Resection of Primary Mediastinal Non-Seminomatous Germ Cell Tumors

A 28-Year Experience at Memorial Sloan-Kettering Cancer Center

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Introduction: Surgical resection of residual tumor mass in responders to platinum-based chemotherapy has evolved as the preferred treatment of primary mediastinal nonseminomatous germ cell tumors (PMNGCTs). We reviewed a single institution's operative experience with these rare tumors.

Methods: We reviewed charts of patients resected for PMNGCT at Memorial Sloan-Kettering Cancer Center between July 1980 and April 2008. Analyses included Kaplan-Meier survival with univariate log-rank comparisons and Cox multivariate regression.

Results: Fifty-seven patients were identified and followed up for a median of 5.3 years. Fifty-four of them received platinum-based preoperative chemotherapy, and 28 (49%) had limited stage I/II disease. Preoperative tumor markers normalized or decreased in 79% of patients. The most common surgical approach was anterolateral thoracotomy with partial sternotomy ("hemiclamshell," 38.6%). An R0 resection was achieved in 91% of the patients with a major morbidity of 17.5% and no postoperative deaths. The median overall survival was 31.5 months. Factors correlating with better survival on univariate analyses were necrosis or teratoma versus residual cancer on final pathology ($p = 0.001$), R0 resection ($p = 0.03$), normalized or decreased postchemotherapy/preoperative tumor markers ($p < 0.001$), normalized postoperative tumor markers ($p = 0.004$), stage I/II disease ($p = 0.03$), and surgery after 2000 versus 1980–1999 ($p = 0.01$). An exploratory multivariate analysis suggests that normalized or decreased postchemotherapy/preoperative tumor markers is the strongest independent predictor of improved survival.

Conclusions: In a cohort of PMNGCT patients in which 91% of the patients underwent complete posttherapy resection, response to chemotherapy, measured by normalized or decreased preoperative tumor markers, was the strongest predictor of improved survival.

Key Words: Germ Cell Tumor, Mediastinal Mass, Tumor Markers, Surgery.

(*J Thorac Oncol.* 2011;6: 1236–1241)

Primary mediastinal nonseminomatous germ cell tumors (PMNGCTs) are primarily a disease of children and young men, usually presenting in the second to fourth decades of life. Mediastinal origin of NSGCTs is in and of itself considered an independent predictor of poor prognosis compared with those of gonadal origin.[1] Although rare, the diagnosis should be considered in any young male with an anterior mediastinal mass and may represent up to 5% of anterior mediastinal masses in adults and 10 to 15% in children. There are several histological types including embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma, and mixed types containing seminomatous components combined with elements of those previously mentioned. Nonseminomatous and nonteratomatous subtypes account for ~15% of these tumors, teratomas 45%, combined subtypes 5%, and pure seminomas 35%.[2]

These large anterior mediastinal masses often present with pain and compression syndromes such as pericardial tamponade or superior vena cava syndrome. Although prior histological diagnosis by means of surgical biopsy or large or fine-bore needle is preferable, treatment may be started on the basis of increased tumor markers. Serum alpha fetoprotein is increased in up to 80% of NSGCTs and beta-human chorionic gonadotropin (β-HCG) in up to 35% of NSGCTs.

The mainstay of treatment is aggressive, multidrug chemotherapy. Surgery is largely considered an adjuvant treatment for resection of tumor residua in patients responding to chemotherapy. At certain specialty centers, surgery is considered even in cases of chemotherapy nonresponders, given the overall ineffectiveness of second-line chemotherapy and lack of other good treatment options.[3,4] Despite

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Disclosure: The authors declare no conflicts of interest.

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Presented at the annual meeting of the American College of Surgeons, Chicago, Illinois, October 11–15, 2009.

ISSN: 1556-0864/11/0607-1236

treatment, outcomes are generally poor, with 5-year survival rates reported between 30 and 48%.[1,4–7]

The purpose of this study was to analyze a single institution's surgical experience with PMNGCT. Our primary goals were to identify significant predictors of outcome and survival in a surgical cohort resected at a single major referral center and to examine the operative approaches to resection of these tumors.

METHODS

We retrospectively reviewed the medical records of patients with PMNGCT resected at Memorial Sloan-Kettering Cancer Center (MSKCC) from 1980 to 2008. Data from nonoperative patients and those not resected at our institution were not collected and are beyond the scope and intent of this study. Data points collected included basic patient demographics, method of preoperative diagnosis/biopsy, information on preoperative chemotherapy regimens, alpha fetoprotein, β-HCG, and lactate dehydrogenase tumor marker status (including prechemotherapy, postchemotherapy/preoperative, and postresection), operative data (including surgical approach and resection details), tumor stage, pathology (including preoperative biopsy and postresection histology), and survival outcomes.

All preoperative and operative biopsies were reviewed at MSKCC. All death events were confirmed by online search of the Social Security Death Index. All patients were required to have their primary resection at MSKCC. Decisions to proceed with surgery were at the joint discretion of the oncologist and surgeon. In general, patients considered for resection are those with response to chemotherapy documented by normalized or decreased tumor markers and with tumor residua felt to have reasonable potential for complete resection. Nevertheless, given the absence of viable alternative treatment options, selected patients with increasing tumor markers and disease burden with potential for complete resection may also be offered surgery.

A previously described staging system by Moran and Suster[2] was adapted to postoperatively stage patients based on pathology reports of the resected specimen (Table 1). Time to recurrence, overall survival (OS), and progression-free survival (PFS) from time of surgery were estimated using the Kaplan-Meier method. Comparison between groups was performed by log-rank test (for univariate analysis) and Cox proportional hazards regression stratified by surgery period (before 2000 versus 2000+) (for multivariate analysis). Although small sample size prohibited robust multivariable testing, an exploratory multivariate analysis was performed. This study was approved by the MSKCC Internal Review Board.

TABLE 1. PMNGCT Staging

Stage I	Well circumscribed tumor without microscopic invasion into adjacent structures
Stage II	Tumor confined to mediastinum with macroscopic and/or microscopic infiltration into adjacent structures (pleura, pericardium, great vessels)
Stage III	Tumor with metastases
IIIA	Metastases to intrathoracic sites (lymph nodes, lung, etc.)
IIIB	Metastases to extrathoracic sites

Adapted from *Cancer*. 1997;80:681–690.
PMNGCT, primary mediastinal nonseminomatous germ cell tumors.

RESULTS

Patient and Tumor Characteristics

Fifty-seven patients undergoing primary resection for PMNGCT at MSKCC between July 1980 and April 2008 were identified. Demographics and results are summarized in Table 2. Fifty-six of the patients (98.2%) were male, and the median age was 30 years (range 18–50 years). The median postoperative follow-up time among patients who did not die was 5.3 years (range 0–14 years). The most common method of preoperative biopsy was anterior mediastinotomy (Chamberlain procedure) (28/57, 49%), and the most common preoperative tumor histologies were mixed PMNGCT (21/56, 43%) and Yolk Sac tumors (16/56, 29%). All except three patients received preoperative chemotherapy with a combination of bleomycin, etoposide, and cis-platinum or etoposide, ifosfamide, and cis-platinum. Preoperative tumor markers were normalized or decreased in 81.8% (45/55) of patients; 42.1% (24/57) presented with metastatic disease before treatment, most often to the lung.

Surgery and Complications

Details of surgery and complications are outlined in Table 2. A single surgeon (M.S.B.) performed 65% of the resections; 88% were performed by three surgeons. Thirty-six patients (63%) were resected by anterior thoracotomy with partial median sternotomy (hemiclamshell) or bilateral anterior thoracotomy with transverse sternotomy (clamshell) surgical approaches. The median length of surgery was 240 minutes (range 120.0–480.0 minutes). Estimated median blood loss was 510 mL (range 11.0–2200.0 mL). The median length of hospital stay was 7 days (range 4–47 days). Lung (41/57, 71.9%) and pericardium (39/57, 68.4%) were the most common additional structures resected with the tumor. An R0 (complete macroscopic and microscopic) resection was accomplished in 91% (49/54) of patients. Ten patients (17.5%) experienced grade 3 or 4 complications, according to the Common Terminology Criteria for Adverse Events version 3.0.[8] In cases where severity of morbidity could not be ascertained from chart review, major morbidity (grade 3 or 4) was assumed. There were no deaths within the 30-day perioperative period.

Recurrence and Survival

Twenty-six patients recurred, with a median time to recurrence of 15 months (95% confidence interval [CI]: 4.8–not reached). Single-site recurrence occurred in 19 patients: four in the mediastinum, six in the lungs, four in bone, two in liver, two in brain, and one in the chest wall. Combined mediastinal and lung recurrence occurred in four patients. One patient presented with combined liver, lung, and mediastinal recurrence, and one with back (soft tissue), mediastinal, and pleural recurrence. Recurrence was diagnosed in one patient based on increasing β-HCG levels with no identifiable site of tumor growth.

TABLE 2. Patient, Tumor, and Treatment Characteristics

Variable	N/Total Evaluable (%)
Median age (yr)	30 (18–50)
Gender, male	56/57 (98.2%)
Preoperative biopsy	
Chamberlain	28/57 (50%)
Fine needle aspiration	11/57 (20%)
Core needle biopsy	5/57 (9%)
Other	13/57 (21%)
Preoperative histology on biopsy	
Mixed	24/56 (43%)
Yolk sac	16/56 (29%)
Teratoma	4/56 (7%)
Embryonal	2/56 (3%)
Choriocarcinoma	1/56 (2%)
Other	9/56 (16%)
Median prechemotherapy STM	
AFP (ng/mL)	899 (0–66,500)
β-HCG (mIU/mL)	0 (0–17,052)
Preoperative STM	
Normalized or falling	45/55 (81.8%)
Rising	10/55 (18.2%)
Preoperative chemotherapy	54/57 (94.7%)
Metastatic disease	24/57 (42.1%)
Lungs	23/57 (40.4%)
Liver	2/57 (3.5%)
Brain	2/57 (3.5%)
Bone	2/57 (3.5%)
Non-mediastinal lymph nodes	2/57 (3.5%)
Other	4/57 (8.8%)
Operative approach	
Hemiclamshell	22/57 (38.6%)
Clamshell	14/57 (24.6%)
Median sternotomy	18/57 (31.6%)
Posterolateral thoracotomy	3/57 (5.3%)
Additional structures resected	
Lung	41/57 (71.9%)
Pericardium	39/57 (68.4%)
Phrenic nerve	12/57 (21.1%)
Large vessels	6/57 (10.5%)
Diaphragm	3/57 (5.3%)
Heart/atrium	2/57 (3.5%)
Other	10/57 (17.5%)
Completeness of resection	
R0	49/54 (90%)
R1	3/54 (6%)
R2	2/54 (4%)
CTCAE Grade 3 or 4 morbidity	10/57 (17.5%)
Pulmonary embolism	2/57 (3.5%)
Pneumonia	2/57 (3.5%)
Stroke	1/57 (1.8%)
Endocarditis	1/57 (1.8%)
Phrenic nerve palsy	1/57 (1.8%)
Renal failure	1/57 (1.8%)
Sepsis	1/57 (1.8%)
SVC thrombosis	1/57 (1.8%)
Final pathology stage	
Stage I	11/52 (21.2%)
Stage II	17/52 (32.7%)
Stage IIIA	22/52 (42.3%)
Stage IIIB	2/52 (3.8%)
Final pathology	
Necrosis	15/57 (26.3%)
Teratoma	12/57 (21.1%)
Cancer	30/57 (52.6%)

STM, serum tumor markers; AFP, alpha fetoprotein; β-HCG, beta-human chorionic gonadotropin; CTCAE, common terminology criteria for adverse events; SVC, superior vena cava.

Patients included in the cohort had a median survival of 4.5 months (range 1–24 months) between start of chemotherapy and surgery. The median OS after start of chemotherapy was 33.8 months. Although we report this as an estimate of survival from time of chemotherapy, we caution that this median is not truly comparable with estimates reported in unselected groups inclusive of patients who start chemotherapy but do not progress to surgery. Instead, it only applies to patients who live long enough and are deemed operable after their chemotherapy treatment, and comparisons to survival results in patients receiving chemotherapy alone are fraught with bias.

Patients who did not die during the study time were followed for a median of 5.3 years after surgery. Twenty-six deaths were observed, only four of which occurred without prior recurrence. The median PFS and OS from time of surgery were 9.1 and 31.5 months, respectively. PFS and OS at 2 years were 46 and 56%, respectively (Figure 1).

Predictors of improved OS on univariate analysis included the presence of necrosis or teratoma versus residual carcinoma in the final specimen ($p = 0.001$; Figure 2), Stage I/II versus IIIA/IIIB ($p = 0.03$; Figure 3), normalized or decreased postchemotherapy/preoperative ($p < 0.001$; Figure 4) and postresection markers ($p = 0.004$), and R0 versus R1/R2 resection ($p = 0.03$). In addition, patients who had

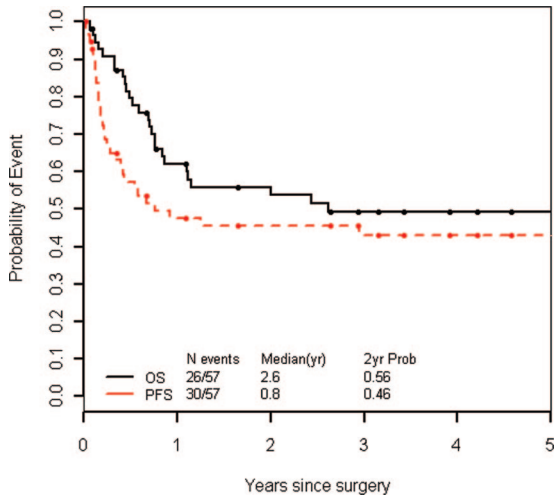

FIGURE 1. Overall survival and progression-free survival.

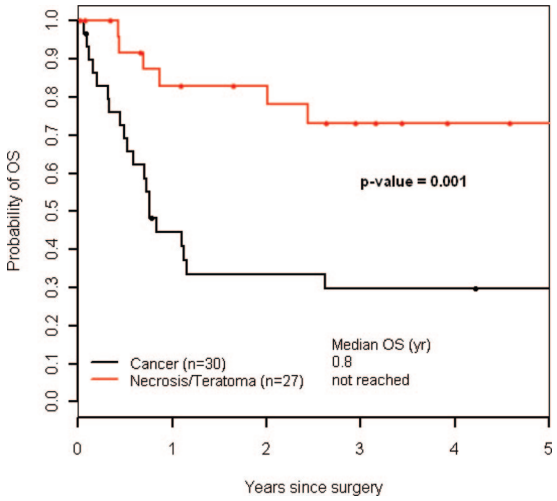

FIGURE 2. Overall survival by pathology in the final specimen (necrosis or teratoma versus residual carcinoma).

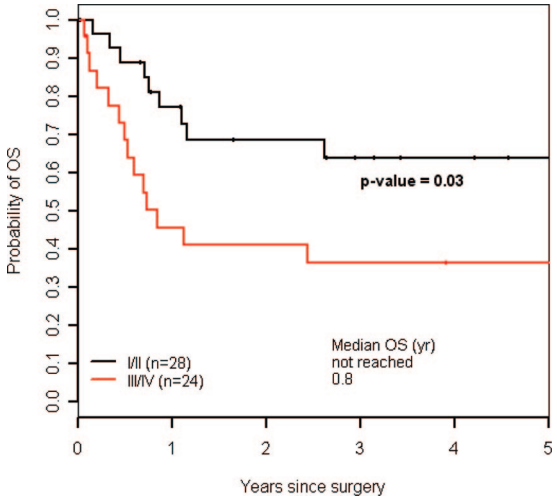

FIGURE 3. Overall survival by pathological stage (I/II versus IIIA/IIIB).

surgery more recently (year 2000 and later) had better survival compared with patients treated before year 2000 (p = 0.01). Limited sample size prevented a reliable, robust multivariate analysis allowing for inclusion of all factors to be significant in our univariate analysis. In a limited, exploratory multivariate analysis stratified by period of surgery (<2000 versus 2000+), having increasing preoperative tumor markers (hazard ratio = 3.2; 95% CI = 1.1–9.4; p = 0.04) was independently associated with worse survival (Table 3). The other two variables included in the model (final pathology and pathological staging) approached but did not reach statistical significance (p values 0.05 and 0.07, respectively). Although all the factors mentioned above, with the exception of the pathological stage, were univariately associated with PFS, having residual carcinoma in the final specimen was the only predictor in an exploratory-adjusted multivariate analysis (hazard ratio = 5.0; 95% CI = 1.6–15.1; p = 0.005; Table 4).

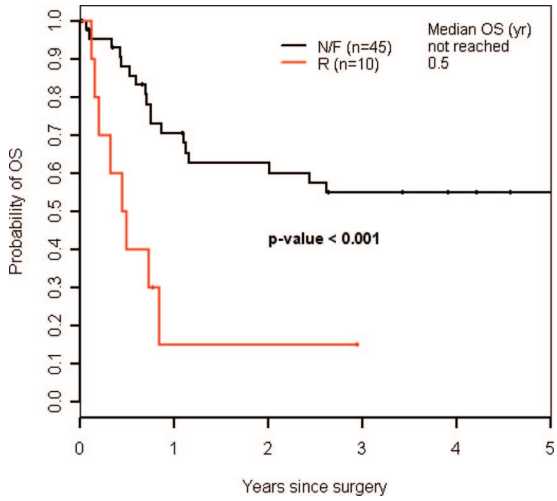

FIGURE 4. Overall survival by perioperative change in tumor markers (normalized or decreased versus increased).

DISCUSSION

PMNGCT remains an aggressive disease of young men with poor survival. Lack of durable response and resistance to first-line chemotherapy regimens, associated hematologic malignancies, and malignant transformation of the primary tumor to nongerm cell tumor elements have been cited as reasons for these poor outcomes.[9–14] In addition, no factors have been found that can reliably and selectively identify patients with no remaining viable cancer in tumor residua after initial treatment.[15] Postchemotherapy adjuvant surgery with the goal of resecting all tumor residua has evolved as a mainstay of therapy in the hopes of achieving durable remission in these patients.[4,12,15]

This study represents the surgical experience with PMNGCT at a single specialty center with operations performed by a limited number of highly experienced surgeons, with exclusion of patients receiving resections of their primary mass at outside institutions. Overall, results of this study are largely congruent with the findings of previous reports from other similar centers (and our own), citing postchemotherapy/preoperative and postoperative normalization of tumor markers, complete (R0) resection of all tumor residua, the absence of extramediastinal disease (i.e., limited stage), and absence of residual viable tumor in the resected specimen as factors predictive of better outcomes.[3–7,10,12,14] Vuky et al.,[4] in a previous report from our institution, reported a 2-year survival rate of 38% in patients undergoing resection. Predictors of worse survival on univariate analysis included persistent malignancy in the postresection specimen, the need for extramediastinal resection, and increasing postchemotherapy markers. Multivariate analyses were not reported. A larger, more recent experience in 158 patients by Kesler et al.[6] from Indiana University found persistent tumor in the resection specimen and increased postresection markers to be associated with worse survival on multivariate analysis. Of note, 11% of the 158 patients in this study were resected at outside institutions.

As mentioned, this study largely confirms the findings of these studies, with univariate analyses identifying preop-

TABLE 3. Factors Associated with OS on Univariate and Multivariate Analysis

	N	Median OS (mo)	OS at 2 yr	Univariate Analysis *p*	Multivariate Analysis HR (95% CI)	Multivariate Analysis *p*
Year				0.01	Stratification factor	
2000–2008	28	Not reached	0.72			
1980–1999	29	10.4 (5.4–not reached)	0.41			
Final pathology				0.001		
Necrosis/teratoma	27	Not reached	0.83		1	Ref
Cancer	30	9.1 (5.8–31.5)	0.33		3.2 (1.0–10.0)	0.05
P stage				0.03		
I/II	28	Not reached	0.69		1	Ref
III/IV	24	10.1 (5.3–not reached)	0.41		2.4 (0.9–5.9)	0.07
Preoperative marker				<0.001		
Normalized/falling	45	Not reached	0.63		1	Ref
Rising	10	5.6 (1.4–10.1)	0.15		3.2 (1.1–9.4)	0.04
Postoperative marker				0.004	Not included in the model	
Normalized/falling	38	Not reached	0.62			
Rising	11	8.3 (3.9–13.2)	0.14			
Complete resection				0.03	Not included in the model	
R0	49	2.4 (1.4–not reached)	0.4			
R1/R2	5	Not reached	0.61			

OS, overall survival; CI, confidence interval; HR, hazard ratio.

TABLE 4. Factors Associated with PFS on Univariate and Multivariate Analysis

	N	Median PFS (mo)	PFS at 2 yr	Univariate Analysis *p*	Multivariate Analysis HR (95% CI)	Multivariate Analysis *p*
Year				0.03	Stratification factor	
1980–1999	29	5.2 (1.9–18)	0.30			
2000–2008	28	Not reached	0.62			
Final pathology				<0.001		
Necrosis/teratoma	27	Not reached	0.75		1	Ref
Cancer	30	3 (1.8–6.5)	0.21		5.0 (1.6–15.1)	0.005
P stage				0.31		
I/II	28	35.4 (2.6–not reached)	0.55		1	Ref
III/IV	24	5.2 (1.8–not reached)	0.37		1.1 (0.5–2.5)	0.85
Preoperative marker				0.002		
N/F	45	35.4 (5.2–not reached)	0.51		1	Ref
R	10	2.3 (0.7–3.4)	0.1		2.4 (0.9–6.1)	0.07
Postoperative marker				<0.001	Not included in the model	
N/F	38	Not reached	0.54			
R	11	2.2 (1.5–3)	0.09			
Complete resection				0.01	Not included in the model	
R0	49	Not reached	0.51			
R1/R2	5	2.4 (1.5–3)	0.2			

PFS, progression-free survival; CI, confidence interval; HR, hazard ratio.

erative and postoperative normalization or decrease in tumor markers, complete (R0) tumor resection, absence of extramediastinal disease (as represented by limited stage I/II), and absence of tumor in the pathological specimen to be associated with improved OS. All the mentioned factors, with the exception of stage, also correlated with improved PFS. Our exploratory multivariate analysis identified normalizing or decreasing preoperative tumor markers as independent predictors of better OS, with limited pathological stage and absence of cancer in the residual tumor also approaching statistical significance. Not surprisingly, only absence of tumor in the resected specimen showed a strong association with PFS on multivariate analysis.

Although our cohort spans over almost three decades, there were no remarkable changes in the chemotherapy protocols or patient demographics during this time. Nevertheless,

it is expected that the cumulative surgeon and institutional experience with these patients, improvements in perioperative and critical care, and possible changes in patient selection for resection may have impacted the chance of survival over time. We stratified the analysis by surgery period, which accounts for potential secular trends in the baseline risk of death of PMNGCT patients.

Although certainly influenced by the study's retrospective nature, reported major morbidity was relatively low, with no mortality within the 30-day postoperative period. Our surgical approach heavily favors a hemiclamshell or clamshell exposure to insure maximal exposure of all affected structures and best chance of complete resection. As we have previously reported, this approach has been shown to afford excellent exposure to the mediastinum and bilateral lung fields, which is required in the resection of these locally aggressive tumors often involving lung and other mediastinal structures.[16] This approach is well tolerated by patients with minimal or no respiratory compromise attributable to the sternotomy and/or anterior thoracotomies.

With this approach, complete microscopic and macroscopic (R0) resection of tumor was achieved in 91% of patients and was found to be a significant predictor of survival on univariate survival (having only five patients with incomplete resection prevented the inclusion of this variable in the univariate model). As mentioned above, the importance of complete resection of all tumor residua has been echoed in other reports, with durable survival outcomes (although vanishingly rare) seen even in the face of increased tumor markers or enlarging masses before surgery.[3,4] Our staging schema was found to be a prognostic factor on univariate analysis only and is not likely to add much clinical relevance or benefit. In our opinion, it is best used as a marker of extramediastinal disease, a known predictor of worse outcomes in these patients.

In summary, complete radical resection of residual tumor mass after platinum-based chemotherapy for PMNGCT can be accomplished in most of appropriately selected patients with normalized or decreased tumor markers and may offer meaningful long-term survival benefits. Nevertheless, given poor alternative options in this aggressive disease, surgery may also be offered even to patients with increasing postchemotherapy markers if it is thought complete resection can be accomplished. Unfortunately, hope for cure remains bleak in this subset of patients and supports ongoing investigation of other salvage modalities for primary treatment failure.

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