

# Melanomas of the vulva and vagina

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## ABSTRACT

**INTRODUCTION:** Malignant melanoma is a rare type of cancer in the vagina and vulva associated with a poor prognosis due to late diagnosis and early dissemination. Only a limited amount of literature exists on the condition. This study elucidates the effect of current treatment.

**METHODS:** All patients diagnosed with malignant melanoma in the vagina or vulva at Aarhus University Hospital, Skejby, Denmark, in the period from 1996 to 2013 were included. Data were collected from the electronic patient records and from the Danish Pathology Register.

**RESULTS:** A total of 17 patients were included. The average age at the time of diagnosis was 77 years and the median overall survival time was 21.9 months. The five-year survival in this study was 17.7%.

The majority of the melanomas were nodular and all of the superficially spreading melanomas were found in the vulva only. Malignant melanoma in the vagina has a poorer prognosis than in the vulva as it is diagnosed later.

**CONCLUSIONS:** Early diagnosis and staging of this cancer is important. Positron emission tomography-computed tomography should be the standard method for staging the disease. Older women with vaginal discharge should always have a gynaecological examination. The primary treatment is resection of the tumour, but future treatment might be a combination of resection and immunotherapy.

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Malignant melanoma (MM) is a cancer derived from the melanocytes. It is by far the most malignant type of skin cancer. In Denmark, in the period from 2008 to 2012, 974 men and 1,111 women were diagnosed annually with malignant melanoma [1].

This type of cancer is cutaneous in 90% of the cases. Malignancy increases with sun exposure to the area of the cancer, e.g. more cases are seen on the extremities, head and neck, and the torso. However, MM is also seen in mucous membranes, e.g. in the vagina and vulva, but these anatomical sites are very rare, and this cancer is not induced by sun exposure. The annual incidence in the vagina alone is 0.46 per million women [2].

The cutaneous melanomas are often seen among younger women, whereas the melanomas in the vagina and vulva are usually seen among older women [2]. The vagina and the vulva are areas on the body where in-

spection and early diagnosis are difficult. The patients see their doctor late in the course and that influences the overall survival rate. The most typical symptoms from the vagina and vulva are postmenopausal bleeding/discharge and stinging in the area or discovering a filling [3]. These symptoms prompt women to see their general practitioner (GP). A limited number of patients will experience no symptoms, and will therefore not be diagnosed early - or will be diagnosed incidentally.

MM metastasises, most often to regional lymph nodes, the liver, the lungs and the brain. MM can be divided into five types:

- Superficially spreading melanoma
- Nodular melanoma
- Lentigo maligna
- Acral lentiginous melanoma
- Amelanotic melanoma.

Because MM in the vagina and vulva is very rare, it is uncertain which treatment is the best. In Denmark, treatment is centralised to the gynaecological and oncological departments in Rigshospitalet and Aarhus University Hospital, Skejby. If the diagnosis is suspected, the woman is referred to one of these centres for further diagnostics. The main focus of this study was to investigate if current treatment is sufficient and to explore what might be changed in the future to improve the overall survival among these patients.

## METHODS

All patients diagnosed with MM in the vagina or vulva at Aarhus University Hospital, Skejby, in the period from 1996 to 2013 were included. Data were collected from the electronic patient records and from the Danish Pathology Register. For some of the patients, the tumour initially appeared to be a carcinoma, but the diagnosis was later corrected to an MM. These patients were also included in the study.

The hospital files of all the patients were meticulously read and reviewed. We searched for data on the following variables: age at the time of diagnosis, symptoms, time from diagnosis to operation, other treatments, comorbidity, parity, any earlier operation in the genitals internally or externally. Information was collected about the histology and resection lines after the

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first operation. Finally, the stage of the cancer was evaluated in each patient according to the following variables: imaging diagnostics, lymph node metastases, other metastases, time from operation to relapse, treatment of relapse, time from diagnosis to death and the cause of death.

*Trial registration:* not relevant.

## RESULTS

In total, 17 patients were included with the diagnosis of a MM in the vagina or vulva. The median overall survival time was 21.9 months.

Mostly older women suffer from this cancer.

**Table 1** shows the distribution of malignant melanoma

in the vulva and vagina according to age at the time of diagnosis and at death, symptoms, histology, image diagnostics and recurrence. In this study, the mean age at diagnosis was 77 years.

Ten of the 17 patients visited the GP primarily because of vaginal bleeding, four felt stinging in the area and three felt pain. As secondary symptoms, two patients had experienced itching and two reported weight loss. However, the frequency of some of the symptoms might be underreported, since several of the patients' files did not include information about the expressed lack of stinging, pain, and itching and weight loss.

In eight of the patients, the melanoma was located in the vagina and in nine women in the vulva. Three of the four patients who were still alive when the study was conducted had vulvar melanoma. Four of the melanomas were of a superficially spreading type and 13 were of a nodular type. Of the four patients still alive when the study was conducted, one was of the nodular and three of the superficially spreading type. All of the four superficially spreading cancers were located to the vulva.

Five patients received a positron emission tomography/computed tomography (PET/CT) to clarify the spreading of the cancer. Two of these also underwent magnetic resonance imaging (MRI). Three women had a MRI and a CT combined, and one patient had a CT only. Two patients had an X-ray of the thorax, in one case combined with an MRI and in the other combined with ultrasound of the liver. Six patients had no imaging diagnostics performed of any type (Table 1).

Six of the 17 patients had a resection of the tumour as their primary procedure based on suspicion and were diagnosed from this operation. Eleven had a biopsy and subsequently the primary operation. The time from diagnosis to operation varied from 17 to 55 days. For the ten patients with a biopsy diagnosis, the mean time from diagnosis to operation was 33 days. One of the 17 patients was evaluated as inoperable.

Only five of the 16 operated women had free resection lines. Three of the 11 patients who did not have free lines had a reoperation; the remainder did not. In the eight women who were not re-operated, the cancer had already spread and six of the women rejected further treatment. One of the eight women with dissemination had radiation therapy and one was treated with immunotherapy.

During the primary operation, lymph node metastases were found in six patients at the time of diagnosis, whereas five patients did not have lymph node metastases. In the remaining six patients, the presence of lymph node metastases was not investigated either by surgery or by imaging diagnostics. Among the four patients who were still alive at the time the study was conducted, only one had lymph node metastases.

**TABLE 1**

Patient characteristics, histology, treatment, and imaging diagnostics.

	At diagnosis (N = 17)	At death (N = 13)	Overall (N = 17)	Alive (N = 4)
Age, mean (range), yrs	77.0 (47-95)	81.7 (63-96)		
Overall survival, median, mo.s	21.9			
5-year survival <sup>a</sup> , %	17.7			
<i>Symptoms at diagnosis, n (%)</i>				
Bleeding	10 (58.2)			
Itching	2 (11.8)			
Pain	3 (17.7)			
Local sting	4 (23.5)			
<i>Treatment, primary, n (%)</i>				
Surgery	16 (94.1)			
No surgery	1 (5.9)			
Free resection lines	5 (31.3)			
<i>Relapse<sup>b</sup>, n (%)</i>				
Relapse	9 (52.9)			
Alive with relapse	2 (22.2)			
<i>Treatment, relapse<sup>b</sup></i>				
Surgery	4 (44.4)			
Radiation therapy	3 (33.3)			
Immunotherapy <sup>c</sup>	2 (22.2)			
No treatment	2 (22.2)			
<i>Histology, n (%)</i>				
Nodular			13 (76.5)	1 (25)
Superficial spreading			4 (23.5)	3 (75)
<i>Image diagnostics, n (%)</i>				
PET/CT			3 (17.7)	
PET/CT + MRI			2 (11.8)	
CT + MRI			3 (17.7)	
CT			1 (5.9)	
X-ray thorax + MRI			1 (5.9)	
X-ray thorax + ultrasound liver			1 (5.9)	
No imaging			6 (35.3)	

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

a) n = 3.

b) n = 9.

c) 1 patient had immunotherapy and surgery, 1 had immunotherapy and radiation therapy.

Five patients had distant metastases. These were located in the urethra, lung, liver, brain, vagina or perianally. Of the four patients still alive when the study was conducted, the same patient who had lymph node metastases also had metastases in the vagina from the primary vulvar tumour.

Nine patients out of 17 had a relapse during the study period. Furthermore, five of the remaining eight had advanced cancer and either died shortly after or had metastases. Two of the four patients who were still alive at the time the study was conducted had suffered a relapse. The average time from operation to relapse among the nine patients was 9.5 months. Of the nine women with relapse, four had a reoperation and three had radiation therapy. One from each of these groups also had immunotherapy. Two patients had no further treatment. Of the two patients who were still alive at the time of the study and who had suffered a relapse, one had surgery and the other had surgery and immunotherapy.

Thirteen of the included patients had died at the time of the study. All except one had died due to their malignant melanoma. The cause of death in the final patient remains unknown, but she died 123 months after surgery. The time from diagnosis to death ranged from two months to 123 months. However, only one patient lived longer than 22 months. The average time from diagnosis to death in the 13 patients was 21.9 months (overall survival). When removing the one patient who lived for 123 months, overall survival drops to 13.5 months. The four remaining living patients had been alive from one year and ten months to 14 years. Only three of the 17 women lived longer than five years with their disease, corresponding to a five-year survival rate of 17.7%. As this cancer mostly affects older women, some comorbidity is observed. Seven of the 17 patients had hypertension, two had a breast cancer and two had had one or more basal cell carcinomas.

## DISCUSSION

The primary aim of this study was to evaluate the current treatment of malignant melanoma in the vagina and in the vulva in our department.

It is of utmost importance to diagnose the malignant melanoma as early as possible since mortality is high once the cancer has spread. A gynaecological examination at the annual health check with the GP should therefore be compulsory, even in older women. In Denmark, gynaecological screening by cervical smear is performed to discover human papillomavirus (HPV)-dysplasia or cervical cancer. This screening is discontinued when the woman turns 64 years of age. However, if a tumour is present, it will probably be detected during these screenings, and the screening can therefore detect both diagnoses.



Malignant melanoma in the vulva.

Some older women might have symptoms and neglect them or simply not realise that they are symptoms. Therefore, it seems logical to offer older women a gynaecological examination at their annual health check.

In the present study, 76.5% of the patients had a melanoma of nodular type. Only 23.5% was of the superficially spreading type. All the superficially spreading histology types were located to the vulva and three of the living patients had a melanoma of the superficially spreading type. In another study, the authors agreed that the nodular type has the poorest prognosis [4]. 53% of the women had a melanoma in the vulva and 47% had a melanoma in the vagina.

In a previous study, the vaginal melanomas appeared to be more aggressive than the vulvar melanomas and relapses occurred more often in the vulva [5]. This is in line with our findings. Hence, three of the living women had a melanoma in the vulva and only one in the vagina. Apart from the fact that this site is associated with more relapses, it is also more difficult to discover a vaginal melanoma, as previously mentioned.

The current primary treatment is resection. It is very important to achieve free resection lines of 8 mm or more at the first operation. However, in the present study, even though the lines were free, relapse was still seen in two out of five patients with a free resection line. These two patients had metastases at the time of diagnosis; one in the lymph nodes and the other in the urethra. However, in a previous study it was noted that "More radical procedures have not resulted in better loco regional control or survival compared with wide local excisions with 1 to 2 cm of margin" [5]. Therefore, it is difficult to conclude on the basis of this study that what the size of the resection lines should be if the disease has already spread.

PET/CT is known to be the best instrument with which to detect metastases and all patients should therefore undergo PET/CT in future diagnostics.

One patient was treated with radiation therapy due

to a lack of free resection lines. Despite this, the patient's cancer progressed with liver and lung metastases, which might have been missed or not visible at the time of the radiation therapy. Another patient who lacked free resection lines also had metastases in two lymph nodes and in the vagina. This woman chose immunotherapy (IntronA (interferon alfa-2b) and interleukin (IL)-2) and received six series. But about 14 months after she concluded this treatment, she had a relapse or possibly progression. She had another resection and started ipilimumab treatment, but the disease progressed. This patient chose a new experimental treatment with T-cells and IL-2. The patient was still alive at the time of the study, but there is no data yet to determine whether the new treatment was successful or not. To determine this, we will need a longer follow-up period.

In another study, the T-cell treatment is described as quite promising for the future [5]. However, we need more data to draw any conclusions regarding this treatment. One study implied that post-operative radiation therapy is an appropriate treatment for melanoma in the vagina [6]. However, this could not be confirmed by the present study because of the small number of patients treated with radiation therapy.

The average age at the time of diagnosis was 77 years in this study. In another study, it was 72 years [7]. In general, the survival rate in the literature is low; ranging from 10% [8] to 8.4-17.5% [9]. In this study we found a five-year survival rate on 17.7%. Our survival rate is in the higher end of the spectrum, presumably because of our small sample size compared with some of the other studies reported. One study included 85 patients [10].

#### Weakness

This study has a small sample size of 17 patients. Many factors such as comorbidity and other risk factors can affect the outcome. Some of the findings might therefore be coincidental and conclusive statements cannot be made. Only four patients were still alive at the time of this study and two of the four patients were diagnosed less than two years previously. A longer follow-up period is needed.

#### CONCLUSIONS

From this study it is impossible to propose specific changes that may improve the overall survival. The disease is rare and its treatment individual. Primary resection with free resection lines and preoperative PET/CT to know the stage of the disease before treatment is necessary.

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