CLINICAL STUDY

Squamous cell carcinoma of the oral cavity

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Abstract

**Objectives:** A number of treatment modalities are available in the management of oral cavity cancer. These are surgery (operation OP), irradiation (radiotherapy RT), chemotherapy (CHT), or complex therapy performed as a combination of the later three methods with various survival rates. A multidisciplinary team approach in every individual case is required.

**Background and methods:** Authors analysed retrospectively a group of 622 patients (553 men, 69 women), mean age 58.6 years (range 23–88 years) hospitalised in the Department of Oral and Maxillofacial Surgery, Faculty Hospital and Faculty of Medicine Comenius University in Bratislava within the years 1992–2001 with primary untreated histologically confirmed squamous cell carcinoma of oral cavity (beside cancer of the lip and salivary glands). Gender, age, location and TNM staging of the disease, clinical and histopathological evaluations of the neck lymph nodes and relationship to the treatment modalities were recorded. The authors compared some parameters of the results obtained during their previous study within the years 1977–1986 (453 patients).

**Results:** The number of cases with squamous cell carcinoma of oral cavity increased by 37.31% in total as well as that of cases with advanced disease, especially stage IV (318 patients=56.6%) increased by 7.6%. In the studied group there occurred cases that were clinically falsely negative by N0 (11.04%) as well as falsely positive by N1 (39.1%) when examined by palpation of lymph nodes. The overall 5-year survival rate remained at the same level (55.4%), the early and late stages did not change the survival rate at the 5th year (I=75.1%, II=69.9%, III=47.5%, IV=25.1%). Regarding the complexity of treatment, the best 5-year survival rates showed the complex three-modal therapy (CHT + OP + RT=23.5%), comparing to the dual (OP + RT or CHT + RT=19.4%) and mono-modal therapy (OP or RT alone=17.2%). In the complex therapy, the mean disease-free interval improved (30.2 vs 39.4 months) due to a change in the sequence of therapy modalities.

**Conclusion:** The increase in the number of cases with advanced disease has a warning trend. The reasons of this trend remain unclear. In spite of the fact that the overall 5-year survival was found not to improve, the quality of life regarding the mean disease-free interval in the group of patients under the complex treatment is considered to be a positive result (*Tab. 3, Fig. 4, Ref. 27*). Full Text (Free, PDF) www.bmj.sk.

Key words: squamous cell carcinoma, oral cavity, treatment, survival.

The incidence of head and neck squamous cell carcinoma in Central and Eastern Europe is still increasing to reach the 4th place as a cause of death among males (1). A number of treatment modalities are available for the management of oral cavity cancer. These are surgery, irradiation, chemotherapy, or a complex combination of them. Regardless of the cancer treatment standards and schedules some differences may occur by the approaches depending on individual philosophy and local traditions influenced by technical and economic conditions. The opin-
ions on best outcomes may change in the course of time on the basis of obtained long-term results. Besides various survival rates, the quality of life of patients suffering from cancer disease remains very important. The aim of the study was to provide other workplaces with our usual approach to the treatment of different locations and stages of oral cavity cancer and our experience with 5-year survival.

Patients

The total of 622 patients (553 men, 69 women), mean age 58.6 years (range 23–88 years) with an untreated primary squamous cell carcinoma of oral cavity were included into this study. All of them were in-patients at the Department of Oral and Maxillofacial Surgery, Faculty Hospital and Faculty of Medicine Comenius University in Bratislava from January 1992 till December 2001. The group of consecutive patients were gathered from the region of Western Slovakia with about 1.5 million inhabitants.

The diagnoses included the locations according to the International Classification of Diseases – Oncology, 10th revision from 1994 as follows: the tongue (C01, C02.1, C02.2, C02.3, C02.8), the upper (C03.0) and the lower jaws (C03.1), the floor of the mouth (C04.0, C04.1, C04.8), the palate (C05.0) and the maxillary sinus (C31). A group of unspecified locations (C06.0, C06.2) revealed mostly the retromolar and buccal regions. Cancer of the lips (C00.0, C00.1, C00.6) and salivary glands (C07, C08.0, C08.1) were excluded from the study. Histopathology confirmed the diagnosis of squamous cell carcinoma in all cases. TNM classification and staging (2) were established on the basis of clinical evaluation, orthopantomography, chest x-rays, skull projections, sonography of the neck and in most patients also computerized tomography and magnetic resonance imaging.

Consultation of a multidisciplinary team consisting of a radiotherapist, chemotherapist and maxillofacial surgeon in the presence of every patient preceded the start of the treatment. Individual treatment plans were consulted for the optimal expected outcome by single or combined modalities. The complex therapy included all three modalities: chemotherapy (CHT), surgery (operation OP) and radiotherapy (RT). Operations followed by irradiation (OP + RT) or concomitant chemoradiotherapy (CHT + RT) represented the dual therapy. Radiotherapy alone or operations alone were performed. Non-cooperative patients who refused the treatment plan were excluded from further study.

Limitations of chemotherapy were represented by poor health, most frequently by poor parameters of full blood count (haemoglobin >10 g/dL, platelets >100x10^9/L, white cell count >3.5x10^9/L especially neutrophils >1.5x10^9/L) as well as renal and liver function tests (3, 4). The neoadjuvant chemotherapy was received by patients within five days after cisplatin or carboplatine, and 5-fluorouracyl protocol took place in three cycles with a 28-day free interval (5). However the patients with progression of the disease received chemotherapy in one or two cycles only and thereon were treated by another treatment modality. The adjuvant chemotherapy with methotrexat was indicated (6) in some individual cases only and was not part of the regular primary treatment plan. Intraarterial chemotherapy was not applied in the consecutive patients.

Surgery was managed by radical resection of the tumour site with/without simultaneous neck dissection. In cases with clinically negative neck the standard procedure was represented by elective unilateral or bilateral neck dissection in the level I and IIa (7, 8) should carcinoma of the tongue and floor of the mouth be involved, depending on invasion to the midline structures. In tumours of the floor of the mouth with extent of T2 and more at least a superficial mandibulectomy with preservation of the mandibular continuity was performed routinely. In cases where segmental mandibulectomy was performed, reconstructive plates were preserved in the space of resected bone segments. No free flaps with microsurgery were performed due to regular application of radiotherapy.

Patients received external irradiation as soon as possible but not earlier than three weeks postoperatively. A total dose of 60–75 Gy was applied during the curative radiotherapy within 6–7 weeks, a total dose of 10–20 Gy during the palliative radiotherapy within 2–5 weeks depending on the degree of local reaction. None of the patients underwent brachytherapy in the following period.

Chemotherapy and radiotherapy took place at specialized departments localised in the capital city Bratislava or in the region of Western Slovakia. The surviving patients were followed up at the Department of Oral and Maxillofacial Surgery in Bratislava. Their follow-up period took at least five years, at longest 14 years, mean follow-up was 7.5 years. The follow-up in the first year was done once in every two months, in the second year every three months, in the third year every four months, in the fourth and the fifth years the surviving patients visited hospital twice per year. The chest x-ray was performed every year. The indications for sonography of the neck and liver, orthopantomography and computerized tomography were dependent on clinical findings revealed and evaluated during the follow-up.

Oncomarkers were found to be of no practical value in monitoring the recurrence of squamous cell carcinoma of the oral cavity (9).

Should no limitations occur in cases of recurrence, adjuvant radiotherapy or chemotherapy were usually applied. The secondary intraoral/neck surgery was performed occasionally by local/ regional recurrences, otherwise this surgery was avoided (10). Some patients required salvage surgery (haemorrhage control, tracheostomy, gastrostomy etc.)

Methods

The analysis was retrospective using the patient’s medical records was done. Within the records gender, age, location and TNM staging of the disease, the primary clinical and histopathological evaluations of the neck lymph nodes and relationship to the local, locoregional or distant metastatic recurrence two years from beginning of the treatment were followed. The statistical evaluation was based on the Student’s paired t-test. The difference
Squamous cell carcinoma of the oral cavity by gender

Fig. 1. Squamous cell carcinoma of the oral cavity by gender.

OVERALL SURVIVAL

Fig. 2. Overall survival.

SURVIVAL BY STAGING

Fig. 3. Survival by staging.

was recognised to be statistically significant once p was less than 0.05. The Kaplan-Meier estimation (11) was not used for 5-year survival rates and the date of death of the followed patients were confirmed by mail, or their family members had announced the dates. However the autopsy protocols were mostly not available to exclude non-cancer reasons of death. Out of the total of 622-patient group only 366 patients (58.8 %) regularly visited the Department of Oral and Maxillofacial Surgery in Bratislava.

Results

Within the analysed ten-year period in the group of patients (Fig. 1), the mean age differed with gender (men 55.2 years, women 62.0 years), ranging from 23 to 88 years.

The squamous cell carcinoma was located on the tongue (n=228 of cases, 36.66 %), upper jaw (n=14, 2.25 %), lower jaw (n=75, 12.06 %), floor of the mouth (n=235, 37.78 %), palate (n=6, 0.96 %), maxillary sinus (n=8, 1.29 %), retromolar and buccal regions (n=56, 9.0 %).

In spite of the accessibility of oral cavity by direct examination, these malignancies still were detected as late as in their late stages. The clinical stage I occurred in 40 patients (7.1 %), stage II in 147 patients (26.2 %), stage III in 117 patients (20.8 %) and stage IV in 318 patients (56.6 %). Distant metastases were evident at primary evaluation in six patients (four pulmonary and two skeletal metastases), the extent T1 of the primary tumour was noted in oral cavity in three of them, four of them had clinically negative neck N0.

Comparing the palpation and histopathological results obtained from 305 of the patients who underwent primary neck dissection false clinical findings were found in clinically NO negative necks in 20 patients=11.04 % (false negative by palpation). By clinically N1 41.43 % of the lymph nodes were without histologically confirmed malignant spread (false positive by palpation). Lymph nodes enlarged more than 6 cm in diameter (N3) were always positive by histopathology (Tab. 1).
Tab. 3. Comparison of staging in the two compared ten-year studies.

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>1977–1986 n</th>
<th>%</th>
<th>1992–2001 n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>31</td>
<td>7</td>
<td>40</td>
<td>7.1</td>
</tr>
<tr>
<td>II</td>
<td>68</td>
<td>15</td>
<td>147</td>
<td>26.2</td>
</tr>
<tr>
<td>III</td>
<td>130</td>
<td>29</td>
<td>117</td>
<td>20.8</td>
</tr>
<tr>
<td>IV</td>
<td>224</td>
<td>49</td>
<td>318</td>
<td>56.6</td>
</tr>
<tr>
<td>Total</td>
<td>453</td>
<td>100.0</td>
<td>622</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The received treatment (chemotherapy = CHT, operation = OP, radiotherapy = RT) and various combinations are indicated in Table 2. In the largest group treated by irradiation alone (n=217) the curative external radiotherapy was received by 77.6 % of the patients, the rest of them (22.4%) were irradiated palliatively. Second by frequency came the combination of surgery followed by radiotherapy (n=191), the three-modal complex therapy was undertaken by 85 of the patients. In the cases of retromolar location and that on the root of of the tongue chemoradiotherapy was combined. Surgery alone was used in cases of small extent, i.e. T1, especially with exophytic growth.

Out of the followed 366 patients, recurrence occurred up to two years in 196 of cases (55.4 %), especially in the late stages of III and IV (45.0 % of all recurrences) with mean interval of 12.5 months. The recurrences were local (n=56, 28.57 %), regional (n=19, 9.69 %) or locoregional (n=119, 60.71 %). Distant metastases to the lungs developed in two of the cases (1.03 %).

The overall survival rate up to the 5th year in the followed group of 366 patients was 55.01 % (n=201) (Fig. 2). The 5-year survival by staging is showed in Figure 3 (stage I=75.1 %, stage II=69.9 %, stage III=47.5 %, stage IV=25.1 %). Regarding the complexity of treatment, the best 5-year survival rates were observed in complex therapy performed as a combination of three modalities (CHT, OP, RT=23.5 %) when compared to dual (OP + RT or CHT + RT=19.4 %) and mono-modal forms of therapy (OP or RT alone=17.2 %) as seen in Figure 4.

In the first half of the investigated period (years 1992–1996) the preferred sequence in the therapy combined of three modalities was chemotherapy in three or two cycles (depending on progression) followed by operation and finally by irradiation (CHT-OP-RT=38 of patients), the mean disease-free interval was that of 30.2 months. Since1997 this approach has changed and the primary concomitant chemoradiotherapy was – followed by surgery (CHT + RT OP=47 of patients), the mean disease-free interval was that of 39.4 months.

Discussion

The analysed group of patients is not sufficiently large for comprehensive study due to its fairly unhomogenous structure regarding the different locations. Due to this reason the results are not comparable very well with larger investigations of other authors. That is why we compared the results to our previous 10-year study (12). Oral cancer disease has affected more men than women, however, the male/female ratio has become less pronounced (9.8:1 vs 7.9:1). Similar trends have been reported in literature regarding the gender (13, 14).

A total increase by 37.31 % was observed in the number of patients with squamous cell carcinoma of oral cavity from the same territory (453 vs 622 of cases). Unfortunately, besides this negative indicator also the number of patients at late stages increased by 7.6 %, especially at stage IV (Tab. 3). This fact is difficult to explain, some of the causes may be of subjective origin e.g. incorrect approach of patients to their health due to social changes. Objectively the hospital network has been reduced, the fact of which has deteriorated the health care service accessibility.

The interesting finding of three patients with T1N0M1 may lead to considerations about second primary cancer in their cases (15). The metastatic spread, found at the first presentation of a patient, was recognized as a bad prognostic factor (16, 17, 18). So the precise evaluation of cervical lymph nodes is of vital importance (19, 20). Bad anatomical conditions due to short neck, wrong position of patient’s head by assessment, non-systematical palpation, or incorrect record are crude subjective errors. Beside this, the involvement of deep groups of lymphatic nodes or the microscopic metastatic deposits can escape clinical detection. As opposed to the later, in clinical N1 falsely positive findings can be achieved by palpation due to overevaluation of e.g. enlarged submandibular salivary gland. Sometimes some of the lymph nodes may be overlooked by the operating surgeon or the pathologist. Therefore proper cooperation, awareness of both, typical and more unusual distributions of spread, the size of nodal metastases and the frequency of extracapsular spread allows the pathologist to focus his assessment on the specific nodal group and to produce standardized pathology reports (21).

The overall 5-year survival (54.82 % vs 55.08 %) remained at a similar level with no statistical significance (p>0.05). The early and late stages did not change much by the survival at the 5th year (stage I=75.12 % vs 75.24 %, stage II=70.88 % vs 71.15 %, stage III=47.54 % vs 46.82, stage IV=25.76 % vs 26.11 %).

In therapy combined of three modalities within the period of years 1992–1996 with CHT-OP-RT as well as in that of 1997–
2001 with chemoradiotherapy followed by surgery (CHT+RT OP), the difference of 9.2 months in the disease-free interval was significant (p>0.05). Patients also suffered less from xerostomia which is a usual and very bothering sequel of oncological treatment (22, 23, 24). Hence, the quality of life was subjectively qualified by patients as normal for a longer period of time (25, 26, 27).

Conclusion

A warning moment was found, namely the increase in the number of advanced squamous cell carcinoma in oral cavity however the subjective and objective reasons remain unclear.

The study shows that the feedback from general practitioners is not sufficient to obtain more reliable information on survival of patients suffering from oral cancer despite the serious character of the disease.

In spite of the found facts, the overall 5-year survival has not improved, the quality of life regarding disease-free interval in the group of patients under the complex treatment reveals a positive result and trend.

References


