RESEARCH ARTICLE

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Received: 26.03.2020
Acceptance: 12.07.2020
DOI: 10.18521/ktd.708364

Konuralp Medical Journal
e-ISSN1309–3878
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A 20-Year Retrospective Analysis of Skin Cancers: Comparison of the First and Second Decades

ABSTRACT

Objective: The incidence of skin cancer increases day by day depending on environmental factors. Developing diagnostic and pathological methods provide correct typing of skin cancers.

Methods: This retrospective analysis included patients who presented to and were scheduled for treatment at Sivas Cumhuriyet University Plastic Reconstructive and Aesthetic Surgery Clinic between January 1, 2000 and December 31, 2019 due to skin cancer and carcinoma in situ. The results were divided two groups as first ten years and second ten years. The groups were compared among themself in terms of cancer type, age, gender and localization.

Results: 619 cases of 652 skin cancer and in situ carcinoma results were detected. When the groups were compared in terms of tumor types detected, there was a significant increase in MM, Bowen's disease, and rare NMSC subtypes other than SCC and BCC in the second decade ($p<0.001$). Comparison of NMSC and MSC rates between the groups showed that the incidence of MSC had increased significantly from 5.2% to 10% in the past 10 years ($p<0,05$).

Conclusions: Rare Non-melanocytic skin cancer group includes many types of carcinoma, there are various treatment protocols. Furthermore, many members of this group are known to be more aggressive than Basal cell carcinoma and squamous cell carcinoma. There are no consensus especially for approaches targeting lymph nodes. Closely following is necessary for early detection of recurrences and metastases.

Keywords: Skin Cancer, Non-Melanocytic Skin Cancer, Melanocytic Skin Cancer, Merkel Cell Carcinoma, Malignant Eccrine Poroma, Malignant Nodular Hidradenoma

Cilt Kanserlerinin 20 Yıllık Retrospektif Analizi: Birinci 10 Yıl İle İkinci 10 Yılın Karşılaştırılması

ÖZET

Amaç: Çevresel faktörlere bağlı olarak cilt kanserlerinin insidansı gün geçtikçe artmaktadır. Gelişen tanısal ve patolojik metotlar kanserlerin daha doğru tiplendirilmesine yardımcı olmaktadır.

Gereç ve Yöntem: Çalışmamızda cilt kanserleri ve in situ karsinom nedeniyle 1 Ocak 2000-31 Aralık 2019 tarihleri arasında kliniğimizde tedavi amacıyla başvuran ve tedavisi planlanan hastalar dahil edildi. Hastalar ilk on yıl ikinci on yıl olarak iki gruba ayrıldı. Gruplar; kanser tipi, yaş, cinsiyet ve lokalizasyon açısından karşılaştırıldı.

Bulgular: 619 vakaya ait 652 cilt kanseri ve insitu karsinom tespit edildi. Gruplar karşılaştırıldığında ikinci on yılda malign melanoma, Bowen hastalığında ve nadir gözlenen Non Melanositik Cilt Kanseri (NMCK)'nin alt tiplerinde anlamlı bir artış olduğu gözlendi ($p<0,001$). NMCK ve Melanositik Cilt Kanseri (MCK) karşılaştırıldığında MCK insidansının son 10 yılda %5.2 den % 10 a yükselmesi istatistiksel açıdan anlamlı idi ($p<0,05$).

Sonuç: Nadir gözlenen NMCK'ler çeşitli tedavi protokolleri olan pek çok karsinom tiplerini içermektedir. Ayrıca bu grubun pek çok üyesinin Bazal Hücreli Kanser ve Skuamöz Hücreli Kanserden daha agresif seyrettikleri bilinmektedir. Özellikle lenf nodlarına karşı yaklaşım hakkında ortak bir konsensüs bulunmamaktadır. Rekürens ve metastazların erken tespit edilebilmesi için yakın takip gereklidir.

Anahtar Kelimeler: Deri Kanseri, Melanositik Olmayan Deri Kanseri, Melanositik Deri Kanseri, Merkel Hücreli Karsinom, Malign Ekrin Poroma, Malign Nodüler Hidradenom

INTRODUCTION

Non-melanocytic skin cancers (NMSC) are the 5th most common type of cancer, while melanomas rank 19th (1). Malignant melanoma (MM) accounts for only 2% of all skin cancers but is the most common cause of skin cancer-related deaths (2). Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common types of NMSC, while other rarer subtypes such as Merkel cell carcinoma (MCC), Porocarcinoma (PC), and Hidradenocarcinoma account for less than 1% of cases (3). According to Turkish Cancer Statistics data (2015), the number of newly reported cases of melanocytic skin cancer increased from 330 in 2011 to 618 in 2015. For NMSCs, 4,450 new cases were reported in 2011 and this figure jumped to 8,800 in 2015 (4). The aim of this study was to determine changes in the incidence and distribution of skin cancers between the first and second decades of a 20-year period.

MATERIAL AND METHODS

This retrospective analysis included patients who presented to and were scheduled for treatment at Sivas Cumhuriyet University Plastic Reconstructive and Aesthetic Surgery Clinic between January 1, 2000 and December 31, 2019 due to skin cancer and carcinoma in situ. The patients were divided into two groups: those who presented between January 1, 2000 and December 31, 2009 comprised Group 1 and those who presented between January 1, 2010 and December 31, 2019 comprised Group 2. Both groups were evaluated in terms of age, sex, tumor type, number of cases, localization, reconstruction method and increase in tumor type. Patients whose patient files and pathology results were not reached, these were excluded from the study. Ethical approval for the study was obtained from the Cumhuriyet University Ethics Committee. (Decision no:2020-01/41).

Statistical Analysis: The collected data were uploaded to the SPSS (version 23.0) software package and tested for normal distribution using the Kolmogorov–Smirnov test. Data analyses included descriptive statistics (frequency, percent, etc.), as well as chi-square test in 2x2 and multicell tables for discrete qualitative data and Mann–Whitney U test for measured data because they did not meet parametric test assumptions. The type I error level was 0.05.

RESULTS

Data pertaining to 619 patients were accessed and a total of 652 skin cancers and in situ carcinomas were identified. Of this patient group, 40.9% (n=253) were in Group 1 and 59.1% (n=366) were in Group 2. When all lesions were evaluated, 61.4% (n=393) of the cancers were BCC, 27.5% (n=176) were SCC, 7.97% (n=51) were MM, and 3.13% (n=20) were other NMSC subtypes. NMSC accounted for 90.3% (n=589) of all lesions, MSC for 7.8% (n=51), and the prevalence of Bowen's disease was 1.8% (n=12). (Table 1 and 2).

Table 1. Distributions of Subtypes of Carcinomas and Anatomical Location

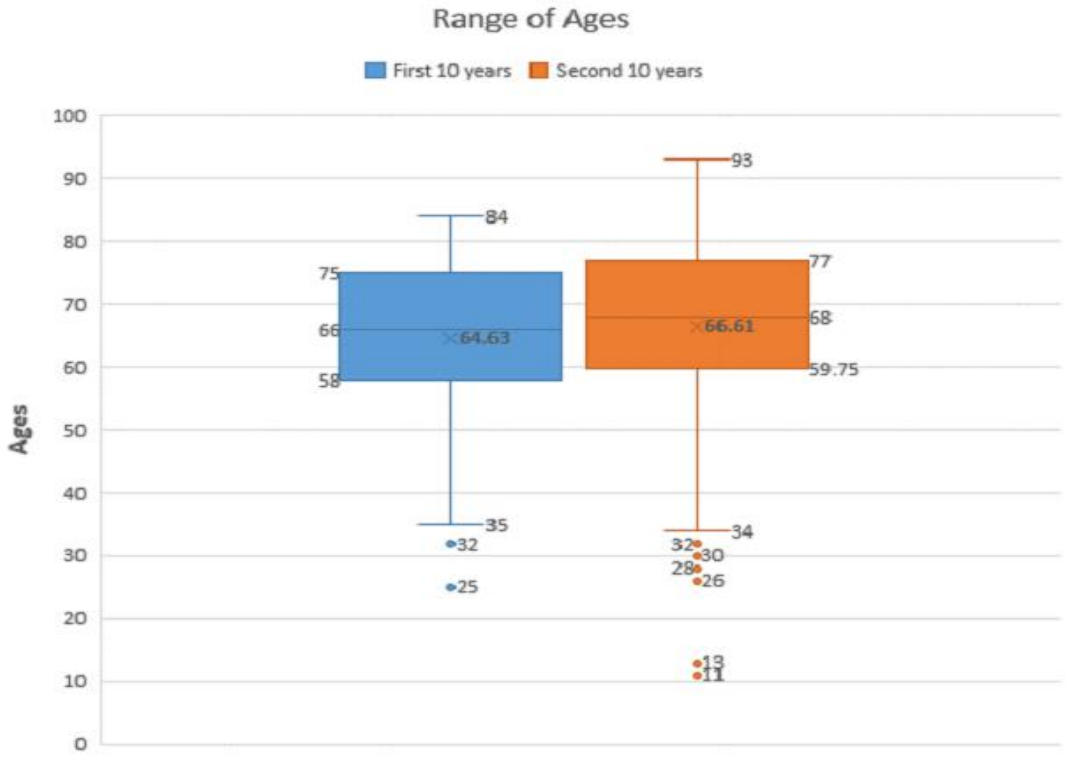
	Basal Cell Carsinoma		Squamous Cell Carsinoma		Malignat Melanoma		Bowen Diasases		Others		TOTAL
Groups	I	II	I	II	I	II	I	II	I	II	
Scalp	4	30	5	10	2	3	0	1	0	0	55
Forehead	26	17	3	2	2	4	0	0	0	1	55
Nose	50	66	2	13	1	0	0	0	0	2	134
Ear	5	6	1	2	0	0	0	0	0	1	15
Periorbital area	53	47	2	7	1	1	0	0	0	2	113
Lower lip	2	2	34	34	2	2	0	1	0	1	78
Upper lip	5	6	4	6	0	0	0	1	0	0	22
Cheek	25	31	6	10	2	4	0	2	0	0	80
Lower extremite	2	3	12	5	1	13	0	1	0	4	41
Upper extremite	0	1	6	7	1	6	1	3	0	3	28
Trunk	1	5	2	0	2	3	0	2	2	4	21
Neck	2	4	2	1	0	1	0	0	0	0	10
Total	175	218	79	97	14	37	1	11	2	18	652

Table 2. Uncommon Types of NMSC

Uncommon Types of NMSC	Group 1	Group 2
Dermatofibrosarcoma Protuberans	0	5
Basosquamous Cell Carsinoma	0	1
Spindle Cell Carcinoma	0	2
Sebaceous Carcinoma	0	1
Merkel Cell Carsinoma	2	1
Caposi Sarkoma	0	1
Verrucous Carcinoma	0	1
Malignant Nodular Hidradenoma	0	1
Epithelioid sarcoma	0	1
Malignant Eccrine Poroma	0	2
Total	2	16

The study sample comprised 39.1% female (n=242) and 60.9% male (n=377) patients. Analysis of sex distribution by group showed that Group 1 included 153 males (60.5%) and 100 females (39.5%), while Group 2 included 224 (61.2%) males and 142 (38.8%) females. Mean age was 65.9 ± 13.6 (11–93) years in the entire patient group, 64.7 ± 12.1 (25–84) years in Group 1, and 66.4 ± 14.1 (11–93) years in Group 2. (Graphic1)

When the two groups were compared based on the median age of patients diagnosed with the different cancer types, there were no significant age differences except for BCC ($p<0.05$) (Table 3).



Graphic 1. Range of ages

Table 3. Statistical analysis of age and tumour subtypes

	Mean Ranks For Ages	Median ± SD (min-max)	Results
BCC			
The first ten years (n:74)	112.41	67 ± 12.787	p:0.005*
The second ten years (n:193)	142.28	(26-93)	
SCC			
The first ten years (n:46)	72.23	69 ± 11.744	p:0.884
The second ten years (n:96)	71.15	(25-90)	
MM			
The first ten years (n:6)	25.50	62 ± 20.465	p:0.461
The second ten years (n:37)	21.43	(11-90)	
Bowen			
The first ten years (n:1)	5.00	65 ± 14.514	p:0.751
The second ten years (n:10)	6.10	(34-85)	
Other			
The first ten years (n:2)	13.00	67 ± 14.902	p:0.528
The second ten years (n:18)	10.22	(33-87)	

*$p<0.05$; Mann Whitney U test was used.

When the first and second decades were compared in terms of the types of cancers detected, there was no significant difference for male patients (p>0.05). However, there was a significant increase in other rare NMSCs in female patients (p<0.05). Comparison of MSC and NMSC subgroups revealed that the incidence of MSC had increased from 27.8% (n=5) to 72.2% (n=13) in females and from 27.3% (n=9) to 72.7% (n=24) in males, but these differences were not statistically significant (p>0.05).

The most common type of skin tumor in Group 1 was BCC (n=175, 64.6%), followed by SCC (n=79, 29.2%). The incidence of MM was 5.2% (n=14). Bowen's disease was detected in only one patient, while other NMSCs accounted for 0.7% of the lesions (n=2). MCC was detected in two patients who had an NMSC other than SCC or BCC. Among the NMSCs, 68.3% (n=175) were BCC, 30.8% (n=79) were SCC, and 0.8% (n=2) were other rare NMSC subtypes. Lesions in non-head and neck locations accounted for 11.1% (n=30).

Similarly, the most common skin cancers in Group 2 were BCC (57.2%, n=218) and SCC (25.5%, n=97). MM was detected in 9.7% (n=37) and Bowen's disease in 2.9% (n=11) of the patients. Other NMSC subtypes were detected in a total of 16 lesions (4.7%). In the past 10 years there were 333 cases of NMSC (90%) and 37 cases of MSC (10%). Of the NMSCs, 65.4% (n=218) were BCC, 29.1% (n=97) were SCC, and 5.4% (n=18) were other rare NMSC subtypes. Sixty lesions (15.7%) occurred in non-head and neck localizations.

When the groups were compared in terms of tumor types detected, there was a significant increasement in MM, Bowen's disease, and rare NMSC subtypes other than SCC and BCC in the second decade (p<0.001). Comparison of NMSC and MSC rates between the groups showed that the incidence of MSC had increased significantly from 5.2% to 10% in the past 10 years (p<0.05) (Table 4). In terms of tumor location, there was a significant increase in tumors located on the scalp and decrease in those located on the forehead and periorbital region (p<0.05) (Table 4).

Table 4. Statistical analysis of groups

	Group 1 n (%)	Group 2 n (%)	Results
Sex			
Female	100 (39.5)	142 (38.8)	X^2: 0.033
Male	153 (60.5)	224 (61.2)	p:0.867
Total	253	366	
Types of Carsinomas			
BCC	175 (66.6)	218 (57.2)	
SCC	79 (29.2)	97 (25.5)	
MM	14 (5.2)**	37 (9.7)**	X^2: 20.064
Bowen	1 (0.4)**	11 (2.9)**	p<0.001**
Others	2 (0.7)**	18 (4.7)**	
Total	271	381	
Distributions of Carcinomas			
NMSC	256 (94.8)	333 (90.0)	X^2: 4.934
MSC	14 (5.2)	37 (10.0)	p:0.026*
Total	271	370	
Anatomic Distributions of Carcinomas			
Scalp	11 (4.1)**	44 (11.5)**	
Forehead	31 (11.4)**	24 (6.3)**	
Nose	53 (19.6)	81 (21.3)	
Ear	6 (2.2)	9 (2.4)	
Periorbital region	56 (20.7)**	57 (15.0)**	X^2: 23.609
Lower lip	38 (14.0)	40 (10.5)	p:0.014**
Upper lip	9 (3.3)	13 (3.4)	
Cheek	33 (12.2)	47 (12.3)	
Lower Extremite	15 (5.5)	26 (6.8)	
Uppeer Extremite	8 (3)	20 (5.2)	
Trunk	7 (2.6)	14 (3.7)	
Neck	4 (1.5)	6 (1.6)	
Total	271	381	
Region			
Head and neck	241 (88.9)	321 (84.3)	X^2: 2.913
Other	30 (11.1)	60 (15.7)	p:0.088
Total	271	381	

*p<0.05 **Chi square test was used; Bonferroni test was used for subgroups.

Recurrences accounted for 5.1% (n=33) of all lesions. Reconstruction techniques used were primary repair in 21.2% (n=138), graft in 34.4% (n=224), and flap in 42.8% (n=279) of the lesions. Distant flaps were used in 5.39% (n=15) of flap reconstructions, while the rest utilized local flaps. Tumor-related amputation was performed in 1.4% (n=9) of the patients. Two patients refused surgery and were referred for radiotherapy.

DISCUSSION

Skin cancers are among the most common cancers. The most frequent type of skin cancer is BCC, which is more benign than other types. SCC and other rare NMSC subtypes tend to be more aggressive. Although MMs are responsible for most skin cancer-related deaths, high rates of recurrence and metastasis have also been reported for NMSCs such as MCC, Porocarcinoma, and sebaceous carcinoma. These tumors reportedly account for less than 1% of NMSCs (5), but their incidence in the second decade of our series was 4.7%, which is substantially higher than rates reported in the literature.

Merkel cell carcinoma is an aggressive neuroendocrine skin tumor (6). The number of patients diagnosed increases each year, which is believed to be due in part to the advanced methods used for the diagnosis of this tumor (7). Although 75% of cases are diagnosed as local disease, recurrence rates are high, at 30% (7,9). Even in localized disease, lymph node involvement can occur in 25% of cases (10). One of the most important prognostic factors is lymph node involvement (8,11-13). However, there is no consensus on elective lymph node dissection. Involvement is detected in about 30% of patients who undergo sentinel lymph node biopsy (SLNB) (6). Like other neuroendocrine tumors, it is radiosensitive (14). A total of three MCCs were identified in our series. Of the two patients with tumors located on the back, axillary single node metastasis was detected in one patient and involvement of four inguinal lymph nodes was detected in the other patient. No lymph node involvement was detected in the one patient in the second decade.

Hidradenocarcinoma has an incidence of less than 0.001% (15,16). Because it is so rare, the treatment protocols used are a subject of debate. It has local recurrence rates up to 50% and metastasis rates of around 60% despite wide excision, which is the generally accepted treatment method (17,18,19). As dermal lymphatic invasion, nerve sheath involvement, deep structure infiltration, positive resection margins, highly anaplastic morphology, and extracapsular lymph node spread are associated with high recurrence rates, these patients have been recommended adjuvant radiotherapy (20,21). Furthermore, successful outcomes have been reported regarding preoperative radiotherapy (22). Although some authors recommend prophylactic lymph node dissection because of high lymphatic involvement (23,24), it has also been emphasized that SLNB provides tumor-free survival, even if the number of the cases is limited (25-27). Due to high recurrence and metastasis rates, antihormone therapy to prevent spread has also been proposed as beneficial for the treatment of these tumors in receptor-positive cases (27). A 67-year-old woman in our series had a MNH on her lower lip. No lymphatic involvement or distant metastasis was detected at the time of diagnosis. The patient underwent wide excision and is currently in her second postoperative year of follow-up with no recurrence or metastasis.

Porocarcinoma accounts for 0.005–0.01% of skin tumors (28,29). Metastatic disease is present in 22.3% of patients at the time of diagnosis (30). It is an aggressive tumor with recurrence and metastasis rates of about 20% despite curative surgery (29,30). The generally accepted treatment is surgical excision. Poor prognostic factors include lymphovascular invasion, high mitosis, tumor thickness over 7 mm, irregular tumor margins, and poor differentiation (32,33). In addition, tumor location is also an important factor for prognosis. Primary lesions in the upper and lower extremities, trunk, hips, and genital area are associated with higher risk of lymph node metastasis than tumors located in the head and neck region. SLNB is recommended for patients in the high-risk group (29). Lymph node positivity is reported to increase to 50% for tumors that are poorly differentiated (34,35). Despite reports that response to radiotherapy and chemotherapy was poor (36) and radiotherapy had no effect on survival, radiotherapy can be used for patients with positive surgical margins and those not eligible for surgery (37). There were two cases of MEP in our series. One was located on the lower eyelid of a 75-year-old patient, while the other was located in the gluteal region of an 83-year-old patient, both of whom were women. No lymphatic involvement or distant metastasis was detected at the time of diagnosis in the patient with the eyelid tumor. She underwent wide excision and has been under follow-up for 1.5 years. The tumor located in the gluteal region was reported to be carcinoma in situ.

Dermatofibrosarcoma protuberance (DFSP) is a soft tissue sarcoma with an incidence of four per million (38). It typically grows slowly and has less than 5% likelihood of regional or distant metastasis unless it transforms into a high-grade fibrosarcoma (39,40). Histopathologically, 3–20% of DFSPs contain fibrosarcomatous changes, and this finding is described as an independent risk factor for recurrence and distant metastases (39,41,42). Other risk factors for recurrence are a clean resection margin narrower than one millimeter or a positive surgical margin and tumor

size. Recurrence is more common with tumors larger than five centimeters (41). Most distant metastases are found in the lungs, but they are also known to metastasize to the bone, soft tissue, liver, kidneys, gastrointestinal tract, and lymph nodes (38). While metastasis was not observed in any of our cases, one of our patients presented with a fifth relapse.

Epithelioid sarcoma (ES) is a rare type of sarcoma with a reported incidence of 0.02–0.05 per 100,000 (43,44). There are two types of ES, proximal and conventional. The conventional type usually occurs in distal locations in the upper extremities, and is seen in adolescents and young men (45). The proximal type is less common, located on the trunk, and has poorer prognosis (46). It also occurs very rarely in the perineum, penis, and vulva (47,48). Treatment planning is based entirely on the presence or absence of lymphatic involvement and distant metastasis. Lymphatic involvement has been reported at rates of 10–80% (49-52). Preoperative evaluation of lymphatic involvement is important due to the high risk. Therefore, many authors recommend SLNB for accurate staging (50,52,53). Pre- or postoperative radiotherapy reduces local recurrence rates and is recommended as an adjunct to radical surgical treatment (50,53). In our patient, the tumor was located in the perineal region and the patient underwent wide excision, bilateral groin dissection, and chemoradiotherapy. While receiving radiotherapy, metastasis developed on the skin of the vulva at postoperative five months. The vulvar metastasis was controlled with wide surgical excision. However, the patient died one and a half years later due to distant metastasis and recurrence.

Sebaceous carcinoma is an aggressive adnexal tumor with two types, ocular (OSC) and extraocular (EOSC). The ocular type is more common but more aggressive than the extraocular type (54). As few cases of EOSC have been described, a definite consensus regarding treatment has yet to be reached, and there are conflicting views in the literature. The generally accepted treatment is wide tumor resection (55). Different figures have been reported regarding its lymphatic involvement and metastasis rates. Lymphatic metastasis rates of 1.3–16% and non-lymph node metastasis rates of 0.4–10% have been reported (55,56). Due to these different rates, there are different attitudes regarding the use of sentinel lymph nodes. Some authors report that subclinical nodal spread is rare for EOSC and few SLNBs are positive (57-59), while others argue that EOSC is a locally aggressive tumor with a high likelihood of regional nodal metastasis and that regional nodal dissection together with a wide local excision should be considered optimal (55). For optimal treatment, SLNB may be helpful in determining subclinical lymphatic involvement in high-risk patients, particularly those with tumors thicker than two millimeters, tumors with a Clark stage over 4, lymphovascular invasion, perineural invasion, bone infiltration, and anaplasia or poorly differentiated tumors (55,60). Although the role of adjuvant radiotherapy is controversial, radiotherapy can be given after complete tumor resection either alone or in combination with chemotherapy (55). Primary radiotherapy alone is not recommended due to high recurrence rates (56,58,60). It can be used in patients who refuse surgery or cannot undergo surgery due to comorbidities, and there are also publications that recommend its postoperative use after resection (55). Our patient was an 85-year-old man with nasally located cancer. Although his cervical lymph nodes were positive at the time of diagnosis, he did not consent to neck dissection and was lost to follow-up.

Detection of spindle cells in pathologic examination is suggestive of spindle squamous cell carcinoma, spindle-cell melanoma, pleomorphic undifferentiated sarcoma, and leiomyosarcoma in diagnosis (61). Spindle and basal cells may also be found in the sarcomatous type of BCC (62). In fact, it has been emphasized that basal cells may be overlooked in some cases (62-65). This subtype exhibits aggressive behavior and has metastatic potential (62). The spindle cell variant of SCC is rare. While it can be seen in sun-exposed regions and radiotherapy areas (66). It is a poorly differentiated form of SCC (61) and progresses more aggressively (62). The spindle variant of MM is in the vertical growth phase. Like the SCC variant, it occurs in sun-exposed areas (62). It is detected as widespread metastatic disease (67,68). In our series, spindle cell carcinoma was detected in two patients, both patients were over 70 years of age and the tumors were located on the face. The pathology department reported them as spindle cell carcinomas, with no subtyping.

In this study, the quantitative increase observed in MM, Bowen's disease, and rare types of NMSC in the second decade was statistically significant. The increase in Bowen's disease may be considered a result of early diagnosis.

The number of patients with MM is increasing daily worldwide (69) and our country (70). The increase in our series is consistent with the literature. This increase has also been observed in the pediatric age group (71). Pediatric malignant melanoma (PMM) accounts for 1–4% of all cases of melanoma (72). Although prognosis is more favorable in the pediatric age group (72-74), MM is a deadly disease and should be treated aggressively. Diagnosing PMM can be difficult, even for experienced physicians. Misdiagnosis in this age group has been reported at around 40% (75,76). Nodular PMMs may exhibit a pyogenic granuloma-like morphology (76,77). In the pediatric age group, PMM should not be overlooked in the differential diagnosis of pigment-free lesions with benign morphology. The treatment protocol is the same as

the protocol for adults. However, sentinel lymph node involvement occurs at a higher rate than in adults (72). Two of the MM patients in the second decade were in the pediatric age group and MM was detected incidentally. One patient was 13 years old and presented with a long-standing unpigmented granulomatous lesion on the front of the thigh. The result of incision biopsy was reported as PMM. Sentinel sampling was performed in this case because Breslow's depth was 6 mm. SLNB was positive and the patient underwent lymph node dissection. MM involvement was not observed in any of the nodes dissected after the sentinel lymph node. The other patient presented because of a nail change and excisional biopsy was performed upon observation of irregular pigmented lesions on the anterior surface of the tibia. The pathology result was reported as superficial spreading MM. The Breslow's depth of the tumor was 0.5 mm. Both of patients are in the second year of postoperative follow-up with no recurrence or metastasis. Although there were a small number of pediatric patients in our study, pediatric patients represented 3.9% of all cases of MM detected in 20 years.

The most important limitation in our study is that the hospital in which we are working has a patient profile limited with local region and it is a single center study. Although small skin cancers are treated in state hospitals in our region, metastic tumors such as SCC, MM, big size tumors and rare forms are consulted and this contributes positively to our work.

The pathological differential diagnosis of rare NMSC subtypes such as MCC, MNH, MEP and sebaceous carcinoma includes BCC and SCC. Different immunohistochemical dyes are used for differential diagnosis (79-82). This increase may be due to an increase in the number of cases or it may be related to more accurate diagnosis with advanced detection methods and staining techniques. As this group includes many types of carcinoma, there are various treatment protocols. Furthermore, many members of this group are known to be more aggressive than SCC and BCC. However, for many types of cancer there are a limited number of cases in the literature and no clear consensus regarding treatment. This creates as limitation, especially for approaches targeting lymph nodes. Treatment protocols are based on case reports and a few case series. It should be kept in mind that without the correct approach and follow-up planning, morbidity and mortality will be higher, especially in patients with aggressive types. This increases the importance of closely following patients for early detection of recurrences and metastases.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval: The approval of Cumhuriyet University Ethical Committee was satisfied. Decision no:2020-01/41.

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