Parameters and outcomes in 525 patients operated on for oral squamous cell carcinoma

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Abstract

Purpose

This report analyzed the outcomes of patients undergoing surgery fororal squamous cell carcinoma (OSCC) to identify the value ofprognostic factors.

Material and methods

A total of 525 patients were studied who had undergone surgery for oral squamous cell carcinoma (OSCC) between 2000 and 2011, of whom 222 had received postoperative radiation-therapy (PORT) and or chemoradiation-therapy (PORTC).

For each patient, personal data, histological findings, treatment and outcome were recorded and analyzed statistically. Survival curves were calculated using the Kaplan–Meier algorithm, and the difference in survival among subgroups was examined.

Results

The overall survival (OS) and disease-specific survival (DSS) 5-year survival rate in the 525 patients were respectively 71.38% and 73.18%. The differences in the overall survival and disease-specific 5-year survival were significant ($p < 0.05$) for age < 40 years, site of origin, N status, staging, grading, osseous medullar infiltration, and perineural invasion. In patients undergoing radiation therapy, only perineural invasion negatively influenced the survival prognosis. In 150 pT1

cases of tongue and floor-of-mouth cancer, an infiltration depth (ID) > 4 mm was statistically correlated with poorer prognosis.

Conclusions

The results demonstrate an improvement in the 5-year OS and DSS rates during the past decade compared with the previous decade.Univariate analysis revealed that age, tumor staging, and lymph node involvement, extracapsular spread, grading, perineurial invasion, infiltration depth, and osseus medullary invasion were associated significantly with overall survival and disease-specific survival.

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Keywords

Oral cancer

Squamous cell carcinoma

Head and neck cancer

1. Introduction

Oral squamous cell carcinoma (OSCC), the most common form of head and neck cancer, remains difficult to treat, and its prognosis is often uncertain. The main treatment for this disease is still surgery: postoperative radiation-therapy (PORT), alone or in association with chemotherapy (postoperative chemo-radiation therapy; PORTC), is used as adjuvant treatment to enhance surgical outcomes or simply apalliative treatment (Shah and Gil, 2009).

The literature shows that the 5-year survival rate can be quite different, ranging from 58% to 94% (Wildt et al., 1989, Lindeløv et al., 1990,Loree and Strong, 1990, Tytor et al., 1990, Shingaki et al., 1995, Chen et al., 1999, Chandu et al., 2005, Sessions et al., 2002, Kademani et al., 2005, Koo et al., 2006, Bell et al., 2007, Rogers et al., 2009, Amit et al., 2013). In a recent International Collaborative Study (Amit et al., 2013), several clinicians have asserted that variability in overall survival (OS) and in disease-specific survival (DSS) is a factor of the variability of observation period, patients' features, surgeons' expertise, percentage of starting tumors compared with advanced ones, quality of radiotherapy, and the use of adjuvant treatments (Kessler et al., 2008). Analysis of clinico-pathological parameters is a determinant of prognosis and for the treatment of the disease (Garzino-Demo et al., 2006).

The aim of the study was to analyze how the clinico-pathological parameters affect the overall OS and the DSS of 525 patients who were referred for primary surgical treatment.

2. Material and methods

2.1. Patients

To address the research purpose, the investigators designed and implemented a retrospective study design. The study population was composed of 525 patients presenting for evaluation and treatment for OSCC at the Division of Maxillofacial Surgery, Città della Salute e della Scienza University Hospital, Torino, Italy.

A total of 303 patients underwent PORT or PORTC therapy postoperatively at the Division of Radiotherapy and Chemotherapy of the University of Turin.

The sites in the oral cavity were divided into subsites: the lateral border of the tongue was divided into anterior (2/3 anterior border) and posterior (1/3 posterior border) parts. The buccal mucosa (cheek) was separated into the buccal mucosa, buccal mucosa–retromolar trigone, and buccal mucosa–maxillary gingiva. In the floor of the mouth, only the anterior and intermediate parts were considered, as it is difficult to separate the posterior part from the posterior part of the tongue.Table 1 shows the distribution of tumors according to site and stage. The tongue (222 cases, 42.29%) buccal mucosa (79 cases, 15.05%), floor of the mouth (65 cases, 12.38%), and mandibular gingiva (78 cases, 14.86%) were the sites most commonly involved.

The primary treatment for patients involved surgery in all cases: 203 (38.66%) were managed by local excision alone, while 322 cases (59.23%) were treated with ‘en bloc’ surgery of the primary tumor in combination with neck dissection (ND). In 44 cases (8.38%) the neck dissection was deferred until the later appearance of metastases.

Unilateral dissection was performed in 245 patients (46.67%). Simultaneous bilateral neck dissection in 77 patients (12.57%) when tumor invasion of the midline or near the midline structures was observed, or when positive nodes were found bilaterally preoperatively. Supraomohyoid neck dissection (SOHND), including nodes at levels I, II, and III with preservation of the sternocleidomastoid muscle,internal jugular vein, and spinal accessory nerve, was performed in 183 patients who were clinically N0 and had primary tumors less than 3 cm in diameter. Modified neck dissection (MRND) was performed in 122 N + patients with a single node less than 3 cm in diameter. When there was suspicion of invasion to more than two nodes, extranodal spread, or nodes greater than 3 cm in diameter, radical neck dissection (RND) or extended neck dissection (END) was performed (17 patients).

The distribution according to Broders' grading classification was 146 G1 (27.81%), 301 G2 (57.33%), and 78 G3 (14.86%) (Table 1). Lesions diagnosed as undifferentiated carcinoma (G4), carcinoma in situ, orverrucous carcinoma (OVCC) were not included in the study, as they are considered to be different types.

In the histological analysis, the tumor resection margin (TRM) was negative in 471 (89.71%) and positive in 54 (10.29%) of the specimens.Dysplasia at the resection margin was absent in 244 cases (46.48%), mild in 200 cases (38.1%), and severe in 81 cases (15.43%).

In the histological analysis, the bone invasion was absent in 421 cases (80.20%), present with cortical bone invasion in 34 cases (6.47%), and present with medullary invasion in 70 cases (13.33%); perineural invasion (PNI) was observed in 102 cases (19.43%) but was absent in 423 cases (80.57%); extra-nodal spread (ECS) was found microscopically in only 17 patients (3.24%).

Infiltration depth (ID) was measured on a surgical specimens in 150 pT1 cases, localized in floor of the mouth and tongue: in 48 cases (30% of 150 cases) ID was greater than 4 mm, whereas in 102 cases (70% of 150 cases), ID was less than 4 mm.

Finally, the distribution of patients according to tumor stage was 201 (38.29%) in stage I, 102 (19.43%) in stage II, 62 (11.80%) in stage III, and 160 (30.48%) in stages IV (Edge et al., 2010).

3. Methods

The patient population comprised 309 men (58.86%) and 216 women (41.14%), a gender ratio of 1.4:1. Their mean age was 63.0910.7 years (range 22–91 years); in 485 patients age was greater than 40 years (92.38%) and in 40 the age was less than 40 years (7.62%). All patients were of white ethnicity.

The following parameters were studied and analyzed: histopathologic parameters, adjuvant therapy, and survival rate.

All 525 patients enrolled in the study underwent surgical treatment as follows: initial radical surgery for the primary tumor; preservation of the mandibular continuity whenever possible by means of marginal resection of the jaw and the mandibular swing procedure; radical neck dissection in cases with major tumor invasion; primary reconstruction, traditional or microsurgical, considering the type of defect and performance status of the patients; and elective tracheotomy for the early postoperative period for cancer involving tongue or floor of the mouth.

Surgical specimens were sutured to polystyrene sheets before fixation in 10% buffered formalin. The specimens were examined in the laboratory after 24–48 h of fixation. Histological assessment was made in sections stained with hematoxylin and eosin (HE).

Representative sections containing the full thickness of the tumor were used for histopathologic gradings and for analyzing other histopathological parameters.

To evaluate the PNI, we referred to the most widely accepted description of PNI: tumors in close proximity to a nerve that involve one-third of its circumference and/or the presence of tumor cells within any of the three layers of the nerve sheath (Liebig et al., 2009,Woolgar, 2006).

Pathology reports for all tumors exhibiting bone invasion were reviewed. Bone invasion was categorized as absent, cortical when limited to the cortex, or medullary when extension into cancellous bone was present (Wong et al., 2000).

Tumor infiltration depth (ID) was measured by an experienced head–neck pathologist, using digital microscopic imaging and computerized measurements (RVC, Research Assistant 6, Soest, The Netherlands); it was defined as the maximum depth (in millimeters) of tumor infiltration below the mucosal surface. In the case of ulcerated or exophytic tumors, the reconstructed mucosal surface was used (Melchers et al., 2012). A cut-off of 4 mm of ID was adopted in 150 pT1 cases of the tongue and floor of the mouth.

Distance from invasive carcinoma to surgical margins for both mucosal and deep margins was measured histologically with the use of a stage micrometer. The guidelines defined a histologic distance from invasive carcinoma to surgical margins of 5 mm as clear, 1–5 mm as close, and 1 mm as involved (Loree and Strong, 1990, Batsakis, 1999).

The presence of dysplasia and the degree was observed and reported.

External beam radiation therapy (EBRT), with or without chemotherapy, was used to enhance loco-regional control (LRC) for cases with unfavorable pathological features. PORT was given to 222 patients (41.29%; in the Division of Radiotherapy and Oncology of the University of Turin) selected based on the following clinico-pathologic features: pT3 and pT4, positive or close surgical margins, poor cellular differentiation, perineural infiltration, involvement of multiple neck nodes, or ECS. The total dose at the primary site was 54–66 Gy, according to the limits of the surgical border obtained. For the neck, the doses were 50–66 Gy, according to the type of node invasion observed histologically. In very high-risk cases (T3 tumor with close or positive surgical margins or multiple pathological positive lymph nodes with ECS or N3 neck) POCRT protocols were adopted. In these cases, monitored epithelial grown factor receptor (EGFR)–targeted therapy, such as cetuximab, was used.

All patients were monitored with the following: monthly clinical visits in the first year postoperatively and every 2 months from the second year onward; ultrasonography of the neck every 3 months in the first and second year, and every 6 months from the third year onward;computed tomography (CT) or magnetic resonance imaging (MRI) of head and neck every 6 months in the first and second years and once per year from the third year onward.

Survival curves were calculated using the Kaplan–Meier algorithm. Time zero was defined as the date of a patient's surgical intervention. Surviving patients were included in the total number at risk for death only up to the time of their last follow-up. Therefore, the survival rate changed only when death had occurred. The calculated survival curve was most likely estimated to be the true survival curve. A log-rank test was used to explore the differences between the survival curves stratified for the variable of interest.

Survival probability was calculated using the product–limit method (Kaplan–Meier), with the 95% confidence interval (CI) computed as 1.96 SE. The difference in survival among subgroups was tested using the log-rank statistic. The level of statistical significance was set at 0.05. Statistical analyses were performed using STATA 8 software.

4. Results

The overall survival rate (OS) 5 years postoperatively was 71.38%, whereas the disease-specific survival rate (DSS) at 5 years was 73.18 % (Table 1). There was no recurrence in 355 patients (67.71%), whereas 170 (33.29%) of them developed a recurrence during the period of observation, consisting of a local recurrence a neck recurrence in 72 and 98 patients, respectively. Of the latter 98 patients with a neck recurrence, 54 developed neck metastases in the untreated neck, whereas 44 patients developed a neck recurrence in the previously treated neck. The mean interval between surgery and loco-regional recurrence was 15.67 months (range 1–48 months). Kaplan–Meier OS and DSS curves are presented in Fig. 1.

The OS (Fig. 2) was plotted according to gender: the difference in survival between male and female was statistically significant ($p = 0.0056$).

The OS percentage at 5 years since surgery in accordance with the age of the patients was respectively 68.80% (age > 40 years) and 62.88% (age < 40th years); the difference was statistically significant ($p = 0.0042$) (Table 1).

The OS percentages at 5 years since surgery according to stage I, II, III, and IV were 84.40%, 80.53%, 63.97%, and 52.81%, respectively. The difference in survival between stages was statistically significant (p = 0:0001) (Table 1). The DSS percentage at 5 years since according to stage as follows: stage I OS = 84.40%, DDS = 89.41%; stage IIOS = 80.53%, DDS = 82.28%; stage III OS = 63.97%, DDS 64.17%; and stage IV OS = 52.81%, DDS 55.47%. The difference between stages was statistically significant ($p < 0.0001$) (Table 1). The DSS curve (Fig. 3) was plotted according to the American Joint Committee on Cancer (AJCC) 2010 staging classification.

The OS rates stratified according to pN were as follows: Nx (withoutneck dissection, local excision alone), 80.05%; N0, 76.99%; N+, 54.94%; and N+ with extranodal spread, 15.15%. The difference in OS according to pN status was statistically significant (p = 0:0001) (Table 1). The DSS rates stratified according to pN were: Nx 85.19; N0 82.93; n+ 57.11, and N+ with extranodal spread 18.18. The difference in DSS according to pN status was statistically significant ($p < 0.0001$). The

DSS curve plotted according to pN status (recorded from histological reports) is depicted in (Fig. 4).

The 5-year survival rates in the groups stratified according to the site of origin were as follows: anterior part (2/3) of the lateral border of the tongue OS = 78.30%, DDS = 81.71; posterior part (1/3) of the tongue OS = 61.63%, DDS = 64.71; cheek OS = 77.09%, DDS = 79.20; floor of the mouth OS = 73.35%, DDS = 76.11; trigonum–cheek OS = 69.58%, DDS = 71.23; buccal mucosa–maxillary gingiva, OS = 68.56%, DDS = 70.16; mandibular gingiva OS = 72.70%, DDS = 74.27. The differences in OS and DDS between anterior part of the tongue and posterior part of the tongue were statistically significant ($p < 0.05$). Similar results were not observed between buccal mucosa and trigonum ($p > 0.05$).

The probability of the patients surviving 5 years (OS) after the time of diagnosis according to Broder's tumor grades G1, G2, and G3 were 79.92%, 69.46%, and 60.24%, respectively ($p = 0.0044$). The 5-year DDS rates in the groups stratified according to the grading were as follows: G1 = 85.52; G2 = 71.11; G3 = 61.74. The DSS curve (Fig. 5), plotted according to grading, is depicted in Fig. 5.

The probability of patients with a positive resection margin surviving (OS) for 5 years was 61.82%, whereas the survival rate (OS) was 72.51% when the surgical margins were negative ($p = 0.065$). The difference in DSS according to TRM status were not statically significant ($p = 0.072$).

The DSS survival curve plotted according to the status of the resection margins is given in Fig. 6.

The difference in OS and DSS according to presence of dysplasia(absent: OS = 73.33%, DSS = 77.86%; mild: OS: 72.31%, DSS = 74.33%; severe: OS = 62.90%, DSS: 63.43%) at the resection margins was statistically significant (OS, $p = 0.0043$; DSS, $p = 0.0038$).

The 5-year OS in the groups stratified according to osseous infiltration was 58.87% with presence of medullary invasion, 62.12% with only cortical invasion, and 74.50% without invasion ($p = 0.0134$). The 5-year DDS in the groups stratified according to osseous infiltration (Fig. 7) was 61.72% with presence of medullary invasion, 70.18% with only cortical invasion and 76.67% without invasion ($p = 0.0144$). The DSS survival curve plotted according to the osseous invasion is given inFig. 6.

The 5-year OS in patients with perineural invasion (Fig. 8) was 57.23%, whereas the rate in patients without perineural invasion was 75.88% (p = 0.0028). The 5-years DSS in patients with perineural invasion was 63.44%, whereas the rate in patients without perineural invasion was 83.55% (p = 0.0001). The DSS curve plotted according PNI is depicted in Fig. 7.

Statistical analysis was used to evaluate the efficacy of PORTC. In the 222 patients who underwent postoperative radiation therapy, a 5-year OS rate of 56.73% and DSS rate of 60.12% were observed; in the 303 patients who did not undergo postoperative radiation therapy, the 5-year OS rate and DSS were 82.87% and 83.33%, respectively (Table 1). In patients receiving radiation therapy, the presence of osseus-vascular invasion and positive resection margins did not influence the cumulative survival probability at 5 years; only perineural invasion negatively influenced the 5-year survival curves (p = 0.0000).

Tumor infiltration depth ID was measured in 150 pT1 cases of the tongue and floor of the mouth, and a cut-off of 4 mm of ID was adopted to evaluate survival probability: in 102 patients with ID less than 4 mm, a 5-year DSS rate of 95.15% was observed; in the 48 patients with ID greater than 4 mm, the 5-year DSS rate was 72.27 (p = 0000). The DSS curve plotted according to tumor infiltration depth is given in Fig. 8.

5. Discussion

A series of 525 patients who underwent OSCC were retrospectively analyzed to identify the prognostic value of clinicopathological parameters.

The OS and DSS rate for the patients with OSCC reported in our series are within the range reported in the literature (Wildt et al., 1989,Lindeløv et al., 1990, Loree and Strong, 1990, Tytor et al., 1990,Shingaki et al., 1995, Chen et al., 1999, Chandu et al., 2005, Sessions et al., 2002, Kademani et al., 2005, Koo et al., 2006, Bell et al., 2007,Rogers et al., 2009, Amit et al., 2013). Generally it is difficult to compare our outcomes directly with others because of variations in case mix, selection for treatment, and presentation of outcome data.Table 2 summarizes findings from of the literature.

Age at diagnosis is correlated with a poor prognosis (Shah and Gil, 2009). In our series, the survival rate in patients aged less than 40 years was significantly lower than in patients with aged more than 40 years.

The site of origin of oral cancer is an important prognostic factor(Woolgar, 2006, Scully and Bagan, 2009). In this series, the OS and DSS at 5-year after diagnosis were slightly lower for lower and posterior sites in the oral cavity. Stage, size, and anatomical differences (richness of the blood supply, lymphatic drainage, and anatomical barriers) probably contributed to this difference in prognosis.

The TNM classification of AJCC relates well to the prognosis and overall survival: the earlier the tumor stage, the better the prognosis and the less complicated the treatment (Garzino-Demo et al., 2006, van der Schroeff and Baatenburg de Jong, 2009, Jerjes et al., 2010). At the same time, logistic regression analysis revealed that the higher the pathological TNM stage, the worse the prognosis (Woolgar, 2006). Our data are in line with these results. However there is growing concern that TNM staging is insufficient to accurately map or classify OSCC, the biological impact of which may be related to volume and pathological aggressiveness of disease (Scully and Bagan, 2009).

Several features of the primary tumor have a very significant bearing on outcome. The main clinical predictors were presence positive nodes and of ECS (Wildt et al., 1989, Lindeløv et al., 1990, Loree and Strong, 1990, Tytor et al., 1990, Shingaki et al., 1995, Chen et al., 1999,Sessions et al., 2002, Kademani et al., 2005, Chandu et al., 2005, Koo et al., 2006, Bell et al., 2007, Kessler et al., 2008, van der Schroeff and Baatenburg de Jong, 2009, Shah and Gil, 2009, Rogers et al., 2009,Amit et al., 2013). Our results confirm the well-established relationship between cervical node metastasis and reduced rates of survival: in this series, there was no difference in the 5-year OS and DDS rates of patients without neck treatment and pN0 cases. The prognosis in patients with one or more lymph node metastases (54.94%) was twice as poor as for N0 patients, and the decrease of the DDS became dramatic in the presence of ECS (18.18%).

The World Health Organisation (WHO) grading system (Pindborg et al., 1997) recommends 3 categories of OSCC: well differentiated, moderately differentiated, and poorly differentiated. This usually depends on the subjective pathological assessment of the degree ofkeratinization, cellular and nuclear pleomorphism, and mitotic activity(Woolgar, 2006). It is a significant predictor of loco-regional failure andtumor recurrence (Shah, 1990, Jerjes et al., 2010, Kademani et al., 2005). The analysis in the present study showed that tumor grade was significantly related to nodal disease at the time of diagnosis and that the DSS rate was lower in poorly differentiated tumors.

The results of this anatomo-pathological revision showed that the status of the surgical margin did not have a significant impact on DSS and OS. In reality, not many studies showed a significant correlation between the width of the free margin (quantity of normal tissue at the closest margin) and the local recurrence rate. Many problems in assessing surgical margins are correlated with tissue shrinkage and its degree, which differs according to different locations and tissues (e.g., gingival vs. oral floor, mucosal vs. deep connective tissue). This technical trouble may explain the controversy that exists regarding the quantity of normal tissue to be removed around the OSCC and the lack of impact of positive surgical margins on prognosis (Vikram et al., 1984,Loree and Strong, 1990, Ravasz et al., 1991, Jacobs et al., 1993, Spiro et al., 1999, Sutton et al., 2003, Kovács, 2004, Binahmed et al., 2007,Upile et al., 2007). More consistent is the data (Upile et al., 2007) on the correlation between the presence of severe dysplasia and local control. These findings prompted us to study the impact on prognosis of the severe dysplasia at the surgical margins, and our data confirm that the presence of dysplasia is negatively correlated with prognosis.

The AJCC staging system (American Joint Committee for Cancer Staging and End-Results Reporting, 1977, Edge et al., 2010) for OSCC continues to classify tumors with invasion through cortical bone as T4, which by definition assigns the patient to stage IV disease with resultant prognostic and management implications. However in the literature, bone invasion is not an independent prognostic factor when confounding variables such as tumor size and involved surgical margins are taken into consideration (Platz et al., 1983, Soo et al., 1988a, Soo et al., 1988b, Dubner and Heller, 1993, Overholt et al., 1996,Edge et al., 2010). Ebrahimi et al. (2011) in a retrospective single-institution analysis, demonstrated that tumor size and medullary bone invasion are independent predictors of reduced survival; in contrast, tumors with bone invasion limited to the cortex have a similar prognosis to those without bone invasion. These data were confirmed in our cohort of patients. The adverse effect of medullary involvement appears to result, at least in part, from an increased risk of distant metastatic failure.

In our cohort of 525 patients, the presence of PNI is found to be related to poor DSS. Effectively, PNI is associated with disease recurrence, an increased probability of regional and distant metastasis, and an overall decrease in 5-year survival rate (Fagan et al., 1998, Soo et al., 1988a,Soo et al., 1988b, Rahima et al., 2004, Woolgar, 2006, Tadbir et al., 2009). There is a strong tendency toward neural invasion in late-stage carcinoma but no association with early-stage SCC of the tongue (Sethi et al., 2009). The same reports demonstrated that younger patients with OSCC had a significantly worse N stage, more PNI, and higher rates of treatment failure and mortality when compared to an older patient population (Soudry et al., 2010). The preponderance of evidence suggests that PNI is a significant prognostic indicator of the ability of OSCC to spread to cervical lymph nodes and therefore should be weighed heavily when considering neck dissection or the use of adjunctive treatment (Chandu et al., 2005, Rahima et al., 2004,Woolgar, 2006, Shah and Gil, 2009).

Two modalities that probably contributed to improved survival during the last decade (Garzino-Demo et al., 2006) are wider resections and greater use of PORT and PORTC

(Amit et al., 2013). However in our experience, in patients receiving POCRT, the presence of osseus and positive resection margins did not influence the cumulative survival rate at 5 years; only perineural invasion negatively influenced the 5-year survival curves.
Not all OSCC cN0 patients have the same risk of cervical metastases. An elective neck dissection should be performed when this risk is greater than 20–25%. The localization and the size of the T stratify the risk of occult metastases (Gourin et al., 2008). Despite these additional criteria, still 20–30% of patients who were cN0 and did not undergo neck dissection, developed metastases during the follow-up (Pitman, 2000). Tumor infiltration depth is an independent predictor for nodal status in pT1 to pT2 OSCC (Pentenero et al., 2005, Huang et al., 2009). Different studies (Pentenero et al., 2005) indicate the impact on the prognosis of both tumor infiltration depth and tumor thickness. Tumor infiltration is considered a better predictor for nodal status. However, in the literature there is a huge variability in the values of infiltration (1.5–10 mm) that are able to affect the prognosis (Spiro et al., 1986,Nathanson et al., 1989, Fakih et al., 1989, Al-Rajhi et al., 2000,Gonzalez-Moles et al., 2002, Po Wing et al., 2002, Kurokawa et al., 2002, O-charoenrat et al., 2003). As did Melchers et al. (2012), we considered 4 mm as cut-off of the infiltration depth.
We have presented an analysis of a cohort of 525 patients treated over an 11-year period from a single institution. Further studies should analyze the influence of prognostic factors and the results of therapy for each subsite of the oral cavity. The limitation of the study is that it is a retrospective study.

6. Conclusion

Age, tumor staging, lymph node involvement, extracapsular spread, grading, perineural invasion, infiltration depth, and osseus medullary invasion seem to be the most predictive factors in patient prognosis. They were significantly associated with OS and DDS.
The results of the current study demonstrate a significant improvement in the 5-year OS and DSS rates among patients with OCSCC during the past decade compared with the previous decade.

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None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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