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Analysis of local recurrence rates after surgery alone for rectal cancer

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Abstract. Local recurrence (LR) continues to be a major problem following surgical treatment for rectal cancer, and proposed ways of reducing this remain controversial. The aim of this study was to review results from published surgical series in which adjuvant therapies were not used. A Medline search identified series published between January 1982 and December 1992 with follow-up on at least 50 patients with rectal cancer treated surgically for cure, without adjuvant therapy. Fifty one papers reported follow-up on 10,465 patients with a median LR rate of 18.5%. LR was 8.5%, 16.3% and 28.6% in Dukes' A, B and C patients respectively, 16.2% following anterior resection and 19.3% following abdominoperineal resection. Nine papers (1,176 patients) reported LR rates of 10% or less. LR was 7.1% in 1,033 patients having total mesorectal excision and 12.4% in 476 patients having extended pelvic lymphadenectomy. Routine cytocidal stump washout in 1,364 patients was associated with 12.2% LR, however a higher proportion (41%) also underwent total mesorectal excision. In 52% of cases, LR was reported to have occurred with no evidence of disseminated disease. Surgical technique is an important determinant of LR risk. LR rates of 10% or less can be achieved with surgery alone in expert hands.

Résumé. Les récidives locales (LR) représentent toujours un problème majeur après traitement chirurgical des cancers du rectum et les moyens de réduire cette incidence sont toujours sujets à controverse. Le but de cette étude est de faire une revue des résultats des séries publiées de traitement chirurgical sans traitement adjuvant. A l'aide de Medline les séries publiées entre janvier 1982 et décembre 1992 avec un follow-up portant sur au minimum 50 patients traités par une chirurgie curatrice sans traitement adjuvant ont été identifiés. Cinquante-et-un articles portant sur 10465 patients avec un taux de récidive locale moyen de 18.5% ont été publiés. Les récidives locales sont respectivement de 8,5% en case de Dukes A, 16,3% en cas de Dukes B, 28,6% en cas de Dukes C, 16,2% après résection antérieure basse et 19,3% après amputation abdomino-périnéale. Neuf articles (1176 patients) publient des récidives locales de moins de 10%. Le taux de récidive locale est de 7,1% chez 1033 patients ayant subi une excision totale du méso-rectum et de 12,4% chez 476 patients ayant subi une lymphadénectomie pelvienne étendue. Le lavage de routine du moignon rectal avec un cytostatique a été réalisé chez 1'364 patients avec un taux de récidive locale de 12,2% bien qu'une proportion élevée (41%) avait subi également une excision du méso-rectum. Dans 52% des cas, la récidive locale est observée alors même qu'il n'y a pas d'évidence d'une dissémination de la maladie. La technique chirurgicale est un facteur déterminant important dans la survenue d'une récidive locale. Des taux de récidive de 10% ou moins peuvent être obtenus avec la chirurgie seule réalisée par des mains expertes.

The trend towards preservation of the anal sphincter has improved the quality of life for patients with rectal cancer, but has not reduced the risk of local recurrence (LR) [1–4]. LR is more common in rectal than colonic cancer [5, 6], and reported rates vary widely, from 3 to 50% [7, 8]. Importantly, LR is seldom cured and produces debilitating symptoms which are difficult to palliate [9–12], and in some patients is the only site of treatment failure [10, 13].

Numerous approaches have been used in an attempt to reduce LR rates. These include complete excision of the mesorectum [14], pelvic lymph node dissection [15–19], rectal stump washout with cytocidal agents [20], pre- and postoperative adjuvant radiotherapy [9, 21–27], and adjuvant chemotherapy [28–30].

Quirke et al. demonstrated the importance of adequacy of rectal excision by showing that involvement of radial resection margins was highly predictive of LR [31]. Utilising the technique of total mesorectal excision (TME). Heald achieved a 10 year actuarial LR rate of 4% in 200

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consecutive patients undergoing curative anterior resection (AR) [32]. Extended pelvic lymphadenectomy (EPL), which incorporates en bloc removal of internal iliac lymph nodes, has also been reported to reduce LR [15, 16]. LR can be reduced by up to 40% with adjuvant radiotherapy [33], and further by combined radiotherapy and chemotherapy [29, 30]. However, LR rates in control groups of trials demonstrating improvements with adjuvant therapy have all exceeded 18% [34, 35]. Furthermore these treatments are expensive and have significant toxicity.

The question of whether surgery alone, without adjuvant therapy, can achieve acceptable LR rates remains controversial. In this study LR rates after surgery alone for rectal cancer have been examined by reviewing results of published series over a 10 year period.

Methods

Selection of papers

A Medline search was undertaken for papers published in English from January 1982 to December 1992 reporting the results of surgical treatment for rectal cancer. Papers reporting follow-up on at least 50 patients surviving rectal excision with curative intent were selected. Patients in adjuvant therapy trials randomised to surgery alone were included, as were retrospective and prospective series. Those patients surviving a curative operation, who were therefore at risk of developing LR, were selected from each paper. Papers were excluded if adjuvant therapy was used in more than 10% of cases, or if information regarding LR and treatment intent (curative vs palliative) was lacking or unclear. Where the same patients were represented in more than one paper, the most recent complete report was used.

Definitions

Curative surgery was defined as removal of all macroscopic disease at operation, whether histologically confirmed or not. Local recurrence was defined as recurrent tumour within the pelvis or perineum. Rectal cancer was defined according to distance from the anal verge on rigid sigmoidoscopy. Alternative definitions were re-categorised as follows; lower two thirds of the rectum and below the peritoneal reflection were defined as "within 12 cm", and below the sacral promontory and rectosigmoid as "within 20 cm".

Case mix was defined by the original Dukes' classification [36]. Patients staged by Modified Dukes', Astler-Coller, TNM, ACPS or Japanese Research Society systems were re-classified according to the matrix for staging system conversion established by the 1990 World Congress of Gastroenterology Working Party on Clinicopathological Staging [37]. The method (prospective vs retrospective) and length of follow-up were recorded. Average follow-up was defined as either mean or median follow-up, or the mid-point of a reported follow-up range.

Analysis

Data was extracted onto a standard proforma and entered into a computerised database. LR rates were determined for patients with Duke' A, B and C disease, and for patients undergoing abdominoperineal resection (APR) and AR. LR rates were also determined for patients undergoing TME and EPL when these techniques were specified in the paper. No attempt was made to collate survival data because of wide variations in reporting of survival figures [38].

Statistical analysis was descriptive rather than comparative because of the diverse nature of series included [39]. Data obtained by combining patients from different series has been prefixed as "pooled". Other data are described by median (range) values, and the Spearman's rank correlation (r_s) was used to test for association between follow-up time and LR.

Results

Overall LR

Fifty one papers were included in the study (Table 1), reporting data on 10,465 patients. The median LR rate for all series was 18.5% with a range of 3 to 50%. The pooled LR rate was 18.8%.

In 22 series both isolated LR (no evidence of disseminated disease) and total LR rates were reported. Pooled LR for these 3,838 patients was 11.3% and 21.5% for isolated and total LR respectively. Thus 52% of these patients with LR had no evidence of disseminated disease.

Tumour stage and definition

Dukes stage was determined for 7,544 patients of whom Dukes' A, B and C cancers comprised 25%, 40%, and 35% respectively. LR according to Dukes' stage was determined for 6,158 patients. Pooled LR rates increased with increasing stage of disease (Fig. 1). For rectal cancer defined as a lesion lying within 12 cm (1,156 patients), 16 cm (1,225 patients) and 20 cm (4,385 patients) of the anal verge, the pooled LR rates were 18%, 16.9% and 18.3% respectively. When rectal cancer was not defined (3,699 patients), the pooled LR rate was 20%.

Surgical procedure and technique

Specific information regarding surgical procedure (AR vs APR) was available on 6,188 patients. The pooled LR rate for 3,577 patients (derived from 30 papers) who underwent AR was 16.2%, and for 2,601 patients (dervied from 24 papers) who underwent APR was 19.3%.

Nine series reported total LR rates of 10% or less (Table 1). Of the 1,176 patients involved, 695 underwent TME and 64 had EPL while surgical technique was not specified for the remaining 417 patients. The case mix, according to Dukes' stage, for series with LR of 10% or less was similar to the case mix for all series combined (Fig. 2).

Of the 10,465 patients, 1,033 had TME (8 papers) and 476 underwent EPL (4 papers). Two papers reported separate series of patients undergoing EPL and conventional surgery [15, 19]. The pooled LR rates for TME and EPL were 7.1% and 12.4% respectively. The case-mix, according to Dukes' stage, for patients undergoing TME was not different from the combined data from all series, whereas patients undergoing EPL tended to have slightly more advanced disease (Fig. 2).

Table 1. List of papers included in the study

Ist Author	Year	Reference	Number patients	LR rate (%)	Surgical technique
Adloff	1984	69	113	32	NS
Amato	1991	65	147	11	EPL
Athlin	1988	70	99	37	NS
Balslev	1986 (controls)	9	247	18	NS
Belli	1988	51	72	4	TME
Braun	1992	86	119	14	NS
Carlsson	1987	87			
	Series I		100	24	NS
	Series II		231	38	NS
Cawthorn	1990	52	122	7	TME
Colombo	1987	53	89	11	TME
Dahl	1990 (controls)	21	128	21	NS "minimal touch"
Danzi	1986	88	83	10	NS
Dixon	1991	54	227	4	TME
Domergue	1989	89	58	25	NS
Feil	1988	80	90	20	NS
Fick	1990	90	58	14	NS
Fisher NSABP R-01	1988 (controls)	28	184	25	NS
Gerard (EORTC)	1988 (controls)	23	175	28	NS (early IMA ligation)
Gillen	1986	91	66	20	NS
GITSG	1985 (controls)	29	58	24	NS
Glass	1985	18	73	14	EPL
Heimann	1986	92	320	16	NS
Hojo	1989	15			
	Extended		192	14	EPL
	Standard		245	19	NS
Jatzko	1992	55	249	13	TME, 'no touch'
Karanjia	1990	7	152	3	TME
Kennedy	1985	93	90	24	NS
Kirwan	1989	3	67	4	TME
Lasson	1984	75	102	16	NS
Leff	1985	78	128	14	NS
Localio	1983	94	360	13	NS
Malmberg	1986	95	83	19	NS
McDermott	1985	68	934	20	NS
Michelassi	1988	19	83	16	NS
			64	9	EPL
Moran	1992	56	55	7	TME
Neville	1987	96	373	19	NS
Nilsson	1984	8	68	50	NS
Pahlman	1984	97	197	38	NS
Pheils	1983	98	193	10[a]	NS
Phillips	1984	99	848	15	NS
Pollett	1983	2	334	7	NS
Reed	1988	100	78	31	NS
Rich	1983	101	142	30	NS
Rosen	1985	76	119	23	NS
Rubbini	1990	102	183	24	NS
Secco	1989	71	90	22	NS
Stockholm	1987 (controls)	25	274	20	NS
Sweeney	1989	103	84	18	NS
Theile	1982	72	210	12	NS
Tonak	1982	104	224	23	NS
Treurniet-Donker	1991 (controls)	26	84	33	NS
Williams	1985	105	148	17	NS
Zirngibl	1990	64	1153	23	NS

[a] Isolated LR only
NS = not specified; EPL = extended pelvic lymphadenectomy; TME = total mesorectal excision

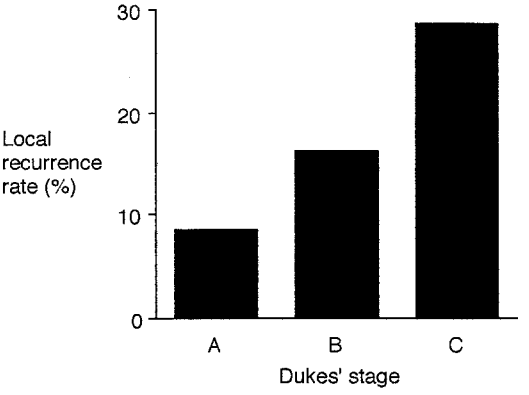

Fig. 1. LR rates according to Dukes' stage. Pooled data on 6,158 patients

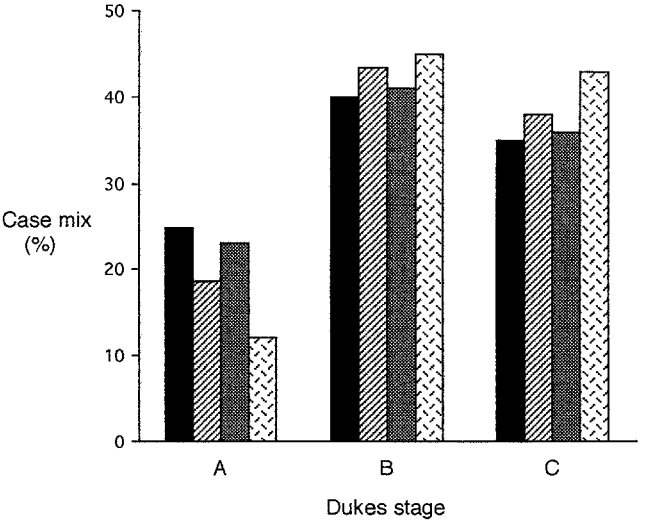

Fig. 2. Case mix, defined by Dukes' stage. Pooled data for all series combined, nine series with LR rate of 10% or less, eight series of TME, and 4 series of EPL. ■ All series; ▩ TME; ▨ <10% LR; ⊡ EPL

Follow-up

Fifteen papers reported prospective follow-up with median (range) LR of 20 (3–38%), 26 papers reported retrospective follow-up with 17.5 (4–38)% LR, and no information

was given regarding the nature of follow-up in 10 papers with 19.5 (4–50)% LR.

The median average duration of follow-up for the 51 series was 60 (range 24–256) months and minimum follow-up was 24 (6–216) months. For the nine series with LR of 10% or less, average follow-up was 68 (32–156) month and minimum follow-up 24 (12–60 month). The eight TME series had a shorter average follow-up time of 45 (32–78) months and minimum follow-up of 24 (6–72) months. The correlation between minimum ($r_s = 0.25$; $P = 0.09$) and average ($r_s = 0.2$; $P = 0.25$ respectively) follow-up times and LR rate were not statistically significant.

Cytocidal washout

Rectal stump washout with a cytocidal agent (water, providine-iodine, cetrimide or mercuric perchloride) was undertaken routinely in 10 series, involving 1,364 patients, with a pooled LR rate of 12.2%. Forty one percent of these patients also underwent TME and 11% had EPL. When separated according to TME, EPL, or other, the pooled LR rates for patients having cytocidal washout were only 1 to 2% less than pooled LR for the groups as a whole.

Discussion

The aim of this study was to review LR rates after surgery, without adjuvant therapy, in the treatment of rectal cancer. Widely ranging LR rates have been published reflecting, in part, the effect of surgeon-related variance on outcome [40–42]. Surgeon-related variance may exceed the influence of specific interventions such as adjuvant therapy [43] which calls into question the relevance of some clinical trials in which control patients appear to have suffered unacceptably high LR rates [40]. On the other hand there have been very few randomised trials assessing oncological aspects of surgical technique in colorectal cancer [44] and a number of important questions remain unanserwed. In the absence of hard scientific information concensus may be obtained by literature review, however reviews are inevidably open to selection and interpretation bias [45]. In the present study we have attempted to minimise these biases by standardising both the selection criteria and the way in which selected papers were analysed.

It is acknowledged that the scientific validity of this approach is limited by the nature of the material it has to draw upon [39, 46] and that the results need to be interpreted cautiously [45, 47]. The series reporting LR of 10% or less, and those of TME and EPL, come mainly from specialist colorectal units whereas the remainder arose from a mixture of specialist units, non-specialist units, multinstitutional and regional studies which would be expected to give rise to much greater surgeon-related variance [40–42]. The data has therefore been carefully summarised and presented in descriptive form only. No attempt was made to use comparative statistical analysis which would be inappropriate for such a diverse aggregate of studies [39, 46, 47]. Despite this the data clearly demonstrates that a number of surgeons have been able to achieve good results, in terms of LR rates, with surgery alone.

"Curative" surgery is usually defined macroscopically, by the surgeon at the time of operation, even though this underestimates the incidence of histologically positive margins in rectal cancer by 50% [31]. One would expect a better outcome after histologically defined, rather than macroscopically defined, curative surgery. This introduces a potential source of bias which might explain lower LR rates in some series. However in carefully reviewing the nine papers in which LR rates of 10% or less were reported, six defined curative surgery macroscopically [2, 3, 7, 51, 52, 54], three did not define it [18, 56, 88] and none defined curative surgery microscopically.

Disease stage is strongly associated with LR risk (Fig. 1). The present study found no differences in case mix between patients treated in series with LR of 10% or less compared with the case mix of all series combined. Those treated with TME also had a similar case mix whereas patients treated with EPL had more advanced disease (Fig. 2). The results of TME, in particular, have sometimes been attributed to case mix or selection bias [48, 49] but we found no evidence of this.

The hypothesis that LR may be prevented by careful dissection encompassing the fascial planes confining the rectum and surrounding mesentery [14] is consistent with the view that LR usually reflects incomplete removal of tumour [10, 11, 31, 35, 50]. Pooled LR in the TME group, derived from eight different series [3, 7, 51–56], was 7.1%. TME may reduce the risk of leaving behind microscopic deposits, especially discontinuous spread [14, 31, 57], insuring against the tendency to "cone down" on the mesorectum when approaching the rectal wall below the tumour [58]. Careful sharp dissection around the mesorectum, rather than blunt extraction, also offers the potential benefits of reduced transfusion requirements [59, 60], preservation of autonomic nerves [61], and avoidance of inadvertent tumour perforation [62–64]. The safety of TME is supported by a median 30 day mortality in the 8 TME series of 2.5% (range 1.6% to 5.4%) [3, 7, 51–56].

EPL was associated with LR of 12.4% despite a higher proportion of Dukes' B and C patients [15, 18, 19, 65]. EPL should incorporate en bloc excision of the mesorectum [66]. The value of adding an aorto-iliac lymph node dissection remains unproven, yet risks damage to the presacral nerves and inferior pelvic plexus, resulting in a higher incidence of urogenital dysfunction [15, 17]. Whether or not this added morbidity is justified in the routine treatment of rectal cancer can really only be established by undertaking a prospective randomised trial [66].

Surgical wounds are a fertile medium for exfoliated tumour cells [20, 67]. Irrigating the rectal stump with a cytocidal washout solution may prevent implantation [20] although this hypothesis has not been formally tested in man. The pooled LR rate for those series in which it was stated that cytocidal washout was used routinely was 12.2%. However, when separated according to surgical technique. LR rates were only marginally less with routine cytocidal use, in keeping with the fact that true anastomotic recurrences make up a minority of all LR [11, 68]. Like EPL, the value of cytocidal could be evaluated by randomised clinical trial, although if the true benefit were small, a very large study would be required to prove it.

Prospective studies reported only slightly higher LR rates than retrospective studies, perhaps because LR usually gives rise to symptoms and is not easily confused with other conditions. There was also no significant correlation between follow-up time and LR rate because most, but by no means all, LR are evident within two years [35] and the vast majority of series had follow-up times well in excess of that. The lowest LR rate for rectal cancer reported anywhere to date was from an independently audited prospective series with a median follow-up of more than 7 years [32].

LR rate was slightly higher after APR than AR and this may reflect a higher risk of LR with low-lying lesions [19, 68–72]. Other factors, such as stapled versus hand-sewn anastomoses [73–78], distal resection margin [2, 7, 79], and tumour differentiation [19, 69, 80] were not specifically addressed by this study.

It is important to recognise the difference between the distal mural resection margin and the radial (or "lateral") resection margin. With the exception of locally advanced or poorly differentiated tumours, malignant cells are rarely found in the bowel wall for more than a centimetre or so beyond the distal end of the tumour [2, 7, 79]. Microscopically involved radial resection margins, on the other hand, frequently exhibit discontinuous spread [14, 31, 57] and are highly predictive of LR in patients undergoing conventional surgery [31]. Furthermore disease within the mesorectum may not be apparent to the surgeon [31]. The adequacy of the distal resection margin is therefore not the same for the bowel wall and the mesorectum. After TME positive radial margins occurr less frequently and, when they do, are more predictive of systemic than local recurrence [52]. Radial margins are clearly of major prognostic importance [31, 52] and should aid in the selection of patients most likely to benefit from adjuvant therapy [82]. The pathological methods for detailed examination of radial resection margins have been well described [31, 52, 83], are applicable in the clinical setting [84], and should be routinely performed.

The wide range of LR rates with surgery alone indicate that rectal cancer should be treated by surgeons with a special interest and training in the management of this disease. In expert hands LR rates of 10% or less can be achieved with surgery alone. Post-operative adjuvant chemo-radiotherapy carries a 2% mortality [30], and has a detrimental effect on long term bowel function [85]. Such treatment may be best reserved for patients with inadequately excised tumours, as judged clinically and pathologically, rather than all tumours penetrating beyond the bowel wall.

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