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Temporal trends in the proportion cured for cancer of the colon and rectum: A population-based study using data from the Finnish Cancer Registry

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Colorectal cancer is the third most common cancer worldwide and the second most common cancer in Europe. Cumulative relative survival curves for both cancer of the colon and cancer of the rectum generally plateau after ~6–8 years. When this occurs, "population" or "statistical" cure is reached. We analyzed data from the Finnish Cancer Registry over a 50-year period using methods that simultaneously estimate the proportion of patients cured of disease (the cure fraction) and the survival time distribution of the "uncured" group. Our primary aim was to investigate temporal trends in the cure fraction and median survival of the uncured by age group for both cancer of the colon and rectum. For both cancers, the cure fraction has increased dramatically over time for all age groups. However, the difference in the cure fraction between age groups has reduced over time, particularly for cancer of the colon. Median survival in the uncured has also increased over time in all age groups but there still remains an inverse relationship between age and median survival, with shorter median survival with increasing age. The reasons for these impressive increases in patient survival are complex, but are highly likely to be strongly related to many improvements in cancer care over this same time period.
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Key words: colorectal cancer; cure models; survival; colon cancer; rectum cancer

Colorectal cancer is the third most common cancer worldwide and the second most common cancer in Europe where it accounts for 13% of all incident cancer cases and 12% of all cancer deaths.[1] There is large geographical variation in the incidence rates with nearly a 4-fold higher incidence rate in more-developed compared with less-developed regions of the world.[2] Population-based studies of cancer patient survival are important as they provide a measure of the combined effects of diagnostic and treatment improvements. Such information is relevant for clinicians, patients and health administrators.

Patient survival for both cancer of the colon and cancer of the rectum has improved over the past few decades.[3–7] In population-based studies, patient survival is typically measured using the cumulative survival function (relative survival or cause-specific survival). An alternative approach, which may provide greater insights, is to simultaneously estimate the proportion of patients cured together with the cumulative survival function of the "uncured."[8] We make use of recent advances in methodology and software to study temporal trends in survival of patients diagnosed with cancer of the colon and rectum in Finland over a 50-year period.

Material and methods

Data

Data were obtained from the Finnish Cancer Registry, which has registered all diagnosed cases of cancer since 1953. Notification has been compulsory since 1961. For solid tumors the completeness of the registration is over 99%.[9] The patient data are linked to the mortality register (maintained by Statistics Finland) to obtain information on date and cause of death in addition to identifying individuals dead with cancer that had not previously been reported to the registry. The cancer register is routinely matched with the central population register to verify that those individuals classified by the registry as being alive, in fact, exist and are alive and resident in Finland.

We studied patients diagnosed in the period 1953–2003 with follow-up to the end of 2004. We excluded patients if the tumor was registered solely on death certificate information, was incidentally diagnosed at autopsy or if histopathology was classified as other than adenocarcinoma (Table I). Patients who emigrated were censored at the date of emigration. Patients older than 80 years of age at diagnosis were excluded from the analyses as cure models are less reliable for older age groups. Surgical intervention, the only potentially curative treatment until very recently, is less common in this age group. Two patients with colon cancer and 2 with rectal cancer were excluded because of incomplete information on date of death.

Statistical methods

It is standard in population-based studies to use relative survival as the measure of cancer patient survival. Relative survival is the ratio of observed (all-cause) to expected survival and provides a measure of excess mortality associated with diagnosis of the disease. It has the advantage that the cause of death information is not required[10] and it captures both mortality directly because of the cancer as well as indirect mortality (*e.g.*, increased risk of non-cancer mortality caused by the treatment).

The point of statistical cure is defined as the point during follow-up at which the patients still alive no longer experience excess mortality compared with the general population. That is, the patients are considered "statistically cured" from the point that they experience the same mortality as individuals without cancer of the same age and sex. The point of statistical cure occurs when the cumulative relative survival curve plateaus and the value at which it plateaus is the estimated cure fraction (Fig. 1). Two groups of patients may have the same cure fraction but the point of cure may be reached sooner in one group. The distribution of survival times for the uncured provides a measure of how fast the cure point is reached.

The concept of statistical cure applies at a grouped level and is distinct from "medical cure" at an individual level, where all cancerous cells in the body have been eradicated. It is, however, difficult to determine with any certainty that an individual has been

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TABLE I – INCLUSIONS AND EXCLUSIONS FOR PATIENTS AGED LESS THAN 80 YEARS AT DIAGNOSIS, BY PERIOD OF DIAGNOSIS

Period of diagnosis	Included	Exclusions	
		Death certificate/autopsy only	Not adenocarcinoma
(a) Cancer of the colon			
1953–1964	2,904 (89.7%)	249 (7.7%)	84 (2.6%)
1965–1974	3,739 (92.1%)	141 (3.5%)	179 (4.4%)
1975–1984	5,562 (91.5%)	188 (3.1%)	328 (5.4%)
1985–1994	7,337 (91.7%)	144 (1.8%)	517 (6.5%)
1995–2003	8,212 (91.4%)	185 (2.0%)	612 (6.8%)
Total	*27,754 (91.4%)*	*907 (3.0%)*	*1,720 (5.7%)*
(b) Cancer of the rectum			
1953–1964	2,539 (93.8%)	146 (5.4%)	22 (0.8%)
1965–1974	3,491 (97.3%)	63 (1.8%)	34 (1.0%)
1975–1984	4,679 (96.8%)	61 (1.3%)	94 (1.9%)
1985–1994	5,324 (96.2%)	63 (1.1%)	150 (2.7%)
1995–2003	5,852 (95.3%)	64 (1.0%)	224 (3.6%)
Total	*21,885 (96.0%)*	*397 (1.7%)*	*524 (2.3%)*

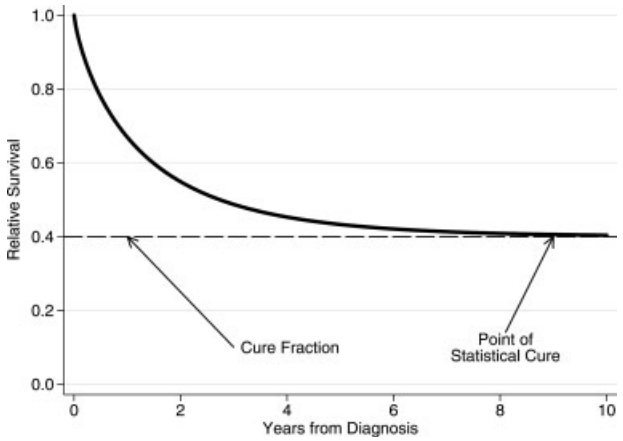

FIGURE 1 – Hypothetical cumulative relative survival curve where the estimated cure fraction is 0.4.

medically cured, and medical cure cannot be studied using cancer registry data. Statistical cure is perhaps the ultimate measure of long-term survival in population-based cancer studies, but has rarely been used in practice because of difficulties in its estimation.

The statistical models we use for estimating the cure fraction are similar to those described by Verdecchia *et al*.[8] and Lambert *et al*.[11] We assume that a proportion, π, of patients will be cured (experience the same mortality as the general population) whereas the remaining $1 - \pi$ will experience excess mortality compared with the general population. The models provide estimates of both the proportion cured along with the distribution of survival times for the uncured.

Algebraically the models can be expressed as follows. The overall survival, $S(t)$, is the product of the expected survival, $S^*(t)$, and the relative survival. We assume that the relative survival is made up of 2 components, the "cured" and the "uncured." Thus,

$$S(t) = S^*(t)\big(\pi + (1-\pi)S_u(t)\big)$$

where π is the proportion cured of disease and $S_u(t)$ is the relative survival function for the uncured. For the models in this article, we assume that the survival times of the uncured have a Weibull distribution, *i.e*.

$$S_u(t) = \exp(-\lambda t^\gamma)$$

We summarize parameter estimates in terms of the cure fraction, the median survival time of the uncured and the time at which 90% of the uncured are dead. We restrict followup to 10 years since we would expect cure to be reached within this period and sparse data toward the end of followup may lead to instability in the cure models.

Estimation of the model parameters is obtained using maximum likelihood on the individual level data. The estimation procedure is similar to that of De Angelis *et al*.,[12] but extended to model both parameters in the Weibull distribution.[11] The models are fitted using freely available software for the Stata package.[13]

Modeling approach

We are chiefly interested in the trends in the cure fraction and the survival of the uncured as a function of calendar year of diagnosis and age at diagnosis. We defined 4 age groups <50 years, 50–59 years, 60–69 years and 70–79 years. To model the effect of year of diagnosis, we used restricted cubic splines with 5 knots (2 external and 3 internal). These provide a flexible way to model nonlinear trends.[14] The cure fraction models have 3 components that may vary over time and by age groups, namely the cure fraction, π, and the 2 Weibull parameters (λ and γ). The 2 Weibull parameters model the survival distribution of the uncured group. Each model component included the restricted cubic spline terms for year of diagnosis and terms for age group. In addition, an interaction between each age group and a linear effect of year of diagnosis were included. Full interactions between the age groups and restricted cubic spline terms were investigated, but all cases did not result in a significant improvement in fit using the likelihood ratio test and so only the age group and linear calendar time interactions were included in the analyses. We present results based on patients diagnosed up to and including 1999. Cure is a long-term measure and although the model will estimate cure and associated measures up to 2003 these, by definition, will be based on a degree of extrapolation. The survival distribution of the uncured group was summarized by median survival and the time at which 90% of the uncured group would be dead.

To assess the fit of the cure models, we also calculated the Ederer II life table estimates of relative survival.[15] Separate cure models were fitted for each combination of age group and period of diagnosis, and then compared with the life table estimates.

Interpreting the results of cure models

With traditional methods for studying temporal trends in patient survival, we plot estimates of 5-year relative survival for different periods of diagnosis and attempt to correlate the observed trends with changes in factors that may affect survival (primarily changes in clinical practice). A common problem is that an observed trend may be consistent with several competing hypotheses. When using cure models we study trends in both the cure fraction along with some summary measure of the survival of the uncured thereby giving greater possibilities to distinguish between the many competing explanations for an observed trend.

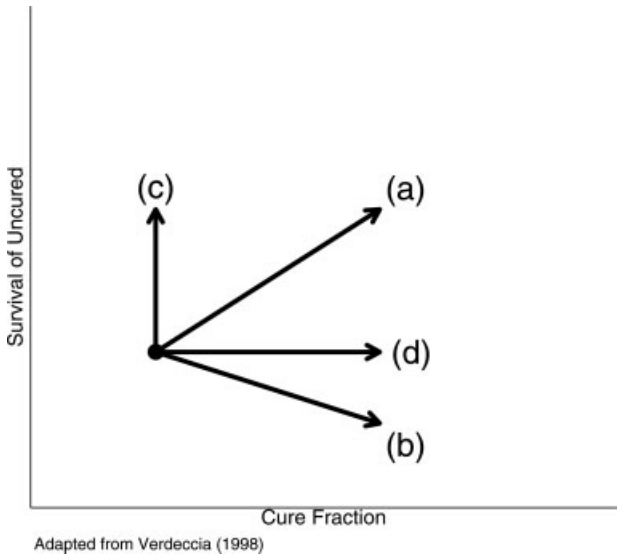

FIGURE 2 – Hypothetical changes in the cure fraction and median survival of the uncured between the 2 periods of diagnosis.

Consider, for example, the hypothetical situation where we compare patient survival between the 2 calendar periods of diagnosis. The black dot in Figure 2 represents the estimated cure fraction and median survival of the uncured at baseline and the arrows represent various scenarios for how these measures could change between the 2 periods of diagnosis.

Scenario (a) represents a general improvement; we have cured a higher proportion of patient in the latter period and those we are unable to cure have a longer median survival time. Scenario (b) might be termed "selective improvement" and could arise if, for example, improvements in treatment enable us to cure those patients who previously would have had a longer survival time (among the uncured). Scenario (c) might occur following improved palliative care or, alternatively, introduction of new diagnostic techniques that bring forward the time of diagnosis without affecting the time of death, that is, lead time bias (see Dickman and Adami,[16] Fig. 2). Here, we are faced with the same dilemma as with traditional methods in that 2 competing hypotheses may explain the same observed data. In this situation, knowledge of changes in clinical practice can guide our interpretation. Lead-time bias is often suggested as a possible explanation for improvements in patient survival when using traditional methods. An advantage in cure models is that the cure fraction cannot be affected by lead-time bias so an observed increase in the cure fraction must be due to other factors. Note that we make a distinction between the effect of earlier diagnosis and lead-time bias. It is quite possible, and certainly desirable, that earlier diagnosis will lead to greater potential for cure. The resulting increase in the cure proportion reflects a true clinical benefit independent of lead-time bias (a statistical artifact that would also exist in this scenario).

Scenario (d) might occur if, during the latter period, we introduced a diagnostic procedure (*e.g.*, PSA screening for prostate cancer) that resulted in inclusion of additional patients who experience no excess risk. There are, of course, other explanations for these 4 scenarios as well as other scenarios, but we believe that these examples provide a basis for interpreting the results of cure models.

Results

Patients

There were 27,754 patients with cancer of the colon and 21,885 patients with cancer of the rectum included in the analyses (Table I). The number of cases of both cancers has been increasing rapidly over time. This is partly due to an increasing population, but the age-standardized incidence rate of particularly colon and also rectal cancer has increased in Finland.[17,18] It is possible that the relatively higher increase in colon cancer incidence can be due to differences in how the rectosigmoid cancers are referred during the time period, but the most pronounced increase in incidence is seen for right-sided colon cancers. The proportion of patients excluded because of death certificate/autopsy only has decreased over time for both cancer types. The proportion of patients excluded as the tumor was not an adenocarcinoma increased over time for both cancer of the colon and rectum.[19] Of the patients included in the analyses for cancer of the colon, 2,903 (10.5%) were aged <50 years; 4,440 (16.0%) were 50–59; 8,763 (31.6%) were 60–69 and 11,648 (42.0%) were 70–79. Of the rectal cancer patients included, 1,798 (8.2%) were aged <50 years; 3,980 (18.2%) were 50–59; 7,443 (34.0%) were 60–69 and 8,664 (39.6%) were 70–79. The stage distribution by period of diagnosis has remained relatively stable in Finland over time (data not shown), but interpretation is complicated by the high proportion of patients for whom there were no stage details (10.7 and 10.2% in 1953–1964 for cancer of the colon and cancer of the rectum, respectively, with the corresponding figures for 1995–2003 being 17.7 and 20.4%) and the usual issue of stage migration.

Exploratory analyses

Initially, separate models were fitted by age group and period of diagnosis. The fitted values of the estimated relative survival curves for each age group as a whole and also the estimated relative survival curves for those uncured can be seen in Figures 3 and 4 for cancer of the colon and rectum, respectively. For the relative survival curves for the group as whole, the empirical life table estimates obtained using the Ederer II method are also shown. It can be seen that the mixture cure fraction model provides a good fit to the data with perhaps the only noticeable exception being the oldest age group for the periods 1953–1964 and 1965–1974 for cancer of the colon, where there is a slight underestimate of the proportion cured of their disease. For both cancer of the colon and rectum there is a clear improvement in relative survival over time for all age groups, with the greatest improvement for the oldest age group, who started from a lower base. For both cancer types, the 5-year relative survival estimates obtained using the Ederer II life table estimate of relative survival are very similar to the model based estimates. However, the relative survival curves tend not to reach a plateau, indicating statistical cure, until some time after 5 years of followup.

Cancer of the colon modeling results

Figure 5 shows the estimated cure fraction and the median survival of the uncured group as a function of calendar year of diagnosis by age group. Table II shows the model-based estimates of the cure fraction, the median survival of the uncured group and the time at which 90% of the uncured group are dead for a selection of years. There has been a clear increase in the proportion cured of their disease in all age groups with the increase fairly constant over time. There has been a large reduction in the difference in the cure fraction between the age groups over time, with the youngest age group now having a slightly lower cure fraction. For the uncured group, the median survival for all age groups was approximately constant until the early 1960s and then rapidly increased until the early 1980s, after which the rate of increase was reduced. In 1999, median survival of the uncured group was estimated at over 1.5 years for the youngest age group and about 1 year for the oldest age group. The time at which 90% of those in the uncured group are dead has also increased for all age groups.

Cancer of the rectum modeling results

Figure 6 shows the estimated cure fraction and the median survival of uncured group as a function of calendar year of diagnosis by age group. Table III shows the model-based estimates of the

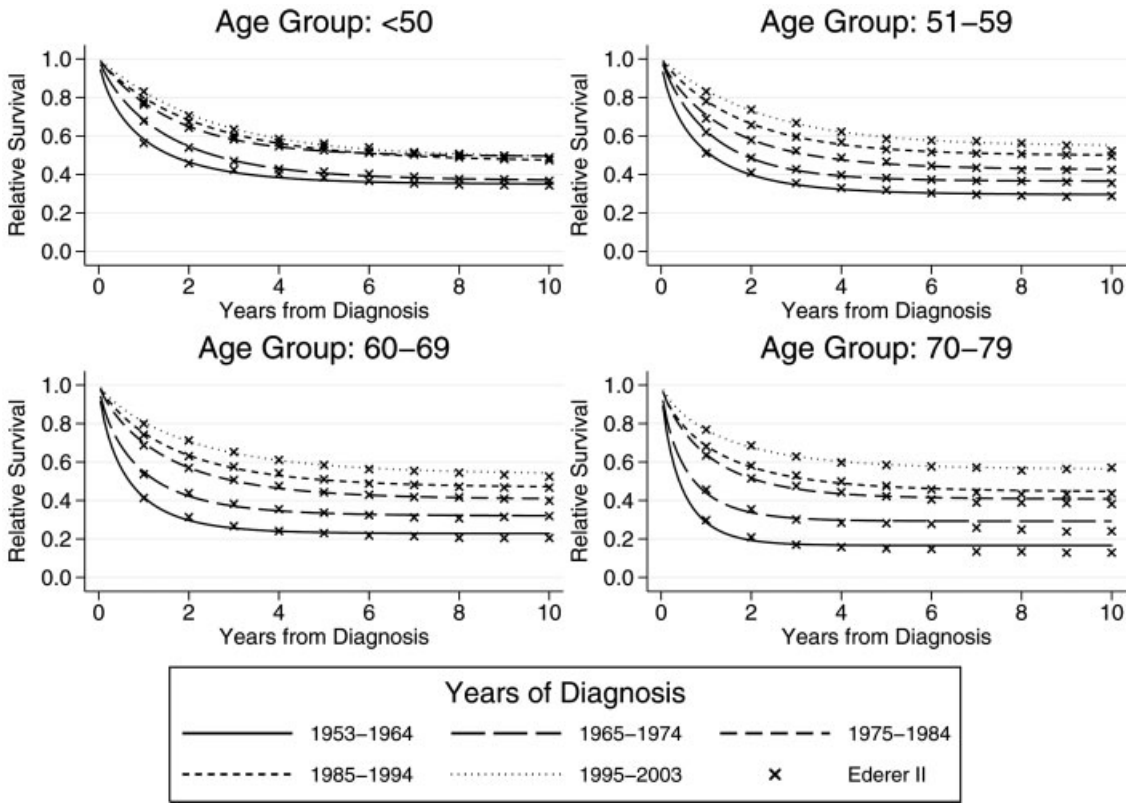

FIGURE 3 – Cancer of the colon: predicted relative survival curves by age group.

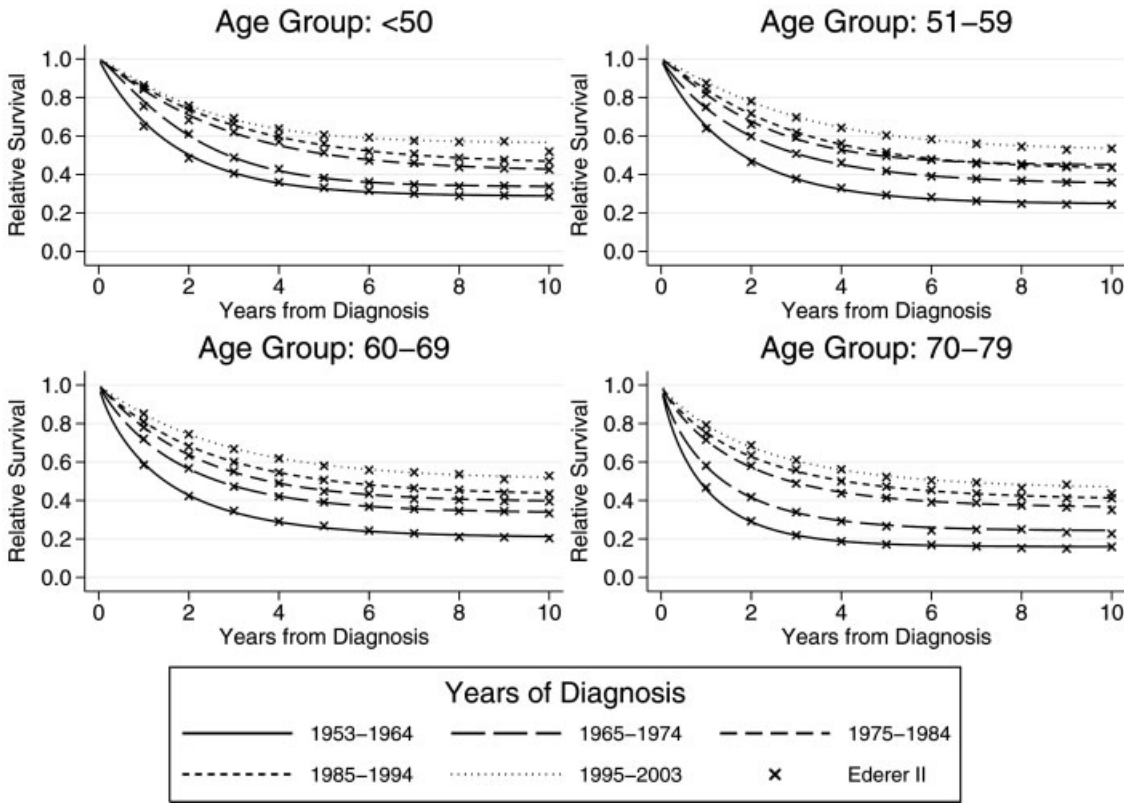

FIGURE 4 – Cancer of the rectum: predicted relative survival curves by age group.

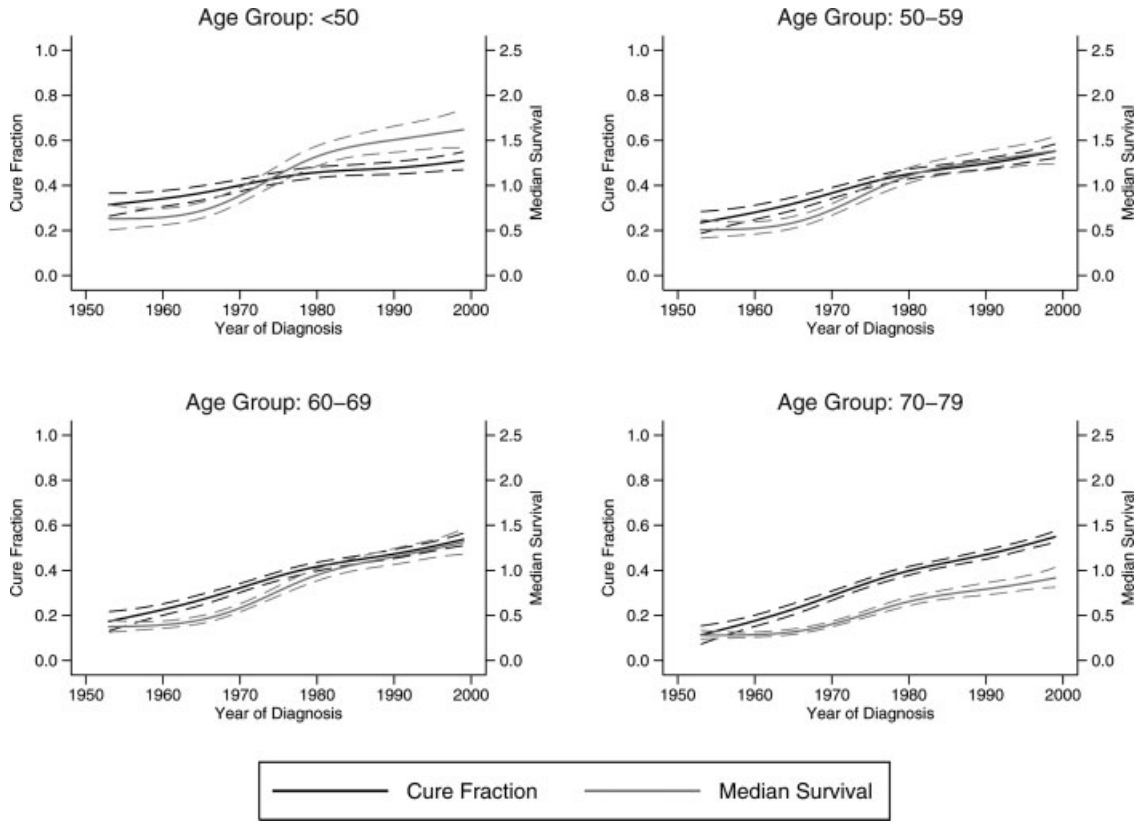

FIGURE 5 – Cancer of the colon: estimated cure fraction and median survival of the uncured group, with 95% confidence intervals presented by age group.

TABLE II – CANCER OF THE COLON: MODEL BASED ESTIMATES

Year	Age group (years)			
	<50	50–59	60–69	70–79
(a) The cure fraction (%)				
1960	34.1 (30.6–37.6)	28.0 (24.8–31.2)	22.6 (20.1–25.1)	17.6 (15.1–20.1)
1970	40.0 (37.3–42.7)	36.6 (34.2–39.0)	32.2 (30.2–34.2)	28.8 (26.7–30.8)
1980	45.8 (43.4–48.2)	45.0 (42.9–47.2)	41.6 (39.7–43.6)	39.8 (37.9–41.7)
1990	47.8 (45.0–50.5)	49.7 (47.4–52.0)	47.3 (45.3–49.3)	47.0 (45.0–49.0)
1999	51.0 (47.0–54.9)	55.3 (52.2–58.4)	53.8 (51.0–56.5)	54.9 (52.3–57.5)
(b) Median survival for the uncured group (years)				
1960	0.65 (0.56–0.75)	0.52 (0.46–0.60)	0.39 (0.36–0.44)	0.29 (0.26–0.32)
1970	0.89 (0.81–0.98)	0.73 (0.67–0.80)	0.58 (0.54–0.63)	0.40 (0.37–0.43)
1980	1.32 (1.21–1.44)	1.11 (1.03–1.20)	0.95 (0.88–1.02)	0.65 (0.61–0.70)
1990	1.51 (1.37–1.66)	1.27 (1.17–1.39)	1.15 (1.06–1.24)	0.79 (0.73–0.86)
1999	1.62 (1.42–1.85)	1.38 (1.24–1.55)	1.31 (1.18–1.46)	0.92 (0.81–1.03)
(c) Time at which 90% of the uncured group are dead (years)				
1960	3.02 (2.58–3.53)	2.43 (2.10–2.80)	1.90 (1.69–2.15)	1.26 (1.12–1.41)
1970	3.64 (3.24–4.08)	2.99 (2.69–3.34)	2.55 (2.31–2.81)	1.73 (1.58–1.90)
1980	4.76 (4.27–5.31)	4.02 (3.65–4.44)	3.77 (3.43–4.13)	2.73 (2.48–2.99)
1990	5.14 (4.56–5.79)	4.41 (3.97–4.91)	4.46 (4.04–4.93)	3.45 (3.09–3.84)
1999	5.20 (4.36–6.19)	4.54 (3.92–5.24)	4.91 (4.25–5.68)	4.08 (3.48–4.78)

cure fraction, the median survival of those uncured group and the time at which 90% of the uncured group are dead. For all age groups the estimated cure fraction was approximately constant for the first 10 years, followed by a rapid increase until the mid 1970s where it appeared to stabilize until the late 1980s whereupon it started to increase again. The difference in the cure fraction between the age groups has reduced over time with the estimated values being similar for the 4 age groups in 1999 (Table IIIa). The median survival for the uncured group has a constant increase until the late 1980s whereupon the improvement ceased and numerically declined. The time at which 90% of the uncured group has died shows a similar pattern to median survival, *i.e.*, with a continuous improvement with calendar time until the last few years when a small decrease was seen.

Discussion

The cure fraction and median survival of the uncured group have increased over time for both cancer of the colon and rectum. The cure fraction is now broadly similar for both types of cancer,

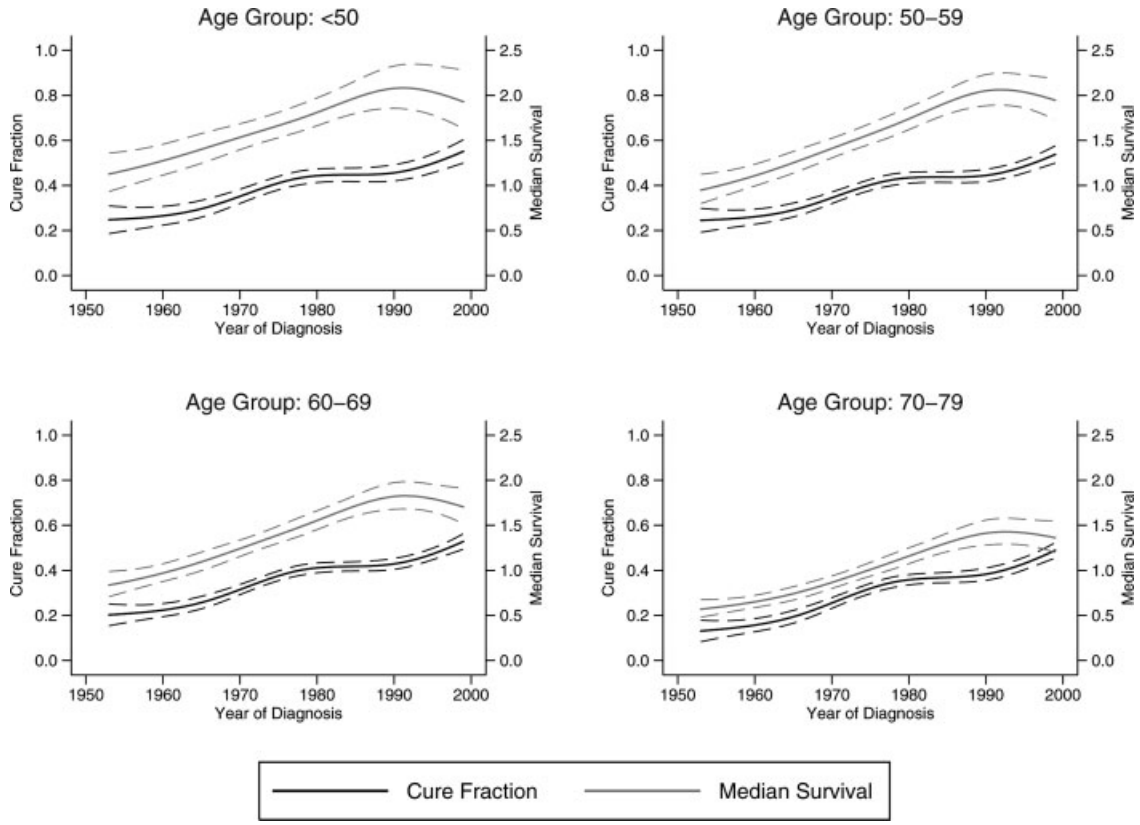

FIGURE 6 – Cancer of the rectum: estimated cure fraction and median survival of the uncured group, with 95% confidence intervals presented by age group.

TABLE III – CANCER OF THE RECTUM: MODEL BASED ESTIMATES

Year	Age group (years)			
	<50	50–59	60–69	70–79
(a) The cure fraction (%)				
1960	26.5 (22.3–30.7)	26.1 (22.7–29.4)	22.3 (19.4–25.3)	15.7 (12.8–18.6)
1970	35.2 (32.0–38.3)	34.5 (31.9–37.1)	31.5 (29.2–33.7)	25.5 (23.1–27.9)
1980	44.3 (41.3–47.3)	43.4 (40.9–45.8)	41.1 (38.9–43.3)	35.8 (33.5–38.1)
1990	45.6 (42.0–49.2)	44.4 (41.7–47.2)	42.9 (40.4–45.3)	38.3 (35.5–41.0)
1999	55.1 (50.0–60.3)	53.8 (49.9–57.6)	52.8 (49.4–56.3)	48.9 (45.5–52.3)
(b) Median survival for the uncured (year)				
1960	1.27 (1.11–1.46)	1.11 (0.99–1.23)	0.97 (0.88–1.07)	0.65 (0.59–0.72)
1970	1.53 (1.40–1.68)	1.41 (1.31–1.52)	1.24 (1.15–1.34)	0.87 (0.80–0.94)
1980	1.81 (1.66–1.97)	1.74 (1.62–1.87)	1.55 (1.45–1.66)	1.16 (1.07–1.25)
1990	2.08 (1.86–2.33)	2.05 (1.88–2.23)	1.82 (1.68–1.97)	1.41 (1.28–1.56)
1999	1.93 (1.63–2.28)	1.95 (1.73–2.19)	1.70 (1.52–1.91)	1.36 (1.20–1.55)
(c) Time at which 90% of the uncured are dead (years)				
1960	4.25 (3.67–4.93)	4.02 (3.55–4.55)	3.95 (3.49–4.48)	2.74 (2.42–3.10)
1970	4.89 (4.36–5.47)	4.75 (4.31–5.23)	4.68 (4.25–5.14)	3.53 (3.19–3.91)
1980	5.27 (4.73–5.86)	5.20 (4.73–5.72)	5.15 (4.71–5.63)	4.33 (3.93–4.76)
1990	6.22 (5.36–7.21)	6.17 (5.51–6.90)	6.09 (5.46–6.79)	5.59 (4.90–6.37)
1999	5.56 (4.43–6.98)	5.53 (4.72–6.48)	5.37 (4.59–6.28)	5.25 (4.43–6.24)

but median survival of the uncured group is still higher for cancer of the rectum. The reasons for these improvements over time are complex and likely because of many interrelated factors. However, much of the improvement is likely because of improved patient care, both surgical and nonsurgical (radiation, pharmacological and supportive). The data provide no direct relationships, at an individual level, between the changes in patient care and improved survival, but it is useful to review what these changes are and how they may have contributed to improved survival. Whenever possible, we have identified studies from Finland presenting changes in the patterns of care. However, since such studies have frequently not been reported, we have primarily identified studies from the other Nordic countries having a very similar health care structure. Also, several examples of joint clinical trials between these countries are present.

Surgical and anesthesiological techniques have become more sophisticated over time and the proportion of patients safely resected has increased over time for both cancer of the colon and rectum.[20–23] The age of the patient at which surgeons are prepared to operate has increased over time,[20,21] which may partially

explain the reduction in the difference in the proportion cured between age groups. Some of the trends over time are likely to be due to the "learning period" when gradually introducing new techniques within and between hospitals. A learning period is also seen when individual doctors/teams become more familiar with and skilled in a particular technique.[24–26] Although we do not have information on trends in surgical factors in Finland as a whole, we have some information from the Department of Surgery of Helsinki University Central Hospital from 1966 to 2005 for cancer of the colon and rectum combined[27,28] (Personal Communication, Professor Heikki J. Järvinen, Helsinki University Central Hospital). The percentage of primary tumors operated on increased from 83% in 1966–1975 to 97% in 1996–2005. The frequency of radical operations (RO) also increased over the same time period from 61 to 80%. The operative mortality fell from 6.5% in 1966–2005 to 2.8% in 1996–2005.

The approximate linear increase with time in the cured fraction in cancer of the colon suggests that the various factors responsible for the improvements have had a constant net effect. This linear effect is much steeper in the highest age groups reflecting the greater possibilities to resect the colon cancer safely.[20] During the late 1960s/early 1970s improvements may be related to improvements in postoperative care, particularly with the creation of intensive care units in Finland. During the late 1990s improvements may be associated with adjuvant chemotherapy in stage III.[29]

In contrast to the almost linear increase in the cured fraction for cancer of the colon, different factors have influenced this fraction much more unevenly in cancer of the rectum. Rectal cancer surgery is more demanding than colon cancer surgery,[30,31] and the general improvements in anesthesiology and postoperative care seen in the late 1960s/early 1970s were relatively more important in cancer of the rectum than in cancer of the colon. The steep increase during the 1990s seen in all age groups likely reflects the marked decrease in the risk of a local failure after rectal cancer surgery seen after the introduction of total mesorectal excision and increased use of preoperative radiotherapy or postoperative radiochemotherapy.[32] A local failure is a much less clinical problem in cancer of the colon than in cancer of the rectum.[33,34] There is now a similar proportion being cured for cancer of the colon and cancer of the rectum (compare Tables II and III). The exception is those aged 70–79 where the cure fraction for cancer of the rectum remains lower. One reason for this could be the greater risks involved with surgery for cancer of rectum leading to a reluctance to operate on some of these individuals. Similar 5-year survival for cancer of the colon and cancer of the rectum has also been reported in one county in Sweden[4] and in Sweden as a whole.[6]

Also the evolution with time in the median survival of the uncured group differs between cancer of the colon and cancer of the rectum. Metastatic disease has been the predominant cause of death in cancer of colon through the decades whereas in cancer of the rectum a local failure has also been frequent until the last decade.[24–26,34–36] The natural course of a local failure is longer than that of distant metastases, liver being most frequently involved. Thus, the median survival of the uncured group has always been much longer in cancer of the rectum, however, with a gradually decreasing difference with time reflecting the decreasing importance of the local failures after cancer of the rectum.

Potential reasons for longer survival of the uncured group are better general health in society, supportive care activities, less postoperative mortality after a palliative bowel resection,[20,23,37] systemic chemotherapy and possibilities to resect metastatic disease, *e.g.*, in the liver. Changes in the stage distribution of the patients could also partially explain these changes. The more rapid increase in median survival seen in cancer of the colon during the 1970s may reflect generally better health, more awareness of the relevance of supportive care activities and above all less postoperative mortality after a bowel resection. Before the improvements in the postoperative care during late 1960s/early 1970s, patients were rarely resected in the presence of metastatic disease because of a very high postoperative mortality.[23,38] Postoperative mortality after a palliative resection has continued to be higher than after a curative resection through the decades, but there is no longer a fear to resect the primary, if possible, even if metastatic disease is present.[37] During the 1970s the first patients also received palliative chemotherapy with 5-fluorouracil alone, however, only with limited influence on median survival.[39] Slightly more effective chemotherapy using 5-fluorouracil modulated with methotrexate or leucovorin was not introduced until during the late 1980s/early 1990s.[40] However, knowledge of the palliative effects benefiting many patients[41] meant that more patients were offered this treatment prolonging median survival about 4–6 months.[40,42] Irinotecan and oxaliplatin were not used until the last years of the 1990s and may then have contributed to a further prolongation of median survival (about 2–3 months) for cancer of the colon. These drugs are also used in metastatic cancer of the rectum and with the same efficacy.[43] However, the reason why survival has not continued to improve during the last 5-year period for cancer of the rectum may be related to the marked decrease in local failure rates (having a longer natural course than metastatic disease). Finally, possibilities to resect local recurrence and liver and lung metastases have increased, however, only in few individuals,[35] and thus has only limited effects on the population. Further, since some patients can be cured by this surgery it may actually decrease median survival of those not cured.

There are some limitations in using cure models. First, the models will still estimate the cure fraction even when it is not reasonable to do so. For example, women with breast cancer experiences excess mortality for at least 30 years subsequent to diagnosis.[44] However, for cancer of the colon and rectum it is likely to be a reasonable assumption. Second, we have used the Weibull distribution to model the distribution of the uncured group. Although this will generally provide reasonable estimates of the cure fraction and associated parameters, in some situations the Weibull distribution may not be flexible enough to capture the shape of the survival distribution and biased estimates can result.[11] This tends to occur in older age groups and is one reason why we excluded the oldest age group in the analyses presented here. We are currently developing methods to overcome this problem.

Cure models have been applied previously for cancer of the colon in Finland.[12] However, we believe that our analysis has a number of advantages to the previous analysis. First, our analysis is over a longer period and excludes individuals aged over 80, which is important as we observed that use of the Weibull model for elderly age groups leads to biased estimates of the cure fraction. Second, we use median survival as a summary measure for survival of the uncured group, while the previous analysis used mean survival, which can be unstable because of the skewed nature of survival data. Third, we have included year of diagnosis as a continuous factor using restricted cubic splines, as opposed to broad categories of time, allowing improved understanding of the changes over time. Fourth, we have included interactions between year of diagnosis and age group. This is important as for both cancer types the effect of age varies over time for both the cure fraction and the survival distribution of the uncured group. Finally, we have also modeled both parameters in the Weibull distribution, which we have previously shown to be important in reducing bias when fitting cure models.[11]

We believe cure models to be a valuable tool for studying temporal trends in patient survival and, in particular, gaining insights into the underlying reasons for these trends.

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References

1. Ferlay J, Bray F, Pisini P, Parkin DM. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5, version 2.0 ed. Lyon: IARC Press, 2004.
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137–50.
3. Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sorensen HT. Population-based study of short- and long-term survival from colorectal cancer in Denmark, 1977–1999. Br J Surg 2005;92:873–80.
4. Dahlberg M, Pahlman L, Bergstrom R, Glimelius B. Improved survival in patients with rectal cancer: a population-based register study. Br J Surg 1998;85:515–20.
5. Angell-Andersen E, Tretli S, Coleman MP, Langmark F, Grotmol T. Colorectal cancer survival trends in Norway 1958–1997. Eur J Cancer 2004;40:734–42.
6. Birgisson H, Talback M, Gunnarsson U, Pahlman L, Glimelius B. Improved survival in cancer of the colon and rectum in Sweden. Eur J Surg Oncol 2005;31:845–53.
7. Dickman PW, Hakulinen T, Luostarinen T, Pukkala E, Sankila R, Soderman B, Teppo L. Survival of cancer patients in Finland 1955–1994. Acta Oncol 1999;38 (Suppl 12):1–103.
8. Verdecchia A, De Angelis R, Capocaccia R, Sant M, Micheli A, Gatta G, Berrino F. The cure for colon cancer: results from the EUROCARE study. Int J Cancer 1998;77:322–9.
9. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncol 1994;33:365–9.
10. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961;6:101–21.
11. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modelling the cure fraction in population-based cancer survival analysis. Biostatistics 2007;8:576–94.
12. De Angelis R, Capocaccia R, Hakulinen T, Soderman B, Verdecchia A. Mixture models for cancer survival analysis: application to population-based data with covariates. Stat Med 1999;18:441–54.
13. Lambert PC. Modelling of the cure fraction in survival studies. Stata J 2007, in press.
14. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–61.
15. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note No. 10 ed. Bethesda MD: End Results Evaluation Section, National Cancer Institute, 1959.
16. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. J Intern Med 2006;260:103–17.
17. Finish Cancer Registry: Cancer in Finland 2002–2003. Cancer Society of Finland Publication No. 66.
18. Malila N, Hakulinen T. Epidemiological trends of colorectal cancer in the Nordic countries. Scand J Surg 2003;92:5–9.
19. Thorn M, Bergstrom R, Kressner U, Sparen P, Zack M, Ekbom A. Trends in colorectal cancer incidence in Sweden 1959–93 by gender, localization, time period, and birth cohort. Cancer Causes Control 1998;9:145–52.
20. McArdle CS, McKee RF, Finlay IG, Wotherspoon H, Hole DJ. Improvement in survival following surgery for colorectal cancer. Br J Surg 2005;92:1008–13.
21. Davila JA, Rabeneck L, Berger DH, El-Serag HB. Postoperative 30-day mortality following surgical resection for colorectal cancer in veterans: changes in the right direction. Dig Dis Sci 2005;50:1722–8.
22. Mitry E, Bouvier AM, Esteve J, Faivre J. Benefit of operative mortality reduction on colorectal cancer survival. Br J Surg 2002;89:1557–62.
23. Makela J, Haukipuro K, Laitinen S, Kairaluoma MI. Palliative operations for colorectal cancer. Dis Colon Rectum 1990;33:846–50.
24. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356:93–6.
25. Wibe A, Eriksen MT, Syse A, Myrvold HE, Soreide O. Total mesorectal excision for rectal cancer—what can be achieved by a national audit? Colorectal Dis 2003;5:471–7.
26. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. Br J Surg 2002;89:1142–9.
27. Turunen MJ, Peltokallio P. Surgical results in 657 patients with colorectal cancer. Dis Colon Rectum 1983;26:606–12.
28. Jarvinen HJ, Ovaska J, Mecklin JP. Improvements in the treatment and prognosis of colorectal carcinoma. Br J Surg 1988;75:25–7.
29. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444–50.
30. Hohenberger W, Reingruber B, Merkel S. Surgery for colon cancer. Scand J Surg 2003;92:45–52.
31. Wiggers T. Surgery for rectal cancer. Scand J Surg 2003;92:53–6.
32. Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol 2003;42:476–92.
33. Sjovall A, Granath F, Cedermark B, Glimelius B, Holm T. Loco-regional recurrence from colon cancer: a population-based study. Ann Surg Oncol 2007;14:432–40.
34. Pahlman L, Glimelius B. Local recurrences after surgical treatment for rectal carcinoma. Acta Chir Scand 1984;150:331–5.
35. Sjovall A, Jarv V, Blomqvist L, Singnomklao T, Cedermark B, Glimelius B, Holm T. The potential for improved outcome in patients with hepatic metastases from colon cancer: a population-based study. Eur J Surg Oncol 2004;30:834–41.
36. Read TE, Mutch MG, Chang BW, McNevin MS, Fleshman JW, Birnbaum EH, Fry RD, Caushaj PF, Kodner IJ. Locoregional recurrence and survival after curative resection of adenocarcinoma of the colon. J Am Coll Surg 2002;195:33–40.
37. Beham A, Rentsch M, Püllmann K, Mantouvalou L, Spatz H, Schlitt H, Obed A. Survival benefit in patients after palliative resection vs non-resection colon cancer surgery. World J Gastroenterol 2006;12:6634–8.
38. Adams C, Fielding JW, Morton DG. Surgery for colon cancer. In: Bleiberg H, Kemeny N, Rougier PHJW, eds. Colorectal cancer: a clinical guide to therapy. London: Martin Dunitz, 2002.93–113.
39. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. Br Med J 2000;321:531–5.
40. Ragnhammar P, Hafstrom L, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in colorectal cancer. Acta Oncol 2001;40:282–308.
41. Superiority of sequential methotrexate, fluorouracil, and leucovorin to fluorouracil alone in advanced symptomatic colorectal carcinoma: a randomized trial. The Nordic Gastrointestinal Tumor Adjuvant Therapy Group. J Clin Oncol 1989;7:1437–46.
42. Glimelius B. Palliative treatment of patients with colorectal cancer. Scand J Surg 2003;92:74–83.
43. Kohne CH, Cunningham D, Di CF, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, Baron B, Pignatti F, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol 2002;13:308–17.
44. Brenner H, Hakulinen T. Are patients diagnosed with breast cancer before age 50 years ever cured? J Clin Oncol 2004;22:432–8.