**Effect of Radiation Therapy on Survival in Patients With Resected Merkel Cell Carcinoma**

A Propensity Score Surveillance, Epidemiology, and End Results Database Analysis

Julian A. Kim, MD, MS; Audrey H. Choi, MD

**IMPORTANCE** Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine malignant neoplasm that can be highly aggressive and ultimately lethal. However, the cumulatively low incidence rate has made it difficult to accrue patients to prospective randomized trials.

**OBJECTIVE** To determine whether patients with MCC in the Surveillance, Epidemiology, and End Results (SEER) database who received radiation therapy after resection demonstrate improved survival.

**DESIGN** The study population consisted of SEER patients with histologically confirmed MCC who underwent surgical resection between January 1, 1998, and December 30, 2006. Cox proportional hazards regression models were used to determine factors associated with MCC-specific and overall survival. Propensity scoring with matched pairs was used to perform Kaplan-Meier survival analysis comparing patients who underwent surgery plus radiation therapy vs those who underwent surgery alone.

**SETTING AND PARTICIPANTS** National database study of participants at least 20 years old with MCC, matched for age, sex, race/ethnicity, diagnosis period, tumor size, disease stage, surgery of the primary site, type of lymph node surgery, and geographic region. Exclusion criteria included survival of less than 4 months and metastatic disease.

**MAIN OUTCOMES AND MEASURES** Disease-specific survival and overall survival.

**RESULTS** Factors that were independently associated with the use of radiation therapy included marital status, disease stage, and type of lymph node surgery. Factors associated with both MCC-specific and overall survival included age and disease stage. Propensity scoring and matched-pair analysis resulted in 269 matched pairs of patients and demonstrated that patients who received radiation therapy had improved overall survival ($P = .03$) but not MCC-specific survival ($P = .26$).

**CONCLUSIONS AND RELEVANCE** The improvement in overall survival among SEER patients who receive radiation therapy following surgical resection of MCC may be a result of selection bias or unmeasured factors and not radiation therapy.
Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine malignant neoplasm that can be highly aggressive and ultimately lethal. Although the exact cause of MCC is unknown, evidence suggests prolonged sun exposure is contributory,\textsuperscript{1,2} as well as possible alterations in p53 and Merkel cell polyomavirus expression in MCC cells.\textsuperscript{3,4} The incidence of MCC is rising: from 1986 to 2001, it increased 3-fold.\textsuperscript{5} However, the cumulatively low incidence rate has made it difficult to accrue patients to prospective randomized trials.

Surgical therapy is the primary treatment for cutaneous MCC. Although it is generally well accepted that adjuvant systemic chemotherapy is not indicated in patients with surgically resected MCC, the use of radiation therapy has remained an area of intense interest and debate. Early studies\textsuperscript{6,7} of radiation therapy to the MCC excision site demonstrated low local recurrence rates, although most investigations were limited by a small sample size, few patient follow-up data, and the lack of a matched comparison group. However, radiation therapy of both the primary MCC site and the regional lymph node bed is becoming widely adopted, without compelling supportive data.

The primary aim of this study was to examine whether radiation therapy following surgical resection of cutaneous MCC was associated with MCC-specific and overall survival using Cox proportional hazards regression models and propensity score matching techniques. Propensity scoring and matched-pair analysis are methods that reduce covariate imbalance between patients in treatment and control groups,\textsuperscript{8} allowing for the analysis of treatment effect among matched pairs of individuals. A secondary aim of this study was to determine factors that are associated with the use of adjuvant radiation therapy in patients with resected MCC in the United States.

Methods

Study Population
The Surveillance, Epidemiology, and End Results (SEER) database is a national database that captures information from approximately 14% of the US population. Patients included in the present study (1) were at least 20 years old; (2) were diagnosed between January 1, 1998, and December 30, 2006, with histologically confirmed MCC (International Classification of Diseases for Oncology, Third Edition codes 8246 and 8247, for cutaneous neuroendocrine tumor and MCC, respectively); and (3) had cutaneous MCC of the head and neck (codes C44.0-44.4), trunk (code C44.5), upper extremity (code C44.6), lower extremity (code C44.7), or other nonspecified cutaneous location (codes C44.8-44.9).

Exclusion criteria included the following: unstaged disease, unknown tumor size, unknown radiation therapy status, unknown lymph node surgery status, patient survival of less than 4 months, metastatic disease at the time of diagnosis, and unknown patient demographics needed for propensity score matching.

Variables of Interest
In addition to the histological and anatomical site codes listed previously, age, sex, race/ethnicity, diagnosis period, and geographic region, as well as tumor size, disease stage, surgery of the primary site, and type of lymph node surgery, were used as variables for the study. Diagnosis periods were grouped as 1998 to 2000, 2001 to 2003, and 2004 to 2006. Tumor size was classified as 2 cm or smaller or larger than 2 cm. For disease stage, localized disease was defined as limited to the primary site (MCC stages I and II). Regional disease was defined as MCC spread beyond the primary site of origin (MCC stage III). Surgery of the primary site was categorized as local tumor destruction or radical excision. Local tumor destruction included local tumor destruction, local tumor excision, biopsies followed by excision, and Mohs surgery. Radical excision included wide local excision and local amputation. Type of lymph node surgery included no lymph nodes removed, sentinel lymph node biopsy, and removal of regional lymph nodes. Individual SEER registries were classified as the following geographic regions: East (Connecticut and New Jersey), Midwest (Iowa and Detroit, Michigan), South (Kentucky, Louisiana, and Atlanta, Georgia), and West (Hawaii, New Mexico, Utah, and Seattle, Washington, as well as California, excluding San Francisco, San Jose, and Los Angeles, and San Francisco–Oakland, San Jose–Monterey, and Los Angeles). In current medical practice, the determination of MCC grade is not uniform; for this reason, histological grade was not included as a variable in the analyses.

Statistical Analysis
Univariate analysis was performed using \( t \) test for testing of differences between means and Pearson \( \chi^2 \) test for testing of differences between proportions. The significance level was set at \( P < .05 \).

Multivariate analysis of factors associated with the use of radiation therapy was performed using logistic regression and stepwise elimination of nonsignificant covariates to produce a full-effects model. Interactions between covariates were tested by including the interaction term in the logistic regression model, with significant \( P \) values included in the final logistic regression model if the interaction was determined to be clinically or biologically relevant. Adjusted odds ratios (95% CIs) were calculated for each covariate. Cox proportional hazards regression models were used to determine covariates associated with MCC-specific and overall survival. Covariates were tested for interactions by including the interaction term in the Cox proportional hazards regression model. Hazard ratios (95% CIs) were reported for each covariate in the Cox proportional hazards regression model, with the significance level set at \( P < .05 \). All analyses were performed using statistical software (SAS, version 9.2; SAS Institute, Inc).

Propensity Score Matching Procedures and Survival Analyses
Propensity scores to determine the conditional probability of receiving radiation therapy were generated using logistic regression.\textsuperscript{9} The logit of the propensity score was then used for patient matching with the calipers set in the method.\textsuperscript{10} A 1:1 patient matching with replacement was used to pair each patient who received surgery alone with another patient who received surgery plus radiation therapy whose propensity score was within the designated caliper size.\textsuperscript{11}
A total of 269 matched pairs of patients who had surgery alone or surgery plus radiation therapy was generated from the propensity score and matching procedure. The standardized difference for each covariate between the 2 patient groups was then calculated and compared before and after the matching process to determine covariate balance between the 2 groups.10

For survival analysis of the propensity score–matched pairs, the censored data version of the sign test by Klein and Moeschberger12 was used. Kaplan-Meier survival analysis was also used.

Results

Univariate and Multivariate Analyses of Factors Associated With the Use of Radiation Therapy

A total of 747 patients comprised the final study population, of which 343 had surgery alone and 404 had surgery plus radiation therapy. To determine factors associated with the use of radiation therapy following surgical resection of MCC, univariate and multivariate analyses were performed. Statistically significant covariates in the univariate analyses were age (P = .003), diagnosis period (P = .02), marital status (P = .045), tumor size (P = .02), disease stage (P < .001), and type of lymph node surgery (P < .001).

To determine which covariates were independently associated with the use of radiation therapy, multivariate logistic regression was performed. A strong interaction between surgery of the primary site and type of lymph node surgery (P = .007) was found, and this interaction term was included in the final logistic regression model because a possibility exists that the interaction could influence the decision to administer radiation therapy. When adjusting for other factors, age was no longer significantly associated with the use of radiation therapy (Table 1). Patients who had localized disease had an approximately 50% lower odds of having radiation therapy following surgical resection compared with patients who had regional disease (odds ratio, 0.50).

The results of the multivariate analysis specific to surgery of the primary site, type of lymph node surgery, and their interaction are summarized in Table 1. Among patients who had local excision of the primary MCC, those who underwent sentinel lymph node biopsy had a more than 3 times higher odds of receiving radiation therapy after surgery compared with patients who had local excision and no lymph node biopsy procedure (odds ratio, 3.12). By contrast, in patients who had radical excision of the primary MCC, those who subsequently underwent lymph node dissection had an almost 2-fold higher odds of undergoing radiation therapy compared with those who had no lymph node surgery (odds ratio, 1.95).

Effect of Radiation Therapy on MCC-Specific and Overall Survival Using Cox Proportional Hazards Regression Models

Multivariate analysis using Cox proportional hazards regression models was performed to determine which covariates were independently associated with MCC-specific and overall survival. The following 2 significant interactions were included in the Cox proportional hazards regression model for MCC-specific survival: sex × disease stage (P = .02) and surgery of the primary site × disease stage (P = .04). No interactions were included in the Cox proportional hazards regression model for overall survival.

Results of the Cox proportional hazards regression model are summarized in Table 2. Covariates significantly associated with MCC-specific survival included age (hazard ratio, 1.03), nonwhite race/ethnicity (hazard ratio, 0.29), and the interaction between surgery of the primary site and disease stage. Radiation therapy was not significantly associated with MCC-specific hazard of death: the hazard ratio for no radiation therapy was 0.94. Similarly, tumor size, surgery of the primary site, tumor histological findings, and type of lymph node surgery were not significantly associated with MCC-specific hazard of death.

When examining the interactions of disease stage with sex and surgery of the primary site, localized disease stage was significantly associated with a lower risk of MCC-specific death among all anatomical sites in women except the lower extremity (Table 3). In men, localized disease stage in the head and neck was associated with a reduced risk of death (hazard ratio, 0.38).

Several covariates were significantly associated with overall survival. Increasing age (hazard ratio, 1.04; 95% CI, 1.03-1.06) was associated with a greater hazard of death. Female sex (hazard ratio, 0.55; 95% CI, 0.42-0.72), localized disease (hazard ratio, 0.64; 95% CI, 0.50-0.83), and tumor size of 2 cm or
less (hazard ratio, 0.77; 95% CI, 0.60-0.99) were significantly associated with a decreased hazard of death. Patients who underwent sentinel lymph node biopsy had a lower hazard of death compared with those who had no lymph node surgery (hazard ratio, 0.59; 95% CI, 0.40-0.88). Finally, in contrast to MCC-specific survival, a lack of radiation therapy was significantly associated with a higher hazard ratio of death from all causes (hazard ratio, 1.28; 95% CI, 1.01-1.63).

In summary, radiation therapy was not associated with MCC-specific survival by multivariate Cox proportional hazards regression analysis. Multivariate analysis demonstrated a significant association of radiation therapy with a reduced hazard of death from all causes.

**Propensity Scoring and Matched-Pair Analysis**

Propensity scoring was used to generate a subset of patient pairs who were matched based on similar patient and tumor characteristics. Table 4 summarizes the covariate balance between the surgery alone group and the surgery plus radiation therapy group before and after propensity score matching. In general, an absolute standardized difference of less than 10% indicates good covariate balance between 2 groups.

Significant differences existed between the 2 groups for tumor site and size, geographic region, specific diagnosis periods, surgery of the primary site, and type of lymph nodes surgery before propensity scoring and matching, which were corrected by the matching process (Table 4). Before matching, the proportions of patients with tumors of 2 cm or less were 65.0% in the surgery alone group and 56.7% in the surgery plus radiation therapy group (standardized difference, −17.1%). After matching, the proportions of patients with tumors of 2 cm or less were 62.1% in the surgery alone group and 61.0% in the surgery plus radiation therapy group (standardized difference, −2.3%). Similar reductions in standardized differences to less than 10% were observed with the disease stage and type of lymph node surgery covariates.

**Survival Analysis of Propensity Score-Matched Patient Pairs**

Kaplan-Meier survival analysis was used to plot the survival estimates for MCC-specific and overall survival of 269 propen-
Although diagnosis period was significantly associated with the administration of radiation therapy in univariate analysis, this association of radiation therapy with improved overall survival may be related to selection bias or differences in unmeasured factors between groups. The sensitivity analysis of the Cox proportional hazards regression model demonstrates that the results may be significantly altered by hidden bias, which suggests that incorporation of other unmeasured factors into a revised analysis may result in a lack of association of radiation therapy with overall survival.

Recent work investigating viral and protein abnormalities found in MCC cells continues to add to the body of knowledge regarding this disease. Since Feng et al. published their discovery of the Merkel cell polyomavirus in human MCC cells in 2008, several other investigators have studied Merkel cell polyomavirus and the transcription factor p63 as prognostic factors in MCC. Although the studies have shown that most MCC cells contain Merkel cell polyomavirus DNA, they did not consistently demonstrate that the presence of viral DNA correlated with disease-specific or overall survival. The few studies on p63 expression in MCC cells report this to be a poor prognostic factor, with Asislo et al. and Hall et al. showing decreased survival associated with p63 expression. It is possible that these new factors, other undiscovered factors, or covariates uncaptured by SEER are related to the improvement in overall survival demonstrated in the radiation therapy group of this study.

The results of the present study also provide insight into patient and clinical factors that are associated with the use of radiation therapy following surgical resection of MCC in the United States. The fact that approximately 40% of the patients in the study did not undergo radiation therapy suggests that adjuvant radiation therapy has not become standard medical care for all patients with MCC in the United States. Although diagnosis period was significantly associated with the administration of radiation therapy in univariate analysis, multivariate analysis indicates that diagnosis period was not independently associated with radiation therapy, suggesting that the recent decades have not demonstrated a trend toward more radiation therapy.
To date, no prospective randomized clinical trials have tested whether radiation therapy in addition to surgery improves disease-specific or overall survival in patients with MCC. The use of SEER data for studying patients with uncommon tumors, such as MCC, allows the analysis of outcomes of many patients, but inherent limitations exist in the use of SEER data.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Before Matching</th>
<th>After Matching</th>
<th>Standardized Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery Alone</td>
<td>Surgery and Radiation Therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 343)</td>
<td>(n = 404)</td>
<td>(n = 269)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>74.9 (12.4)</td>
<td>72.2 (12.6)</td>
<td>−1.7</td>
</tr>
<tr>
<td>Median</td>
<td>77</td>
<td>75</td>
<td>NA</td>
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<tr>
<td>Sex, No. (%)</td>
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<td></td>
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<tr>
<td>Female</td>
<td>149 (43.4)</td>
<td>172 (42.6)</td>
<td>−1.8</td>
</tr>
<tr>
<td>Male</td>
<td>194 (56.6)</td>
<td>232 (57.4)</td>
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<tr>
<td>Race/ethnicity, No. (%)</td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
<td>325 (94.8)</td>
<td>386 (95.5)</td>
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<tr>
<td>Nonwhite</td>
<td>18 (5.2)</td>
<td>18 (4.5)</td>
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<td>Diagnosis period, No. (%)</td>
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<td>1998-2000</td>
<td>72 (21.0)</td>
<td>59 (14.6)</td>
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<td>2001-2003</td>
<td>135 (39.4)</td>
<td>153 (37.9)</td>
<td>−3.1</td>
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<td>2004-2006</td>
<td>136 (39.7)</td>
<td>192 (47.5)</td>
<td>15.9</td>
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<td>Marital status, No. (%)</td>
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<td>Married</td>
<td>197 (57.4)</td>
<td>261 (64.6)</td>
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<tr>
<td>Unmarried</td>
<td>146 (42.6)</td>
<td>143 (35.4)</td>
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<td>Geographic region, No. (%)</td>
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<tr>
<td>East</td>
<td>66 (19.2)</td>
<td>59 (14.6)</td>
<td>−12.4</td>
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<tr>
<td>Midwest</td>
<td>30 (8.7)</td>
<td>45 (11.1)</td>
<td>5.6</td>
</tr>
<tr>
<td>South</td>
<td>42 (12.2)</td>
<td>48 (11.9)</td>
<td>−1.1</td>
</tr>
<tr>
<td>West</td>
<td>205 (59.8)</td>
<td>255 (63.1)</td>
<td>6.9</td>
</tr>
<tr>
<td>Tumor histological finding, No. (%)</td>
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<tr>
<td>MCC</td>
<td>339 (98.8)</td>
<td>400 (99.0)</td>
<td>1.7</td>
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<tr>
<td>Cutaneous neuroendocrine carcinoma</td>
<td>4 (1.2)</td>
<td>4 (1.0)</td>
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<td>Tumor site, No. (%)</td>
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<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>137 (39.9)</td>
<td>164 (40.6)</td>
<td>1.3</td>
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<tr>
<td>Trunk</td>
<td>44 (12.8)</td>
<td>55 (13.6)</td>
<td>2.3</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>93 (27.1)</td>
<td>110 (27.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>69 (20.1)</td>
<td>72 (17.8)</td>
<td>−5.9</td>
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<tr>
<td>Other</td>
<td>0</td>
<td>3 (0.7)</td>
<td>12.2</td>
</tr>
<tr>
<td>Tumor size, cm, No. (%)</td>
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<td></td>
<td></td>
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<tr>
<td>≤2</td>
<td>223 (65.0)</td>
<td>229 (56.7)</td>
<td>−17.1</td>
</tr>
<tr>
<td>&gt;2</td>
<td>120 (35.0)</td>
<td>175 (43.3)</td>
<td>NA</td>
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<td>Disease stage, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>215 (62.7)</td>
<td>179 (44.3)</td>
<td>−37.5</td>
</tr>
<tr>
<td>Regional</td>
<td>128 (37.3)</td>
<td>225 (55.7)</td>
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<tr>
<td>Surgery of the primary site, No. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Local tumor destruction</td>
<td>155 (45.2)</td>
<td>172 (42.6)</td>
<td>−5.3</td>
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<tr>
<td>Radical excision</td>
<td>188 (54.8)</td>
<td>232 (57.4)</td>
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<td>Type of LN surgery, No. (%)</td>
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<tr>
<td>No LNs removed</td>
<td>210 (61.2)</td>
<td>191 (47.3)</td>
<td>−28.3</td>
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<tr>
<td>SLNB NOS</td>
<td>65 (19.0)</td>
<td>80 (19.8)</td>
<td>2.2</td>
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<tr>
<td>Regional LNs removed</td>
<td>68 (19.8)</td>
<td>133 (32.9)</td>
<td>30.0</td>
</tr>
</tbody>
</table>

Abbreviations: LN, lymph node; MCC, Merkel cell carcinoma; NA, not applicable; NOS, not otherwise specified; SLNB, sentinel lymph node biopsy.
The SEER database does not capture information regarding margin status after surgical resection or about radiation therapy dose, the timing of radiation therapy, and whether radiation therapy was administered to only the primary tumor site or included the regional lymph nodes. In addition, the inclusion of other important covariates, such as the Charlson comorbidity index or some other indicator of performance status, would help to reduce selection bias and balance the 2 study groups.20

In conclusion, although the present findings suggest an improvement in overall survival associated with the use of radiation therapy following surgical resection of MCC, the lack of improvement in MCC-specific survival brings into question the therapeutic value of radiation therapy for these patients. A prospective randomized national or international study could address this issue, although it may be difficult to accrue patients because of strong physician bias. For the present, patients and physicians should be aware that selection bias or bias related to confounders may be the reason why overall survival is improved in patients with MCC who undergo radiation therapy.

ARTICLE INFORMATION
Author Contributions: Drs Kim and Choi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kim.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Administrative, technical, and material support: Kim.
Study supervision: Kim.
Obtain funding: Kim.
Conflict of Interest Disclosures: None reported.
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REFERENCES
NOTABLE NOTES

Notable Noses

Walter H. C. Burgdorf, MD; Leonard J. Hoenig, MD

Although the nose is a small organ, it is centrally located and subject to scrutiny. A number of skin disorders primarily affect the nose, causing potentially embarrassing lesions. Some people have turned their nasal maladies to advantage, using them to make a statement about life.

In 1987, President Ronald Reagan was treated for a basal cell carcinoma on the nose. At a White House briefing, he pointed to a small Band-Aid on his nose and said: “This is just a small billboard that says... ‘stay out of the sun.’”1 His remarks helped raise public awareness about the rising epidemic of skin cancer in the United States.

Unusual noses often evoke humorous responses, prompting some comedians to poke fun at their proboscises. One of the great comedians and movie stars from the first half of the 20th century was W. C. Fields (1880-1946), who suffered from rosacea and rhinophyma, developing a large red nose that became part of his comic persona. Field’s red nose at times needed special attention from makeup and camera crews to neutralize its bright color. In 1941, Fields received radiotherapy for his rhinophyma, but his nose became infected and kept the actor out of the public eye for almost a month.2 Radiotherapy was used to treat acne and rosacea during that era, and its beneficial effects were probably due to a reduction in the size and number of sebaceous glands.

A “W. C. Fields nose” is today synonymous with these dermatologic conditions. In a radio broadcast, Fields traded insults with ventriloquist Edgar Bergen’s famous dummy, Charlie McCarthy, who asked: “Is it true, Mr. Fields, that when you stood on the corner of Hollywood and Vine, 43 cars waited for your nose to change to green?”3

The nose has also been used as a subject by artists who themselves suffered from nasal disorders. Andy Warhol (1928-1987) was an outstanding American pop artist who underwent dermabrasion in 1957, presumably to treat rhinophyma. Cosmetic surgery of the nose later became the focus of his early 1960s painting “Before and After,” which depicts an enlarged version of a black and white advertisement for plastic surgery. It shows 2 profiles of the same woman, before and after an operation on her nose. On the left is a big, curved nose, and on the right, is the surgically corrected, cute, turned-up nose. Warhol’s artwork teaches us something about who we are. In “Before and After,” we find symbolically portrayed our own perceived deficiencies and hopes for something better.

There is much to learn about dermatology from studying the nose, especially those that are notable. In the process we can also learn some interesting lessons about life.

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REFERENCES

