REVIEW ARTICLE

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Primary Malignant Melanoma of the Vulva

An Aggressive Tumor for Modeling the Genesis of Non-UV Light-associated Melanomas

Boel K. Ragnarsson-Olding

From the Department of Oncology, Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden

Correspondence to: Boel K. Ragnarsson-Olding, Department of Oncology, Radiumhemmet, Karolinska University Hospital, SE-171 76 Stockholm, Sweden. Tel: +46 8 5177 2733. Fax: +46 8 5177 6290. E-mail: boel.ragnarsson-olding@kus.se

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Malignant melanomas appear in such sun-shielded areas as the vulva, challenging conventional knowledge that they are associated with UV radiation. Based on 1 442 patients with vulvar melanomas the tumors' epidemiology, clinical manifestations, histopathology, molecular genetics, treatment strategies, and prognosis were surveyed. Despite their sun-shielded location and rare incidence, vulvar melanomas were, on average, more dense than melanomas on the body surface and nearly the density of melanomas in chronically sun-exposed skin of the head and neck. Vulvar melanomas differed markedly from cutaneous melanomas, as evidenced by histopathological lesions and molecular genetics. Most melanomas were located on the glabrous skin as opposed to the hairy skin within the vulva and differed significantly in biological properties. The prognosis for the patients was poor, and in the 11 largest studies of surgical strategies, none offered a significant survival advantage. Tumor thickness and ulceration were usually significant predictors of (poor) prognosis in multivariate analyses along with macroscopic amelanosis, angioinvasion or DNA non-diploidy in some reports. Clear-cut biological differences between vulvar and cutaneous melanomas and between melanomas within different vulvar sites provide new paths for extensive research on melanomagenesis and for potential therapies. Additionally, studies of vulvar and other extracutaneous melanomas should characterize subgroups of cutaneous melanomas and identify their cause(s), which are apparently not linked to UV radiation.

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At least two good reasons compel us to study primary melanomas of the vulva. First, although rare in absolute numbers (0.1 to 0.15 per 10^5 females in population-based studies) (1, 2) these tumors are almost twice the density, on average, of cutaneous melanomas on the whole body surface (Table 1) (3). Accordingly, the vulvar melanoma is not merely an odd tumor but, rather, exemplifies the possible product of etiological factors other than UV radiation. Such factors could be tissue-specific or derive from environmental toxins, drugs, or viruses. The vulvar melanoma shares this property with other melanomas located in sun-shielded areas, preferentially mucosal membranes. Second, the diversity of the tumor, its late detection, its biological aggressiveness and the failure of any effective therapy create a lingering, grim prognosis and impel the design of more effective therapeutic strategies than are now available.

As an anatomical site for pursuing cancer research, the vulva provides an opportunity not only to compare melanomas in sun-protected areas with those in chronically or intermittently exposed skin areas but also to compare two different compartments within the vulva itself (Fig. 1). They are hairy skin with dermal appendages of hair and hair follicles, sebaceous and sweat glands in contrast with glabrous skin moistened by water diffusing through the thinned squamous epithelium and by mucous glands (4). Embryologically, the vulva represents a collision of germ layers at the junction of cloacal endoderm, urogenital ectoderm, and paramesonephric mesoderm.

In this communication, reports on vulvar melanoma are reviewed and placed in the framework of biological differences from cutaneous melanomas followed by comments on therapeutic strategies and prognosis.

VULVAR MELANOMAS IN THE FRAMEWORK OF EXTRACUTANEOUS MELANOMAS: MELANOMA DENSITY

Melanomas emerging in sun-protected areas of the body, in the mucous membranes, and often in the border zone between skin and mucous membrane (5) are here named *extracutaneous melanomas*. Those melanomas often become

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Table 1

Malignant melanoma of the vulva within nationwide consecutive series in Sweden 1960 through 1996

Tumors	No.	Percent	Density[1] ratio
Cutaneous melanomas (male and female)	32 154	–	
Cutaneous melanomas (female)	16 693 of all cutaneous melanomas	51.9	
Vulvar melanomas observed	310 of all female cutaneous melanomas	1.9	
expected[2]	170 of all female cutaneous melanomas		
observed/expected			1.9[3]
Vulvar malignancies	4 345	–	
Vulvar melanomas	310 of all vulvar malignancies	7.1	

[1]Density refers to the number per square unit of body surface.
[2]Given a vulvar area amounting to 1% of the body surface (114).
[3]Decreasing from 2.5 (1960–1984) to 1.9 (1960–1996) because of an increasing incidence of cutaneous melanomas and a relatively stable incidence of vulvar melanomas.

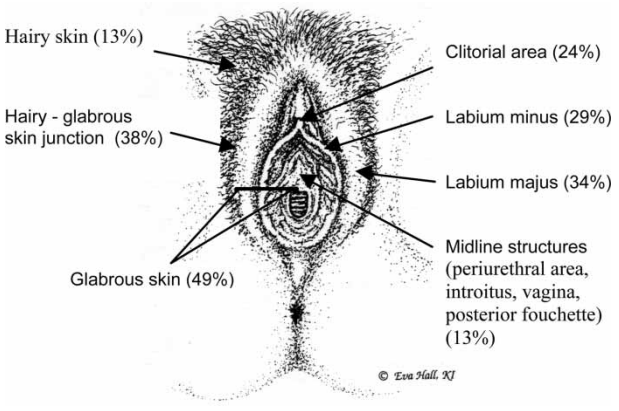


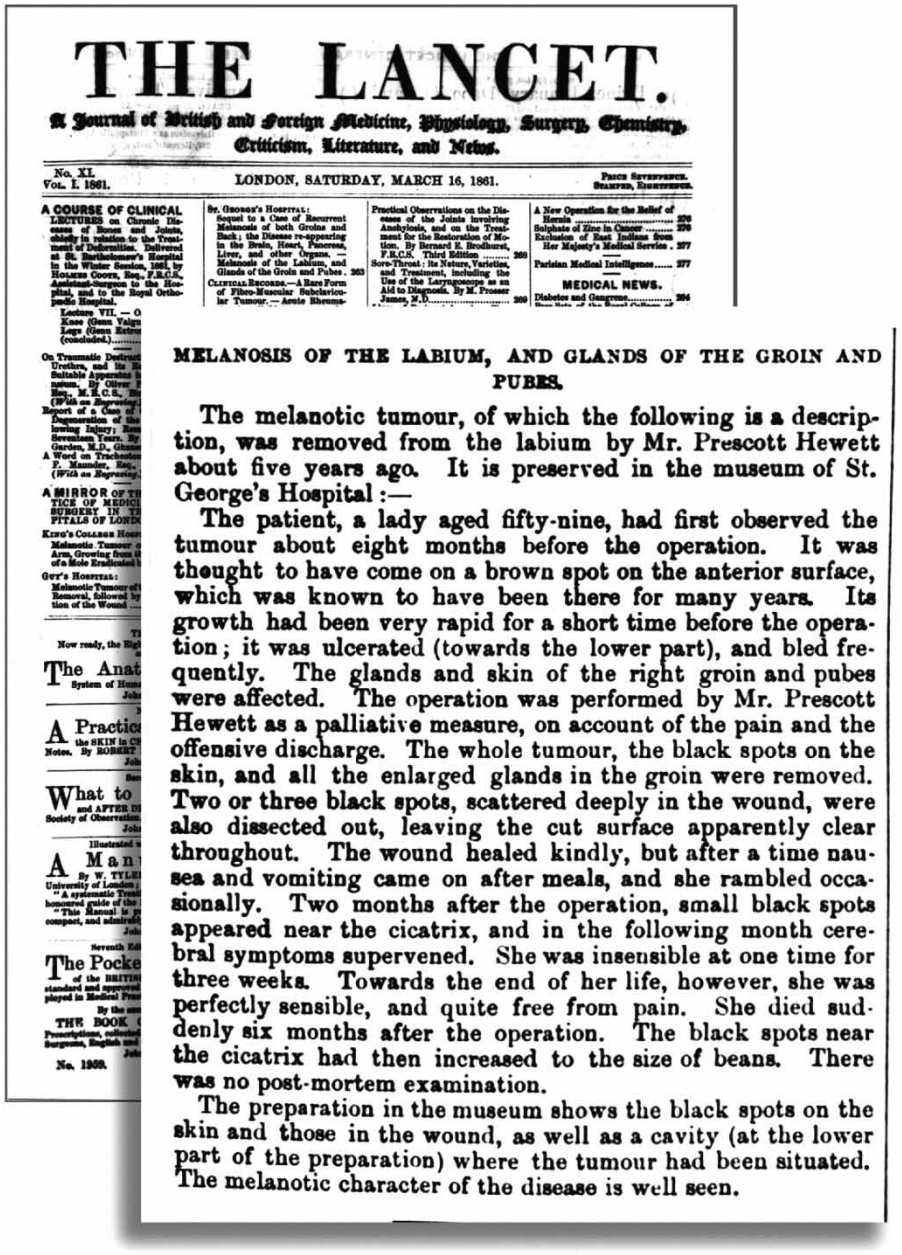
Fig. 1. Anatomy of the vulva. In parentheses is the incidence of melanomas located to histological compartments (left) from 182 patients in one report (3) and to gross structures (right) calculated from 644 patients in 13 reports (3, 12, 16–19, 22, 23, 25, 26, 29, 79, 102).

serious therapeutic problems either by evading early detection and thus advancing to considerable size before their diagnosis or because of extreme biological aggressiveness. The true incidence of extracutaneous melanomas is difficult to determine, and seldom are the figures reported derived from whole geographic regions or national populations. However, in Sweden and the other Scandinavian countries, the law decrees that all primary malignancies must be reported to a national agency. Accordingly, since 1958 about 98% (6) of all malignant primary tumors in Sweden have been recorded at the Swedish National Cancer Registry. Between 1960 through 1996, a total of 32 154 patients with cutaneous melanomas were reported to the Registry, l6 693 of them females (see Table 1) (7). During the same time interval, 3 598 patients with a primary extracutaneous melanoma were registered. Eye melanomas were the most common (2 837), whereas melanomas derived from the vulva (310) and anus/rectum (224) were more numerous than tumors in the sino-nasal cavity (148), mouth (14), vagina (35), penis (23), or urethra (7).

However, comparing subgroups of melanomas in absolute numbers is deceptive, because it does not take into account the size of the area in which the tumors emerge. Recently the *density* (i.e. the number per square unit of body surface) of cutaneous melanomas in various body areas has been evaluated (8). According to that report the density of invasive cutaneous melanomas in the face was calculated to be 2.3 times higher than the density on all other body skin. This over-representation quotient of melanomas on the facial skin is very similar to that in the vulva versus the whole body skin (1.9) (Table 1), which again emphasizes the deception in calculating only the absolute number of melanomas. Furthermore, the similarity in melanoma density between the most sun-exposed and one of the most sun-shielded areas of the body is compelling for seeking new causative factors, in addition to UV radiation, of melanomagenesis.

REPORTS ON VULVAR MELANOMA

The first description of vulvar melanoma was cited briefly in 1824 by Cullen and Carswell in an autopsy report (9). However, apparently, the first case study on primary vulvar melanoma was published in the *Lancet* in 1861 by Prescott Hewett at St. George's Hospital in London (10) under the title, 'Melanosis of the labium and glands of the groin and pubes' (Fig. 2) (further historical notes in (11)). From 1861 to date more than 1 800 cases of vulvar melanoma have been described in publications. The exact figure is difficult to compute, because several descriptions have appeared both as single case histories and as inclusions in case series. According to one review, fewer than 400 cases were published between 1861 and 1970 (12). As documented in the MedLine Database and PubMed, all published case series of vulvar melanoma amounting to 10 or more cases, during 1970 to 2002, have been reviewed, and the 1 442 cases compiled, with their references, are displayed in Table 2. Series have sometimes been updated with



THE LANCET.

A Journal of British and Foreign Medicine, Physiology, Surgery, Chemistry, Criticism, Literature, and News.

No. XI. Vol. I. 1861. LONDON, SATURDAY, MARCH 16, 1861. Price Sevenpence. Stamped, Eightpence.

A COURSE OF CLINICAL LECTURES on Chronic Diseases of Bones and Joints, chiefly in relation to the Treatment of Deformities. Delivered at St. Bartholomew's Hospital in the Winter Session, 1861, by HOLMES COOTE, Esq., F.R.C.S., Assistant-Surgeon to the Hospital, and to the Royal Orthopædic Hospital.

Lecture VII. — On Knee (Genu Valgum Legs (Genu Retrum (concluded).

ST. GEORGE'S HOSPITAL: Sequel to a Case of Recurrent Melanosis of both Groins and Back; the Disease re-appearing in the Brain, Heart, Pancreas, Liver, and other Organs. — Melanosis of the Labium, and Glands of the Groin and Pubes. 363

CLEISTOGENESIS.—A Rare Form of Fibro-Muscular Subclavicular Tumour. — Acute Rheumatism.

Practical Observations on the Diseases of the Joints involving Anchylosis, and on the Treatment for the Restoration of Motion. By Bernard E. Brodhurst, F.R.C.S. Third Edition 369

Sore-Throat: its Nature, Varieties, and Treatment, including the Use of the Laryngoscope as an Aid to Diagnosis. By M. Prosser James, M.D. 369

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A MIRROR OF THE PRACTICE OF MEDICINE AND SURGERY IN THE HOSPITALS OF LONDON.

KING'S COLLEGE HOSPITAL: Melanotic Tumour ... Arm, Growing from a ... of a Mole Eradicated ...

GUY'S HOSPITAL: Melanotic Tumour of ... Removal, followed by ... tion of the Wound ...

Now ready, the Eighth ...

The Anat... System of Hum... John...

A Practic... the SKIN in Ch... Notes. By ROBERT ... John...

What to ... and AFTER D... Society of Observation. ... John...

Illustrated ...

A Man... By W. TYLER ... University of London; ... "A systematic Treat... honoured guide of the ... "This Manual is p... compact, and admirably ... John...

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THE BOOK ... Prescriptions, tabular ... Surgeons, English and ... John...

No. 1909.

MELANOSIS OF THE LABIUM, AND GLANDS OF THE GROIN AND PUBES.

The melanotic tumour, of which the following is a description, was removed from the labium by Mr. Prescott Hewett about five years ago. It is preserved in the museum of St. George's Hospital:—

The patient, a lady aged fifty-nine, had first observed the tumour about eight months before the operation. It was thought to have come on a brown spot on the anterior surface, which was known to have been there for many years. Its growth had been very rapid for a short time before the operation; it was ulcerated (towards the lower part), and bled frequently. The glands and skin of the right groin and pubes were affected. The operation was performed by Mr. Prescott Hewett as a palliative measure, on account of the pain and the offensive discharge. The whole tumour, the black spots on the skin, and all the enlarged glands in the groin were removed. Two or three black spots, scattered deeply in the wound, were also dissected out, leaving the cut surface apparently clear throughout. The wound healed kindly, but after a time nausea and vomiting came on after meals, and she rambled occasionally. Two months after the operation, small black spots appeared near the cicatrix, and in the following month cerebral symptoms supervened. She was insensible at one time for three weeks. Towards the end of her life, however, she was perfectly sensible, and quite free from pain. She died suddenly six months after the operation. The black spots near the cicatrix had then increased to the size of beans. There was no post-mortem examination.

The preparation in the museum shows the black spots on the skin and those in the wound, as well as a cavity (at the lower part of the preparation) where the tumour had been situated. The melanotic character of the disease is well seen.

Fig. 2. The first publication on malignant melanoma of the vulva in 1861 (10).

new patients, and in those instances only the number of patients in the updated report is included in this grand total.

Two such reports are not included here, both based on the National Cancer Database, USA, and both derived from the time period 1985–1994, but with a large, unexplained discrepancy in numbers of cases. Whereas one reports only 193 cases of non-cutaneous melanomas from female genitalia, without further details (13), the other one (14) mentions 569 cases of vulvar melanoma.

INCIDENCE

Almost all reported cases of vulvar melanoma originated from individual hospitals and multicenter institutions (see Table 2). However, two reports on the age-standardized, population-based incidence of vulvar melanoma have been published: one from the USA covering approximately 10% of the American population (2), and one from Sweden, covering virtually the whole Swedish population (1). Both investigations showed similar results. The American series consisted of 203 cases of vulvar melanoma collected from multiple, population-based regional cancer registers in USA during 1973–1987. From that series, the average age-standardized incidence of vulvar melanoma was calculated at 0.10 per 100 000 of the country's female population per year. The incidence was stable during the 15-year observation period. The Swedish national series included 219

Table 2

Compiled reports on malignant melanoma of the vulva (n = 1 442 patients) from 1970 onwards (only series including 10 cases or more)

No. of cases	Period	Source of patient series	Reference no.
12	1977–1987	One center University of Vienna, Austria	Vavra et al., 1991 (115)
13	1971–1983	One center University of Munich, Germany	Baltzer et al., 1986 (116)
14	1930–1968	One center Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, Italy	Cascinelli et al., 1971 (117)
14	1938–1978	Cancer Control Agency of British Columbia, Canada	Iversen & Robins, 1980 (118)
14	1972–1982	One center New York University Medical Center, USA	Beller et al., 1986 (119)
14	1982–1991	Two centers St Bartholomew's Hospital & the Royal Marsden Hospital, UK	Neven et al., 1994 (102)
14	1980–2000	One center University of Virginia, USA	Irvin et al., 2001 (120)
15	1950–1978	One center Queen Elizabeth Hospital, Tyne and Wear, UK	Edington, Monaghan, 1980 (22)
16	1938–1982	One center University of Iowa Hospital, IA, USA	Benda et al., 1986 (42)
16	1961–1981	One center University Hospital of Groningen, The Netherlands	Bouma et al., 1982 (121)
16	1964–1982	One center Jackson Memorial Hospital/University of Miami Medical Center, USA	Jaramillo et al., 1985 (21)
16	1973–1988	One center Indiana University Hospital, IN, USA	Look et al., 1993 (23)
18	1975–1991	One center Queen Elizabeth Hospital, UK	Piura et al., 1992 (24)
19	1949–1984	One center University of Michigan Medical Center, USA	Johnson et al., 1986 (25)
23	1927–1973	One center Roswell Park Memorial Institute, NY, USA	Karlén et al., 1975 (26)
24	1964–1984	One center Royal Marsden Hospital, London, UK	Davidsson et al., 1987 (106)
26	1927–1986	One center Roswell Park Memorial Institute, NY, USA	Rose et al., 1988 (43)
29	1950–1968	One center Mayo Clinic, MN, USA	Yackel et al., 1970 (27)
30	1944–1970	One center MD Anderson Hospital and Tumor Institute TX, USA	Morrow & Rutledge, 1972 (12)
30	1951–1987	One center Netherlands Cancer Institute, The Netherlands	Tasseron et al., 1992 (44)
30	1970–1995	One center Duke University Medical Center, Durham, UK	DeMatos et al., 1998 (18)
40	1978–1995	One center Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, Italy	Raspagliesi et al., 2000 (122)
41	1979–1989	Database of the Scottish Melanoma Group, UK	Blessing et al., 1991 (62)
44	1934–1973	One center Memorial Sloan–Kettering Cancer Center, NY, USA	Chung et al., 1975 (28)
45	1930–1975	One center Long Island Jewish Hillside Med. Center, NY, USA	Ariel et al., 1981 (123)
48	1950–1980	One center Mayo Clinic, MN, USA	Podratz et al., 1983 (98)
50	1957–1982	Regional Cancer Registry, West Midlands Region, UK	Bradgate et al., 1990 (16)
50	1955–1987	Multicenter Australia	Woolcott et al., 1988 (29)
51	1970–1997	One center	Verschraegen et al., 2001 (20)

Table 2 (*Continued*)

No. of cases	Period	Source of patient series	Reference no.
		MD Andersson Cancer Center, TX, USA	
71	1983–1990	Multicenter USA[1]	Phillips et al., 1994 (79)
75	1956–1987	One center Norwegian Radium Hospital, Norway	Scherstrøen et al., 1995 (17)
80	1949–1990	One center Memorial Sloan–Kettering Cancer Center, NY, USA	Trimble et al., 1992 (124)
89	1978–1991	Five centers Germany	Räber et al., 1996 (19)
203	1973–1987	US National Cancer Institute Surveillance, Epidemiology and End Results Program[2]	Weinstock, 1994 (2)
219	1960–1984	Nationwide, Sweden National Cancer Registry	Ragnarsson-Olding et al., 1993 (1)

[1]Prospective study.
[2]Covering approximately 10% of the USA population.

consecutive cases of vulvar melanoma (1) compiled from the Swedish National Cancer Registry during 1960–1984, with follow-up until 1995. The annual age-standardized incidence decreased continuously *from 0.27 to 0.14 per 100 000 women* during the 25 years or, by 3.2% annually, mainly because of a decrease among younger age groups. Concomitantly, the national age-standardized incidence of female cutaneous melanomas increased by almost 6% annually (15). An additional study from a regional cancer register in the West Midlands Region, UK that included 50 individuals has been reported (16). Another series of 75 patients from the Norwegian Radium Hospital presumably represents a vast majority of patients with vulvar melanoma in Norway during 1956–1987 (17), because that hospital is the national center for the treatment of female genital malignancies. Neither of these two series reports any age-standardized, population-based incidence of vulvar melanoma. Overall, the age profile among patients with vulvar melanoma tends towards the older age group in most reports (1, 2, 16–20). That is, the patients' mean age usually exceeded 60 years at the first presentation of the tumor, varying between 54 (20) and 68 (1).

CLINICAL RECORDS

Symptoms and clinical features

The wide array of non-specific symptoms, or combinations thereof, bringing the patient to her doctor has been compiled from 14 series of vulvar melanoma studies (3, 12, 16, 18, 19, 21–29). Lump, polyp, and/or mole (44%), bleeding (31%), pruritus (18%), discharge and irritation (16%) were the most common symptoms in the compiled series. In one series (3), unexpectedly, polyps (36%) and amelanotic tumors (27%), not moles, nevi, brown spots or melanosis (together 13%) were cited as the most common clinical manifestations of melanoma of the vulva. The amelanotic tumors were almost exclusively found in the vulva's glabrous skin and often described as 'reddish'. Vulvar melanomas with a similar frequency (34%) of macroscopic amelanosis had been reported previously (26). Similarly, as early as 1953, Allen and Spitz found that melanomas in multiple mucosal membranes lacked visible pigmentation in about half the tumors (30).

Clinical staging is of paramount importance in evaluating the progression of tumors and the efficacy of particular treatment strategies. Even if no consensus exists as to the most convenient method for staging of vulvar melanoma, most authors currently prefer the four-stage system suggested by the American Joint Committees on Cancer (AJCC) with a revision in 2001 (31). In that staging modality, primarily designed for cutaneous melanomas, tumor thickness according to Breslow (32), invasion level according to Clark et al. (33), tumor ulceration, and spread of the tumor are pertinent parameters. Tumor size, however, is not a consideration in the AJCC staging system. Nor is the AJCC staging system as suitable if one seeks to separate the prognostic impact of tumor thickness, invasion level, and ulceration on survival in an unbiased way. Furthermore, the Clark level cannot be used for the glabrous skin of the vulva, which lacks a clear-cut stratification of the subepithelial fibrous tissue in papillary and reticular layers (5). An alternative, purely anatomical microstaging system has been suggested by Chung et al. (28), in which Clark's staging is combined with tumor thickness, as used by some authors (34).

A simple, clinical three-stage classification system (35, 36) harmonizes with the intention of testing clinical and histopathological parameters separately as predictors of survival (18, 37, 38). In this system Stage I denotes a localized primary melanoma with or without satellites within 5 cm, Stage II a melanoma with regional lymph node metastases and/or in-transit metastases, and Stage III a melanoma with distant metastases beyond the regional lymph nodes. This system is also convenient for investiga-

tions of retrospective series encompassing patients from many hospitals over long periods of time. The drawback is, however, that high- and low-risk groups cannot be differentiated within Stage I.

The staging system aimed at genital carcinomas and suggested by the International Federation of Gynecology and Obstetrics (FIGO) (39) is also used by some. However, in our opinion, the latter system is less convenient for classifying vulvar melanomas, because it takes into account mainly the tumor's diameter and its extension inside the vulva and to adjacent tissues. Yet, the diameter of vulvar melanoma is of minimal prognostic value (16, 17, 29, 34) whereas vertical growth and tumor thickness are crucial prognostic parameters for vulvar as well as cutaneous melanomas. In all staging systems, an 'understaging' of Stage II may occur in retrospective patient series because of varying routines for detecting metastases in the hospitals from which the patients' records are collected, as well as varying diagnostic tools used over time.

LOCALIZATION TO ANATOMICAL AND HISTOLOGICAL SITES

The primary localization of the vulvar melanomas to the gross anatomical structures of the vulva as judged from the clinical records is displayed in Fig. 1. Those data are based on 644 patients in 13 reports. Since Fig. 1 represents a simplified division that does not take into account a secondary extension of the tumor, melanomas extending over two or more anatomical structures of the vulva without a clinician's assessment of the primary site have been omitted. The labia majora were the most common primary sites. Anatomical and histological sites are not completely congruent, because the labia majora consists of a lateral cover of hairy skin and a medial one of glabrous skin (Fig. 1), and approximately 30–40% of melanomas emerge at the mucocutaneous border of the vulva according to a previous report (5). This is in accordance with 38% in the Swedish report (3), in which the histological compartments where melanomas emerged were noted (Fig. 1). Significant biological differences were found between melanomas in those compartments (see below) (11, 37).

PATHOLOGY

During the last 50 years, histopathologic research on melanomas and particularly cutaneous melanomas has advanced notably. In 1953, Allen and Spitz (30) asserted that 'only a small added increment of depth of invasion' sharply worsened the prognosis for the patients. In 1969, Clark et al. (33) presented a microstaging system linked to survival (Clark's level I–V) that stratified melanomas within the dermis. Breslow (32) then developed another microstaging method by which the tumor volume could be indirectly estimated by measuring the maximal thickness of the lesion. An important vantage point for the assessment of melanoma progression and prognosis came with the recognition that a vertical growth phase was necessary for the emergence of metastases (40), although this opinion has been questioned recently (41). A vertical growth phase occurs in almost all reported vulvar melanomas and tallies with enlarged tumor thickness (3, 16, 17, 25, 42–44).

It is fair to presume, as Cochran and co-workers do (45), that the histogenetic type of melanoma gives some clue to the tumor's pathogenesis and that continuously recording different subtypes of melanoma in epidemiological studies is worthwhile because of increasing evidence that the causative agents differ. For example, *superficial spreading melanoma (SSM)* (33) of the skin is evidently linked to sun exposure especially among fair-skinned Caucasians. These tumors account for virtually the entire increase in incidence of cutaneous melanomas during the last recent decades according to large-scale national (46) and multinational surveys (47, 48). *Lentigo maligna melanoma (LMM)* of the skin is also generally believed to be caused by UV radiation (49). In contrast, *nodular melanoma (NM)* of the skin does not seem to increase (46) but rather to decrease (47, 48) over time. A recent report indicates that the density of NM is higher in the chronically sun-exposed face than in other skin areas (8) but there is no information on the trend of density over time. In conclusion, at present no convincing evidence connects NM with solar exposure.

In the 1970s, Reed (49) and Arrington et al. (50) described *acral lentiginous melanoma (ALM)*, a melanoma found in volar, palmar, and subungual skin, i.e. glabrous skin rarely exposed to direct sunlight. The current opinion is that ALM occurs at the same rate in all races (51–53) but these sites and this melanoma type are prevalent among populations with a more-or-less dark complexion like Blacks, Asians, and Hispanics. Recent data indicate that ALM is decreasing in frequency in Sweden (46). An interesting aside is that the ALM type of melanoma also predominates among Sinclair swine, and an amazing perception is that the order of incidence for the tumors' histogenetic types in these animals (ALM 70% $>$ NM 20% $>$ SSM 10%) (54) is similar to the incidence in both human volar skin (i.e. 71%, 17%, and 8%, respectively) (55) and in glabrous skin of the vulva (57%, 22%, and 4%) (3). Furthermore, in one series (3), the incidence of vulvar histogenetic subtypes reversed that for cutaneous melanoma (46) within the same geographic area and time period (Table 3), and this seems logical because of the apparent linkage of SSM to sun exposure.

Mucosal lentiginuous melanoma (MLM), apparently the mucous membrane counterpart of ALM and histologically indistinguishable from it, was originally described by Clark et al. in 1979 (56). McGovern called attention to the frequent occurrence of the MLM type in vulvar as well as

Table 3

Number of cutaneous (CMM) and vulvar melanomas (MMV) by histogenetic subtypes among Swedish females in two studies 1960–84

Histogenetic type[1]	CMM n = 251[2] (%)	MMV n = 198[3] (%)	RR	χ^2	p-value
SSM	118 (46.8)	7 (3.5)	0.08		
NM	32 (12.7)	40 (20.2)	1.67		
AL M/MLM	15 (6.0)	103 (52.0)	9.16	17.24	0.001
Others	87[4] (34.5)	48[5] (24.2)	0.70		

[1]SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma; MLM, mucosal lentiginous melanoma. For description see text.
[2]Population based sample among 8 248 females with a primary CMM (46).
[3]Consecutive, nationwide series of primary MMV (3).
[4]Lentigo maligna melanoma and unclassifiable melanoma.
[5]Mixed melanoma and unclassifiable melanoma.

in other mucocutaneous melanomas, but he emphasized the need for large series of such melanomas in which the histogenetic patterns were accurately delineated (57).

The literature offers no general consensus as to the incidence of histogenetic types of vulvar melanoma (Table 4). MLM dominated in two reports (3, 42). In addition, Clark et al. stated that most melanomas of the vulva were of the MLM type. Surprisingly, in two series, from the UK (16) and Norway (17) respectively, not a single case of MLM was found. The reason is unknown, but in the Norwegian report criteria for histogenetic types cited were from Clark et al. 1969 (33), i.e. before the histological features of ALM in glabrous skin were clearly delineated (49, 50) or linked to those of MLM (56, 57). Furthermore, the absence of micro-photodocumentation, except in two reports (3, 42), makes comparison difficult. However, one must emphasize that accurate typing is sometimes difficult to achieve so that a picture of mixed histogenetic types, often in different compartments of the histological section, occasionally results (3). Of interest, a recent investigation suggests a classification of cutaneous melanomas based on genomic aberrations which emphasizes tumor anatomical site and sun-exposure pattern rather than histogenetic type in defining a distinct type of melanoma (58). It is at present unclear whether this classification is a practicable way of classifying melanomas (see 'Molecular genetic aspects').

Melanocytic nevi of the vulva. Remnants of dermal melanocytic cells adjacent to and contiguous with cutaneous melanomas have been noted for many years in 10–32% of cutaneous melanomas (59, 60). These cells are generally believed to be precursors of melanomas, preferentially of the SSM type (61) and hence often named 'pre-existing' nevi. They have been mentioned in communications about vulvar melanomas, but not localized to a specific site in the vulva (16, 62) except in one series (3). In the latter, pre-existing nevi were found adjacent to melanomas only in vulvar hairy skin (in 35% of such melanomas) but never near those in glabrous skin. Thus, melanomas in the glabrous skin may arise 'de novo', i.e. emerge directly from transformed melanocytes, not from nevocellular nevi.

A survey of *atypical melanocytic nevi* of the genital type (AMNGT) has been published by Clark et al. (63), based on a selected series of 56 patients whose vulvar pigmented lesions were submitted for consultation to the authors. Of

Table 4

Histogenetic types of malignant melanoma (all stages) of the vulva

No. of cases	Types[1] (%)				Reference no.
	SSM	MLM	Mixed	NM	
16	19	63	0	19	Benda et al., 1986 (42)
19	26	11	0	63	Johnsson et al., 1986 (25)
26	53	8[2]	0	23	Rose et al., 1988 (43)
50	56	0	0	28	Bradgate et al., 1990 (16)
30	33	27[2]	0	43	Tasseron et al., 1991 (44)
75	60	0	0	19	Scherstroen et al., 1994 (17)
30	37	27[2]	0	NA[3]	DeMatos et al., 1998 (18)
182	4	57	6	22	Ragnarsson-Olding et al., 1999 (3)
51	40	4	0	56	Verschraegen et al., 2001 (20)

[1] For description and explanation of histogenetic types see text and Table 3; mixed melanomas, combination of SSM+MLM.
[2]Named 'melanoma with lentiginous pattern', or acral lentiginous melanoma.
[3]Data not available.

these tumors, 36 were diagnosed as AMNGT, 14 as dysplastic nevi, and 6 as common dermal nevi. AMNGT, often having a mushroom-cap shape, were found mostly in the labium majus or occasionally in the perineum, whereas dysplastic nevi appeared predominantly in the labium minus or perineum. Distinctive features of the stroma were attributed to different nevi, and together with the melanocytic cytology they were instrumental in typing the lesions and in differentiating atypical nevi from melanomas.

Macroscopic amelanosis in vulvar melanomas and in melanomas of several mucosal membranes was reported long ago (26, 30), although the implication for prognosis was not investigated. In the Swedish series (3), a high incidence of macroscopical amelanosis in melanomas (27%) was detected and often described as 'reddish' by the patients' physicians. A point of emphasis is that some melanomas (16%) with macroscopic amelanosis contain small amounts of microscopic melanin (3). Macroscopical amelanosis might depend on a predominance of reddish, sulfur-containing pheomelanin over brown-black eumelanin. Alternatively, some melanoma cell clones could somehow lose the ability to produce melanin during the tumor's progression.

Far beyond the scope of this presentation are the details of *melanogenesis* encompassing many new biochemical aspects of eu- and pheo-melanin synthesis, various melanin precursors involved in red-ox processes in the melanocyte, the structure and wide array of receptors and their governing genes for multiple hormones, enzymes, and signaling substances involved in melanin production by melanosomes. This broad, multidisciplinary, and rapidly expanding field of research has been extensively reviewed elsewhere (64). In this context, though, two aspects of melanin function should be emphasized. First, although melanin is necessary for the protection of keratinocytes and basal cells and helps to inhibit carcinoma formation, it also seems to be mandatory for the emergence of melanomas. A supportive observation is that human albinos, who have a normal number of melanocytes but lack the ability to produce melanin even by the age of 20, often display basal cell and squamous cell carcinomas but very rarely a malignant melanoma (65, 66). Since 1952, only 27 albino patients with melanomas have been documented, seven such tumors occupying extracutaneous sites (66–72). Second, melanins may also serve as a filter binding environmental xenobiotics, industrial chemicals, or drugs taken up by skin, mucous membranes, and eyes (73, 74). These findings recall the observation by Norris almost 150 years ago (75) that his patients with cutaneous melanomas often lived in heavily polluted industrial environments. Accordingly, when considering alternatives to UV radiation-caused DNA damage as possible inducers or promoters of melanomas, one might propose as candidates numerous exogenous or endogenous factors bound to the melanins.

Ulceration in cutaneous malignant melanomas is common in large patient series (76, 77). In the Swedish series of vulvar melanomas (3), those with ulcerations varied from 91% in the glabrous skin to 65% in the hairy skin, at all clinical stages. This lesion is of significant prognostic value, as explained below (37). Additional pathological and histopathological lesions found in patients with vulvar melanomas are detailed elsewhere (16, 18, 37, 42, 44, 78, 79).

Site-specific pathological features of malignant melanomas in vulvar compartments

As an anatomical site for pursuing cancer research, the vulva provides an opportunity to compare melanomas within two different tissues at the same sun-protected area, i.e. the hairy and glabrous skin compartments. This has been done histologically (see Fig. 1) in an investigation of 182 cases (3). The majority of these primary melanomas, or 49%, were located in the glabrous skin and only 13% in the hairy skin of the vulva. Some 38% of the cases encompassed both the glabrous and hairy skin, as was apparent from the histological sections. The higher density of melanomas in the vulva as compared with the average density of the body surface refers largely to those in the glabrous skin. Significant biological differences between the hairy and glabrous vulvar skin compartments are given in Table 5. The reason(s) for differences between melanomas in the hairy and glabrous skin is unclear. However, indications are that tumors emerging in the glabrous skin are more aggressive than those in hairy skin, because all the significant differences except pre-existing nevi are well-known signs of poor prognosis in cutaneous melanomas (80, 81). The crucial questions bearing on the whole process of melanomagenesis are: why do melanomas emerging in two different compartments within the same small sun-shielded area differ at all, and what is the biological impact of individual tissue factors? Interestingly, no significant difference in histogenetic type, except for NM, was found between the two compartments, and the MLM dominated in both. This might give support to recent suggestions that anatomical site and local tissue factor(s) rather than

Table 5

Comparison between lesions in the hairy and glabrous skin of the vulva[1]

	Vulvar melanoma (%)		
	Hairy skin	Glabrous skin	p-value
Preexisting nevi	34.8	0	< 0.001
Macroscopic amelanosis	4.3	38.9	0.002
> 10 mitoses/10 HPF	0	32.9	0.002
Ulceration	65.2	91.1	0.005
Microscopic amelanosis	4.3	23.3	0.041
Nodular melanoma	8.7	27.8	0.052

[1]Data from (11, 37).

histogenetic type defines a distinct type of melanoma (see below).

MOLECULAR GENETIC ASPECTS

Studies of the molecular genetics of primary vulvar and other extracutaneous melanomas (excluding ocular melanomas) are rare. Variations in DNA copy numbers (82) have been used to study genomic abnormalities in differing types of melanomas (83–85). Of interest, extracutaneous melanomas most closely resemble acral melanomas, but not the cutaneous of SSM type, which predominate among cutaneous melanomas. These mucosal and acral tumors frequently have more distortions in chromosome arms 1q and 6p, and also more chromosomal alterations than other melanomas. However, in a recent report (58) the authors suggest that the differences in chromosomal alterations of melanomas depend on anatomical location and sun-exposure pattern rather than histogenetic type. These findings are extended by the findings of significant differences in histological lesions between melanomas in the vulvar glabrous skin and hairy skin (3).

In a series of 50 vulvar malignancies subjected to combined chromosome banding and cytogenetic analyses, three out of three vulvar melanomas displayed complex karyotypes with multiple aberrations in several chromosomes but most commonly in chromosome 1, specifically 1p12-q41 (86).

Two other genetic aspects of vulvar and other mucosal melanomas have been addressed, namely mutations in the H-, K-, and N-ras oncogene (87) and in the p53 tumor suppressor gene (TP53) (88). The ras proto-oncogene family has been implicated in basic cellular processes such as signal transduction and cellular proliferation/differentiation. Several studies have demonstrated that the N-ras oncogene is the predominant gene activated in cutaneous melanomas exposed to UV radiation (89–93) and that exon 2, codon 61, is the preferential site of mutation. The mutations in melanomas from chronically sun-exposed skin significantly outnumber those in mucous membranes (87), supporting the concept of a positive correlation between UV radiation and mutations in the N-ras oncogene.

The occurrence and importance of TP53 mutations in cutaneous melanomas is controversial, varying from 0% to 32% (94, 95). In a recent investigation comparing mucosal and cutaneous (from chronically sun-exposed skin) melanomas (88), TP53 mutations were found about equally frequent (34% and 26%, respectively). Furthermore, a relatively high fraction of the mutations in mucosal melanomas were C→T transitions at dipyrimidine sites. Previous reports claim that such mutations reflect DNA damage associated with UV radiation in sun-related basaliomas and squamous cell carcinomas of the skin (96, 97) but, obviously, such mutations in the TP53 in melanomas are introduced by mechanisms other than or in addition to UV radiation.

TREATMENT

Surgery has been and is still the major choice of treatment for patients with localized vulvar melanomas. Discussions generally focus mainly on two aspects of the surgical treatment: namely, the extent of local tumor excision and the rationale for prophylactic lymph node dissection.

Surgical procedures for vulvar melanoma have often been adapted from the traditional methods for removing squamous cell carcinomas of the vulva despite obvious differences in the two tumors' growth patterns, biological processes, and clinical behavior. Each of many surgical variations entails a different technique. Basically, one of five modalities is used: (a) wide local excision of the tumor, (b) hemivulvectomy, (c) partial vulvectomy, i.e. removal of a large area of the vulva but with retention of as much normal function as possible, especially the clitoris, prepuce, and frenulum, (d) total vulvectomy (synonymous with 'simple vulvectomy'), removal of the total vulva, and (e) radical vulvectomy, including total vulvectomy but with a wider excision. Each of these variants could include lymph node dissection, either therapeutic (delayed), i.e. removal of clinically overt metastatic nodes, or elective (prophylactic) and could comprise unilateral, bilateral, superficial, and/or deep lymph node dissection or combinations thereof.

Surgical strategies described in major reports during the last 20 years are listed in Table 6. For the sake of simplicity, these techniques are grouped into four categories; therefore, the few publications with pre- and postoperative treatments included have been omitted from Table 6. The various surgical treatments produced no significant difference in survival rate, and local recurrence rates were as high as 32–41% despite extensive surgical treatment (17, 98). However, in one series encompassing patients in the FIGO Stage I only (78), a significantly (p-value 0.006) longer recurrence-free interval was found after radical vulvectomy with bilateral lymph node dissection, although there was no significant decrease in tumor-specific death (not shown in Table 6). The first sites to which vulvar melanomas metastasized could be assessed in two reports (17, 18) (Table 7). Most authors agree that patients treated by local excision, hemi- or vulvectomy usually suffer from loco-regional recurrences whereas distant metastases were more often found in patients subjected to radical surgery including lymph node dissection. Consequently, conservative treatment with a wide local excision has turned out to be as effective as vulvectomy for tumor-specific survival. However, retrospective reports should be interpreted cautiously, because of the risk that indigenous selection bias among treatment groups could have skewed the results. For example, a tendency might prevail to treat thin melanomas with local excision and large ones with vulvectomy, but

Table 6

Surgical treatment modalities for malignant melanoma of the vulva

Treatment	Prodratz et al., 83(98) USA (n = 48)[1]	Davidsson et al., 87(106) UK (n = 32)	Rose et al., 88(43) USA (n = 26)	Bradgate et al., 90(16) UK (n = 50)	Tasseron et al., 91(44) Netherl. (n = 30)	Trimble et al., 92(34) USA (n = 80)	Räber et al., 96(19) Germany (n = 89)	Scherstroen et al., 96(17) Norway (n = 65)	DeMatos et al., 98(18) USA (n = 30)	Ragnarsson-Olding et al., 99(37) (Sweden) (n = 123)	Verschraegen et al., 2001(20) USA (n = 51)
Local excision, only or hemivulvectomy, only	1	10	9	18	6	12	15	17	9	30	17
Local excision, or hemivulvectomy with lymph node dissection[2]	3	–	3	3	2	6	7	–	10	5	14
Vulvectomy (of any kind)[3], only	1	9	4	10	3	12	17	22	3	40	2
Vulvectomy (of any kind)[3] with lymph node dissection[2]	41	9	10	13	15	47	30	26	8	23	12
Difference between treatment groups in terms of:											
Recurrence-free interval	NA[4]	NS[5]	NA	NA	NA	NA	NA	NS	NS	NA	NA
Survival	NA	NS	NS	NS	NA	NS	NS	NS	NS	NS	NS

[1]Number of patients in parentheses.
[2]Lymph node dissection of any kind; uni- and bilateral, superficial and deep, and combinations thereof.
[3]Vulvectomy of any kind; named partial, simple, total, and radical.
[4]Data not available.
[5]Statistically not significant.

large melanomas could also have been treated with local excision for palliative reason.

As mentioned before, for patients with cutaneous melanomas, changing opinion presages a shift to less extensive excision. Yet, because the width of the tumor-free margins for removing vulvar melanomas is rarely recorded in exact millimeters or centimeters, that factor is difficult to analyze statistically. Even two reports (43, 78) that did mention free margins measured in centimeters included only instances of local excision, not vulvectomy or hemivulvectomy. Without exact information on the width of surgical margins in all surgical modalities those modalities are difficult to compare. Particularly for melanomas located at the medial part of the vulva with its shortage of submucous fat tissue, free margins towards deep tissues, the urethra, and the vagina are difficult to achieve. The only prospective (multicenter) study of vulvar melanoma (79) compared the outcomes of 34 females subjected to 'radical hemivulvectomy' with those of 37 females given a 'radical vulvectomy'. No significant advantage of either method was found with respect to tumor recurrence (survival not reported) but, again, the failure to specify surgical margins impaired interpretation of the results. Yet, reports on surgeries for vulvar melanoma have so far not connected tumor *thickness* with surgical *margins*. Several reports on cutaneous melanomas bear out the importance of this connection (99–101).

Controversies remain regarding the advantage of elective (prophylactic) lymph node dissection in vulvar melanoma with respect to the tumors' recurrence and/or the patients' survival (17, 34, 44, 102). Randomized trials of elective lymph node dissection in patients with cutaneous melanomas showed no advantage of elective over therapeutic (delayed) modes in terms of local recurrence or survival (103). Of course, such trials are very difficult or impossible to conduct on small series of vulvar melanomas. The two traditional variations of lymph node dissections, elective and therapeutic, have today extended to a third variant, the 'selective lymph node dissection', in pioneering work by Morton et al. (104) in which the first drainage lymph node, the 'sentinel node', is identified and removed with subsequent dissection of the rest of the nodes if melanoma cells are present. This technique for treating vulvar melanomas has so far been reported for only a few patients, the largest group (four cases) being reported by Abramova et al. (105).

Table 7

Sites of first recurrences in patients with vulvar melanoma

Sites	DeMatos et al. (18) N = 18[1] (100%)	Scherstroen et al. (78) N = 43[1] (100%)
Local tissues, only	3 (17)	11 (26)
Regional lymph nodes, only	4 (22)	7 (16)
Local tissues+regional lymph nodes	0 (0)	4 (9)
Distant tissues, only	2 (11)	14 (33)
Local+distant tissues	9 (50)	7 (16)

[1] Number of patients

The high incidence (50%) of distant metastases in patients with microscopically negative lymph nodes treated with radical vulvectomy (78) makes this drastic procedure hard to justify as a routine practice. Presumably, the same conservative principles that prevail for surgery to treat cutaneous melanomas should be applied to vulvar melanomas. Several authors (16, 18, 20, 34, 37, 43, 44, 78, 102, 106) have questioned the benefit of vulvectomy and have advocated individualizing the treatment depending on the tumor's prognostic factors (see below). The width of the free surgical margins should be dictated by the thickness of the tumor growth. However, because of the biological aggressiveness of these melanomas, a surgical resection margin of at least 2 cm is suggested given that the histological margin is the same.

PROGNOSTIC FACTORS AND SURVIVAL

In Stage I cutaneous melanoma, *tumor thickness* and *ulceration* have been well documented as independent predictors of survival. For example, in a composite group of about 17 600 patients with cutaneous melanomas from 10 centers worldwide, these predictors were the most significant (80). These two factors evidently reflect very aggressive tumor growth that infiltrates and destroys the epidermis or mucosal membrane. Ulceration has been thought to correlate with increased tumor thickness, but Balch et al. emphasized its value as an independent, adverse prognostic factor, and others agree (107, 108).

The prognosis for patients with vulvar melanoma has been expressed as different end-points such as recurrence-free interval, emergence of lymph node metastases, or tumor-specific survival. The series are usually small, and Stage II is presumably often underestimated, regardless of the staging system used, because of the failure to recognize lymph node metastases. Common use of current, more sophisticated techniques may correct this staging error. In contrast with the accord as to prognostic factors for cutaneous melanomas, at present no such consensus exists on the most important predictors of outcome for vulvar melanomas, which have been reported mainly as univariate analyses.

In some univariate analyses, *ulceration* became a significant determinant of disease-free survival or long-term survival (16, 37, 78), but in only one report of multivariate analysis (37) did it emerge as an independent variable.

Tumor thickness according to Breslow (32) was a significant determinant in univariate analyses (16, 17, 37, 79), but in only two reports (37, 79) was it an independent variable in multivariate analyses. The reason(s) for these discrepancies is unclear. One should keep in mind, however, that the number of patients in the various series was small. Furthermore, the profiles of patients differed, e.g. the FIGO staging as employed in the Norwegian study (78) excluded the largest tumors still localized.

In the Norwegian report (78), only angioinvasion and DNA non-diploidy of melanoma cells were independent variables for long-term survival in multivariate analyses but when these patients were assessed for disease-free interval the type of primary surgery was also an independent variable. A noteworthy point is that angioinvasion in cutaneous melanoma had no significant impact on survival according to multivariate analyses by several authors (81, 109, 110). They have noted their experience that shrinkage artifacts make the determination of invasion into the small, thin-walled vessels (representing neoangiogenesis) very difficult.

In the prospective multicenter study by Phillips et al. (79) comprising 71 patients with vulvar melanomas, tumor invasion into capillaries and central localization of the tumor in the vulva emerged as the only independent variables positively correlated with lymph node status. When disease-free interval was used as an endpoint, the AJCC stage was the only independent prognostic factor, but AJCC staging includes tumor thickness. However, tumor thickness was an independent variable when tested in the absence of AJCC stage. Ulceration seems not to have been tested.

Macroscopic amelanosis was apparently ignored as an independent predictor of survival until the Swedish series identified it as such (37). Combined with tumor thickness and ulceration, macroscopic amelanosis increased the imminence of death (expressed as relative hazards, in multivariate analyses) fivefold although its means of negatively impacting survival remain unknown. However, amelanotic cutaneous melanomas tend to be aggressive and denote a poor prognosis (81).

At this writing, no general agreement has confirmed whether the poor prognosis for individuals with vulvar melanomas is caused by late detection of the tumor (patient's or doctor's delay) or by the natural aggressiveness of these tumors. Prognostic markers are hitherto diversified and conflicting in various reports on vulvar melanoma, as indicated above. However, the frequent occurrence of distinctive markers like ulceration, amelanosis, and an almost invariable vertical growth phase in addition to excessive tumor thickness should indicate that aggressive growth is a key.

Survival. The survival of patients with vulvar melanoma is gloomy. The average 5-year survival rate ranges from 27% to 60% as calculated by individual investigators (Table 8). However, the figures are based on patient series including all clinical stages. One reason for a better prognosis among patients with cutaneous melanoma is early detection of the tumor. For example, the 5-year survival rate of patients with localized cutaneous melanoma (clinical Stage I) improved from about 50% in 1960 to 92% in 1990–94 in Sweden, whereas no time trend for improving survival was observed among patients with regional or

Table 8

Tumor-specific survival in malignant melanoma of the vulva

Survival (per cent)		Observation period	No. of patients	Reference
5-year	10-year			
46	37	1956–87	75	Scherstroen et al., (17)
35	22	1957–82	50	Bradgate et al., (16)
47	44	1960–84	219	Ragnarsson-Olding et al., (1)
27	NA[1]	1970–97	51	Verschraegen et al., (20)
60	50	1973–87	203	Weinstock et al., (2)

[1] Data not available.

distant metastases (111). No similar analyses of survival trends in large series of patients with vulvar melanoma have been published.

CONCLUDING REMARKS

Recent research provides strong indications that vulvar melanomas and other mucous membrane melanomas are biologically different from cutaneous melanomas, both histopathologically and genetically. Although UV radiation is the main etiologic factor of cutaneous melanomas, subgroups of such tumors apparently do not stem from UV radiation. It is fair to assume that melanomas of the acral lentiginous and mucosal lentiginous type, and possibly also of the nodular type, belong to those subgroups. Biological differences evident not only between melanomas in chronically sun-exposed skin and the sun-protected vulva, but also between melanomas in the vulvar hairy and glabrous skin compartments, i.e. within the same sun-shielded area, offer strong incentives for studying etiological factors other than UV radiation. The recently found, surprisingly close similarity in density of melanomas emerging in chronically sun-exposed head-and-neck skin and sun-protected vulva lend further support to such investigations. Melanins and their precursors as well as xenobiotics such as drugs and carcinogenic environmental toxins, filtered and bound to melanins, are feasible etiological candidates along with viruses. Oral contraceptives and hormone replacement therapy have also been suggested as risk factors because of the occurrence of an estrogen receptor in melanomas (112), but large epidemiological studies (reviewed in (113)) have failed to show an increased risk to develop cutaneous melanoma. One might also propose that endogenous tissue factors bound preferentially to the glabrous skin, its cellular content, and extracellular matrix are the responsible agents, whatever their nature. The need for cooperative studies between workers in basic research and clinical science is evident if the genesis of extracutaneous melanomas is to be understood. The prognosis for patients with vulvar melanomas in terms of survival rate is still poor, and advanced tumor thickness, ulceration, and amelanosis make it even worse. There is no evidence that a radical, mutilating vulvectomy improves the survival time significantly over that after a local excision with wide, tumor-free surgical margins. Unquestionably, prospective multicenter studies are needed that include consecutive series of vulvar and other extracutaneous melanomas with well delineated and mutually agreed clinical and histopathological classifications and photographic documentation.

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