Clinical Case Reports

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CASE REPORT

Leptomeningeal metastasis of uterine cervical cancer 17 years after primary tumor treatment

Takahiro Oike[1], Tatsuya Ohno[1], Shin-Ei Noda[1], Tomomi Murata[2], Takashi Hirakawa[2], Junko Hirato[3], Mio Furuya[3], Hiro Sato[1], Yuka Hirota[1], Takashi Minegishi[2] & Takashi Nakano[1]

[1]Department of Radiation Oncology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
[2]Department of Obstetrics and Gynecology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
[3]Department of Pathology, Gunma University Hospital, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

Correspondence
Takahiro Oike, Department of Radiation Oncology, Gunma University Graduate School of Medicine, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81-27-220-8383; Fax: +81-27-220-8397; E-mail: oiketakahiro@gmail.com

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Key Clinical Message

Leptomeningeal metastasis (LM) of uterine cervical cancer is extremely rare. A 54-year-old woman with uterine cervical cancer treated with surgery and radiotherapy developed LM manifesting as ptosis 17 years later. Although rare, LM should be considered in patients with a history of uterine cervical cancer presenting with cranial nerve symptoms.

Keywords

Cancer cell dormancy, leptomeningeal metastasis, oculomotor nerve metastasis, ptosis, uterine cervical cancer.

Introduction

Leptomeningeal metastasis (LM) occurs in 3–8% of cancer patients [1, 2]. In most cases, LM develops secondary to lung, breast, gastrointestinal, or hematopoietic malignancies, or malignant melanoma [3]. LM from gynecologic malignancies is rare, and when present, it is associated with ovarian cancer [4]. LM of uterine cervical cancer is extremely rare. Yust et al. [5] reported that 0.03% (4/13289) of cervical cancer cases registered in the MD Anderson Cancer Center database developed LM. Here, we report a unique case of LM of uterine cervical cancer presenting with ptosis due to oculomotor nerve invasion 17 years after treatment of the primary tumor.

Case Report

A 54-year-old woman with uterine cervical cancer [Federation of Gynecological Oncologists (FIGO) stage Ib] underwent radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy in 1996. Pathological examination of the surgical specimen revealed nonkeratinizing squamous cell carcinoma of the uterine cervix. Immunohistochemical staining of the tumor was positive for p16, a marker for human papillomavirus (HPV) infection in uterine cervical cancer (Fig. 1A and B) [6]. The pathological stage was pT1bN1M0. Two of the 21 resected internal-iliac lymph nodes were positive for malignant cells. Therefore, the patient received radiotherapy; X-ray irradiation to the pelvis with a dose of 50 Gy in 25 fractions and four sessions of electron boost to the vaginal stump. After completion of radiotherapy, the patient was followed up yearly for 16 years and showed no signs of disease. In a systemic work-up performed in December 2010, contrast-enhanced computed tomography (CE-CT) showed no evidence of local recurrence or distant metastasis.

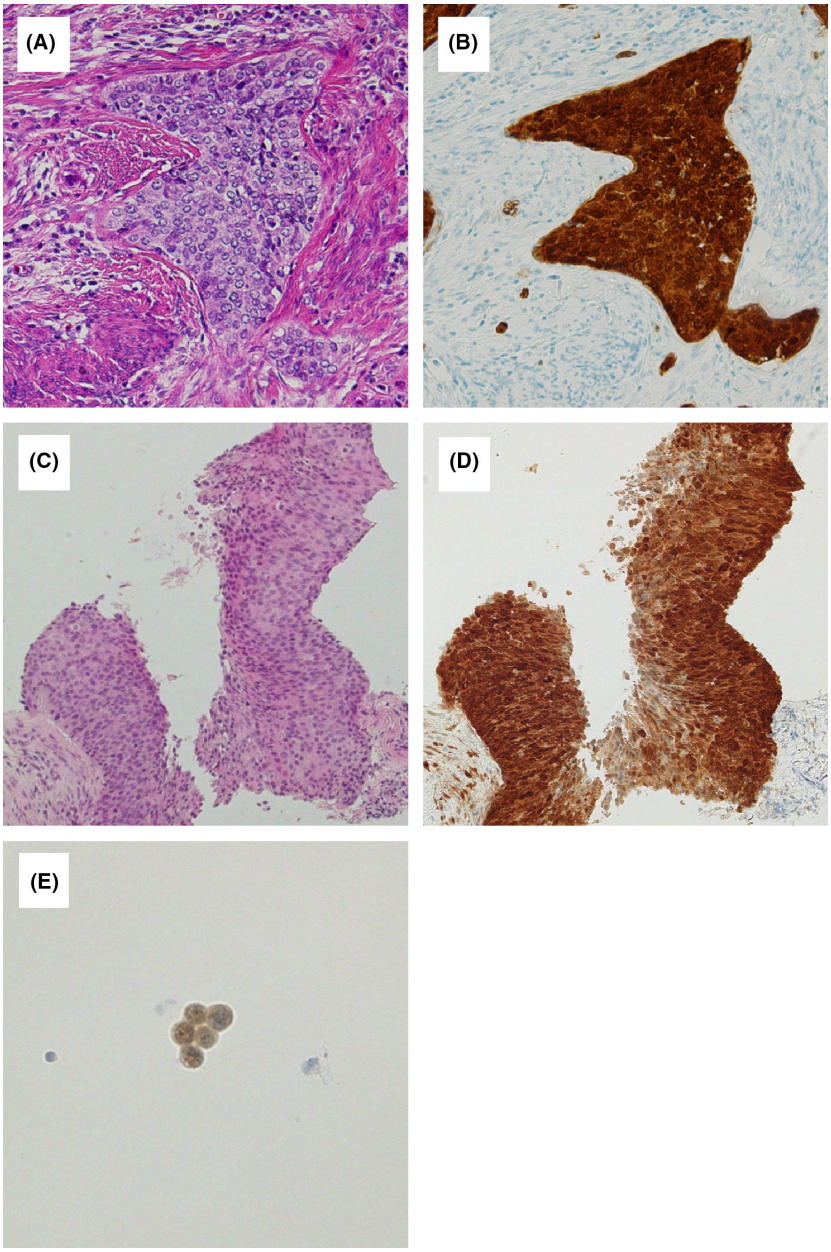

Figure 1. Microphotographs showing the results of pathological examination. (A, B) Hematoxylin and eosin staining (A) and immunohistochemical staining (B) of a surgical specimen showing squamous cell carcinoma positive for p16. (C, D) Hematoxylin and eosin staining (C) and immunohistochemical staining (D) of a biopsy specimen of the lumbar spine showing metastatic squamous cell carcinoma positive for p16. (E) Immunohistochemical staining of a cerebrospinal fluid cytology specimen showing p16-positive atypical cells fairly conclusive for metastatic cancer from the uterine cervix.

In November 2012, the patient presented with back pain. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) combined with CT showed a spinal mass with increased FDG uptake at L2 and L3. CT-guided needle aspiration biopsy of the lumbar spine revealed squamous cell carcinoma positive for p16, consistent with metastasis of the patient's primary carcinoma of the uterine cervix (Fig. 1C and D). Systemic work-up, including otological and gynecological evaluations, gastrointestinal endoscopy, ultrasonography (thyroid, mammary glands, and abdomen), and CE-CT, was unremarkable, except for the lumbar spine lesions. The patient was treated with three-dimensional conformal radiotherapy (3D-CRT) at a dose of 40 Gy in 20 fractions

followed by stereotactic body radiotherapy (SBRT) at 30 Gy in 10 fractions. After completion of radiotherapy, the PET-CT images demonstrated the decrease in FDG uptake in the L2 and L3 lesions (Figure S1), and the patient had no residual pain.

In October 2013, the patient presented with back pain extending into the right thigh. PET-CT suggested a spinal metastatic lesion at Th12, possibly accounting for the presenting symptoms. The patient was treated with 3D-CRT at a dose of 40 Gy in 20 fractions followed by SBRT at 30 Gy in 10 fractions. After completion of radiotherapy, the PET-CT images demonstrated the decrease in FDG uptake in the Th12 lesion (Figure S2), and the patient had no residual pain.

In January 2014, she presented with right upper leg weakness. Manual muscle testing revealed Grade 2 strength in the right upper leg. PET-CT suggested a metastatic lesion at L1 possibly accounting for the presenting symptoms. The patient was treated with 3D-CRT at a dose of 40 Gy in 20 fractions followed by SBRT at 30 Gy in 10 fractions.

Simultaneously with the leg weakness, the patient developed left eyelid ptosis, nausea, and vomiting. Neurological examination revealed left mydriasis, decreased left pupillary light reflex, and left eye movement limitation (i.e., limitation in adduction, supraduction, and infraduction), suggesting oculomotor nerve paralysis. Physical examination and laboratory tests showed no signs of infection or diabetes. Brain CT was unremarkable; however, magnetic resonance imaging (MRI) showed abnormal gadolinium enhancement in the swollen left oculomotor nerve (Fig. 2), with no midbrain abnormalities or leptomeningeal enhancement. Magnetic resonance angiography did not reveal a brain aneurysm. Cerebrospinal fluid cytology showed p16-positive atypical cells fairly conclusive for metastatic cancer from the uterine cervix (Fig. 1E). Taken together, the patient was diagnosed with LM with left oculomotor nerve invasion secondary to uterine cervical cancer. She received SBRT at a dose of 30 Gy in 10 fractions for the left oculomotor nerve lesion. In March 2014, she developed aspiration pneumonia. Despite intensive medical treatment, her general condition worsened gradually, and she died in late April 2014. Permission for an autopsy was not granted.

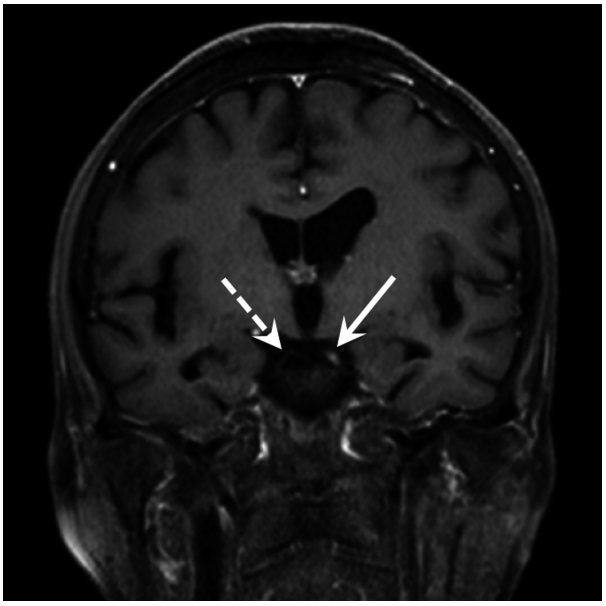

Figure 2. MRI of the brain showing abnormal gadolinium enhancement in the swollen left oculomotor nerve (solid arrow). The right oculomotor nerve is indicated by a dotted arrow.

Discussion

LM of uterine cervical cancer is extremely rare. To the best of our knowledge, there are only 19 cases of this disease reported in the English-language literature (Table 1, Fig. 3) [2, 3, 5, 7–17]. A literature review highlighted two unique features of the present case: (1) oculomotor nerve metastasis causing ptosis, and (2) the longest interval (17 years) from primary tumor treatment to the onset of LM.

Previous research points out four mechanisms to cause LM; hematogenous spread, meningeal seeding from hemispheric brain metastasis, direct extension from subdural or extradural tumors, and direct extension from sites outside but adjacent to the central nervous system [13]. Hematogenous spread is the commonest mechanism for LM. This is in line with the fact that the frequency of LM in the squamous cell carcinoma of the uterine cervix is low because hematogenous spread is not common in this disease [13]. Interestingly, in our case, LM occurred following multiple metastases to the vertebral bones. This indicates that the LM in this case occurred by direct extension from the vertebral bone metastases via spinal canal. To the best of our knowledge, no previous case of LM from the uterine cervix demonstrates vertebral bone metastasis prior to LM (Fig. 3), suggesting that this mechanism is uncommon especially in the uterine cervical cancer.

LM can show diverse symptoms (Fig. 3). Signs of meningeal irritation such as headache, nausea, and vomiting are frequently reported. Symptoms that can be caused by single cranial nerve involvement, such as vision loss, hearing loss, and ptosis, are less frequent. The present case (taken together with those reported in the literature) indicates that, although rare, LM should be included in the differential diagnosis of patients with a history of uterine cervical cancer who present with cranial nerve symptoms.

Table 1. Review of the literature on leptomeningeal metastasis of uterine cervical cancer.

Year	Age	Stage	Pathology	Primary Therapy	Interval to LM (M)	LM symptom	CNS CT abnormalities	CNS Gd-MRI abnormalities	CSF malignancy	Metastatis outside CNS	Therapy for LM	ITCTx agent	Survival after LM (M)	References
1975	47	IB	Sq	RT	40	Headache, nausea, vomiting, vertigo, tinnitus	NA	NA	Positive	Paraaortic/ pelvic LN	CSRT, ITCTx	MTX+ MeCCNU	0.5	[7]
1987	53	IVb	Sq	RT, CTx	1.5	Headache, nausea, vomitting	Parietal lobe involvement	NA	Positive	Lung	BSC	–	0.5	[3]
1996	36	Ib	Ad	RT, Sg	24	Headache, nausea, vomiting, vertigo	NA	Leptomeningeal enhancement	Positive	Bladder	WBRT, ITCTx	MTX	0.5	[8]
2004	39	NA	NE	NA	0	Headache, facial palsy, hearing loss, dysarthria	NA	Leptomeningeal enhancement	Negative	NA	NA	NA	NA	[9]
2004	44	IVb	AdSq	CTx	0	Headache, vomiting, vision loss, seizures	Unremarkable	NA	Positive	Unremarkable	WBRT, ITCTx, CTx	MTX	4	[10]
2004	51	IIb	Sq	CCRT	40	Headache, nausea, photophobia	Unremarkable	Unremarkable	Positive	Letroperitoneal LN	ITCTx	MTX	3.2	[11]
2006	30	Ib	Sq	Sg	144	Blurred vision, ocular pain	NA	Optic nerve enhancement	Positive	Unremarkable	Focal RT(orbit), ITCTx	MTX	2.2	[2]
2006	64	IIIb	Sq	CCRT	31	Paraparesis, paresthesia	NA	Leptomeningeal enhancement	Positive	Lung, liver, peritoneum, skin	WBRT	–	NA	[12]
2007	39	IIb	Sq	CCRT	9	Seizures	SAH, contusion	SAH, contusion	Positive	NA	NA	NA	NA	[13]
2007	50	Ib	Sq	NA	0	Headache	Falx cerebri/optic nerve involvement	NA	Positive	Unremarkable	NA	NA	NA	[14]
2008	58	NA	Sq	CCRT	34	Headache, dizziness, photophobia	Unremarkable	Leptomeningeal enhancement	Positive	Supraclavicular/ letroperitoneal LN	WBRT, ITCTx	MTX+ Thiotepa	6.5	[15]
2009	47	IIIb	Ad	CTx, Sg, CTx	10	Headache, disquieting attitude, disorientation	Unremarkable	NA	Positive	Unremarkable	BSC	–	1.8	[16]
2009	54	Ib	NE	CCRT, Sg	19	Dizziness, paraparesis, ataxia	Intraventricular nodule	Leptomeningeal enhancement, nodules	Negative	Liver	WBRT, Focal RT(spine), CTx	–	7	[17]
2009	63	IIb	Ad	CCRT, Sg	31	Facial palsy, hearing loss, paraparesis	Unremarkable	Leptomeningeal enhancement	Positive	Liver	Focal RT (brain, spine)	–	3	[17]
2013	NA	IIb	Sq	NA	6.3	NA	NA	NA	NA	Skin, pelvic LN	NA	NA	4.3	[5]
2013	NA	IIa	Sq	NA	48	NA	NA	NA	NA	Unremarkable	NA	NA	2.3	[5]
2013	NA	Ib	AdSq	NA	57	NA	NA	NA	NA	Lung	NA	NA	11.5	[5]

Table 1. Continued.

Year	Age	Stage	Pathology	Primary Therapy	Interval to LM (M)	LM symptom	CNS CT abnormalities	CNS Gd-MRI abnormalities	CSF malignancy	Metastatis outside CNS	Therapy for LM	ITCTx agent	Survival after LM (M)	References
2013	NA	IVa	Ad	NA	2.3	NA	NA	NA	NA	Unremarkable	NA	NA	3.5	[5]
2015	64	Ib	Sq	Sg, RT	209	Ptosis, nausea, vomiting	Unremarkable	Oculomotor nerve enhancement	Positive	Multiple vertebrae	Forcal RT (oculormotor nerve)	–	3	Current case

The present case and that reported by Portera et al. [2] showed LM 17 years and 12 years after primary tumor treatment, respectively (Fig. 3). These cases indicate that uterine cervical cancer can cause distant metastasis after a long period of dormancy. The long-period dormancy is common in cancers such as breast cancer and prostate cancer. For these types of cancer, the underlying mechanisms have been partially elucidated, for example, activation of micro-RNA miR-23b and TGFβ family proteins [18, 19]. However, since a long period of dormancy as in our case is rarely observed in uterine cervical cancer, the underlying mechanisms are poorly understood. Recently, Ignatius et al. [15] reported that HPV-45 infection is a possible factor contributing to the long-period dormancy of uterine cervical cancer although this has not been validated by other groups. In the present case, insufficient amounts of specimen prevented further molecular analysis. Further studies focusing on micro RNA, TGFβ, HPV genotype, and other molecular features for cancer dormancy, are warranted to improve patient survival in cases similar to the present case.

The number of reports of LM of uterine cervical cancer is growing steadily (Figure S3), which can be attributed (at least in part) to the recent prevalence of diagnostic modalities such as CT and MRI. Our literature review indicated that MRI with gadolinium enhancement is a useful tool for detecting LM, and its sensitivity is higher than that of CT (Fig. 3). In contrast to the improvement in diagnostic technologies, the prognosis for this disease remains poor (Figure S4). Radiotherapy and/or intrathecal chemotherapy are performed in 82% (9/11) of cases. In radiotherapy, focal irradiation of the symptomatic lesions is preferred over total craniospinal irradiation, considering the general condition of the patients. Methotrexate is the main chemotherapeutic agent for intrathecal administration. Although 45% (5/11) of reported cases were treated with combined focal radiotherapy and intrathecal chemotherapy, the survival benefit of combination treatment is not evident. We treated the oculomotor nerve lesion with focal irradiation using SBRT, however, it was ineffective for the symptoms. This was contrast to the sufficient pain resolution by radiotherapy in the spinal metastases. The difference in the total dose (30 Gy for the oculomotor nerve lesion versus 70 Gy for the spinal lesions) might affect the difference in the treatment response, indicating the need for high dose in the palliative irradiation for LM. Another possible reason for the ineffectiveness of radiotherapy on the oculomotor nerve symptoms is that the oculomotor nerve invasion had led to irreversible functional loss which was difficult to be recovered by any anti-tumor treatment. Taken together, these findings indicate that early intervention with best supportive care is important

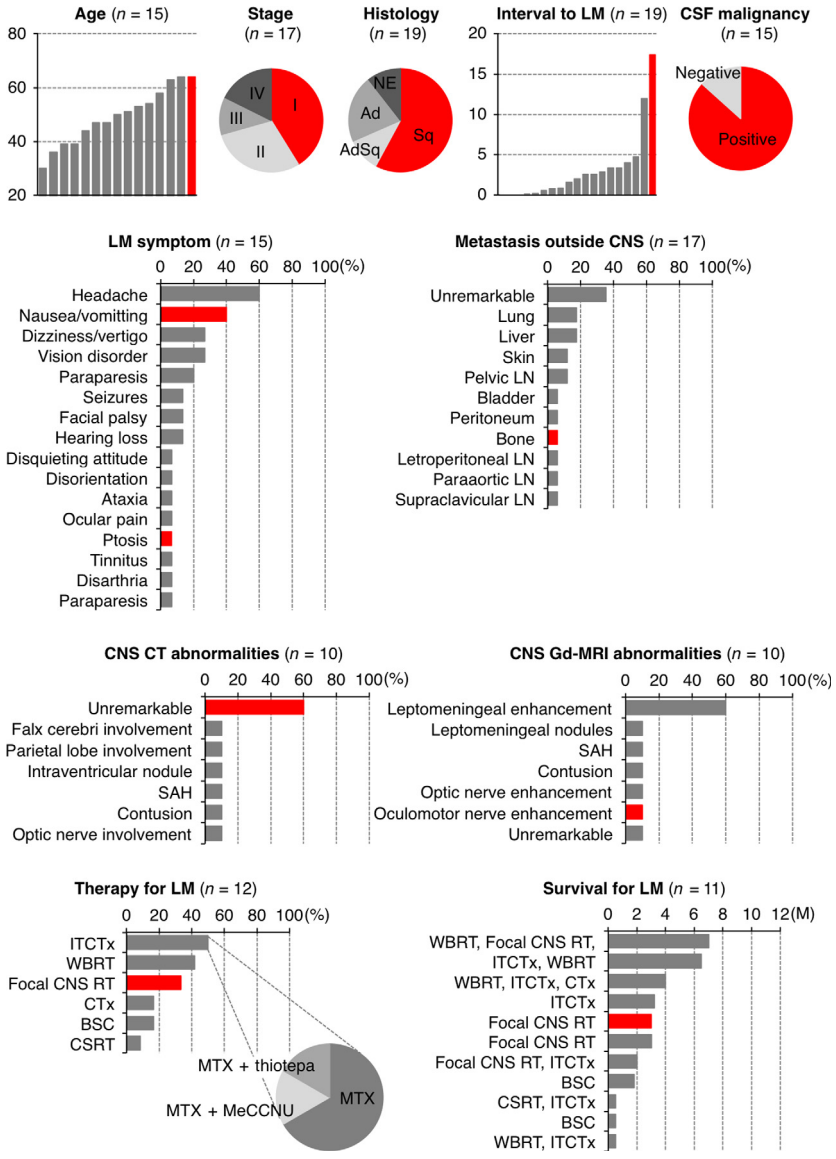

Figure 3. Graphic summary of the current case and other reported cases of leptomeningeal metastasis of uterine cervical cancer, showing patient characteristics, examination findings, treatment modalities, and prognosis. Detailed information is provided in the Table 1. The current case is indicated in red. Sq, squamous cell carcinoma; Ad, adenocarcinoma; AdSq, adenosquamous cell carcinoma; NE, neuroendocrine carcinoma; LM, leptomeningeal metastasis; CSF, cerebrospinal fluid; CNS, central nervous system; LN, lymph node; SAH, subarachnoid hemorrhage; Gd, gadolinium; ITCTx, intrathecal chemotherapy; WBRT, whole brain radiotherapy; RT, radiotherapy; CTx, chemotherapy; BSC, best supportive care; CSRT, craniospinal radiotherapy; MTX, methotrexate; M, month.

to improve the quality of life of patients with this intractable disease.

The level of SCC, a tumor maker for squamous cell carcinoma, according to disease course should be discussed (Figure S5). At the time of diagnosis, the SCC level was within normal limit as is often the case with nonkeratinizing type squamous cell carcinoma of the uterine cervix. However, interestingly, this case showed abnormally high SCC levels at the time of diagnosis for L2/3 metastasis and thereafter. This may suggest that the SCC level in this case reflects a certain context of the tumor cells that contributed to bone metastasis and LM, and that the SCC level should be carefully followed up even it was unremarkable at the time of diagnosis.

In summary, we report a case of LM of uterine cervical cancer presenting with oculomotor nerve invasion causing ptosis. To the best of our knowledge, the present case shows the longest period of dormancy (17 years from

primary tumor treatment to the onset of LM) reported to date. Awareness of early neurological symptoms may facilitate early diagnosis and intervention to improve the patients' quality of life.

Informed consent

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images.

Acknowledgments

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Conflict of Interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. PET-CT images taken before and after radiotherapy for L2 and L3 lesions.
Figure S2. PET-CT images taken before and after radiotherapy for Th12 lesion.
Figure S3. Cumulative number of publication reporting leptomeningeal metastasis of uterine cervical cancer.
Figure S4. Survival after leptomeningeal metastasis (LM) of uterine cervical cancer across the ages.
Figure S5. SCC levels according to disease course. Meta, metastasis; LM, leptomeningeal metastasis.