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DO ACUTE SIDE-EFFECTS DURING RADIOTHERAPY PREDICT TUMOUR RESPONSE IN RECTAL CARCINOMA?

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Patients given preoperative radiotherapy (31.5 Gy in 18 fractions) in a prospective, randomized trial of presumably operable rectal adenocarcinoma, were examined for a possible relation between bowel toxicity manifested as diarrhoea, and tumour size in the operative specimen, in addition to recurrence rate. The group requiring drugs for diarrhoea had significantly smaller tumours at surgery (2.5 cm versus 3.5 cm, $p < 0.05$). Patients without significant radiation-induced diarrhoea had also more recurrences (37.5% against 14.3%, $p = 0.01$). The disease-specific survival rate was also significantly better ($p = 0.02$) at 1.5 and 10 years in patients with diarrhoea WHO grade 3 and 4; 89.5%, 75.9% and 65.1% compared to 83.5%, 49.3% and 44.4% in patients with no or minimal radiation-induced loose bowels. These results indicate that the reaction of the normal bowel to radiation may correlate to radiation sensitivity of tumours derived from the same tissue.

The present analysis was initiated after observing a patient with diarrhoea of WHO grade 3 during radiotherapy, dying of perforated gastric ulcer after a radiation dose of 26.25 Gy. Autopsy disclosed no residual tumour in the rectum. We therefore postulated that the patient had increased radiosensitivity both in the tumour and the normal gut, as the ulcers were found within the treatment fields. To our knowledge, no study of the relative intrinsic radiosensitivity of normal tissue and corresponding tumour from the same patient had previously been undertaken (1). Normal tissue side-effects observed during radiotherapy most likely reflect among other factors also variability in genetic determinants of intrinsic radiosensitivity. It is well known that cells from different normal tissues vary in radiosensitivity. As a cancer is genetically derived from host cells, we wanted to test the hypothesis that acute normal tissue reactions from the bowels during radiotherapy correlate with the radioresponsiveness of tumours. We therefore retrospectively compared the antitumour effects in patients with side-effects (diarrhoea WHO grade 3–4) requiring treatment with patients with less or no diarrhoea during preoperative radiotherapy for primarily operable rectal cancer. All the data recording was done prospectively as part of a protocol comparing preoperative radiation with surgery alone in a randomized study (2).

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Material and Methods

From May 1976 to December 1985, 159 patients were given preoperative radiotherapy in a prospective, randomized trial of primarily operable rectal cancer and were compared with patients treated by surgery alone (2, 3). All patients had a biopsy-proven rectal adenocarcinoma with the lowest margin of tumour below 15 cm from the anal verge, measured by rigid sigmoidoscopy. No upper age limit was defined. In the present study, only data from radiated patients were examined to assess the recurrence rate and to evaluate tumour response.

Radiotherapy. All radiotherapy was given at the Department of Oncology, Haukeland Hospital, by megavoltage equipment (a cobolt 60 source or a linear accelerator using 25 or 8 MV photons). The entire minor

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pelvis, hypogastric, inferior mesenteric, lymph nodes up to the lower margin of the first lumbar vertebra were treated in two opposed anterior and posterior 'chimney fields', as suggested by Kligerman (4). The lateral borders were the tips of the spinal wings in the abdomen and 1.5 cm lateral to the pectineal line in the pelvis. The lower field margin included the obturator foramen. The lower margin was extended to include the perineum in distal tumours, defined as below 5 cm from the anal verge. The daily dose was 1.75 Gy, 5 fractions a week for a total of 31.5 Gy.

Gastrointestinal side-effects. The side-effects were graded according to the WHO criteria (1). As radiation-induced loose bowels are difficult to discern from the diarrhoea caused by tumour itself, we decided to divide the patients into two groups: Group 1: No or slight diarrhoea (WHO grade 0, 1 and 2) and group 2: Diarrhoea sufficiently severe to be treated by drugs (WHO grade 3 and 4). The drugs given were loperamide hydrochloride and diphenoxylate chloride.

Surgery. The operation was carried out 2 to 3 weeks after completion of the radiotherapy. The standard surgery was 'en bloc' resection of the rectum and lower sigmoid with involved adjacent tissue and regional lymph nodes up to or above the origin of the inferior mesenteric artery. A minimal touch technique was used with high ligation of the inferior mesenteric artery. The decision whether the patient should have an abdominoperineal resection (APR) or a low anterior resection (LAR) was made by the surgeon at the operation. The operation was considered radical when there was no macroscopical tumour left behind and free margins were observed histopathologically. The largest tumour diameter was measured from the operative specimen and the tumour was staged according to Astler-Coller's modification of Dukes' classification system (5).

Follow-up. The patients were seen every sixth month for two years, and thereafter at least once yearly until 5 years after the operation; the control routines are described in detail elsewhere (1). When recurrences were suspected by clinical examination or by elevation of CEA, the diagnosis was verified by barium enema, colonoscopy, ultrasonography, or CT scan. Visible or palpable recurrences in the perineum or at the anastomosis were always verified by biopsy.

Statistical analysis. To estimate the significance of differences between means, Student's t-test (two-tailed) was used. Mann-Whitney U test was used to compare non-parametric data and χ^2- or Fisher's exact probability test was used to analyse 2×2 tables. The Kaplan-Meier method was used in the Medlog data package for survival analyses, and the differences in survival were tested by the log-rank test (Mantel-Haenszel test) (6–8).

Results

In all 159 patients were randomized to radiation for rectal cancer in the present analysis. One patient refused radiation after being randomized, in another patient the diagnosis of rectal cancer was altered by the pathologist to prostatic cancer, leaving 157 fully evaluable patients. The clinical characteristics of the patients are shown in Table 1. There were 116 patients with no or only slight diarrhoea during radiotherapy (group 1), whereas 41 patients had diarrhoea that required drug treatment (group 2) Table 2. There were no differences between the two groups in the distribution of the known risk factors; Age, sex, tumour localization or number of quadrants involved by tumour.

One patient died of perforated gastric ulcer before operation, after having been given 26.25 Gy radiation. However, no tumour was seen at autopsy. Another patient, who had no clinical evident residual tumour after radiation, was not operated due to high age and reduced general condition. In addition, two patients had their primary tumour removed by trans-anal extirpation. The others were treated by either APR or LAR, including 6 with liver metastases at operation. Thus, 131 patients were operated on for cure, 96 (83%) of all patients in group 1 and 35 (85%) in group 2 respectively (Table 2).

The tumour diameter was significantly larger ($p < 0.05$) in group 1 than in group 2 (median 3.5 and 2.5 cm respectively) at the time of surgery (Table 3). There was no correlation with tumour stage in the two groups. There was, however, a trend towards fewer positive lymph nodes, 3 or 35 (7%) in group 2 after radiation, compared with 21/96 (21%) in group 1 after radiation ($p = 0.06$, one-sided test). In 7 patients no tumour was left after radiotherapy

Table 1

Clinical characteristics of patients receiving 31.5 Gy radiation for rectal cancer by opposed chimney fields

Diarrhoea grade	Group 1 WHO 0, 1, 2 (n = 116)	Group 2 WHO 3, 4 (n = 41)	
Age			
Median	65	66	
Range	30–86	42–88	N.S.
Sex			
Male	65	27	N.S.
Female	51	14	N.S.
Symptom duration			
Median	6.7	6.5	N.S.
Range	0–48	0–108	
Tumour location (cm from anal verge)			
Median	8	9	N.S.
Range	1–15	1–15	
Quadrants involved by tumours			
1	53	20	N.S.
2 and 3	41	15	N.S.
4	22	6	N.S.

Table 2

Operative status of patients having preoperative radiation for rectal cancer according to grade of diarrhoea

Diarrhoea grade	WHO 0, 1, 2 (n = 116)	WHO 3, 4 (n = 41)
Operated patients		
Curative resection	96	35
No curative surgery		
Metastases	7	3
Local inoperable	1	0
Metastases + local inoperable	2	0
No operation		
Metastases	3	1
Local inoperable	1	0
Poor general condition	4	1
Patient refused surgery	2	0
Died of gastric perforation during RT	0	1

Table 3

Tumour size (largest diameter) in resected specimens correlated with diarrhoea during preoperative radiation therapy

Diarrhoea grade	Group 1 WHO 0–2	Group 2 WHO 3–4
Median	3.5	2.5
Range*	0–8	0–6

* Three (3.1%) tumours in group 1, and 4 (11.4%) tumours in group 2 were erradicated by 31.5 Gy radiation alone.

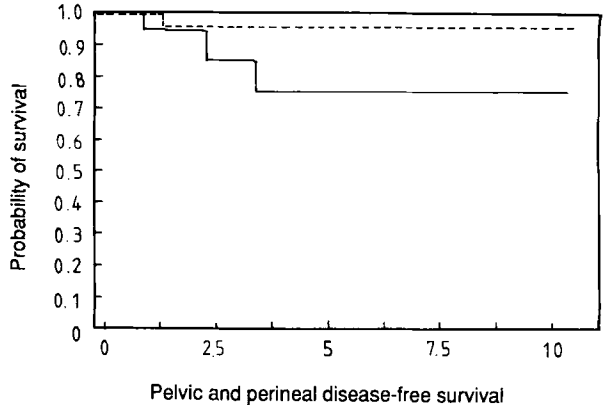

Fig. 1. Local disease-free survival for operable rectal cancer patients having 31.5 Gy irradiation in 18 fractions according to presentation of side-effects: Group 1: Diarrhoea WHO grade 0–2, ——. Group 2: Diarrhoea WHO grade 3–4, – – –. Time in years.

Table 4

Recurrence after radiation according to WHO grade of diarrhoea

Diarrhoea grade	Group 1 WHO 0, 1, 2	Group 2 WHO 3, 4	
All patients (n)	116	41	
Local failure	27 (23.3%)	3 (7.3%)	p = 0.04
Metastases	30 (25.9%)	7 (17.1%)	p = 0.6
Total failure	57 (49.1%)	10 (24.4%)	p < 0.01
Failure after (n) curative resection	96	35	
Local failure	17 (17.7%)	2 (5.7%)	p = 0.10
Metastases	20 (20.8%)	3 (8.6%)	p = 0.10
Total failure	36 (37.5%)	5 (14.3%)	p < 0.05

(one of these was assessed at autopsy and one only clinically assessed, but followed for 5 years with no signs of recurrence). Of interest is that 4 (11.4%) of these patients belonged to group 2 against only 3 (3%) in group 1. This difference was, however, not statistically significant.

For all 157 patients the actuarial disease-free survival rates at 1, 5 and 10 years were 93%, 53% and 53%, against 100%, 77% and 77%, respectively in group 1 and group 2 ($p = 0.009$). When all pelvic recurrences, some of which had concurrent distant spread, were analysed (Fig. 1), the corresponding figures were 96.8%, 73.5% and 73.5%, against 100%, 97.1% and 97.1%, again favouring the group with most acute side-effects ($p = 0.016$). If only pelvic and perineal recurrences without distant spread were analysed the corresponding figures were 96.8% at 1 year, 75.1% at 5 and 10 years in group 1 against 100% at 1 year and 97.1% at 5 and 10 years in group 2 ($p = 0.02$).

The recurrence rate of patients operated for cure at a median follow-up time of 54 months, was 37.5% in group 1 but only 14% in group 2. This difference was statistically significant ($p = 0.01$), (Table 4). Within group 2 there was also a trend towards fewer recurrences in those patients who had severe diarrhoea. No difference in survival between the groups was seen. However, the disease-specific survival (death of rectal cancer and treatment-related complications up to 30 days after surgery) was significantly lower in group 1 compared to group 2 ($p = 0.02$) (Fig. 2). The disease-specific survival at 1, 3, 5, and 10 years was in group 1 83.5%, 68.8%, 49.3% and 44.4%, against 89.5%, 86.8%, 75.9% and 65.1% in group 2.

Discussion

The radioresponsiveness of human tumours reflects the radiosensitivity of the tissue or origin. Thus, seminomas are exquisitely radiosensitive, reflecting the extreme radiosensitivity of the testicular germinative tissue. Lymphomas, leukaemias and plasmocytomas are also radiosensitive, reflecting the radiation response in hematopoetic tissue. In vitro lymphoma, neuroblastoma and myeloma cell lines showed greater radioresponsiveness than normal cell lines derived from bladder, cervix or colon (9). There is, however, significant variation in radiosensitivity between different normal cell types, for instance fibroblasts and lymphocytes (10). Among the radiobiological processes studied, cellular ability to repair

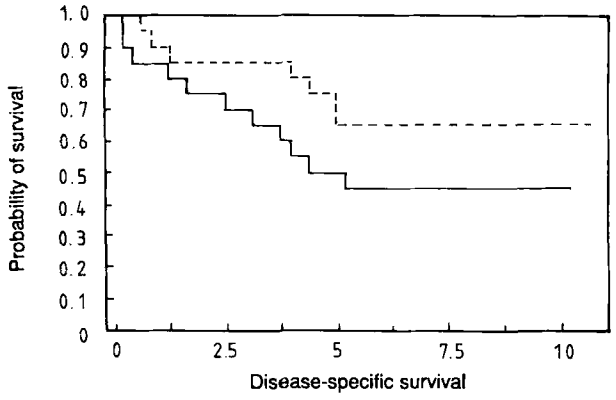

Fig. 2. Disease-specific survival (dead of rectal cancer and complications within 30 days from surgery) for patients having 31.5 Gy irradiation in 18 fractions according to presentation of side-effects: Group 1: Diarrhoea WHO grade 0–2, ——. Group 2: Diarrhoea WHO grade 3–4, – – –. Time in years.

sublethal radiation damage, reassortment, reoxygenation of hypoxic sites, and cellular repopulation have been shown to determine radioresponsiveness. It is, however, unlikely that any simple correlation can be established (1).

Due to comparable values of the terminal slope of the cell survival curves, an inherent difference in radiosensitivity of tumour cells has been largely ignored (9). It seems that the steepness of the initial slope of the cell survival curve in human tumour cell lines, a measure of cellular radiosensitivity, correlates well with clinical responsiveness (11). The intrinsic cellular radiosensitivity as quantified by the in vitro SF_2 varied in human tumour cell lines from cancer of the uterine cervix, melanoma and head and neck squamous cell carcinomas in a manner well compatible with the observed clinical radioresponsiveness, but corrections may be necessary (12). The radiosensitivity of normal cells is governed by the same factors as in tumours, and varies with the tissue in question. The repair of radiation damage seems to be an important factor for the observed normal tissue toxicity, as shown for the rare autosomal disorder ataxia telangiectasia, where the greatly increased normal tissue sensitivity to radiation has been correlated to a defect in DNA repair mechanisms (13).

In patients, the observed normal tissue toxicity during fractionated radiotherapy varies greatly from patient to patient. It may reflect the random nature of radiation effects, but it is likely that at least some part of the variation reflects intrinsic normal tissue radiosensitivity. In the treatment of rectal carcinoma, the most common side-effect during treatment is diarrhoea, reflecting the effect of radiation in the bowel, the same epithelium the tumour is derived from.

The patients in this controlled, randomized trial of preoperative radiotherapy were all treated at the same institution, were given the same information about diet during radiotherapy, and the same drugs (loperamide hydrochloride and diphenoxalate chloride) for diarrhoea during treatment. As shown in Table 1, the clinico-pathological characteristics including the number of quadrants involved, indicate similar tumour sizes before radiation in the two groups of patients. No patient had severe anorexia during radiation leading to significant changes in the anterior-posterior diameter during radiotherapy, which could have increased dosage in patients with decreasing anterior-posterior dimensions during radiation. The finding of smaller tumours and less recurrences in the group with severe diarrhoea indicates that the correlation between bowel sensitivity and tumour sensitivity to radiation is not by chance due to subgroup analysis. As there is no means to predict which patient will get side-effects during radiotherapy, the evaluation of a possible correlation between normal tissue sensitivity and tumour tissue sensitivity can only be assessed retrospectively. The difference was significant both for local tumour control and overall recurrences. The same reduction of both local and distant tumour spread is reported after a mesorectal excision for rectal cancer (14), thus implying that better local tumour control may reduce distant spread.

It must be borne in mind that the patients in the present study were not radiated with the intent of local tumour sterilization, but for eradication of tumour projections, early lymphatic spread and to decrease tumour cell viability before surgical manipulation. Both tumour and normal tissue effects are expected to be on the linear part of the sigmoid dose–response curves. With radiotherapy given to a high-dose level, permanent tumour control and complete responses should be related to long-term side-effects when investigating a possible correlation between tumour response and side-effects. Such a correlation was found in an RTOG study of radiotherapy in advanced pelvic malignancies (15). Using high-dose weekly fractions with misonidazole, 6 or 46 patients had complete response. Of these, 4 of 6 (67%) had high-grade late complications in the bowel, against 30% and 26% in patients with partial or no response respectively. Good tumour response was thus related to late bowel toxicity, although longer survival in patients with good response partially could explain the increased long-term toxicity.

The present finding is further supported by the demonstration of significantly more radiosensitivity in 5 fibroblast lines established from women exhibiting unusually severe clinical response to radiation for treatment of breast cancer compared with 6 women with normal reactions (16). In the human skin a close correlation between late radiation damage (teleangiectasias) was observed in both right and left treatment field where difference radiation doses were applied, providing further evidence for the existence of patient-to-patient differences in factors influencing the radiation sensitivity of normal tissues (17, 18). However, this individual variation is not necessarily dominated by a genetic component expressed equally in all cells.

Conclusion

We have presented evidence that early side-effects of radiation manifested as diarrhoea predict the radiation effect on tumour and the prognosis of patients given radiotherapy. If the findings in the present investigation can be verified by other studies, it could imply that one should increase the tumour dose in patients with no or slight symptoms during bowel radiotherapy, provided the total dose is kept below a limit leading to severe long-term side effects.

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