Melanoma and the management of lymph nodes

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1. ***Does the timing of lymph node dissections alter survival?***

* Does improved staging translates into improved survival? Does early lymphadenectomy for occult metastasis have a survival advantage?

* Halsted: *yes!*

* Fischer, Cady: *no!*

2. ***Is the time span between occult and clinically evident metastatic disease (16 months) really important from a survival point of view?***

3. ***Did the historical Elective Lymph Node Dissections (ELND's) improve survival?***

* Accepted concept was, and still is, that patients with intermediate thickness melanoma (1-4mm) have an increased risk of nodal disease without a high risk of distant disease.

* Yes, ELND did improve survival, but only marginally so:

* WLE (Wide Local Excision) vs. WLE + ELND: DFS at 5 years: 51,3% vs. 61,7% with p= 0,09

4. What is a SLN?

* Sentinel node is the first node that receives lymph from a primary neoplasm.
* Drainage pattern is determined by anatomical site and variations in lymphatic anatomy.
* The discordancy between lymphoscintigraphic and clinically defined nodal basins is 5% for extremity melanoma, 14% for upper extremity melanoma, 25% for truncal melanoma and 48% for head and neck melanoma.

5. ***Which are the drainage sites on the torso?***

* 2 Lines determine the direction of draining in truncal melanomas i.e.
* -Midline anterior and posterior
* -Sappey's line (umbilicus /iliac crest/L2)
* Sydney Melanoma Unit has developed computer programmes with three dimensional maps

6. ***The technique of SLNB?***

* Lymphoscintigraphy and blue dye

* Sites of uptake are marked (on the lymphoscintigram and on the patient's skin). In the operating room 2-4ml of a dye is injected intra-dermally at the biopsy scar.

* To decrease the miss rate, all SLN's with more than 10% of the ex-vivo radioactivity of the "hottest" SLN should be removed.

7. ***How successful is the hunt for (affected) sentinel nodes?***

* Clinical examination is not sensitive.

* Preoperative Ultrasound and FNAC followed by lymphoscintigraphy and SLNB yield a detection rate of 100% for micrometastases.

* The SLN could be identified in 95% of attempted cases.

8. Can we predict if a SLN is going to be positive?

- Statistically significant predictors for positive SLN are:
  - Increasing Breslow thickness:
    - <1mm: 3% SLN +
    - 1-2mm: 13% SLN +
    - 2-3mm: 22% SLN +
    - >4mm: 35-65% SLN +
  - The extent of tumour lymphangiogenesis, ulceration, younger age, absence of regression.

9. ***How is the SLN evaluated for metastatic disease?***

9.1 Intra-operative evaluation
- * Frozen section
- * Imprint cytology
- * RIHC (Rapid Immunohistochemistry)

9.2 A detailed pathologic analysis

9.3 Immunohistochemistry (IHC) for S100

9.4 Recent advances: PCR

10. What is the negative predictive value of SLNB?

If the SLNB is negative or micrometastatic (<0,1mm tumour), the lymph node basin is truly negative in 95% of patients.

12. What is the positive predictive value of SLNB?

If the SLNB is positive, 20% of patients have other positive lymph nodes in the basin. This increases with the diameter of tumour in the SLNB, the density of the dendritic leucocytes in the paracortex as well as with the poor prognostic factors of the primary.

13. *After the SLN has been identified and analysed, should a Completion Lymph Node Dissection (CLND) be performed?*

* If the SLN is positive: yes. But patients with very limited tumour burden in the SLN (<0.1mm) are probably unlikely to benefit from a CLND.
* If the SLN is negative or technically inconclusive: perhaps not But poor prognostic factors of the primary such as tumour thickness, ulceration, angiolymphatic invasion and mitotic index might influence this decision.

14. Any false negative SLN's?

* The risk of nodal recurrence after a negative SLNB is <5%

* Nodes obliterated by tumour may not take up blue dye or radioisotope

15. Any false positive SLN's?

IHC may inadvertently report false positive SLNB due to phagocytic cells containing melanocyte antigens

16. More than one sentinel node?

* More than one sentinel node is almost the rule: average number of SLN's per basin is 1,8.

* More than one basin: patients with a melanoma around the waist will have a 17,7% probability of dual drainage to the axilla and groin.

17. Is there an oncological down side to lymph node dissection?

* Regional immunity is probably affected.

18. What is the prognostic value of negative SLN's in terms of DFS?

* 5 Year DFS survival in thin melanomas and negative SLNB's: 85,3%

* 5 Year DFS survival in thick (4mm) melanomas and negative SLNB's: 47%

19. What is the prognostic value of positive SLN's in terms of DFS?

* Three histopathological parameters of positive SLNB's predict a poor prognosis: tumour burden, tumour penetrative depth >2mm and infiltration of the SLN capsule.

20. Possible contra-indications for SLNB?

19.1 Where previous surgery (e.g. skin flaps) has resulted in disruptions of the lymphatic vessels.

19.2 A melanoma thickness of less than 1mm without additional risk factors such as a previous shave biopsy, angiogenesis etc.

19.3 Desmoplastic melanoma. Unconfirmed studies show a 1-2% incidence of positive SLNB's even in thick desmoplastic melanomas.

21. The million dollar question: Does the timing of lymphadenectomy impact on survival? Is there a survival benefit in early lymphadenectomy (SLNB +/ - CLND) versus ThLND (wait and see)?

* YES, but a qualified yes.

* A meta-analysis of 6 studies (n=2633) indicated that there is a significant lower risk of death for patients who underwent SLNB+/-CLND compared to patients who underwent ThLND (CI 1.28-2.00; P< 0001). The median survival was 119 months for the SLNB+/-CLND group vs. 62 months for the ThLND group.

* The qualified yes is because these 6 studies were (published) retrospective series and not RCT,s.