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Case report

Pazopanib-mediated long-term disease stabilization after resection of a uterine leiomyosarcoma metastasis to the brain: A case report

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ABSTRACT

A 48-year-old woman underwent a total abdominal hysterectomy after preoperative diagnosis of multiple uterine leiomyomas. The histopathological diagnosis was leiomyosarcoma (LMS). After 47 months, multiple lung metastases were detected and resected. The patient was also diagnosed with pelvic bone metastasis and received six cycles of adjuvant chemotherapy with gemcitabine plus docetaxel and local radiation therapy to control the pain. Seventy-seven months from the initial diagnosis, she had a headache and developed left hemiparesis and aphasia. Imaging studies detected a solitary brain metastasis in the right frontal lobe. The patient underwent a craniotomy and resection of the lesion, which was a confirmed metastasis from uterine LMS by histopathology. One month after the craniotomy, the patient experienced lower abdominal pain, and a pelvic metastasis was detected. She was prescribed oral pazopanib (800 mg per day). For twelve months, she remained asymptomatic, but gradually, pelvic pain increased due to pelvic mass growth. After 14 months of pazopanib treatment, pazopanib was discontinued. To date, for 18 months after the brain surgery, she is alive with disease, and the brain metastasis has not recurred.

1. Introduction

Brain metastasis of uterine leiomyosarcoma (LMS) is rare (Wroński et al., 1994 Aug; Honeybul & Ha, 2009 Mar; Yamada et al., 2011 Dec; Rose et al., 1989 Mar 1; Fleming et al., 1984 Oct). Several case reports suggest a resection of brain metastases of uterine LMS could result in longer survival, for which controlling systemic disease is a prerequisite (Wroński et al., 1994 Aug; Honeybul & Ha, 2009 Mar; Yamada et al., 2011 Dec; Gadducci et al., 1996 Jul). However, adjuvant therapies after brain surgery have not been established. Radiotherapy after brain surgery can lower recurrence rates, but long-term toxic side effects of radiation, such as cognitive decline, decrease quality of life, and radiation cannot control systemic disease. Pazopanib is approved for soft tissue sarcomas and penetrates the blood-brain barrier (BBB) (Iwamoto et al., 2010 Aug). Several case reports in other malignancies suggest that pazopanib treatment could elicit survival benefits for patients with brain metastases in addition to controlling systemic disease (Jacobs et al., 2013 Mar 1; Hingorani et al., 2014). We present the first case report of long-term disease stabilization with pazopanib treatment after a resection of solitary brain metastasis from uterine LMS.

2. Case report

A 48-year-old multiparous woman underwent a total abdominal hysterectomy for what was thought to be multiple uterine leiomyomas. Final histopathology revealed uterine LMS, and she was referred to our hospital.

Subsequent positron emission tomography/computed tomography (PET/CT) showed no metastatic lesions, and she was followed up without further surgery or adjuvant therapy. Forty-seven months after the initial diagnosis, a biannual follow-up computed tomography (CT) scan revealed multiple lung metastases, and video-assisted thoracic surgery (VATS) was performed. The surgical specimens were confirmed LMS metastases. Shortly after the VATS procedure, the patient developed pelvic pain, and PET/CT imaging suggested a pelvic bone metastasis. She was treated with six cycles of adjuvant chemotherapy with gemcitabine and docetaxel, and local radiation therapy was administered to control the pain. Seventy-seven months after the initial diagnosis, she had a gradually worsening headache, and 2 weeks later, she developed left hemiparesis and aphasia with a Karnofsky performance scale (KPS) score of 40. Magnetic resonance imaging (MRI) revealed a solitary 58 mm × 45 mm lesion in the right frontal lobe with a midline shift (Fig. 1). The patient underwent a craniotomy and complete resection of the lesion, after which she showed no neurological deficit, and her KPS score improved to 90. Immunohistochemical findings of the resected metastatic brain tumor were positive for alpha-smooth muscle

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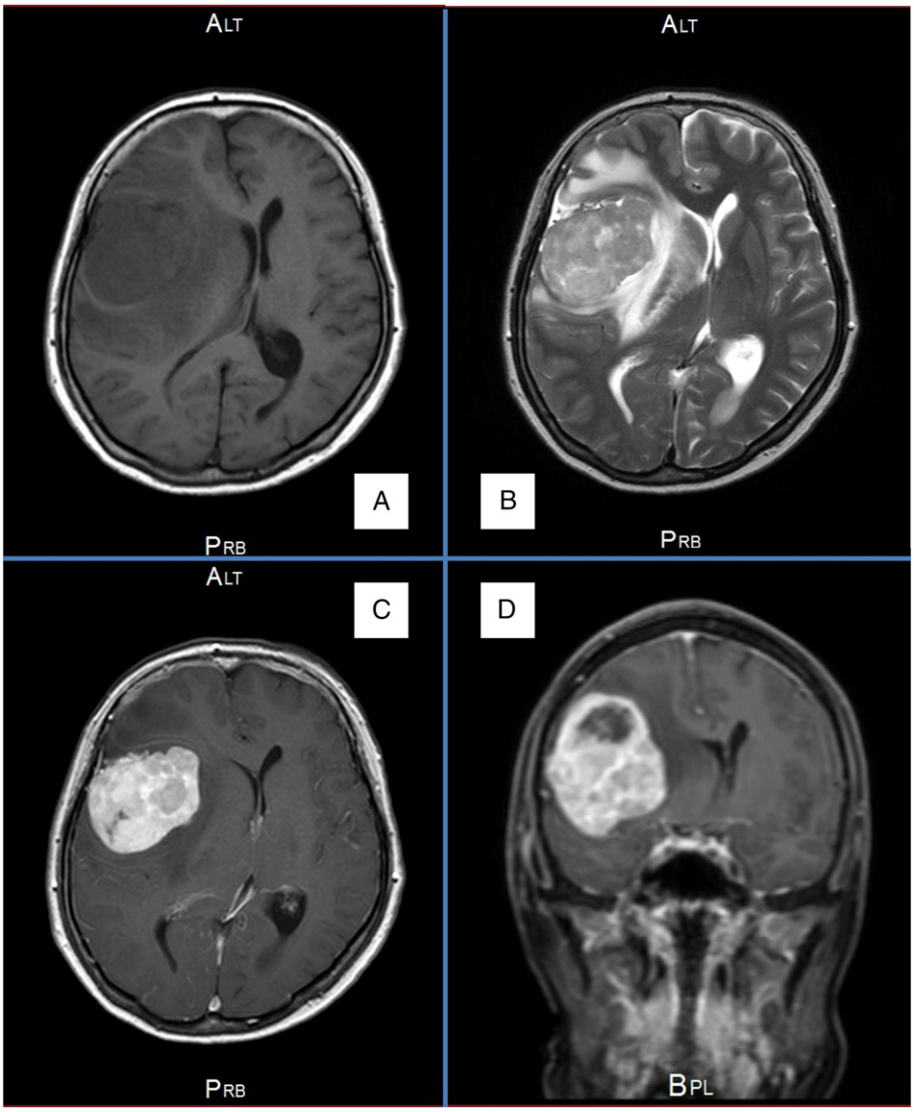

Fig. 1. MRI images of the solitary brain metastatic lesion in the right frontal lobe. A: T1 image, B: T2 image, C and D: Gadolinium-enhanced MRI.

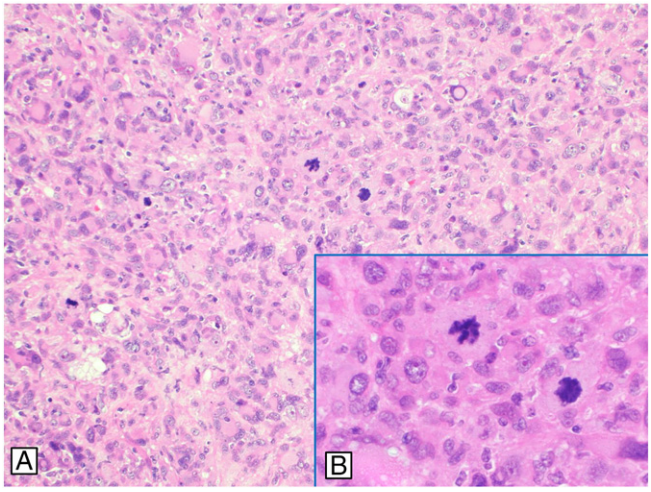

Fig. 2. Microscopic findings of the resected metastatic brain tumor. Marked cellular pleomorphism, nuclear atypia, and mitotic figures are present. A: Hematoxylin and eosin (H&E), ×20, B: The inset of A, ×40.

actin, vimentin, desmin, and epithelial membrane antigen staining, and LMS metastasis to the brain was confirmed (Figs. 2 and 3). One month after the craniotomy, she experienced lower abdominal pain that required opioids, and a CT scan revealed a pelvic mass that was suggestive of recurrence and was unresectable (Fig. 4). The patient was informed about an increased risk for intracranial hemorrhage by using pazopanib. One month after the brain surgery, she began oral pazopanib (800 mg per day). One month later, she was free of pain, and no opioid was necessary. She experienced mild diarrhea and mild hypertension, both of which were well-controlled.

For 12 months, the patient remained asymptomatic. There was no recurrence of brain metastasis. However, the pelvic lesions gradually enlarged, causing a severe pain. Therefore, 14 months after starting pazopanib, it was discontinued. To date, she remains alive with disease, 18 months after the brain surgery.

3. Discussion

Uterine LMS is aggressive in nature, and prognosis of recurrent LMS is very poor. The risk of recurrence after complete resection of uterus-limited LMS, which was estimated to be 70% after 2 years in a retrospective study, is high (Major et al., 1993 Feb 15). The most common sites of uterine LMS metastasis are the lung, pelvis, and vagina (Rose et al., 1989

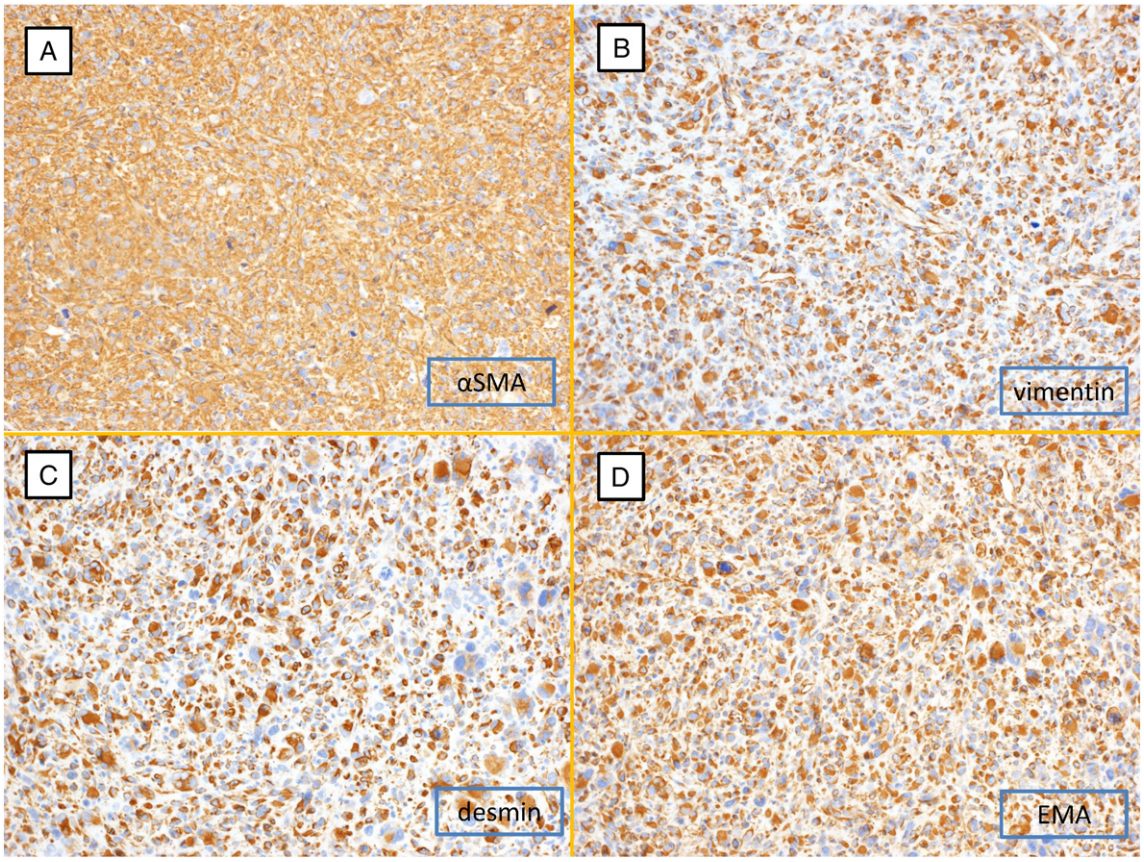

Fig. 3. Immunohistochemical findings of the resected metastatic brain tumor. A: Alpha-smooth muscle actin staining, ×20. B: Vimentin staining, ×20. C: Desmin staining, ×20. D: Epithelial membrane antigen (EMA) staining, ×20.

Mar 1; Mayerhofer et al., 1999 Aug), but brain metastasis is rare. To the best of our knowledge, only case reports of uterine LMS metastasis to the brain are available (Wroński et al., 1994 Aug; Honeybul & Ha, 2009 Mar; Yamada et al., 2011 Dec). Yamada et al. reviewed in their case report that there had been 21 such cases (Yamada et al., 2011 Dec). Brain metastasis incidence has been reported to be 1 in 19 (Rose et al., 1989 Mar 1) and 1 in 4 from autopsies of patients with uterine LMS (Fleming et al., 1984 Oct). In a retrospective study of brain metastases from gynecologic malignancies, 4 cases out of 139 cases of gynecologic malignancies were uterine LMS (Nasu et al., 2013 Feb). Because of its rarity, there has been no established management for uterine LMS metastasis to the brain.

For recurrence of uterine LMS, combination chemotherapy, such as gemcitabine and docetaxel, may be a treatment option (Hensley et al., 2002 Jun 15), but it is meant to be palliative and is not curative. Additionally, conventional cytotoxic agents that have proven to be effective for LMS do not cross the BBB. Only surgical resection can prolong survival. In a retrospective study by Leitao et al., pulmonary and extrathoracic metastasectomy of recurrent uterine LMS resulted in a survival benefit when complete resection was achieved (Leitao et al., 2002 Dec). In cases of a solitary brain metastasis of uterine LMS with well-controlled systemic disease, long-term survival, namely 1–2 years, after brain surgery can be expected, as presented and reviewed in multiple case reports (Wroński et al., 1994 Aug; Honeybul & Ha, 2009 Mar; Yamada et al., 2011 Dec; Gadducci et al., 1996 Jul). On the other hand, in patients with progressive and uncontrolled systemic metastases, survival is very poor, even after an aggressive brain surgery (Honeybul & Ha, 2009 Mar). Moreover, whole-brain radiotherapy (WBRT) after brain surgery can greatly lower brain metastasis recurrence rates (Patchell et al., 1998 Nov 4), but long-term toxic effects of WBRT, such as cognitive decline, should be considered when systemic disease remains under control and long-term survival is expected. Yamada et al. pointed out that in patients with uterine LMS metastasis to the brain, postoperative radiation therapy might not offer survival benefits (Yamada et al., 2011 Dec). Furthermore, when brain metastasis recurrence can be decreased, systemic disease should be controlled. Adjuvant therapy that is effective for both systemic and brain-specific disease after brain surgery is needed.

Pazopanib is a multi-targeted tyrosine kinase inhibitor that impairs angiogenesis and is approved for soft tissue sarcoma treatment. It is small enough to penetrate the BBB and has been used in a phase II study for patients with glioblastoma (Iwamoto et al., 2010 Aug). One case report showed prolonged survival after pazopanib therapy for patients with papillary renal cell carcinoma and brain metastases (Jacobs et al., 2013 Mar 1). Another case report described a patient with renal cancer and brain metastasis who survived for 3 years after WBRT and subsequent pazopanib (Hingorani et al., 2014). Pazopanib was used to treat the patient in our case report to control the pelvic lesions and prevent brain metastasis recurrence. It was well-tolerated, and to date, there has been no brain metastasis recurrence, and, although they have since progressed, the pelvic lesions remained under control for a year.

We can study the role of pazopanib by relieved symptoms, tumor size reduction assessed by imaging studies including ultrasonography, CT and MRI, and treatment response assessed by fluorodeoxyglucose PET/CT (except for brain metastases). If resected specimens are obtained, the immnohistochemical expression of platelet-derived growth factor receptor (PDGFR) can be investigated as a predictive marker for response of pazopanib, although it has not been clinically applicable. As for brain metastasis, resectable uterine leiomyosarcoma metastatic to the brain is very rare, and to the best of our knowledge, immunohistochemical investigation has not proceeded.

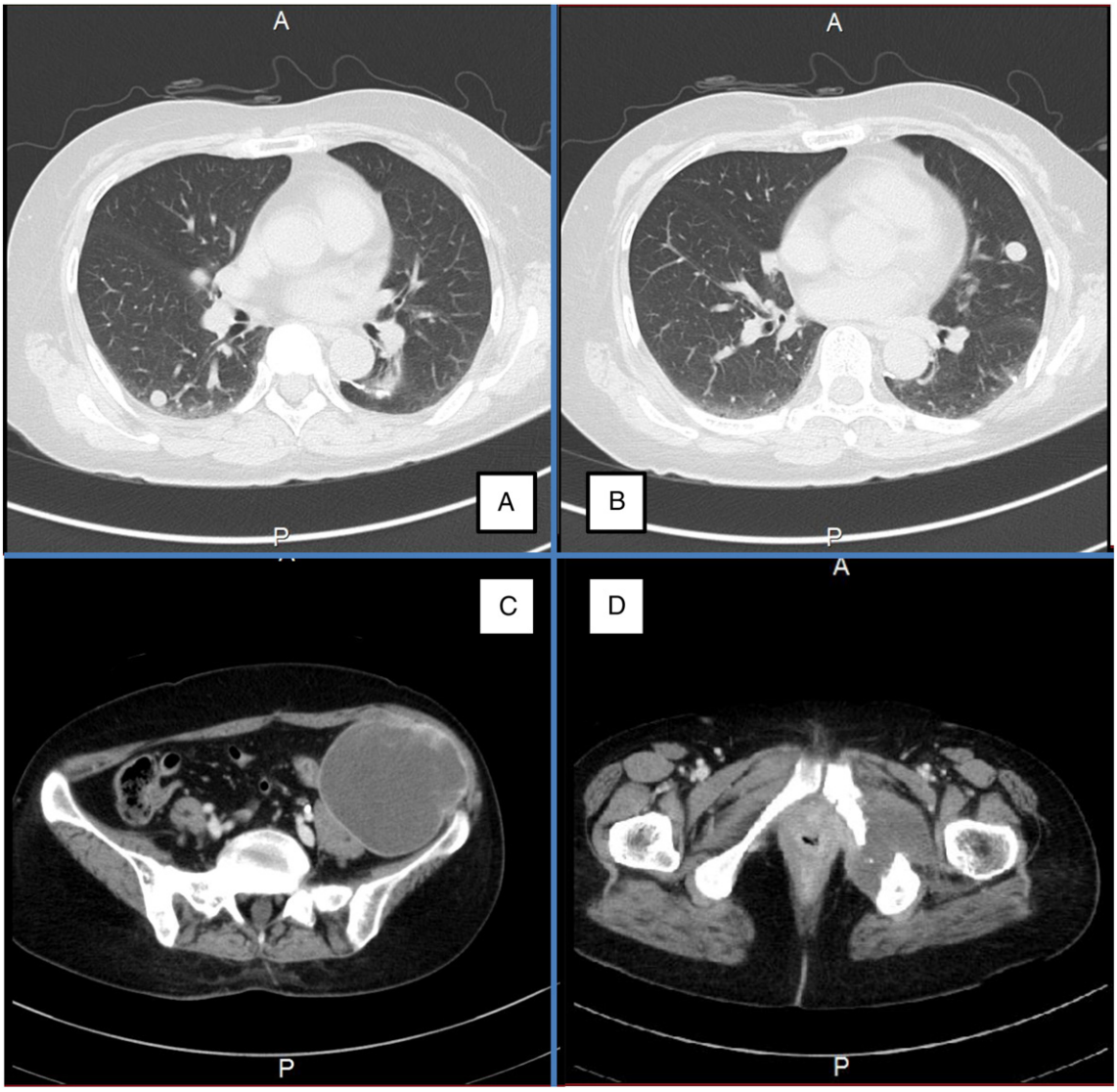

Fig. 4. CT images of the lung and pelvis. A and B: Multiple small metastatic lesions in bilateral lung fields on chest CT. C: A cystic lesion in the left pelvis. D: A 5-cm tumor and a lytic lesion of the pubic bone.

It is unknown whether pazopanib was actually effective for preventing recurrence of brain metastasis or whether complete resection of the brain metastasis contributed to the favorable prognosis in this patient. The patient enjoyed a prolonged symptom-free survival from the surgery for the brain metastasis.

4. Conclusion

Long-term disease stabilization was obtained with pazopanib treatment after resection of a uterine LMS brain metastasis. Pazopanib, with its ability to penetrate the BBB, could replace WBRT after resection of solitary brain metastasis and might lower brain metastasis recurrence rates and control systemic disease.

Disclosure

Written informed consent for this report was obtained from the patient. The authors have no conflicts of interest to declare.

References

Fleming, W.P., Peters 3rd, W.A., Kumar, N.B., Morley, G.W., 1984 Octt. Autopsy findings in patients with uterine sarcoma. Gynecol. Oncol. 19 (2), 168–172.

Gadducci, A., Landoni, F., Sartori, E., Zola, P., Maggino, T., Lissoni, A., Bazzurini, L., Arisio, R., Romagnolo, C., Cristofani, R., 1996 Jull. Uterine leiomyosarcoma: analysis of treatment failures and survival. Gynecol. Oncol. 62 (1), 25–32.

Hensley, M.L., Maki, R., Venkatraman, E., Geller, G., Lovegren, M., Aghajanian, C., Sabbatini, P., Tong, W., Barakat, R., Spriggs, D.R., 2002 Jun 15. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J. Clin. Oncol. 20 (12), 2824–2831.

Hingorani, M., Dixit, S., Maraveyas, A., 2014. Pazopanib-induced regression of brain metastasis after whole brain palliative radiotherapy in metastatic renal cell cancer progressing on first-line Sunitinib: a case report. World J. Oncol. 5 (5–6), 223–227.

Honeybul, S., Ha, T., 2009 Marr. Leiomyosarcoma of the uterus metastatic to the brain: a case report. Arch. Gynecol. Obstet. 279 (3), 391–393. http://dx.doi.org/10.1007/s00404-008-0717-1 (Epub 2008 Jul 1).

Iwamoto, F.M., Lamborn, K.R., Robins, H.I., Mehta, M.P., Chang, S.M., Butowski, N.A., Deangelis, L.M., Abrey, L.E., Zhang, W.T., Prados, M.D., Fine, H.A., 2010 Augg. Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American brain tumor consortium study 06-02). Neuro-Oncology 12 (8), 855–861. http://dx.doi.org/10.1093/neuonc/noq025 (Epub 2010 Mar 3).

Jacobs, C., Kim, D.W., Straka, C., Timmerman, R.D., Brugarolas, J., 2013 Mar 1. Prolonged survival of a patient with papillary renal cell carcinoma and brain metastases using

pazopanib. J. Clin. Oncol. 31 (7), e114–e117. http://dx.doi.org/10.1200/JCO.2012.46.0501 (Epub 2013 Jan 14).

Leitao, M.M., Brennan, M.F., Hensley, M., Sonoda, Y., Hummer, A., Bhaskaran, D., Venkatraman, E., Alektiar, K., Barakat, R.R., 2002 Decc. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. Gynecol. Oncol. 87 (3), 287–294.

Major, F.J., Blessing, J.A., Silverberg, S.G., Morrow, C.P., Creasman, W.T., Currie, J.L., Yordan, E., Brady, M.F., 1993 Feb 15. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer 71 (4 Suppl.), 1702–1709.

Mayerhofer, K., Obermair, A., Windbichler, G., Petru, E., Kaider, A., Hefler, L., Czerwenka, K., Leodolter, S., Kainz, C., 1999 Augg. Leiomyosarcoma of the uterus: a clinicopathologic multicenter study of 71 cases. Gynecol. Oncol. 74 (2), 196–201.

Nasu, K., Satoh, T., Nishio, S., Nagai, Y., Ito, K., Otsuki, T., Hongo, A., Hirashima, Y., Ogura, T., Shimada, M., 2013 Febb. Clinicopathologic features of brain metastases from gynecologic malignancies: a retrospective study of 139 cases (KCOG-G1001s trial). Gynecol. Oncol. 128 (2), 198–203. http://dx.doi.org/10.1016/j.ygyno.2012.11.001 (Epub 2012 Nov 8).

Patchell, R.A., Tibbs, P.A., Regine, W.F., Dempsey, R.J., Mohiuddin, M., Kryscio, R.J., Markesbery, W.R., Foon, K.A., Young, B., 1998 Nov 4. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. J. Am. Med. Assoc. 280 (17), 1485–1489.

Rose, P.G., Piver, M.S., Tsukada, Y., Lau, T., 1989 Mar 1. Patterns of metastasis in uterine sarcoma. An autopsy study. Cancer 63 (5), 935–938.

Wroński, M., de Palma, P., Arbit, E., 1994 Augg. Leiomyosarcoma of the uterus metastatic to brain: a case report and a review of the literature. Gynecol. Oncol. 54 (2), 237–241.

Yamada, S., Yamada, S.M., Nakaguchi, H., Murakami, M., Hoya, K., Matsuno, A., 2011 Decc. A case of multiple brain metastases of uterine leiomyosarcoma with a literature review. Surg. Oncol. 20 (4), e127–e131. http://dx.doi.org/10.1016/j.suronc.2011.04.001 (Epub 2011 May 25).