NOWOTWORY Journal of Oncology • 2005 • volume 55
Number 3 • 207–212

Analysis of survival and prognostic factors in patients with cutaneous melanoma after therapeutic lymphadenectomy

Andrzej Pieńkowski[1], Zbigniew I. Nowecki[1], Piotr Rutkowski[1], Małgorzata Symonides[2], Włodzimierz Ruka[1]

The aim of the study was to perform a single-institution analysis of factors influencing the clinical outcomes of cutaneous melanoma (CM) patients undergoing therapeutic lymphadenectomy (LND).
Patients and methods. The data of 353 consecutive melanoma patients with metastases to regional lymph nodes who underwent radical LND from 1985 to 2001 was analyzed. For statistical analysis 10 clinico-pathological factors were chosen: gender, primary lesion thickness (Breslow), CM level of invasion (Clark), ulceration of CM, CM site, number of metastastatic lymph nodes, maximal diameter of metastatic lymph node(s), presence of nodal extracapsular invasion, percentage of metastatic nodes in comparison to all dissected nodes, type of nodal metastases: macrometastases (defined as clinically detected metastases confirmed cytologically) vs. micrometastases (positive nodes as a result of sentinel lymph node biopsy in non-palpable regional basin). Additionally, we evaluated the influence of adjuvant radiotherapy. Survival time was calculated from the date of LND. Median follow-up time was 27 months for survivals.
Results. Estimated 5-year overall survival (OS) ratio was 44% and 5-year disease free survival (DFS) rate was 35%. The independent predictors of poor OS according to multivariate analysis were: extracapsular melanoma invasion ($p<0.0001$), primary lesion Breslow thickness >3mm ($p= 0.007$), male sex ($p=0.011$) and CM site in head/neck region ($p=0.05$). The negative factors for DFS were: nodal extracapsular melanoma extension ($p<0.0001$) and male sex ($p<0.0001$). There were no significant differences in OS and DFS for patients treated or not with adjuvant radiotherapy, although patients undergoing adjuvant radiotherapy as a selective group demonstrated worse prognostic factors.
Conclusions. The most important single factor influencing patient outcome after therapeutic lymphadenectomy due to regional basin lymph node metastases is nodal extracapsular extension of melanoma cells.

Ocena przeżyć i czynników rokowniczych u chorych na czerniaka skóry po leczniczej limfadenektomii

Celem pracy była jednoośrodkowa analiza czynników wpływających na wyniki leczenia chorych na czerniaka, poddanych leczniczej limfadenektomii (LND)
Chorzy i metody. Poddano analizie dane 353 kolejnych chorych z przerzutami do regionalnych węzłów chłonnych, u których wykonano radykalną LND w latach 1985-2001. Do analizy statystycznej włączono 10 czynników rokowniczych: płeć pacjenta, grubość nacieku zmiany pierwotnej, mierzona w milimetrach, poziom naciekania zmiany pierwotnej według skali Clark'a, występowanie bądź brak owrzodzenia ogniska pierwotnego, stwierdzone w badaniu histopatologicznym, umiejscowienie ogniska pierwotnego, liczbę węzłów chłonnych zajętych przez przerzuty, największy wymiar największego objętego przerzutem węzła chłonnego lub konglomeratu węzłów chłonnych, stwierdzenie lub brak nacieku poza torebką węzła chłonnego, odsetek objętych przez przerzuty węzłów chłonnych w stosunku do całkowitej przebadanej liczby węzłów chłonnych w preparacie pooperacyjnym, typ przerzutu do węzła lub węzłów chłonnych: makroprzerzut (wykryty na podstawie badania klinicznego, potwierdzony przedoperacyjnie wynikiem cytologicznym punkcji cienkoigłowej), vs mikroprzerzut (przerzut do węzła chłonnego, stwierdzony na podstawie wyniku badania histopatologicznego usuniętego węzła wartowniczego). Dodatkowo w analizie statystycznej uwzględniono wpływ uzupełniającej radioterapii. Czas przeżycia obliczano od daty limfadenektomii. Mediana czasu obserwacji dla żyjących wyniosła 27 miesięcy.
Wyniki. Oszacowany odsetek 5-letnich przeżyć całkowitych wyniósł 44%, a 5-letnich przeżyć wolnych od nawrotu choroby – 35%. Analiza wielowariantowa wykazała, że istotny niekorzystny wpływ na przeżycia całkowite mają: występowanie

[1] Department of Soft Tissue/Bone Sarcoma and Melanoma
[2] Department of Anesthesiology
Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology Warsaw, Poland

nacieku poza torebką węzła chłonnego (p<0,0001), grubość nacieku zmiany pierwotnej >3 mm (p=0,007), płeć męska (p=0,011) i umiejscowienie ogniska na głowie lub szyi (p=0,05). Natomiast w odniesieniu do przeżyć bezobjawowych istotnymi i niezależnymi niekorzystnymi czynnikami rokowniczymi są: stwierdzenie nacieku poza torebką węzła chłonnego (p<0,0001), płeć męska (p<0,0001). Oceniając skuteczność uzupełniającego napromieniania nie stwierdzono istotnych statystycznie różnic w przeżyciach całkowitych i bezobjawowych między grupami chorych leczonych i nie leczonych tą metodą, pomimo tego, że napromieniana grupa chorych charakteryzowała się gorszymi czynnikami rokowniczymi.
Wnioski. Najistotniejszym pojedynczym czynnikiem wpływającym na wyniki leczenia chorych na czerniaka po limfadenektomii terapeutycznej z powodu przerzutów do węzłów chłonnych regionalnego spływu jest obecność nacieku pozatorebkowego.

Key words: cutaneous melanoma, lymphadenectomy, extracapsular invasion, lymph node, radiotherapy, prognosis
Słowa kluczowe: czerniak skóry, limfadenektomia, naciek pozatorebkowy, węzeł chłonny, radioterapia, rokowanie

Introduction

The incidence of cutaneous melanoma has been increasing throughout the recent years. The most important factor determining the prognosis of melanoma patients is regional lymph node involvement (stage III according to the American Joint Committee on Cancer – AJCC 2002) [1]. However, the detailed contemporary analyzes of factors influencing clinical outcome in such a group of patients are rare in literature. The risk of disease recurrence in patients after therapeutic lymphadenectomy (LND) is high and ranges from 50% to 70% [2]. Similarly, the survival analysis cumulates the subsets of patients with 5-year survival rates from 24% to 69% [3]. This group of patients may profit significantly from finding new experimental, adjuvant treatment. Thus the main problem is to find the criteria, which may identify patients with a high risk of dissemination and unfavorable outcome i.e. those that may benefit from adjuvant treatment.

The main aim of this study was to perform a large, retrospective single-institution analysis of factors influencing the clinical outcomes of stage III melanoma patients undergoing therapeutic lymph node dissection. We analyzed the spectrum of possible and established prognostic factors in relation to overall and disease free survival after radical lymph node dissection. We have also made an effort to analyze the value of adjuvant treatment with radiotherapy.

Material and methods

Between 12/1985 and 12/2000 374 consecutive patients with histologically proven cutaneous melanoma and regional lymph node metastases underwent radical therapeutic lymphadenectomy at the M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland.

For purpose of the analysis all patients had to meet the following criteria:

- stage III melanoma (according to AJCC 2002) with regional nodal metastases detected by lymphatic mapping and sentinel node (SLN) biopsy (91 patients) or clinically and cytologically confirmed (262 patients);
- metastases to only one regional basin;
- absence of distant and in-transit metastases;
- nformed consent.

In the group of 374 patients, 21 cases were excluded from the analysis (5.6%), due to simultaneous therapeutic LND performed in two basins (14 cases) or elective lymphadenectomy (7 patients). All in all the analyzed group consisted of 353 patients, who fulfilled the presented criteria. The initial clinicopathological stage of melanoma was determined by pathological evaluation of the primary lesion and dissected lymph nodes, as well as by physical examination and routine imaging examinations (chest X-ray, ultrasonography of the abdominal cavity). Patient characteristics are summarized in Table 1. In the analyzed group the median Breslow thickness of the primary tumor was 4 mm (in the SLN biopsy group and clinically and cytologically confirmed metastatic group: 3.8 mm and 4.9 mm, respectively). Primary tumor ulceration was distributed equally in both groups. In 91 analyzed patients the original procedure consisted of lymphatic mapping (corresponding to 18.6% of all – both positive and negative – SLN biopsies). We performed preoperative lymphoscintygraphy combined with intraoperative vital blue-dye [Patent Blau V®] lymphatic mapping and intraoperative lymphoscintygraphy with a hand-held gamma-detecting probe [Neoprobe 1000®, Neoprobe Corp., Dublin, OH, USA or Navigator®, RMD Watertown, MA, USA]. During routine pathologic examination SLNs were cut serially along the major axis and HE stained. Paraffin embedded specimens were examined in light microscopy (x40; x200). In doubtful cases additional immunohistochemical staining (S 100, HMB 45) was performed. Final pathological examination after LND revealed extracaspular extensions of melanoma cells in 37.4% cases (34/91) of involved lymph nodes in patients with positive SLN biopsy and in 56.5% cases (148/262) after LND due to clinically detected metastases.

The clinical and pathological parameters examined for prognostic value were: primary lesion thickness according to Breslow (≤3 mm vs 3-8 mm vs ≥8 mm), primary tumor level of invasion according to Clark, ulceration of primary tumor, primary lesion site (trunk vs. extremities vs. head/neck), gender, presence of nodal extracapsular invasion, percentage of metastatic nodes in comparison to all dissected nodes, maximal diameter of metastatic nodes, number of metastatic nodes (1 vs 2-3 vs ≥4), type of nodal metastases: macrometastases (defined as clinically detected metastases confirmed cytologically) vs. micrometastases (defined as positive result of sentinel lymph node biopsy in non-palpable regional basin).

Median follow-up time was 27 months for survivors. Overall survival (OS) time was calculated from the date of LND to the date of the most recent follow-up or death. Similarly, disease-free survival (DFS) time was estimated from the date of lymph node dissection to the date of the most recent follow-up or disease recurrence. For survival analysis the Kaplan-Meier method in combination with the log-rank test was used for univariate analysis. Cox's proportional hazard regression model was used for multivariate analysis for variables with p≤0.1 in univariate analysis. Contingency tables were analyzed by the chi-square test. Differences were considered statistically significant if p-values were <0.05. Additionally (non-randomly)

Table I. Patient characteristics

Variable	No = 353
Demographical	
Gender:	
female	182 (52%)
male	171 (48%)
Age:	
range (min, max)	(19, 87)
mean (standard deviation SD)	54 (15)
median	53
Clinical	
Primary site:	
extremities	182 (52%)
trunk	134 (38%)
head/neck	17 (4.5%)
unknown	20 (5.5%)
Maximal diameter of metastatic nodes:	
≤3cm	239 (68%)
>3cm	103 (29%)
data not available	11 (3%)
Microstaging of primary lesion	
Clark level of invasion:	
I+II	39 (11%)
III	114 (32%)
IV	76 (22%)
V	70 (20%)
data not available	54 (15%)
Ulceration of primary tumor:	
present	140 (40%)
absent	109 (31%)
data not available	104 (29%)
Breslow thickness:	
≤ 1mm	19 (5%)
> 1 – 2≤	29 (8%)
> 2 – 4≤	62 (18%)
> 4	144 (41%)
data not available	99 (28%)
Microstaging of lymph nodes	
Number of metastatic nodes	
1 node	136 (39%)
2-3 nodes	98 (28%)
4 and more nodes	117 (32.5%)
data not available	2 (0.5%)
Percentage of metastatic nodes:	
≤12%	124 (35%)
12-31%	116 (33%)
>31%	111 (31.5%)
data not available	2 (0.5%)
Type (burden) of nodal metastases:	
micrometastases (positive SLN biopsy)	91 (26%)
macrometastases (clinically and cytologically detected)	262 (74%)
Extracapsular invasion:	
present	182 (52%)
absent	169 (47.5%)
data not available	2 (0.5%)
Treatment	
Lymphadenectomy:	
cervical	20 (5%)
axillary	171 (49%)
inguinal	29 (8%)
ilio-inguinal	81 (23%)
ilio-obturatory-inguinal	52 (15%)
Adjuvant radiotherapy:	
yes	82 (23%)
no	271 (77%)

we evaluated the influence of adjuvant radiotherapy using Cox's model for multivariate analysis.

Results

The 5-year overall survival (OS) rate (± standard error) of the entire group of melanoma patients (computed from the date of lymph node dissection) was 44% (±4%). In an univariate analysis the following factors were found to have significant negative impact on OS: presence of extracapsular tumor extension from involved lymph nodes ($p<0.001$) [Figure 1], male gender ($p=0.05$), primary tumor site on the trunk or in the head/neck region ($p=0.02$), primary melanoma thickness > 3 mm ($p=0.01$), number of metastatic lymph nodes >1 ($p=0.007$), percentage of involved nodes >12% ($p=0.001$) and macrometastases ($p=0.007$). No significant correlations were found between OS and primary tumour ulceration, Clark level or maximal diameter of metastatic nodes.

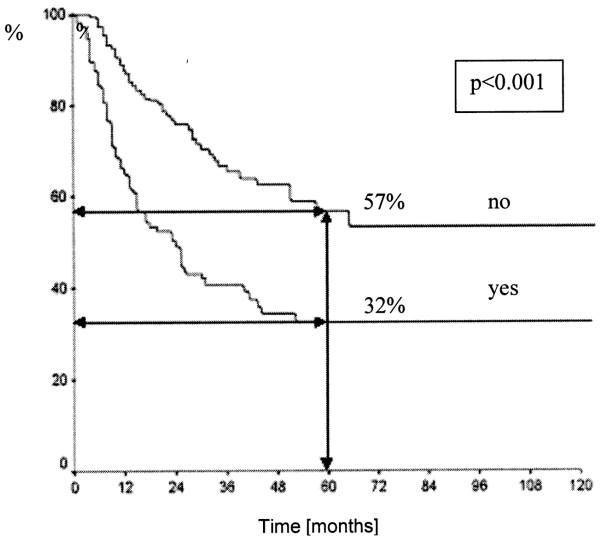

Figure 1. Overall survival according to the presence of extracaspular extension of nodal metastases

Multivariate analyses disclosed that the following factors had an independent, negative impact on overall survival in stage III melanoma patients: extracapsular melanoma invasion of fat tissue surrounding metastatic lymph nodes ($p<0.0001$), primary tumor thickness > 3 mm ($p=0.007$), male sex ($p=0.011$) and head/neck primary tumor location ($p=0.04$) (Table II).

Table II. Predictive factors influencing the OS of the entire group of patients according to multivariate analysis

Variable	DF	Wald	P	Risk
Extracapsular extension	1	16.703	<0.0001	2.404
Breslow thickness > 3mm	1	7.344	0.007	1.470
Male gender	1	6.408	0.011	1.776
Primary site (extremity)	2	5.853	0.054	1.000
Primary site (head/neck)	1	4.324	0.038	2.847
Primary site (trunk)	1	3.236	0.072	1.492

The 5-year disease free survival (DFS) rate was 35% (±3%). The following factors significantly negatively influenced DFS in univariate analysis (calculated from the date of lymphadenectomy to the date of relapse): male sex (p=0.019), primary tumor non-extremity localization (p=0.05), primary tumor thickness >3 mm (p=0.02), primary tumor Clark level >III (p=0.008), presence of extracapsular invasion in involved lymph nodes (p<0.001), percentage of involved nodes >12% (p<0.001), number of metastatic lymph nodes >1 (p<0.001), and macrometastases (p=0.02). In multivariate analysis, only nodal extracapsular extension (p<0.0001) and male gender (p<0.0001) correlated independently with poorer disease-free survival (Table III).

Table III. Predictive factors influencing the DFS of the entire group of patients according to multivariate analysis

Variable	DF	Wald	P	Risk
Extracapsular extension	1	21.808	<0.0001	2.272
Male gender	1	13.361	<0.0001	1.897
Breslow thickness >3 mm	**1**	**2.923**	**0.087**	**1.220**

Taking into account the fact, that most of the other authors and the new AJCC 2002 staging classification do not analyze the presence of extracapsular invasion of melanoma cells in nodal metastases, which seems to be the strongest prognostic factor in our analysis, we performed a simulation of multivariate analysis for OS after excluding this parameter. Negative, statistically important (p<0.01) factors for OS were: male gender, Breslow thickness >3mm, the number of metastatic nodes >1, primary tumor site on the trunk and macrometastases. Moreover, analyzing the prognostic significance of the number of metastatic nodes and the presence of extracapsular extension, we found that these features are dependent on each other: the more metastatic nodes the higher the risk of extracapsular extension (Table IV).

Table IV. Correlations between the number of metastatic nodes and the presence of extracapsular extension

Number of metastatic nodes	Extracapsular extension of melanoma cells		
	No	Yes	Total
1	93 (55.0%)	43 (23.7%)	136 (39.0%)
2-3	51 (30.2%)	47 (25.8%)	98 (28.0%)
>3	25 (14.8%)	92 (50.5%)	117 (33.0%)

We also performed a separate analysis of the outcome of patients treated (RTH/+/) or not (RTH/-/) with adjuvant radiotherapy after lymphadenectomy. We have not found significant differences in OS and DFS between these two groups of patients. Therefore, we evaluated the distribution of those prognostic variables, which were found to be important in the above-mentioned analyses. We have found that patients treated with adjuvant radiotherapy had a significantly higher rate of extracapsular extension (89%) as compared to patients, who were not irradiated (41%) (p<0.001). In patients undergoing radiotherapy the primary tumor was more frequently situated in the head/neck region (9%), as compared to patients not treated with radiotherapy (3.5%) (p=0.005). It could be concluded, that the group of patients with adjuvant radiotherapy demonstrated worse prognostic factors. Thus we decided to compare OS and DFS in the subgroup of patients treated or not with radiotherapy, who were characterized by extracaspular extension within the metastatic nodes. We found that the OS time was longer for the RTH/+/ group, as compared with the RTH/-/ group (41% versus 22%, not significant statistically – n.s.) (Figure 2). Similarly in the case of DFS the curves estimated for patients with extracapsular extension of melanoma cells have shown significant differences between the RTH/+/ and the RTH/-/ groups with a significant benefit discernible for the former (28% versus 12%, n.s.).

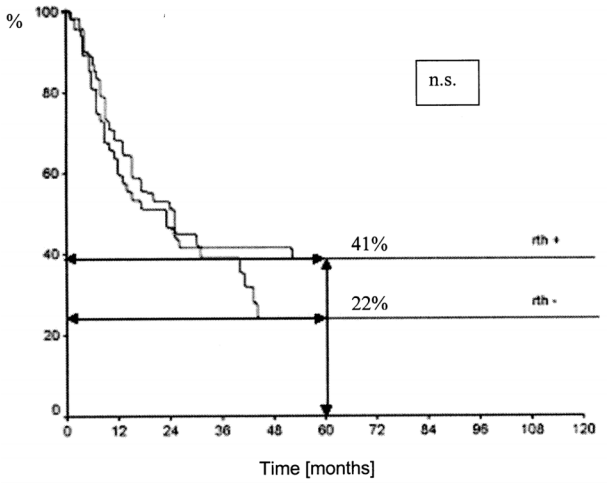

Figure 2. Overall survival in patients with extracapsular invasion treated (rth+) or not (rth-) with adjuvant radiotherapy

Discussion

Our one-institution study presents a remarkable homogenous group of 353 patients with melanoma metastases to regional lymph nodes as all of whom were operated on by the same staff of surgeons. This implies that the presented results are reliable and comparable with other large studies [2-10].

The presence of metastases to regional lymph nodes is one of the most important factors negatively affecting the clinical outcome of patients with cutaneous melanoma. This heterogeneous group of patients (although generally with poor outcomes) cumulates cases with very different prognosis (5-year survival rate ranges from 24%

to 69%). This is the reason for searching for factors, which may help in the selection of high- and low-risk patients.

The results of the study demonstrate that extracapsular extension of melanoma cells in lymph nodes is the strongest single factor negatively influencing the prognosis of stage III patients, both in univariate and multivariate analysis for overall and disease-free survival. This hypothesis is supported by the observation of Cascinnelli et al., who showed that the presence of metastatic melanoma cells into soft tissue adjacent to the lymph node is a more important prognostic factor than the number of metastatic nodes [10]. This factor was included into the new revised AJCC staging system for melanoma, however its role is unclear and underestimated. According to a multivariate analysis after the exclusion of this variable (which seems to be related to the number of metastatic nodes) the most important negative prognostic factors become the metastases to more than one node and clinically detected macrometastases. In most of the studies the authors did not include the extracapsular extension for prognostic analyses [3, 4, 7, 8], which has contributed to the reinforcement of the clinical importance of these two other factors. The results of this study suggest that in case of nodal extracapsular extension the relevance of detecting melanoma metastases by sentinel node biopsy or clinically/cytologically is similar. The survival value of sentinel lymph node biopsy can be proven only in prospective, randomized trials [11]. The other issue is the determination of the compartmentation of the number of metastatic nodes in relation to patient survival. We suggest that the dichotomization of this parameter in two subgroups: one metastatic node versus more than one nodal metastases is the most effective method and simpler than that proposed by Balch [3]. Moreover, it has been proven that the size of the metastases is not a useful factor for prognosing survival in melanoma patients. This factor has been eliminated from the current staging system, while the number of involved lymph nodes has been included [1] as the crucial factor.

Another interesting hypothesis analyzed in this study is the prognostic value of the percentage of metastatic nodes in relation to the total number of dissected and pathologically evaluated nodes. This parameter, rarely presented in the literature [10,12], has shown its prognostic significance both for overall and disease-free survival in an univariate analysis. The percentage of metastatic nodes may characterize the quality of the surgical procedure as well as the postoperative pathological examination.

The second significant prognostic factor in multivariate analysis was patient gender. Male patients have a 1.776 fold higher risk of death than women, and a 1.897 higher risk of recurrence. The explanation of this phenomenon warrants further analyses [6, 7, 13-15].

Patients with lymph node metastases pose as the most important therapeutic problem in melanoma and the target for adjuvant therapy. However, the results of clinical trials with experimental drugs (e.g. interferon or vaccines) are disappointing. Another technique used in the adjuvant treatment of stage III melanoma is radiotherapy. The literature data is controversial [16, 17], but most of the authors suggest that the indication for adjuvant radiotherapy may be multiple nodal metastases or the presence of extracapsular extension. Although the patients undergoing adjuvant radiotherapy as a selective group demonstrated worse prognostic factors, they did not show significant differences in OS and DFS as compared to not irradiated patients. This implies the survival benefit of adjuvant radiotherapy after radical lymph node dissection due to melanoma metastases in a selected group of patients.

In conclusion, our data suggests, that the most important factor influencing patient outcome after therapeutic LND due to regional basin lymph node metastases is nodal extracapsular extension of melanoma cells. The number of involved regional lymph nodes is an important prognostic factor in patients without extracapsular nodal invasion. There were no significant differences in overall and disease-free survival for patients treated, or not, with adjuvant radiotherapy after therapeutic LND although the patients undergoing adjuvant radiotherapy as a selective group demonstrated worse prognostic factors

Piotr Rutkowski MD, PhD
Department of Soft Tissue/Bone Sarcoma and Melanoma
M. Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology
W. K. Roentgena Str. 5
02-781 Warsaw, Poland
e-mail: rutkowskip@coi.waw.pl

References

1. Balch Ch M, Buzaid AC, Soong SJ et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 2001; 19: 3635-48.
2. Reeves M, Coit D. Melanoma. A Multidisciplinary Approach for the General Surgeon. *Surg Clin N Am* 2000; 80: 581-601.
3. Balch Ch M, Soong SJ, Gershenwald JE et al. Prognostic factors analysis of 17.600 melanoma patients: validation of the American Joint Committee on Cancer Melanoma Staging System. *J Clin Oncol* 2001; 19: 3622-34.
4. Kretschmer L, Preusser KP, Marsch WC, Neumann C. Prognostic factors of overall survival in patients with delayed lymph node dissection for cutaneous malignant melanoma. *Melanoma Res* 2000; 10: 483-9.
5. 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.
6. Coit D, Rogatko A., Brennan M. Prognostic factors in patients with melanoma metastatic to axillary or inguinal lymph nodes. *Ann Surg* 1991; 214: 627-36.
7. Balch C, Soong SJ, Murad T et al. A multifactorial analysis of melanoma. Prognostic factors in melanoma patients with lymph node metastases (stage II). *Ann Surg* 1981; 193: 377-88.
8. Morton D, Wanek L, Nizze J et al. Improved long – term survival after lymphadenectomy of melanoma metastatic to regional nodes. *Ann Surg* 1991; 214: 491-501.
9. Drepper H, Biess B, Hofherr B et al. The prognosis of patients with stage III melanoma. *Cancer* 1993; 71: 1239-46.
10. Cascinelli N., Vaglini M., Nava M. et al. Prognosis of skin melanoma with regional node metastases (stage II). *J Surg Oncol* 1984; 25: 240-7.

11. McMasters KM, Reintgen DS, Ross MI et al. Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. *J Clin Oncol* 2001; 19: 2851-5.
12. Bevilacqua R, Coit D, Rogatko A et al. Axillary dissection in melanoma. Prognostic variables in node positive patients. *Ann Surg* 1990; 212: 125-31.
13. Callery C, Cochran A, Roe D et al. Factors prognostic for survival in patients with malignant melanoma spread to the regional lymph nodes. *Ann Surg* 1982; 196: 69-75.
14. Karakousis C, Hena M, Emrich L. et al. Axillary node dissection in malignant melanoma: Results and complications. *Surgery* 1990; 108: 10-17.
15. Nowecki ZI, Rutkowski P, Nasierowska-Guttmejer A, Ruka W. Sentinel lymph node biopsy in clinically N0 melanoma patients – one institution experience. *Melanoma Res* 2003; 13: 35-43.
16. Creagan E, Cupps R, Ivins J et al. Adjuvant radiation therapy for regional nodal metastases from malignant melanoma. A randomized, prospective study. *Cancer* 1978; 42: 2206-10.
17. Fuhrman D, Lippold A, Borrosch F et al. Should adjuvant radiotherapy be recommended following resection of regional lymph node metastases of malignant melanomas? *Brit J Dermatol* 2001; 144: 66-70.

Paper received: 12 January 2005
Accepted: 7 March 2005