

Analysis of the surgical management of patients with recurrent cervical cancer after radiotherapy and chemotherapy.

Análise do manejo cirúrgico de pacientes com câncer cervical recidivado após radioterapia e quimioterapia.

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A B S T R A C T

Objectives: To analyze the results of morbidity and survival after curative and palliative surgery in recurrent cervical cancer patients who underwent chemoradiation as their primary treatment. Another goal was to assess the factors associated with curative and non-curative procedures. **Methods:** This was a retrospective cohort consisting of patients undergoing surgery curative and palliative from January 2011 to December 2017 at a high complexity oncology center. Outcome of morbidity was reported according to the Clavien-Dindo classification, and survival analysis was carried out using the Kaplan-Meier method. To assess the factors associated with the procedures, a univariate analysis using the Mann-Whitney U test was performed. **Results:** Two radical hysterectomies, three pelvic exenterations with curative intent, and five palliatives pelvic exenterations were performed. In the curative group, there were major complications in 40% of the cases, and the median survival time was 16 months. In the palliative group, there were major complications in 60% of the cases, and the median survival time was 5 months. Advanced staging (p-value= 0.02), symptoms (p-value=0.04), tumor size greater than five centimeters (p-value=0.04), and more than three organs involved (p-value=0.003) were factors significantly associated with non-curative surgery. **Conclusions:** The morbidity rates of this study were higher in palliative group, and the median survival time was lower in the palliative group than the curative group, but this difference in survival was not statistically significant. Advanced stage, symptoms, tumor size and number of organs involved are factors that should be taken into consideration when indicating surgical salvage.

Headings: Uterine Cervical Neoplasms. Pelvic Exenteration. Hysterectomy. Recurrence.

INTRODUCTION

Cervical cancer is the fourth most frequent neoplasm in the female population in the world¹. Approximately 70% of this type of neoplasm occurs in less developed countries, where the risk of death is three times higher². In Brazil, 60% of cervical neoplasms are diagnosed in advanced stages³.

The standard treatment for locally advanced lesions is chemotherapy associated with radiotherapy⁴. In this scenario, the recurrence rate varies from 15% to 30%, with a minority of these cases eligible for surgery^{5,6}. Prognostic factors that decrease recurrence or increase survival rates are: (i) a disease-free interval greater than two years after the completion of primary treatment^{7,8}, (ii)

tumor size less than four centimeters⁹, (iii) negative margins after an exenteration^{7,10}, (iv) negative lymph nodes¹¹, and (v) surgery with curative intention⁷.

Surgeries in recurrent cases that had an initial treatment with radiotherapy and chemotherapy vary in complexity. A hysterectomy can be performed when the lesions are small and restricted to the uterus and/or vagina, and pelvic exenteration is chosen when the lesions involve adjacent structures^{12,13}.

Relevant studies on the management of patients with advanced pelvic disease of cervical origin were diverse. They included primary exenterative procedures^{7,11}, pelvic exenteration as the only surgical modality^{10,11,14,15}, other pelvic neoplasms^{8,10,16,17}, or isolated radiotherapy as primary treatment^{18,19}. Studies specifically focusing on patients

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that underwent surgery due to recurrent cervical cancer after chemoradiation are rare, and involve a small number of patients⁵.

This study aimed to analyze the results of morbidity and survival after curative and palliative surgery in patients with cervical cancer who recurred after primary treatment with chemotherapy and radiotherapy. Another goal was to assess the factors associated with curative and non-curative procedures.

METHODS

A retrospective cohort consisting of cervical cancer patients undergoing curative or palliative surgery between January 2011 and December 2017 was carried out at the High Complexity Oncology Center of Ijuí, Ijuí, state of Rio Grande do Sul, Brazil. This center serves and treats cancer patients who have free health insurance provided by the federal government. It covers a population of over 1.5 million people in 120 municipalities in the northwest region of the state of Rio Grande do Sul.

A total of 227 patients with invasive cervical neoplasms that were staged, treated, and followed-up at the High Complexity Oncology Center of Ijuí were first included. These cases were staged according to the International Federation of Gynecology and Obstetrics⁴ in initial (IA1, IA2, IB1, IB2, IIA1), locally advanced (IB3, IIA2, III, IVA), or metastatic (IVB). In total, 68 patients who had initial lesions and eight patients with visceral metastases were excluded because they were not treated with chemoradiotherapy.

Locally advanced cases (n=151) were initially treated with conventional (2D) pelvic radiotherapy (50.4 Gy) combined with weekly cisplatin in a dose of 40 mg/m² for six weeks and four subsequent high-dose (7 Gy) brachytherapy sessions. In the follow-up, it was observed that 76 patients recurred or progressed with the disease.

Of these, 64 were not considered for surgery due to systemic disease progression or tumor infiltration in the pelvic wall. Subsequently, 12 cases were indicated for surgery, and 10 underwent surgery and were analyzed in this study. Surgical indications were based on clinical and imaging exams. The clinical exams performed included (i) gynecological examination to assess invasion of adjacent structures and extension to the pelvic wall and (ii) palpation of the inguinal and supraclavicular lymph nodes. The imaging exams consisted of chest and total abdominal computed tomography (CT) and pelvic floor magnetic resonance imaging.

The operated cases were divided into curative or palliative groups based on the surgical outcome and pathology report. Surgical management was classified as curative, also known as surgical salvage, when free margins were reached. The surgery was classified as palliative when patients presented positive margins, retroperitoneal lymph node metastasis or peritoneal implants in the surgical exploration period.

Postoperative complications were divided according to the Clavien-Dindo classification²⁰. Complications were considered minor when belonging to classes I or II, and major when classified as III, IV, or V. These groupings were used to report outcome of morbidity.

The categorical and continuous variables collected from medical records were age, staging, time interval between completion of primary treatment and recurrence, symptoms in recurrence, tumor size, surgical margins, resection types, number of structures involved, and complications. Information about death and disease status was collected until February 2019.

Statistical analysis was performed using the Statistical Package for the Social Sciences software version 25.0. Categorical variables were described by relative and absolute values, and the continuous variables were presented as minimum, maximum, and median values.

A survival analysis was carried out using the Kaplan-Meier method. To assess the factors associated with curative or non-curative procedures, a univariate analysis using the Mann-Whitney U test was performed. P-values=0.05 were considered statistically significant in both analyses. A multivariate analysis using the Cox proportional hazard regression model was not carried out due to the small sample size.

This study was approved by the Research Ethics Committee of the University of Cruz Alta under the document number 2,354,150. Patient consent was not required due to the nature of this study.

RESULTS

Recurrence or progression of the disease was seen in 76 cases (50.3%) after completion of treatment with radiotherapy and chemotherapy. Of these, 54 cases (71%) were above stage II at admission. Surgery was indicated for 12 cases (15.78%), but two patients (2.63%) refused to receive intervention. The procedures performed are shown in Figure 1.

Regarding patients submitted to surgery, the age ranged from 27 to 62 years, and 40% of them were in stage IIB. The time interval between completion of initial treatment and recurrence ranged from three to 21 months. Symptoms at diagnosis were observed in 90% of the patients (Table 1).

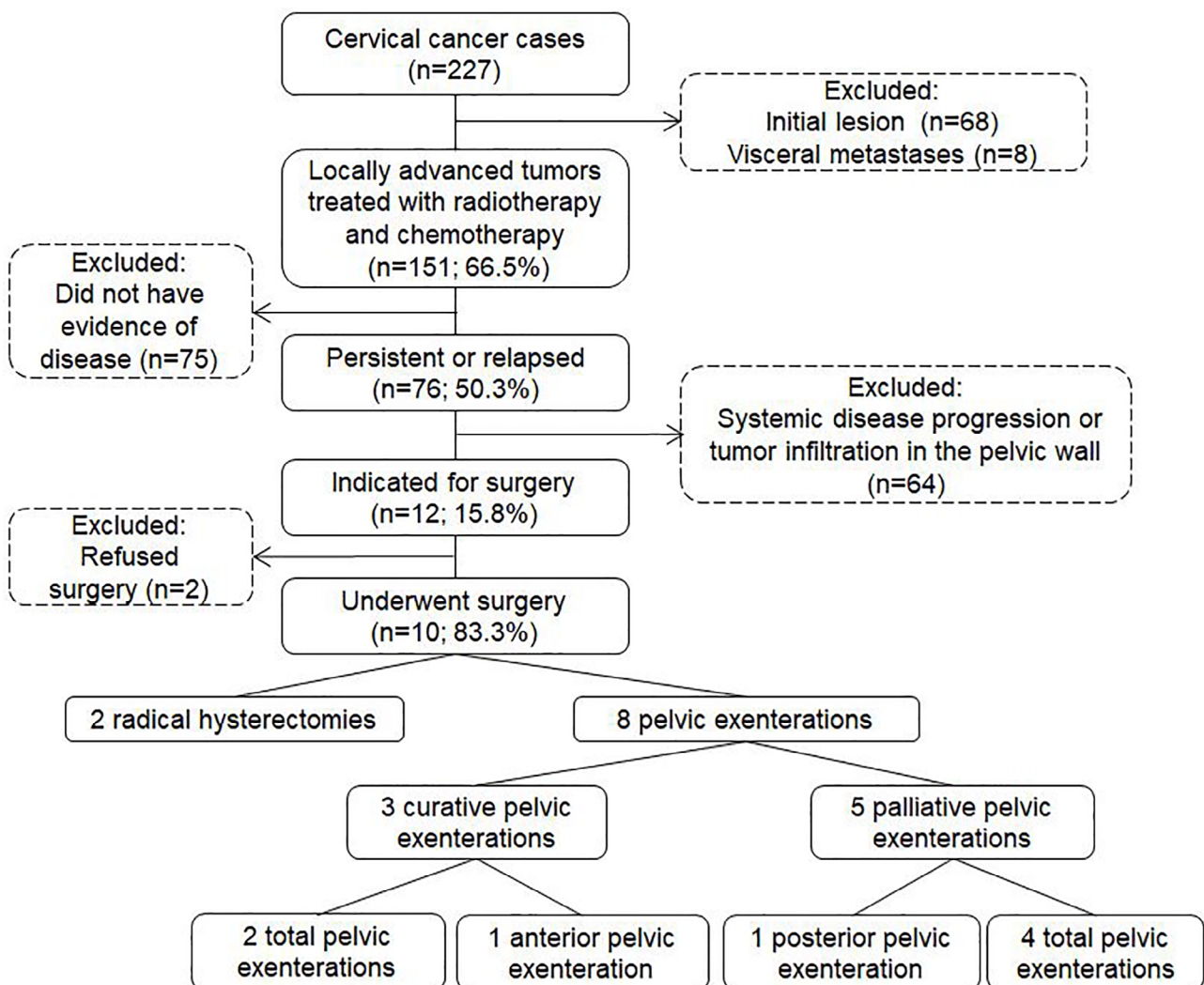


Figure 1. Flowchart of the study with the distribution of cases according to the types of surgery performed.

All tumors were squamous cell carcinoma. Perineural, vascular, and lymphatic invasion were present in all surgical specimens. The tumor diameter ranged from two to nine centimeters. The number of organs involved ranged from one to five (Table 2).

In the curative intent group, the uterus was the only structure involved in one case; uterus

and vagina were involved in two cases; and uterus, vagina and bladder in two other cases.

During exploratory laparotomy, two patients were found to have peritoneum implants in the pelvis, one had paraaortic lymph node metastasis, and another patient developed ovarian metastasis. All of these patients underwent palliative pelvic exenteration.

Table 1. Clinical characteristics of ten recurrent cervical cancer patients.

Variable	Curative Group (n=5)	Paliative Group (n=5)	p-value
Age (min-max)	36 (27 - 62)	44 (30 - 57)	0.98
Stage*			0.02
IB3	1	0	
IIA2	1	0	
IIB	3	1	
IIIB	0	2	
IIIC1	0	1	
IVA	0	1	
Relapse time [†] (min-max)	7 (3 - 21)	5 (3 - 8)	0.25
Symptoms			0.04
Asymptomatic	1	0	
Vaginal bleeding / discharge	3	1	
Pelvic pain	1	0	
Vaginal bleeding / discharge and pelvic pain	0	2	
Rectovaginal fistula	0	2	

*According to the International Federation of Gynecology and Obstetrics classification. [†]Time interval between completion of primary treatment and recurrence in months.

Table 2. Pathological characteristics of ten recurrent cervical cancer patients.

Variable	Curative Group (n=5)	Paliative Group (n=5)	p-value
Lesion size (min-max)*	5 (2 - 7)	6 (2.6 - 9)	0.04
Number of organs involved	2 (1 - 3)	4 (3 - 5)	0.003
1	1	0	
2	3	0	
3	1	1	
4	0	1	
5	0	3	
Margins			0.07
Clear	5	1	
Positive	0	4	

* Largest tumor diameter in centimeters.

Uterus, vagina, and paraaortic lymph nodes were affected in one case after posterior exenteration. After total pelvic exenteration, uterus, vagina, bladder, and rectum were affected in one case; uterus, vagina, bladder, rectum, and ovaries in another case; and uterus, vagina, bladder, rectum, and peritonitis in two other cases. Regarding the anatomopathological examination, the lateral margins were microscopically affected in four of the five patients who underwent palliative pelvic exenteration.

Regarding postoperative complications, there were two major complications in the curative intent group: (i) a death due to urinary sepsis after total pelvic exenteration, and (ii) an abdominal wall abscess after radical hysterectomy. In the palliative pelvic exenteration group, there were three major complications: (i) a urinary fistula after posterior pelvic exenteration, (ii) a pelvic hollow abscess, and (iii) a systemic inflammatory response syndrome requiring hemodialysis (Table 3).

The rate of tumor recurrence in the group undergoing surgical salvage was 66%.

One case had progression of the disease in the bladder after radical hysterectomy, one case had progression of the disease in the peritoneum after anterior pelvic exenteration, and one case had inguinal lymph nodes after total pelvic exenteration. All patients undergoing surgical salvage carried out pelvic and paraaortic lymphadenectomy.

The median survival time was five months in the palliative group, and 16 months in the curative group; however, this difference was not statistically significant (p -value=0.06) (Figure 2). Up to February 2019, all the patients in the palliative group were dead, and only two patients in the curative group were alive.

In the univariate analysis, it was found that advanced stages (p -value=0.02), presence of significant symptoms such as rectovaginal fistulas or vaginal bleeding/vaginal discharge associated with pelvic pain (p -value=0.04), tumor size greater than five centimeters (p -value=0.04), and more than three organs involved (p -value=0.003) were factors significantly associated with non-curative surgery.

Table 3. Surgical characteristics of ten recurrent cervical cancer patients.

Variable	Curative Group (n=5)	Paliative Group (n=5)	p-value
Surgery type			0.68
Total pelvic exenteration	2	4	
Anterior pelvic exenteration	1	0	
Posterior pelvic exenteration	0	1	
Radical hysterectomy	2	0	
Reconstruction type			0.26
Ureteroileostomy + terminal colostomy	1	2	
Double-barreled wet colostomy	1	2	
Terminal colostomy	0	1	
Ureteroileostomy	1	0	
Without reconstruction	2	0	
Complications*			0.93
II	2	2	
IIIA	0	1	
IIIB	1	1	
IV	0	1	
V	1	0	

*According to the Clavien-Dindo classification.

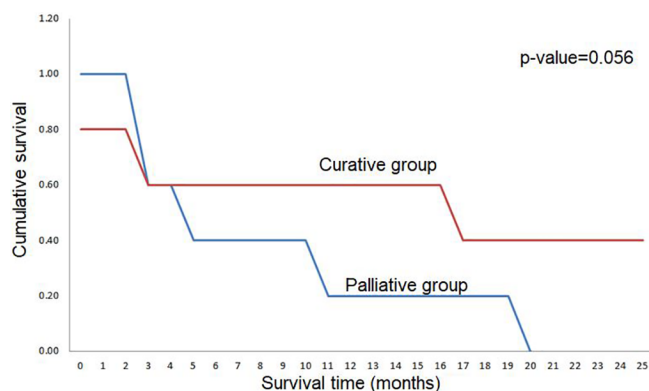


Figure 2. Survival analysis according to the Kaplan-Meier method.

DISCUSSION

Teixeira et al.³ showed that, in Brazil, 60% of cervical neoplasms are diagnosed at advanced stages. In our survey, 70% of all the cases were locally advanced or metastatic.

Our study analyzed radical hysterectomies and exenterative procedures only in recurrent cervical cancer patients who underwent chemotherapy and radiotherapy as their primary treatment. This type of study is rare in the literature and typically includes a small sample size⁵.

For the preoperative evaluation of recurrent disease, clinical and imaging examinations were performed. Peritoneal implants and compromised lymph nodes may go unnoticed in clinical restaging. Therefore, intraoperative evaluation of resectability is important^{21,22}. In our study, additional findings in the exploratory phase of laparotomies were observed: (i) peritoneal implants in two patients, (ii) paraaortic lymph node metastasis in one case, and (iii) ovarian metastasis in another case.

A positron emission tomography (PET/CT) scan is the most sensitive noninvasive test to determine any sites of distant disease. It can also differentiate a recurrent lesion from inflammatory or scarring changes^{23,24}. A recent study carried out with 40 patients with recurrent gynecological pelvic neoplasms analyzed the impact of PET/CT on pelvic exenteration candidates.

This exam changed the original surgery plan in 15 patients (37.5%), because it showed no disease in four cases, and showed unresectable or metastatic disease in 11 cases. However, even with PET/CT, six patients had findings of extra pelvic disease or lymph node metastasis during the surgical approach²⁵. Therefore, it should be performed prior to exenteration whenever possible. The associated cost and the low availability through free health insurance are limiting factors for the use of PET/CT.

Hysterectomy as a salvage surgery procedure can be performed if the lesion is small and limited to the uterus¹². A group from India⁵ analyzed 20 recurrent cervical cancer cases, of which seven underwent hysterectomy with bilateral pelvic lymphadenectomy. Two pelvic relapses were reported in their follow-up. Another recent study evaluated the effectiveness of hysterectomy in controlling pelvic disease in 40 patients with residual cervical cancer after radiotherapy and/or chemotherapy. It was shown that radical hysterectomy is more effective than extrafascial hysterectomy in local control¹⁹. Two cases in our study underwent radical hysterectomy, of which one recurred with pelvic disease.

When opting for pelvic exenteration, it is necessary to reestablish intestinal and/or urinary transits. In the case of simultaneous urinary and intestinal shunts, double-barreled wet colostomy is an interesting option. It does not require enteroenteric anastomosis, it is possible with a single stoma, and has a low morbidity rate²⁶. The need for longer surgical time and the risk of anastomotic fistulas in previously irradiated sites were factors considered for ostomy in patients undergoing exenterative procedures.

The improvement of surgical techniques and perioperative management, in addition to a more careful selection of patients, have reduced the mortality and morbidity rates in complex pelvic surgeries¹¹. In our study, the rates of mortality and major complications were 10% and 60%, respectively.

Radical hysterectomy is easier than a pelvic exenteration, however it also has complications. The Memorial Sloan-Kettering Cancer Center reported fistulas in 48% of the 21 operated women²⁷. The separation of adjacent structures to the uterus becomes challenging in an irradiated pelvis.

The indications for salvage surgery come from retrospective studies. Some factors to be considered to indicate surgery include: performance status, comorbidities, disease-free interval after completion of chemo-irradiation, tumor size, surgery with curative intention, and absence of signs and symptoms that suggest a compromised pelvic wall, e.g., lower limb edema, lumbocytalgia, and hydronephrosis^{7-11,22,28-30}. In our study the operated patients were young, had no comorbidities, and had good performance status.

The time between the end of primary treatment and recurrence correlates with overall survival and the disease-free interval. According to Marnitz et al.⁷, the overall survival at five years was 16% for those who relapsed within two years, and 28% when the interval was between two and five years (p -value=0.01). A retrospective study⁸ was carried out with gynecological tumor patients who were submitted to pelvic exenteration after treatment with radiotherapy. Of those patients, 66% had cervical cancer. Results showed a recurrence rate of 50%, and a shorter overall survival time for those who required surgery within two years after the end of the initial treatment. Comparatively, in our study, no patient had a disease-free interval greater than two years after completion of radiotherapy and chemotherapy.

The tumor size has been one of the criteria for identifying who would benefit from surgical

management; however the cutoff point is not clearly defined. A Korean study⁹ showed, through a multivariate analysis, that a tumor larger than four centimeters is a predictive factor for recurrence after exenterative procedures. However, a Brazilian cohort on pelvic exenteration for gynecological tumors found that the number of organs involved was more relevant than tumor diameter regarding survival. Perineural invasion was also relevant in cancer-specific and progression-free survival³¹. In our cohort, perineural invasion was present in all surgical specimens.

Palliative pelvic exenteration is a controversial and largely debated topic²². This procedure was carried out in patients with significant symptoms such as rectovaginal fistula and vaginal bleeding / discharge associated with pelvic pain. It was only considered if there were no other effective therapies available. Our study indicated that besides the significant symptoms, advanced stage, tumor size greater than five centimeters, and more than three organs involved were factors significantly associated with non-curative surgery. Median survival time in the palliative group was low (five months).

Marnitz et al.⁷ reported that the two-year survival rate was 60% for patients treated with curative intent and 10.5% for those treated with palliative intent (p -value=0.0001). A study¹⁶ with 13 patients with gynecological malignancies undergoing palliative total pelvic exenteration reported two procedure-related deaths, a morbidity rate of 38.4%, an overall two-year survival rate of 15%, and a cancer-specific survival rate of 20%. Only three patients survived more than 12 months.

The main limitation of our study is the retrospective analysis of a small number of cases, which decreased the statistical power of the study.

There are a few pelvic recurrence cases that occur after radiotherapy and chemotherapy that are eligible for surgery. Therefore, the publication of studies with a considerable sample size from a single health center will be scarce.

Positive aspects of our study include: (i) the homogenization of the sample, (ii) the clear methods in relation to the origin of the patients submitted to surgical procedures, and (iii) the Brazilian pioneering spirit of the study, which may serve as a basis for the elaboration of a multicenter study.

CONCLUSION

The morbidity rates of this study were higher in the palliative group. The median survival time was lower in the palliative group than in the curative group, but this difference in survival was not statistically significant. Advanced stage, symptoms, tumor size, and number of organs involved are factors that should be taken into consideration when indicating surgical salvage.

R E S U M O

Objetivos: Analisar os resultados de morbidade e sobrevida após cirurgias curativas e paliativas em pacientes com câncer cervical recidivado após tratamento primário com radioterapia e quimioterapia. Outro objetivo foi avaliar os fatores associados aos procedimentos curativos e não curativos. **Métodos:** Coorte retrospectiva de pacientes submetidos à cirurgias curativas e paliativas, entre janeiro de 2011 a dezembro de 2017, em um centro de alta complexidade em oncologia. O desfecho da morbidade foi relatado de acordo com a classificação de Clavien-Dindo e a análise de sobrevida foi realizada pelo método de Kaplan-Meier. Para avaliar os fatores associados aos procedimentos, foi realizada análise univariada pelo teste U de Mann-Whitney. **Resultados:** Foram realizadas duas histerectomias radicais, três exenterações pélvicas com intenção curativa e cinco exenterações pélvicas paliativas. No grupo curativo, houve complicações maiores em 40% dos casos, e o tempo mediano de sobrevida foi 16 meses. No grupo paliativo, houve complicações maiores em 60% dos casos, e o tempo mediano de sobrevida foi 5 meses. Estadiamento avançado ($p=0,02$), sintomas ($p=0,04$), tamanho do tumor maior que cinco centímetros ($p=0,04$) e mais de três órgãos envolvidos ($p=0,003$) foram fatores significativamente associados a cirurgia não curativa. **Conclusões:** As taxas de morbidade foram maiores no grupo paliativo, e o tempo mediano de sobrevida foi menor no grupo paliativo do que no grupo curativo, entretanto esta diferença na sobrevida não teve significância estatística. Estádio avançado, sintomas, tamanho tumoral e número de órgãos envolvidos são fatores que devem ser levados em consideração na indicação de resgate cirúrgico.

Descritores: Neoplasias do Colo do Útero. Exenteração Pélvica. Histerectomia. Recidiva.

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