

Improvement in colorectal cancer survival: A population-based study

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Abstract

The aim of this study was to explore the reasons for improvement in colorectal cancer survival. Trends in relative survival among 5874 patients diagnosed with colorectal cancer over a 24-year period in a well-defined French population were analysed. The 5-year relative survival rate, excluding operative mortality, increased from 49.2% to 56.3% between the periods 1976–1987 and 1988–1999. In multivariate analysis, stage at diagnosis and adjuvant chemotherapy were both associated with better survival after surgery with curative intent. Survival trends differed markedly by age. The improvement in overall survival for older patients can be attributed to the increase in the proportion of patients resected for cure. For younger patients, there was an increase in the proportion of patients operated for cure, but also an improvement in stage-specific survival, particularly for stage III tumours, suggesting an impact of adjuvant chemotherapy.

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1. Introduction

With some 36000 incident cases in France each year, colorectal cancer is the second most common cancer in women and the third most common in men [1]. Prognosis remains poor, but improvement in survival has been reported recently in some European countries [2–5] and in the United States of America (USA) [6]. Improved diagnostic procedures, earlier diagnosis and improved therapeutic procedures have been suggested to explain survival trends [2,4,5,7]. Community-based studies including all cases

diagnosed in a well-defined population represent the only feasible approach for assessing real improvement in prognosis in non-selected series. Such studies are rare, because they require accurate and detailed data collection, which is seldom available from general cancer registries. Two recent population-based studies have reported important changes in the management of rectal cancer with improvement in survival [4,5]. We have demonstrated previously how reduced operative mortality plays a major role in the improvement of overall survival after curative surgery [8]. The purpose of this project was to study colorectal survival trends over a 24-year period in a well-defined French population in order to explore the reasons for improvement in survival, over and above the impact of reduced operative mortality.

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2. Patients and methods

2.1. Patients

A population-based registry for digestive tract cancers was established in the Côte d'Or administrative area (Burgundy, France) in 1976. It covers a resident population of 506 800 inhabitants, according to the 1999 census. Information on new cases is collected from public and private pathology laboratories, university and local hospitals, the regional cancer institute, private surgeons, oncologists and gastroenterologists, general practitioners and death certificates. No cases were registered based on death certificates only, but these were used to identify missing cases. Due to the involvement of the entire medical profession, it can be assumed that virtually all newly diagnosed cases of colorectal cancer are recorded. The quality and completeness of the registry is certified every 4 years by an audit of the National Committee on Population-Based Cancer Registries.

A total of 5873 new cases of colorectal cancer (3199 males, 2674 females, median age 73 years) registered between 1976 and 1999 were included. Tumour sites were classified according to the tenth revision of the International Classification of Diseases (ICD-10) [9], regrouped into 3 anatomic sub-sites. The right colon (caecum (C18.0), appendix (C18.1), ascending colon (C18.2), hepatic flexure (C18.3) and transverse colon (C18.4)); the left colon (splenic flexure (C18.5), descending colon (C18.6) and sigmoid colon (C18.7)); and the rectum (recto sigmoid junction (C19) and rectal ampulla (C20)). Anal cancer cases (C21) were not included. The stage of disease at diagnosis was classified according to the UICC classification for resected cancers [10]. Patients with visceral metastasis or those operated without resection were classified as having advanced-stage disease. Those who underwent resection but were not properly staged were classified as stage unknown (7 patients, 0.12% of the population). Vital status in January 2002 was known for 5870/5873 patients (99.9%), of these 4425 were deceased and 1445 alive.

2.2. Statistical analysis

Operative mortality was defined as death within 30 days of surgery. Mortality rates were estimated in the intervals 0–1 months, 1–12 months and 1–5 years after surgery. Mortality rates were calculated as the number of deaths divided by the number of person-years at risk. In order to evaluate the causes of improvement in survival over and above the reduction in operative mortality, we estimated conditional probability of surviving beyond 30 day after surgery. Only patients alive at day 30 after surgery were retained in the analysis and their survival time was calculated from that time until the date of death or the census date.

Associations between categorical data were analysed using χ^2 tests for heterogeneity.

The significance of covariates was tested by the likelihood ratio test. Relative survival is defined as the ratio of the observed survival rate to the expected survival rate in that particular area in a population of the same gender and age distribution as the cases estimated from population life tables. This provides an estimate of patient survival, which is corrected for non-colorectal causes of death. Relative survival was estimated in univariate or multivariate analysis by means of STATA[®] algorithms (Stata Corporation, College Station, TX, USA) based on methodology defined by Estève and colleagues [11] and developed by Paul Dickman [12].

3. Results

3.1. Trends in overall survival

Median overall survival increased from 16.4 months for patients diagnosed during 1976–1979 to 40.5 months for 1988–1991 and has remained almost stable since then for patients diagnosed up to 1999. The 5-year relative survival rate increased from 37.8% (1976–1979) to 53.4% (1988–1991) and was 52.1% for 1996–1999. The corresponding relative survival curves by period of diagnosis (Fig. 1) confirm the progressive improvement in prognosis up to 1991 with little subsequent change.

Operative mortality after curative surgery decreased from 12.0% during the 1976–1979 period to 8.1% and 5.3% during 1980–1983 and 1984–1987, respectively. It remained almost stable thereafter: 4.9%, 6.0% and 5.6% for 1988–1991, 1992–1995 and 1996–1999, respectively. After exclusion of operative mortality, the differences in survival between 1976–1979 and 1984–1987 decreased markedly (Fig. 2) and we grouped patients

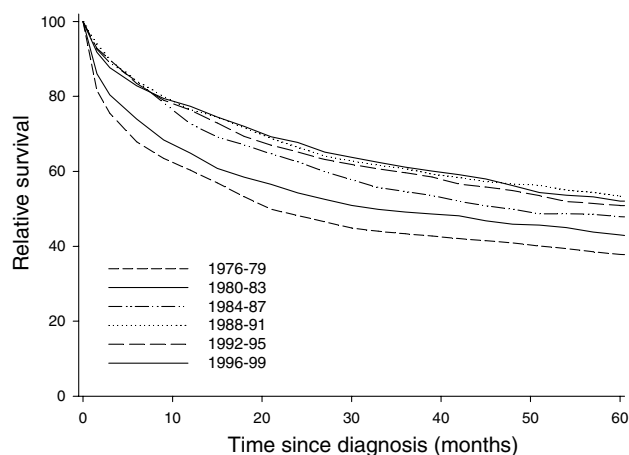


Fig. 1. Relative survival by period of diagnosis among all colorectal cancer patients – Côte-d'Or, Burgundy, France.

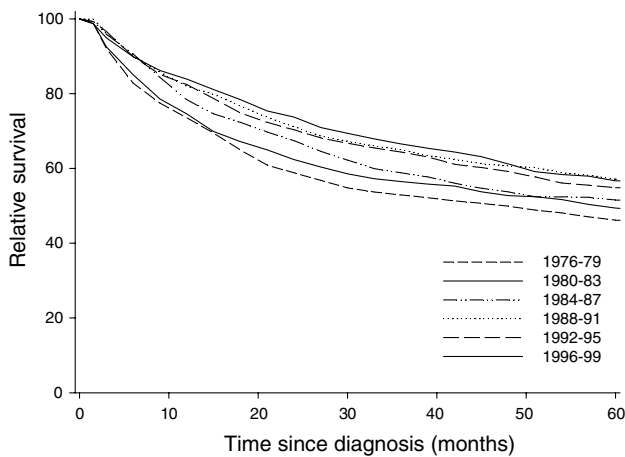


Fig. 2. Relative survival by period of diagnosis, after exclusion of operative mortality among colorectal cancer patients – Côte-d'Or, Burgundy, France.

into two 12-year periods (1976–1987 and 1988–1999) for further analysis.

Mortality rates decreased not only in the post-operative period (Table 1) but also during the 1–12 month period after surgery and, to a lesser extent, over the 13–60 month period after surgery. The overall 5-year survival rate excluding operative mortality (survival up to 5 years of those who survived the first month after surgery) increased from 37.7% to 45.7% and the corresponding 5-year relative survival rate from 49.2% to 56.3% between 1976–1987 and 1988–1999. The 5-year

relative survival rates were, respectively, 50.3% and 58.0% ($P < 0.001$) in patients under 75 years of age and 47.1% and 53.6% ($P < 0.001$) in patients aged 75 years and over.

3.2. Trends in survival after resection with curative intent, excluding operative mortality

All patients with stages I and II tumours were resected with curative intent, and their survival was compared with that of patients with stage III tumours. In case of stage III disease, 97.3% of patients were resected for cure during 1976–1987 and 98.7% during 1988–1999 (Table 2). Very few advanced tumours were treated for cure: 3.1% during 1976–1987 and 8.6% during 1988–1999. The distribution of stage at diagnosis among patients resected for cure did not change between 1976–1987 and 1988–1999, but for all patients combined the proportion of patients with stages I–II cancers rose from 46.0% to 52.1% and the proportion with advanced disease fell from 34.8% to 26.7% (Table 2). The improvement in stage at diagnosis was more important in patients aged 75 years and over than in younger patients.

The proportion of patients resected with curative intent rose from 65.7% during 1976–1987 to 75.4% during 1988–1999 ($P < 0.001$). The proportion rose from 71.7% to 77.9% for patients under 75 years ($P < 0.001$) and from 57.5% to 72.1% for older patients ($P < 0.001$). After curative surgery there was no change in 5-year survival rates for patients aged 75 years and over, but there

Table 1

Mortality rates and 95% confidence interval (CI) by period of diagnosis and time since diagnosis: patients diagnosed with colorectal cancer in Côte d'Or, 1976–1999

Period of diagnosis	Time since diagnosis		
	0–1 Month (95% CI)	2–12 Months (95% CI)	13–60 Months (95% CI)
1976–1979	2.09 (1.76–2.49)	0.46 (0.41–0.53)	0.19 (0.16–0.21)
1980–1983	1.41 (1.17–1.71)	0.44 (0.39–0.50)	0.16 (0.14–0.18)
1984–1987	0.76 (0.58–0.98)	0.34 (0.30–0.39)	0.17 (0.15–0.19)
1988–1991	0.70 (0.54–0.88)	0.30 (0.26–0.34)	0.14 (0.12–0.15)
1992–1995	0.82 (0.65–1.03)	0.30 (0.26–0.34)	0.15 (0.13–0.16)
1996–1999	0.82 (0.66–1.03)	0.28 (0.24–0.32)	0.15 (0.13–0.17)

Table 2

Stage, age and intent of treatment by period of diagnosis: colorectal cancer, Côte d'Or, 1976–1999

Age (years)		All patients		Patients operated with curative intent	
		Period of diagnosis		Period of diagnosis	
		1976–1987 <i>n</i> (%)	1988–1999 <i>n</i> (%)	1976–1987 <i>n</i> (%)	1988–1999 <i>n</i> (%)
Under 75	Stage I–II	752 (48.4)	944 (53.4)	752 (67.4)	944 (68.6)
	Stage III	344 (22.1)	382 (21.6)	337 (30.2)	378 (27.5)
	Advanced ^a	459 (29.5)	441 (23.0)	26 (2.3)	54 (3.9)
75 and over	Stage I–II	484 (42.6)	710 (50.4)	484 (72.1)	710 (69.9)
	Stage III	173 (15.2)	292 (20.7)	166 (25.4)	287 (28.2)
	Advanced ^a	478 (42.1)	407 (28.9)	3 (0.5)	19 (1.9)

^a Advanced stage = metastatic cases (UICC stage IV) and unresectable cases.

was a significant improvement in patients under 75 years (Table 3). In this age group, the 5-year relative survival probability increased significantly from 64.9% to 72.7% ($P = 0.003$).

For stages I–II tumours, 5-year relative survival rates increased from 78.0% to 82.3% ($P = 0.14$). Corresponding rates for stage III tumours were 35.8% and 44.2% ($P = 0.006$), respectively (Table 3). Trends in survival were different between age groups (Table 3, Fig. 3). For patients under 75 years, there was a significant improvement in survival for stage III tumours ($P = 0.001$) but no significant change for stages I–II tumours ($P = 0.31$). For older patients, 5-year survival for stages I–II and stage III did not change significantly between 1976–1987 and 1988–1999.

The number of lymph nodes examined is a major determinant of stage after curative surgery. The median number of lymph nodes examined after surgery with curative intent was 6 for 1976–1987 and 7 for 1988–1999. The frequency of cases with no examined lymph nodes fell slightly from 16.2% to 14.4% whereas the number of patients with 8 and more examined lymph nodes increased from 40.1% to 45.1% ($P = 0.04$).

After curative surgery and exclusion of post-operative deaths, the proportion of patients who received adjuvant chemotherapy between 1976–1987 and 1988–1999 increased from 0.8% to 6.4% for stages I–II tumours and from 3.9% to 27.7% for stage III tumours. Patients aged 75 years and over were less likely to receive adjuvant chemotherapy than younger patients. During 1988–1999, 0.8% of patients aged 75 years and

over with stages I–II tumours received adjuvant chemotherapy, compared with 10.3% for younger patients. These rates were, respectively, 9.1% and 40.6% for stage III tumours. For 1988–1999, patients under 75 years with stage III tumours operated with curative intent had a significantly improved 5-year survival rate after adjuvant chemotherapy: 60.7% compared with 41.2% in patients without adjuvant chemotherapy ($P = 0.002$).

Multivariate models were fitted to estimate prognostic factors associated with conditional relative survival after curative surgery (Table 4). After exclusion of operative mortality, stage and adjuvant chemotherapy were strongly associated with relative survival in younger patients, whereas stage was the only significant factor associated with relative survival for patients aged 75 years and over. When considering patients under 75 years, the hazard ratio associated with the period of diagnosis became just significant (HR 0.85, 95% CI 0.72–1.00, $P = 0.046$) when adjuvant chemotherapy was introduced into the regression model whereas it was highly significant (HR 0.77, 95% CI 0.66–0.90, $P = 0.001$) for the model without adjuvant chemotherapy. This was not observed for patients aged 75 years and over for whom period of diagnosis was not significantly associated with relative survival either in the model without adjuvant chemotherapy (HR: 0.87, 95% CI 0.68–1.13, $P = 0.3$) or in the model with adjuvant chemotherapy (HR: 0.92, 95% CI 0.71–1.19, $P = 0.6$). This strongly suggests that adjuvant chemotherapy in itself could partly explain the period difference in survival among patients under 75 years of age at diagnosis.

Table 3

Five-year actuarial and relative conditional survival after curative surgery by period and age: colorectal cancer, Côte d'Or, 1976–1999

	Period of diagnosis	<i>n</i>	5-Year actuarial survival (95% CI)		5-Year relative survival (95% CI)	
<i>Under 75 years</i>						
All stages	1976–1987	1024	57.5	(54.5–60.5)	64.9	(61.4–68.2)
	1988–1999	1291	67.9	(65.1–70.5)	72.7	(69.8–75.5)
					<i>P</i> = 0.0037	
Stages I–II	1976–1987	707	69.1	(65.6–72.4)	78.2	(74.1–81.7)
	1988–1999	922	77.0	(74.0–79.7)	82.7	(79.4–85.5)
					<i>P</i> = 0.31	
Stage III	1976–1987	317	31.6	(26.6–36.8)	35.7	(30.0–41.5)
	1988–1999	369	45.5	(40.1–50.7)	48.6	(42.8–54.2)
					<i>P</i> = 0.001	
<i>75 years and over</i>						
All stages	1976–1987	572	41.4	(37.4–45.4)	68.0	(61.1–74.0)
	1988–1999	897	43.3	(39.8–46.8)	67.9	(62.4–72.8)
					<i>P</i> = 0.45	
Stages I–II	1976–1987	428	48.1	(43.3–52.7)	78.0	(69.6–84.4)
	1988–1999	642	51.9	(47.6–55.9)	82.2	(74.2–86.5)
					<i>P</i> = 0.21	
Stage III	1976–1987	144	21.7	(15.4–27.5)	36.9	(25.7–48.0)
	1988–1999	255	21.8	(16.6–27.5)	34.1	(25.8–42.6)
					<i>P</i> = 0.74	

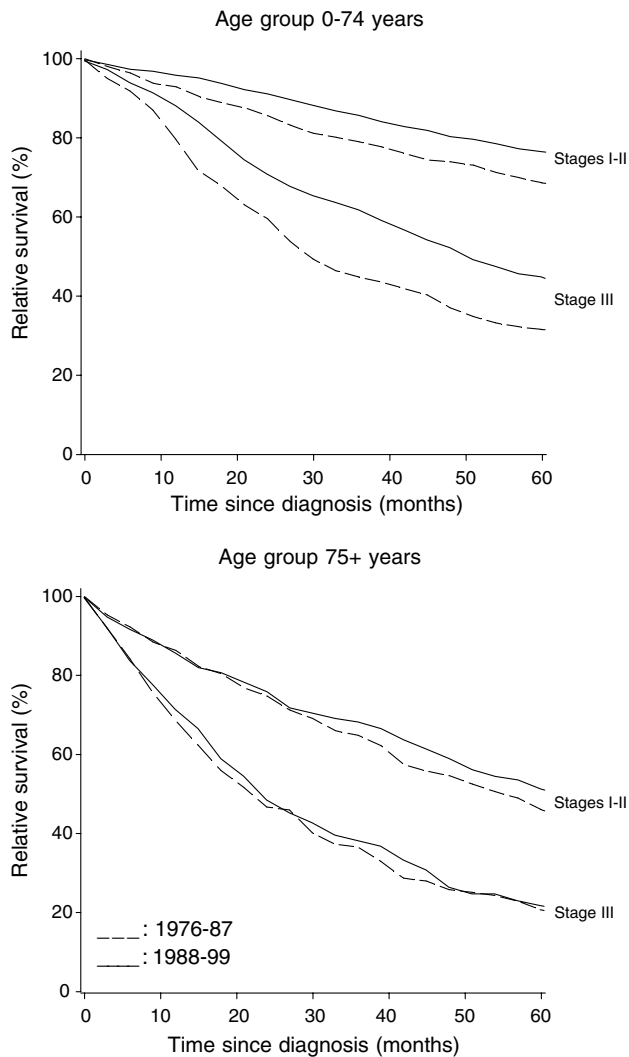


Fig. 3. Conditional relative survival after curative surgery for stages I–II and III tumours by period and age among colorectal cancer patients – Côte-d’Or, Burgundy, France.

Table 4

Multivariate analysis of factors associated with conditional relative survival for patients with stages I–III tumours operated for cure: colorectal cancer, Côte d’Or, 1976–1999

		Hazard ratio	95% CI	P
<i>Under 75 years</i>				
Period of diagnosis	1976–1987	1		
	1988–1999	0.85	0.72–1.00	0.046
Stage	I–II	1		
	III	4.01	3.41–4.72	<0.001
Adjuvant chemotherapy	no	1		
	yes	0.68	0.52–0.88	0.003
<i>75 years and over</i>				
Period of diagnosis	1976–1987	1		
	1988–1999	0.87	0.68–1.13	0.30
Stage	I–II	1		
	III	3.98	3.05–5.21	<0.001

3.3. Trends in survival for advanced tumours

As a consequence of an earlier diagnosis, relative frequency of advanced tumours fell from 34.8% to 26.7% between 1976–1987 and 1988–1999. Trends were marked for elderly patients: the relative frequency of advanced tumours fell from 42.1% to 28.9% ($P < 0.001$) for these patients, whereas it fell from 29.5% to 25.0% ($P = 0.03$) for younger patients. Overall, there was a significant increase in 1-year relative survival from 29.9% (26.9–33.0) to 39.3% (35.9–42.7) but no significant improvement in 2-year (14.5–16.8%) or 5-year relative survival (7.6–9.6%) between 1976–1987 and 1988–1999. For younger patients, there was a significant increase in 1-year relative survival from 30.1% (25.9–34.3) to 45.2% (40.5–49.8) and in 2-year relative survival from 13.8% (10.8–17.2) to 23.5% (19.6–27.6) but not for 5-year relative survival (from 8.2% to 9.3%). There was no significant improvement in 1-year (from 29.7% to 32.1%), 2-year (from 15.5% to 19.4%) or 5-year relative survival (from 5.9% to 11.3%) for elderly patients.

Six percent of patients with advanced tumours were treated by palliative chemotherapy during 1976–1987 and 26.7% ($P < 0.001$) during 1988–1999. Corresponding rates were 9.2% and 44.1% ($P < 0.001$) for patients under 75 years, and 2.9% and 8.0% ($P = 0.001$) for older patients.

4. Discussion

Colorectal cancer survival increased dramatically over the 24-year period between 1976 and 1999 in France. The aim of this population-based study was to explore the reasons for this improvement. Whereas results from specialised centres may be misleading due to referral bias, cancer registries allow the analysis of true epidemiological trends. Cancer survival improvement may be related to progress in diagnostic or therapeutic procedures. We have shown in a previous study that reduced operative mortality between 1976–1979 and 1983–1987 was one reason for the improvement in survival after curative surgery [5,8]. For operated patients, this was the major cause for the improvement in overall survival observed between 1976–1979 and 1984–1987. This decrease in operative mortality, however, did not fully explain all the differences in survival rates between periods, and we performed the present analysis to point out the respective roles of other potentially involved factors, such as stage at diagnosis or chemotherapy.

After exclusion of operative mortality, survival differences between 1976–1979, 1980–1983 and 1984–1987 fell markedly with a gap between the first three periods and the last three. This suggests a change in a short period of time secondary to the introduction of new diagnostic

methods and/or therapeutic means. Survival remained stable between 1988–1991 and 1995–1999.

Stage at diagnosis is the major determinant of survival differences between populations [13]. In a study including three European cancer registries, differences in rectal cancer survival were no longer significant after checking for stage [14]. Improved information with an earlier visit to the doctor in case of digestive symptoms, more widespread use of endoscopy and a more resolute attitude on the part of surgeons are likely to have been responsible for most of these trends.

Trends in survival varied between age groups. In contrast to younger patients, survival rates after curative surgery and stage-specific survival remained stable among patients aged 75 years and over. But the absolute number of elderly patients resected with curative intent increased from 653 during the period 1976–1987 (57% of the patients) to 1016 during the period 1988–1999 (72% of the patients), which can be considered as progress. In this group of patients the use of adjuvant or palliative chemotherapy was marginal. This lack of survival improvement for older patients was also reported by Martijn and colleagues [4], elderly people being less likely to receive (neo)adjuvant radiochemotherapy for their rectal cancer than younger patients.

The interpretation of survival trends is more complex in younger patients. As for elderly patients, the proportion of patients operated with curative intent increased between 1976–1987 and 1988–1999. There was also an improvement in survival for stage III tumours. As stage definition depends on diagnostic technology and medical practice, stage determination varies with time and place. With a more careful staging of cancer, a fraction of cancers that would previously have been classified as localised are found to be at a more advanced stage [15]. This stage migration phenomenon (Will Rogers) results in improved survival at all stages. It has an important confounding effect on stage-specific survival comparisons between populations and must be considered when attempting to interpret survival differences between areas and over time [13,16]. It has been demonstrated that the proportion of stage III tumours increases significantly with the number of lymph nodes examined and that at least eight nodes had to be examined to stage colorectal cancer correctly [17]. Since the frequency of patients with eight or more examined lymph nodes slightly increased, a migration in stage can partly explain our results.

Adjuvant chemotherapy could explain, at least partially, survival improvement for stage III tumours in younger patients. Adjuvant chemotherapy for stage III colon cancer is associated with a 6–12% survival improvement in controlled trials [18]. Since the publication of these trials at the beginning of the 1990s, adjuvant chemotherapy has been recommended for stage III colon cancer and its use increased from 3.9% before 1988 to 7.1% during 1989–1990 and 54.9% during 1997–

1998 [19]. This increase was particularly marked in younger patients, with 86.1% of stage III patients under the age of 65 years being treated during the 1997–1998 period, compared with 24.4% of those over 75 years for the same period ($P < 0.0001$) [19]. In the present analysis, we observed an improved survival for patients treated with adjuvant chemotherapy compared with patients who were not, but this is a non-controlled population-based study and results could be biased by patient selection. Multivariate analysis provides strong arguments to support the impact of adjuvant chemotherapy.

Substantial advances in rectal cancer management occurred over the last two decades, mainly total mesorectal excision and radiotherapy combined with surgery [19,20]. Earlier diagnosis has also allowed more effective treatment with an increase in resection rates and sphincter-saving procedures [5]. These improvements probably explain the dramatic increase in relative survival observed in France (from 35.4% for the 1978–1981 period to 57.0% for the 1985–1989 period) [5] as well as in The Netherlands [4].

In conclusion, colorectal cancer survival has improved over the last few decades. Survival improvement in elderly patients was mostly due to a decrease in operative mortality and an increase in the resection rate. For younger patients, in addition to what was observed for older patients, a significant stage-specific survival improvement was observed after curative surgery for stage III tumours. The results suggest that adjuvant chemotherapy improves survival among stage III patients, but this requires further confirmation.

Conflict of interest statement

None declared.

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