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The Value of Follow-up in Patients Treated for Squamous Cell Carcinoma of the Head and Neck

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Clinical findings, treatment and results have been recorded prospectively in 661 patients with carcinoma of the head and neck. With an average follow-up of 3 years 7813 follow-up consultations revealed 220 recurrences. The overall "recurrence pick-up rate" and subsequent "cure rate" was 1:36 and 1:113 consultations, respectively. Laryngeal carcinomas treated with radiotherapy and oral carcinomas receiving radiotherapy and limited resections showed recurrence "cure-rates" of 1:89 and 1:110, respectively. For other tumour sites the average "cure-rate" was 1:238. Only 39% of the recurrences were detected through physical examination. Follow-up consultations revealed 9.1% of second primaries. More time should be spent on training patients to recognise symptoms and signs of recurrence. Routine follow-up is rarely indicated beyond the third year after completion of treatment, or in patients for whom we have little to offer in terms of curative treatment.

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INTRODUCTION

ONE OF the main objectives of follow-up of patients treated for malignant disease is to discover and treat early recurrences. The benefit of prolonged routine follow-up in terms of increased survival has been questioned for several types of carcinomas [1–4]. In a previous retrospective study on squamous cell carcinoma of the head and neck we found that successful treatment of recurrences was almost exclusively achieved in patients with laryngeal carcinoma initially treated with irradiation alone [5].

Since 1983 we have prospectively recorded relevant clinical data and the outcome of all follow-up consultations of patients treated for squamous cell carcinoma of the head and neck. In this study we have evaluated to what extent our follow-up regimen has been effective in detecting early recurrences and, once a recurrence was detected, whether further treatment resulted in cure. Furthermore, we have recorded how the recurrences were detected—through symptoms or signs that the patients reported or by physical examination at scheduled follow-up consultations.

PATIENTS AND METHODS

From May 1983 to May 1988, 807 consecutive and previously untreated patients with confirmed squamous cell carcinoma of

the head and neck were admitted to our department. The clinical findings, treatment, results and outcome of all follow-up consultations have been recorded prospectively. Excluded from the present study were 50 patients with disseminated disease, other serious illnesses or poor general condition which made treatment with curative intent impossible. In addition we excluded 96 patients in whom initial control of the primary tumour and/or neck metastases was not achieved (i.e. where the operative findings or histological examination of the surgical specimens showed an incomplete resection and patients who at the first appointment 6 weeks after completion of the treatment had residual tumour locally, regionally or at distant sites). Our study focusses on the remaining 661 patients who were considered "free of disease" 6 weeks after the completion of the therapy.

Of the 661 patients 77% were male and 23% female, ranging in age from 27 to 88 years (mean 63 years). Table 1 presents the material according to site and the UICC classification of 1982 [6]. In general, the smaller tumours (T1-2) received radiotherapy with surgery for suspected residual tumour and the larger combined radiotherapy and surgery. In cases where resection of part of the mandible was considered necessary surgery had preceded radiotherapy. Radiotherapy was given in once-a-day fractions of 2 Gy 5 days a week from an external megavolt source and directed towards the primary site and usually both sides of the entire neck. The primary site received 66–80 Gy. Most cases of oral carcinomas, not involving the mandible, received external irradiation of 47–50 Gy and an additional 20–30 Gy as brachytherapy for the primary tumour. The clinically negative neck received 47–50 Gy and the positive neck 50 Gy with an

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Table 1. Clinical classification (UICC 1982) according to site of the primary tumour

Classi- fication	Site of primary tumour						Un- known primary	Total
	Oral cavity	Meso- pharyn- geal	Naso- pharyn- geal	Hypo- pharyn- geal	Sino- nasal	Larynx		
T1	64	9	1	9		104	—	187
T2	72	27	4	9		62	—	174
T3	20	7	4	2		28	—	61
T4	52	27	11	26		76	—	192
Tx	—	—	—	—	34*	—	13	47
NO	173	32	4	14	30	237	—	490
N1	23	25	9	25	3	15	6	106
N2-3	12	13	7	7	1	18	7	65
Total	208	70	20	46	34	270	13	661

* UICC of 1982 has no classification for sinonasal carcinomas.

additional boost of 10 Gy to the nodes followed by neck dissection.

All follow-up consultations were recorded. The localisation and time of recurrences as well as the results of further treatment were also noted. For deceased patients death certificates were obtained and autopsy records were reviewed when available. We also recorded how the recurrences were detected: (1) by symptoms or signs that the patients reported at the scheduled consultations or by separate consultations requested by the patients or (2) at physical examination at scheduled consultations. For second malignancies the criteria proposed by Warren and Gates [7] were applied. Basal cell carcinomas of the skin were not included.

In general the patients are seen at the out-patient clinic every 2–3 months the first 2 years, and every 3–4 months the following 3 years. After 5 years follow-up was usually discontinued. The consultations included general ear, nose and throat examination, supplemented with endoscopic examination when indicated, and relevant blood tests. An X-ray of the chest and panendoscopy (hypopharyngo-, oesophagoscopy-, laryngo- and bronchoscopy) was not a compulsory part of the work-up. None of the patients were lost to follow-up and the minimum time of follow-up was 2 years.

The SAS 6.03 software for personal computers (SAS Institute Inc., Cary, North Carolina, USA) was used for storage, processing and statistical evaluation (χ^2) of the data.

RESULTS

Table 1 shows the T and N classification according to the anatomical site of the primary tumour. Half of the patients had stage III or IV disease. 239 patients (36%) received combined radiotherapy and surgery of the primary tumour and 120 (18%) combined treatment of the neck (Table 2). Of the 661 patients judged to be "free of disease" at the first consultation 6 weeks following the completion of the primary treatment, 220 (33%) developed recurrences. In 131 (20%) the first site of recurrence was locally, 54 (8%) regionally and 35 (5%) at distant sites.

Figure 1 reveals the incidence of recurrences according to the site of the primary tumour. 55 (42%) of the 131 local recurrences were in laryngeal carcinomas, and of these 36 (65%) were salvaged. Secondary treatment of local recurrences in laryngeal carcinomas was with one exception successful only in patients

Table 2. Treatment of primary tumour and neck

Treatment of primary tumour	Treatment of neck				Total
	None	Surgery	Combined irradiation surgery	Irradiation	
Surgery	48	2	—	—	50
Combined irradiation/ surgery	14		59	166	239
Irradiation	151		61	160	372
Total	213	2	120	326	661

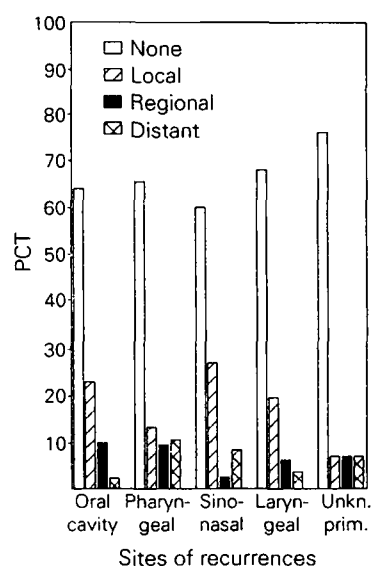


Fig. 1. Incidence (%) and site of recurrences according to site of primary tumour.

initially treated with irradiation alone. Local recurrences of oral carcinomas were seen in 48 patients (37%) of whom 19 (40%) were successfully treated. The initial treatment for these was radiotherapy alone or radiotherapy combined with limited resections in 17 patients and radiotherapy combined with extensive resections in 2 patients. Of the remaining 28 (21%) local recurrences 6 were salvaged.

Of 54 regional recurrences 6 (11%) were salvaged. 12 regional recurrences occurred in patients who had not received treatment of the neck and of these 4 were salvaged. Among 28 neck recurrences initially treated with elective radiotherapy 2 were successfully treated. None of the recurrences in patients with initial positive necks were salvaged. Of the 35 recurrences at distant sites 1 patient (3%) was salvaged. Figure 2 shows the treatment results of recurrences. With an average of 3 years follow-up the absolute and relative survival was 56% and 77%, respectively for the material as a whole (Fig. 3).

The total number of follow-up consultations was 7813 which gives a overall recurrence "pick-up rate" of 1 recurrence in 36 consultations and an overall "cure rate" of 1 cure in 113 consultations. Laryngeal and sinonasal carcinomas had the best "cure-rate" (1:89 and 1:87, respectively) and pharyngeal carcinomas the worst, with 1 cure in 160 consultations for

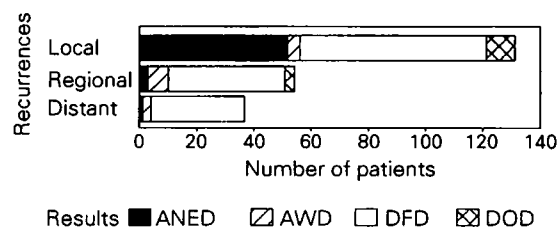


Fig. 2. Results according to site of first recurrence. ANED: alive, no evidence of disease, AWD: alive with disease, DFD: dead from disease, DOD: dead other diseases.

hypopharyngeal carcinomas and no cures for meso- and nasopharyngeal carcinomas (Table 3). If patients with laryngeal and oral carcinoma are left out, the "cure rate" was 1:238 per follow-up consultations. The patients who developed recurrence accounted for one-third of the total number of consultations.

61% (135/220) of the patients had noticed symptoms or signs such as pain, soreness, increased hoarseness or a lump in the neck suggesting some irregularity that eventually led to the diagnosis of recurrence. In particular, symptoms and signs suggesting a regional recurrence were often noticed by the patients (42 out of 54). The remaining 85 patients (39%) had no apparent symptoms and recurrence was diagnosed through the physical examination at the scheduled follow-up consultations (Table 4). The survival rate was somewhat better for patients in whom a recurrence was detected through symptoms and signs presented by the patients compared with recurrences detected through the physical examination, but the difference was not statistically significant.

Figure 4 shows that 76% of the recurrences were diagnosed during the first 2 years, 11% in the third and 13% later than 3 years following the completion of the primary treatment. The distribution of the site of recurrences was equal for all time periods. Table 2 shows that 59 patients received combined

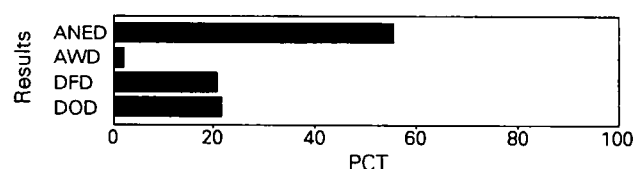


Fig. 3. Survival for material as a whole.

Table 4. How recurrences were diagnosed—through symptoms and signs presented by the patients or by physical examination at scheduled consultations

Site of recurrences	Symptoms presented by patients	Physical examination	Total
Local	75	56	131
Regional	42	12	54
Distant	18	17	35
Total	135 (61%)	85 (39%)	220

treatment of the primary tumour and neck node metastases and these patients accounted for approximately 850 consultations. None of the recurrences in 90 patients having carcinomas of meso- and nasopharynx were salvaged (Table 1). These patients had 930 consultations (Table 3). Only 3 of the 19 recurrences among 46 patients with carcinomas of the hypopharynx were salvaged (Tables 1 and 3).

Table 5 shows that 60 patients (9.1%) developed second primary tumours. 5 (8%) of the secondary tumours (4 within the head and neck region) were diagnosed through the clinical examination at scheduled consultations. In the remaining tumours the diagnosis was obtained through symptoms or signs presented by the patients which lead to further examination

Table 5. Second malignant neoplasms according to the site of the index tumour

Site of index tumour	Sites of secondary tumours				Total (%)
	Head and neck	Lung	Oesophagus	Other sites	
Oral cavity	14	6	4	2	26 (12,5)
Mesopharynx	2	3	3	2	10 (14,3)
Hypopharynx	0	1	0	3	4 (8,7)
Sino-nasal	0	0	0	2	2 (5,9)
Larynx	5	4	1	7	17 (6,3)
Unknown primary	0	0	0	1	1 (7,7)
Total	21	14	8	17	60 (9,1)

Table 3. Rate of recurrences (local, regional and distant) and cures in patients judged "free of disease" following primary treatment

	No. of consultations	No. of recurrences	Recurrence "pick-up" rate	No. of cures*	Recurrence "cure-rate"
Oral cavity	2533	74	1/34	23	1/110
Mesopharynx	686	20	1/34	0	0
Nasopharynx	244	7	1/35	0	0
Hypopharynx	481	19	1/25	3	1/160
Sinonasal	346	13	1/27	4	1/87
Larynx	3373	84	1/40	38	1/89
Unknown primary	150	3	1/50	1	1/150
Total	7813	220	1/36	69	1/113

* 14 patients alive with disease are not included.

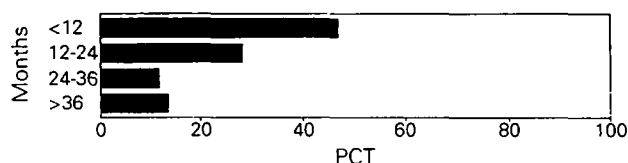


Fig. 4. Time from completion of treatment to diagnosis of recurrence.

either in our department, through consultation with a private physician or at the local hospital. Multiple primary tumours developed at a constant rate of approximately 2.8% per year and accounted for an excess mortality of 5.2%. 20 patients (33%) are alive, and of these 9 had the second malignancy within the head and neck region, 4 were localised in the lungs and 7 at other sites.

DISCUSSION

Follow-up of patients treated for carcinoma has several objectives: (1) early detection and treatment of recurrences, (2) registration and amelioration of complications that the treatment may have caused, (3) provision of support and help, (4) detection and treatment of secondary neoplasms and finally (5) evaluation of treatment results and endpoint reporting.

The search for recurrences of carcinoma at routine follow-up consultations presupposes that new manifestations of the disease are more likely to be cured if detected at the earliest possible moment. This hypothesis has been investigated for cancer of the breast [1, 8], colon [2, 3] bronchial carcinoma [4] and in a large regional follow-up programme covering several types of cancer [9]. All these studies showed that regular follow-up is of limited benefit in terms of increased survival.

The present prospective study shows that with our primary treatment regimen, successful treatment of recurrences was possible almost only in local recurrences, and in particular for laryngeal carcinomas initially treated with radiotherapy and oral carcinomas treated with radiotherapy alone or radiotherapy combined with limited resections. The result of secondary treatment of patients with local recurrences who had received combined treatment with radiotherapy and extensive surgery as well as for regional and distant disease was disappointing. These findings concur with our previous retrospective study [5] and with Wolfenberger [10], the only other study addressing the effectiveness of follow-up in patients with head and neck carcinoma that we are aware of. Follow-up with the intention of detecting curable recurrences is thus only meaningful in patients for whom we still have treatment options left. Some of the unsuccessfully treated recurrences may have gained some palliation, but to what extent this has increased the time of survival is unknown.

In almost two-thirds of the patients it was symptoms or signs that the patients themselves noticed that eventually led to the diagnosis of recurrence. The patients' ability to recognise symptoms and signs suggesting renewed tumour growth was especially marked for regional recurrences. It may be that our follow-up regimens should be intensified the first 2 years after completion of the treatment in patients not receiving treatment of the neck and in patients treated with elective radiotherapy of the neck. Nevertheless it is our opinion that considerably more time should be spent on informing patients about the possible symptoms and signs that could occur, and in instructing them to contact either our out-patients' clinic, their local hospital or physician as soon as alarming symptoms occur. We believe this

to be an important aid in detecting early recurrences. It is noteworthy that the survival rate was somewhat better for patients in whom a recurrence was detected through symptoms compared with recurrences detected through the physical examination. Further it has been shown that recurrences rarely occur later than 3 years after the completion of the primary treatment and follow-up beyond the third year is thus of little effect in terms of detecting recurrences.

The majority of our patients have undergone high-dose radiotherapy and/or mutilating operations resulting in functional and cosmetic disability. Many of these patients will need some sort of rehabilitation. Moreover there are several patients who need psychological readjustment and, for some patients, working ability has been affected. It is the responsibility of the institutions treating these patients to initiate and maintain functional adjustment, substitutional therapy, psychological, social and work-related adjustment. Long-term follow-up is necessary to cope with all kinds of rehabilitation. However, these consultations need not be on a regular basis, but can be tailored according to the individual needs.

If the sole purpose of follow-up is detection of recurrences the regular follow-up in many patients with tumours with a low "cure-rate" (pharynx and sinonasal cavities) and also a number of patients with advanced oral and laryngeal carcinomas can be omitted because these patients, in case of recurrence cannot be offered additional treatment with curative intent. If we further take into consideration that approximately 500 consultations were performed later than 3 years following the completion of the primary treatment it appears that a considerable number of follow-up consultations are redundant. Without excluding the consultations necessary for long-term follow-up of functional, social and psychological adjustments our estimate suggests that the number of consultations could be reduced by approximately one-third.

The patients attitude towards the follow-up consultations is also of importance. Prior to consultations most patients are anxious that a recurrence will be found. If the examination turns out well the patients are relieved and this may induce a feeling of security. This feeling may sometimes be false and lead to neglect of alarming symptoms. Thus, the effect of the follow-up regimen may sometimes cause a delay in the diagnosis of a recurrence.

Multiple primaries occur at a rate of approximately 3–6% a year [11–13]. After the third year following completion of detection and treatment these tumours are more of concern than recurrences. Surprisingly only 8% of the secondary neoplasms were detected through clinical examinations, indicating that our follow-up in this respect was insufficient. It should be noted that neither regular panendoscopic examination nor chest X-ray was part of our follow-up programme. The value of panendoscopy in the follow-up of patients with head and neck cancer is still debated [14, 15]. Such examinations may detect a number of oesophageal and bronchial carcinomas [16, 17], but due to the poor survival rates of these tumours [18] the cost-effectiveness of routine panendoscopy in every patient with head and neck cancer is questionable [17].

As a consequence of the findings in this study the follow-up regimens should be reconsidered. Follow-up on a regular basis is rarely indicated beyond the third year after completion of treatment and should be limited to the patients for whom we still have treatment options left. For patients who have undergone combined treatment with radiotherapy and large resections we have little to offer in terms of curative secondary

treatment. The follow-up in these patients should mainly be one of care-taking and support-giving and can be made on an individual basis. A modest estimate reveals that approximately one-third of the follow-up consultations can be dropped without reducing the number of early detected recurrences that can be offered secondary treatment, and without reducing the care and support that we are obliged to give. The means, personnel and time hereby made available could be better utilised.

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Progressive Loss of Antiemetic Efficacy During Subsequent Courses of Chemotherapy

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The maintenance of the antiemetic efficacy of a combined protocol (intravenous methylprednisolone, oral thiethylperazine and oral amitriptyline) during six consecutive courses of adjuvant FAC chemotherapy (5-fluorouracil, doxorubicin, cyclophosphamide) was analysed in 107 female breast cancer patients who completed the six planned courses of treatment. A continuous decrease in complete (no vomiting episodes) and major protection rate (0–2 vomiting episodes) was evident during chemotherapy. Complete protection rate decreased from 62.6% in the first course to 48.6% in the sixth ($P < 0.05$, χ^2 test). The respective figures for major protection rate were 76.6% and 58% ($P < 0.01$, χ^2 test). These data, together with other from the literature, should be taken into consideration when reviewing the overall results of current antiemetic trials, which usually only mention the results obtained in the first course of chemotherapy.

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INTRODUCTION

WITH VERY few exceptions [1–5], antiemetic trials only report the results obtained during the first course of chemotherapy. A question which usually arises when reading the positive results of many recent antiemetic trials is whether or not the efficacy is maintained during subsequent cycles of chemotherapy.

Adjuvant FAC (5-fluorouracil, doxorubicin, cyclophosphamide) chemotherapy for breast cancer provides a useful model for answering this question, since it induces considerable emesis and the great majority of patients usually receive the planned six courses of chemotherapy.

In this paper, we present the results of a study in which the