Sentinel Lymph Node Dissection and Malignant Melanoma
David G. Hanks, B.Sc., MD, FRCS(C)
Kamloops, BC

Outline
- Background
  - History
  - MSLT-I summary
- Indications
- Community perspective
- Training and certification
- The future

Background - ELND
- 1970's Elective Lymph Node Dissection (ELND) standard of care
- Large randomized trials showed no overall survival benefit to ELND
- 1990's trend towards observation of regional nodes rather than ELND as standard of care

Background - SLND
- 1960 Gould et al
- Parotid cancer
- 1977 Cabanas
- Lymphatic mapping for penile cancer
- Promise of accurate nodal staging with reduced morbidity encouraged the development of SLND by Morton and others

Background - MSLT-I
- Natural evolution to adopt SLND in melanoma with the hope that survival benefit would eventually be proven
- 1992 first published description of SLND for early stage melanoma
- 1994 Morton et al opened the Multicenter Selective Lymphadenectomy Trial (MSLT-I). Results of third in-term analysis recently published

Multicenter Selective Lymphadenectomy Trial (MSLT-I)

References:
Background – MSLT-I

- Median follow up 5 yrs
- No overall survival benefit to early vs. delayed CLND
- Melanoma specific 5 yr survival
  - 90.2% if SLN negative
  - 72.3% if SLN positive

Background – MSLT-I

- Rate of regional metastasis
  - 18.6% in observation arm
  - 19.4% in SLN arm
  - Positive SLN (16%) + FN SLN (3.4%)
- Improved survival in subset of node positive patients for early vs. delayed CLND
- Average number of nodes at CLND significantly higher with delayed vs. immediate

Background – MSLT-I Training

- Prior to trial each center completed 30 training cases and
  each surgeon completed 15 SLND in combination with CLND
- In first 25 cases during trial
  - FN rate = 10%
  - FN rate in subsequent cases during the trial
    - FN rate = 3.4%
  - BUT technique changed during the study
  - AND no mention of FN rate during the training phase

Indications

- Should we be doing SLND in melanoma patients?
- If so which patients?

What is the role of SLND in melanoma?

- Does the available evidence support the sentinel node hypothesis?
- Does the sentinel node accurately predict prognosis?
- Does SLND directed therapy result in improved regional control?
- Does the SLND directed therapy improve survival?
- What is the morbidity of SLND?

Does the available evidence support the sentinel node hypothesis?

- Yes, when there is lymphatic spread it usually occurs in an orderly fashion through the nodal basin
- Current techniques accurately identify the SLN
- 30-50% of cases with positive SLND the SLN is the only site of metastasis
Does the available evidence support the sentinel node hypothesis?

- **MSLT-I**
  - Sentinel nodes detected were clinically significant
  - Rate of regional relapse in observation arm same as combined rates of positive SLN and regional relapse in SLN arm
  - Sidney Melanoma unit cohort (n=946)
  - Observation arm had SLN marked and then followed by exam and U/S
  - Almost all regional relapses occurred in the SLN

7. Thompson, JF. ANZ J. Surg. 2006;76:100-103

Does the sentinel node accurately predict prognosis?

- Lymph node metastases are the single most important prognostic factor in melanoma
- Confirmed in numerous retrospective studies
- AJCC staging revised in 2002 include result of SLND
- **MSLT-I**
  - Significant decrease in overall survival with positive SLN (90.2% vs. 72.3%)

Does SLND result in improved regional control?

- Yes
- Many series show a higher rate of relapse following CLND done for gross disease vs. CLND following positive SLND
- **MSLT-I**
  - 39% N1 in observation arm vs. 70% in SLND arm
  - 26% N3 in observation arm vs. 1.6% in SLND arm
  - Average # of positive nodes on CLND 3.4 in observation arm vs. 1.4 in SLND arm


Does SLND improve survival?

- Possibly
- Some patients with stage III disease will be cured by CLND. But does intervening early improve survival?
- No study has shown overall survival benefit to SLND or therapies directed by SLN
- Several large series have suggested survival benefit to ELND in subset of node positive patients

Does SLND improve survival?

- **MSLT-I**
  - Significant improvement in disease free survival
  - Subset analysis shows improved melanoma specific survival for early (SLND guided) CLND vs. delayed CLND in node positive patients (72.3 vs. 52.4%)
  - Indirect evidence from higher incidence of N3 and lower incidence of N1 disease in observation arm

Multicenter Selective Lymphadenectomy Trial (MSLT-I)

- Immediate SLND (40%)
- Observation (40%)
- Regional nodal CLND
- Node negative: Observe
- Node positive: CLND
What is the Morbidity of SLND

- Lymphoedema 0.66-1.5%
- In transit metastasis
  - MSLT-I no difference between observation and SLN arm
- Allergic reaction to blue dye 0.4%
- Other
  - Wound infection 1%
  - Seroma/hematoma 2.3%
  - Nerve injury 0.23%
  - DVT 0.09%


Current Indications

- Intermediate thickness (1-4 mm)
- Thin lesions (<1 mm)
  - Clarke’s level IV or V
  - Ulceration
    - (mitotic rate, regression)
- Thick lesions (>4 mm)
  - Selected cases with negative staging?
  - Patient factors **

Current Indications

- Thin lesions
  - Low risk
    - < 5% chance of regional nodal metastasis
  - High risk
    - 10% chance of regional metastasis

Current Indications

- Thick lesions
  - > 40% risk of regional metastasis
  - But 60-75% risk of distant metastasis
  - Controversial
  - Individualized approach
  - Identification of subset with regional metastases only
    - Accurate staging
    - ? Role of PET scan

Current Indications

- Thick lesions
  - In one series SLN status very strongly predictive of prognosis
    - 82% vs. 42% 5 yr survival for limb lesions
    - 52% vs. 8% 5 yr survival for lesions on the trunk

Community Perspective

- Same as in larger centers
- New SLN surgeon vs. new SLN service
- Challenges to setting up SLN service
  - Resources and personnel
  - Funding for the probe
  - Training the team
  - Training the surgeon
Melanoma vs. Breast Cancer

- Adopted early as stand alone
- Accuracy accepted
- Attempts to prove survival benefit of CLND
- SLND directed adjuvant therapy less effective

Melanoma vs. Breast Cancer

- Slow to be adopted as stand alone
- Much fuss over FN rate
- Little concern over survival benefit of CLND
- Axillary staging crucial to adjuvant therapy

Training and Certification

- Theoretical ideal is a crossover series for each surgeon
- SLND followed by CLND
- Determination of identification rate and false negative rate
- BUT CLND not currently standard of practice
- Unacceptable morbidity for training purposes
- AND number of cases required to accurately determine FN rate much to high

Training and Certification

To be 95% certain of surgeons with true false negative and nonidentification rates of <5% has these capabilities to within a range of 0-7% would take how many cases? (breast cancer)

750 patients with 300 node positive basins


Training and Certification

- No large studies for melanoma specifically designed to examine the learning curve for SLND
- MSLT-I suggests 55 cases
- Data difficult to interpret due to evolution of technique during study (lymphoscintography)

Training and Certification

- Much more data from Breast Cancer studies
- NSABP-32, ALMANAC
- Large trials comparing outcomes for stand alone SLND vs. ALND
- Both required a prerandomization phase to eliminate negative effects of procedural variations on results


ALMANAC Prerandomization

- Standardized course
- 13 surgeons, each did 40 cases with SLND followed by ALND
**ALMANAC Prerandomization**

- 520 patients (32.5% positive axillae)
- Average of 2 SLN per patient
- Overall FN rate = 5.9%
- Overall ID rate = 96.5% (dye+radioisotope)


**NSABP-32 Prerandomization**

- Standardize technique for surgery, pathology and nuclear medicine
  - Didactic teaching
  - Onsite mentoring
  - Validation series of 5 SLND followed by ALND
- Data collection from and monitoring of Pathologist as rigorous as for surgeons

May 1999 to Feb 2003
- 187 surgeons completed training
  - Up to Nov 1999 - 56/187 successful
  - After Nov 1999 - 131/187 successful
- Success defined as performing the technique according to strict guidelines and adhering to data collection protocols

**Analysis of learning curve data**
- No relationship between position of case on the curve and the chance of FN or non-identification after the first case
- The learning curve was one case?!
Training and Certification

- Process must involve the institution
  - The SLN team
  - Surgeon
  - Pathologist
  - Radiology/Nuclear Medicine
- Surgeons
  - Standardized training course
  - Review of literature
  - Mentored cases (n>5)

The Future of SLND

- Stratify risk of other (non-SLN) nodal disease in setting of positive SLN.
  - Therapeutic SLND?
  - MSLT II
  - Role of PCR (Sunbelt trial)
  - Non-surgical assessment of SLN

Summary

- SLND is an accurate and useful staging technique for melanoma
- Therapeutic benefit to SLND guided CLND
  - Regional control
  - Possible survival benefit?
- Training and certification should involve entire SLN team