

## PAPERS AND ORIGINALS

## Outcome in colorectal carcinoma: seven-year study of a population

DAVID N CLARKE, PETER F JONES, C DOUGLAS NEEDHAM

### Summary and conclusions

All 433 patients with colorectal cancer who presented in the north-east of Scotland during 1968 and 1969 were followed up for seven years or until death intervened. The incidence of colorectal cancer in the region was the highest recorded in Great Britain. Half the patients were incurable at the time of diagnosis. Nevertheless, of the 195 survivors of radical resection 146 (75%) did not die of carcinoma during the next seven years. Men with "curable" rectal cancer showed a substantially lower corrected survival rate (42%) than women (70%), but this was due to intercurrent disease not recurrence. Comparable figures for colonic carcinoma showed no difference between men (75%) and women (77%).

The overall picture of colorectal cancer has apparently not changed for 20 years. Nevertheless, earlier diagnosis and timely operation—possibly with adjuvant chemotherapy—may produce useful long-term results.

### Introduction

Carcinoma of the large bowel is the second most common malignant tumour in Great Britain but there have been few studies of its occurrence and course in the population of a defined area. The north-eastern (Grampian) region of Scotland is such an area, and during 1968 and 1969 the population was fairly static. Virtually every patient with major disease is treated in one of the hospital units in Aberdeen, where pathological and radiological records are also kept, and there are close relations between hospital and general practice. These conditions greatly

help the long-term study of disease. We believe that we have traced every new case of carcinoma of the colon and rectum diagnosed in the region during 1968 and 1969 and have followed up all but two of these patients for seven years from diagnosis or until death intervened.

Nearly all patients in the region who require elective or emergency gastrointestinal operations are treated in one of the four general surgical units in Aberdeen: a few are treated in the district hospital in Elgin or in the two nursing homes in Aberdeen. The results reflect the outcome of standard surgical treatment in a combined teaching and district general hospital.

### Materials and methods

All instances in which carcinoma of the colon or rectum was diagnosed for the first time in patients living in the landward area of the then North-eastern Regional Hospital Board during 1968 and 1969 were included. Sources of information used were (1) the Central Diagnostic Index of the Aberdeen Hospitals; (2) reports of all necropsies performed in Aberdeen; (3) biopsy or operation reports prepared in the university's department of pathology, which provides a morbid histology service for the whole region; (4) the North-east Regional Malignant Disease Register; (5) registrars of births, deaths, and marriages; and (6) all reports of a radiological examination that identified a carcinoma of large bowel.

In every case identified the notes were scrutinised by one of us, and for patients who did not have a resection the diagnosis of colorectal carcinoma was accepted only when there was clear-cut biopsy, radiological, or postmortem confirmation. For every patient we obtained some follow-up data over seven years or until death intervened. This information was obtained from the hospital case notes, the records of registrars of deaths, direct inquiries to patients, and, most valuably and consistently, by written and spoken communication with the family doctor.

The term right colon includes caecum and ascending and transverse colon, and left colon includes splenic flexure and descending and sigmoid colon. Carcinoma of the rectosigmoid junction was classified as rectal carcinoma. Squamous carcinoma of the anal canal was excluded from the survey.

For patients who had a resection we judged whether the surgeon believed that a radical resection had been performed: patients so classified are referred to as the "radical-treatment" group. During 1968-9 very little use was made of chemotherapy or radiotherapy for colorectal cancer in Aberdeen.

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**Results**

**SEX AND AGE OF PATIENTS AND SITE OF TUMOUR**

Out of 264 patients with carcinoma of the colon, 157 (59%) were women. Of the 169 cases of rectal carcinoma, however, only 85 (50%) were women. Table I groups the 433 patients according to age, sex, and site of tumour. A total of 289 patients (67%) were at least 65 years old, and 129 (30%) were 75 years or older. Carcinoma of the rectum showed the greatest prevalence in patients aged 65-74 years. The mean age at presentation was  $68.1 \pm SD 12.0$  years. Age did not differ significantly between patients undergoing radical and non-radical treatment, except that women given radical treatment for rectal cancer had a mean age of 64.3 years:  $p < 0.03$ . Table II shows the sites of all tumours.

TABLE I—Distribution of patients according to age, sex, and site of tumour.

Age group (years)	Men		Women		Total
	Colon	Rectum	Colon	Rectum	
≤54	12	6	21	10	49
55-64	22	17	31	25	95
65-74	42	41	50	27	160
≥75	31	20	55	23	129
Total	107	84	157	85	433

TABLE II—Sites of carcinoma in the 433 patients (percentages given in parentheses)

	No of patients studied	Right colon			Left colon			Rectum
		Caecum + ascending colon	Hepatic flexure	Transverse colon	Splenic flexure	Descending colon	Sigmoid colon	
Men	191	36 (19)	6 (3)	12 (6)	10 (5)	9 (5)	34 (18)	84 (44)
Women	242	66 (27)	7 (3)	23 (10)	8 (3)	5 (2)	48 (20)	85 (35)
Total	433	102 (24)	13 (3)	35 (8)	18 (4)	14 (3)	82 (19)	169 (39)

**INCIDENCE**

In the Grampian region during 1968-9, 433 patients had colorectal cancer diagnosed for the first time. The estimated population of the region was 441 100, so the yearly overall incidence of colorectal carcinoma was 49/100 000. Table III gives the incidence rates by age, sex, and site of tumour.

TABLE III—Incidence rates (per 100 000 population) of colonic and rectal carcinoma at various ages in Grampian region (estimated population 441 100)

Age group (years)	Colon		Rectum	
	Men (n=107)	Women (n=157)	Men (n=84)	Women (n=85)
25-34	2	6	2	0
35-44	6	11	2	6
45-54	17	22	6	13
55-64	46	56	38	45
65-74	124	110	124	58
≥75	223	188	139	80
All ages	25	34	20	18

Overall incidence 49/100 000.

**TREATMENT AND OUTCOME OF OPERATION**

Forty-eight of the 433 patients (11%) had no operation: of these, 38 were unfit for laparotomy and in 10 the diagnosis was made only at necropsy. The remaining 385 (89%) came to laparotomy (table IV; fig 1), but only 215 (50% of all cases) were at operation considered to be potentially curable by resection, and these constitute the radical-treatment group. Of the 101 patients treated by palliative resection, almost all had palpable hepatic metastases.

Of the 88 patients having a radical operation for rectal carcinoma, 48 had an abdominoperineal resection and 40 an anterior resection.

Perioperative mortality (deaths within one month after operation) accounted for 66 (17%) of all operated patients and 20 (9%) of the radical-treatment group. The high mortality after radical resection

was due largely to deaths in men with colonic cancer, one of whom died from anastomotic leakage, one from adhesive intestinal obstruction, and seven from cardiorespiratory complications.

**PALLIATIVE-TREATMENT GROUP**

As might be expected, only 26 (12%) of the 218 patients who did not receive radical treatment survived for more than one year after presentation, and only 7 (3%) were alive after two years. Four patients lived more than six years, one then dying from metastases from a carcinoma of the caecum. The three patients who lived more than seven years must have been wrongly classified: two men had adherent rectal tumours, thought to be incompletely removed, but the adhesions were presumably fibrotic; the third patient had a palpable nodule in the liver, but it was not subjected to biopsy.

**RADICAL-TREATMENT GROUP**

Although only half the patients received radical treatment, the much better outlook for this group (table V) warrants more-detailed examination.

Crude long-term survival rates in elderly populations only poorly indicate the effects of a disease or its treatment because they ignore the cause of death. In all age groups considered here men in the

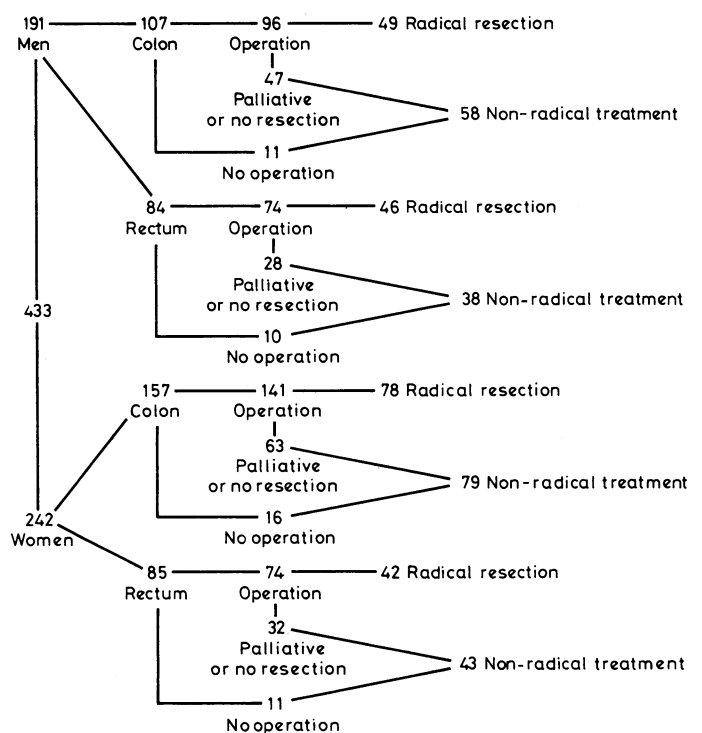


FIG 1—Flow diagram showing treatment and potential curability of all patients in study.

UK have a shorter life expectation than do women—that is, age-specific death rates are higher for men. It might therefore be thought that the poorer survival of men undergoing radical operations for carcinoma of the rectum (table V) was due to their greater age-specific death rate (particularly as they were older than the women in this group). This difficulty, however, can be overcome by comparing the actual longevity of the four groups of patients undergoing radical operations with the age-adjusted and sex-adjusted life expectation of the general Scottish population as derived from the Registrar General's (Scotland) life tables, which are based on census and mortality returns. Comparing the actual survival of each of the four radical-treatment groups with the life expectation of their age-adjusted and sex-adjusted peers in the general population gives a more meaningful "corrected" survival rate (table VI). Because the Registrar General's life tables cannot give adequate data for survival beyond 85 years our tables exclude follow-up data obtained after that age. Figure 2 and table VI show that the poor prognosis of men with carcinoma of the rectum remained after this age and sex correction: it was clearly

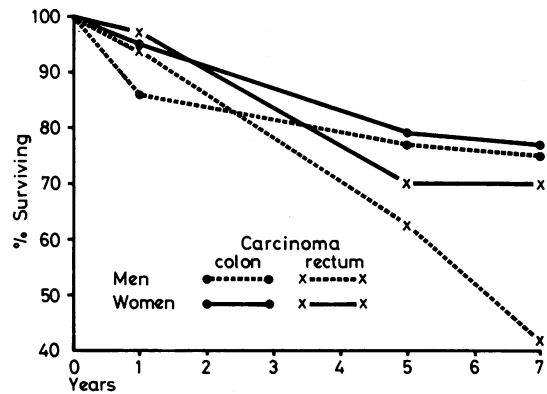


FIG 2—Survival rates, corrected for age and sex, of all radically treated patients.

TABLE IV—Operability and resectability of colonic and rectal carcinoma, and perioperative mortality (percentages given in parentheses)

Site of cancer	No of patients	Laparotomy				Perioperative mortality	
		No resection	Palliative resection	Radical resection	Total	Total	Radical resection
Colon { Men	107	19 (18)	28 (26)	49 (46)	96 (90)	29 (30)	9 (18)
Colon { Women	157	22 (14)	41 (27)	78 (50)	141 (90)	14 (10)	5 (6)
Rectum { Men	84	16 (19)	12 (14)	46 (55)	74 (88)	12 (16)	4 (9)
Rectum { Women	85	12 (14)	20 (24)	42 (49)	74 (87)	11 (15)	2 (5)
Total	433	69 (16)	101 (23)	215 (50)	385 (89)	66 (17)	20 (9)

TABLE V—Outcome seven years after radical resection

Site of cancer	No of patients	Deaths				Survivors
		Perioperative	Metastatic	Other causes	Total	
Colon { Men	49	9	5	9	23	26
Colon { Women	78	5	17	12	34	44
Rectum { Men	46	4	14	15	33	13
Rectum { Women	42	2	13	2	17	25
Total	215	20	49	38	107	108

TABLE VI—Corrected life expectancy five and seven years after radical resection (excludes 14 patients aged over 85)

Site of cancer	No of patients	At 5 years			At 7 years		
		Observed alive	Expected alive	Corrected percentage expectation of living	Observed alive	Expected alive	Corrected percentage expectation of living
Colon { Men	46	28	36.6	77	25	33.4	75
Colon { Women	70	47	59.6	79	43	55.6	77
Rectum { Men	45	21	34.0	62	13	31.2	42
Rectum { Women	40	25	36.0	70	24	34.4	70

evident at five years and continued to deteriorate to seven years, although the other three groups stabilised at five years.

None of the 108 patients who survived for seven years showed evidence of metastasis, save for two who died shortly after completing their seventh year.

Delay in diagnosis had no detrimental effect on outcome: those whose diagnosis was made over six months after the onset of symptoms survived marginally longer than those seen within six months. This was true for both rectal and colonic tumours.

**Discussion**

Our results provide firm evidence that colorectal cancer is unduly common in north-east Scotland. When the incidence rates are compared with those recorded during 1963-6 in other parts of Great Britain (table VII) the rates in the Grampian area are the highest and come close to the very high incidence found in some North American States.<sup>1, 2</sup> The higher incidence

of carcinoma of the large bowel among women was confined to colonic tumours (table VII), especially those in the caecum (table II). The overall incidence of caecal tumours in our series was high. Many more rectal carcinomas arose in old men than in old women (table I).

The mean age at presentation was 68, and two-thirds of the patients were over 65 at diagnosis. Out of 18 patients diagnosed before they were 45, only six survived for over seven years, thus supporting the belief that young patients have a poor prognosis.<sup>3</sup>

Distressingly, at the time of diagnosis half the patients (218) were either dead (10 cases) or already incurable by present methods (table IV; fig 1). These included 38 who were unfit for any operation, 69 (16% of all patients in the series) whose tumours were irremovable, and 101 (23% of the whole series) who underwent palliative resection. These findings were closely similar to those in the Birmingham Region,<sup>4</sup> where of over 12 000 patients, 52% were incurable at the time of diagnosis and 22% inoperable.

The operability rate was high in both colonic (90%) and rectal cancer (88%), and the resectability rate averaged 73%. Relatively fewer men with rectal tumours had a resection, possibly because in the depths of the male pelvis several tumours appeared to be fixed and were believed to be inoperable: the two long-term "incurable" survivors show that these adhesions may be inflammatory, and surgeons should not be too easily deterred.<sup>5</sup>

Comparing our figures with those from other centres discloses considerable differences. Few regional surveys are comparable with ours, and those from Birmingham,<sup>4</sup> Malmö,<sup>6</sup> and Connecticut<sup>7</sup> are apparently the only ones based on a known population with a five-year follow-up. Table VIII gives as far as possible the results from these centres. Aberdeen and Malmö had the

We chose a seven-year follow-up period after noting long survival of a few patients with metastatic disease, and indeed two of our patients lived for seven years before dying in this way. Since we could not determine Duke's grading in each case we grouped patients according to whether they had received radical or non-radical treatment. This proved to have great significance. When a patient was regarded as potentially curable at the time of resection, then, irrespective of the pathological grading of the tumour and spread to lymph nodes, the probability of surviving seven years without recurrence was 75-77% of normal expectation when the tumour was in the colon, 70% when the patient was a woman with a rectal carcinoma, and 42% for a man with carcinoma of the rectum. Even though this last figure was due to intercurrent disease (table V), not recurrence

TABLE VII—Comparative incidence rates of colonic and rectal carcinoma/100 000 population during 1963-6.\* (All figures except those for Grampian region taken from UICC report<sup>1</sup>)

	Colon		Rectum			
	Men	Women	Men	Women	Men	Women
Grampian region	25.3	34.1	Grampian region	19.9	Grampian region	18.5
Liverpool	24.7	33.0	South-west England	19.8	South-west England	16.5
South-west England	22.8	32.0	Birmingham	19.5	Birmingham	15.0
Oxford	20.0	26.8	Sheffield	18.2	Oxford	13.7
Scotland†	19.0	25.0	Oxford	17.6	Sheffield	13.2
Birmingham	18.6	24.5	Liverpool	15.5	Liverpool	12.0
Sheffield	18.4	24.0	Scotland†	14.5	Scotland†	11.1

\* Figures for 1968-9 not published. Changes in incidence do not occur rapidly enough to invalidate comparison of figures assembled within a decade.<sup>13</sup>

† Includes Grampian region.

TABLE VIII—Outcome of colorectal cancer: summary of reports

	Total patients	% treated by operation	% treated by resection	% treated by radical resection	Operative mortality (%)		% survival 5 years after radical resection (corrected for age and sex)
					Overall	Radical resection	
Birmingham, England (1950-61) <sup>4</sup>	12 494	78		48			Colon 52, rectum 49
Connecticut, USA (1955-9) <sup>7</sup>	16 370		Colon 76, rectum 74	Colon 37, rectum 39			Colon 79: men 76, women 81; rectum 70: men 69, women 71;
Malmö, Sweden (1958-67) <sup>6</sup>	960	89	76	66		9.7	Colon 68, rectum 54
Aberdeen, Scotland (1968-9)	433	89	73	50	17	9	Colon: men 80, women 80; rectum: men 66, women 70
Leeds, England (1955-68) <sup>9</sup>	550	98	90	74	10.6	9.6	Rectum 56
St Mark's Hospital, London (1948-72) <sup>8</sup>	3 163	93	93	80		2.1	Rectum: men 68, women 76

same operability rate (89%), which exceeded that in the Birmingham region (78%). Malmö, Connecticut, and Aberdeen had similar resectability rates (73-76%), but the proportion of patients regarded as potentially curable varied from 37% in Connecticut to 66% in Malmö, Aberdeen and Birmingham showing figures of 50% and 48% respectively. We cannot explain these variations, but clearly in all centres too many patients presented too late.

The operative mortality rate in our series (17%) warrants detailed scrutiny. The perioperative mortality rate for palliative operations was 27% and for the potentially curative operations 9%. The average age of the 20 patients who died after radical resection was 74. All but one of these (who leaked from an anastomosis) had a "medical" cause of death, including myocardial infarction (four cases), pulmonary emboli (four), heart failure (four), and bronchopneumonia (two). The 46 deaths among the 170 patients who had a palliative operation reflects the very grave state of many of these patients. Eighteen of the 46 were fit only for a laparotomy because of advanced irremovable disease, and 15 had emergency operations for perforation of the colon or intestinal obstruction. Even in the radical group, in which we would certainly hope for a lower mortality rate, most deaths apparently occurred in elderly people who were already ill with other diseases. With modern prophylactic measures, however, we should be able to eliminate deaths from embolism.

or metastasis, the difference between the survival of men with rectal cancer and that in other groups was remarkable. Correction of the data for age and sex should provide full allowance for the ordinarily expected poorer male life expectancy. Indeed, this was apparently the case for men with colonic disease; but the unduly large number of deaths caused not by cancer but by intercurrent disease, and occurring especially between the fifth and seventh years, suggests a general deleterious effect arising from rectal carcinoma in men.

Comparing the five-year survival figures, corrected for age and sex, with those from other centres (table VIII) shows both similarities and differences. In the four regional surveys there is no explanation for the differences in operability and resectability and for the relatively low survival in the radical group at five years in the Birmingham region. Although the specialist centres at St Mark's Hospital, London,<sup>8</sup> and at Leeds<sup>9</sup> operated on far more patients and had a higher percentage of potentially curable patients, corrected survival in the radical group was similar to that in the regional surveys. The only feature common to all these reports was that men with carcinoma of the rectum fared less well than women, although there was no information whether this was due to intercurrent disease or to recurrent carcinoma.

The general picture of colorectal cancer in Britain appears to be as grave as when Slaney<sup>4</sup> reported on the Birmingham region in the 1950s. In only half our patients was a radical operation

with a view to cure possible. The results in this radical group, however, show the major part played by timely operation in colorectal cancer. Most deaths in this group were from liver metastases which were occult at the time of operation: hence adjuvant chemotherapy—possibly by postoperative portal-vein infusion<sup>10</sup>—may further improve the results of operation.

Can anything be done for the half who present with inoperable disease? The only action available at present is to achieve earlier diagnosis. That a long history before diagnosis does not adversely affect outcome only underlines the variability of malignancy between one patient and another. Knowing that a carcinoma is probably present for five years before it is clinically recognised<sup>11</sup> is a great stimulus to act on any suspicion of carcinoma and to initiate useful investigations. Some patients still report to the outpatient department only after they have complained for months of rectal bleeding or diarrhoea, and several of these have a palpable rectal tumour. Hospital doctors must remember the vital role of sigmoidoscopy in diagnosing rectal neoplasms just out of reach of the finger, the great importance of adenomas of the rectum or sigmoid,<sup>11</sup> and that single contrast barium enemas may be misleading (and even double contrast enemas be difficult to interpret) in the proximal colon.<sup>12</sup>

Although results may not have changed much in the past 20 years, it is important not to be fatalistic about the outcome of colorectal cancer, especially since timely operation can produce such useful long-term benefit.

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# Synergistic effects of a combined salbutamol-nitroprusside regimen in acute myocardial infarction and severe left ventricular failure

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## Summary and conclusions

The haemodynamic effects of a simultaneous infusion of salbutamol and nitroprusside were measured in 20 patients with acute myocardial infarction and severe left ventricular failure. Six patients also had clinical manifestations of cardiogenic shock. Ten patients received salbutamol first with the subsequent addition of nitroprusside; in the other 10 patients nitroprusside was infused first. Salbutamol was infused at a constant rate of 20 µg/min in all patients, while the dose of nitroprusside, which averaged 51.25 µg/min, was adjusted to reduce left ventricular filling pressure (measured as pulmonary artery end-diastolic pressure) to approximately 15 mm Hg with reference to sternal angle.

Cardiac index increased in all patients from a mean of 1.8 to 2.6 l/min/m<sup>2</sup> while pulmonary artery end-diastolic pressure fell significantly from 24 to 16 mm Hg. The adverse effects were small in most patients: heart rate

did not increase significantly and systolic arterial pressure fell on average from 112 to 96 mm Hg. Ten of the 20 patients survived to leave hospital.

Nitroprusside accounted for most of the fall in filling pressure irrespective of treatment sequence, whereas both drugs contributed to the augmented cardiac output. The haemodynamic benefits of this combined regimen were considerably greater than those achieved by either drug alone. Thus salbutamol and nitroprusside have synergistic effects which influence favourably the two principal manifestations of left ventricular dysfunction after extensive myocardial infarction.

## Introduction

Salbutamol is a relatively specific β<sub>2</sub>-adrenergic receptor agonist with important haemodynamic effects due principally to reduction in peripheral arteriolar tone.<sup>1</sup> The drug improves cardiac output in patients with severe left ventricular dysfunction after myocardial infarction but has little effect on left ventricular filling pressure.<sup>2</sup> Most patients with a critical haemodynamic state after infarction have both reduced output and pulmonary oedema with excessive filling pressure; salbutamol is therefore of limited value. Nitroprusside has been recommended because it reduces both arteriolar and venous tone and decreases filling

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