CASE REPORT

# Primary malignant melanoma of cervix – A rare entity with limited therapeutic option

**Kanddy Loo Chin Yee, MRCOG (UK)[1], Syadwa Abdul Shukor, FRCR (UK)[2], Wee Wee Sim, FRCOG (UK)[1]**

[1]Gynaeoncology Unit, Department of O&G, Sarawak General Hospital, Malaysia, [2]Department of Radiotherapy Unit, Sarawak General Hospital, Malaysia

## SUMMARY

**Primary malignant melanoma of cervix (PMMC) is an extremely rare entity, accounting for 2% of the overall incidence of malignant melanoma (MM), which is 1% of all malignancy. We reported a case of PMMC in a 57-year-old woman. She presented with postmenopausal bleeding with no other significant symptoms. General examination was unremarkable with no suspicious mole elsewhere. Speculum and vaginal examination revealed a huge cervical mass with no pigmentation, with clinical stage 1B3 disease. Histopathological examination confirmed MM. She had three cycles of neoadjuvant chemotherapy with cisplatin, vincristine and dacarbazine, after which she underwent radical hysterectomy and pelvic lymphadenectomy. Histopathological examination confirmed stage 1B3 PMMC with close radial margin (1mm margin). She was planning for postoperative adjuvant radiotherapy, but she defaulted on the treatment. She succumbed to disease recurrence nine months after the surgery. There is little consensus on the standard treatment for PMMC. All therapeutic decisions made in this case were based on literature reviews. Surgery remains the mainstay of treatment. Radical hysterectomy may confer survival benefits compared to total hysterectomy alone. While nodal involvement is an important prognosticating factor, the role of regional lymphadenectomy is debatable. Adjuvant therapy with chemotherapy or radiotherapy seems to confer no survival benefits. Radiotherapy was planned for this patient as the margins were close. The prognosis for this condition is generally poor.**

## INTRODUCTION

Primary malignant melanoma of cervix (PMMC) is an extremely rare entity. Malignant melanoma (MM) accounts for only 1% of all malignancies, of which 3-7% occurs in female genital tract and 2% occurs primarily in cervix. Most of the literatures on PMMC are case reports and case series. In the largest review done by Pusceddu et al.[1], there were only 78 cases of PMMC reported in literatures over 200 years (1889-2009), signifying the rarity of the condition. There is little consensus on the standard treatment for PMMC. In Malaysia, to our best knowledge, PMMC has not been reported, and therefore, we would like to share our experience in managing this rare condition.

## CASE REPORT

A 57-year-old para 1 woman was referred from the district hospital, presented with postmenopausal bleeding for one year with no other significant symptoms. She had no prior cervical screening, and nor did she have any medical illness. There was no family history of malignancy.

General examination revealed a well-built woman with no cervical lymphadenopathy and normal abdominal examination. Retrospective examination showed that there was no suspicious mole elsewhere. Speculum examination revealed a huge polypoidal cervical mass >4cm with no pigmentation. The mass replaced the entire cervix. Biopsy was taken. Bimanual vaginal examination showed a hard cervical tumour of >4cm with no vaginal, parametrium or pelvic sidewall involvement. Rectal examination revealed smooth mucosa with external compression anteriorly. She was staged at 1B3 cervical carcinoma.

Staging computed tomography showed heterogeneous enhancing soft tissue mass in the region of the lower uterine body and cervix, measuring 5×7.4×4.2cm. It abutted the urinary bladder with an enlarged left internal iliac node of 1 cm. There was no distance metastasis.

Histopathological examination (HPE) of cervical biopsy showed tumour tissue which exhibited epithelioid to spindle with hyperchromatic nuclei, with some prominent nucleoli. Mitoses were brisk. Some contained melanin pigments. There was no junctional activity seen. The tumour cells stained strongly positive for S100, HMB 45 and Melan A. It was concluded as PMMC as three out of four diagnostic criteria by Morris and Taylor were fulfilled.

Considering the size of the tumour, a multidisciplinary discussion was done with the clinical oncologist and a consensual decision was made for neoadjuvant therapy. She tolerated three cycles of cisplatin, vincristine and dacarbazine chemotherapy. The reassessment CT scan showed stable disease, and she underwent radical hysterectomy and pelvic lymph node dissection (PLND). HPE confirmed stage 1B3 PMMC with close radial margin (1mm margin) and from vaginal cuff (3mm margin). She recuperated well after the surgery with no residual urinary symptoms. She was planned for adjuvant radiotherapy because of unsatisfactory surgical margin, but unfortunately, she defaulted due to the COVID-

*This article was accepted: 09 May 2022*
*Corresponding Author: Kanddy Loo Chin Yee*
*Email: klcygirl@yahoo.com*

**Table I: Summary of the details of review by Pusceddu et al., Yuan et al., and Sun et al., as well as comparison with the index case**

| Characters | Pusceddu et al. | Sun et al. | Yuan et al. | Index case |
|---|---|---|---|---|
| Age of diagnosis | 65.7% over 50-year-old<br>Median age 59 | Age range 38–80<br>Median age 56.5<br>Mean age 57 | Age range 42–78<br>Median age 62 | 57-year-old |
| Presenting complaints | • Vaginal bleeding (72%)<br>• Vaginal discharge (22%)<br>• Abdominal pain<br>• Dyspareunia, Haematuria, Asymptomatic | • Vaginal bleeding (86%)<br>• Vagina discharge (7%)<br>• Urinary incontinence (7%)<br>• Vaginal bleeding (86%)<br>• Vagina discharge (7%) | • Vaginal bleeding | • Vaginal bleeding |
| | Main presenting complaint was vaginal bleeding | | | |
| Stage at diagnosis | Stage I – 41%<br>Stage II – 34.4%<br>Stage III – 18.0%%<br>Stage IV – 6.5% | Stage I – 50%<br>Stage II – 35.7%<br>Stage III – 7.1%%<br>Stage IV – 7.1% | Stage I – 35.7%<br>Stage II – 42.8%<br>Stage III – 21.5%<br>Stage IV – 0% | Stage 1B3 |
| | Approximately 75 – 80% of cases were diagnosed in early stage | | | |
| Treatment modalities | 79% (62/78) underwent surgery<br>• Majority had total abdominal hysterectomy – 53/62 (85%)<br>• Local excision in 7/62 (11%)<br>• 1 total pelvic exenteration and one surgery not specified<br>19 had chemotherapy with 2 neoadjuvant chemotherapy | 78.6% (11/14) underwent surgery<br>• 1 had neoadjuvant chemotherapy<br>• 3 – adjuvant chemotherapy<br>• 3 – adjuvant radiotherapy<br>• 3 – BCG, interleukin-2, interferon<br>3 remaining cases – 2 received no treatment; 1 had chemotherapy and immunotherapy | 71.4% (10/14) underwent surgery<br>• 6 radical hysterectomy and 4 total hysterectomy<br>• 8 received PLND<br>• 1 received preop radiotherapy<br>• 1 received preop radiotherapy and chemotherapy<br>3 only received chemotherapy and radiotherapy<br>1 received chemotherapy due to physically unfit for surgery | Neoadjuvant chemotherapy (cisplatin, dacarbazine and vincristine) followed by radical hysterectomy and bilateral pelvic lymph node dissection |
| Survival | • Mean survival – 22.9 months<br>• Median survival – 12 months<br>• 10.7% survived more than 5 years<br>• Majority (85%) died within 3 years<br>• 5-year survival rate<br>  • I – 18.8%<br>  • II – 11%<br>  • III and IV – 0% | • Overall survival – 3–70 months<br>• Median survival – 13.7 months | • Survival >2 years – 50%<br>• Survival >5 years – 14.3% | Survival time – 13 months |

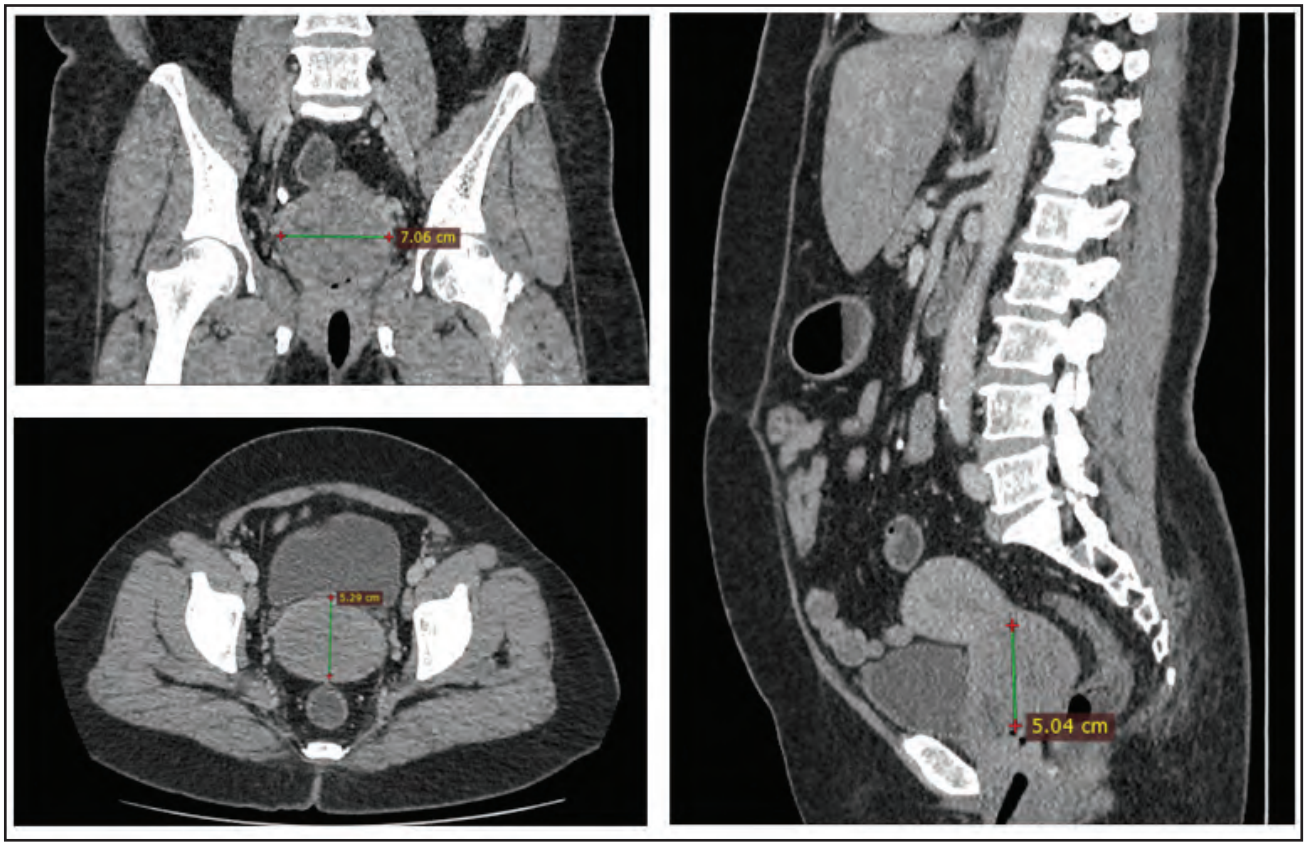


**Fig. 1:** Computed tomography imaging of the case before treatment

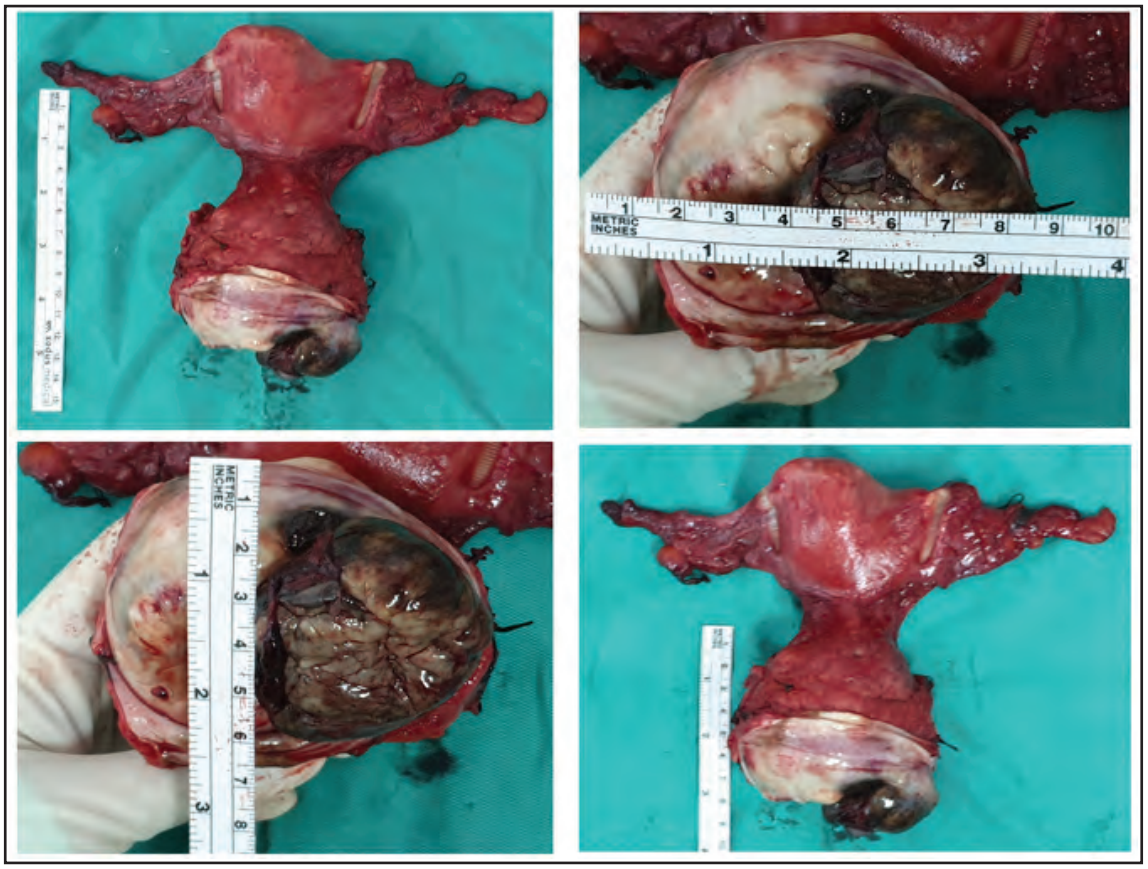


**Fig. 2:** Images of the resected specimen

19 pandemic. Multiple attempts have been made to contact patient but to no avail. She presented again nine months later with extensive pelvic recurrence with bowel involvement and bilateral obstructive uropathy. She revealed that the reason for defaulting further treatment was because of the fear of COVID-19 infection, and she was not contactable due to poor communication signal in her village. She succumbed to the disease eventually.

## DISCUSSION

Managing this case posed a challenge due to our lack of experience in handling such an unprecedented case. We performed a literature search to guide the management of this case. The main literatures included are by Pusceddu et al., Sun et al.,[2] and Yuan et al.[3] Sun et al., performed a review on 14 cases of PMMC diagnosed in Tianjin Medical University Cancer Institute and Hospital from January 1972 to February 2017. Yuan et al., reviewed 14 cases in Cancer Hospital of Chinese Academy of Medical Science from January 1, 1981 to December 31, 2014. The summary of these three literatures is detailed in Table I.

### Surgery and lymphadenectomy

In concurring with the general management of MM elsewhere, the mainstay of management of PMMC is surgery. Literature has proven the survival benefits of surgery in PMMC but there is still a lack of consensus on the type of surgery. There are generally two schools with regards to the radicality of surgical treatment. Some authors think that oncological resection to obtain an optimal surgical margin of 2cm is necessary.

On the other hand, in view of the poor prognosis, a more conservative approach can be advocated. In the review by Sun et al.,[2] 11 out of 14 cases had surgery, out of which nine were radical hysterectomy. It was proven that those with surgery had significantly better overall survival compared to those without surgery, regardless of the type of surgery. On top of demonstrating similar findings of better overall survival with surgery (47.9 vs. 7.75 months; p=0.047),[3] Yuan et al concluded that radical hysterectomy conferred longer survival compared to total hysterectomy only (66.8 vs. 19.5 months, p=0.016).

The role of lymphadenectomy in improving survival is still debatable. Historically, Jones et al., suggested prophylactic regional lymph node dissection as 30% of clinically normal lymph nodes contained microscopic metastasis.[4] However, Cantuara et al., advocated lymphadenectomy for grossly involved lymph nodes.[5] The more recent review by Sun et al had only one patient who underwent PLND while Yuan et al had eight patients who received PLND, all of which were negative for metastasis. Both reviews failed to demonstrate the beneficial effect of routine PLND. For our case, we have decided on a more radical surgical approach, including PLND.

### Neoadjuvant and adjuvant chemotherapy

There were anecdotal case reports by Min et al.,[6] and Liu et al.,[7] demonstrating successful treatment with neoadjuvant chemotherapy. Min et al reported a case of PMMC with parametrial and iliac lymph nodes involvement, treated with two cycles of cisplatin and dacarbazine, followed by radical hysterectomy, right salpingoophorectomy and pelvic lymphadenectomy. Postoperatively, four cycles of same chemotherapy regime were given concurrently with pelvic irradiation. The outcome was good, with no disease recurrence up to 24 months of follow-up. In another report by Liu et al., where the disease was staged at 1B1 with tumour size up to 4cm, two cycles of cisplatin, dacarbazine and vincristine were given. Subsequently, radical hysterectomy and pelvic lymphadenectomy were performed, followed by postoperative chemotherapy. Patient had survived 30 months of follow-up without recurrence.

The main challenge in this case was the size of the tumour, for which oncological resection might not be achieved with optimal margin. Considering the size, we employed the strategy of neoadjuvant chemotherapy in the hope of shrinking the tumour to get optimal surgical margin without compromising adjacent organs. Unfortunately, the size remained similar after three cycles of neoadjuvant chemotherapy.

Dacarbazine has been the most widely used chemotherapeutic agent for MM with a response rate of 15-20% as a single agent.[8] In combination with cisplatin and vincristine, dacarbazine can achieve a response rate but 25-30%,[9] but this regime is not more superior than dacarbazine alone in prolonging survival. Survival analysis by Sun et al showed that adjuvant chemotherapy did not confer survival benefits.[2]

### Radiotherapy

Generally, MM is not a radiosensitive tumour. This treatment modality has been used as adjuvant, neoadjuvant therapy and as palliative intend in some literatures. Sun et al demonstrated no survival benefit from adjuvant radiotherapy.[2] Nevertheless, adjuvant radiotherapy may be considered in cases where there is a close margin or involvement of lymph node or parametrium.

### Immunotherapy and targeted therapy

Immunotherapy has been approved for the treatment of metastatic MM as it has been proven to improve survival in that context.[10] For PPMC, reports on the use of immunotherapy have demonstrated contradicting results. Pusceddu et al., reported disappointing results of treatment with Bacille Calmette-Guerin (BCG), interferon, and interleukin-2 in seven cases.[1] Sun et al demonstrated no survival benefit with immunotherapy in the survival analysis.[2] The evidence on targeted therapies against mutations like BRAF, KIT, MEK1/MEK2 and VEGF are emerging and maybe the way forward in the treatment of PMMC. The use of immunotherapy in our patient was out of context due to the cost and indication.

## CONCLUSION

PMMC has a poor prognosis. Despite 80% of cases being diagnosed at early stage of Stage I and II, only 10-15% of patients survive more than 5 years,[1,4] with most patients succumbed within three years of diagnosis. The management

PMMC largely depends on the anecdotal experience from case reports and case series, as clinical trials and research are scarce. The behaviour of PMMC is unpredictable, as evidenced by contradicting results of treatment strategies other than surgery. Targeted therapies may have a promising future in the management of PMMC. Hence, research on tumour biology is of paramount importance to understand the disease better. For this patient, it is indeed very unfortunate that the patient has defaulted on her adjuvant treatment. Nevertheless, given the fact that this disease has a very poor prognosis, the adjuvant radiotherapy might not change the outcome.

## ACKNOWLEDGEMENT

We would like to thank the family of the deceased for allowing us to publish the case report. Our gratitude goes to Department of O&G, Oncology, Pathology and Radiology of Sarawak General Hospital for its participation in managing the case.

## CONSENT

Written informed consent was taken from the patient from the start of managing the case for publication.

## CONFLICT OF INTEREST

There was no conflict of interest.

## REFERENCES

1. Pusceddu S, Bajetta E, Carcangiu ML, Formisano B, Ducceschi M, Buzzoni R. A literature overview of primary cervical malignant melanoma: an exceedingly rare cancer. Critic Rev Oncol Hematol 2012; 81: 185-95.
2. Sun H, Chen Y, Chen Y, Liu D, Yan Z, Meng B, et al. Primary malignant melanoma of cervix: 14 cases and literature review. Melanoma Res 2018; 28(6): 578-85.
3. Yuan G, Wu L, Li B, An J. Primary malignant melanoma of the cervix: report of 14 cases and review of literature. Oncotarget 2017; 8(42): 73162-7.
4. Jones HW, Droegmueller W, Mokowski EL. A primary melanocarcinoma of the cervix. Am J Obstet Gynecol 1971; 111: 959-63.
5. Cantuaria G, Angioli R, Fernandez-Abril A, Penalver M. Primary malignant melanoma of the uterine cervix: case report and review of the literature. Prim Care Update Ob Gyns 1998; 5: 159-60.
6. Min KJ, Kim YS, Hong JH, Lee JK,Yang DS. Primary malignant melanoma of uterine cervix: a suggestion of new scheme of treatment combination. Chin J Cancer Res 2014; 26(3): 351-4.
7. Liu ZQ, Wang H, Zhang X, Qing Xu. Primary malignant melanoma of the cervix: a case report. Oncol Lett 2014; 8: 2661-3.
8. Bajetta E, Del Vecchio M, Nova P, Fusi A, Daponte A, Sertoli MR, et al. Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-alpha2b in metastatic melanoma. Ann Oncol 2006; 17: 571-7.
9. Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist 2011; 16(1): 5-24.
10. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with Ipilimumab in patients with metastatic melanoma. New Engl J Med 2010; 363(8): 711-23.