

## **MERKEL CELL CARCINOMA**

Date Developed: May, 2008

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The recommendations contained in this guideline are a consensus of the Alberta Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

## BACKGROUND

Merkel Cell Carcinoma is rare and accounts for less than 1% of cutaneous malignancies. The mean patient age at diagnosis is about 75 years; only 5% of cases occur before 50 years of age and overall, the two-year survival rate for MCC is 50-70%. The overall 5-year survival rates range from 30% to 64%.<sup>1,2,3,4,5,6</sup>

## GUIDELINE GOALS AND OBJECTIVES

To improve the diagnoses, treatment and follow-up for all stages of Merkel Cell Carcinoma (MCC)

## GUIDELINE QUESTIONS

- What is the widely accepted staging classification for Merkel Cell Carcinoma?
- What is the most appropriate treatment for MCC Stage I-IV?
- What are the management strategies for recurrence of MCC?
- How should a patient with MCC be followed?

## DEVELOPMENT PANEL

This **guideline** was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, dermatologists, nurses, pathologists, and pharmacists. **Evidence** was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

## SEARCH STRATEGY

The MEDLINE (1966 through April 2009), CINAHL, Cochrane, ASCO Abstracts and proceedings, and CANCERLIT databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Search terms included: Merkel cell and cancer or Merkel cell carcinoma.

## RECOMMENDATIONS

### Staging

No widely accepted or standardized staging classification based upon prognosis is available. Memorial Sloan-Kettering Cancer Center's (MSKCC) developed a four tier staging system based on clinical presentation for patients with MCC. MSKCC's staging system shown below is the most commonly used staging system consistent with the American Joint Committee on Cancer.<sup>7</sup>

STAGE		LOCALIZED DISEASE	LYMPH NODE	METASTASIS
I	Primary lesion $\leq$ 2 cm	+	-	-
II	Primary lesion > 2 cm	+	-	-
III	Positive lymph node	+/-	+	-
IV	Distant metastasis	+/-	+/-	+

History, physical examination, and relevant investigation should guide further treatment.

### Treatment

Patients with MCC, a tumor that is amenable to surgery and is considered both radiosensitive and chemosensitive, benefit from management in a multidisciplinary manner.

### Stage I and II

SLN biopsy	Sentinel lymph node biopsy to precede excision if possible
Surgery	<ul style="list-style-type: none"> <li>Wide local excision has been recommended whenever possible</li> <li>Mohs micrographic surgery could be considered as a tissue-sparing technique when the tumor is in a sensitive area such as head and neck</li> </ul>
Radiation	<ul style="list-style-type: none"> <li>Adjuvant radiation therapy to the primary site should be considered. Adjuvant radiation therapy to the regional lymph node basin is recommended if a sentinel node biopsy cannot be performed.</li> <li>50 Gy to the surgical bed and the draining regional lymphatics, delivered in 2 Gy fractions</li> <li>For patients with unresected tumors or tumors with microscopic evidence of spread beyond resected margins, higher doses of 56 Gy to 65 Gy have been recommended</li> </ul>
Follow-up	<p><u>Year 1: Every 1 to 3 months</u></p> <ul style="list-style-type: none"> <li>Physical exam including complete skin and regional lymph node exam</li> <li>Chest x-ray (optional)</li> </ul> <p><u>Year 2: Every 3 to 6 months</u></p> <ul style="list-style-type: none"> <li>Physical exam including complete skin and regional lymph node exam</li> <li>Chest x-ray (optional)</li> </ul> <p><u>Years 3+: Annual</u></p> <ul style="list-style-type: none"> <li>Physical exam including complete skin and regional lymph node exam</li> <li>Chest x-ray (optional)</li> </ul>

**Stage III**

Surgery	<ul style="list-style-type: none"> <li>• Wide local excision has been recommended whenever possible</li> <li>• Mohs micrographic surgery could be recommended as a tissue-sparing technique when the tumor is in a sensitive area such as head and neck</li> <li>• Completion lymph node dissection or radiation therapy or both should be given to the nodal basin if the SN is positive</li> </ul>
Radiation	<ul style="list-style-type: none"> <li>• Adjuvant radiation therapy to the primary site and to the regional lymph node basin if there is macroscopic, clinically positive disease .</li> <li>• 50 Gy to the surgical bed and the draining regional lymphatics, delivered in 2 Gy fractions</li> <li>• For patients with unresected tumors or tumors with microscopic evidence of spread beyond resected margins, higher doses of 56-65 Gy have been recommended</li> </ul>
Chemotherapy	<p>If sentinel lymph node positive consider adjuvant chemotherapy:</p> <ul style="list-style-type: none"> <li>• Cisplatin, or Carboplatin</li> <li>• Etoposide</li> <li>• Topotecan (in older patients)</li> </ul>
Follow-up	<p><u>Year 1: Every 1 to 3 months</u></p> <ul style="list-style-type: none"> <li>• Physical exam including complete skin and regional lymph node exam</li> <li>• Chest x-ray (optional)</li> </ul> <p><u>Year 2: Every 3 to 6 months</u></p> <ul style="list-style-type: none"> <li>• Physical exam including complete skin and regional lymph node exam</li> <li>• Chest x-ray (optional)</li> </ul> <p><u>Years 3+: Annual</u></p> <ul style="list-style-type: none"> <li>• Physical exam including complete skin and regional lymph node exam</li> <li>• Chest x-ray (optional)</li> </ul>

**Stage IV**

Chemotherapy	<p>Systemic chemotherapy is the treatment most often used for patients with stage IV</p> <p>Because of morphologic and immunohistochemical similarities, the regimens employed are similar to those used for patients with small cell lung cancer:</p> <ul style="list-style-type: none"> <li>• Cisplatin, or Carboplatin</li> <li>• Etoposide</li> <li>• Topotecan (in older patients)</li> <li>• Doxorubicin</li> </ul>
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Radiation	As indicated
Surgery	As indicated
Follow-up	<u>Year 1: Every 1 to 3 months</u> <ul style="list-style-type: none"> <li>Physical exam including complete skin and regional lymph node exam</li> <li>Chest x-ray (optional)</li> </ul> <u>Year 2: Every 3 to 6 months</u> <ul style="list-style-type: none"> <li>Physical exam including complete skin and regional lymph node exam</li> <li>Chest x-ray (optional)</li> </ul> <u>Years 3+: Annual</u> <ul style="list-style-type: none"> <li>Physical exam including complete skin and regional lymph node exam</li> <li>Chest x-ray (optional)</li> </ul>

### **Recurrence**

- Local or regional recurrences individualize treatment
- Disseminated recurrence, treat as Stage IV

### **Prognosis and Follow-up Evaluation**

- Patients should be monitored closely for recurrence of locoregional or distant disease. Lymph node or distant metastatic disease has a uniformly grave prognosis; however, there may be a role for chemotherapy in prolonging survival.

Given the complex issues in dealing with this aggressive tumor, patients are best served by being cared for in a tertiary care setting with a multidisciplinary approach.

## **DISCUSSION**

Merkel cell carcinoma is an aggressive tumour and stage of the disease has been identified as the strongest predictor of survival in 1 large series (stage I, 81% 5-year survival rate; stage II, 67% 5-year survival rate; stage III, 52% 5-year survival rate; stage IV, 11% 2-year survival rate).<sup>8</sup> Although disease-specific survival rates based on stage are reported infrequently in other studies, 5-year survival rates have been reported as 44% to 68% for localized disease (stages I and II) and 23% to 42% for regional or distant metastatic disease (stages III and IV).<sup>9,10</sup> The reported overall recurrence rate ranged from 40% to 45% in several large series but reportedly was as high as 77% on the head and neck.<sup>11,12,13</sup> Higher recurrence rates in smaller series may be influenced by unintentional retrospective and tertiary center bias. The median time to recurrence consistently is reported as approximately eight months, with the majority of recurrences (90%) occurring within 2 years of diagnosis.<sup>14,15,16</sup>

Ultraviolet (UV) radiation may be an etiological factor in MCC<sup>17</sup> as most tumours are located on sun-exposed areas of the skin.<sup>18,19</sup> Geographic locations have revealed a correlation between solar UV-B indexes and regional differences in MCC incidence. Lunder and Stern report a 100-fold increase in MCC incidence in patients with psoriasis who were treated with systemic UV-A and methoxsalen.<sup>20</sup>

Indirect evidence of an association between MCC and immunosuppression is plentiful. In 1 large series, 14.5% of patients with MCC were receiving or had received immunosuppressive therapy.<sup>21</sup> Penn and first reported 41 patients with MCC after the transplant, among a total of 4,560 patients with skin cancers.<sup>22</sup> In contrast to MCC in the general population, 49% of transplantation patients with MCC were frequently younger than or equal to  $\leq 50$  years. The ratio of post transplantation melanoma to MCC is 6:1 compared with 65:1 in the general population.<sup>23</sup> Several other cases of MCC associated with iatrogenic immunosuppression have been reported.<sup>24,25</sup>

In patients with human immunodeficiency virus or acquired immunodeficiency syndrome, the relative risk of MCC is 13.4 compared with the general population.<sup>26</sup> An increased rate of other malignancies in patients with MCC further supports an impaired immune status in the pathogenesis of some cases of MCC. An increased risk of MCC as a second primary malignancy has been identified among patients with multiple myeloma, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and melanoma.<sup>27</sup> Several cases of MCC have been linked to chronic arsenic exposure, implicating this carcinogen in the pathogenesis of MCC in those patients.<sup>28</sup>

### Prognosis and Follow-up Evaluation

MCC has been compared with malignant melanoma because of its similar aggressive behavior.<sup>29,30,31,32,33</sup> The local recurrence rate is 26% to 44% after primary treatment. As many as 30% of patients have regional lymph node involvement at the time of diagnosis with a 55% rate of regional lymph node relapse after treatment and a 34% to 49% rate of distant metastasis.<sup>34,35,36,37,38</sup> Survival rates reportedly are 68% for women and 36% for men at 3 years.<sup>39,40</sup> Given the relative rarity of the tumor, no large multicenter randomized trials have been conducted to assess stage, treatment modality, recurrence rate, and overall survival. There have been reports of patients with spontaneous resolution of MCC.<sup>41,42,43</sup> Almost all patients with metastatic disease eventually die of the disease.<sup>44</sup>

### Presentation

MCC is rarely suspected at the time of initial presentation. It generally presents as cutaneous disease only, however, some patients present with evidence of regional or distant metastasis.

The most common location of metastasis is the draining lymph node basin (27-60%), distant skin (9 – 30%), lung (10 – 23%), central nervous system (18%), bone (10 – 15%), and liver (30%)<sup>45,46</sup> Other reported areas of distant metastasis include testis, pancreas, heart, bone marrow, pleura, parotid, gastrointestinal tract, prostate and bladder.

### Differential Diagnosis

<ul style="list-style-type: none"> <li>• Basal Cell Carcinoma</li> <li>• Squamous Cell Carcinoma</li> <li>• Cyst</li> <li>• Pyogenic granuloma</li> </ul>	<ul style="list-style-type: none"> <li>• Malignant Melanoma</li> <li>• Lymphoma cutis</li> <li>• Lipoma</li> </ul>
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## Work-up

### **Physical Examination**

- The primary skin lesion is generally asymptomatic.
- Patients with disseminated disease may have constitutional symptoms (eg, fatigue), localizing signs (eg, hemoptysis, neurologic defect, adenopathy secondary to metastasis), or both.
- MCC most commonly presents as a blue or red solitary, dome-shaped nodule or firm plaque
- Lesions are most often smaller than 2 cm in greatest dimension, but may exceed 15 cm in diameter.<sup>47</sup>
- Lesions on the head and neck typically are smaller than lesions in other locations.<sup>48</sup>
- The most common locations for MCC include the head and neck region and the extremities, however, any mucosal or cutaneous site may be affected
- The surface is often shiny with telangiectasias.
- Ulceration is uncommon.

### **Biopsy**

- H & E
- Immun-histochemistry (to include CK-20, CK-7, and/or thyroid transcription factor-1)

### **Tests**

- Chest x-ray is indicated to exclude cutaneous metastases from small cell lung cancer
- Sentinel lymph node biopsy to determine the presence or absence of lymph node disease
- Additional studies as clinically indicated (consider CT scan of chest/abdomen)

## **IMPLEMENTATION STRATEGY**

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

## **EVALUATION STRATEGY**

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

## **DECLARATION OF CONFLICT OF INTEREST**

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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**REFERENCES**

- <sup>1</sup> Veness MJ, Perera L, McCourt J, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. *Aust N Z J Surg.* 2005;75:275–281.
- <sup>2</sup> Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol.* 2006;142:693–700.
- <sup>3</sup> Morrison WH, Peters LJ, Silva EG, Wendt CD, Ang KK, Goepfert H. The essential role of radiation therapy in securing locoregional control of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys.* 1990;19:583–591.
- <sup>4</sup> Pacella J, Ashby M, Ainslie J, Minty C. The role of radiotherapy in the management of primary cutaneous neuroendocrine tumors (Merkel cell or trabecular carcinoma): experience at the Peter MacCallum Cancer Institute (Melbourne, Australia). *Int J Radiat Oncol Biol Phys.* 1988;14:1077–1084.
- <sup>5</sup> Wong KC, Zuletta F, Clarke SJ, Kennedy PJ. Clinical management and treatment outcomes of Merkel cell carcinoma. *Aust NZ J Surg.* 1998;68:354–358.
- <sup>6</sup> Yiengpruksawan A, Coit DG, Thaler HT, Urmacher C, Knapper WK. Merkel cell carcinoma. Prognosis and management. *Arch Surg.* 1991;126:1514–1519.
- <sup>7</sup> Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23: 2300–2309.
- <sup>8</sup> Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23: 2300–2309.
- <sup>9</sup> Eng TY, Boersma MG, Fuller CD, Cavanaugh SX, Valenzuela F, Herman TS. Treatment of Merkel cell carcinoma. *Am J Clin Oncol.* 2004;27:510–515.
- <sup>10</sup> McAfee WJ, Morris CG, Mendenhall CM, Werning JW, Mendenhall NP, Mendenhall WM. Merkel cell carcinoma: treatment and outcomes. *Cancer.* 2005;104:1761–1764.
- <sup>11</sup> Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23: 2300–2309.
- <sup>12</sup> Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. *Arch Otolaryngol Head Neck Surg.* 2001;127:149–154.
- <sup>13</sup> Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol.* 2001;8:204–208.
- <sup>14</sup> Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. *Arch Otolaryngol Head Neck Surg.* 2001;127:149–154.

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- <sup>15</sup> Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol*. 2001;8:204–208.
- <sup>16</sup> Eng TY, Naguib M, Fuller CD, Jones WE 3rd, Herman TS. Treatment of recurrent Merkel cell carcinoma: an analysis of 46 cases. *Am J Clin Oncol*. 2004;27:576–583.
- <sup>17</sup> Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. *Cancer Epidemiol Biomarkers Prev*. 1999;8:153–158.
- <sup>18</sup> Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol*. 2005;23: 2300–2309.
- <sup>19</sup> Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol*. 2001;8:204–208.
- <sup>20</sup> Lunder EJ, Stern RS. Merkel-cell carcinomas in patients treated with methoxsalen and ultraviolet A radiation. *N Engl J Med*. 1998;339:1247–1248.
- <sup>21</sup> Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol*. 2001;8:204–208.
- <sup>22</sup> Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. *Transplantation*. 1999;68:1717–1721.
- <sup>23</sup> Buell JF, Trofe J, Hanaway MJ, et al. Immunosuppression and Merkel cell cancer. *Transplant Proc*. 2002;34:1780–1781.
- <sup>24</sup> Robak E, Biernat W, Krykowski E, Jeziorski A, Robak T. Merkel cell carcinoma in a patient with B-cell chronic lymphocytic leukemia treated with cladribine and rituximab. *Leuk Lymphoma*. 2005;46:909–914.
- <sup>25</sup> Takabayashi M, Sakai R, Sakamoto H, et al. Merkel cell carcinoma developing after antithymocyte globulin and cyclosporine therapy for aplastic anemia. *Anticancer Drugs*. 2003;14:251–253.
- <sup>26</sup> Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet*. 2002;359: 497–498.
- <sup>27</sup> Vlad R, Woodlock TJ. Merkel cell carcinoma after chronic lymphocytic leukemia: case report and literature review. *Am J Clin Oncol*. 2003;26:531–534.
- <sup>28</sup> Ho SY, Tsai YC, Lee MC, Guo HR. Merkel cell carcinoma in patients with long-term ingestion of arsenic. *J Occup Health*. 2005;47:188–192.
- <sup>29</sup> Goessling W, McKee P, Mayer R. Merkel cell carcinoma. *J Clin Oncology*, 2002; 20: 588-598.
- <sup>30</sup> Aasi SZ, Leffell DJ: Cancer of the skin. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds.: *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2005, pp 1717-44.

- <sup>31</sup> Gollard R, Webber R, Kosty MP, Greenway HT, Massullo V, Humberson C: Merkel cell carcinoma: Review of 22 cases with surgical, pathologic and therapeutic considerations. *Cancer* 2000; 88:1842-1851.
- <sup>32</sup> Hitcock CL, Bland KI, Laney III RG, Franzini D, Harris B, Copeland III EM: Neuroendocrine Merkel cell carcinoma of the skin: Its natural history, diagnosis and treatment. *Ann Surg* 1988; 207:201-207.
- <sup>33</sup> Safai B. Management of skin cancer. In Devita V, Hellman S, Rosenberg S, ed. *Principles and Practice of Oncology*, Philadelphia: JB Lippincott; 1997:1905.
- <sup>34</sup> Hitcock CL, Bland KI, Laney III RG, Franzini D, Harris B, Copeland III EM: Neuroendocrine Merkel cell carcinoma of the skin: Its natural history, diagnosis and treatment. *Ann Surg* 1988; 207:201-207.
- <sup>35</sup> Silva EG, Mackay B, Goepfert H, et al: Endocrine carcinoma of the skin (Merkel cell carcinoma). *Pathol Annu* 1984; 19:1-30.
- <sup>36</sup> Best TJ, Metcalfe JB, Moore RB, Nguyen GK: Merkel cell carcinoma of the scrotum. *Ann Plast Surg* 1994; 33:83.
- <sup>37</sup> Goepfert H, Remmler D, Silva E, Wheeler B: Merkel cell carcinoma (endocrine carcinoma of the skin) of the head and neck. *Arch Otolaryngol* 1984; 110:707-712.
- <sup>38</sup> Kurul S, Mudun A, Aksakal N, Aygen M: Lymphatic mapping for Merkel cell carcinoma. *Plast Reconstr Surg*. 2000; 105:680-683.
- <sup>39</sup> Goepfert H, Remmler D, Silva E, Wheeler B: Merkel cell carcinoma (endocrine carcinoma of the skin) of the head and neck. *Arch Otolaryngol* 1984; 110:707-712.
- <sup>40</sup> Canales LI, Parker A, Kadakia S: Upper gastrointestinal bleeding from Merkel cell carcinoma. *Am J Gastroenterol* 1992; 87:1464-1466.
- <sup>41</sup> Feun LG, Sararaj N, Legha SS, Silva EG, Benjamin RS, Burgess MA: Chemotherapy for metastatic Merkel cell carcinoma. *Cancer* 1988; 62:683-685.
- <sup>42</sup> Redmond III J, Perry J, Sowray P, Vukelja SJ, Dawson N: Chemotherapy of disseminated Merkel-cell carcinoma. *Am J Clin Oncol* 1991; 14:305-307.
- <sup>43</sup> Queirolo P, Gipponi M, Peressini A, et al: Merkel cell carcinoma of the skin: Treatment of primary, recurrent, and metastatic disease—review of clinical cases. *Anticancer Res* 1997; 17:673-678.
- <sup>44</sup> Abeloff: *Clinical Oncology*, 3rd ed. Copyright © 2004 Churchill Livingstone, An Imprint of Elsevier
- <sup>45</sup> Goessling W, McKee P, Mayer R. Merkel cell carcinoma. *J Clin Oncology*, 2002; 20: 588-598.
- <sup>46</sup> Aasi SZ, Leffell DJ: Cancer of the skin. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds.: *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2005, pp 1717-44.

<sup>47</sup> Gollard R, Webber R, Kosty MP, Greenway HT, Massullo V, Humberson C: Merkel cell carcinoma: Review of 22 cases with surgical, pathologic and therapeutic considerations. *Cancer* 2000; 88:1842-1851.

<sup>48</sup> Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23: 2300–2309.