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## Original Paper

# Substantial Variation in Therapy for Colorectal Cancer Across Europe: EUROCARE Analysis of Cancer Registry Data for 1987

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To provide a quantitative description of the treatments applied to malignant colorectal cancer across Europe, we analysed all cases (11 333) of colorectal cancer registered in 1987 by 15 Cancer Registries in eight European countries. In a third of cancer registries, therapy was known for all cases, in the others 1-15% of registrations lacked treatment information. Eighty per cent of all patients received surgical resection, ranging from 58% (Estonia) to 92% (Tarn). The proportion of resections decreased with advancing age (85-73% for colon cancer; 85-70% for rectal cancer for <65 years to >74 years, respectively). Only 4% of colon cancer patients received adjuvant or palliative chemotherapy, range 1-12%. Sixteen per cent of rectal cancer patients received radiotherapy with great inter-registry variability (1-43%). Since the proportion of surgically resected patients correlated positively with the 5-year relative survival probability reported by the recently published EUROCARE study, this may be part of the explanation for the major differences in survival for these cancers among different European populations. The most likely determinant of this correlation is stage at diagnosis, but, quality of, and access to surgery, as well as access to endoscopy, may differ among countries and registry areas, and these may also contribute to inter-country survival differences. Copyright © 1996 Elsevier Science Ltd

**Key words:** rectal neoplasms, colonic neoplasms, treatment, colon and rectal surgery, registries, survival

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## INTRODUCTION

BASED ON combined data collected by 30 population-based cancer registries for cases diagnosed during 1978-1985 and analysed by EUROCARE, the 5-year relative survival for colorectal cancer patients in Europe was approximately 40%

[1]. However, there were conspicuous geographical variations in this statistic: from over 45% in cancer registries from Switzerland, South-east Netherlands and Finland to less than 35% in cancer registries from England and Poland [1].

The aim of the present study was to provide a quantitative description of the types of treatment applied to colorectal cancer in European countries, based on information routinely collected by cancer registries during 1987. This may help us to understand why there are marked between-country differences in survival from these cancers across Europe. The study was carried out within the EUROCARE network of cancer registries, under the auspices of an EC Concerted Action programme, responsible for evaluating and standardising population-based cancer survival data and reporting on cancer patient survival and care practices in Europe.

## PATIENTS AND METHODS

The study analysed all the colorectal (ICD-9 153,154) [2] cancers occurring in 1987 in 15 European populations, for whom relatively complete data on treatment were available,

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covered by cancer registries in eight countries. Only malignant invasive tumours, as defined by ICD-O behaviour code 3 or higher [3] were considered; *in situ*, uncertain and borderline tumours were excluded, as were carcinoids and non-epithelial tumours. Both microscopically verified and non-verified cases were included, but cases known to registries by death certificate only (DCO) or discovered incidentally at autopsy, were excluded.

Table 1 shows a breakdown of the total 11 333 colorectal cancer cases according to participating cancer registry and country. The registries of Finland and Estonia cover the entire populations of those countries. France, The Netherlands, Switzerland and the U.K. are represented by two or more registries. Italy and Poland are represented by single registries covering small areas. Most of the cases were from registries in Northern Europe and almost 50% were from the two U.K. registries. Table 1 also provides information on the distribution by sex, age and cancer site according to registry. The proportion of males ranged from 44% (Finland) to 59% (Côte d'Or). 43% of cases were over 74 years of age, varying between 28% (Estonia and Cracow) and 46% (Geneva and Basel). The number of colon cancer cases was usually slightly higher than that of rectal cancer. The proportion of cases confirmed either histologically or cytologically ("microscopically verified") generally ranged between 80% (Mersey) and 99% (Basel and Eindhoven), but in Cracow only 45% of cases were "microscopically" confirmed.

The major sources of information for most cancer registries

are medical records and pathology files and sometimes death certificates, to collect a minimal set of information for routine cancer incidence studies.

Cancer registries were asked to provide information on whether patients underwent surgical resection and/or radiotherapy, chemotherapy or other treatment. If surgical resection, radiotherapy, chemotherapy or other treatment was mentioned in the registry file, it was entered as such; if none were mentioned, the item was entered as "therapy not known". Detailed information on type of surgery, or radiotherapeutic or chemotherapeutic regimen adopted was not requested. However, to provide as complete a picture as possible on therapy, the participating registries were asked to re-check the clinical records of patients for whom no information on treatment had been recorded. Two large registries (Finland and Thames) did not perform this check.

Surgical resection was defined as any surgical intervention which removed the tumour, whether with radical or palliative intent. When only by-pass surgery was performed, it was classified as "other treatment", although the Finnish cancer registry could not separate by-pass surgery from resection as defined above.

Because the age-distributions of patients differed between registries, the proportions of patients given particular types of treatment were age-adjusted using the direct method, i.e. the proportion of cases treated in each 10-year age group (<35, 35-44, 45-54, 55-64, 65-74, 75+) for each registry was applied to the age distribution of the total series of cases. The age-stratified homogeneity test was used for testing treatment differences between cancer registries or between countries [4].

## RESULTS

Table 2 shows the (age-adjusted) percentages of colorectal cancer patients who received surgical resection either alone or in association with chemotherapy or radiotherapy, and the percentages of patients given "other treatments" (symptomatic or palliative, including chemotherapy, radiotherapy and by-pass surgery). In 8% of cases, there was no information on therapy. Overall, 80% of patients received surgical resection, varying from 58% (Estonia) to 92% (Tarn) by registry, with Estonia, Amiens, Cracow and Mersey cancer registries less than 70%.

Tables 3 and 4 show, for colon and rectum, respectively, the percentages of patients treated surgically, according to registry and age. The proportion treated surgically decreased with advancing age: from 85 to 73% for colon cancer, and from 85 to 70% for rectal cancer. This trend was evident for both cancer sites in most cancer registries. The proportion of treated patients aged over 74 ranged from 43% (Estonia) to 94% (Doubs) for colon cancer, and from 33% (Amiens) to 82% (Tarn, Rotterdam and Basel) for rectal cancer. Fairly large differences between registries, with respect to proportions receiving surgery, were also evident in the younger and in the middle age-group.

In addition to between-country variability, there was considerable variability within countries, which was particularly significant in France, Switzerland and the U.K. for both colon and rectal cancers (all ages,  $P < 0.005$ ). No treatment differences in relation to sex were observed (not reported in Table).

Table 5 shows the age-standardised percentages of colon cancer patients who received chemotherapy, and rectal cancer patients given radiotherapy. Overall, only 4% of patients with

Table 1. Colorectal cancer cases by registry, sex, age, site and microscopic verification (MV)

Registry	No. of cases (%)	Males %	>74 years of age %	Colon %	MV%
Estonia	415 (4)	45	28	54	87
Finland*	1422 (13)	44	38	58	95
France					
Côte d'Or	244 (2)	59	43	69	98
Calvados	249 (2)	54	41	57	98
Doubs	175 (2)	53	37	56	98
Tarn	200 (2)	53	45	59	97
Amiens	249 (2)	53	37	59	95
Italy					
Varese	421 (4)	49	39	62	90
The Netherlands					
Eindhoven	389 (3)	52	36	68	99
Rotterdam	732 (6)	48	42	66	97
Poland					
Cracow	200 (2)	45	28	51	45
Switzerland					
Basel	485 (4)	54	46	63	99
Geneva	184 (2)	48	46	71	95
U.K.					
Mersey	1163 (10)	49	40	60	80
Thames*	4805 (42)	48	44	62	87
Total	11 333 (100)	49	43	61	90

\*No re-check of therapy data.

Table 2. Colorectal cancer cases according to registry and therapy. Age-standardised percentages

Registry	Therapy		
	Surgical resection* %	Other treatments† %	Not known (%)
Estonia	58	39	2
Finland‡	82	13	6
France			
Côte d'Or	86	14	—
Calvados	81	16	3
Doubs	89	11	—
Tarn	92	4	4
Amiens	67	29	4
Italy			
Varese	72	27	1
The Netherlands			
Eindhoven	89	10	—
Rotterdam	87	12	—
Poland			
Cracow	60	25	15
Switzerland			
Basel	89	10	1
Geneva	79	21	—
U.K.			
Mersey	66	27	7
Thames‡	83	3	14
Total	80	12	8

\*Surgery with or without radiotherapy or chemotherapy. †Includes radiotherapy or chemotherapy when given alone, as well as other symptomatic treatments. ‡No re-check of therapy data.

colon cancer received chemotherapy: varying from about 1% in Côte d'Or, The Netherlands and Mersey to 12% in Estonia and Doubs. Almost all colon cancer cases treated with chemotherapy also received surgical resection. Sixteen per cent of rectal cancer patients received radiotherapy, with great variability between registries (1–43%). Overall, radiotherapy for rectal cancer was associated with surgical resection in 75% of cases. The proportion of colon cancer patients receiving chemotherapy decreased with advancing age (from 11% under 65 years, to 1% over 75 years) as did the proportion of rectal cancer patients receiving radiotherapy (from 20% under 65 years to 10% over 75 years).

### DISCUSSION

This study reveals that the proportion of colorectal cancer patients who received surgical resection varied widely within Europe in 1987. Surgical resection was performed in over 80% of colon and rectal cancer cases in four of the five French areas, The Netherlands, one of the two Swiss areas, Thames (U.K.) and Finland. By contrast, Estonia, Cracow, Mersey (U.K.) and Amiens reported that less than 70% of patients underwent surgical treatment, while Varese and Geneva had intermediate figures.

In the Finnish cancer registry, with a high proportion of surgical resections, this category may include a small number

Table 3. Surgical resection in colon cancer patients according to registry and age. Age-standardised percentages

Registry	Age-groups			
	<65 %*	65–74 %	>74 %	All %†
Estonia	74	68	43	59
Finland‡	91	87	70	81
France	92	91	80	87§
Côte d'Or	92	96	78	87
Calvados	100	93	89	93
Doubs	92	96	94	94
Tarn	100	93	91	94
Amiens	80	79	54	69
Italy				
Varese	84	87	56	73
The Netherlands	90	92	85	89
Eindhoven	88	94	87	90
Rotterdam	92	90	84	88
Poland				
Cracow	52	55	65	59
Switzerland	97	93	78	88§
Basel	97	96	82	90
Geneva	96	88	67	81
U.K.	84	86	73	80§
Mersey	73	75	56	66
Thames‡	87	89	77	83
Total	85	86	73	80¶

\*Age-standardised percentages (four age categories: <35, 35–44, 45–54, 55–64). †Age-standardised percentages (six age categories: <35, 35–44, 45–54, 55–64, 65–74 and >74). ‡No re-check of therapy data. §Test for homogeneity within country:  $P < 0.005$ . ||Test for homogeneity within country:  $P = 0.396$ . ¶Test for homogeneity between countries:  $P < 0.001$ , between registries:  $P < 0.001$ .

of cases that received a by-pass operation only. Note that, although this registry was unable to re-check its "therapy not known" cases (6% of total), 76% of these were histologically verified, suggesting that some of them had been resected. In contrast, the Cracow registry had a low proportion of surgical resections (60%) and the highest proportion of "therapy not known" (15%). Before verification, these figures were 54% and 30%, respectively, suggesting that the remaining 15% of unknown therapy patients included very few who were resected.

Cases notified to the registries by death certificate only were excluded from this analysis. These are patients who were not admitted to hospital, and for whom only palliative or no therapy was given; generally they remain at home for the terminal phase of their illness. Some cancer registries with a low proportion of DCOs actively sought clinical information on cases initially identified through death certificates, leading to the inclusion of unfavourable cases. The proportion of DCO cases was highest in Poland and Thames (U.K.) and lowest in Switzerland and Varese, so it is unlikely that the proportion of DCO cases substantially affected the proportion of treated patients. Furthermore, a recent study has provided

Table 4. Surgical resection in rectal cancer patients according to registry and age. Age-standardised percentages

Registry	Age-groups			
	<65 %*	65-74 %	>74 %	All %†
Estonia	75	67	35	57
Finland‡	91	85	76	84
France	87	88	59	77§
Côte d'Or	86	94	73	84
Calvados	81	76	44	66
Doubs	86	100	68	83
Tarn	94	89	82	88
Amiens	85	86	33	66
Italy				
Varese	76	82	53	69
The Netherlands	90	89	80	86
Eindhoven	94	97	76	88
Rotterdam	90	85	82	86
Poland				
Cracow	72	60	58	63
Switzerland	90	86	76	86§
Basel	92	88	82	87
Geneva	83	79	58	72
U.K.	85	83	72	80§
Mersey	78	70	54	66
Thames‡	88	86	76	83
Total	85	82	70	78¶

\*Age-standardised percentages (four age categories: <35, 35-44, 45-54, 55-64). †Age-standardised percentages (six age categories: <35, 35-44, 45-54, 55-64, 65-74 and >74). ‡No re-check of therapy data. §Test for homogeneity within country:  $P < 0.005$ . ||Test for homogeneity within country:  $P = 0.191$ . ¶Test for homogeneity between countries:  $P < 0.001$ , between registries:  $P < 0.001$ .

evidence that the proportion of DCO cases does not affect colon cancer survival figures [5].

In most registries, the frequency of surgical treatment decreased with advancing age, while the proportion of patients treated symptomatically, or for whom no information on therapy was recorded, increased with age. Stage is not necessarily more unfavourable for elderly patients with colorectal cancer [6], but concomitant disease may more frequently contraindicate surgery.

This study gives an indication of the application of chemotherapy and radiotherapy for colon and rectal cancers, respectively. However, registries often could not distinguish between the adjuvant or palliative intent of these therapies. In 1987, radiotherapy was known to be efficacious in rectal cancer [7], mainly to decrease the risk of local recurrence in Dukes' B and C, which constitute up to 60% of cases. The large variation between registries in the application of radiotherapy for rectal cancer (range 1-43%) certainly reflects different clinical attitudes, but may also be related to the availability of radiotherapy facilities. Studies showing that adjuvant chemotherapy could be efficacious in colon cancer appeared only after 1987 [8]. Chemotherapy was, in fact, only given to 1-12% of patients.

Table 5. Chemotherapy (CT) in colon and radiotherapy (RT) in rectal cancer patients according to registry. Age-standardised percentages (in parentheses CT or RT associated with resection)

Registry	Colon CT		Rectum RT	
	%	%	%	%
Estonia	12	(9)	15	(14)
Finland*	6	(5)	14	(13)
France	7†	(6)	28†	(19)
Côte d'Or	1	(1)	26	(16)
Calvados	9	(9)	43	(20)
Doubs	12	(12)	37	(30)
Tarn	9	(8)	18	(16)
Amiens	8	(5)	14	(12)
Italy				
Varese	3	(2)	22	(15)
The Netherlands	1‡	(1)	23‡	(18)
Eindhoven	1	(1)	27	(24)
Rotterdam	1	(1)	22	(14)
Poland				
Cracow	2	(1)	2	(0)
Switzerland	3§	(2)	17†	(10)
Basel	3	(2)	12	(8)
Geneva	5	(2)	34	(14)
U.K.	4†	(3)	13†	(10)
Mersey	1	(1)	1	(1)
Thames*	5	(4)	16	(12)
Total	4	(4)	16	(12)

\*No re-check of therapy data. †Test for homogeneity within country:  $P < 0.001$ . ‡Test for homogeneity within country:  $P = 0.183$ (RT),  $P = 0.574$ (CT). §Test for homogeneity within country:  $P = 0.275$ . ||Test for homogeneity between countries:  $P < 0.001$ , between registries:  $P < 0.001$ .

Our findings on the proportion of surgical resections for colorectal cancers in 1987 can help the interpretation of the EUROCARE finding of significant between-country differences in colon and rectal cancer survival (cases occurring between 1978 and 1985). Within the 15 cancer registry areas of this study, the age-adjusted proportion of patients who received surgical resection correlated positively with the 5-year relative survival probability (Pearson's  $r = 0.7$ ,  $P = 0.02$  for colon and Pearson's  $r = 0.6$ ,  $P = 0.05$  for rectum). The most likely determinant of this correlation is stage at diagnosis: both proportion of resected patients and survival probability correlate with this variable. However, quality of, and access to surgery, as well as access to endoscopy, may differ among countries and registry areas [9], and these may also contribute to inter-country survival differences. Unfortunately, the staging information routinely available to registries is incomplete and insufficiently standardised, and more detailed comparisons are not possible.

Because cancer registries aim to record all the colorectal cancer cases in defined areas, the findings of this study are not influenced by the socio-demographic factors that often affect access to individual hospitals. These population-based results therefore probably reflect the real health care situation in the

areas considered, although one small caveat would be that registries, particularly small ones, may be more likely to be present in areas where the local medical community has above-average interest in oncology, and this could positively influence the standard and availability of care in those areas.

In conclusion, the proportion of patients undergoing surgical resection for colorectal cancers varied widely across Europe in 1987. Since this variation correlates positively with the 5-year survival probability for these cancers (as reported in the EURO CARE study [1]), it may be part of the explanation for the major differences in survival for these cancers among European populations. Factors such as diagnostic procedures and their relation to stage, which determine treatment and in particular whether a patient is resected, are currently being investigated by the EURO CARE group.

1. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J, eds. *Survival of Cancer Patients in Europe*. Lyon. International Agency for Research on Cancer (IARC) Sci. Publ. No 132, 1995.
2. *International Classification of Diseases*, 9th revision. Geneva, WHO, 1977.
3. *International Classification of Diseases for Oncology*, 1st edition. Geneva, WHO, 1976.
4. Breslow NE, Day NE. Classical methods of analysis of grouped data. In *Statistical Methods in Cancer Research*, Vol. 1: *The Analysis of Case-Control Studies*. Lyon. International Agency for Research on Cancer (IARC) Sci. Publ. No. 32, 1980, 122–159.
5. Sant M, Capocaccia R, Verdecchia A, et al. Comparison of colon cancer survival among European countries. The EURO CARE study. *Int J Cancer* 1995, **63**, 43–48.
6. Kronborg O. Staging and surgery for colorectal cancer. *Eur J Cancer* 1993, **29A**, 575–583.
7. Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy. *Br J Surg* 1994, **81**, 7–19.
8. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon cancer. *N Engl J Med* 1990, **322**, 352–358.
9. McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *Br Med J* 1991, **302**, 1501–1505.

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