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Klinik Çalışma - Araştırma / *Original Article*

The Clinical and Histopathological Characteristics of Cutaneous Malignant Melanoma

Malign Melanomların Klinik ve Histopatolojik Özellikleri

Cavit ÇÖL[1], Gündüz TUNÇ[2], Kemal YANDAKÇI[2], Oğuz HASDEMİR[1], Erol YALÇIN[2]

[1]*Department of General Surgery, Medical Faculty of Abant İzzet Baysal University, Bolu;*
[2]*Department of (1st) General Surgery, Yıldırım Beyazıt Training and Research Hospital, Ankara*

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Objectives: The most effective method of treatment of cutaneous malignant melanoma (CMM) is surgical excision performed in the early stages. Our aim was to evaluate the descriptive characteristics of CMM.

Patients and Methods: Fifty-five patients with malignant melanoma (32 males, 23 females; mean age 50.9±12.9; years, range 26 to 76 years) were evaluated retrospectively. Surgical excision alone was performed on stage I and II patients. Regional lymph-node dissection was performed together with surgical excision on patients with palpabl lymph nodes (stages III and IV) detected during preoperative examination. Descriptive characteristics such as anatomical locations, histological subtypes and stages of the CMM were examined; the tumor size and thickness, adjuvant chemotherapy and immunotherapy rates, local recurrence rates were evaluated.

Results: Palpabl lymph nodes were identified in 74% (n=41) of the patients. Lymph-node dissection was performed together with surgical excision on these patients. The average tumor thickness and tumor size were 2.1±1.3 mm and 21.7±11.6 mm respectively.

Conclusion: Width of surgical margins and wide surgical resection with lymph-node dissection for CMM will have no effect on loco-regional recurrence, distant metastases and survival rates. The complications and benefits must be meticulously evaluated before application of lymph-node dissection.

Key Words: Lymph node excision; melanoma/pathology/surgery.

Amaç: Deri malign melanomlarının en etkili tedavi yöntemi erken dönemde yapılacak cerrahi eksizyondur. Bu çalışmada malign melanomun tanımlayıcı özelliklerinin saptanması amaçlandı.

Hastalar ve Yöntemler: Malign melanom saptanan 55 hastanın (32 erkek, 23 kadın; ort. yaş 50.9±12.9; dağılım 26-76) dosyaları geriye dönük olarak incelendi. Evre I ve evre II hastalara yalnızca cerrahi eksizyon yapıldı. Ameliyat öncesi dönemde palpabl lenf nodu tespit edilen evre-III ve evre-IV hastalarda cerrahi eksizyonla birlikte bölgesel lenf nodu diseksiyonu yapıldı. Malign melanomların yerleşim yerleri, histolojik alt türleri ve evreleri gibi tanımlayıcı özellikleri incelendi; tümör çapı ve derinliği, yardımcı kemoterapi ve immünoterapi oranları, lokal yineleme oranları değerlendirildi.

Bulgular: Kırk bir hastada (%74) palpabl lenf nodu tespit edildi. Bu hastalara cerrahi eksizyonla birlikte bölgesel lenf nodu diseksiyonu yapıldı. Ortalama tümör çapı 21.7±11.6 mm, tümör derinliği ise 2.1±1.3 mm bulundu.

Sonuç: Cerrahi sınırların genişliği ve lenf nodu diseksiyonu ile lokal yineleme, uzak metastazlar ve yaşam süresi arasında anlamlı bir ilişki olmadığı saptandı. Bölgesel lenf nodu diseksiyonu yapmaya karar verirken diseksiyondan beklenen yararlar ve olası komplikasyonlar göz önünde bulundurularak karar verilmelidir.

Anahtar Sözcükler: Lenf nodu eksizyonu; melanoma/patoloji/cerrahi.

Correspondence (İletişim adresi): Dr. Cavit Çöl. Abant İzzet Baysal Üniversitesi Tıp Fakültesi Genel Cerrahi Anabilim Dalı, 14280 Bolu.
Tel: 0374 - 253 46 56 Faks (Fax): 0374 - 253 45 59 e-posta (e-mail): col_c@ibu.edu.tr

During the past 20-30 years, a noticeable increase has been observed in the incidence of and mortalities due to cutaneous malignant melanoma (CMM) derived from melanosites in comparison to other cancers. The incidence of CMM is greater in Europe than in Asia, and according to research the occurrence is approximately 15-30 cases in every 100,000.[1-3]

Cutaneous malignant melanoma is generally localized in the head-neck region and the extremities which are exposed to sunlight. The combination of positive family history, fair complexion, number of nevi, exposure to sun and chromosomal alterations seem to be implicated in the pathogenesis of CMM.[4]

The most effective method of treatment of CMM is surgical excision performed in the early stages. Although the effect of surgical excision is indisputable, discussions still continue on the issues of the width of the excision, lymph node dissection (LND), adjuvant chemotherapy, immunotherapy and radiotherapy.[5-9]

PATIENTS AND METHODS

Between the years 1995-2002, surgical treatment for CMM was carried out on fifty-five patients (32 males, 23 females; mean age 50.9±12.9; range 26 to 76 years), at the Social Security Ankara Training Hospital. These patients were evaluated in this retrospective study according to clinical and histopathological characteristics.

Regional LND was performed together with surgical excision on the patients with palpable lymph nodes (stages III and IV) during the preoperative examination (group I). Surgical excision alone was performed on the stage I and II patients (group II). In this retrospective study, definitive characteristics such as anatomical location, the histological subtypes and the stages of the CMM according to the American Joint Committee of Cancer (AJCC) classification were examined; the tumor size and tumor thickness, the rates of application of adjuvant chemotherapy and immunotherapy, the rates of local recurrence and the time of occurrence of these recurrences in both groups of patients were evaluated. Adjuvant immunotherapy was carried out on stage II patients, while stage III patients received adjuvant chemotherapy. The adjuvant immunotherapy protocol applied is as follows: a $20x10^6$ Ü/m^2/day I.V. Interferon-α-2b infusion given five days a week for a month at the induction, and $10x10^6$ Ü/m^2/day S.C. or I.M. Interferon-α-2b three days a week at the consolidation. The adjuvant chemotherapy protocol was carried out as three five day courses of 200 mg/m^2/day Dacarbazine (DTIC) given at one-month intervals.[10,11] The chi square and student's t-test were used for statistical analysis and p value of <0.05 was accepted as statistically significant. Patients were observed for a period ranging from two months to 6.5 years (an average of 4.2 years) and the follow-ups were carried out by physical examination only.

RESULTS

Cutaneous malignant melanoma was localized in the head and neck region of nine patients, the upper extremities of eight patients, lower extremities of 26 patients and thoraco-abdominal region of 12 patients. In terms of histological subtypes, 35 patients had nodular melanoma, 12 had superficial spreading melanoma, five had acral lentigo and three had Hutchinson's melanotic freckle (lentigo maligna). The evaluation of the preoperative findings of the patients with CMM according to AJCC categorization showed that one patient was at stage IA, six were at stage IB, four at stage IIA, three at stage IIB, 37 at stage III and four at stage IV (Table 1).

Clinical findings

Palpable lymph nodes (PLN) were identified in 74% of the patients (n=41) during the preoperative clinical examination (group I). Lymph node dissection was performed together with surgical excision on these patients, 25 of which were male, 16 female with an average age of 51.3±11.9 years. In the 14 patients who did not receive LND (group II), the number of males and females were equal and the average age was 49.6±15.9 (Chi-square=0.5, $p>0.05$). The width of the CMM lesion was found to be on average 21.2±6.6 mm in group I and 18.5±4.6 mm in group II ($t=0.8$, $p>0.05$). The average tumor

Table 1. The clinical and histopathological characteristics of 55 patients who had CMM

	Group I	(n=41)	Group II	(n=14)	Total	(n=55)
Sex	25M/16F		7M/7F		32M/23F	
Age	51.3±11.9		49.6±15.9		50.9±12.9	
Tumor size (mm)	21.7±11.6		19.0±9.6		21.0±11.1	
Tumor tickness (mm)	2.1±1.3		1.4±1.2		2.0±1.1	
Number of local recurrence	17		1		18	
Number of adjuvant chemotherapy	32		6		38	
Number of adjuvant immunotherapy	30		6		36	
Anatomical site of CMM	Head and neck	4	Head and neck	5	Head and neck	9
	Thorax	5	Thorax	3	Thorax	8
	Abdomen	4	Abdomen	0	Abdomen	4
	Upper extremity	6	Upper extremity	2	Upper extremity	8
	Lower extremity	22	Lower extremity	4	Lower extremity	26
Histologic subtype of CMM	Lentigo maligna	2	Lentigo maligna	1	Lentigo maligna	3
	Sup spreading	6	Sup spreading	6	Sup spreading	12
	Acral lentigo	4	Acral lentigo	1	Acral lentigo	5
	Nodular	29	Nodular	6	Nodular	35
Clinical stage of CMM	Stage IA	0	Stage IA	1	Stage IA	1
	Stage IB	0	Stage IB	6	Stage IB	6
	Stage IIA	0	Stage IIA	4	Stage IIA	4
	Stage IIB	0	Stage IIB	3	Stage IIB	3
	Stage III	37	Stage III	0	Stage III	37
	Stage IV	4	Stage IV	0	Stage IV	4
Pathologic stage of CMM	Stage IA	0	Stage IA	1	Stage IA	1
	Stage IB	0	Stage IB	11	Stage IB	11
	Stage IIA	0	Stage IIA	9	Stage IIA	9
	Stage IIB	0	Stage IIB	9	Stage IIB	9
	Stage III	21	Stage III	0	Stage III	21
	Stage IV	4	Stage IV	0	Stage IV	4

CMM: Cutaneous malignant melanoma.

thickness was 2.05±0.8 mm in group I and 1.35±0.7 mm in group II (t=1.15, p>0.05).

Histopathological results

Lymphatic metastasis was identified in 25 of the patients (60%) receiving LND and 16 were reported to have reactive lymphadenitis after a histopathological examination. Metastasis was identified on only one lymph node in eight patients and on more than one node in 17 patients diagnosed with lymph node metastasis.

In the patients receiving LND, the average number of dissected lymph nodes was 15.0±4.8 while the number of metastatic lymph nodes was found to be 1.5±1.0. According to the pathological classification carried out during the postoperative period, 12 patients were found to be at stage I, 18 at stage II, 21 at stage II and four at stage IV. This means that 16 of the patients identified as being at stage III according to the preoperative findings were at stages I and II in the pathological classification.

Adjuvant therapy

The median follow-up period was 4.2±1.7 (range 2-6.5) years. Following surgical treatment patients at stage II received adjuvant immunotherapy, and those at stage III received adjuvant chemotherapy. Seventy-eight percent of the patients at stage I and 42% of those at

stage II received chemotherapy (Dacarbazine, DTIC) (Chi square=6.05 p<0.05). Similarly, 68% of group I patients and 42% of those in group II received adjuvant immunotherapy (Interferon-α-2b) (Chi square= 4.24; p<0.05) (Table 1). The number of loco-regional recurrence was 41% (n=17) in group I and 7% (n=1) in group II after 4.2±1.7 years of follow-up. While the mean time of recurrence was 6.2±1.2 months in group I, recurrence appeared in one patient in group II during the two months immediately following the operation.

DISCUSSION

Ninety percent of malignant melanomas are localized on the skin, the remaining 10% occurring on the retina, mucous membranes and internal organs. Although CMM constitute only 2-3% of skin cancers, over half of the skin cancers which cause mortality are malignant melanomas. The age and sex distribution, anatomic site of CMM, histopathological subtypes and clinical classification according to the AJCC of the patients involved in this study are similar to those of other series in the literature, and no significant difference was found between the two groups, other than the clinical stages.

Lymph-node dissection

It appears that LND is an effective independent factor on survival and more important than the diameter and tumor thickness on the evaluation of the stage of disease and prognosis. The matter of which patients LND needs to be performed upon should be discussed.[12] While some studies recommend that LND be performed on patients with CMM whose tumors are more than 1 mm thickness,[13] others defend that the indications of LND be based not upon the tumor thickness but on clinical and operative findings.[4] The thickness of most of the tumors of the patients in this series exceeded 1 mm and had a mean of 2.0±1.1 mm The mean tumor thickness of the patients with and without PLN were found to be 2.05±0.8 mm and 1.35±0.7 mm respectively. Similarly, the mean diameter of tumors in group I patients was 21.2±6.6 mm, while that of group II patients was 18.5±4.6 mm Although the thickness and diameter of the tumors of the patients with PLN were greater than those of the patients without PLN, the difference is not significant (p>0.05). However, the fact that the tumor thickness is greater in patients with PLN should be interpreted as a finding which supports the thesis that tumor thickness should be used as a sign of advanced stages in CMM.[14,15]

According to published studies, the rate of lymphatic metastasis in CMM ranges from 15-20%.[16,17] In the current retrospective clinical study, metastasis was identified in one or more than one of the lymph nodes of 25 out of the 41 CMM patients with PLN indications who received LND. According to the results of this study, while the rate of lymphatic metastasis in CMM patients was 45% in general, this rate rose to 60% with PLN. Both these findings are considerably high in comparison to the rates of lymphatic metastasis found in the literature. The reason for this could be the fact that most of the patients were at the advanced stages of the disease.

Complete performance of surgical excision in CMM, knowledge of the state of the regional lymph nodes, and the performance of therapeutic LND on those with lymphatic metastasis are accepted as the most critical points for the classification of patients and the evaluation of survival.[12,16,18]

Differences are observed in each individual in the number of lymph nodes in both the inguinal region and the axillary region and in the structure of lymphatic tissue. However, the complete removal of the regional lymphatics is important for both the evaluation of the presence of lymphatic metastasis, and for the success of therapeutic lymphadenectomy. In the cases of this study, the mean numbers of dissected lymph nodes and metastatic lymph nodes were found to be 15.0±4.8 and 1.5±1.0 respectively. These numbers are considered to be sufficient for therapeutic lymph node dissection.

When elective LND is performed on CMM patients, it is performed unnecessarily on many patients who do not have lymphatic metastasis.

However, post-LND complications such as lymphodema, infected wounds and paresthesia can be observed in patient.[17] In the current study, out of 25 patients who received LND, lymphodema was observed in one, infected wounds in four, and parasthesia in one patient. If routine elective LND had been performed in our institution, unnecessary LND would have been performed on 55% of the patients. This study has shown that the rate of lymphatic metastasis rises to 60% in CMM patients with PLN during the preoperative period. These results show both the importance of behaving selectively in order to reduce the number of patients receiving unnecessary LND and how even the findings of preoperative clinical examinations can reduce the number of unnecessary LND by half.

In recent years, new methods have been developed in order to evaluate the lymphatic structure of CMM patients and to accurately identify which patients require LND. Radiological screening of lymphatics in the preoperative period and biopsy of the sentinel lymph node are the most current practices. The antimony sulfur colloid lymphoscintigraphy technique used in the identification of the sentinel lymph node is a cheap, non-invasive technique that can be carried out at low levels of radiation with high degrees of accuracy.[19] Lymphatic mapping/sentinel lymph-node biopsy (LM/SLNB) technique is a multi-disciplinary approach, carried out routinely in many centers today, requiring the cooperation of surgeons, histopathologists and sometimes radiology-nuclear medicine experts.[20-24] Sentinel lymph-node biopsy has developed over the past decade as a minimally invasive technique to assess regional lymph node status in patients with malignancy. Sentinel lymph node biopsy is now widely available, and most cancer surgeons offer this as part of their diagnostic protocol for patients.[25,26] The LM/SLNB technique reduces the length of time spent in hospital, the length of the operation, the costs and loss of workforce, in addition to securing almost 100% accuracy in the indication of LND in the preoperative period.[21,27]

Prognosis

One of the important factors in making the prognosis of CMM is the existence of the invasion and metastasis of deep tissues.[28] Adjuvant chemo-immunotherapy is frequently performed on advanced stage CMM with deep invasion. However, research shows that such treatment carried out during advanced stage CMM does not have a significant effect on survival.[7,29] For this reason, the most effective treatment for the disease is surgical excision, and the success of the treatment depends on early identification of the disease, excision with normal margins of surgical resection, and performance of regional LND on patients with lymphatic metastasis.

Over a mean period of 4.2 years, the rate of local recurrence was found to be 32.7% and 41% for the group of patients with LND. Only one case of local recurrence was observed in the patients who did not receive LND. Wide surgical excision, therapeutic lymphadenectomy, chemotherapy and immunotherapy are used in the treatment of local recurrence and metastasis in CMM. The fact that the rate of local recurrence was high in the group of patients receiving LND was put down to their being at the advanced stages of the disease. Since it appeared at a very early stage, the single case of recurrence in the group of patients not receiving LND was put down to inadequate surgical technique or unidentified in-transit metastasis.

The rate of recurrence in local advanced CMM is high. Surgery should be performed in a way that ensures local control of the disease in order to reduce the distant metastasis and locoregional recurrence of the disease. In recent years significant advancements have been recorded in the area of adjuvant chemotherapy and immunotherapy in the treatment of CMM.[4,18] The most important agent used in immunotherapy is interferon-2-α, however, interferon-β and interferon-γ are also used. The results of chemotherapy carried out with Dacarbazine alone in comparison to those of combined chemotherapy have been shown to have less toxic side effects and to be just as effec-

tive.[29] There are contradicting studies on the issue of the effect of adjuvant systemic chemotherapy and immunotherapy on the survival of patients with nodal eclipse.[9,30,31] Furthermore, only 20% of patients receive positive outcomes from chemotherapy. Interferon treatment is very expensive and some patients show intolerance.

In the current series, adjuvant chemotherapy with dacarbazine and immunotherapy with interferon-2-α was carried out on patients at the advanced stages. Sixty-nine percent of patients received adjuvant chemotherapy in the postoperative period, while 65% received immunotherapy (Table 1).

The fact that its treatment requires a multidisciplinary approach and that its incidence has increased over the past decades in relation to other cancers has led to CMM becoming an important public health problem. The most important method of protection against CMM is avoidance of excessive exposure to sunlight and ultraviolet. Early diagnosis and treatment with surgical excision are the most important factors affecting survival. The surgical treatment of CMM is complete surgical excision of the tumor with a 1 cm margin, and if the margins are clear histopathologically, no further local surgery is needed.[29] The width of surgical margins and wide surgical resection for CMM will have no effect on loco-regional recurrence, distant metastases and survival rates. The complications and benefits must be meticulously evaluated before application of LND. Education of the public on the subject of CMM, taking preventative measures against the disease and developments in methods of treatment will reduce the incidence and mortality of this disease in the future.

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