Rectal cancer after pelvic irradiation

M D Levitt FRACS **D M Millar** FRCS **J O Stewart** FRCPath *Departments of Surgery and Pathology, Colchester General Hospital, Colchester, Essex CO4 5JL*

Keywords: rectal cancer; pelvic irradiation; histopathology

Summary

During a 6 month period in 1988 five women were treated at Colchester General Hospital for carcinoma of the rectum, each more than 10 years after undergoing pelvic irradiation. Although irradiation has not been proven to induce human colorectal cancer, considerable circumstantial and experimental evidence supports this belief. Features suggestive of radiation-induced colorectal cancer are the presence of radiation-damaged bowel adjacent to the carcinoma and a mucus-secreting ('colloid') histological pattern.

The increasing number of women being exposed to rectal irradiation in the course of treatment of gynaecological malignancy may result in an increase in the incidence of radiation-induced rectal cancer. Awareness of this potential long-term complication is important when planning follow-up of patients subjected to pelvic radiotherapy.

Introduction

Although colorectal carcinoma following abdominal and pelvic radiotherapy is well documented, a direct cause-effect relationship has not been proven. During a period of 6 months in 1988, five women underwent resection for rectal cancer at the Colchester General Hospital, each more than 10 years after pelvic radiotherapy. This has prompted a review of the association between irradiation and colorectal cancer and of the need for follow-up of the rectum in patients who have received pelvic radiotherapy.

Results

The essential clinical details of the five patients are recorded in Table 1.

Discussion

Irradiation is one of the most potent and well documented environmental carcinogens in man[1].

Table 1. Clinical details

	Radiotherapy details						*Subsequent rectal cancer Pathology*	
Case No.	*Reason for radiotherapy*	*Dose [cGy]*	*Route*	*Additional therapy*	*Latency period (years)*	*Operation performed*	*Tumour*	*Adjacent bowel*
1	Induction of menopause for menorrhagia	1200 (app)	External	Nil	>40	Abdomino-perineal resection	Well differentiated adeno-carcinoma of lower ⅓ of rectum. No lymph node involvement. Solitary metastasis in left lobe of liver.	Normal
2	Cervical carcinoma	8000 (at pt A)	External + implant	Nil	20	Abdomino-perineal resection	Poorly differentiated mucus-secreting adenocarcinoma of lower ⅓ of rectum. No lymph node involvement. Liver clear.	Dense post-irradiation rectal fibrosis
3	Endometrial carcinoma	4500	External	Abdominal hysterectomy	30	Abdomino-perineal resection	2 distinct, synchronous rectal carcinomata involving almost entire rectum, both poorly differentiated mucus-secreting lesions (Figure 1). No lymph node involvement. Liver clear.	Chronic proctitis with fibrosis affecting intervening rectum
4	Invasive bladder carcinoma	5000	External	Nil	12	Abdomino-perineal resection	Well differentiated adeno-carcinoma of lower ⅓ of rectum. No lymph node involvement. Liver clear.	Marked fibrosis and muscular hypertrophy of rectum and sigmoid
5	Endometrial carcinoma	3000 (at pt A)	Implant	Abdominal hysterectomy	16	Anterior resection	2 distinct, synchronous lesions of upper ⅓ of rectum and distal sigmoid colon, both moderately differentiated, mixed mucus-secreting adenocarcinomata. No lymph node involvement. Liver clear.	Fibrosis of intervening bowel wall; goblet cell hyperplasia of intervening mucosa (Figure 2).

0141-0768/90/030152-03/$02.00/0

Yet evidence in the literature linking irradiation and colorectal cancer is largely inconclusive and often contradictory. For example, one follow-up study[2] has shown a greater than expected incidence of carcinoma of the rectum in women previously irradiated for benign uterine bleeding (×3.32) and for cervical carcinoma (×1.4); another has shown no such increase after irradiation for benign uterine bleeding[3]. However, the former study is hampered by incomplete follow-up of the irradiated group (43%) and the latter by the short duration of follow-up (mean=6.7 years), making interpretation of the conclusions difficult in both studies.

Other authors have observed higher than expected mortality rates from rectal cancer among women previously irradiated for cervical carcinoma (×2.8)[4], for benign uterine bleeding (×1.53)[5] and for ankylosing spondylitis (×1.7)[6]. A subsequent report has found this last observation to be independent of any increased risk of rectal carcinoma due to the association of ulcerative colitis with ankylosing spondylitis[7]. Observations relating to mortality rates, however, may not reflect a real increase in the incidence of rectal cancer but may represent a poorer prognosis for cancers occurring incidentally in irradiated bowel or in previously irradiated patients. Similar arguments diminish the significance of the observed increase in mortality from colonic cancer among Japanese atomic bomb survivors[8].

The issue is further clouded by the apparent, possibly genetic, link between gynaecological and rectal malignancy irrespective of the mode of treatment of the gynaecological cancer. Bailar[9] found a higher incidence of rectal cancer among women previously treated for cervical or endometrial carcinoma by surgery alone than by radiotherapy alone (×2.14 vs ×1.41). On the other hand, another study has shown that the increased risk of the late development of rectal cancer after treatment for endometrial cancer was conferred only to those women who had been treated by radiotherapy[10].

Finally, experimental irradiation of rat colon has established the carcinogenic potential of irradiation in this animal[11]. Although this observation cannot necessarily be applied to the human colon, one comprehensive analysis[12] calculated that the relative risk in humans of developing colorectal carcinoma after irradiation for gynaecological malignancy is increased by 2-3 fold (2.0-3.6).

In view of the high incidence of colorectal cancer in Western populations it is clear that not all post-irradiation rectal cancer is in fact radiation-induced. Numerous criteria have been proposed which might distinguish incidental from radiation-induced cancers (Table 2). Most implicate high dose radiation as the principle risk factor[13,14].

Table 2. Proposed criteria for radiation-induced colorectal cancer

Black and Ackerman (1965)
(1) Post-irradiation interval 10 years
(2) Large radiation exposure to bowel
(3) Severe radiation damage to bowel adjacent to tumour
MacMahon and Rowe (1971)
(1) Early radiation proctitis
(2) Subsequent secondary proctitis
(3) Stenosis/induration of recto-vaginal septum

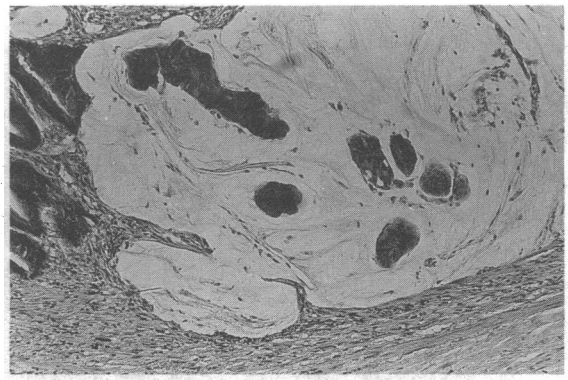

Figure 1. Mucus-secreting adenocarcinoma (case 3). Malignant cells lying within lakes of mucus (H&E, ×42)

Another feature linked with radiation-induced carcinoma is the presence of a mucus-secreting (or 'colloid') histological pattern (Figure 1). This has been found significantly more frequently than expected in the two largest published series of post-irradiation colorectal cancer[15,16] and is the only histological variety of colon cancer to date in irradiated animals[11].

Unfortunately, none of these criteria, whether taken alone or in combination, can be regarded as absolute confirmation that any given tumour is radiation-induced. For example, the reported post-irradiation interval or 'latency period' is highly variable. In the largest published series[16] the peak incidence of post-irradiation colorectal cancer was from 5 to 10 years after the completion of radiotherapy while one carcinoma was seen 45 years after irradiation. This report confirms a wide range of post-irradiation intervals (12-40 years). As yet, however, the influence of radiation dose upon the latency period has not been considered in detail in the literature. It is possible that higher doses of irradiation might be associated with the earlier appearance of colorectal cancer. Hence, radiation-induced rectal cancer might occur at widely variable intervals following completion of radiotherapy depending upon the dosage of irradiation directed at the rectum.

Not surprisingly there is also incomplete agreement about the dose of irradiation most likely to predispose to subsequent colorectal cancer. Although radiation damaged bowel adjacent to the carcinoma (indicative of moderate to high doses of radiotherapy) has been identified in 70% of post-irradiation cancers[16], others have concluded that lower doses of radiotherapy are more likely to induce colorectal cancer[2,17]. Experience with irradiated rat colon, however, has shown an essentially linear relationship between dose and the subsequent rate of cancer induction[11].

We have also noted a wide range of radiation dosage in the present series but it is our impression that higher doses producing radiation damaged bowel are more likely to be associated with subsequent development of carcinoma. The occurrence of nearby synchronous carcinomata within radiation-affected bowel in two of the five cases reported adds weight to this impression of a 'field effect'; ie cancer arising out of mucosa rendered unstable by prior irradiation.

The presence of mucus-secreting adenocarcinoma in three of the cases in this series and of obvious goblet cell hyperplasia alongside the primary tumour in one (Figure 2) reinforces the proposed link between bowel irradiation and this histological pattern.

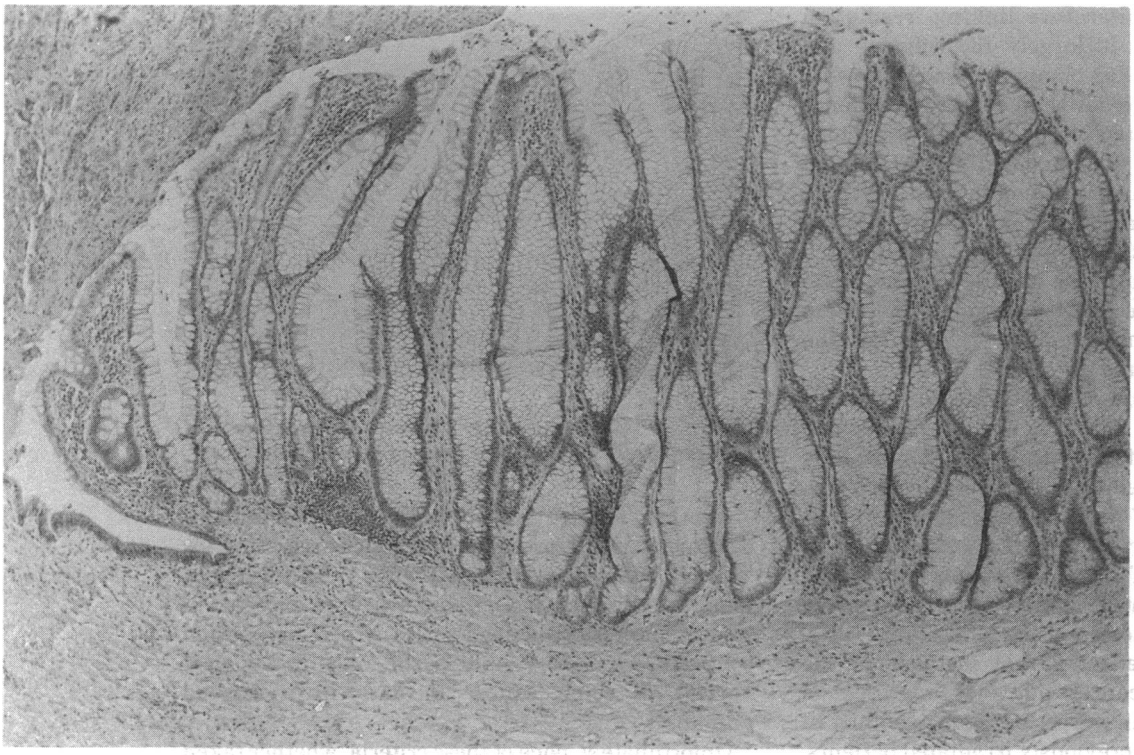

Figure 2. Goblet cell hyperplasia adjacent to carcinoma (case 5: H&E, ×17)

Experimental irradiation of rat small intestine[18] has also been shown to produce a significant increase in goblet cells both in absolute and relative terms. We regard these microscopic appearances as suggestive of radiation-induced cancer.

With radiotherapy now forming at least part of the treatment of virtually all patients with cervical cancer, the number of women exposed to rectal irradiation has increased. The incidence of radiation-induced rectal cancer may also be set to increase over the next 10-20 years. Until irradiated patients can be shown not to be at increased risk of subsequent rectal cancer, consideration should be given to surveillance of the rectum at post-radiotherapy follow-up examinations.

Acknowledgment: The authors thank Dr Jennifer Dyson, Consultant Pathologist, The Whittington Hospital, London for her assistance in the preparation of the photomicrographs.

References

1 UNSCEAR. Sources and effects of ionizing radiation. 1977 report to the General Assembly of the United Nations Scientific Committee on the Effects of Atomic Radiation. New York: United Nations, 1977
2 Palmer JP, Spratt DW. Pelvic carcinoma following irradiation for benign gynecological diseases. *Am J Obstet Gynecol* 1956;**72**:497-505
3 Corscaden JA, Fertig JW, Gusberg SB. Carcinoma subsequent to the radiotherapeutic menopause. *Am J Obstet Gynecol* 1946;**51**:1-12
4 Dickson RJ. Late results of radium treatment of carcinoma of the cervix. *Clin Radiol* 1972;**23**:528-35
5 Smith PG, Doll R. Late effects of X-irradiation in patients treated for metropathia haemorrhagica. *Br J Radiol* 1976;**49**:224-32
6 Court Brown WM, Doll R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965;**2**:1327-32
7 Smith PG, Doll R, Radford EP. Cancer mortality among patients with ankylosing spondylitis not given X-ray therapy. *Br J Radiol* 1977;**50**:728-34
8 Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. VII. Mortality. *Radiat Res* 1982;**90**:395-432
9 Bailar JC. The incidence of independent tumors among uterine cancer patients. *Cancer* 1963;**16**:842-53
10 Index tumors of the breast and reproductive organs. In: Schoenberg BS, ed. *Multiple primary malignant neoplasms. The Connecticut experience, 1935-1964*. New York: Springer-Verlag, 1977:82-3
11 Denman DL, Kirchner FR, Osborne JW. Induction of colonic adenocarcinoma in the rat by X-irradiation. *Cancer Res* 1978;**38**:1899-905
12 Sandler RS, Sandler DP. Radiation-induced cancers of the colon and rectum: assessing the risk. *Gastroenterology* 1983;**84**:51-7
13 Black WC, Ackerman LV. Carcinoma of the large intestine as a late complication of pelvic radiotherapy. *Clin Radiol* 1965;**16**:278-81
14 MacMahon CE, Rowe JW. Rectal reaction following radiation therapy of cervical carcinoma. *Ann Surg* 1971;**173**:264-9
15 Shu-Wen J, Beart RW, Reiman HM, Gunderson LL, Ilstrup DM. Colon and anorectal cancer after pelvic irradiation. *Dis Col Rectum* 1987;**30**:953-8
16 Castro EB, Rosen PP, Quan SH. Carcinoma of the large intestine in patients irradiated for carcinoma of cervix and uterus. *Cancer* 1973;**31**:45-52
17 Rubin P, Ryplansky A, Dutton A. Incidence of pelvic malignancies following irradiation for benign gynecologic conditions. *Am J Roentgenol* 1961;**85**:503-14
18 Becciolini A, Fabbrica D, Cremonini D, Balzi M. Quantitative changes in the goblet cells of the rat small intestine after irradiation. *Acta Radiol Oncol* 1985;**24**:291-9

(Accepted 26 June 1989)