ACTA RADIOLOGICA

Vol. 21
Fasc. 6

ONCOLOGY

1982

COMBINED IRRADIATION AND THREE-DRUG CHEMOTHERAPY IN INOPERABLE COLORECTAL CARCINOMA

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Irradiation has a major role in treatment of inoperable colorectal carcinoma, either alone or followed by surgery (WANG & SCHULZ 1962, KLIGERMAN & URDANETA-LAFEE 1974, STEVENS et coll. 1976, RAO et coll. 1978, TIERIE 1978). Experience in combined irradiation and chemotherapy is limited, but some reports indicate that the effect of irradiation might be improved by addition of 5-fluorouracil (MOERTEL et coll. 1969, VONGTAMA et coll. 1975, WASSIF 1976). In these trials single-drug chemotherapy was used whereas the toxicity and the local tumour response of irradiation combined with multidrug chemotherapy was evaluated in the present series. Based on cumulative data on the effect of chemotherapeutic agents on colorectal carcinoma, a 3-drug regimen consisting of 5-fluorouracil, methotrexate and cyclophosphamide was used (CARTER & FRIEDMAN 1974, WASSERMAN et coll. 1975).

Material and Methods

Forty patients with inoperable or not radically resected tumours in the rectum or rectosigmoideum were treated in the period from May 1976 to November 1978. All cases were adenocarcinomas, microscopically. Twenty-one patients had a measurable tumour within the irradiation field and could thus be included in the evaluation of the tumour response. The remaining 19 patients were only included in the toxicologic evaluation. Characteristics of the 2 groups of patients are given in Table 1. Before beginning of the treatment, distant metastases were found in 21 patients, but only a few of these had measurable distant metastases. Therefore, it was not possible to evaluate the effect of the chemotherapeutic drugs alone.

Irradiation was given with 8 MV photons on 2 opposed anterior and posterior fields against the small pelvis and the para-aortic lymph nodes up to the lower level of L 2. The central dose was 3.12 Gy twice weekly for 6 weeks to a total dose of 37.44 Gy. This was equivalent to a CRE value of 1 380 reu.

Chemotherapy, which was started at the same time as irradiation, consisted of 5-fluorouracil, methotrexate and cyclophosphamide. The drugs were given during 15 days with an interval of 3 weeks before a new treatment cycle was begun. The planned total treatment period was 9 months. For 5-fluorouracil the dose was 600 mg/m^2 intravenously once weekly, for methotrexate 25 mg/m^2 intravenously once weekly, and for cyclophosphamide 100 mg/m^2 orally every third day. In the first two series, when chemotherapy was given simultaneously with irradiation, the doses of 5-fluorouracil and methotrexate were reduced to 75 per cent on days 1 and 8; on day 15, the doses never exceeded 50 per cent.

Definition of response. The local tumour response was evaluated by ultrasound scanning, palpation and rectoscopy combined with biopsy and, in some patients, confirmed at a second operation. Complete response (CR) was defined as a total disappearance of the tumour, and partial response (PR) as a more

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Table 1

Forty patients with microscopically confirmed adenocarcinoma in rectum or rectosigmoideum

	Age (years)	Sex (male/female)	No. of patients with a primary tumour	No. of patients with a recurrent tumour	No of patients with distant metastases before start of treatment
21 evaluable patients	Median 57 Range 38–78	10/11	13	8	11
19 non-evaluable patients	Median 59 Range 43–73	14/5	12	7	10

than 50 per cent reduction in tumour size without development of new tumours within the radiation fields. The response duration was measured from the beginning of treatment until local progression or death.

Results

Tumour response. Eight of the 21 patients with a measurable tumour achieved CR and a further 5 patients PR (thus CR+PR=13/21, 62%). Of the 8 CR patients 4 were considered locally cured. However, 2 of these patients died due to distant metastases, and one patient was alive with metastases but without local recurrence 50 months after the beginning of treatment. Primary tumour size, duration of remission and present status for the patients who achieved CR are given in Table 2. The 5 patients with PR and the remaining 8 non-responding patients all died due to progressive disease.

Of the 19 non-evaluable patients, 2 were still alive without evidence of disease 43 and 48 months after beginning of the treatment.

Acute side effects. Acute toxicity was evaluated in all 40 patients. The main toxic effects were nausea and vomiting, especially on the days following injection of the drugs. Six patients suffered from stomatitis during treatment. Seven patients had pollakiuria which in 2 patients continued for several months after completion of the radiation therapy. Fifteen patients had diarrhoea and in 7 a loss of weight of more than 2 kg occurred. All patients without progressive disease had regained their loss of weight within one month after completion of the irradiation.

Leukopenia below 2×10^9/l occurred in 12 patients and thrombopenia below 100×10^9/l in 5 patients. In 3 cases, the myelosuppression caused sepsis which was successfully treated with antibiotics.

Alopecia occurred in 6 patients during the treatment. Three of these patients required wigs. No treatment-related effects on liver or kidney functions were found.

Table 2

Patients who achieved complete tumour remission

Case No.	Tumour size (cm)	Duration of remission (months)	Present status
1	14×12	4+	Dead without local recurrence
2	20×20	67+	Alive without evidence of disease
3	15×15	50+	Alive with distant metastases but without local recurrence
4	8×4	9.5	Dead with local progression
5	3×3	16+	Dead without local recurrence
6	5×6	30	Dead with local progression
7	10×10	9	Dead with local progression
8	3×2	27	Dead with local progression

Late side effects. The long observation period made it possible to examine late complications, such as fibrosis or fistulation in the irradiation area. Nine patients, who died due to progressive disease within 6 months after beginning of treatment, have not been included in the evaluation of the frequency of late complications. Of the remaining 31 patients 2 were operated upon for ileus due to extensive fibrosis, and a further 3 patients suffered from fistulation. However, 2 of these had had repeated fistulation before beginning of the treatment. Thus, the frequency of late complications was 3/31. No deaths related to the treatment occurred.

Discussion

When irradiation is applied as the only treatment of patients with inoperable colorectal carcinoma

long term remissions from 0 to 16 per cent have been reported (WANG & SCHULZ, STEVENS et coll., RAO et coll., TIERIE). Although it is difficult to compare these results with the present ones, it was found inspiring to achieve complete tumour remission in 8 of 21 patients with large inoperable tumours (Table 2). The high response rate (CR+PR) of 62 per cent may be due to a drug-induced enhancement of the irradiation effect. However, increased effects are noted not only in tumours but also in normal tissues (PHILLIPS & FU 1978). Until now it has been difficult to demonstrate a therapeutic synergism of combined chemotherapy and irradiation (BLEEHEN 1981, PECKHAM & COLLIS 1981). Thus, it may be possible to achieve equally good results by increasing the radiation dose, but the high incidence of metastases outside the radiation fields may advocate a combination of the two types of treatment.

In the present series, early toxicity following the combined treatment was moderate, but in 3 cases late complications, such as fibrosis and fistulation, developed. These complications may, however, have arisen as a result of irradiation alone, especially when taking the large irradiation field and the fractionation schedule into consideration (ROSWIT 1974). When irradiation is combined with 5-fluorouracil in the treatment of gastrointestinal tumours, late complication rates of about 5 per cent have been reported (DANJOUX 1979). However, in one report, late serious complications without predictable acute reactions occurred in 7 of 24 patients (29%) given pelvic irradiation and 5-fluorouracil (DANJOUX & CATTON 1979). In the present series a far lower frequency of late complications was observed, but as in the series reported by DANJOUX & CATTON acute toxicity was not predictable for late side effects, which emphasizes the importance of evaluating early as well as delayed reactions following new treatment modalities.

In conclusion, it was found that the combined treatment was effective and that toxicity was acceptable. Based on the present results, a randomized series of combined treatment of patients with resectable adenocarcinoma in the rectum and rectosigmoideum was started. The patients were allocated for either observation or irradiation combined with 5-fluorouracil and methotrexate. However, the side effects following the combined treatment were so severe and unacceptable that the randomized trial had to be closed (SPARSØ et coll., in preparation). Therefore, this combined regimen cannot be recommended until the reason for the discrepancy between frequency and severity of the complications in the preliminary series and the following randomized trial has been evaluated.

SUMMARY

Forty patients with inoperable or not radically resected tumours in the rectum or rectosigmoideum were treated with irradiation combined with 5-fluorouracil, methotrexate and cyclophosphamide. The acute toxicity was moderate, but 3 patients developed late complications such as fibrosis and fistulation in the irradiated area. Twenty-one patients had a measurable tumour within the radiation fields and were included in the evaluation of the tumour response. Of these patients 8 achieved complete and 5 partial tumour remission. Nevertheless, it is emphasized that this treatment cannot be recommended because of severe complications observed in a following randomized series of patients receiving irradiation combined with 5-fluorouracil and methotrexate.

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