Arch Bronconeumol. 2011;**47(3)**:134-137

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Original Article

Surgery of female genital tract tumour lung metastases

Guillermo González Casaurrán,[a,*] Carlos Simón Adiego,[a] Rafael Peñalver Pascual,[a,b] Nicolás Moreno Mata,[a] Miguel Ángel Lozano Barriuso,[b] Federico González Aragoneses[a]

[a]*Servicio de Cirugía Torácica, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[b]*Servicio de Oncología Radioterápica, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

ARTICLE INFO

Article history:
Received July 18, 2010
Accepted October 30, 2010

Keywords:
Drug therapy
Pulmonary metastases
Surgical procedures
Uterine neoplasms

ABSTRACT

Introduction: Lung metastases originating from tumors of the female genital tract are rare. Due to this rarity and their variable histology, it has been difficult to compare different patient series.
Material and methods: A retrospective study of patients who underwent resection of lung metastases of female genital tract tumors (uterine, fallopian and cervical cancer) during the period from 01/01/1989 to 12/31/2006. Epidemiological, diagnostic and treatment data were collected. Non-parametric tests and the survival analysis were performed using the Kaplan-Meier curves and the log-rank test.
Results: During the study period, 27 underwent resection. Mean disease-free interval (DFI) from initial diagnosis to the diagnosis of metastasis was 58 months (1-195 months). Mean survival from the diagnosis of metastasis was 94 months. The overall 5-year survival after diagnosis of metastasis was 84.1%. A second surgery for metastasis was performed on 5 patients (18.5%). Survival after second surgery of metastases was 80.5 months. Five-year survivals from diagnosis of metastasis were: endometrial carcinoma 100%; cervical cancer 62.5%; uterine sarcoma 60%. Adjuvant hormone therapy was prescribed in15 out of 16 patients with endometrial carcinoma. There was a statistically significant difference in survival depending on the histological type and disease free interval.
Conclusion: Surgical treatment of lung metastases originating from female genital tract tumors (mainly endometrial carcinoma) is associated with a high long-term survival.

Cirugía de las metástasis pulmonares de tumores del tracto genital femenino

Palabras clave:
Tratamiento médico
Metástasis pulmonares
Procedimientos quirúrgicos
Neoplasias uterinas

RESUMEN

Introducción: Los tumores del tracto genital femenino constituyen una etiología poco frecuente de metástasis pulmonares. Debido a esto y a su variada histología, la comparación de resultados ha resultado complicada hasta la fecha.
Material y métodos: Estudio retrospectivo de pacientes intervenidos de metástasis pulmonares de tumores del tracto genital femenino (cuerpo, trompa y cuello de útero) en el periodo 01/01/1989-31/12/2006. Se recogen datos referentes a aspectos epidemiológicos, de diagnóstico y tratamiento. Se han utilizado tests no paramétricos, y el análisis de supervivencia se ha realizado con curvas de Kaplan-Meier y el *log-rank test*.
Resultados: Durante el periodo descrito se ha intervenido a 27 pacientes. Intervalo libre de enfermedad (ILE) desde el diagnóstico inicial al de metástasis pulmonares 58 meses (1-195 meses). Mediana de supervivencia desde el diagnóstico de metástasis 94 meses. Supervivencia global tras diagnóstico de metástasis a 5 años: 84,1%. Segunda cirugía de metástasis: 5 pacientes (18,5%). Supervivencia tras segunda cirugía de metástasis: 80,5 meses. Supervivencia desde el diagnóstico de metástasis a 5 años: carcinoma de endometrio 100%; cáncer de cérvix 62,5%; sarcoma uterino 60%. Recibieron hormonoterapia adyuvante 15 de 16 pacientes con carcinoma de endometrio. Hallamos diferencias estadísticamente significativas en la supervivencia en función de: tipo histológico, e intervalo libre de enfermedad.

*Corresponding author.
E-mail address: ggcasaurran@gmail.com (G. González Casaurrán).

0300-2896/$ - see front matter

Conclusión: El tratamiento quirúrgico de las metástasis del tracto genital femenino (principalmente de las de carcinoma de endometrio) se asocia a una elevada supervivencia a largo plazo.

Introduction

The *International Registry of Lung Metastases* (IRLM) has shown an overall post-resection five-year survival of pulmonary metastases of 36%, as well as the existence of different variables (disease-free interval, number of metastases resected, and complete or incomplete resection) used to create prognostic groups.[1] This study also demonstrated the role of histological type as an independent prognostic factor. In this regard, metastases of sarcoma and epithelial tumors (with a 5-year survival of 30-60%) occupy an intermediate place between germ-cell/Wilms tumors and melanoma.[2-7] Tumors of the female genital tract constitute 18% of the pulmonary metastases treated surgically in our Thoracic Surgery unit, and they present the peculiarity of including tumors in varying locations (uterus, cervix, ovaries, fallopian tubes) and type (adenocarcinoma, epidermoid carcinoma, sarcoma, etc.), which make it difficult to compare results. This study intends to analyze survival in these cases and those factors that are an influence.

Material and Methods

Ours is a retrospective study of all those patients who had undergone curative resection of pulmonary metastasis of female genital tract tumors (uterine body, fallopian tubes and cervix) in the period between January 1, 1989 and December 31, 2006, in the Hospital General Universitario Gregorio Marañón (Madrid). Ovarian tumors were not included due to their limited prevalence (two cases). One uterine tube tumor was grouped with the endometrial adenocarcinoma. The following variables were analyzed: age at the diagnosis of the primary tumor/at the diagnosis of the metastasis; disease-free interval (DFI); overall survival, 5-year survival; IRLM group;[1] histological type; degree of differentiation; stage of the primary tumor (following the staging system by the International Federation of Gynecology and Obstetrics [FIGO]);[8] post-op mortality (first 30 days after surgery); number of metastases resected; mean size of metastasis (mean diameter); type of surgical approach; type of resection; and degree of lymph node affectation (following the classification by Mountain et al. for bronchogenic carcinoma).[9] The quantitative variables are expressed as averages and their range, and they are analyzed using non-parametric tests. The survival analysis was calculated with Kaplan-Meier curves, *log-rank test,* and the Breslow test. Data analysis was carried out using SPSS 13.0 software.

Results

We found 27 patients who had undergone surgery in the 18-year study period. Mean age at diagnosis of pulmonary metastasis was 62 (33-77). Mean follow-up was 94 months (11-280 months). We classified the tumors found according to their histological type: 16 cases endometrial carcinoma (59.2%); 6 cervical cancer (22.2%) (4 adenocarcinoma and 2 cervical epidermoid carcinoma); 5 uterine sarcoma (18.5%). We found 5 poorly-differentiated tumors (18.2% G3). The stage of the primary tumor at the time of diagnosis is reflected in table 1.

Table 1
Initial stage

	Stage I	Stage II	Stage III	Stage IV
Endometrial carcinoma	50%	12%	38%	
Cervical cancer	50%	33%	16%	
Uterine sarcoma	80%		20%	

In 25 cases (92.6%), initial gynecological surgery consisted of total hysterectomy and double annexectomy**.** Twenty-three patients (85.2%) received pelvic and/or para-aortic radiotherapy after surgery of the primary tumor.

The mean number of pulmonary metastases resected was 1. Out of the total number of cases, 18 (66.7%) presented only one metastasis, 5 (18.5%) presented two, and 4 (14.8%) presented more than two. Mean size was: endometrial carcinoma, 18 mm (7-40); cervical cancer, 15 mm (10-30); uterine sarcoma, 19.5 mm (1-67).

The most frequently used surgical approach for resecting the pulmonary metastases was thoracotomy 81.2% (n = 22), followed by sequential bilateral thoracotomy 7.4% (n = 2), unilateral video-assisted thoracoscopy 3.7% (n = 1), sequential bilateral video-assisted thoracoscopy 3.7% (n = 1), and video-assisted thoracoscopy + thoracotomy 3.7% (n = 1). Lung resection consisted of: wedge resection, 81.5% (n = 22); lobectomy, 11.1% (n = 3); segmentectomy, 3.7% (n = 1); and atypical resection + parietectomy, 3.7% (n = 1). Perioperative mortality was 3.7% (one patient). Thirteen patients (48.1%) were in group I of the IRLM, 11 (40.7%) in group II, and 3 (11.1%) in group III. Lymphadenectomy (generally systematic or selective sampling) was performed in 8 patients (26.6%). 62.5% (n = 5) were N0, 12.5% (n = 1) N1, and 25% (n = 2) N2.

Table 2 shows the adjuvant treatment received after the appearance of lung metastases. 55.5% of patients (15 of the 16 patients with endometrial carcinoma) received adjuvant hormone therapy. The only patients that received chemotherapy did so after initial gynecological surgery (cervical cancer, n = 1), or after tumor progression (4 out of 5 patients with uterine sarcoma).

Table 3 and figure 1 reflect the data for age at diagnosis of lung metastasis, DFI (after resection of the primary tumor); mean survival, 5-year survival and relapse rate after lung metastasis resection. We found a 5-year survival after metastasis surgery of 84.1% (100% in patients with endometrial carcinoma).

Mean progression-free survival after the first metastasis surgery was 63 months (7-280 months). Mean survival after the first lung

Table 2
Types of treatment after the first metastasis surgery

	2nd Surgery	3rd Surgery	Lung RTx	HTx	Adjuvant CTx
Endometrial carcinoma	2 (12.5%)		2 (12.5%)	15 (93.75%)	0%
Cervical cancer			1 (16.6%)		0%
Uterine sarcoma	3 (60%)	2(40%)			0%
Total	5 (18.5%)	2 (7.4%)	3 (11.1%)	15 (55.5%)	0%

CTx: chemotherapy; HTx: hormone therapy; RTx: radiotherapy.

Table 3
Survival and relapse rate

	Age at diagnosis of metastasis (years)	DFI (months)	Survival after metastasis resection (months)	5-year survival	Relapse rate
Endometrial	74 (51-77 y)	68.5 (16-195)	122.5 (29-183)	100%	25%
Cervical	45.5 (33-65 y)	19.5 (1-67)	66 (11-280)	62.5%	50%
Sarcoma	59 (45-62 y)	47 (14-97)	49 (17-179)	60%	100%
Total	62 (33-77 y)	58 (1-195)	94 (11-280)	84.1%	44%

DFI: disease-free interval.

metastasis resection was 94 months (11-280), and 64 months (14-105) after the second metastasis surgery. Out of the 5 patients who had undergone surgery for the second time (3 uterine sarcomas and two endometrial carcinomas), 2 died (one due to tumor progression at the intra-extrapulmonary level, and another due to a second primary tumor). Out of the 3 remaining patients, two relapsed at the intra- and extrapulmonary levels, and one case is in complete remission after 63 months.

Two patients with uterine sarcoma underwent a third metastasis resection. The disease-free interval after the second metastasis surgery was 20 months. Survival after the third metastasis surgery was 44 and 80 months. One patient suffered intra-extrapulmonary relapse and died as a result, and the other patient has recently presented relapse at the intra-extrapulmonary level.

Four patients relapsed with endometrial carcinoma after pulmonary metastasis surgery (25%; 4/16) at the lung level. Two of them underwent a second surgery for lung metastasis (one patient died from mantle-cell lymphoma, and another is disease-free 84 months after the 2nd surgery), and the other 2 received lung radiotherapy (one in complete remission, and another expired 70 months after lung RT).

Three patients suffered cervical cancer relapse (50%; 3/16): 2 at the lung level and 1 at the intra-extrapulmonary level, all of whom died due to tumor progression. One patient underwent lung RT, dying 4 months later.

All the patients who had undergone surgery for uterine sarcoma metastasis suffered relapse (5/5): 4 at the lung level, one at the intra-extrapulmonary level (pulmonary and retroperitoneal relapse). Three patients underwent a second metastasis surgery and two underwent a third. Currently, two patients are still alive, having had relapses in several extrapulmonary locations.

We found statistically significant differences in survival depending on the histological type. Survival was greater in the patients with endometrial carcinoma compared to the patients with uterine sarcoma or cervical cancer (p = 0.023 Breslow test). There were also differences for disease-free interval after the surgery of the primary tumor, the survival being greater in those with DFI > 24 months (p = 0.054 Breslow test). When we analyzed the subgroups, we could not confirm statistically significant differences for DFI.

The overall relapse rate was 44% (table 3). We found statistically significant differences in the relapse rate for one variable: histological type (the relapse was more frequent in patients with uterine sarcoma and cervical cancer compared with patients with endometrial carcinoma, p = 0.012).

Discussion

Female genital tract tumors are an infrequent cause of pulmonary metastasis. For example, according to an article published in our setting, only 2% of surgically-treated lung metastasis in a third-level hospital were secondary to endometrial adenocarcinoma.[10] The 5-year survival of patients who underwent resection oscillates from 32.9-46.8%.[11-20] The studies published after the IRLM tend to group the lung metastases by location and histology, knowing the different biological behaviors, and the differences in adjuvant treatment. For this reason, we are going to analyze the data and classify it by histological types and location.

Endometrial carcinoma is the most frequent neoplasm in the female genital tract. As has been reported in two studies, the incidence of lung metastases in this pathology is 6-8.7%, (80% metachronic and 20% synchronic).15,18 The five-year survival after the diagnosis of metastasis in these studies was 24-53%.15,18 The factors found for good prognosis were the presence of unilateral metastasis and a DFI of more than 24 months.[15] In our study, survival is clearly higher (100% at 5 years), which may be due to the fact that we had resected hardly any multiple (33% vs. 86% in one of the studies cited) or synchronic (mean DFI 68 vs. 27 months) metastases. We also believe that the use of hormone therapy could have had an influence (following the Bonte model[21] with 20 mg/24 h tamoxifen for 7 days and 500 mg/24 h medroxyprogesterone acetate for 21 days, cyclically), which is used as a life-long adjuvant therapy, as supported by the experience with hormone therapy of the first study cited.[15] However, the absence of a control group that did not receive hormone therapy does not allow us to affirm that this model is better

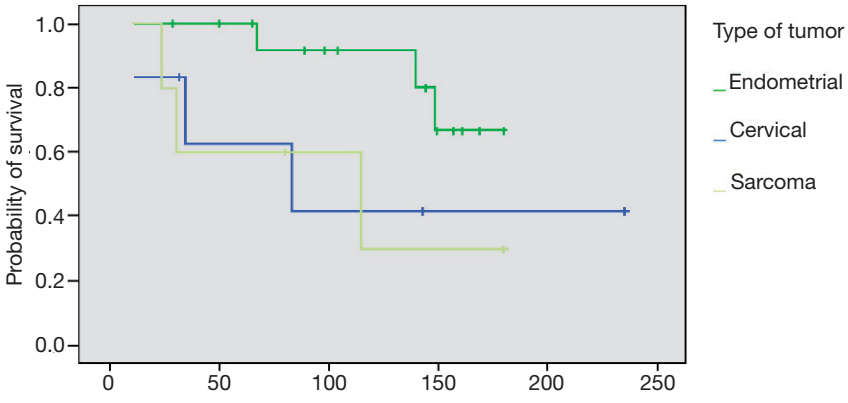

Figure 1. Survival according to type of location/histology.

than the current approach of awaiting new relapses before initiating hormone treatment (progestogen and/or tamoxifen, or aromatase inhibitors) or chemotherapy (cisplatin/doxorubicin +/– paclitaxel).[22]

As for the cervical cancer metastases, to begin with we find there is a lack of homogeneity among the groups studied (some are predominantly adenocarcinoma, others epidermoid carcinoma). Second of all is the rarity of its appearance (2.1-10% of cervical cancer with develop lung metastasis). Five-year survival ranges between 0 and 52%, with the majority of the current studies claiming between 25 and 36%. The prognostic factors found in said studies are: number of metastases and histology (epidermoid has the best prognosis), while the role of other factors, such as DFI, lymph node affectation or the size of the metastasis, is still not clear.[13,14,16,17,19] Finally, we should also highlight that the scarcity of cases does not allow for comparisons with other studies and that our therapeutic approach in this type of tumors does not diverge from that used in other centers, with radical surgery that may or may not be associated with adjuvant chemotherapy based on cisplatin/carboplatin.[23]

Uterine sarcomas constitute 4-9% of malignant uterine tumors. The relapse rate in the initial stages is 73.5%. The recurrences are usually in the pelvic area, although 48% of the cases described also presented lung metastasis.[12,17,20] Metastases of uterine sarcoma seem to have an intermediate prognosis between cervical cancer and endometrial carcinoma according to the medical literature, although in our study they seem to have a poorer prognosis (although not statistically significant) than cervical cancer. Five-year survival is estimated at 20-46.8%. Factors for poor prognosis are the presence of either bilateral metastases or those greater than 2 cm, or a DFI of less than 24 months.[12,17,20] According to some authors, adjuvant chemotherapy (based on doxorubicin for high-grade leiomyosarcoma/sarcomas or ifosfamide for carcinosarcoma) seems to increase the recurrence-free general survival in soft-tissue sarcoma.[20,24] In the case of low-grade endometrial stromal sarcoma positive for estrogen receptors, adjuvant hormone therapy with aromatase inhibitors or progestogen seem to reduce the rate of distant relapse.[22,25]

In closing, we would like to highlight some facts. First of all, the high rate of recurrence in the metastases of cervical cancer and uterine sarcoma (mainly at the pulmonary level) warrant researching new regional or systemic adjuvant chemotherapy models (new drugs, intensification chemotherapy, regional perfusion with chemotherapy- ILuP, stop-flow technique, etc.).[26-28] Secondly, the heterogeneity and rarity of these cases require their inclusion in multi-center clinical assays.

Conclusion

Surgical treatment of lung metastases originating from tumors of the female genital tract (mainly endometrial carcinoma) is associated with high long-term survival.

References

1. Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, et al. Long–term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg. 1997;113:37-49.
2. Schnorrer M, Ondrus D, Cársky S, Hornák M, Belan V, Kausitz J, et al. Management of of germ cell testicular cancer with pulmonary metastases. Neoplasma. 1996;43: 47-50.
3. Godzinski J, Tournade MF, De Kraker J, Ludwig R, Weirich A, Voute PA, Burgers JM, Habrand JL, Sandstedt B, Ducourtieux M. The role of preoperative chemotherapy in the treatment of nephroblastoma: the SIOP experience. Semin Urol Oncol. 1999; 17:28-32.
4. Barth A, Wanek LA, Morton DL. Prognostic factors in 1521 melanoma patients with distant metastases. J Am Coll Surg. 1995;181:193-201.
5. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg. 2007;84:324-8.
6. Casson AG, Putnam JB, Natarajan G, Johnston DA, Mountain C, McMurtrey M, et al. Five-year survival after metastasectomy for adult soft tissue sarcoma. Cancer. 1992;69:662-8.
7. Putnam JB, Roth JA, Wesley MN, Johnston MR, Rosenberg SA. Survival following aggressive resection of pulmonary metastases from osteogenic sarcoma: analysis of prognostic factors. Ann Thorac Surg. 1983;28:516-23.
8. Benedet JL, Bender H, Jones H, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int Gynaecol Obstet. 2000;70:209-62.
9. Mountain FC, Dresler CM. Regional lymph node classification for lung cancer staging. Chest. 1997;111:1718-23.
10. Ayarra J, Jiménez R, Congregado M, Girón JC, Gallardo G, Triviño AI, et al. Cirugía de metástasis pulmonares en 148 pacientes. Análisis de sus factores pronósticos. Arch Bronconeumol. 2008;44:525-30.
11. Fuller AF, Scannell JG, Wilkins EW. Pulmonary resection for metastases from gynecologic cancers: Massachusetts General Hospital experience, 1943-1982. Gynecol Oncol. 1985;22:174-80.
12. Levenback C, Rubin SC, McCormack PM, Hoskins WJ, Atkinson EN, Lewis JL. Resection of pulmonary metastases from uterine sarcomas. Gynecol Oncol. 1992; 45:202-5.
13. Shiromizu K, Kasamatsu T, Takahashi M, Kikuchi A, Yoshinari T, Matsuzawa M. A clinicopathological study of postoperative pulmonary metastasis of uterine cervical carcinomas. J Obstet Gynaecol Res. 1999;25:245-9.
14. Anderson TM, McMahon JJ, Nwogu CE, Pombo MW, Urschel JD, Driscoll DL, et al. Pulmonary resection in metastatic uterine, and cervical malignancies. Gynecol Oncol. 2001;83:472-6.
15. Otsuka I, Ono I, Akamatsu H, Sunamori M, Aso T. Pulmonary metastasis from endometrial carcinoma. Int J Gynecol Cancer. 2002;12:208-13.
16. Yamamoto K, Yoshikawa H, Shiromizu K, Saito T, Kuzuya K, Tsunematsu R, et al. Pulmonary metastasectomy for uterine cervical cancer: a multivariate analysis. Ann Thorac Surg. 2004;77:1179-82.
17. Clavero JM, Deschamps C, Cassivi SD, Allen MS, Nichols, 3rd FC, Barrette BA, et al. Gynecologic cancers: factors afecting survival after pulmonary metastasectomy. Ann Thorac Surg. 2006;81:2004-7.
18. Bouros D, Papadakis K, Siafakas N, Fuller AF. Natural history of patients with pulmonary metastases for uterine cancer. Cancer. 1996;78:441-7.
19. Tellis CJ, Beechler CR. Pulmonary metastasis of carcinoma of the cervix. Cancer. 1982;49:1705-9.
20. Berchuck A, Rubin SC, Hoskins WJ, Saigo PE, Pierce VK, Lewis JL. Treatment of uterine leiomyosarcoma. Obstet Gynecol. 1988;71:845-50.
21. Bonte J. The endometrial carcinoma as a model for hormone-dependency and hormone-responsiveness of gynaecological cancers. Eur J Obstet Reprod Biol. 1984;18:335-41.
22. NCCN Clinical practice guidelines in oncology. Uterine neoplasms V1.2010. Available from: http://www.nccn.org.
23. NCCN Clinical practice guidelines in oncology. Cervical cancer V1.2010. Available from: http://www.nccn.org.
24. Sarcoma meta-analysis collaboration (SMAC). Adyuvant chemotherapy for localised resectable soft tissue sarcomas in adults. Cochrane Database Syst Rev: CD001419.
25. Reich O, Regauer S. Hormonal therapy of endometrial stromal sarcoma. Curr Opin Oncol. 2007;19:347-52.
26. Pedrazzoli P, Ledermann JA, Lotz JP, Leyvraz S, Aglietta M, Rosti G, et al, European Group for Blood and Marrow Transplantation (EBMT) Solid Tumors Working Party. High dose chemotherapy with autologous hematopoietic stem cell support for solid tumors other than breast cancer in adults. Ann Oncol. 2006;17:1479-788.
27. Grootenboers MJ, Heeren J, van Putte BP, Hendriks JM, Van Boven WJ, Van Schil PE, et al. Isolated lung perfusion for pulmonary metastases, a review and work in progress. Perfusion. 2006;21:267-76.
28. Pilati P, Mocellin S, Miotto D, Rossi CR, Codello L, Foletto M, et al. Stop-flow technique for loco-regional delivery of antiblastic agents: literature review and personal experience. EJSO. 2002;28:544-53.