

Original article

Is there a role for locoregional surgery in stage IV breast cancer?



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ABSTRACT

Current guidelines do not recommend locoregional surgery for Stage IV breast cancer at presentation despite some studies suggesting a survival benefit. We aimed to assess outcomes in patients with Stage IV breast cancer who underwent surgery.

In a cohort study of all Stage IV breast cancers diagnosed at our tertiary-referral specialist centre between 2006 and 2012, we assessed patient survival in the context of demographics, histopathology, metastatic burden, and type of surgery performed.

One hundred and nine patients were included; 52 underwent surgery. Patients in the surgery group had longer 5-year-survival ($p = 0.003$). Survival was also significantly longer in those with just one site of metastatic disease ($p < 0.001$). Patients with axillary cytology positive for regional metastases were less likely to proceed to surgery.

Locoregional surgery does confer a survival advantage in Stage IV breast cancer. Assessment of pre-operative axillary cytology may preclude some patients from proceeding to potentially beneficial locoregional surgery.

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Introduction

Stage IV breast cancer is defined as any breast cancer with distant metastases [1]. Current guidelines do not recommend surgical intervention for Stage IV disease at presentation, instead recommending systemic endocrine or chemotherapy [2]. Surgery can be considered for poorly controlled local disease or fungating tumours. However, some studies have suggested a benefit for local surgery in the presence of metastatic disease.

A number of studies have shown a significantly longer survival for patients with stage IV disease who undergo surgery versus those who don't [3–7]. In some studies, this survival advantage has persisted on multivariate analyses [3], even when corrected for age, comorbidity, tumour grade, histology and metastasis site [4]. Other studies have found the survival benefit only in certain groups; such as those with visceral disease but not bony disease [5] or younger patients and those without comorbidity [8]. Multimodal

locoregional therapy in the form of radiotherapy, surgery or both was also found to be associated with better survival, even on multivariate analysis [9,10].

However, contradictory evidence is also available [11]. In a separate matched pair analysis of Stage IV patients who underwent surgery or no surgery, incorrect classification and frequency of oligometastases was felt to account for most of the apparent benefit of surgery [12]. All of these studies are generally small, cohort studies with multiple confounding factors and published results from a randomised trials to assess surgery in Stage IV disease are awaited [13–15].

Axillary staging techniques have evolved over recent years and the use of axillary fine needle aspiration cytology (FNAC) to identify axillary metastases [16–18] allows earlier staging of patients with distant (Stage IV) disease. FNAC was initially heralded as a diagnostic technique which avoids the need for two axillary surgeries, namely sentinel lymph node biopsy (SLNB) and subsequent axillary lymph node dissection (ALND) [19]. However, since adaptation of the results of the Z0011 trial [20], preoperative FNAC has proved potentially detrimental to patients with low volume axillary disease who are triaged to ALND when SLNB may have

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sufficed [19]. The value of FNAC is now said to be in its ability to triage patients to staging, avoiding surgery in Stage IV disease. However, this is only of value if there is no benefit from surgery in Stage IV disease.

The aim of our study was to assess differences in survival outcomes in patients with Stage IV breast cancer who underwent surgery. We aimed to compare outcomes in those who underwent surgery in the form of sentinel lymph node biopsy (SLNB) versus axillary lymph node dissection (ALND). We also aimed to compare disease burden and outcomes to patients who underwent no surgery at all. Finally, we aimed to assess the impact of axillary ultrasound on predicting Stage IV disease and altering surgical management.

Methods

We performed a retrospective cohort study from a prospectively maintained database. We identified all patients diagnosed with Stage IV breast cancer within three months of their original diagnosis of invasive breast carcinoma between 2006 and 2012 at our tertiary referral centre in the West of Ireland. We collected data regarding patient demographics, radiological and pathological diagnosis, surgery performed, final histopathology, staging results, sites of distant metastases, adjuvant treatments, disease progression or regression and overall survival. If there was doubt about the presence of metastatic disease on original reports, these images were independently re-reviewed by a consultant radiologist.

Patients attending our triple assessment breast cancer clinics routinely undergo clinical examination, mammography, breast and axillary ultrasound and core breast biopsy, and may undergo axillary fine needle aspiration cytology (FNAC) if an abnormal lymph node is detected on ultrasound. Patient results are discussed at multidisciplinary meeting prior to proceeding to surgery or systemic therapy. Patients with normal axillary ultrasounds proceed to SLNB whereas patients with lymph node cytology positive for metastatic disease proceed to ALND. All patients with nodal metastases identified at SLNB or FNAC undergo computed tomography (CT) and isotope bone scanning. National guidelines require surgery (if surgery is the first treatment) to be performed within four weeks

of discussion at multi-disciplinary meeting [21]. Other patients are occasionally diagnosed with metastatic disease first due their presenting symptoms and undergo standard triple assessment after distant imaging.

Collected data was entered into an Excel (Microsoft) spreadsheet and analysed using SPSS Version 22 (IBM). Categorical variables were analysed using Chi-squared test and Fisher's Exact test whereas continuous variables were analysed via *t*-test and ANOVA. Cox multivariate regression survival analysis was performed to assess for factors contributing to survival differences.

Results

A total of 109 patients were diagnosed with Stage IV breast cancer between 2006 and 2012 at our institution. Of these patients, 52 underwent surgery and 57 didn't. The means by which patients were selected to undergo surgery are shown in Fig. 1.

Overall patient characteristics are shown in Table 1.

Patients who underwent surgery were less likely to have bony metastases, had fewer sites of metastases and were less likely to have a positive axillary ultrasound (Table 2).

There was no difference in individual surgeon preference for performing surgery. Patients in the surgery group were shown to have longer overall survival (Fig. 2).

Survival was also significantly longer in those with just one site of metastatic disease ($p < 0.001$), whereas number of individual lesions did not affect survival ($p = 0.352$) (Table 3).

Assessing overall survival further by multivariate Cox regression analysis we found that at 24 months follow-up surgery remained significantly associated with improved survival, as did number of metastatic sites and use of chemotherapy (Table 4).

Positive axillary US was associated with fewer patients undergoing surgery (Table 2). As expected, in those who did advance to surgery, we found that positive axillary ultrasound and FNAC were associated with patients proceeding directly to ALND and bypassing SLNB (Table 5). Positive axillary US was associated with a shorter time to staging scans and a decreased likelihood of proceeding to surgery prior to staging, which approached statistical significance (Table 5).

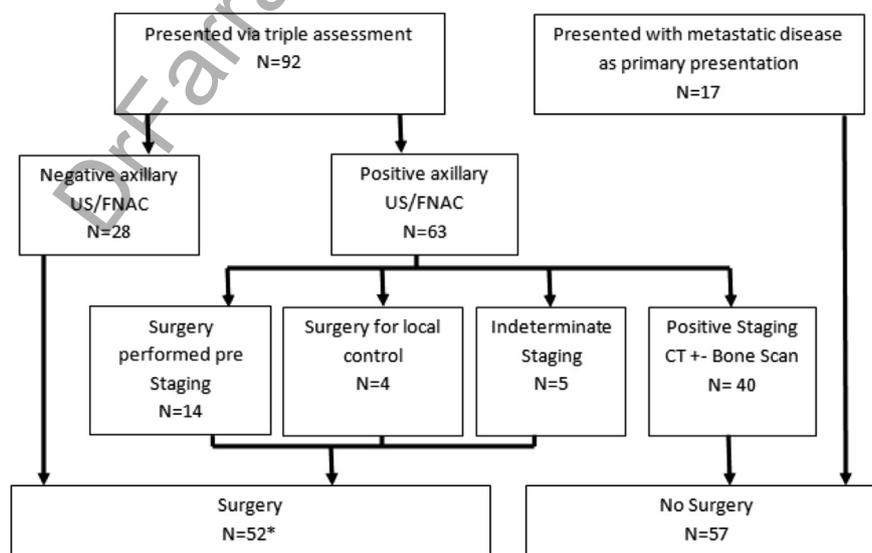


Fig. 1. Means by which 109 Stage IV breast cancer patients were triaged to surgery or no surgery. *Twenty-eight patients proceeded to surgery directly following negative axillary assessment and were only staged following positive SLNB; fourteen patients underwent surgery prior to staging due to delays in accessing imaging within national guidelines for primary breast surgery; five patients initial staging imaging was indeterminate but metastatic disease confirmed on follow-up imaging, four patients required surgery for local control and data regarding preoperative axillary status was not available for one patient.

Table 1

Characteristics of total cohort of 109 patients with Stage IV breast cancer. SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection, Luminal A = ER/PR+ve, HER2/neu–ve, Luminal B = ER/PR+ve, HER2/neu+ve, Triple Negative = ER/PR–ve, HER2/neu–ve. *7 patients who underwent SLNB firstly then proceeded to subsequent ALND. **Mean overall survival calculated at follow-up timepoint of April 2014.

	Number (109)	%
Surgery performed	52	47.7
- SLNB	14	
- ALND*	45	
Chemotherapy	68	62.4
- Neoadjuvant or primary	42	38.5
- Adjuvant	27	24.8
Radiotherapy	64	58.7
- For metastatic disease only	17	15.6
Female gender	107	98.2
Mean age at diagnosis	62.1 years (± 13.1)	
Year of diagnosis:		
- 2006	5	4.6
- 2007	15	13.8
- 2008	14	12.8
- 2009	18	16.5
- 2010	7	6.4
- 2011	27	24.8
- 2012	23	21.1
Mean radiological size	38.7 mm (± 20.8)	
Mean histological size ($n = 52$)	47.9 mm (± 29.1)	
Positive axillary US/FNAC	65	59.6
Bony metastases	73	67
Visceral metastases	66	60.6
Single organ metastases	69	63.3
- Bone only	38	
- Visceral only	31	
Single metastatic lesion	15	13.8
Subtype:		
-Luminal A	63	57.8
- Luminal B	17	15.6
- Triple negative	7	6.4
- ER-ve/HER2+ve	12	11
Mean overall survival**	29.5 months (± 22.1)	

Discussion

We have shown a mean overall survival of 29.5 months for patients with metastatic breast cancer, which is in line with internationally reported data [22]. Our results have shown that there is a survival benefit for patients with Stage IV breast cancer who proceed to surgery. However, the number of metastatic sites also significantly predicts survival, with patients with only one metastatic site having longer survival. In those who do undergo surgery, axillary lymph node dissection does not augment this survival benefit. Finally, positive axillary US selects patients for earlier staging scans, thus reducing the number of patients with Stage IV disease proceeding to potentially beneficial surgery.

Our results mirror results in a number of other cohort studies of surgery in Stage IV disease [3–6] and a recent meta-analysis [7]. Most significantly, our study also shows that number of sites of metastases is a significant predictor of survival. Cady et al. identified 27% of their cohort of Stage IV patients as having oligometastatic disease [12]. Oligometastatic disease refers to a state where only one or more (but usually ≤ 2) organs are involved by a single metastatic lesion [22]. In a case series of oligometastatic disease only, Kobayashi et al. found an overall median survival of 185 months, much longer than would be expected with Stage IV disease [22]. In this series, overall survival was significantly prolonged in patients with single site metastatic disease also [17]. The Cady series found that patients with oligometastatic disease accounted for 26% of their patient cohort who survived more than 5 years; and that oligometastatic disease accounted for the largest proportion of true stage IV 5-year survival [12]. There have been other reports of

Table 2

Comparison of patients who underwent surgery versus those who didn't. Patients who underwent surgery had longer overall mean survival. However, they also had significantly fewer metastatic lesions and fewer sites of metastases.

	Surgery (n, %)	No surgery (n, %)	P
Bony metastases	26 (50.9)	47 (83.9)	0.001
Visceral metastases	29 (55.8)	37 (64.9)	0.555
> 1 metastatic site	10 (19.2)	30 (52.6)	<0.001
> 1 metastatic lesion	39 (75)	55 (96)	0.001
Mean radiological size	37.6 mm	39.7 mm	0.662
Positive axillary US/FNAC	28 (53.8)	37 (64.9)	0.021
Nodes			
- Assessed pathologically	15.8 \pm 7.6	0.3 \pm 0.4	<0.001
- Positive	7.7 \pm 8	0.3 \pm 0.4	<0.001
Surgeon:			
- 1	19	13	
- 2	12	7	
- 3	8	17	
- 4	10	8	
- 5	3	7	0.112
Grade of carcinoma:			
- 2	24 (48)	33 (67)	
- 3	26 (52)	15 (31)	0.068
Subtype:			
- Luminal A	29	34	
- Luminal B	12	5	
- Triple Negative	7	5	
- ER/PR-ve/HER2+ve	2	5	0.207
Mean age at diagnosis	62.2 years	62.1 years	0.953
Surgery pre Staging	42 (80%)	–	–
Mean time to surgery	19 days	–	–
Mean time to CT	21.3 days	11.1 days	0.004
Mean time to bone scan	24.7 days	14.3 days	0.008
Chemotherapy	40 (76.9)	28 (49.1)	0.018
Radiotherapy	33 (63.5)	31 (54.4)	0.680
- To metastases only		17	
Mean survival			
- At 2 years follow-up	22.1 months	16 months	<0.001
- At 5 years follow-up (n52)	35.8 months	20.2 months	0.003

Figures in bold indicate statistical significance.

much longer than expected survival in certain cohorts of patients with metastatic breast cancer [23]. Patients with solitary bone metastases, in particular, have been shown to have longer survival and benefit from early intervention [24]. This suggests that certain patients with an oligometastatic phenotype may benefit from aggressive local therapy. However, it has also been suggested that the survival benefit seen in these patients may actually reflect the indolent nature of their disease rather than any specific treatment intervention [25], a theory which requires further study. Nevertheless, if patients are expected to have a prolonged survival, then local control of their primary tumour is an important component of their management. A recent meta-analysis of surgery in Stage IV disease has suggested an evidence base for primary tumour resection for appropriately selected patients [7]. However, the selection criteria for such patients remains to be identified and the authors were not able to extract enough evidence from the available published data to make firm recommendations.

We have shown no additional benefit for ALND over breast surgery with SLNB alone, although the SLNB only group in our cohort is small. Previous studies have not specifically addressed whether ALND is required to confer a survival advantage. Two previous studies have found similar results to ours, where ALND does not statistically alter patient survival significantly [26,27]. Other studies have not assessed the difference between SLNB alone and ALND in Stage IV disease [4]. As far back as the NSABP-B4 trial comparing radical mastectomy with total mastectomy alone, the survival benefit of ALND in breast cancer treatment has been

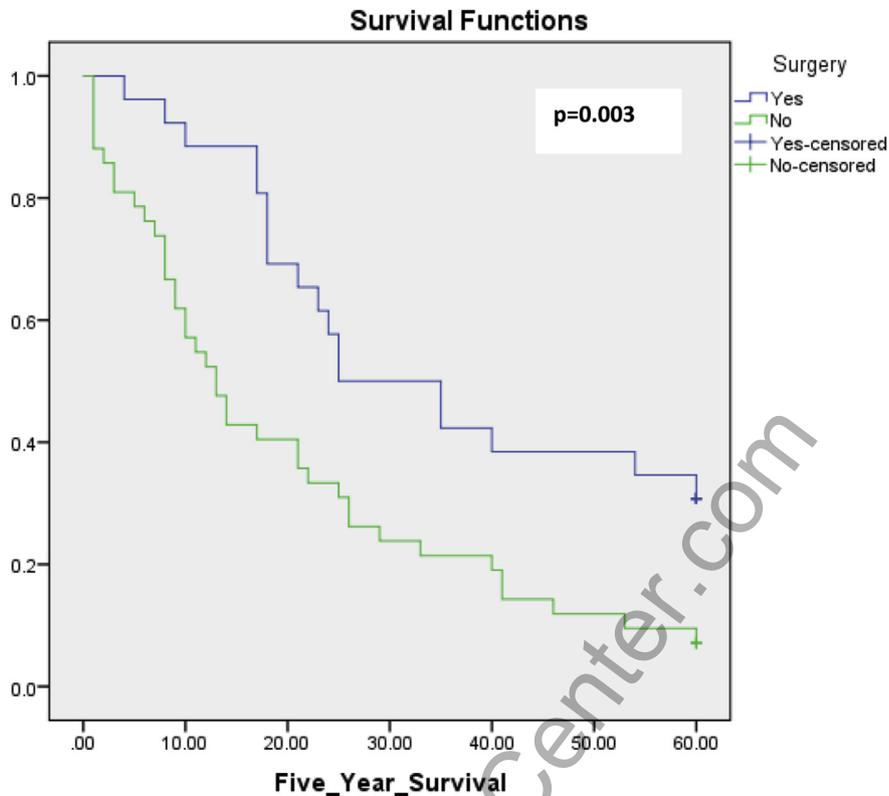


Fig. 2. Five year survival comparison in patients who underwent surgery versus those who didn't ($p = 0.003$).

questioned [28]. In recent years ALND has been omitted in early stage node positive disease in patients undergoing breast conserving therapy, following the Z0011 trial [20]. Certainly, there has been some benefit shown for ALND in patients with a heavier

axillary metastatic burden and no distant disease [29]. However, our data suggests there is no survival benefit for ALND once distant metastases has occurred, although studies with larger numbers are required to confirm this finding.

Table 3

Factors affecting survival in this cohort of patients with Stage IV breast cancer with 3 year ($n = 86$) and 5 year ($n = 52$) follow-up available. Surgery and number of sites of metastases were significantly associated with longer survival at both time points.

Survival	At 3 years follow-up (months)	<i>P</i>	At 5 years follow-up (months)	<i>P</i>
Surgery	28.1		35.8	
No surgery	17.8	<0.001	20.2	0.003
SLNB	21.5		20.2	
ALND	27.3	0.430	34.8	0.363
Chemotherapy	25		31.8	
None	20.1	0.178	21.7	0.120
Radiotherapy	23.5		29.3	
None	19.8	0.240	20.6	0.076
Axillary US				
- Positive	20.1		24.4	
- Negative	28.3	0.022	28.3	0.566
Grade				
- 2	18.8		20.7	
- 3	19	0.971	12.7	0.101
Single site	20.4		33.3	
Multi-site	16	0.001	17.2	0.001
Single lesion	26.7		36.8	
Multiple lesions	21.5	0.251	24.8	0.207
Bony mets	24		24.2	
No bony mets	20.9	0.048	36.2	0.143
Visceral mets	20.9		24.7	
No visceral mets	24.6	0.215	29.4	0.374
ER+ve	21.5		22	
ER-ve	17.4	0.348	18	0.534
HER2/neu+ve	21.1		22.4	
HER2/neu-ve	18.5	0.598	18.9	0.660
Triple negative	19	0.926	20.4	0.984

Figures in bold indicate statistical significance.

Preoperative axillary US combined with FNAC has been shown to be a very useful method of staging the axilla and determining axillary management. It is an excellent way of identifying extensive nodal metastases; a negative axillary US has negative predictive value of 97.7% for excluding N2/N3 disease [16] and a positive axillary US with biopsy has 99.9–100% specificity [17,18]. Preoperative axillary US with selected biopsy will correctly identify approximately 50% of patients with axillary nodal metastases [19], a finding which was replicated in our study here. Axillary US with biopsy can triage patients directly to axillary lymph node dissection, skipping a 2 stage sentinel lymph node procedure [19]. However, axillary US will have relatively less utility in the current climate where surgeons wish to omit ALND for minimal nodal metastases in early breast cancer [19]. Surgeons, who have adapted their practice following the Z0011 trial [20] may find axillary US of

Table 4

Multivariate Cox regression analysis for survival shows that surgery, chemotherapy and number of sites of metastases are independent significant predictors of survival.

	B	SE	Wald	Df	Sig
Surgery	1.094	0.442	6.128	1	0.013
Chemotherapy	0.268	0.126	4.524	1	0.033
Radiotherapy	0.548	0.381	2.074	1	0.150
Bony mets	0.309	0.308	1.009	1	0.315
Visceral mets	-0.303	0.389	0.605	1	0.437
Single site	1.386	0.621	4.991	1	0.025
Single met	-0.888	0.714	1.547	1	0.214
ER + ve	0.888	0.63	1.794	1	0.180
Grade	0.257	0.431	0.354	1	0.552
Phenotype	-0.223	0.283	0.625	1	0.429

Figures in bold indicate statistical significance.

Table 5

Comparison of patients who had a positive axillary US versus those who had a negative axillary US. As expected axillary positivity was associated with patients proceeding directly to ALND and bypassing SLNB. However, axillary positivity also resulted in less patients proceeding to surgery prior to staging and a shorter time delay to staging scans.

	Positive axillary US	Negative axillary US	P
Surgery	28 (40.5%)	14 (56%)	0.497
Chemotherapy	42 (60.8%)	16 (64%)	0.601
Radiotherapy	37 (53.6%)	17 (68%)	0.729
	30 (43.4%)	4 (16%)	0.015
> 1 metastatic site	62 (89.8%)	20 (80%)	0.291
> 1 metastatic lesion			
Bony metastases	43 (62.3%)	17 (38%)	0.931
Visceral metastases	42 (60.8%)	13 (52%)	0.583
SLNB	0	9 (36%)	0.000
ALND	28 (100%)	9 (36%)	0.002
Subtype			
- Luminal A	33	18	0.137
- Luminal B	9	3	1.000
- Triple Negative	11	2	0.329
- ER/PR–ve, HER2+ve	6	1	0.667
Time to CT	16.25 days	30.9 days	0.004
Time to Bone scan	19.1 days	31.2 days	0.024
Surgery pre staging	12 (17.3%)	9 (36%)	0.090

Figures in bold indicate statistical significance.

limited benefit, due to its inability to reliably distinguish between minimal and advanced nodal disease [19]. It has been suggested that axillary US may maintain its usefulness by assessing for multiple abnormal nodes, with triaging to SLNB for those with minimal nodal metastases [19] and triaging patients with multiple nodal metastases to distant staging to identify Stage IV disease. Our study has shown that axillary US does triage patients to earlier staging and reduces the number of Stage IV patients proceeding to surgery prior to staging. However, as there is a potential survival benefit associated with surgery in these patients, it appears that all patients who do not present with symptoms of disseminated, heavy-burden metastatic disease should proceed to primary breast surgery with SLNB.

Our study has confirmed findings of other similar retrospective series, namely that there is benefit to be gained from surgery in a subset of Stage IV breast cancer patients. We have additionally collected data on a wide range of potential confounding factors and used multivariate analysis to confirm that surgery is an independent predictor of longer survival in our cohort of patients with Stage IV disease. We have also newly identified that diagnosis of Stage IV disease after SLNB rather than axillary US/FNAC does not adversely affect outcome in these patients, and in fact offers a potential survival advantage. Therefore, avoidance of node sampling at axillary US (if small volume disease is identified) in preference to performing SLNB can be safely practiced without affecting outcomes for patients with distant metastases.

Like all retrospective studies however, our paper does have some limitations. Selection bias is an almost universal problem with retrospective analysis. Patients in our study who underwent surgery had a lower burden of both distant metastatic disease and axillary nodal disease, which may directly impact their survival. We attempted to account for this by performing multivariate analysis and found both surgery and single site disease to be independent predictors of improved survival. Of note, the majority of our patients were not known to be Stage IV when they proceeded to surgery, thus eliminating surgeon preference as a major selection bias. However, it may well be that patients' lower volume of metastatic disease is what has contributed to their improved survival. A number of randomised controlled trials are currently in progress [15] in an attempt to address the question of surgery in Stage IV

disease without the inherent biases of retrospective review. To date, preliminary results from 2 trials have shown no survival advantage for surgery in Stage IV disease [13,14]. The results presented from India so far, however, were after a short duration of follow-up [14]. The Indian study has subselected patients with a lower volume of metastatic disease (≤ 2 viscera involved) and a predicted life expectancy of > 1 year from diagnosis [14]. Longer term results from this study may help determine if there is true survival benefit for surgery in Stage IV oligometastatic disease. To date, the study from Turkey shows there is some benefit from surgery for patients with isolated bone metastases [13].

Conclusions

In summary, our data confirms that surgery of the primary tumour does confer a survival advantage in selected patients with Stage IV breast cancer. However, survival is no different in those undergoing ALND compared to SLNB alone. The survival benefit is most marked in patients with low volume metastases, in one distant organ. It remains to be established whether this survival benefit is directly related to the surgery performed or whether it relates to the natural history of the oligometastatic phenotype. Positive axillary cytology may triage patients with Stage IV breast cancer to non-operative management and preclude them from proceeding to potentially beneficial locoregional surgery.

Conflict of interest statement

The authors declare no conflicts of interest.

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