Article is available online at http://www.webio.hu/por/2003/9/3/0184

ARTICLE

Clinical Significance of Sentinel Lymph Node Involvement in Malignant Melanoma

Gabriella LISZKAY, Gábor PÉLEY, István SINKOVICS, Ilona PÉTER, Zsolt OROSZ, Zsuzsa FEJÔS, Béla HORVÁTH, István KÖVES, Katalin GILDE, Miklós KÁSLER

National Institute of Oncology, Budapest, Hungary

In the period 1997–2002, sentinel lymph node (SLN) surgery was performed on 179 primary skin melanoma patients, one to two months after the removal of the primary. Staining with patent blue was combined with an isotope technique. Histological evaluation of the sentinel lymph nodes was performed in serial sections. Immunohistochemical detection of S100, HMB-45, or Melan-A was used in the case of suspected micrometastases. Demonstration of positive sentinel lymph node was followed, preferably within 2-3 weeks, by regional block dissection. In these cases interferon-α2 in low doses or BCG immune therapy were applied as adjuvant therapy. Bimonthly follow-up of the patients included physical examination and the use of imaging techniques as specified in the melanoma protocol. Sentinel lymph node surgery was successful in 177/179 cases (98%). Positive sentinel lymph node was identified in 26/177 patients (14.7%). In node positive patients the thickness of the primary tumour was significantly greater than that of node negative ones (p<0.00001). Patients with micrometastases had significantly poorer symptom-free and overall survival by the Mantel-Cox test than those of the other group (p=0.0001 and p=0.0007 respectively). Comparison of the tumor thickness and positive SLN by discriminance analysis, yielded 81.7% and 79.9%, respectively for correct classification rates. Based on our study and data from the literature, we suggest SLN-positivity as equally strong poor prognosis factor for skin melanoma as the tumor thickness. (Pathology Oncology Research Vol 9, No 3, 184–187)

Keywords: sentinel lymph node, melanoma, prognosis, tumor thickness

Introduction

Involvement of regional lymph nodes is one of the most significant prognostic factor in malignant melanoma affecting the selection of the therapy.[6,9,10] The sentinel lymph node (SLN) biopsy is a minimally invasive method that helps to evaluate the status of the lymph node region of the primary tumor. Its principles were described by Cabanas in penis carcinoma[5] and the patent blue technique for its clinical use in malignant melanoma was worked out by Morton somewhat later, in the 90's.[12] With the advent of this methodology the decade long dispute about elective block dissection could finally be settled. The application of radioisotopes[2] raised the diagnostic accuracy from 85-90% to 95-99%.[1,12,13] Pathological analysis of the SLN specimen raised several new questions regarding the definition of tumor metastasis, but the accepted guideline defines it as a tissue of the size equal or larger than 2 mm.[3,19] This recommendation does not accept smaller sized metastasis to affect clinical decisions. Here we have analysed the clinical and prognostic significance of SLN surgery in a large group of skin melanoma patients followed for 5 years.

Received: August 15, 2003; *accepted:* Sept 15, 2003

Correspondence: Gabriella LISZKAY MD, Department of Dermatology, National Institute of Oncology, Ráth György u. 7-9., 1122 Budapest, Hungary. Phone: 36 1 224 8600, fax: 36 1 224 8620, E-mail: liszkay@oncol.hu

Patients and Methods

We have performed SLN surgery on 179 patients treated at the Department of Dermatology, National Institute of Oncology, Budapest during the period from November 1997 to September 2002. Most of the primary malignant melanomas of the skin represented moderate to high risk for dissemination and the rest were thin melanomas show-

Table 1. Clinicopathological characterisitics of malignant melanoma with and without sentinel node involvement

	Number of patients	*M*	*F*	*Age (year)*		
SLN–	151	85	66	52		
SLN+	26	13	13	54		
Localization (%)	Lower extr	Upper extr	Trunk	other		
SLN–	55	31	64	1		
SLN+	13	1	12	0		
Breslow (mm)	<1.0	1.01-2.00	2.01-4.0	>4.0	nd	
SLN–	36	59	27	13	16	
SLN+	1	6	11	8	0	
Clark stage	I	II	III	IV	V	nd
SLN–	9	25	49	63	1	4
SLN+	0	0	7	11	7	1
Histology	SSM	NM	ALM	nd		
SLN–	84	40	4	23		
SLN+	10	9	6	1		

ing signs of spontaneous regression. The sentinel lymph node surgery was combined with wide excision (1-2 cm margins) of the primary malignancy. Patients who had been operated in an other institution underwent SLN biopsy 1-2 months after primary tumour excision. The clinical details of the patients and the pathological characteristics of their tumours are summarised in *Table 1*.

The SLN biopsy was carried out with the double labelling (99mTc –human colloid serum albumin and patent blue) method combined with dynamic lymphoscintigraphy. Surgery was conducted under general anaesthesia and in a few cases under local anaesthesia. The histological evaluation of the sentinel lymph nodes was performed on serial sections according to ADASP recommendations.[3,19] Micrometastasis equal or larger than 2 mm was determined. Smaller sized groups of tumor cells were reported but not considered metastatic SLN. For the immunohistochemical detection of melanoma cells S-100, HMB-45, Melan-A was used in the case of suspected micrometastases. Diagnosis of positive SLN was followed by regional block dissection within a week.

Patients with melanoma of >1 mm thickness or those showing signs of regression were given low dose interferon-α2 (3-5 ME, 3 times a week) or BCG therapy, at a 6 weekly basis. In harmony with our melanoma protocol patients were regularly tested by physical and imaging examinations (chest X-ray, abdominal ultrasonography and bone scan, CT and MRI, when needed).

Data have been analysed by F-test, the Mantel-Cox regression model and by discrimination analysis.

Results

SLN surgery was successful in 177/179 cases (98%). The failures (2 cases) occured in the learning phase. Complications subsequent to the SLN surgery included: development of seroma (30%) and patent blue pigmentation (20%), one patient reacted with an anaphylactic shock to the injection of the patent blue dye.

Presence of metastasis in the sentinel lymph node was verified in 26 cases (14.7%). In two patients the subsegment block dissection was proved to be positive (7.6%). The clinical and pathological sentinel node negative and positive patient's characteristics are given in *Table 1*. Data indicate that SLN positive melanoma occurred more frequently on the lower extremities and are more frequently of the acrolentiginous type. Histological signs of spontaneous regression were noted in 46 cases (25.9%). However, only in 1/26 sentinel node positive patient was found to have a regressing primary tumor (3.8%).

The follow up period ranged from 1-59 months (mean 22,1). In 18/151 sentinel node negative patients progression developed (11.9%). Lymph node recurrence in the SLN region was detected in 4 cases (false negative ratio: 4/30 =13.3%). Three patients developed local and in-transit metastasis (3/151 = 1,9%), while hematogenic metastasis was found in 11 patients (11/151 = 7,3%).

In the SLN positive group 11/26 (42.3%) patients experienced progression. Lymph nodes beyond the SLN region were found to be positive in one patient and in transit metastasis in another. Hematogenic dissemination was demonstrated in 8/26 patients (30.8%).

In the group of SLN negative patients the average tumor thickness was 1,9 mm in contrast to the 4,1 mm thickness with the node positive patients (F-test, $p<0,00001$). The average tumor thickness in patients showing SLN negativity and tumor progression (3.3 mm) was smaller compared the tumors where SLN was positive (6.0 mm, $p=0,057$, F-test). Finally, the thickness of the primary tumors in SLN positive patients without progression was significantly smaller (3.0 mm) compared to progressing tumors (6.0 mm, $p<0.01$, F-test).

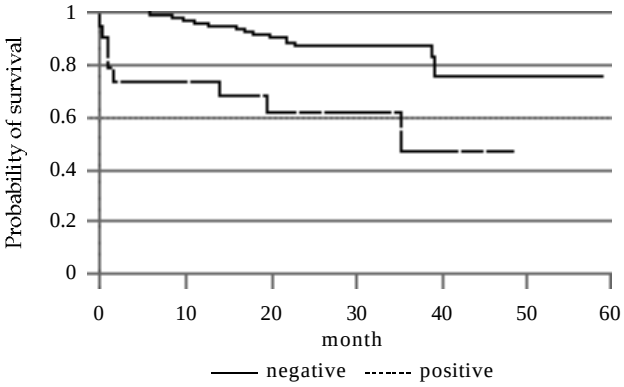

Figure 1. Disease-free survival of melanoma patients following sentinel lymph node (SLN) surgery. thick lane: SLN metastasis negative patients, thin lane: SLN metastasis positive patients

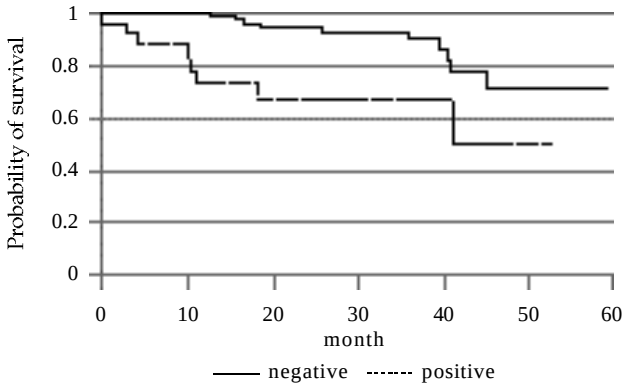

Figure 2. Overall survival of melanoma patients following sentinel lymph node (SLN) surgery. thick lane: SLN metastasis negative patients, thin lane: SLN metastasis positive patients

The disease-free (DFS) and overall survival (OS) rates of the sentinel node negative and positive patients were calculated by the method of Kaplan-Meier (*Figures, 1,2*, respectively). For each parameter the Mantel-Cox model disclosed significant difference in favour of the sentinel node negative patients (p=0,0001 and p=0,0007, respectively).

Last, we have compared the predictive value of the Breslow thickness to the SLN positivity for OS by discriminance analysis. These studies indicated that both factors have a comparably high poor prognosis predictive value for OS in case of skin melanoma (Breslow=81.7%, SLN+=79.9%).

Discussion

Although the clinical benefit of sentinel lymph node dissection is still a controversial matter to some authors,[6] the fact, that the sentinel lymph node status has become an integral part of the new melanoma staging and has ben introduced into the clinical practice of surgical management of malignant melanoma.[4] In the National Institute of Oncology we have been performing sentinel lymph node biopsy for 5 years.[8] The method has proved in our handsto have 98% diagnostic accuracy. Sentinel lymph node positivity in skin melanoma was found in 14.7% of the patients. Both rates are in harmony with literature data which state that the ratio of sentinel lymph node positive patients may range from 10 to 40%.[6,15,16]

At present, the sentinel lymph node status is considered the most important prognostic factor in melanoma. Analysis of the clinical data of 4218 patients who had undergone sentinel lymph node surgery demonstrated that the most essential predictor of sentinel lymph node positivity was the thickness of the primary tumour.[7] In this respect melanomas showing signs of spontaneous regression may be exceptions even though the prognostic significance of regression characteristics is rather controversial. We have to mention however, that it is the sentinel lymph node examination that may yield useful information about the biological significance of the regression features.[11]

Our own observations are also in line with the statement that the primary tumors of the SLN positive patients are significantly thicker than those of the SLN negative ones. On the other hand, thickness of the primary tumor is still a strong indicator for tumor progression, since the SLN positive patients whose tumor progressed showed significantly greater thickness than those without dissemination.

In our patient group regression signs were identified only in one of the SLN positive patients. However, we think that because of the rather uncertain clinical course of thin, regressing tumours, SLN surgery does represent an important source of information from the point of view of clinical staging.

The disease-free and overall survival rates of the SLN positive patients were significantly poorer compared to SLN negative ones. The question arises whether all patients benefit from early block dissection. Some authors suggest that one should make the intervention depending on the extent of the involvement of lymph nodes. Based on our own results we support this notion.[6,8]

There is an ongoing debate on the relative value of the Breslow thickness and SLN positivity in the prediction of disease outcome in melanoma. The discriminance analysis of our data found no significant differences between the two parameters indicating that both factors should be included in the prediction of the outcome of the disease.

Based on own experience and internationally accepted guidelines[4] as well as recommendations of the Hungarian Consensus Conference on Melanoma we recommend the sentinel lymph node surgery in all cases of primary malignant melanoma except those of absolute good prognosis, i.e. <1 mm thick, not ulcerated, does not show signs of regression and depth of invasion <Clark level III. In such cases surgery seems unnecessary. Furthermore,

in cases of ulcerated, >4 mm thick tumours, it is not worth performing SLN biopsy either because prognosis is very poor, independent of the result of the intervention.

Acknowledgement

Authors are indebted to Dr. István Gaudi for the performance of the mathematical analyses.

References

1. *Alazraki MT, Eshima LA:* Lymphoscintigraphy, the sentinel node concept, and the intraoperative gamma probe in melanoma, breast cancer, and other potential cancers. Semin Nucl Med 27: 55-67, 1997
2. *Alex JC, Krag DN:* Gamma-probe-guided localization of lymph nodes. Surg Oncol 2: 137-147, 1993
3. Association od Directors of Anatomic and Surgical Pathology. ADASP recommendations for processing and reporting lymph node specimens submitted for evaluation of metastatic disease. Am J Surg Pathol 25: 961-963, 2001
4. *Buzaid AC, Balch CM:* Proposed change of TNM classification. Mel Res 11 Suppl: S4-S5, 2001
5. *Cabanas RM:* An approach for the treatment of penile cancer. Cancer 39: 456-466, 1977
6. *Coldiron MB:* Sentinel node biopsy: who needs it? Int J of Dermatol 39: 807-811, 2000
7. *Kirkwood JM, Hunt Strawdwrman M, Ernstoff MS, et al*. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 14:7-17, 1996
8. *Krag DN, Meijer SJ, Weaver DL, et al:* Minimal access surgery for staging of malignant melanoma. Arch Surg 130: 654-658, 1995
9. *Lens MB, Dawes M, Newton-Bishop JA:* Tumour thickness as a predictor of occult lymph node metastases in patients with stage I and II melanoma undergoing sentinel lymph node biopsy. Br J Surg 89:1223-1227, 2002
10. *Liszkay G, Péley G, Farkas E, et al.* Sentinel node biopsy for melanoma in 103 patients. Early follow-up study. EJSO 28: 357, 2002
11. *Moore MP, Kinne DW.* Axillary lymphadenectomy: A diagnostic and therapeutic procedure. J Surg Oncol 66: 2-6, 1997
12. *Morton DL, Wen DR, Wong JH, et al*. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 127: 392-399, 1992
13. *Reintgen D, Balch CM, Kirkwood J, et al*. Recent advances in the care of the patient with malignant melanoma. Ann Surg 225: 1-14, 1997
14. *Ronan GS, Eng MA, Briele AH, et al.* Thin malignant melanomas with regression and metastases. Arch Dermatol 123: 1326-1330, 1987
15. *Ross MI.* Surgical management of stage I and II melanoma patients: approach to the regional lymph node basin. Semin Surg Oncol 12: 394-401, 1996
16. *Ross MI, Reintgen D, Balch Ch:* Selective lymphadenectomy: Emerging role of lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. Semin Surg Oncol 9: 219-223, 1993
17. *Starz H, Gerstel C, Bachter D, et al:* Two simple morphometric parameters permit a clinically relevant staging of the sentinel node metastases in malignant melanoma and merkel cell carcinoma. Eur J Nucl Med 26 (Suppl): S68, 1988
18. *Taylor A, Murray D, Herda S, et al.* Dynamic lymphoscintigraphy to identify the sentinel and satellite nodes. Clin Nucl Med 21: 755-758, 1996
19. *Tímár J, Csuka O, Orosz Z et al:* Molecular pathology of tumor metastasis. II. Molecular staging and differential diagnosis. Pathol Oncol Res 8: 204-219, 2002