Resection of Pulmonary Metastases in 148 Patients: Analysis of Prognostic Factors

Javier Ayarra Jarne, Rafael Jiménez Merchán, Miguel Congregado Loscertales, Juan Carlos Girón Arjona, Gregorio Gallardo Valera, Ana Isabel Triviño Ramírez, Carlos Arenas Linares, and Jesús Loscertales

Servicio de Cirugía General y Torácica, Hospital Universitario Virgen Macarena, Sevilla, Spain

OBJECTIVE: To evaluate the prognostic factors for survival in a series of patients who underwent surgery for pulmonary metastases from primary tumors in distinct organs.

PATIENTS AND METHODS: This was a retrospective study of 148 patients operated between May 2001 and May 2007. Multivariate analysis was used to evaluate overall survival. Patients scheduled for tumorectomy were included provided their primary tumor was controlled and they had no extrathoracic recurrence and adequate cardiorespiratory function. The influence of the following prognostic factors was analyzed: number and diameter of the metastases, lymph node infiltration, complete resection, and, above all, histological type. A significance level of 95% was used.

RESULTS: A total of 90 men (60.81%) and 58 women (39.19%) were operated. The mean (SD) age was 56.5 (9.7) years. The actuarial survival at 6 years was 30.3% (n=45) and the median survival was 34 months. The factors that affected survival were the number of metastases (*P*<.05), diameter of the lesions (*P*<.05), lymph node infiltration (*P*<.05), complete resection (*P*<.05), and, above all, histological type (*P*<.05). Tumorectomy was the most commonly performed operation.

CONCLUSIONS: These results suggest that, in the absence of other therapeutic options and contraindications, we should operate on patients in whom the primary tumor is controlled and in whom complete resection can be performed. Even if factors associated with poor prognosis are present, the outcomes are always better than when surgery is not performed, particularly in view of the relatively low morbidity and mortality associated with this type of surgery.

Key words: *Pulmonary metastases. Pulmonary resection. Video-assisted thoracoscopic surgery. Risk factors. Prognosis. Survival.*

Cirugía de metástasis pulmonares en 148 pacientes. Análisis de sus factores pronósticos

OBJETIVO: Evaluar los factores pronósticos de supervivencia en una serie de pacientes intervenidos por metástasis pulmonares de diferentes tumores y órganos.

PACIENTES Y MÉTODOS: Se ha realizado un estudio retrospectivo de 148 pacientes intervenidos entre mayo de 2001 y mayo de 2007, y se ha aplicado un análisis multivariante para valorar la supervivencia global. Los criterios de inclusión fueron: control del tumor primario, sin recurrencia extratorácica y función cardiorrespiratoria suficiente, siempre con intención de tumorectomía. Se valoró qué influencia tenían en el pronóstico los siguientes factores: número de metástasis, diámetro de éstas, adenopatías invadidas, cirugía completa y, sobre todo, tipo histológico, para un nivel de significación del 95%.

RESULTADOS: En total se intervino a 90 varones (60,81%) y 58 mujeres (39,19%). La edad media ± desviación estándar era de 56,5 ± 9,7 años. Se obtuvo una supervivencia actuarial a 6 años del 30,3% (n = 45), con una mediana de supervivencia de 34 meses. Los factores que influyeron en el pronóstico fueron el número de metástasis (p < 0,05), el diámetro de éstas (p < 0,05), la presencia de adenopatías invadidas (p < 0,05), la cirugía completa (p < 0,05) y, sobre todo, el tipo histológico (p < 0,05). La tumorectomía fue la intervención más realizada.

CONCLUSIONES: Los resultados avalan que aceptemos para tratamiento quirúrgico a los pacientes sin otra posibilidad terapéutica a quienes pueda realizarse una resección completa, que tengan el tumor primario controlado y no presenten otras contraindicaciones, pues, aunque en presencia de ciertos factores empeora la supervivencia, los resultados son siempre mejores que con la abstención quirúrgica, máxime si se tienen en cuenta las cifras relativamente bajas de morbilidad y mortalidad con este tipo de cirugía.

Palabras clave: *Metástasis pulmonares. Resección pulmonar. VATS. Factores de riesgo. Pronóstico. Supervivencia.*

Introduction

The presence of distant metastases is a sign of systemic spread and the most important negative prognostic factor in patients with cancer. After the liver, the lung is the organ most commonly affected by metastases—lung metastases are present in 20% to 54% of all cancers. They can be resected in 15% to 25% of cases, achieving a 5-year survival

Correspondence: Dr J. Ayarra Jarne
Servicio de Cirugía Torácica, Hospital Universitario Virgen Macarena
Avda. Dr. Fedriani, s/n
41071 Sevilla, Spain
E-mail: javierayarra@tecnifip.com

Manuscript received August 15, 2007. Accepted for publication February 9, 2008

of 30% to 40% whether through surgery alone or with associated chemotherapy.[1] Sarcomas show a particular tendency to metastasize to the lung; the majority present in the first 2 years and usually develop without lymph node involvement.[2]

The first metastasectomy is attributed to the French surgeon Sedillot who, in 1855, resected a chest wall tumor with a single pulmonary metastasis.[3] In 1883, Kronlein[4] reported a case arising from a sarcoma of the chest wall and that was treated surgically; the patient survived 7 years. In 1933, in the United States of America, Barney and Churchill[5] treated a metastasis from a renal carcinoma, with a survival of 23 years, and in 1944, Blalock[6] published another case of colorectal origin. In 1947, Alexander and Haight[7] published the first series (25 cases), which included some major resections, and in 1965 Thomford and coworkers[8] published the results of 205 metastasectomies, achieving a 5-year survival of 30.3%. There were many other publications during that decade, though with widely varying outcomes due to the heterogeneity of the samples.

The International Registry of Lung Metastases was set up to cover the need to unify patient selection criteria. Its results were published in 1997 and included 5206 patients from various hospitals in the United States and Europe.[9] Although the true benefit of surgery in this field is still under discussion, it is generally accepted that without surgery the mean survival of patients is 10 months, with a 5-year survival below 5%, whereas surgical treatment has achieved survival rates of 21% to 43% at 5 years.[10]

Some tumors, such as choriocarcinoma, osteosarcoma, testicular tumors, and melanoma, have a tendency to produce single lung metastases, whereas others, such as soft tissue sarcomas (85%), breast cancer (60%), and tumors of the colon and kidney, give rise to multiple metastases.[11] It must be realized that when a patient with a known extrathoracic tumor presents a solitary pulmonary nodule, there is a 24% probability that it is a metastasis; the probability is 3% if a primary tumor has not been documented.[12] However, single metastases are uncommon and an exhaustive search must therefore be performed as surgical treatment is not as effective if multiple metastases are present.[13]

The initial criteria for performing metastasectomy, described by Ehrenhaft[14] in 1958, have been extended and the current consensus is as follows: *a)* the primary tumor must be controlled and this must be confirmed with all available techniques; *b)* there must be no metastases in other organs (if there is another single metastasis and it is decided to perform surgery, the pulmonary metastasis should be excised in a second operation); *c)* all nodules must be excised, although the maximum accepted number has not been defined; *d)* lung function tests must ensure respiratory function will be adequate after the operation; and *e)* there must be no major contraindications to this type of surgery.[9] At the present time, there are other unanimously accepted indications: *a)* that effective chemotherapy is available after surgery; *b)* when there is difficulty differentiating between a metastasis and a primary tumor; *c)* that there is no other nonsurgical treatment available; and *d)* for symptomatic pulmonary metastases (hemoptysis, hemothorax, pneumothorax, etc).

TABLE 1
Localization of the Primary Tumor

Colon	50
Breast	23
Osteosarcoma	13
Soft tissue sarcoma	10
Cutaneous melanoma	10
Lung	9
Rectosigma	9
Thyroid	5
Liver	5
Kidney	5
Germ-cell tumors	4
Endometrium	3
Leiomyosarcoma	3
Thymus	3
Mature teratoma	2
Pancreatic adenocarcinoma	1
Esophagus	1
Bladder	1
Squamous cell carcinoma	1
Parotid mucoepidermoid tumor	1
Gall bladder	1
Ovary	1

TABLE 2
Type of Resection

Unilateral wedge resection	122
Bilateral wedge resection	14
Lobectomy (2 VATS)	8
Segmentectomy	8
Wedge resection plus lobectomy (ipsilateral)	3
Pneumonectomy	3
Lobectomy to complete a pneumonectomy	3

Abbreviation: VATS, video-assisted thoracic surgery.

Patients and Methods

Between May 2001 and May 2007, a total of 161 operations were performed on 148 patients (13 of these were reoperations for new metastases) with a mean (SD) age of 56.5 (9.7) years (range, 15-78 years); 58 patients were women (with 62 operations) and 90 were men (with 99 operations).

Eighty-eight percent of the patients were asymptomatic and the metastasis was discovered in control studies performed for follow-up of the primary tumor. A basic radiologic study was performed in all patients and was diagnostic in 93%, though not specific. Conventional computed tomography (CT) was performed in 44% and helical CT in the remainder. Positron emission tomography (PET), which was performed in 16 patients, had significant negative predictive value and was more effective at detecting possible mediastinal lymph node involvement than nodules smaller than 8 mm (Figure). Fibreoptic bronchoscopy was performed in all patients to exclude endobronchial lesions. Tumor staging studies, which varied according to the disease (abdominal CT with contrast, PET, scintigraphy), had already been performed in all patients, and lung function tests based on the forced vital capacity, forced expiratory volume in 1 second, and carbon monoxide diffusion capacity were performed in all cases. Ventilation-perfusion scans were only performed on those patients in whom pneumonectomy was considered.

The sites of the primary tumors are shown in Table 1. That tumor had to be controlled and show no signs of recurrence in order for the patient to be included. The types of resection used

TABLE 3
Surgical Approach

Lateral thoracotomy	79
Videothoracoscopy	58
Bilateral lateral thoracotomy	11
Posterolateral thoracotomy	4
Video-assisted thoracic surgery	2
Midline sternotomy	4
Right videothoracoscopy and left thoracotomy	1
Left videothoracoscopy and right thoracotomy	1
Bilateral anterolateral and transsternal thoracotomy (clamshell)	1

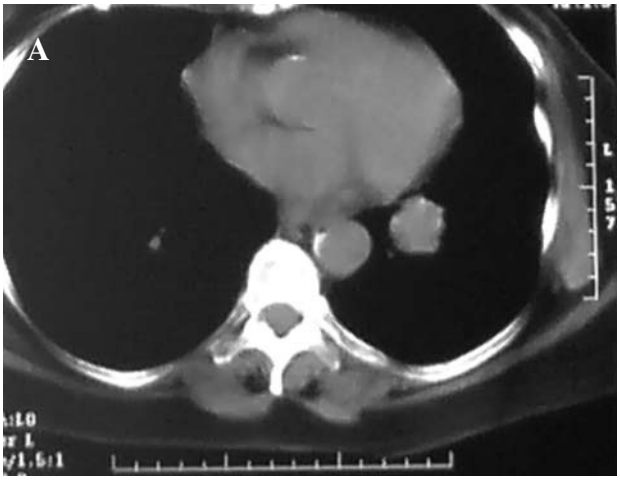
to treat the lesions are shown in Table 2. The lesions treated by thoracoscopy were localized by direct visualization in 27 patients, by instrumental palpation in 17, digital palpation in 14 (minimally extending 1 of the entry incisions), and by the preoperative insertion of a hook-wire under CT guidance in 9 patients in whom the lesion was central or was less than 1 cm in diameter.

The surgical technique chosen was wedge resection with a margin of 1 to 2 cm, performed using endostaplers (3.5 mm Endo GIA, Autosuture); over the past 3 years we have buttressed the suture margins with polyglycolic acid sheaths in order to prevent air escape. In no case did we perform enucleation. Lobectomy was only performed when the lesion was larger than 4 cm, centrally situated, or multilobar. When the resection was performed by video-assisted thoracoscopic surgery (single metastasis of less than 4 cm on CT scan or to obtain material for diagnosis), 3 entry ports were used: 1 in the seventh or eighth intercostal space in the midaxillary line, a second in the third or fourth space in the anterior axillary line, and a third in the fifth or sixth space in the posterior axillary line. When lobectomy was performed by video-assisted thoracoscopic surgery, a small submammary incision of 4 to 5 cm was also made. Lymph node resection was not performed systematically in all patients. The criterion applied was to excise lymph nodes with a macroscopic appearance suggestive of malignant disease on examination of the mediastinal space.

We have analyzed the influence of the following factors on the prognosis: number of metastases, diameter of the metastases, lymph node infiltration, complete resection, and, above all, histological type, using a significance level of 95%.

Statistical Analysis

Survival and the multivariate data were analyzed using the BMDP statistical package (Statistical Software, Los Angeles, California, USA). Survival curves were calculated using the Kaplan-Meier method and the differences between groups were analyzed by ranges. Significance was taken as a *P* value less than .05. This statistical analysis was used to evaluate the prognostic factors. The Cox model was used for the multivariate analysis.



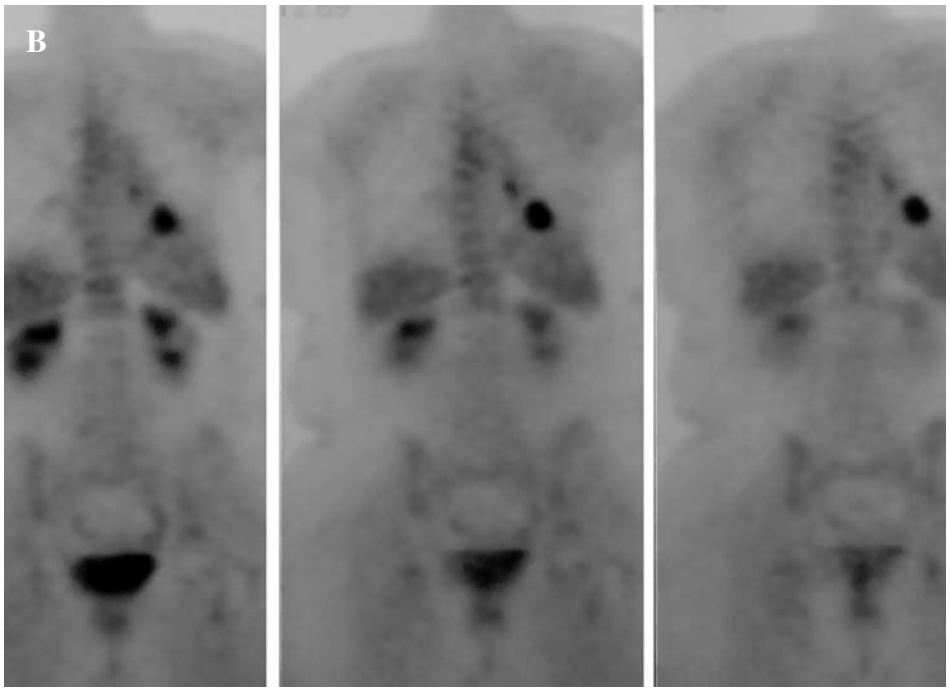


Figure 1. Single pulmonary metastasis in a patient operated for carcinoma of the breast. Computed tomography shows its localization in the left lower lobe *(A)* and positron emission tomography confirms the suspicion *(B)*.

Results

The surgical approaches used are shown in Table 3. With regard to the number of metastases with postoperative pathological confirmation, 88 were single, 59 were multiple and unilateral, and 14 were bilateral. There was a mean of 2.2 metastases per patient (range, 1-13). Based on the pathology report, the mean size of the metastases was 2.90 cm.

The length of postoperative stay was 7.4 (3) days (range, 4-19 days). Complications occurred in 17 patients (10.6%) and were generally minor: 10 apical pneumothoraces and 6 cases of prolonged air leakage that resolved completely. There was 1 empyema that resolved with drainage and 1 lung abscess in a patient who died. Two other patients died, 1 due to pulmonary thromboembolism and the other to postoperative liver and kidney failure; these 3 deaths represented 1.86% of the study group.

The mean actuarial survival calculated at 6 years, with a follow-up of 2 to 72 months, was 30.3% and the median survival was 34 months. When resection was complete (n=147), 3-year survival was 32.2%, and this fell to 11% when the resection was incomplete (n=14); none of these latter patients was alive at 5 years (significant difference, *P*=.003). The number of metastases resected also had a significant effect, as the mean survival was 38 months with less than 4 metastases and 21 months with 4 or more (*P*=.002). The diameter of the tumors also had a significant effect: the mean survival with metastases less than 3.5 cm was 37.2 months vs 28 months when the diameter was larger (*P*=.004).

However, the most important predictive factor appeared to be the histological type of the primary tumor. Germ-cell tumors, which have an excellent response to chemotherapy, presented a 5-year survival of 66%, whereas this survival fell to 19.3% in patients with metastases from melanomas. There was a large group with intermediate results (breast, colon, and kidney), with a 5-year survival of 34.5%-37.3% (*P*=.002).

Lymph node disease was found in 26.4% of the 37 patients with synchronous metastases, and this was classified as N2 in 9 cases (6.4%). The 5-year survival was of 30.3% in patients with no lymph node disease vs 9% in patients with N2 disease (*P*=.003). We did not find significant differences between the N0 and N1 groups.

Discussion

The International Group for the Study of Lung Metastases was set up in 1997 and included important thoracic surgery teams from Europe and the United States.[9] The aim was to select certain prognostic factors and calculate the survival of patients treated surgically for this disease. The group reached the conclusion that there were 3 important prognostic factors: the disease-free interval (worse prognosis if less than 36 months), single or multiple metastases, and resectability. Based on these factors, 4 groups were defined with median 5-year survivals that varied between 61 and 14 months. Other factors, including tumor histology, type of pulmonary resection, lymph node disease, and complete resection, have been added since that time.

All our patients satisfied the required selection criteria: *a)* controlled primary tumor, confirmed through various radiographic studies (CT, magnetic resonance imaging, ultrasound, scintigraphy, etc, depending on the case), endoscopy, blood tests (carcinoembryonic antigen in digestive tract tumors, human chorionic gonadotropin in gonadal tumors, etc); *b*) no extrapulmonary metastases (for which PET was useful for confirmation) except in certain cases of liver metastases in colorectal carcinoma; *c)* a wide surgical margin or, likewise, complete resection, giving survivals of 63% at 3 years and 51% at 5 years, vs 33% and 23%, respectively, when resection was incomplete; *d)* the number and size of the metastases (better with 1 or 2 metastases than with more than 2, and 3 cm was an evaluable size for establishing a prognosis; survival was of 48% for smaller metastases and 27% for larger ones); *e)* the unilateral or bilateral localization of the lesions did not have any effect[15]; and *f)* functional studies demonstrated the criteria required for performing a successful operation.

In our experience, the prognostic factors that were important were the histological type (with very good results when the primary tumor was of germ-cell origin[16] and very poor results when it was a melanoma); the disease-free period (a better prognosis when this was greater than 12 months; when it exceeded 36 months it was no longer considered to be a predictive factor)[9]; and the absence of mediastinal lymph node infiltration. A number of studies have reported major prognostic value for the presence of mediastinal lymph node involvement,[17] as its presence leads to a higher rate of recurrence and a lower survival,[18] with a better prognosis being found when only 1 lymph node station was affected.[19] However, other publications have not found these differences.[20] This factor was found to be important in our study.

The following aspects were considered to be important when deciding on the surgical approach: that it should be the least aggressive; that, in the majority of cases, it should permit manual palpation; and that all resections required can be performed. We believe that the 2 approaches that satisfy these requirements are midline sternotomy for bilateral metastases, and lateral thoracotomy for unilateral disease. We only considered bilateral anterior thoracotomy with transverse sternotomy for nodules with a posterior localization, particularly in the left hemithorax, as this type of resection is difficult via a sternotomy. A sequential lateral thoracotomy may also be used in these cases, with a recommended period between procedures of 6 weeks.[21] We do not have any experience in the use of extended pneumonectomy[22] for this type of surgery; this approach may be acceptable, given the better survival achieved, though it could appear to be very aggressive.

The role of videothoracoscopy in the treatment of unilateral metastases continues to be highly controversial. Many of the studies that recommended against the use of this technique were performed with early-generation instruments. Attention is drawn to the study by MacCormack and coworkers,[23] in which 56% of the metastases detected had not been diagnosed previously. We believe that these criteria should at least be reviewed today, after the appearance of the new-generation CT machines, particularly the thin-section helical CT. When

the results with these new machines were compared with those of high resolution CT, they had a sensitivity of 82.3% vs 75% with the latter machine, and a sensitivity of 61.5% vs 48% with high resolution CT for the detection of nodules smaller than 6 mm.[24] Thus, videothoracoscopy may be used when fewer than 3 lesions are detected in the preoperative studies, they have a peripheral, unilateral localization, and they are smaller than 3 cm in diameter; it may also be used for diagnostic purposes with bilateral lesions, and for lesions not associated with sarcoma. Some authors have published their results, which are equal to or better than thoracotomy.[25] In addition, it should also be remembered that videothoracoscopy has less effect on lung function, although any difference disappears with time. Ninomiya and coworkers[26] found a decrease of 21.3% in the vital capacity with video-assisted thoracoscopic surgery compared to 61% with conventional surgery. Landrenau and coworkers[27] compared postoperative pain and exercise after the use of each type of surgery and the results were much better after videothoracoscopy. Reoperation has also been shown to be easier when the first operation is performed by video-assisted thoracoscopic surgery,[28] finding fewer and looser adhesions and better tolerance to the operation.[29] In any case, reoperation has not led to poorer results with regard to overall survival, as found in the series by Muñoz-Llarena and coworkers.[30] Finally, it has been shown that when only unilateral lesions are found, contralateral examination to search for other possible metastases is not necessary.[31]

Although localization of the lesion or lesions is sometimes difficult by videothoracoscopy, it is usually simple when they are subpleural, as they are immediately visible or may be indicated by an area of atelectasis. It is sometimes necessary to make several passes with an instrument in order to localize the lesion, or even to perform digital palpation through one of the entry ports. The placement of a hook-wire under CT guidance[32] some hours before the operation may be used to help locate the lesion, a common technique in our hospital, and also methylene blue injection.

The type of surgical resection that should be chosen is one that enables the nodule or nodules to be resected with a 1 to 2 cm margin and that spares as much lung tissue as possible. When these 2 conditions are satisfied, metastasectomy can be performed with mechanical staplers, electrocautery, or laser. Rolle and coworkers[33] state that the use of laser permits a larger number of metastasectomies to be performed than with the electrosurgical scalpel or staplers, and also leads to fewer lobectomies due to its greater ability to preserve parenchyma. In addition, patients who are disease-free except for recurrent metastases can benefit from up to 4 reoperations.[34]

Lobectomy is only indicated when it is not possible to perform metastasectomy due to incomplete resection, large or centrally located lesions, or multiple lesions in a single lobe. Pneumonectomy is only indicated in highly selected cases with large, centrally located lesions, or in endobronchial lesions, which are relatively common when the origin is the colon, kidney, or breast. The treatment of a lesion due to carcinoma should be more restrictive than for a sarcoma, and 5-year survival is 20%.[35] In the presence of lymph node invasion (28.6% of cases), survival is lower and the treatment is not considered curative.

We also consider the disease-free interval to be an important predictive factor as the 5-year survival was 43% in those patients operated after a disease-free interval greater than 24 months and the median survival was of 49 months, whereas only 8% of those who did not have this period free of disease were still alive at 5 years, and the median survival was 29 months (P=.004).

After complete resection, and with a perioperative mortality of 0.5% to 1%, the 5-year survival is 25% to 35% and the 10-year survival 15% to 25%. These figures refer to those cases with the following prognostic indicators: short duplication time; the longer the disease-free interval the better (with a disease-free interval over 36 months, the 5-year survival was greater than 46%); and the number of metastases (better with a single lesion [40% survival at 5 years and 30% at 10 years] than with more than 4 lesions [5-year survival of 25% and 10-year survival of 15%]).

An additional factor of undeniable importance is the histological type: germ-cell tumors have the best prognosis (5-year survival of up to 68%) and melanomas the worst (21% survival at 5 years). Thanks to metastasectomy, which may be repeated on 3 or 4 occasions, survival in cases of sarcoma, which often metastasize to the lung, have a greater tendency to recurrence, and are resistant to conservative treatments, has increased from 17% to 48% after surgery.[36] There is a large group that we could define as having an intermediate response, with survivals around 38% at 5 years and 18% at 10 years; the origin of the lesions in these cases is the ovaries, breast, kidney, colon, and others.[37]

Although the choice of local treatment may appear insufficient for a systemic disease, it is supported by the results. All patients for whom there are no other therapeutic options and in whom complete resection can be performed, in whom the primary disease is controlled, and who do not present contraindications should be accepted. Even if factors associated with poor prognosis are present, the outcomes are always better than when surgery is not performed, particularly in view of the relatively low morbidity and mortality associated with this type of surgery.[38]

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