PET/CT for Melanoma

The Trundholm Sun Chariot, "anterior view" app 1350 BC
The National Museum of Denmark, Copenhagen
54 x 35 x 29 cm (width, height, depth).
The cause of this increased incidence remains incompletely explored – sunlight is known to play an important role.
Progressive advances in melanoma therapy, clinical screening, and imaging have provided steadily improved survival.
Factors with most significant impact on staging

Primary tumor thickness ulceration

Presence of regional satellite or distant metastasis

Several other factors have prognostic significance
Malignant melanoma localized to the skin i.e. no metastatic disease

<table>
<thead>
<tr>
<th>Tumor Size (mm)</th>
<th>1 year</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>99%</td>
<td>95-90</td>
<td>88-83</td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>99-98</td>
<td>87-77</td>
<td>79-64</td>
</tr>
<tr>
<td>2.0-4.0</td>
<td>99-95</td>
<td>79-63</td>
<td>64-51</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>95-90</td>
<td>67-45</td>
<td>32-52</td>
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Primary tumor thickness is of critical importance (regardless of stage)
And the single best predictor of survival
Stage I: <2 mm (no ulceration or metastasis)

Stage II: High risk primaries without metastasis
1-2 mm + ulceration
>2 mm +/- ulceration

Stage III: Satellite metastasis and/or regional lymph node metastasis

Stage IV: Distant metastasis
1) distant skin, nodes, subcutaneous tissue
2) lung
3) other visceral metastasis
In patients with **regional lymph node** involvement, 35% die within the first 3 years after initial treatment.

Patients with **metastasis to the brain or organs** usually die within months.

Melanoma may **recur** in up to 50% of melanoma survivors. The risk is greatest during the first years after diagnosis.
In high-risk patients imaging offers an indispensable adjunct to clinical and surgical staging.

US, CT, MRI, FDG PET/CT are used in different situations.
Purpose of imaging

Prognostication of clinical node negative patients

Detection of occult disease in clinical node positive in patients with late diagnosis

Detection recurrence

Surveillance/follow-up?
**Sentinel node biopsy**
Prognostication of clinical node negative patients

**FDG-PET/CT**
Detection of occult disease in clinical node positive patients *with late diagnosis*

Recurrence

In node negative patients: no need to go further with respect to imaging.

Patients with regional lymph node involvement expect to undergo diagnostic imaging at the time of diagnosis; the detection rate is low particularly in asymptomatic patients with microscopically disease nodes.

**US, FDG-PET/CT**
Survillance/follow-up ?
Contemporary Diagnostic Imaging Modalities for the Staging and Surveillance of Melanoma Patients: a Meta-analysis

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Background
Meta-analyses were performed to examine the utility of ultrasonography, computed tomography (CT), positron emission tomography (PET), and a combination of both (PET-CT) for the staging and surveillance of melanoma patients.

Method
Patient-level data from 74 studies containing 105,228 patients (between January 1, 1990, and June 30, 2009) were used to derive characteristics of the diagnostic tests used. Meta-analyses were conducted by use of Bayesian bivariate binomial models to estimate sensitivity and specificity. Diagnostic odds ratios [i.e., true-positive results/false-negative results/(false-positive results/true-negative results)] and their 95% credible intervals (CrI) and positive predictive values were used as indicators of test performance.

Results
Among the four imaging methods examined for the staging of regional lymph nodes, ultrasonography had the highest sensitivity (60%, 95% CrI = 33% to 83%), specificity (97%, 95% CrI = 88% to 99%), and diagnostic odds ratio (42, 95% CrI = 8.08 to 249.8). For staging of distant metastases, PET-CT had the highest sensitivity (80%, 95% CrI = 63% to 93%), specificity (87%, 95% CrI = 84% to 97%), and diagnostic odds ratio (25, 95% CrI = 3.68 to 195.7). Similar trends were observed for melanoma surveillance of lymph node involvement, with ultrasonography having the highest sensitivity (96%, 95% CrI = 86% to 99%), specificity (99%, 95% CrI = 96% to 100%), and diagnostic odds ratio (1075, 95% CrI = 226.6 to 16,950). For distant metastases, PET-CT had the highest sensitivity (86%, 95% CrI = 78% to 93%), specificity (91%, 95% CrI = 79% to 97%), and diagnostic odds ratio (67, 95% CrI = 20.42 to 229.7). Positive predictive values were likewise highest for ultrasonography in lymph node staging and for PET-CT in detecting distant metastases.

Conclusion
Among the compared modalities, ultrasonography was superior for detecting lymph node metastases, and PET-CT was superior for the detection of distant metastases in both the staging and surveillance of melanoma patients.

J Natl Cancer Inst 2011;103:129–142

74 studies, 105,228 patients
Meta-analysis
Sensitivities, specificities
PPV, NPV

Staging & surveillance
US is superior for lymph nodes
PET/CT for distant metastases
Primary staging

A

Lymph node metastases

Primary staging
US
CT
PET
PET–CT

Sensitivity

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Specificity

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Stage III

Stage IV
CT alone is not as accurate as PET/CT and has high false positive rates.

Pulmonary lesions are often visualised better with CT (relatively low spatial resolution of the PET-camera, and respiration artifacts decreases PET accuracy particularly in the lung basis).
Clinical examples

Case 3
Specific clinical questions:
Deliniate the anatomic relationship between the tumor and surrounding tissue before surgery
Superior to PET/CT in liver, brain, and heart where background activity is a limiting factor.
Brain imaging has little utility in asymptomatic patient (not a screening tool)
Recurrence

50% of patients treated for early stage melanoma

- 20% local
- 50% regional lymph nodes
- 30% distant sites (lungs)

Metastasectomy in selected patients is associated with improved survival
In patients with clinical evidence of recurrence, PET/CT influences treatment planning, particularly in those patients with locoregional recurrence or suspected distant metastasis. App 30% change in management due to upstaging.
Strategy in recurrence

A

Lymph node metastases

Surveillance

US
CT
PET
PET-CT

Distant metastases

Surveillance

CT
PET
PET-CT

Sensitivity
Specificity
Recurrence

Longitudinal follow-up involves a multidisciplinary approach based on clinical and imaging findings.

Currently *no consensus guidelines* exist to dictate routine follow-up with FDG PET.

Close clinical observation is recommended (NCCN).

FDG PET may have a role in high risk patients. 
Impression: institution specific.
PET/CT has rapidly gained acceptance as the imaging modalities of choice for identifying metastatic melanoma but have often been applied without regard to tumor-specific risk strata or known benefits.

Table 4

<table>
<thead>
<tr>
<th>Site and risk level</th>
<th>5-y recurrence probability, %</th>
<th>PPV, % (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>US</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>5</td>
<td>83 (36 to 100)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>15</td>
<td>94 (68 to 100)</td>
</tr>
<tr>
<td>High risk</td>
<td>30</td>
<td>98 (83 to 100)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>5</td>
<td></td>
</tr>
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<td>High risk</td>
<td>30</td>
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*The 95% confidence intervals (CIs) were calculated by assuming the total number of patients in the study was 100.
Inclusion of equivocal findings on PET/CT does not increase sensitivity for metastatic disease and only results in decreased diagnostic accuracy
The diagnostic odds ratio: \( \frac{(TP/FN)}{(FP/TN)} \). Its value ranges from zero to infinity, with a higher value indicating better discriminatory power. A value of 1.0 is expected for tests with no difference detected between disease and non-disease groups.
The results of this meta-analysis indicate that the anatomical site (regional node, M-stage) to be evaluated was more important than the clinical scenario (ie, staging or surveillance).

For the assessments of lymph node metastasis, ultrasonography was superior to CT, PET, and PET-CT. PET-CT had the highest positive predictive value.

For the surveillance of distant metastasis; the higher number of false-positive results (ie, lower specificity) from PET-CT lead to the loss of precision. OBS! Old data.

For patients at low risk of metastasis, the positive predictive value of PET-CT (ie, 33%, 95% CI = 9% to 61%) indicated that use of PET-CT is not warranted without additional clinical indications.

**PET/CT is superior in high risk patients**
**PET/CT is superior for the detection of distant metastasis**
Summer Evening on the Skagen Southern Beach with Anna Ancher and Marie Krøyer, P. S. Krøyer, 1893