Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Melanoma of the lower genital tract: Prognostic factors and treatment modalities

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HIGHLIGHTS

- Melanomas of the lower genital tract are rare and aggressive malignancies
- Therapeutic approach is based on current data concerning gynecologic cancers and standard management of cutaneous melanomas.
- Primary treatment includes surgery, if feasible, to obtain free margins, with loco-regional lymph nodal assessment.
- Adjuvant treatment is unproven and therapy for advanced/metastatic genital melanomas is limited with a poor prognosis.
- These tumors may harbor mutations in relevant genes/pathways for which targeted therapies are under investigation

ARTICLE INFO

Article history:
Received 24 February 2018
Received in revised form 16 April 2018
Accepted 17 April 2018
Available online xxxx

Keywords:
Melanoma
Vulva
Vagina
Cervix
Surgery
Target therapy

ABSTRACT

Primary melanomas originating from the gynecological tract are rare and aggressive cancers. The vulva is the most frequent site (70%), followed by vagina and more rarely by cervix. The clinical outcome of patients with female genital tract melanoma is very poor, with a 5-year overall survival (OS) of 37–50% for vulvar, 13–32% for vaginal, and approximately 10% for cervical melanoma. In this systematic review, we analyzed the pathogenesis and the different factors influencing the prognosis of melanomas of the lower genital tract, with particular emphasis on biologic variables that may influence new therapeutic approaches. We evaluated the different treatment modalities described in the literature, in order to offer a possible algorithm that may help the clinicians in diagnosing and treating patients with these uncommon malignancies.

Contents

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https://doi.org/10.1016/j.ygyno.2018.04.562
0090-8258/

1. Introduction

Melanomas arise from melanocytes, of which their precursors migrate during the phase of gastrulation from the neural crest through the embryonic mesenchyme to their final tissue destination [1]. Whereas skin and eye melanocytes have a protective function against UV radiations, mucosal melanocytes could have antimicrobial properties and potentially play a role in innate immune defense system. The pathogenesis of mucosal melanomas is largely unknown. UV radiations are unlikely to be involved, since these tumors arise on surfaces not exposed to sun. Although all melanocytes share the same embryologic origin, the microenvironment in their final destinations might be various, and therefore cutaneous and mucosal melanocytes could differ in adhesion molecules or intracellular signaling pathways involved in their growth.

Mucosal melanomas are rare and have a poorer prognosis than cutaneous melanomas [1]. The National Cancer Database between 1985 and 1994 revealed that 91.2% of the melanomas were cutaneous, 5.2% were ocular, 1.3% were mucosal and 2.2% were of unknown origin [2]. The Surveillance Epidemiology and End Results (SEER) database between 1988 and 2010 reported a 5-year OS of 34% for mucosal melanomas, 78% for ocular melanomas, and 89% for cutaneous melanomas [3].

For localized cutaneous melanomas, when the primary tumor is larger than 1 mm, surgical excision with margins proportional to the microstage of the primary lesion with lymphatic mapping and sentinel lymph node [SLN] biopsy is the mainstay of treatment (Melanoma Treatment (PDQ) https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032516/).

This allows identifying patients who may avoid the morbidity of systematic regional lymphadenectomy and those who may benefit from adjuvant therapy [4]. Conversely, if SLN is positive, a complete regional lymphadenectomy must be subsequently performed. The Multicenter Selective Lymphadenectomy Trial I [MSLT-I] randomly allocated 2001 patients with cutaneous melanoma to undergo either wide local excision [WLE] plus postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or WLE and SLN biopsy [SNB] biopsy with immediate lymphadenectomy if SLN was positive [4]. The final results showed that the 10-year disease- free survival [DFS] was significantly better in the SNB arm when compared with the observation arm, both among patients with intermediate-thickness (1.20 to 3.50 mm) melanomas (hazard ratio (HR) = 0.76; 95% confidence interval (CI) = 0.62–0.94), and among those with thick (>3.50 mm) melanomas (HR = 0.70, 95%CI = 0.50–0.96) [4].

There are no established guidelines for adjuvant treatment of high-risk cutaneous melanoma after surgical excision. A meta-analysis of 15 trials showed that adjuvant interferon [IFN]-α improved DFS (HR = 0.86, 95% CI = 0.81–0.91) and OS (HR = 0.90, 95% CI = 0.85–0.97) in patients with high-risk melanoma, with absolute differences in 5-year and 10-year DFS of 3.5% and 2.7%, and 5-year and 10-year OS of 3.0% and 2.8%, respectively [5].

The role of adjuvant radiotherapy on the clinical outcome of patients with pathologically positive nodes is still debated [6]. However, although melanoma has been considered as radioresistant, radiotherapy delivered with high dose per fraction (>400 cGy) appears to be able to improve the local control of the disease in advanced cases [7]. Compared with photon beams, carbon ion beams seem to achieve a better dose distribution. Recent reports have shown promising results for carbon ion beams in mucosal melanomas, including gynecological melanoma [8].

Dacabazine has been considered as the standard drug treatment for metastatic disease, while no significant improvement in response rates and OS has been observed with platinum-based regimens [9]. The combination of chemotherapy and immunotherapy (*i.e.* bio-chemotherapy) has obtained overall good response rates, but this did not reflect in any survival benefit, with increased toxicities. Conversely, immune checkpoint inhibitors, such as ipilimumab, pembrolizumab, and nivolumab, and molecularly targeted agents, such as BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib, cobimetinib) have shown satisfactory results [10].

However, whereas cutaneous melanomas often show BRAF mutations, mucosal melanoma, including those of the female genital tract, more often present c-KIT or NRAS mutations [11]. These mutations cause aberrant signaling in MAPK and PI3K/AKT signaling pathways, thus representing potential targets for molecular therapy in patients with advanced/metastatic mucosal melanomas [12,13].

In this systematic review, we firstly analyzed the incidence and the overall prognosis of genital melanomas, underlying the different prognostic factors and pathogenesis as opposed to cutaneous melanomas. We subsequently evaluated the different treatment modalities described in the literature, to offer a possible algorithm that may help the clinicians in diagnosing and treating patients affected by these rare and aggressive diseases.

2. Gynecological melanomas

2.1. Epidemiology

Primary melanomas originating from the gynecological tract are rare and aggressive cancers. Vulvar melanoma represents 2.4–10% of all vulvar malignancies, with an incidence of approximately 0.48 to 1.4 per 1,000,000 women annually [14,15]. Although the vulvar skin accounts for only 1–2% of body surface area, 3–7% of melanomas in women occur in this site.

Vulvar melanoma usually occurs in the fifth or sixth decade of life, with a mean and median onset age ranging from 54 to 76 years [11,15–18].

A large epidemiological Swedish study on gynecological melanomas showed that 75% of the 219 patients with vulvar melanoma were older than 60 years of age [19]. The age-standardized incidence decreased from 0.27 to 0.14 per 100,000 women (decrease of 3% per year) over the period of 25 years of observation. This was in contrast with the trend in incidence of cutaneous melanomas, which increased of almost 6% per year in the same interval time.

The analysis of 324 vulvar melanomas and 125 vaginal melanomas included in the SEER database between 1992 and 2005 reported an annual age-adjusted incidence of these malignancies in the female population of 0.87 per 1,000,000 in blacks, 0.75 per 1,000,000 in American-Indians, 1.03 per 1,000,000 in Asians and pacific islanders, 1.22 per 1,000,000 in Hispanics, and 1.90 per 1,000,000 in non-Hispanic whites [20].

Please cite this article as: A. Gadducci, et al., Melanoma of the lower genital tract: Prognostic factors and treatment modalities, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.04.562