Colorectal cancer in ulcerative colitis patients: survival curves and surveillance

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■ **BACKGROUND** Survival curves can provide useful information for designing cancer surveillance programs.

■ **OBJECTIVE** To outline how to derive the density and hazard functions from the survival curve and to use this information to make recommendations regarding cancer surveillance in patients with ulcerative colitis.

■ **DISCUSSION** The hazard of cancer or dysplasia remains low during the first decade of ulcerative colitis but rises exponentially thereafter. After 40 years, approximately 20% of patients with ulcerative colitis acquire cancer or dysplasia per year.

■ **CONCLUSION** A reasonable recommendation for cancer surveillance based on information from survival curves would be a colonoscopy with biopsy approximately 10 years after the onset of ulcerative colitis, and repeated every 3 years for the next decade, every 2 years for the subsequent decade, and every year thereafter. Prophylactic proctocolectomy is an option after 40 years of disease due to the extremely high cancer risk, but data supporting this option are sparse.

■ INDEX TERMS: COLORECTAL NEOPLASMS; COLITIS, ULCERATIVE; SURVIVAL ANALYSIS ■ CLEVE CLIN J MED 1994; 61:272–275

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VALUABLE information regarding the risk of disease or death and the outcome of treatment is often reported in the form of survival curves. For surveillance of cancer, the shape of the survival curve may dictate when to commence screening, how often to screen, and when screening is no longer worthwhile. Physicians involved in cancer surveillance can apply information from the survival curve to clinical decision-making.

SURVIVAL CURVES AND DERIVED INFORMATION

A *survival curve* depicts the proportion of a population free of an outcome (ie, death for a true survival curve or cancer for a cancer-free survival curve) on the ordinate vs a measure of time (ie, age or duration of disease) on the abscissa. At time 0, the proportion surviving is 1.0; as time progresses, the proportion surviving diminishes.

As an example, in *Figure 1*, the plot of survival [S(t)] vs age approximates the true survival curve

of the US population.[1] At birth, everyone is alive. Due to the nonnegligible mortality rate in the first year of life in the United States, the curve drops sharply in the first year. Survival declines only minimally from age 1 through age 80 but declines markedly thereafter, until it approximates 0 at age 95.

The *mean survival time* of a population, a valuable piece of information, can be obtained from the survival curve. In this example, the mean survival time is the mean life expectancy of the US population, approximately 75 years. This measure is calculated as the integral from birth to age 100 of the survival function (the area under the curve).

The *density function* can be generated directly from the survival curve. It can provide information regarding mortality frequency; in *Figure 1*, the density curve approximates the frequency of deaths in the US population at different ages. Density is a plot of the opposite of the first derivative of survival vs time. Mathematically, density function = $-dS(t)/dt$. During the first year of life, the number of deaths is relatively high. From age 1 to age 60, the number of deaths is very low. After age 60, the number of deaths increases with a peak at the point of inflection of the survival curve. By age 95, the number of deaths is relatively low because nearly everyone has died by then. Although this function supplies useful information such as the most frequent age at death, it says nothing of the mortality rate, the most important measure of risk. However, the density curve can be used to calculate the best measure of true risk, the *hazard rate*.

A curve of hazard rates can be obtained from either the survival curve or the density curve. The annual risk of dying is a hazard rate; it can be estimated by dividing the number of people dying in a given year by the number alive at the beginning of the year. Mathematically, the hazard function can be calculated from the survival curve by dividing the opposite of the first derivative of the survival function (the density function) by the survival at the beginning of the interval. Thus, hazard function = $-(dS[t]/dt)/S(t)$.

The hazard curve in *Figure 1* approximates the hazard function for death in the US population. For the first year of life, the hazard rate is relatively high and similar to the density function. The hazard of dying remains very low until age 60, when it increases. One can use the hazard function as a meaningful measure of risk to design surveillance programs and to optimize patient management decisions.

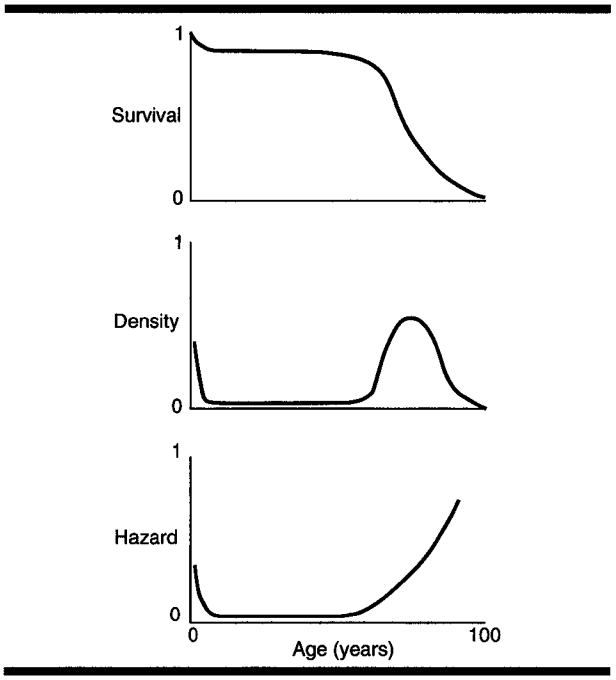

FIGURE 1. Approximations of survival, frequency of death (density function), and hazard of death as functions of age for the US population. See reference 1.

HOW SURVIVAL CURVES MODIFY CANCER SURVEILLANCE IN ULCERATIVE COLITIS

Patients with chronic ulcerative colitis are at an increased risk of acquiring colorectal cancer; the risk is directly related to the extent and duration of the colitis and to older age at the onset of symptoms.[2] Many patients eventually undergo a proctocolectomy because of intractable disease or malignant transformation. Although common, surgery is not inevitable. Surveillance programs are designed to identify patients at extremely high risk of dying of cancer, ie, patients with a premalignant lesion (dysplasia) or early, surgically curable cancer. Patients at extremely high risk should undergo proctocolectomy, while in others, surgery is delayed as long as possible.

The only acceptable method for detecting dysplasia at present is colonoscopy with biopsy, a costly and potentially morbid procedure. The belief that surveillance and subsequent proctocolectomy for neoplasia can reduce cancer mortality has fostered the institution of several screening programs.[3–8] Most of these programs recommend annual colonoscopy in patients with pancolitis after 10 years of disease and total proctocolectomy if dysplasia or cancer is de-

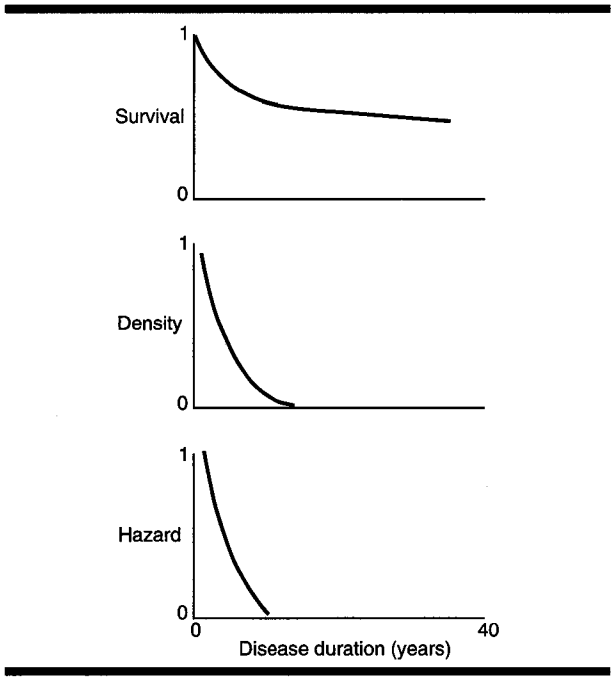

FIGURE 2. Hypothetical cancer-free survival, frequency of cancer (density function), and hazard of cancer as functions of duration of ulcerative colitis in a common model of cancer incidence.

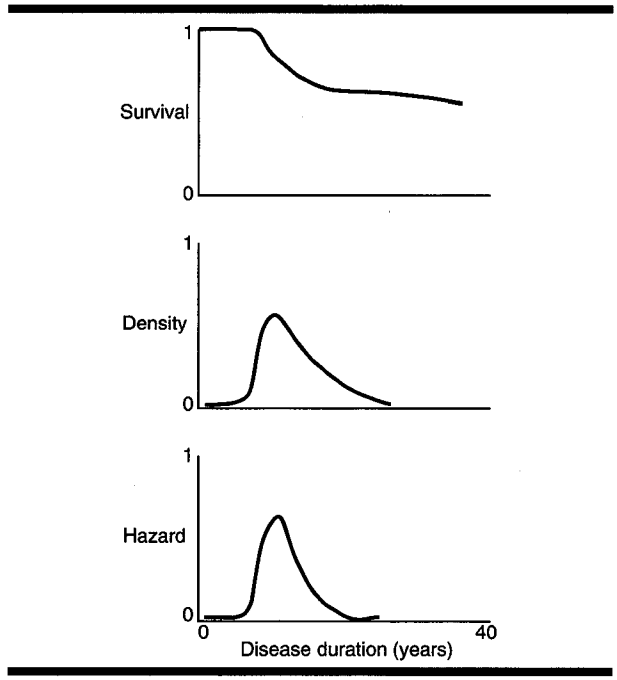

FIGURE 3. Hypothetical cancer-free survival, frequency of cancer (density function), and hazard of cancer as functions of duration of ulcerative colitis in a model of cancer detection after a lag period.

tected. However, these parameters may not be optimal or efficient, and one might reduce the number of tests without altering effectiveness by basing screening test frequency on the shape of the actual survival curve.

Hypothetical models of cancer incidence

For screening to be useful, it should start when the hazard rate becomes unacceptably high and stop when the hazard either diminishes or becomes so high that delaying intervention may be unsafe. For example, *Figure 2* demonstrates a hypothetical set of survival, density, and hazard functions based on an exponentially declining model of risk. A model of exponential decline fits many clinically observed diseases where there is a high early mortality rate that diminishes over time. If this model were true for cancer incidence in patients with ulcerative pancolitis, the risk of colorectal cancer would steadily diminish with time until, after 40 years of disease, there would be virtually no cancer detected. Because cancer is observed at a high rate after 40 years of disease, this model does not fit the data.

Figure 3 demonstrates another set of hypothetical survival, density, and hazard functions where no cancer is detected for the first 10 years, cancer is mostly detected between years 10 and 30, and little if any cancer is detected in patients who are cancer-free after 30 years of disease. This model assumes that cancer is acquired at only one stage of life and is very rare before or after that stage. Such a survival curve with a long lag period and exponential decline afterward is observed for cancer incidence after certain industrial exposures. If this model were correct for cancer incidence in ulcerative colitis patients, screening should begin after the lag period (10 years of disease) and stop after 30 years of disease. However, the actual curves present a different picture.

True incidence of dysplasia or cancer

The curves shown in *Figure 4* approximate the actual survival, density, and hazard functions for the development of cancer or dysplasia in patients with extensive ulcerative colitis followed in a surveillance program.[9] The survival curve was determined using the product-limit method on data from 99 patients followed in a single referral center. Although there is a lag period of approximately 10

years, the hazard increases exponentially thereafter.

These curves indicate there is no need to screen a patient before 10 years of disease. However, after 40 years of disease the risk of cancer may be inordinately high. In fact, after 40 years of disease the approximated annual hazard is greater than 0.20 (ie, 20% of cancer-free patients will acquire cancer in the next year), a risk few patients will accept.[10] Unfortunately, available data determining survival after 40 years of disease are sparse, and a hazard rate of 20% can only be considered an approximation.

Because the hazard rate is so high, it has been proposed that prophylactic total proctocolectomy be performed after 40 years of disease to obviate this extremely high cancer risk.[10] However, the decision whether to perform a prophylactic proctocolectomy requires more information than the cancer risk alone. Surgical alternatives such as ileal-pouch anal anastomosis, social and life-style concerns, cancer fears, and occupational factors all influence the decision-making process.

Hazard rates also can help the clinician to decide how often to schedule screening tests to achieve maximum benefit for a given cost.[11] For a surveillance program to be maximally effective, the interval between tests should shorten as the hazard rate increases. Because hazard rates for cancer or dysplasia rise inexorably as the duration of ulcerative colitis increases, the screening interval should shorten accordingly.[9] A reasonable, convenient, and efficient surveillance approach is to perform no screening tests for the first 10 years of disease, test every 3 years for the next 10 years of disease, test every 2 years between years 20 and 30, and test annually thereafter.[10]

Although these recommendations represent conclusions drawn from information obtained from the shape of the survival curve, whether this surveillance approach can be as effective as annual testing in reducing cancer-related mortality remains to be determined. Clinicians can use their knowledge of the survival curve and of the associated risks to make informed management decisions that minimize the risk of mortality from cancer while delaying proctocolectomy as long as is reasonable.

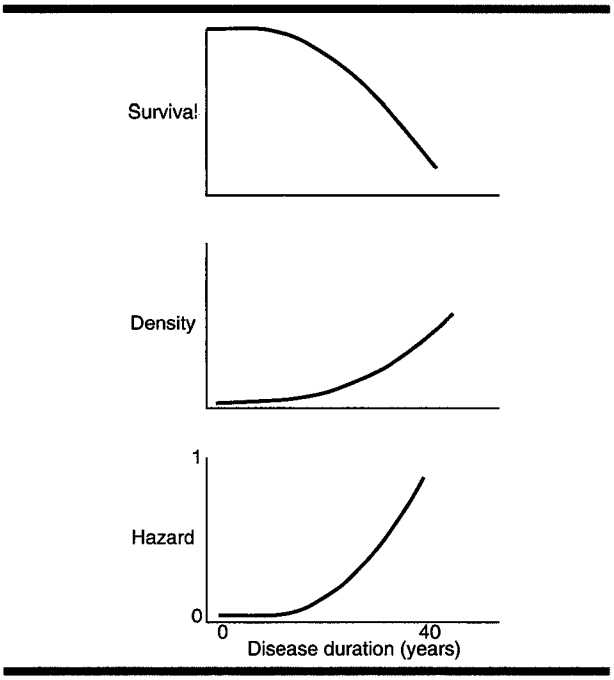

FIGURE 4. Approximation of the dysplasia- or cancer-free survival, frequency (density function), and hazard as functions of duration of ulcerative colitis in patients enrolled in a surveillance program. Based on data from reference 9.

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