Published online:04/10/2015 Published print:10/2015

ORIGINAL PAPER

doi: 10.5455/medarh.2015.69.293-297
Med Arh. 2015 Oct; 69(5): 293-297
Received: July 15th 2015 | Accepted: September 15th 2015

Evaluation of 6 Patients with Genital Melanoma from Onset of Symptoms to Death: Evaluate the Factors Affecting the Prognosis of the Disease

Marjan Shokrani

Department of Surgery, Imam Khomeini Hospital, Department of Surgery, Valiasr Hospital, Department of Chemotherapy and Radiotherapy, Cancer Hospital, Tehran university of Medical Sciences, St. Gharib, Tehran, Iran

Corresponding author: E-mail: Marjanshokrani@gmail.com

ABSTRACT

Background: Genital melanoma is a rare but deadly cancer in women and the prognosis is often poor. **Purpose**: This study assesses the impact of possible risk factors on the end prognosis of the patients, with the ultimate goal of improving survival of disease. **Methods**: This is a report of 6 patients diagnosed and treated as genital melanoma. Parameters reviewed included: age at diagnose, presenting symptoms, location size and Breslow depth of lesion, stage at diagnose, adjuvant therapies, hysterectomy and salpingo-oophorectomy, metastasis or recurrence in follow-up, chemotherapy for metastatic disease. **Results**: The mean age at the time of diagnosis, was 44.67 years, the average size of lesion was 2.91 cm; the average Breslow depth of lesion was 1.93 mm. The mean interval between the onsets of symptoms to diagnosis was 16.7 months; the average life expectancy was 23.5 months. There is no significant relationship between the initial location of the lesion and prognosis (P: 0.98). Patients diagnosed in < 7 months, were in lower stages at diagnose (P: 0.018), and the survival of them was better (P: 0.035). Patients diagnosed in early stages had better survival at last (P: 0.035) Adjuvant radiotherapy improves survival markedly (P: 0.018). Hysterectomy and salpingo-oophorectomy had no significant effect on prognosis (P: 0.7). Chemotherapy in metastatic disease had no significant effect on prognosis (P: 0.46). **Conclusion**: The survival markedly improved if the disease diagnosed in a short distance from onset of symptoms and specially in early stages. Adjuvant radiotherapy can improve the survival significantly, but for the early hysterectomy and salpingo-oophorectomy and also for chemotherapy in metastatic disease, the impact on prognosis is uncertain, but positive.

Key words: Melanoma/ Genital melanoma/ Adjuvant radiotherapy/ Hysterectomy and salpingo-oophorectomy / Mucosal melanoma

1. INTRODUCTION

Malignant melanoma is a cancer that originates from melanocytes of the skin. Melanocytes are cells originate from the neural crest; migrate to the epidermis and form the melanin pigments. The pigments are responsible for skin color variations, as well as moles. When these cells do not respond to the growth control mechanisms in the body, malignant melanoma is present. So, malignant melanoma can occur in any part of the body where melanocytes spread. Primary tumor of melanocytes usually begins in a mole and then the attacker can invade the lymph nodes in the adjacent area or distant parts of the body. In contrast of skin melanomas, non-skin melanomas are very uncommon; they can be primary present in the eye, skull, nails and mucosal membranes (mouth, nose, esophagus, urinary tract, genitalia, and anus) (1). In this study, we decided to examine a very uncommon type of the melanoma, genital melanoma. But it is so aggressive and the prognosis is very bad, among others.

A very small percentage of melanomas occur in the genital area. It has been said, the genital melanoma

include less than 1% of the total melanomas (2) and 3% of melanomas in women (3). The prevalence of genital melanoma in women is more than men. Rarely, genital melanoma also can occur in men, some cases of penile melanomas and scrotal melanomas have been recorded (4). However, the vast majority of cases is in women and involves vulva and vaginal areas. Most of the lesions are discovered accidentally during a gynecological examination. Common symptoms are pain, bleeding, and vaginal discharge (5, 6). When these lesions appear on the vulva, they can affect labia minor, labia major or clitoris.

As genital melanoma symptoms are similar to other disorders in this area, these patients often misdiagnoses for example as: genital infections, irregular menstruation or other malignancies in this area; and sometimes treatments are inappropriate (6). When they return because of the lack of response to treatment, and diagnosed with a closer evaluation, disease spread and evidence of invasion or metastasis can be seen. In other hand, if the location of primary melanocytic lesion was more accessible, the changes in its appearance could easily be recognized by the patients. So that, with the development of the first changes in moles, such as increase in size, change in colors, change margins and etc. the patient was referred to a doctor (1). So doctors have enough time to take the necessary tests to diagnosis and starting main treatment immediately and at last, the deaths, recurrence, spread of disease, and need more extensive surgery reduced.

Articles and researches in this field are very limited. Perhaps the most important factor is the low prevalence of the disease and limitation of the number of cases.

This study with completing knowledge of the past is a continuation of previous researches, and is a part of the future researches will expand. It is hoped that with the promotion of medicines in this area.

2. METHODS

This study is a case series study. All genital melanoma cases referred, diagnosed and treated in the hospitals of Tehran University of medical sciences (Iran) (Imam Khomeini hospital, Valiasr hospital and cancer hospital) in the period 2001-2015 were evaluated. Due to the limited number of cases, all of them were examined.

To collect samples all the patients admitted to these hospitals as Genital melanoma were reviewed and followed upped. In the course of examining the patients information including age, sex, initial symptoms at admission, interval from onset of symptoms to admission and diagnosis, size and depth and extent of invasion of lesion at diagnosis according to the pathology reports, anatomic location of the lesion, the stage of the disease based on FIGO(Federation of gynecology and obstetrics) staging system in admission, the method used in surgery with or without extensive primary surgery like hysterectomy and salpingo-oophorectomy, adjunctive therapies such as chemotherapy, radiotherapy, the response to treatment in patients, recurrent or metastasis in follow up, the treatment used in patients with metastatic disease and its benefits in survival, disease prognosis and survival of patients after treatment; were evaluated. Data on target and classified variables were analyzed using SPSS software (Version 23; SPSS INC). To display quantities variables, we used Mean ± SD, and for qualitative variables, the frequency and percentage. Less than 0.05 was considered significant. To examine the relationship between variables, the chi-square analysis, Anova and t-Test were used. To assess survival of disease we used Kaplan Meier analysis. Although the population of our study is small, because of the importance of the effect of predictive risk factors in the prognosis of the disease, all p values mentioned; it may be enlightening and helpful for future studies.

3. RESULTS

The prevalence of genital melanoma is 6 among all patients admitted to the hospitals of Tehran University of Medical Sciences (Imam Khomeini Hospital Valiasr hospital and Cancer Hospital), during the years 2001-2015, as genital cancer. The average age at diagnosis was 44.67±5.88 years (range, 48.67-40.17). All patients diagnosed with genital melanoma, were women. 2 patients (33.3%) referred with symptoms of mass in labia major, 1 patient (16.7%) with a mass in the vaginal canal and vaginal bleeding, 3 patients (50%) only with vaginal bleeding. In 2 patients (33.3%) the lesion was in Vulva, in 2 cases (33.3%) in the Vulva and a third of vaginal canal and in 2 other patients (33.3%) in the Vulva, third of the vagina and a third of urethra. The mean interval from onset of symptoms to diagnosis in the first group was 6.36 ± 5.5 months(range, 1-10), for the second group 6.5 ± 3.5 months(range, 4-9) and in the third group 9.5 ± 3.53 months(range, 7-12) (P: 0.70). Also, the average life expectancy from the time of diagnosis, in the first group 33.23 ± 25.50, (range, 2-49) in the second group 23 ± 18.38 (range 10-36) and in the third group24±5.65 (range, 20-28) (P: 0.98). The average duration from onset of symptoms until diagnosis of genital lesions as malignant melanoma was 7.16 ±4.07 months (range, 3.83-9.84). The average life expectancy after diagnosis in patients were diagnosed in less than 7 months from the start of symptoms was 42.5 ± 9.19 months, and in the other group diagnosed after 7 months of symptoms was 14 ± 10.95 months (P: 0.035). The average size of tumors at diagnosis, according to pathology report was 2.91 ±0.80 cm (range, 2.33-3.5) Average Breslow depth of lesions based on pathology reports at the time of referral was 1.93 ± 1.28 mm (range, 0.9-2.8) (Figure 1) None of the patients had distant metastases at presentation. According to the pathology reports, 4 patients (66.6%) had lymph node involvement, and 2 patients (33.3%) had no spread to the lymph nodes. In the first admission, 1 patients (16.7%) was in the stage IB (T1bN0M0) of FIGO, 1 patients (16.7%) in stage II (T3N1aM0), one (16.7%) in stage IIIA (T2N1aM0) and 3 patients (50%) in stage IIIB (T1bN2aM0, T2N2aM0, T2N2BM0). Patients were divided into two groups based on the stages of disease in admission(Stage I&II, and stage III) The average age of patients diagnosed in stage I & II was 38.5± 4.95 years, and in patients with stage III it was 47.5 ± 3.40 years (range, 14.67-24) (P: 0.057). The mean interval from on-

patients	Age	Sex	SYM	Size	BD	L	Stages (FIGO)	STD	MOS	HS	AR	MIF	CM	DTD
1	42	F	Mass in labia major	2	2	Vulva	1B(T1B-N0M0)	1.00	WLE & LAD	No	Yes	Yes	Yes	49.00
2	52	F	Mass in labia major	3	.8	Vulva	3B(T1b-N2aM0)	10.00	WLE & LAD	No	No	Yes	No	2.00
3	49	F	Mass in va-gina	4	3.6	Vulva &Vagina	3B(T-2N2aM0)	9.00	WLE & LAD	No	No	Yes	Yes	10.00
4	35	F	Vaginal bleeding	2	.2	Vulva &Vagina	2(T2N0M0)	4.00	WLE & LAD	Yes	Yes	Yes	Yes	36.00
5	45	F	Vaginal bleeding	3	2	Vulva &Vagina &Urethra	3A(T-2N1aM0)	7.00	WLE & LAD	Yes	Yes	Yes	No	28.00
6	45	F	Vaginal bleeding	3.5	3.00	Vulva &Vagina &Urethra	3B(T-2N2BM0)	12.00	WLE & LAD	Yes	No	Yes	Yes	16.00

Table 1. Clinical data and histologic features of patients with primary Genital melanoma. Age, year; F, Female; M, Male; SYM, Symptoms; Size, Centimeter; BD, Breslow Depth of lesion, millimeter; L, Location of lesion; FIGO, International Federation of Gynecology and Obstetrics; STD,Distance between symptoms to diagnosis, month; MOS, Method Of Surgery; WLE, wide local excision; LAD, lymphadenectomy; HS, Hysterectomy and Salpingo-oophorectomy; AR, Adjuvant Radiotherapy; MIF, Metastases in Follow-up; CM, Chemotherapy fot metastatic disease; DTD, Distance between Diagnoses to Death, month.

set of symptoms to diagnosis in patients with stage I&Π was 2.5 ± 2.12 months (range, 1-4) and in patients with stageIII was 9.59 ± 2.08 months(range, 7.66-11.33) (P: 0.018). The average life expectancy after diagnosis in patients with stage I&Π was 42.5 ± 9.19months (range 36-49) and in patients with stageIII it was 14 ± 10.59 months (range, 4.67-24) (P: 0.035) (Figure 2). The mean duration from diagnosis of disease to death (related to disease) in all patients was 23.5 ± 17.47 months (range 11.33-36.83). All patients have been operated with WLE (Wide Local Excision) and bilateral inguinal lymphadenectomy. During the surgery 3 patients (50%) had hysterectomy and salpingo-oophorectomy and bilateral inguinal lymphadenectomy and 3 patients (50%) had not. In patients who have had hysterectomy and salpingo-oophorectomy, average life expectancy from the time of diagnosis was 26.67 ± 10.06 months(range, 16-36), and in contrast in patients had not hysterectomy and salpingo-oophorectomy it was 25.14± 20.33 months (range, 2-49) (P: 0.70) (Figure 3). Following surgery, 3 patients (50%) had received full course of adjuvant radiation therapy, and 3 patients (50%) had not. in patients who had received adjuvant radiotherapy, the median survival from the time of diagnosis was 37.67 ± 10.59 months(range, 28-49) and in other group that had not undergone radiotherapy was 9.33 ±7.02 months(range, 2-16) (P: 0.018) / Figure 4).

Patients after initial treatment and in the course of investigation were referred again with evidence of metastases. Following the detection of metastases in patients 4 patients (66.7%) treated with a full course of chemotherapy with Dacarbazine (DTIC), and 2 patients (33.3%) did not receive the full course of chemotherapy (due to the unwillingness or death in the course of therapy). In metastatic disease who received chemotherapy average life expectancy from the time of diagnosis was 27.75 ± 18 months(range, 12-44.67) and in the other group did not receive chemotherapy it was 18.38± 15 months(range, 2-28) (P: 0.46) /Figure 5)

4. DISCUSSION

The prevalence of genital melanoma is generally very low. Some studies in this field are retrospective review of patients who have been evaluated in other studies, so in these studies, statistical population is acceptable. But in other studies that are initial studies of patients, examined population is often limited, as in our study. In some previous studies, vaginal bleeding was listed as the primary symptom of the patient (5, 6, 10). In previous studies the primary site of lesion associated with the period from onset of symptoms to diagnosis, prognosis and outcome, was not studied in this way. In the present study we examined this factor as a possible risk factor; the results are as follows: In 2 patients (33.3%), the first lesion was in Vulva, in 2 cases (33.3%) in the Vulva and a third of vaginal canal and in 2 patients (33.3%), the Vulva and a third of the vagina and a third of urethra. The mean interval from onset of symptoms to diagnosis of the first group was 5.5 months in the second group 6.5 months, and in the third group it was 9.5 months. There

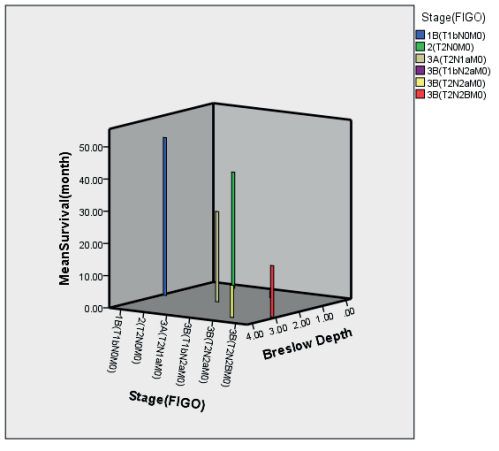

Figure 1. The relationship between Stage of disease at Diagnose (FIGO), Breslow Depth of lesion (mm) and Mean Survival (month)

is no significant relationship between the primary site of lesion and interval between the onset of symptoms and diagnosis. (P: 0.70). Average life expectancy from diagnosis In the first group was 25.50 month, in the second group 23 months and in the third group24 months (P: 0.98), so a significant correlation between the location of first lesion in genitalia and the prognosis of disease was not seen. Average period from onset of symptoms to diagnosis of lesion as genital melanoma, in past studies was not mentioned specifically, which in our review estimated 7/16 months. Perhaps the most important reason of this late diagnosis is the low average age of our patients compared to the average age of other studies. So they treated more time with other diagnoses that are more common for their age. In previous studies rapid detection was listed as a factor affecting prognosis (8). patients who diagnosed in less than 7 months from the started symptoms, finally have average life expectancy of 42.5 month, and in contrast, the patients diagnosed after the 7 months from the started symptoms, life expectancy was 14 months (P: 0.035). A significant relationship was seen between the period late from symptoms to diagnose the disease and future outcome of patients. Average size of lesion in past studies was 3 cm that in this study estimated 2.91 cm (9). Average depth of lesions base on Pathology reports was 1.93 mm in current study but it was reported 2.8mm in past studies (7). None of the patients had metastasis in time of referring. After surgery base on pathology reports in 4 patients (66.6%) regional lymph nodes were involved and in 2 patients (33.3%)

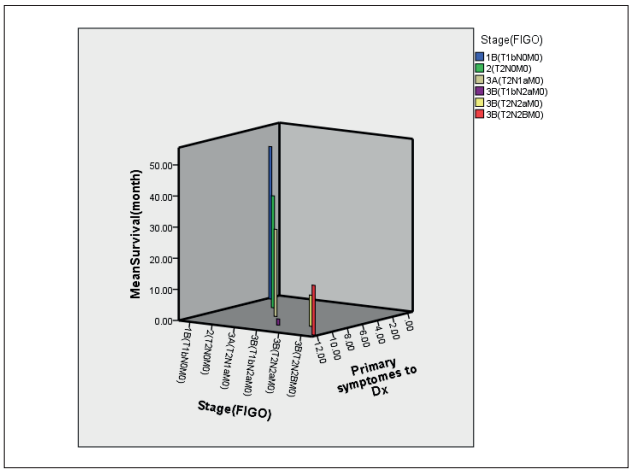

Figure 2. The relationship between Stage of disease at Diagnose (FIGO), Distance between primary symptoms to Diagnoses (month) and Mean Survival (month)

were not. All of them had complete lymphadenectomy, in primary surgery. Patients were classified by the FIGO staging system. 1 people of patients (16.7%) in referring time were in stage IB of FIGO, 1 (16.7%) in stage II, 1 (16.7%) in stage IIIA and 3 (50%) in the stage IIIB. Mean age in patients with stage I&Π was 38.5 year, and in patients with stage III was 47.5 years (P: 0.057). There is no significant correlation between the age of patients at the time of diagnose and the stage of disease. The mean interval from onset of symptoms to diagnosis in patients with stage I&Π was 2.5 months, in patients with stage III was 9.59 months (P: 0.018). It means a significant relationship between the interval from onset of symptoms to diagnosis and stage of disease in primary admission,

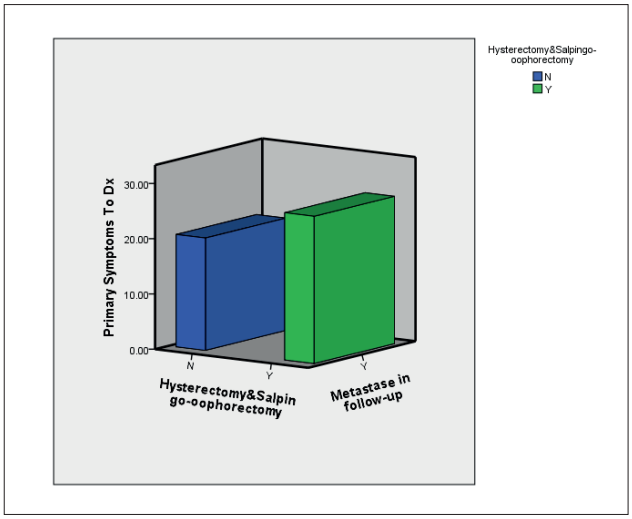

Figure 3. The relationship between Hysterectomy and Salpingo-oophorectomy, Metastases in Follow-up and Mean Survival (month)

is seen. The average life expectancy after diagnosis in patients with stage I&Π was 42.5, months; in patients with stage III was 14months (P: 0.035). It seems that there is a relationship between the primary lesion stage and the final prognosis of the disease. Evaluation of the relationship between stage of disease and interval from onset of symptoms to diagnosis and also the prognosis is an

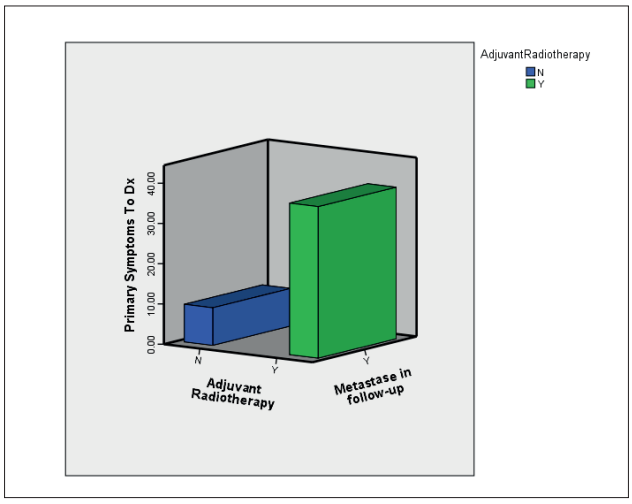

Figure 4. The relationship between Adjuvant Radiotherapy, Metastases in Follow-up and Mean Survival (month)

important new finding of this study. Unfortunately, the average life expectancy of our patients after treatment was 23.5 months and all of them died before 5 years, this despite the fact that in previous studies 5-years survival was estimated 17.5% (9). It seems that the reason is late diagnosis of the disease in our study population, so that most patients shortly after diagnosis and initial treatment develop metastases and died. all of the patients after diagnosis had operated with WLE (Wide Local Excision) and bilateral inguinal lymphadenectomy. During

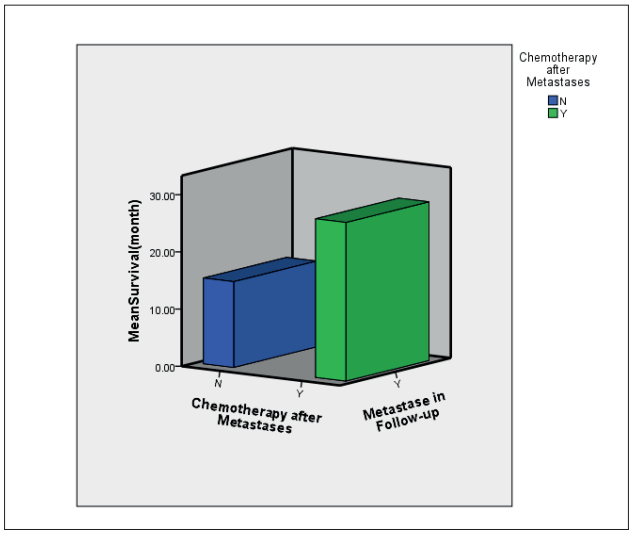

Figure 5. The relationship between Chemotherapy of Metastatic Disease, Metastases in Follow-up and Mean Survival (month)

the operation 3 of 6 patients (50%) had hysterectomy and salpingo-oophorectomy and 3 patients had not.

In patients who have had hysterectomy and salpingo-oophorectomy average life expectancy from the time of diagnosis was 26.67 months and in contrast in other group who had not hysterectomy and salpingo-oophorectomy was 25.14 months(P: 0.70). According to the results, it seems that early hysterectomy and salpingo-oophorectomy have no significant correlation with the final prognosis of the disease. In some past studies, it was mentioned (5, 6, 8). Following surgery, 3 of 6 patients (50%) had received full course of adjuvant radiation therapy and 3 had not. in patients who had received adjuvant radiation therapy, average life expectancy from the diagnosis was 37.67 months, and the other group, that have not undergone radiotherapy, was 9.33 months (P: 0.018). There was a significant association between adjuvant radiotherapy and survival of patients. Adjuvant radiation therapy in previous studies only was listed as a factor that can have a positive impact in survival of disease (5, 8, 9). Patients after treatment in the course of the study re-visited with evidence of metastases. In the past studies the use of Dacarbazine in the treatment of metastasis melanoma was listed as the most acceptable chemotherapy protocol (11). In our study, we used this protocol in some patients and evaluated the effect of it in final prognosis. Following the detection of metastases in patients, 4 patients (66.7%) treated with a full course of chemotherapy with Dacarbazine (DTIC) and 2 patients (33.3%) did not (due to the unwillingness or death in the course of therapy). In metastatic disease who received chemotherapy, the average survival from the time of diagnosis was 27.75 months, and in the other group who had not received the chemotherapy it was 18.38 months (P: 0.46).

And it means there was no significant association between chemotherapy of metastatic disease, and improving their survival, although its impact is positive. Based on the findings of this study, it seems that the most influential factor in the poor prognosis of genital melanoma in our patients is late diagnosis due to the lack of specific clinical symptoms, so patients will find too late and due to poor clinical suspicion is his first visit in some cases, This factor leads to a higher stage diagnosis and therefore the prognosis is poor.

It also seems that early adjuvant treatment with radiotherapy in addition to surgery improves prognosis markedly. We found a positive association between the primary extensive surgery such as hysterectomy and salpingo-oophorectomy and the prognosis of disease, but it is not significant. As well as, the impact of chemotherapy with Dacarbazine on patients who had metastases in follow-up, on the prognosis was positive, but it is not extensible. So we need more researches in this area.

CONFLICT OF INTEREST: NONE DECLARED.

REFERENCES

1. Singer M, Matthew GM. Anal Melanoma. Clin Colon Rectal Surg. 2006; 19: 78-87.
2. Ragnarsson-olding BK, Nilson BR, Kanter-lewensohn LR, et al. Malignant Melanoma of the Vulva in a nationwide, 25-years study of 219 Swedish Females: Clinical observation and histopathologic features. Cancer. 1999; 86: 1273-1284.
3. Ariel IM. Malignant Melanoma of the Female Genitalia system: a report of 48 patients and review of the literature. J Surg Oncol. 1981; 16: 371-383.
4. Christensen WN, Friedman KF, Woodruff JD, et al. Histologic Characteristics of Vulvar Nevocellular Nevi. J Cutan Pathol. 1987; 14: 87-91.
5. Kristiansen SB, Anderson R, Cohen DM. Primary malignant melanoma of the cervix and review of literature. Gynecology and oncology. 1992; 47(3): 398-403.
6. Zamiati S, Sahraoui S, Jabri L, et al. Primary Malignant Melanoma of the Cervix Uter: a propos of 1 case with review of the literature. Gynecol Obstet Fertil. 2001; 29(5): 381-385.
7. Wechter ME, Gruber SB, Haefner HK, et al. Vulvar melanoma: a report of 20 cases and review of the literature. American academy of dermathology. 2004; 50: 554-562.
8. Simoes M, Cunha V, Nabais H, et al. Primary Malignant Melanoma of the Uterine Cervix - case report and review. Eur J Gynecol Oncol. 2011; 32(4): 448-451.
9. Ried G, Schmidt RW, Roberts JA, et al. Primary melanoma of the vagina: a clinicopathologic analysis. Obstetrics and gynecology. 1989; 74: 190.
10. Yucesoy G, Kus E, Muezzinoglu B, et al. Primary malignant melanoma of the cervix: report of a case. Arch gynecology and obstetrics. 2011; 279(4): 573-575.
11. Seronne L, Zeuli M, Sega FM, et al. Dacarbazine-based chemotherapy for metastatic melanoma: thirty year experience overview. J Exp Clin Cancer Res. 2000; 19(1): 21-34.
12. David E. Precursors to melanoma and their mimics: nevi of special sites. Modern pathology. 2006; 19: s4-s20.
13. Simoes M, Cunha V, Nabais H, et al. Primary malignant melanoma of the uterine cervix: case report and review. Eur journal of gynecology and oncology. 2011; 32(4): 448-451.
14. Vaysse CH, Pautier P, Filleroa TH, et al. A large retrospective multicenter study of vaginal melanomas implications of or new management. Melanoma research. 2013; 23(2): 138-146.