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Pathology of Rectal Adenocarcinoma following Preoperative Adjuvant Radiotherapy and Chemotherapy

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SUMMARY

The study group comprised 13 patients (mean age 68 years) with clinically fixed and biopsy proven moderately differentiated rectal adenocarcinoma (8 high rectal, 5 low-mid rectal) who received synchronous courses of preoperative combination chemotherapy and pelvic radiotherapy (radiotherapy alone in 3 cases) over a period of 8-20 weeks prior to surgical resection. All cases showed varying degrees of mural and mesorectal fibrosis. Three cases did not differ otherwise from usual rectal adenocarcinoma while 4 had a 20-30% diminution in expected tumour area. In 6 cases tumour could not be definitely identified grossly – 1 showed a 50% reduction in tumour bulk while 5 had only residual microscopic foci from 0.6 - 4 mm in maximum dimensions. Only 3 cases had involvement of the mesorectal circumferential radial margin. Four involved lymph nodes in 2 cases were partially hyalinised and calcified. Preoperative combination adjuvant therapy can produce marked regressive morphological changes in rectal adenocarcinoma. The implications of this are discussed.

INTRODUCTION

Early work by Papillon[1] illustrated the preservative and curative potential of locally applied irradiation in the treatment of limited cancers of the rectum and anus. Stevens *et al*[2] reported that preoperative radiotherapy decreased local pelvic recurrence and increased 5 year survival in 97 patients with recto-sigmoid adenocarcinoma. Of these the tumour field was sterilised in nine cases and there were only residual microscopic foci in another three. Others have noted preoperative radiotherapy to give decreased local recurrence rates[3,7] (although this is not universally accepted[8]), increased 5 year survival,[13,7] improved resectability[5,6,9] and facilitation of local excision in medically unfit patients.[10] Regression of disease in involved lymph nodes producing "down staging" has also been reported.[3,4,7] It appears that radiotherapy is more effective when combined with chemotherapy[6,11] although there is some debate as to whether preoperative or post operative treatment is better.[6] These potential benefits are presumably as a result of regression in the tumour tissue induced by the adjuvant therapy. Morphological aspects of this are described in this paper.

METHODS

The 13 patients (9 male) aged between 48 and 84 years (mean 68) had biopsy proven rectal adenocarcinoma (8 high rectum, 5 low-mid rectum) and clinically fixed, tethered lesions (2 had evidence of liver metastases). In all cases potential for curative surgical resection was considered clinically to be either borderline or not possible. After diagnosis they received pelvic radiotherapy comprising 40 Gray in 20 fractions over a period of 4 weeks. Three patients were unfit for chemotherapy with one having had a recent myocardial infarct. Three received concomitant chemotherapy comprising folinic acid with 5-Fluorouracil as a bolus and infusion

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over 48 hours[12] as 2-3 cycles at 2 week intervals. The remaining patients had a 5 day infusion of 5-Fluorouracil (1 gm/m^2) during the first 5 days of radiotherapy. All proceeded to operative resection at 18-20 weeks after starting radiotherapy. The resection specimens were opened, immersed in 10% formalin and fixed for 48 hours. Serial transverse sections of the tumour, bowel wall and mesorectum were obtained according to Quirke *et al*[13] and any mesenteric lymph nodes sampled (mean of 8 per case). The sections were stained with haematoxylin and eosin for microscopy and tumour graded as well, moderately or poorly differentiated. Two dimensional measurements of the tumour and distances to the mesorectal circumferential radial margin and serosa were assessed grossly and verified using the microscope stage Vernier scale. An approximate estimate of the percentage of residual tumour was determined from the gross and histological measurements; these were assessed in combination with the amount of replacement fibrosis and/or granulation tissue seen along the expected tumour front which was extrapolated between residual tumour foci. Information on pre-treatment tumour dimensions for comparison against actual residual tumour size was not available. A Dukes' stage was derived from the depth of invasion and the lymph node status.

RESULTS

On biopsy and resection specimens the tumours were all moderately differentiated rectal adenocarcinoma, not otherwise specified. They did not show any de-differentiation in the resection specimens and were ulcerated on gross inspection. The maximum histological dimensions ranged from 0.6 mm to 50 mm and distances to the mesorectal circumferential radial margin 0 mm to 25 mm (Table). All showed evidence of mural and mesorectal fibrous reaction and in 3 cases (2 received no concurrent chemotherapy) the tumour did not differ otherwise from usual adenocarcinoma. In cases 1- 4, 7 and 13 tumour could not be confidently identified on gross examination - histology in 5 of these cases showed an ulcer base of thickened, inflamed fibromuscular connective tissue with a partially re-epithelialised surface (Figure 1). This was due to therapy induced regression in the tumour tissue: case 3 showed an approximate 50% reduction in tumour bulk while in cases 1, 2, 4, 7 and 13 carcinoma was only identifiable microscopically (maximum dimensions 0.6 - 4 mm). Residual foci were seen in various layers of the bowel wall from the submucosa to the mesorectum associated with chronic inflammation, fibrosis, tumour necrosis and calcification (Figure 2). There were also foci

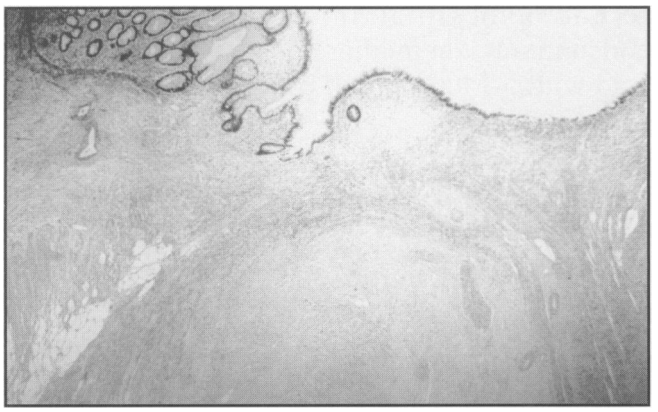

Fig 1. An ulcer base of thickened, inflamed fibromuscular connective tissue and a re-epithelialised surface. No residual tumour.

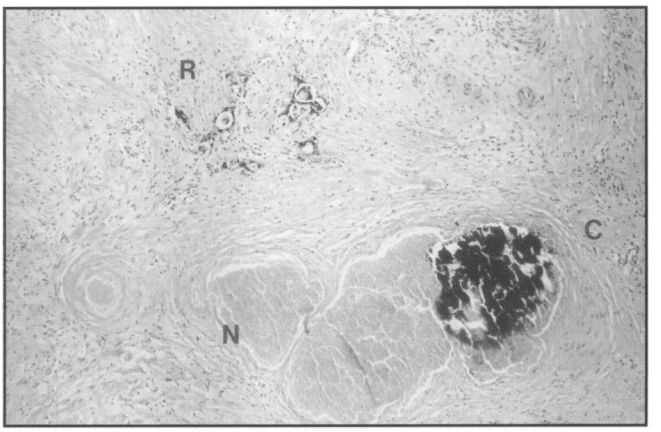

Fig 2. Case 1 Mesorectal reaction with residual microscopic carcinoma (R), tumour necrosis (N) and dystrophic calcification (C).

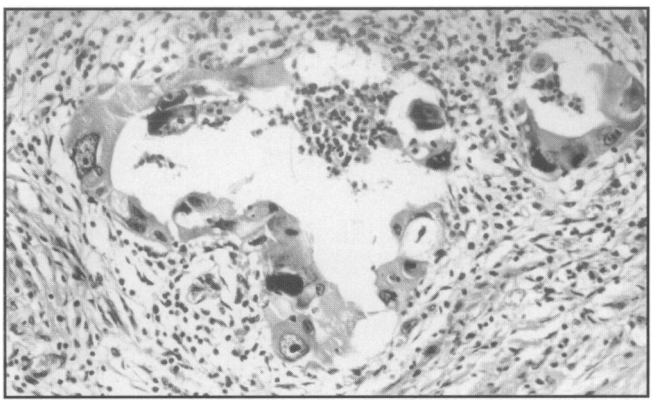

Fig 3. Residual submucosa tumour foci. The tumour cells show bizarre nucleoli– and nucleomegalic degenerative radiotherapy type changes, necrosis and apoptosis.

of partially degenerate tumour acini encased in an inflammatory and fibrous reaction with constituent epithelium showing bizarre nucleolo – and nucleomegalic degenerative radiotherapy type changes, necrosis and apoptosis (Figure 3). In addition 2 cases showed hyalinisation and calcification in 4 involved lymph nodes. Carcinoma involved (to within 1 mm) the mesorectal circumferential radial margin of resection in 3 cases.

The bowel adjacent to the tumours showed variable degrees of low grade mucosal chronic inflammation – presumably radiotherapy related. Some of the mesorectal vessels were also thickened.

TABLE

Rectal Adenocarcinoma receiving preoperative adjuvant therapy

Case	*Gross (mm)*	*Tumour Histology*		*Stage*	*Comment*
		Maximum Dimension (mm)	*Distance (mm) from serosa (s), deep Radial Limit (l)*		
1	Ulcer 13 x 10	0.6	1 (s) 15 (l)	C_1	Tumour necrosis/calcification
2	Ulcer 30 x 30	4	2 (s) 20 (l)	D	Tumour gland atypia. Regressive changes in 2 involved nodes
3	Ulcer 30 x 15	14	9 (l)	C_1	50% tumour viable. Regressive changes in 2 involved nodes
4	Ulcer 30 x 30	4	1 (s) 6 (l)	B	Healing ulcer
5	Ulcer 45 x 40	45	1 (l)	C_1	Tumour viable
6	Ulcer 50 x 30	50	5 (s) 25(1)	B	Tumour viable
7	Ulcer 40 x 30	1	8 (s) 10 (l)	B	2 microscopic (1 mm) foci at muscular/mes orectum junction
8	Ulcer 32 x 32	32	0 (l)	C_2	Tumour viable
9	Ulcer 37 x 30	27	2 (s) 0 (l)	B	70-80% tumour viable
10	Ulcer 40 x 35	33	4 (s) 7 (l)	B	70-75% tumour viable
11	Ulcer 40 x 30	25	15 (l)	A	60-70% tumour viable
12	Ulcer 40 x 40	35	5 (s) 15 (l)	D	80-90% tumour viable
13	Ulcer 8 x 8	2	3 (l)	C_2	2 microscopic (< 1 mm) foci at mucosa and mesorectum

NOTE: Dukes' Stage

A = tumour confined to the wall
B = tumour through the wall
C_1 = tumour in regional lymph nodes
C_2 = tumour in the regional suture tie limit node

DISCUSSION

This study demonstrates that preoperative combination adjuvant therapy can potentially produce marked morphological changes of regression in the bowel wall involved by rectal adenocarcinoma. Presumably this is the basis for the suggestion that it results in improved 5 year survival and decreased local recurrence rates[2-7, 11] and is therefore, currently, the subject of large, standardised international trials. Tumour regression has been previously described in rectal adenocarcinoma receiving either preoperative radiotherapy alone[2, 4] or in combination with chemotherapy.[9] These authors noted significant changes in the majority of lesions with total or sub-total regression in a minority. The effects were more noticeable in Dukes A/B tumours but particularly if they were exophytic, mobile and well to moderately differentiated[4] where a flat, well demarcated ulcer with a re-epithelialised surface resulted.[9] The extent of residual tumour could not be assessed by endoluminal ultra-sound or gross examination but only by microscopy which showed viable, degenerate and necrotic tumour associated with mucin pools. Adjuvant therapy did not induce any de-differentiation in the tumour and preoperative biopsy histology could not reliably predict which tumours would respond to treatment or give an accurate determination of stage of disease.[9] Two issues of practical importance have tentatively emerged. Firstly, Marks *et al*[10] suggested that tumour response to preoperative radiotherapy could facilitate full thickness disc or hemi-circumferential local excision in select patients who were either not medically fit for radical surgery, or, where radical surgery offered limited benefits but for whom sphincter preservation was important. Thirteen of 14 patients retained good sphincteric control and had three year actuarial local recurrence and survival rates of 23% and 61% respectively. Similarly, others have noted the benefit of sphincter preservation[5, 6] and improved local resectability.[5, 6, 9] The most important indicator of local recurrence and prognosis is involvement of the mesorectal circumferential radial margin of resection[13] and improved clearance can be obtained by meticulous surgical technique with excision of an intact mesorectum.[14] However Schaldenbrand *et al*[9] also noted preoperative combination therapy to improve resectability in 4 out of 13 clinically fixed and tethered lesions. Furthermore 4 out of 6 cancers not resected for cure had no viable residual tumour in the marginal mesorectal fibrosis – it is of note that only 3 of our clinically fixed cases involved the circumferential radial resection margin. Secondly, adjuvant therapy diminishes the size and harvest of normal mesorectal lymph nodes but, as in breast cancer,[15] can also induce regression in those involved by tumour.[4, 9] In the present study 2 cases had 4 involved nodes which showed partial hyalinisation and calcification. Horn *et al*[4] noted "down staging" of disease with lymph node involvement in 18.4% of irradiated cases versus 27.5% of controls. Overall prognosis was not changed but they postulated a potential role for preoperative treatment in transferring node positive patients to a better prognostic category. Others have also reported a decreased incidence of involved nodes.[3, 7]

Preoperative combination adjuvant therapy can induce marked morphological regression of rectal adenocarcinoma and possibly even involved lymph nodes in some patients. This has obvious implications for the pathologist in surgical reporting. Surgeons submitting these specimens should inform the pathologist about preoperative adjuvant therapy. It may also facilitate improved local surgical resection – the biological significance of so-called "down staging" requires more extensive study. Further investigations should also address why there is a spectrum of complete, partial and non-response of rectal carcinoma to neo-adjuvant therapy.

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