Epidemiology of Extracutaneous Melanoma in the Netherlands

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Abstract

Background: Reliable population-based incidence and survival data on extracutaneous melanoma (ECM) are sparse.

Methods: Incidence data (1989-2006) from the Netherlands Cancer Registry were combined with vital status on January 1, 2008. Age-adjusted annual incidence rates were calculated by direct standardization, and the estimated annual percentage change was estimated to detect changing trends in incidence. Additionally, we carried out cohort-based relative survival analysis.

Results: Ocular melanomas were the most common ECM subsite with European standardized incidence rates (ESR) of 10.7 and 8.2 per 1,000,000 person-years for males and females, respectively. In comparison, for cutaneous melanoma (CM), the ESRs for men and women were 122 and 155 per million person-years, respectively. No statistically significant trends in the incidence of ECM were detected, whereas an annual increase of 4.4% for men and 3.6% for women was detected in the incidence of CM. Relative survival for ECM was poor, but differed largely between anatomic subtypes ranging from a 5-year relative survival of 74% for ocular melanomas to 15% for certain subsites of mucosal melanomas.

Conclusions: Of all ECM subsites, ocular melanomas had the highest incidence and the best survival. Mucosal melanomas were the second most frequent subsite of ECM. Five-year relative survival for all ECM subtypes was worse if compared with CM. No statistically significant trends in the incidence of (sub)sites of ECM were determined.

Impact: This study gives insight into the relative sizes of the different subgroups of ECM as well as an estimate of 5-year survival, which varies substantially by subsite.

Introduction

Although rare, melanomas can arise at noncutaneous sites. Such extracutaneous melanomas (ECM) include ocular, meningeal, and mucosal melanomas, or melanomas on exceedingly rare sites such as the adrenal gland, kidney, lung, or soft tissue. Ocular melanomas arise in the eye and adnexa, whereas meningeal melanomas occur in the dura mater or leptomeninges. Mucosal melanomas may occur at different anatomic sites, such as in the head and neck region, female or male genitals, esophagus, anorectally, or very rarely in the urinary tract or biliary tract (1).

Most of the available epidemiologic data on ECM are restricted to anatomic sites and are not based on well-described populations, e.g., from geographic regions or national databases (2-5). Thus, population-based incidence and survival data on ECM are sparse. In 2005, McLaughlin et al. published incidence data on ECM from the United States and showed that ocular melanoma was more common among men (men, 6.8 cases per million; women, 5.3 cases per million women, age-adjusted to U.S. population standard in 2000), whereas mucosal melanomas were more common among women (women, 2.8 cases per million; men, 1.5 cases per million men; ref. 6). Unfortunately, trends in ECM incidence and survival were not reported. Comparable European data are not available.

In general, ECMs are rare (incidence rates <10 per 1,000,000 person-years; refs. 2-6) and have a poor prognosis, with 5-year survival estimates ranging from 4% to 60% (1). As opposed to cutaneous melanomas (CM), the prognosis for ECM is poor due to late diagnosis. As most ECMs are not visible, early presenting signs and symptoms are often absent. Additionally, ECMs seem to be biologically more aggressive than most CMs (1).
In the Netherlands, the age-adjusted incidence rate of CM increased significantly by 3.3% in men and by 2.2% in women between 1989 and 1998 (7). This was likely due to increases in sun exposure, and partly due to increased awareness (7). Because the effects of sun exposure are considered to be small or absent for the development of ECM, no changes in incidence rates are expected to occur over time for ECM.

The objective of this study was to contribute to the very limited information on population level regarding this rare group of cancers by assessing incidence rates, relative survival, and time trends in the incidence of ECM of different anatomic sites in the national general population-based Netherlands Cancer Registry between 1989 and 2006.

Materials and Methods

Data
Incidence data from 1989 until 2006 according to sex, calendar year of diagnosis, and anatomic site were obtained from the nationwide population-based Cancer Registry in the Netherlands. This registry receives lists of newly diagnosed cases on a regular basis from the FALGA network, the registry of histopathology and cytopathology in the Netherlands. All pathology departments in the country participate in this nationwide network. In addition to these records, lists of hospitalized cancer patients are provided by the medical record departments, and these are also checked. Sequentially, the medical records of patients with newly diagnosed primaries are collected. From these, trained tumor registrars summarize relevant information. Duplicate records are removed (8).

From both hospital records and the death registry of the Central Bureau for Genealogy (which registers all deceased in the Netherlands via the municipal civil registries), vital status on January 1, 2008 was obtained. We recorded survival for the periods between primary melanoma diagnosis and date of death or the latest date of follow-up. Patients who were alive at their last date of follow-up were considered censored.

Anatomic sites of ECM were identified based on the International Classification of Disease for Oncology, 9th and 10th revision (ICD-9, ICD-10), and were regrouped in the melanoma of the central nervous system (brain, benign brain tumors, meninges, and other central nervous system; ICD codes: 1921-1922, C70-C71), ocular melanoma (eye, eye lids, orbita, choroid, corpus ciliare, and the eye muscles; ICD codes: 1900-1909, C69), or mucosal melanoma of the ear-nose-throat region (nasal cavity, middle ear, sinuses, larynx, lip, pharynx, and oral cavity; ICD codes: 1404, 1430, 1439, 1452, 1453, 1600-1609, C00-C09, C11-C14, C30-C33), genitals (for males, penis and other not otherwise specified male genitals; for females, cervix uteri, ovary, vagina and other female genitals, but excluding the vulva; ICD codes: 1840-1848, 1871-1877, C52, C53, C56, C57, C60, C63), vulva (ICD code: C51), gastrointestinal tract (esophagus and anus/anal canal; ICD codes: 1504, 1505, 1541-1548, C15, C20-C21), lung (ICD codes: 1625, C34, C38) or urinary tract (including urinary bladder; ICD codes: 1881, C68), and ECM of other sites (such as adrenal gland, kidney, soft tissue; ICD codes: 1890, C49, C74, C77). ECM of the stomach, small intestine, and colorectal are exceedingly rare and can be metastases of an occult primary melanoma. Therefore, ECM registered as the subsites stomach, small intestine, and colorectal (ICD codes 1521, 1570, C16, C17 and C18) were excluded from analyses (n = 10).

The Netherlands Cancer Registry records are assumed to be complete from 1989 onwards (9). However, data collection before 2003 on ocular melanomas was incomplete because, at the time, ocular melanomas that were not pathologically confirmed were not systematically included in the Netherlands Cancer Registry. Likewise, vulvar melanomas were not systematically reported prior to 1993 because a unique ICD code was lacking. Consequently, we included only data from 2003 and 1993 onwards for ocular and vulvar melanomas, respectively.

Analysis
For each site, incidence rates were calculated stratified by sex and calendar year. Annual incidence rates were age adjusted by direct standardization according to the European standard population, resulting in European standardized incidence rates (ESR) per 1,000,000 person-years. Subsequently, 3-year moving averages of the ESR were calculated. To detect changing trends in ECM incidence over time, the estimated annual percentage change (EAPC) was calculated. The EAPC was estimated by fitting a regression line with the following equation: $y = mx + b$, where $y = \ln\ ESR$ and $x = \text{calendar year}$. The EAPC is then equal to $100 \times (e^m - 1)$. This method assumes that the incidence rates increase or decrease at a constant rate in the study period (1989-2006). For each EAPC, 95% confidence intervals (95% CI) were calculated using the standard error of $m$ obtained with the regression line (7). EAPCs were calculated separately for men and women, for CM, all mucosal melanomas, and mucosal melanomas of the vulva and ear-nose-throat region.

Additionally, join-point analyses were carried out to determine if significant changes in the time trends were present and, if so, when they occurred (10). In join-point analyses, linear line segments are connected on a log scale to identify changes in the EAPC values over time (10).

Relative survival was estimated in a cohort-based analysis by dividing the crude survival among cancer patients by the expected survival from the general population based upon the same age and sex distributions as has been described earlier (11). Relative rather than crude survival was estimated because this reflects the excess mortality among the cancer patients rather than the overall survival experience of the patients, including the non-cancer-related deaths. Standard errors were calculated according to Greenwood’s method (12).

All calculated $P$ values were two-sided and considered significant if $P < 0.05$. All analyses were done using SPSS.
16.0 (SPSS Inc.), except relative survival which was calculated using the SAS computer package, version 9.1 (SAS Institute Inc.).

Results

Between 1989 and 2006, a total of 3,134 primary invasive ECMs were registered among Dutch citizens age ≥18 years. In comparison, the Netherlands Cancer Registry recorded 42,124 primary invasive CMs in the same period. The number of melanomas with an unknown primary was <0.2%, and these were considered to have a cutaneous origin in this study.

Incidence

Table 1 summarizes the number of incident melanoma cases diagnosed between 1989 and 2006 by anatomic location and sex. During this period, a total of 42,124 CMs were diagnosed. The age-standardized incidence rates (ESR) of CM were 122 and 155 per million person-years for males and females, respectively (Table 1). The male to female rate ratio was 0.79.

Between 2003 and 2006, ECM made up 6.4% of all invasive melanomas. The proportion of ECM was slightly higher among men (7.0% versus 6.0%).

During this period, ocular melanomas were the most commonly occurring subsite of ECM and represented 87% and 68% of all ECM among men and women, respectively. The ESRs of ocular melanoma were 10.7 and 8.2 per 1,000,000 person-years for males and females, respectively. Thus, the male to female rate ratio of ocular melanomas was 1.3.

After excluding ocular melanomas reported before 2003 and vulvar melanomas reported before 1993 (see Materials and Methods for explanation), 1,502 incident primary ECMs among 1,493 patients were eligible for further analyses.

Patients with ECM had a median age at diagnosis of 68 years, whereas CM patients had a median age of 53 years. Median ages at diagnosis and the 25th and 75th percentile of patients with different melanoma subtypes are presented in Table 1. Overall, ECM patients are generally older at diagnosis than CM patients, and male ECM patients are younger at diagnosis (median age, 65 years) than female ECM patients (median age, 71 years).

Table 1. Invasive cutaneous and extracutaneous melanomas in the Netherlands National Cancer Registry

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Men</th>
<th>Women</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incident cases (n)</td>
<td>ESR 1989-2006 (rate*)</td>
<td>Incident cases (n)</td>
</tr>
<tr>
<td>Skin</td>
<td>17.723</td>
<td>121.9</td>
<td>24.401</td>
</tr>
<tr>
<td>Nonskin, nonmucosal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system§</td>
<td>6</td>
<td>0.038</td>
<td>7</td>
</tr>
<tr>
<td>Ocular§</td>
<td>373</td>
<td>10.67</td>
<td>322</td>
</tr>
<tr>
<td>Others§</td>
<td>1</td>
<td>0.01</td>
<td>4</td>
</tr>
<tr>
<td>Nonskin, mucosal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear-nose-throat§</td>
<td>122</td>
<td>0.880</td>
<td>139</td>
</tr>
<tr>
<td>Genitals§</td>
<td>48</td>
<td>0.338</td>
<td>121</td>
</tr>
<tr>
<td>Vulva</td>
<td>n.a.</td>
<td>n.a.</td>
<td>214</td>
</tr>
<tr>
<td>Gastrointestinal tract§</td>
<td>53</td>
<td>0.382</td>
<td>78</td>
</tr>
<tr>
<td>Lung§</td>
<td>6</td>
<td>0.045</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract§</td>
<td>1</td>
<td>0.007</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviation: n.a., not applicable.

*ESR, expressed in 1 per 1,000,000 person-years.

†Calculated 5-year cumulative overall survival relative to the general Dutch population standardized for age and gender.

‡Median age at diagnosis in years (25-75 percentile).

§The extracutaneous localizations were defined as: central nervous system, including brain, benign brain tumors, meninges and other central nervous system; ocular, including melanoma of the eye and its adnexa, such as the eye lids, orbita, choroidia, corpus ciliare and the eye muscles; and others, including adrenal gland, kidney, and soft tissue; and mucosal melanomas, which were subdivided into several categories, such as ear-nose-throat, which includes sinonasal and oropharyngeal mucosal melanomas (larynx, lip, pharynx, oral cavity, nasal cavity, middle ear, and sinuses); genitals, which included, for males, penis and other NOS (not otherwise specified) male genitals, and for women, female genitals including cervix uteri, ovary, vagina and other female genitals, but excluding the vulva; gastrointestinal tract, which included oesophagus and anus/anal canal; and urinary tract, which included urinary bladder and other urinary tract structures.

∥Only data from 2003 until 2006 were included for ocular melanomas since the Dutch Cancer Registry was incomplete for ocular melanomas before 2003.
Mucosal melanomas, such as vulvar (ESR 1.06) and ECM of the ear, nose and throat (ESR 0.88 for males and 0.71 for females), also contributed substantially to the total ECM incidence. The male to female rate ratio of mucosal melanomas was 0.48.

Only 13 incident primary ECM within the central nervous system were reported in the total study period (1989-2006), resulting in extremely low ESRs for men and women (0.038 and 0.052 per million person-years, respectively).

Relative survival

Five-year relative survival for CM unstratified for gender was 86% overall between 1989 and 2006. Relative survival of all ECM subtypes was poor compared with those of CM. However, there are large differences in 5-year relative survival estimates among ECM subtypes. Of all ECMs, ocular melanomas had the best 5-year relative survival of 74%, whereas vulvar melanomas had a 5-year relative survival of 40%. The 5-year relative survival of different subsites of mucosal melanomas varied between 15% and 40% (Table 1).

Trends in incidence

For both sexes, the ESR for CM increased significantly between 1989 and 2006 (Table 2). For males, the ESR for CM increased by 4.4% (95% CI, 3.9-4.9%) per year. Increases among females were 3.6% (95% CI, 2.9-4.2%).

The age-adjusted incidence rates of all mucosal melanomas and of the selected mucosal of the ear-nose-throat region (Fig. 1) showed an increasing, but nonsignificant trend among women (EAPC, 1.8%; 95% CI, −0.5 to 4.2%; and EAPC, 2.8%; 95% CI, −0.1 to 6.8%, respectively). For men, lower increases were observed in the annual incidence of all mucosal melanomas and those of the ear-nose-throat region (EAPC, 1.0%; 95% CI, −1.8 to 3.8; and EAPC, 1.1%; 95% CI, −4.4 to 7.1, respectively). The estimated increase in the incidence of vulvar melanoma between 1993 and 2006 was only 0.3% (95% CI, −2.6 to 3.4).

Despite apparent changes in trend, no statistically significant join points were shown in the join-point analyses that were carried out (results not shown).

Table 2. European standardized incidence rates for melanomas of different locations in 3-year periods between 1989 and 2006

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>n</td>
<td>ESR*</td>
<td>n</td>
<td>ESR*</td>
<td>n</td>
<td>ESR*</td>
<td>n</td>
<td>ESR*</td>
</tr>
<tr>
<td>Skin</td>
<td>1,900</td>
<td>88.5</td>
<td>2,154</td>
<td>96.0</td>
<td>2,600</td>
<td>111.6</td>
<td>3,007</td>
<td>124.1</td>
</tr>
<tr>
<td>Mucosal†</td>
<td>28</td>
<td>1.95</td>
<td>29</td>
<td>2.54</td>
<td>38</td>
<td>1.97</td>
<td>47</td>
<td>3.21</td>
</tr>
<tr>
<td>Ear-nose-throat†</td>
<td>18</td>
<td>0.88</td>
<td>17</td>
<td>0.81</td>
<td>16</td>
<td>0.72</td>
<td>23</td>
<td>1.00</td>
</tr>
<tr>
<td>Ocular‡</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>2,91</td>
<td>124.7</td>
<td>3,15</td>
<td>130.8</td>
<td>3,7</td>
<td>150.8</td>
<td>4,06</td>
<td>161.2</td>
</tr>
<tr>
<td>Mucosal†</td>
<td>71</td>
<td>2.89</td>
<td>89</td>
<td>3.65</td>
<td>83</td>
<td>2.58</td>
<td>111</td>
<td>3.21</td>
</tr>
<tr>
<td>Ear-nose-throat†</td>
<td>15</td>
<td>0.60</td>
<td>22</td>
<td>0.88</td>
<td>22</td>
<td>0.87</td>
<td>30</td>
<td>1.19</td>
</tr>
<tr>
<td>Vulva‡</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>35</td>
<td>1.42</td>
<td>55</td>
<td>2.12</td>
</tr>
<tr>
<td>Ocular‡</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

*European standardized incidence rate, expressed in 1 per 1.000,000 person-years.
†Subcategories of the extracutaneous melanomas that were tested for an incidence trend were: mucosal melanomas, including all mucosal melanomas (ear-nose-throat, genitals, vulva, gastrointestinal tract, lungs and urinary tract); ear-nose-throat, including only the sinonasal and oropharyngeal mucosal melanomas (larynx, lip, pharynx, oral cavity, nasal cavity, middle ear and sinuses); and vulvar mucosal melanomas.
‡Before 1993 there were no separate ICD codes registered for vulvar melanomas. Both in 1993 and 1994, 16 vulvar melanomas were registered.

Discussion

Incidence

Our results show that, between 2003 and 2006, about 6.4% of all primary melanomas in the Netherlands were ECMs. This proportion is similar to those in previous reports (4-6.8%; refs. 6, 13). In general, ECM patients, especially those with mucosal melanomas, are older...
at diagnosis than CM patients. Similarly, Chang et al. observed a median age of ~70 years for mucosal melanomas (14).

No statistically significant time trend in ECM incidence was seen, whereas an annual increase in age-adjusted standardized CM incidence among both sexes was observed.

Ocular melanoma was the most common ECM subsite, and its incidence was somewhat higher than reported by McLaughlin et al. (ESR males, 10.7 versus 6.8 per million person-years; females, 8.2 versus 5.3 per million person-years; ref. 6). The male to female rate ratio of 1.3, however, was similar (6).

Mucosal melanomas were the second most frequent subsite of ECM, and the incidence we report is in agreement with the U.S. data reported in McLaughlin’s article (ESR men, 1.8 versus 1.5 per million person-years; women, 2.8 versus 2.8 per million person-years; ref. 6). The male to female rate ratio for mucosal melanomas was 0.48, which seems to be rather consistent throughout the literature (6, 14, 15), and the female predominance is most likely a reflection of the lack of a male counterpart for vulvovaginal lesions (15).

The incidence of vulvar melanoma in our study (ESR, 1.1 per million person-years) is similar to that of a previously published study from Sweden (1960-1984; ref. 3). In that study, however, the annual age-standardized incidence of vulvar melanoma decreased by 3.2% annually (mainly due to a decrease among younger age groups; ref. 3), whereas our results showed no definite trend in incidence (EAPC, 0.3%; 95% CI, -2.6% to +3.4%). Nonetheless, the Swedish data are outdated (data up to 1984) and were based on a consecutive series of cases rather than a population-based sample (3).

Relative survival

Five-year relative survival proportions of ECM subtypes, except ocular melanoma, were poor compared with CM (86%) and differed substantially between subsites. Preferably, we would have stratified for the clinical stage of disease at diagnosis in the survival analysis, which was not possible due to low numbers of incident ECM.

Of all ECM subsites, primary ocular melanoma had the best survival, with a relative 5-year survival of 74% (95% CI, 67-81%). Estimates from the Collaborative Ocular Melanoma Study (1) were slightly lower (60%), but the 5-year disease-specific survival of 75% published by Chang et al. (14), is comparable. Our estimate may be somewhat underestimated due to the fact that we could only use data from 2003 until 2006 and vital status on January 1, 2008, resulting in a relatively short follow-up for part of the patients with ocular melanoma in our dataset and hence relatively many patients being censored alive.

Vulvar melanomas in our dataset resulted in a 5-year survival proportion of 40% (95% CI, 31-49%), comparable with the 50% reported by Weinstock on U.S. data (16).

The survival proportion for gastrointestinal melanoma was calculated to be 15% (95% CI, 8-22%), slightly better than the overall crude 5-year survival of 6% presented in a Dutch case series of anorectal melanoma (63 cases, 1960-1995; ref. 17). Although we included anorectal as well as esophageal melanomas in this subsite, survival estimates for patients with anorectal and esophageal melanomas did not substantially differ in our dataset (data not shown).

Reflection

The poor survival proportions estimated for ECM could obviously reflect the often advanced stages in which ECMs are diagnosed. However, ECM and CM also differ substantially in their clinicopathologic and molecular aspects. Even between subgroups of CM, such as acral melanoma and chronic versus nonchronic sun-exposed melanomas, the genetic makeup and morphologic features differ (18). The clinical heterogeneity of melanoma can, in part, be explained by distinct sets of genetic alterations. Approximately 80% of melanomas in skin without chronic sun-induced damage contain a mutation in either BRAF or NRAS, whereas cutaneous melanoma arising in nondamaged skin, as well as acral and mucosal melanomas do not (19). Instead, these tumors frequently display increased gene copy number of cyclin-dependent kinase 4 and cyclin D1. Oncogenic BRAF mutations in ocular melanoma are rare, if not absent, or restricted to only a subset of cells in posterior uveal melanomas (20-23). However, somatic mutations in the heterotrimeric G protein α-subunit, GNAQ, are frequently observed in uveal melanoma, but rarely in other melanomas (24). Mutations and/or copy number increases of receptor tyrosine kinase KIT have been detected in 39% of mucosal melanomas, 36% of acral melanomas,
and 28% of melanomas on chronically sun-damaged skin (25). These genetic changes commonly result in various alternative routes to mitogen-activated protein kinase activation and hence proliferation. However, upstream oncogenic mutations in BRAF, NRAS, KIT, and GNAQ will activate additional signaling cascades specific for that tumor type and therefore contribute to the diversity in melanoma biology, prognosis, and response to therapy.

**Future research**

Future epidemiologic research on ECM should include large (international) datasets. This would enable researchers to stratify for clinical stage at diagnosis in survival analysis and therefore to study how much of the poor prognosis of ECM is due to delayed diagnosis. It would also allow for studying the male to female ratios reported and time trends in incidence and survival, and investigate possible geographic gradients in comparison with CM. Ideally, these datasets would be population based to avoid biases occurring from selected patient groups. Whenever possible such international databases should include aspects that may explain the clinical heterogeneity, such as the morphologic features and mutational status of an ECM. If treatment were to be adequately collected, the effects of targeted therapies such as imatinib for c-KIT mutated mucosal melanomas could be studied.

**Conclusions**

With incidence rates for different subsites of extracutaneous melanoma ranging from ≤0.1 per million person-years for ECM of the lung or urinary tract up to about 10 to 11 per million person-years for ocular melanomas among men, ECM is a rare type of melanoma. Of all ECM subsites, ocular melanomas had the highest incidence (10.7 and 8.2 per million person-years for men and women, respectively) and the best survival with a 5-year relative survival of 74%. Mucosal melanomas, such as vulvar melanomas, were the second most frequent subsite of ECM. Five-year relative survival for mucosal melanomas ranged between 15% and 40%, and survival for all ECM subtypes was worse if compared with the 86% 5-year relative survival for CM. Also in contrast with CM, no statistically significant trends in the incidence of (subsites of) ECM were determined.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

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