Multimodality Management of Merkel Cell Carcinoma

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Hypothesis: Merkel cell carcinoma is a rare dermal neuroendocrine carcinoma whose optimal treatment and prognostic factors are poorly defined. We hypothesize that high-risk patients with Merkel cell carcinoma are best treated with multimodality therapy.

Design: A retrospective review of all patients (N = 33) with Merkel cell carcinoma treated at the Massachusetts General Hospital from January 1, 1980, to August 24, 1997. Median follow-up time was 37 months (range, 6-157 months).

Patients: Adequate data for evaluation were available for 31 patients. Male to female distribution was 14 men and 17 women, with a median patient age of 68 years.

Main Outcome Measure: Stage at presentation; factors associated with recurrence; and the effects of surgery, radiation therapy (XRT), and chemotherapy on recurrence, salvage, and survival rates.

Results: There were 12 extremity, 11 head and neck, and 8 truncal tumors. There were 22 isolated primary tumors, 8 with additional clinically positive lymph nodes, and 1 with distant disease. Therapy was local excision with or without XRT in 19 patients, local resection and lymphadenectomy with or without XRT in 8 patients, and XRT alone in 4 patients with head and neck tumors. Fifteen patients developed recurrences (7 local, 8 nodal, and 10 distant). Median time to recurrence was 8 months (range, 3-48 months). There were 7 tumor-related deaths, 6 of which were associated with truncal lesions (P<.001). No locoregional recurrences occurred in patients with margins of resection of 2 cm or greater or adequate XRT. A multivariate analysis selected truncal location (P = .005) and nodal disease (P = .05) as predictors of mortality. Remission was possible in 5 patients with locoregional and 2 patients with distant recurrences.

Conclusions: Merkel cell carcinoma is an aggressive dermal cancer with frequent nodal metastases; truncal tumors have the worst prognosis. Locoregional recurrence correlates with inadequate margins and lack of XRT, but remission is possible with multimodality therapy.

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Merkel cell carcinoma (MCC), a neuroendocrine carcinoma of the dermis, is an extremely rare and aggressive malignant neoplasm. This tumor has a high propensity for local recurrence (20%-75%), regional nodal metastases (31%-80%), and distant metastases (26%-75%).

Approximately one third of patients eventually die of their disease.

Toker11 first described MCC in 1972, and the first published series appeared in 1982.1 Since that time, slightly over 600 cases have been reported in the literature. Merkel cell carcinoma has a distinctive appearance, presenting clinically as a red to violaceous intradermal nodule. The lesion typically increases rapidly in size over a few weeks to months. Recommended management has usually been surgical excision of the primary lesion, with wide margins (1-3 cm) advocated by most authors.2,10,11,13 In addition, some have recommended a prophylactic lymphadenectomy due to the propensity for early occult spread to regional nodes.14,15 More recently, sentinel lymph-node mapping has been used in MCC to detect the presence of regional nodal metastases. This technique allows one to perform selective lymph-node dissection.16

Most authors have recommended adjuvant radiation therapy (XRT) for local control, but a survival benefit has not been demonstrated. Meeuwissen et al17 demonstrated a substantial benefit in both time to recurrence and disease-free survival when XRT was used. While MCC is sensitive to multiple chemotherapy agents (cisplatin, doxorubicin hydrochloride, vindesine sulfate, and fluorouracil), the experience of most authorities is that the response has been short-lived. Owing to the rarity of Merkel cell carcinoma...
SUBJECTS AND METHODS

The medical records of 33 patients identified through the cancer data registry with MCC treated at the Massachusetts General Hospital, Boston, from January 1, 1980, to August 24, 1997, were reviewed. Median follow-up was 37 months (range, 6-157 months). Adequate data for evaluation were available for 31 patients (94%). Demographic data were collected and clinical outcomes recorded. Individual physicians were contacted when necessary to complete follow-up data. We determined location and stage at presentation; the incidence of other malignant neoplasms; factors associated with recurrence; and the effects of surgery, XRT, and chemotherapy on recurrence, salvage, and survival rates.

Disease-free survival curves were estimated using the Kaplan-Meier method. Patients who were alive and disease free at the most recent follow-up were treated as censored for this analysis. Factors associated with outcome were compared using a univariate log-rank test Cox regression. An optimal multivariate model was selected using a forward and backward selection procedure. A 2-tailed Fisher exact test was used for analysis of local and regional recurrence.

of this tumor and the lack of a standardized approach to treatment, it has been difficult to adequately evaluate the proper role and regimen for chemotherapy. The purpose of this study was to analyze our experience with MCC and determine which factors in patient presentation affected outcome and to help clarify the optimal treatment of these patients.

RESULTS

PREDICTORS OF DISEASE-FREE SURVIVAL RATES

The median patient age was 68 years (range, 34-81 years). There were 14 men and 17 women and all patients were white. Thirteen patients (42%) had a total of 17 previously treated or coexisting malignant neoplasms (Table 1). The size of the primary lesions varied from 0.5 to 15 cm (median, 2 cm) and did not affect the outcome. Demographic data, tumor location, regional nodal status, and effect of treatment on outcome are presented in Table 2. While the incidence of MCC was roughly equal between the sexes, there was a trend for female patients to have a better outcome by univariate analysis (P = .09). Twenty-two patients (71%) presented with stage I disease, 8 patients (26%) presented with stage II disease (clinically positive nodes), and only 1 patient (3%) presented with distant disease (stage III) at diagnosis. Primary treatment included local excision with or without XRT in 19 patients, local resection and lymphadenectomy with or without XRT in 8 patients, and XRT alone in 4 patients with head and neck tumors. Fifteen patients (48%) developed recurrences (7 local, 8 nodal, and 10 distant).

Univariate, statistically significant predictors of disease-free survival were location of the lesion (P < .001), age 55 years or older (P = .002), and regional nodal status at the time of diagnosis (P = .002). A multivariate survival model selected only truncal location (P = .005) and nodal disease (P = .05) as statistically significant, independent predictors of survival. With these variables in the model, there were no additional clinical treatments or demographic variables that independently predicted mortality at a significant level. Lesions occurring on the trunk had an extremely poor prognosis (Figure 1), with 6 of the 7 deaths occurring in this group and only 2 of the 8 patients with truncal lesions surviving free of disease (at 96 months and 12 months). Both of these patients underwent wide excision of their lesions, with XRT of 45 Gy or more to the tumor bed and regional nodes and adjuvant chemotherapy. Of the 8 patients with clinically positive regional nodes at the time of presentation,
only 4 survived (Figure 2). Two of these 4 survivors received XRT to the nodal bed, 1 received XRT and a therapeutic lymph-node dissection, and 1 only received a therapeutic lymph-node dissection. Of the 4 patients with positive nodes at the time of diagnosis who did not survive, none received adequate XRT to the nodal bed in the immediate postoperative period. Of the 23 patients who had clinically negative regional nodes at presentation, only 2 subsequently developed nodal disease.

TREATMENT

Radiation therapy of 45 Gy or more to the primary site and/or regional nodes appeared to confer a benefit \((P = .08)\), with no treatment failures among the 9 patients who received this dose (Figure 3). Within this group, 4 patients had head and neck lesions (4.5 cm on the right cheek, 1.7 cm on the right eyebrow, 1.2 cm on the left upper eyelid [39 Gy], and 3 cm on the left cheek) whose margins were either positive (3 patients) or within 1 mm (1 patient). Due to the limits of resection, XRT was the primary treatment modality in these patients. All of these patients were alive and free of disease at 8, 33, 60, and 92 months, respectively.

Three of 6 patients who received chemotherapy survived, compared with 21 of 25 patients who did not receive chemotherapy. Thus, the administration of chemotherapy was associated with a worse outcome by univariate analysis \((P = .02)\). This difference disappeared in multivariate analysis since many of these patients had truncal lesions and positive regional nodes, and that was the main determinant of their outcome. There were in fact 2 patients with distant metastases who were treated with chemotherapy and were free of disease at 33 and 96 months, respectively.

Seven patients had margins of resection of 2 cm or larger. None of these patients experienced a local recurrence, compared with 7 local recurrences in 24 patients with margins of resection less than 2 cm \((P = .16)\). Two of the 7 patients with wide excisions subsequently died of distant disease. As a result, a margin of resection of 2 cm or larger vs less than 2 cm did not significantly affect the survival rate. Median time to recurrence for the entire series was 8 months (range, 3-48 months).

Recurrence developed locally in 4 patients and in regional nodes only in 1 patient. All 5 of these patients were curable with XRT and/or reexcision (mean disease-free survival, 40 months).

COMMENT

The rarity of Merkel cell carcinoma has contributed to its undertreatment. From both our series of patients and the previously reported combined experience in the literature, it is clear that MCC is an aggressive but also curable lesion. Understaging combined with undertreatment leads to local recurrence and distant failure. Shaw and Rumball\(^9\) point out that, in many respects, MCC is similar to aggressive melanoma. Both skin tumors are of neural tissue origin and found almost exclusively in whites. They both tend to follow a predictable pattern of spread to the regional lymph nodes followed by systemic disease. The occurrence or spread of MCC may reflect a predisposition to developing cancer. Thirteen patients (42%) had previous malignant neoplasms. Four of these patients had experienced 2 prior separate malignant neoplasms. This is a higher multiple cancer rate for this age group than even the expected single cancer rate of 1 in 3 for male and 1 in 4 for female patients. This study represents the first documentation...
of an increased malignant neoplasm rate among patients with MCC.

WHAT DETERMINES outcome in patients with MCC? In our series, the tumor size had no effect on survival rates, similar to the findings of Victor et al. Six patients with large tumors (4-10 cm) were disease free at 8, 12, 24, 37, 96, and 113 months. By contrast, 3 of the 7 deaths occurred in patients with primary tumors smaller than 2 cm. There was a trend for women to have a better prognosis than men, similar to melanoma. A more favorable prognosis for women with MCC has also been found by other authors.

Figures 1 and 2 demonstrate that location and nodal status at presentation are correlated with outcome. Again this is similar to melanoma, for which truncal lesions and positive lymph nodes are poor prognostic factors; however, this is the first time truncal location has been shown to carry such a poor prognosis for MCC. Truncal location resulted in mortality in 6 (75%) of 8 patients, compared with no deaths among the 12 patients with extremity lesions and 1 death among the 11 patients with head and neck lesions. The poor outcome of patients with truncal tumors may reflect a wider potential array of lymphatic basins for dissemination relative to extremity and head and neck lesions; it may also be due to earlier systemic spread. Our observation that the 2 truncal lesion survivors received more aggressive therapy than the non-survivors suggests that multimodality treatment does make a difference. Both survivors received wide excision and XRT to the tumor bed and regional nodes in excess of 45 Gy, and 1 patient also received chemotherapy. By contrast, of the 6 nonsurvivors, only 1 patient had an optimal wide excision and none received optimal XRT in the perioperative period.

Due to the propensity for early nodal spread and the significant negative impact nodal disease has on outcome, many have felt that prophylactic lymph-node dissection is warranted. These authors demonstrate improved locoregional control but no impact on survival. No comment is made about complications of the lymph-node dissection (edema, infection, and pain), so it is not clear at what cost this local benefit was obtained. Our study confirms the findings of the previous studies. Although the 8 patients in our series who underwent lymphadenectomy did not develop nodal recurrences, there was no survival benefit. None of these patients experienced any significant complications from the nodal dissection. At the very least, the information on nodal status may be useful in selecting patients for further adjuvant therapy. In this regard, the report by Messina et al employing the sentinel node technique is promising, with no false negatives, although the follow-up is limited (median, 10.5 months).

Since a truncal location of tumor and node positivity have a significant negative impact on survival, what is the optimal treatment of these high-risk patients as well as all patients with MCC? Almost all authors advocate wide local excision, and we strongly agree with this. This reduces the incidence of local recurrence but does not improve survival. Our findings confirm this and indicate that a 2-cm margin, when possible, is the appropriate width of excision to obtain local control. None of the 7 patients with margins of resection of 2 cm or larger experienced a local recurrence, whereas one third of patients with narrower margins did. In anatomical locations where wide margins cannot technically be obtained, XRT has been useful in local control with long-term survival rates. Our 4 patients with facial lesions treated primarily by XRT suggest that this is a reasonable alternative, although the sample size does not allow a satisfactory statistical analysis.

Radiation therapy is an important component in the treatment of MCC. All 9 patients who received XRT of 45 Gy or greater to the primary tumor bed and to the regional nodal bed were alive and free of disease at the time of this report (Figure 3). This result, in conjunction with the 4 disease-free head and neck primary tumors that were treated primarily with XRT, supports the benefit of XRT for outcome. This is the first time that XRT as the only therapy for MCC has been shown to have a curative role. With a larger sample size, it is likely that the benefit of XRT for survival (P = .08) would have achieved statistical significance. While most studies have demonstrated the benefit of XRT for local control, the study by Meeuwen et al and our study are the only studies also confirming the benefit for survival.

The use of chemotherapy is unproven but advisable for high-risk patients (ie, truncal lesions or nodal disease). Multiple agents have been demonstrated to be active against MCC. Although the administration of chemotherapy was associated with a worse outcome in our series, this clearly reflects a selection bias, as demonstrated by the multivariate analysis. The fact that 2 patients with distant metastatic disease were alive and free of disease at 32 and 96 months may suggest that some lasting benefit is gained from chemotherapy. Given the extremely low incidence of this tumor, it is unlikely that anything more than anecdotal treatment reports will appear in the literature.

When treatments fails with either local recurrence or nodal disease, patient should undergo resection, followed by XRT greater than 45 Gy to the site. At the time of this report, we had 5 such patients, with mean disease-free survival of 40 months. This is in agreement with the 50% to 60% success rate reported by Meland and Jackson.

Our recommendations for the treatment of MCC are based on its aggressive behavior, which requires an aggressive treatment plan. To minimize local recurrence, lesions should, whenever anatomically possible, be widely excised with a 2-cm margin. They should also receive postoperative XRT to the primary site if wide margins have not been obtained or if the primary lesion is located on the trunk. At the time of the resection the status of the draining lymph nodes should be ascertained. Results using the sentinel-node mapping technique suggest that this is as applicable here as it has been shown to be in patients with melanoma. Patients with positive lymph nodes should undergo formal lymph-node dissection, followed by XRT to the nodal bed. Patients who choose not
to have a complete lymph-node dissection should probably undergo XRT to the regional nodes, especially if they have a truncal lesion. Patients with truncal lesions or positive nodes are at high risk for distant metastatic disease, and systemic chemotherapy should be seriously considered. When lesions recur, a combined modality approach of reexcision, lymphadenectomy, XRT, and chemotherapy should be used, unless contraindicated. The combination of wide local excision, regional lymphadenectomy, and postoperative XRT has the potential to achieve cure in greater than 90% of patients.


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REFERENCES


DISCUSSION

Richard Swanson, MD, Worcester, Mass: I congratulate Dr Ott and his colleagues at the Massachusetts General Hospital for doing an excellent job analyzing data regarding this rare tumor so they can help us with treatment guidelines. The rarity of this tumor is clear from the fact that only 2 cases per year were seen at the Massachusetts General Hospital over 17 or 18 years. At our own institution, the University of Massachusetts Memorial Health Care Cancer Center, we have seen 5 cases over 7 years. This represents less than 0.1% of all cancer cases seen during this period. Obviously with such a rare tumor it would difficult to conduct a randomized prospective trial to definitely answer questions regarding optimal treatment. Thus, we need to formulate treatment decisions from retrospective analysis such as that presented today.

From your data you’ve made recommendations about... treatment regarding aggressive surgery and radiotherapy. Your suggestions are similar to those found in the literature. From our own small experience, and from my reading of the literature, I’m impressed by the radio-sensitivity of these tumors. This leads me to wonder whether aggressive surgery is necessary if radiotherapy will be used.

Specifically, from your data you recommended... excision when possible with postoperative radiotherapy. If all patients receive 45 Gy to the primary, do we need the 2-cm margin? You state that 4 who’ve had neck cancers were treated primarily with radiotherapy without a wide excision and all are alive without disease. You also stated that 9 patients who had over 45 Gy radiotherapy enjoyed disease-free survival. Other than the 4 head and neck cancer patients, did any of these 9 patients have less than 2-cm margins? Perhaps radiotherapy alone or radiotherapy after a simple excision of the primary without regard to achieving wide margins would be sufficient. I’d appreciate your comments about that point.

You recommended sentinel lymph-node biopsy, or suggest a sentinel lymph-node biopsy would be helpful in determining positive nodes, and then you recommend a formal lymph-node dissection and radiotherapy to the nodal region for positive nodes. I agree that a sentinel-node biopsy is reasonable to identify positive nodes, and I agree that patients with positive nodes should have treatment of those nodes; the question is, what is necessary to treat the sentinel node—positive but clinically negative nodal basin? From your data and the literature I suspect that over 45 Gy in radiotherapy to the nodal region would be sufficient, and dissection would not be necessary. Do you have specific data that argue for the addition of node dissection to radiotherapy in the subset?

In summary, can we treat patients with MCC with excision of the gross tumor without concern about margins followed by sentinel-node biopsy and radiation therapy to the primary and to the node region for positive nodes without formal node dissection?

Peter Deckers, MD, Farmington, Conn: I’d like to speak to just the opposite of what Dr Swanson spoke about. Let me put it this way. I think all of us who have done lymphadenectomies, either in the groin or the axilla, over the years have been impressed with the fact that if you add radiotherapy to well-done axillary dissections or well-done groin dissections, then you don’t really gain anything by that from the point of view.
of survival or local control, but you do significantly increase the morbidity, ie, lymphedema of the arm or lymphedema of the leg. So what I'm asking is can you give me solid evidence that the radiotherapy after an adequate groin dissection or an adequate axillary dissection for clinically positive disease makes a real difference?

Charles Shoemaker, MD, Newport, RI: Just a few observations. One, we reviewed this entity at the New England cancer meeting a couple of years ago, and it's a very rare lesion. I heard the comment, “What does it look like?” Our experience was you took the lesion out, then you found out it was MCC and it was too late to get a picture. Histologically, the lesion starts in the deep layers of the skin, so the top layer of skin may not be involved, so it's just a heaping up of the skin, and looking back at notes, it's sort of pink in color.

The other part of our review supports your last comment—be very aggressive about the recurrences, because some patients are salvageable.

The third comment relates to Dr Deckers' comment. Surgeons from Memorial Sloan-Kettering are very aggressive about doing lymph-node dissection for lesions arising in the head and neck, but do not employ postoperative radiation.

William Cook, MD, North Andover, Mass: It just happens that 2 days ago I had a call from one of our local oncologists, who had an MCC tumor patient they thought was controlled over the past 4 or 5 years and that patient has presented with a solitary nodule in the lung. Dr Ott, would you comment on the nature of your distant metastases as to how often you see, or might expect to see, a solitary pulmonary nodule as an expression of recurrence, or whether I should be thinking about this being a different kind of tumor; obviously, I'll find out. If it turns out to be a recurrence of the MCC tumor, what would you propose besides resection of the lesion as far as additional therapy?

Dougald MacGillivray, MD, Portland, Me: I have 2 questions. One is the method of detection of distant metastases. Have you used octreotide scans in evaluating these patients? We recently had a patient who had an unsuspected distant metastasis detected this way. This patient was on immunosuppression after having a renal transplantation and had very rapid progression of disease. In my review of the literature there have been anecdotal reports of these tumors associated with immunosuppression. Were any of your patients on immunosuppression?

Dr Ott: Thank you very much, Dr Swanson. In terms of the several issues, I'll work back a little bit in reverse order. Several of these patients did have immunosuppressed states. As I said, there was a high incidence of associated malignancies in these patients, and several of them were actually undergoing chemotherapy prior to the development of their MCC. I do think that there probably is some immunosuppression involved with development of this tumor. Certainly, octreotide scans have been reported in the literature as being used clinically to detect metastases. I'm aware of one positive scan similar to yours as well. These do have somatostatin receptors. The octreotide scan is said to be 80% to 83% sensitive in detecting neuroendocrine tumors, and MCC is a neuroendocrine tumor. Only 1 patient in our series had the scan, and it was positive.

In terms of Dr Cook's questions and his patient with the lung metastases, his patient is almost identical to one of the patients in our series. Our patient developed an isolated lung metastasis 26 months after resection of the initial skin lesion. The patient underwent chemotherapy with cisplatin and Adriamycin and is presently at 33 months disease free. The patient did not have resection of that isolated lesion as part of the patient's treatment.

Merkel cell cancer, when it's looked at by a pathologist, looks exactly like small cell carcinoma lung. In fact, when a skin lesion is detected, it's very important to make sure that the patient does not have a primary somewhere else and that the skin lesion is not a metastasis. Neuroendocrine tumors of the gut and small cell of the lung can metastasize to the skin, so it is important to exclude these other tumors.

In terms of the metastatic pattern, we've had metastases to the lung. We've had them to the bone. We've had them to other areas of the skin, to the liver, to the small bowel, to the kidney, to the brain, and to nodes. So in a sense it behaves very similar to an aggressive melanoma, and it can basically show up anywhere.

Dr Shoemaker's comments about the lesion's appearance on the skin: Yes, it's an intradermal lesion. The Merkel cell receptor is located at the base of the hair follicle, and it's believed to arise in that area, and it does cause a heaping up of the skin with sort of a reddish/purple discoloration. The vast majority of times, the lesion is excised, believing that it's a benign intradermal process. When it ultimately comes back as MCC, it is usually a surprise. So you're right; it's very uncommon to have a great photograph of an MCC until it's in the pathology lab.

In terms of the whole question of surgery and radiation therapy, this is an extremely radiosensitive tumor. In the 4 cases of the head and neck lesions, 2 of those cases had clinically positive neck nodes, and all of those cases received radiation to the primary as well as to the neck on that side. All 4 patients had regression of the primary or nodal disease. All 4 patients are now alive at 8, 33, 60, and 92 months out and are free of disease. I think there is certainly room for treating these patients with radiation as the primary form of therapy. There was 1 patient who had a positive single lymph-node biopsy in the groin and then received subsequent radiation to that area without surgical resection and is among the patients who are disease free 3 to 4 years out from their initial treatment. Certainly this is a radiosensitive tumor, but due to the small numbers, it is difficult to test whether surgery vs radiotherapy is better or whether they should be combined.

As to my own opinion of using both surgery and radiation therapy, yes, there is a higher incidence of lymphedema and morbidity from that combined approach. And, yes, there are patients in our series who had just lymphadenectomy without radiation therapy and are free of disease at 3 to 4 years. I can think of 2 in our series of survivors who did not have radiation. Having reviewed the data, my point is that more of these patients could have been cured. Due to the rarity of this disease, we're never going to know how little we can get away with. We are therefore stuck with erring on the side of being more aggressive and combining therapies. That was the basis of this entire paper. That applies particularly to the nodal disease. To Dr Swanson's question about whether it is adequate just to simply excise the primary and give radiation therapy to control the primary, I think the answer to that is probably yes. All of us here are surgeons, and we would feel much more comfortable doing a wide excision of 2 cm which will also cure the primary. Certainly curative surgery is preferable to surgery and radiation when possible in treating the primary tumor. It is nice to have a tumor which gives one both options.