Radiotherapy in the Treatment of Ameloblastoma and Ameloblastic Carcinoma

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ABSTRACT

Objective: To determine the efficacy of radiotherapy in the treatment of ameloblastoma and ameloblastic carcinoma.

Patients and Methods: Two patients with ameloblastoma and 3 patients with ameloblastic carcinoma were treated with radiotherapy alone (1 patient) or surgery and postoperative radiotherapy (4 patients) at the University of Florida between 1973 and 2004. Follow-up ranged from 10 months to 3.3 years; no patient was lost to follow-up.

Results: Local control was achieved in all 5 patients. No patient developed regional or distant metastasis. One patient died of intercurrent disease at 2.1 years; 4 patients were alive and disease-free. No significant treatment-related complications were observed.

Conclusion: Adjuvant postoperative radiotherapy improves the likelihood of local control after surgery when margins are close or microscopically positive. Limited data suggest that radiotherapy alone may occasionally control patients with unresectable tumours.

Key Words: Ameloblastoma, Head and neck neoplasms, Radiotherapy, Treatment outcome

INTRODUCTION

Ameloblastomas are benign, locally invasive tumours constituting 1% of all tumours and cysts arising in the mandible and maxilla. They account for 11% of all odontogenic tumours. Approximately 80% arise in the mandible (most commonly in the molar-ramus region) and the remainder occur in the maxilla.1-4 Ameloblastomas arising in soft tissues are rare.5 Most patients are diagnosed in the third to fifth decade of life.3,6,7 However, the tumour grows slowly and probably starts to develop between early childhood and young adulthood.2,8 Gender distribution varies but is probably about 1:1. Most authors report an equal racial distribution.2,4 The most common presentation is a painless swelling of the jaw. Additional symptoms include malocclusion, pain, tooth mobility, ill-fitting dentures or bridges, periodontal disease, ulceration, paresthesia, and/or anesthesia of the affected area.3,4,6,7

Histologically, ameloblastomas arise from cell remnants of the embryonic tooth, particularly the dental lamina or inner enamel epithelium. They are composed of a central area of stellate epithelial cells known as the stellate reticulum and are surrounded by a periphery of vacuolated columnar epithelial cells. The peripheral cells are regarded as the reserve cells. The stellate reticulum may undergo squamous metaplasia.9,10

Ameloblastomas exhibit various histological patterns; the 2 most common are follicular and plexiform. Others include acanthomatous, granular, basaloïd, and desmoplastic. These patterns may exist singly or in combination. The tumours are also subdivided into 4 variants based on overall histologic architecture including solid, multicystic, multicystic plus solid, and unicystic types. Apart from the unicystic variant, which has a lower recurrence rate, the histological pattern does not influence clinical behaviour.9,10 Gross morphology and location are more important in predicting tumour aggressiveness.12,13
Two rare forms of malignancy are associated with ameloblastoma: malignant ameloblastoma and ameloblastic carcinoma. The cardinal feature of malignant ameloblastoma is metastatic spread. The histologic appearance of the primary and metastatic lesions is indistinguishable from benign ameloblastoma. In contrast, the primary and metastatic lesions of an ameloblastic carcinoma show histologically malignant epithelial features similar to an epidermoid carcinoma.\textsuperscript{14,15}

Regional nodal metastases and/or hematogenous dissemination may occur.\textsuperscript{15-18} Seventy five percent of distant metastases arise in the lungs, while the remaining lesions occur predominantly in the bones (i.e., skull, vertebrae, ribs, and femur). The median survival after development of distant metastases is 2 years.\textsuperscript{19}

Surgery is the mainstay of treatment for ameloblastoma and ameloblastic carcinomas. The optimal treatment for ameloblastic carcinomas is resection with wide margins. However, because ameloblastomas are benign, the extent of the resection is controversial. Less aggressive resections are often employed to avoid the potential morbidity associated with wide excisions.\textsuperscript{20} Recurrence rates of ameloblastomas are as high as 15\% to 25\% after wide resection and 65\% to 90\% after less extensive operations such as curettage.\textsuperscript{9,20-25} The initial surgical intervention offers the best chance of cure and reducing the risk of developing metastases.

Ameloblastomas have been reported to be radio-resistant and, thus, radiotherapy (RT) has generally been reserved for palliation of patients with unresectable tumours.\textsuperscript{26} Most recently, RT has been employed with some degree of success.\textsuperscript{27} Isolated case reports exist describing the efficacy of chemotherapy and, in general, it appears to be relatively ineffective.\textsuperscript{28}

The aim of this report is to present our experience with RT in the treatment of patients with ameloblastomas and ameloblastic carcinomas, and to review the pertinent literature.

**PATIENTS AND METHODS**

Five patients were treated with curative intent with RT alone (1 patient) or following surgery (4 patients) at the University of Florida between 1973 and 2004. A tissue diagnosis was available in all patients. Four patients had a tumour located in the maxilla and 1 patient had a mandibular lesion. Two patients had ameloblastomas and 3 had ameloblastic carcinomas. Four patients were treated for lesions that were recurrent after one or more operations. No patient presented with regional node involvement or distant metastasis.

Four patients underwent resection (Table 1). Margins were close in 2 patients and microscopically positive in 2 patients. RT doses ranged from 63 to 72 Gy. Three patients received once-daily RT, 1 patient received twice-daily fractionation, and 1 patient was treated with a combination of the 2 techniques. One elderly patient was treated with RT alone for an advanced recurrent tumour of the maxilla (Table 1). Follow-up ranged from 10 months to 3.3 years. No patients were lost to follow-up. All living patients were contacted or seen within 1 month of data analysis. Local control was defined as no evidence of disease at the primary site on subsequent physical examinations and/or radiographic studies until last follow-up or death. Death from intercurrent disease was defined as death without evidence of recurrent tumour.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Primary site</th>
<th>Histology</th>
<th>Prior treatment</th>
<th>Surgery</th>
<th>Resection</th>
<th>Radiotherapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70/m</td>
<td>Maxilla</td>
<td>Ameloblastic carcinoma</td>
<td>Surgery x 1</td>
<td>Partial maxillectomy</td>
<td>Close</td>
<td>66.4 Gy/46 fx/QD/BID</td>
<td>NED 3.3 years</td>
</tr>
<tr>
<td>2</td>
<td>70/m</td>
<td>Mandible</td>
<td>Ameloblastic carcinoma</td>
<td>None</td>
<td>Segmental mandibulectomy</td>
<td>Close</td>
<td>66 Gy/33 fx/QD</td>
<td>NED 2.1 years</td>
</tr>
<tr>
<td>3</td>
<td>56/m</td>
<td>Maxilla</td>
<td>Ameloblastic carcinoma</td>
<td>Surgery x 1</td>
<td>Total maxillectomy</td>
<td>(&lt;0.5 mm)</td>
<td>Microscopically positive</td>
<td>NED 0.83 years</td>
</tr>
<tr>
<td>4</td>
<td>82/m</td>
<td>Maxilla</td>
<td>Ameloblastoma</td>
<td>Multiple operations</td>
<td>-</td>
<td>72 Gy/60 fx/BID</td>
<td>NED 2.1 years</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61/m</td>
<td>Maxilla</td>
<td>Ameloblastoma</td>
<td>Multiple operations</td>
<td>Maxillectomy</td>
<td>Microscopically positive</td>
<td>NED 2.1 years</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: m = male; fx = fractions; QD = once-daily fractionation; BID = twice-daily fractionation; NED = no evidence of disease; DID = dead of intercurrent disease.
RESULTS
Local control after RT was observed in all 5 patient (100%). No patient developed a regional or distant recurrence.

Four patients are alive and disease-free and 1 patient died of intercurrent disease. No patient suffered a severe treatment-related complication.

DISCUSSION
Surgery
Surgery is the optimal treatment for patients with ameloblastoma and ameloblastic carcinoma. The optimal surgical approach remains controversial. Conservative options include enucleation, curettage, cryotherapy, electrocautery, marsupialization, or any combination of the above. Wide resection involves segmental or rim resection of the mandible or maxilla.\textsuperscript{20,24,25}

Conservative resections have resulted in high local recurrence rates. Sehdev et al reported local recurrences in excess of 90% in a series of 92 patients with ameloblastoma treated with curettage alone.\textsuperscript{21} With a mean follow-up of 3 years, Sampson and Pogrel reported a 100% local recurrence rate in 11 patients undergoing curettage for ameloblastoma.\textsuperscript{20}

Some authors have emphasized the importance of distinguishing unicystic from the solid or multicystic variant of ameloblastoma; the latter warrants more aggressive surgical intervention. Muller and Slootweg reported a series of 84 patients and observed local recurrence rates of 75% versus 20% after conservative resection of multicystic versus unicystic ameloblastomas.\textsuperscript{25} Following wide resection for multicystic tumours, the recurrence rate declined to 15%. In addition, they noted that 95% of local recurrences developed within 5 years after surgery.

Gardner and Pecak reported that conservative surgical treatment should be considered only in the presence of unicystic lesions when extraosseous spread has not occurred.\textsuperscript{12} They concluded that unacceptably high recurrence rates occur in the multicystic or solid variant, which often exhibits invasion into the intertrabecular spaces of the cancellous bone, making complete resection with conservative methods exceedingly difficult. In addition, Gardner and Pecak concluded that ameloblastomas in the posterior part of the maxilla should be treated more aggressively than similar lesions in the mandible, due to the proximity of vital structures and difficulty of treating subsequent recurrences.\textsuperscript{12}

Due to the high risk of local recurrence, optimal resection requires a more than 1 cm margin of uninvolved cancellous bone surrounding the primary tumour.\textsuperscript{29,30} However, local recurrence rates are as high as 15% to 25% after wide resection. Reportedly, salvage surgery can control 80% of mandibular tumours but only 40% of maxillary tumours.\textsuperscript{21,30} Therefore, patients at high risk for developing recurrence after surgery should be considered for adjuvant therapy.

Radiotherapy
There are relatively few data pertaining to the efficacy of RT. Robinson reported one of the first series, in which 18 patients were treated with RT alone; 13 patients (72%) developed a local recurrence.\textsuperscript{1} RT consisted of orthovoltage external beam RT, radium needles, or radon seeds.\textsuperscript{1} Sehdev et al reported on 11 patients treated at the Memorial Sloan Kettering Cancer Center with RT between 1921 and 1951.\textsuperscript{21} Although the tumour initially responded in some patients, all eventually experienced progression of persistent disease or a local recurrence.

Recently published studies analyzing the efficacy of megavoltage therapy in the management of ameloblastoma have questioned the proposition that these tumours are inherently radioresistant. Gardner reported on 3 patients treated with megavoltage RT (40, 45 and 55 Gy, respectively); all 3 responded initially but later recurred.\textsuperscript{31} Based on these results, Gardner concluded that RT can produce regression of an ameloblastoma, particularly the part which causes expansion of the jaw or has invaded the adjacent soft tissues but that it is not appropriate treatment for ameloblastomas and should be reserved for unresectable tumours.\textsuperscript{31}

Atkinson et al published a case series of 10 patients treated at Princess Margaret Hospital between 1958 to 1982.\textsuperscript{27} Two patients underwent total excision and postoperative RT and 1 patient underwent subtotal excision and RT; all 3 remained alive and disease-free at 27 months, 30 months, and 5 years after treatment. Seven patients were treated with RT alone; 1 patient had persistent disease and required further treatment and the remainder experienced slow regression of the tumour which remained locally controlled in all 6 patients.

In a case report and review of the literature, Miyamoto et al asserted that ameloblastoma is radiosensitive.\textsuperscript{32} They proposed guidelines for treatment planning as follows: 1) RT portals should include the entire tumour...
volume with a 2 cm margin, 2) lymph nodes should not be included unless clinical involvement is suspected, and 3) doses of at least 45 to 50 Gy in 4 to 5 weeks using 1.8 Gy fractions are necessary to control the tumour.

All 5 of our patients treated with surgery and RT (4 patients) or RT alone (1 patient) have remained disease-free after treatment.

Chemotherapy
Experience with chemotherapy is minimal in the treatment of ameloblastoma and is largely limited to isolated cases. Lanham described a case report of ameloblastoma metastatic to the lungs and submandibular nodes treated with doxorubicin, cisplatin, cyclophosphamide, dacarbazine, and 5-fluorouracil; the tumour failed to respond. Duffey et al reported a case of ameloblastoma with dissemination to cervical lymph nodes, liver, and lungs treated with multi-agent chemotherapy. The tumour did not respond to treatment. In contrast, Grunwald et al described a case of ameloblastoma metastatic to the lungs and pleura, which exhibited response to paclitaxel and carboplatin.

CONCLUSIONS
Our experience indicates that the probability of controlling local recurrence of ameloblastoma and ameloblastic carcinoma with surgery and adjuvant RT is high. All of the 4 patients in our series treated with surgery and RT remained locally controlled after treatment. There are few data in the literature pertaining to the efficacy of RT alone. It appears that RT alone probably controls approximately half of those treated. Thus, patients who have tumours that are amenable to gross total resection should be treated surgically.

We currently employ adjuvant RT in patients with ameloblastomas that have been resected with positive margins and in whom salvage surgery would likely be ineffective. RT alone for gross disease is employed only by default if the disease is unresectable. Ameloblastic carcinoma is treated in the same manner as other more common oral cavity carcinomas with surgery and postoperative RT depending on the pathologic findings. Indications for RT include close or positive margins, multiple positive nodes, extracapsular invasion, and perineural invasion.

RT doses range from 60 to 70 Gy using once- or twice-daily fractionation. In patients with ameloblastic carcinoma, regional nodal irradiation should be considered.

REFERENCES

Continuing Medical Education in Journal of the Hong Kong College of Radiologists available on Membership & Learning Management System

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