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ORIGINAL ARTICLE – COLORECTAL CANCER

Relative Survival is an Adequate Estimate of Cancer-Specific Survival: Baseline Mortality-Adjusted 10-Year Survival of 771 Rectal Cancer Patients

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ABSTRACT

Background. The objective of the present investigation is to assess the baseline mortality-adjusted 10-year survival of rectal cancer patients.

Methods. Ten-year survival was analyzed in 771 consecutive American Joint Committee on Cancer (AJCC) stage I–IV rectal cancer patients undergoing open resection between 1991 and 2008 using risk-adjusted Cox proportional hazard regression models adjusting for population-based baseline mortality.

Results. The median follow-up of patients alive was 8.8 years. The 10-year relative, overall, and cancer-specific survival were 66.5 % [95 % confidence interval (CI) 61.3–72.1], 48.7 % (95 % CI 44.9–52.8), and 66.4 % (95 % CI 62.5–70.5), respectively. In the entire patient sample (stage I–IV) 47.3 % and in patients with stage I–III 33.6 % of all deaths were related to rectal cancer during the 10-year period. For patients with AJCC stage I rectal cancer, the 10-year overall survival was 96 % and did not significantly differ from an average population after matching for gender, age, and calendar year ($p = 0.151$). For the more advanced tumor stages, however, survival was significantly impaired ($p < 0.001$).

Conclusions. Retrospective investigations of survival after rectal cancer resection should adjust for baseline mortality because a large fraction of deaths is not cancer related. Stage I rectal cancer patients, compared to patients with more advanced disease stages, have a relative survival close to 100 % and can thus be considered cured. Using this relative-survival approach, the real public health burden caused by rectal cancer can reliably be analyzed and reported.

Colorectal cancer is among the most common malignancies, accounting for ~1.2 million new cases and over 600,000 deaths in 2008.[1] With this high prevalence, colorectal cancer has a substantial public health impact. Rectal cancer comprises approximately one third of all colorectal malignancies. Because the incidence increases with age and ~60 % of all patients survive 5 years, rectal cancer patients have a relevant risk of dying from causes other than rectal cancer itself.[2] Indeed, the risk of dying from other causes varies considerably, mainly according to gender, age, and calendar year of operation.[3,4] For example, the risk of dying within 10 years is 16.7 % for an average 65-year-old woman in 2000 but 66.4 % for an 80-year-old man in the United States.[5] This imbalance in analyzing the real public health burden appears to be resolvable by only counting the deaths caused by rectal cancer and ignoring other causes of death using the cancer-related survival approach.[6] However, it is often difficult or even impossible to establish the exact cause of death,

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especially in retrospective cohort studies, and the fallacy of cancer-specific death is well known.[7] The occurrence of a fatal pulmonary embolism in an end-stage cancer patient represents a typical debate whether or not this should be classified as a cancer death. Furthermore, even if the cause of death is known, it might have been determined in a biased manner.[8,9]

We assessed the long-term survival in a homogenous sample of patients with rectal cancer undergoing resection through application of the relative survival approach and analyzed the fraction of cancer versus non-cancer-related death in the overall group and in different subsets. We aimed to understand whether the relative survival approach is a hope—or just hype—for better understanding the public health importance of rectal cancer.

PATIENTS AND METHODS

The present study was based on the retrospective colorectal database of the authors' institution, one of the largest tertiary care centers in Switzerland. Several previous publications from our research group were based on this valuable database.[10–14] Overall, 818 patients undergoing primary open resection for histologically proven rectal cancer at a single institution between January 1991 and December 2008 were identified. A total of 47 patients were excluded because the long-term prognosis based on American Joint Committee on Cancer (AJCC) stage was the main focus of the present study. In-hospital mortality occurred in 22 patients [2.7 %, 95 % confidence interval (CI) 1.8–4.0]. In addition, 25 patients were excluded because they underwent a transanal tumor resection leading to incomplete tumor staging. A total of 771 patients thus remained for analysis (Fig. 1).

Data Collection and Definitions

Data on the patients' demographics, comorbidities, operative details, postoperative mortality, morbidity, and histological results were retrospectively ascertained from medical charts. Tumor height, defined as the distance between the tumor and the anal verge, was gathered from results from the rigid rectosigmoidoscopy, endorectal sonography, MRI scans and colonoscopy, in that order. Operation time was ascertained from the operation protocol. All operations were performed or supervised by experienced colorectal surgeons and were performed as highly standardized procedures. Since 2004, neoadjuvant radiotherapy or radiochemotherapy was routinely administered according to an interdisciplinary tumor board decision for patients with cT3/4 or cN + disease.[15] In patients who underwent neoadjuvant treatment, adjuvant chemotherapy was routinely provided to patients with node-positive disease according to preoperative staging. In patients without neoadjuvant treatment, the indication for adjuvant treatment was based on the postoperative pathological findings.[15]

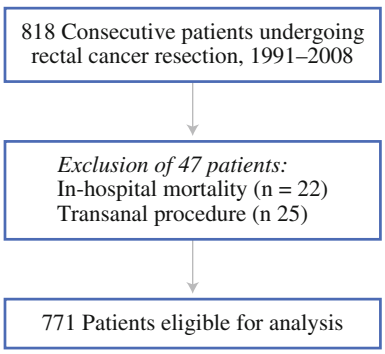

FIG. 1 Patient selection

Follow-Up

The 5-year follow-up was performed according to national guidelines.[16] The patients and their general practitioners were contacted by mail and by telephone to obtain information about their survival status. If no information was available, the local residents' registration offices were contacted to achieve the most complete follow-up possible.

Definition of Outcome Measures

The relative survival (S_r) of patients with rectal cancer after successful resection was defined as the main outcome. The relative survival represents the ratio of the observed (=overall) survival (S_{ov}) of the patients with rectal cancer and the expected survival (S_e), where the expected survival is the survival of a group of the general population with similar characteristics (gender, age, calendar year) than the study cohort except for the risk factor (rectal cancer) analyzed [$S_r = S_{ov}/S_e$]. The expected survival was calculated on the basis of life tables showing the probability of death before a person reaches his or her next birthday for each age. In consequence death due to rectal cancer alone (v) in a single time period equals the total number of deaths in the rectal cancer patient cohort (λ = overall hazard of death in the rectal cancer cohort) minus the expected number of deaths (λ^*) in the general population (background mortality or expected hazard of death in the general population), [$v = \lambda - \lambda^*$].

For cancer-specific survival, cancer-specific and cancer-consequent deaths were counted, whereas other deaths were censored. A death was accounted as cancer specific if the clinical records rendered the death likely to be a consequence of the rectal cancer (primary tumor and/or

metastatic disease). For, example the death of a patient with diffuse liver metastasis and evident liver failure was accounted as a cancer-specific death. A death occurring during adjuvant chemotherapy (e.g., due to pulmonary embolism, pneumonia, or renal failure) was accounted as cancer-consequent death.[17]

Statistical Analyses

Statistical analyses were performed using the R statistical software (www.r-project.org). A two-sided p value of <0.05 was considered statistically significant. Continuous data are expressed as mean ± standard deviation.

The population tables regarding background mortality for the relative survival analyses were obtained from the Swiss National Statistical Office.[18] The relative survival analyses were conducted using the R package "relsurv" using the Ederer estimator.[19] Population mortality rates were included as time-dependent covariates (multiplicative Cox regression model).[20]

RESULTS

Patient Characteristics

A total of 771 patients with histologically proven adenocarcinoma of the rectum were included in the present analysis. The median follow-up was 8.8 years (range 0.1–21.3 years) for patients alive at the time of the study. A total of 367 patients died during the follow-up. In 198 (54 %) patients the death was clearly tumor related, and in 71 patients (19 %) the death was not tumor related. In 98 patients (27 %) the cause of death remained unknown. These 98 patients were excluded for the analysis of cancer-specific survival. Table 1 summarizes the patient characteristics.

TABLE 1 Patient characteristics and perioperative outcome ($N = 771$)

Characteristic	Variable	Value[a]
Follow-up (years)		6.1 ± 4.2
Age (years)		65.4 ± 11.9
Gender	Male	496 (64.3 %)
	Female	275 (35.7 %)
Age	<65 years	371 (48.1 %)
	≥65 years	400 (51.9 %)
Body mass index (kg/m^2)		25.5 ± 4.3
ASA stage	II	588 (76.3 %)
	III/IV	183 (23.7 %)
AJCC stage	I	222 (28.8 %)
	II	196 (25.4 %)
	III	198 (25.7 %)
	IV	155 (20.1 %)
Tumor distance from anal verge (cm)		8.1 ± 4.2
Neoadjuvant therapy	No	475 (61.6 %)
	Yes	296 (38.4 %)
Operation	Anterior resection	695 (90.1 %)
	Abdominoperineal resection	76 (9.9 %)
Operation time (min)		181.9 ± 74.3
Surgery	Elective	742 (96.2 %)
	Urgent	29 (3.8 %)
Resection	R0	619 (80.3 %)
	R1/2	152 (19.7 %)
Adjuvant therapy	No	442 (57.3 %)
	Yes	329 (42.7 %)
Perioperative outcome		
Length of hospital stay (days)		23.6 ± 13.2
ICU referral	No	451 (58.5 %)
	Yes	320 (41.5 %)

ASA American Society of Anesthesiologists, *AJCC* American Joint Committee on Cancer, *ICU* intensive care unit

[a] Values are expressed as n (%) or mean ± standard deviation

Survival Analysis

Figure 2 (left) depicts the relative and overall survival curves for the entire cohort. On the basis of gender, age, and calendar year at the time of operation, the expected 10-year survival was 73.0 %, reflecting the fact that 27 % of the population would have died of any cause (e.g., baseline mortality). The observed 10-year overall survival was 48.7 % (95 % CI 44.9–52.8), with the corresponding total overall mortality of 51.3 % (100 − 48.7 %). Subtracting the baseline mortality (27.0 %) from the total overall mortality (51.3 %) resulted in an excess mortality of 24.3 %. This percentage represents the deaths solely due to rectal cancer. Consequently, 47.3 % of all deaths (excess mortality divided by overall mortality: 24.3/51.3 %) were related to rectal cancer during the 10-year period. The 10-year relative survival was 66.5 % (95 % CI 61.3–72.1). The relative survival dropped to ∼67 % during the first 6.5 years and remained stable thereafter, with only a slight drop to ∼66 %, thus indicating that the vast majority of rectal cancer death occurred before 6.5 years of follow-up. Figure 2 (right) also depicts cancer-specific survival excluding the 98 patients with unknown cause of death. The 10-year cancer-specific survival estimate of 66.4 % (95 % CI 62.5–70.5) and the shape of the survival curve were similar compared with the relative survival, thus confirming the results of the relative survival analysis. The corresponding 5-year relative, overall, and cancer-specific survival rates were 72.1 % (95 % CI 68.2–76.2), 62.6 %

(95 % CI 59.2–66.2), and 73.0 % (95 % CI 69.6–76.6), respectively.

When censoring all cancer-related deaths in our cohort, the non-cancer-related 10-year survival was estimated with 70.6 % (95 % CI 66.6–74.9). The expected 10-year survival of the cohort was 73.0 %, which is included in the 95 % CI of the non-cancer-related survival, sustaining the comparability of our cohort with the external comparison population.

When limiting the analysis to curatively treated patients with stage I to III rectal cancer with complete tumor resection, the expected 10-year survival was 72.7 %, and the observed 10-year overall survival was 58.9 % (95 % CI 54.6–63.5). The baseline mortality was 27.3 %, and the excess mortality due to rectal cancer was 13.8 % (observed overall survival minus baseline mortality, e.g., 41.1–27.3 %). Therefore, 33.6 % of all deaths (excess mortality divided by overall mortality, e.g., 13.8/41.1 %) were related to rectal cancer. The 10-year relative survival was 80.8 % (95 % CI 74.9–87.2).

Survival Analysis Based on Different AJCC Stages

The expected 10-year survivals were 75.8, 71.2, 70.5, and 74.3 % for patients with AJCC stage I, II, III, and IV rectal cancer, respectively. The 10-year overall survival rates were 72.0 % (95 % CI 65.3–79.3), 55.0 % (95 % CI 74.5–63.6), 46.8 % (95 % CI 39.7–55.2), and 7.9 % (95 % CI 4.3–14.5) for AJCC stages I, II, III, and IV, respectively. Figure 3 displays the resulting relative, overall, and cancer-specific survival patterns of the subgroups generated according to the AJCC staging system. The 10-year relative survival rates were 96.2 % (95 % CI 87.3–105.9), 76.3 % (95 % CI 66.0–88.2), 66.3 % (95 % CI 56.3–78.1), and 10.0 % (95 % CI 5.5–17.9) for AJCC stages I, II, III, and IV, respectively. For patients with AJCC stage I rectal cancer, the 10-year overall survival did not differ significantly from that of the average Swiss population after matching for gender, age, and calendar year ($p = 0.151$). For the more advanced tumor stages, however, survival was significantly impaired ($p < 0.001$). These results were confirmed by nearly similar cancer-specific survival rates, which were 89.4 % (95 % CI 84.3–94.9), 79.6 % (95 % CI 73.1–86.8), 63.4 % (95 % CI 55.5–72.3), and 10.9 % (95 % CI 6.1–19.5) for AJCC stages I, II, III, and IV, respectively. Of note, for each stage, the CIs for relative and cancer-specific survival overlapped.

DISCUSSION

To our knowledge, this is one of the first investigations in the literature of a homogeneous sample of consecutive rectal cancer patients providing relative survival by adjusting for the population-based baseline mortality. The

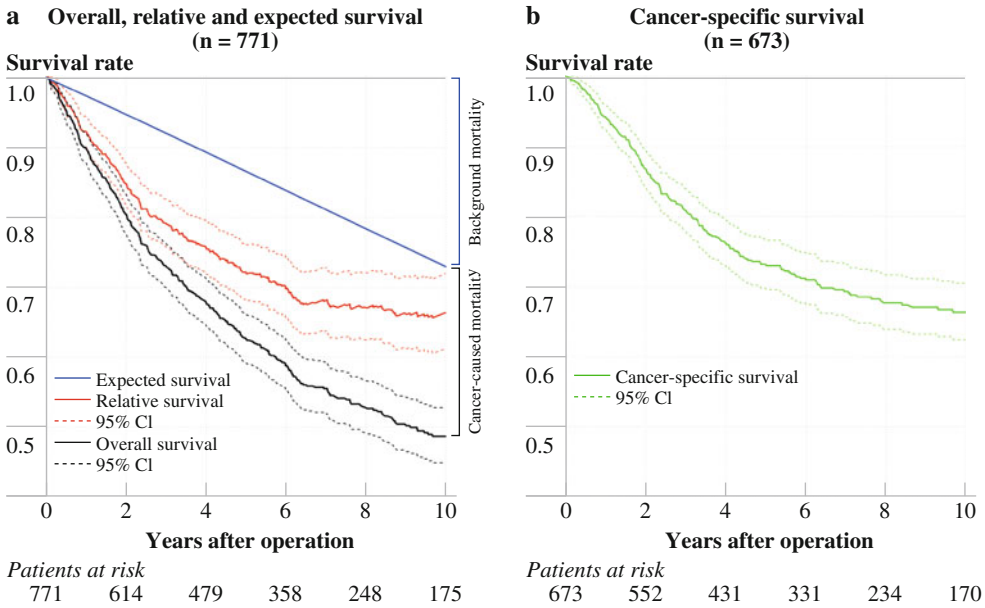

FIG. 2 Overall, expected, relative, and cancer-specific survival. *Left* usual Kaplan–Meier curve for the overall survival (*black solid line*). Additionally, expected survival according to age and gender at the time of operation (*blue line*) and relative survival (*red line*) are shown. *Right* usual Kaplan–Meier curve for the cancer-specific survival after excluding 98 patients with an unknown cause of death. The number of rectal cancer patients at risk is provided below the *plots*. Overall, relative, and cancer-specific survival curves are provided with 95 % CIs. The expected survival divides the overall survival in the background mortality and the cancer-caused (excess) mortality

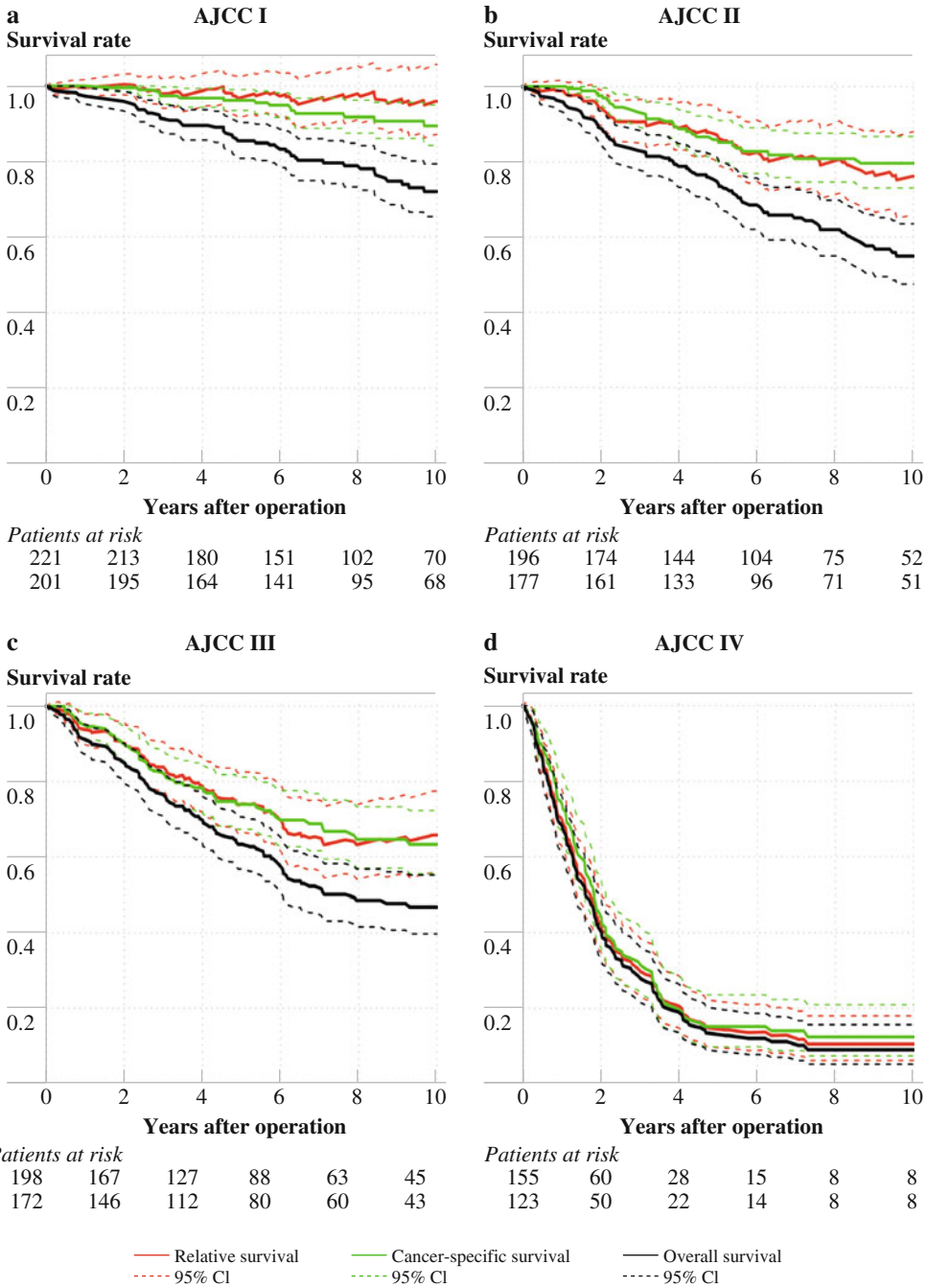

FIG. 3 Relative, cancer-specific, and overall survival stratified by the four AJCC stages. Each panel displays relative (*red lines*), cancer-specific (*green lines*), and overall survival (*black lines*) curves for one AJCC stage. These curves are provided with 95 % CIs. For each plot, the number of rectal cancer patients at risk is given below the plots (*lower line* relative survival, *upper line* cancer-specific survival). Cancer-specific survival was calculated after excluding patients with an unknown cause of death

present study yields three key results. First, only half of the observed deaths of stage I to IV rectal cancer patients and only one third of stage I to III rectal cancer patients undergoing resection were related to rectal cancer. This surprising result emphasizes the cardinal importance of adjusting for baseline mortality to obtain conclusive results. Second, in a 10-year perspective of our series, with a relative survival of 96.2 % and a cancer-specific survival of 89.4 %, most patients with stage I rectal cancers can be considered cured. However, more advanced disease stages were associated with lower survival rates, confirming that the staging system currently in use is a precise and reliable prognostic factor. Third, a relevant fraction of cancer-related deaths occurred after the commonly reported 5-year follow-up, thus highlighting the importance of longer follow-up periods to avoid the underestimation of the real burden caused by rectal cancer.

To estimate the survival of cancer patients, cancer-specific survival and relative survival are concurring approaches. Both methods are widely accepted and valuable, but cancer-specific survival is usually used in clinical trials, whereas relative survival is mainly used in

epidemiologic studies and population-based analyses. However, according to Sarfati et al.,[17] "There is no sound theoretical justification for this dichotomy, and both methods have their pros and cons."

The main source of possible bias for the relative survival approach is the lack of comparability between the cohort of interest and the external comparison group. In the present study, the noncancer life expectancy of the study cohort and the life expectancy of the reference population were nearly identical, precluding a relevant violation of the assumption of comparability.[17] Moreover, in the calculation of relative survival, the external comparison population is assumed to be free from the specific cancer in question, allowing the assumption that any excess mortality among the cancer patients is in fact due to the cancer under investigation. In reality, however, the comparison group is usually a population that includes some patients with the cancer in question. Nonetheless, it has been demonstrated that this effect is very small and of little relevance because death due to rectal cancer is rare outcome in the general population.[21]

The most important potential source of bias in the cancer-specific survival approach is misclassification of the underlying cause of death.[17,22,23] Between two relatively clear extremes where death can be directly attributed to cancer or not, there are a lot of deaths for which cancer might have contributed to some extent. Even if the correct cause of death is exactly known (e.g., pneumonia 2 years after lobectomy for lung cancer), it is impossible to accurately ascribe such individual deaths as being fully cancer specific or not.[17] This is not a data quality issue but rather a conceptual issue.[17,24] Therefore, cancer-specific survival is inevitably prone to subjective decisions, and the relative survival approach may be more appropriate.[24] The overall impact of the public health problem of rectal cancer is better captured by the relative survival approach than by the cancer-specific survival. For example, elderly and frail patients might be harmed through the cancer treatment, with it contributing to or even causing their death. The delayed death of such a patient is probably not ascribed as being cancer specific, causing a potential bias. In contrast, the relative survival approach accounts for this bias because all observed deaths independently of their cause are compared, with the number of deaths expected to occur based on the comparison with the general population. To estimate the real burden caused by rectal cancer, all deaths have to be considered because they might be a consequence of rectal cancer treatment.

The 10-year relative survival of 66 % for all disease stages found in the present investigation compares favorably with previous studies that reported a relative survival for colorectal cancer of less than 60 %.[3,25–28] Of course, the vast majority of available relative survival data for rectal cancer is based on cancer registries and not on clinical investigations. Cancer registries typically house the data from patients treated with and without surgery. Furthermore, for cancer registries, a relevant percentage of data on cancer staging might be incorrect and thus may introduce a strong bias, preventing a fair comparison with the present analysis.

Randomized controlled trials represent the gold standard of study designs. As a result of random allocation, balanced patient groups are generated, thus minimizing the bias between the different study arms. Under these circumstances, the relative survival approach is not adequate. Conversely, noncontrolled studies might well profit from the relative survival approach independently of the disease under investigation if a causal relationship between the disease and the death is not unequivocally known. This approach is not limited to, e.g., colorectal, breast, or prostate cancer patients with a reasonable long survival time but is also applicable in diseases such as diabetes.

Particularly when considering the necessary long-term follow-up period desired for survival analyses, the methodical drawback of a retrospective design must often be accepted. Lack of international comparability is another drawback of conventional survival analysis because there are large differences in the background mortality among different nations.[1] To deal with these issues, cancer registries usually apply the methodically more demanding relative survival approach.[29] Because the survival of a cohort is compared with the survival of the general population, an adjustment for the international differences in life expectancies is easily performed.[4,8,30] Unfortunately, until recently, this approach was rarely used in clinical studies because this method is considered more challenging than standard survival analyses.[28] However, population-based mortality tables for many countries are now readily accessible online.[19,31]

This study has several limitations. This is a cohort study and not a prospective trial. However, for the research question at hand, a cohort study may be the most appropriate study design. Although a study using cancer registries would include much larger patient numbers, this study has the high resolution of a clinical investigation, with which cancer registry usually cannot compete. Moreover, cancer registry data are prone to a relevant amount of incorrect or missing data.[32,33] The relative survival is a very good estimate of the cancer-specific survival, which can be achieved without the difficulties associated with using death certificates, but it is not free of bias.[34] The relative risk approach might lead to an overestimation of survival in low-mortality cancers such as stage I rectal cancer. This might be caused by some of the patients changing their lifestyle after successful treatment for colorectal cancer and an earlier diagnosis and treatment

of other potentially fatal conditions resulting from the follow-up investigations. However, in the present study, cancer-specific and relative survival yielded nearly identical results, thus indicating that most stage I rectal cancer patients can be considered cured, even with long-term follow-up.

The present study demonstrated that retrospective investigations of survival after rectal cancer resection should provide baseline mortality-adjusted results, at least as a sensitivity analysis. Overall survival only partially represents the public health impact of a certain disease. Conversely, the relative survival reflects much better the cancer-specific survival, which is often difficult to assess, particularly in retrospective cohort studies. The relative survival approach represents a powerful method to differentiate between cancer-related versus non-cancer-related deaths. Using this approach, the real burden caused by rectal cancer can reliably be analyzed and reported. Therefore, the relative survival approach is definitely a hope—and not just hype—for better understanding the public health importance of rectal cancer.

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