestinal (34.5%), 7 lung (24.1%), 4 urogenital (13.8%) and 3 trunk and limbs (10.3%). Adenocarcinoma (48.3%) was the commonest pathology. Twelve patients (41.4%) had metastases only to the breast. Seven breast metastases (24.1%) were diagnosed simultaneously with the primary malignancies, and 2 breast metastases (6.9%) were detected before the primary. The 12-month OS rate was 55.2% and the median survival was 5 month (1–60 months). Sixteen patients (55.2%) received surgical resection of the in-breast metastases, and their OS was not significantly different from those biopsy-only patients.

Conclusions: Surgical resection of metastases to the breast from extra-mammary malignancies could achieve similar survival outcome compared to patients who only received core needle biopsy, with potential of improving the quality of life for patients with breast ulceration, huge mass and inflammatory changes.

Keywords: Metastasis to the breast; extra-mammary malignancy; surgical resection; survival outcomes; individualized patient data analysis

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Introduction

Secondary neoplasms of the breast comprised 3% of the breast tumors and the majority were metastases from the contralateral breast (1-3). Non-hematological metastasis to the breast was approximately 0.3–0.4% of contemporary malignant mammary tumors (1,3,4). It remains controversial whether surgical resection of either the primary tumor or the metastatic site would improve patients' survival outcomes. Retrospective and population-based studies had shown that primary surgery would be associated with improved survival in stage IV breast cancer, in asymptomatic colorectal cancer and even in male stage IV breast (5-8). In prospective randomized trials, primary surgery might be beneficial in selective patients with conflicting evidence.

Surgical resection of liver metastatic lesions has been widely accepted for with liver metastases from colorectal cancer and neuro-endocrine tumors (9,10). Hepatic resection for liver metastases from breast cancer before progression of disease even with chemotherapy might result in better outcomes of selected patients or allow time off from systemic chemotherapy (11,12). However, it remains unclear whether the surgical resection of metastasis to the breast from extra-mammary malignancies would improve survival outcome.

Methods

Patients and clinicopathological characteristics

The individual patient data (IPD) meta-analysis was performed according to the method previously reported (13,14). There were 129 abstracts identified during 2009–2016 by searching the PubMed by searching with keywords such as “metastasis to the breast”, “extra-mammary malignancy”, “in breast metastasis”, “secondary neoplasms of the breast” and “extra-mammary cancer metastatic to the breast”. Twenty-one duplicates were excluded after screening by the content of abstracts. Thirty-five irrelevant studies were excluded after eligibility evaluation, and 49 studies without therapeutic or survival information were also excluded. There were 25 cases reported by 24 studies and 4 previously unreported cases from PUMC Hospital (altogether 29 cases) included. The clinicopathological characteristics and overall survival (OS) by 4 and 12 months were compared respectively among all patients and several subgroups of patients. Patients who might potentially benefit from surgical resection of the metastatic lesion to the breast were identified (*Figure 1*).

Statistical analysis

The OS time was defined as the time from the date of diagnosis of breast metastasis from extra-mammary malignancy to death. OS were analyzed by the Kaplan-Meier curve method, and were compared by means of the log rank test for all patients and each subgroup. The significance threshold was set at $P < 0.05$. All analyses were conducted using SPSS software, version 18.0 (SPSS, Inc. Chicago, IL, USA)

Results

Descriptive information of the study cohort

There were 25 cases reported by 24 studies and 4 previously unreported cases from PUMC Hospital (altogether 29 cases) included in this IPD meta-analysis (*Figure 1* and *Table 1*). The breast symptoms included 22 lumps (75.9%), 4 huge mass (13.8%), 3 inflammation (10.3%), 1 ulceration (3.4%) and 1 non-palpable lesion (3.4%). There were 2 male patients (6.9%) with breast metastasis and 3 patients with bilateral breast metastasis (10.3%). The primary malignancies included 10 gastrointestinal tract (34.5%), 7 lung (24.1%), 4 urogenital (13.8%) and 3 trunk and limbs (10.3%) and adenocarcinoma (48.3%) was the commonest primary pathology. There were 12 patients (41.4%) with breast as the only distant metastases. Seven (24.1%) patients' breast metastases were diagnosed simultaneously with the primary malignancies, and 2 (6.9%) breast metastases were detected before the primary. Sixteen patients (55.2%) received surgical resection of the in-breast metastases, including 14 extended lumpectomies, 2 mastectomies and 5 sentinel lymph node biopsies.

Comparison of OS among all patients and subgroups of patients

The 12-month OS rate was 55.2% and the median survival was 5 months (1–60 months). The comparison of OS events by 4, 6, 9 and 12 months among different subgroups of patients showed that the 4-month OS events were different among different pathology of the primary cancer ($P = 0.016$) and between whether there were other extra-mammary metastases ($P = 0.007$) (*Table 2*). Patients with primary adenocarcinoma and with only in-breast metastasis showed less OS events compared to patients with sarcoma, melanoma or other primary cancer pathology and to patients with systemic metastases during the first 4 months

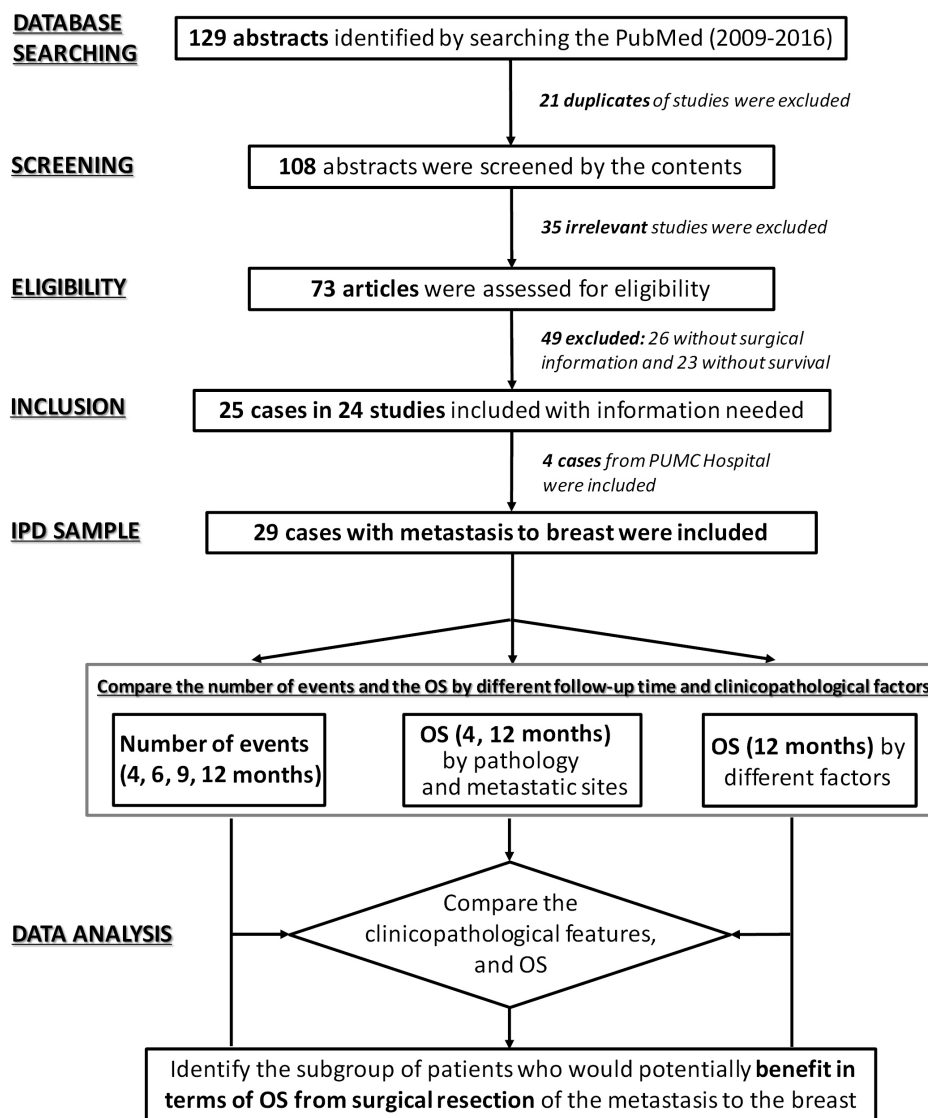


Figure 1 Diagram of the research design. There were 129 research abstracts identified from January, 2009 to October, 2016 by searching the PubMed database with keywords such as “cancer metastasize to the breast”, “malignancy metastasis to the breast” and “metastasis in the breast from extramammary malignancies”, and with the searching of “similar articles” on the PubMed website. Twenty-one duplicates of studies were excluded and the remaining 108 abstracts were screened by the study contents. After another 35 irrelevant studies were excluded, there were 73 articles further assessed for eligibility. Forty-nine studies were excluded including 26 studies without sufficient surgical and other therapeutic information, and 23 studies without survival and follow-up data. The 25 cases reported by the 24 studies with another 4 cases from PUMC Hospital (altogether 29 cases) with sufficient information of surgical treatment and survival were included in this IPD meta-analysis. The OS by different follow-up time (by 4, 6, 9 and 12 months) and clinicopathological factors were compared.

(Figure 2). However, there was no significant difference between these two subgroups of patients if the comparison was performed by 12 months (Figure 2). The comparison of 12-month OS between patients received surgical resection of the in-breast metastatic lesion and those without surgery

showed no significant difference in survival outcomes among all patients and subgroups of patients, regardless of whether the in-breast metastasis was found before or after the primary malignancy, and of whether breast was the only distant metastasis site (Figure 3).

Table 1 Clinicopathological characteristics and survival of the 29 cases with malignancy metastasize to the breast

Case reference	Primary tumor					Breast metastasis					Survival							
	Author and reference	Year	Sex/age	Site	Pathology	Local treatment	systematic treatment	Symptom	Laterality	Multifocal (Y/N/IBC)	Diameter (cm)	Surgery (Y/N)	Breast procedure	Other metastasis (Y/N)	Diagnosis interval (mo)*	Follow-up (mo)	Death (Y/N)	OS (mo)
Jeong YJ <i>et al.</i> (15)	2014	F/47		Lung	Adenocarcinoma	Surgery	NA	Lump	Uni	N	1.3	Y	Lmp+ SLNB	N	36	23	0	23
Yokouchi M <i>et al.</i> (16)	2014	F/66		Dorsum	Liposarcoma	Surgery	No	Lump	Uni	N	3.2	Y	Lmp	N	17	60	0	60
Kharmoum S <i>et al.</i> (17)	2014	F/43		Conjunctiva	Melanoma	No	Chemo	Lump	Uni	N	2.0	Y	Lmp	Y	24	4	1	4
Khalifeh I <i>et al.</i> (18)	2009	F/56		Peritoneum	Serous carcinoma	Surgery	Chemo, endocrine	Inflammatory	Bi	IBC	NA	Y	Bilateral Mx + SLNB	Y	-11	5	0	5
Li J <i>et al.</i> (19)	2011	F/47		Rectum	Adenocarcinoma	Surgery	Chemo	Lump	Uni	N	3	N	CNB	Y	36	4	0	4
Kim SJ <i>et al.</i> (20)	2013	F/41		Stomach	Adenocarcinoma	NA	NA	Inflammatory	Uni	IBC	Whole breast	N	CNB	N	0	5	1	5
Orguç S <i>et al.</i> (21)	2012	F/12		ilium	Ewing sarcoma	NA	Chemo	Lump	Uni	N	3.5	N	CNB	Y	5	2	1	2
Perin T <i>et al.</i> (22)	2011	F/46		Colon	Adenocarcinoma	Surgery	Chemo	Lump	Uni	N	1	Y	Lmp+ SLNB	Y	36	16	1	16
Maounis N <i>et al.</i> (23)	2010	F/73		Lung	Adenocarcinoma	Pleural drainage, pleurodesis	Chemo	Lump	Uni	N	NA	Y	Lmp	N	0	6	1	6
La Rosa S <i>et al.</i> (24)	2015	F/50		Ileum	NET	Surgery	NA	Npbc	Uni	N	0.4	Y	Lmp+ SLNB	Y	56	28	0	28
Wilsher MJ <i>et al.</i> (25)	2012	F/58		Dorsum	Melanoma	Surgery	NA	Lump	Uni	N	NA	Y	Lmp	Y	24	4	1	4
Shen YW <i>et al.</i> (26)	2015	F/52		Lung	Adenocarcinoma	No	Chemo	Inflammatory	Uni	IBC	5.0	Y	CNB	0	0	9	1	9
Solami L <i>et al.</i> (27)	2014	F/44		Kidney	Unknown	No	No	Lump	Uni	N	1.5	Y	Lmp+ SLNB	Y	0	4	1	4
Sibartie S <i>et al.</i> (28)	2011	F/56		Uterus	Sarcoma	Surgery	NA	Lump	Uni	N	NA	Y	Lmp	Y	36	4	1	4
Ho YY <i>et al.</i> (29)	2009	M/50		Colon	Adenocarcinoma	Surgery	Unknown	Lump	Uni	N	1.5	N	CNB	Y	60	12	0	12
Ternier F <i>et al.</i> (30)	2010	F/29		Epencephalon	Medulloblastoma	Surgery, radiation	NA	Lump	Uni	N	NA	N	CNB	Y	60	14	1	14
Aitelhaj M <i>et al.</i> (31)	2014	F/55		Cervix	Squamous carcinoma	Radiation	Chemo	Lump	Uni	N	2.0	Y	Lmp	Y	8	3	1	3
Mirrielees JA <i>et al.</i> (32)	2014	F/67		Lung	Unknown	No	Hospice care	Lump	Uni	N	2.0	N	CNB	Y	0	2	1	2
Mirrielees JA <i>et al.</i> (32)	2014	F/58		Lung	Adenocarcinoma	Surgery, radiation	Chemo	Lump	Uni	N	1.3	N	CNB	N	36	29	1	29

Table 1 (continued)

Table 1 (continued)

Case reference	Primary tumor				Breast metastasis						Survival							
	Author and reference	Year	Sex/age	Site	Pathology	Local treatment	systematic treatment	Symptom	Laterality	Multifocal (Y/N/IBC)	Diameter (cm)	Surgery (Y/N)	Breast procedure	Other metastasis (Y/N)	Diagnosis interval (mo)*	Follow-up (mo)	Death (Y/N)	OS (mo)
Ko K <i>et al.</i> (33)	2012	F/47		Lung	Adenocarcinoma	No	Chemo	Lump	Uni	N	1.0	N	CNB	Y	36	5	0	5
Yu H <i>et al.</i> (34)	2016	F/31		Duodenum	Adenocarcinoma	Surgery	Chemo	Lump	Uni	N	2.5	Y	Lmp	N	18	2	0	2
Wang T <i>et al.</i> (35)	2011	M/38		Rectum	Adenocarcinoma	Surgery	Chemo	Mass	Uni	N	6.2	Y	Mx	N	84	4.8	1	4.8
Makhdoomi R <i>et al.</i> (36)	2013	F/28		Rectum	Adenocarcinoma	NA	NA	Lump	Bi	Y	3.0	N	FNA	N	9	2	0	2
Framarino-del-Malatesta M <i>et al.</i> (37)	2015	F/49		Pleura	Malignant mesothelioma	Unknown	NA	Lump	Uni	N	3.0	N	CNB	N	0	9	0	9
He CL <i>et al.</i> (38)	2015	F/48		Stomach	Adenocarcinoma	No	Chemo	Mass	Uni	N	8.9	N	CNB	N	-1	5	0	5
Zhou YD <i>et al.</i> [§]	2016	F/30		Thymus	NET	Surgery	Chemo	Ulceration	Bi	Y	NA	N	CNB	Y	48	13	1	13
Zhou YD <i>et al.</i> [§]	2016	F/53		Ovary	Papillary serous carcinoma	CRS surgery	Chemo	Lump	Uni	Y	1.0	Y	Lmp	N	0	12	0	12
Zhou YD <i>et al.</i> [§]	2017	F/33		Colon	Adenocarcinoma	Surgery	Chemo	Lump	Uni	N	2.2	Y	Lmp	Y	2	4	1	4
Zhou YD <i>et al.</i> [§]	2017	F/66		Lung	Unknown	No	Chemo	Lump	Uni	Y	2.8	Y	Lmp	Y	21	1	1	1

* , Time interval by month between the diagnosis of primary tumor and of the breast metastasis. Minus time interval indicated metastasis to the breast was diagnosed before primary tumor; § , unpublished cases from the Peking Union Medical College (PUMC) Hospital. Chemo, chemotherapy; NPBC, non-palpable breast cancer; Uni, unilateral; Bi, bilateral; IBC, inflammatory breast cancer; Lmp, lumpectomy; SLNB, sentinel lymph node biopsy; Mx, mastectomy; CNB, core needle biopsy; FNA, fine needle aspiration; OS, overall survival; NA, not available; NET, neuroendocrine tumor.

Table 2 Comparison of the number of OS events by clinicopathological factors of the cases with malignancy metastasize to the breast

Factors	Patients (No.)	Follow up time (months)/number of events (No.)							
		4 m		6 m		9 m		12 m	
		No.	P ^a	No.	P	No.	P	No.	P
Age			0.365		0.328		0.427		0.427
<40	7	2		3		3		3	
40–59	18	5		6		7		7	
≥60	4	2		3		3		3	
Gender									
Male	2	0	0.338	1	0.840	1	0.777	1	0.777
Female	27	9		11		12		12	
Primary tumor location			0.181		0.625		0.581		0.581
Respiratory	7	2		3		4		4	
Digestive	10	1		3		3		3	
Urogenital	4	3		1		3		3	
Trunk & limbs	3	2		1		2		2	
Other	5	1		3		1		1	
Pathology			0.016		0.102		0.098		0.098
Adenocarcinoma	14	1		4		5		5	
Sarcoma	3	2		2		2		2	
Melanoma	2	2		2		2		2	
Other	7	1		1		1		1	
Breast symptoms			NA		0.786		0.546		0.546
Lump	26	9		11		11		11	
Inflammatory	3	0		1		2		2	
Breast laterality			NA		0.372		0.344		0.344
Unilateral	26	9		12		13		13	
Bilateral	3	0		0		0		0	
Breast focality			0.482		0.883		0.756		0.756
Unifocal	21	8		10		10		10	
Multifocal	3	0		1		1		1	
Inflammatory	3	1		1		2		2	
Breast surgery			0.163		0.227		0.377		0.377
No	13	2		3		4		4	
Yes	16	7		9		9		9	
Other metastasis			0.007		0.077		0.154		0.154
No	12	0		3		4		4	
Yes	17	9		9		9		9	
Diagnostic interval			0.568		0.945		0.603		0.603
Breast after primary	20	7		8		8		8	
Simultaneously	7	2		4		5		5	
Breast before primary	2	0		NA		NA		NA	

^a, P values were calculated using log-rank test. Bold type indicates statistical significance. NA, not available.

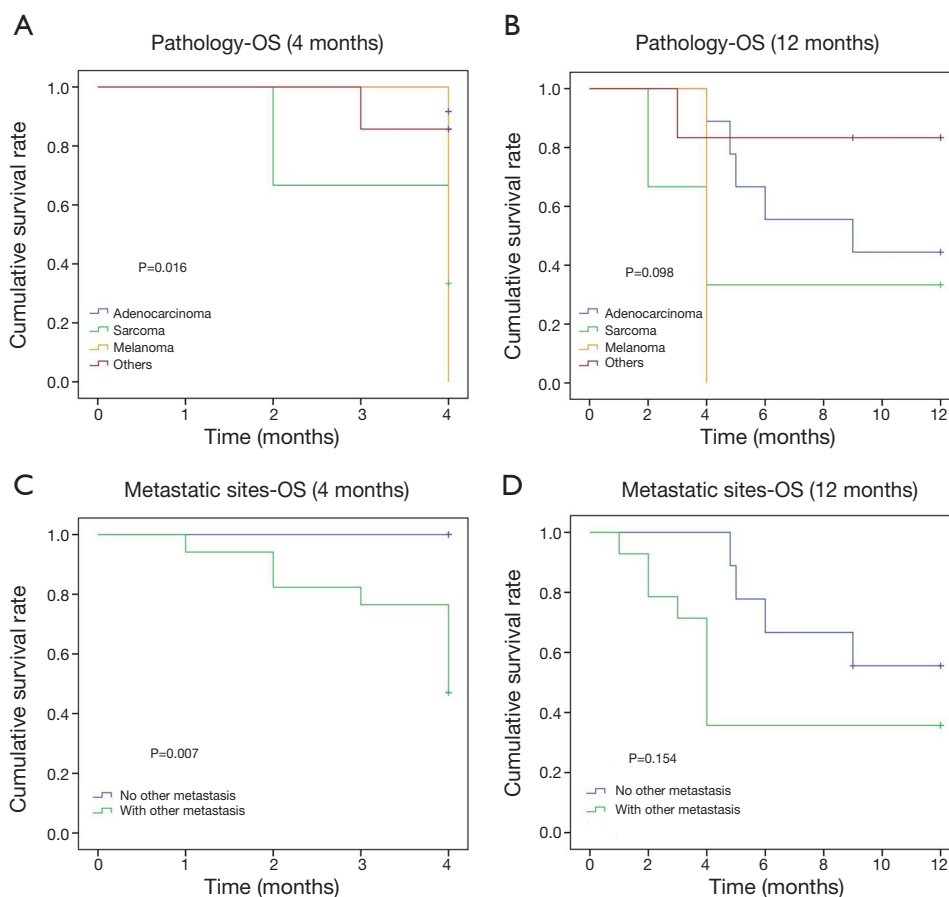


Figure 2 Kaplan-Meier survival curves for the comparison of OS among patients with different pathology of primary cancer and between patients with or without other metastatic sites. (A,B) for comparison of OS by 4- and 12-month follow-up time among patients with different primary cancer pathology; (C,D) for comparison of OS by 4- and 12-month follow-up time among patients with or without other metastatic sites. P values were calculated using log-rank test. OS, overall survival.

Discussion

Extramammary non-hematological metastasis to the breast comprised 0.3–0.4% of malignant breast tumors (1,4). On one hand, surgical resection of primary tumor of metastatic breast cancer is associated with favorable outcomes among selective patients in prospective randomized trials as well as in retrospective and population-based studies (5,7,8). On the other hand, surgical resection of liver, lung and even brain metastatic lesion might also be beneficial in certain primary cancers and in selective patients (9,10,39,40). It remained unclear whether surgical management of in-breast metastasis from extra-mammary malignancies would improve survival outcome.

The commonest primary malignancy site developing in-breast metastases was the gastrointestinal tract (34.5%)

with lung (24.1%) as the second, while the commonest pathology of primary was adenocarcinoma (48.3%). A large series of intramammary metastases of 280 cases from Abbas *et al.* showed that the three commonest primary malignancies as melanoma (17.5%), ovarian carcinoma (14.6%) and lung cancer (14.3%) (3), while another large series of 169 cases from Williams *et al.* showed as skin (39.6%), respiratory (24.3%) and gynecological (14.2%) cancers (41). The metastases to the breast could either be multifocal (10.3%) or be bilateral cancers (10.3%). Interestingly, there were 2 males colorectal cancer patients with metastasis to the breast, which was also reported by Zhou *et al.* and Luo *et al.* (2,42). Because in-breast metastasis might be misdiagnosed with breast cancer especially when it was found before the primary malignancy, as 2 cases (6.9%) were reported in this study and one of them underwent bilateral

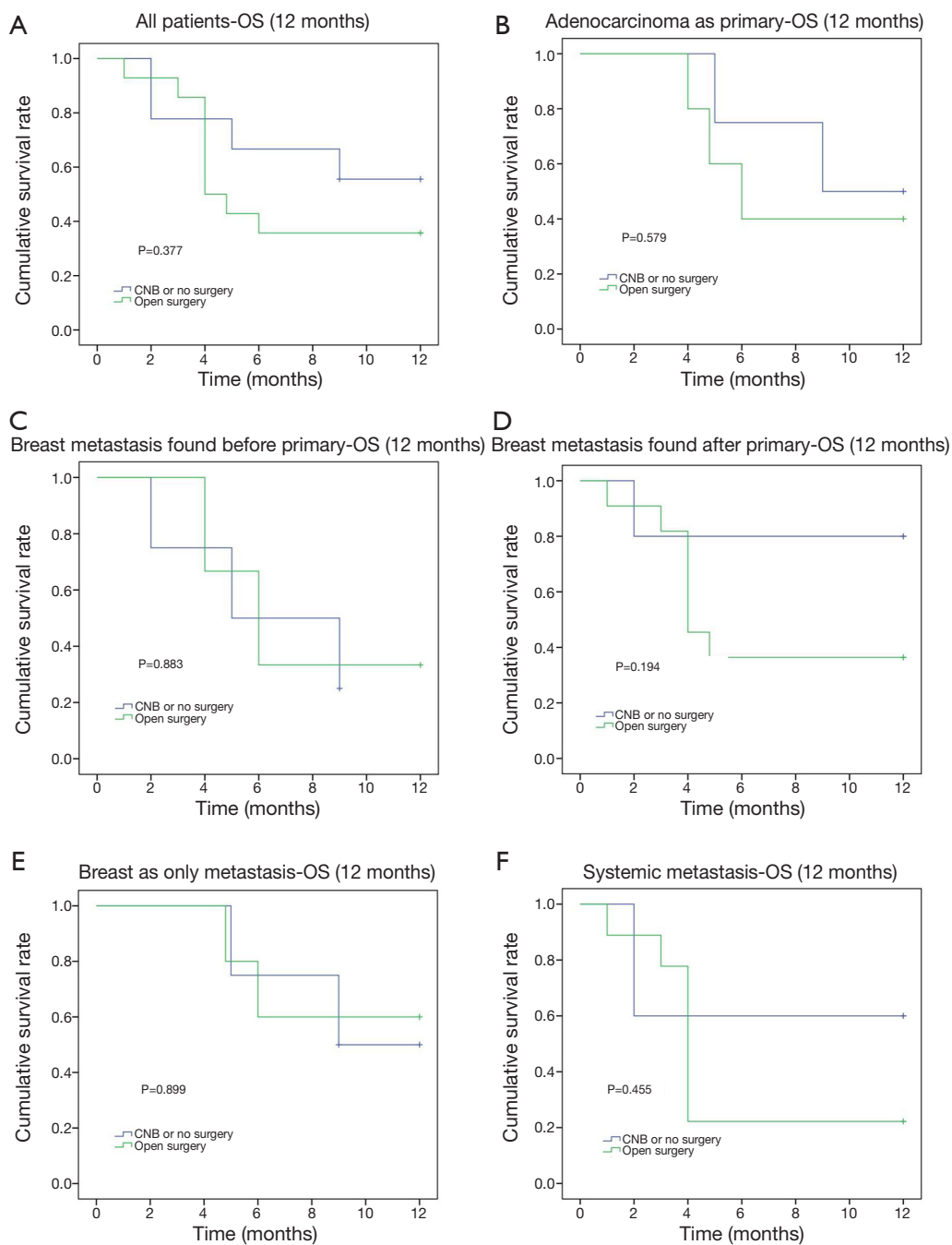


Figure 3 Kaplan-Meier survival curves for comparison of OS between patients received surgical resection of the metastatic tumor in the breast and those without surgery. The comparison was performed in all patients (A); in patients with adenocarcinoma as the primary malignancy (B); in patients whose breast metastasis was found before the primary cancer (C); in patients whose breast metastasis was detected after the primary cancer (D); in patients with metastasis only to the breast (E); and in patients with systemic metastasis other than metastasis in breast (F). P values were calculated using log-rank test. OS, overall survival.

mastectomies + sentinel lymph node biopsies (18,38). In 12–31% of cases metastases to the breast they have been reported as the first finding leading to a diagnosis of an extramammary cancer.

The median OS of metastases to the breast from extramammary solid tumors was 9.2–24 months (2,41,42). Study from Williams *et al.* showed better survival among patients who underwent surgical resection for in-breast metastases (41). In our study the 12-month OS rate was 55.2%, and the median survival was 5 month (1–60 months). In all patients as well as in all subgroups of patients, surgical resection of the metastatic lesion in the breast could achieve similar prognostic outcome in terms of 12-month OS. Considering breast local symptom such as huge mass (13.8%), inflammation (10.3%) and ulceration (3.4%) might compromise the patients' quality of life, surgical management could potentially improve selective patients' quality of life and achieve 12-month OS non-inferior to those patients without surgery.

Our study had several limitations. Firstly, the PubMed database searching might not find all studies suitable for this IPD analysis. Secondly, it was a retrospective IPD study with very limited number of cases and short follow-up time. Since the individual patient's surgical and survival information from large case series was usually unavailable, cases included in this IPD analysis were usually from case reports, resulting in selection bias. Thirdly, patients included in this study were from all over the world thus might be treated quite differently and the OS was acquired from different studies instead of direct follow-up of the patients. Fourthly, also due to the limited number of included cases, Cox analysis could not be performed to identify the OS related prognostic factors.

In conclusion, surgical resection of metastases to the breast from extra-mammary malignancies could achieve similar survival outcome compared to patients who only received core needle biopsy, with potential of improving the quality of life for patients with breast ulceration, huge mass and inflammatory changes.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.08.18>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. Since this is a retrospective study without any intervention or treatment to patients, the Ethics Committee Board just approved it without giving an ID. Informed consent was waived.

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