Table 1 Distribution of 40 851 patients who had surgery for colorectal cancer between 1995 and 2004 by age group and gender.

Year of surgery	Total (n = 40 851)	1995–6 (n = 7952)	1997–8 (n = 6266)	1999–2000 (n = 7665)	2001–2 (n = 9093)	2003–4 (n = 9875)
Age group (years)						
18–49	3642	827 (10.4%)	646 (10.3%)	650 (8.5%)	765 (8.4%)	754 (7.6%)
50–64	14 978	3058 (38.5%)	2414 (38.5%)	2855 (37.2%)	3225 (35.5%)	3426 (34.7%)
65–79	18 518	3412 (42.9%)	2678 (42.7%)	3539 (46.2%)	4230 (46.5%)	4659 (47.2%)
≥ 80	3713	655 (8.2%)	528 (8.4%)	621 (8.1%)	873 (9.6%)	1036 (10.5%)
Male to female ratio						
18–49		1.16	1.45	1.19	1.23	1.21
50–64		1.56	1.67	1.51	1.57	1.52
65–79		1.50	1.45	1.56	1.59	1.45
≥ 80		1.21	1.10	0.91	0.87	0.87

ated histology and advanced pT-stage were greater in the over 80 age group. However, the frequency of regional lymph node metastasis and liver metastasis was lower than in other groups. Consequently, the frequency of pathological Stage II and Stage IV was greater and lower, respectively, in the over 80 age group compared with the other age groups.

In all age groups, 78% of CRC patients underwent an R0 resection. In the over 80 year age group, however, the scope of lymph node dissection (both peri/paracolic and central lymph node) was markedly less extensive, and the mean number of lymph nodes examined was significantly smaller than for other age groups. There was a significant decrease in the administration of adjuvant chemotherapy for patients with Stage III disease in the over 80 age group. Preoperative radiotherapy was also applied less frequently to patients with rectal cancer aged over 80 (0.3%) compared with the other age groups (2.1%).

Survival

The OS and CSS after surgery for CRC stratified by age group and pathological stages are shown in Table 3. With increasing age, the 5-year OS of patients with Stage I disease decreased from 0.97 in patients aged 18–49 to 0.85 in those over 80, although differences between the 18–49 and 50–64 age groups were not statistically significant. A decreased OS with increasing age was also observed in Stage II and Stage III disease. In Stage IV disease, although there was no stepwise decrease, the OS of patients over 80 years was significantly lower than that of other age groups. While differences in CSS among each stage were smaller than those in OS, the CSS of the over 80 age group was significantly lower than for other age groups in any stage as well as OS. Apart from the issue of the over 80 age group, it is noteworthy that OS and CSS of the youngest patients were not inferior to other age groups.

Univariate analysis for identifying predictors of OS is shown in Table 4. Among 18 factors investigated, 15 were associated with a difference in OS. Multivariate Cox regression analysis showed that age group was an independent predictor of OS (hazard ratio 1.45, 95% CI 1.34–1.58, $P < 0.001$). An additional 15 factors were also prognostic for OS (except for history of CRC and number of CRCs). The highest hazard ratio was pathological stage, followed by the presence of residual tumour.

The impact of treatment patterns

A total of 12 850 and 14 932 propensity score-matched pairs of patients with pT3 and pT4 disease, respectively, who had R0 surgery were extracted from the entire cohort to examine the impact of central lymph node dissection and adjuvant chemotherapy on OS. In the matched cohort, the OS of patients with central lymph node dissection and with adjuvant chemotherapy was significantly better than those without. The estimated hazard ratio for central lymph node dissection was 0.800 (95% CI 0.738–0.869, $P < 0.001$) and for adjuvant chemotherapy it was 0.723 (95% CI 0.671–0.776, $P < 0.001$), but these differences were insignificant in the group aged over 80 years (Fig. 1).

Discussion

The main strength of this study was its access to the large-scale cancer registry database collected from JSCCR member institutions. The key finding was the significant differences in clinical and pathological characteristics and survival after surgery between elderly

Table 2 Tumour and treatment characteristics stratified by age group (n = 40 851).

	Age group (years)											
	Total (n = 40 851)		18–49 (n = 3642)		50–64 (n = 14 978)		65–79 (n = 18 518)		< 80		≥ 80 (n = 3713)		P Difference between < 80 and ≥ 80
Characteristics	Mean age 64.9 ± 11.4 SD		Mean 42.8 ± 6.0 SD		Mean 58.0 ± 4.2 SD		Mean 71.2 ± 4.1 SD		(n = 37 138)		Mean 83.6 ± 3.3 SD		
Tumour related characteristics													
Serum CEA, preoperative*													
Low	20 356	58.7%	1969	62.2%	7706	59.6%	9075	58.1%	18 750	59.2%	1606	53.8%	< 0.001
High	14 319	41.3%	1195	37.8%	5215	40.4%	6532	41.9%	12 942	40.8%	1377	46.2%	
Multiple primary cancer													
No	34 645	88.3%	3320	94.9%	13 130	91.2%	15 176	85.4%	31 626	88.7%	3019	84.4%	< 0.001
Yes	4601	11.7%	180	5.1%	1269	8.8%	2592	14.6%	4041	11.3%	560	15.6%	
History of colorectal cancer													
No	37 743	97.6%	3418	98.4%	13 962	98.3%	16 983	97.0%	34 363	97.7%	3380	96.6%	< 0.001
Yes	943	2.4%	56	1.6%	242	1.7%	525	3.0%	823	2.3%	120	3.4%	
Number of colorectal cancers													
1	38 795	95.0%	3484	95.7%	14 333	95.7%	17 472	94.4%	35 289	95.0%	3506	94.4%	0.061
≥ 2	2056	5.0%	158	4.3%	645	4.3%	1046	5.6%	1849	5.0%	207	5.6%	
Tumour location													
Right colon	11 938	29.2%	801	22.0%	3487	23.3%	6052	32.7%	10 340	27.8%	1598	43.0%	< 0.001
Left colon	12 766	31.3%	1020	28.0%	4753	31.7%	5967	32.2%	11 740	31.6%	1026	27.6%	
Rectum	16 147	39.5%	1821	50.0%	6738	45.0%	6499	35.1%	15 058	40.5%	1089	29.3%	
Macroscopic tumour type†													
Type 0–3	39 026	98.1%	3450	97.3%	14 325	98.1%	17 690	98.2%	35 465	98.1%	3561	98.1%	0.525
Others	756	1.9%	94	2.7%	275	1.9%	318	1.8%	687	1.9%	69	1.9%	
Tumour size‡													
< 2/3	18 544	50.8%	1692	51.5%	7087	53.0%	8401	50.8%	17 180	51.7%	1364	41.3%	< 0.001
≥ 2/3	17 968	49.2%	1591	48.5%	6290	47.0%	8145	49.2%	16 026	48.3%	1942	58.7%	
Liver metastasis													
No	35 449	87.6%	3117	86.6%	12 804	86.2%	16 217	88.5%	32 138	87.4%	3311	90.6%	< 0.001
Yes	4995	12.4%	483	13.4%	2051	13.8%	2116	11.5%	4650	12.6%	345	9.4%	
Peritoneal dissemination													
No	38 257	94.7%	3335	92.8%	14 032	94.6%	17 418	95.1%	34 785	94.7%	3472	95.3%	0.082
Yes	2120	5.3%	257	7.2%	800	5.4%	890	4.9%	1947	5.3%	173	4.7%	
Pulmonary metastasis													

Table 2 (Continued).

Characteristics	Age group (years)												P Difference between < 80 and ≥ 80
	Total (n = 40 851)		18–49 (n = 3642)		50–64 (n = 14 978)		65–79 (n = 18 518)		< 80		≥ 80 (n = 3713)		
	Mean age 64.9 ± 11.4 SD		Mean 42.8 ± 6.0 SD		Mean 58.0 ± 4.2 SD		Mean 71.2 ± 4.1 SD		(n = 37 138)		Mean 83.6 ± 3.3 SD		
No	37 628	97.5%	3361	97.7%	13 823	97.4%	17 052	97.4%	34 236	97.5%	3392	97.4%	0.498
Yes	981	2.5%	80	2.3%	365	2.6%	447	2.6%	892	2.5%	89	2.6%	
Histology[§]													
Well, Mod	37 962	92.9%	3291	90.4%	14 012	93.6%	17 285	93.3%	34 588	93.1%	3374	90.9%	< 0.001
Por, Muc, Sig	2889	7.1%	351	9.6%	966	6.4%	1233	6.7%	2550	6.9%	339	9.1%	
pT-category													
pT1, pT2	10 166	25.1%	868	24.1%	3998	26.9%	4592	25.0%	9458	25.7%	708	19.2%	< 0.001
pT3, pT4	30 335	74.9%	2734	75.9%	10 843	73.1%	13 786	75.0%	27 363	74.3%	2972	80.8%	
pN-category													
pN0	22 689	56.6%	1702	47.6%	8154	55.6%	10 580	58.2%	20 436	56.1%	2253	61.9%	< 0.001
pN +	17 370	43.4%	1874	52.4%	6507	44.4%	7605	41.8%	15 986	43.9%	1384	38.1%	
Lymphatic invasion													
No	12 645	31.6%	1056	29.6%	4670	31.9%	5817	32.1%	11 543	31.7%	1102	30.3%	0.035
Yes	27 369	68.4%	2513	70.4%	9985	68.1%	12 331	67.9%	24 829	68.3%	2540	69.7%	
Venous invasion													
No	15 580	39.1%	1329	37.4%	5658	38.8%	7103	39.2%	14 090	38.9%	1490	41.1%	0.005
Yes	24 282	60.9%	2224	62.6%	8929	61.2%	10 995	60.8%	22 148	61.1%	2134	58.9%	
pStage													
I	8333	20.4%	655	18.0%	3267	21.8%	3825	20.7%	7747	20.9%	586	15.8%	< 0.001
II	12 914	31.6%	946	26.0%	4382	29.3%	6062	32.7%	11 390	30.7%	1524	41.0%	
III	12 375	30.3%	1306	35.9%	4497	30.0%	5512	29.8%	11 315	30.5%	1060	28.5%	
IV	7229	17.7%	735	20.2%	2832	18.9%	3119	16.8%	6686	18.0%	543	14.6%	
Treatment-related characteristics													
Scope of Peri/paracolic lymph node dissection[¶]													
< 10 cm	10 492	28.4%	783	24.6%	3481	25.9%	4825	28.6%	9089	27.1%	1403	40.9%	< 0.001
≥ 10 cm	26 460	71.6%	2398	75.4%	9964	74.1%	12 067	71.4%	24 429	72.9%	2031	59.1%	
Central lymph node dissection													
No	16 905	45.7%	1206	37.6%	5471	40.6%	7858	46.5%	14 535	43.3%	2370	70.2%	< 0.001
Yes	20 064	54.3%	1999	62.4%	8014	59.4%	9044	53.5%	19 057	56.7%	1007	29.8%	
Residual tumour													

Table 2 (Continued).

Characteristics	Age group (years)												P Difference between < 80 and ≥ 80
	Total (n = 40 851)		18–49 (n = 3642)		50–64 (n = 14 978)		65–79 (n = 18 518)		< 80		≥ 80 (n = 3713)		
	Mean age 64.9 ± 11.4 SD		Mean 42.8 ± 6.0 SD		Mean 58.0 ± 4.2 SD		Mean 71.2 ± 4.1 SD		(n = 37 138)		Mean 83.6 ± 3.3 SD		
R0	30 728	77.9%	2642	74.9%	11 188	77.3%	14 141	79.1%	27 971	77.9%	2757	77.4%	0.363
R1	3060	7.8%	300	8.5%	1136	7.9%	1326	7.4%	2762	7.7%	298	8.4%	
R2	5658	14.3%	587	16.6%	2143	14.8%	2421	13.5%	5151	14.4%	507	14.2%	
Number of lymph node examined (mean ± SD)													
Colon and rectum	16.5 ± 14.4		21.2 ± 17.6		17.8 ± 15.2		15.6 ± 13.3		17.0 ± 14.7		11.8 ± 10.4		< 0.001
Colon	15.3 ± 12.8		19.6 ± 16.1		16.0 ± 13.1		14.8 ± 12.3		15.6 ± 13		12.3 ± 10.6		
Rectum	18.5 ± 16.4		23.0 ± 19.0		20.0 ± 17.2		16.9 ± 15.0		19.0 ± 16.7		10.6 ± 9.8		
Number of lymph node metastasis													
Mean ± SD	1.7 ± 3.8		2.5 ± 6.4		1.8 ± 3.9		1.5 ± 3.2		1.7 ± 3.9		1.2 ± 2.7		< 0.001
Adjuvant chemotherapy for pStage III													
No	5120	47.9%	435	39.0%	1584	40.6%	2321	48.9%	4340	44.5%	780	84.1%	< 0.001
Yes	5567	52.1%	681	61.0%	2317	59.4%	2422	51.1%	5420	55.5%	147	15.9%	

Missing data for each characteristic were excluded from analysis.

*Low, below cut-off value; High, above cut-off value.

†0 = superficial, 1 = protuberant, 2 = expansive ulcerating, 3 = infiltrative ulcerating, others = diffusely ulcerating or unclassified.

‡Tumour size, proportion of the tumour in relation to the circumference of the bowel.

§Wel, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Por, poorly differentiated adenocarcinoma; Muc, mucinous carcinoma; Sig, signet ring carcinoma.

¶Peri/para-rectal nodes distal to rectal cancer were classified into < 4 cm or ≥ 4 cm categories.

Table 3 Survival after surgery stratified by age group and pathologic stage (n = 40 851).

			Overall survival					Cancer-specific survival				
			Years after surgery		P			Years after surgery		P		
pStage	Age group	No. of cases	3 years	5 years	Age 18–49	Age 50–64	Age 65–79	3 years	5 years	Age 18–49	Age 50–64	Age 65–79
I	18–49	655	0.981	0.972				0.989	0.979			
	50–64	3267	0.974	0.974	0.830			0.989	0.979	0.933		
	65–79	3825	0.940	0.940	< 0.001	< 0.001		0.986	0.964	0.067	0.001	
	≥ 80	586	0.845	0.845	< 0.001	< 0.001	< 0.001	0.958	0.935	< 0.001	< 0.001	< 0.001
II	18–49	946	0.938	0.909				0.957	0.933			
	50–64	4382	0.931	0.885	0.059			0.953	0.920	0.254		
	65–79	6062	0.885	0.817	< 0.001	< 0.001		0.937	0.896	0.001	< 0.001	
	≥ 80	1524	0.780	0.659	< 0.001	< 0.001	< 0.001	0.904	0.857	< 0.001	< 0.001	< 0.001
III	18–49	1306	0.836	0.748				0.854	0.770			
	50–64	4497	0.826	0.735	0.357			0.748	0.765	0.683		
	65–79	5512	0.786	0.684	< 0.001	< 0.001		0.835	0.754	0.173	0.139	
	≥ 80	1060	0.647	0.504	< 0.001	< 0.001	< 0.001	0.745	0.653	< 0.001	< 0.001	< 0.001
IV	18–49	735	0.306	0.202				0.317	0.212			
	50–64	2832	0.309	0.213	0.543			0.328	0.232	0.203		
	65–79	3119	0.281	0.195	0.284	0.008		0.307	0.219	0.991	0.047	
	≥ 80	543	0.200	0.136	< 0.001	< 0.001	< 0.001	0.240	0.177	0.001	< 0.001	< 0.001
All	18–49	3642	0.785	0.724				0.800	0.742			
	50–64	14 978	0.795	0.734	0.217			0.817	0.764	0.007		
	65–79	18 518	0.770	0.692	0.001	< 0.001		0.817	0.761	0.017	0.581	
	≥ 80	3713	0.670	0.558	< 0.001	< 0.001	< 0.001	0.777	0.720	0.020	< 0.001	< 0.001

Table 4 Univariate and multivariate analysis for overall survival.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age group						
< 80/≥ 80 years	1.69	1.60–1.79	< 0.001	1.45	1.34–1.58	< 0.001
Gender						
Male/Female	0.86	0.83–0.90	< 0.001	0.83	0.79–0.87	< 0.001
Serum CEA, preoperative*						
Low/High	3.14	3.01–3.27	< 0.001	1.65	1.56–1.74	< 0.001
Multiple primary cancers						
No/Yes	1.37	1.29–1.44	< 0.001	1.41	1.32–1.52	< 0.001
History of CRC						
No/Yes	0.90	0.79–1.02	0.114	0.99	0.84–1.17	0.902
Number of CRCs						
1/≥ 2	1.02	0.94–1.12	0.573	1.00	0.90–1.11	0.986
Tumour location						
Colon/Rectum	1.02	0.99–1.06	0.220	1.12	1.06–1.17	< 0.001
Macroscopic tumour type†						
Type 0-3/Others	2.33	2.09–2.58	< 0.001	1.47	1.28–1.69	< 0.001
Tumour size‡						
< 2/3/≥ 2/3	2.25	2.16–2.35	< 0.001	1.19	1.12–1.25	< 0.001
Histology§						
Well,mod/Por,muc,sig	2.27	2.15–2.41	< 0.001	1.64	1.52–1.77	< 0.001
Lymphatic invasion						
No/Yes	2.59	2.47–2.73	< 0.001	1.38	1.28–1.49	< 0.001
Venous invasion						
No/Yes	2.26	2.16–2.36	< 0.001	1.25	1.17–1.33	< 0.001
Pathological stage						
I/II	2.06	1.88–2.25	< 0.001	1.50	1.32–1.70	< 0.001
I/III	4.00	3.67–4.35	< 0.001	2.68	2.36–3.03	< 0.001
I/IV	20.38	18.75–22.15	< 0.001	5.41	4.64–6.30	< 0.001
Treatment period						
1995–9/2000–4	0.88	0.85–0.91	< 0.001	0.79	0.75–0.83	< 0.001
Residual tumour						
R0/R1–R2	7.66	7.37–7.96	< 0.001	2.37	2.16–2.60	< 0.001
Peri/paracolic lymph node dissection¶						
< 10 cm/≥ 10 cm	0.71	0.68–0.74	< 0.001	0.90	0.85–0.96	< 0.001
Central lymph node dissection						
D0-2/D3	0.70	0.68–0.73	< 0.001	0.72	0.68–0.76	< 0.001
Adjuvant chemotherapy						
No/Yes	1.39	1.33–1.44	< 0.001	0.85	0.81–0.90	< 0.001

Missing data for each characteristic were excluded from the analysis. The number of patients analysed are given in the 'Total' column in Table 2.

*Low, below cut-off value; High, above cut-off value.

†0 = superficial, 1 = protuberant, 2 = expansive ulcerating, 3 = infiltrative ulcerating, others, diffusely ulcerating or unclassified.

‡Tumour size is the proportion of the tumour in relation to the circumference of the bowel.

§Wel, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; Por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; sig, signet ring carcinoma.

¶Peri/para-rectal nodes distal to rectal cancer were classified into < 4 cm or ≥ 4 cm categories.

patients with a cut-off value of 80 years and younger patients. Our results were in accord with most previously published reports that demonstrated female predominance and a shift towards right colon distribution in elderly patients [11–13]. Mucinous and poorly differentiated histology, multiple primary cancer and history

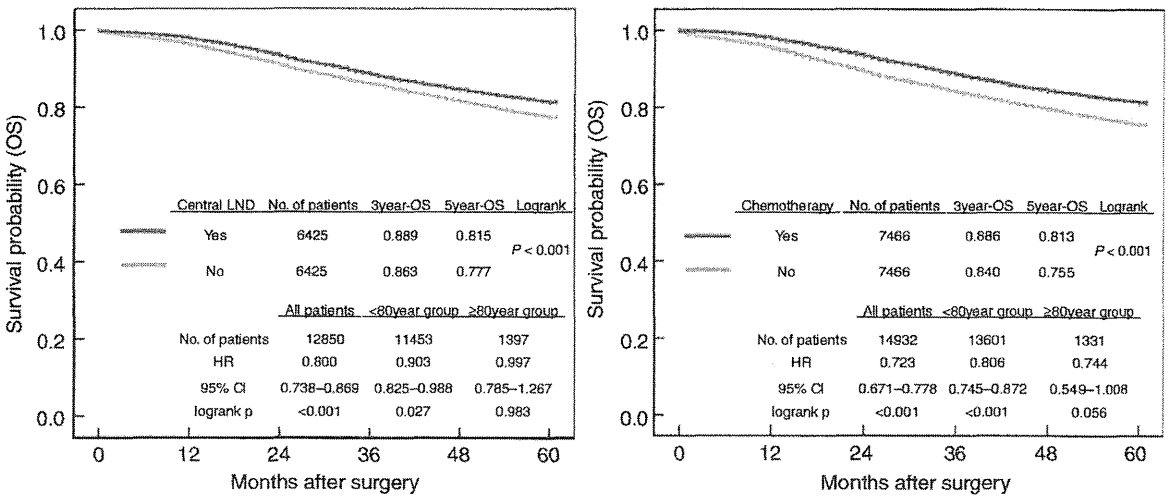

Figure 1 Kaplan–Meier plots for overall survival (OS) according to central lymph node dissection in the propensity score matched patients with pT3/pT4 colorectal cancer who underwent R0-resection (a) stratified by central node dissection (b) stratified by adjuvant chemotherapy.

of CRC were also characteristic, as previously described [14,15].

It is well known that CRC with methylation of *h*MLH1 occur more commonly in the right colon of elderly patients, especially women [16]. Accumulation of *h*MLH1 methylation is thought to be causative for microsatellite instability (MSI) of CRC. The coincidence between the characteristics of CRC in elderly patients and that of CRC with MSI may provide information regarding carcinogenesis in the elderly [17].

In the present study, CRC in the over 80 age group was more locally advanced at presentation in terms of tumour size, pT stage and preoperative serum CEA levels, but metastatic disease was less frequent in patients over 80 years than in younger patients. Thus, a large proportion of pT3/pT4-N0 or Stage II disease was observed in the over 80 age group.

In general, elderly patients are less likely to be offered optimal treatment because they are more likely to have comorbidity or age-determined deteriorating organ function. In the present study, we evaluated the curability of surgical resection, the extent of lymph node dissection and administration of adjuvant chemotherapy as treatment patterns. For curability by surgical resection, there was no difference in the R0 resection rate between age groups, as reported in a previous study [9]. In contrast, the extent of lymph node dissection was significantly reduced in patients aged over 80. Additionally, both the number of lymph nodes examined (NLNE) and the number of lymph node metastases (NLNM) were significantly lower in the over 80s. The smaller NLNM presumably resulted from a smaller NLNE. Given the reduced scope for lymph node dissection effects on NLNE and NLNM, the selection bias of treatment on survival may occur through stage migration or unidentified mechanisms.

Although the majority of patients with Stage III disease in this study did not receive adjuvant chemotherapy, the frequency of administration of was extremely low in patients aged over 80, and the magnitude was far greater than that of any of the other factors investigated in this study. Although several studies have suggested that elderly patients could derive benefit from adjuvant chemotherapy without a significant increase in adverse effects [18,19], the definition of 'elderly' patients can be anywhere between age 65 and 75 years. Moreover, patients aged over 80 are often excluded from clinical trials. In a large-scale pooled analysis of adjuvant chemotherapy consisting of 3351 patients with colon cancer, only 23 (0.7%) were aged over 80 [20]. Thus, to date, the efficacy and safety of adjuvant chemotherapy for people aged 80 and over is unknown.

Because the number of patients who received preoperative radiotherapy was extremely small, the efficacy of therapy could not be evaluated in this study. Furthermore, downstaging effects of preoperative therapy were not determined in terms of NLNE (data not shown).

Consistent with previously published reports [3–9], this study revealed significant differences in OS between the over 80s and younger counterparts in all pathological stages of disease. Even in the earliest stage of disease, the difference in 5-year OS between patients aged over 80 and the 18–49 year age group was 12.7%, and increased to 25% in Stage II and 24.4% in Stage III

disease. Differences in 5-year CSS of every pathological stage of disease between the age groups were also significant, although they were less pronounced than for OS.

The gap between OS and CSS in elderly patients might be partly explained by diminished life expectancy and increased operative mortality [6–8]. Because of a paucity of information regarding treatment-related death in this study, we cannot comment further on this. A large-scale nationwide survey on operative mortality and mortality revealed that 30-day mortality and operative mortality, defined as death within index hospitalization up to 90 days, were 1.1 and 2.3%, respectively, among 19 070 patients who underwent right hemicolectomy (cancer in 92.6%) in Japan [21]. In this report, multivariate logistic regression analysis proved age to be an independent factor that significantly affected operative mortality. The 30-day mortality rate for emergency surgery (that accounted for 8.4% of the entire cohort) was reported to be as high as 6.0%. It is well documented that emergency surgery is associated with higher mortality rate, and 5-year OS of patients having emergency surgery was significantly worse than those operated on electively [22]. Moreover, elderly patients more frequently presented with large and obstructive tumours requiring emergency surgery [23].

Thus operative mortality may be a major factor that affects OS in elderly patients. A shorter CSS in the over 80 age group suggests, however, that a worse OS was not only a result of operative mortality but also age-specific oncological factors such as the high malignant potential of disease, less aggressive treatment patterns and other unidentified factors [9]. Although the impact of central node dissection and administration of adjuvant chemotherapy on OS was not definitely demonstrated in patients aged over 80, partly in the propensity score-matched cohort, our findings warrant further investigation.

Limitations of the study include patient and treatment selection bias. Furthermore, because of a paucity of information such as performance status, comorbidity, duration of hospitalization, operative urgency (emergency or elective) and operative morbidity, the study is inappropriate for evaluation of the short-term results of surgery. The study may also be confounded by other important contributing factors because of insufficient information on other variables. The study was also limited in its generalizability because the study population included patients who presented to the leading institutes for colorectal cancer surgery in Japan. Because patients without follow-up information were excluded from the analyses, survival probabilities in the present study could be over- or underestimated.

The study demonstrated significant differences in tumour characteristics and treatment patterns between patients aged over 80 and their younger counterparts. Even after adjustment for available confounders, differences in survival persisted, and age *per se* was a robust prognostic factor. To determine more appropriate healthcare for aged patients with CRC, an increased understanding of changes in biochemical and molecular factors that occur with ageing is required.

Ethical statement

This study was exempted from review by the Tochigi Cancer Center's institutional review board, because it used pre-existing data with no personal identifiers.

Conflicts of interest

None declared.

Author contributions

K.K.: Contributed to conception and design of the study, acquisition, analysis and interpretation of data, drafting and revision of manuscript. M.A.: Contributed to acquisition and interpretation of data, revision of manuscript. H.O., H.K. and K.S.: Contributed to interpretation of data, revision of manuscript.

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Editor's choice

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It has taken one generation of surgeons and anaesthetists for old age not to be any more a contra-indication for elective major abdominal surgery. The change has largely been driven by improved peri-operative non-surgical care although of course surgical craftsmanship has progressed. When things do go wrong our ICU colleagues have provided patients with a safety net that is slowly, but surely, lowering 30-day mortality rates for colorectal resection. The population is getting older and we are able to offer safe curative resections in octogenarians. Is that as far as we can or should go? The paper by Kotake *et al.* examines patterns of treatment and the outcome in well over 3700 octogenarians. They confirm that octogenarians have less extensive resections, minimal access to adjuvant chemotherapy and show distinctive clinical and pathological features. Overall survival and disease free survival are both lower in octogenarians and, as expected, age is a robust independent predictor of survival. Information on the physiological status of these patients is lacking but would have been helpful. Nevertheless there is much to take away from this study and it raises many questions. The life expectancy of octogenarians falls within the standard 3 and 5 year colorectal cancer follow-up schemes and previous studies have shown beneficial effects of adjuvant chemotherapy in octogenarians. To my mind this study confirms that we should not be too nihilistic when we treat octogenarias with colorectal cancer.

Alexander Engel
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ORIGINAL ARTICLE

Influence of extent of lymph node dissection on survival for patients with pT2 colon cancer

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Abstract
Purpose The optimal extent of lymph node dissection for early-stage colon cancer (CC) remains undefined. This study assessed the influence of the extent of lymph node dissection on overall survival (OS) in patients with pT2 CC.
Methods We retrospectively examined data from the multi-institutional registry system of the Japanese Society for Cancer of the Colon and Rectum and used a propensity score matching method to balance potential confounders of lymph node dissection. We extracted 463 matched pairs from 1433 patients who underwent major resections for pT2 CC between 1995 and 2004.
Results Lymph node metastasis was found in 301 (21.0 %) of 1433 patients with pT2 CC. In this cohort, significant independent risk factors for lymph node metastasis were lymphatic invasion and venous invasion. Patients who underwent D3 or D2 lymph node dissection did not significantly differ in OS, either among the propensity score-matched cohort (estimated hazard ratio [HR] 0.85, 95 % confidence interval [CI] 0.536–1.346, P=0.484) or in the cohort as a whole (HR 0.720, 95 % CI 0.492–1.052, P=0.089).
Conclusions For patients with pT2 CC, D3 lymph node dissection did not add to OS. D2 lymph node dissection may be adequate for pT2 CC.

Keywords pT2 colon cancer · Lymph node metastasis · Lymph node dissection · Overall survival · ?Propensity score matching

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Introduction

Colorectal cancer (CRC) is the fourth leading cause of cancer death worldwide [1]. In Japan, approximately 110,000 new cases of CRC are diagnosed annually, with a trend toward increasing proportion of early-stage disease [2, 3]. With the advent of CRC screening programs and promotion of early CRC detection, curative treatment is expected to further increase.

Although controversy exists, efficacy of local excision with regard to organ and function sparing and oncological outcome was suggested for selected patients with pT1 and pT2 rectal cancer [4, 5]. For colon cancer (CC), however, mostly because of anatomical inaccessibility, local excision is focused around colonoscopic technique; generally, the selection criteria for colonoscopic resection are limited to pT1 disease with favorable histologic features [6, 7]. Otherwise, major resection is the standard therapy, with a laparoscopic approach gradually becoming an option of choice [8]. In major resection, the importance of lymph node dissection (LND) up to the origin of the primary feeding artery has been appreciated for locally advanced CC (cT3 and cT4) [7, 9, 10]. However, the optimal extent of LND for early-stage CC, especially for pT2 CC, remains undefined. Paucity of high-quality data on this subject from controlled trial indicates the need for further research.

The present study therefore assessed the influence of extent of LND on oncological outcomes of patients with pT2 CC who underwent major resection, using a large-scale CRC database.

Materials and methods

Definition of N stage and scope of LND

In this study, N stage and scope of LND were classified according to the sixth edition of the Japanese Classification of Colorectal Carcinoma [11]. N1 is defined as metastasis to epicolic and paracolic lymph nodes (pericolic nodes) located within 5 cm from the tumor, N2 as metastasis to pericolic lymph nodes located 5–10 cm away from the tumor and intermediate lymph nodes along the primary feeding artery, and N3 as main lymph nodes at the root of the primary feeding artery. All of these are defined as regional lymph nodes. D1 LND is defined as removal of pericolic nodes located within 5 cm from the tumor, D2 LND as removal of pericolic nodes located within 10 cm from the tumor and intermediate nodes, and D3 LND as removal of all regional nodes including main nodes (Fig. 1).

Data collection

The database of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) maintains prospectively collected clinical and pathological data for more than 170,000 patients with CRC treated between 1974 and 2005 at member hospitals located all over Japan. The present study is based on anonymized data of 1433 patients with pT2 CC extracted from the JSCCR database. First, we identified 2430 patients with pT2 CC from 41,644 patients who underwent surgery for invasive adenocarcinoma (pT1–4) of the colon and rectum between 1995 and 2004. We then excluded 514 patients with missing data for age or pathologic lymph node status and/or lost to follow-up and 483 patients who underwent procedures less extensive than D2 LND.

Statistical analysis

Univariate analysis used frequency and proportionality for categorical variables and mean with standard deviations for continuous variables. We analyzed correlations of lymph node metastasis (LNM) and baseline variables including demographic-, tumor-, and treatment-related characteristics. Multivariate binary logistic regression analysis was then performed to identify predictors for LNM.

Then, influence of lymph node dissection on overall survival (OS) was explored by the propensity score matching method, which is a tool to adjust a treatment effect for measured confounders in non-randomized studies. To identify potential predictors to guide selection of LND extent, we assessed 16 variables through univariate analysis; these variables were then used as covariates in a multivariable binary logistic regression in which the extent of LND was the dependent variable. The estimated probabilities were used as propensity scores. Using the propensity scores, the entire cohort was matched by a 1:1 nearest-neighbor matching method with a caliper of 0.01, and the balance of the covariates between the matched pairs was then examined. The primary outcome of interest of this study was OS, which was calculated in months

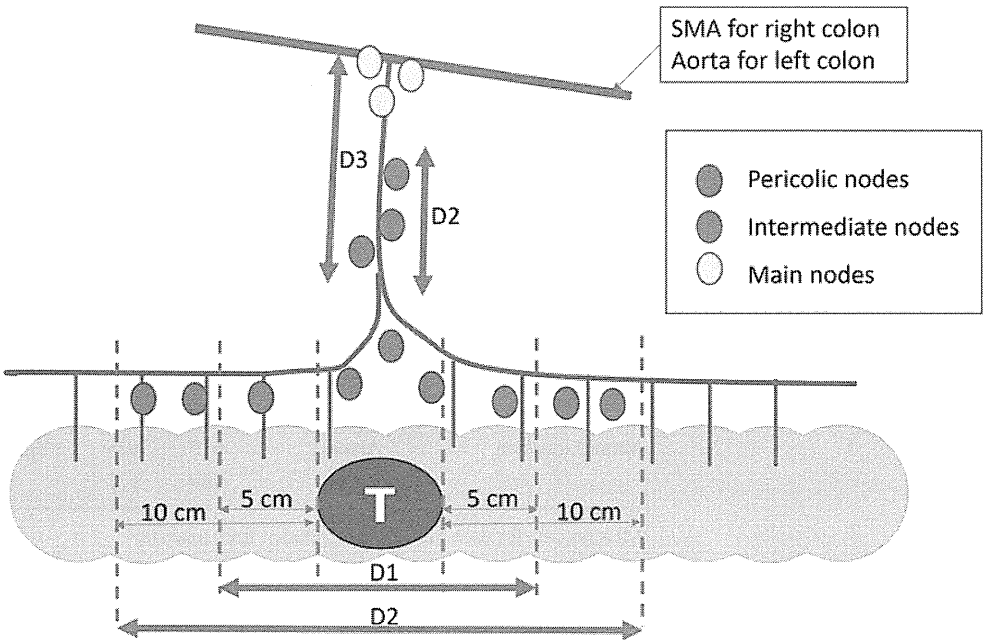

Fig. 1 Lymph node station and scope of lymph node dissection using Japanese classification

from date-of-surgery. We used the Kaplan–Meier method of survival analysis for both cohorts, the log-rank test for comparison of the survival curves, and Cox-proportional hazard model for estimating the hazard ratio. Statistical analyses were performed using SPSS Statistic version 22 (IBM Corporation, Somers, NY), SPSS plug-in of PSMATCHING2, and R version 2.15.0 (R Foundation for Statistical Computing; http://www.r-project.org). $P<0.05$ was considered significant.

Results

Table 1 shows the basic clinicopathological characteristics of the 1433 patients as a whole, divided by presence of LNM. Histologically confirmed LNM was found in 21.0 % of the patients (301/1433), of whom 17.2 % (246/1433) had pN1 disease, 3.4 % (49/1433) had pN2, and 0.78 % (6/774) had pN3. Of the 10 variables examined (treatment year, age, sex, preoperative serum carcinoembryonic antigen, tumor location, tumor size, macroscopic tumor type, histology, lymphatic and venous invasion), lymphatic invasion (odds ratio [OR] 4.105, 95 % confidence interval [CI] 2.813–5.991, $P<0.001$) and venous invasion (OR 1.479, 95 % CI 1.076–2.034, $P<0.001$) were independent predictors for LNM in multivariate analysis.

Table 2 shows variables for the entire cohort, indicating those who underwent D3 LND (774 patients) and D2 LND (659 patients). Significant differences were seen in six of 14 tested variables. In this cohort, both number of lymph node examined (NLNE) and number of metastatic lymph nodes (NMLN) were significantly larger in the D3 group than in the D2 group (Table 3). The OS for the D3 group was slightly higher than in the D2 group, but not significantly so. The estimated hazard ratio (HR) for OS of the D3 versus D2 groups was 0.720 (95 % CI 0.492–1.052, $P=0.089$).

We extracted 463 propensity score-matched pairs from the entire cohort. Table 4 shows that the selected variables in the propensity score-matched cohort were well balanced between the D3 and D2 groups. In this cohort, OS curves of the D3 and D2 LND groups overlapped each other, with an estimated HR of 0.85 (95 % CI 0.536–1.346, $P=0.484$) (Fig. 2). Although NLNE of the D3 group was larger than that of the D2 group in these matched pairs, OS between the two groups did not differ significantly even if both NLNE and NMLN were included in

Table 1 Predictive factors for lymph node metastasis (LNM)

		Univariate analysis			Multivariate analysis		
		LNM −	LNM+	*P*	OR	95 % CI	*P*
Treatment year	1995–1999	545	143	0.844			
	2000–2004	587	158				
Age group (years)	<70	705	191	0.708			
	≥70	427	110				
Sex	Male	635	158	0.264			
	Female	497	143				
Serum CEA, preoperative	≤cutoff	799	222	0.084			
	>cutoff	147	28				
Tumor location	Right colon	520	132	0.519			
	Left colon	612	169				
Tumor size	<2 cm	241	70	0.265			
	≥2 cm	776	189				
Macroscopic tumor type[a]	Type 0–2	1075	286	0.965			
	Type 3–4	37	10				
Histology	Well, mode	1106	291	0.312			
	Por, muc, sig	26	10				
Lymphatic invasion	Absent	557	55	<0.001	1		
	Present	569	245		4.105	2.813–5.991	<0.001
Venous invasion	Absent	689	126	<0.001	1		
	Present	429	172		1.479	1.076–2.034	0.016

Missing data for each factor were excluded from analysis

CI confidence interval, *OR* odds ratio, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *muc* mucinous carcinoma, *sig* signet ring carcinoma

[a] Type 0, superficial; 1, protuberant; 2, expansive ulcerating; 3, infiltrative ulcerating; 4, diffusely ulcerating

Table 2 Characteristics of the 1433 patients who underwent major surgical resection for pT2 colon cancer, according to the scope of lymph node dissection

		D2 LND	D3 LND	*P*
Number of patients (*N*=1433)		659	774	
Year of surgery	1995–1999/2000–2004	291/368	397/377	0.007
Age group (years)	<70/≥70	376/283	520/520	<0.001
Sex	Male/female	367/292	426/348	0.805
Serum CEA, preoperative	≤cutoff	441	580	0.003
	>cutoff	89	86	
	Missing	129	108	
Multiple primary cancer	Absent/present	575/84	690/84	0.267
Adjuvant chemotherapy	No	377	448	0.011
	Yes	146	208	
	Missing	136	118	
Tumor location	Right colon/left colon	309/350	343/431	0.329
Tumor size	<2 cm	177	134	<0.001
	≥2 cm	411	554	
	Missing	71	86	
Macroscopic tumor type[a]	Type 0–2	625	736	0.819
	Type 3–4	21	26	
	Missing	13	12	
Histology	Well, mod	645	752	0.387
	Por, sig, muc	14	22	
Laparoscopic approach	No/yes	537/122	686/88	<0.001
Lymphatic invasion	Absent	271	341	0.233
	Present	383	431	
	Missing	5	2	
Venous invasion	Absent	382	433	0.589
	Present	268	333	
	Missing	9	8	
Lymph node metastasis, histological	Absent/present	530/129	602/172	0.220

A missing category was created and reported in this univariate analysis

wel well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *muc* mucinous carcinoma, *sig* signet ring carcinoma

[a] Type 0, superficial; 1, protuberant; 2, expansive ulcerating; 3, infiltrative ulcerating; 4, diffusely ulcerating

the variables used for matching (data not shown). In addition, D3 LND showed no survival benefit over D2 LND for neither patients with positive node (logrank P=0.925) nor negative node (logrank P=0.414).

Discussion

This study analyzed multi-institutional CRC registry data regarding extent of LND for pT2 CC. The strengths of this study

Table 3 Number of lymph nodes examined and number of lymph nodes found to be metastatic in patients who underwent major resection for pT2 colon cancer, in both the entire cohort and in the propensity score-matched cohort

		Entire cohort (*n*=1433)			Propensity score-matched cohort (*n*=926)		
		D2 LND	D3 LND	*P*	D2 LND	D3 LND	*P*
Number of lymph node examined	Mean	11.58	17.74	0.007	11.63	18.08	0.011
	SD	11.43	11.49		11.18	12.01	
Number of metastatic lymph nodes	Mean	0.36	0.53	0.001	0.38	0.45	0.095
	SD	1.01	1.89		1.07	1.15	

Table 4 Characteristics of the 926 patients who underwent major resection for pT2 colon cancer in the propensity score-matched cohort, according to the scope of lymph node dissection

		Propensity-score matched cohort (n=926)		
		D2 LND	D3 LND	P
Number of patients		463	463	
Year of surgery	1995–1999/2000–2004	226/237	231/232	0.742
Age group (years)	<70/≥70	300/163	293/170	0.632
Sex	Male/female	254/209	279/184	0.096
Serum CEA, preoperative	≤/> cutoff value	345/56	349/51	0.876
	Missing	62	63	
Multiple primary cancer	Absent/present	420/43	402/61	0.061
Adjuvant chemotherapy	No/yes	273/119	274/110	0.676
	Missing	71	79	
Tumor location	Right colon/left colon	206/257	211/252	0.741
Tumor size	<2/≥2 cm	105/303	86/323	0.281
	Missing	55	54	
Macroscopic tumor type[a]	Type 0–2	445	437	0.126
	Type 3–4	8	18	
	Missing	10	8	
Histology	Well, mod	453	452	0.825
	Por, sig, muc	10	11	
Laparoscopic approach	No/yes	397/66	408/55	0.283
Lymphatic invasion	Absent/present	199/263	200/263	0.606
	Missing	1	0	
Venous invasion	Absent/present	265/192	265/195	0.600
	Missing	6	3	
Lymph node metastasis, histological	Absent/present	369/94	368/95	0.953

A missing category was created and reported in this univariate analysis

wel well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *muc* mucinous carcinoma, *sig* signet ring carcinoma

[a] Type 0, superficial; 1, protuberant; 2, expansive ulcerating; 3, infiltrative ulcerating; 4, diffusely ulcerating

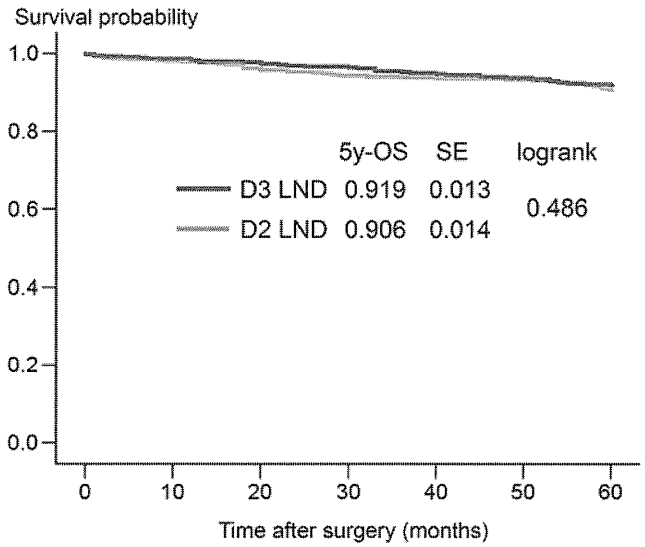

Fig. 2 Overall survival of patients with pT2 colon cancer, by whether they had undergone D3 or D2 lymph node dissection, in the propensity score-matched cohort

were its access to the large-scale database and its ability to adjust available confounders by propensity score matching analysis to address internal validity. In the present study, incidence of histologically proven LNM was 21.0 % (301/1433 cases), and predictors for LNM were lymphatic and venous invasion in patients with pT2 CC. These results coincided well with previous reports [12–15].

In this cohort, 5-year OS after surgery of patients in the D3 group was slightly higher than in the D2 group, but did not significantly differ. As we thought this result might reflect a selection bias in that D3 LND was prone to be applied to younger patients, during earlier treatment years, for larger tumors, performed as open surgery, etc., we adjusted these confounding factors by propensity score matching method. These statistical accommodations clearly showed the equivalence of 5-year OS between the two groups.

Major surgery with LND has been regarded as a standard care of invasive CC, except for pT1 with favorable histologic features, although little high-level evidence on the survival effects of LND extent [16–18], especially for pT2 CC [13, 14, 19]. Recently, excellent oncological outcomes for CC

have been reported through complete mesocolic excision and central vascular ligation technique [9, 20]. The essentials of this surgical procedure are mobilization of the bowel along embryological and anatomical planes to obtain clear margins, high ligation of the primary feeding arterial vessel, and resection of an adequate bowel resection for LND, which would be almost identical to D3 LND except for wider range of bowel resection [20]. Our previous study, which also used JSCCR registry data, associated D3 LND for pT3 and pT4 CC with a significant survival advantage over D2 LND [10]. In that previous series, incidence rate of pN3 was 4.9 % (326/6580) and was approximately 4 % higher as that in pT2 of the present study.

As shown in the present study, survival for patients with pT2 CC after major surgery is quite favorable. According to JSCCR data, the 5-year OS rate for patients with stage I CC is >90 %, and cumulative 5-year recurrence rate was low as 3.7 % [7]. For such a small proportion of recurrence, the benefit of postsurgical adjuvant chemotherapy is estimated to be very small, even assuming a 20 % risk reduction for undergoing the FOLFOX regimen for stage III disease [21]. As the prognosis is so good and the incidence of pN3 so low, the question arises whether D3 LND contributes to local control or survival for pT2 CC.

The basis for more extensive LND for CC has been mainly rationalized by studies on lymphatic flow in diseased bowel segments, analysis of pathologic specimens, and mapping of lymph nodes. Hida et al. reported analysis of pathologic specimen using clearing methods that showed rates of LNM from pT2 CC to intermediate nodes and main nodes to be 20 and 0 %, respectively, and distance from tumors to metastatic pericolic nodes was exclusively less than 5 cm [12]. Nevertheless, in their study, the rate of LNM to intermediate lymph node was somewhat higher than LNM to pN2 in the present study (3.4 %); they therefore speculated that removal of intermediate node and both sides of 5-cm bowel resection margin could be a curative treatment for pT2 CC. Furthermore, Hashiguchi et al. analyzed incidence and distribution of LNM and NLNE of pT2–4 CC by LND extent and concluded that removal of main nodes and pericolic LNs beyond 5 cm from the tumor did not improve staging accuracy or survival benefit over not removing these nodes, even for pT4 disease [22]. Because of a lack of information on accurate location of pericolic nodes, we cannot comment further on range of bowel resection.

NLNE closely affects prognosis in CRC regardless of presence of LNM, and increased NLNE is significantly associated with decreased risk of recurrence and cancer death, at least in patients with pT3–4 CC [23–27], which is partly explained by stage migration. Another possible mechanism would be improved clearance of micrometastasis and/or isolated tumor cells, which have been shown to predict poorer survival [28]. For example, in a study of patients with stage I and II CC, Faerden et al. reported 5-year recurrence rates of 23 and 8 %, respectively, for patients with and without micrometastasis; their 5-year disease-free survival also differed significantly [29]. Currently, the ongoing Enroute+ study is intended to determine the efficacy of adjuvant chemotherapy for stage I and II CC patients with micrometastasis [30]. In the present study, even if NLNE was significantly larger for the D3 group (mean 17.4 nodes) than for the D2 group (mean 11.5 nodes), the difference was not reflected in OS. For survival analysis using a large-scale database of Surveillance, Epidemiology, and End Results (SEER) by Maggrard et al. [31], NLNE for accurate staging of T2 CC was estimated to be 10 lymph nodes. Given the probability and spread of LNM is associated with pT stage, LND of adequate extent in pT2 CC for accurate staging and removal of both visible and invisible LNM could be less than that for pT3–4 disease.

However, whether accuracy of clinical assessment of T staging is as high as 70–80 % is contested [32]. Nakafusa et al. reported that 30 % of putative cT2 tumors were revealed to be pT3 [33]. In this light, D3 LND should be standard surgery for uncertainly staged cT2 tumor, whereas cT2 tumors with clear diagnostic accuracy could be treated with D2 LND. On this issue, JSCCR guidelines for colorectal carcinoma state: "Although there is insufficient evidence describing the area of dissection for cT2 cancer, at least D2 dissection is necessary. However, D3 dissection can be performed, because about 1 % of cT2 cancer is accompanied by main lymph node metastases and because preoperative diagnosis of depth of invasion is not very accurate" [7]. Our findings may provide a rationale for this statement of JSCCR guidelines.

Finally, this study had several limitations inherent to its retrospective nature and its being a non-randomized study. Non-randomized studies may be confounded by other variables. Although we adjusted for baseline differences between patients using propensity score, the retrospective nature of the study meant that the variables were limited to those for which data were available for. Also, as patients without follow-up information were excluded from the analyses, survival probabilities in the present study could be over- or underestimated. In spite of these limitations, our findings were significant and warrant further investigations to find the optimal extent of LND for pT2 colon cancer.

Ethical statement This study was considered exempt by the Tochigi Cancer Center's institutional review board because it used preexisting data without personal identifiers.

Conflict of interest None.

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ORIGINAL ARTICLE

Gender differences in colorectal cancer survival in Japan

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Abstract

Background A gender difference in survival has been documented in colorectal cancer (CRC) patients, although the underlying mechanism remains undefined. This study aimed to gain improved insight into this difference, with a special focus on improved cancer-specific survival.

Methods The study population consisted of 82,402 patients with invasive CRC who had undergone surgery in Japan between 1985 and 2004. To estimate improved survival, multivariate adjustment using patient demographics and tumor characteristics was performed.

Results Patient characteristics changed over time. The 5-year survival rates increased from 66.5 to 76.3 % during the study period. Higher survival rates persisted in women over time (multivariate-adjustment model—hazard ratio [HR] 0.87, 95 % confidence interval [CI] 0.85–0.90). Patients who received surgery during the period 2000–2004 had significantly longer survival than those during the period 1985–1989 (men: HR 0.70, 95 % CI 0.67–0.74; women: HR 0.72, 95 % CI 0.67–0.76). However, there was no gender difference regarding improved survival.

Conclusions A reduced risk of cancer-specific death for women relative to men persisted over time; however, enhancement of survival was equally observed in both genders. Identification of factors associated with gender differences and changes over time in CRC survival may serve as targets for further improvement.

Keywords Colorectal cancer · Gender differences · Cancer specific survival · Improvement in survival

Introduction

Colorectal cancer (CRC) remains a serious health problem. It is the second most common cancer in women and the third in men, accounting for ≥1.3 million newly diagnosed cases annually worldwide [1]. Current estimates indicate that the incidence of CRC could increase to >2 million in the near future [1]. In contrast to such a steeply increasing incidence, a downward trend in CRC mortality has been observed in some countries, suggesting a potential improvement in CRC survival in recent years [2, 3]. According to the CONCORD-2 study that analyzed survival regarding 11 common cancers in >25 million cases collected from 67 countries, the CRC survival rate increased over the period from 1995−2009, and the 5-year relative survival rates >60 % in 22 countries [4]. A report from the Epidemiology and End Results (SEER) program in the United States indicated an indisputable improvement in CRC survival between 1970 and 1973 and between 2004 and 2010 [5]. In particular, the 5-year relative survival rates of patients with colon and rectal cancer increased by 14.8 and 19.7 %, respectively, during these periods [5]. In Japan, small but significant improvements in the 5-year relative survival rate of 1.2 % for colon cancer and 2.9 % for

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Q 2 日本の大腸癌の治療成績は？

A 以下に大腸癌の短期・長期治療成績を具体的に示す。

1．大腸癌の生存率・再発率

わが国には全数調査に基づく大腸癌の生存率の計測値は存在しないが，代替値としての罹患[1]と死亡[2]の推移をみると，両者の乖離幅は着実に拡大しており，生存率の改善傾向が示唆されている（図1）。生存率の比較的網羅性の高い計測値としては，地域がん登録による5年相対生存率がある。1993～2005年までを4期に区分した5年相対生存率は経年的に高まっており，結腸癌の遠隔，直腸癌の領域と遠隔では前期（1993～1996年）と後期（2003～2005年）の生存率の差は推計学的に有意である（図2）[1]。このように高まりつつある日本の大腸癌の生存率は経済協力開発機構（OECD）参加諸国のなかで最も高率である[3]。

大腸癌治療ガイドライン[4]には大腸癌全国登録2000～2004年症例の部位別，進行度（Stage）別の累積5年生存率が収載されている。

大腸癌の再発に関する大規模データは乏しく，大腸癌治療ガイドライン[4]に収載されている大腸癌研究会のデータがわが国では最大規模である。再発率は直腸癌が高率であり，直腸癌の

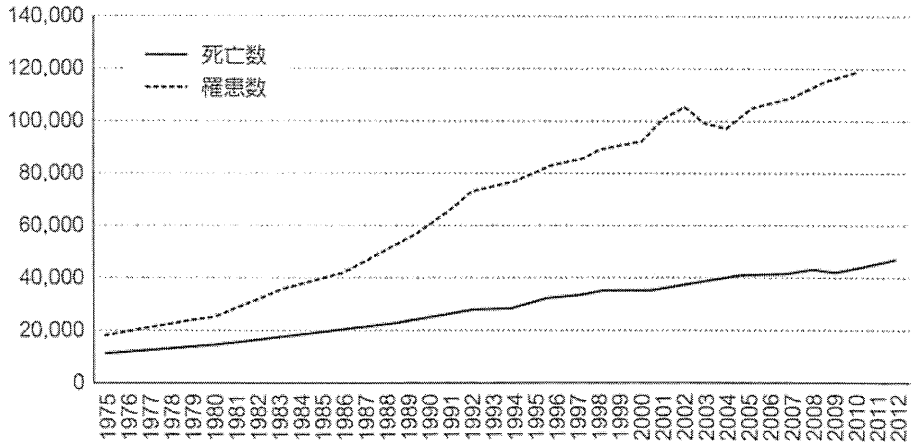

図1　大腸癌の罹患数と死亡数の推移
罹患数と死亡数の乖離幅の拡大から，生存率の改善を読み取ることができる。
（文献1，2をもとに作成）

Gastric Cancer
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ORIGINAL ARTICLE

Exploratory phase II trial in a multicenter setting to evaluate the clinical value of a chemosensitivity test in patients with gastric cancer (JACCRO-GC 04, Kubota memorial trial)

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Abstract

Background Although postoperative adjuvant chemotherapy with S-1, an oral fluoropyrimidine, has become a standard of care for gastric cancer in Japan, nonresponders may suffer from the cost and adverse reactions without clinical benefit. This multicenter exploratory phase II trial was conducted to see whether a chemosensitivity test, the collagen gel droplet embedded culture drug sensitivity test (CD-DST), can adequately select patients for chemotherapy.

Methods The CD-DST using four different concentrations of 5-fluorouracil was conducted with resected specimens from preregistered patients who underwent gastrectomy with D2 or more extensive lymphadenectomy. Patients who were histopathologically confirmed to have stage II or greater disease without distant metastasis were eligible for final enrollment. All patients underwent protocol-specified adjuvant chemotherapy with S-1. Three-year relapse-free survival was compared between patients determined as sensitive by the CD-DST (responders) and those deemed insensitive (nonresponders). Appropriate cutoff values for in vitro growth inhibition were defined when the hazard ratio for relapse in responders and the log-rank *P* values were at their minimum.

For the JACCRO-GC04 Group.

The investigators in the Japan Clinical Cancer Research Organization Gastric Cancer 04 (JACCRO GC-04) Group are listed in the Appendix.

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