

# Self-reported Symptoms to Monitor Recurrent Head and Neck Cancer—Analysis of 1,678 Cases

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**Abstract.** *Aim: The aim of this article was to study the clinical significance of subjective symptoms of recurrence in patients treated for primary head and neck cancer. Materials and Methods: Clinical data of 1,678 patients with squamous cell carcinoma of the head and neck admitted at the Department of Oto-rhino-laryngology-Head and Neck Surgery, Oslo University Hospital during a period of 15 years (1983-1997) were analyzed. Results: A total of 525 (31%) patients had recurrence during follow-up, 74% of these within the first two years after primary treatment. Subjective symptoms indicating recurrent disease were reported by 67%. The remaining recurrences were detected in asymptomatic patients at scheduled consultations. Prognosis was better among patients with subjective symptoms of recurrent disease after treatment for primary tumors of the oral cavity and larynx. Those with recurrence from other tumor sites had no difference in prognosis between symptomatic and asymptomatic patients. Conclusion: The high proportion of patients with subjective symptoms indicates that there is a potential to make follow-up routines more effective. Individualized and flexible procedures, taking into account patient's self-reported symptoms, may help speed-up the process and thus improve prognosis. This could also lead to a more efficient use of resources by reducing the number of redundant examinations of low-risk patients.*

The rationale for post-treatment surveillance in head and neck cancer is that early detection of either recurrence or secondary malignant tumors (SMTs) will allow for appropriate treatment and better survival and functional outcome.

While primary treatment programs for head and neck cancers have become relatively uniform at most centers, there

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*Key Words:* Squamous cell carcinoma, head and neck cancer, recurrence, follow-up, surveillance, survival, salvage therapy.

is no consensus regarding post-treatment surveillance. The three key issues are i) time intervals between clinical consultations; ii) which diagnostic techniques should be included in the follow-up program, and iii) the overall duration of post-treatment monitoring. National and international expert groups present different recommendations (1-3), but no relevant comparisons of prognosis in relation to follow-up routines are available.

The majority of recurrences occur during the first two years after completion of primary treatment (4, 5). Consequently, follow-up should be particularly close during this time, the standard interval being every 3-4 months. Theoretically, a recurrence may appear in-between scheduled visits, and may grow for several weeks or even months before it is diagnosed. In previous studies, we observed that many of our patients reported to have registered clinically alarming symptoms long before the recurrence was diagnosed at the appointed consultations (4-6). From this we concluded that if patients' self-reported symptoms could be added as part of post-treatment monitoring, this would potentially shorten the time to additional treatment. Other authors have drawn similar conclusions (7-9).

Recurrent disease is a signal of aggressive tumor biology and early detection and immediate additional treatment is imperative. In this study we investigated the rate of self-reported symptoms in-between scheduled consultations in order to explore the potential to speed-up the process of detecting recurrent disease. The outcome was analyzed and compared between those with subjective symptoms *versus* patients with silent recurrences that were not detected until scheduled clinical examination. Our findings indicate that a more flexible follow-up, with clinical consultations only when needed, could reduce the rate of redundant examinations of low-risk patients.

## Materials and Methods

*Study population.* Demographic and relevant clinical data were collected prospectively for all previously untreated patients with malignant disease admitted during a 14-year period (from 1983 to 1997) to the Department of Oto-rhino-laryngology, Rikshospitalet,

Oslo University Hospital, Norway, in close collaboration with the medical oncology team at Radiumhospitalet, Oslo University Hospital.

One of the authors (MB) has received authorization from the Norwegian Data inspectorate to compile and analyze the data, and the study was approved by the local ethical committee. Classification was initially performed according to the 3rd edition (1982) of the International Union against Cancer and subsequently updated to the 1997 (6th) edition.

The database comprises of 2,341 patients with squamous cell carcinoma (Snomed 80,703 and 80,713) of the head and neck. Patients with tumors of the lips, thyroid, lungs and unknown primary were excluded from the study. Also excluded were patients with distant metastases, serious comorbidities, mental disorders or previous extensive treatment for carcinoma of the aerodigestive tract (89 patients). Excluded were also 272 patients (12%) with residual tumor manifestations after completed therapy. Six patients were lost to follow-up and seven of the patients' records were incomplete. The total number of excluded patients was 374 resulting in 1,678 (72%) eligible patients. There was no significant difference in site or stage when comparing the excluded and eligible patients.

**Treatment.** Head and neck surgeons and oncologists at our Institution have agreed on a treatment protocol for all sites and stages of head and neck cancer. Treatment was planned at joint meetings of the head and neck surgeons, oncologists and a nurse specialized in oncology, taking into consideration each patient's mental and physical condition. Any essential supplementary investigations were performed ahead of the treatment conference. Treatment for recurrence, when feasible, depended on what treatment options that was still available. Neo-adjuvant chemotherapy was administered to 69 patients (10).

Particular attention was paid to informing patients on symptoms and signs that might indicate a local or regional recurrence or a new malignant tumor. Patients were strongly urged to contact the outpatient clinic immediately in the case of 'alarming' symptoms between scheduled appointments. In cases of recurrence or SMT, it was recorded whether the diagnosis was made through symptoms presented at scheduled appointments or through symptoms that led patients to request a consultation between scheduled appointments, or as a result of only the clinical examination in an asymptomatic patient.

SMTs (second malignant tumors) were defined according to the criteria established by Warren and Gates (11) and subsequently modified (12), as follows: (i) both were malignant tumors, (ii) the first and second tumors were geographically separate and (iii) the second tumor did not represent a metastasis from the first tumor.

**Follow-up procedure.** The follow-up regimen comprised of 4-6 visits during the first year and 2-3 consultations during the second and third years after completed therapy. After three years' follow-up, patients who were 'free of disease' and did not suffer from serious treatment-related complications were usually discharged from regular surveillance. Thereafter, the referring hospital or family physician was in charge of follow-up with particular attention being paid to nutrition, dental problems and thyroid function. At regular intervals we retrieved follow-up data for all patients monitored by other departments and physicians. Patients treated for recurrence, SMT or serious complications, were followed

at our outpatient clinic for as long as it was considered necessary. The final follow-up was in December 2010.

In this study we have no exact data as to the number of follow-up consultations. At the first follow-up consultation (4-6 weeks after completion of treatment), a contrast-enhanced computerized tomography (CT) scan of the primary site and neck was performed in all patients to evaluate the treatment response and this provided baseline data for comparison in case of future events. Further CT scans or magnetic resonance imaging (MRI) was not performed unless there was suspicion of loco-regional recurrence, SMT or serious treatment-related complications. Initially an annual chest x-ray of the lungs was performed. Later it was decided to skip the annual chest x-ray, because the yield in terms of detection of metastases and SMT's and successful salvage was too low. Chest x-ray or CT scans of the lungs were only performed in a case of suspicion of lung disease. From 1999, ultrasound evaluation of the neck, supplemented with fine needle aspiration cytology (Fnac) became standard at each consultation.

**Statistics.** The data were stored and analyzed by means of the SAS software v.9.3 (SAS Institute, Cary, NC, USA). Chi-square tests were performed for categorical data. Kaplan-Meier plots and log-rank tests were used to assess rates of recurrence and survival. Patients dead of causes unrelated to the index tumor as well as those alive with no evidence of disease were treated as censored values.  $p < 0.05$  were considered statistically significant.

## Results

Table I presents the demographic and clinical characteristics of the 1,678 patients judged as "free of disease" after completed primary treatment. Of these, 525 (31%) developed a recurrence during follow-up.

Twenty seven patients (19%) had simultaneous recurrences at two sites. In the analysis these dual recurrences were allocated to the site that was assumed to have worst prognosis. Accordingly, 16 cases of simultaneous relapse locally and regionally were considered regional recurrences and 11 cases of simultaneous local or regional recurrence and relapse at distant sites were classified as distant recurrences. Patients who died during treatment or were unable to complete treatment as planned were considered dead from the index tumor.

Figure 1 presents the distribution of recurrences according to type (local, regional, distant) *versus* time from primary treatment. The majority (74%) of recurrences occurred within the first two years after primary treatment of the index tumor and 26% the 3rd year and later. A total of 4.3% of the total number of patients had a recurrence beyond three years following primary treatment. This represents 14% of all recurrences (n=525) among the patients in our study.

Local, regional and distant failures accounted for 60%, 25% and 15% of the recurrences, respectively (Figure 1). Local recurrence continued to occur until the 11th year after treatment (data not shown). Both regional and distant metastases were

Table I. Distribution of 1,678 patients versus tumor characteristics and treatment. Mean age for all patients: 64 years (range 20-90 years). Neo-adjuvant chemotherapy with cisplatin and 5-fluorouracil was given to 69 patients with advanced disease.

Stage	I+II		III+IV		Total	
	N	%	N	%	N	%
Patients	904	(54)	774	(46)	1678	(100)
Gender						
Male	710	(55)	590	(45)	1300	(77)
Female	194	(51)	184	(49)	378	(23)
Site						
Oral cavity	335	(58)	244	(42)	580	(35)
Parotid gl	4	(31)	9	(69)	13	(0.8)
Oropharynx	45	(27)	122	(73)	167	(10)
Nasopharynx	1	(3)	33	(97)	34	(2)
Hypopharynx	21	(22)	75	(78)	96	(6)
Sino-nasal	26	(37)	44	(63)	70	(4)
Larynx	472	(66)	247	(34)	719	(43)
T						
T1	527	(93)	41	(7)	568	(34)
T2	377	(78)	108	(22)	485	(29)
T3	197	(100)	-	(-)	197	(12)
T4	428	(100)	-	(-)	428	(26)
N						
N0	877	(70)	373	(30)	1250	(74)
N1	27	(16)	147	(84)	174	(10)
N2	207	(100)	-	(-)	207	(12)
N3	47	(100)	-	(-)	47	(3)
Treatment						
Surgery	130	(85)	23	(15)	153	(9)
RT	524	(59)	369	(41)	893	(53)
Surgery + RT	159	(53)	143	(47)	302	(18)
RT + surgery	91	(28)	239	(72)	330	(20)

RT, Radiotherapy.

infrequent after the 3rd year. The majority of recurrences at distant sites were located to the lungs. Only two patients with solitary lung metastases were successfully salvaged.

Overall, 67% of recurrences were brought to attention through symptoms presented by the patients at scheduled appointments. Of these, only 4.7% had been in contact with the clinic in-between scheduled appointments.

A total of 77% of recurrences originated from tumors originally located to the oral cavity and larynx; 193 and 208 patients, respectively. As expected, the salvage rate was higher for patients with early-stage tumors, compared to advanced-stage tumors. Being diagnosed with a recurrence was the decisive factor in terms of prognosis, and salvation of a second recurrence was practically non-existent.

Figure 2 shows survival of recurrence by tumor site after completed therapy. The rate of recurrence was highest in early-stage tumors, 30%, compared to 8% for advanced tumors. The survival after recurrence of laryngeal and oral cavity tumors was significantly better than for recurrent

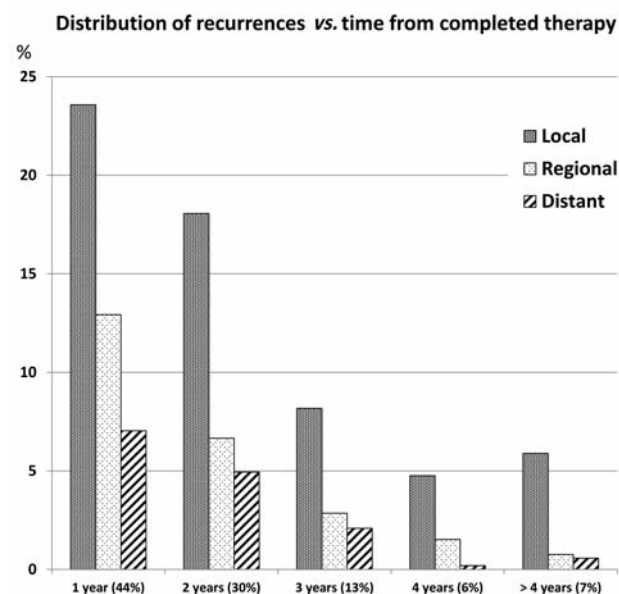


Figure 1. Distribution of recurrences (local, regional and distant) versus time from completed therapy (N=525).

pharyngeal and parotid gland tumors, that had extremely low salvage rates. Gender and patient age did not correlate with rate of recurrences or outcome after salvage treatment.

Survival was better among patients with subjectively symptomatic recurrences in the oral cavity and larynx compared to those without subjective symptoms. When entering all tumor subsites in the analysis, however, prognosis was not statistically different between symptomatic and asymptomatic patients (data not shown).

A total of 305 SMT's (skin tumors not included) were diagnosed during follow-up. Of these, 16% were located to the upper aerodigestive tract, 66% to the lungs and 18% to the esophagus. Out of all SMT's, 50% were diagnosed through symptoms presented by patients. SMT's continued to occur up to 15 years post-treatment. Prognosis was very poor for this group of patients. There was no association between treatment modality and the occurrence of SMT's.

Figure 3 shows the outcome among patients diagnosed with recurrent disease. At three years follow-up, 73% of patients were free of disease. In all, 70% of the patients with a recurrence, died from their disease, the majority of these (77%) within the first two years.

## Discussion

Prognosis for head and neck cancer remains remarkably unchanged despite progress in diagnostic and therapeutic techniques. The possible occurrence of recurrent disease is

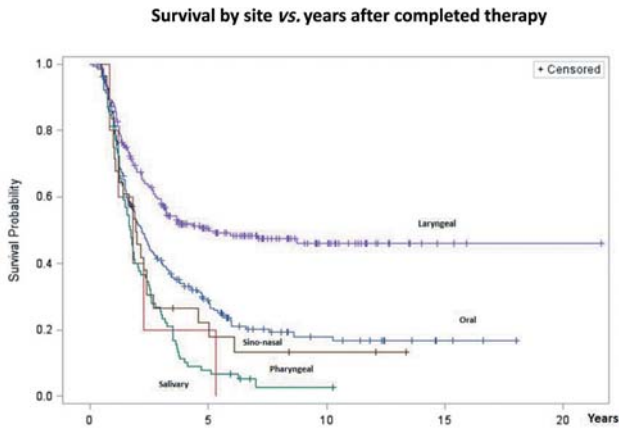


Figure 2. Survival by site versus years after completed therapy (all patients, N=1,678).

the decisive factor for prognosis. This is the rationale for regular follow-up consultations in order to detect a recurrence as early as possible. Unfortunately, there exists little evidence to show that this regimen actually improves the final outcome. Our study indicates that the value of routine examinations of asymptomatic patients is questionable. We need to educate our patients so that they can take active part in the surveillance and encourage them to report back in case of critical symptoms. This may require a more flexible organization but in the end resources can be saved.

The current single-center analysis is based on a dataset of prospectively recorded information including clinical data on 1,678 patients with long-term follow-up. The study addresses two key issues: i) the rate of subjective symptoms of recurrent disease after primary treatment, ii) the organization of follow-up routines.

The first two years after completed primary treatment is when the risk of a recurrence is at its highest after treatment of primary head and neck cancer. During this time patients are cautiously monitored, with a traditional frequency of 3 to 4 months at most centers. The frequency of follow-up appointments from three years and onward varies. Most commonly, consultations continue until the 5th year after completed primary treatment (1, 7, 13-15).

Regular clinical consultations require considerable resources and it can be questioned whether follow-up routines actually help save more lives. One obvious risk with regular consultations is that if a recurrent disease starts in-between consultations, it could have time to grow and become clinically advanced long before being diagnosed at next appointment.

A total of 23% of all patients in our study had a recurrence within the first two years after completed primary treatment. The outcome after additional treatment

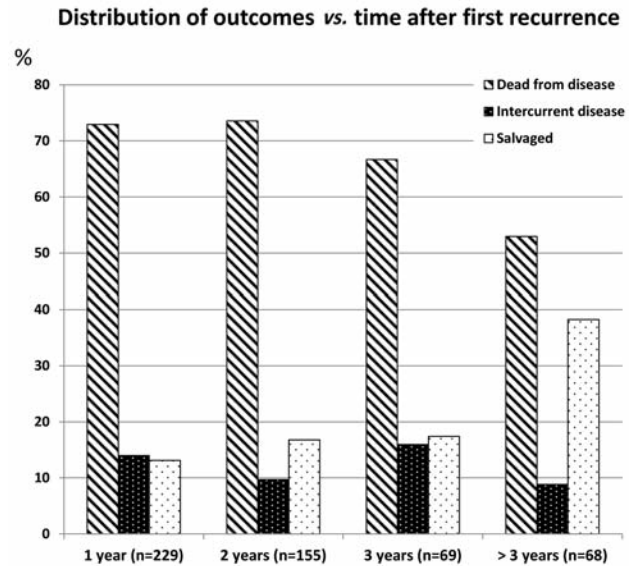


Figure 3. Distribution of outcomes versus time after first recurrence (N=525).

was decisive in terms of prognosis. In general, the earlier the stage of recurrence when detected, the better the prognosis. In the study, 67% of patients with recurrent disease had subjective symptoms that had occurred in the interval in-between scheduled check-ups. Unfortunately, the majority of these patients did not contact our clinic earlier than planned. A large group of those with subjective symptoms were early-stage oral and laryngeal (glottic) tumors, probably due to the fact that local failures in these areas give early symptoms. These two groups were found to have significantly more favorable prognosis after treatment of recurrent disease. With all tumor sites compiled, however, there was no survival benefit when the recurrence was diagnosed through patients' self-reported symptoms, compared to those detected by clinical examination of asymptomatic patients. Treatment results were generally poor for advanced recurrent tumors regardless of type of treatment. As reported by others, extensive treatment had a high prize in terms of morbidity and even death (16). With disseminated recurrent disease, including metastases to the lungs, survival was less than a year (17).

We believe that time to treatment of the recurrence could have been shortened if patients with symptoms had contacted us earlier. Unfortunately, we were unable to evaluate time to treatment among the few (4,7%) patients that actually did contact us earlier than planned. Potentially, a more flexible follow-up routine with monitoring by phone or online services and with specialized nurses as first line contact could save resources. For selected, low-risk patients, it may even be sufficient with regular phone consultations. A total of 73%

of the patients in our study were cured from their primary tumor without signs of recurrent disease. Beyond 3 years, only 4,3% of all patients developed a recurrence, representing 14% of the total number of relapses. At 3 years post-treatment there were approximately 1,136 of 1,678 patients alive without signs of recurrent disease. It seems irrational that time and resources should be spent on regular attendance of patients that are likely to be permanently cured.

The majority of patients with late recurrences had poor prognosis, regardless of given treatment. Thus, in terms of cost-benefit, the low risk of a late recurrence and the poor survival once diagnosed, does not seem to justify extended monitoring of all asymptomatic patients (18). Interestingly, other authors (19, 20) found that given a choice, patients preferred a regimen that allowed them to contact the clinic only when needed. In addition to that, many of the patients preferred to communicate with a qualified nurse rather than a physician (21). Some authors are skeptical to letting patients take an active part in follow-up programs. Lester and Wight brought to attention the risk of neglecting symptoms (22). The need for active monitoring of patients was also addressed in a study by Pagh *et al.* where 86% of all head and neck cancer patients had severe morbidity issues after completed therapy (23). In our opinion, follow-up should take into account the individual capabilities. We must realize that communication has changed compared to what it once was. Online services offer great advantages with regard to sharing information and also lead to increased awareness of medical conditions.

We believe that in selected cases, patient's self-reported symptoms should be considered as a sensitive and effective tool to improve post-treatment surveillance. With adequate information, patients can be educated to take active part in follow-up. With a flexible organization and gradual training of patients, post-treatment monitoring could become more effective, thereby saving more lives.

## Conflicts of Interest

The Authors declare no conflicts of interest.

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*Received March 3, 2016*

*Revised April 20, 2016*

*Accepted May 4, 2016*