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ORIGINAL ARTICLE

Results of surgery plus postoperative radiotherapy for patients with malignant parotid tumor

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Abstract
Purpose The latest version of the World Health Organization (WHO) histologic classification of salivary gland malignancies was published in 2005. To contribute to data accumulation on the basis of this latest version, a retrospective study was performed.
Materials and methods Participants comprised 27 patients who underwent postoperative radiotherapy between 2000 and 2013. Two, eight, and 17 patients were allocated to low, intermediate, and high-grade groups, respectively, in accordance with the latest WHO classification. The radiation field included the tumor bed and ipsilateral regional lymph nodes for 25 patients. The radiation dose was 46–60 Gy (median 56 Gy).
Results Median duration of follow-up was 41 months. Five-year locoregional control was 89 %. Two patients experienced local recurrence and 7 patients developed distant metastases. No patients in the low or intermediate-grade groups developed distant metastases. Overall 3 and 5-year survival for all patients were 81 and 75 %, respectively. Five-year overall survival for patients in the low and intermediate-grade groups was 100 %, compared with 59 % for patients in the high-grade group ($p = 0.03$).
Conclusion Favorable locoregional control was achieved for patients with malignant parotid tumors who underwent surgery plus postoperative radiotherapy. Patients with high-grade tumors frequently experienced distant metastases and prognosis was poor.

Keywords Malignant parotid tumor · Surgery · Postoperative radiotherapy · WHO classification

Introduction

Malignant parotid gland tumors are rare, accounting for 1–3 % of all head and neck carcinomas [1]. These tumors comprise a complex and diverse group with different outcomes. Histologically, salivary gland tumors are the most heterogeneous group of tumors of any tissue in the body [2]. Assessment of prognostic factors is very difficult, because of their biologic and histologic heterogeneity. In 1972, the first version of the World Health Organization (WHO) histologic classification of salivary gland malignancies was published. It has since been revised twice, in 1991 and in 2005. In the latest version, salivary gland malignancies are divided into three broad categories—pathologically low, intermediate, and high-grade tumors (Table 1) [3].

Surgery is the mainstay of treatment for malignant parotid tumors. Several studies have identified important prognostic factors, for example T3-4 tumor, close or

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Table 1 Classification of salivary gland malignancies into three pathological groups

Low grade	Intermediate grade	High grade
Acinic cell carcinoma	Mucoepidermoid carcinoma, intermediate-grade type	Mucoepidermoid carcinoma, high-grade type
Mucoepidermoid carcinoma, low-grade type	Adenoid cystic carcinoma, cribriform and tubular type	Adenoid cystic carcinoma, solid-type
Polymorphic low-grade adenocarcinoma	Sebaceous carcinoma	Oncocytic carcinoma
Epithelial myoepithelial carcinoma	Adenocarcinoma NOS, intermediate-grade type	Salivary duct carcinoma
Clear cell carcinoma NOS	Myoepithelial carcinoma	Adenocarcinoma NOS, high-grade type
Basal cell adenocarcinoma	Lymphoepithelial carcinoma	Carcinoma ex pleomorphic adenoma, invasive type
Cystadenocarcinoma		Carcinosarcoma
Mucinous adenocarcinoma		Squamous cell carcinoma
Adenocarcinoma NOS, low-grade type		Small cell carcinoma
Carcinoma ex pleomorphic adenoma, non-invasive and microinvasive type		Large cell carcinoma
Metastatic polymorphic adenoma		
Salivary gland neuroblastoma		

For the low-grade group 5-year overall survival was 85 %

For the high-grade group 5-year overall survival was 50 %

positive resection margins, high-grade or undifferentiated tumor, perineural invasion, skin or bone invasion, and lymph node metastases, and postoperative radiotherapy is recommended as part of the adjuvant treatment for patients at high risk of locoregional recurrence [4–7]. In some of these reports, analysis was performed on the basis of the WHO histologic classification. As far as we are aware, however, the latest version has not been used in any other. This retrospective study was undertaken to contribute to data accumulation based on the latest version of the WHO histologic classification.

Materials and methods

This study was approved by the institutional review board at our hospital before the retrospective review of patient information.

Patient population

Between January 2000 and September 2013, 33 patients with malignant parotid tumors underwent postoperative radiotherapy at our institution. Patients who had T3-4 stage, multiple lymph node metastases, close or positive margin, or pathological high grade disease were treated with postoperative radiotherapy. Three patients with other coexisting malignancies and two patients treated with incomplete radiotherapy (<45 Gy) were excluded from this analysis. Furthermore, 1 patient with malignant peripheral nerve sheath tumor was also excluded, because this entity was not listed in the latest version of the WHO classification. Data for the remaining 27 patients were analyzed. Table 2 outlines characteristics of the patients.

In this study, tumors were classified into 3 groups (pathologically low, intermediate, or high-grade), in accordance with the latest version of the WHO classification, by two pathologists. Two, 8, and 17 patients were allocated to the low, intermediate, and high-grade groups, respectively. Tumors were retrospectively staged in accordance with the 2010 American Joint Committee on Cancer staging system. Stages T1, T2, T3, and T4 were observed for 7, 37, 19, and 37 % of patients, respectively, and Stages I, II, III, and IVa were observed for 7, 26, 26, and 41 % of patients, respectively.

Treatment

All patients underwent definitive surgery and postoperative radiotherapy sequentially. Surgery consisted of total parotidectomy alone and total parotidectomy with neck dissection for 6 and 21 patients, respectively. Microscopically positive margins were observed for two patients (7 %). The median time between surgery and postoperative radiotherapy was 35 days (range 20–67 days). For 2 patients (7 %) without lymph node metastasis the radiation field included the tumor bed only. For the other 25 patients (93 %) the radiation field included the tumor bed and ipsilateral regional lymph nodes (Levels I–III, AJCC Cancer Staging Manual). The prescribed dose was 46–60 Gy (median

Table 2 Patient characteristics

Age	Gender	Malignant histology	Pathologically malignant grade	T stage	Stage	N stage	Radiation dose
74	M	Mucoepidermoid carcinoma	High	2	IVa	+	60 Gy
41	M	Adenoid cystic carcinoma	Intermediate	2	II	−	56 Gy
51	F	Adenoid cystic carcinoma	Intermediate	2	II	−	50 Gy
84	M	Clear cell adenocarcinoma	High	3	III	+	50 Gy
78	M	Adenocarcinoma NOS	Intermediate	2	II	−	60 Gy
56	M	Adenocarcinoma NOS	High	2	III	+	46 Gy
16	F	Adenocarcinoma NOS	Intermediate	1	I	−	50 Gy
72	M	Adenocarcinoma NOS	High	4	IVa	−	60 Gy
20	M	Adenoid cystic carcinoma	Intermediate	2	II	−	60 Gy
38	M	Adenocarcinoma NOS	Intermediate	2	II	−	60 Gy
64	F	Mucoepidermoid carcinoma	Low	3	III	−	60 Gy
64	F	Mucoepidermoid carcinoma	High	4	IVa	+	50 Gy
74	M	Salivary duct carcinoma	High	4	IVa	−	60 Gy
24	F	Carcinoma ex pleomorphic adenoma	High	2	II	−	60 Gy
65	M	Adenocarcinoma NOS	High	4	IVa	+	60 Gy
75	F	Carcinoma ex pleomorphic adenoma	High	4	IVa	−	60 Gy
53	M	Carcinoma ex pleomorphic adenoma	High	3	III	−	50 Gy
72	M	Mucoepidermoid carcinoma	Intermediate	4	IVa	+	50 Gy
41	F	Adenoid cystic carcinoma	Intermediate	3	III	−	60 Gy
56	M	Carcinoma ex pleomorphic adenoma	High	2	III	+	50 Gy
27	M	Mucoepidermoid carcinoma	Low	2	II	−	50 Gy
74	M	Adenocarcinoma NOS	High	4	IVa	−	50 Gy
32	M	Salivary duct carcinoma	High	1	I	−	50 Gy
48	M	Carcinoma ex pleomorphic adenoma	High	4	IVa	−	50 Gy
71	F	Carcinoma ex pleomorphic adenoma	High	4	IVa	−	60 Gy
59	F	Carcinoma ex pleomorphic adenoma	High	4	IVa	+	60 Gy
78	M	Carcinoma ex pleomorphic adenoma	High	3	III	−	56 Gy

56 Gy) in 23–30 fractions over 4.6–6 weeks. For patients with histologically positive or close margin and/or clinically unsatisfactory safety surgical margin, the prescribed dose was 56–60 Gy; for patients with complete resection, the prescribed dose was 46–50 Gy. Follow-up consisted of routine physical examination and imaging studies of the head and neck. Twenty patients underwent chemotherapy concurrently with radiotherapy. The patients in the high-grade group received chemotherapy in principle. Some patients in other groups were added on the basis of the impression of the surgeons. Tegafur–gimeracil–oteracil combination, tegafur–uracil, carboplatin, and cisplatin plus tegafur–gimeracil–oteracil combination were administered to 14, 3, 2, and 1 patient, respectively. Patients were examined medically every 6 months for 1 year, then annually thereafter.

End points and statistical analysis

The end points analyzed were overall survival and locoregional control. All events were measured from the date of surgery. One, 3, and 5-year estimates of the probability of overall survival and locoregional control were calculated by use of the Kaplan–Meier method, and statistical analysis was performed by use of two-sided log-rank tests. Statistical analysis was performed with GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA).

Results

Median follow-up was 41 months (range 5–153 months). Overall survival for the entire patient population at 1, 3, and 5 years was 93, 81, and 75 %, respectively (Fig. 1). When the survival of patients in the low and intermediate-grade groups was compared with that in the high-grade group, a significant difference was observed ($p = 0.03$, Fig. 1).

Two patients experienced local recurrence, detected after 4 and 40 months. No patients experienced nodal metastasis. For the entire patient population, 3 and 5-year estimates of local control were 96 % and 89 %, respectively. Both of the

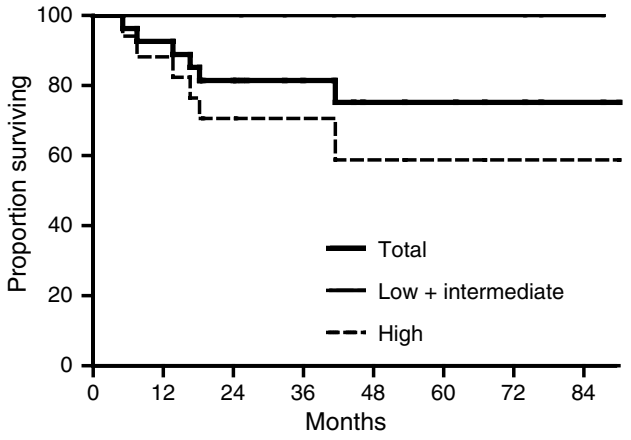

Fig. 1 Kaplan–Meier survival curves for all patients, for the pathologically low and intermediate-grade groups, and for the high-grade group. There was a significant difference between the last 2 groups ($p = 0.03$)

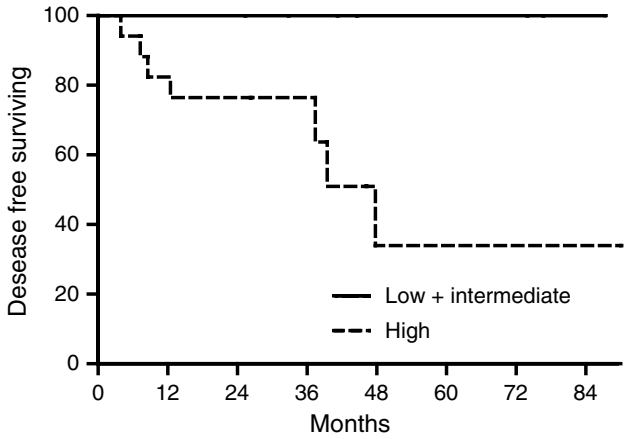

Fig. 2 Kaplan–Meier disease-free curves for the low and intermediate-grade groups, and for the high-grade group. There was a significant difference between the 2 groups

patients with local recurrence were in the high-grade group. For the high-grade groups, 3 and 5-year estimates of local control were 94 % and 78 %, respectively.

Eleven sites of distant metastasis were observed among 7 patients, all in the high-grade group. Bone, lung, liver, and brain metastases were observed in 4, 4, 2, and 1 patient, respectively. The sites of metastases partly overlapped.

Disease-free survival in the low and intermediate-grade groups was significantly different from that in the high-grade group ($p = 0.01$, Fig. 2).

Five-year overall survival for patients with T1, T2, T3, and T4 was 100, 75, 80, and 70 %; that for patients with Stages I, II, III, and IV was 100, 86, 86, and 58 %, respectively. Although stratification by T stage and Stage was performed, no significant difference was found between those groups. Likewise, radiation dose, cervical lymph node status, close/positive margins, neck dissection, or use of chemotherapy had no significant effect on overall survival.

Discussion

The latest version of the WHO histologic classification of salivary gland malignancy has been in use for approximately a decade. However, relatively few data based on this classification have been accumulated, because of the infrequency of this disease. Although the number of patients in this study was not large, several findings were observed.

Vander Poorten et al. reported that histology was not an independent prognostic factor for disease-free survival [8]. Recently, Al-Mamgani et al. also reported that histological types were not significant predictors for disease-free survival [9]. In this study, however, both overall survival and disease-free survival were significantly poor for patients in the high-grade group. A possible explanation of this discrepancy is that evaluation was performed on individual histology in the first 2 studies. The small number of patients for which individual histology was conducted could result in insufficient statistic power. In our study, evaluation was performed on the broad categories. The WHO histologic classification worked well. In the high-grade group, distant metastases were frequently observed, and resulted in poor prognosis. Strategies against distant metastases are thus required for the pathologically high-grade group.

Systemic chemotherapy has a limited, palliative effect in the treatment of recurrent, advanced unresectable, and metastatic malignant salivary gland tumors. Because of the rarity of these tumors, large-scale randomized control

Table 3 Five-year locoregional control after surgery alone or surgery followed by radiotherapy

Author and Ref.	Year	Patients (*n*)	Surgery	+ Post-operative radiotherapy
Fu et al. [12]	1977	100	46 %	86 %
Fitzpatrick [13]	1986	403	27 %	73 %
Tran et al. [14]	1986	133	53 %	75 %
Armstrong et al. [6]	1990	46	66 %	73 %
Frankenthaler et al. [15]	1991	178	80 %	88 %
Mendenhall et al. [16]	2005	224		89 %
Pohar et al. [17]	2005	163	63 %	89 %
Chen et al. [18]	2006	140	80 %	92 %
Al-mamgani et al. [9]	2011	186		89 %
Present study	2015	27		89 %

trials are not feasible for investigation of tumor management. There is no evidence to validate use of chemotherapy in the postoperative adjuvant setting. The most active single agents include cisplatin, epirubicin, doxorubicin, and 5-fluorouracil [10]. Selection of chemotherapeutic agents is also challenging. A randomized control trial comparing single-agent vinorelbine with the combination of vinorelbine plus cisplatin for patients with a variety of histologic subtypes of malignant salivary gland tumor showed that the combination regimen was more active, with a 44 % overall response compared with 20 % for monotherapy [11]. Although data for chemotherapy are limited, chemotherapy should be used as a strategy against distant metastases in the pathologically high-grade group.

Five-year locoregional control of 73–92 % has been reported after use of postoperative radiotherapy (Table 3) [6, 9, 12–19]. Our results showed locoregional control was comparable with that in previous studies. Given the good local control, the radiation doses of 50–60 Gy and radiation fields (tumor bed ± ipsilateral regional lymph nodes) used in our study seemed appropriate for the low and intermediate-grade groups. In the study performed by Al-Mamgani et al., the incidence of occult nodal metastasis was 31 % for patients treated with elective neck dissection. However, no nodal metastasis was found in our study. Satisfactory regional control was achieved by use of our treatment regimen. Local control in the high-grade group was, however, relatively low compared with that in the low and intermediate-grade groups. A dose of 60 Gy, at least, was preferable for this group.

In conclusion, this analysis reveals that surgery and postoperative radiotherapy result in satisfactory local control for patients with low or intermediate-grade malignant parotid gland tumors. Patients in the pathologically high-grade group frequently experienced distant metastases and their prognosis was poor. Adjuvant systemic chemotherapy is required for that group. Thus, pathological groups based on the WHO classification are predictors of relapse pattern, and individual strategy can be established for each group.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All applicable institutional guidelines for the care were followed.

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