Significance of Self-reported Symptoms as Part of Follow-up Routines in Patients Treated for Oral Squamous Cell Carcinoma

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Abstract. *Background: There is little evidence to prove that frequent out-patient consultations lead to better prognosis in patients treated for oral squamous cell carcinoma. Furthermore, there is no consensus regarding the timing and number of follow-up consultations or the duration of monitoring after completed therapy. Materials and Methods: We prospectively recorded demographic and clinical data of 537 patients treated over a period of 15 years with complete follow-up of 18 years in a tertiary academic Center. Results: Out of 537 patients considered free of disease after treatment, 196 (36%) developed recurrent disease during follow-up. Self-reported symptoms led to diagnosis of the recurrence in 78% of the cases. Only 22% of recurrences were detected through physical examination of asymptomatic patients. There was no difference in disease-free survival in-between these two groups. Conclusion: Follow-up routines are indispensable as part of cancer treatment but can be more cost-efficient when patients are educated and encouraged to report subjective symptoms. Trained personnel in collaboration with head and neck specialists can handle parts of follow-up routines.*

The principle rationale in follow-up of head and neck cancer patients is to detect possible tumor recurrences and secondary malignant tumors (SMT) at a stage when additional treatment is still an option (1). Several international and national boards of head and neck oncologists and surgeons advocate a follow-up regimen that lasts for a minimum of 5 years with periodic appointments at fixed intervals (2-4). The reasoning behind this principal rule of post-treatment surveillance is that regular and frequent consultations should allow physicians to detect and cure recurrences at an early stage, thereby improving prognosis (2-5). There is, however, no consensus as to the timing and frequency of consultations and no established standard with respect to examination routines. More disturbingly, there a lack of evidence to show that regular follow-up in fact results in improved post-recurrence survival (6).

In previous analyses of post-treatment outcomes, we found that the majority of recurrences occurred within the first three years after completed therapy (7). Routine follow-up beyond three years was shown to be cost-ineffective with respect to patient survival, as late recurrences were rare and had a poor salvage rate (7-9). Moreover, at retrospective analysis, we found that patients' self-reported symptoms had led to the discovery of a recurrence in two-thirds of cases while only one third were detected through clinical examinations at routine consultations. With respect to prognosis it made no difference whether recurrences were detected by the patient or the physician (8). Other authors have reported similar results (6, 10-14).

More than 25 years after our first report, this is a critical follow-through of our previous observations (7). We used prospectively recorded, demographic and clinical data from patients with squamous cell carcinoma of the oral cavity (OSCC) collected over a period of 15 years and with follow-up data up to 18 years. The investigation included data on incidence and time of appearance, site of recurrence, post-salvage disease-free survival and the frequency of SMTs. The focus of the present study was to explore whether the detection of recurrences were based on patients' self-reported symptoms or diagnosed at scheduled consultations with asymptomatic patients. The ultimate aim of our analysis was to search for guidance when trying to economize post-treatment surveillance after treatment of oral cancer.

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Materials and Methods

Over a period of 15 years (1983 through 1997), demographic and relevant clinical information was collected in a prospective manner for previously untreated patients admitted to our Department. All consultations and treatment decisions were in close collaboration with Radiumhospitalet, the centre that provided radiotherapy and chemotherapy when applicable. Jointly we are an academic tertiary referral centre that recruit patients mainly from the South-eastern part of Norway, covering a population of approximately 1,500,000 people.

One of the authors (M.B.) holds an authorization from the Norwegian Data Inspectorate to collect and evaluate data from patients admitted to our department. The local Ethical Committee and the Ministry of Health approved the study. Data on long-time follow-up (up to 18 years; the latest recorded follow-up date was October 15th, 2010) was collected by review of records on patients treated at our clinic supplemented by outpatient charts, autopsy protocols, direct contact with the local hospitals, family physicians, patients themselves or next of kin. Classification of disease was initially performed according to the 3rd edition (1982) of the International Union against Cancer (UICC) and later transformed and updated according to the 4th edition (1997). Some of the data was included in previous reports (8).

Patients. The database in the current investigation comprises 742 patients with primary squamous cell carcinoma of the oral cavity (lips and salivary glands not included). Of these, 205 patients (28%) were excluded; with the largest group representing 106 patients with residual disease after completed therapy and 50 patients judged unfit to undergo any treatment. Another 42 patients had a history of previous malignant disease for which treatment options were exhausted. Five patients with distant metastases (M+) on admittance were also excluded (Table I). These strict demands concerning exclusion criteria concur with Haas *et al*. (15). Patients with residual disease or who were unfit for treatment received palliative treatment. All of these patients died within 2-3 years either from the index tumour or from comorbidity.

Follow-up. Patients were given specific information regarding symptoms and signs that could signify a locoregional recurrence or a new malignant tumour. They were encouraged to take immediate contact with our outpatient clinic if such symptoms should occur between scheduled appointments. In the database, we labelled patients according to whether the recurrence was detected from patients' symptoms at the scheduled appointments or appointments on request. Alternatively, the physician at clinical examinations of an asymptomatic patient discovered the recurrence.

Our institutional follow-up regimen involved 4-6 consultations the first year and 2-3 appointments the second and third year following completed treatment. At the first follow-up consultation, all patients underwent contrast-enhanced computerized tomography (CT) scan of the primary site and the neck. In selected cases, we used ultrasound (US) and fine needle aspiration cytology (FNAC) for additional evaluation of the neck.

After 3 years, unless prevented by treatment morbidity, patients "free of disease" continued consultations at other institutions or with family doctors. Patients treated for a recurrence, a second malignant tumour (SMT) or any other serious morbidity were followed at our outpatient clinic for as long as considered necessary. SMTs were defined according to the criteria established by Warren and Gates (16).

Table I. *Patient selection*.

Categories	Number (%) of patients
All patients	742
M+ at diagnosis	5
Incomplete files	1
Lost to follow-up	1
Previous malignancy	42
Unfit for treatment	50
Recidual tumour	106
All patients excluded	205 (28)
Eligible patients	537 (72)

Treatment. Treatment was determined from clinical staging. Between 1983 and 1991, standard treatment for oral cancer was radiotherapy (RT) of both the primary site and the neck, followed by supplemental surgery in cases where the locoregional tumour manifestations were considered operable. In 1991, we changed our treatment policy in favour of primary surgery when possible, followed by post-operative radiotherapy in cases with histologically unclear margins. Patients with primary tumours judged inoperable received external radiotherapy alone in fractions of 2 Gy/day, 5 days a week. Selected cases (43 patients) with advanced disease received neoadjuvant chemotherapy with cisplatin and fluorouracil (5-FU) either prior to radiotherapy or prior to radiotherapy followed by surgery. Ninety-six patients were treated with brachytherapy in doses 20-50 Gy. Regardless of the radiation scheme, all patients received a total dose of 60-70 Gy to the primary site, while levels I-IV received 50-60 Gy. The time between surgery and radiotherapy rarely exceeded 6 weeks. The treatment program is in accordance with the Danish consensus program (17). Treatment of recurrences included whatever treatment option was available: surgery, radiotherapy and/or chemotherapy.

Histopathology. In patients treated with primary surgery, all specimens, including preoperative frozen sections, were thoroughly reviewed by a senior pathologist. Infiltration beyond 3 mm was set as cut-off to determine whether to apply subsequent radiotherapy. Patients with regional spread received radiotherapy of the ipsilateral neck independently of whether a neck dissection was performed or not. When the primary tumour was located medially or affected the midline, both sides of the neck were irradiated. Only a few selected cases underwent bilateral neck dissection. When the tumour was located in bone or close to bone, a bone-resection was performed and combined with reconstruction.

Statistical analysis. The data were stored and analyzed by means of the SAS software v.9.3 (SAS Institute, Cary, NC, USA). Categorical data were analyzed using the Chi-square test, survival data was investigated according to Kaplan-Meyer using the Log-rank test. All survival analyses were cancer-specific. Patients dead from other causes and patients free of disease were set as censored values. *p*-Values <0.05 were considered statistically significant.

Results

Table II lists clinical and treatment details of the 537 patients who entered surveillance, all considered "free of disease" following initial treatment; 60% were stage I+II and 40% stage

Table II. *Demographic and clinical data of patients considered "free of disease".*

Parameters	Stage I+II	Stage III+IV	Sum (range/%)	Statistics
All patients	323	214	537	
Gender				
Male	198	139	337	
Female	125	75	200	*p*=0.39
Age mean (range in years)	61	64	63 (21-86)	
Follow-up mean (range in years)			3.8 (3-20)	
Subsite (ICD10)				
Tongue (C02)	134	66	200 (37)	
Floor of mouth (C04)	79	46	125	
Gingiva (C03)	52	78	130	
Bucca+palate (C05,06)	58	24	82	*p*<0.01
Treatment*				
Surgery	88	9	97	
Surgery+Radiation	132	79	211	
Radiation+Surgery	72	70	142	
Radiation	31	56	87	*p*<0.01

*43 patients with advanced disease received neoadjuvant chemotherapy, cisplatin and 5-FU.

III+IV tumours. The overall mean age was 63 years (range=21-86 years) with a male predominance (63%) and a mean follow-up of 3.8 years (range=3-20 years). Tongue tumors, being the largest subsite, represented 37% of the material. Stage of disease was equally distributed between subsites.

Recurrence was diagnosed in 196 (36%) patients. For the remaining 344 patients (64%) there was no history of relapse at the last follow-up contact and these patients were thus considered permanently cured for the index tumour. Self-reported symptoms led to the diagnosis of the recurrence in 153 patients (78%), while only 43 patients (22%) were detected at scheduled clinical examinations of asymptomatic patients (Figure 1). The rate of symptom-related recurrences was highest the first year after treatment, particularly recurrences at the primary site. Collectively local recurrences amounted to 72%.

Cases with dual recurrence were assigned to the subsite with worst prognosis. Accordingly, seven cases with simultaneous local and regional recurrence were classified as regional failures. Similarly, three cases with simultaneous local and regional recurrences and a concurrent distant metastasis were denominated distant failures. SMT was diagnosed in 28 patients and of these 10 were within the head and neck, five were in the lung and one in the oesophagus. All head and neck SMTs were discovered from symptoms reported by the patients, while lung tumours chiefly were detected through annual chest image.

All 19 recurrences (10%) at distant sites occurred within 3 years and all but four regional failures within the 3rd year of follow-up. Local recurrences, on the other hand, continued to occur up to the 10th year from treatment. Figure 2 demonstrates that 78% of the recurrences appeared within the 2 first years and 12% during the 3rd year after treatment. A mere 11% of the recurrences were detected later than the third year after treatment. Neither the subsite of the primary tumour nor the gender or age of the patient had any correlation with site or rate of recurrences.

Thirty percent of the patients treated for recurrences were alive at the last follow-up contact. Regardless of the stage of the tumors, the salvage rate was highest for recurrences detected during the first year (Figure 3). After the first year, there was a decline in salvage rate by time from completed treatment. Out of the recurrences diagnosed after two years, only half (21/44) were salvaged.

Overall, there was no significant difference in post-salvage disease-free survival when comparing the group of patients in whom recurrence was detected through symptoms and those where recurrence was detected through physical examination. The salvage rate of recurrences in patients with advanced disease was, as expected, very poor. Only 2% of these patients were alive and well at the end of this study.

Discussion

The results of the present study address the issue of post-treatment consultations for patients after primary treatment of OSCC. There are considerable variations in-between different Centres regarding follow-up schedules and supplemental investigations (18, 19), but most Institutions recommend a close follow-up during the first two years (2, 11, 15). It remains largely unproven, however, that regular and frequent consultations translate into improved survival once the recurrence is detected (18).
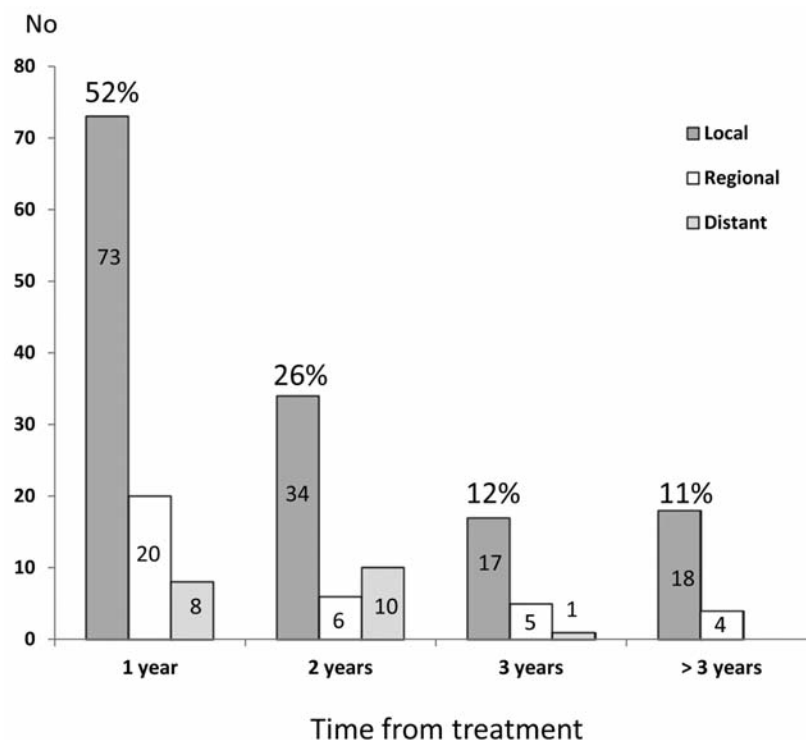
Figure 1. *The distribution of the 196 recurrences (78%) that were detected through symptoms presented by patients vs. years after treatment. One hundred and one of the recurrences (52%) were detected during the first year.*

In the current report, we present results from a single Institution with prospectively recorded clinical data with a follow-up of maximum 18 years. The study included 537 patients that were free of disease after treatment of primary oral cancer. In all, 78% of recurrences occurred during the first two years and only 11% later than three years after the end of treatment. In the majority of cases (76%), patient-reported symptoms led to detection of the recurrence rather than in scheduled examinations of asymptomatic patients. In terms of survival, there was no difference in prognosis related to whether the patient or the physician first discovered the relapse, which is in accordance with our previous findings (8).

Post-treatment monitoring is an indispensable part in the management of head and neck cancer and the efficacy has been debated since our first reports (7, 8, 10, 11, 18, 20-23). The incidence of recurrences is highest shortly after completed therapy and according to some authors these early recurrences have a better chance of being successfully treated (2, 11, 15). Patients with head and neck cancer often have lifestyle issues with an inherent tendency to ignore symptoms of disease. It has been argued that a fixed schedule with monthly consultations during the first year followed by consultations every second month during the

second year would reduce patients inclination to suppress symptoms and lead to better compliance (15). The question is whether such intensive monitoring in fact improves treatment results. The findings of this report clearly indicate that this is not the case.

One argument to advocate prolonged follow-up is the need for continuous psychosocial support to patients who have undergone therapy. Another argument is that it gives the clinician a chance to detect late recurrences and SMTs at a stage when salvage could still be an option (24-27). Data from the current investigation shows that late recurrences had disappointingly poor prognosis and that prolonged surveillance did not improve the outcome. This is in accordance with previous studies from our group and others (9, 28).

Some authors have reported that prognosis was better when the new tumor was detected at an asymptomatic stage (29). Radiographic imaging of the lungs with Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) and possibly Positron Emission Tomography (PET) allows for early detection and is by many recommended as part of regular consultations (2, 19, 21, 30). Ultrasound-guided fine needle aspiration (US-FNAC) has been shown to be superior to CT and MRI in monitoring possible regional recurrences at
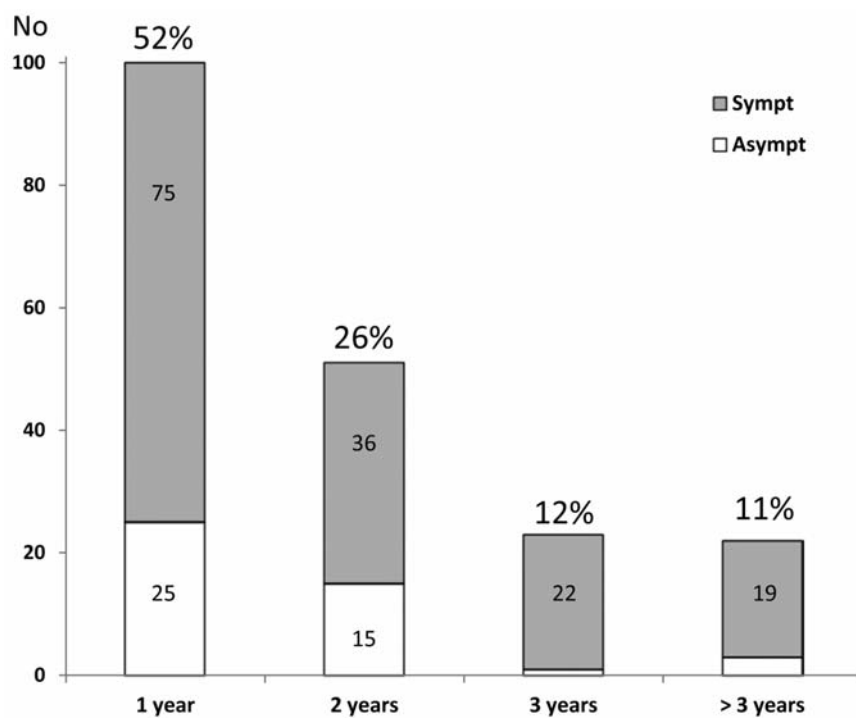
Figure 2. *Type of recurrence detection vs. year from treatment for 196 patients with recurrence of primary squamous cell carcinoma of the oral cavity.*
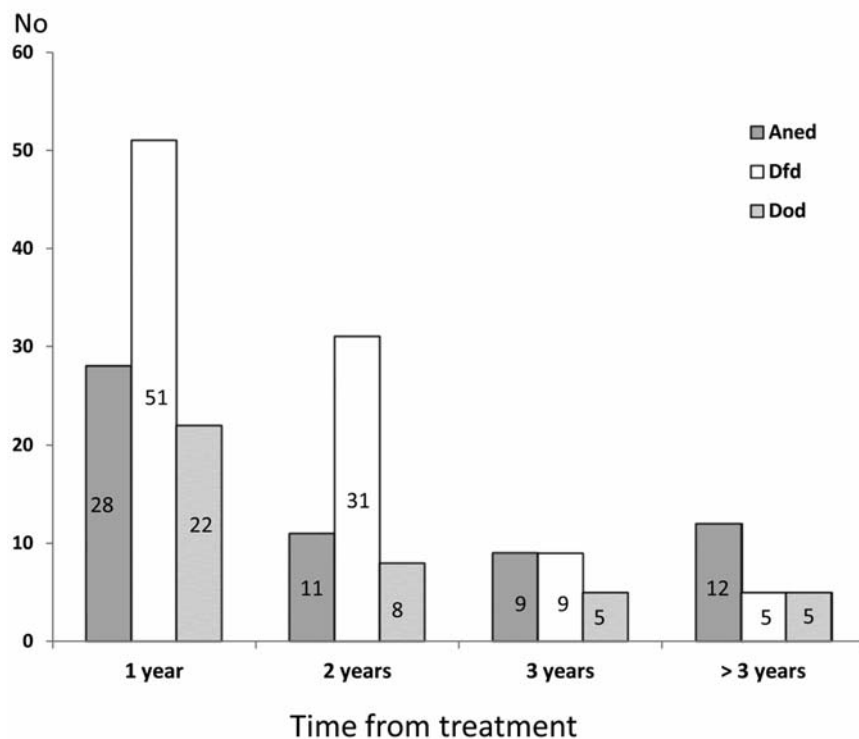

Figure 3. *Status of patients who experienced recurrences according to time period from treatment. Aned=alive, no evidence of disease, Dfd=dead from recurrence of oral cancer, Dod= dead from other disease.*

an asymptomatic stage (31). Consequently, at many centres US-FNAC is a compulsory part of follow-up consultation (32).

Clinical examination alone is not sufficient in the monitoring of patients treated for oral cancer. The message from our report is that self-reported symptoms is a significant guidance and should be included as part of the follow-up regimen. A brief education of patients should improve sensitivity (28). A self-reporting system improves patients' awareness and prevents the passive attitude that otherwise can be seen among those who take part in surveillance programs based on standard consultations.

In our investigation, we found a survival rate of 70% after treatment of OSCC. From that, we can roughly estimate that approximately 900 of our scheduled consultations were superfluous. According to our opinion, standard routines with frequent regular check-ups for up to five years, tend to be expensive and time consuming.

When patients are well-educated and made aware of critical clinical symptoms, well-trained and specialized nurses can manage the need for counselling by scheduled telephone-consultations.

In case of alarming symptoms and treatment-related complications, clinical arrangements can be organised. This flexible surveillance strategy could be as efficient, secure and reliable as regular outpatient consultations on a fixed schedule. In support of this view, Trinidade and co-workers found that after completed treatment, the patient preferred to communicate with a qualified nurse rather than the physician (23). Likewise, Kothary reported that 84% of patients with head and neck cancer felt that follow-up visits were too frequent and that 2/3 of the patients were in favour of a system based on self-reporting of problems (12).

In view of the discrepancies in post treatment surveillance and imbalance between efforts invested and benefits gained, a large-scale randomized trial comparing standard and low-intensity post treatment surveillance has been suggested (10). Such studies should include self-referral and interaction with allied health personnel.

Conclusion

We challenge the current national and international tradition of surveillance of OSCC. There is an alarming imbalance between the efforts and expenses invested in post-treatment follow-up and the benefits gained in term of outcomes. Most recurrences in our study were detected through patient-reported symptoms. This indicates a potential release of resources to examine and treat new patients of regular consultations of asymptomatic patients. Shortening the institutional follow-up period would save additional time and expenses. A de-centralized follow-up procedure with telephone interviews and questionnaires organized by qualified allied health personnel would be even more cost-effective.

Conflicts of Interest

None.

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