Second Neoplasms in Patients with Merkel Cell Carcinoma

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BACKGROUND. Merkel cell carcinoma (MCC) has been associated with a high incidence of other skin tumors and hematological malignancies. The purpose of this study was to analyze data from the Israel Cancer Registry regarding the incidence of second neoplasms in patients with MCC and their impact on survival.
METHODS. Sixty-seven patients in whom MCC was diagnosed between 1983 and 1999 were included. Data were collected on age, gender and ethnic origin, dates of diagnosis of MCC and any other neoplasm, and date and cause of death, if applicable. Comparison of MCC-specific survival, estimated by the Kaplan–Meier product limit method, between patients with no other neoplasm and those with second primary tumors was performed by log rank test. Age-specific standardized incidence ratio (SIR) was calculated using 5751 age- and ethnic-matched malignant melanoma patients as a control group.
RESULTS. Seventeen patients (25%) had a second neoplasm before, concomitant with, or after the diagnosis of MCC; 2 of them also had a third primary tumor. The SIR was 2.8 (95% CI; range, 1.38–4.22), significantly higher than the control group. Almost half the tumors were squamous cell carcinomas, either skin or head and neck, and most of the remainder were hematological malignancies or breast and ovarian adenocarcinomas. On univariate analysis, the presence of another neoplasm, regardless of its chronology, was associated with higher MCC-specific mortality (65% vs. 40% for patients with MCC only; $P = 0.022$). Analysis of only those patients in whom a second neoplasm developed during follow-up after treatment for MCC yielded an estimated actuarial risk of developing a second primary of 2.1% for each year of observation.
CONCLUSIONS. There is a high incidence of second neoplasms, including noncutaneous solid tumors, in patients with MCC. The presence of these neoplasms, whether they appear before, after, or simultaneously with MCC, is associated with a higher MCC-specific mortality. ***Cancer*** **2001;91:1358–62.**
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Merkel cell carcinoma (MCC) is a rare and highly malignant tumor of the skin, first described by Toker[1] in 1972. Originally presumed to originate from the Merkel cell, a component of the amine precursor uptake and decarboxylation (APUD) system,[2] MCC now is considered a neuroendocrine tumor. Its diagnosis requires, in addition to the characteristic histologic features, either the presence of membrane-bound dense-core neurosecretory granules on electron microscopy[3,4] or positive findings on immunohistochemical staining for cytokeratin, chromogranin, and neuron-specific enolase.[5,6] The clinical course of MCC is often aggressive and lethal, characterized by frequent and rapid recurrences, either locoregional or distant.[7,8]

Data concerning the epidemiologic and clinical features of MCC

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are still limited. Studies on small series of patients have indicated an association of MCC with other skin tumors[9,10] as well as with hematologic malignancies.[11,12,13] In our previous report of 40 Israeli patients with MCC,[14] we described an excessive rate of second neoplasms, including solid nonskin cancers, documented, to our knowledge, for the first time in this patient population. In the current article, we review and update the data from the Israel Cancer Registry on the incidence of second neoplasms in MCC and analyze their impact on clinical outcome.

MATERIALS AND METHODS

According to the Israel Cancer Registry, between August 1983 and December 1999, a diagnosis of MCC was made in 67 patients. The histologic diagnosis was established by light microscopy and was supported by immunohistochemical staining or electron microscopy or both. Age, gender, ethnic origin, dates of diagnosis of MCC and any accompanying neoplasm, and date and cause of death, if applicable, were recorded in each case. The incidence of second neoplasms in the MCC study group was compared with the incidence of second neoplasms in age-, ethnic-, and period-matched controls including 5751 patients with malignant melanomas registered in the Israel Cancer Registry. The standardized incidence ratio (SIR) of a second neoplasm was calculated with a 95% confidence interval (CI).

Patients with no other neoplasms were compared by log rank test with patients who had second primary tumors. MCC-specific survival, defined as the time from diagnosis of MCC to death from MCC, if applicable, was estimated by the Kaplan–Meier product limit method. Patients who died of other causes, including other neoplasms, were considered lost to follow–up.

RESULTS

The epidemiologic characteristics of the patient population are summarized in Table 1. The vast majority were Ashkenazi Jews, evenly distributed by gender. Most of the patients were elderly. Their age distribution is shown in Table 2. Only 5 patients (8%) were younger than 50 years. The median age of the whole MCC group was 73 years (range, 19–90 yrs), and for the 17 patients with second neoplasms, 72 years (range, 51–84 yrs); this difference was not statistically significant.

The incidence of second neoplasm in the MCC group was significantly higher than that in the age-matched malignant melanoma control group: 25% (17 of 67) vs. 5.8% (332 of 5751). The calculated SIR for second neoplasm was 2.8 (95% CI; range, 1.38–4.22; $P < 0.05$).

TABLE 1
Epidemiologic Features of Patients

Features	No.	%
Gender		
Male	35	52
Female	32	48
Age (yrs)		
Median	73	
Range	19–90	
Ethnic origin		
Ashkenazi Jews	54	81
Sephardic Jews	11	16
Arabs	2	3

TABLE 2
Age Distribution

Age (yrs)	No. of patients (%)
< 50	5 (8)
50–59	10 (15)
60–69	11 (16)
70–79	29 (43)
> 80	12 (18)

At the time of diagnosis of MCC, 12 patients had a personal history of another neoplasm. The median length of time between the diagnosis of the previous tumor and the diagnosis of MCC was 4 years (range, 2–34 yrs). In 4 additional patients, a second neoplasm developed after the diagnosis of MCC (median time period, 3 yrs; range, 1–3 yrs). One patient presented with a synchronous tumor at the periphery of the MCC specimen. In addition, two of the patients who had a second neoplasm were diagnosed as having a third primary tumor. For one of these patients, the third tumor was discovered at the time of diagnosis of MCC and, for the other patient, one year later. Thus, out of our population of 67 patients with MCC, 17 (25%) had 19 additional neoplasms (Fig. 1).

Descriptions of the second neoplasms are presented in Table 3. Almost half the tumors were squamous cell carcinomas, occurring either in the skin ($n = 4$) or head and neck ($n = 3$). Of the remainder, most were hematologic malignancies ($n = 7$) or breast and ovarian adenocarcinomas ($n = 4$). One patient was operated for an anaplastic meningioma 3 years before the diagnosis of MCC.

On univariate analysis, the presence of another neoplasm, either before, after, or concomitant with the diagnosis of MCC, was associated with a significantly higher MCC-specific mortality (Fig. 2). Whereas

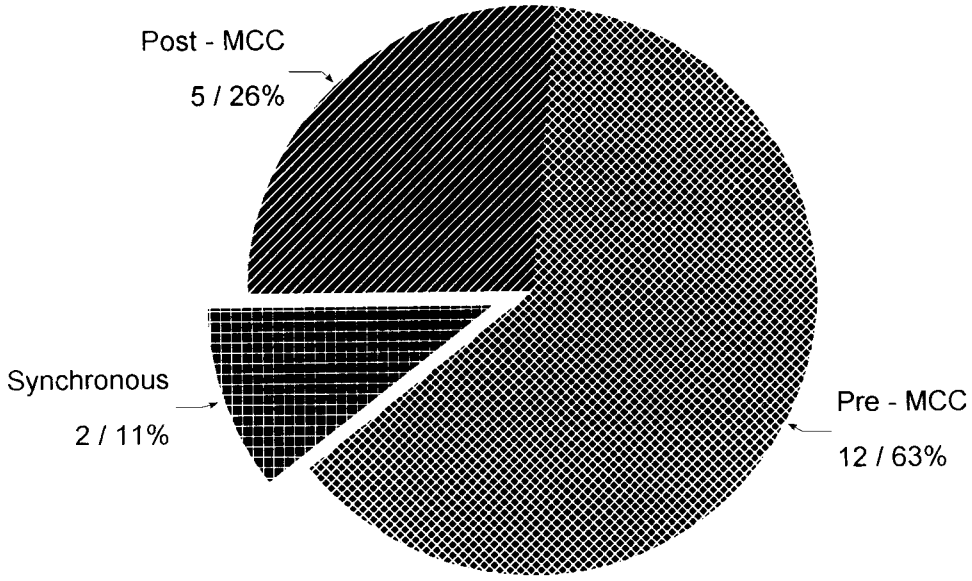

FIGURE 1. Chronology of second neoplasms relative to MCC.

TABLE 3
Second Neoplasms

	Patients (n = 17)[a]		Chronology (yrs)[b]	%
Squamous cell carcinoma	7			36.9
Nonskin		3		15.9
Larynx			1 −2	5.3
Tonsil			1 −24	5.3
Parotid			1 +1	5.3
Skin		4	−2, 0, 0, +3	21.0
Hematologic malignancies	7			36.9
Chronic lymphocytic leukemia		3	−3, −3, −4	15.9
Non-Hodgkin lymphoma		4	−19, −18, −4, +1	21.0
Adenocarcinoma	4			21.0
Breast		2	−19, +2	10.5
Ovary		2	−10, +3	10.5
Meningioma	1		−3	5.2

[a] Two patients had two additional neoplasms.
[b] Relative to MCC.

11 of the 17 patients (65%) with other tumors died of generalized metastatic MCC, only 20 of the remaining 50 patients (40%) did so ($P = 0.022$). Of the six patients with second neoplasms who did not die of MCC, five were alive at the time of analysis. One woman died of non-Hodgkin lymphoma.

A separate analysis was performed for patients in whom a second neoplasm developed during follow-up after treatment for MCC. As shown in Figure 1, there were 5 such patients (7.6%). Considering that the average follow-up period from diagnosis of MCC was 3.6 years (range, 0.25–10 yrs), the estimated actuarial risk of developing a second primary cancer after MCC was 2.1% for each year of observation. The malignancies diagnosed after treatment for MCC included breast, ovarian, parotid, and skin carcinomas, as well as non-Hodgkin lymphoma. Four of these patients (80%) died of MCC at 24, 25, 34 and 50 months after its diagnosis, and 1 patient, with squamous cell carcinoma of the skin, was alive at the time of analysis.

DISCUSSION

For the current study, the entire database of the Israel Cancer Registry was reviewed and analyzed to better define the relation between MCC and the development of other cancers.

Comparison of the epidemiologic features of the population comprising our database with the features of populations reviewed in the literature[9,15] yielded a high consistency. The mean reported age at diagnosis of MCC was 68 and 69 years, respectively, with 92% of the patients older than 50 years; the incidence of MCC was almost equal between the sexes. The fact that all the patients in our series were Caucasians, mostly belonging to the lighter Ashkenazi subpopulation, is also in accordance with previous reports.[11,16]

We noted a high incidence (25%) of second neoplasms among our population of MCC patients. This rate was significantly higher than that for the age-matched control group of patients diagnosed during the same period with an equally deadly cutaneous neoplasm, malignant melanoma. Moreover, 2 of the study patients had a third primary tumor, bringing the total incidence of second primary tumors to 19 (28%).

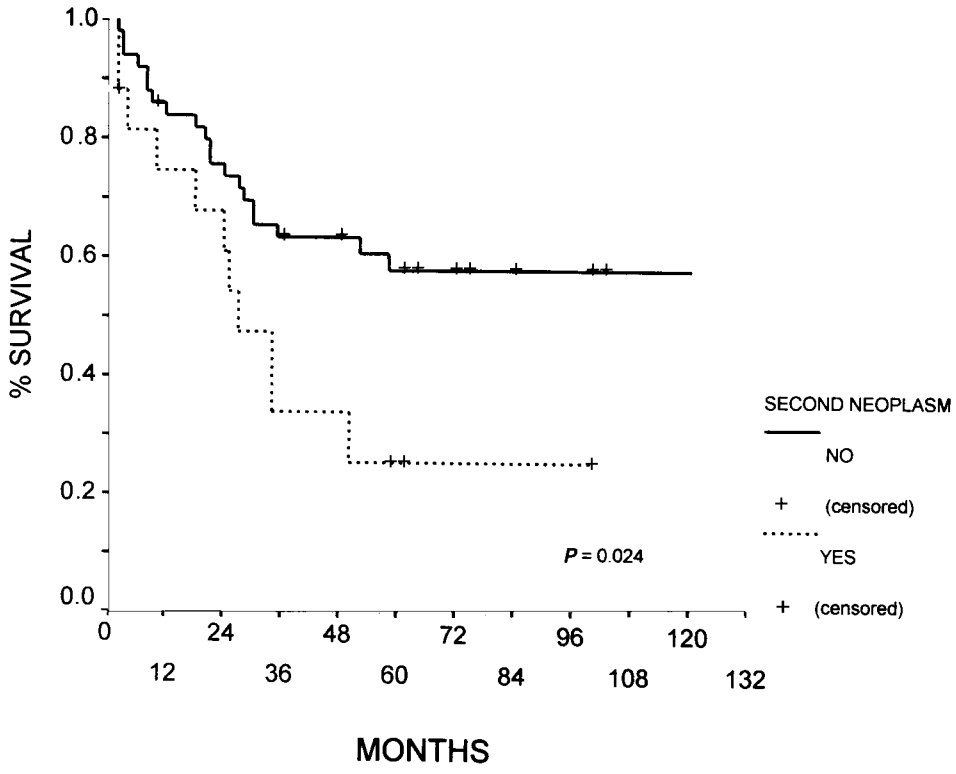

FIGURE 2. MCC-specific survival by presence of a second neoplasm.

As opposed to previous reports,[11–13] which related MCC to skin and hematologic malignancies only, our series found that almost half the second neoplasms were nonskin solid tumors. We believe this finding supports the assumption in our previous study[13] that MCC is associated with an increased risk of second cancers in general. It is noteworthy that, with the exception of one meningioma, all of the nonskin solid tumors in our series were breast and ovarian carcinomas or head and neck cancers.

The majority of the second primary tumors preceded the diagnosis of MCC. This is not surprising considering that most of the MCC tumors in our patients were diagnosed in the last 10 years, thereby covering many more person-years of observation before than after this point of reference. This asymmetry precludes any definitive conclusion regarding the chronology of second malignancies relative to MCC.

One finding that has an immediate clinical implication is the high risk of occurrence of other neoplasms during the course of follow-up after treatment for MCC, namely 2.1% for each year of observation. As many of these subsequent neoplasms are amenable to early detection and, therefore, successful treatment, it is important for clinicians to be highly aware of this possibility during routine follow-up of these patients.

The existence of a second malignancy, whether preceding, copresenting, or following MCC, was associated with a higher MCC-specific mortality. Of the 17 patients with second primary tumors, 11 died of MCC. We suggest that this finding may be linked, at least in part, to the underlying reason for the association of MCC with second neoplasms.

One explanation for the high risk of other skin cancers in patients with MCC may be the possible contributory role of sunlight in the development of MCC, as suggested by several reports.[9,16] Other investigators[11,17,18] have linked MCC to various immune-compromised conditions. The relation between some of the neoplasms that have been associated with MCC, including those in our own series, and impaired immunity has already been well established (chronic lymphocytic leukemia, non-Hodgkin lymphoma, etc.). Whether the neoplasms related to MCC represent predisposing immune-compromised conditions for its development or are the result of a common predisposing immune-compromised situation is still unclear. There also may be a genetic aspect. Vortmyer et al.[19] found cytogenic changes in chromosome 1 that resembled the genetic changes in neoplasms of neural crest origin. In a cytogenetic analysis of 12 specimens of MCC,[20] 3 were shown to be devoid of the Y chro-

mosome. Even though the significance of the Y chromosome loss remains unclear, such a major cytogenetic disturbance could be relevant to the high risk of other cancers. The recently reported[21] basic dysregulations of the cell cycle in MCC, namely, a high expression of the antiapoptotic gene *bcl-2* and high mutation rate of the proapoptotic gene *p53* in MCC specimens, also may play a role. In any case, regardless of whether the association between MCC and other cancers has an immunologic or genetic basis, or both, the association could be relevant to the poorer outcome of affected patients.

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