

## RESEARCH ARTICLE

# Prognostic Factors and Clinical Outcome in Parotid Gland Tumors: a Single Institution Experience from the Eastern Black Sea Region of Turkey

Mustafa Kandaz\*, Gulsen Soydemir, Zümrüt Bahat, Emine Canyılmaz, Adnan Yoney

## Abstract

**Purpose:** To review clinical characteristics, treatment outcomes and prognostic factors in patients with parotid gland tumors treated with surgery and postoperative radiotherapy. **Materials and Methods:** We retrospectively reviewed 69 patients with parotid gland tumors, with a median follow-up of 52 months (range, 2-228 months), and a median radiotherapy dose of 60 Gy (range, 30-69 Gy). **Results:** There were 24 (35%) females and 45 (65%) males, at a ratio of 1/1.9. Median age at presentation was 58.9±17.2 (range 13-88) years. The most common histology was adenoid cystic carcinoma (33%) and mucoepidermoid carcinoma (28%). The mean overall survival (OS) was 65.3±8 (95% confidence interval [CI], 49.6-81.1) months and the median overall survival was 40.0 ± 7 (95% CI, 26.2-53.7) months. The -1, -3, -5 and -10 year OS rates were 78%, 52.4%, 35.3% and 19.6% respectively. The mean disease free survival (DFS) was 79.2±10 (95% CI, 59.3-97.1) months and the median disease free survival was 38±13 (95% CI, 7.05-88.7) months. The -1, -3, -5 and -10 year DFS rates were 71.9%, 50.1%, 43.7% and 30.1% respectively. On univariate analysis, the OS was significantly better with female sex ( $p<0.005$ ), < 50 age ( $p<0.021$ ), T stage ( $p<0.0001$ ), absence of lymph node involvement ( $p<0.0001$ ), lower tumor grade ( $p<0.0001$ ), absence of lymphovascular invasion ( $p<0.002$ ), absence of perineural invasion ( $p<0.0001$ ), absence of extracapsular extension ( $p<0.0001$ ), surgical margin negativity ( $p<0.006$ ), ≤60 Gy radiotherapy dose ( $p<0.0001$ ) and absence of distant metastasis ( $p<0.027$ ). **Conclusions:** Employing existing standards of postoperative radiotherapy is a possible treatment that was found to be mainly effective in patients with parotid gland carcinomas.

**Keywords:** Parotid gland cancers - patients characteristics - clinical outcome - prognostic factors

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## Introduction

Parotid carcinoma is very heterogeneous and rare disease. Approximately 4% of head-and neck-cancers and 0.5% of all human cancers (Al-Mamgani et al., 2012). Mucoepidermoid carcinoma, squamous cell carcinoma, adenocarcinoma and adenoid cystic carcinomas are the most histological types (Alterio et al., 2011).

The mainstay treatment is surgical resection and in well-selected patients with low grade tumor removed with resection free margins ≥5 mm, early-stage parotidectomy alone might be sufficient. Other patients, combined modality treatment of surgery and postoperative radiotherapy (RT) is needed (1). Some different studies shown that, surgery and postoperative RT (PORT) improved locoregional control (LRC), overall survival (OS) and disease-free survival (DFS) compared to one modality alone (Al-Mamgani et al., 2012).

PORT is indicated for patients with tumor size >4cm, tumor with deep lobe settlement, high grade tumor, lymph node involvement, advanced stage, positive surgery margins, perivascular and perineural invasion, nerve infiltration, recurrent tumor and soft tissue extension (Alterio et al., 2011).

In this study we evaluated clinical outcomes and prognostic factors in patients with parotid carcinomas treated with surgery and RT at our institution.

## Materials and Methods

### Patients selection

We retrospectively analyzed the data of 69 patients treated with surgery and RT for parotid carcinomas from January 1997 and December 2014. Locoregional clinical staging was performed using clinical examinations and computed tomography (CT) and/or magnetic resonance

(MR) and/or PET-CT. Distant metastases were detected using total-body CT, abdominal ultrasonography (USG) and/or MR. Surgical procedure (superficial or total parotidectomy, lymph node dissection) were recorded. Different surgical approaches depended on tumor location, histological characteristic and stage. Ipsilateral neck dissection was performed in patients of high-grade tumors, radiological or clinical evidence of lymph node metastasis or with the risk of lymph node involvement.

**Treatment**

PORT was given to patients in advanced stage, positive surgical margins, recurrent tumor, high grade histology and presence of lymph node metastasis. Ipsilateral neck lymph nodes were irradiated in patients of pathological lymph nodes or, as elective treatment, in high-risk patients. Total PORT dose was planned ranged from 60 Gy to 66 Gy for negative and positive microscopic surgical bed margins, respectively, and from 50 Gy to 60 Gy for negative and positive nodes with or without extracapsular extension, respectively. RT was performed with linear accelerator of 6 MV- energy and/or cobalt-60. RT was performed with some patients IMRT and some cases with 2-D and/or 3-D conformal technique. One daily fraction of 1.8 to 2 Gy for 5 days/week was used for all patients. When the tumor infiltrated the skin or was located in the superficial lobe, a waterequivalent bolus was added for all of the treatment duration and/or a mixed photon-electron beam technique was used according to personalized treatment plans. The spinal cord doses was limited between 45 Gy to 50 Gy. Head and neck mask was used for immobilization, simulation of all therapy phases. When computed tomography-based treatment was planned, organ at risk contouring and dose prescription and target volume were performing according to the International Commission on Radiation Units (ICRU) 62 guidelines. Radiotherapy-related acute and late mucosa, soft tissue, skin and temporomandibular joint toxicity was commentate according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system.

**Follow-up**

Follow-up was performed every 3 months for the first 2 years, every 6 months for the subsequent 3 years, and once a year thereafter. Clinical and radiological examinations were performed for each visit.

**Statistical methods**

In this study, clinical outcome was evaluated of disease-free and overall survival. Disease-free survival was evaluated between the end of PORT and the occurrence of local and/or distant recurrence. The association between clinical outcome (distant metastasis and local recurrence) and tumor characteristics (stage, grade, lymph node metastasis, positive surgical margins, extracapsular extension and perineural invasion) were analyzed. The association between total dose applied, surgical technique and toxicity (mucosa, soft tissue and skin) was also appraised.

Survival rates were calculated using Kaplan-Meier

technique. All significant tests and statistical significance were accepted for a calculated p value of <0.005.

**Results**

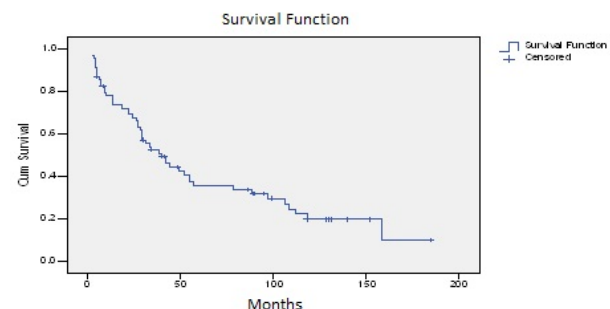
*Patients characteristics*

A total of 69 patients of parotid carcinomas. There were 24 (35%) females and 45 (65%) males, for a ratio of 1/1.9. Median age at presentation was 58.9±17.2 (range 13 to 88) years. Of the 69 patients, 18 (26%) occurred in <50 years and 51 (74%) in ≥50 years. The most common histology was adenoid cystic carcinoma (33%), mucoepidermoid carcinoma (28%), malign mixt tumor (18.5%) and squamous cell carcinoma (10%). The rarer histology was undifferentiated carcinom (3%), ductal carcinom (1.5%), pleomorphic carcinom (1.5%), acinic cell carcinom (1.5%), adenosquamous carcinom (1.5%) and papiller adenocarcinom (1.5%). Pathological T stage: 2 (3%) patients in stage I, 32 (46%) patients in stage II, 29 (42%) patients in stage III and 6 (9%) patients in stage IV. 39 (57%) patients had lymph node involvement. Pathological grade were low grade in 5 (7%) patients, intermediate grade in 42 (61%) patients and high grade in 22 (32%) patients. Lymphovascular invasion was seen in 29 (42%) patients. Perineural invasion was seen in 33 (48%) patients. 4 (6%) of patients had extracapsular spread.

*Treatment characteristics*

Gland excision was performed to all patients. 8 (12%) patients underwent unilateral functional neck dissection, 27 (39%) patients underwent unilateral radical neck dissection. Surgical margins were negative in 30 (43%), positive in 31 (45%) and close (<5mm) in 8 (12%) patients.

All patients (one patient with benign parotid tumors, radiotherapy was indicated only in case of recurrent disease) were treated with surgery followed by



**Figure 1. Overall Survival**

**Table 1. Acute Toxicity**

		Skin lesions	Oral mucositis
Grade 0-patients	(%)	0	0
Grade I-patients	(%)	12 (17.4%)	16 (23.2%)
Grade II-patients	(%)	38 (55.1%)	39 (56.5%)
Grade III-patients	(%)	13 (18.8%)	10 (14.5%)
Grade IV-patients	(%)	6 (8.7%)	4 (5.8%)

**Table 2. Patient Characteristics of Log-rank Univariate Analysis for Overall Survival**

	Mean (month) 95%CI	Median (month) 95%CI	p	Survival rate 1 year (%)	Survival rate 3 year (%)	Survival rate 5 year (%)	Survival rate 10 year (%)
General	65.3±8 49.6-81.1	40.0±7 26.2-53.7		78	52.4	35.3	19.6
Gender							
Female	100.0±15 70.6-130.7	97.0±23 51.3-142.6	0.005	91.7	64.9	60.3	35.3
Male	46.6±7 31.3-61.9	29.0±6 16.1-41.8		70.8	45.6	20.8	10.7
Age							
<50	84.4±11 61.4-107.5	106.0±41 24.2-187.7	0.021	88.9	82.5	50.8	30.5
≥50	55.0±8 37.8-72.2	29.0±2 24.1-33.8		72.1	39.1	30	15.6
Histology							
Adenoid cystic Ca	58.5±9 40.7-76.4	52.0±11 30.0-73.9		78.3	60.9	37.7	8.8
Mucoepidermoid Ca	84.7±18 49.0-120.4	44.0±35 0.0-114.4		89.5	53.7	46	30.7
Malign mixt tumor	66.1±19 28.1-104.0	34.0±19 0.0-72.5		69.2	46.2	36.9	27.7
Squamous cell Ca	30.8±11 8.9-52.7	18.0±6 5.1-30.8	0.524	71.4	42.9	14.3	-
Ductal Ca	-	-		-	-	-	-
Undifferentiated Ca	-	-		50	-	-	-
Pleomorphic Ca	-	-		-	-	-	-
Acinic cell Ca	-	-		-	-	-	-
Adenosquamous Ca	-	-		-	-	-	-
Papiller Adeno Ca	-	-		-	-	-	-
T stage							
I	68.0±44 0.0-155.3	5 -	0.0001	50	50	50	50
II	103.9±12 78.7-129.1	108.0±14 79.0-136.9		90.4	76.7	65.5	40.7
III	32.2±5 20.8-43.7	27.0±3 19.9-34.0		72.4	31	9.1	-
IV	20.8±9 2.4-39.2	6.0±4 0.0-15.6		50	33.3	-	-
N stage							
Negative	90.5±12 67.0-114.1	78.0±31 16.9-139.0	0.0001	84.4	65.7	53.1	35.2
Positive	34.6±6 21.8-47.3	26.0±3 18.6-33.3		69.7	34.8	13.9	3.5
Grade							
Low	165.7±16 133-198.4	-		-	-	-	75
Intermediate	67.5±8 50.0-85.0	44.0±7 30.0-57.9	0.0001	88	58.5	37.3	20.2
High	31.3±8 14.9-47.8	13.0±2 7.1-18.8		53.6	29.2	16.2	-
Lymphovasculer invasion							
Yes	36.7±7 22.1-51.4	27.0±4 18.2-35.7	0.002	65.5	31	15.8	7.9
No	85.2±11 62.9-107.5	78.0±25 27.2-128.7		87.4	68.6	50.4	29.6
Perineural invasion							
Yes	30.3±5 18.6-42.0	26.0±7 10.6-41.3	0.0001	63.2	22.1	11.9	-
No	96.9±11 73.6-120.1	97.0±29 39.3-154.6		91.6	80	57	36.4
Extracapsuler extension							
Yes	10.2±5 0.0-21.3	4.0±2 0.0-7.9	0.0001	25	-	-	-
No	68.8±8 52.4-85.2	42.0±9 24.0-59.9		81.3	55.7	37.5	20.8

**Table 3. Treatment Results of Log-rank Univariate Analysis for Overall Survival**

	Mean (month)	Median (month)	p	Survival rate 1 year (%)	Survival rate 3 year (%)	Survival rate 5 year (%)	Survival rate 10 year (%)
	95%CI	95%CI					
<b>Surgical margin</b>							
Negative	82.9±12 58.0-107.8	52.0±32 0.0-116.2	0.006	86.2	68.2	45.2	28.8
Positive	38.6±7 23.9-53.2	27.0±5 17.0-36.9		67.7	35.5	19.7	5.3
Close	67.9±14 40.0-95.7	-		87.5	60	60	60
<b>Radiotherapy dose</b>							
≤60Gy	89.5±11 66.9-112.1	97.0±38 21.8-172.1	0.0001	85.4	67.6	50.5	33.9
>60Gy	30.5±5 19.4-41.6	24.0±5 12.5-35.4		66.7	29.6	12.7	-
<b>Concurrent chemotherapy</b>							
Yes	62.7±33 0.0-128.1	29.0±25 0.0-78.0	0.988	75	50	25	25
No	67.5±8 50.4-84.6	40.0±6 26.6-53.3		78	52.4	36	18.9
<b>Local recurrence</b>							
Yes	67.9±14 39.7-96.1	52 26.3-77.6	0.633	88.2	58.8	30.3	22.7
No	65.5±9 46.2-84.7	38.0±6 25.0-50.9		70.7	50.4	36.7	18
<b>Distant metastasis</b>							
Yes	46.2±8 29.4-63.0	31.0±6 17.9-44.0	0.027	67.7	45.2	21.3	8.5
No	86.6±12 61.2-111.7	49.0±32 0.0-113.4		86.8	58.7	48.7	30.5
<b>Treatment options</b>							
Primer	67.7±9 49.7-85.7	40.0±7 25.6-54.3	0.929	75.5	53.8	37.5	18.3
Relaps	59.9±18 23.4-96.3	33.0±14 5.1-60.8		81.8	45.5	22.7	22.7

postoperative radiotherapy (PORT). Radiation dose were given 42 (61%) patients ≤60 Gy and 27 (39%) patients >60 Gy. The fractional dose 1.8/2Gy daily. 9 (13%) patients received tumor bed irradiation. 52 (75%) patients were treated with tumor bed and unilateral neck nodal irradiation and 8 (12%) patients were treated with tumor bed and bilateral neck nodal irradiation. 5 (7%) patients underwent concurrent chemotherapy.

#### Toxicity

Acute toxicity was noted by seeing skin lesions and oral mucositis. 12 (17.4%) patients had grade I skin lesions, 38 (55.1%) patients had grade II, 13 (18.8%) patients had grade III and 6 (8.7%) patients had grade IV. 16 (23.2%) patients had grade I oral mucositis, 39 (56.5%) patients had grade II, 10 (14.5%) patients had grade III and 4 (5.8%) patients had grade IV. Acute toxicity was shown in table 1. None of the patients developed grade 3 and 4 late toxicity of soft tissues, skin or oral mucosa.

#### Locoregional recurrences and distant metastasis

Median follow-up 52 months (range, 2-228 months). 17 (25%) patients developed locoregional recurrences (5-126 months). 12 of the relapse cases were seen in treatment area and 5 of them were in the neighbourhood. The

locoregional recurrences cases included, 12 (71%) male, 6 (35%) adenoid cystic carcinoma, 5 (29%) mucoepidermoid carcinoma, 8 (47%) lymph node involvement, 7 (41%) positive surgical margin, 6 (35%) lymphovascular invasion, 7 (41%) perineural invasion and grade 2-3 was seen in all patients. After locoregional recurrence was average survival 30 (range, 2-96) months.

31 (45%) patients developed distant metastasis to the lungs in 19 (61%) patients (lungs plus bone in 2, lungs plus brain 1, lungs plus liver 3), brain in 4 (13%) patients, liver in 1 (3.5%) patients, bone in 6 (19%) patients and mediastinal lymph node metastasis in 1 (3.5%) patients (9 patients had both locoregional and distant metastasis). The distant metastasis cases included, 22 (71%) male, 13 (42%) adenoid cystic carcinoma, 8 (26%) malign mixt tumor, 18 (58%) lymph node involvement, 17 (55%) positive surgical margin, 15 (48%) lymphovascular invasion, 16 (52%) perineural invasion. After distant metastasis was average survival 18 (range, 0-86) months.

#### Survival analysis

The mean overall survival (OS) 65.3±8 (95% confidence interval [CI], 49.6-81.1) months and the median overall survival 40.0 ± 7 (95% CI, 26.2-53.7) months. The -1, -3, -5 and -10 year OS rates were 78%,

52.4%, 35.3% and 19.6% respectively (figure 1.) (table 2.).

The mean disease free survival (DFS) 79.2±10 (95% CI, 59.3-97.1) months and the median disease free survival 38±13 (95% CI, 7.05-88.7) months. The -1,-3,-5 and -10 year DFS rates were 71.9%, 50.1%, 43.7% and 30.1% respectively.

On univariate analysis, the OS was significantly better with female sex ( $p<0.005$ ),  $< 50$  age ( $p<0.021$ ), T stage ( $p<0.0001$ ), absence of lymph node involvement ( $p<0.0001$ ), lower tumor grade ( $p<0.0001$ ), absence of lymphovascular invasion ( $p<0.002$ ), absence of perineural invasion ( $p<0.0001$ ), absence of extracapsular extension ( $p<0.0001$ ), surgical margin negativity ( $p<0.006$ ),  $\leq 60$  Gy radiotherapy dose ( $p<0.0001$ ) and absence of distant metastasis ( $p<0.027$ ) (Table 3.).

## Discussion

Parotid tumors represent 1-5% of all head and neck tumors and 0.1-0.5 of all human tumors (Lima et al., 2005; Kaur et al., 2014). Malignant parotid neoplasms have low incidence and heterogeneity of histological types (Mercante et al., 2014). Our retrospective study included 69 patients who had surgery and PORT. We evaluated in this study clinical outcome and the incidence of acute toxicity.

Parotid glands tumors occurs more commonly between the 6. and 7. decades (Alterio et al., 2011; Al-Mamgani et al., 2012; Mercante et al., 2014). The mean age in our study was, 58.9 years. The male/female ratio in our study was 1.9/1.

Various studies have shown mucoepidermoid carcinoma, adenoid cystic carcinoma and adenocarcinoma are the most common histology affecting parotid glands (Nascimento et al., 1986; Feinstein et al., 2011; Al-Mamgani et al., 2012; Mercante et al., 2014). The most frequently recorded histological types in our series were adenoid cystic carcinoma followed by mucoepidermoid carcinoma and malign mixt tumor.

Parotid gland's cancers is mostly diagnosed at a locally advanced stage (Ito et al., 2005; Al-Mamgani et al., 2012; Mercante et al., 2014). In our study; 46% occurred in stage T2, 42% stage T3 and 9% stage T4.

Some studies have shown that the lymph node is involved at the time of diagnosis (Koivunen et al., 2002), but some studies have shown often there is lymph node involvement at the time of diagnosis (Al-Mamgani et al., 2012; Mercante et al., 2014). In our series, was 57% had lymph node involvement. Parotid glands cancers oftenly dont have extracapsular extension at the time of diagnosis (Mercante et al., 2014). In our study, there was 6% extracapsular extension. Parotid glands cancers is mostly diagnosed at intermediate and high grade (Al-Mamgani et al., 2012). In our series, 61% occurred in intermediate grade and 32% high grade.

Surgery and/or neck dissection remains the primary treatment option for parotid malignancies (Al-Mamgani et al., 2012; Mercante et al., 2014). In our study there was 51% neck dissection in patients.

Radiotherapy doses, of at least 60 Gy,  $>65$  Gy and 70 Gy were thus recommended for microscopically

negative and positive margins and gross residual disease, respectively (Terhaard et al., 2005). In our study applied the same protocol.

Different acute and late treatment toxicities have been described when RT was delivered to the patients (Garden et al., 1997) soft tissue fibrosis, bone and temporal lobe necrosis, hearing loss, frozen temporomandibular joint, brachial plexopathy. These toxicities could be related to different factors: dose, fraction, radiotherapy technique and size of treatment field. In our study, the acute toxicity was observed in all patients, but late toxicity was not observed.

Large studies in literature have shown age, sex, T stage, N stage, grade and perineural invasion as the most common important prognostic variables for parotid gland malignancy (North et al., 1990; Hocwald et al., 2001; Iqbal et al., 2014). In line with the literature data, in our univariate analysis, the OS was prognostic factors with gender, age, T stage, N stage, tumor grade, lymphovascular invasion, perineural invasion, extracapsular extension, surgical margin, radiotherapy dose and distant metastasis. The DFS was prognostic factors with gender, T stage, N stage, tumor grade, lymphovascular invasion, perineural invasion, extracapsular extension, surgical margin and radiotherapy dose.

In conclusion, We believe that our findings contribute significantly to the awareness of the demographic and pathologic features of parotid gland tumors in the Turkish population and that they are similar to what has been reported elsewhere in the world.

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