Online Resource 1: Melanoma - clinical data review

Article title: Running for Time: Circadian Rhythms and Melanoma

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Survival rate by stages

Survival rates are estimated according to nearly 60,000 patients analysed within the '2008 AJCC Melanoma Staging Database'. The presented data explains observed survival rates that include patients diagnosed with melanoma who may have later died from other causes, i.e. heart disease. It is therefore possible to assume higher survival percentages for melanoma patients. Generally, it is assumed that that the outcome is better for melanoma spread only to distant parts of the skin or distant lymph nodes rather than to other organs, and if the blood level of lactate dehydrogenase (LDH) is normal.

Stage IA: The 5-year survival rate is around 97%. The 10-year survival is around 95%.
Stage IB: The 5-year survival rate is around 92%. The 10-year survival is around 86%.
Stage IIA: The 5-year survival rate is around 81%. The 10-year survival is around 67%.
Stage IIB: The 5-year survival rate is around 70%. The 10-year survival is around 57%.
Stage IIC: The 5-year survival rate is around 53%. The 10-year survival is around 40%.
Stage IIIA: The 5-year survival rate is around 78%. The 10-year survival is around 68%.*
Stage IIIB: The 5-year survival rate is around 59%. The 10-year survival is around 43%.
Stage IIIC: The 5-year survival rate is around 40%. The 10-year survival is around 24%.
Stage IV: The 5-year survival rate is about 15% to 20%. The 10-year survival is about 10% to 15%.
*Observed survival rate is higher for stage IIIA cancers than for some stage II cancers. This might be due to a less advanced primary tumor in IIIA cancers, although this should be additionally clarified.*

The outcome of melanoma depends on the stage at presentation. It is estimated that 82-85% of melanoma patients present with localized disease, 10-13% with regional disease, and 2-5% with distant metastatic disease. An excellent prognosis (5 year survival achieved in more than 90% patients) is given to patients with localized disease and primary tumors (1.0 mm or less in thickness). For patients with localized melanomas (more than 1.0 mm in thickness), survival rates range from 50-90%. The likelihood of regional nodal involvement increases with increased tumor thickness. If the regional nodes are involved, survival rates drop substantially (20-70%, depending primarily on the nodal tumor burden). Long-term survival in patients with distant metastatic melanoma is less than 10%. However, even with stage IV, some patients have a more indolent clinical course that is biologically quite distinct from most patients with advanced disease [1].

**Surgical treatment:**

*Surgical treatment is based on* standard protocols for surgical margins wide excision of primary melanoma as follows:

<table>
<thead>
<tr>
<th>Tumor thickness</th>
<th>Recommended clinical margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5-1 cm</td>
</tr>
<tr>
<td>≤1.0 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01-2 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>2.01-4 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

Routine elective lymphadenectomy or irradiation of regional lymph nodes is not recommended (stage IIB). Sentinel lymph node biopsy in melanoma with a tumor thickness of >1 mm and/or ulceration is necessary for precise staging (stage IIB). It should be followed by a complete lymphadenectomy of regional lymph nodes, if the sentinel node was found positive for metastases (III, C) [2]. This procedure however, has no proven effect on overall survival [3]. Sentinel lymph node biopsy should be carried out only by skilled teams in experienced centres.

Melanoma stages are defined by the American Joint Committee on Cancer's TNM classification system [4]. Histological features of the primary melanoma—tumor thickness, mitotic rate, and ulceration—are important hallmarks of melanoma prognosis and staging. Most notably, the mitotic rate has emerged in this analysis as a powerful predictive factor of survival [5–8].

**Stage I Melanoma**

**Standard Treatment Options for Patients with Stage I Melanoma**

Current evidence suggests that lesions 2 mm or less in thickness may be treated conservatively with radial excision margins of 1 cm. Elective regional lymph node dissection did not proved beneficial for patients with stage I melanoma. Lymphatic mapping and sentinel lymph node (SNL) biopsy for patients with tumors of intermediate thickness and/or ulcerated tumors, however, may allow the identification of individuals with occult nodal disease who might benefit from regional lymphadenectomy and adjuvant therapy [9–12].
Stage II Melanoma

Standard Treatment Options for Patients with Stage II Melanoma

Current evidence suggests that for melanomas with a thickness between 2 mm and 4 mm, the surgical margins need to be 2 cm or less. Lymphatic mapping and sentinel lymph node (SLN) biopsy have been used to assess the presence of occult metastasis in the regional lymph nodes of patients with stage II disease, which potentially identifies individuals who may be spared the morbidity of regional LND and individuals who may benefit from adjuvant therapy [11,13–16]. To ensure accurate identification of the SLN, lymphatic mapping and removal of the SLN should be performed prior to wide excision of the primary melanoma. Adjuvant treatment after resection (i.e. interferons) has not been shown to have an impact on the overall survival.

Stage III Melanoma

Standard Treatment Options for Patients with Stage III Melanoma

1. Wide local excision of the primary tumor with 1 cm to 3 cm margins, depending on tumor thickness and location [17–21]. Skin grafting may be necessary to close the resulting defect.
2. High-dose or pegylated interferon alpha-2b as adjuvant treatment for patients who have undergone a complete surgical resection but are considered to be at high risk for relapse.
3. Ipilimumab for patients with unresectable disease.

Adjuvant Treatment Options for Patients with Resected Stage III Disease

Prospective, randomized, multicenter treatment trials have demonstrated that high-dose interferon alpha-2b and pegylated interferon do not improve overall survival.

Treatment Options for Patients with Unresectable Stage III Disease

1. Ipilimumab
2. Vemurafenib for patients who test positive for the BRAF V600 mutation by an FDA-approved test.
3. Local therapy for extremity melanoma. For patients with in-transit and/or satellite lesions (stage IIIC) of the extremities, hyperthermic isolated limb perfusion (ILP) with melphalan (L-PAM) with or without tumor necrosis factor-alpha (TNF-alpha) has resulted in high tumor response rates and palliative benefit [17].

Several treatment options for patients with stage III melanoma are under clinical evaluation.

Stage IV and Recurrent Melanoma

Treatment Options for Patients with Stage IV and Recurrent Melanoma

1. Immunotherapy.
2. Signal transduction inhibitors.
3. Chemotherapy.
4. Palliative local therapy.
5. Clinical trials should be strongly considered because of the rapid advances in the development of novel agents and combinations of agents designed to reverse or interrupt aberrant molecular pathways that support tumor growth.

References


