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Combined therapy for oral cavity and oropharyngeal squamous cell carcinoma: Depth of invasion as prognostic factor

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Background. *The aim of the study was to emphasize the importance of surgical management of squamous cell carcinoma (SCC) in the head and neck and to find the most important predictive factor for cervical lymph node metastasis and prognostic factor for survival. The use of multimodality therapy is being discussed as well.*

Patients and methods. *From June 1st, 1992 to May 31st, 1998, 154 patients with oral cavity and oropharyngeal SCC were admitted to the Department of Otorhinolaryngology and Cervicofacial Surgery in the Teaching Hospital of Maribor. The criteria for inclusion into the study were met by 142 patients, but only 62/142 patients entered the multimodality protocol (surgery and postoperative radiotherapy). These 62/142 patients were treated surgically and 49 of them were postoperatively irradiated, while 13/62 declined postoperative radiotherapy. Surgical specimen was evaluated for positive or negative lymph nodes, tumor margins and the depth of invasion. Tumor cells were stained for Ki67 proliferative factor.*

Results. *The depth of invasion was the most important predictive factor for the neck metastases in multivariate model including also the grade, pT and T. pN was found to be important in determining the overall survival using Cox regression model ($p < 0,05$). A statistically important discrepancy between N and pN classification was found. In 23 cases N was overrated and in 3 cases underrated. The overall 5-year disease specific survival was 55 %. Ki67 correlated with the grade of tumor differentiation. No statistically significant correlation was found with lymph node metastases.*

Conclusions. *The depth of invasion is the most important factor determining the occurrence of the neck metastases whereas the N status determines the survival.*

Key words: mouth neoplasms – therapy; oropharyngeal neoplasms – therapy; combined modality therapy; carcinoma, squamous cell; neoplasm invasiveness; survival analysis

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Introduction

The modality of treatment of oropharyngeal and oral cavity squamous cell carcinoma (SCC) is still a matter of debate. Almost all authors use the multimodality therapy approach, and only a few are willing to take a chance with the single modality therapy. Chemotherapy is becoming more and more used in the therapy of head and neck SCC, although its results are inconsistent and benefits not proven.

Regardless of the modality used, the survival of patients with head and neck SCC in the last 50 years has not improved as much as we would like, but the quality of life has, especially with the use of reconstructive procedures. In the management of the head and neck SCC, two questions emerge: 1. How to treat? 2. How much is enough (ultraradical multimodality therapy, close margin surgery)? The answers to these two questions should bring us closer to the final goal: the cure of the patient with less therapy and better quality of life.

We wish to present the results of multimodality approach to the treatment of patients with oral cavity and oropharyngeal SCC at the Department of Otorhinolaryngology and Cervicofacial Surgery in Maribor Teaching Hospital. We tried to identify the most important predictive factors determining regional metastasizing and locoregional prognosis as well as prognostic factor for survival.

Patients and methods

From June 1st, 1992 to May 31st, 1998, 154 patients with oral cavity or oropharyngeal SCC were admitted to our department.

The criteria for the inclusion into the analysis were: 1. histologically proven SCC in the oropharynx or oral cavity, 2. no meta- or synchronous tumors found at panendoscopy, 3. no prior oncological treatment, 4. resectable tumor.

The inclusion criteria for entering the multimodality protocol were satisfied by 142 patients. In 23 of 142 patients, the carcinoma was medically inoperable because of a significant co-morbidity or extent of the disease, whereas 57 patients declined primary radical surgical therapy.

Sixty-two (44 %) of 142 patients were treated surgically and 49/62 (80 %) under multimodality protocol: surgery and postoperative teleradiotherapy with doses ranging from 52 to 56 Gy, while 13/62 declined postoperative radiotherapy.

There were 58 (93 %) males and 4 (7 %) females. The average age of patients was 55.6 years. The youngest one was 31 and the oldest 78 years old.

All patients were preoperatively submitted to screening tests, panendoscopy and neck ultrasound, and had the tumor (re)classified according to cTNM.[1]

The radicality of tumor excision was proven with intraoperative frozen section. Tumor and neck specimens were sent to the Pathohistology Department for the final macro- and microscopical analysis. The following parameters were determined:

1. Depth of invasion measurable from virtual line connecting uninvolved tissue margins to the deepest tumor line.
2. Immunohistochemical detection of Ki-67 proliferating factor.
3. Thickness of tumor measured from the most superficial tumor line to the deepest line of invading tumor.
4. Lymph nodes identified in fibrofatty tissue obtained during neck dissection; the nodes were searched for metastatic cells and extracapsular spread by conventional histological technique and serial sections through lymph node.
5. Tumor classified according to pTNM.

Ki-67 was detected by Immunotech monoclonal antibody Ki-67 antigen (MIB-1) using

standard immunochemistry methods.[2] The average proportion of Ki-67 positive nuclei was calculated for each sample.

The data were analyzed using Statistica for Windows with Student t test, multivariate linear regression models, Kaplan Meier survival analysis and Cox regression analysis.

Results

Intra/transoral excision and comprehensive neck dissection were performed in 41/62 (66 %) patients, and commando operation in 21/62 (34 %) patients. All resections were R0.

The defect was reconstructed with myocutaneous flaps (platysma, PMMF, infrahyoid) in 10/62 cases (16 %), with forearm free fasciocutaneous flaps in 8 cases, local flaps in 13 cases, and primary suture or split thickness skin graft in 31 cases.

Of 62 patients, 51 (83 %) were with tumors classified as stage III or IV.

Bilateral and multilateral neck dissections were performed in 55 and 7 cases, respectively. In each neck specimen, more than 30 lymph nodes were isolated (average 39).

N+/pN0 conversion was observed in 15/62 (24 %) cases and overall 23/62 (37 %) necks were overrated (cN > pN).

Occult metastases were found in only 3/62 (5 %) cases. Using Student t test, we found statistical difference between N and pN for the same cohort of patients ($p = 0.019$).

Kaplan Meier survival curves for the patients treated with multimodality approach ($n = 49$) according to N stage are presented in Figure 1.

In order to identify factors influencing the rate of metastases in regional lymph nodes, we analyzed clinical and pathognomonical factors using multivariate linear regression. The depth of invasion, T stage, thickness and differentiation grade were analyzed. The only statistically important factor was the depth of invasion > 4 mm ($p = 0.0237$).

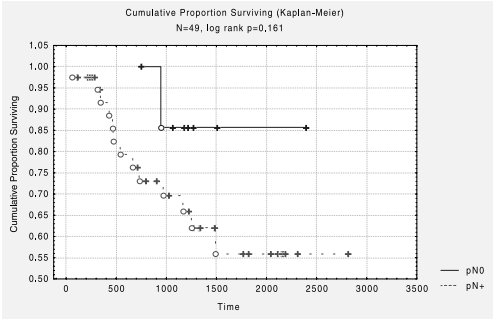

Figure 1. Kaplan Meier survival analysis according to pN stage.

The patients' survival was dependent on pN status ($p = 0.056$) in the model that included pN, pT, G and depth of invasion, using Cox regression for analysis.

A 5-year disease specific survival of the group of patients with oropharyngeal cancer was 74% and those with oral cavity 47 %. The overall disease specific survival was 55 %.

Of 62 patients, 16 died of disease, 3 were lost to follow up, 5 died from locoregional recurrence, 7 from distant metastases and 4 had regional recurrence without any evidence of primary tumor. All patients with regional recurrence (9/16) had positive neck status at the first treatment.

The incidence of locoregional recurrence in combined modality group and in single modality (surgery only) group was 16.3 % and 7.5 %, respectively. The distribution of advanced stage in both groups was statistically similar.

Ki-67 expression correlated to the grade of differentiation and had no statistically significant influence on node metastases. The results are preliminary and the independent research is being performed.

Discussion

In our analysis, we presented a "classical" treatment concept of SCC of the oral cavity or

oropharynx. The most surprising result is low incidence of occult metastases and a high rate of overrated necks. In 24 % of all cases, the clinical suspicion for metastases didn't prove correct. Regional disease is an important survival prognostic factor and Kaplan Meier survival curves are significantly different for pN0 and pN+ status.

The depth of invasion was found to be one of the most important factors determining the occurrence of regional metastases. The depth of invasion > 4mm means a 3 times higher probability of positive neck.[3,4] The depth of invasion is not included in TNM system. The invasion of tumor cells in the surrounding tissue is followed by angiogenesis and matrix lysine. Invasive and antigenic tumor potentials are connected and only together they have prognostic value. The depth of invasion is simple and evident in any gross evaluation of a tumor specimen.

The grade of differentiation does not prove to be the decisive factor in metastasis prognosis. As indicated by our preliminary results, the same holds true for Ki-67.

In our series, a large proportion of admitted patients with resectable and medically operable tumors (57/119) declined further surgical therapy. The reason for their decision is not clear from retrospective analysis. According to the results of some other authors, surgery as single modality treatment for advanced oral cavity or oropharyngeal cancer is definitely more successful than primary radiotherapy.[5,6] Most authors advocate postoperative irradiation in the cases of positive margins, perineural and perivascular spread in the case of extracapsular spread or in the case of multiple positive nodes.[7]

Conclusions

We believe that the depth of invasion should be included in every pathologist report of oropharyngeal and oral cavity SCC because it may influence the decision for further treatment and postoperative irradiation. The depth of invasion is as important for the prognosis as TNM classification. In our study, Ki-67 proliferative factor didn't correlate with metastatic potential of the SCC of the oral cavity and oropharynx.

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