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ORIGINAL ARTICLE

Prolonged facial edema is an indicator of poor prognosis in patients with head and neck squamous cell carcinoma

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Abstract
Objective The purpose of this study was to identify the causes of prolonged facial edema and its associations with other clinical factors.
Summary background data Facial edema sometimes is observed in patients with head and neck squamous cell carcinoma (HNSCC), but its prevalence and association with other factors is unclear.
Methods Between July 2003 and July 2007, the medical records from 264 patients with HNSCC were reviewed. Prolonged facial edema is defined as persistence of edematous status (largest thickness >5 mm by CT scan) for more than 100 days. Clinical data including age, gender, tumor stage, and tumor primary sites were recorded. Statistical analyses were performed to determine the prognostic effect of prolonged facial edema, as well as its relationship to other clinical variables. The etiology of prolonged facial edema was also analyzed.
Results Prolonged facial edema occurred in 32 (12.1%) patients. The etiologies included internal jugular vein thrombosis, local infection, neck lymph nodes dissection, flap reconstruction, and direct vessel compression by tumors or metastatic lymph nodes. There was no significant difference in the incidence of prolonged facial edema in patients receiving different treatment modalities; however, patients receiving neck dissection correlated with the occurrence of late-onset facial edema. In addition to previously demonstrated prognostic factors (T status, nodal involvement and distant metastasis), prolonged facial edema was also identified as independent prognostic indicators for HNSCC patients (P=0.001).
Conclusions Prolonged facial edema may reflect the underlying disease status, and it can be applied as a prognostic marker in patients with HNSCC.

Keywords Facial edema · Head and neck squamous cell carcinoma · Prognosis

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Introduction

Head and neck squamous cell carcinoma (HNSCC), including cancers originating from the oral cavity, oropharynx, hypopharynx, and larynx, is the fifth most common cancer in men and the eighth most common cancer in women worldwide [1]. HNSCC is a common cancer in Taiwan where it ranks fourth as a cause of cancer-related death in men [2], probably owing to habitual consumption of betel nuts [3] by middle-age men. Despite adaptation of multimodality therapies, including combinations of surgery, radiotherapy, and

chemotherapy to the treatment of HNSCC, the prognosis of advanced HNSCC remains poor. More reliable clinical predictors of outcome are needed to select high-risk patients who may benefit from receiving more aggressive therapy.

Facial edema is a common clinical problem with diverse etiology. The causes of facial edema include trauma [4], allergic reaction [5, 6], venous thrombosis [7, 8], infection [9, 10], and benign [11] or malignant conditions [12–14]. Clinical history and physical examination are essential in the evaluation of facial edema. In cancer patients, facial edema is also a common presentation in patients with different types of cancers such as sarcoma [12], adenocarcinoma [13], and lymphoma [14]. The causative factors of cancer-related facial edema include superior venous cava syndrome [15], internal jugular vein thrombosis [7, 8], and neck infection [9, 10]. Imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are useful for delineating etiology of persistent facial edema and planning for treatment strategy. Being a frequent clinical problem in HNSCC, however, the prevalence rate and clinical significance of prolonged facial edema has not been documented well. In this retrospective study, we attempted to identify the etiology and to investigate the clinical significance of prolonged facial edema in patients with HNSCC.

Patients and methods

Patient population and treatment of HNSCC

Data from the medical records of 264 patients with pathology-proven HNSCC diagnosed and treated at the Taipei Veterans General Hospital between July 2003 and July 2007 were retrospectively analyzed. Clinical information collected for subsequent analysis included age at diagnosis, gender, primary tumor site, and clinical TNM status based on the American Joint Committee on Cancer staging system [16]. "TNM" stand for tumor size (status of spread), lymph nodes involvement, and distant metastasis. To simplify analysis, patients were divided into subgroups based on T status (T1+T2 or T3+T4; T3+T4 regard as advanced T status), nodal status (N0 or N+ for any N), and M status (M0 or M1 for distant metastasis).The median follow-up was 17.9 months (range, 0–63.5 months). The characteristics of all the patients are shown in Table 1.

All 264 patients received definitive treatment, including primary chemoradiotherapy (CRT), surgery alone, or surgery plus postoperative radiotherapy/CRT. Selection of treatment modality (primary CRT or surgical intervention) was based on the desire of the patient and resectability of the tumor, as determined by head and neck surgeons. If patients were at a high risk of recurrence (as indicated by, e.g., positive surgical margins, extracapsular nodal spread, bone invasion, nodal disease, perineural invasion, and lymphovascular embolism), postoperative CRT was given. Patients received radiotherapy consisting of conventional fractionated dose of 1.8 or 2 Gy, one fraction per day, 5 days per week, using three-dimensional conformal radiotherapy or intensity-modulated radiotherapy technique through the high-energy (6 MV X-ray beam) linear accelerators (Clinac 2100 C, 2100CD, Varian, Palo Alto, CA). The irradiation field included the primary tumor bed and neck lymphatics either unilaterally or bilaterally, depending on the type of tumors and the risk factors for recurrence. All target volumes were contoured slice by slice on the treatment-planning CT simulation images. Radiation dose was 70–74 Gy to the gross disease, 60–66 Gy to the high-risk areas, and 50–54 Gy to the low-risk areas. For patients with distant metastasis on initial presentation (n=17), palliative chemotherapy was arranged for symptomatic relief.

Definition of prolonged facial edema

Facial edema is the build-up of fluid in the face. Severe facial edema can be evaluated by clinical examination and imaging. In this study, prolonged facial edema is defined as an episode of subcutaneous fluid accumulation, with largest thickness ≥5 mm identified by image (CT or MRI) and persistence of edematous status in image for more than 100 days. The image study is taken initially at the time of diagnosis or followed up every 2 to 3 months. The representative CT scans of facial edema cases are shown in Fig. 1.

Statistical analysis

The Kaplan–Meier estimate was used for survival analysis, and the log-rank test was used for univariate analysis of prognostic factors [17]. The Cox proportional hazard model was applied in multivariate survival analysis to test the independent prognostic factors. The χ^2 test (for values >5) or Fisher's exact test (for values ≤5) was applied for comparison of dichotomous variables. A $P<0.05$ was considered to be statistically significant. All statistical analyses were performed by SPSS 13.0 (SPSS, Chicago, IL, USA).

Results

Characteristics of study population and the impact of treatment modality on the development of prolonged facial edema

The characteristics of both study populations with/without prolonged facial edema are shown in Table 1. The overall prevalence of prolonged facial edema was 12.1%. All characteristics were similar in both groups except N status,

Table 1 Baseline characteristics of 264 patients with squamous cell carcinoma of the head and neck

Characteristics	No facial edema (n=232) (87.9%)	Facial edema (n=32) (12.1%)	P value
Age	55 (26–95)[a]	52.5 (34–89)[a]	0.270
Gender			
Male	211 (91%)	29 (91%)	0.952
Female	21 (9%)	3 (9%)	
Primary Site			
Oral Cavity	106 (45.7%)	14 (43.8%)	0.479
Oropharynx	22 (9.5%)	0 (0%)	
Hypopharynx	68 (29.3%)	13 (40.6%)	
Larynx	35 (15.1%)	5 (15.6%)	
Salivary gland	1 (0.4%)	0 (0%)	
T stage			
0	0 (0%)	0 (0%)	0.151
1	12 (5.2%)	3 (9.3%)	
2	77 (33.2%)	5 (15.6%)	
3	73 (31.5%)	10 (31.3%)	
4	70 (30.2%)	14 (43.8%)	
N stage			
0	89 (38.4%)	8 (25%)	0.001
1	34 (14.7%)	1 (3.1%)	
2	105 (45.3%)	19 (59.4%)	
3	4 (1.7%)	4 (12.5%)	
M stage			
0	218 (94.0%)	29 (91.7%)	0.470
1	14 (6.0%)	3 (9.3%)	
TMN stage			
I	5 (2.2%)	1 (3.1%)	0.325
II	33 (14.2%)	3 (9.4%)	
III	48 (20.7%)	3 (9.4%)	
IV	146 (62.9%)	25 (78.1%)	

[a] Median age with age range in parenthesis

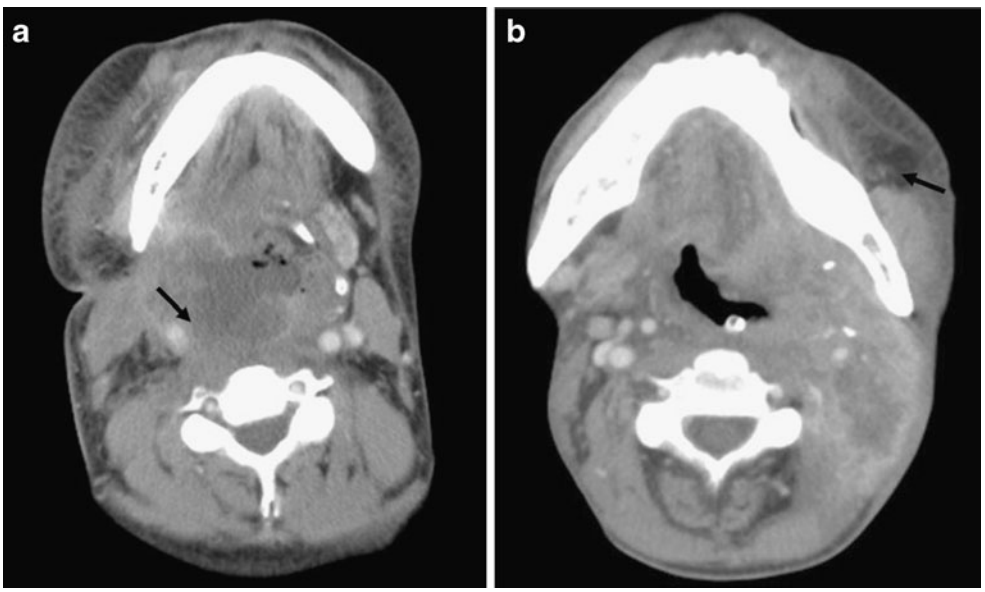

Fig. 1 Facial CT showed subcutaneous fluid accumulation of more than 5 mm thickness. **a** Right internal jugular venous thrombosis (*black arrow*). **b** Local infection with abscess formation (*black arrow*)

which showed a more advanced N status (N3+N4) in patients with prolonged facial edema (71.9% vs. 47%; $P=0.001$).

To elucidate whether patients treated with surgery and postoperative radiotherapy±chemotherapy are more prone to develop facial edema and to investigate the impact of treatment modality on the development of facial edema, we compared the incidence of facial edema in patients receiving primary radiation±chemotherapy, surgery and postoperative radiation±chemotherapy, and other treatment modalities (surgery alone, chemotherapy alone, or conservative treatment). However, the incidence of facial edema is not higher in the surgical-treated group in comparison with other groups (Table 2). This result suggests that prolonged facial edema is not correlated with the treatment modality. In contrast, it may reflect the underlying status of disease.

The clinical significance of the timing in developing prolonged facial edema

To investigate the clinical significance of the timing in developing prolonged facial edema, we firstly analyzed the interval between diagnosis and first appearance of persistent facial edema. Among the 32 patients with prolonged facial edema, we found that the occurrence time of edema after diagnosis ranged from days 0 to 658. The first quartile day was 0, medium day was 54, and the third quartile day was 216. We therefore defined the early onset group as occurrence of facial edema on day 0 ($n=10$, 27.8% of prolonged facial edema cases) and the late onset group as development of edema after day 0 ($n=22$, 72.2% of prolonged facial edema cases). The causative factors of prolonged facial edema between these two groups were compared. As shown in Table 3, patients received neck lymph node dissection were significantly associated with late-onset facial edema (20% vs. 68%, $P=0.011$). There was no significant correlation between the timing of facial edema and other clinical factors such as internal jugular vein thrombosis (10% vs. 9%, $P=0.935$), local infection (30% vs. 14%, $P=0.272$), flap reconstruction (20% vs. 32%, $P=0.491$), and direct compression of vessels by tumor or metastatic lymph nodes (20% vs. 32%, $P=0.491$). In addition, the duration of facial edema also showed no difference between these two groups (mean, 224 vs. 287 days, $P=0.35$; data not shown). These results suggest that patients received neck lymph nodes dissection is significantly associated with the development of late-onset facial edema.

Patients with prolonged facial edema were associated with a worse outcome

To investigate the prognostic significance of prolonged facial edema, univariate survival analysis of the prognostic variables was performed in 264 patients with HNSCC, and the result demonstrated that four factors were associated with an adverse impact on survival (Table 4): advanced T disease ($P=0.004$), nodal involvement ($P=0.002$), distant metastasis ($P<0.001$), and facial edema ($P<0.001$; Fig. 2). To identify the independent prognostic factors in HNSCC, multivariate Cox regression analysis was performed. The result showed that prolonged facial edema is an independent prognostic indicator for HNSCC ($P<0.001$). In addition, other three factors also demonstrated their independent prognostic effect [advanced T disease ($P=0.030$), nodal involvement ($P=0.028$), and distant metastasis ($P=0.011$)].

Follow-up of patients with facial edema

Among our 32 patients with prolonged facial edema, seven (21.9%) remain alive and free from disease, six (18.8%) are alive but have had disease recurrence or metastasis, and 19 (59.4%) died due to cancer or its related complications. The proportion of deaths due to cancer or its related complications was significantly higher in HNSCC cases with prolonged facial edema than HNSCC cases without prolonged facial edema (59.4% vs. 28.2%, $P<0.001$; Table 5).

Discussion

The present study showed that prolonged facial edema is not a rare symptom in patients with HNSCC, with a

Table 2 Correlation between the treatment modality and the development of facial edema in 264 patients with head and neck squamous cell carcinoma

Treatment modalities	Primary RT±CT ($n=85$)[a]	OP+postop RT±CT ($n=112$)[b]	Others[c] ($n=67$)	P value
Facial edema	12 (14.1%)	15 (13.4%)	5 (7.5%)	0.396
No facial edema	73 (85.9%)	97 (86.6.%)	62 (92.5%)	

RT radiation, *CT* chemotherapy, *OP* operation, *postop* postoperation

[a] Eight patients had RT only and 77 patients combined with chemotherapy

[b] Twenty-six patients had RT only and 86 patients combined with chemotherapy

[c] Forty-nine patients had surgery alone, 17 patients had chemotherapy alone, and one patient had conservative treatment

Table 3 The causative factors of prolonged facial edema in 32 patients with HNSCC

Characteristics	Early onset (n=10)	Late onset (n=22)	P value
IJV thrombosis			
Yes	1 (10%)	2 (9%)	0.935
No	9 (90%)	20 (91%)	
Local infection			
Yes	3 (30%)	3 (14%)	0.272
No	7 (70%)	19 (86%)	
Neck LN dissection			
Yes	2[a] (20%)	15 (68%)	0.011
No	8 (80%)	7 (32%)	
Flap reconstruction			
Yes	2[a] (20%)	7 (32%)	0.491
No	8 (80%)	15 (68%)	
Compression of vessels by tumor directly			
Yes	2 (20%)	7 (32%)	0.491
No	8 (80%)	15 (68%)	

HNSCC head and neck squamous cell carcinoma, *IJV* thrombosis, internal jugular venous thrombosis, *LN* lymph nodes

[a] Two patients accepted primary neck LN dissection and flap reconstruction, with prolong facial edema after surgical intervention

prevalence rate of 12.1%. Patients with this symptom also suffered from difficulty in breathing and cosmetic problems. The major causes of facial edema in our 32 patients were internal jugular vein thrombosis, neck infection, lymph node dissection, flap reconstruction, and compression of blood vessels by tumor or metastatic lymph nodes. However, other common causes of facial edema (e.g., trauma or injury to the face, allergic reactions, superior vena cava syndrome, and secondary malignancy) were not found in this study.

Regarding the influence of treatment modality on the development of facial edema in HNSCC cases, previous studies suggest that postoperative facial swelling is a common complication after neck dissection and flap

Table 4 Univariate analysis of prognostic factors in 264 patients with head and neck squamous cell carcinoma

Variable	Patients (%)	Relative risk	95% CI	P value (log-rank)
Age (yr)				
≥65	75 (28.4)	1.000		
<65	189 (71.6)	0.692	0.395–1.212	0.198
Gender				
Male	240 (91.0)	1.000		
Female	24 (9.0)	1.632	0.595–4.478	0.342
Tumor site				
Oral cavity	119 (45.1)	1.000		
Oropharynx	22 (8.3)	0.879	0.306–2.528	0.811
Hypopharynx	81 (30.7)	1.884	1.103–3.217	0.020
Larynx	40 (15.2)	1.298	0.651–2.589	0.458
Other[a]	2 (0.8)			
T status				
T1+T2	97 (36.7)	1.000		
T3+T4	167 (63.3)	2.241	1.296–3.877	0.004
N status				
N0	97(36.7)	1.000		
N+	167(63.3)	2.364	1.371–4.075	0.002
M status				
M0	247 (93.6)	1.000		
M1	17 (6.4)	3.690	1.816–7.498	<0.001
Facial edema				
No	232 (87.9)	1.000		
Yes	32 (12.1)	3.032	1.789–5.139	<0.001

[a] Other: 2 patients got salivary gland tumor and could not be enrolled to analysis due to limited numbers (n=2)

T status, status of tumor spread or tumor size; N status, status of lymph node involvement; M status, status of distant metastasis; RR, relative risk; 95%CI, 95% confidence interval

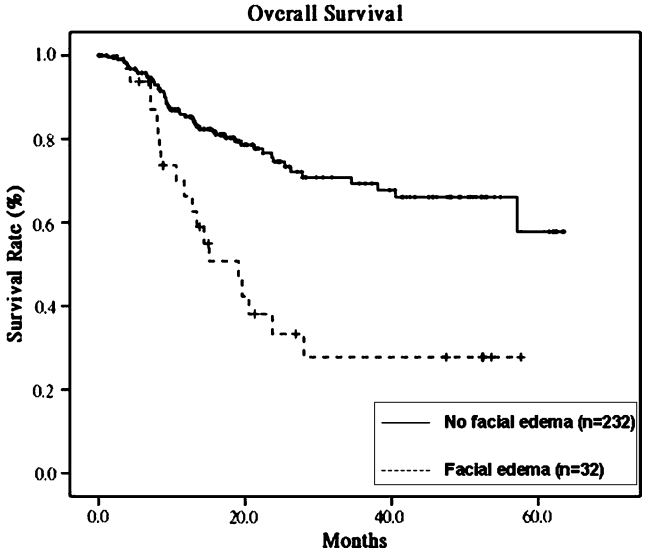

Fig. 2 Facial edema is an indicator of poor prognosis in patients with squamous cell carcinoma of the head and neck (n=264, P<0.001)

reconstruction: Ahn et al. [18] reported facial swelling in 33–54% patients after bilateral neck dissection, and Ueda et al. [19] also reported severe facial edema in two of seven patients who received pectoralis major myocutaneous flap reconstruction. It may attribute to the changes in vessel architecture and lymphatic drainage, resulting in the circulatory disturbance in the corresponding part of the face. However, there was no difference in the incidence of occurrence of prolonged facial edema in patients receiving different treatment modalities (e.g., primary radiotherapy± chemotherapy, surgery plus postoperative radiotherapy± radiotherapy, conservative treatment, etc.) in our study. The possible explanation is that surgery and postoperative radiotherapy-induced facial edema resulted from transient lymph edema, and the symptom is often mild and difficult to define and record. In our study, prolonged facial edema was defined as persistence of edematous status for more than 100 days. The subsequent analysis supports the fact that the prognostic effect of facial edema is existence in cases with persistent symptoms. This result highlights the clinical significance of prolonged facial edema in HNSCC: Persistence of edema does not correlate with the treatment modality; in contrast, it reflects the underlying disease status.

Table 5 Multivariate analysis of prognostic factors in 264 patients with head and neck squamous cell carcinoma

Factors	RR	95%CI	*P* Value
T status			
T1+T2	1.000	1.062–3.241	0.030
T3+ T4	1.855		
N status			
N0	1.000	1.072–3.318	0.028
N+	1.886		
M status			
M0	1.000	1.243–5.286	0.011
M1	2.563		
Facial edema			
No	1.000	1.516–4.407	<0.001
Yes	2.585		

T status status of tumor spread or tumor size, *N status* status of lymph node involvement, *M status* status of distant metastasis, *RR* relative risk, *95%CI*, 95% confidence interval

The timing of the onset of facial edema is a critical issue in clinical aspect. To understand the impact of the causative factors on the timing of edema occurrence, we divided patients into two groups: patients with early versus late onset of facial edema. We found that patients who received neck dissection had a higher incidence to develop late-onset facial edema. This result suggests that, although radical surgery does not increase the incidence of overt facial edema of HNSCC cases, the neck dissection procedure still has an impact on the development of late-onset facial edema. However, the prognostic significance of early- versus late-onset facial edema cannot be demonstrated in our series due to the limited number of edema cases. Further large-scale analysis to identify the clinical and biological difference between early- and late-onset facial edema is mandatory.

Other major causative factors of prolonged facial edema in our series were internal jugular vein thrombosis and neck infection. Internal jugular vein thrombosis is not a common presentation in patients with HNSCC: Prim et al. reported that jugular vein thrombosis is only in one of 54 patients with HNSCC [7]. Thrombosis of the jugular vein is more frequent in patients with infection and in cases receiving flap reconstruction [8]. In our study, internal jugular vein thrombosis occurred in three cases: One case was associated with neck infection, one with radical neck dissection, and one with flap reconstruction. In all three cases, low molecular weight heparin was given and resulted in recanalization. Neck abscess or neck infection may be a primary manifestation of head and neck cancer [10]. In our study, six patients with infection developed a high fever and local inflammatory swelling of the cheek. Blood culture revealed *Staphylococcus aureus* in one patient and *Pseudomonas aeruginosa* in the other. Four patients recovered after empiric treatment with antibiotics, and one patient died from severe sepsis.

Although its etiology was variable, prolonged facial edema was uniformly an indicator of poor outcome in our study. This might be explained by the association of facial edema with more advanced lymph node involvement. However, the actual mechanism is still unclear and will need further investigation. Mild or moderate facial edema is

difficult to define and record, and it can be easily neglected by the clinician. Therefore, the prognostic significance of the transient, mild facial edema is hard to investigate. Nevertheless, mild facial edema, which is not picked up in our retrospective study, may not be correlated with a poor prognosis. Further confirmation study is necessary to clarify the difference in prognostic effect in prolonged versus mild, transient facial edema of HNSCC cases.

In conclusion, prolonged facial edema occurs in a certain proportion of HNSCC patients. It is not correlated with the treatment modality, and development of persistent edema may reflect the underlying aggressiveness of HNSCC. Prolonged facial edema is an independent prognostic indicator for HNSCC patients. We suggest that finding the causative factor and aggressive treatment of underlying disease is important in managing HNSCC patients presenting with prolonged facial edema.

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