



## Studying Surgical Margin of skin melanoma of the face and its relapse after surgical treatment in patients referring to Razi Hospital and Cancer Institute of Imam Khomeini Hospital during 1992-2010

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### ABSTRACT

Melanoma is a malignant neoplasm caused by the uncontrolled growth of melanocytes and the production of skin pigmentation. Melanoma treatment varies depending on the type and location. To treat melanoma cutaneous (MC), different surgical treatments are used and for histological treatment of the of melanoma lesions, surgical resection is the standard treatment. However, margin optimal resection for treatment of MC is of controversial issues. The aim of this study was to obtain the desired size and safety margins for melanoma surgery, to examine 4-year survival rate, recurrence rate, and its variants in patients with melanoma who underwent surgery were clear margin. The study population was patients diagnosed and hospitalized with melanoma by a pathologist to perform a surgical resection from 1992 until 2010 in the Department of Plastic and Reconstructive Surgery of Razi Hospital and Cancer Institute of Imam Khomeini Hospital. Demographic information of the patients was recorded in the prepared form, and in the first stage of the procedure, with the observed macroscopic lesions margin determined by the anatomical contours. Then the lesion was resected with 5, 1-2 cm margin. Depending on the extension of the lesion, this procedure was performed under local anesthesia with IV sedation. Samples were sent to pathology and positive and negative margins of the cut were determined, and in case of negative resection of the point, surgical resection was done with flap or graft. In case of positive margin, the first stage of the procedure was repeated, so that the environmental margins were negative. In the presence of thicknesses higher than one millimeter, sentinel lymph node biopsy was performed, and in the presence of positive lymph nodes in clinical examination, with video actions neck lymph node dissection was performed. Three months after surgery, local recurrence was assessed. Duration of follow-up was 4 years that was carried out regularly once every three months and follow up of patients was through phone calls, visits, and patient re-interviews were conducted. During the treatment and follow-up of tumor characteristics, the surgical findings and disease recurrence in the demographic data were recorded. In this study, 85 people 57 of whom were male (67.1%) and 28 females (32.9%) were studied whose mean age was  $65.7 \pm 18.0$  (100-17) years. The average size of the primary lesion macroscopically is  $3.04 \pm 1.7$  (8.20-0.48) cm and margins mean size was  $1.95 \pm 1.2$  (6-0.3) cm. In pathology, the average number of nodes was  $1.10 \pm 3.09$  with a median of zero (21-0). The average duration of relapse in Razi Hospital was  $36.9 \pm 7.7$  months, and in Cancer Institute, it was  $23.09 \pm 2.9$  months where comparison between the two groups showed no statistically significant difference. Local recurrence average duration was  $14.9 \pm 11.1$ , regional recurrence was  $15.8 \pm 3.3$ , and systemic recurrence was  $17.1 \pm 5.1$  months and comparing three groups showed no statistically significant difference ( $P=0.977$ ). Comparing the average size of the initial macroscopic lesions in Razi Hospital and Cancer Institute did not show statistically significant differences. In comparing the size of surgical margins in terms of the presence or absence of recurrence, no statistically significant difference was observed. In comparing the mean size of surgical margins in three groups of local, regional, and systemic recurrences no statistically significant difference was observed. Moreover, by using Tukey test, no significant correlation was observed between any of the groups. The 4-year survival rate was 95.3% and the recurrence rate was 52.9%, and the rate of local recurrence was less than systemic or regional recurrence. According to the findings, the size of the surgical margins is likely not to be associated with the recurrence and survival. It can be advised that for maintaining the beauty and function of the face, depending on the type of pathology and the depth of the surgical margins, consider 1-2 cm meters depth of the lesion and after surgical resection send the margins to pathological examination. In case of negativity, the restoration in the affected area was done using flaps or grafts.

**Key words:** melanoma, skin, Surgical margin, the rate of relapse

## INTRODUCTION

Melanoma neoplasm is a malignancy that appears with uncontrolled growth of melanocytes manifested by increased production of skin pigmentation. Melanoma is an important problem in medicine, melanoma accounted for the 75% of skin cancer deaths[1]. The incidence of melanoma is increasing [2]. The standard treatment in most melanoma is surgical resection: a small tumor with a margin of one centimeter is resected from the healthy skin around the lesion. In some deeper lesions, there may be need for resection with a margin of more than 2 cm of healthy skin around the lesion, because the margin of tumor resection depends on the thickness of the tumor and to close the lesion, skin graft or complete healing is often used[3]. Treatment of primary melanoma varies depending on the position and type. The standard treatment in primary malignant cutaneous melanoma is resection with a safe margin of healthy skin around the lesion. However, the desirable width of safety margin is unknown so far. The purpose of the surgeon from treatment is prevention of relapse and long-term recovery from the disease with minimal surgical morbidity, short hospital stay, and beautiful and functional results that are strongly influenced by the width of the margin of resection. For many years, proper margin of resection in primary cutaneous malignant melanoma is of controversial issues[4-6]. In a study in 1963, Petetsen et al reported that surgical resection of the primary tumor with a margin of at least 5 cm is necessary and this invasive procedure was considered to prevent local recurrence. However, this method requires the use of skin grafts or surgery flaps, leading to increased morbidity and unacceptable aesthetic and functional results [7]. Local recurrence in malignant melanoma is of the symbols of the poor prognosis associated with poor healing as well as regional and distant metastases risk [8]. The need for thicker tumors resection with poor prognosis is of controversial cases. Some surgeons started cutaneous melanoma resection with narrower margins. In contrast, some studies have reported that, there is no reason for the treatment of melanoma differently from other tumors. This is while in other studies different margins of resection volume in melanoma were reported [9]. In the treatment of melanoma, the margin of resection is very important, and if this margin is very narrow, it will have better aesthetic results but weaker recovery and more relapse associated in long run. Thicker primary melanomas, especially in the head and neck and limbs, primary melanoma lesions and lymph node metastasis of melanoma of factors are associated with an increased risk of relapse. As melanoma is a malignant lesion involving the skin the most and its main treatment is surgery, about the resection of this tumor in different areas of the body, there are different opinions, especially in the facial area. The resection of the tumor causes impaired muscle function and facial aesthetics and psychological problems for the patient. Even a bit more width in the affected area of resection margins can interfere with the function of tissues, mouth, and nose. Thus, calculating the amount of margin is important. Moreover, considering the importance of the type of tumor, tumor location, tumor grade, tumor resection margin size, reduced morbidity, reduced relapse after surgery, physical and psychological effects, applicability and cost-effectiveness of the project findings, and as with knowing a safe margin in most patients and using it for patients who need such a surgery later cause to have better beauty and high performance while having good rate of recurrence and morbidity. Therefore, the present study was conducted to evaluate Surgical margin melanoma of the skin of the face and recurrence rates after surgical treatment in patients referring to Razi Hospital and Cancer Institute of Imam Khomeini Hospital during 1992-2010.

## MATERIALS AND METHODS

This study is a descriptive cohort study, and the study population was the patients hospitalized for resection of tumors from 1992 to 2010 in the department of plastic and reconstructive surgery of Razi Hospital and Cancer Institute of Imam Khomeini Hospital. All the people who had the inclusion criteria were enrolled. The inclusion criteria included consent to participate in the research project, patients to undergo resection for face melanoma diagnosed by pathologists, and exclusion criteria was death for other reasons than melanoma. At first, demographic data of the patients were recorded in the pre-prepared information forms. In the first stage of the procedure, macroscopic observing of the margin of the anatomical lesions was found, based on that the lesion with margins of 2.5, 1 cm was resected. Depending on the extension of the lesion, this procedure was performed under local anesthesia with IV sedation. Samples were sent to pathology and positive and negative margins of the cut were identified, and in case of negative pathology results, surgical resection was restored with flap or graft. In the case of the positivity of the margin, the first stage of the procedure was repeated until the margins of the environment became negative. In case of margins higher than one-millimeter thickness, biopsy of the guard lymph nodes of the neck was performed. In the presence of positive lymph nodes in clinical examination, with video actions neck lymph node dissection was performed. Three months after local recurrence was evaluated. In the subsequent visits, patients were evaluated every three months. It should be noted in this study, recurrence refers to re-creation of the lesion at the site of the cut. To assess margins, the cuts were resected parallel to the surgical margins and were kept in Formalin for 24 hours, and the day after surgery were reported. The sections were stained with hematoxylin and eosin.

Duration of follow-up was 4 years and the follow-up contact was through phone calls, interviews, and re-visits. The way to prevent exit from the study was through completing files and persistent follow-up of the patients' recurrence to the clinic for examination. During the treatment and follow-up, tumor characteristics, surgical findings, and disease recurrence in the demographic data were recorded. Information required by the plan was recorded using the information in the file and data from follow-up interviews with patients on pre-prepared information sheets. All data were analyzed with SPSS software version 16. To analyze data, the mean of quantitative variables such as age, size, surgical margins, lesion size, and frequency of qualitative data such as gender and recurrence rate were calculated. To compare the quantitative variables between different groups, Mannwithney U test, T test, One Way ANOVA, and Tukey HSD were used. Using Kaplan-Meier, recurrence time was calculated, and the normality of the distribution of the samples was evaluated using the Kolmogorov-Simonov test.

**Table 1: Frequency of qualitative variables**

Variables	Sub groups	Frequency number (percentage)	
Palpable lymph nodes at initial examination	Has	18 (21.2%)	
	Does not have	67 (78.8%)	
	Total	85 (100%)	
The primary lesion area	Cheek	40 (47.1%)	
	Forehead		
	Nose	18 (21.2%)	
	Ear	5 (5.9%)	
	Neck	4 (4.7%)	
	Lip	2 (2.4%)	
	Other areas of face	11 (12.9%)	
	Total	85 (100%)	
	Histopathology	Nedolar	21 (41.2%)
		Lentigomligna	18 (35.3%)
SSM		9 (17.6%)	
Opioid		2 (3.9%)	
Lentigomaligna+ SSM		1 (2%)	
	Total	51 (100%)	
The thickness of the primary lesion segmentation based on Breslow		59 (69.4%)	
	Less than or equal 0.75	4 (4.7%)	
		13 (15.3%)	
	0.76 to 1.5	9 (10.6%)	
		85 (100%)	
Clark Staging primary lesion	Level 1	3 (5.3%)	
	Level 2	3 (5.3%)	
	Level 3	6 (10.5%)	
	Level 4	22 (38.6%)	
	Level 5	18 (31.6%)	
	Level 1/ Level 2	2 (3.5%)	
	Level 3 / Level 2	1 (1.8%)	
	Level 4 / Level 3	2 (3.5%)	
	Total	57 (100%)	
Lymph node pathology	Positive	3 (3.5%)	
	Negative	41 (48.2%)	
	unknown	41 (48.2%)	
	Total	85 (100%)	
Adjuvant therapy	Did not receive	56 (65.9%)	
	received	Radiotherapy	6 (7.1%)
		Chemotherapy	16 (18.8%)
		Interferon	1 (1.2%)
		Radiotherapy+ Interferon	2 (2.4%)
		Radiotherapy+ Chemotherapy	2 (2.4%)
		Chemotherapy+ Interferon	2 (2.4%)
	Total	85 (100%)	
Relapse	Did not have	40 (47.1%)	
	Had	Local	4 (4.7%)
		Regional	23 (27.1%)
		Systemic	4 (4.7%)
		Locoregional	10 (11.8%)
		Regional+ Systemic	2 (2.4%)
		Local+ Regional+ Systemic	2 (2.4%)
	Total	85 (100%)	
Death	Survived	81 (95.3%)	
	Died	4 (4.7%)	
	Total	85 (100%)	

**Findings**

In this study, 85 people 57 of whom were male (67.1%) and 28 females (32.9%) were studied whose mean age was  $65.7 \pm 18.0$  (100-17) years. The average size of the primary lesion macroscopically is  $3.04 \pm 1.7$  (8.20-0.48) cm and margins mean size was  $1.95 \pm 1.2$  (6-0.3) cm. In pathology, the average number of nodes was  $1.10 \pm 3.09$  with a median of zero (21-0).

In subjects studied recurrence time was  $29.5 \pm 3.8$  months, which was  $36.9 \pm 7.7$  months in Razi Hospital and  $23.09 \pm 2.9$  months at Cancer Institute. The average duration of local recurrence was  $14.9 \pm 11.1$  months, regional recurrence was  $15.8 \pm 3.3$  months, and systemic recurrence was  $17.1 \pm 5.1$  months and comparing three groups showed no statistically significant difference ( $P = 0.977$ ). Comparing the average size of the primary lesion microscopically in Razi Hospital and Cancer Institute did not show statistically significant differences. In addition, the mean size of surgical margins in Razi Hospital and Cancer Institute did not show statistically significant differences (Table 2).

**Table 2: Comparison of the average size of the primary lesion microscopically and size of surgical margins between the Razi Hospital and Cancer Institute of Imam Khomeini Hospital**

P-value	Total	Cancer Institute	Razi Hospital	Variable
0.468	$1.7 \pm 3.04$	$1.8 \pm 3.15$	$1.5 \pm 2.74$	The initial lesion size in cm
0.188	$1.2 \pm 1.95$	$1.1 \pm 1.84$	143232	surgical margins size in cm

The average size of surgical margin was  $1.95 \pm 1.2$  cm. This mean in those who had a recurrence was  $2.05 \pm 1.21$  cm and in the group without relapse was  $1.83 \pm 1.18$  cm that was not statistically significant difference ( $P = 0.340$ ). The average size of surgical margins in patients with local recurrence was  $2.20 \pm 1.63$  cm, in the group with regional recurrence was  $1.83 \pm 0.94$  cm, and in patients with systemic recurrence was  $1.67 \pm 0.65$  cm and by using Tukey test the relationship between any of the groups not significant ( $P = 0.745$ ).

**Table 3: Comparison of the frequency of lesion area in terms of the presence or absence of recurrence**

P-value	Have a relapse	Have a relapse	Lesion area
0.358	23 (57.5%)	17 (37.8%)	cheek
	7 (17.5%)	11 (24.4%)	Forehead
	3 (7.5%)	2 (4.4%)	Nose
	1 (2.5%)	4 (8.9%)	Ear
	25%	2 (4.4%)	Neck
	1 (2.5%)	1 (2.2%)	Lip
	3 (7.5%)	8 (17.8%)	Other areas of the face
	40 (100%)	45 (100%)	Total

**Table 4: Comparison of tumor thickness in terms of the presence or absence**

P-value	Have a relapse	Have a relapse	Thickness
0.459	25 (62.5%)	34 (75.5%)	Less or equal to 0.75 mm
	3 (7.5%)	1 (2.2%)	0.76 to 1.5 mm
	8 (20%)	5 (11.1%)	1.51 to 4 mm

In the present study, four-year survival rate was 95.3% and the rate of recurrence was 52.9% of which 8.9% was local recurrence. In the four-year follow-up period in patients studied, the time without relapse of the disease was  $29.5 \pm 3.8$  months.

**DISCUSSION AND CONCLUSION**

Melanoma treatment varies depending on the type and location of melanoma. For the treatment of MC, different surgical treatments are used [10] and for histological treatment of melanoma lesions, the standard treatment is surgical resection [11]. However, margin optimal resection for treatment of MC is of controversial issues [12]. In this study, four-year survival rate was 95.3% but the rate of recurrence was 52.9% however 8.9% of that it was local recurrence. In various studies, the incidence of local recurrence is reported differently, which is due to different definitions of local recurrence in various studies. Overall, the incidence of local recurrence is low [13]. The rate of local recurrence in studies is from 0.8% to 3.8% and according to different location and time of follow-up is different [14-16]. In some studies, it is reported that with longer follow-up, local recurrence rate increases and the highest recurrence that can be cited is in the pursuit of five years [17,18].

Local recurrence is of events of importance for the patient, and survival rates after local recurrence has been reported as very different in studies. In the present study, the time for local relapse was less than regional and

systemic relapse recurrence, but there was no significant difference between them. Local recurrence is associated with poor prognosis, but independently does not show prognostic marker of survival [19]. In this study, the time when the disease was not associated with relapse was longer in Razi hospital. However, there were no statistically significant differences between the two groups. The macroscopic size of the primary lesion in Razi hospital sector was lower, but no statistically significant difference was obtained between the two treatment groups. Surgical margins size in Razi Hospital was more its size in Cancer Institute, but there was no significant difference between the two groups. Surgical margins size in patients who had relapse was higher, but compared with patients who did not have relapse showed no significant difference. This is also confirmed by other studies [13-20]. The average size of surgical margins in patients who had local recurrence was higher, but there were no show significant differences between three groups. Also in this study, tumor thickness did not show significant correlation with recurrence and the size of the primary lesion was not associated with the surgical margins. Other studies are consistent with the findings of this study.

Breslow and Macht more than two decades ago reported that disease prognosis is directly linked to tumor thickness and for skin melanoma with low thickness of tumor, margin of one centimeter is secure [21]. Some studies that have been done using Mohs technique have not reported the use of narrow margins [22-25]. Given the recurrence of tumor is high, most surgeons recommend wide resection margins for better control of local recurrence, and tumor thickness does not affect surgical margins.

So far, about the depth of resection margins no accepted guidelines are accepted in the American Academy of Dermatology and the International Association of Cancer [26]. In various studies, by systematic review and research clinical trial margins narrow and broad terms of survival, local recurrence at follow-up period of 5-16 years have been compared and reported the impact of the margin and local recurrence in the survival as uncertain [27-30]. According to the findings in this study, the size of the surgical margins is not associated with recurrence and survival. Therefore, Plastic and Reconstructive Surgeons can be advised for maintaining the beauty and function of the face, depending on the type of pathology and the depth of the surgical margins, consider 1-2 cm meters depth of the lesion and after surgical resection send the margins to pathological examination. In case of negativity, the restoration in the affected area was done using flaps or grafts. It is suggested that in future studies, this study be done with different margins and more follow-up periods.

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