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Original Contribution

RECURRENCE RATES OF PRIMARY NONMELANOMA SKIN CANCERS

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ABSTRACT

Purpose: To investigate the recurrence rate and the importance of factors associated with their development after treatment of non-melanoma skin cancers (NMSC).

Methods: This retrospective study includes 1630 patients (840 men and 790 women) registered in 1996 in Bulgaria with NMSC. Patients were followed for an average 122.8 months.

Results: The overall recurrence rate was 6.3%. Tumor localization (face, head and neck), T-stage (tumor size over 2 cm) and histological type (adenoid carcinomas) are significant risk factors for recurrences. The applied treatment is a very important factor related with the risk of recurrences. The recurrence rate is low after surgical excision (6,4%), superficial contactherapy (4,0%) and cryotherapy (6.6%), but after electrodesiccation it is high (11.7%). The presence of one recurrence is a significant risk factor for subsequent recurrence. Relapses occur after an average of 48.5 months (6÷118 months). The highest recurrence rate is during the first year - 17.5%. In subsequent years the recurrence rate decreases and during the tenth year it is just 3.9%, but the risk of recurrences remains long time.

The higher risk of new malignant conditions such as recurrences, multiple skin cancers and second primary tumors after treatment of NMSC require skin cancer survivors to be continuously followed up for a long time.

Conclusion: Right selection of treatment method, depending on the characteristics of the tumor and the patient and better skills of doctors are the necessary conditions to achieve high therapeutic efficiency.

Key words: recurrence rate, non-melanoma skin cancers, risk factors

INTRODUCTION

Non-melanoma skin cancers (NMSC) are the most common cancers affecting both sexes among Caucasians and their incidence is increasing significantly in recent years (1). Data from the National Cancer Registry in Bulgaria show (2) that in 2009 there were 2231 new cases with NMSC and only 104 died from the disease. NMSC cover 12.4% of the total cancer incidence and only 0.6% of total cancer mortality.

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The high incidence rate and low mortality rate lead to a large number of persons with a history of skin cancer. In 2009 skin cancer survivors in Bulgaria were 55 701 and skin cancer prevalence rate covers 21.3% of the total cancer prevalence. Patients experienced NMSC are the largest group of cancer patients, both in Bulgaria and among all white populations (2).

Treatment of the large number of patients with NMSC, subsequent scarring, mutilation and disability convert into significant medical, social and economic problem for the society. The burden of skin cancer is even greater because of higher risk among survivors for new malignant conditions such as: 1.recurrences, 2.multiple skin cancers, 3.second primary tumors (1, 3).

Recent studies have shown that the recurrence rate depends on many risk factors. Such factors

include the anatomical localization of primary tumor, its size and clinical stage (TNM classification) and male sex, presence of photosensitive skin, age over 60 years at the diagnosis of the first tumor, histological type and immunological status (1). Treatment should be consistent with the characteristics of the tumor. It is as much better, as the smaller is the rate of recurrences.

The aim of this study is to investigate the recurrence rate and the importance of factors associated with their development after treatment of NMSC.

METHODS

This retrospective study includes 1630 patients (840 men and 790 women) registered in 1996 in Bulgaria with non-melanoma skin cancers (NMSC). Each patient has only one skin tumor, histologically proven. Patients were observed up to the end of 2006. Information on patients was obtained from the regional oncology dispensaries at the permanent address of the patient.

Questionnaire specifically designed for this study was used. It contains seven groups of questions about patient, primary tumor, treatment methods, presence of recurrence, repeated recurrences, lymph and visceral metastases.

For statistical analysis the following variables: gender, age, residence, comorbidities, TNM classification, histological type and anatomical localization of the tumor, treatment of primary tumors and recurrences were used. Codes of International Classification of Diseases - 9th revision (173.0-173.9) are applied.

RESULTS

Patients were followed for an average 122.8 months and the overall recurrence rate was evaluated.

The number of recurrences in the observation group was 103 or 6.3% is the overall recurrence rate.

There were 61 recurrences in men - 7.3% overall recurrence rate and 42 recurrences in women - 5.3% overall recurrence rate. Recurrence rate in men is higher, but the estimated relative risk, although higher was not statistically significant (RR = 1.37; 95% CI = 0.93÷2.00; p> 0.05).

Recurrence rate does not correspond to the incidence rate of NMSC by age groups. We found that the most affected by the disease are the age groups 70-74 years - 319 patients or 19.6% of all observed, followed by the group 65-69 years – 313 or 19.2%. The highest incidence of recurrences is in the group 50-54 years - 12.0%, followed by the group 40-44 years - 9.5 % and the group 55-59 years - 9.3%. Advanced age is associated with a risk for skin cancers developing, but not a risk factor for recurrences.

Among urban populations the number of recurrences is 57 or 6.2% overall recurrence rate and among rural population recurrences are 46 or 6.4% overall recurrence rate. There is no significant difference between the recurrence rate among urban and rural population.

The analysis according to anatomical localization of primary tumor is found that the recurrence rate is greatest in the lower limbs - 15.8% (6 recurrences of 38 primary cancers), followed by the frequency of recurrences of head and neck - 7.3% (8 recurrences of 109 tumors) and face - 6.4% (74 recurrences of 1163 tumors). A statistically significant risk of recurrence after treatment of tumors of the lower limbs is established (RR = 2.78; 95% CI = 1.19÷6.5; p <0.05). An increased risk of recurrences in carcinoma of the head and neck and face is found, but results are not significant (respectively, RR = 1.17; 95% CI = 0.59÷2.35; p = 0.65 and RR = 1.07; 95% CI = 0.89÷1.14; p = 0.91).

In our study, the recurrence rate in tumors with diameters less than 2 cm (T1) is 5.8% and for tumors with a diameter greater than 2 cm (T2-4) it is 10.4%. We find a significantly increased risk of tumor recurrence in T2-4-tumors compared to T1-tumors (RR = 1.54; CI = 1.03÷2.31; p = 0, 04).

The calculation of the recurrence rate according to histological type shows that adenoid carcinomas recur most often - 40% recurrence rate. There is a statistically significant risk for relapse in adenoid carcinomas compared to all other NMSC (RR = 9.88; 95% CI = 1.67÷58.49; p=0.001). Squamous cell carcinomas (total, regardless of the degree of differentiation) have a higher recurrence rate (8.0%) rather than solid

basal cell carcinomas (5.6%), but the risk is not significant. In situ carcinomas do not recur.

Surgical excision is the most commonly applied method of treatment in the followed group - 657 cases or 40.3% of all patients. The recurrence rate is low – 6, 4%. There is no significant risk of recurrence after surgical treatment.

Radiotherapy methods are often used in the treatment of skin cancers. The incidence rate in contactherapy was 4,0% and there is no significant risk for relapse. In conventional radiotherapy the recurrence rate is 13.2% and the risk was statistically significant (RR-2.03; CI = 1.46÷3.62; p = 0.0004). In interstitial brachytherapy the recurrence rate is low (4, 5%), but this method is rarely used.

Cryotherapy was applied in 106 patients or 6.6% and overall recurrence rate was 6, 6%. There is no significant risk of recurrence after cryotherapy.

Electrodesiccation and curettage is carried out in 94 patients or 5.8% of all treated patients. Relapses occurred in 11 or 11.7% recurrence rate. This represents 10.7% of all 103 relapse. A statistically significant risk for the occurrence of recurrences after electrodesiccation of NMSC is found (RR=1.93; CI = 1.06÷3.5; p = 0.03).

After the treatment of 103 patients with recurrences in 14 cases second recurrences occur - 13.6% overall recurrence rate. The analysis of data show that the second recurrences are more common in men, cancers of the face and large primary tumors (T3-T4), but the results were not statistically significant (p>0.05). The presence of one recurrence is a significant risk factor for a second recurrence (RR = 1.93; CI = 1.06÷3.5; p = 0.03).

Relapses occur after an average of 48.5 months (6÷118 months). The highest recurrence rate is during the first year - 17.5%. In the first three years are developed almost half of all recurrences - 48.5 %. In subsequent years the recurrence rate decreases and during the tenth year it is just 3.9%.

DISCUSSION

NMSC are characterized by diverse clinical manifestations and marked tendency to relapse. The tumor can recur repeatedly for many years after the initial treatment, and therefore the treatment of some NMSC can be prolonged and ineffective. In our study the overall recurrence rate is low – 6.31%. According to various authors the recurrence rate varies quite a range of 2-7% to 30-40% (4, 5, and 6).

Factors that contribute to the development of recurrences are very different. Some authors (7) found that men have a higher risk of relapse. In our study the recurrence rate in men is greater but the estimated risk, although higher was not significant.

NMSC affect the older patients. We established that the recurrence rate does not correspond to the incidence rate of NMSC by age groups. The age is associated with risk for developing skin cancers, but is not a risk factor for relapses.

Analysis of results according to residence of patients found that the incidence of NMSC by region does not correspond to the recurrence rate. There is no significant difference between the recurrence rate among urban and rural populations and geographic areas. We found a high recurrence rate in certain regions of the country - Blagoevgrad (15.8% recurrence rate), Varna (15.0% recurrence rate), Burgas (13.7% recurrence rate) and Plovdiv (11.7% recurrence rate). These results are rather related to local preferences about the methods of treatment than with climatic and geographic conditions.

According to many authors (1, 8) tumor localization correlates with the recurrence rate. Most NMSC are localized in the head region, where the tumors are also most difficult to treat. The particularly high-risk areas are the central region of the face involving the inner can thus, nostrils, and peri-auricular areas (9). Tumors on the scalp and forehead are considered to pose a middle risk of recurrence, whereas the low-risk areas comprise the neck, trunk and extremities (10). Some authors found a high recurrence rate in tumors of the upper limbs (1).

We consider that carcinomas of the face, head and neck are very difficult to treat because of the risk of recurrence, scars, blemishes and disfigurement. Tumors of the body and limbs have a good prognosis. Surprising to us was the high incidence of recurrences in carcinomas of the lower limbs. Multivariate analysis of these

cases showed that the high recurrence rate is associated with the method of treatment. All these tumors were treated by conventional radiotherapy, which proved to be unsuitable for tumors localized in the lower extremities.

Our results confirm the importance of tumor size as a risk factor for recurrence. We believe that the larger the primary tumor, the greater the risk for recurrence. It is found that the recurrence rate is increasing by approximately 7% for every one millimeter of tumor diameter (11).

Calculating the recurrence rate according to the histological type, we found that the highest risk is related with the adenoid carcinomas, especially when they are treated by radiotherapy. We and other authors (9) found a higher recurrence rate in squamous cell carcinomas. There are studies (3, 12) that establish a higher risk for recurrence in basal cell carcinomas. We consider that the high recurrence rate in basal cell carcinomas is rather associated with a large size, difficult to treat localization and inappropriate treatment method than the histological type only.

The applied treatment is a very important factor related with the risk of recurrences. The more effective therapeutic method, the lower the recurrence rate is (1, 3, 4, 5, 6, 13).

The distribution of patients according to the observed therapeutic methods is given in **Table1.**

Table 1.*Distribution of cases according to treatment methods*

	Treatment	Frequency	Percent
1	Surgicalexcision	657	40,3
2	Contactherapy	545	33,4
3	Conventional radiotherapy	143	8,8
4	Cryotherapy	106	6,5
5	Electrodesiccation	94	5,8
6	Local application of drugs	8	,5
7	Interstitial brachytherapy	44	2,7
8	Photodynamic therapy	2	,1
9	Electro-chemotherapy	2	,1
10	Combined therapy	29	1,8
	Total	1630	100

The most frequently used treatment method in Bulgaria is the surgical excision, followed by radiotherapy, cryotherapy and electrodesiccation and curettage. Laser therapy, photodynamic therapy, electro-chemotherapy and topical medications are occasionally used in certain indications. Due to the small number of cases the results of these methods are not significant.

Distribution of recurrences according to the treatment methods is given in **Table 2.**

Mohs micrographic surgery was not applied routinely. We believe as other authors (4, 5) that surgical excision remains the first treatment of choice for NMSC.

Three radiation techniques were available: interstitial brachytherapy, superficial contact therapy and conventional radiotherapy. The radiotherapist chose the treatment technique according to tumour parameters and patient characteristics (age, performance status).

Superficial contact therapy was routinely used in all small tumors when excision efficiency is impossible or undesirable. Interstitial brachytherapy is an effective, but difficult to implement method that requires special conditions and highly trained doctors. Therefore, it is rarely applied.

Conventional radiotherapy is often used, but overall recurrence rate is high. Multifactorial analysis of data showed that these results are related to the large size and ulcer-infiltrative growth of tumors treated with this method.

Table 2.*Distribution of recurrences according to treatment methods*

	Treatment	Cases with recurrences	Recurrence rate
1	Surgicalexcision	42	6,4%
2	Contactherapy	22	4,0%
3	Conventional radiotherapy	19	13,2%
4	Cryotherapy	7	6,6%
5	Electrodesiccation	11	11,7%
6	Local application of drugs	0	0
7	Interstitial brachytherapy	2	4,5%
8	Photodynamic therapy	0	0
9	Electro-chemotherapy	0	0
10	Combined therapy	0	0
	Total	103	6,3%

In accordance with other results (1, 4, 14) we establish that the recurrence rate in surgical excision is similar to the recurrence rate in superficial contactherapy and both therapeutic modalities are associated with a low recurrence rate. Thus, radiotherapy can be considered as a simpler alternative for the treatment of NMSC, especially in elderly individuals where the long-term cosmetic outcome is of a lesser concern than in younger subjects. The results also show that radiotherapy could be the preferred option for recurrent tumours, providing comparable, if not better, results than simple excision.

In Bulgaria electrodesiccation and curettage were not performed very often, except in very small and superficial tumor lesions. Electrodesiccation and curettage is a common treatment modality in Europe, but the results are highly variable. In skilled hands curettage can approach the efficacy of surgical excision, with cure rate of 90% or higher (15, 16, 17, 18).

Cryotherapy also not commonly used in our country. We believe that the efficacy of cryotherapy was significantly inferior to excision or radiotherapy, especially for unselected tumours and for head tumours

Other treatment options like photodynamic therapy (PDT), electro-chemotherapy, local application of imiquimod and 5-FU are rarely used in certain indications and local preferences in different centres.

Combination therapy is rarely applied in special cases, like resistant to treatment tumors, large size and localization difficult to access. In these patients overall recurrence rate is 8.2%. It should be noted that the success of the treatment administered depends largely on the skills of doctors and their experience. In skilled hands the treatment methods achieve high efficacy, with cure rate of 90% or higher (1, 19). However, for the inexperienced physicians the recurrence rates of over 30% are not uncommon, due to a poor technique or inappropriate selection of patients. We agree with other authors (17, 20) that the supervision and more intensive teaching of dermatology residents results in a much lower recurrence rates.

Recurrences occur most often during the first years after treatment of NMSC, but the risk of their occurrence remains long time. In addition, the development of a relapse increases the risk for second and subsequent relapses. It is therefore necessary, skin cancer survivors to be continuously followed up for the appearance of recurrences and second primary cancers.

The conducted study allowed us to determine the recurrence rate after the treatment of NMSC and to identify factors associated with risk of their occurrence. Our results are similar to those obtained by other authors (1, 21, 22) and show that tumor localization (face, head and neck), T-stage (large tumor size) and the method of treatment are significant predictors of the risk of recurrence.

Right selection of treatment method, depending on the characteristics of the tumor and the patient and better skills of doctors are the necessary conditions to achieve high therapeutic efficiency.

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