NOWOTWORY Journal of Oncology • 2004 • volume 54
Number 4 • 363–366

The prognosis after lymphadenectomy for stage III melanoma metastatic to inguinal nodes

Krzysztof Herman, Andrzej L. Komorowski, Wojciech M. Wysocki

Introduction. The aim of this study was to identify the prognostic factors affecting the outcome of melanoma patients after inguinal lymphadenectomy.
Material and methods. We analysed 96 patients with melanoma of the lower extremity and its nodal metastases treated between the years 1988 and 2000.
Results. Patient staging: 2 pts. – IIIA; 19 pts. – IIIB; 75 pts. – IIIC. Ulceration of primary lesion – 47 pts (49%). Estimated overall survival rates (OS): 50.7% at 2 yrs and 16.8% at 5 yrs. In case of pts with nodal metastases operated less than 12 months from initial treatment the 2 and 5-year survival rates were 43.5% and 9.7%, respectively, and in patients with nodal involvement detected over12 months after initial surgery – 66.1% and 32.4%, respectively (p=0.002). Multivariate Cox's analysis of independent factors pointed at a rapid nodal metastases (p=0.009), involvement of deep nodes (p=0.015) and ulceration of primary site (p=0.049) as unfavourable parameters influencing prognosis.
Conclusions. Although in stage III melanoma of the lower extremity prognosis is poor, ilioinguinal lymphadenectomy may be beneficial. Unfavourable factors affecting survival include ulceration of primary site, deep node involvement and inguinal metastases discernible less than 12 months after primary treatment.

Rokowanie u chorych na czerniaka z przerzutami do węzłów chłonnych pachwinowych (III) poddanych wycięciu węzłów chłonnych

Wprowadzenie. Celem pracy jest ocena czynników prognostycznych u chorych na czerniaka skóry kończyn dolnych, po wycięciu pachwinowego układu chłonnego.
Materiał i metodyka. Przeanalizowano dane dotyczące 96 chorych na czerniaka skóry kończyn dolnych z przerzutami do regionalnych węzłów chłonnych, leczonych w okresie od 1988 r. do 2000 r.
Wyniki. Stwierdzono w zaawansowaniu IIIA – 2 chorych, IIIB – 19 chorych i IIIC – 75 chorych. U 47 chorych (49%) stwierdzono owrzodzenie zmiany pierwotnej w obrębie kończyny. Całkowity odsetek przeżyć dwuletnich wyniósł 50,7%, przeżyć pięcioletnich 16,8%. Wśród chorych operowanych z powodu przerzutów do węzłów chłonnych w okresie poniżej 12 miesięcy od wycięcia zmiany pierwotnej przeżycia dwuletnie wyniosły 43,5%, a przeżycia pięcioletnie 9,7%. W grupie operowanych w czasie powyżej 12 miesięcy od wycięcia zmiany pierwotnej przeżycia dwuletnie wyniosły 66,1%, natomiast pięcioletnie 32,4% (p=0,002). W wieloczynnikowej analizie Coxa niezależnymi niekorzystnymi czynnikami rokowniczymi były: krótki czas do stwierdzenia przerzutów w węzłach chłonnych (p=0,009), zajęcie węzłów chłonnych biodrowych (p=0,015) i owrzodzenie zmiany pierwotnej (p=0,049).
Wnioski. Rokowanie dla chorych na czerniaka skóry kończyn dolnych z przerzutami do węzłów chłonnych jest poważne, jednak wycięcie węzłów chłonnych pachwinowych i biodrowych może znacznie poprawiać rokowanie. Owrzodzenie zmiany pierwotnej, zajęcie przez przerzuty węzłów chłonnych biodrowych oraz stwierdzenie przerzutów w węzłach chłonnych wcześniej niż 12 miesięcy od wycięcia zmiany pierwotnej były niekorzystnymi czynnikami prognostycznymi.

Key words: melanoma, lymphadenectomy, inguinal lymph node metastases
Słowa kluczowe: czerniak, wycięcie węzłów chłonnych, przerzuty do węzłów pachwinowych

Introduction

The occurrence of metastases within inguinal lymphnodes in patients with malignant melanoma of the lower extremity is an important prognostic factor for the course of the disease. The extent of surgical excision of the lymphatic basin in this area (superficial versus superficial

Department of Surgical Oncology
Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Kraków Branch, Poland

and deep) is not well established. Elective lymphadenectomy is no longer performed in patients with melanoma of the lower limb. Most surgeons advocate *en bloc* excision of both the superficial and deep inguinal lymphnodes after confirming the presence of nodal metastases. It must be kept in mind that deep inguinal lymphadenctomy is associated with significant rise in morbidity and therefore some centres limit surgery to superficial inguinal lymphadenectomy. At the same time attempts are made to define factors influencing the appearance of deep inguinal metastases.

The aim of the current study was to assess the prognostic factors affecting patients with melanoma of the lower extremity and metastases to the superficial and/or deep inguinal lymphnodes (stage III, AJCC/UICC 2002).

Material and methods

We analysed the cases of 112 patients with primary malignant melanoma of the lower limb and metastases to superficial and/or deep inguinal lymphnodes verified by aspiration cytology operated between 1985 and 2000 in the Department of Surgical Oncology of the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in Kraków, Poland. Sixteen patients were excluded from analysis due to non-cancer related death, insufficient data on primary melanoma site or loss from follow-up, i.e. the final retrospective analysis was performed on 96 patients.

Statistical analysis was performed with the aid of the Statistica PL 5,1G (Statsoft Polska, Kraków, Poland).

Results

In 78% of patients the primary site of malignant melanoma was within the foot or the lower leg. The primary lesion was excised in the Department of Surgical Oncology in 54% of patients. The excisions were performed with clear surgical margins of at least 15 mm. Table I presents the data concerning the primary found in our patients.

In 21 patients (22%) metastases to the inguinal lymphnodes were diagnosed synchronously with the primary site. In this group the excision of primary lesion and inguinal lymphadenectomy was performed synchronously. In 50 patients (52%) inguinal lymphadenectomy was performed within 12 months after the excision of primary site. In the remaining 25 patients (26%) selective lymphadenectomy was performed more than 12 months after the excision of the primary site.

Mean age at the lymphadenectomy procedure was 53.3 years (22-85). Table II presents basic demographic data of the analysed group.

Table I. Characteristics of the primary tumour

Primary site of melanoma (%)	
Foot	37 (38)
lower leg	38 (40)
thight	21 (22)
diameter, mm, mean (range)	25 (5-98)
clear margins, mm, mean (range)	15 (0-40)
ulceration (%)	47 (49)
Breslow scale, mm, mean (range)	6.5 (1-30)
Clark stage (%)	
I	1 (1)
II	4 (4)
III	20 (21)
IV	34 (36)
V	21 (22)
n/a	16 (17)

n/a – data non-available

Table II. Basic characteristics of the analysed group (n = 96)

Age, mean (range)	53 (22-85)
women (%)	71 (74)
stage TNM-UICC 2002	
IIIA	2 (2%)
IIIB	19 (20%)
IIIC	75 (78%)

The mean number of the excised superficial inguinal lymphnodes was 7 (2-20). The mean number of metastatic superficial inguinal lymphnodes was 3 (0-7). The mean number of the excised deep inguinal lymphnodes was 4 (1-12). The mean number of metastatic deep inguinal lymphnodes was 2 (0-7).

Metastatic superficial inguinal lymphnodes were present in 89 patients (93%). Deep inguinal lymphnodes contained metastases in 46 patients (49%). Histological examination did not reveal involvement of superficial nodes in 7 of these patients.

The Kaplan-Meier estimation of survival was 50.7% at 2 years and 16.8% at 5 years. In the subgroup of patients undergoing inguinal lymphadenectomy within first 12 months after primary site excision estimation of survival was 43.5% at 2 years and 9.7% at 5 years. In the group undergoing inguinal lymphadenectomy 12 months after the primary site excision survival was estimated at 66.1% ate 2 years and 32.4% at 5 years (Figure 1).

Multivariate Cox's analysis has suggested that a short time lapse between the primary site excision and lymphadenectomy (p=0.009), the involvement of deep inguinal lymphnodes (p=0.015) and ulceration of the

Table III. Cox's multivariate analysis of independent factors influencing survival

Factor	Relative risk	P-value
time between primary excision and lymphadenectomy, years	2.53	0.0009
deep nodes involved	2.79	0.015
ulceration of primary site	1.69	0.049

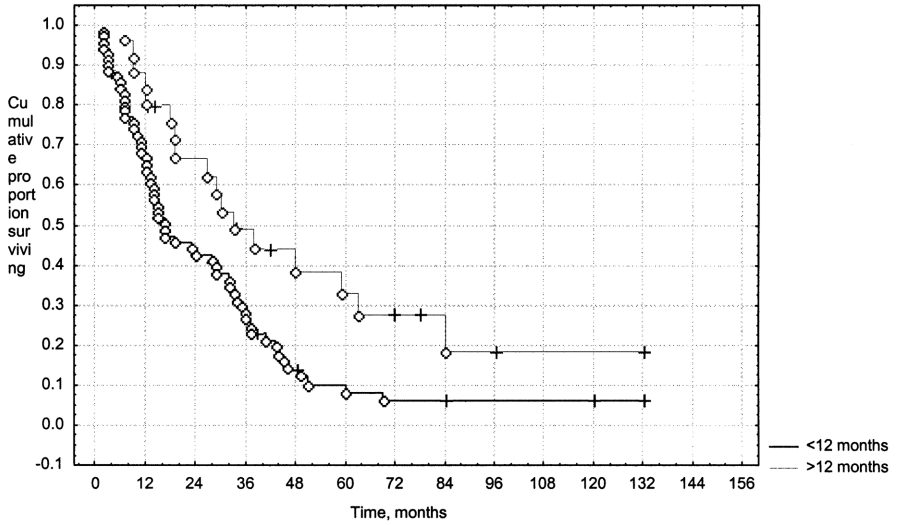

Figure 1. Kaplan-Meier estimation of survival of patients undergoing lymphadenectomy within 12 months after primary site excision and more than 2 months after primary surgery for melanoma

primary site (p=0.049) are unfavourable factors for survival (Table III).

Discussion

Superficial and deep inguinal lymphnodes are considered to be the regional lymphatic basin for malignant melanoma of the lower extremity. Metastases found in this area are determinants of stage III melanoma according to the AJCC/UICC staging system. The treatment of choice for these patients is primary site excision with wide surgical margins and *en bloc* excision of deep and superficial inguinal lymphnodes. Despite such aggressive surgical treatment the prognosis for this subset of melanoma patients is poor. According to different authors, the 5 years survival rates vary between 20% and 40% [1, 2]. The most important factors influencing survival are: the number of involved inguinal lymphnodes, extracapsular infiltration and diameter of the biggest metastatic inguinal lymphnode.

In the presented group, one of the factors influencing survival was the length of the disease free interval between excision of the primary lesion and inguinal lymphadenectomy. The prognosis was worse for patients with metastases found within inguinal lymphnode basin no later than 12 months after excision of the primary lesion. This observation is in concordance with data presented by Hughes [3]. Hughes noticed that short disease free interval negatively influenced risk for dissemination, but did not reach statistical significance in terms of overall survival.

The observed influence of the ulceration of the primary lesion on the long-term survival of patients with lymphnode metastases is an interesting finding. Mann has observed a similar phenomenon [4]. The determination of the clinical course of the disease in patients with involvement of inguinal lymphnodes acc. to the primary site characteristics has already been mentioned in several studies. Buzaid [5], Strobbe [6] and White [7] report that the thickness of infiltration according to Breslow influences survival. In a large meta-analysis of almost 16000 melanoma patients Balch found tumour thickness and ulceration to be among the most important prognostic factors [8]. In our study it was the ulceration of the primary site on the lower limb that negatively correlated with survival. On the other hand, ulceration of the primary site was not found to be statistically significant in the studies by Strobbe [6] and Kretschmer [9].

There is an ongoing debate concerning the extent of dissection in patients with melanoma involvement of the inguinal lymphnodes. This aggressive surgical approach was also a standard treatment in our department. The opponents of this approach stress the significant increase in morbidity after superficial and deep inguinal lymphadenectomy when compared to superficial lymphadenectomy only. The main complications after deep lymphadenectomy include healing impairment and increased lymphoedema formation in the lower extremity [10]. In order to avoid these complications some authors are trying to identify the factors allowing to identify the subset of patients with a high risk of developing deep inguinal lymphnode involvement. The status of the superficial inguinal lymphnodes may suggest the status of deep inguinal nodes. Among these predictive factors Mann [4] points out: >3 involved nodes and diameter of the biggest involved node >3 cm. Strobbe, in a recent work, [11] examined the status of the Cloquet node as a predictor of deep nodal status, but it was shown not to be an efficient predicting tool. In conclusion Strobbe has suggested performing deep lymphadenectomy in every patient with positive inguinal nodes [11].

On the other hand a study presented by Hughes [3] suggests, that deep inguinal lymphnodes dissection can be performed with a relatively low complication rate. In this study there was no statistical difference between the complication rate after superficial lymphadenectomy as compared with deep and superficial lymphadenectomy [3]. Also a recent study by Lawton shows that by using

a technique of preserving the muscle fascia the rate of lymphoedemas after deep node dissection can be significantly limited without increasing the recurrence risk [12]. If these results are confirmed it would suggest superficial and deep lymphadenectomy to be of the greatest value in patients with superficial lymph node involvement.

In our study group the involvement of deep inguinal lymphnodes was associated with poorer prognosis. It is of particular interest that Mann [4] and Hughes [3] did not find the involvement of deep inguinal lymphnodes to be an important factor influencing survival. Basing on this data, both they and Balch [13] advocate an aggressive surgical approach in patients with clinical or radiological suspicion of the deep inguinal lymphnode involvement. This aggressive approach allows to obtain a 5-year survival at 25-35%. The extent of surgery in patients with no signs of deep inguinal lymphnode involvement still remains arbitrary. This is caused by the lack of an efficient tool to identify patients with the highest potential benefit from superficial and deep lymphnodes excision [4]. Assuming this to be true, the authors of the present report support the aggressive surgical approach in patients without deep lymphnode involvement.

The other issue concerning the attempts at omitting deep lymphnode dissection is the problem of "skip metastases". In our material we had found 7 patients with deep inguinal lymphnode involvement without metasteses in superficial inguinal lymphnodes. The frequency of this phenomenon is estimated at 2-10% [6]. This situation is caused either by the existence of non-typical lymphatic drainage omitting the superficial inguinal lymphnodes, or by the presence of micrometastases within superficial nodes overlooked during routine pathological examination [6].

In order to achieve a unified surgical approach for patients with metastases within superficial inguinal lymphnodes, multicentered randomized trials are necessary.

Andrzej Komorowski MD
Department of Surgical Oncology
Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Kraków Branch, Poland
ul. Garncarska 11
31-115 Kraków, Poland
alkomorowski@wp.pl

References

1. Coit DG, Rogatko A, Brennan MF. Prognostic factors in patients with melanoma metastatic to axillary or inguinal lymph nodes. A multivariate analysis. *Ann Surg* 1991; 214: 627-36.
2. Buzaid AC, Ross MI, Balch CM et al. Critical analysis of the current American Joint Comitee on Cancer staging system for cutaneous melanoma and proposal of a new staging system. *J Clin Oncol* 1997; 15: 1039-51.
3. Hughes TMD, A'Hern RP, Thomas JM. Prognosis and surgical management of patients with palpable inguinal lymph node metastases from melanoma. *Br J Surg* 2000; 87: 892-901.
4. Mann GB, Coit DG. Does the extent of operation influence the prognosis in patients with melanoma metastatic to inguinal nodes? *Ann Surg Oncol* 1999; 6: 263-71.
5. Buzaid AC, Tinoco LA, Jendiroba D et al. Prognostic value of size of lymph node metastases in patients with cutaneous melanoma. *J Clin Oncol* 1995; 13: 2361-8.
6. Strobbe LJA, Jonk A, Hart AAM et al. Positive iliac and obturator nodes in melanoma: survival and prognostic factors. *Ann Surg Oncol* 1999; 6: 255-62.
7. Balch C. Cutaneous melanoma: Prognosis and treatment results worldwide. *Semin Surg Oncol* 1992; 8: 400-14.
8. Kretschmer L, Neumann C, Preuser K-P et al. Superficial inguinal and radical ilioinguinal lymph node dissection in patients with palpable melanoma metastases to the groin. An analysis of survival and local recurrence. *Acta Oncol* 2001; 40; 72-8.
9. Urist MM, Maddox WA, Kennedy JE et al. Patient risk factors and surgical morbidity after regional lymphadenectomy in 204 melanoma patients. *Cancer* 1983; 51: 2152-6.
10. Balch CM, Ross MI. Melanoma patients with iliac nodal metastases can be cured. *Ann Surg Oncol* 1999; 6: 230-1.
11. Strobbe LJ, Jonk A, Hart AA et al. The value of Cloquet's node in predicting melanoma nodal metastases in the pelvic lymph node basin. *Ann Surg Oncol* 2001; 8: 209-14.
12. Lawton G, Rasque H, Ariyan S. Preservation of muscle fascia to decrease lymphedema after complete axillary and ilioinguinofemoral lymphadenectomy for melanoma. *J Am Coll Surg* 2002; 195: 339-51.
13. White RR, Stanley WE, Johnson JL et al. Long-term survival in 2505 patients with melanoma with regional lymph node metastasis. *Ann Aurg* 2002; 235: 879-87.

Paper received: 4 November 2003
Accepted: 9 February 2004