Jpn. J. Cancer Res. **90**, 705–710, July 1999

Improvement of Survival Over Time for Colon Cancer Patients by Anatomical Sub-sites

Yoshikazu Kawazuma,[1] Hideo Tanaka, Hideaki Tsukuma, Wakiko Ajiki and Akira Oshima

[1]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511

The aims of this study are to describe and to evaluate improvement of survival over time for colon cancer patients by anatomical sub-sites. Data on 661 patients newly diagnosed as having colon cancer at Osaka Medical Center for Cancer and Cardiovascular Diseases from 1978 to 1991 were examined in this study. Corrected survival was calculated with the Kaplan-Meier method according to the period of diagnosis: early period (1978–84) and later period (1985–91). Factors concerning the difference in survival between the two periods were examined with the Cox proportional hazards regression model according to sub-site. Five-year corrected survival of the patients with left colon cancer improved significantly (60 to 72%; $P<0.01$), probably due to advances in treatment, while that of patients with transverse colon cancer also improved significantly (39 to 67%; $P<0.01$), mainly because of progress in diagnosis. The five-year corrected survival of those with right colon cancer did not increase (57 to 46%; $P=0.14$), owing to lack of improvement in stage at diagnosis. Among the three sub-sites, the right showed the worst five-year survival in the later period. We concluded that survival of patients with right colon cancer, differing from the other anatomical sub-sites, did not improve, possibly because of lack of symptoms. The screening programs for colon cancer introduced in Japan in 1992 may be expected to improve the survival of patients with colon cancer, including that of the right colon.

Key words: Colon cancer — Sub-site — Survival — Improvement over time

The incidence of colon cancer has been increasing remarkably in Japan. The age-standardized incidence rate per 100,000 population (standardized to the world population) was 7.7 for males and 7.0 for females in 1975, and had increased to 30.7 and 17.8 in 1993 for males and females, respectively.[1)] Colon cancer is the third most common cancer for males and the fourth most common cancer for females in Japan.[1)] Studies of survival of patients with colon cancer are of great interest, as success in diagnosis and treatment can be measured according to survival. Proximal and distal colon cancer are considered to have somewhat different etiologies,[2, 3)] and sometimes show dissimilar symptoms.[4)] Although survival of colon cancer patients has increased during the past decades,[5)] it is unclear if this increase applies to each anatomical sub-site. The aims of this study are to describe and to evaluate the improvement of survival over time for colon cancer patients by sub-site based on reliable information on diagnosis according to sub-site from a hospital-based cancer registry in Osaka.

[1] To whom correspondence and requests for reprints should be addressed.
E-mail: xkawazum@iph.pref.osaka.jp

SUBJECTS AND METHODS

Subjects Candidates for study subjects were 880 consecutive patients with colon cancer newly diagnosed at Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC) between January 1978 and December 1991. They were identified through the hospital cancer registry (HCR) of the OMCC.[6)] In cases with multiple colon cancers, only the tumor at the most advanced stage or the largest in size was included in the analysis. Of the 880 cases, the following were excluded: 36 with an unknown anatomical sub-site, 125 detected through screening for colon cancer, 20 with mucosal carcinoma, and 38 with adenomatous polyps having a small carcinomatous region. The remaining 661 cases were enrolled in this study. Of those, 488 were both diagnosed and treated at the OMCC, and 173 were diagnosed at OMCC but treated in other hospitals.

Data for this analysis were obtained primarily from the HCR of the OMCC. When patients were diagnosed at OMCC but treated at other medical facilities, information on the extent of their disease and histological differentiation was supplemented with data from the Osaka Cancer Registry (OCR), a population-based cancer registry covering Osaka Prefecture.[5)] Colon cancer cases were categorized into three anatomical sub-sites: right (cecum and

ascending), transverse (hepatic flexure, transverse, and splenic flexure), and left (descending and sigmoid). In both the HCR and OCR, extent of disease at diagnosis was classified into three stages,[6] based on pathological and/or clinical extent of disease: 1) localized, confined to the original organ (corresponding to T1-3 N0 M0 in the TNM classification[6]); 2) regional, direct extension to adjacent organs or tissues and/or regional lymph nodes (corresponding to T4 N0 M0 or any T N1, 2 M0); and 3) distant, metastases to remote organs and/or distant lymph nodes (corresponding to M1). Histological differentiation coded according to the International Classification of Disease for Oncology (ICD-O) was re-categorized into high (grade I), low (grades II, III and IV) and unknown (grade or differentiation not determined or not stated).

Follow-up methods Routinely, the HCR of the OMCC annually updates information on the vital status of registered patients, referring to records of hospital visits, death certificates issued in the hospital, and files of the OCR. When a patient's vital status is unknown as of 5 years after diagnosis, HCR inquires as to the presence or absence of resident registration. Causes of death are identified by documents such as death certificates or OCR data, and classified as original cancer death, other cancer death or non-malignant tumor death.[5] Among the study subjects, 355 (54%) were alive, 300 (45%) were dead and 6 (1%) were lost to follow-up as of five years from the date of diagnosis. Of the 300 dead patients, 213 (71%) had died of colon cancer and 69 (23%) had died of other causes. In the remaining 18 (6%) patients, the cause of death was unknown because death certificates were unavailable.

Statistical analysis Five-year survival from the date of diagnosis was estimated with the Kaplan-Meier method according to the period of diagnosis: early period (1978–84) and later period (1985–91). In these analyses, only colon cancer deaths were considered as events, while deaths from other than colon cancer, including unknown causes of death and lost to follow-up, were considered as censored to describe mortality attributable to colon cancer.[7] The differences in survival curves between the two periods and among the three sub-sites were assessed with the log-rank test. Factors concerning the difference of survival between the two periods were examined with the Cox proportional hazards model. All study variables were categorized and coded as dummy variables to avoid assumptions about gradations of the effect. Unknown grade of histological differentiation and stage at diagnosis were regarded as independent categories. Analyses were performed with PROC LIFETEST and PROC PHREG of the SAS computer programs.[8] All tests were two-sided, and a *P*-value of less than 0.05 was considered as statistically significant.

RESULTS

Characteristics of study subjects Table I shows the distribution of selected characteristics according to the anatomical sub-site and the period of diagnosis. In cases with left colon cancer, distribution of age, sex, histological differentiation and stage at diagnosis seemed to show no remarkable changes during the two study periods. In transverse colon cancer, localized disease increased from 27 to 56% during the two study periods. With right colon cancer, patients aged 65 years old and over increased from 54 to 62%, localized disease was reduced from 39 to 23%, and lesions with a high grade decreased from 47 to 40% between the earlier and later periods. For each sub-site, the proportion of patients who underwent abdominal ultrasonography or computed tomography increased remarkably.

Univariate analysis of survival Table II shows the corrected five-year survival of the study subjects according to the anatomical sub-site and the period of diagnosis. The five-year survival of patients with right colon cancer was 57% in the early period (1978–84) and decreased to 46% in the later period (1985–91), although the difference was not significant (log-rank test: $P=0.14$). In the patients with transverse cancer, the five-year survival improved significantly from 39 to 67% ($P<0.01$). In the cases with left cancer, the five-year survival improved significantly from 60 to 72% ($P<0.01$).

Fig. 1 shows the cumulative corrected survival curves of the study subjects diagnosed in the later period according to anatomical sub-site. The left colon cancer patients showed the best survival rate, the right the worst and the transverse intermediate. Differences among the three survival curves were statistically significant ($P<0.01$).

Multivariate analysis for survival Table III shows the later to early period hazards rate ratios (HRs) according to anatomical sub-site. In the left colon cancer patients, age and sex adjusted HR was 0.65 (95% confidence interval [CI]: 0.46–0.92). HR was reduced to 0.58 (95% CI: 0.41–0.82) after an additional adjustment for histological differentiation and to 0.44 (95% CI: 0.31–0.62) after further adjustment for stage at diagnosis.

In the transverse colon cancer patients, the age and sex adjusted HR was 0.43 (95% CI: 0.23–0.82). An additional adjustment for histological differentiation still showed a significant reduction of HR (HR=0.51; 95% CI: 0.27–0.99), while there was no significant improvement after further adjustment for stage at diagnosis (HR=1.22; 95% CI: 0.58–2.55).

In the patients with right cancer, the age and sex adjusted HR was 1.41 (95% CI: 0.89–2.23). However, further adjustment for histological differentiation and stage at diagnosis reduced the HR to 1.08 (95% CI: 0.66–1.74).

Table I. Distribution of Selected Characteristics by Anatomical Sub-sites and Period of Diagnosis

	Anatomical sub-sites														
	Left (*N*=410)					Transverse (*N*=89)					Right (*N*=162)				
	1978–1984		1985–1991		$P^{a)}$	1978–1984		1985–1991		$P^{a)}$	1978–1984		1985–1991		$P^{a)}$
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Total	195	(48)	215	(52)		33	(37)	56	(63)		72	(44)	90	(56)	
Age															
−64	118	(61)	134	(62)	0.71	13	(39)	32	(57)	0.11	33	(46)	34	(38)	0.30
65−	77	(39)	81	(38)		20	(61)	24	(43)		39	(54)	56	(62)	
Sex															
Male	116	(59)	132	(61)	0.69	22	(67)	43	(77)	0.30	35	(49)	39	(43)	0.50
Female	79	(41)	83	(39)		11	(33)	13	(23)		37	(51)	51	(57)	
Histological differentiation															
High	112	(57)	107	(50)	0.12	14	(42)	30	(54)	0.19	34	(47)	36	(40)	0.59
Low	52	(32)	57	(27)		9	(32)	18	(32)		23	(32)	30	(33)	
Unknown	31	(16)	51	(24)		10	(30)	8	(14)		15	(21)	24	(27)	
Stage at diagnosis															
Localized	98	(50)	103	(48)	0.12	9	(27)	33	(56)	0.08	28	(39)	21	(23)	0.11
Regional	51	(26)	41	(19)		10	(30)	14	(24)		21	(29)	26	(29)	
Distant	37	(19)	54	(25)		11	(33)	9	(15)		15	(21)	31	(34)	
Unknown	9	(5)	17	(8)		3	(9)	3	(5)		8	(11)	12	(13)	
CT															
Done	22	(11)	58	(27)	<0.01	5	(15)	16	(29)	0.15	10	(14)	26	(29)	0.02
Not done	173	(89)	157	(73)		28	(85)	40	(71)		62	(86)	64	(71)	
Echo															
Done	73	(37)	161	(75)	<0.01	17	(52)	45	(80)	<0.01	33	(46)	73	(81)	<0.01
Not done	122	(63)	54	(25)		16	(48)	11	(20)		39	(54)	17	(19)	

a) *P*-value for χ^2 test.

Table II. Five-year Corrected Survival Rates by Anatomical Sub-sites and Period of Diagnosis

	No. of cases	Anatomical sub-sites														
		Left (*N*=410)					Transverse (*N*=89)					Right (*N*=162)				
		1978–1984		1985–1991		$P^{a)}$	1978–1984		1985–1991		$P^{a)}$	1978–1984		1985–1991		$P^{a)}$
Total	661	59.8	(3.5)	72.2	(3.1)	0.01	38.8	(8.6)	66.5	(6.4)	0.01	56.5	(6.0)	46.1	(5.6)	0.14
Age																
−64	364	59.0	(4.6)	72.5	(3.9)	0.04	52.8	(3.9)	63.3	(8.8)	0.52	63.6	(8.4)	44.3	(8.9)	0.10
65−	297	60.9	(5.7)	71.8	(5.1)	0.18	30.0	(5.1)	70.4	(9.4)	<0.01	49.7	(8.5)	47.3	(6.7)	0.67
Sex																
Male	401	56.8	(4.7)	72.2	(4.0)	0.02	35.4	(10.4)	63.2	(7.6)	0.03	63.7	(8.1)	48.0	(7.1)	0.10
Female	260	64.2	(5.5)	72.2	(5.1)	0.33	45.5	(15.0)	76.9	(11.7)	0.10	48.1	(8.8)	43.3	(8.2)	0.65
Histological differentiation																
High	333	70.8	(4.4)	82.9	(3.7)	0.04	49.0	(13.6)	83.2	(6.9)	0.02	53.7	(9.0)	69.0	(7.8)	0.24
Low	189	41.6	(7.0)	70.3	(6.3)	<0.01	—		43.8	(12.4)		60.9	(10.2)	28.2	(8.4)	0.02
Unknown	139	—		51.9	(7.2)		10.0	(9.5)	50.0	(17.7)	0.14	55.8	(13.6)	32.6	(10.0)	0.23
Stage at diagnosis																
Localized	289	81.1	(4.0)	94.0	(2.4)	0.01	—		100.0	(0.0)		81.0	(7.7)	95.2	(4.7)	0.15
Regional	163	54.2	(7.1)	78.0	(6.5)	0.02	50.0	(15.8)	38.5	(13.5)	0.80	55.1	(11.1)	60.7	(9.7)	0.64
Distant	157	3.2	(3.1)	19.1	(5.8)	0.01	9.1	(8.7)	—			0.0	(0.0)	0.0	(0.0)	0.21
Unknown	52	66.7	(15.7)	81.9	(9.5)	0.39	—		—			—		40.4	(15.5)	

a) *P*-value for log-rank test.
b) Survival rates are not shown when numbers of cases are less than 10.
( ) : standard error.

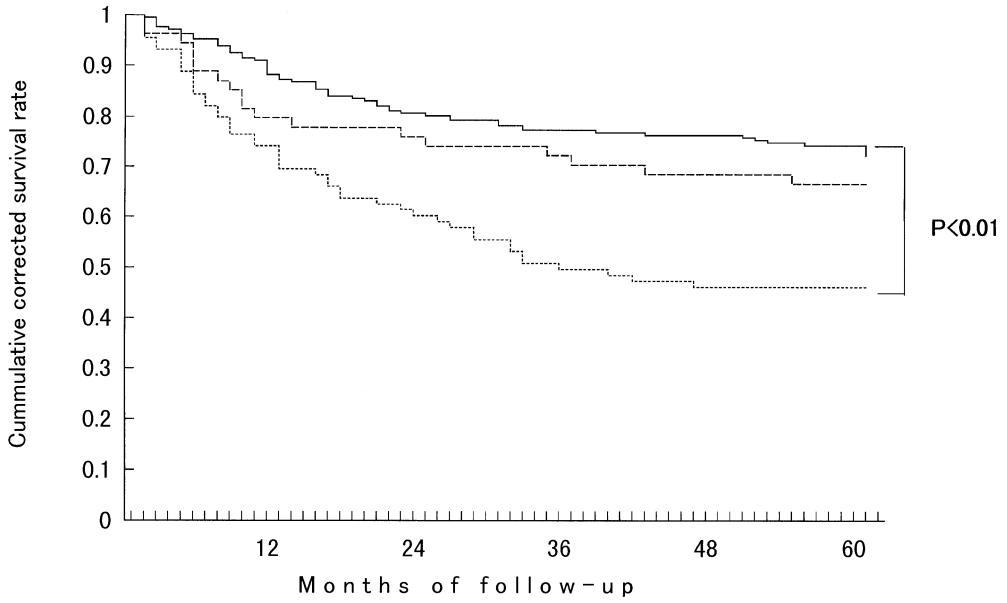

Fig. 1. Corrected survival of colon cancer by anatomical sub-site (1985–91). The numbers of patients at risk according to the months of follow-up (12, 24, 36, 48, 60) were as follows. Left, 215, 185, 166, 157, 153, 142; transverse, 56, 43, 40, 37, 36, 35; right, 90, 61, 51, 42, 39, 39. —— left, ---- transverse, ····· right.

Table III. The Later (1985–91) to Early (1978–84) Period Hazard Rate Ratio Adjusted for Prognostic Factors

Variables for adjustment	Anatomical sub-sites					
	Left (*N*=410)		Transverse (*N*=89)		Right (*N*=162)	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
	0.66 (0.47–0.92)	0.02	0.43 (0.23–0.82)	0.01	1.41 (0.89–2.23)	0.14
Age, sex	0.65 (0.46–0.92)	0.01	0.43 (0.23–0.82)	0.01	1.41 (0.89–2.23)	0.15
Age, sex, differentiation	0.58 (0.41–0.82)	<0.01	0.51 (0.27–0.99)	0.05	1.37 (0.86–2.19)	0.18
Age, sex, differentiation, stage at diagnosis	0.44 (0.30–0.62)	<0.01	1.22 (0.58–2.55)	0.60	1.08 (0.66–1.74)	0.77

DISCUSSION

Data from the HCR of the OMCC were used in this study, which was specifically focused on the anatomical sub-sites. With the HCR data, the proportion of cases with unspecified sub-site was below 4%, while it was approximately 30% in the OCR.[9)]

We made several efforts to reduce the selection biases that often accompany a hospital-based study. First, not only patients treated at the OMCC but also cases treated at other medical institutes were included in this study, because the latter had significantly more advanced disease than the former and the proportion of the latter was significantly higher in 1985–91 (31%) than in 1978–84 (21%). Excluding these cases, therefore, might have overestimated survival[10)] in patients diagnosed from 1985 to 91. Record linkage with the OCR was conducted to compensate for incomplete information on these cases. The staging scheme adopted in population-based cancer registries in Japan[11)] was used in this study to maintain comparability with the HCR data. Second, patients with clinical diagnosis only were included in order to avoid overestimating

survival, since in such cases histological confirmation is often not attempted because of advanced disease.[10, 12]

Study subjects were restricted to patients who were diagnosed before 1992, when a colorectal cancer screening program was integrated into a public health service in Japan.[13] Cases detected through screening or health check-ups were excluded, as well as patients with mucosal cancer and adenomatous polyps having a small carcinomatous region. In this study, therefore, the effects on survival owing to the lead-time and length biases often introduced by a screening program[12, 14] were eliminated or reduced to an almost negligible level. If these excluded cases had been included in the analyses, the survival would have been overestimated in the later period, because the number of excluded cases diagnosed in the later period was greater than that in the early period (151 vs. 30, respectively).

Improvement of survival over time for colon cancer patients by anatomical sub-sites was examined in this study. Since the extent of disease and histological differentiation, as well as sex and age at diagnosis, are all important prognostic factors of colon cancer,[12, 15] the Cox proportional hazards model was employed for adjustment of differences in the distribution of these prognostic factors. In the transverse colon cancer patients, proportions of the localized stage and higher differentiation were increased and survival improved significantly in the later period, but no significant reduction of the HR remained after an additional adjustment for stage at diagnosis according to age, sex and differentiation. The higher proportion of disease at an earlier stage and with a higher grade in the later period, which was probably due to improvements in diagnostic techniques, were considered to have led to improved survival. Patients with abdominal symptoms would have consulted doctors earlier in the later period, and their doctors might have used fecal occult blood tests, barium enema, and colonoscopy more frequently for diagnosis in patients with such symptoms. These potential factors might be related to the earlier detection of transverse colon cancer.

In cases with left colon cancer, survival increased significantly in spite of the similar distributions of age, sex, histological differentiation and stage at diagnosis. The HR remained even more reduced after adjustment for the stage. Stage migration[16] could have existed; however, improvement of not only stage-specific survival but also over-all survival may suggest the effectiveness of treatment.[17] Active treatment for metastasis detected by CT or echo might partially explain the increased survival among the patients with distant metastasis.[18]

In the patients with right colon cancer, the proportion of disease at the localized stage and that of higher differentiation and survival did not improve during the study period. The HR still remained at around 1.0 after adjustment for differentiation and stage. It was suggested that cases with right colon cancer had not been successfully diagnosed even in the later period, possibly because of lack of symptoms. True survival benefits for patients with right colon cancer will be expected from the screening programs employing fecal occult blood tests, which were introduced in Japan in 1992. Although differences in some biological behaviors of cells and related tissues by sub-site were reported, their effects on survival were controversial.[2, 19, 20] We do not have any plausible explanation as to why some biological behaviors would be associated with poor survival of right colon cancer patients. Further study is expected to clarify the effects of differences in biological behaviors of cells and related tissues on survival of colon cancer patients by anatomical sub-site.

We concluded that improvement of survival over time for colon cancer patients and related factors might differ according to the anatomical sub-site. Survival of patients with transverse colon cancer has improved significantly, mainly because of earlier diagnosis. That of patients with left colon cancers has ameliorated significantly, probably due to advances in treatment. Survival of the right colon cancer cases, however, has not improved because stage at diagnosis and treatment have remained the same, possibly due to the asymptomatic nature of right colon cancer.

The screening programs for colon cancer introduced in Japan in 1992 may be expected to improve survival, including that in patients with right colon cancer. Effectiveness of these screening programs should also be assessed by anatomical sub-site based on population-based cancer registry data of high quality in order to completely exclude selection biases.

ACKNOWLEDGMENTS

We wish to express our gratitude to the Osaka Cancer Registry for providing access to registry data. We also wish to thank Ms. Noriko Kinoshita, Ms. Yoko Koyama and the staff of the Hospital Cancer Registry of the Osaka Medical Center for Cancer and Cardiovascular Diseases for technical assistance. This study was supported in part by a grant for the New 10-year Strategy for Cancer Control, Prevention of Cancer, from the Ministry of Health and Welfare.

(Received March 18, 1999/Revised April 30, 1999/Accepted May 7, 1999)

REFERENCES

1) The Research Group for Population-based Cancer Registration in Japan (5-3). Cancer Incidence in Japan in 1992–1993: Estimates Based on Data from Population-based Cancer Registries. *Jpn. J. Clin. Oncol.*, **28**, 641–647 (1998).

2) Chen, V. W., Fenoglio-Preiser, C. M., Wu, X. C., Coates, R. J., Reinols, P., Wickerham, D. L., Andrews, P., Hunter, C., Stemmermann, G., Jackson, J. S., Edwards, B. K. and the National Cancer Institute Black/White Cancer Survival Study Group. Aggressiveness of colon carcinoma in blacks and whites. *Cancer Epidemiol. Biomarkers Prev.*, **6**, 1087–1093 (1997).
3) Ji, B. T., Devesa, S. S., Chow, W. H., Jin, F. and Gao, Y. T. Colorectal cancer incidence trends by subsite in urban Shanghai, 1972–1994. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 661–666 (1998).
4) Wolmark, N., Wieand, H. S., Rockette, H. E., Fisher, B., Grass, A., Lawrence, W., Lerner, W., Cruz, A. B., Volk, H., Shibata, H. and Evans, J. The prognostic significance of tumor location and bowel obstruction in Dukes B and C colorectal cancer. *Ann. Surg.*, **198**, 743–752 (1983).
5) Osaka Cancer Registry. "Survival of Cancer Patients in Osaka 1975–89," pp. 30–39 (1998). Osaka Foundation for Prevention of Cancer and Circulatory Diseases, Osaka.
6) Henson, D. E., Lawrence, W. J. and Klatt, G. R. Colon and rectum. *In* "AJCC Cancer Staging Manual," 5th Ed., ed. I. D. Fleming, J. S. Cooper, D. E. Henson, R. V. P. Hutter, B. J. Kennedy, G. P. Murphy, B. O'Sullivan, L. H. Sobin and J. W. Yarbro, pp. 83–90 (1997). Lippincott-Raven, Philadelphia.
7) Parkin, D. M. and Hakulinen, T. Survival analysis. *In* "Cancer Registration, Principles and Methods," IARC Scientific Publications No. 95, ed. O. M. Jensen, D. M. Parkin, R. MacLennan, C. S. Muir and R. G. Skeet, pp. 159–176 (1991). International Agency for Research on Cancer, Lyon.
8) SAS Institute Japan. "SAS/STAT Software: Changes and Enhancements through Release 6.12" (1997). SAS Institute, Inc., Cary, NC.
9) Osaka Cancer Registry. Total numbers of incident cases and crude and age-standardized average annual incidence rates according to detailed primary site and sex, 1980–1989 (Table 12-2). *In* "Cancer Incidence and Mortality in Osaka 1963–89," p. 209 (1993). The Shinohara Publishers, Osaka.
10) Prior, P., Woodman, C. B. J. and Collins, S. International differences in survival from colon cancer: more effective care versus less complete registration. *Br. J. Surg.*, **85**, 101–104 (1998).
11) Tanaka, H., Hiyama, T., Hanai, A., Fujimoto, I. and The Research Group for Population-based Cancer Registration in Japan. Interhospital differences in cancer survivals in Japan. *Jpn. J. Clin. Oncol.*, **23**, 191–198 (1993).
12) Esteve, J., Benhamou, E. and Raymond, L. Estimation of survival distribution. *In* "Statistical Methods in Cancer Research Volume IV: Descriptive Epidemiology," IARC Scientific Publications No. 128, pp. 213–245 (1995). International Agency for Research on Cancer, Lyon.
13) Oshima, A. A critical review of cancer screening programs in Japan. *Int. J. Technol. Assess. Health Care*, **10**, 346–358 (1994).
14) Berrino, F., Esteve, J. and Coleman, M. P. Basic issues in estimating and comparing the survival of cancer patients. *In* "Survival of Cancer Patients in Europe: The EUROCARE Study," IARC Scientific Publications No. 132, ed. F. Berrino, M. Sant, A. Verdecchia, R. Capocaccia, T. Hakulinen and J. Esteve, pp. 1–14 (1995). International Agency for Research on Cancer, Lyon.
15) Sant, M., Capocaccia, R., Verdecchia, A., Gatta, G., Micheli, A., Mariotto, A., Hakulinen, T. and Berrino, F. Comparisons of colon-cancer survival among European countries: The EUROCARE Study. *Int. J. Cancer*, **63**, 43–48 (1995).
16) Feinstein, A. R., Sosin, D. M. and Wells, C. K. The Will Rogers phenomenon. *N. Engl. J. Med.*, **312**, 1604–1608 (1985).
17) Koyama, Y. and Kotake, K. Overview of colorectal cancer in Japan. *Dis. Colon Rectum*, **10** (Suppl.), s2–s9 (1997).
18) Nordinger, B., Vaillant, J. C., Guiguet, M., Balladur, P., Paris, F., Bachellier, P. and Jaeck, D. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. *J. Clin. Oncol.*, **12**, 1491–1496 (1994).
19) Lothe, R. A., Peltomäki, P., Meiling, G. I., Aaltomen, L. A., Nyström-Lahti, M., Pylkkänen, L., Heimdal, K., Andersen, T. I., Møller, P., Rognum, T. O., Fosså, S. D., Haldorsen, T., Langmark, F., Brøgger, A., de la Chapelle, A. and Børresen, A.-L. Genomic instability in colorectal cancer: relationship to clinicopathological variables and family history. *Cancer Res.*, **53**, 5849–5852 (1993).
20) Thibodeau, S. N., Bren, G. and Schaid, D. Microsatellite instability in cancer of the proximal colon. *Science*, **260**, 816–819 (1993).