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Advances in diagnosis and treatment of metastatic cervical cancer

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ABSTRACT

Cervical cancer is one of the most common cancers in women worldwide. The outcome of patients with metastatic cervical cancer is poor. We reviewed the relevant literature concerning the treatment and diagnosis of metastatic cervical cancer. There are two types of metastasis related to different treatments and survival rates: hematogenous metastasis and lymphatic metastasis. Patients with hematogenous metastasis have a higher risk of death than those with lymphatic metastasis. In terms of diagnosis, fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and PET-computed tomography are effective tools for the evaluation of distant metastasis. Concurrent chemoradiotherapy and subsequent chemotherapy are well-tolerated and efficient for lymphatic metastasis. As for lung metastasis, chemotherapy and/or surgery are valuable treatments for resistant, recurrent metastatic cervical cancer and chemoradiotherapy may be the optimal choice for stage IVB cervical cancer. Chemotherapy and bone irradiation are promising for bone metastasis. A better survival is achieved with multimodal therapy. Craniotomy or stereotactic radiosurgery is an optimal choice combined with radiotherapy for solitary brain metastases. Chemotherapy and palliative brain radiation may be considered for multiple brain metastases and other organ metastases.

Keywords: Diagnosis; Neoplasm Metastasis; Therapeutics; Uterine Cervical Neoplasms

INTRODUCTION

Cervical cancer is one of the most common malignant tumors affecting women [1]. According to the American Joint Committee on Cancer (AJCC), cervical cancer patients with the International Federation of Gynecology and Obstetrics stage I to IV tumors (any AJCC tumor [T] stage), any lymph node (LN) stage, and M1 (distant metastasis of peritoneal spread and involvement of supraclavicular lymph node [SCLN], mediastinal lymph node [MLN], or para-aortic lymph node [PALN]; lung; liver; bone; or brain) at primary presentation, or who have persistent/recurrent disease outside the pelvis, are classified as metastatic cervical cancer patients. Thirteen percent of cervical cancer patients are diagnosed at advanced stages. The 5-year survival rate for metastatic cervical cancer is 16.5% compared to 91.5% for localized cervical cancer [2]. In contrast to patients with early-stage cervical cancer and locally advanced cervical cancer who have access to conventional treatments including

surgery, chemotherapy, or radiotherapy (RT), there is no standard treatment for patients with metastatic cervical cancer because of its heterogeneous manifestations. Currently, the median survival time is only 8 to 13 months [3]. This article will focus on some of the important findings in metastatic cervical cancer.

PATIENTS WITH LYMPHATIC METASTASIS

For patients with metastatic cervical cancer, if the involved sites outside of the pelvic organs are all LNs, the type of metastasis is designated as lymphatic metastasis.

DIAGNOSIS

Historically, methods of detecting LN status include computed tomography (CT), magnetic resonance imaging (MRI), lymphadenectomy, and lymphangiogram. CT and MRI are considered the preferred tools for the clinical evaluation of invasive cervical cancer [4]. Diffusion-weighted MRI has emerged as a new technique for detecting pelvic LN metastases in patients with cervical cancer. However, large-scale, high-quality trials are in desperate need to evaluate its clinical value for the discrimination of metastatic from non-metastatic pelvic LNs in patients with cervical cancer [5].

Recently, positron emission tomography (PET) is becoming common for the preoperative examination and diagnosis of metastatic cervical cancer. PET-CT, in which PET is combined with CT images to improve anatomical accuracy, has also become prevalent. In patients of reproductive age, 18F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is absorbed by the ureter physiologically. ^{18}F-FDG-PET has emerged as an effective tool to evaluate extra-pelvic metastases including LNs with superior sensitivity and specificity compared to CT or MRI, and it is considered the most useful among non-invasive diagnostic imaging methods [6,7]. FDG-PET may also offer maximal benefits by selecting appropriate recurrent cervical cancer patients for salvage therapy with precise restaging information [8].

Besides, PET or PET-CT improve primary treatment planning in cervical cancer with MRI-defined suspected distant nodal metastasis. In one study [9], 47 patients were enrolled for suspected metastasis to PALN with (n=8) or without (n=31) other distant nodal involvement, iliac LN (n=6), or SCLN metastasis (n=2). Additional PET or PET-CT had a positive clinical effect in 21 (44.7%) of the 47 patients. The positive effects included disclosing additional curable sites (n=8), down-staging (n=6), and offering metabolic biopsy (n=4) or a change to palliation (n=3). Staging/restaging (p=0.006) was associated with a better prognosis [10]. There were significant correlations between the metabolic tumor volume, total lesion glycolysis, and LN metastasis (p=0.017 to 0.032) [11].

In addition to PET-CT, PET-MRI has emerged as another diagnostic tool in recent years. Diagnostic confidence was significantly higher for PET-MRI in malignant (p<0.01) and benign lesions (p<0.05). Considering the reduced radiation dose and superior lesion discrimination, PET-MRI may serve as a powerful alternative to PET-CT in the future [12]. Moreover, PET-MRI also revealed a significant and strong correlation between tumor metabolism and higher cellularity in cervical cancer lesions [13].

However, a recent study demonstrated that the efficacy of PET or PET-CT in the detection of LN metastasis in cervical cancer is limited by the region of the LN, the size of the metastasis lesion in the LN, and the pathological type of primary tumor. Because of its limited spatial resolution, PET or PET-CT is not suitable for detecting small lesions, early-stage screening, and diagnosing primary lesions [14]. Further improvements in diagnostic technology including PET-MRI, the investigation of new positron tracers, and the analysis of data from various combinations of tracers are likely to make PET particularly useful for diagnosis and therapeutic strategy planning [15].

TREATMENT

For LN metastasis, the risk of mortality increases tremendously based on the most distant level of LN involvement at diagnosis [16]. Within a stage, patients with PET-positive LNs had a significantly worse survival than those with PET-negative LNs (p<0.001) [17]. In addition, a high FDG intake, which is measured by the standard uptake value (SUV), is related to poor survival of the primary tumor [18].

One study aimed to determine whether concurrent chemoradiotherapy (CCRT) is efficient for improving prognosis compared to chemotherapy in patients with stage IVB cervical cancer who have distant lymphatic metastasis. In a study, 24 patients who received CCRT (n=10) or chemotherapy (n=14) were enrolled. The complete response rates were 60% and 0% after CCRT and chemotherapy (p<0.01), respectively. CCRT were favorable prognostic factors for the improvement of progression-free survival (PFS; 7.8 months vs. 40.5 months) significant for the improvement of overall survival (OS; 18.4 months vs. 63.7 months). Grade 3 or 4 leukopenia were more common in the patients treated with CCRT (24.4% vs. 9.1%, p=0.03). Grade 3 proctitis occurred as a late RT-related toxicity in only one patient (10%) who was treated with CCRT. However, no differences in the rate and pattern of disease recurrence were observed between CCRT and chemotherapy [19].

For isolated LN recurrence, salvage RT with concurrent chemotherapy after radical surgery in cervical cancer is also recommended. In one study, 22 cervical cancer patients with LN recurrence who had previously undergone radical hysterectomy and pelvic LN dissection were treated with salvage RT with (n=18) or without (n=4) chemotherapy. Various chemotherapy regimens were used (5-fluorouracil [5-FU] + cisplatin [FP], n=11; paclitaxel + carboplatin, n=7). The median total RT dose was 60 Gy (range, 40 to 70 Gy). Patients treated with CCRT achieved longer 5-year PFS and OS rate (72.9% and 60%; p=0.009). Treatment failure after salvage RT occurred in 14 (63.6%) of the 22 patients (in field, two; out of field, 10; both in and out of field, two). Grade 3 acute skin (n=2) and hematologic toxicity (n=1) developed in three patients [20].

1. Treatment for patients with PALN metastases

The incidence of extrapelvic disease at the initial management of patients treated for locally advanced cervical cancer is high, ranging from 10% to 30%, particularly in PALN (21%) [21]. Among patients with PALN metastasis, the tumor SUV is higher in patients with PET-positive LNs compared to others [22]. An SUV (^{18}F-FDG PET; max) greater than or equal to 3.3 and a nodal involvement greater than 5 mm for PALN are significant adverse factors of prognosis [23,24].

When para-aortic disease occurs, two types of therapy are used. The first choice is surgical resection. PALN resection not only is beneficial for detecting potential LN metastases of cervical cancer patients, but also provides a therapeutic effect [25]. Initially, the operation was performed by laparotomy, but this procedure was abandoned because of its high complication rate (10% to 16%) [26]. In the 1990s, with the development of laparoscopy and its low morbidity, short hospital stay, and reduced delay prior to RT, the concept of para-aortic surgery arose, first via the transperitoneal approach [27]. Compared to laparotomy, the extraperitoneal laparoscopic approach substantially reduces perioperative morbidity, particularly the incidence of RT-induced complications. Moreover, extraperitoneal laparoscopic para-aortic lymphadenectomy for pretherapeutic surgical staging is a safe and feasible procedure that should be considered as a tool to provide accurate information for LN positive patients who require extended-field radiation (EFRT) and/or chemotherapy [28-30]. In one study that included 44 women with histologically proven PALN metastasis, laparoscopic lymphadenectomy was performed in 40 patients. The patients underwent conventional fractionation of 50.4 Gy to the para-aortic and pelvic regions. In addition, MRI-guided brachytherapy was performed to the cervix with 5 to 6 single doses of 5 Gy for a total dose of 25 to 30 Gy. All of the patients received cisplatin-based chemotherapy, except for five patients who received carboplatin and one patient who received radiation only. Cisplatin and carboplatin were administered once per week. There was no grade 4 or 5 acute radiation toxicity. In all, 11% of the patients had grade 3 gastrointestinal late toxicities, and 19% of the patients had grade 3 genitourinary late toxicities. The 2 and 5 years OS rates were 68.4% and 54.1%, respectively. Of the 44 patients, 43 remained tumor-free in the para-aortic region. The author concluded that excellent pelvic and para-aortic control could be achieved by lymphadenectomy followed by EFRT with concurrent chemotherapy [31]. Pretreatment surgical PALN dissection or sampling is feasible with low complication rates and short delays in starting treatment [32]. However, considering the complicated laparoscopic procedure, the expensive equipment, and the recent emerging tumor recurrence complications [33], the application of surgery is limited.

The alternative type of therapy is CCRT. Nowadays, curative doses of EFRT can be safely delivered to patients with metastatic cervical cancer who present with only PALN metastasis [34].

When combined with concurrent chemotherapy, the sensitivity of RT increased. In one study, totals of 13 and 19 patients underwent EFRT and EFRT with concurrent chemotherapy. The 5-year OS rate was 40% for patients who underwent CCRT as compared to 18% for patients who had EFRT alone, with median survival of 29 and 13 months, respectively [35]. One study enrolled 46 stage IB-IVA cervical cancer patients (51.1%) who received concurrent chemotherapy. Seventy patients (77.8%) had complete remission. The 5-year OS and PFS were 62.6% and 43.9%, respectively [36]. Another study reviewed the results of 33 women with stage IB-IVB cervical cancer who were treated with EFRT and concurrent platinum-based chemotherapy. Each patient received a total dose of 59.4 Gy, including a three-dimensional conformal boost to the PALN, and 41.4 to 50.4 Gy of external beam RT to the pelvis. Patients also underwent six or seven applications of high-dose rate brachytherapy. Twelve women received monthly FP (5-FU 1,000 mg/m^2/day and cisplatin 20 mg/m^2/day), 11 women received weekly cisplatin (30 mg/m^2), seven women received paclitaxel (135 mg/m^2/day) plus cisplatin (75 mg/m^2/day) at 3-week intervals, and three women received paclitaxel (135 mg/m^2/day) plus carboplatin (area under the curve [AUC] 5) at 3-week intervals. More than three-quarters of the patients showed a complete response, and 15 had no evidence of disease. Severe acute

and late gastrointestinal toxicity were observed in three and four patients, respectively. These results suggested that EFRT with concurrent chemotherapy is feasible in women with uterine cervical carcinoma and positive PALN with acceptable late morbidity and a high survival rate despite its substantial acute toxicity [37]. The other study (n=13) also confirmed the role of concurrent chemotherapy combined EFRT [38].

Ke et al. [39] studied 46 stage IB1-IVA cervical cancer patients with positive PALNs. Neoadjuvant, concomitant, and adjuvant chemotherapy with paclitaxel and carboplatin were administered for one cycle before RT, two cycles during RT, or three cycles after RT. All of the patients received extended-field intensity modulated RT (EF-IMRT) (50.4, 1.8 Gy per fraction) and intracavitary brachytherapy (the point "A" dose of 20.0 to 30.0 Gy in 5.0 Gy per fraction). Twenty-six patients were treated with a boost dose of 6.0 to 8.0 Gy in 2.0 Gy per fraction to positive PALNs. The 3-year PFS and OS rate were 46.2% and 61.2%. This study demonstrated that EF-IMRT and intracavitary brachytherapy combined with chemotherapy are safe and effective for stage IB1-IVA cervical cancer with positive PALNs [39].

A phase I/II study evaluated the role of weekly paclitaxel and cisplatin chemotherapy concurrent with extended-field irradiation in women with cervical cancer metastatic to the PALNs. A total of 29 patients were enrolled. The maximum tolerated dose was determined to be 40 mg/m^2 for cisplatin and 40 mg/m^2 for paclitaxel administered weekly for six cycles concurrently with EFRT. The para-aortic region received 45 Gy in 30 fractions after the 25 days of pelvic radiation, whereas the pelvic region received 45 Gy in 25 fractions. A parametrial boost of 5.4 to 9.0 Gy in 1.8 Gy fractions utilizing AP/PA fields was given based on the extent of parametrial involvement. The author concluded that this modality showed a higher disease-free survival (DFS) in relation to historical data with an approximate survival rate of 56% to date and an estimated 48-month survival rate of 50% [40].

Moreover, FP treatment was also associated with better patient survival. In one study, of 40 cervical cancer patients with isolated PALN metastasis at the initial diagnosis and all patients received RT. Among them, 14 patients received FP (two to four cycles of cisplatin at 75 mg/m^2 and 5-FU at 1,000 mg/m^2), and 16 patients received weekly concurrent cisplatin (40 mg/m^2) for a total of four to six cycles and the other patients received RT alone. Hematologic toxicity occurred in three patients who received FP therapy. The 3-year OS rates were 70.7%, 31.3%, and 37.5% in the patients who received FP, weekly cisplatin, and RT alone (p=0.028) [41]. Also, patients treated with high dose of radiation had a longer OS. The conventional 45 Gy is not sufficient for patients with LN metastasis. Doses greater than or equal to 50.4 Gy for treating PALN may result in better disease control [42]. Another study showed that a dose greater than 54 Gy for positive PALN metastasis in EFRT is safe [43]. In some studies, the 5-year OS rate were 47% to 77% for patients undergoing a 50 to 60 Gy radiation dose to the para-aortic area [36,37,44].

2. Treatment for patients with SCLN metastasis

The overall frequency of left SCLN metastasis in patients with metastatic cervical cancer is approximately 8.6% with or without PALN metastasis [45]. The frequency of metastasis is much higher in the subset of patients who undergo surgical staging for their cervical cancer and who have been found to have positive PALNs. The 5-year OS rate of patients with SCLN metastasis was 16.5% [10]. For patients with SCLN metastasis, different SUVs represent different outcomes. Patients with high SUV (>8) or low SUV (<4.3) have a lower 3-year OS rate compared to those with intermediate SUVs (between 4.3 and 8) [23]. Moreover, a latency

period of less than 2 years, squamous cell carcinoma antigen (SCC-Ag) levels ≥4 ng/mL, and recurrence extending beyond SCLN were significant adverse prognostic factors [46].

For patients presenting with both PALN and SCLN metastases, curative CCRT and subsequent chemotherapy are feasible with acceptable late toxicity in spite of a high rate of acute hematologic toxicity. In one study, 25 patients with both PALN and SCLN metastases received a mean 59.4 Gy to the PA and left supraclavicular areas and 50.4 Gy to the pelvis, followed by 30 Gy of high-dose rate brachytherapy in six fractions. All patients received platinum-based chemotherapy simultaneously. The median survival of the patients with SCLN and PALN metastases was 32 months [47], much higher compared to 7.5 months before report (with the longest surviving for 16 months) [48].

Another study also evaluated the outcomes of cervical cancer patients (n=7) with SCLN involvement and who received RT with chemotherapy. All of the patients also had positive PALNs. The RT field was designed to include the entire pelvis, the involved PALNs, and the SCLN area. The median SCLN RT dose was 66.6 Gy (range, 60 to 75.6 Gy). The FP regimens consisted of 40 to 60 mg/m^2 of cisplatin by intravenous infusion given on day 1 and 5-FU at a dose of 1,000 mg/m^2/day given as a continuous infusion on days 1 to 5. Chemotherapy was repeated every 3 weeks. The 5-year OS rates and PFS rates were 55.6% and 44.4%, respectively. The acute hematologic toxicities were as follows: G3/4 leukopenia in six patients (66.7%), G3 anemia in one patient (11.1%), and G3/4 thrombocytopenia in two patients (22.2%). These data suggested RT with chemotherapy as an active therapy can be expected to provide favorable results, although there is an increased risk of G3/4 hematologic toxicity [49].

PATIENTS WITH HEMATOGENOUS METASTASIS

Hematogenous dissemination is relatively unusual, and it most commonly involves the lungs (36.3%), bone (16.3%), liver, brain, and other sites can also be involved. Half of the patients with hematogenous dissemination died within 6 months. Sixty-nine point two percent of patients with a single metastasis and 82.7% of patients with multiple metastases died within 1 year [50]. A recent study including 30 patients (n=30) with disseminated cervical cancer of different types of metastasis indicated that patients with hematogenous metastasis had a 5.3-fold higher risk of death compared to those with lymphatic metastasis [51]. Chemotherapy has been used for recurrent or metastatic disease, but it has a limited influence on survival [52]. Clearly, we are in need of better treatment options for cervical cancer patients with hematogenous metastasis. The use of RT and multiagent chemotherapy are good choices [53].

1. Cervical carcinoma metastatic to the lung

For patients with cervical cancer, 4.16% to 7.7% patients develop lung metastasis [54]. The number of metastatic nodules, pulmonary metastasectomy, the disease-free interval (DFI) between the primary gynecologic procedure, and postoperative platinum based chemotherapy can influence clinical outcomes [55,56].

Patients with one or two pulmonary metastases had a 5-year DFS advantage over patients with three or four metastases [57]. Pulmonary metastases were detected in 83.9% patients within 2 years after the initial treatment of cervical cancer. The median PFS was 13 months. The median survival after lung metastasis was 18 months with 2- and 5-year survival rates of 37.7% and 7.5%, respectively. The metastases were mainly distributed to the inferior lobe

of the right lung. Regular CT lung screening is recommended for patients with stage IA-IIB cervical cancer during their follow-up period [58].

1) Operation

When cervical malignancy metastasizes to the lungs, surgery is a good choice because it provides a survival advantage [58,59]. The preferable conditions for pulmonary metastasectomy are as follows: the absence of hilar and MLN metastasis by roentgenographic findings; less than four pulmonary lesions; a DFI greater than 24 months; metastases up to approximately 3 cm in diameter; and no elevation in serum tumor markers [60]. For the surgical approach, wedge resection with a disease-free margin of 2 cm or more from the tumor edge was appropriate for lesions smaller than 3 cm in diameter, and lobectomy with LN dissection was necessary for lesions 3 cm or more in diameter [61].

One study evaluated the results of six cervical cancer patients (n=6) who underwent resection for pulmonary metastases, the median survival in those cervical cancer patients was 36 months. The authors concluded that pulmonary resection may provide a survival advantage for selected patients who have cervical malignancies with metastases isolated to the lungs [62]. In addition to that, it is beneficial for suspicious thoracic metastasis in cervical cancer patients [63].

Shiromizu et al. [64] conducted a study that involved a total of 519 patients with invasive cervical carcinoma (stage IB-IIB). The frequencies of pulmonary metastases were 6.4% (24/377) and 11.3% (16/142) in the patients with negative and positive pelvic LNs, respectively. Among the 24 patients with negative LNs, 15 had pulmonary metastasis only. The overall 5-year survival rate of these 15 patients was 36% after relapse. The prognosis of 12 patients (46%) with one to three pulmonary metastases was better after surgical resection and/or chemotherapy.

Above all, active surgical resection of the pulmonary lesion(s) and further chemotherapy is recommended to improve the prognosis [64].

2) Non-operative therapy

The responders to chemotherapy survived longer than the non-responders. Therefore, appropriate chemotherapy can prolong the survival of patients with pulmonary metastasis from uterine carcinoma [65].

The combination of carboplatin (300 mg/m^2, every 4 weeks) and 5'-DFUR (doxifluridine) (1,200 mg/day, 4 days per week) [66] or peplomycin, adriamycin, and cisplatin (peplomycin at a dose of 5 mg/day, continuous intravenous drip on days 1 to 7, adriamycin at a dose of 40 mg/m^2 intravenous on day 1, and cis-platinum at a dose of 40 mg/m^2, continuous intravenous drip on day 1, repeating at 5 to 6 weeks intervals) [67] are useful regimens for cervical carcinoma with pulmonary metastasis. A FP regimen (cisplatin 75 mg/m^2 and 5-FU 800 mg/m^2 every 4 weeks) was also evaluated. Fifty patients with radiologically proven pulmonary metastases were treated with chemotherapy. The 1- and 3-year OS rates after FP chemotherapy were 62% and 17.6%, respectively. The 1- and 3-year PFS rates were 36.7% and 14.3%, respectively. We conclude that a FP regimen is safe and reasonably effective for the management of patients with pulmonary metastases after primary treatment for invasive carcinoma of the cervix who are not eligible for surgical metastasectomy [68]. Aside from intravenous chemotherapy administration, bronchial arterial infusion chemotherapy [69] and subcutaneous infusion (bleomycin) [70] are potent treatments for pulmonary metastases of uterine cervical

cancer. For stage IVB cervical carcinoma with lung metastasis, no recurrence occurred after chemotherapy (paclitaxel, carboplatin 1 course) followed by CCRT with weekly cisplatin 20 mg/m^2 and continued chemotherapy with paclitaxel and carboplatin [54].

For large solitary pulmonary metastatic tumors, surgery combined with chemotherapy (plus RT for stage IVB) is able to provide a better prognosis. For patients who are not candidates for surgery, chemoradiotherapy may be the optimal choice for primary metastatic cervical cancer (stage IVB). Chemotherapy is valuable for resistant, recurrent metastatic cervical cancer.

2. Cervical carcinoma metastatic to the bones

Bone metastases from the carcinoma of the uterine cervix were observed in 0.8% to 23% of all cases [71-74]. The rates of metastasis in each of the four clinical stages have been reported as follows: 4.0% in stage I, 6.6% in stage II, 8.0% in stage III, and 22.9% in stage IV. The most frequent site of metastasis was the vertebral column [75], particularly the lumbar spine (48%). For 67% of cases, lesions of the bone were detected within 1 year after completion of the initial treatment, and 75% of patients died within 1 year after detection of the metastasis [72]. Patients younger than 45 with bone metastasis at the time of the cervical cancer diagnosis have a poorer prognosis than elderly patients [76]. Bone metastasis can cause severe pain, pathological fracture, and disability. The diagnosis of bone metastasis is confirmed by a bone biopsy or positive results on more than two modalities including a bone scan, FDG-PET, X-ray, and MRI. Plain radiograph and bone CT are useful modalities for evaluating metastatic bone disease. MRI depicts the soft tissue extension to a better advantage. In addition, a bone scan is a useful diagnostic tool for the detection of distant metastases and to differentiate the isolated distant metastasis from diffuse metastasis [77]. Patients with stage I and stage II carcinoma of the cervix may not require a bone scan [78,79]. Currently, there is no specific widely accepted guideline for the treatment of patients with bone involvement. Patients who do not receive therapy for bone metastasis survive for less than 6 months [80].

1) Surgery

For resectable bone metastasis, surgery should be considered. Pasricha et al. [81] reported a 36-year-old female presented with carcinoma of uterine cervix had remained healthy for 39 months after the surgical excision of bone metastasis. Hamanishi et al. [82] reported a 38-year-old woman who had a timely hemipelvectomy for lateral recurrent cervical cancer had reduced tumor pain and prolonged survival whereas other non-invasive treatments were not effective. However, most patients with bone metastasis die within 1 year, treatment should aim not only at prolonging their lifespan but also improving the patient's quality of life and palliating their pain.

2) Chemotherapy and/or bone irradiation

RT provided moderate palliation for treatable patients [83]. However, although local RT was useful for pain relief, it did not affect the prognosis [84]. RT provides good palliation for treatable patients, but the remission achieved is short lasting. Lesions of the bone treated by RT followed by cisplatin-based chemotherapy for patients with good general condition may be considered [85].

In one study, among 105 patients with bone metastasis, the median bone metastasis-free survival was 27 months. Most patients received a radiotherapeutic dose of 3,000 cGy (median, 3,000 cGy; range, 1,800 to 14,000 cGy) to bone metastasis, and approximately 60%

of the patients showed improvements in pain. The median survival after bone metastasis was 10 months, and it was longer in the patients who received RT with or without chemotherapy than in the patients who received chemotherapy alone as a salvage therapy (12 months vs. 7 months, p=0.01) [86]. When the treatment objective is pain relief, a single dose of 8 Gy treatment prescribed to the appropriate target volume is recommended as the standard dose-fractionation schedule for symptomatic and uncomplicated bone metastases [87]. However, a total dose of 30 Gy in 10 fractions is also considered as a standard method with lower rates of pathological fracture and spinal cord compression [88,89]. With regard to chemotherapy, except for intravenous administration, palliative transcatheter arterial chemoembolization/embolization could be a suitable treatment method for symptomatic bone metastases because it is minimally invasive, repeatable, effective, and rapid-acting [90]. Moreover, an intratumor injection of sizofiran and OK-432 with RT was effective for osteolytic bone metastases [91]. When combined with bisphosphonate administration, chemotherapy showed promising effects [92]. However, neither bisphosphonates nor denosumab have any positive effects on the survival of patients with bone metastasis [93].

3. Cervical carcinoma metastatic to the brain

Brain metastasis from uterine cervical cancer is rare (0.5% to 1.2%) [94] and is usually considered incurable. Patients presenting with intracranial pressure and cerebellar syndrome, such as headache, nausea, vomiting, seizure, and extremity weakness, are considered to have brain metastasis. Patients who have brain metastasis from cervical cancer are considered to have poor prognoses, particularly when it is detected late in the course of the disease. The median survival from the diagnosis of brain metastasis to death was 2.3 months [95]. Treatment depends on the number and location of the metastases, the presence of metastases at other organs, and the clinical status. Factors related to good prognoses are: age younger than 50 years, good performance status, single brain metastasis, and no extracranial metastasis [96]. Lung metastasis appears to be related to brain metastasis and may be regarded as a risk factor. Brain metastasis of cervical carcinoma can be either single (one metastasis; 50.6%) or multiple (≥two metastases; 49.4%) [97]. Most brain metastases are located in the supratentorial region of the brain, which may be related to the vascularity and spatial characteristics of this region [94,98]. Brain scans can be beneficial for metastasis detection [99]. Currently, no satisfactory therapeutic and standard effective treatments have been established.

1) Conventional surgery combined with chemotherapy and/or brain irradiation
One study encompassed 12 patients with brain metastasis from cervical cancer. Eight patients received whole-brain irradiation and steroids, three received steroids alone, and one underwent surgery followed by irradiation. The median dose was 3,750 cGy (range, 3,000 to 4,000 cGy) given over a median of 11 fractions (range, 10 to 20 fractions). Two of the four patients with solitary lesions received a stereotactic boost to the tumor site. All of the patients who received whole-brain irradiation experienced improvements in their symptoms. Five patients who received chemotherapy after brain irradiation had a median survival of 4.4 months compared to 0.9 months for those who received no additional treatment after brain irradiation (p=0.016). The chemotherapy regimens included topotecan, etoposide, docetaxel, cisplatin, and cisplatin plus ifosfamide. The patients who received brain irradiation (n=9) had a median survival of 3.0 months compared to 0.5 months for those who were treated with steroids alone (n=3; p=0.267). The median survival from the diagnosis of brain metastasis for the patients who underwent craniotomy was 6.2 months compared to 1.3 months for the six patients who were treated with whole-brain irradiation (p=0.024). This clinical trial

suggested that chemotherapy after brain irradiation appeared to have improved survival. Moreover, surgery combined with postoperative irradiation also showed survival benefits compared to RT alone [95].

2) Stereotactic radiosurgery combined with chemotherapy and/or brain irradiation
Except for conventional surgery, stereotactic radiosurgery (SRS) has advantages for the control of local brain metastasis and may also be used in inaccessible lesions. A study evaluated the survival benefit of SRS [100]. Seventy-seven patients with 90 metastatic brain tumors were treated with SRS. Among these patients, 10 with 17 metastatic brain tumors had their primary lesions controlled, and no other distant metastases were included in the current study. The median prescribed isocenter dose was 30 Gy (range, 30 to 45 Gy), and the median prescribed peripheral dose was 25 Gy (range, 12 to 30 Gy). The 3-year local control rates and OS rates were 90.0% and 51.9%, respectively. Although based on a very small number of patients, the best survival was noticed in patients receiving SRS either alone or in combination with other treatment modalities [101].

Another study also reported on the use of SRS for the management of brain metastases from cervical cancer. Thirteen patients with brain metastases from cervical cancer were managed with a Gamma-knife radiosurgery (GKRS). GKRS was chosen as the only treatment in four patients and was performed in combination with whole-brain radiotherapy (WBRT) in nine patients. GKRS was conducted simultaneously with WBRT within a 1-month interval in six patients and was chosen as the salvage treatment after WBRT in three patients. The mean number of metastatic brain lesions per patient was 5.7 (range, 1 to 16). The median cumulative tumor volume was 23.7 cm^3 (range, 2.7 to 40.2 cm^3), and the median marginal dose covering the tumors was 14 Gy of a 50% isodose line (range, 8 to 25 Gy). Nine patients showed relief from their main neurological symptoms after GKRS. The median length of time that the patients spent in an improved neurological state was 11.1 weeks (range, 2 to 39.6 weeks). The local and distant control rates were 66.7% and 77.8%, respectively. The median survival from the date of GKRS until death was 4.6 months (range, 1.0 to 15.9 months). The 6- and 12-month survival rates after GKRS were 38% and 15%, respectively. A pairwise comparison of the median survival time between GKRS alone and GKRS with WBRT demonstrated a statistically significant difference (1.2 months vs. 4.6 months, p=0.012). GKRS with WBRT appears to improve the duration of survival compared to GKRS alone for brain metastases from cervical cancer. Patients with relatively poor performance were more likely to be treated with GKRS alone instead of a combination modality [102]. Another study also demonstrated that extended survival can be achieved with more aggressive treatment such as surgery or SRS [103].

We also reviewed some case reports that showed similar results to the above studies (**Table 1**) [99,104-114].

In summary, as the studies demonstrated, the treatment of brain metastases has evolved over the years from WBRT alone to multimodal therapy including surgical resection (craniotomy) or SRS followed by WBRT and/or chemotherapy. A better survival is achieved with multimodal therapy (craniotomy followed by WBRT) compared to craniotomy alone or WBRT alone. The worst survival is observed in patients with no treatment [97]. SRS either alone or in combination with another treatment modality also shows greater benefits [100-103]. The decision between conventional craniotomy plus adjuvant RT and radiosurgery must be made on an individual basis, considering the size, number, and location of the lesions,

Table 1. Summary of the treatment and overall survival in the cervical cancer patients with brain metastases

Study	Age (yr)	Histology	Site	Treatment	Systemic disease control	Outcome*
Kumar et al. (1992) [104]	-	-	Solitary metastasis	Surgery+WBRT	-	7 mo
Kumar et al. (1992) [104]	-	-	Multiple brain metastases	WBRT	-	2 mo
Robinson et al. (1997) [105]	68	Moderately differentiated squamous cell carcinoma	An isolated subtentorial cerebellar mass	Surgery+WBRT (whole brain 30 Gy with 10 Gy subtentorial boost)	Yes	6 yr
Cormio et al. (1999) [106]	51	-	A solitary right frontal lobe lesion	Surgery+chemotherapy (3 cycles of cisplatin)	Yes	11 mo
Omari-Alaoui et al. (2003) [107]	48	Undifferentiated invasive squamous carcinoma	Isolated left cerebellum	Surgery+WBRT (whole brain 30 Gy with boost in posterior fosse of 15 Gy)	Yes	8 mo
Omari-Alaoui et al. (2003) [107]	67	Poor differentiated invasive squamous carcinoma	Three space occupying lesions in the posterior fosse	WBRT (30 Gy)	Yes	2 mo
Tajran et al. (2003) [108]	59	Moderately differentiated papillary adenocarcinoma	A right temporal-parietal lobe lesion	WBRT (45 Gy)	Yes	4.5 mo
Wuntkal et al. (2004) [109]	44	Poorly differentiated adenosquamous carcinoma	Carcinomatous meningitis	Radiation therapy+chemotherapy (intrathecal methotrexate parenteral dexamethasone and 5 cycles of systemic carboplatin)	No	5 mo
Amita et al. (2005) [110]	54	Poorly differentiated squamous cell carcinoma	Isolated left parieto-occipital lobe metastasis	Surgery+WBRT (whole brain 30 Gy with boost in posterior fosse of 10 Gy)	Yes	6 mo
Cordeiro et al. (2006) [111]	31	Poorly differentiated carcinoma	A left occipital lesion	Surgery+WBRT	Yes	5 yr
Cordeiro et al. (2006) [111]	31	Poorly differentiated adenosquamous carcinoma	A right hemispheric cerebellar lesion	WBRT	No	1 mo
Brown et al.(2007) [112]	60	-	A large right occipital CNS metastasis	SRS (16 Gy)+chemotherapy (6 cycles of paclitaxel [175 mg/m² and carboplatin [AUC, 5])	Yes	5 mo
Park et al. (2010) [113]	48	Moderately differentiated squamous cell carcinoma	Multiple	WBRT (30 Gy)+steroids	Yes	6 mo
Marongiu et al. (2012) [114]	48	Poorly differentiated squamous cell carcinoma	A left parietal lesion	WBRT+chemotherapy	No	11 mo
Marongiu et al. (2012) [114]	34	Small cell neuroendocrine carcinoma	A left postrolandic lesion	Surgery	Yes	11 mo
Erdis (2014) [99]	67	Squamous cell carcinoma	Solitary metastasis	WBRT (30 Gy)	No	Long-term disease-free survival

AUC, area under the curve; CNS, central nervous system; WBRT, whole brain radiotherapy; SRS, stereotactic radiotherapy.
*Outcome, from the date of diagnosis of brain metastasis to the date of death.

clinical conditions, and available technology [111]. Craniotomy is usually performed in larger, symptomatic lesions or if a histological diagnosis is required. SRS is less invasive and is more suitable for inaccessible lesions or when patients are not eligible for surgery [115]. We can also conclude that the optimal dose of RT is 30 Gy for the entire brain, and the dose boost to the focal is approximately 10 to 15 Gy.

Chemotherapy alone may be considered initially in patients with multiple brain metastases and other organ metastasis because it may control both brain metastasis and other metastatic

organs [116]. Cisplatin is the most frequently used drug. However, topotecan could be a reasonable option based on its activity against cervical cancer and its ability to cross the blood-brain barrier [117]. There has been no specific study with regard to the best dose and regimen for patients with brain metastasis. Meanwhile, for brain metastasis with multifocal metastases, palliative brain radiation is a more appropriate therapy. For solitary brain metastases in the absence of systemic disease, the use of craniotomy is an optimal choice combined with RT [105]. Although all of these treatments are available, the median survival from the diagnosis of brain metastasis to death is short.

PROBLEMS AND PROSPECTS

Until now, most studies on therapeutic methods for patients with metastatic cervical cancer have contained patients with both primary and metastatic or recurrent diseases because of the lack of enrolled patients with first-diagnosed metastatic cervical cancer. Patients with more than two metastatic sites who received more than one prior systemic therapy had dismal outcomes [118]. In recurrent cervical cancer patients, if the patient received prior chemotherapy, chemo-resistance may occur through several changes in drug transport, leading to reduced intracellular accumulation and activated drug detoxification by elevated levels of intracellular scavengers, including glutathione, the apoptotic cell death pathway, etc. [119]. Moreover, prior ionizing radiation can cause the failure of RT [120]. Because of the different biological characteristics of patients with primary stage IVB cancer compared to patients with metastatic or recurrent cervical cancer, studies that focus only on stage IVB cervical cancer are in desperate need. Some studies have demonstrated that the use of RT and multiagent chemotherapy in patients with stage IVB cervical carcinoma and good performance status were well-tolerated and resulted in higher survival rates [53]. In addition, the effectiveness of chemoradiotherapy for lymphatic metastasis has been confirmed according to the above mentioned data. However, whether chemoradiotherapy is effective for stage IVB cervical cancer patients with hematogenous metastasis remains unclear. In addition, the effects of radical hysterectomy require confirmation. Meanwhile, there have not been enough studies concerning patients with cervical cancer metastatic to the liver and MLN to draw any conclusions about treatment and survival. And many of the references are small sized retrospective studies. Therefore, future large sized and prospective studies are required to provide more confirmative information.

CONCLUSIONS

For cervical cancer patients, there are two types of metastasis: hematogenous metastasis and lymphatic metastasis. Patients with hematogenous metastasis have a higher risk of death than those with lymphatic metastasis. In terms of diagnosis, PET or PET-CT is an effective tool to evaluate distant metastasis including hematogenous metastasis and LN metastasis. For treatment, CCRT and subsequent chemotherapy are well-tolerated and efficient for lymphatic metastasis. Moreover, for hematogenous metastatic to different organs, it is more beneficial to undergo surgery when applicable. Regarding cervical carcinoma metastatic to the lungs, for large solitary pulmonary metastatic tumors, surgery combined with chemotherapy (plus RT for stage IVB) is able to provide a better prognosis. For those who are not candidates for surgery, chemoradiotherapy may be the optimal choice for primary metastatic cervical cancer (stage IVB). Chemotherapy is valuable for resistant, recurrent

metastatic cervical cancer. For cervical carcinoma metastatic to the bone, concurrent chemotherapy and bisphosphonate administration is promising. For cervical carcinoma metastatic to the brain, palliative brain radiation is a more appropriate therapy for brain metastases with multifocal metastases. The use of craniotomy is an optimal choice combined with RT for solitary brain metastases. Chemotherapy may be considered initially in patients with multiple brain metastases and other organ metastasis.

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