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Multivisceral Resection for Locally Advanced Gastric and Gastroesophageal Junction Cancers—11-Year Experience at a High-Volume North American Center

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Abstract

Introduction The oncologic benefit of multivisceral en bloc resections for T4 gastroesophageal tumors has been questioned, given the increased morbidity associated. We thus sought to investigate the surgical and oncologic outcomes of curative-intent en bloc multivisceral resections for T4 gastroesophageal carcinomas.

Methods Between 2005 and 2016, 35 of the 525 patients who had gastric or EGJ carcinomas underwent curative-intent multivisceral resections for direct invasion or adhesion to adjacent organs.

Results Postoperative complications occurred in 16(46%), 10 of which were Clavien-Dindo ≥ 3 (29%). Ninety-day mortality was 3%. The R0 resection rate was 94% (33). Direct organ invasion (pT4b) was confirmed on pathological analysis in 14 (40%) and did not affect survival. The majority (28, 80%) had lymph node involvement with a high nodal disease burden and was associated with decreased survival. Overall 5-year survival rate was 34%, and the vast majority of recurrences were distant/peritoneal (81%). On multivariate analysis, positive lymph nodes (H.R. 21.2; 95%CI 2.34–192) and R1 resection (H.R. 5.6; 95%CI 1.02–30.9) were predictors of survival.

Conclusion Multivisceral resections for T4 gastric and GEJ adenocarcinomas, in combination with effective systemic therapy, result in prolonged long-term survival with acceptable morbidity. Complete resection to negative margins should remain a mainstay of curative-intent treatment in carefully selected patients.

Keywords Gastric cancer · Locally advanced · T4 · Surgery

Introduction

Gastric cancer is the fifth most common cancer in the world.[1] While the North American incidence of distal gastric cancers has decreased over time, proximal gastric and gastroesophageal junction (GEJ) adenocarcinomas are on the rise.[2–4] Due to the late appearance of symptoms, the majority of patients with gastroesophageal tumors present with advanced disease .[3]

Curative-intent surgery for gastroesophageal tumors requires complete tumor resection with negative margins and regional lymphadenectomy. When tumors directly invade surrounding organs, multivisceral en bloc resection is traditionally required to achieve complete resection with negative margins. For gastric and GEJ cancers, the most commonly invaded organs include liver, spleen, transverse colon, and pancreas.[5–8] En bloc resection of such adjacent organs with the stomach, while oncologically sound, are associated with significant morbidity and mortality, including bleeding, anastomotic and pancreatic leaks, prolonged hospital stay, cardiorespiratory complications, and even death.[5–10] Debate remains whether these potential consequences of aggressive, curative-intent surgery actually outweigh any long-term survival benefits of disease control.[7,10–12] Prior studies examining this question have been hampered by including historical patients from an era in which systemic therapies were largely considered ineffective, or have not examined the outcomes of multivisceral resection for locally infiltrative gastric and GEJ adenocarcinoma patients as a group.

We thus sought to review the short-term surgical and long-term oncologic outcomes of en bloc multivisceral

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resection for locally advanced gastric and GEJ carcinomas at a high-volume center from a modern era cohort including up to date systemic therapy.

Methods

Patient Selection

A prospectively collected institutional gastric and esophageal cancer database at the Montreal General Hospital of the McGill University Health Centre was queried from 2005 to 2016. All patients with clinical T4b lesions diagnosed in the preoperative setting or as an intraoperative finding who underwent curative-intent en bloc multivisceral resections were included. Patients undergoing non-curative-intent surgery and multivisceral resection for any reason other than suspected invasion of adjacent organs were excluded from the final analysis. Resections of the pleura, pericardium, mesentery, azygos vein, thoracic duct, or diaphragm were not considered multivisceral resections and were excluded (Fig. 1). This study was approved by the McGill University Health Center's (MUHC) institutional review board.

Data Collection

Patient demographic data, comorbid status, pre-operative staging, preoperative neoadjuvant therapy, type of surgery, number and type of organs resected, postoperative length of stay, and final pathology results were recorded. Primary outcomes assessed were postoperative morbidity, mortality, and overall survival.

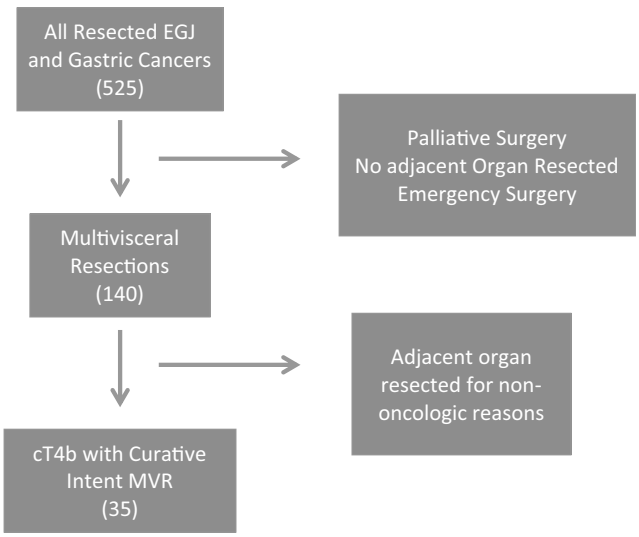


Fig. 1 Patient selection algorithm

Preoperative Staging

Preoperative assessment for gastric and esophageal cancer at our institution routinely includes esophago-gastroduodenoscopy (EGD), computed tomography (CT) of the chest, abdomen and pelvis, and whole-body positron emission tomography–computed tomography (PET-CT). Endoscopic ultrasound is used selectively. Patients are routinely discussed in a dedicated upper A GI cancer multidisciplinary oncology conference was attended by gastrointestinal surgeons, medical and radiation oncologists, and oncology liaison nurses to determine the optimal therapeutic approach for each patient. The locally preferred care plan for suitable patients with adenocarcinomas T3+ and/or N+ is 3 cycles of platinum-based triplet systemic cytotoxic chemotherapy (primarily docetaxel/cisplatin/5-flourouracil) pre- and postsurgery, with intervening en bloc anatomical resection and D2 lymphadenectomy, in accordance with Japanese and European guidelines for gastric and EGJ adenocarcinomas.[13,14]

Postoperative Surveillance

All patients were followed with history, physical examination, and routine bloodwork including tumor markers every 3 months for 2 years, then every 6 months for 3 years, then annually. CT chest/abdomen/pelvis was performed every 3 months for 2 years, and EGD was performed at 6 months and then annually. PET-CT, diagnostic laparoscopy, and other specialized tests were performed selectively as needed.

Statistical Analysis

Data was analyzed using descriptive statistics to characterize categorical variables. Kaplan-Meier method and log-rank test were used to estimate and analyze survival. To identify prognostic factors associated with overall survival, we used univariate and multivariate Cox proportional hazard models. Multivariate models were constructed by forward selection in a stepwise fashion, incorporating variables with a P value < 0.2 on univariate analyses (Cox) or variables of clinical significance independent of the results on the univariate analysis. P values < 0.05 were considered significant. Descriptive statistics are presented as median (interquartile range) or number (%) as indicated. Statistical analysis was performed using Stata version 13 (Statacorp, USA).

The study was approved by the ethics review board at McGill University.

Results

Of 525 patients with gastric or GEJ cancer resection in the database, a total of the 35 patients met inclusion criteria (71%

female, median age 64.5 (16) years). The majority were of the American Society of Anaesthesiology (ASA) class ≤ 2 (19, 54%). The most common primary tumor sites were EGJ and gastric body, accounting for 37% each. Local organ invasion was suspected preoperatively in 15 patients (43%). The distribution of surgeries performed was total gastrectomy in 14 (40%), esophagogastrectomy in 11 (31%), subtotal gastrectomy in 8 (23%), and extended total gastrectomy/distal esophagectomy with pedicalized jejunal interposition in 2 (6%). The majority of patients had adenocarcinomas (94%), of which 23 (66%) were poorly differentiated. Sixteen patients (46%) received pre- and postoperative chemotherapy, 4 patients (11%) received neoadjuvant therapy only, and 7 (20%) received adjuvant therapy alone, leaving 8 patients (23%) who did not receive any adjuvant therapy. Characteristics of study patients are presented in Table 1. Of the 15 patients who were not able to receive any neoadjuvant therapy, the most common reasons included uncontrollable bleeding (4 patients), poor performance status (4 patients), complete obstruction (3 patients), and perforation (1 patient).

The most commonly resected organ was pancreas (49%) followed by spleen (34%) and liver (29%). Fifteen patients (43%) required resection of two or more neighboring organs. All cases were performed open. Median length of stay was 10 (13) days. Serious complications (Clavien-Dindo ≥ 3) occurred in 10 (29%). These included anastomotic leak (9%), pancreatic/duodenal stump leak (9%), enterocutaneous fistula (6%), and bile leak after liver resection (6%). One patient (3%) died in the hospital on postoperative day #20 due to pulmonary embolism (Table 2).

Although all tumors were adherent to resected organs intraoperatively, direct organ invasion (pT4b or ypT4b) was confirmed on final pathological analysis in only 14 (40%). Median lymph node retrieval was 33 (28). Lymph node involvement (LN(+)) was identified in the majority of cases (80%), with a high nodal disease burden (46% with pN3 disease). Negative resection margins were achieved in 33 patients (94%). Pathologic outcomes are presented in Table 3.

Median length of follow-up after surgery was 31 (25) months. Estimated median survival was 38 months (95% CI 22–61). Disease-free survival (DFS) and overall survival (OS) at 1, 3, and 5 years were 70 and 88%, 26 and 51%, and 20 and 34%, respectively (Fig. 2). Thirteen patients are still alive at the time of publication, and five have survived more than 5 years. All of the five long-term survivors had R0 resections: only one of them was LN (+), two were truly pT4b on final pathology, and one had more than one adjacent organ resected. Of the 22 patients who experienced recurrences during the study period, only 3 (9%) were loco-regional, 9 (26%)

Table 1 Patient demographic and clinical characteristics

Gender, no. (%)	
Male	10 (29)
Female	25 (71)
Age, median (IQR)	64.5 (16)
Follow-up in months, median (IQR)	31 (25)
ASA class, no. (%)	
1	1 (3)
2	18 (51)
3	16 (46)
Tumor site, no. (%)	
GEJ	13 (37)
Fundus	3 (9)
Body	13 (37)
Antrum	6 (17)
Suspicion of cT4b, no. (%)	
Preoperative	15 (43)
Intraoperative	20 (57)
Surgery, no. (%)	
Esophagectomy	11 (31)
Extended total gastrectomy/distal esophagectomy	2 (6)
Total gastrectomy	14 (40)
Subtotal gastrectomy	8 (23)
Adjuvant therapy, no. (%)	
None	8 (23)
Only neoadjuvant therapy	4 (11)
Only adjuvant therapy	7 (20)
Both	16 (46)

Table 2 Postoperative outcomes

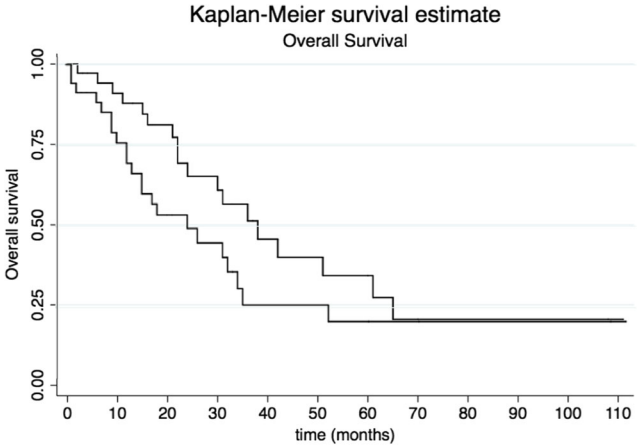
Surgical outcomes, no (%)	
90-day mortality	1 (3)
Readmissions (within 30 days post d/c)	4 (11)
Reoperation	6 (21)
Major complications (Clavien-Dindo ≥ 3)	10 (29)
Any complications	16 (46)
ICU requirement	5 (14)
Length of stay in days, median (IQR)	10 (13)
Clavien-Dindo, no. (%)	
0	19 (54)
1	2 (6)
2	4 (11)
3a	3 (9)
3b	4 (11)
4a	2 (6)
5	1 (3)
Major complications (Clavien-Dindo ≥ 3), no. (%)	
Anastomotic leak	3 (9)
Enterocutaneous fistula	2 (6)
Duodenal and pancreatic stump leak	3 (9)
Bile leak	2 (6)
Death (pulmonary embolism, pericarditis)	1 (3)

Table 3 Pathologic characteristics

Organs resected, no. (%)	
1	20 (57)
2	9 (26)
3 or more	6 (17)
Resected organs, no. (%)	
Pancreas	17 (49)
Spleen	12 (34)
Liver	10 (29)
Colon	6 (17)
Lung	6 (17)
Other organs	6 (17)
Histology, no. (%)	
Adenocarcinoma	33 (94)
Squamous cell carcinoma	2 (6)
Differentiation, no. (%)	
Well-differentiated	3 (9)
Moderately differentiated	7 (20)
Poorly differentiated	25 (66)
pT, no. (%)	
T3	19 (54)
T4a	2 (6)
T4b	14 (40)
pN, no. (%)	
N0	7 (20)
N1	3 (9)
N2	9 (26)
N3	16 (46)
Lymphadenectomy, no. (%)	
D1	4 (11)
D2	30 (86)
D3	1 (3)
Total LN, median (IQR)	
Total	33 (28)
Positive	9 (12)
Resection, no. (%)	
R0	33 (94)
R1	2 (6)

were peritoneal, and 10 (29%) were distant organ metastases. Clinico-pathologic characteristics of the long-term survivors are presented in Table 4.

Overall survival did not differ significantly by tumor T stage (pT3 vs. pT4; Fig. 3), but was significantly different between LN (+) and LN (−) patients (Fig. 4). Five-year overall survival was 83% for pLN(−) and 11% for pLN(+) ($p = 0.001$) (Fig. 4). On multivariate analysis, positive lymph nodes (H.R. 21.2; 95% CI 2.34–192, $p = 0.007$) and R1 resection (H.R. 5.6; 95% CI 1.02–30.9, $p = 0.047$) were identified as independent factors associated with poorer survival.



	12 mo	36 mo	60 mo
Overall Survival, %	88	51	34
Disease free survival, %	70	26	20

Fig. 2 Overall and disease-free survival

Discussion

This study describes the surgical and oncologic outcomes after multivisceral resection for locally advanced gastric and GEJ adenocarcinomas. While the utility of such aggressive resections has been questioned,[15–17] this work confirms that long-term survival and local disease control is achievable in carefully selected patients, with comparable 5-year overall survival (31%) to similar reports.[6–8] Furthermore, complete R0 resection was achieved in 94% of cases, greater than that reported in previous works (58–84%).[5,7,9,18–20]

This work uniquely examines MVR for locally advanced gastric and GEJ cancers in a number of ways. Firstly, while several other reports of patient cohorts exist for MVR, in many cases these include resection of gallbladder, small bowel, diaphragm, transverse colon mesentery, and other tissues,[21,22] which were not considered truly "multivisceral" in our study due to the relatively low morbidity of resection of such structures. Furthermore, while other works include patients in whom organ resection was done for non-oncologic reasons, such as splenectomy for iatrogenic injury,[5,8] we only included patients in whom organ resection was undertake en bloc and for suspicion of direct tumor invasion. As such, our data represent patients who underwent complex resections for truly advanced disease.

As with any aggressive surgical intervention, patient selection is of paramount importance. Our series represents a cohort of highly selected patients for whom the oncologic benefits of multivisceral resection were deemed to outweigh the risks of serious perioperative morbidity. In general, these patients were relatively young (median age 64) and were fit enough to also tolerate systemic therapy in the majority of cases.

Table 4 Five-year survivors' characteristics

#	Age	ASA	Sx	MVR	LOS	CD	pT	pN	R	Systemic therapy	F/U	REC	L/D
1	37	1	EG	Lu	10	0	T4b	0	R0	Postoperative CT	108	No	L
2	79	3	STG	Li	7	0	T4b	N1	R0	Pre- and post CT	111	No	L
3	55	2	STG	C	10	3a	T3	0	R0	Pre- and post CT	65	Distant	D
4	61	2	STG	C	6	0	T3	0	R0	Preoperative CT	70	No	L
5	61	2	EG	P, S, A	7	1	T3	0	R0	Pre and post CT	60	No	L

ASA American Society of Anesthesiology score, *Sx* surgery, *STG* subtotal gastrectomy, *EG* partial esophagectomy with gastric pull-up, *OR* organs resected, *Lu* lung, *Li* liver, *C* colon, *P* pancreas, *S* spleen, *A* adrenal gland, *LOS* length of stay (days), *CD* Clavien-Dindo complication score, *R* resection, *NA* neoadjuvant therapy, *A* adjuvant therapy, *F/U* follow-up, *REC* recurrence, *L/D* living or deceased at last follow-up

Complete surgical resection with negative histologic margins is known to be a major factor in improving survival and reducing the risk of loco-regional recurrence in patients with esophagogastric cancers.[23,24] Multivisceral en bloc resection to negative margins is thus required for tumors found to be infiltrating adjacent organs at the time of surgery, but only if the morbidity of such resections does not outweigh the oncologic benefits. Previous work has demonstrated that a 5-year survival can be similar among MVR patients compared to those who undergo single organ resection alone,[12] and even patients undergoing non-curative resections can experience a survival benefit from such an approach.[18] However, debate remains regarding the long-term survival benefits versus the short-term risk of morbidity and mortality from such an aggressive surgical approach.[17,25] This work reports an acceptable rate of major complications and only one in-hospital mortality, which is in line with or better than outcomes reported in previous series.[8–10,12] These outcomes are, despite including patients undergoing extended total gastrectomies and distal esophagectomies, procedures with considerably higher baseline complication rates from total or subtotal gastrectomy alone.

Survival time without surgery for locally invasive gastroesophageal cancers is universally poor, even with systemic therapy. Since surgery is a mainstay of any curative-intent treatment regimen, it is difficult to exactly quantify survival in resectable patients who do not undergo surgery. However, recent data in low volume metastatic disease patients who responded favorably to chemotherapy demonstrates a median survival increase of 15 months for surgical resection over systemic therapy alone.[26] These data support primary tumor resection in conjunction with systemic therapy to achieve local/regional disease control even for advanced disease.

It is important to note that the true local invasion rate in our series on final pathological analysis was only 42%. These results recapitulate numerous studies demonstrating limited accuracy in pre- and intraoperative prediction of tumor invasion. The positive predictive value of CT scan to predict adjacent organ invasion has been reported to be no better than 50%[20] and EUS accuracy for advanced T stage is less than 50%.[27,28] Furthermore, pre- and intraoperative clinical assessment accuracy for presumed T4 lesions has been reported to range widely from 13.8 to 89%. Several explanations have been proposed to explain to the low accuracy of intraoperative T stage determination. Desmoplastic reaction that can be mistaken for local

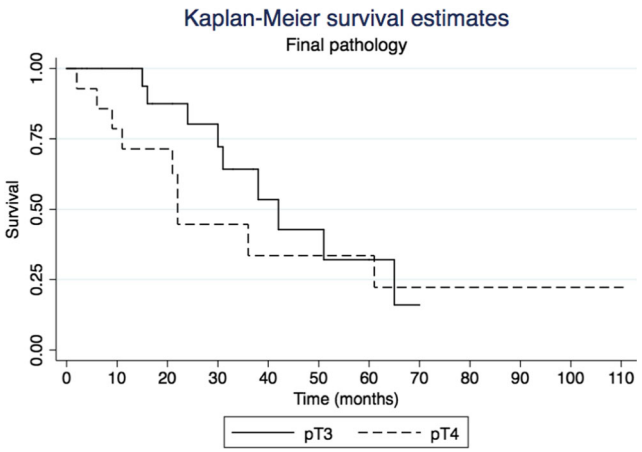
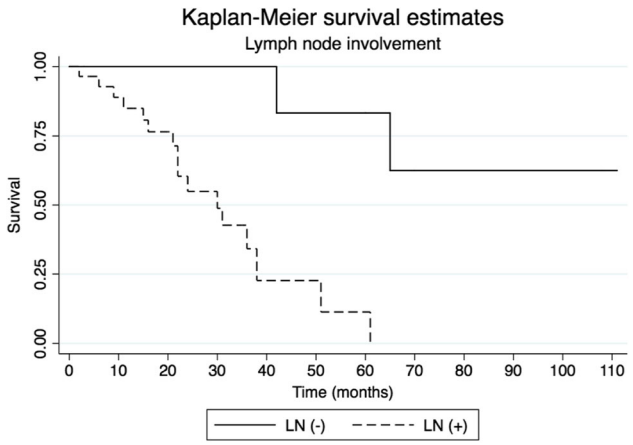


Fig. 3 Overall survival by final pathology T stage. P = N.S



Survival rate, %	12 mo	36 mo	60 mo
LN (+)	85	34	11
LN (-)	100	100	83

Fig. 4 Overall survival by N stage. $P = 0.014$

invasion is a main factor, and this is especially true when posterior gastric wall tumors extend to the capsule of the pancreas. Thus, a sizeable proportion of patients in our series, as in previous reports,[7,10,20,29] underwent MVR without oncologic benefit. While it may seem unnecessarily risky to undertake such extensive resection when true tumor invasion is indeterminate, multivariate analysis identified R1 resection to be an independent predictor of poor long-term survival in our study, while type and number of additional organs resected did not influence survival. This has also been shown in numerous other series.[6,7,9,12,22,29,30] Therefore, if surgery is to be undertaken in patients with bulky gastric and GEJ cancers, complete surgical resection to negative margins is essential.

Patients were offered neoadjuvant chemotherapy in accordance with Japanese and European guidelines for gastric and EGJ adenocarcinomas.[13,14] Even though North American guidelines advocate the use of chemoradiation for EGJ carcinomas independent of the histologic type, there is also abundant evidence that supports the use of neoadjuvant chemotherapy for gastric and EGJ adenocarcinomas.[31–37] Considering that after curative-intent resection for esophageal and EGJ adenocarcinomas the majority of recurrences are distant and that our local control of disease is rather high, with an R0 resection rate over 94%, we favor the use of systemic cytotoxic chemotherapy to enhance systemic control of the disease. We believe the use of chemoradiation potentially might have decreased the pathologically confirmed T4b tumors. However, this is unlikely to have reduced the rate of adjacent organ, since tumor fibrosis and radiation effects often make intraoperative determination of local tumor extension difficult, and can give the appearance of direct invasion.

Lymph node involvement was another independent predictor of reduced long-term survival in our cohort, with a 5-years survival of 11 vs. 83% for LN (+) vs. LN (−) cases respectively. This association is well-documented in the gastric cancer literature.[7,9,10,12,22,29] Furthermore, 86% of cases of recurrent disease in our cohort were distant or peritoneal metastases, with only three loco-regional recurrences. Thus, while extensive resection can achieve excellent local disease control, these results highlight the systemic nature of locally advanced gastric and esophageal cancers, and therefore reinforce the importance of systemic therapy in combination with surgery to achieve disease control.

Since a significant proportion of the recurrences in our cohort were peritoneal (22 patients, 41%), the possibility to provide directed treatment to this subset of patients with intraperitoneal therapies such as HIPEC is interesting. However, although evidence for HIPEC in peritoneal metastases is promising, it is still very limited and this is not currently part of our practice. We believe the role of HIPEC in the treatment of gastric cancer, and specially in peritoneal metastasis, is still evolving and larger studies are required before it can be accepted as a standard of care.[38,39]

The limitations of this study include the retrospective nature of data collection and the small case numbers. This work represents 11 years of experience at a high-volume center presently performing approximately 150 gastric and esophageal cancer resections annually, indicating that true multivisceral, a non-palliative resection of gastric and GEJ cancers in North America is rare. In our institution, we do not register detailed demographic data, such as ethnic origin, income, occupation, or educational level of our patients. This limitation along with the relatively low number of patients precludes us to perform an in-depth demographic analysis and limits widely generalizable conclusions and minutely detailed statistical analyses. Nevertheless, this review does provide granular insight that may help inform patient selection decisions in these complex cases.

Conclusion

Multivisceral resections for locally invasive gastric and GEJ adenocarcinomas, in combination with systemic therapy, result in prolonged long-term survival with acceptable morbidity. Complete resection to negative margins should remain a mainstay of curative-intent treatment in carefully selected patients.

Compliance with Ethical Standards

This study was approved by the McGill University Health Center's (MUHC) institutional review board.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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