Effect of Routine Follow-up After Treatment for Laryngeal Cancer on Life Expectancy and Mortality

Results of a Markov Model Analysis

Savitri C. Ritoe, MD[1]
Femmie de Vegt, MSc, PhD[2]
Inger M. Scheike, MSc[2]
Paul F. M. Krabbe, MSc, PhD[3]
Johannes H. A. M. Kaanders, MD, PhD[4]
Frank J. A. van den Hoogen, MD, PhD[1]
André L. M. Verbeek, MD, PhD[2]
Henri A. M. Marres, MD, PhD[1]

[1] Department of Otorhinolaryngology-Head and Neck Surgery, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

[2] Department of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

[3] Department of Medical Technology Assessment, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

[4] Department of Radiation Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

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Address for reprints: Savitri C. Ritoe, MD, Department of Otorhinolaryngology-Head and Neck Surgery, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands; Fax: (011) 0031-243540251; E-mail: s.ritoe@kno.umcn.nl

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BACKGROUND. Routine follow-up is offered to all patients with laryngeal cancer who are treated with curative intent. Although time and resources are devoted to surveillance, the effect of asymptomatic recurrence detection is not well understood. For this study, the authors evaluated the effect that routine follow-up may have on life expectancy and disease-specific mortality rate for patients with laryngeal cancer.

METHODS. Using a Markov model, a cohort simulation was performed on 4 hypothetical age groups of patients with laryngeal cancer. Three different follow-up strategies were compared—the current schedule, no follow-up, and the perfect follow-up—in which all recurrences were detected asymptomatically. Sensitivity analyses were performed to study the impact of variations in the transition rates on life expectancy.

RESULTS. Compared with no follow-up, the current schedule showed a gain in life expectancy with a range from 0.3 years to 1.5 years that decreased with advancing age. Abolishing the current follow-up schedule raised the disease-specific mortality rate; the increase ranged from 2.8% to 5.9%. Variations of ±25% in the transition rates produced only a modest effect on life expectancy.

CONCLUSIONS. A small reduction in life expectancy was observed when follow-up was withheld from the majority of patients. Disease-specific mortality rates rose when no follow-up was provided. These rates probably were overestimated. A simplified version of the current follow-up protocol may be implemented. ***Cancer* 2007;109:239–47.** © *2006 American Cancer Society.*

KEYWORDS: Markov model, follow-up, laryngeal cancer, life expectancy, mortality.

Posttreatment surveillance is part of the treatment protocol for patients with laryngeal cancer, because it is believed that the detection of asymptomatic recurrences or second primary tumors is an important factor in prolonging life expectancy (LE). Follow-up also is intended to reduce disease-specific mortality (DSM). The other objectives of follow-up—detection and treatment of complications, evaluation of medical treatment, and provision of psychosocial support—were not considered in the current study.

Several studies have been published on the value of follow-up for patients with head and neck cancer. Some authors advocate thorough follow-up, citing a substantial incidence of recurrences and second primary malignancies. Others recommend limiting surveillance to the first years after curative treatment.[1–3] Unfortunately, this debate is hampered by a lack of comparative empirical data. Postoncologic surveillance has been evaluated for several other malignancies; however, no benefit has been observed for patients with breast cancer or colon carcinoma.[4–7]

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This lack of benefit may be caused by the differences between postoncologic surveillance programs and nationwide primary cancer screening programs. Patients who already have received oncologic treatment but go into recurrence have a poorer prognosis compared with patients who have primary malignancies. Some other factors probably also are involved: the limited therapeutic options in the event of cancer recurrence and are applicable to both the postoncologic surveillance and the general screening programs: the detection of slow-growing tumors (length-time bias) and the magnitude and adjustment of the lead time.[8–11]

According to the current protocol, patients who have received curative treatment for laryngeal cancer continue to visit our clinic regularly, nearly 22 times over a period of 10 years. Surveillance is more intensive during the first years after treatment. One objective is to detect recurrences, because the rate of recurrence is higher early during follow-up. Another objective is to treat any posttreatment complications that may arise. After they receive curative treatment, all patients enter the follow-up program, which includes a routine visit every 2 months during the first year of follow-up, a visit every 3 months in the second year, and a visit every 4 months in the third year. In the fourth and fifth years, the patient is seen every 6 months. Many patients are screened annually for up to 10 years. Between their prescheduled visits, the patients are free to make another appointment if they notice any symptoms (extra or additional visits).[12] The follow-up schedule adopted at our clinic conforms to the nationwide recommendations for laryngeal cancer treatment in the Netherlands.[13,14] There is no internationally accepted standard protocol.

It is not deemed ethical to conduct a randomized controlled trial in which 50% of the patients are excluded from routine follow-up without strong evidence that such surveillance is ineffective. In the current study, we evaluated the effect of the current follow-up protocol on LE and DSM. These effects were calculated and were compared with the results from 2 alternative schedules: a schedule that abolished all routine visits and another schedule that adhered to a perfectly conducted, routine follow-up in which all cancer recurrences were detected asymptomatically. This exercise was performed with a Markov model, and the results were combined with data on the current follow-up of patients with laryngeal cancer as observed in a previous study.[12]

MATERIALS AND METHODS

The Study Population

Measured data were derived from a cohort of 402 patients with laryngeal cancer who were referred to our clinic between January 1990 and January 1995. All patients had squamous cell carcinoma and were treated with curative intent. The most common site involved was the glottic region (62.7%) followed by the supraglottic region (37.1%) and the subglottic region (0.2%). The peak incidence was in the seventh decade of life, and the ratio of men to women was 8.6:1.0. The mean duration of the follow-up program was 61 months (median, 66 months). The 5-year overall survival rate for all 402 patients was 73%. During the follow-up, 156 patients developed recurrent cancer.

In 94 patients (60.2%), recurrent cancer developed at the primary tumor site or in a cervical lymph node. Fifteen patients (9.6%) developed a primary tumor in the head and neck region, and 17 patients (10.9%) developed a primary tumor in the lungs. Distant metastases were detected in 15 patients, and 15 patients developed a malignancy elsewhere in the body.

Patients with recurrent cancer were divided according to the presence of symptoms that indicated the recurrence (yes or no) and by the mode of detection (at a routine visit or at an additional visit in between routine visits). Thirty-seven patients had a malignancy detected in the preclinical phase at a routine visit, and 101 patients had symptoms that indicated recurrent cancer detected either at a routine visit or at an additional visit.

The Markov Model

Markov models are implemented for clinical problems in which the risk of an event is continuous over time. For the current study, we used a Markov chain model that was developed previously and was intended to evaluate the effectiveness of presymptomatic detection of breast cancer recurrence.[15] The model allowed us to make a comparison between the current protocol and various alternatives.

The progression of disease is described by the model as a finite sequence of discrete states of illness, also referred to as health states.[16] Consistent with a Markov model, we assumed that a patient is always in 1 of these health states. Transitions are possible between the various states. The model starts at a fixed stage of disease or a certain occasion within a treatment protocol. A hypothetical group of patients of the same age enters the model directly after receiving treatment for laryngeal cancer. During follow-up, the patients are cycled through this model and become redistributed in a specific time span. Because the calculations are based on proportions and rates, the absolute number of patients entered in the model is irrelevant to the outcome of the exercise.

A Markov chain model was designed to describe the history of laryngeal squamous cell carcinoma.

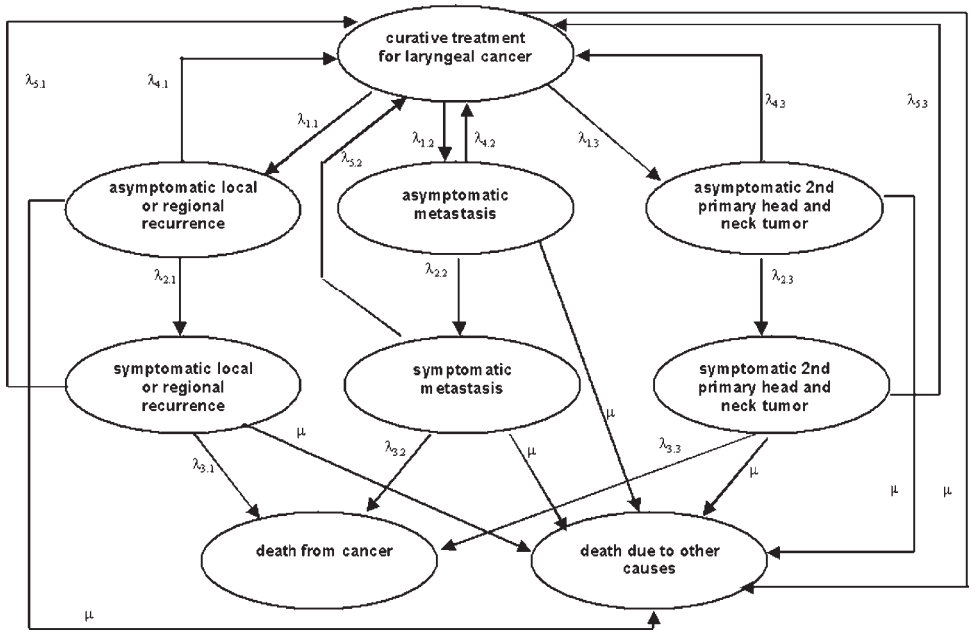

FIGURE 1. Markov chain model representing the history of patients who have received curative treatment for squamous cell laryngeal carcinoma. The Greek letter λ indicates the disease progression rate, the *i* in $\lambda_{i,j}$ refers to the progression from 1 health state to another, and *j* indicates recurrent disease (either local or regional recurrence, metastasis, or second primary head and neck cancer).

The model recognizes 7 health states and 2 states of death (Fig. 1).

At first, all patients are subsumed under the health state *curative treatment for cancer*. At the end of a cycle, a fraction of the initial cohort is apportioned to subsequent states according to the transition probabilities. Patients may remain in the same state; they may develop asymptomatic or symptomatic locoregional recurrence; they may develop second primary head and neck cancer or metastases; or they may die of some other cause. The onset of recurrent cancer is not detectable. The recurrence will be detected, either asymptomatically or in light of symptoms, as the disease progresses. Subsequently, patients may recover from the recurrent cancer; or they may die of recurrent cancer or of some other unrelated cause. At the end of the simulation, all patients eventually end up in the absorbing states of *death from cancer* or *death from other causes*.

In this study, cohort simulations were performed on 4 hypothetical groups of patients aged 40 years, 50 years, 60 years, or 70 years who were cycled through the model separately. The duration of each cycle was 1 year.

Transition rates

Transition rates are defined as the proportion of patients who shift from 1 state to another during a fixed 1-year interval. These rates are depicted in the model by Greek letters (λ indicates the disease progression rate, and μ indicates the natural mortality rate. The *i* in $\lambda_{i,j}$ refers to the progression from 1 health state to another, and *j* refers to recurrent cancer (either local or regional recurrence, metastasis, or second primary head and neck cancer). The rates presented here were derived from a study by Ritoe et al.[12] and were supplemented by findings from the literature and assumptions based on academic knowledge.[17] The μ (death from other causes) depends on age and sex and is considered to be equal for each health state. Mortality rates and general LE are derived from the Central Bureau of Statistics (Statistics Netherlands, 2002).[18] Table 1 lists all of the transition rates that were used for the calculation of the 3 different follow-up strategies.

Calculation of transition rates

Calculations were performed by using the cancer recurrence and survival data measured by Ritoe et al.[12] Table 1 shows all of the transition rates for the 3 strategies—the current follow-up protocol, no follow-up, and the perfect follow-up—when all recurrences are detected asymptomatically.

From curatively treated to the asymptomatic state: λ_1

This transition is not constant over time for locoregional recurrences or metastases. Almost 90% of all locoregional recurrences develop in the first 3 years of follow-up.[19] Metastases also are found predominantly during the first years of follow-up.[20] For locoregional recurrences and metastases, this transition can be described by an exponential declining function $R = R_0 \cdot {}^{-\lambda 1 \cdot t}$, where R is the number of patients who are recurrence free at time zero, λ_1 is the average recurrence rate per year, and t is the time in years. The recurrence rate declined on an S-curve. Data needed for the calculation were the proportion

TABLE 1
Transition Rates for the Current Follow-up, No Follow-up, and the Perfect Follow-up

Transition*	Current follow-up	No follow-up	Perfect follow-up†
Curatively treated to asymptomatic state			
$\lambda_{1.1}$	0.039	0.039	0.039
$\lambda_{1.2}$	0.002	0.002	0.002
$\lambda_{1.3}$	0.114	0.114	0.114
Asymptomatic to symptomatic state			
$\lambda_{2.1}$	4.196	4.196	4.196
$\lambda_{2.2}$	3.798	3.798	3.798
$\lambda_{2.3}$	1.791	1.791	1.791
Symptomatic state to death from cancer‡			
$\lambda_{3.1}$	0.107	0.109	0.106
$\lambda_{3.2}$	1.100	1.364	0.937
$\lambda_{3.3}$	0.109	0.111	0.107
Asymptomatic state to curatively treated‡			
$\lambda_{4.1}$	0.165	0	0.737
$\lambda_{4.2}$	0	0	0
$\lambda_{4.3}$	0.316	0	0.923
Symptomatic state to curatively treated‡			
$\lambda_{5.1}$	0.484	0.803	0.803
$\lambda_{5.2}$	0	0	0
$\lambda_{5.3}$	0.362	0.440	0.440
Any health state to death from other causes§			
μ			

* λ Indicates the disease progression rate; μ indicates the natural mortality rate. The i in $\lambda_{i.j}$ refers to the progression from 1 health state to another, and j refers to disease recurrence.
† All recurrences are detected asymptomatically.
‡ Varies by follow-up strategy.
§ Depends on age and gender.

of patients who develop a new tumor during 2 years, 3 years, 5 years, and 7 years of follow-up.

Second primary tumors develop with a constant rate in time. Our recurrence rate was consistent with findings in the literature.[17] The formula for recurrences that develop at a constant rate is given by $\lambda = (-l/t) * \ln (R_t/R_0)$. In this equation, λ is the transition rate, R_t/R_0 is the fraction of the cohort that is recurrence free at time t, and t is the time at which the recurrence-free time is measured. Data needed for this calculation are the percentage of recurrence-free patients after 2 years, 3 years, 5 years, and 7 years of follow-up.

The value of λ_1 was calculated for the 3 types of recurrences: locoregional recurrences ($\lambda_{1.1} = 0.039$), metastases ($\lambda_{1.2} = 0.002$), and second primary tumors ($\lambda_{1.3} = 0.114$). The value of λ_1 was not altered by changing the current follow-up protocol to either *no follow-up* or the *perfect follow-up*.

From the asymptomatic state to the symptomatic state: λ_2

Data on all visits to our outpatient clinic, both routine and extra visits, were collected from the patients' medical records. For this analysis, we needed to calculate the mean sojourn time (MST) (the length of time the tumor spent in the detectable preclinical stage). The time between the last visit and the visit at which an asymptomatic tumor was detected was derived from the patient's record. The mean of these numbers defined the MST ($MST = 1/\lambda_2$). The value for λ_2 was calculated for the 3 recurrence types: locoregional recurrences ($\lambda_{2.1} = 4.196$), metastases ($\lambda_{2.2} = 3.798$), and second primary tumors ($\lambda_{2.3} = 1.791$). The value of λ_2 was not altered by changing the current follow-up protocol to *no follow-up* or the *perfect follow-up*.

From the symptomatic state to death by cancer: λ_3

The mortality rate of symptomatic patients was considered to be constant. The mathematical relation between survival and time can be described by a decreasing exponential function: $S_t = S_0 * e(-m * t)$, where S_t is the number of symptomatic patients with cancer recurrence at time t, S_0 is the number of symptomatic patients with cancer recurrence at time zero, m is the mortality rate per year (ie, the transition rate λ_3), and t is the time when survival is measured. According to the Declining Exponential Approximation of Life Expectancy method,[16] the relation between LE and the mortality rate (m) is $LE = 1/m$. Combining the 2 formulas results in $m = (-1/t) * \ln(S_t/S_0)$. The data required for this calculation were 1) the survival rate of symptomatic patients through time and 2) the mortality rate of patients with a specific type of recurrence, In the group of 156 patients who had recurrent cancer, 73 patients died of cancer. Only 2 of those patients had a prolongation of survival beyond 5 years of follow-up. Thus, 85 patients remained alive 5 years after the detection of recurrent cancer (54.5%).

The calculated λ_3 values were as follows: Of 94 patients who had locoregional recurrences, 39 patients died of cancer within 5 years (survival $= [94 - 39]/94 = 0.585$; $m = \lambda_{3.1} = 0.107$; LE = 9.3 years). Of 15 patients who had metastases, 10 patients died of cancer within 1 year (1-year survival = 0.333; $m = \lambda_{3.2} = 1.100$; LE = 0.9 years). Of 43 patients who had second primary tumors, 18 patients died of cancer within 5 years (5-year survival = 0.581; $m = \lambda_{3.3} = 0.109$; LE = 9.2 years). When this formula was applied, a lead time of 2 months for symptomatic recurrences was assumed.

From the asymptomatic state to curatively treated: λ_4

This transition is calculated by using the percentage of tumors detected asymptomatically at a routine visit and the percentage of asymptomatic patients who are treated with curative intent. Using the formula asymptomatic detection rate * cure rate gives the transition rate λ_4.

Among 156 patients with recurrent cancer, the recurrences in 37 patients were detected asymptomatically at a routine visit. Of these 37 patients, 26 were treated with curative intent.

The numbers of different types of recurrence were as follows: Of 19 patients who had screen-detected locoregional recurrences, 14 patients were treated with curative intent; of 5 patients who had screen-detected metastasis, zero patients were treated with curative intent; and, of 13 patients who had screen-detected second primary tumors, 12 patients were treated with curative intent. Applying the formula, provides us with the following values for λ_4: locoregional recurrence, $\lambda_{4.1} = 0.165$; metastasis, $\lambda_{4.2} = 0$; and second primary tumor, $\lambda_{4.3} = 0.316$.

When no routine visits take place, the detection of any cancer recurrences will be based on symptoms. Therefore, λ_4 will be equal to zero in all cases. In the perfect follow-up, all recurrences are detected asymptomatically, thereby resulting in different values for λ_4.

From the symptomatic state to curatively treated: λ_5

This transition is calculated by using the formula asymptomatic detection rate * cure rate, yielding the transition rate λ_5. Of 66 patients who had locoregional recurrences detected, 53 patients were treated with curative intent; of 9 patients who had metastases detected, zero patients were treated with curative intent; and, of 25 patients who had second primary tumors detected, 11 patients were treated with curative intent. Applying the formula provides the value of λ_5 for locoregional recurrence ($\lambda_{5.1} = 0.484$), metastasis ($\lambda_{5.2} = 0$), and second primary tumor ($\lambda_{5.3} = 0.362$).

In case of *no follow-up*, all recurrences will be detected symptomatically, resulting in different values for λ_5. In the *perfect follow-up*, all recurrences are detected asymptomatically. Because treatment still is possible in the symptomatic state, however, λ_5 is considered to be equal to the value for *no follow-up*.

From the curatively treated, asymptomatic, or symptomatic state to death by other causes: μ

Death from other causes was described in a mathematical function fitted to the data obtained from Statistics Netherlands. The following formula yielded an almost perfect fit: $\mu = e\ (0.1202 * ((t + \text{age}) - 106.0123) + 0.0002 * ((t + \text{age}) - 106.1023\ ** 2)$, where μ is the mortality rate per year; *age* is the age at which a specific cohort of men or women started (in years); and t is the time measured (in years).

Model assumptions

Changing the current follow-up protocol does not alter the proportion of patients entering the subclinical disease state (λ_1). It is not expected that the number of routine visits will have any influence on the mean sojourn time, ie, the time in which preclinical cancers are detectable. Therefore, the transition from the asymptomatic state to the symptomatic state (λ_2) was expected to be the same for each of the follow-up strategies. Calculation of the transition rate from the symptomatic state to death from cancer (λ_3) was based on the findings in the previously conducted study. However, because survival was calculated from the date recurrent cancer was detected, we had to take into account the lead time by which the detection date was brought forward for the asymptomatically discovered malignancies. In that study, the lead time for local or regional cancer recurrences was estimated to be 1 month. For metastases and second primary head and neck malignancies, would be somewhat longer. In the current study, we assumed that stopping surveillance because of the symptomatic detection of recurrence would postpone detection by approximately 2 months. The reverse was assumed when all recurrences were detected asymptomatically. Accordingly, during the perfect follow-up, the lead time was assumed to increase by 2 months.

Changing the current follow-up protocol influences λ_4 (the transition from an asymptomatic state to curative treatment for cancer) and λ_5 (the transition from a symptomatic state to curative treatment for cancer), because the number of patients in each state is altered. When follow-up is no longer executed, all recurrences will be detected in a symptomatic state; therefore, the transition from the asymptomatic state to the curatively treated state will be reduced to zero. In case of *no follow-up*, all recurrences will be detected symptomatically, resulting in different values for λ_5. In the *perfect follow-up*, all recurrences are detected asymptomatically. Because treatment still is possible in the symptomatic state, however, λ_5 is considered equal to the value for *no follow-up*. The μ (death from other causes) was considered the same for each health state: It was equal to the natural death rate of the general population and, thus, increased with age.

Patients cycled the model only once, and it was assumed that patients developed only 1 type of recurrence. This can be justified by the observation that, in our clinic, the strict routine follow-up schedule is abandoned when patients have developed a malignancy. The recurrence rate for all types of malignancies was assumed to be equal for men and women.

Effect Measures: LE and DSM

In the Markov model, each patient is assigned a number of credits for the length of time spent in a

TABLE 2
Effect of 3 Follow-up Strategies on Life Expectancy, and Cancer-Related Death, in Patients Ages 40 Years, 50 Years, 60 Years, and 70 Years

	Aged 40 years		Aged 50 years		Aged 60 years		Aged 70 years	
Follow-up schedule	Men	Women	Men	Women	Men	Women	Men	Women
Life expectancy, y								
Current follow-up	27.8*	30.2	22.2	24.9	16.2	19.2	10.5	13.1
No follow-up	26.6	28.7	21.4	23.9	15.8	18.5	10.2	12.8
Perfect follow-up†	31.9	35.0	24.7	28.0	17.5	20.9	11.0	13.9
In the general population	37.0	41.2	27.7	31.9	19.1	23.1	11.8	14.9
Cancer-specific mortality, %								
Current follow-up	42.7	46.4	33.6	37.9	23.9	28.6	14.7	18.9
No follow-up	48.3	52.3	38.5	43.2	27.9	33.1	17.5	22.2
Perfect follow-up†	24.3	26.9	18.4	21.2	12.6	15.3	7.3	9.6

* Base value for sensitivity analysis.

† All recurrences are detected asymptomatically at a routine visit.

specific health state. The LE is the sum of all credits obtained during the simulation and is determined by the route of states that each patient has taken. The outcome of LE for the current protocol was calculated for the separate age groups and was compared with 2 other situations: no follow-up and the perfect follow-up, in which all cancer recurrences are detected asymptomatically. Using the Markov model, the DSM rates were calculated.

Sensitivity Analysis

Estimates of the value of transition rates contain a certain amount of uncertainty. A sensitivity analysis was performed to investigate the impact of variations in the transition rates on the results. All transition rates were varied by ±25% of their value. They were varied grouped together, ie, λ_1 was varied for all types of malignancies together ($\lambda_{1.1}$, $\lambda_{1.2}$, $\lambda_{1.3}$). The impact on the absolute length of LE and the gain in life years was determined for men aged 40 years, because it was expected that variations would have the greatest impact in this age group. The impact was then compared with their LE in the current follow-up protocol (27.8 years). First, all transition rates were varied individually, and the results were displayed; then, we investigated the effects of a model that included the most positive and most negative assumptions for all parameters in 1 model.

The Markov model was constructed with the software Tree Age DATA 4.0. Statistical software (SAS version 8.2) was used to calculate the parameters LE and DSM and to perform the sensitivity analysis.

RESULTS

LE and Mortality

The difference between the current follow-up strategy and no follow-up with respect to LE showed a decrease that ranged from 1.2 years to 0.8 years for men aged 40 years and 50 years and a decrease of from 0.4 years to 0.3 years for men aged 60 years or 70 years. In women, the impact of discontinuing follow-up had a slightly greater impact on reducing LE. The increase in the DSM rate seems high in the group of patients aged 40 years (5.6% for men and 5.9% for women). This percentage quickly reduces to 2.8% and 3.3% for men and women aged 70 years, respectively. When the perfect follow-up schedule is conducted, the estimated increase in LE in men aged 60 years and 70 years will be 1.3 years and 0.5 years, respectively. The results are summarized in Table 2.

Sensitivity Analysis

In the sensitivity analysis, the most important parameter for determining LE turned out to be variations in λ_1. When the number of patients who developed an asymptomatic cancer recurrence was raised by 25%, the LE declined by 1.2 years. Decreasing the asymptomatic recurrence rate resulted in an increased LE of 1.6 years. However, this transition rate is not influenced by the follow-up program. The variation in λ_3 also influenced LE. The percentage of patients who die after developing recurrent cancer, however, will be influenced particularly by their remaining therapeutic options after recurrence. The influence of changes in the other transitions rates lead only to small changes in the LE. Table 3 lists all

TABLE 3
Sensitivity Analysis: Range ±25% for All λ Values in Men Aged 40 Years With a Life Expectancy of 27.8 Years

Transition	Basis value	−25%	Life expectancy, years	Life years gained*	+25%	Life expectancy, years	Life years gained*
Curatively treated to asymptomatic state							
$\lambda_{1.1}$	0.039	0.029	29.4	+1.6	0.049	26.6	−1.2
$\lambda_{1.2}$	0.002	0.002			0.002		
$\lambda_{1.3}$	0.114	0.086			0.142		
Asymptomatic to symptomatic state							
$\lambda_{2.1}$	4.196	3.146	27.8	0	5.246	27.8	0
$\lambda_{2.2}$	3.798	2.848			4.748		
$\lambda_{2.3}$	1.791	1.341			2.241		
Symptomatic state to death from cancer							
$\lambda_{3.1}$	0.107	0.080	29.4	+1.6	0.134	26.5	−1.3
$\lambda_{3.2}$	1.100	0.825			1.375		
$\lambda_{3.3}$	0.109	0.082			0.136		
Asymptomatic state to curatively treated†							
$\lambda_{4.1}$	0.165	0.124	27.3	−0.5	0.206	28.4	+0.6
$\lambda_{4.2}$	0	0.1			0.1		
$\lambda_{4.3}$	0.316	0.237			0.395		
Symptomatic state to curatively treated†							
$\lambda_{5.1}$	0.484	0.363	26.8	−1.0	0.605	28.6	+0.8
$\lambda_{5.2}$	0	0.1			0.1		
$\lambda_{5.3}$	0.362	0.272			0.452		

* Compared with life expectancy in the current follow-up protocol.
† Instead of 0.0, 0.1 was used in this calculation.

of the variations in transition rates and their calculated LE ranges. Table 4 lists the boundaries within which LE can differ, from most positive to most negative, in the sensitivity analysis for all $\lambda_{i.j}$, ranges.

TABLE 4
Sensitivity Analysis for Men Aged 40 Years of Age: Gain in Life Expectancy (in Years) Based on the Most Positive and Most Negative Set of Transition Rates

	$\lambda_{i.j}$ Transition rates	
Variable	Most positive	Most negative
Life expectancy, y	31.6	23.3
Gain in life-years	+3.8	−4.5

DISCUSSION

Because the general population is aging and more women are smoking, more individuals will suffer from laryngeal cancer.[21] Accordingly, more patients will enter the follow-up program, thereby expanding the screening population. Previously, we addressed the value of the follow-up program for patients with laryngeal cancer in the Netherlands.[12] The current study, using data on follow-up in our clinic did not demonstrate any extension of survival nor any reduction in cancer-specific mortality for patients with asymptomatically detected recurrences compared with symptomatic patients. Nonetheless, it would be unethical to withdraw patients from the current follow-up protocol without knowing how it would influence their LE and DSM. That knowledge can be produced with a Markov model that simulates the LE of patients who are treated curatively for laryngeal cancer.

The LE and DSM values were compared for 2 situations: follow-up of patients according to the existing protocol and withholding posttreatment surveillance from patients. To establish the maximal gain for these parameters, the values also were calculated for the perfect situation, in which all cancer recurrences are detected asymptomatically.

When conducting a simulation study, one objective is to describe reality in a form in which alterations of reality can be estimated. When reading the results as calculated by the model, it should be kept in mind that these are not and should not be considered measured data.

When we carefully examine our results of stopping routine surveillance on LE and DSM rates, the impact seems large. This is inconsistent with the previously conducted studies on routine follow-up.[12,22] There are some points to be considered when evaluating the results of this study. The majority of patients with laryngeal cancer are men aged $\geq$60 years. This group of patients accounts for 65% of all patients with laryngeal cancer in our clinic. The LE in this group is reduced only slightly when they obtain no follow-up. In younger patients and in women, the effect on LE reduction is greater. This reflects the overall longer LE in these groups in the general population. We assumed that death from natural causes would be the same in the patients with laryngeal cancer and in the general population, but it is not very likely that this is true. However, we found no data in the literature on this mortality rate.

Furthermore, the lead time for asymptomatic cancer detection was estimated at 2 months. There are indications that this is an overestimate.[19] Therefore, the actual difference between the symptomatic group and the symptomatic group may be reduced even more.

To simplify the calculations, all patients in the model developed only 1 type of malignancy. It should be kept in mind that some patients go on to develop a third tumor (31%), a fourth tumor, or even more. However, this risk will not be influenced by offering routine follow-up.

Previously reported data indicate that asymptomatic patients are offered treatment with curative intent more often than symptomatic patients. However, no difference in cancer-specific mortality was observed.[12] This difference in treatment will show up when follow-up modalities are varied.

The LE and DSM values were determined for the situation in which a perfect follow-up schedule is conducted. The maximal gain in LE that could be obtained in elderly patients turned out to be disappointing.

The current sensitivity analysis made it clear that the greatest variation in LE was obtained by varying 2 values: the proportion of patients entering the subclinical disease state (λ_1) and the transition rate from the symptomatic state to death by cancer (λ_3). The influence of routine visits on these transition rates is either small or nonexistent. When the transition rate is varied from an asymptomatic or symptomatic state to a curatively treated stage (λ_4 and λ_5), the differences in LE are small. The number of routine visits influences these parameters. Applying more sensitive diagnostic tests to increase the asymptomatic detection rate would be expensive. A previous study showed that the objective of conducting more routine visits to increase asymptomatic detection is not attainable because of the high number of prescheduled visits that would be needed to increase the asymptomatic detection rate.[19]

The most serious disadvantage of using a model is that it oversimplifies the study population. Some of the implications of this are discussed above. The main problem is how to construct the model. Questions may be raised about the assumption that patients can enter the symptomatic states only by passing through the asymptomatic states. We decided on this model because it already had been used in a study of screening for breast cancer. Yet a different model also would have been suitable in which the symptomatic and asymptomatic states are seen as separate entities. However, it is doubtful that using such a model would have yielded a better outcome for routine follow-up. Another problem is that not all patients enter the follow-up program with the same prognosis. A previous study indicated that patients who continued to smoke after their initial treatment ran a greater risk of developing recurrent cancer compared with patients who ceased smoking. In addition, a poor histologic grade and a T2, T3, or T4 tumor classification of the primary malignancy will contribute to an increased risk of developing cancer.[19] Once patients have received excessive treatment for an extensive primary malignancy, fewer therapeutic options will remain in the event of recurrent cancer. Mortality rates from cancer are high—>90%—in postlaryngectomy patients with recurrent disease. Furthermore, our model ignores the differences in cancer recurrence between patients with limited or extensive index tumors.[22] It will be difficult, however, to include all clinical prognostic factors in the process of modeling.

Because LE in the general population is longer in women, changes in the follow-up program will have more influence on them. Because the number of women with laryngeal cancer is increasing, it is important to show the results for the female population.[21] Whether the increased LE for women compared with men applies to patients with laryngeal cancer is dubious. In our previous studies, the local/regional recurrence rate in women appeared to be the same as that in men.[12] However, the mode of detection in women may not be comparable. The reason is that, in the current follow-up program, cancer recurrences in women usually are detected at a routine visit while symptoms are present,[12] although the implication this difference is not quite clear.

Based on the results of this study, we conclude that the current follow-up schedule has limited influence on LE in elderly patients. Follow-up should not be abolished. Rather, it should be reduced in length and intensity. The emphasis should not be on detecting asymptomatic cancer recurrence; instead, the

objective should be to provide the necessary treatment and care in case of recurrence.

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