Current Treatment of Cutaneous Melanoma

Carlos Corvera, M.D.
Associate Professor of Surgery
UC San Francisco

Topics for Discussion

- What is a sentinel lymph node (SLN)?
- Utility of sentinel lymph biopsies: therapeutic or staging?
- Thin Melanoma and Sentinel Node Dissection
- Groin Mapping Superficial/Deep
- Timing of Sentinel Node Procedure
- What should you do with a positive sentinel lymph node (+) SLN?

Malignant Melanoma

- Brief review of surgical treatment
  - Primary lesion
  - Regional LN’s
  - Clinically (-) / normal LN’s controversial topic
- Microscopic invasion is an important predictor of outcome
- Two systems:
  - Clark’s levels: depth of invasion
  - Breslow’s thickness
- Breslow’s
  - More reproducible/less subjective
  - Tumor thickness conveys more prognostic information

Surgical Treatment

- Lymph Regional nodes:
  - Direct relationship b/w primary tumor thickness, and LN mets
  - LN’s mets are a poor prognostic sign.
- Management: AJCC clinical stage III
  - FNA, or open bx to confirm metastatic melanoma
  - If (+), ---> a complete regional lymph node dissection
- Prognosis: (depends on # of + LN’s found) but is approx. 20%-50%
Clinically Normal Lymph Nodes

- Thin (<1mm) Melanoma:
  - In situ, 0.5 cm margin is enough
  - Low rate of LN involvement (<5%)
  - Wide excision of primary with at least 1-cm margin

- Intermediate (1-4mm) - assoc. 20-25% occult LN metastasis
  - 2cm excision margin, procedure considered outpatient.
  - Trials elective vs therapeutic LN dissection
    - No survival difference.
    - These results argue against elective

- Thick (>4mm)
  - Increased risk of regional metastasis
  - Increased incidence occult systemic at Dx.
  - Exc. With 2 cm margin

Sentinel Lymph Node Biopsy

- Elective Lymph Node Dissection (ELND) standard of care prior to 1990's
- Randomized trials failed to show survival benefit with ELND
- Standard of care drifted towards observation of regional nodal basins

Background

- 1977 Cabanas
  - Lymphatic mapping for penile cancer

- 1992 Morton fine-tuned and developed SLN technique with accurate staging and decreased morbidity

- Continued controversy of “standard of care”

Therapy vs Staging

- Management of early stage Melanoma-controversy. Hypothesis:
  - Primary --> Reg. LN's --> Distant sites

- Delayed LND vs. Elective LND

- SLN approach: Morton et al. 1992
  - 223 pts. ID'ed SLN in 194 pts (82%)
  - A complete LND was performed in all cases
  - Only 2/194 (1%) were mets found in non-SLN’s
**Therapy vs Staging**

- Morton’s results indicate that the SLN histology is representative of the remaining nodal basin.
- Therefore, nodal staging could be completed by SLN bx alone.
- Currently, identification of SLN ~98%

**Lymphatic Mapping**

- Pre-op lymphoscintigraphy
  - Inject 0.5-0.8 mCi
  - Image documents drainage patterns
Locating the Sentinel Node

Recording Ex-vivo Count

Sentinel Node
Recording Background

Wide Local Excision of Primary Lesion

Staging?

- Reviewed effects on tumor thickness, ulceration, Clark level, location, and SLN status on dz-free survival
- 580 pts (95%) successful SLN bx.
  - SLN positive=85 pts (15%)
  - SLN negative=495pts (85%)
- SLN status was the most significant prognostic factor with respect to dz-free and dz-specific survival

Sentinel Lymph Node Status

- Compared with (+)SLN, a (-)SLN was associated with 58.6% and 38.5% increase in DFS and DSS
- The presence of positive SLN is the most important predictor of recurrence and survival.

Gershenwald et al., Journal of Clinical Oncology, Vol 17, No.3 (March), 1999: pp 976-983
Therapeutic?

Essner et. al. - matched paired analysis
534 pts. LM, SL, SCLND vs ELND
- Equivalent 5yr. Rates of dz-free survival and overall survival
- No signif. Difference in recurrence

Conclusion: Sentinel Node is therapeutically equivalent to ELND

MSLT-I

Multicenter Selective Lymphadenectomy Trial

WE + Observation 40%
Node negative Observe
Node positive CLND

16% of pts undergoing SLN had positive node
3.4% of SLN “negative” pts recurred in nodal basin
15.6% in Observation arm had nodal relapse
19.4% total in SLN group vs 15.6% observation
Removing unnecessary microscopic disease w/SLN

MSLT-I

Median follow-up 5 yrs
No overall survival benefit
Disease-free survival better in SLN group
78.3% vs. 73.1% (p=0.009)
Among patients with nodal metastasis*
SLN with CLND 72.3% 5yr overall survival
Observation with CLND at time of clinical disease 52.4% 5yr overall survival
Case #1

- 39 yo male
- Lower extremity melanoma 0.8mm
- Clark level IV
- No ulceration

Wide excision alone? SLN?

Thin Melanoma

- Long-term follow-up of patients with lesions < 1.0mm
- Most do well with wide excision alone
- 3-4% will have recurrence

What factors may predict for SLN positivity
- Breslow depth
- Clark level
- Ulceration
- Mitotic rate > 0
- Age
- Male gender
- Primary tumor site
- Presence of regression

JWCI Experience

- 1732 pts
- Breslow depth < 1.0mm
- Wide excision alone (1cm margin)
- Prognostic variables
  - Breslow depth
  - Clark level
  - Ulceration
  - Primary tumor site
  - Age
  - Sex

Results

Univariate analysis
- Sex p<0.001
- Breslow thickness p<0.001
- Clark level p<0.001
- Age (<50, >50) p=0.08
- Breslow thickness
  - <0.25mm = 0%
  - 0.26-0.50mm = 1.1%
  - 0.51-0.75mm = 4.3%
  - 0.76-0.99mm = 8.5%

Multivariate analysis
- Sex (male nearly 4x higher risk)
- Breslow thickness
- Age (grouped 30, 30-39, 40-49, 50-59, 60-69, >70)
- Risk decreased as age increased
- Nomogram developed based on age, thickness, sex
- Risk varies from 0.1% to 17.4%
High Risk Features

- Ulceration
- Increased mitotic rate
- Angiolymphatic invasion

Patients with thin melanoma with these high risk features should undergo WLE + SLN bx.

Case #1

- 39 yo male
- Lower extremity melanoma 0.8mm
- Clark level IV
- No ulceration

Wide excision alone? SLN?
Nomogram predicts 14%
Sentinel Node Dissection

- Superficial node only
- Superficial node and Deep node
- If Superficial node positive?
  - Extent of completion dissection?

Indications for Pelvic SLN/ Complete Dissection

- Deep SLNB if separate lymphatic channel
- Pelvic dissection if superficial SLN positive?
  - 4 or more positive inguinal nodes identified
  - Gross inguinal disease identified during groin dissection
  - Pelvic nodal metastases identified clinically or radiographically
  - Lymphoscintigraphic drainage into pelvis that was not biopsied during original SLN (case specific)
Case #2

71 yo male with melanoma of Right arm
8.3 mm Breslow Depth
Clark level IV
No ulceration
Mitotic rate = 0
Clinically node negative

Lymphatic Mapping by SPEC

Is there a benefit to SLNB in patients with T4 melanoma?

Sabel et al., Cancer 2009

Single institution review
227 pts with T4 melanoma underwent SLNB
107 (47%) positive
Angiolymphatic invasion and ulceration strongest predictors of nodal involvement
Median f/u 43 months
**SLNB and T4 Melanoma**

- Local regional recurrence rate (LRR) overall 22%
  - SLN- LRR = 11%
  - SLN+ LRR = 34%
- Distant disease-free survival (DDFS) at 5 years
  - SLN- DDFS = 85.3%
  - SLN+ DDFS = 47.8%
- Overall survival (OS)
  - SLN- OS = 80%
  - SLN+ OS = 47%

**CONCLUSIONS**

- Clinically node negative T4 pts should be offered SLNB
- SLN status is the most significant prognostic sign among these patients
- T4 patients with negative SLN in the absence of ulceration have an excellent prognosis and should not be considered candidates for adjuvant Interferon

**SLNB and T4 Melanoma**

- Patients T4 melanoma, SLN+, no ulceration*
  - DDFS = 95%
  - OS = 90%
- Patients T4 SLN-, WITH ULCERATION
  - HR = 5.78 for DDFS

* Most did not receive adjuvant Interferon

**T4 and Beyond!**
Postoperative 8 Weeks

Recurrent Disease 18 months

Advanced Scalp Melanoma
Large Nodal Metastasis

Case Presentation
62 year-old man guard at our Cancer Center.

Noticed enlarging ulcerating mass on the top of his head.

PREOPERATIVE STAGING
In-transit Metastases

- Unfavorable outcomes 5-year survival rates ~ 25-30%

Treatments:
- Excision to clear margin when possible
- Alternative: Isolated Limb Perfusion
- Laser Treatment
- Amputation (rare)

Advanced In-transit Melanoma

Laser Treatment

Recurrent Refractory Melanoma
Stage IV Melanoma

- Metastasectomy: Predictors of Survival
  1. Initial dz stage
  2. DFI after treatment of Melanoma
  3. Initial site of Disease
  4. Extent of Disease: single site vs Multiple
  5. Ability to achieve a complete resection.

- Pre Ipilimumab/ Pre-operative PET
- Postoperative PET
- MIP: Whole body PET
- Axial fusion

Chemotherapy

- Dacarbazine (DTIC) only approved chemo for Melanoma—Marginal benefit with mod side effects.
- Temozolamide compared to DTIC modest benefit.
- Vaccines response rate ~ 2.6 %.
- Immunotherapy: most promising
  - Monoclonal antibody
  - Interferon–based therapy.

BRAF mutations

- 40-60% of cutaneous melanomas carry mutations in BRAF
- 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (BRAFV600E)
- BRAFV600E activates the MAPK-ERK pathway resulting in enhanced proliferative potential
Vemurafenib (PLX4032): Phase I/II study

- 32 patients with BRAF V600E mutation and without previous treatment
- 24 partial response, 2 complete response
- Median progression-free survival > 7 months
- Side effects included arthralgia, rash, nausea, fatigue and SCC.
  - 10 patients had cutaneous SCC (total of 35 carcinomas)
  - 34/35 were keratoacanthoma type
  - Median time to appearance was 8 weeks
  - No other SCC were observed


Ipilimumab (Yervoy) in Treatment of Cancer

- CTLA-4:
  - Down-regulates T-cell activation
- Ipilimumab (Yervoy):
  - Fully human monoclonal antibody
  - Blocks CTLA-4 receptor
  - Potentiates T cell activation

**Ipilimumab: Mechanism of Action**

- **T-cell activation**
- **T-cell inhibition**
- **T-cell potentiation**

**IPILIMUMAB blocks CTLA-4**

**Study 024: Phase III Placebo-Controlled Trial of First-line DTIC ± IPI**

**SCREENING**
- Previously untreated, unresectable Stage III or IV melanoma (N = 502)

**INDUCTION**
- Ipilimumab 10 mg/kg q3w x4
- Placebo q3w x4
- Dacarbazine 850 mg/m² q3w x8
- Dacarbazine 850 mg/m² q8w

**MAINTENANCE**
- Ipilimumab 10 mg/kg q12w
- Placebo q12w

**Study 024: Overall Survival**

- IPI + DTIC vs Placebo + DTIC
- HR 0.72
- p-value <0.001
- Median OS 11.2 vs 9.1 months

**Study 024: Progression-Free Survival**

- IPI + DTIC vs Placebo + DTIC
- HR 0.76
- p-value 0.006
**Study 024: Duration of Response (DoR)**

- **IPI + DTIC** vs **Placebo + DTIC**
- Median DoR 19.3 vs 8.1 months
- *p*-value 0.03

Conclusions

- IPI (10 mg/kg) + DTIC improved overall survival in patients with previously untreated metastatic melanoma compared to DTIC + placebo.
- Durable responses were observed in the IPI + DTIC group compared to the DTIC + placebo group.
- Adverse events observed were consistent with those seen in earlier studies of IPI.

However, rates of the following events differed from the expected based on prior studies:
- Higher rates of elevated ALT and AST
- Lower rates of gastrointestinal events
- No GI perforations

Thank You