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).
Introduction

Melanoma of the skin

Victims of sun worship
Background - mortality

Melanoma of the Skin - Mortality

Died from Melanoma (no. of persons)

Year

Malignant melanoma localized to the skin i.e. no metastatic disease

<table>
<thead>
<tr>
<th>Tumor Size (mm)</th>
<th>Survival (%)</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>
<td></td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>99-98</td>
<td>87-77</td>
<td>79-64</td>
<td></td>
</tr>
<tr>
<td>2.0-4.0</td>
<td>99-95</td>
<td>79-63</td>
<td>64-51</td>
<td></td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>95-90</td>
<td>67-45</td>
<td>32-52</td>
<td></td>
</tr>
</tbody>
</table>
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.
Purpose of imaging

The Astronomical clock/Orloj. Prague
Purpose of imaging

- Prognostication of clinical node negative patients
- Further diagnosis in clinical node positive patients
- Occult disease in patients with late diagnosis
- Recurrence in survivors
- Surveillance/follow-up
Purpose of imaging

**Sentinel node biopsy**
Prognostication of clinical node negative patients

**PET or PET/CT**
Further diagnosis in clinical node positive patients
Occult disease in patients with late diagnosis
Recurrence in survivors
Surveillance/follow-up?
Definition

"Any lymph node receiving direct lymphatic drainage from a primary tumor site"
Theory

The SLN will most likely be the first affected by metastasis.

Few biopsies help avoiding histologic sampling errors.

Minimal invasive
SLN as prognostic factor

N = 347

Topping A et al BJPS 2004
SLN as prognostic factor

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Negative SLN</th>
<th>Positive SLN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>198</td>
<td>160</td>
<td>38</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td></td>
<td>50 months</td>
<td>38 months</td>
</tr>
<tr>
<td>Recurrence</td>
<td>26</td>
<td>16 (10%)</td>
<td>10 (26.3%)</td>
</tr>
<tr>
<td>Mean time to recurrence</td>
<td></td>
<td>31.3 months</td>
<td>14.2 months</td>
</tr>
<tr>
<td>Site of first recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>10</td>
<td>4 (2.5%)</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>Nodal</td>
<td>1</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Systemic</td>
<td>15</td>
<td>11 (6.9%)</td>
<td>4 (10.5%)</td>
</tr>
</tbody>
</table>

Primary tumor thickness

| T1 (≤0.75 mm)                  | 21       | 21 (100%)    | 0 (0%)       |
| T2 (>0.75 mm, ≤1.5 mm)         | 88       | 79 (89.8%)   | 9 (10.2%)    |
| T3 (>1.5 mm, ≤4.0 mm)          | 75       | 54 (72%)     | 21 (28%)     |
| T4 (>4.0mm)                    | 14       | 6 (42.9%)    | 8 (57.1%)    |

Fincher TR et al Amj J Surgery 2003
SLN as prognostic factor

SLN-status is a significant predictor of (local and systemic) recurrence

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>No recurrence (n = 160)</th>
<th>Recurrence (n = 38)</th>
<th>Univariate P value</th>
<th>Multiple covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI P value</td>
</tr>
<tr>
<td>Male sex</td>
<td>57%</td>
<td>62%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>50 years</td>
<td>51 years</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Clark level &gt; III</td>
<td>71%</td>
<td>85%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Axial Location</td>
<td>57%</td>
<td>62%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Tumor Depth (mean)</td>
<td>1.7 mm</td>
<td>3.1 mm</td>
<td>&lt;0.0001</td>
<td>1.2 1.04–1.5 0.03</td>
</tr>
<tr>
<td>Positive SLN</td>
<td>17%</td>
<td>38%</td>
<td>0.01</td>
<td>3.0 1.2–7.5 0.02</td>
</tr>
</tbody>
</table>

Covariate influence on disease-free survival for patients with a positive SLNB (n = 38)

<table>
<thead>
<tr>
<th>Covariate influence</th>
<th>No recurrence (n = 38)</th>
<th>Recurrence (n = 38)</th>
<th>Univariate P value</th>
<th>Multiple covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial location</td>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI P value</td>
</tr>
<tr>
<td>&gt;1 positive node</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor depth (mean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of nodal disease, micro versus macro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fincher TR et al Amj J Surgery 2003
Detection of SN

**Preoperative**
Lymphoscintigraphy
  - dynamic
  - static

**Peroperative**
Gammaprobe detection
Blue dye

1. Epidermis
2. Dermis
   - stratum papilare
   - stratum retikulare
3. Subcutis
Why scintigraphy?

- To produce an accurate map of the pattern of lymphatic drainage from the primary tumor site in each patient
- To find the number of SLN
- To separate the first SLN from the other nodes
- To guide biopsy (marking on the skin)
Detection of SN

0.05 mL, 5 MBq
99mTc-Nanocoll per depot
Injected perilesional/peritumoral

Avoid contamination of the skin
The tracer

$^{99m}$Tc-Nanocoll

Particle size 2.5 - 1000 nm

Negative surface charge

Opsonalization ($C3$, $C4B$, $C5$)

<table>
<thead>
<tr>
<th>A</th>
<th>HSA Microcolloid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rhenium sulfide</td>
</tr>
<tr>
<td></td>
<td>Stannous fluoride</td>
</tr>
<tr>
<td></td>
<td>Sulfur colloid (unfiltered)</td>
</tr>
<tr>
<td></td>
<td>Sulfur colloid (filtered)</td>
</tr>
<tr>
<td></td>
<td><strong>HSA Nanocolloid $^{99m}$Tc-Nanocoll</strong></td>
</tr>
<tr>
<td></td>
<td>Antimony sulfide</td>
</tr>
<tr>
<td></td>
<td>Dextran</td>
</tr>
</tbody>
</table>

Ranges of Particle Sizes, nm

1 10 100 1000 10000
Two separate lymphatic vessels reach 2 sentinel nodes

1 in parotid region
1 in right submandibular region.

Multiple draining node fields are common in head and neck

More than one SLN

Patient at end of study. Sentinel node (SNs) are marked on skin with "X." Melanoma site on nose is indicated by thick arrow.
Sentinel node can be seen in left submandibular region (straight arrow). Another sentinel node can be seen in right midcervical area (level III) (curved arrow). Such contralateral drainage is not uncommon in head and neck.
Two sentinel nodes in the right axilla.
One second-tier node in the right axilla.
Sentinel node in the right triangular intermuscular space (curved arrow)
Lymphatic channels passed directly through body wall to sentinel node in retroperitoneal area (vertical arrow) and sentinel node in right para-aortic region (horizontal arrow).
In 13% of patients with lymph node metastasis, the node involved with tumor has substantially less activity than the hottest node (McMasters KM et al J Clin Oncol 2001)
When not to use SNB

Clinical metastasis in regional node (node positive)

Do US and FNA.

If malignancy is confirmed, FDG-PET/CT is recommended before surgery.
Contemporary Diagnostic Imaging Modalities for the Staging and Surveillance of Melanoma Patients: a Meta-analysis

Yan Xing, Yulia Bronstein, Merrick I. Ross, Robert L. Askew, Jeffrey E. Lee, Jeffrey E. Gershenwald, Richard Royal, Janice N. Comnier

Manuscript received February 12, 2010; revised October 5, 2010. Accepted October 12, 2010.

Correspondence to: Janice N. Comnier, MD, MPH, Department of Surgical Oncology, Unit 444, The University of Texas M.D. Anderson Cancer Center, 1400 Holcombe Boulevard, Houston, TX 77030-4009. E-mail: jcomnier@mdanderson.org.

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 [e, true-positive results/falsenegative 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 (90%, 95% CrI = 83% to 93%), specificity (97%, 95% CrI = 88% to 99%), and diagnostic odds ratio (42, 95% CrI = 8.08 to 249.81). For staging of distant metastases, PET-CT had the highest sensitivity (80%, 95% CrI = 53% to 93%), specificity (87%, 95% CrI = 54% to 97%), and diagnostic odds ratio (25, 95% CrI = 3.58 to 198.7). Similar trends were observed for melanoma surveillance of lymph node involvement, with ultrasonography having the highest sensitivity (96%, 95% CrI = 85% to 99%), specificity (69%, 95% CrI = 95% to 100%), and diagnostic odds ratio (1675, 95% CrI = 226.8 to 15,920). 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 = 29.42 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

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

74 studies,
105.228 patients
Meta-analysis
Sensitivities, specificities
PPV, NPV
Primary staging

A. Lymph node metastases

B. Distant metastases

- Primary staging
  - US
  - CT
  - PET
  - PET–CT

- Surveillance
  - CT
  - PET
  - PET–CT

Sensitivity

Specificity
Recurrence

50% of patients treated for early stage melanoma

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

Metastasectomy in selected patients is associated with improved survival

No evidence-based guidelines
Clinical practice patterns vary widely.
Strategy in recurrence

A

Lymph node metastases

Primary staging

US
CT
PET
PET-CT

Surveillance

US
CT
PET
PET-CT

Distant metastases

Primary staging

CT
PET
PET-CT

Surveillance

CT
PET
PET-CT

Sensitivity

Specificity
## Table 4
Positive predictive value (PPV) estimates for surveillance for ultrasonography (US), computed tomography (CT), positron emission tomography (PET), and PET-CT, stratified by level of risk and metastatic site.

<table>
<thead>
<tr>
<th>Site and risk level</th>
<th>5-y recurrence probability, %</th>
<th>PPV, % (95% CI)</th>
</tr>
</thead>
<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 52 (12 to 88)</td>
<td>83 (36 to 100)</td>
</tr>
<tr>
<td>Intermediate risk 15</td>
<td>94 (68 to 100)</td>
<td>78 (43 to 95)</td>
</tr>
<tr>
<td>High risk</td>
<td>98 (83 to 100) 90 (68 to 99)</td>
<td>95 (81 to 100)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>5 13 (27 to 32)</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk 15</td>
<td>34 (16 to 52)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>55 (38 to 73)</td>
<td></td>
</tr>
</tbody>
</table>

*The 95% confidence intervals (CIs) were calculated by assuming the total number of patients in the study was 100.*
Clinical examples
Clinical examples
Clinical examples
Clinical examples

Case 3
The diagnostic odds ratio: \[(\text{TP}/\text{FN})/(\text{FP}/\text{TN})\]. 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**
Surveillance after surgical treatment of melanoma: Futility of routine chest radiography


Russell F. Brown, MD, Arnold J. Spector, PhD, Lee J. Haggard, MD, Deborah H. Haskew, MD, SUNY, James S. Lovato, MD, Marshall H. Uretz, MD, Michael J. Edwards, MD, Charles H. Sophocles, MD, MBA, Kevin M. Schievits, MD, PhD, Robert G. Hagan, MD, PhD

Accepted 15 July 2010, published online 30 August 2010.

Abstract
Current recommendations by the National Comprehensive Cancer Network and other groups suggest that follow-up of cutaneous melanoma may include chest radiography (CXR) at 6- to 12-month intervals. The aim of this study was to determine the clinical efficacy of routine CXR for recurrence surveillance in melanoma.

Methods
Post hoc analysis was performed on data from a prospective, randomized, multi-institutional study on melanoma ±1.0 mm in Breslow thickness. All patients underwent excision of the primary melanoma and sentinel node biopsy with completion lymphadenectomy for positive sentinel nodes. Yearly CXR and clinical assessments were obtained during follow-up. Results of routine CXR were compared with clinical disease states over the course of the study.

Results
A total of 1,235 patients were included in the analysis over a median follow-up of 74 months (range, 12–138). Overall, 210 patients (17.0%) had a recurrence, most commonly local or in-transit. Review of CXR results showed that 4,218 CXR were obtained in 1,235 patients either before, or in the absence of, initial recurrence. To date, 88% (n = 3,722) of CXR showed no evidence of recurrence. Of CXR associated with recurrence, 7.7% (n = 38) of surveillance CXR were read as "abnormal." Overall, 99% (n = 4,180) of CXR were read as either "normal" or found to be falsely positive.

Background
Chest radiography (CXR)

Overall, 99% (n = 4,180) of CXR were read as either "normal" or found to be falsely positive.

0.9% (n = 38) of all CXR were TP. Among these 35 revealed widely disseminated disease (multiorgan or bilateral pulmonary metastases); 3 (0.07%) had isolated pulmonary metastases amenable to resection. Sensitivity and specificity for surveillance CXR in detecting initial recurrence were 7.7% and 96.5%, respectively.

Conclusion
The routine use of surveillance CXR provides no clinically useful information in the follow-up of patients with melanoma. CXR does not detect recurrence at levels sufficient to justify its routine use and, therefore, cannot be recommended as part of the standard surveillance regimen for these patients.
Ultraspecific tracers

- Melanin biosynthesis
- Metallopeptide
  (melanocortin type 1 receptors)

Initial experience in γ-emitting radioisotopes has gradually shifted to positron-emitting isotopes due to the requirement of high sensitivity, especially if the completion of SNB is the focus.
Introduction and aim:
18F-MEL050, a melanoma PET probe with high specificity and avidity for melanin. The imaging potential was examined using small-animal PET in a model of murine malignant melanoma.
The authors implanted in the mouse dorsal foot metastatic melanoma cells with a propensity to metastasize in the popliteal lymph node (PLN). After PLN metastasis developed, $^{18}$F-MEL050 was injected either perilesionally or intravenously with a dose that was 15-fold higher in the systemic than in the local route.
Superior melanoma-specific tracer accumulation in metastatic PLNs when the local route was used, with sensitivities of 100% and 60% and node-to-background ratios of 48 and 6.8 for local and systemic administrations, respectively.

Both injection routes were able to detect lung metastases commonly seen in this tumor model.
MK Čiurlionis
Saulės pasveikinimas
1906-8