Skin Cancers
Emerging Trends and Treatment Approaches

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Learning Objectives

- Dysplastic Nevi
- Melanoma
- NMSC
- BCC
- SCC
ABCDE of Melanoma

➢ Assymetry
➢ Border Irregularity
  ➢ irregular, notched or scalloped
➢ Color
➢ Diameter
  ➢ more than 6mm
➢ Enlargement
  ➢ any change in the lesion over a period of time
Dysplastic Nevus

- Clinically defined as atypical mole
- Specific histology criteria
- 3 important features
  - Possible simulants of melanoma
  - Markers for increased risk of melanoma
  - Debate whether they are precursors of melanoma
New term is FAMM (familial atypical mole and melanoma)

Diagnostic criteria:

- The occurrence of malignant melanoma in 1 or more first- or second-degree relatives
- The presence of numerous (often >50) melanocytic nevi, some of which are clinically atypical
- Many of the associated nevi showing certain histologic features
Increased risk of melanoma

- Meta-analysis of 49 studies (Olsen et. al, 2010)
- 1 atypical nevi – relative risk of developing melanoma is 3.63
- 42% of melanomas were found in individuals with >25 common nevi
- High-risk group: >25 common nevi and >1 atypical nevi
Debate about grading by pathologists (mild, moderate, severe)

Practical approach
- Mild – no further excision
- Severe – assume melanoma in-situ and re-excise with 0.5 cm margins
- Moderate – difficult decision, refer to derm
Dysplastic Nevus

➢ Possible simulants of melanoma?
  ➢ YES

➢ Markers for increased risk of melanoma?
  ➢ YES

➢ Debate whether they are precursors of melanoma
  ➢ UNKNOWN, most applicable to severely dysplastic nevi
Potentially Malignant Moles

**Congenital**

Large CMN (>20cm)

**Acquired**

ATYPICAL

**NO URGENCY TO REMOVE SMALL CONGENITAL MOLES IN BABIES!!!**
Excision of all Benign Moles

➢ Not practical
  ➢ Very high expense, resource utilization, morbidity

➢ For 20 y.o. individual, lifetime risk of a regular mole transforming into melanoma by age 80
  ➢ 1 in 1,364 for men
  ➢ 1 in 10,800 for women
Melanoma

➢ Malignant Tumor of Melanocytes (skin pigment cells that make melanin)

➢ Melanoma can occur at the site of preexisting moles,

BUT

Most of the cases arise DE NOVO !!!

➢ Diagnosis usually made after age of 18 years
Important Risk Factors

- Genetics
- Environment – excessive exposure to UV light
- Moles
  - atypical, giant, high number of moles
- Skin Type
- Immunosuppression
  - transplant patients
UVB range (290-320nm)
- New evidence shows UVA-induced damage
- Excess, acute, intermittent UV exposure at any point in life can be a risk factor
- If >5 sunburns, double melanoma risk
2007 Meta-analysis of 19 studies of indoor tanning and melanoma
- Overall relative risk of 1.75
- International Agency for Research on Cancer classified tanning beds as “carcinogenic to humans”

NIH
- Exposure to sunbeds/lamps is known to be human carcinogen
## Melanoma genetics

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected genetic alterations in malignant melanomas</th>
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</thead>
<tbody>
<tr>
<td>Gene type</td>
<td>Gene</td>
</tr>
<tr>
<td>Oncogenes</td>
<td>BRAF</td>
</tr>
<tr>
<td></td>
<td>NRAS</td>
</tr>
<tr>
<td></td>
<td>AKT3</td>
</tr>
<tr>
<td>Tumour suppressors</td>
<td>CDKN2A</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
</tr>
<tr>
<td></td>
<td>APAF-1</td>
</tr>
<tr>
<td></td>
<td>p53</td>
</tr>
<tr>
<td>Others</td>
<td>Cyclin D1</td>
</tr>
<tr>
<td></td>
<td>MITF</td>
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</table>
Types of Melanoma

- Superficial Spreading Melanoma
- Nodular Melanoma
- Lentigo Maligna Melanoma
- Acral Lentiginous Melanoma
- Amelanotic Melanoma
- Ocular Melanoma
- Mucosal Melanoma
Superficial Spreading Melanoma

➢ Most common type
➢ 70% of all melanomas
➢ Diagnosed between ages of 30 and 50
Superficial Spreading Melanoma
Nodular Melanoma

- 2nd Most common type
- 15-30% of all melanomas
- Diagnosed in the 6th decade of life
- Typically blue to black nodules that rapidly enlarge over several months
  - can be ulcerated and bleed
Nodular Melanoma
Lentigo Maligna Melanoma

- Minority of melanomas
- Most frequently – 7th decade
- Most commonly present on the face (especially nose and cheek)
Lentigo Maligna Melanoma
Acral Lentiginous Melanoma

➢ Relatively uncommon
➢ Tends to affect Asians and Blacks
➢ Typically occurs on palms, soles or nail
Acral Lentiginous Melanoma
Acral Lentiginous Melanoma
Amelanotic Melanoma

Diagnostic aids
Dermoscopy

- Non-invasive diagnostic technique for the in vivo observation of pigmented skin lesions
- Allows better visualization of surface and subsurface structures
- Magnification of these various instruments range from 6x to 40x and even up to 100x
Melanoma Workup

- Biopsy suspicious lesion
  - Ideally excisional biopsy, but can use punch biopsy

- H&P

- Complete Skin Exam
# Biopsy Report

## Histopathological Reporting of Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (Breslow depth)</td>
</tr>
<tr>
<td>Mitoses/mm²</td>
</tr>
<tr>
<td>Level of invasion (Clark)</td>
</tr>
<tr>
<td>Regression, tumor infiltrating lymphocytes, presence of plasma cells</td>
</tr>
<tr>
<td>Ulceration</td>
</tr>
<tr>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Microscopic satellites</td>
</tr>
<tr>
<td>Associated nevus</td>
</tr>
<tr>
<td>Margins</td>
</tr>
</tbody>
</table>
Melanoma Workup

- Stages 0 and IA – wide excision
- Any thickness >1mm, ulcerated lesion or high mitotic rate, consider sentinel node biopsy
- CXR (optional)
- LDH (optional)
- Further imaging (CT +/-PET, MRI)
Sentinel node is the 1st site deposition of metastatic cells

- Identified using lymphoscintigraphy and dye injection
- Tc-99 and blue dye injected around primary tumor
- Hand-held gamma counter used
- Hot node is biopsied and examined using H&E stains and immunohistochemistry
  - S-100, HMB45
Conclusions

➢ SNB false negative rate is very low (3.4%)
➢ SNB still an excellent prognosis tool
  ➢ Excellent staging technique
  ➢ If SN negative, 83% disease free survival which provides reassurance to patients
➢ No clear evidence whether completion lymph node dissection is necessary
  ➢ Most likely lead time bias
  ➢ MSLT 2 trial of SN + immediate CLND vs. delayed CLND!
Melanoma treatment

- Melanoma In-situ and LM
  - Localized disease, usually “curable”

- Invasive Melanoma
  - Advanced treatment approaches
MIS / LMM treatment

- Surgery
  - Wide excision (5mm margins)
  - Slow Mohs (rushed permanent section + subsequent stage)
  - Mohs

- Topical
  - Imiquimod (Aldara 5% cream) – Lentigo Maligna

- Radiation Therapy

- Laser Treatment
Excision

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended Clinical Margins</th>
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<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>≤ 1.0 mm</td>
<td>1.0 cm (category 1)</td>
</tr>
<tr>
<td>1.01 - 2 mm</td>
<td>1.2 cm (category 1)</td>
</tr>
<tr>
<td>2.01 - 4 mm</td>
<td>2.0 cm (category 1)</td>
</tr>
<tr>
<td>&gt; 4 mm</td>
<td>2.0 cm</td>
</tr>
</tbody>
</table>

- Margins may be modified to accommodate individual anatomic or cosmetic considerations.
- For in situ melanomas, pathologic confirmation of a negative peripheral margin is important (category 2B).
Mohs

➢ Advantages
  ➢ Complete margin evaluation
  ➢ Tissue conservation
  ➢ Immediate reconstruction vs. staged excision

➢ Disadvantages
  ➢ Difficult to identify malignant melanocytes (DDx. benign melanocytic hyperplasia, pigmented AKs)
  ➢ False positives even when immunostains are used

➢ Slow Mohs
  ➢ Modified staged surgery allows margin control
  ➢ Standard excision, then rushed permanent sections
  ➢ Reduced recurrence rates 0-5%
  ➢ Disadvantages: prolonged opened wound, greater infection risk and formation of early granulation tissue
Topical Imiquimod (Aldara)

- Immune response-modifier
- Acts on Toll-like receptor 7, releases IFN-α and TNF – α
- Off-label, first reported in 2000
- Clearance rates 66-100%
- Alternative treatment
  - Large and/or cosmetically sensitive areas in elderly and poor surgical candidates

Disadvantages
- Optimal treatment regimen not identified
- Concern for recurrence with invasive disease (22% of MIS on initial biopsy have invasive disease)
Non-invasive, destructive treatment option

2nd line treatment

appealing for elderly and poor surgical candidates

Up to 95% clearance rates

Surface doses of 20Gy once weekly for 4-5 weeks

Disadvantages

Poor cosmetic outcome (skin pallor, atrophy, telangiectasia)

Induction of other tumors in the future at radiation site
Several different lasers used for MIS
- Argon, CO$_2$, Q-switched Alex, Q-switched Nd:YAG)
- Claimed short treatment duration, minimal postop care, excellent cosmesis, BUT

Currently **NOT a recommended therapy!**

**Disadvantages**
- High recurrence rates
- Inadequate margin control
- Inadequate laser targeting of tumor
Invasive Melanoma 5yr survival

- AJCC 2009 staging system
- Database of 30,946 patients

- Stages I and II
  - 40-95% survival

- Stage III
  - 40-78% survival

- Stage IV
  - 15-20% survival
Invasive Melanoma treatment

- Surgery
  - Wide excision
  - Mohs
- Immunotherapy
  - Interferon
  - Vaccines
  - Ipilimumab
- Radiation Therapy
- Chemotherapy
  - Dacarbazine (DTIC)
  - Temozolomide (po form, pro-drug of MTIC, the active metabolite of DTIC)
  - High dose IL-2
  - Other drugs including cisplatin, vinblastine, BCNU/fotemustine, taxol/taxotere
- Novel Targeted Agents ***
  - BRAF inhibitors (vemurafenib, dabrafenib)
  - MEK inhibitors (trametinib, cobimetinib)
Melanoma Summary

➢ Early diagnosis is critical
  ➢ Better survival with thinner melanomas
  ➢ New diagnostic tools available

➢ New data regarding genetics of melanoma

➢ New targeted therapies for advanced melanomas
Part 2
Non-Melanoma Skin Cancers

➢ Most common malignancy in humans
  ➢ Most are Basal Cell Carcinomas
  ➢ Up to 25% Squamous Cell Carcinomas

➢ Most are related to UV light exposure
  ➢ BCC - Brief, intermitted UV radiation (eg. holidays)
  ➢ SCC - Cumulative UV radiation
  ➢ Other factors include:
    ➢ ionizing radiation, arsenic or organic chemicals, human papillomavirus infection, immunosuppression and genetic predisposition
Most common skin cancer

- Arise from pluripotential cells within the basal layer
- Mutation in PTCH gene on chromosome 9q, aberrant Hh (Hedgehog) signalling pathway
Basal Cell Carcinoma

- Nodular BCC
- Pigmented BCC
- Superficial BCC
- Infiltrating BCC
- Sclerosing or morpheaform BCC
Nodular BCC
Nodular BCC

- Most common subtype (60% tumors)
- Mainly head and neck, over age 60
- Pearly/translucent, skin-toned pink papule or plaque
  - +/- telangiectasias
  - +/- raised border
- Pigmented BCC especially in darker skin (black to brown)
2nd most common subtype (15% tumors)
Mainly torso, younger patients
Well-defined, pink to red, minimally elevated papules or plaques that commonly have a thin pearly border
DDx: Bowen’s, psoriasis, dermatitis, tinea, lichenoid AK
Sclerosing or Morpheaform BCC

- About 3% of all BCC
- Also known as desmoplastic BCC, fibrosing BCC and scar-like BCC
- Affects head and neck of older individuals
- Indurated, flat to slightly elevated papule or plaque with a white to yellow scar-like appearance
Treatment

- History – duration, rate of growth, prior therapy, fam hx, prior radiation, immunosupression
- Physical exam – palpate the depth, lymph node exam, full skin exam
- Biopsy
  - Shave for shallow therapy (e.g. curettage)
  - Punch from the center – more ideal

BCC General Treatment

➢ Surgical
  ➢ Curettage and electrodessication
  ➢ Cryosurgery with liquid nitrogen
  ➢ Excisional surgery
  ➢ Mohs micrographic surgery

➢ Non-Surgical
  ➢ Imiquimod
  ➢ Photodynamic Therapy (PDT)
  ➢ Interferon-α
  ➢ Radiation Therapy
  ➢ Lasers
Advantages

➢ Works best in nodular or superficial BCC
➢ Cheap
➢ Short (<5 mins)

Disadvantages

➢ Cannot examine tumour margins histologically
➢ Success operator-dependent
➢ Healing by secondary intention -> longer healing + potential for scarring
➢ Not recommended for recurrent, large tumours
Excisional Surgery

➢ Advantages
  ➢ Can examine surgical margins histologically
  ➢ 5 year cure rate 99% for primary BCC and 95% for recurrent BCC
  ➢ Shorter healing time than curettage

➢ Disadvantages
  ➢ More costly
  ➢ Sacrifice normal tissue (minimum 4 mm margins)
Mohs

➢ Gold Standard

➢ Advantages
  ➢ Tissue sparing
  ➢ Allows exam of 100 percent of peripheral and deep surgical margins
  ➢ Lowest 5 year recurrence rate
  ➢ Excellent for recurrent BCC treatment

➢ Disadvantages
  ➢ Very time consuming
Imiquimod 5% cream

- Immune response modifier
- FDA: biopsy-proven, small (<2cm) primary superficial BCC

- Not indicated for
  - Morpheaform
  - Infiltrative
  - Nodular
  - Recurrent BCC
  - Head lesions
Application of tumor-localizing photosensitizing agent and subsequent activation with visible light -> tumor destruction

- 5-aminolevulinic acid (ALA) – Levulan
  - Blue light (410 nm)
  - FDA: hypertrophic AK’s only

- Methylaminolevulinate (MAL) – Metvix
  - Red light (635 nm)
  - FDA: Non-hypertrophic AK’s
Cure rates

- Superficial BCC: 62-91%
- Nodular BCC: 50-92%

Main Disadvantage: high recurrence rate
Advantages

➢ Useful for non-surgical candidates
➢ Difficult to treat locations
➢ Unresectable tumours

Disadvantages

➢ Not recommended for younger than 60 years of age
➢ Cannot examine skin margins
Lasers – Possible future?

➢ CO lasers described in several studies
  ➢ Mid-dermal ablation
  ➢ 51 BCC’s, 100% cure for superficial BCC’s

➢ PDL (595 nm) – Shah et. al, 2009
  ➢ 4 treatments every 2-4 weeks
  ➢ Complete histologic clearance in 11 out of 12 BCCs, 1.5cm or smaller

➢ Long-pulsed Alexandrite laser (755nm) - Wasserman et. al, 2010
  ➢ 3 patients, 4 treatments each, complete clearance
Squamous Cell Carcinoma

- AK
- SCC in situ
- SCC
- Keratoacanthoma
SCC in situ

- Full-thickness intraepidermal carcinoma
- Subtypes
  - Bowen’s Disease
  - Erythroplasia of Queyrat
- Lesions enlarge slowly, over years
- Seldom progression to invasive carcinoma
  - Dermis invasion – 26 %
  - Metastases – up to 16%
Most common head, neck and arms of men
Lesions on sun-exposed sites – better prognosis
Mucosal SCC – greater recurrence and metastases
Oral carcinomas – lower lip in men
  UV exposure, tobacco use, poor oral hygiene, immunosuppression
Verrucous Carcinoma – distinct variant
Keratoacanthoma
SCC Treatment Options

- **Surgical**
  - Curettage and electrodessication
  - Cryosurgery
  - Excisional surgery
  - Mohs micrographic surgery

- **Non-Surgical**
  - Imiquimod
  - Radiation Therapy
Dysplastic Nevi
- Increased risk factors for melanoma
- Don’t necessarily all need to be excised

Melanoma
- Early Diagnosis is Key
- SLN prognostic method
- New targeted therapies

NMSC
- Mohs is the gold standard
- Future therapies, including lasers