Primary Malignant Melanoma of the Cervix: An Integrated Analysis of Case Reports and Series

Aiping Min², Aizhen Fu³, Meiyuan Huang⁴, Hongjing Wang⁵ and Huan Chen¹*

¹ Department of Obstetrics 1, Zhuzhou Central Hospital, Zhuzhou, China, ² Department of Obstetrics and Gynecology, People’s Hospital of Leshan, Leshan, China, ³ Department of Obstetrics and Gynecology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China, ⁴ Department of Pathology, Zhuzhou Central Hospital, Zhuzhou, China, ⁵ West China Second University Hospital, Sichuan University, Chengdu, China

Melanoma, also known as malignant melanoma, is a type of malignant tumour that originates from melanocytes in the basal layer of the epidermis. Primary malignant melanomas of the female genital tract are rare. Similarly, primary malignant melanoma of cervix, which originates from cervical melanocytes, is an extremely rare disease and the second most common type of female melanoma in women aged between 15 to 44 years worldwide. To date, primary malignant melanoma of the cervix is characterized by poor patient prognosis and little consensus exists regarding the best treatment therapy. The situation is worsened by lack of clinical studies with large samples. Notably, surgery remains the preferred treatment option for patients with primary malignant melanomas of the cervix. Current treatments are based on Federation International of Gynecology and Obstetrics(2018) staging with reference to National Comprehensive Cancer Network guidelines. This study is in order to find a more suitable treatment modality for primary malignant melanoma of cervix. Therefore, we first conducted an integrated analysis of case reports and series to assess the impact of various factors on the prognosis of such patients. In summary, this is the first pooled analysis including 149 cases of primary cervical melanoma. We found that patients who underwent radical hysterectomy-based surgery, those with non-metastatic lymph nodes and those who underwent lymphadenectomy had significantly higher survival rates. In patients who had RH-based surgery, survival rates at the 24m time point of those who did not add other treatments was higher than those who did, but for those who had total hysterectomy-based surgery, the addition of other treatments to prolong median survival may be considered. In the overall analysis, age and lymphadenectomy were associated with increased and reduced risk of death in these patients, respectively. Although there is no statistical difference, stage III&IV, TAH, lymphatic metastases increase the risk of death; whereas radical hysterectomy was associated with reduced risk of death. In the subgroup analysis, for patients who have undergone radical hysterectomy-based surgery, lymphadenectomy reduces the risk of death, while lymphatic metastases and complementary other treatments increase the risk of death. For patients who have undergone total hysterectomy-based surgery, complementary treatment reduces the risk of death. In
INTRODUCTION

Melanoma, also known as malignant melanoma (MM), is a type of malignant tumour that originates from melanocytes in the basal layer of the epidermis (1). It is considered one of the most aggressive cancer diseases due to its high malignancy and treatment resistance (2). Notably, MM patients have a survival period of less than 5 years (3), although they have very good prognosis if the disease is detected in its early stages (4). Globally, disease accounts for approximately 0.03% of all newly diagnosed cancers (5). Previous studies have shown that the high mortality rate is due to the aggressive metastatic potential of melanoma cells (6). Previous estimates have shown that approximately 132,000 and 48,000 new malignant melanoma cases and deaths, respectively, occur each year (7). In fact, MM is ranked the fifth most common cancer in the world, and its incidence is on the rise (8). Primary MMs of the female genital tract are rare, accounting for only 3-7% of all mucosal melanomas (9). On the other hand, primary malignant melanoma of the cervix (PMMC) is an extremely rare disease that originates from cervical melanocytes (10). It is the second most common type of female melanoma in women aged between 15 to 44 years worldwide (11).

Melanoma is a highly malignant tumor with a poor prognosis (12), while that of PMMC worse (13). To date, little consensus has been reached regarding the best treatment therapy for PMMC. Lack of clinical studies involving large sample sizes has also contributed to scarcity of optimal treatment options. Nevertheless, surgery remains the preferred treatment option (13, 14). The current treatments are based on FIGO staging with reference to NCCN guidelines (15). This study is in order to find a more suitable treatment modality for PMMC. Therefore, we first conducted an integrated analysis of case reports and series to assess the impact of various factors on the prognosis of such patients.

METHODS

Data Sources and Search Strategy

In this section, we describe a comprehensive analysis based on published case report data. Briefly, we searched three public databases, namely PubMed, EMBASE and the Cochrane Library, for case reports published from their inception until 31st January 2022. The search strategy involved the following terms: (((Cervixes) OR (Uterine Cervix)) OR (Cervix, Uterine)) AND (Primary malignant melanoma). In addition, we performed a secondary search of the reference lists across relevant articles to identify additional eligible reports. Two independent reviewers (Aiping Min and Aizhen Fu) conducted the literature search, study selection and data extraction. Any discrepancy between them was resolved through consensus and arbitration by a third author (Meiyuan Huang).

Study Selection Criteria

All studies describing primary malignant melanoma of the cervix, with clinical information on the patients regardless of sample size, were included in this study. Conversely, articles that met the following criteria were excluded from the study: Primary melanoma of other genital tract origin, genital tract melanoma of undeterminable origin, reviews, books, as well as irrelevant. In cases where studies had overlapping data, we selected the study with the larger sample size.

Data Extraction

The following data were recorded: year of publication, patient’s age at diagnosis, patient’s symptoms, FIGO stage, whether surgery was performed, mode of surgery, presence or absence of lymphatic metastases, use of other treatment modalities and overall survival (OS) in months. If the patient’s clinical information was mentioned in another article, and the corresponding full text was not available, we marked the survival status with UNCERTAIN.

Outcomes and Statistical Analysis

Outcomes assessed were age and OS. The definition for survival time was based on data from the individual participants reported. Missing and unidentifiable data were specified as NA, thus were not included in the statistical analysis. Categorical data were presented as frequencies and percentages. On the other hand, continuous data that conformed to normal distribution were presented as means and standard deviations (SD), while non-normally distributed data were presented as medians (range). In addition, Kaplan-Meier survival curves were generated to estimate OS of patients, and differences across subgroups compared using the Log-rank test. Statistical analysis was performed using the SURVIVAL package implemented in R language (16). A multivariate analysis of these predictors of survival for overall and subgroups was conducted using a Cox proportional risk model. Data followed by P<0.05 were considered statistically significant.

RESULTS

Search Results and Eligible Studies

The aforementioned search strategy resulted in a total of 233 articles across the screened databases. Finally, 113 articles, containing 149 cases, were found to be eligible and therefore included in the analysis. A summary of the main features of the included studies is outlined in Table 1, whereas the procedure for literature search and selection is shown in Figure 1.
| Authors | Age | Symptom | Figo | Surgery | Lymph | Treatment | Survival(m) | Status |
|---------|-----|---------|------|---------|--------|-----------|-------------|--------|
| 1889 (17) | 40 | NA | NA | yes not defined | NA | NA | NA | NA |
| 1923 (18) | NA | VB | IIIB | NA | NA | no | 0.1 | uncertain |
| 1944 (19) | 64 | VB, A pain | IB | TAH + PV | NA | no | 156 | uncertain |
| 1950 (20) | 62 | VB | IB | TAH | NA | R | 1.2 | uncertain |
| 1954 (21) | NA | NA | NA | NA | NA | no | UK | NA |
| 1954 (22) | NA | VB and VD | IIIB | TAH + LND | NA | R | 21 | uncertain |
| 1959 (23) | 68 | Post coital VB and VD | IB | LE | NA | R | 23 | uncertain |
| 1959 (24) | 49 | Post coital VB and VD | IIIA | No | NA | R | 11 | uncertain |
| 1961 (25) | 64 | UK | IB | TAH + BSO | NA | no | UK | NA |
| 1961 (26) | 46 | Asymptomatic | IIIB | No | yes | R | 6 | 1 |
| 1966 (27) | 50 | VB and VD | IB | TAH + LND | NA | R | 21 | uncertain |
| 1967 (28) | 72 | VB and VD | IB | No | NA | R | UK | NA |
| 1959 (29) | 57 | VB | IIIA | TAH + BSO | NA | R | 12 | uncertain |
| 1970 (30) | 69 | Dyspareunia | IB | LE | NA | R | 62 | uncertain |
| 1970 (31) | 72 | VD | IIIA | LE + VULV | NA | R | 24 | uncertain |
| 1971 (32) | 39 | Asymptomatic | IIIA | TAH + BSO + PLND + PV + VULV | no | C+R | 168 | 1 |
| 1976 (33) | 70 | VB and VD | IIIB | TAH + BSO | NA | C+R | 10 | 1 |
| 1979 (34) | 44 | VB | IB | TAH + BSO | NA | I | 12 | 0 |
| 1979 (35) | 62 | VB | IB | TAH + BSO | NA | C+R | 19 | uncertain |
| 1979 (36) | 48 | UK | NA | TAH + BSO + LND | NA | C | 14 | uncertain |
| 1980 (37) | 26 | VB and VD | IIIB | Total pelvic exenteration | no | no | 11 | 0 |
| 1981 (38) | 65 | VB | IIIB | RH+PLND | yes | C | 10 | 1 |
| 1981 (39) | 45 | VB | IIIA | RH+PLND+PV | yes | no | UK | NA |
| 1981 (40) | 52 | VB | IB | TAH+BSO+PV | NA | no | 18 | 1 |
| 1986 (41) | 74 | VB | IIIA | RH+BSO+PLND+PV | no | no | UK | NA |
| 1987 (42) | 46 | VB and VD | IV | LE | NA | R | 5 | uncertain |
| 1988 (43) | 47 | VB | IIIA | No | NA | C+R | UK | NA |
| 1988 (44) | 58 | VB | IIIB | No | NA | R | 9 | 1 |
| 1989 (45) | 52 | VB | IB | TAH+PLND+PV | no | R | 25 | 1 |
| 1989 (46) | 20 | VB | IV | LE | yes | C | 5 | 1 |
| 1990 (47) | 64 | VB | IB | RH+BSO+PLND | no | R | 48 | 0 |
| 1990 (48) | 71 | UK | IB | TAH+VULV+LND | no | no | UK | NA |
| 1990 (49) | 35/58 | VB/VB | IV/IA | RH+BSO+PLND | no/no | no | 17/5 | 0/0 |
| 1991 (50) | 30 | VB and A pain | IB | RH+BSO+PLND+PV | yes | R | 34 | 0 |
| 1991 (51) | 62/60/ | VB, VB, VB | III/III/ | no/RH/RH | NA | C+/R/no | 14/12/10 | 1/1/0 |
| 1992 (52) | 37 | VB | IB | No | NA | R | 15 | 1 |
| 1992 (53) | 63 | VB | IV | TAH+BSO | NA | C+R | 12 | 0 |
| 1992 (54) | 70 | VB | IIIA | TAH+LND+VAG | NA | no | UK | NA |
| 1993 (55) | NA | Asymptomatic | IA | RH + BSO + LND + PV | NA | R | 66 | uncertain |
| 1994 (56) | 70 | VB | IB | RH | NA | no | 18 | uncertain |
| 1995 (57) | 78 | VB | IB | TAH+BSO+LND | NA | no | 27 | uncertain |
| 1996 (58) | 72 | VB | IB | LE | NA | R | UK | NA |
| 1997 (59) | 19 | NA | NA | RH+BSO+PLND+PV | NO | C | UK | NA |
| 1997 (60) | 57 | VB | IIIA | TAH+BSO+PV | no | C | 18 | 1 |
| 1998 (61) | 66 | VB, A pain | IIIB | No | NA | R | 6 | 1 |
| 1998 (62) | NA | VB | IIIB | TAH+BSO+LND+PV | NA | no | 48 | uncertain |
| 1998 (63) | 51 | VB | NA | TAH+BSO | NA | C+i | 13 | 1 |
| 1998 (64) | 70 | VB | IIIA | RH+BSO+PLND+PV | NA | R | 29 | 0 |
| 1999 (65) | NA | VB | Hematuria | IIIB | NA | NA | R | 9 | uncertain |
| 1999 (66) | 76 | VB | IB | RH+BSO+PLND | no | no | 30 | 0 |
| 1999 (67) | 71 | VB | IVB | RH+BSO+PLND | no | C | 2.75 | 1 |
| 1999 (68) | 70 | VB | IIIA | RH+BSO+PLND+PV | yes | R | 29 | 1 |
| 1999 (69) | 63 | VB | IB | TAH+BSO | NA | C | 10 | 1 |
| 2000 (70) | 73 | VB | VD | No | NA | R | 8 | 1 |
| 2001 (71) | 33 | VB, A pain | IB | RH+BSO+PLND | yes | no | 6 | 0 |
| 2001 (72) | 31 | VB | IIIA | TAH+BSO+LND | no | no | 10 | 1 |
| 2001 (73) | 50 | VB | IB | RH+PLND | no | R | 24 | 0 |
| 2002 (74) | 70 | VB, A pain | IB | RH+PLND | no | R | 6 | 1 |
| 2003 (75) | 26/70 | VB, and asymptomatic | IIIA/IB | TAH+salpingorectomy/residual cervix+PV +PLND | NA/no | I/no | 11/5 | 0/0 |
| 2003 (76) | 67 | VB | IIIA | TAH+BSO+PLND+PV | no | no | 12 | 1 |

(Continued)
| Authors | Age | Symptom | Figo | Surgery | Lymph | Treatment | Survival (m) | Status |
|---------|-----|---------|------|---------|-------|-----------|--------------|--------|
| 2003 (77) | 70 | VB | LE | NA | NA | C | 4 | 1 |
| 2004 (78) | NA | VB | NA | NA | NA | NA | NA | NA |
| 2005 (79) | 39 | VB, A pain | IIIB | RH+BSO+PLND+PV | yes | C+R | 6 | 1 |
| 2005 (80) | 82 | NA | NA | NA | yes | R | NA | NA |
| 2005 (81) | 45* | Post coital VB and VD | NA | RH+PLND/RH+PLND/RH+PLND/RH+PLND | NA | C+R/C+I | 42/42/6//0/1/1// | 84 | 0 |
| 2005 (82) | 54 | VB | IIA | RH | NA | C+R | 8 | 1 |
| 2006 (83) | 38 | VB | IB1 | RH+BSO+PLND | no | R | 24 | 0 |
| 2007 (84) | 63 | Asymptomatic | NA | Residual cervix+PLND | no | no | 12 | 0 |
| 2008 (85) | 43 | VB and VD | IIIB | TAH+BSO+PLND+VAG | no | C | 65 | 1 |
| 2009 (86) | 40 | VB | II | RH+PLND | yes | C+R | 18 | 0 |
| 2009 (87) | 61 | VB | IB | RH+BSO+PLND | no | no | 10 | 0 |
| 2009 (88) | 58 | VB | IIIB | RH+PLND | NA | C | NA | NA |
| 2009 (89) | 61 | vaginal spotting | IB1 | RH+BSO+PLND | no | no | 120 | 0 |
| 2009 (90) | 67 | VB | IIA | TAH+BSO+PLND+PV | no | C+I | 6 | 0 |
| 2009 (91) | 40 | NA | NA | TAH | NA | NA | NA | NA |
| 2009 (92) | 61 | NA | NA | TAH | NA | NA | NA | NA |
| 2010 (93) | 65 | VB | IB1 | no | NA | NA | NA | NA |
| 2010 (94) | 72 | NA | NA | yes not defined | NA | R | NA | NA |
| 2010 (95) | 50 | Contact VB | NA | yes not defined | NA | R | NA | NA |
| 2011 (96) | 34 | VB | IV | total pelvic extirpation | yes | R | 96 | 0 |
| 2011 (97) | 75 | VB | IB1 | RH+BSO+PLND | NA | C+R | 5 | 1 |
| 2011 (98) | 67 | VB | IB1 | RH+BSO+PLND+PV | no | no | NA | NA |
| 2012 (99) | 76 | VB | NA | TAH+BSO+PLND | yes | NA | NA | NA |
| 2012 (100) | 66 | VB | IB1 | RH+PLND+TV | yes | R | NA | NA |
| 2013 (101) | 63 | AVD and occasional VB | IIIA | RH+BSO+PLND+PV | no | no | 40 | 0 |
| 2013 (102) | 35 | AVD and irregular VB | IIA | TAH+PLND | yes | no | 6 | 1 |
| 2014 (103) | 35 | VB and abdominal pain | IB1 | NA | NA | NA | NA | NA |
| 2014 (104) | 46 | VB | IB2 | RH+BSO+PLND | yes | C+R | 24 | 0 |
| 2014 (105) | 65 | VB | IB1 | RH+BSO+PLND | no | C | 30 | 0 |
| 2014 (106) | 49 | VB | IIA2 | TAH+BSO+PLND | no | NA | NA | NA |
| 2014 (107) | 42 | VB | IIB | no | yes | R | 5 | 1 |
| 2014 (108) | 51 | VB | IIB | TAH+BSO+PLND | no | C | 10 | 0 |
| 2015 (109) | 43 | VB | IB1 | RH+PLND | no | R+I | 20 | 0 |
| 2015 (110) | 43 | VB | IB1 | RH+BSO+PLND | NA | NA | NA | NA |
| 2015 (111) | 73 | VB | IB2 | RH+BSO+PLND | no | C+I | 7 | 1 |
| 2016 (112) | 61 | VB | IB1 | RH+BSO+PLND | no | NA | 16 | 1 |
| 2016 (113) | 70 | left thigh pain | IV | no | yes | argon laser | 2 | 1 |
| 2016 (114) | 68 | VB | IB2 | RH+BSO+PLND | no | no | 60 | 0 |
| 2017 (115) | 47 | AVD | IB2 | RH+PLND | yes | C+R | NA | NA |
| 2017 (116) | 64 | VB and dyspareunia | IIB | RH+PLND | no | R | 21 | 0 |
| 2017 (117) | 66 | VB | IIIA | RH+BSO+PLND+TV | no | C+PD | 13 | 1 |
| 2017 (118) | 61 | VB | IIB | RH+PLND | NA | I | 193 | 0 |
| 2017 (119) | 74 | VB | IB2 | RH+PLND | NA | C | 33 | 1 |
| 2017 (120) | 56 | VB | IIB | no | NA | C+R | 5 | 1 |
| 2017 (121) | 74 | VB | IIA1 | TAH+PLND | NA | C+I | 28 | 1 |
| 2017 (122) | 77 | VB | IB1 | TAH | NA | no | 25 | 1 |

(Continued)
Patients’ Clinicopathological Characteristics

A total of 149 patients with PMMC were recruited in this study. Seven cases with missing data were excluded. The remaining cases had a median age of 58 years at diagnosis. Among the 149 patients, 126 (126/149) were suffered from vaginal bleeding or vaginal discharge, 2 due to contact bleeding, 7 asymptomatic, one each for acute pain in the lower abdomen, dyspareunia, left thigh pain, urinary incontinence, and 11 because of unknown reasons. FIGO staging guidelines stratified 56 patients into stage I, 45 into stage II, 18 into stage III, 8 in stage IV and 22 for whom staging information was not available. Notably, 7 patients had no surgical information, while 20 had no surgery and 7 (4.6%) only had local excision. On the other hand, 77.1% (115/149) of patients were treated with surgery, 46.9% (70/149) patients had surgery based on radical hysterectomy (RH), 2 of whom had...
total pelvic exenteration, 28.2%(42/149) patients had surgery based on total hysterectomy (TAH), while 3 had surgery but not defined at all. In addition, 25 and 38 exhibited presence and absence of lymph node metastases, respectively, while corresponding information was not available in the remaining patients. For the 25 patients with lymph node metastases, lymphadenectomy was performed in 17 cases. Furthermore, 79 and 60 patients underwent and did not undergo lymphatic resection, respectively, with the rest of the cases lacking corresponding information. Finally, 68 patients received whereas 37 did not receive treatment other than surgery, which included radiotherapy, chemotherapy, immunotherapy (interferon-γ or interleukin-2), PD/PD-1 inhibitors, oncolytic virus Rigvir®, argon laser, Argon helminknife. Among the 68 patients, 18 patients received chemotherapy, 6 patients received chemotherapy+immunotherapy, 1 patients received chemotherapy+PD, 14 patients received chemotherapy+radiotherapy, 1 patients received chemotherapy+radiotherapy +immunotherapy, 3 patients received immunotherapy, 2 patients received others(oncolytic virus Rigvir®, argon laser, Argon helminknife) treatment, 4 patients received PD, 17 patients received radiotherapy, 1 patients received radiotherapy +immunotherapy, 1 patients received radiotherapy +PD.

**Patient Prognosis and Survival Rates**

A total of 99 patients had information on survival time and status, of whom 39 survived (5-193 months) while 60 died. Corresponding information was not available for 32 patients, whereas the survival status of 18 patients could not be determined owing to a lack of full text. We generated Kaplan–Meier survival curves to evaluate OS of the patients, and obtained a median OS of 18 months in the cohort (Figure 2). Next, we employed log-rank tests under stratified covariates (FIGO stage, Surgery or not, the extent of surgery, Lymphatic metastases or not, Lymphadenectomy or not, Supplementary treatment or not), to explore underlying factors that may affect patient prognosis. Results indicated that prognosis of patients significantly decreased with stage progression (P=0.00069; Figure 3). Notably, patients who did not have surgery had significantly worse prognosis compared to those who had RH-based and TAH-based surgery (P<0.0001), while those who had RH-based surgery had better prognosis than those who had TAH-based surgery (Figure 4). Moreover, patients with non-lymphatic metastases had higher median survival times than those with lymphatic metastases, albeit with no statistical significance (P=0.056; Figure 5). Patients who underwent lymphadenectomy exhibited better prognosis than those who did not undergo the procedure (P<0.0001; Figure 6). Next, we compared surgical results (RH+TAH, RH, TAH) with and without other treatments, and found that in patients who underwent surgery(RH+TAH), there was no statistically significant differences in patient prognosis between groups with or without the addition of other treatment modalities (P=0.81; Figure 7). However, patients who added chemotherapy and others treatments(oncolytic virus Rigvir®, argon laser, Argon helminknife) had significantly longer median OS than those who
added the remaining treatment modalities. The exception to this was in patients who added radiotherapy or immunotherapy, where survival rates at the 60m time point were significantly higher than others (Figure 8). Moreover, in patients who had RH-based surgery, we found survival rates at the 24m time point of those who did not add other treatments was higher than those who did (Figure 9; P=0.18). In order to exclude possible confounding effects due to inhomogeneous distribution of characteristics between patients with RH and patients with RH +T, we tested if the stage, LS, LM are the same (Supplementary Table). The results found no significant difference between the two groups for Stage, LS, but a significant difference for LM. Similarly, patients who had chemotherapy or other treatments (oncolytic virus Rigvir®, argon laser, Argon heliumknife) exhibited significantly better median OS than those who had the remaining treatments. The exception was observed in patients who underwent radiotherapy, immunotherapy or with no other treatment added, whose survival rates at the 54m were significantly higher than others (Figure 10; P=0.14). In patients who had TAH-based surgery, we found no statistically significant differences in prognosis between the group with or without addition of other treatment modalities. However, the former group had higher median survival times than the latter (Figure 11; P=0.066). Furthermore, patients who added chemotherapy+radiotherapy exhibited significantly longer OS than those who added the remaining treatment modalities. The
median survival time for TAH-based patients with the addition of other treatment modalities was higher than for those who had only TAH surgery (Figure 12; P=0.39).

Results of multivariate Cox hazard model analysis revealed that age, stage III&IV, TAH and lymph metastasis increased the risk of death, whereas RH and lymphadenectomy was associated with reduced risk of death (Figure 13). In both the univariate and multifactorial cox regression risk models, only age and lymphatic resection showed consistency and could therefore be used as independent prognostic factors (Table 2). For patients who have undergone RH-based surgery, lymphadenectomy reduces the risk of death, while lymphatic metastases and complementary other treatments increase the risk of death (Figure 14). For patients who have undergone TAH-based surgery, lymphadenectomy seems to have little effect, while complementary treatment reduces the risk of death (Figure 15).

DISCUSSION

Primary malignant melanoma of the cervix is an extremely rare disease. According to Norris and Taylor (129), cervical melanoma can be diagnosed based on four criteria, namely: presence of melanin in the normal cervical epithelium; absence
of melanoma elsewhere in the body; junction changes in the cervix; and metastasis following a pattern of cervical cancer. The disease is characterized by poor patient prognosis, especially if it is not detected in time or treated correctly (95). Previous studies have shown that the 5-year OS for patients with this cancer is approximately 10% and many patients die within three years of diagnosis (87.5%) (13). However, the present study revealed contrasting results. as evidenced by a 5-year OS of 27% and death rate of 65% within 3 years. We attribute this to the continuous improvement in surgery and other treatment modalities. The main prognostic factor for cervical melanoma is the FIGO stage at the time of diagnosis (13). This is consistent with the results the present study, which revealed that median survival time gradually decreased with increasing FIGO stage.

Although no standard treatment modality has been developed for this condition, RH with pelvic lymph node dissection, partial vaginectomy remain the first-choice therapy for patients suitable for the procedure (130, 131). Results of the present study indicated that RH-based surgery did improve patient survival times, which were significantly better than those of patients who had TAH-based surgery and those who did not have surgery. However, a total hysterectomy was performed in some cases.
FIGURE 8 | Kaplan-Meier survival curves for OS in patients of surgery (RH+TAH) plus various treatments vs. no other treatments. The median OS was significantly longer for patients who added chemotherapy and other treatments (oncolytic virus Rigvir®, argon laser, Argon heliknife) than for those who added the remaining treatment modalities (Except for radiotherapy. Survival rates of this group at the 54m time point were higher for patients than other groups.) C: chemotherapy R: radiotherapy I: immunotherapy (interferon-γ or interleukin-2) PD : PD-1/PD-L1 Others: oncolytic virus Rigvir®, argon laser, Argon heliknife+Sunitinib no: no other treatment.

FIGURE 9 | Kaplan-Meier survival curves for OS in patients of RH-based surgery with and without other treatments. Survival rates at the 24m, 36m, 48m and 60m time points were significantly higher for patients who did not add other treatment modalities than for those who did.
FIGURE 10 | Kaplan-Meier survival curves for OS in patients of RH-based surgery plus various treatments vs. no other treatments. The median OS was significantly longer for patients who added chemotherapy and other treatments (oncolytic virus Rigvir®, argon laser, Argon heliumknife) than for those who added the remaining treatment modalities (Except for radiotherapy and no other treatment added). Survival rates of these two groups at the 48m time point were significantly higher for patients than others.) C: chemotherapy, R: radiotherapy, I: immunotherapy (interferon-γ or interleukin-2), PD: PD-1/PD-L1 Others: oncolytic virus Rigvir®, argon laser, Argon heliumknife+Sunitinib, none other treatment.

FIGURE 11 | Kaplan-Meier survival curves for OS in patients of TAH-based surgery with and without other treatments. The median OS for them are 20m, 12m respectively.
Adjuvant pelvic radiotherapy may be considered for patients with positive surgical margins, parametrial involvement or histologically positive nodes. On the other hand, patients who are not suitable for radical surgery may be subjected to definitive external pelvic radiotherapy with/without brachytherapy, primarily for palliative purposes (131). Although our results were consistent with this conclusion, we believe that adjuvant other treatments are counterproductive in patients who have
undergone RH-based surgery. This conclusion is contrary to common sense. It may be related to the following reasons: 1. The difference in LM numbers between the two groups was significant, while the median survival time was significantly lower for patients with lymph node metastases than for those without; 2. The sample size of patients supplemented with other treatments was not large enough; 3. Each case came from a different study unit, so there was some variation in the quality of the procedure even for radical surgery. If the extent of surgery is inadequate, for example TAH, adjuvant other treatments may improve their median survival time.

Immunotherapy, particularly immune checkpoint inhibitors, has shown great promise in cancer treatment (132), whereas immunotherapy based on immune checkpoint blockade is efficacious in treating melanoma (133). Although some studies have suggested that anti-PD-1 is associated with better OS compared to anti-CTLA4 in advanced/recurrent female genital tract melanoma (134), our results demonstrated that PD agents were not superior to the other adjuvant treatment modalities in patients with PMMC. This may be due to the small sample size of patients enrolled in this study.

In summary, this is the first pooled analysis including 149 cases of primary cervical melanoma. We found that patients who underwent RH-based surgery, those with non-lymph nodes metastatic and those who underwent lymphadenectomy had significantly higher survival rates. Based on the results of the analysis, the addition of other treatment options for patients who undergoing RH-based surgery is subject to further study, but for those who had TAH-based surgery, the addition of other treatments to prolong median survival may be considered. Notably, age and lymphadenectomy were associated with increased and reduced risk of death in these patients,

**TABLE 2 | Clinical factors effect on overall survival by univariate and multivariate cox proportional hazard regression analysis.**

| Characteristics                      | Univariate analyzes | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | HR(95% CI)          | P value               |
|                                      |                     | HR(95% CI)            | P value               |
| age                                  | 1.022(1.002-1.042)  | 0.0306                | 1.0546(1.01249-1.0984)| 0.0105               |
| Stage I                              |                     |                       |
| II                                   | 1.8260(0.9725-3.427) | 0.061046 | 0.7676(0.21393-2.7545)| 0.6850 |
| III                                  | 4.7650(2.1692-10.469)| 0.000101 | 4.1698(0.72557-23.9643)| 0.1095 |
| IV                                   | 1.3890(0.4026-4.792) | 0.602981 | 3.1280(0.45096-21.6976)| 0.2485 |
| No Surgery                           | 1                   |                       |
| RH                                   | 0.1523(0.07749-0.2993)| 4.7(6e-08) | 0.2443(0.03559-1.6767)| 0.1516 |
| TAH                                  | 0.2986(0.14636-0.6011) | 0.000745 | 1.9431(0.16396-23.0273)| 0.5985 |
| No lymphadenectomy                   | 1                   |                       |
| lymphadenectomy                      | 0.3143(0.1851-0.5336) | 1.82e-05 | 0.2260(0.06244-0.8182) | 0.0235 |
| No lymph metastasis                  | 1                   |                       |
| lymph metastasis                     | 2.11(0.9717-4.583)  | 0.0591                | 4.0186(0.94152-17.1519)| 0.0603 |
| No treatments or only surgery        | 1                   |                       |
| Treatments other than surgery        | 1.4290(0.741-2.757)  | 0.287                 | 0.7562(0.23845-2.4186) | 0.6376 |

**FIGURE 14 | Multivariate Cox hazard model analysis for RH-based patients. Lymphadenectomy reduces the risk of death, while lymphatic metastases and complementary other treatments increase the risk of death.**
respectively. Although there was no statistically significant difference, stage III&IV, TAH and lymph metastasis increased the risk of death, whereas RH was associated with reduced risk of death. For patients who have undergone RH-based surgery, lymphadenectomy reduces the risk of death, while lymphatic metastases and complementary other treatments increase the risk of death. For patients who have undergone TAH-based surgery, lymphadenectomy seems to have little effect, while complementary treatment reduces the risk of death. Future collaborative epidemiological studies are needed to further validate these findings. Therefore, via summarizing previous reports, the recommended treatment procedure for PMMC are radical hysterectomy and lymphadenectomy. The addition of other treatment options for patients who undergoing RH-based surgery need further study.

**DATA AVAILABILITY STATEMENT**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**ETHICS STATEMENT**

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

**AUTHOR CONTRIBUTION**

HC wrote the manuscript. AM and AF participated in the search strategy development. AM assisted in acquisition, analysis, or interpretation of data for the current work. HC prepared figures and tables. HW contributed to study concept and design. HC and MH double-checked the data and corrected the error in the tables. All authors contributed to critical manuscript revision.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.913964/full#supplementary-material

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**FIGURE 15** | Multivariate Cox hazard model analysis for TAH-based patients. Lymphadenectomy seems to have little effect, while complementary treatment reduces the risk of death.
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