Abstract. Aim: The aim of this study was to analyse the outcome of patients with oral and maxillofacial (OMF) cancer. The emphasis was to evaluate the outcome of patients with second primary cancer. Patients and Methods: A total of 649 patients were retrospectively evaluated (male: 457; female: 192). All patients were treated for a primary cancer at the department of OMF surgery, Eppendorf University Hospital, Germany. All patients were reclassified (UICC TNM-system, 1992). The follow-ups were analysed separately for primary and second primary cancer. Results: Seventy-seven of 649 patients developed a second cancer (11.9%; male: 50; female: 27). Second primaries were synchronous (18.2%) or metachronous (76.6%; necropsy: 5.2%). The index tumor was located in the OMF region in 49 patients (63.6%). The incidence of second cancer inside the OMF region was 49 cases (7.5% of all patients). The mean survival differed significantly between patients with one cancer and those with two (127 months vs. 48 months p<0.001). However, these differences were not significant when survivals were calculated with diagnosis of the index tumor as the reference time-point. About a third of second primaries in the OMF region succeeded a primary of other organs. Conclusion: Patients who develop second cancer are younger than single OMF cancer patients at the time-point they acquire their index tumor. Successful therapy for a primary cancer that had developed inside or outside the OMF region expands the life-span of cancer patients. These patients are at risk of developing second primaries. Inspection of the upper aerodigestive tract should be included in the follow-up of cancer patients who survive cancer that originated in other organs. Tumor markers are needed to define this subgroup of cancer patients.

The risk for second cancer in patients with oro-maxillofacial (OMF) malignancies varies between 1.8% and 4.3% up to 30% (1-3). These data are predominantly gained from squamous cell carcinoma of the mucosa of the upper aerodigestive region. Warren and Gates (4) were the first who published criteria that should be fulfilled when a malignant tumor is to be recognized as a second primary. During the last 50 years studies were conducted by many experienced investigators (5-27). They found interrelationships between index tumors and second malignancies, both in functionally and histogenetically related organs, and those with similar carcinogen exposure. The aim of this study was to determine the number of patients with second cancer treated in a single surgical unit and their prognosis compared to those who experienced one malignancy only, in order to provide a basis for further diagnostic and therapeutic strategies.

Patients and Methods

Patients. The files of patients treated for a squamous cell carcinoma of the OMF region (ablative or reconstructive surgery) were evaluated. All patients had been treated at the department of OMF surgery, Eppendorf University Hospital, Germany. Data for a total of 695 patients were collected. Forty-six patients were excluded from the evaluation due to insufficient data. The term "treatment" refers to surgery, radiotherapy, chemotherapy or a combination of these treatments. The majority of the patients were treated for a primary tumor in the OMF region. However, our evaluation of cancer patients included the record of any malignant tumor, irrespective of localization. The calculation of survival times started with the diagnosis of the index tumor. The calculation of survival after second primaries started with the diagnosis of this tumor. This method has been used in several other survival studies on second cancer, thus providing comparable data.

Classification. A second primary cancer was defined according to Warren and Gates (4). The proposals of de Vries and Gluckman (28) for the differentiation of histopathological identical tumors were applied in relevant cases. The time-related categorization of second primaries was adapted from Moertel (18). An index tumor is the first diagnosed malignant tumor in patients with two or more malignancies. The term simultaneous tumor was applied for those malignancies that were diagnosed at the same time or during the
staging of the first malignancy. A *synchronous* second primary was that diagnosed within 6 months of the index tumor, a *metachronous* tumor after 6 months following the diagnosis of the index tumor. The topographic relationships of the tumors were analysed according to Kapsinow (29). The histological grading was performed according to Broders. All squamous cell carcinomas of the OMF region were reclassified according to the UICC Tumor-Node-Metastasis (TNM) Classification, 1992 (30).

**Risk factors.** A family history of cancer and internal diseases were regarded as endogenous risk factors and compared between patients with and without second primaries. Alcohol and nicotine consumption were regarded as exogenous risk factors. The self estimation of the patients and the data quality of the records had to be accepted due to the retrospective study design.

**Statistics.** Deviations from a Gaussian distribution were calculated using the Lilliefors-test. In random samples with patient numbers lower than 50, the Shapiro-Wilks test was applied. The comparison of two variables was calculated with the Chi-square test according to Pearson. The survival times were calculated according to the product-limit method of Kaplan and Meier. The calculations were performed with the Statistical Package for the Social Sciences (SPSS) Software Package (SPSS Inc., Chicago, USA).

The level of significance for differences between values was defined as follows: 0.05 > p > 0.01: significant; 0.01 > p > 0.001: very significant; p < 0.001 highly significant.

**Results**

**Patient overview.** We evaluated 649 patients with cancer of the OMF region. One hundred and ninety-two (29.6%) were female and 457 (70.4%) were male, the male to female ratio being 2.4:1. Out of 649 patients, 77 patients had a second cancer (77/649=11.9%), 27 (34.2%) out of 77 (100%) being female and 50 (64.9%) being male. Second primaries were synchronous in 18.2% and metachronous in 76.6%. Second primaries of a further four patients (5.2%) were diagnosed following necropsy. The index tumor was located in the OMF region in 63.6% (49 patients) and outside in 36.4% (28 patients). The incidence of second cancer inside the OMF region was 49 or 7.5% of all patients. The mean survival time of patients with one cancer was 127 months and of patients with a second primary 48 months.

**Age at the time of the diagnosis.** The mean age of patients with an index tumor was 58.5 years (minimum:11 years, maximum: 100 years, median: 57 years). In females, the mean age was 62.4 years and higher than in males (56.8 years; p<0.001).

**Exogenous and endogenous risk factors**

**Alcohol and smoking.** Four hundred and thirty-three patients reported regular smoking (66.7 %), 362 out of 649 (55.8%) consuming 20 to 40 cigarettes daily. One hundred and eighty-four were non-smokers (28.4%). In 32 patients, no information was obtained. Regular intake of alcoholic beverages was reported by 243 patients (37.44%) and in 128 patients alcohol addiction was proven (19.7%). The combination of heavy smoking and alcohol consumption was revealed in 123 patients (19%). To elucidate the effect of these on oral cancer, we investigated 479 patients with an index tumor of the oral cavity and oropharynx separately. Within this subgroup, 354 patients (73.9%) were smokers, 300 (62.6%) declaring heavy smoking. A chronic alcohol addiction was known for 116 patients (24.2%) with carcinoma of the oral cavity. The combination of chronic alcohol intake and smoking was identified in 115 patients. These are 93.5% of 123 patients with a combined abuse. Only 6.5% of the patients with heavy smoking and drinking habits developed their index tumor outside the oral cavity or oropharynx.

**Family history of cancer.** Sixty-four out of 649 patients declared that cancer had occurred in parents, sisters or brothers (9.9%). In 224 patients, this association was denied (34.5%). However, the vast majority of files (n=361, 55.6%) did not address this item sufficiently for analysis.

**Further diseases.** Additional diseases were recorded in the minority of patients while 424 (65.5%) had no obvious further disease. The number of additional diseases is listed in Table I. The influence of additional diseases on the prognosis is analysed below.

<table>
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<tr>
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<tr>
<td>Lung</td>
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<td>9.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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</tr>
<tr>
<td>Liver</td>
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<td>2.0</td>
</tr>
<tr>
<td>Combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus and cardiovascular diseases</td>
<td>27</td>
<td>4.1</td>
</tr>
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<td>1.1</td>
</tr>
<tr>
<td>Lung and cardiovascular</td>
<td>13</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table Ib. Localization of second cancer (%).

<table>
<thead>
<tr>
<th>Localization of second cancer</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and oropharynx</td>
<td>63.6</td>
</tr>
<tr>
<td>Skin and lips</td>
<td>7.8</td>
</tr>
<tr>
<td>Other OMF regions</td>
<td>6.5</td>
</tr>
<tr>
<td>Other regions or organs</td>
<td>20.8*</td>
</tr>
</tbody>
</table>

*Of which: lung 31.3%, esophagus 18%, prostate 12.5%, bladder 12.5%, colon 12.5%, pancreas: 6.2%, breast: 6.2%.
Site of the index tumor. Out of 649 patients, the index tumor was located in the oral cavity and oropharynx in 479 (73.8%). A further 94 patients developed a squamous cell carcinoma of the lips or facial skin (47 each, 14.5% each). The epipharynx was the origin of the index tumor in 7 patients (1.1%), the larynx in 4 (0.6%). The subgroup "other OMF regions" included adenoid cystic carcinoma of salivary glands, carcinoma of the maxillary sinus or lacrimal gland. A further 28 patients had an index tumor outside the OMF region. These patients were exclusively affected by second primaries of the OMF region.

Stage of the index tumor. According to the UICC criteria the minority of patients was in stage grouping I (85 patients, 13.1%). A further 98 patients (15.1%) were in stage grouping II, 105 (16.2%) in stage grouping III. In 197 patients (30.4%) the disease was in stage grouping IV. However, in about a quarter of patients (25.2%) the staging of the disease was not classified. Restricted to index tumors of the oral cavity and oropharynx, these carcinomas (n=479 (100%)) were in stage I: 60 patients (12.5%), stage II: 79 patients (16.5%), stage III: 93 (19.4%), with the majority (n=187 (39.0%)) being stage IV (not classified: 60 (12.5%)).

In the group with carcinomas of the facial skin and lips, the index tumor was treated in stage I in 23 patients (24.5%), stage II in 19 (20.2%), stage III in 11 (11.7%) and stage IV in 7 (7.4%). The remaining 34 patients could not be exactly classified. Comparing these two groups, the differences in stage grouping were highly significant (p<0.001). The frequency of stage I lip carcinoma was unexpectedly high and the frequency of stage IV carcinoma low.

Grading of the index tumor. Well-differentiated carcinoma (G I) was diagnosed in 160 (24.7%) of 649 patients. The majority of carcinomas were moderately-differentiated (G II, n=354 (54.5%)). A poorly-differentiated tumor (G III) was noted in 56 patients and anaplastic carcinomas were rare (4, i.e. 0.6%). The differentiation was not given in the histopathological diagnosis of 75 cases (11.6%). The further evaluation of tumor differentiation was restricted to these 574 patients. We found a significant dependence of tumor grading on localisation for well-differentiated lip tumors and poorly-differentiated carcinomas of "other OMF regions" only (p<0.05). The results are summarized in Table II.

Treatment. Out of 649 patients, 532 underwent ablative surgery (82%). A single therapeutic tool, i.e. surgery or radiotherapy or chemotherapy, was chosen in about every second patient (n=322 (49.2%)), 234 of these 322 only surgical (36.1% of all patients). Radiotherapy only was applied in 80 patients (12.3%) and chemotherapy only in 8 (1.2%). A combination of two methods was applied in 295 patients (45.4%). Irradiation followed by ablative surgery was performed in 137 patients (21.1%) while in 102 (15.7%) surgery preceded the irradiation. In 41 patients a cytostatic...
chemotherapy preceded the resection of the tumor. A combination of three methods was rarely used. No treatment was given in 18 patients. The choice of therapy is shown in Table III.

Overall survival. This analysis included all 649 (100%) patients. We studied the influence of gender, localisation, grading and staging of the tumor and additional diseases on survival. The control period following the index tumor lasted 53.4 months on average. Within this period, 303 patients died (46.7%), 318 survived (49%) and 28 (4.3%) were lost to follow-up. The mean survival time following the diagnosis of the index tumor was 127 months. One year after diagnosis 78.5% of all patients were alive, three years after diagnosis 64.4% and the 5-year survival rate (5YSR) was 58.7%. Half of all patients had died after 88 months. The differences in survival dependent on the gender of the patients were not statistically significant (females: 186 patients, mean survival 120 months, 5YSR 63.6%; males: 435 patients, mean survival 123 months, 5YSR 56.5%; p > 0.05).

The site of the index tumor had some impact on survival. Within the large group of primary oral and oropharyngeal carcinoma the mean survival was 106 months. The 5YSR was 54%. Half of these patients had died after 88 months following the diagnosis. The differences in mean survival times were statistically highly significant when comparing this group and patients with a primary of the facial skin or lips (94 patients (14.5%); mean survival time: 158 months; 5YSR: 72.4%; 50% died 163 months following index tumor diagnosis). Other locations had almost identical mean survival times of 150 to 152 months, except for laryngeal carcinoma (48 months). However, this subgroup is very low in number (4 patients).

The staging of the index tumor had a great impact on survival times. The differences were statistically highly significant (p < 0.001) except for stage II and III index tumors. The mean survival of 85 stage I carcinoma patients (13.1%) was 181 months (5YSR 82%), whilst that of 98 stage II patients (15.1%) was 121 months (5YSR 64%). Ninety-eight months was the mean survival of stage III patients. The mean survival of 197 stage IV patients (30.4%) was 59 months. Five years after the diagnosis, 36.9% were still alive. The survival according to the stage grouping is shown in Figure 1.

The grading of the index tumor had little impact on survival. One hundred and sixty patients (24.7%) with a well-differentiated index tumor survived a mean of 115 months, 5YSR was 61%. A moderately-differentiated tumor was found in 354 patients (54.5%). The mean survival time of this group was 16 months (5YSR 52.9%). Poorly-differentiated carcinoma was recorded for 56 patients (8.6%). The mean survival time of these patients was 103 months (5YSR 54.7%). Patients with anaplastic carcinomas were rare (3 patients, 0.5%). The mean survival time was 13 months. Statistically significant differences in the survival times were noted when comparing well- to moderately-differentiated carcinomas (p < 0.01) and comparing all groups to anaplastic carcinomas (p < 0.001).

Out of 424 patients without further diseases, 399 patients were evaluable for survival calculations (61.5%); 175 died during the control period (27%) and 224 survived (34.5%). The mean survival time of these patients was 128 months (5YSR 61%). These findings were also recorded for the majority of patients with further diseases (comorbidity). However, 60 patients (9.2%) with diabetes mellitus survived for 82 months (mean value) and had a 5YSR of 38%. This
difference was statistically significant ($p<0.01$). Out of a further 60 patients suffering from bronchial diseases, 35 died during the observation period. The mean survival time was 96 months (5YSR 52%). The influence of other diseases on survival was not shown (Table I).

Second cancer

Age at the time of the index tumor. The mean age of second cancer patients at the time of the index tumor was 59.8 years (median: 61 years; standard deviation (SD): 12.2 years). The youngest patient was 30 years old, the oldest 92 years. In females, the mean age was 58.5 years (SD 13.2; median 61 years; minimum 30 years, maximum 81 years). In males, the mean age at the time of the index tumor was 59.9 years (SD 12.0 years, median 60 years, minimum 31 years, maximum 92 years).

Age at the time of the second cancer. The mean age at the time of the second cancer was 64.6 years. This age is significantly higher than the age of patients overall (58.5 years, difference 6.1 years, $p<0.001$). The median is 64 years (SD 11.8 years, minimum 31 years, maximum 100 years). There were no differences in age in patients with second cancer related to their gender ($p>0.05$).

Risk factors. Forty-nine patients (63.6%) were smokers [10 cigarettes/d: n=7 (9.1%); 20-40 cigarettes/d: n=41 (53.2%)]. One patient smoked cigars, 27 denied smoking (34.2%), and in one patient we obtained no information on smoking habits. Heavy drinking was denied by 40 patients (51.9%). Alcohol addiction was proven in 18 patients (23.4%). Modest consumption of alcoholic beverages was found in 10 patients (13%) while 9 patients (11.4%) were non-informative. In patients with second carcinoma, the combination of heavy drinking and smoking (20 to 40 cigarettes/d) accounted for 25 patients (32.4%). Nineteen of these 25 patients (19/77, 24.7%) developed an OSCC, representing 76% of the patients with this combination of abuse. One further patient developed a carcinoma of the lip and the remaining 5 patients of this subgroup developed second primaries outside the OMF region.

Further diseases. No relevant diseases were recorded in 43 patients (55.8%). Cardiovascular diseases were found in 20 patients (26%), diseases of the lung in 13 (16.9%), diseases of the liver in 2 (2.6%) and diabetes mellitus in 9 (11.7%) (Table IV).

Family history of cancer. A history of malignant tumors in parents, sisters or brothers was noted in 19 patients (24.7%). No family history of cancer was recorded in 51 patients (66.2%). Seven patients (9.1%) could not give precise information about this issue.

Localization of the index tumor. In the majority of patients the index tumor was located in the oral cavity or oropharynx. These regions contributed to 48.1% (n=37) of patients with second cancer. Further index tumors were the nasopharynx (n=1, (1.3%)), the lips or facial skin (n=4 each, (total 10.4%)), the larynx (n=2, (2.6%)) and sublingual gland (n=1, (1.3%)). In 28 patients, the index tumor was located outside the OMF region (breast: n=6, uterus: n=3, lung or colon and rectum: n=3 each; bladder, stomach, prostate, thyroid gland: n=2 each; kidney, esophagus: n=1 each. A further three patients had a history of rhabdomyosarcoma, osteosarcoma, or Non-Hodgkin’s lymphoma. (Table V).

Staging of index tumors in patients with a second primary. The data on staging are incomplete due to the fact that primaries outside the OMF region accounted for about one-third of this group. These patients were treated in other hospitals. In 40 out of 49 patients (81.6%) with OMF tumors, we were able to obtain usable data. However, these data were available in only 6 out of 28 patients (21.4%) with index tumor outside the OMF region. Therefore the staging was restricted to OMF carcinoma patients (evaluated: 49 patients). The data are shown in Table VI.
The stage distributions were in accordance with the expected frequency (Chi-square test). We could not find any influence of the index tumor staging on the incidence of second cancers.

**Grading of index tumors in patients with a second primary.**

The distribution of tumor grading in index tumors and second primaries did not differ significantly. Well-differentiated tumors were found in 11 patients (14.3%) of 77 second primaries (100%). The majority of tumors were of grade II (n=32, 41.6%) and a further 6 tumors were poorly-differentiated (G III, 7.8%). In 28 index tumors the grading could not be recorded; 22 of them were outside the OMF. Restricted to OMF index tumors (n=49, 100%), the distribution of grading was: G I=9 (18.36%), G II=29 (59.2%), G III=5 (10.2%). No information on grading was available in 6 tumors (12.2%).

**Localization of the second primary.** Out of 77 second cancers (carcinoma, 100%), sixty tumors were located inside (77.9%) and 16 tumors developed outside the OMF region. In one patient, the second primary could not be exactly determined at necropsy. OMF second primaries were confined to the oral cavity/oropharynx (n=49, 63.6%), the facial skin and lips (n=6; 7.8%) and further oral/maxillofacial regions (n=5; 6.5%).

Sixteen (100%) second primaries outside the OMF region were found in the lungs (n=5; 31.3%), esophagus (n=3; 18.7%), two in each of the prostate, bladder, or colon, and one in each of the pancreas or breast.

**Staging and grading of second primaries.** Sixty out of 77 patients were evaluated (stage I: 18.3%; stage II: 15.0%; stage III: 11.7%; stage IV: 31.7%). Twelve tumors were well-differentiated carcinomas (15.6%), 35 moderately-differentiated (45.5%), and 4 were poorly-differentiated (5.2%). No grading was reported in 26 cases (33.8%).

**Relation of tumor locations in primary and second carcinoma.** Out of 37 (100%) index tumors of the oral cavity, 23 (62.1%) developed in the same organ. In 13 cases (35.1%), the second tumor developed outside the OMF region. In these 13 cases (100%) the tumor was located in the lung (n=5, 38.5%), esophagus (n=3, 23%), prostate (n=2, 15.4%), breast, bladder or pancreas (one each).

Following an index tumor of the facial skin or lips (n=8), the second tumor was multicentric in only one patient. Out of the remaining seven patients, 2 carcinomas developed in the oral cavity and three in distant organs (colon: n=2; bladder: n=1).

Two patients developed the index tumor in the larynx. In one of these two patients the second primary developed in the orbit and in the second the oral cancer occurred with multiple distant metastases. Both patients with a nasopharyngeal carcinoma or sublingual carcinoma developed their second primary inside the oral cavity. Index tumors outside the OMF region (n=28) preceded an SCC of the oral mucosa in 22 (78.6%), of the lips in 5 (17.9%), and of the parotid in 1 patient (3.6%).

**Interval between index and second primary carcinoma.** Out of 77 second primary carcinomas (14.2%) developed within 6 months of the diagnosis of the index tumor. Metachronous tumors were found in 59 patients (76.6%). In 4 cases, the second primary was metachronously diagnosed at necropsy. The mean disease-free interval of these 77 patients lasted 56.1 months. However, the mean variation was extreme (standard deviation 60 months). The shortest interval lasted from zero (12 simultaneous second tumors) to 300 months (1 case). The median was 40.5 months. Only 28.3% of 77 patients had a disease-free interval of 1 year and 44.6% developed the second primary within 2 years, 64.9% within 5 years (Table VII).

A comparison of the disease-free interval following the index tumor of patients with primary OMF cancer to those with a primary outside of this field revealed a mean of 57 months (OMF primary, SD 65.2 months, range <1 month
to 300 months, median 46.5 months) and 54 months (outside the OMF region, SD 53.1 months, range 0 to 180 months, median 36 months). These differences were not statistically different (Student’s t-test, \( p > 0.05 \)).

**Treatment of the second primary.** Forty-eight patients (62.3%) were treated with ablative surgery, 33 of these with surgery only. A combined treatment was performed in 45.5%. Surgery included resection of the tumor with safety margins and efferent lymphatics when indicated. The choice of the chemotherapeutics over time was not further specified. The data are summarized in Table VIII.

**Survival.** Forty-eight patients died during the observation period (62.3%), 24 survived (31.2%) and 5 were lost to follow-up. The mean survival of all second primary patients was 48 months (Figure 2). One year after diagnosis of the second primary, 59% were still alive and after two years 56.6% had died. After a follow-up of 5 years, 29% were alive. Fifty-six patients with a single carcinoma survived at least for five years and had a mean survival time of 127 months. The comparison of survival parameters of the patients suffering from a second primary to those with a single carcinoma reveals a statistically significant difference (\( p < 0.001 \); Figure 3). However, this difference is not revealed when the basis for calculating survival times are the times of diagnosis of the index tumor in both groups (\( p > 0.05 \), Figure 4). Patients with a second primary had a mean survival of 110 months and 71% survived for at least 5 years. The gender had no effect on survival in patients with second primaries (\( p > 0.05 \), Wilcoxon test). There was no effect of differences of the localization of the second primary (oromaxillofacial region vs. other regions) on survival (\( p > 0.05 \)); out of 60 patients (100%) with a second primary in the OMF-region, 19 survived the observation period (31.7%) and 36 died (60%). Five patients were lost to follow-up. The mean survival period was 49 months and 33.3% survived for at least 5 years. Out of 16 patients with second primaries of regions other than the OMF-region, only 4 survived and 12 died (mean survival 33 months, 5YSR: 23%). When the second primaries were subdivided according to the anatomical structures inside the OMF-region, a statistically significant difference was found only when the patients with tumors of the facial skin and lips were compared to second primaries of organs outside the OMF-region.

**Impact of the disease-free period on survival.** Out of 77 second primaries, 14 (18.2%) developed a synchronous second carcinoma. In 12 of these 14 patients this tumor developed simultaneously with the index tumor. Out of these 12 patients, 5 died and 7 survived the evaluation period. The mean survival of these patients was 88 months (5YSR 55%). In 59 patients the second primary developed metachronously (72.7%) with the index tumor, with an interval of 7 months to 25 years. Out of these 59 patients, 40 died within the evaluation period and 19 survived. The mean survival was 40 months (5YSR: 26%). In 4 cases, second primaries were revealed at necropsy. The differences between survival times of patients with synchronous and metachronous second primaries proved to be highly significant (\( p < 0.001 \)).

**Discussion**

This study shows that there is a substantial risk for second cancer in patients with primaries of the OMF region.

**Gender and age.** The male to female ratio was 2.4:1 (all patients). The predisposition of men with OMF cancer compared to women is in accordance with current reports. Within the subgroup with second primaries this relation was reduced to 1.8:1. This ratio varies between 1.6 and 7.4:1 in studies on second cancer patients (4, 31-36).

The mean age of our patients at the time of index tumor diagnosis is in the range of similar studies. The mean age of OMF index tumor patients (58.5 years) differed highly significantly from the age at the time of the second primary (64.6 years; \( p < 0.001 \)). The mean age of second primary cancer patients at the time of their index tumor (59.8 years) did not differ significantly from the mean age of the whole patient group. The age differences of patients at the time of index tumor (mean: 57.6 years) and second primary diagnosis (mean: 62 years) ranged between 0.7 and 5.6 years. Obviously, the longer a patient survives an index tumor, the higher the risk for a second primary is (37).

**Etiology and risk factors.** This study is in accordance with results from the literature indicating that alcohol and smoking abuse support the development of an index or second primary carcinoma of the upper aerodigestive tract (22, 38-42). Moore (40) revealed a six-fold higher risk of

**Table VIII. Therapy for second primary carcinoma (n=77 patients).**

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<tr>
<th>Therapy</th>
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<td>6</td>
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<tr>
<td>Surgery followed by chemotherapy</td>
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<td>Total</td>
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</table>
second carcinomas in patients who did not stop smoking after the index tumor, compared to patients of the same study group who stopped smoking. Later this author noted that abstinence from smoking reduced the risk of second cancer (41). On the other hand, Castigliano (43) could not confirm these conclusions. But Schottenfeld et al. (22) found a four-fold risk for second cancer for patients continuing smoking and drinking after therapy of the primary. These findings were confirmed by Hsairi et al. (39). The self-assessment of abuse often underestimates the amount of consumption. Smokers accounted for a total of 66.7% of patients in our study and 83.4% of them consumed 20 to 40 cigarettes per day. Patients with oral cancer were smokers in 73.9% of cases and 24.2% were certainly addicted to alcohol. A combination of both smoking and drinking was known for 32.4%. Data from other studies suggest the risk for second cancer for patients who smoke is very high (41, 44, 45).

De Vries and Gluckman (28) investigated 59 patients with multiple primaries of the upper aerodigestive tract and concluded that genetic factors play an inferior role for this entity. Our retrospective study could not completely address this issue. Patients with one cancer had a familial history of cancer in 9.9% of cases and 34.5% had no such history (no data: 55.6%). In patients with a second primary, 24.7% had parents or siblings also affected by cancer and 66.2% had none. The difference between both groups was insignificant ($p>0.05$). Larson et al. (46) found 7.2% of second primary cancers also had affected family members.

**Incidence of second primaries.** There are several factors related to the increased diagnosis of second primaries: improvement of diagnostics, successful life-saving therapy for the primary, and an increased medical interest in this subject (28, 47). The incidence differs for second primaries following a primary of the upper aerodigestive tract and/or maxillofacial region. Analysing prospective and retrospective studies, the incidence is between 1.8% (3) and 37% (48). In retrospective studies the incidence is 1.8% (3) and 27% (35). The incidence in our study is 11.9% (all patients), and 7.5% for patients with an index tumor of the OMF region. The remaining 4.4% are tumors of the upper aerodigestive tract following an index tumor outside this region. In prospective studies the incidence varies over about the same range: 2.0% (49) and 37% (48). The differences between the results obtained in retrospective and prospective studies appear to be small. One main reason

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**Figure 2.** Survival following the diagnosis of the second cancer.

**Figure 3.** Survival of patients with and without second cancer (Npl, neoplasm).
for the differences as a whole is probably the definition of the patient groups, in particular, the exclusion of second primaries outside the OMF area from evaluation. Most of the studies, including this one, come from one institution. Therefore, further treatment in other hospitals during the follow-up cannot be entirely excluded (50). This factor could result in an even higher number of second primaries. Regional differences for this entity cannot be determined in a single institution study but are addressed in the review of de Vries and Gluckman (28). Another aspect could be responsible for an underestimation of second primaries: in our study only 4 patients had second primaries on necropsy (5.2% of 77 second primaries). However, Donath et al. (51) analysed the records of 129 necropsies of patients with an index tumor of the oral cavity. They found second primaries in 15%. Therefore, it is likely that the number of second primaries would be higher if all 303 patients, who died during the observation period, had been necropsied.

**Prognostic value of index tumor localisation.** Tumors of the oral cavity and oropharynx were 73.8% of all tumors. These regions accounted for 48.1% of all second primaries. The localization of the index tumor inside the oral cavity and oropharynx was between 12.9% and 55.6% (49, 52). In studies that analysed the oral cavity and oropharynx separately, the percentage of the index tumor was 14.3% to 40% (oral cavity) and 9.8% to 40.7% (oropharynx) (31, 47, 53 - 56). These results are in the same range as our data. The frequency of index tumors of the larynx is surprisingly high in this region. Hordijk and de Jong (49) found 70.6% of the index tumors in the larynx when analysing patients with multiple primaries. The range of laryngeal index carcinomas was between 10.4% and 70.6% (49, 57). The low frequency in our study is caused by the fact the patients with this index tumor were regularly followed up in ENT institutions. The index tumors occurred in the hypopharynx in 2% to 26.1% (53, 57).

The highest incidence is found in cancers of the oral cavity, oropharynx and larynx (31, 47, 49, 52-60). The incidence of second primaries following an index tumor of the oral cavity varies between 9.6% and 30% (32, 33, 35, 47, 49, 54, 55, 61, 62). In our study the incidence was 7.7% (oral cavity and oropharynx) and lower than those previously reported. The highest frequency of second primaries was found for carcinomas of the skin and lips (8.5%). In the current literature, this rate lies between 15.2% and 15.8% (33, 47). Studies focusing on the oropharynx revealed a second primary frequency of 5.5% to 23% (55, 61). Modern screening methods, e.g. positron emission tomography and photodynamic techniques (28), may support screening for multiple primary cancers of the OMF (63, 64).

**Index tumor stage grouping (UICC, 1992).** The stage grouping of the index tumor is dependent on the localization at the time of the diagnosis (65) and has some impact on the prognosis (26, 46) and the incidence of second primaries (32, 46, 66). Vikram et al. (66) reported an increase of second primary incidence in patients with an index tumor stage grouped III or IV. The results of Larson et al. (46) shared the opposite. Their second primary cancer patients were stage I or II in 60.3%. Their findings were confirmed by Day et al. (32). One reason could be the better prognosis for index tumor patients with early stages. Curative treatment increases the probability of survival and the risk for developing multiple primaries (28, 46). Day et al. (32) try to explain their results with the hypothesis that patients with early stages were more engaged in the fight against their disease. This fact was substantiated by the early detection. Mc Donald et al. (67) investigated index tumors of the larynx and substantiated the afore-mentioned...
findings. Two large studies could not provide any evidence of the influence of the index tumor staging on the incidence of second primaries (50, 57). In our study, advanced stage cancer predominated in index cancer patients (57, 65, 68). The localization of the index tumor and the staging were dependent. Carcinoma of the skin and lip were mainly stage I or II, whereas oral cavity tumors were predominantly stage III or IV. The differences were highly significant ($p<0.001$). In patients with OMF second primaries, 18.4% were in stage grouping I, 24.5% in stage II and 20.4% each in stage grouping III or IV. Index primary tumors at stage IV were significantly underrepresented in this group ($p<0.001$). These results support the conclusion of Larson et al. (46) and Day et al. (32) that the incidence of second primaries decreases depending on the progression of the index tumor.

The impact of index tumor grading on the incidence of second cancer. The impact of index tumor differentiation on the development of second primaries was investigated in one study. Larson et al.’s (46) analysis supported their conclusion that patients with well- and moderately-differentiated index tumors had a higher risk of establishing a second primary than those with poorly or undifferentiated index tumors. They explained their result in that patients with a better tumor differentiation probably have a better prognosis. Therefore, their longer life-span increases the risk for second primaries (37). This explanation can be interpreted as an indirect effect of grading of the index tumor on second primary incidence.

In our whole study group the grading of carcinomas was unequally distributed (well-differentiated: 24.7%, moderately-differentiated: 54.5%, poorly-differentiated 8.6%, undifferentiated 0.6%). However, the Chi-square test did not reveal a significant deviation of the expected frequency of second cancer correlated to grading ($p>0.05$). Therefore, we cannot substantiate Larson et al.’s (46) results on the predictive value of index tumor grading on second cancer incidence.

Interval between index tumor and second primary. The difference between synchronous and simultaneous primaries is important when endoscopic techniques are used. Synchronous second tumors are suspected as being present at the time of the index tumor, but were not revealed (28). According to the current literature, the mean interval between both entities in one subject lasts 18 to 68 months (3, 31, 32, 36, 46, 49, 52, 55, 68). The mean value of the present study is 56 months. However, a large proportion of our second primaries were detected within the first year. Second primaries, reported in the literature, occurred in the first year between 20% and 100% (3, 28, 31, 32, 36, 46, 49, 52, 55, 68). We diagnosed 28.3% of all second primaries within the first year and 44.6% within 2 years. However, 35.1% of second primaries occurred 5 years or later. In contrast to other studies, we included index tumors outside the oral and maxillofacial region (36.4% of all second primaries). Applying the concept of field cancerization to our study, the interval between both tumors should last longer due to the implication that the exposure to carcinogens had to act on two independent organ systems in our study (69). However, the interval in both groups was not statistically significantly different (54 and 57 months, $p>0.05$).

Metachronous second primaries were more frequent than synchronous tumors in retrospective studies (32, 34, 46, 49, 50, 52, 55, 57, 62). In such studies, metachronous second primaries occurred in 4.2% (52) to 17.8% (46) and synchronous tumors in 1.1% (17) to 8.2% (46). The relationship of metachronous to synchronous tumors was 9.2% to 2.2% in our study, which was in the same range as results from prospective studies (56, 57, 70). As a consequence the 5YSR should be compared in patients with simultaneous/synchronous and metachronous tumors. This comparison should provide evidence for the hypothetical value of extensive screening for multiple primaries in OMF tumors. However, we identified only two studies that revealed a better prognosis for patients who were identified as multiple primary cancer patients at an early point (71, 72). We could not reveal a better prognosis for patients with metachronous cancer. Panosetti et al. revealed a 5YSR of synchronous vs. metachronous cancer relationship of 18% vs. 55% (57) and in a further study 18% vs. 41% (58). One reason for poorer prognosis could be the compromises of therapy when treating two different entities at the same time (34). Metachronous tumors were more frequent than synchronous tumors in this study and not dependent on the localization of the index tumor.

Topography of index tumors and second primaries. Several studies were aimed at revealing topographic relationships of index and second carcinomas (1, 28, 33-35, 47, 49, 54, 57, 61, 73). Primaries of the oral cavity are frequently succeeded by multicentric cancers. The rate is up to 40% (33). In our study, we found 62.1% multicentric second primaries following an index tumor of the oral cavity and oropharynx. The lungs accounted for 13.5% and the esophagus for 8.1%. These results are in accordance with the literature (47, 49, 54, 55, 61).

Therapy. There are several factors that influence therapy. Among these factors are the staging of the primaries, general health status and the individual agreement of the patient to the offered treatment options. Thus we are not able to establish a special treatment for different sites. However, we found some trends in treatment. Both index and second
primary tumor were surgically treated in most cases. The index tumor underwent ablative surgery in 82%. A combination with radiotherapy was frequently applied. However, 36.1% of all index cases were purely surgically treated. In second cancers the ratios were identical. Steinhart and Kleinasser (74) and others (25, 35, 46, 75) described the positive effects of radiotherapy as an adjunct to surgery. Postoperative radiotherapy in index cancer patients was applied in 15.7% and for second primaries in 2.6% only. The number of patients treated with radiotherapy only differed, not significantly, in primary and second cancer patients (12.3% vs. 7.8%). The value of chemotherapy for therapy of OMF cancer is presently not well established (76). Catimel (76), in a review on guidelines for the chemotherapy of carcinomas of the OMF region, points out that the quality of life following palliative chemotherapy has to be balanced with the final life-span. In our study, only 1.2% of all patients received chemotherapeutics for index cancer treatment. However, chemotherapeutics were used for second primary treatment in 2.6%. In addition to radiotherapy and surgery, the chemotherapy was applied prior to surgery in 6.3% of index cancer patients. Interestingly, chemotheraphy was included in the multimodal treatment regime of second cancer patients in 42.9%. The reasons for these variations are probably the impaired accessibility of second primaries in a previously surgically treated area, multicentricity of the tumors, loss of compliance of surgically treated patients who have to face a second cancer, and restricted re-irradiation in an already irradiated field (28).

**Prognosis.** Crude survival times were calculated. In our study the mean survival times of patients with only one cancer were 127 months and the 5YSR was 56%. In second cancer patients, the mean survival time was 48 months and the 5YSR was 29% (calculation started after the diagnosis of the second cancer).

Following the diagnosis of the index tumor, the survival was 110 months and the 5YSR was 71%. The differences between both groups concerning the times following the diagnosis after second cancer are statistically highly significant (p<0.001) and are in the reported ranges. However, when both groups are compared and the survival after index tumor diagnosis is taken as the parameter, there are no statistically significant differences concerning the survival times (p>0.05).

Most studies do not declare the time point of calculating survival times, especially whether the index or the second cancer diagnosis was the parameter. Although this lack of information impairs the comparability of several studies, agreement exists that second cancer patients have a poor prognosis (1, 28, 32, 46, 48, 54). Day et al. (32) found 75% of second cancer patients died after diagnosis of multiple primaries, while Odette et al. (77) found 50% and Larson et al. (46) 35% during that period. In this study, 41% of second cancer patients died within one year, 43.4% within 2 years and a further 29% after 5 years. Our data support the well-known high mortality within two years following second cancer diagnosis.

**Impact of gender and family history of cancer on the prognosis.** Prognosis appears to be better for women compared to men, both after one and two cancers. The 5YSR of women was 63.6% and of men 56.5% following one cancer. After diagnosis of second cancer, the 5YSR values were 32.5% for women and 27.5% for men. These values indicate a trend towards a better prognosis for women. However, the differences were not statistically significant (p>0.05). Day et al. (32) reported similar results: females had a 5YSR of 50% and males of 39%. However, a statistical analysis of the differences was not provided. We were not able to define any impact of a family history for cancer on the incidence of second primaries. However, data from other studies suggest this impact (78, 79).

**Impact of the co-morbidity on the prognosis.** We found no study on the impact of co-morbidity on the prognosis of second cancer patients confined to entities of the upper aerodigestive tract. Our retrospective data analysis will probably underestimate this issue. Secondly, the diagnosis itself does not provide sufficient knowledge on its severity and impact on morbidity and mortality. The co-morbidity will probably have an enormous impact on therapy decisions. Therefore, it is surprising that such studies have not been published. Patients without other disease than the malignant disease(s) survived for a mean of 128 months. Their 5YSR was 61%. The 60 patients with known diabetes mellitus survived for 82 months, the 5YSR being 38%. This difference is statistically significant (p<0.01). Patients with lung diseases also had significantly reduced survival times. Their 5YSR was 52%, with mean survival being 96 months (p<0.01).

**Impact of the time interval between both tumors in second cancer patients on the prognosis.** Most studies declare that patients with synchronous second primaries have a poorer prognosis than those with metachronous disease (5, 31, 32, 34, 57). Panosetti et al. (57) found 5YSR of 18% and 55% for synchronous and metachronous second primaries. As a rule, the more time that elapses between both cancers the better the prognosis appears to be. Day et al. (32) demonstrated this relationship. The 5YSR of patients with an interval of more than 5 years was 70% compared to patients with a disease-free interval of less than 2 years. These differences were explained by the immune suppression during cancer therapy. Gluckman et al. (59) found contradictory results. In their study, the 5YSR of patients with synchronous second primaries was superior to
those with metachronous cancer. Depending on the localization of the second primary, the 5YSR varied between 20.6% and 10.5% and up to 50% vs. 26.8%. Our results are similar to those of Gluckman et al. (59). The 5YSR of our synchronous second cancer patients was 55% and those with metachronous disease only 28%. These differences are statistically significant (p<0.001).

**Impact of tumor localization on the prognosis.** The localization of the index tumor is an important factor for the prognosis. Patients with oral cavity and oropharynx carcinoma have a 5YSR of 27% to 54% (1, 54, 59). In cases with multiple primaries, the 5YSR falls to 18.2% (54). In our subgroup of patients with index tumors of the oral cavity and oropharynx, the 5YSR was 54%. This result is in accordance with the findings of Lamprecht et al. ((55), 5YSR: 58.3%). In cases with multiple primaries, the proportion falls to 35%. The prognosis is best for index tumors of the lips and skin; these patients survived their tumor in 64.6% (54, 59) and in 74% (this study).

Decisive in the prognosis is the staging. Index tumors of the lip and skin were prognostically better than mucosal carcinomas due to the fact that they were diagnosed at a lower stage. Analysing the impact of localization of second cancer on prognosis, a significant difference was found only between second cancers of the lips and second cancers outside the OMF region. The 5YSR of second primaries affecting the lips was 60% and for those with second cancers outside the OMF-region, the 5YSR was 54%. This result is in accordance with the findings of Lamprecht et al. ((55), 5YSR: 58.3%). In cases with multiple primaries, the proportion falls to 35%. The impact of tumor localization on the prognosis was analysed by Larson et al. (46) who described a proportional decrease of the 5YSR of second cancer patients depending on the decline in tumor differentiation (G I : 40%; G II : 30%; G III: 20%). These results are similar to ours. Statistically significant differences of staging on the prognosis were found for both index and second tumors. Patients with index tumors of stage I had a 5YSR of 82%, of stage II: 64%, III: 50% and IV: 36.9% (p<0.001). The results were similar for second cancer patients. The 5YSR was 22% in stage IV. Larson et al. (46) described the 5YSR of this stage to be 15% while it was 52% in stage I. Surprisingly, our patients in stage II had a better prognosis than those in stage I (68% vs. 36.4%). However, the sample size was small and the differences were not statistically significant (p>0.05). Early detection of these patients seems to be the most important factor for increasing survival rates.

**Impact of therapy on the prognosis.** Jones et al. (1) could find no influence of the type of treatment on the prognosis. The latency period after exposure to a radiation source is approximately 20 years (25, 42, 61, 64). Jones et al. (1) followed their patients up to 15 years and could find no correlation between radiotherapy and an increased incidence of second cancer.

**Conclusion**

Second cancer in patients with primaries of the oral and maxillofacial region is an increasing challenge for surgical treatment. This study describes some epidemiological data concerning diagnosis, treatment and prognosis for these patients. Some risk factors are identified. At present tumor markers are not defined for patients with primaries of the oral and maxillofacial region who are at risk for second malignancies. Molecular genetic studies are required to more precisely differentiate second primaries and distant metastases in oral and maxillofacial cancer patients. About one-third of patients with second primaries in the maxillofacial region had a history of cancer affecting other regions of the body. Maxillofacial surgeons should be involved in the follow-up control of cancer patients who developed primaries in other body sites.

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