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Risk of Basal Cell Carcinoma after Hodgkin's Disease

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Key Words
Basal cell cancer · Hodgkin's disease

Schlüsselwörter
Basaliome · Morbus Hodgkin

Summary
Background: Basal cell cancer is a common skin cancer, yet studies of second tumors after Hodgkin's disease tend to exclude basal cell cancers as second malignant tumors from analysis. Basal cell carcinomas (BCC) are possibly more common in immunosuppressed patients and were recently implicated as indicators of subsequent malignancies. ***Materials and Methods:*** Our database of 1,120 patients with Hodgkin's disease (derived from the tumor registry) was investigated for the occurrence of later BCCs. Kaplan-Meier curves were calculated. ***Results:*** A total of 9 cases of BCC were observed 0–20 years after the diagnosis of Hodgkin's disease. One case relapsed after excision. The probability of second BCC was 2.1% after 15 years of follow-up and 7.1% after 20 years. Statistically, the risk for second BCC was increased only in younger patients and with prolonged follow-up, but not in the total group of patients with Hodgkin's disease. ***Conclusion:*** BCC is not a major threat for the survivors of Hodgkin's disease, but continued follow-up is necessary.

Zusammenfassung
Einleitung: Basaliome sind häufige Hauttumoren und wurden bis jetzt in den meisten Studien der Zweitneoplasien nach Morbus Hodgkin ausgeschlossen. Basaliome haben möglicherweise eine erhöhte Inzidenz bei immunsupprimierten Patienten, und wurden kürzlich als Indikator-Neoplasien für nachfolgende andere Tumoren beschrieben. ***Material und Methoden:*** Wir untersuchten unsere Datenbasis von 1120 Patienten mit M. Hodgkin auf das Auftreten von späteren Basaliomen. Kaplan-Meier-Kurven wurden errechnet. ***Ergebnisse:*** Insgesamt konnten wir 9 Fälle von Basaliomen 0–20 Jahre nach der Diagnose M. Hodgkin beobachten. Die Wahrscheinlichkeit des Auftretens von Zweitbasaliomen beträgt 2,1% nach 15 Jahren Nachsorge und 7,1% nach 20 Jahren. Gegenüber einem Normalkollektiv war das Auftreten von Basaliomen nur bei jüngeren Patienten und bei sehr langer Nachsorge erhöht, nicht jedoch im Gesamtkollektiv der Patienten mit M. Hodgkin. ***Schlußfolgerung:*** Basaliome gehören nicht zu den häufigsten Zweittumoren nach M. Hodgkin. Jedoch ist eine weitere Überwachung der Patienten, auch auf das Auftreten von Basaliomen, erforderlich.

Introduction

Patients treated for Hodgkin's disease have an increased risk to develop second malignant neoplasms. This risk correlates with age, stage of Hodgkin's disease, the treatment received, splenectomy, and certain other factors such as impaired immunity. At 15 years, a cumulative risk in the range of 11–18% to develop second malignant neoplasms was observed in different case series [for review see 1]. Basal cell carcinoma (BCC) is a frequent malignant tumor of the skin which rarely metastasizes. BCCs are associated with increasing age, exposure to sun light, and ionizing radiation [2]. An increased incidence of BCC was suggested in patients with AIDS [3]. In a case report, metastatic BCC was described in a patient infected with HIV [4]. More recently, BCCs were also described as predictors for other cancers such as non-Hodgkin's lymphomas, leukemias and carcinomas [5] and for malignant melanomas [6]. In several case series of second malignant tumors occurring after Hodgkin's disease, BCCs were either not mentioned [7–10] or excluded from analysis [11, 12]. We therefore investigated the incidence and the characteristics of BCCs in our database of 1,120 patients with Hodgkin's disease treated at 5 centers in Munich between 1976 and 1994.

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Materials and Methods

Starting from the database of the Munich tumor registry, 1,120 patients with the diagnosis of Hodgkin's disease treated at 5 hematology centers and the Department of Radiation Oncology were investigated for the development of second malignant tumors. All patients' files were reviewed, and details of the medical history and personal as well as professional health risks were analyzed. Concerning Hodgkin's disease, special interest was given to the date of diagnosis, exact staging, the histological subtype as well as staging procedures, e.g. splenectomy. In addition, duration and dose of radio- and chemotherapy, time to complete remission, time of relapse, further treatment and last follow-up were recorded. Complete follow-up was achieved by contacting either the patients or the treating physicians. In all cases, the patients or the physicians were asked if second tumors, especially secondary skin tumors had developed.

The 1,120 patients had a total follow-up of 10,116 years with a median follow-up of about 8 years. The median age at diagnosis was 31 years, ranging from 2 to 84 years. 55.8% of the patients were male. In the entire group of patients no cases of second spinal cell cancer and 2 cases of malignant melanoma were recorded.

The calculation of the expected number of BCCs was made on the basis of the incidence rates for the ICD (International Classification of Diseases) code 173 of the WHO where all non-melanoma skin cancers are registered. The incidence data are extracted from the 1993 report of the population-based Cancer Registry of Saarland (cancer registry in Southwestern Germany).

The comparison of the actual with the expected number of cases were made using the standardized incidence ratio (SIR). Assuming a Poisson distribution of the observed cancer events, 95% confidence intervals (CI) were calculated [13] for the decision whether or not SIR is statistically different from 1, i.e. whether or not the observed and the expected number of BCCs are statistically different. Kaplan-Meier analysis was performed according to standard methods.

Results and Discussion

A total of 9 cases of BCCs was recorded in our database of 1,120 patients treated for Hodgkin's disease (5 males and 4 females, for details see table 1). There were two groups of patients: in 6 patients the second malignancy was diagnosed at a rather young age (30–48 years), whereas in 3 patients the second malignancy was diagnosed at the usual age for BCCs (50–68 years). Most patients had mantle field irradiation, and most BCCs were located on the trunk and therefore in the field of previous radiotherapy. One patient had a BCC at the right earlobe which was not directly included in the previous radiation field. In one patient the diagnosis of BCC was coincidental to the diagnosis of Hodgkin's disease and therefore not related to any previous treatment for Hodgkin's disease. In another case, BCC was diagnosed 18 months after breast cancer and therefore has to be considered as a third malignancy. In no case metastatic basal cell cancer developed. One patient had a relapse of his basal cell cancer which was again treated by local excision. As can be seen from table 1, BCC occurred 0–20 years after the diagnosis of Hodgkin's disease (mean interval 13.7 years). Kaplan-Meier analysis showed a probability of developing second BCC of 0.1% after 10 years, of 2.1% after 15 years and of 7.1% after 20 years.

With respect to the distributions of sex, age and calendar period of our patient cohort the expected number of BCCs was calculated as 4.6. The SIR was 1.96, with 95% CI ranging from 0.89 to 3.74. Because the value 1 is in the CI of SIR, the observed number of BCC did not statistically differ from the expected. If only young patients (aged less than 40 years at diagnosis of BCC) are considered, in this age group a statistically increased risk of BCC becomes apparent (SIR 10.26, CI between 3.56 and 23.99).

Taken together, in the total group of patients with Hodgkin's disease, no statistically significant increase of cases with BCC was observed. However, younger patients have a low but significant risk. BCC is a common skin cancer and often underreported in studies of cancer incidence. In the International Data Base on Hodgkin's Disease a relative risk of 3.6 for males

Table 1. Cases of BCC occurring after Hodgkin's disease

Patient number, Sex	Age 1, years[a]	Age 2, years[b]	Stage of Hodgkin's disease	Therapy for Hodgkin's disease	BCC in radiation field?	Condition at last follow-up
1, m	15	30	IIIA	CM	yes	alive, CR (6/97)
2, f	16	30	IIA	RX	yes	alive, CR (7/97)
3, m	22	35	IIIA	CM	yes	alive, CR (relapse of BCC 6/97)
4, f	24	43[c]	IIB	RX	no	alive, CR (1/98)
5, m	25	36	IIIA	RX	yes	alive, CR (7/97)
6, m	28	48	IIA	CM	yes	alive, CR (7/97)
7, m	30	50	IIA	CM	yes	alive, CR (4/97)
8, m	52	63	IIB	CM	no	† (pneumonia, 5/92)
9, f	67	67	IIA	RX	N.A.	† (Hodgkin's disease, 6/93)

[a] Age at the time of HD diagnosis.
[b] Age at the time of BCC diagnosis.
[c] Diagnosis of BCC within 2 years of second breast cancer.
RX = Radiotherapy; CM = combined modality; CR = complete remission.

and 3.5 for females was reported without mentioning further details [14]. The conclusion of our study holds true if the database of Rochester, MN, USA, is taken for comparison [15]. In this population-based incidence study, a somewhat higher incidence in the general population was reported (age-standardized incidence/100,000 white residents: 175 cases for males, 124 for females). Damage to skin by ionizing irradiation has to be taken into consideration as an etiologic factor in patients treated for Hodgkin's disease. In a case report, BCC was reported to occur symmetrically over acromioclavicular joints following mantle field irradiation for Hodgkin's disease 18 years earlier [16]. In our collection of cases, 6/8 irradiated cases also have a similar topographic occurrence (BCC in or close to the original irradiation field for Hodgkin's disease). Taken together, at least in our group of patients, BCCs are until now not generally increased after the treatment of Hodgkin's disease. In young individuals, BCCs are uncommon [17]. Following treatment of Hodgkin's disease in young patients, second BCCs appear more frequent. In chronically immunosuppressed patients (recipients of kidney transplants), a 5-fold increase in the incidence of BCC was reported [18]. In Hodgkin's disease, immunity is transiently defective and recovers following successful treatment. As mentioned above, the risk of subsequent BCC after Hodgkin's disease is small and possibly limited to younger patients with more than 10 years follow-up. The prognosis of BCC following Hodgkin's disease is generally good. However, the clinician should be alerted for second skin cancer and unclear skin lesions should be biopsied early. A longer follow-up is necessary to assess later cases of BCC in patients irradiated for Hodgkin's disease.

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