Abstract. Oral squamous cell carcinoma (OSCC) is among the most frequent malignancies worldwide. Ablative surgery for OSCC is the therapy of choice, however, severe disfigurement and loss of function is a consequence of therapy. On the other hand, R0-resection margins following ablative surgery do not guarantee disease-free survival, in particular due to the widespread, interconnecting lymphatic vessels. Therefore, irradiation of the primary and efferent lymphatics is a valuable therapeutic alternative to surgery. The combination of both irradiation and surgery might even improve overall survival. It has been argued that curatively planned irradiation (isodose of the primary: 60-70 Gy) might not routinely be followed by ablative surgery. Indeed, the sequelae of surgery in an irradiated field are well known. The aim of this study was to determine vital tumor cells in the resection specimens of irradiated advanced stage OSCC in order to estimate the effect of radiotherapy. Materials and Methods: One hundred patients (male 78, female: 22, mean age 60.2 years) with primary OSCC (T2: n = 41, T3: n = 26; T4: n = 33) and suspected regional lymph node metastases were externally irradiated up to a total dosage of 70 Gy (single dose 1.4 Gy, twice daily, minimum daily interval 6 hours; 5 days a week). Ablative surgery followed radiotherapy about 3 months later. Results: In 51% of the primaries, specimens showed vital tumor cells after completion of radiotherapy. The evidence of vital tumor cells increased with T-stage and with N-stage, but showed no correlation to grading. Conclusion: Irradiation of the head and neck region following a hyperfractionation scheme in the treatment of advanced stage OSCC offers a 50% chance of deletion of malignant cells. Despite high total dosages and sophisticated irradiation protocols, the number of patients with vital tumor cells is high. Short-term follow-up controls are mandatory in patients who were subjected to a primary radiotherapy. Ablative surgery following irradiation is a salvage option for pre-irradiated OSCC patients.

Oral squamous cell carcinoma (OSCC) is among the most frequent malignancies worldwide. Both radical surgery and irradiation of the primary and efferent lymphatics are valuable therapeutic tools to fight OSCC (1, 10). Improvement of reconstructive head and neck surgery and refinements of irradiation protocols have been established over recent decades (1, 3, 6). However, the overall survival rate of patients with OSCC has not substantially increased over the last thirty years. Efforts to increase the local radiation effect in radiotherapy led to the concept of hyperfractionation (11, 16). This hyperfractionation should result in an improved local control (12). The combination of both irradiation and surgery might even improve loco-regional tumor control and, thus, overall survival (9, 10, 12, 14-17, 19). The effectiveness of this radiation scheme can be studied by the histological investigation of resection specimens following radiotherapy. The aim of this study was to determine vital tumor cells in the resection specimens of irradiated OSCC.

Materials and Methods

One hundred patients with primary OSCC were retrospectively evaluated. Patients with primaries of the lips were excluded, as were patients with T1-tumors. The latter were only surgically treated. All patients with T2-4 OSCC (UICC, 1987) were treated with external beam irradiation following a hyperfractionation scheme with a single dose of 1.4 Gy, twice daily, with at least 6 hours pause between exposures to the radiation source. The total dosage at that time was 70 Gy for the primary and 50 Gy for efferent lymphatics (16). The oral tumor was tattooed with ink prior to radiotherapy in order to provide landmarks for tumor extension after completion of the irradiation. Tumor stage grouping was performed according to the TNM classification system and the documentation requirements of the DOESAK (15). The investigation included the metric description of the oral lesion.
palpation of the neck for regional lymph nodes, ultrasound investigation of the neck, plain and computed radiographs for depicting local extension and regional spread. In cases where bone involvement was likely due to localization of the primary, scintigraphy was carried out. The localization of the primaries was described according to Fries (6). Tumors with overgrowth to different anatomical units of the oral cavity were assigned to the region of maximum tumor involvement. Tumors of the floor of the mouth (inferior level) and of the soft and hard palate (superior level) formed the largest sub-groups.

Resection of the irradiated tumor was carried out about 3 months after completion of the radiotherapy. Histological investigations of the resection specimens were carried out on Haematoxylin-Eosin-stained slices (Department of Oral Pathology, UKE). Grading was performed according to Broders (2).

Results

One hundred patients with primary OSCC were enrolled in the evaluation (female: 22, male: 78; ratio=1:4). The mean age of the patients was 60.2 years (male: 58 years; female: 67.8 years; minimum: 45 years, maximum: 95 years) and was not related to the tumor stage. Patients with T2-tumors constituted the largest sub-group (n=41), followed by T4 (n=33) and T1-tumors (n=26). Concerning the nodal stage, the pre-therapeutic investigations assigned homolateral lymph node spread (N1) in 49 patients, a N2-category in 36 the pre-therapeutic investigations assigned homolateral lymph node spread (N1) in 49 patients, a N2-category in 36, a N3-category in 23 patients. For T1-OSCC, no tumor cells were visible in 20 (83.3%). Again, this ratio decreased with increased N-stage. Six of 10 patients with T3N0-OSCC had microscopically complete tumor regression (69%). In T4-OSCC patients, only 26.9% had no vital tumor cells (n=7/26), restricted to N0 (n=1) or N1 (n=6) stage. In T4-OSCC, only 2 patients were microscopically tumor-free [6.1% of the sub-group, T4N0 (33.3%) and T4N1 (9.1%) each].

Discussion

This study reveals that a high percentage of previously untreated patients with primary OSCC, who were subjected to external radiotherapy following a hyperfractionated irradiation scheme, are at risk of maintaining vital tumor cells in the primary or lymphatics, or both (complete regression of the primary: 51%, lymph nodes: 63%, total: 42%). Despite enormous efforts to increase the radiation effect on cancer cells by means of radiotherapy, including the introduction of hyperfractionated irradiation to head and cancer, resistant cancer cells still remain in many patients after completion of therapy. The risk for maintaining OSCC despite radiotherapy follows the calculated tumor volume and spread, as depicted in the TNM-staging system. This study shows an increase of patients with vital tumor cells with higher T-stage and cancer, resistant cancer cells still remain in many patients after completion of therapy. The risk for maintaining OSCC despite radiotherapy follows the calculated tumor volume and spread, as depicted in the TNM-staging system. This study shows an increase of patients with vital tumor cells with higher T-stage and involvement of regional lymph nodes (4, 5, 8, 9). The poor response of advanced stage OSCC to a combined chemo-radiotherapy was also noted by Valente et al. (18). In their study, 54% of patients showed no neoplastic cells after complete work-up of the resection specimens. This study was based on the light microscopic evaluation of resection specimens by an experienced investigator. Neither immunohistochemical investigations, e.g. identification of proteins indicative of induction of apoptosis mechanism, nor molecular biological techniques, e.g. in situ hybridisation for mutations of tumor-suppressor genes, were used. Therefore, it can not be excluded that the number of patients who would have developed tumor recurrence might even be higher than the ratios that were derived from the light microscopic findings alone.

In fact, despite the increase of total dosage, applicable with the hyperfractionation of external radiation sources in the head and neck region, this measure obviously did not improve the tumor regression, as compared to conventional radiotherapeutic strategies (14, 17, 19). If radiotherapy is applied in advanced stage OSCC, caution has to be
exercised to expect curative therapy. In such patients, after completion of the radiotherapy, ablative surgery is the last option for patients who develop local recurrence. Tumor markers are needed to identify those patients who might benefit from radiotherapy. For example, the application of immunohistochemical identification of the p53 antigen in OSCC prior to radiotherapy was proposed as such a prognostic marker (7). However, this result could not be substantiated by a second study (13).

Expertise is warranted for ablative and reconstructive surgery of those patients who have been subjected to a curatively intended radiotherapy and who develop a local recurrence.

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