Oncocytic Carcinoma of the Parotid Gland

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Objectives/Hypothesis: The incidence of oncocytic carcinoma of the parotid gland is low, so a systematic evaluation of treatment strategies is lacking. We aimed to describe our experiences in treating this malignancy.

Study Design: Retrospective study.

Methods: We reviewed the files for 18 patients (14 males) of oncocytic carcinoma of the parotid gland in our institution from 1991 to 2011. Four patients underwent surgery alone, four surgery and postoperative radiotherapy, nine surgery and postoperative brachytherapy, and one radiotherapy alone. Median follow-up was 36 months (range 2–108 months).

Results: The 5-year local control rate was 66.9%, overall survival 68.6%, disease progression-free survival 46.2%, and 5-year freedom from distant metastasis 61.0%. Clinical N category, local recurrence, and distant metastasis significantly influenced overall survival.

Conclusions: Conservative parotidectomy is not radical enough to treat oncocytic carcinoma of the parotid gland. Elective neck dissection is recommended for patients with cancer stage T2 to 4. Surgery with postoperative 125I brachytherapy leads to good local control for patients with advanced disease or with positive or close resection margins.

Key Words: Oncocytic carcinoma, parotid gland, surgery, brachytherapy.

Level of Evidence: 4.

INTRODUCTION

Oncocytic carcinoma was first reported by Bauer and Bauer in 1953. Its occurrence in the salivary gland is included in the current World Health Organization histological classification of salivary gland tumors. Oncocytic carcinoma accounts for 5% of all oncocytic tumors and less than 1% of all salivary gland tumors. It can occur in major and minor salivary glands, nasal and thoracic cavities, ovary, thyroid gland, and breast and parathyroid gland, the most common site is the parotid gland. Oncocytic carcinoma is characterized by oncocyes with marked cellular atypia, frequent mitosis, destruction of adjacent structures, perineural or vascular invasion, and distant or regional lymph-node metastasis. Its recurrence has been reported to range from 25% to 52% of cases.

Because of the low incidence of oncocytic carcinoma, a treatment strategy has not been established nor systematically evaluated. Similar to most parotid gland carcinomas, surgery is the treatment of choice for oncocytic carcinoma. Radiotherapy is delivered in advanced-stage cases, with positive or close resection margins, and/or regional metastasis. Although chemotherapy is used for treating distant metastasis, the relative roles of radiotherapy and chemotherapy in treatment of this disease remain controversial.

The purpose of this retrospective study was to report our experiences in treating oncocytic carcinoma of the parotid gland, and to evaluate the efficacy of different treatment modalities as well as the factors influencing prognosis.

MATERIALS AND METHODS

Study Population

We reviewed case files for 18 patients (14 males) with oncocytic carcinoma of the parotid gland who were treated at Peking University School and Hospital of Stomatology from 1991 to 2011. Table I summarizes the clinical characteristics of patients. The tumors were staged according to the 6th edition of the International Union Against Cancer (TNM) classification for malignant tumors of the major salivary glands. The diagnosis of oncocytic carcinoma was based on histopathologic and immunohistochemical examination. Among the 18 cases, one originated from a pleomorphic adenoma, and three transformed from oncocytoma. This study was approved by the Ethics Committee of Peking University School and Hospital of Stomatology.

The main symptom at presentation was a pain-free mass. Only seven and four patients presented pain and facial nerve paralysis, respectively. In two patients, the skin overlying the gland was wrinkled. Four patients had enlarged cervical lymph nodes at presentation.

Treatment Strategy

The treatment strategy was determined on a case-by-case basis and was influenced by tumor stage, presence of...
perineural or major vascular invasion, the medical condition of the patient, and their own wishes. Four patients with early disease (stages I and II) underwent surgery alone, specifically superficial or partial parotidectomy preserving the facial nerve. Nine patients with advanced disease (stages III and IV) or with positive or close resection margins (<3 mm) underwent surgery and postoperative external radiotherapy (n = 4) or postoperative 125I brachytherapy (n = 5). Four patients with unresectable disease underwent local debulking surgery (or biopsy alone) and postoperative 125I brachytherapy to preserve the facial nerve, with or without external radiotherapy to the neck. One patient with advanced disease (T4aN2cM0) refused surgery and received only external radiotherapy. The dose of external radiotherapy was 56 to 66 Gy (conventional fractionation; 2 Gy/d; median 60 Gy; mean 60.8 Gy). The actuarial dose delivered to 90% of the target volume with use of a 125I implant was 162 to 197 Gy (median 177 Gy). The activity of 125I (model 6711, China Institute of Atomic Energy; half-life 59.4 days) was 18.5 to 33.3 MBq per seed.

In total, six patients with clinical cervical lymph node involvement or advanced disease (stages T3 and 4) underwent neck dissection; for two patients with clinical stage N0 (determined by physical examination and CT), histopathology revealed cervical metastasis after neck dissection. Six patients with advanced cancer (stages III and IV) received external radiotherapy to the neck with or without neck dissection.

Patient follow-up consisted of routine physical examination and appropriate imaging of the primary site and neck: CT or PET-CT, if necessary.

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**Table 1. Patients Characteristics.**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>56.5(40–86)</td>
</tr>
<tr>
<td>Sex (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
</tr>
<tr>
<td>Duration (months)*</td>
<td>12 (0.5–156)</td>
</tr>
<tr>
<td>UICC stage (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>IVA</td>
<td>6</td>
</tr>
<tr>
<td>IVB</td>
<td>1</td>
</tr>
<tr>
<td>Treatment modality for primary site (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>Surgery (superficial or partial parotidectomy)</td>
<td>4</td>
</tr>
<tr>
<td>Surgery (radical, superficial or partial parotidectomy) + EBRT</td>
<td>4</td>
</tr>
<tr>
<td>Surgery (superficial or partial parotidectomy) + 125I implant</td>
<td>5</td>
</tr>
<tr>
<td>Surgery (debulking operation) + 125I implant</td>
<td>4</td>
</tr>
<tr>
<td>EBRT alone</td>
<td>1</td>
</tr>
<tr>
<td>Treatment modality for neck lymph node (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>Neck dissection</td>
<td>1</td>
</tr>
<tr>
<td>Neck dissection + EBRT</td>
<td>5</td>
</tr>
<tr>
<td>EBRT</td>
<td>1</td>
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</tbody>
</table>

*Data are presented as median (range); EBRT = external beam radiotherapy.

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**Statistical Analysis**

Statistical analysis involved use of SPSS 13.0 for Windows (SPSS Inc, Chicago, IL). The probabilities of local control, freedom from distant metastasis, disease progression-free survival, and overall survival were calculated by the Kaplan-Meier product-limit method. The effect of T stage, N category, UICC stage, local recurrence, and distant metastasis on overall survival were analyzed by univariate analysis with the classical log-rank test. The impact of T stage on cervical and distant metastasis and treatment modality on local control were analyzed by univariate log-rank test. Differences were considered statistically significant with a two-sided \( P < 0.05 \).

**RESULTS**

**Overall Survival and Progression-Free Survival**

Median follow-up was 36 months (range 2–108 months); 5-year overall survival was 68.6%, with mean survival time 6.92 years (95% confidence interval [95% CI] 5.14–8.69 years; Fig. 1). The 5-year progression-free survival was 46.2%, with mean survival time 4.1 years (2.56–5.58 years; Fig. 2). The 5-year progression-free survival for nine patients who received 125I implantation brachytherapy was 77.8%, and 25% for patients who underwent surgery with external beam radiotherapy. Clinical N category, local recurrence, and distant metastasis influenced survival significantly (\( P = 0.001, P = 0.035, P < 0.001 \), respectively). Survival was better, although not statistically significant, for tumors at UICC stages I and II than stages III and IV (\( P = 0.252 \)). The patient who underwent radiotherapy alone died of the disease within 1 year; disease was associated with local progression and metastases to the lung, brain, and liver.

**Local Control**

Excluding the patient who refused surgery, the 5-year local control rate was 66.9%, with mean local control time 5.06 years (95% CI 3.55–6.57 years; Fig. 3). The postoperative local recurrence rate was 35.3% (6 of
17 patients); recurrence occurred at a median of 12 months (range 1.5 and 72 months) after treatment. Local recurrence was lower for patients who received \(^{125}\text{I} \) implantation brachytherapy (1/9) than those who underwent surgery alone (2/4) or surgery with external beam radiotherapy (3/4) (Table II). As well, 5-year local control for patients who received \(^{125}\text{I} \) implantation brachytherapy (88.9\%, with mean local control time 5.89 ± 0.58 years) was significantly better than patients who underwent surgery with external beam radiotherapy (50\%, mean local control time 3.16 ± 1.74 years, \(P = 0.049 \)). Figure 4 shows a patient with stage IV oncocytic carcinoma of the right parotid gland got complete regression 6 months after biopsy and \(^{125}\text{I} \) implantation.

**Cervical Lymph Node and Distant Metastasis**

Excluding the patient who received radiotherapy alone, in three patients without neck dissection and one patient with neck dissection (all stage T2 to 4), cervical lymph node metastasis developed at a median 8 months (range 1.5–42 months) during the period of follow-up.

The 2- and 5-year freedom from distant metastasis rates were 82.4\% and 61.0\%, respectively, with a mean freedom from distant metastasis time 6.45 years (95\% CI 4.63–8.28 years; Fig. 5). Distant metastasis occurred in five patients at a median of 12 months (range 8–48 months). All five patients had cervical lymph node metastasis on admission or after treatment, and four of these were at stage T4. As compared with tumors at stages T1 to 3, tumors at stage T4 had a higher risk, although not statistically significant, of distant metastasis (\(P = 0.059 \)). The most common site of distant metastasis was the lung (4 of 5 cases), then the brain (3 cases), and liver (1 cases).

Table II shows the cervical and distant metastasis information for patients who received different treatments.

**DISCUSSION**

Oncocytic carcinomas of the parotid gland occur most commonly in patients between the ages of 55 and 70 years and shows a significant male predilection, with a ratio of males to females of approximately 2:1.\(^{24–26}\) The patient sample we reviewed had similar characteristics, with median patient age 56.5 years and male to female ratio 3.5:1.

Most cases of parotid gland carcinoma present a hard painless mass, which can be fixed or movable,\(^{7,9,16,17,20,25}\) although approximately one-third of patients present a painful mass or facial paralysis,\(^{7,9,16,20,27}\) as in our cases. The skin overlying the gland can become discolored or wrinkled,\(^{16}\) which we found.

**TABLE II.**

The Local Recurrence, Neck Metastasis, and Distant Metastasis for Patients Who Underwent Different Treatment Modalities.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Local recurrence</th>
<th>Neck metastasis</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (no.) Rate</td>
<td>2/4</td>
<td>1/4</td>
<td>1/4</td>
</tr>
<tr>
<td>Surgery + EBRT</td>
<td>3/4</td>
<td>1/4</td>
<td>2/4</td>
</tr>
<tr>
<td>Surgery + (^{125}\text{I} )</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Debulking Operation + (^{125}\text{I} )</td>
<td>1/4</td>
<td>2/4</td>
<td>1/4</td>
</tr>
</tbody>
</table>

Note: EBRT = external beam radiotherapy; \(^{125}\text{I} \) = \(^{125}\text{I} \) implantation brachytherapy.
Although there is a controversy,6,24 the fine needle aspiration (FNA) biopsy maybe used to help diagnosis.15,26,28

**Treatment Strategy**

Surgery is often the first-choice treatment for oncocytic carcinoma.9,15–17 However, a suitable surgical strategy has not been established. The potential limitations of a conservative surgical approach (superficial or partial parotidectomy) were highlighted by Goode et al., who found a tumor recurrence rate of 55.6% among nine cases of oncocytic carcinoma of the salivary glands.3 Furthermore, Gallego et al. reported lymph node metastasis in the residual parotid gland after superficial parotidectomy.9 In our study, four patients at stages I and II underwent conservative surgery alone; local recurrence occurred in two patients. Therefore, conservative surgery may be inadequate for effective treatment of oncocytic carcinomas of the parotid gland (even for tumors in early stage). Radical parotidectomy is recommended.3

Metastases to the cervical lymph nodes develops in about 40% to 63% patients with oncocytic carcinoma of parotid gland.4,7,15,20,24,25 The existing data support that tumors at stages T2 to 4 have increased risk of cervical metastasis.3,9,16 In our study, nine of 18 patients (all at stages T2 to 4) had clinical positive cervical metastasis detected before and after treatment. The risk of occult metastasis should be considered in patients with oncocytic carcinoma.6 We observed two cases of occult metastasis. Given the high incidence of neck metastasis, elective neck dissection is recommended, especially for tumors at stages T2 to 4.

The role of radiotherapy is controversial for treatment of oncocytic carcinoma.3,4,6,10,18,22,29,30 Several case reports described the positive effect of postoperative radiotherapy, for 1 to 3 years’ local control.18–20 In our study, conventional postoperative external radiotherapy (56–66 Gy) did not have a positive effect on enhancing local control; three of the four patients (stages T2 to 4) showed local recurrence. Further studies are needed to clarify the role of external radiotherapy, particularly the use of high radiation doses (≥66 Gy), which may be needed to achieve good local control.4,20

In terms of tolerance of vital normal tissues, increasing the external radiation dose is difficult. However, 125I seed brachytherapy is a promising alternative to external radiotherapy.31,32 125I brachytherapy can deliver a high radiation dose to the tumor while sparing surrounding tissues. Several reports have analyzed the benefits of 125I brachytherapy alone or with surgery for malignant salivary tumors.14,31,33 Zhang et al. reported 100% local control and no complications in malignant parotid gland tumors treated with conservative surgery and 125I brachytherapy to preserve the facial nerve.14 In our study, 5-year local control for nine patients who received 125I brachytherapy significantly better than for patients...
who underwent surgery with external beam radiotherapy ($P < 0.05$). Five patients who underwent conservative surgery with $^{125}$I brachytherapy were followed for a median of 30 months (range 18–78 months), with no recurrence. And four patients of them, including one patient with mild paralysis before treatment, who refused to sacrifice facial nerves that were near or adherent to tumors, showed well-preserved facial nerve function. Furthermore, we found only one case of local failure among four patients who underwent debulking surgery (or biopsy alone) and $^{125}$I brachytherapy were followed for a median of 18 months (range 12–66 months). Therefore, $^{125}$I implantation brachytherapy, especially combined with surgery, might result in good local control for oncocytic carcinoma of the parotid gland.

**Prognostic Factors**

The prognosis of oncocytic carcinomas is not well characterized. In some reports, patients appear to have good short-term survival, but long-term survival was poor. Distant metastasis was thought to be the most important prognostic factor for patients with oncocytic carcinoma. The distant metastasis rate in our series was as high as 27.8%, which was similar to the study by Nakada et al. (25.9%), but higher than that by Ardekian et al. (2.9%).

Lung was the most common metastasis location, then kidney, brain, liver, and bone. The presence of involved lymph nodes ($P < 0.001$) seems to confer increased risk of distant metastasis. Risk of distant metastasis is greater, although not significantly for tumors at stage T4 than stages T1 to 3 ($P = 0.059$). In our study, prognostic factors for overall survival were clinical N category, local recurrence, and distant metastasis. Advanced T stage may also have an important role in overall survival, but more cases and long-term follow-up are needed to confirm this suggestion.

**CONCLUSION**

Our review of the literature and clinical experience leads us to conclude that conservative parotidecomy is not radical enough to treat oncocytic carcinoma of the parotid gland, even for tumors at an early stage (stages I–II). Aggressive surgery is recommended, and elective neck dissection is recommended for tumors at stages T2 to 4. Conventional postoperative low-dose external radiotherapy ($<66$ Gy) may not have a significant positive effect on local control. Surgery combined with postoperative $^{125}$I brachytherapy leads to good local control for patients with advanced disease or with positive or close resection margins. Clinical N category, local recurrence, and distant metastasis have a significant influence on survival. A study with a larger number of patients and longer follow-up is needed to confirm the best treatment protocol(s) for oncocytic carcinoma of the parotid gland.

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