A Case of Merkel Cell Carcinoma

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The University of Colorado Health Sciences Center holds weekly second opinion conferences focusing on cancer cases that represent most major cancer sites. Patients seen for second opinions are evaluated by an oncologist. Their history, pathology, and radiographs are reviewed during the multidisciplinary conference, and then specific recommendations are made. These cases are usually challenging, and these conferences provide an outstanding educational opportunity for staff, fellows, and residents in training.

SECOND OPINION
Multidisciplinary Consultations on Challenging Cases
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The second opinion conferences include actual cases from genitourinary, lung, melanoma, breast, neurosurgery, and medical oncology. On an occasional basis, ONCOLOGY will publish the more interesting case discussions and the resultant recommendations. We would appreciate your feedback; please contact us at second.opinion@uchsc.edu.

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The patient is an elderly woman with rheumatoid arthritis who was evaluated in our multidisciplinary cutaneous oncology clinic for a new diagnosis of Merkel cell carcinoma.

History
This 74-year-old Caucasian female noted a red nodule on her left forearm approximately 4 months prior to diagnosis. She stated that the lesion started as a small, raised papule and slowly grew in size. Because the lesion was enlarging, the patient sought evaluation by her dermatologist. A biopsy was performed and revealed Merkel cell carcinoma. Positron-emission tomography/computed tomography (PET/CT) scan was performed and did not show evidence of metastatic disease. The patient subsequently underwent wide excision with concurrent sentinel lymph node evaluation. The reexcision specimen revealed an undifferentiated small-cell carcinoma most consistent with Merkel cell carcinoma, with clear margins. One sentinel lymph node harvested from the left axilla was negative for metastatic disease.

The patient then presented for a second opinion regarding further treatment options and follow-up plans. Of note, the patient has a 20-year history of rheumatoid arthritis. She has been treated with oral steroids for approximately 15 years, and at the time of her initial evaluation was on 2 mg of prednisone daily. She was also being treated with infliximab (Remicade) for her rheumatoid arthritis for approximately 2 years prior to her diagnosis of Merkel cell carcinoma.
Her past medical history is also significant for hypertension, which is well controlled on low-dose lisinopril. Her family history is significant for a daughter who died of leukemia in her early 30s. There is no family history of merkel cell carcinoma or melanoma. Her review of systems was pertinent for
arthritic pain, mainly in her wrists. The rest of her review of systems was unremarkable.

**Physical Exam**

**FIGURE 1**

Exophytic Tumor on Left Forearm

Physical exam revealed a well-appearing female in her usual state of health. The patient's cardiac, pulmonary, and abdominal exam were unremarkable. Her left forearm had a 2 × 2 × 2 cm red, exophytic tumor (see Figure 1). There was no palpable cervical, supraclavicular, axillary, or inguinal lymphadenopathy. Examination of her joints revealed ulnar deviation of her right hand and thickening and limited range of motion of her wrists bilaterally. There was no active synovitis.

**Discussion**

This patient is a 74-year-old female with a stage IB MCC on her left forearm. Her lesion is confined to the skin, and there is no evidence of distant or regional metastasis.

**Epidemiology**

Dr. Ragini Kudchadkar: The incidence of Merkel cell carcinoma is low compared to other cutaneous malignancies; however, the number of cases has been steadily rising. Almost 500 new cases are seen in the United States each year. The steady increase in incidence has been attributed to the aging population in the United States. MCC is primarily a disease of the elderly and is extremely rare in those under age 50 (less than 5% of cases). Whites are affected more commonly than blacks. Most tumors primarily occur in the sun-exposed areas of the skin, with almost half the cases occurring on the face or neck. The majority of patients present with localized disease. Regional lymph node involvement at the time of diagnosis occurs in 10% to 30% of cases, while distant metastases occur in only 1% to 4% of cases at initial presentation. The most common sites of distant disease are the liver, lung, and bones.

**Pathologic Review**

**FIGURE 2**
Dr. Kudchadkar: Dr. Fitzpatrick, will you review the pathology for us?

Dr. James Fitzpatrick: This specimen demonstrated features consistent with MCC on routine hematoxylin and eosin (H&E) stains, with a normal epidermis overlying nodular dermal aggregates of small, round cells, and no evidence of vascular or lymphatic extension (see Figure 2). On high power, the nuclei were relatively uniform in appearance, with round hyperchromatic nuclei that demonstrate one to several small nucleoli. Scattered atypical mitotic figures were present. Some of the cells demonstrated scant lightly eosinophilic cytoplasm at one edge of the nucleus (see Figure 2).

In sum, the histologic features are those of a “small blue-cell carcinoma” of the skin. In addition to MCC, the differential diagnosis on H&E for this pattern also includes small-cell carcinoma of the lung, lymphoma, Ewing’s sarcoma, and small-cell melanoma.

Dr. Fitzpatrick: Since it is very difficult to distinguish between some of the tumors in the “small blue-cell carcinoma” differential, a panel of immunoperoxidase stains should always be done. In our laboratory, if MCC is suspected, the initial immunoperoxidase panel consists of a cytokeratin 20 (CK20), neuron-specific enolase (NSE), and thyroid transcription factor-1 (TTF-1).

Merkel cell carcinomas express CK20 in 90% of cases, often with a characteristic perinuclear dotlike pattern. A positive CK20 is also useful because it excludes lymphoma, Ewing’s sarcoma, and small-cell melanoma, as these lesions do not express this cytokeratin; however, about one-third of small-cell carcinomas of the lung express CK20. The TTF-1 is ordered to exclude small-cell carcinoma of the lung, as it is uniformly negative in MCC and positive in more than 90% of small-cell carcinomas of the lung. Although CK20 is most commonly ordered, other cytokeratin stains including pancytokeratin and CAM5.2 are positive in most cases. The NSE is ordered as a confirmatory stain and is usually positive in more than 80% of cases (see Figure 3). In cases that do not coexpress cytokeratin and NSE, we order additional confirmatory stains such as CD117, CD56, epithelial membrane antigen (EMA), chromogranin A, or synaptophysin.

Dr. Rene Gonzalez: Will you review how the sentinel lymph node should be processed and evaluated? Is it evaluated differently than a specimen from a patient with melanoma?

Dr. Fitzpatrick: There is far less experience in evaluating sentinel lymph nodes in patients with MCC, as compared to melanoma, and there is no uniformly agreed on standard for processing them. In general, everyone agrees that sentinel lymph nodes should be bisected and multiple step sections examined by routine H&E. What is not agreed upon is how many step sections should be examined and whether the step sections should be consecutive or cut with skip regions so that different areas of the lymph node can be examined. Intuitively, the latter approach would likely provide the most accurate assessment, although there are no studies to support this.

I think that it would be reasonable to bisect the lymph node and do one H&E and four unstained sections every 1 mm as you step in the block. The H&E stains are examined, and any areas that are suspicious for MCC should be confirmed with a CK20 stain done on one of the adjacent sections. If the initial tumor is CK20-negative, then another stain that is known to be positive for NSE can be used. In sum, a positive sentinel lymph node in MCC should demonstrate cells consistent with Merkel cell carcinoma on routine H&E, and it should be supported by a an immunoperoxidase stain that is consistent with the lineage of the primary tumor.

**Surgery Review**

Dr. Karl Lewis: Dr. Gonzalez will you review the guidelines of surgical excision of a Merkel cell tumor?

Dr. Ricardo Gonzalez: Generally the accepted approach for localized MCC is wide local excision. Although few
would argue with this approach for MCC, the optimal margin width is controversial as no controlled trials have been reported to date. Based on retrospective series, the optimal margin depends on the width of the primary tumor. In general, a small MCC (< 2 cm) should be excised with at least a 1-cm margin, whereas larger lesions (≥ 2 cm) should be excised with a 2-cm margin.[1,2] Using this approach, Allen et al reported on 251 patients with MCC. The median tumor width was 1.5 cm, and the average margin width was 1.1 cm. Local recurrence developed in 8% of patients who underwent a margin-negative resection. Additionally, neither the use of adjuvant radiation therapy (RT) nor the achievement of a surgical margin greater than 1 cm was associated with decreased local recurrence.[1]

Dr. William Robinson:
From a surgical standpoint, do you believe adjuvant treatment is needed after adequate excision?

Dr. Ricardo Gonzalez:
Controversy exists regarding the use of adjuvant RT to the primary site. Local recurrence rates after wide excision are relatively low (4%-14%). However, several groups have reported on the use of adjuvant RT for local and regional control.[2-4] We would favor the use of adjuvant radiotherapy to the primary site for high-risk lesions (≥ 2 cm). Furthermore, adjuvant therapy to the draining lymphatic basin should be considered in patients with clinically evident regional or nodal disease.[2-4]

Dr. Kudchadkar:
Dr. Gonzalez, is a sentinel lymph node evaluation indicated in all patients with a diagnosis of MCC or is there a select population for which you recommend it be done?

Dr. Ricardo Gonzalez:
As with melanoma, the management of regional disease for MCC is central to improving disease control. Unlike melanoma, however, stringent predictive criteria justifying the risks of sentinel node biopsy as a staging modality for MCC are not well described. The risk of managing an otherwise clinically negative lymphatic basin with either radiation or surgery may lead to either overtreatment or a high false-negative rate in the setting of truncal MCC. Unless otherwise contraindicated by comorbidity, sentinel lymph node biopsy should be considered in all patients with MCC. This technique is the most reliable staging technique available with which to direct regional therapy. The incidence of occult nodal disease ranges from 19% to 32%, and appropriate regional therapy may have a significant impact on disease-free survival.[2,5-8]

Dr. Rene Gonzalez:
What is the role of surgical management for micrometastatic disease?

Dr. Ricardo Gonzalez:
Ideal management of micrometastatic disease for MCC remains to be defined and therefore requires a multidisciplinary approach. Based on limited data, first-line management of micrometastatic disease within the draining lymphatic basin should be completion lymphadenectomy (CLND) in the medically fit patient.[2,5-8] Radiation therapy alone should be considered in the setting of unacceptable morbidity associated with CLND. Patients with extracapsular extension or extensive lymph node disease may be managed with CLND and adjuvant RT, as will be discussed later by the radiation oncologist.

**Adjuvant Radiotherapy**

**Dr. Lewis:** Is MCC a radiosensitive tumor?

**Dr. Rusthoven:** MCC is histopathologically similar to small-cell carcinoma and, as such, would be expected to be highly radiosensitive. Several clinical and laboratory-based studies have demonstrated the radiosensitivity of MCC. For example, in a series of 19 patients treated at the Peter McCallum Cancer Institute in Sydney, Australia, local control was achieved in 35 of 36 irradiated fields, which included gross disease in 23 fields.[9] Furthermore, Leonard and colleagues evaluated the response of the MMC13 MCC cell line to gamma irradiation and compared the survival fraction after 2 Gy (SF2) to that of small-cell lung cancer, melanoma, Epstein-Barr virus (EBV) transformed lymphocytes (LCL), and skin fibroblasts. The MMC13 cell line was highly radiosensitive, with an SF2 value similar to that observed for the small-cell lung cancer cell line.[10] Despite these reports of radiosensitivity, however, single-institution retrospective data have been mixed regarding the effect of adjuvant radiotherapy for MCC on local control and survival. Moreover, no prospective randomized trials have addressed this question.

**Dr. Kudchadkar:** What data are available for and against the use of adjuvant radiotherapy in MCC?

**Dr. Kavanagh:** The role of radiotherapy in the treatment of MCC remains controversial. Historical series of patients treated with surgery alone have reported high rates of local and regional relapse, making adjuvant radiotherapy an attractive option. In one case series from M.D. Anderson Cancer Center, investigators reported locoregional control in only 4 of 37 patients treated with surgery alone. The median time to relapse in these patients was only 4.9 months, with 91% of recurrences occurring within 1 year of surgery. Conversely, in 31 patients treated with adjuvant RT, only one in-field...
In the setting of positive SLNB, options for treatment of the regional nodal basins include complete lymph node dissection and regional radiotherapy. A recent report from Dana Farber Cancer Institute included 251 patients with surgically resected MCC and found no benefit of adjuvant radiotherapy on local or regional control. This series reported a local recurrence rate of only 8% after margin-negative resection without radiotherapy, compared to 10% in patients treated with adjuvant RT.[1]

In contrast to the previously mentioned series, an analysis of the largest single-institution series from Memorial Sloan-Kettering Cancer Center included 251 patients with surgically resected MCC and found no benefit of adjuvant radiotherapy on local or regional control. This series reported a local recurrence rate of only 8% after margin-negative resection without radiotherapy, compared to 10% in patients treated with adjuvant RT.[1]

In a meta-analysis of previously published series of nonrandomized patients, investigators compared adjuvant radiotherapy vs surgery alone, identifying 1,254 patients with excised MCC and negative surgical margins. This study found a significant reduction in local (12% vs 39%, P < .001) and regional (23% vs 56%, P < .001) failure rates at 5 years with adjuvant radiation compared to surgery alone. Patients treated with radiotherapy also had a nonsignificant improvement in overall and cause-specific survival compared to those treated with surgery alone.[3]

A recent analysis of the Surveillance, Epidemiology and End Results (SEER) database identified 1,665 patients with MCC, among whom 89% were treated with initial surgical resection. About 40% of these patients were treated with adjuvant radiotherapy, which was associated with a significant improvement in median survival (63 vs 45 months) compared to no radiation. Although a survival benefit was observed for all tumor sizes, the greatest relative benefit was observed among patients with tumors greater than 2 cm (median survival: 50 vs 21 months).[13]

The benefit associated with adjuvant irradiation in this series, however, must be interpreted in the appropriate context, as information regarding surgical margin width, medical comorbidities, performance status, systemic therapy, and radiation dose and field volumes is not available in the SEER database. Although the data from this analysis are compelling due to the large number of patients examined and the profound difference in survival, these limitations prevent conclusions about the causal relationship between adjuvant radiotherapy and survival.

In contrast to the previously mentioned series, an analysis of the largest single-institution series from Memorial Sloan-Kettering Cancer Center included 251 patients with surgically resected MCC and found no benefit of adjuvant radiotherapy on local or regional control. This series reported a local recurrence rate of only 8% after margin-negative resection without radiotherapy, compared to 10% in patients treated with adjuvant RT.[1]

Regional lymph node status has been shown to be the strongest predictor of survival in MCC.[14] Elective treatment of the regional lymph nodes, however, has historically been challenging due to difficulty identifying the appropriate lymphatic basins to treat, particularly in areas with ambiguous lymphatic drainage.

Similar to breast cancer and melanoma, sentinel lymph node biopsy (SLNB) is a sensitive and specific technique for identifying the primary echelon lymphatics and is important in guiding adjuvant therapy. Allen et al reported a significant reduction in the rate of regional nodal recurrence among 54 patients evaluated with SLNB and 17 undergoing elective lymph node dissection, compared to patients with no lymph node evaluation (11% vs 44%, P < .001).[1]

In the setting of positive SLNB, options for treatment of the regional nodal basins include complete lymph node dissection and regional radiotherapy. A recent report from Dana Farber Cancer Institute described the benefit of adjuvant regional radiotherapy in patients with positive SLNB. The authors reviewed 122 cases of clinically node-negative MCC in which SLNB was performed. SLNB was positive in 32% of cases and was highly predictive of recurrence (60% SLNB-negative vs 20% SLNB-positive, P = .03). Adjuvant radiotherapy was associated with a significant improvement in 3-year relapse-free survival among patients with positive SLNB (51% vs 0%, P < .01), but not among patients with negative SLNB (90% vs 70%, P = .26).[6] In patients with positive SLNB treated with complete lymph node dissection, adjuvant RT should be considered in patients with extensive lymph node disease or extracapsular extension.[15]

What then is the overall consensus on the use of adjuvant radiotherapy?

Based on the patterns of failure and risk of locoregional recurrence, it is reasonable to consider adjuvant radiotherapy in the treatment of surgically resected MCC. Although evidence from prospective randomized trials is lacking, the majority of available data suggest a potential benefit of
adjuvant radiotherapy, particularly in the setting of positive surgical margins or a primary tumor greater than 2 cm, and in patients with positive sentinel lymph nodes who have not undergone complete lymph node dissection.

The target volume for adjuvant treatment of MCC includes the surgical bed with wide margins of 4 to 5 cm and the at-risk regional lymphatics. Wide margins are recommended due to the high risk of marginal recurrence, but may be reduced for tumors adjacent to critical structures (eg, orbit, optic nerve, chiasm). For lesions of the head and neck region, the entire ipsilateral cervical lymph node chain should be electively treated. These target volumes are typically treated to 46 to 50 Gy in 2.0 to 2.5 Gy per fraction for postoperative and electively treated volumes, but may be escalated to 60 to 66 Gy for gross residual or unresectable disease.

Treatment can be administered using electrons and/or photons depending on the depth of the primary tumor and regional lymph nodes requiring elective treatment. Tumors of the head and neck region, however, require mixed electron-photon or dedicated photon treatment to adequately cover the electively treated cervical lymph nodes.[16]

### Adjuvant Chemotherapy

**TABLE 1**

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<th>Table 1: Chemotherapy Regimens Used in the Treatment of MCC</th>
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<td><strong>Regimen</strong></td>
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**Is there a role for chemotherapy in the adjuvant setting?**

**Dr. Rene Gonzalez:** There is limited experience with chemotherapy either alone or in combination with radiotherapy in the adjuvant setting. Another confounding factor is the lack of consistency in chemotherapy regimens used in both the adjuvant and metastatic settings. Table 1 summarizes the chemotherapy regimens that have been used in various studies. Most commonly, however, small-cell lung chemotherapy regimens are used, and a few small trials are looking at these regimens in the adjuvant setting.

Poulsen et al performed a randomized trial of the use of radiotherapy combined with carboplatin and etoposide vs radiotherapy alone in 102 high-risk stage I/II MCC patients.[14] At least one high-risk feature was present in all patients. These high-risk features included recurrence after initial therapy, nodal involvement, primary size greater than 1 cm, and gross residual disease after surgery. Radiation was administered to the primary site of disease and to the lymph node basin for a total treatment dose of 50 Gy. Carboplatin at an area under the concentration-time curve (AUC) of 4.5 and etoposide at 80 mg/m² was given on days 1 and 3 during weeks 1, 4, 7, and 10. This study failed to show any survival benefit by the addition of chemotherapy.

Other small studies have supported this lack of benefit from the addition of adjuvant chemotherapy. Kokoska et al treated 35 patients with adjuvant chemotherapy and also showed no improvement in overall survival.[17] Investigators at Memorial Sloan-Kettering Cancer Center performed a retrospective subgroup analysis of 76 patients and did not demonstrate any additional benefit with the addition of chemotherapy.[18] In fact, the use of adjuvant chemotherapy in stage III patients showed a trend (P = .8) toward decrease survival compared to patients with stage II disease who did not receive chemotherapy.[18]

However, most studies do show significant response rates in patients treated for localized disease. Boyle et al saw a significant response rate in MCC when regional nodal disease was treated adjuvantly with carboplatin, with 8 of 20 patients responding.[19] Tai et al studied a larger series of patients with both metastatic and localized disease. Of the patients without metastatic disease, approximately 68% of patients responded.[20]

Overall, little evidence supports the use of chemotherapy in the adjuvant setting at this time. Larger studies with more power need to be performed to truly elucidate the effects of chemotherapy in the adjuvant setting.
Metastatic Disease

Dr. Kudchadkar: Should this patient develop metastatic disease, would there be a role for chemotherapy?

Dr. Lewis: The role of chemotherapy has been studied more often in patients with metastatic disease than in the adjuvant therapy setting. However, a clear benefit in metastatic patients has yet to be revealed. The most common regimens used are combinations of etoposide and platinum or of cisplatin, doxorubicin, and vincristine. Response rates are rather high—mostly between 60% and 70%.

The largest such review assessed 204 patients with locally recurrent and metastatic disease, showing a response of approximately 60% in the metastatic patients.[20] Complete response to chemotherapy was identified in the review, but partial responses were much more common. Although most patients respond to initial treatment, the duration of response is short, and a clear impact on survival has yet to be demonstrated. The median overall survival of patients with metastatic MCC is 10 months.

Many have theorized as to why chemotherapy of a chemosensitive tumor like MCC has not clearly shown survival benefit. The average age of a patient at diagnosis of MCC is 69 years, making MCC primarily a disease of the elderly. Given this elderly population, the toxicities of chemotherapy are significant. The toxic death-rate reported in patients with MCC receiving chemotherapy is between 4% and 8%—much higher than that reported in the treatment of other solid-tumor malignancies.[20-22]

Most of the toxicity seen has been related to bone marrow suppression and neutropenia. However, tumor lysis syndrome and renal failure have been reported in the literature.[18,21] Neutropenic fever and sepsis are not uncommon. Poulsen et al reported neutropenic fever in 60% of patients and sepsis in approximately 40%.[14] These toxicities are seen with the use of chemotherapy in all solid tumors. However, the elderly population of patients with MCC may be more susceptible to these treatment side effects, thus limiting any potential survival benefit.

Dr. Kudchadkar: Are there alternative systemic treatments for MCC besides chemotherapy?

Dr. Rene Gonzalez: Biologic agents have been used in a very limited fashion in patients with MCC. The use of interferon and tumor necrosis factor (TNF) has been reported, but their use at this time is entirely experimental.[23-25] A Japanese group reported tumor regression in localized disease with intratumoral injections of TNF.[25,26] However, the number of MCC patients receiving such treatment is extremely small, and therefore, no definite conclusions can be drawn about the possible effectiveness of these biologic agents.

Susan Hammerman: Are targeted agents such as imatinib (Gleevec) an option for treatment?

Dr. Robinson: MCC expresses the tyrosine kinase receptor KIT, which is the CD117 antigen that can be seen on immunohistochemical stains of Merkel cell tumors, as discussed earlier by Dr. Fitzpatrick. We evaluated nine tumors from MCC patients for KIT immunostaining. Eight of nine tumors expressed KIT, but no activating mutations were found.[27] Therefore, we do not believe that using a drug like imatinib, which targets activating mutations in the c-kit proto-oncogene, would be effective in the treatment of this disease.

Krista Treichel: Could the patient's treatment with infliximab have contributed to her development of Merkel cell carcinoma?

Dr. Kudchadkar: The use of immunosuppressive treatments has been associated with an increased risk of malignancy. One would suspect that the use of anti-TNF agents such as infliximab would increase the risk of the development of MCC, given the fact that TNF has been shown in vitro and in vivo to suppress the growth of MCC.[25,26]

Bongartz et al did an extensive review of the current studies in rheumatoid arthritis patients treated with anti-TNF agents.[28] This analysis included nine trials of 3,493 patients who received anti-TNF antibody and 1,512 patients who received placebo. The overall odds ratio for malignancy was 3.3, and malignancy was more common with higher doses of anti-TNF antibodies. Approximately 37 malignancies were seen in the treatment group, and only 3 in the placebo group. The number needed to harm for 1 additional malignancy to occur was 154. Because of the rarity of MCC, it is not surprising that no cases of Merkel cell have been specifically reported. However, several cases of melanoma have been reported with the use of these agents.

Overall, there is an increased risk of malignancy with the use of infliximab. After diagnosis of Merkel cell carcinoma in our patient, the use of infliximab was discontinued. However, she did remain on oral prednisone for the treatment of her rheumatoid arthritis.

Ms. Hammerman: Given that immunosuppressive agents increase the risk of malignancies, is there any evidence to support an infectious cause?
Until recently there was no direct evidence to support the notion of an infectious agent leading to the development of MCC. However, Feng et al recently reported evidence that polyomavirus may be involved in the development of MCC.[29] This study discovered a new polyomavirus that they coined as Merkel cell polyomavirus (MCV). Ten MCC tumors were evaluated, and eight had detectable MCV sequences. Control tissue was also evaluated and only 5 of 59 demonstrated the virus. Most of the MCC tumors had integrated viral DNA within the tumor genome. Perhaps it is this integration that leads to the clonal expansion of tumor cells.

Recommendations

Dr. Kudchadkar: Recommendations for the initial treatment of MCC are adequate surgical resection and sentinel lymph node evaluation. The use of radiotherapy for adjuvant treatment should be considered, especially in patients with high-risk disease. Chemotherapy is not recommended at this time in the adjuvant setting. For patients with metastatic disease, high chemotherapy response rates are seen. However, chemotherapy should be use with extreme caution in the elderly and in those with poor performance status. Best supportive care in the metastatic setting is a reasonable option for those patients with a poor performance status.

References:

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