SCREENING FOR LOCAL AND REGIONAL CANCER RECURRENT IN PATIENTS CURATIVELY TREATED FOR LARYNGEAL CANCER: DEFINITION OF A HIGH-RISK GROUP AND ESTIMATION OF THE LEAD TIME

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Abstract: Background. All patients treated for laryngeal cancer are offered the same follow-up schedule to detect asymptomatic locoregional recurrences. In this study, we evaluated the prognostic profile of patients for cancer recurrence and estimated the lead time.

Methods. A cohort study was performed between 1990 and 1995. Cox proportional hazards model was used to analyze the prognostic factors. The effect of altering the follow-up for asymptomatic recurrence detection was determined after estimating the lead time.

Results. The variables cT classification, smoking, and histologic grade proved to be prognostic factors. The risk of locoregional failure was 15% in the low-risk group versus 29% in the high-risk group. The estimated lead time was 2 to 4 weeks.

Conclusion. Risk profiles for locoregional relapse were defined. Intensifying the follow-up schedule is not advisable because the lead time is very short. An excessively high number of routine visits would have to be performed to increase the detection rate for asymptomatic recurrences.

Keywords: laryngeal cancer; recurrence; prognostic factor; follow-up; lead time

In the Netherlands, as throughout Western Europe, the most common location of head and neck cancer is the larynx.1 After curative treatment for laryngeal cancer, patients enter a uniform, nationwide follow-up program. They are put on 1 of 2 schedules: a minimum of 17 routine visits at fixed intervals and declining frequencies over a period of 5 years; or 22 routine visits over a period.
of 10 years. The main aim is to detect local or regional cancer recurrence while it is still asymptomatic. This follow-up program was designed on the basis of extensive clinical experience and national consensus. All curatively treated patients are enrolled in this follow-up program. Some of them, as it turns out, run a higher risk of locoregional cancer recurrence than others.

Previous studies on follow-up in head and neck cancer conclude that patients with upper-airway malignancies run a high risk of developing local or regional cancer recurrence and second primary malignancies. In the literature, the locoregional recurrence rate of laryngeal cancer is usually given within the broader context of recurrent head and neck cancer and is mostly used to evaluate a new treatment protocol for a specific tumor stage. Reported recurrence rates range from 16% to 32%, while some studies on advanced primary tumors report rates up to 50%. The most frequent sites of locoregional cancer recurrence are the larynx or neopharynx, including stomal recurrences, followed by the regional lymph nodes. Grau et al found that the duration of follow-up could be shortened because most relapse-related deaths occurred within the first 3 years. However, they did not analyze to what extent asymptomatic recurrence detection is preferable to symptomatic detection in terms of potential survival benefit or cancer mortality reduction.

Several studies concentrated on prognostic factors for local or regional cancer relapse in patients with laryngeal or other head and neck cancers. Although calculations were performed to identify prognostic factors, it was not clear whether these high-risk patients would benefit from intensified screening.

The present study investigated whether it is possible, during the follow-up of curatively treated laryngeal cancer patients, to recognize the clinical risk factors of local or regional cancer recurrence. We defined a low-risk and a high-risk group for locoregional cancer recurrence in an effort to personalize the current follow-up program and perhaps to limit participation in it to high-risk patients. In this paper, we discuss the effect of the follow-up program on therapeutic options, cancer-specific mortality, and survival of patients with asymptomatic locoregional cancer recurrence. The actual asymptomatic recurrence detection rates were used to estimate the lead time (the interval at which a tumor is detected prior to the presentation of symptoms). The estimated lead time was then used to evaluate how intensifying the follow-up schedule would affect the detection rate for asymptomatic recurrences.

**PATIENTS AND METHODS**

A cohort study was performed on all the consecutive patients with laryngeal cancer who were referred to our clinic between January 1990 and January 1995. The following inclusion criteria had to be met: primary tumor of the larynx; histologically proven squamous cell carcinoma; and initial treatment with curative intent.

After treatment, all the patients entered the follow-up program. It comprised a routine visit every 2 months in the first year of follow-up, every 3 months in the second year, and every 4 months in the third year. In the fourth and fifth years, the patient was seen every 6 months. Some patients were screened annually for up to 10 years. Patients were free to make additional appointments if they had complaints or questions. An interview was held at each routine visit or at each extra visit between the prescheduled visits. Furthermore, a complete physical examination was performed on the head and neck, including palpation of the neck region, pharyngoscopy, and laryngoscopy. The otolaryngologist and the radiation oncologist conducted these examinations alternately.

Data were retrieved from the patient’s medical records at the departments of otolaryngology and radiotherapy. Any precise complaints that indicated tumor recurrence and/or physical evidence of tumor recurrence were recorded at each visit.

**Data Analysis.** Data on patient, tumor, and treatment characteristics were collected and stored in a Microsoft Access database designed for the study. Recurrence and survival curves were computed by the Kaplan-Meier method. Differences between patient and tumor variables were tested with the chi-square test, using SPSS version 12.0.1. The univariate and multivariate analyses were performed with the statistical software SAS version 8.2.

Patients with locoregional recurrences were divided into 3 groups: patients with screen-detected asymptomatic locoregional recurrences; patients with symptomatic recurrences detected at a prescheduled visit; and patients with a symptomatic recurrence that was detected at an additional visit. These groups were compared in terms of the therapeutic options applied to the recur-
rence and the effects on cancer-specific mortality and survival. Time to recurrence was calculated using the date of histologic proof of the primary tumor and of the cancer recurrence.

A number of patient and tumor characteristics that were thought to have prognostic influence on local or regional cancer relapse were analyzed: age (dichotomized into ≥65 years vs <65 years); sex; smoking after primary laryngeal tumor detection (continuation vs cessation); daily alcohol consumption (>6 units a day vs none or ≤6); tumor stage (II–IV vs I); histologic differentiation (poor vs well/moderate); cT classification (T2–4 vs T1); cN classification (N+ vs N0); localization (supraglottic vs glottic); and therapy applied to the primary malignancy (radiotherapy alone vs surgery alone, or surgery combined with radiotherapy). Risk factors were determined at the baseline of the initial treatment of cancer except for smoking.

First, the impact of assumed prognostic factors on disease recurrence was studied univariately, together with the 95% confidence interval and p value, by applying the Cox proportional hazards method. All prognostic factors with a p value ≤.1 were analyzed multivariately. The multivariate analysis with a stepwise backward technique was used, including the possible factor combinations, to assess independence of the prognostic factors. The independent risk factors calculated with this technique were used to construct 8 different prognostic profiles. Their rates over time were calculated for each of these profiles.

Next, it was attempted to estimate the lead time, meaning the length of time by which the detection of the locoregional cancer recurrence had been brought forward by the current follow-up schedule. We used the formulas developed to estimate the lead time in the general screening program for breast cancer, which have been described by Straatman et al.13 and Van Gils et al.14 These formulas show that lead time can be described based on the observed prevalence of recurrence detected at a screening examination and on the occurrence of recurrences during intervals between surveillance examinations taking place at times t1, t2, . . . , tn.

The probability that cancer will be detected at screening “J” is given by P [S] ≈ r/λ [1 − e−λΔ]. Detection of a recurrence in the interval between 2 scheduled visits is given by P[I] ≈ rΔT = r/λ [1 − e−λΔ]. Here r = locoregional cancer incidence; 1/λ = mean sojourn time, meaning the time in which preclinical cancers are detectable before becoming clinically manifest. And ΔT = length of the screening interval in years. Actual data of asymptomatic and symptomatic cancer recurrence detection in our study group were used to calculate the mean lead time. With the above mentioned formulas at hand, we then evaluated how altering the number of routine visits during follow-up affected the detection rates for asymptomatic recurrence.

RESULTS

Population. A total of 402 patients with laryngeal cancer met the inclusion criteria. Most of the patients (62.7%) had glottic laryngeal cancer, many (37.1%) had supraglottic laryngeal cancer, and a single patient (0.2%) had subglottic laryngeal cancer. The peak incidence was in the seventh decade of life and the man-to-woman ratio was 8.6:1.0. The mean duration of follow-up was 61 months, with a median of 66 months. The 5-year overall survival rate for the 402 patients was 73%.

Survival. Overall survival calculated from the detection date of the recurrence (date of positive histology) in the 94 patients who had a relapse was 69% at 12 months and 47% at 5 years (Figure 1).

Follow-up Protocol. According to the medical records, the 402 patients made 4639 routine visits to our clinic. Thus, 98% of the planned routine visits took place.15

Local and Regional Cancer Recurrence. A total of 94 (23%) of the 402 patients had a local and/or regional cancer relapse. In 70 patients (74%), it developed at the primary tumor site, whereas 10 of them also had a regional recurrence in the neck.
In 24 patients (26%), cancer recurrence was detected at a lymph node in the neck, without any local relapse.

In the majority of the 70 patients with a local recurrence, the therapy applied was with curative intent (60 of 70, or 86%). By the end of the follow-up period, 33 of the patients who were diagnosed with local cancer recurrence had died (47%); 27 of these 33 (82%) deaths were due to cancer.

In the group of patients with recurrence in the neck (n = 24), 14 of the 24 (58%) patients were treated with the intent to cure. During the follow-up, 17 of the 24 patients died (71%), 13 of them due to cancer (76%). In the 10-year follow-up program, 88% of the local and regional recurrences developed in the first 3 years. The mean interval was 19 months; the median was 12 months (Figure 2).

**Asymptomatic Locoregional Recurrence Detection and Treatment Options, Survival, and Mortality.** Eighty-five of the 94 patients could be assigned to 1 of 3 groups. The first consisted of patients with screen-detected locoregional recurrences (n = 19). The second consisted of patients with a locoregional recurrence detected at a routine visit while symptoms were present (n = 41). And the last group comprised those patients whose tumor had been detected at an additional visit, which was arranged because symptoms had emerged (n = 25). In the 9 patients, the mode of detection was either unknown or the recurrence was detected at an extra visit without symptoms present. There was no difference between the 3 groups with respect to the time interval between the primary malignancy and the recurrent tumor (p = 0.71). The groups were comparable for age, sex, tumor stage, cT classification, cN classification, histology, and therapy (surgery, radiotherapy, or a combination) for the primary tumor.

Furthermore, no difference was found between the types of therapy applied (surgery and/or radiotherapy) for the locoregional recurrence. Also, no difference was found in the intention of the therapy applied, be it curative or palliative. The cause of death—from cancer or due to other reasons—did not differ among the 3 groups. Finally, no difference was found among the groups with respect to survival.15 Table 1 summarizes the number of patients and the p values.

**Risk of Local or Regional Cancer Relapse.** In the univariate analysis, the cT classification, smoking habit, cN classification, localization of the primary malignancy, tumor stage, and histology were found to influence the risk of local or regional cancer relapse. These variables were then analyzed multivariately and were computed again in the patient group to establish their multivariate p values. Primary tumor cT classification (p = .004), continuing to smoke after detection of the primary malignancy (p = .09), and poor histological differentiation (p = .001) proved to be independent prognostic factors (Table 2).

The largest difference in the risk of locoregional cancer relapse was found by applying the dichotomization cT 1 versus cT 2–4. By stratifying the study population according to the 3 prognostic factors mentioned above, 8 groups (I–VIII) could be formed. We calculated the risk that locoregional cancer recurrence would develop in these groups. Table 3 shows the proportion of patients with locoregional cancer relapse during the follow-up period.

A risk of 20% or less was considered a relatively low risk for locoregional cancer recurrence. Therefore group I (n = 114) formed the low-risk group, whereas groups II to VIII (n = 288) were combined to form the high-risk group. This way there would still be a sufficient number of patients in the low-risk group. Moreover, there would be a big difference in risk between the low- and high-risk groups according to Table 3. The same calculation was performed on these 2 groups as on groups I to VIII. The low-risk group had a locoregional failure risk of 15% compared with 29% in the high-risk group over a period of 5 years. There was a significant difference in risk of locoregional recurrence among these groups (p = .004). The overall risk of locoregional failure in all the patients (n = 402) over a period of 5 years was 25% (Figure 3).
Estimating the Lead Time. The length of time by which the detection date was brought forward prior to presentation of symptoms was estimated using the current mode of follow-up examinations (history and physical examination). It was difficult to enter the data derived from our population into the lead-time formula because not all the patients had adhered precisely to the schedule of routine visits. Also, the interval between the routine visits differed each year. To simplify our calculation, the duration of follow-up was limited to 3 years and the interval between the routine visits was set at 3 months on average, meaning that 12 routine visits were conducted. In our patients with laryngeal cancer who were treated with curative intent, the 3-year locoregional relapse rate was approximately 25\% (Figure 3).

Figure 4 shows the predicted asymptomatic screen-detection rates using the formula previously derived, with various lead times of 0.5 to 2 months (third line from below) and a visit interval of 3 months, the average percentage of asymptomatic tumors detected at each routine visit would be 53\%. Monthly intervals (instead of tri-monthly) would increase the detection rate to 76\% (same line shifts to the left). With intervals every 6 or 12 months, the detection rates would be 32\% and 16\%, respectively (same line shifts to the right). In our population, the asymptomatic screen-detection rate turned out to be 20\%. According to Figure 4, the lead time must be approximately 2 to 4 weeks (a point between the lowest line and the second lowest line in the figure).

If the screening interval is set at 1 month and the lead time is set at 0.5 month, according to Figure 4, 50\% of the recurrences will be detected asymptotically. In order to estimate a kind of “number needed to screen” to detect 1 case of asymptomatic recurrence, we made a very rough calculation comprising a cohort of 400 patients developing 100 recurrences within 3 years. In a cohort of 400 patients under surveillance for

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>No.</th>
<th>Assumed high risk</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value (univariate)</th>
<th>p value (multivariate)</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>360</td>
<td>Male</td>
<td>0.83</td>
<td>0.45–1.53</td>
<td>.55</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>53</td>
<td>≥6 units</td>
<td>1.35</td>
<td>0.76–2.39</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>184</td>
<td>≥65</td>
<td>0.98</td>
<td>0.65–1.48</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>Therapy primary tumor</td>
<td>326</td>
<td>Radiotherapy</td>
<td>1.26</td>
<td>0.71–2.22</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>cT classification*</td>
<td>245</td>
<td>T2–4</td>
<td>2.19</td>
<td>1.39–3.47</td>
<td>.0008</td>
<td>.004</td>
</tr>
<tr>
<td>Smoking*</td>
<td>86</td>
<td>Continuation</td>
<td>1.46</td>
<td>0.93–2.29</td>
<td>.10</td>
<td>.09</td>
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<tr>
<td>cN classification</td>
<td>61</td>
<td>N+</td>
<td>1.61</td>
<td>0.95–2.73</td>
<td>.08</td>
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<tr>
<td>Localization</td>
<td>149</td>
<td>Supraglottic</td>
<td>1.78</td>
<td>1.19–2.67</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td>248</td>
<td>II–IV</td>
<td>2.14</td>
<td>1.35–3.38</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Histology (differentiation)*</td>
<td>64</td>
<td>Poor</td>
<td>2.34</td>
<td>1.49–3.68</td>
<td>.0002</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Independent prognostic factor by multivariate analysis.
36 (months) \approx 14,000 \text{ routine visits will achieve 50 screen-detected tumors. A lead time of 1 month would detect approximately 64 asymptomatic recurrences (Figure 4). Therefore, to screen-detect 1 locoregional cancer recurrence, } \frac{14,000}{50} = 280 \text{ or } \frac{14,000}{64} = 219 \text{ routine visits would have to be conducted.}.

**DISCUSSION**

Almost one fourth of the patients who received curative treatment for laryngeal carcinoma at our center were diagnosed with local or regional cancer recurrence. They had all entered the same strict nationwide follow-up program that was set up to detect asymptomatic local and regional cancer recurrences, despite the fact that there were only limited therapeutic options left for some patients who had undergone total laryngectomy for advanced-stage disease.\(^\text{16}\)

Asymptomatic locoregional cancer detection did not lead to differences in the therapy applied, to reductions in cancer-specific mortality, or to improved survival. In addition, the detection date of locoregional cancer recurrence was not found to have been brought forward by the screening program. This suggests that a short lead time should be taken into consideration in screening programs for recurrence in patients treated for laryngeal cancer.

The follow-up program runs for 10 years after treatment for the primary laryngeal tumor. The locoregional recurrences mainly developed in the first 3 years. Thus, the question arises as to whether the follow-up program can be shortened to 3 years. This would not disregard the interests of patients who develop metastases, because most of the distant metastases develop in the same period.\(^\text{17}\) Second primary malignancies in the head and neck region develop at a constant rate over the follow-up period, but their incidence is low compared with locoregional cancer recurrences.\(^\text{18}\)

To determine which patients run a high risk of local or regional cancer recurrence, we analyzed a set of variables to evaluate their prognostic value. Three independent variables were found, and calculations on recurrence rates were performed on

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**Table 3.** Risk of locoregional recurrence during follow-up in relation to combinations of prognostic factors.

<table>
<thead>
<tr>
<th>Histology</th>
<th>cT classification</th>
<th>Smoking Group</th>
<th>Risk by months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Well/moderately differentiated</td>
<td>1</td>
<td>Cessation I</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuation II</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>2–4</td>
<td>Cessation III</td>
<td>0.12</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1</td>
<td>Continuation IV</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cessation V</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuation VI</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>2–4</td>
<td>Cessation VII</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuation VIII</td>
<td>0.33</td>
</tr>
</tbody>
</table>

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**FIGURE 3.** Locoregional recurrence rate for low-risk and high-risk group. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**FIGURE 4.** Detection rate of asymptomatic locoregional recurrences by variation in screening interval and lead time.
combinations of these variables. Localization supraglottic, tumor stage II to IV, and N+ classification seem to be risk factors in the univariate analysis. In the multivariate analysis, however, they proved to be interdependent. Compared with glottic tumors, supraglottic tumors are more often detected at a more advanced stage, including the cT classification. Ultimately, a low-risk group and a high-risk group were formed. The risk of local or regional cancer recurrence in the low-risk group was 15% compared with 29% in the high-risk group during the first 5 years of follow-up. In our opinion, the difference in recurrence risk between the low- and high-risk groups was not large enough to justify restricting participation in the follow-up program to the high-risk group.

The value of the screening program would improve if all the locoregional recurrences were detected at an asymptomatic stage. This could be accomplished by intensifying testing, ie, arranging more frequent routine visits or by developing more sensitive techniques to detect asymptomatic recurrence. Because the majority of patients were no longer asymptomatic when the locoregional recurrence was detected, and the average frequency of routine visits was once every 3 months over the first 3 years of follow-up, it can be expected that only a short time is spent in a detectable preclinical phase (the sojourn time).19 A short sojourn time implies that to detect the lesion earlier, routine follow-up visits should be planned at short intervals. Our estimates point to a lead time of at most 4 weeks.

This very short lead time explains the large number of recurrences that were detected at a routine visit when symptoms were already present. Patients whose symptoms emerged just after a routine visit might not have paid them much attention because of the recent reassurance. It was also possible that some patients waited with their symptoms until the next prescheduled visit. A rough estimate showed that the aim of enhancing the rate of asymptotically detected locoregional recurrences would require an excessive number of prescheduled visits.

CONCLUSION

Despite the great efforts made by patients and physicians to adhere strictly to the follow-up schedule, there are no indications that asymptomatic locoregional recurrence detection results in better treatment options, reduced cancer mortality, or improved survival. Important prognostic factors for local or regional cancer recurrence appeared to be continuation of smoking after treatment, the cT classification of the initial tumor, and the histology. It was possible to define a high-risk group for locoregional cancer recurrence, but the difference in risk between the low-risk and the high-risk groups was not substantial. The percentage of recurrences in the low-risk group is still high. This prevents us from withholding routine follow-up from the low-risk group without investigating how so doing would affect their life expectancy.

To detect more recurrences at an asymptomatic stage, an enormous number of prescheduled visits would have to be added to the follow-up program, due to the (estimated) short lead time. For now, the emphasis of the follow-up program should be on the emotional well-being of the patient and on the treatment of complications of the therapy applied. Patients should be strongly encouraged to refrain from smoking. After the third year of follow-up, the screening program can be discontinued.

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REFERENCES


Screening for Recurrence in Laryngeal Cancer