

Sentinel Lymph Node Dissection and Malignant Melanoma

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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^{1,2}
- 1990's trend towards observation of regional nodes rather than ELND as standard of care

1. Veronesi, U., et al. N. Eng. J. Med. 1997;297(12):627-630
2. Balch CM, et al. Ann. Surg. 1996;224(3):225-266

Background - SLND

- 1960 Gould et al
 - Parotid cancer
- 1977 Cabanas⁴
 - Lymphatic mapping for penile cancer
- Promise of accurate nodal staging with reduced morbidity encouraged the development of SLND by Morton and others

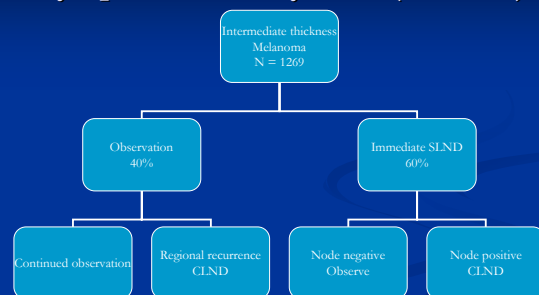
4. Cabanas, RM. Cancer 1997;39:456-466.

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 melanoma⁵
- 1994 Morton et al opened the Multicenter Selective Lymphadenectomy Trial (MSLT-I). Results of third in-term analysis recently published⁶

5. Morton, DL, et al. Arch. Surg. 1992;127(4):392-399
6. Morton, DL, et al. N. Eng. J. Med. 2006;335(13):1307-17

Multicenter Selective Lymphadenectomy Trial (MSLT-I)



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
 - false negative rate 10%
- FN rate in subsequent cases during the trial
 - FN rate = 5%
- 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)⁷
 - 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 SLND⁸
- 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

8. Johnson, TM et al. The role of sentinel lymph node biopsy for melanoma: Evidence assessment. J Am Acad Dermatol 2006;54:19-27

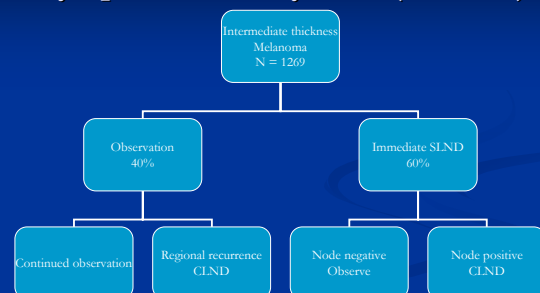
Does SLND improve survival?

- 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 SLND
- Several large series have suggested survival benefit to ELND in subset of node positive patients^{1,2}

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)



What is the Morbidity of SLND

- Lymphoedema 0.66-1.5%⁹
- In transit metastasis
 - MSLT-I no difference between observation and SLN arm
- Allergic reaction to blue dye 0.4%⁹
- Other¹⁰
 - Wound infection 1%
 - Seroma/hematoma 2.3%
 - Nerve injury 0.23%
 - DVT 0.09%

9. Leong, SP et al. Surg Clin North Am, 2003,83:157-185
10. Scheri PS, et al. Anticancer Ther 6(7),1105-1110 (2006)

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
- 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 too 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 basins¹¹

11. PJ Tanis, OE Nieweg, AAM Hart, BBR Kroom, Ann Surg Onc, 2002;9(2):142-147

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 (lymphoscintigraphy)

Training and Certification

- Much more data from Breast Cancer studies
 - NSABP-32¹², ALMANAC¹³
- Large trials comparing outcomes for stand alone SLND vs. ALND
- Both required a prerandomization phase to eliminate negative effects of procedural variations on results

12. Harlow, S.P., Krag, D. N, et al, Ann Surg 2005;241:48-54
13. D Clarke et al., Ann Surg Onc. 2004;11(3):211S-215S

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)

D Clarke et al., Ann Surg Onc. 2004;11(3):2118-2158

ALMANAC Prerandomization

- 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?!

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

NSABP-32 Prerandomization

- 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

NSABP-32 Prerandomization

- Overall
 - Successful in 5 cases 132/187 (70.6%)
 - Successful in > 5 cases 55/187 (29.4%)
- Review after completion of a series of 5 cases
 - 27/56 (48%) successful in ≤ 5 cases
- Review on case by case basis during 5 case series
 - 113/131 (80%) successful in ≤ 5 cases

NSABP-32 Prerandomization

- 819 cases with complete data sets (119 surgeons) used in detailed analysis
 - Overall FN rate = 6.9%
 - Overall Identification rate = 96.2%

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