MALIGNANT MELANOMA

risk factors, clinical presentation and treatment

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Introduction  Malignant Melanoma in Belgium:

- In 2006 a total of 1572 patients were diagnosed with malignant melanoma in Belgium, crude incidence rate in males 8/100,000 person years and in females 12/100,000 person years.
- In females the fifth most frequent occurring tumor (2005)
- In the age group 15-29 years the most important malignancy

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m</td>
<td>f</td>
<td>m</td>
</tr>
<tr>
<td>Absolute numbers (n)</td>
<td>620</td>
<td>873</td>
<td>621</td>
</tr>
<tr>
<td>CR, (n/100,000 person years)</td>
<td>12.2</td>
<td>16.4</td>
<td>12.1</td>
</tr>
<tr>
<td>ESR, (n/100,000 person years)</td>
<td>10.9</td>
<td>14.2</td>
<td>10.5</td>
</tr>
<tr>
<td>CRI, (%)</td>
<td>0.88</td>
<td>1.12</td>
<td>0.81</td>
</tr>
</tbody>
</table>

CR: crude (all ages) incidence rate (n/100,000 person years)
ESR: age-standardised incidence rate, using European Standard Population (n/100,000 person years)
CRI: cumulative risk 0-74 years (%)
Introduction – Malignant melanoma in Belgium:

- In the Flemish region an increase in incidence of malignant melanoma in both sexes was observed between 1999 and 2005.
Introduction – Malignant melanoma in Belgium:

• Comparison with European countries revealed a low incidence of malignant melanoma in males, the incidence rate for females was positioned in the middle of the selected European data.
Geographic variability of MM incidence

# Introduction – Malignant melanoma in Belgium:

- in 2004 275 patients died from metastatic disease

<table>
<thead>
<tr>
<th>Malignant Melanoma of the skin</th>
<th>Males</th>
<th>Females</th>
<th>M/I ratio</th>
<th>M/I ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (n)</td>
<td>I (n)</td>
<td>M/I ratio</td>
<td>M (n)</td>
</tr>
<tr>
<td>Brussels – Capital Region</td>
<td>9</td>
<td>56</td>
<td>0.16</td>
<td>17</td>
</tr>
<tr>
<td>Flemish region</td>
<td>72</td>
<td>364</td>
<td>0.2</td>
<td>95</td>
</tr>
<tr>
<td>Wallon Region</td>
<td>49</td>
<td>200</td>
<td>0.25</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>620</td>
<td>-</td>
<td>145</td>
</tr>
</tbody>
</table>

Malignant melanoma:
- stage by sex, Belgium 2004-2005:
  - Males tend to be diagnosed in a more advanced stage than females
MALIGNANT MELANOMA

- risk factors
- clinical presentation
- treatment
sun exposure

- only preventable causative factor

- sharp short bursts of acute sun exposure childhood and severe sunburn
primary prevention: avoid sunburn and excessive sun exposure

UV intensity (UV-index): influenced by season, time of the day, reflection, ...

Sunscreens (total blockers, high SPF) and protective clothing
skin pigmentation

► skin type 1, linked to polymorphisms in melanocortin-1-receptor (MC1R)
  phenotype: blond or red hair
  blue or green eyes
  fair skin
  freckels
  → doubles the risk

► non-white people: incidence 10-20 x less,
  and present more frequently with cMM on palms and soles
naevi

• number of naevi most powerfull predictor of risk of melanoma

• recent GWAS identifies common variant, flanking CDKN2A locus, associated with high naevus count and melanoma susceptibility (Falchi M, 2009; Bishop T, 2009)

• > 100 naevi, or > 2 clinical atypical naevi, increases risk 5 to 20 fold

clinical atypical naevus

- > 5 mm diameter
- irregular or blurred edge
- irregular or mottled pigmentation
clinical atypical naevus phenotype, atypical mole syndrome (AMS)
dysplastic naevus syndrome (DNS)

- numerous naevi (> 100), with high variability in size and color
- clinical atypical naevi (>2)
- naevi on unusual sites (breasts in females, buttocks, scalp ears, dorsum of feet)

- sporadic DNS: negative family history
- familial DNS: melanoma in at least 2 first degree family members
MALIGNANT MELANOMA

• risk factors

• clinical presentation

• treatment
superficial spreading malignant melanoma (SSMM)

- commonest subtype
- on non-CSD skin
- biologically less aggressive: slow growing initially, develop horizontally before they acquire the capacity for invasion (ABCD rule)
superficial spreading malignant melanoma (SSMM)

- commonest subtype
- on non-CSD skin
- biologically less aggressive: slow growing initially, develop horizontally before they acquire the capacity for invasion (ABCD rule)
nodular malignant melanoma

- common in older men
- on non-CSD
- biologically more aggressive (grow rapidly, vertical growth fase from the beginning)
- does not meet ABCD criteria
- not necessarily associated with high number of naevi or freckles (not in the high risk population)
lentigo malignant melanoma (LMM)

- common in older people
- on CSD skin
- develops in slow growing precursor lesion, lentigo maligna
- once invasive melanoma develops, LMM is as aggressive as other MM of similar thickness
Acral lentiginous malignant melanoma

- Rarest type in caucasian population
- On soles/heels, palms, under the nail
- Occur in all ethnic groups
- Though to be unrelated to sun exposure
Acral lentiginous malignant melanoma (subungual)

naevus

invasive melanoma

in situ melanoma
Frequency distribution of genetic alterations in BRAF, NRAS, and KIT among four groups of melanoma

Early detection of melanoma

ABCD(E) rule
“ugly duck” sign
show images of melanoma
neophobia

• who should be screened?
- clinical atypical nevus phenotype
- positive family history of melanoma

breslow thickness is strongest prognostic factor
Benign melanocytic naevus

Symmetrical
Regular border
Even color
< 6 mm

Superficial spreading malignant melanoma

A: Symmetry
B: Border: irregular border
C: Color: irregular pigmentation,
   shades of black, brown, grey and pink
   (Diameter: > 6 mm)
E: Evolution (change over weeks or months)
"ugly duck sign"
not all cMM adhere to the ABCD rule

neophobia: anything that changes rapidly on the skin (weeks/months)

Amelanotic malignant melanoma

nodular malignant melanoma
Histological diagnosis

- subtype (SSMM, NMM, ALM, LMM, ..)
- growth fase (radiaal, invasief radiaal, verticaal)
- breslow thickness
- clark level
- mitoses/mm2
- ulceration
- regression
- lymphovascular and en perineural invasion/ satelites
- type van afweerrespons door de gastheer
Breslow thickness: strongest prognostic factor

- **horizontal phase**: growth within the epidermis
- **vertical growth**: invasion of the tumor is assessed by **Breslow thickness** = measurement in mm of the distance between the granular cell layer to the deepest identifiable melanoma cell (most important prognostic factor)
New AJCC - TNM classification:

**Table 1. TNM Staging Categories for Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1s</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| T1             | ≤ 1.00         | a: Without ulceration and mitoses ≤ 1mm²  
|                |                | b: With ulceration or mitoses ≥ 1mm²       |
| T2             | 1.01-2.00      | a: Without ulceration     
|                |                | b: With ulceration         |
| T3             | 2.01-4.00      | a: Without ulceration     
|                |                | b: With ulceration         |
| T4             | > 4.00         | a: Without ulceration     
|                |                | b: With ulceration         |

**Table 2. Anatomic Stage Groupings for Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Clinical Staging*</th>
<th>Pathologic Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>N</td>
</tr>
<tr>
<td>0</td>
<td>T1s</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
</tr>
<tr>
<td>II A</td>
<td>T2a</td>
</tr>
<tr>
<td>II B</td>
<td>T3a</td>
</tr>
<tr>
<td>II C</td>
<td>T4a</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
</tr>
<tr>
<td></td>
<td>Any N</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.

*Clinical staging includes microstaging of the primary melanoma and clinical radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

**Pathologic staging includes microstaging of the primary melanoma and pathological information about the regional lymph nodes as partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathological evaluation of their lymph nodes.**

Survival curves from the AJCC Melanoma Staging Database:


Useful tool to calculate prognosis: → http://melanomaprognosis.org/
MALIGNANT MELANOMA

• risk factors

• clinical presentation

• treatment
Treatment of melanoma

- **Locoregional disease (I-III)**
  - Surgical treatment of the primary tumor (wide excision according to breslow thickness)
  - Surgical treatment of regional metastatic melanoma
  - ILP (isolated limb perfusion)
  - Adjuvant therapy for high-risk melanoma

- **Distant metastatic disease (IV)**
  - Systemic treatment of metastatic melanoma
  - Melanoma and radiotherapy
Survival in stage IV patients:

One-year survival rates among 7,972 stage IV patients:

M1a (= skin, subcutaneous tissue or distant lymphnodes and normal LDH): 62%
M1b (= metastasis to the lung (or with combination of lung and skin or subcutaneous metastases) and normal LDH): 53%
M1c (= any other visceral site or at any location with an elevated LDH): 33%

→ Median survival 6-9 months, 5-yr survival rate 1-2%

Different ways to attack melanoma:

**Attack directly the tumorcell:**
- Classical chemotherapy (DTIC, Temozolomide, combination chemotherapy)
- Angiogenesis inhibitors (sunitinib, XL-184, E7080)
- KIT-inhibitors (imatinib, nilotinib)
- BRAF-inhibitors (sorafenib, PLX4032, GSK2118436)
- MEK-inhibitors (GSK1120212)
- Apoptosis-inducers (oblimersen)
- NRAS-Inhibitors

**Stimulate immunesystem to overcome immuno-resistance**
- Interleukin-2
- Interferon-α
- Anti-CTL-4 antibodies (ipilimumab, tremelimumab)
- Anti-PD-1 antibodies
- Vaccination therapy (peptide–based, dendritic cells, ... adoptive Immunotherapy)
- Allovecin-7

**Biochemotherapy**
**Frequency (%) of mutations in kinase signaling pathways in melanoma subtypes**

<table>
<thead>
<tr>
<th></th>
<th>cutaneous</th>
<th>acral</th>
<th>mucosal</th>
<th>uveal</th>
<th>Not specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>40-60</td>
<td>15-20</td>
<td>3-5</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>15-25</td>
<td>10-15</td>
<td>5-15</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>c-KIT (mut)</td>
<td>&lt;2 (CSD 2-17)</td>
<td>10-20</td>
<td>15-20</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>c-KIT (ampl)</td>
<td>0-7 (CSD 6)</td>
<td>25-30</td>
<td>25-30</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>GNαQ</td>
<td>&lt;1 (CSD 5)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>45-50</td>
<td></td>
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<tr>
<td>ERBB4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-20</td>
</tr>
<tr>
<td>PTEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-30</td>
</tr>
<tr>
<td>PIK3CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2</td>
</tr>
<tr>
<td>AKT1/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2</td>
</tr>
</tbody>
</table>

**Fig 2.** Frequency distribution of genetic alterations in BRAF, NRAS, and KIT among four groups of melanoma. Non-CSD, melanomas on skin without chronic sun-induced damage; CSD, melanomas on skin with chronic sun-induced as evidenced by the presence of marked solar elastosis; acral, melanomas on the soles, palms, or sub-ungual sites; mucosal, melanomas on mucosal membranes. One CSD melanoma had a KIT and an NRAS mutation, and one acral melanoma had a KIT and a BRAF mutation.


Davies MA et al Oncogene 2010, 29, 5545-5555
Fig 4. Summary of key molecular pathways in melanoma and current targeted agents in clinical trials. The agents, designated targets, and current investigational status are presented in Table 1. VEGF-TRAP, vascular endothelial growth factor-trap; RTK, receptor tyrosine kinase; SCF, stem cell factor (also known as KIT ligand); ECM, extracellular matrix; TKI, tyrosine kinase inhibitors; UCN-01, 7-hydrosystaurosporine; PDK1, phosphoinositide-dependent kinase 1; AKT, also known as protein kinase B; mTOR, mammalian target of rapamycin; PKC, protein kinase C; IKK, I-κB kinase; I-κB, inhibitor of nuclear factor-κB; NF-κB, nuclear factor-κB; 17-AAG, 17-allylamino-17-demethoxygeldanamycin; 17-DMAG, 17-dimethylaminoethylamino-17-demethoxy-geldanamycin; FAK, focal adhesion kinase; HSP90, heat shock protein-90; CDK, cyclin-dependent kinase.
Background - Ipilimumab

- Ipilimumab is a fully human IgG monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) and potentiates T-cell responses.

2. CTLA-4 ligation on activated T cells downregulates T-cell responses.
• primary prevention (sun-protection) and secondary prevention (early detection) are essential

• standard of care remains good surgical management

• adjuvant therapy (interferon..) may improve relapse free survival- no effect on overall survival

• new therapies (vaccines, BRAF and ckit inhibitors, ipilimumab) hold promise-until now only effect on disease free survival- important questions need to be answered