ORIGINAL ARTICLE

Parotid squamous cell carcinoma: Outcome of multidisplinary management

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Abstract

Purpose: To evaluate the origin and outcome of parotid squamous cell carcinoma (SCC).

Methods: Fifty nine patients were identified with parotid SCC through the hospital data-base, patients' charts, imaging studies and computerized notes.

Results: Fifty of the patients were diagnosed as metastatic SCC from skin primary cancer to parotid lymph nodes; 28% were immunocompromized and 9 patients were diagnosed as primary SCC of the parotid gland, none was immunocompromized. Forty seven patients with metastatic SCC were treated with surgery and post-operative radiotherapy. The rate of neck lymph node metastases was 54%. The median follow up of these patients was 33 months and the 3-year actuarial cause specific survival was 91%. The 3-year actuarial local recurrence free survival (LRFS) and disease free survival rate were 79% and 77% respectively. Positive surgical margin after parotidectomy was the only factor that had statistically significant poor LRFS. Patients with primary parotid SCC had DFS of 100%.

Conclusion: The most common site of the primary tumor was a cutaneous SCC of the face. All patients should be considered for facial nerve sparing radical parotidectomy and adjuvant radiotherapy. Neck dissection or elective neck irradiation for ipsilateral neck is recommended due to high occult LN metastasis.

Key words

Parotid, Parotidectomy, Radiotherapy

1 Introduction

Parotid squamous cell carcinoma (SCC) is either primary, when another primary site of origin is unknown or when it is not present in parotidean lymph nodes, or metastatic. Primary SCC originating in the parotid is a rare and aggressive tumor, with reported incidence of only 0.3% to 1.5%. More commonly, SCC is metastatic to the intraparotid and periparotid lymph nodes from ipsilateral cutaneous malignancy of the face and scalp [1, 2, 3]. When SCC of the parotid is diagnosed, efforts must be made to identify the primary site. When no primary lesion exists or when the SCC is not confined to parotidean lymph nodes, it seems logical to consider it a primary SCC of the parotid. In both metastatic and primary SCC of the parotid, optimal treatment was unclear [4, 5]. The policy of treatment in our institute is facial nerve sparing

parotidectomy followed by adjuvant radiotherapy. The aim of this study is to evaluate patients with parotid SCC to evaluate the origin and determine the outcome of patients who metastasis to the parotid.

2 Patients and methods

Patients were retrospectively identified through the hospital data-base, patients' charts, imaging studies and computerized notes, after receiving the approval of Institutional Review Board.

During the period of 1995 to 2008, fifty nine patients were diagnosed with parotid SCC and were treated in the department of radiation oncology. All patients were selected for this analysis. Fifty of the 59 patients were diagnosed as metastatic SCC to intra or peri-parotid lymph nodes. However, 9 patients were diagnosed as primary SCC of the parotid. Images included CT± MRI head & neck and CT chest and upper abdomen.

Statistical Design: Kaplan-Meier estimates of actuarial survival, disease free survival, local recurrence free survival, were calculated with Graphed prism program (version 5). For comparisons of survival differences, the log-rank test was performed. The *P*-values were double-sided with $p \leq 0.05$ considered statistically significant.

3 Results

Age of patients ranged from 51-91years (Median=73 years). Forty nine patients were female and 10 patients were male. Forty eight of the fifty patients with metastatic SCC had a history of primary disease (Table 1). Of those patients, 47 patients had a history of cutaneous SCC of the face and one patient had a history of SCC of the alveolar mucosa. Two patients had no history of primary lesion, however, one patient developed helix SCC later. The most common sites of cutaneous SCC were the auricle (19 patients) followed by the check (13 patients). Forty one of the fifty patients developed the parotid lesion after a median 7 months of the diagnosis of the primary lesion, and 9 patients presented with concurrent primary lesion. Of the fifty patients, 8 patients presented with ipsilateral neck lymph nodes in level II, and 2 patients had facial palsy. Fourteen patients were immunocompromised; 5 patients had organ transplantation, 6 patients had hematological malignancy and 3 patients had solid malignancy.

Table 1. Patients' characteristics of Metastatic SCC

	NO (50).	**(%)**
Clinical neck L.N	8	(16)
Facial palsy	2	(3)
Neck dissection	44	(88)
Facial preservation	34	(68)
Positive margins	19	(38)
PNI	13	(26)
Grade of disease	GI 6	(12)
	GII 30	(60)
	GIII 14	(28)
Pathologic neck L.N	24 /44	(54)
Occult neck L.N spread	16/36	(44)
Neck LN ECE	9/24	(37)
Parotid RT	47	(94)
Ipsilateral neck RT	42	(84)
Bilateral neck RT	2	
Chemotherapy	13	(26)
Local recurrence	11	(22)
Neck recurrence	0	
Distant metastasis	2 (lung)	
Cause specific death	4	

SCC: squamous cell carcinoma, L.N: lymph node, PNI: perineural invasion, ECE: extracapsular extension, RT: radiotherapy

All 50 patients underwent a parotidectomy. Thirty four (68%) patients had a conservative (facial nerve sparing) parotidectomy. Ten of these patients had positive margins. The remaining 16 (32%) patients had a total parotidectomy with sacrifice of the facial nerve, and nine patients were identified as having positive margins. Ipsilateral neck dissection was performed in 44 (88%) patients. Of those 44 patients, 23 patients had selective neck dissection (SND) of level I-III, 20 patients had modified radical neck dissection (MRND), and one patient had radical neck dissection (RND).

Table 2. Local recurrence (LR) & Treatment modality.

Treatment Modality of metastatic SCC	Number (50) NO. (%)	LR (11) NO. (%)
Surgery alone.	3 (6)	3 /3 (100)
Surgery+ Radiotherapy.	34 (68)	5/34 (14)
Surgery+ Radiotherapy+ Chemotherapy.	13 (26)	3/13 (23)

Positive margins were found in 19 of 50 patients (38%) and peri-neural invasion (PNI) in 13 patients (26%). Nine patients had extra capsular extension (ECE) of parotid L.N with a median 3 L.N pathologically positive (Range: 1-7 L.N). Regarding histological differentiation, 6 patients had grade I, 30 patients had grade II, and 14 patients had grade III. The incidence of pathologically positive neck L.N was 54% (24/44) and 9 of them had ECE. The eight patients, who had clinically positive neck, all had pathological positive disease. Therefore, the incidence of occult cervical metastasis was 44% (16/36) (Table 1). The most common sites of L.N metastasis were level II, level Va and level III respectively.

Table 3. Factors affecting local control

Factors	*P*
Lymph node presentation	0.3
Tumor ≥ 3 cm	0.1
Facial preservation	0.8
Margin positive	0.05
Perineural invasion	0.08
Extracapsular extension	0.4
Grade	0.5
Chemotherapy	0.2

Postoperative radiotherapy (RT) was prescribed to 47 patients (94%) to the parotid region, of whom 42 patients received RT also to the ipsilateral neck, and 2 patients received bilateral neck RT. Therefore, 44 patients received post-operative neck irradiation plus parotid region. The dose was 60 Gy/30 fractions/ 6 weeks for the parotid and positive L.N regions. Lower neck L.N received a prophylactic dose of 50 Gy/25 fractions/5 weeks. Areas of positive margins and ECE were boosted to 66 Gy. The majority of patients were treated with 3D conformal RT. Thirteen patients (27%) received concurrent chemo-radiation in the form of TP (Taxane/Platinum).

3.1 Sites of failure

Eleven patients developed parotid region recurrence (Table 2). Three of these patients did not receive postoperative RT. The incidence of local failure (LF) was 17% for the patients who received postoperative RT (8/ 47). No patient developed neck recurrence. Local recurrence developed in a median follow up 16 months (range, 4 to 27 months). Distant metastasis developed in 2 patients to lung, one of them concurrent with local failure.

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3.2 Survival

Patients with metastatic SCC who were treated with surgery and postoperative RT (47 patients) were analyzed for survival (Figures 1&2). The median follow up was 33 months (range, 10 to 99 months). The 3-year actuarial cause specific survival was 91% (Figure 1). The 3-year actuarial local recurrence free survival (LRFS) and disease free survival (DFS) rate were 79% and 77% respectively (Figure 2).

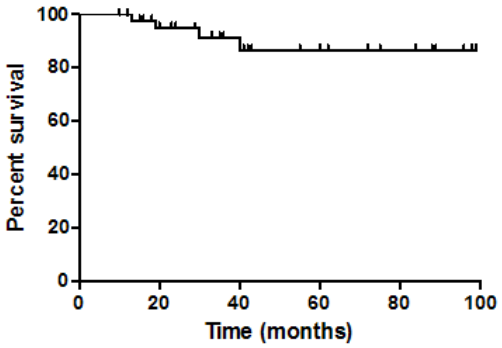

Figure 1. Cause Specific Survival

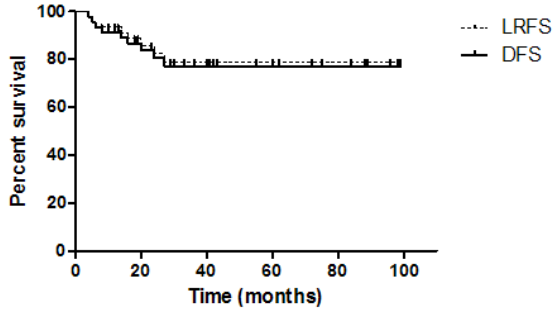

Figure 2. Local Recurrence and Disease Free Survival

Several variables were analyzed for correlations with LRFS (Table 3). Positive surgical margin after parotidectomy was the only factor that was associated with statistically significant poor outcome on LRFS.

4 Discussion

Our data supports previous reports suggesting that parotid SCC is commonly metastasizing from cutaneous SCC. Cutaneous SCC metastasizing to parotid LN is associated with a poor prognosis. However, the relatively good outcome of these patients in our series suggests that combined modality treatment, including surgery and adjuvant radiotherapy, have improved the outcome. Publications support surgery and adjuvant RT as the best practice in resectable tumor [6, 7, 8]. In our series, 17% (8/47) local recurrence rate was observed for patients treated with combined modality. Recent studies reviewed by Veness et al, reported that patients who treated with combined approach can expect 20% to 25% chance of local recurrence [9]. Veness et al, designed a prospective trial and reported that RT improved the local control and DFS (73% vs 54%; *P*=0.004) when compared with surgery alone [10]. In primary parotid SCC, adjuvant radiotherapy is not routine but is usually recommended for high-risk patients, based on grade, stage, and margin of excision to improve local control [11, 12, 13]. In the present study, adjuvant radiotherapy was given to 94% patients.

The local recurrence rate in our study was 17%, in spite of the combined modality of treatment, high dose of RT, and the addition of chemotherapy in 26% of patients. We studied the influence of some clinico-pathological factors on local

recurrence. Positive surgical margin was the only statistically significant factor associated with poor local control (P=0.05) in this study. Khurana et al [14] reported that positive surgical margins were associated with poor local control (P=0.02), as did O'Brien et al, who identified margin positivity as an independent predictor for parotid recurrence [15]. Several other studies have reported on prognostic factors for predicting local control and survival [1, 14, 16]. Joseph et al, observed that the involvement of multiple nodes, extracapsular spread, or vascular and perineural invasion were associated with increasing relapse rates [1]. Veness et al [10], and Margret et al [17, 18], identified extranodal spread as an independent predictor for locoregional recurrence.

Quality of life is an important aim in treatment of parotid tumors. Therefore, facial nerve preservation is important. The extent of surgery is dictated by the extent of tumor, aiming to achieve macroscopic clearance of the tumor and, meanwhile possible, preservation of the facial nerve. Extending the surgery to near-total parotidectomy or sacrificing the facial nerve did not seem to make any significant difference in tumor control [3, 19]. Residual microscopic disease is treated by high dose adjuvant radiotherapy. Eddy et al, recommend that the facial nerve is only sacrificed if it is grossly involved by tumor [20].

Patients with metastatic cutaneous SCC involving the parotid gland had a high incidence of clinical (16%) and occult neck disease (44%). Our findings are consistent with Ying et al [3] (44%) and those of O'Brien et al., who reported a 35% incidence of occult spread in 37 clinically negative necks [5]. Jackson and Ballantyne reported a 24% rate of occult metastatic SCC and recommended elective treatment of the clinically negative neck [21]. Researchers from The University of Texas M. D. Anderson Cancer Center documented a 42% rate of occult metastases [22]. Eddy et al reported a 16% incidence of occult spread in 43 clinically negative necks [20]. Treatment of the clinically negative neck should be considered to reduce the likelihood of failure in cervical nodes [5, 16, 20, 21]. Our data identified no neck failure likely because all patients received neck LN treatment. Whether or not surgery [14, 21] or radiotherapy [23, 24] should be used to treat the clinically negative neck cannot be answered from this study. Elective neck dissection has the benefit of providing additional pathological information with low morbidity and may obviate the need for lower neck irradiation. Patients with clinical involvement of cervical nodes should have a comprehensive neck dissection. Radiotherapy is also delivered to the entire ipsilateral neck if disease is identified in multiple nodes or extracapsular spread in a single node. An undissected ipsilateral neck should be irradiated in the presence of parotid nodal disease even if clinically negative.

A pooled analysis of EORTC [25] and RTOG [26] data in postoperative mucosal head and neck squamous cell carcinoma (HNSCC) demonstrated that combination concurrent platinum chemotherapy and adjuvant radiotherapy improve overall survival and disease-free survival in high-risk patients (extranodal spread and/or positive margin) [27]. Patients with metastatic cutaneous HNSCC with these pathologic features may benefit from means to improve loco-regional control and survival although randomized data in this setting are needed to confirm any hypothesis.

From our data, the median age of patients is 73 years. Older patients may tolerate less toxic and more tolerable chemotherapy. Targeted therapy reduces side effects and optimizes treatment. Epidermal growth factor receptor (EGFR) is over expressed in the majority of mucosal HNSCC. Cetuximab inhibits receptor activity by blocking the ligand binding site. It is used as a radiosensitizer, and improved the survival and loco-regional control [28]. It could be considered for old age patients with a borderline performance status. This needs a further research for cutaneous HNSCC.

In conclusion, clinicians should be aware of the potential for primary cutaneous SCC of the head and neck to metastasize to parotid lymph nodes. All patients with metastatic SCC should be considered for facial sparing radical parotidectomy and adjuvant radiotherapy. Neck dissection or elective neck irradiation for ipsilateral neck is recommended due to high occult LN metastasis. The addition of chemotherapy or targeted therapy may be beneficial and are points of research.

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