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Preoperative Irradiation With and Without Chemotherapy (MFL) in the Treatment of Primarily Non-resectable Adenocarcinoma of the Rectum

Results from Two Consecutive Studies

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Abstract—*Twenty-one consecutive patients with primarily non-resectable adenocarcinoma of the rectum were treated with preoperative split-course radiotherapy* (40 Gy) *and simultaneous sequential methotrexate + 5-fluorouracil + leucovorin (MFL). An initial infusion of methotrexate* (250 mg/m^2) *was followed in the 2nd hour by 5-FU—first a bolus injection* (10 mg/kg) *and then continuous infusion* (35 mg/kg/24 h) *for* 72 h. *Leucovorin rescue* (15 mg *every* 6 h) *was initiated* 24 h *after the initial injection. Radiotherapy* (10 Gy) *was given with two* 2.0 Gy *fractions on days* 1 *and* 2, *and one fraction on day* 3. *The toxicity of the treatment was mostly mild to moderate. Compared with a previous consecutive series comprising* 38 *patients who received preoperative irradiation* (≥40 Gy) *only, with a resectability rate of* 34%, *the* 71% *resectability rate with this treatment seems to be superior.*

INTRODUCTION

TEN to twenty-three per cent of all rectal carcinomas are primarily locally non-resectable, but only half of these have distant metastases at the time of diagnosis [1–3]. Untreated, the patients have a median survival of 6–8 months [4, 5], often with severe suffering from symptoms such as pain, haemorrhage, anal incontinence and urinary or vaginal problems due to overgrowth to neighbouring organs. Compared with the 5-year survival of about 50% among surgically curable patients, patients with a non-resectable tumour have a 5-year survival of 0–5% [4–6]. Radiotherapy usually provides valuable symptom relief and, when delivered preoperatively, may produce tumour regression, resulting in a resectability rate of 39–70% and a prolonged survival [1, 3, 6–12]. The large discrepancy in the resectability rate is probably due to differences in the criteria for non-resectability, in the radiotherapy dose and technique, and in patient selection.

Tumour regression may also occur after chemotherapy, but increased resectability after systemic drug therapy alone has not been reported. 5-Fluorouracil (5-FU) given simultaneously with irradiation has been found to cause greater tumour shrinkage than irradiation alone [13, 14], and experimental and clinical data indicate that continuous infusion of 5-FU during and after irradiation has advantages [15–17].

Sequential methotrexate (MTX) and 5-FU followed by leucovorin has been reported to result in improved response rates in advanced colorectal carcinomas [18]. Drug synergism between MTX and 5-FU given sequentially has been claimed in experimental systems [19–22]. High-dose leucovorin has also been used to enhance the antimetabolic activity of 5-FU [23–27]. Our own experience with a combination designated MFL—methotrexate + 5-fluorouracil + leucovorin—was encouraging in a preliminary series [18], and data from a Nordic multicentre randomized study have indicated that the effect of MFL is superior to that of 5-FU only [28].

Between 1979 and June 1985, consecutive patients with a locally non-resectable adenocarcinoma of the rectum were given preoperative radiotherapy alone. Preliminary results for patients included up to 1983 have been published by Påhlman *et al.* [3]. Since July 1985, irradiation has been combined with a modified MFL regime, which can be given simultaneously with the irradiation, with the continuous infusion of 5-FU during and after the

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irradiation. In this report the resectability rate and short-term survival with the two treatment modalities are presented.

MATERIALS AND METHODS

Definition of non-resectability

Non-resectability was defined as fixation to the pelvic wall, the prostate gland or the base of the urinary bladder, or a large non-mobile tumour at digital examination. Thirteen per cent of the patients with carcinoma of the rectum seen at the Department of Surgery in Uppsala had a primarily non-resectable tumour. The resectability was defined in the same way before and after treatment. Pulmonary X-ray and, when liver metastases were suspected on clinical grounds (pathological liver tests, palpable liver and/or weight loss), ultrasound of the liver were performed in order to exclude patients with metastatic disease.

Preoperative radiotherapy—first series

From 1979 to June 1985, a total of 56 patients (27 women and 29 men, median age 70 years, range 36–92) admitted to the Department of Surgery, Akademiska sjukhuset, Uppsala had a primarily, locally non-resectable carcinoma of the rectum. In 31 of these 56 patients computed tomography (CT) over the pelvic region was performed before treatment. Twelve patients (21%) were excluded from radiation therapy, 10 patients because of high age alone, or in combination with other diseases (range 70–92 years), and two because of generalized disease at the time of diagnosis. Three of these patients underwent surgery without preoperative treatment.

External radiation therapy was given with a three-field technique, one dorsal and the other two fields symmetrically angled 60°, with the patient in the prone position. The target was defined from CT images, previously described [29]. The cranial limit of the target was at L4 and the caudal limit at the anal orifice. The irradiation energy was 8 or 16 MV X-rays, fractioned with 2 Gy measured in the cutting point of the three central axes, 5 days/week, to a planned total dose of 46 Gy. Three weeks later, the patients were re-examined before surgery. If the tumour was still non-resectable, the radiotherapy was continued to 64 Gy in combination with a 5-FU 250 mg i.v. bolus injection three times/week [3].

Preoperative irradiation and drug treatment—second series

Between July 1985 and June 1988, 26 consecutive patients (11 women and 15 men, median age 68 years, range 38–84) admitted to the above Department of Surgery had an adenocarcinoma of the rectum that was considered primarily locally non-resectable. In 12 of the patients magnetic resonance tomography (MRT) over the pelvic region was performed before and after treatment to assess the resectability.

Five of the patients (19%) were not included in the protocol, one patient because of previous radiation therapy for a cervical carcinoma and three because of high age (range 80–84 years) together with generalized disease. The fifth patient was only given radiation therapy, because of a poor general condition at diagnosis.

The treatment was administered in 3 days as shown in Fig. 1. The 5-FU infusion was increased or decreased by 2.5 mg/kg/day after each course according to the toxicity of the previous treatment course in the individual patient. MTX was not given if the serum creatinine level was above 125 μmol/l (upper normal value 107 μmol/l) at diagnosis or if it increased above this level at any time during treatment.

External radiotherapy was given simultaneously with the same target, technique and energy as described above. The irradiation was fractioned, with 2.0 Gy × 2 on days 1 and 2 and 2.0 Gy × 1 on the 3rd day (Fig. 1). This therapy was repeated three times and was given every other week, giving a total absorbed radiation dose of 40 Gy. Three to four weeks later the patients were re-examined with respect to tumour resectability and were then operated upon. The total length of time between diagnosis and surgery was thus about 3 months.

Toxicity and statistics

Toxicity was defined and graded according to the WHO criteria for reporting results of cancer

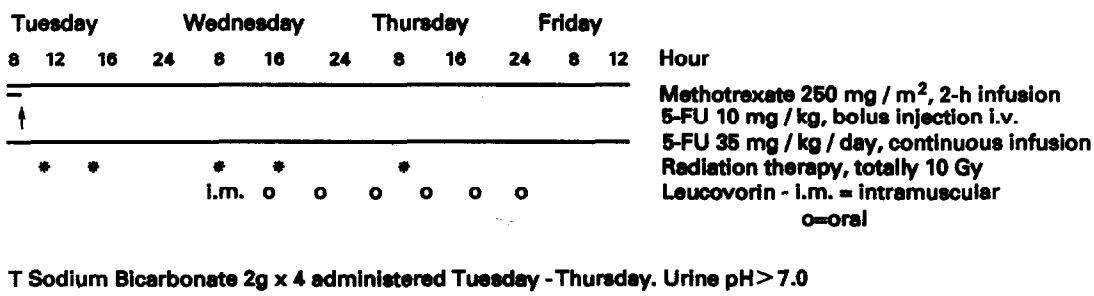

Fig. 1. Treatment schedule, sequential MFL and radiotherapy.

treatment [30]. A patient in whom the rectal tumour could be both macro- and microscopically radically resected and without known generalized disease was considered 'possibly cured'. Cancer-specific survival was defined as death with cancer, and is described with the life table technique [31].

RESULTS

Preoperative radiotherapy—first series

Treatment and toxicity. Thirty-eight of the 44 patients included in the series were given 40 Gy or more. Nine of these patients received a total of 64 Gy, the last 18 Gy in combination with 5-FU. Four of the 38 patients had somewhat shortened treatment (40 Gy), because of high age and generalized disease. In the remaining six patients the radiotherapy course was interrupted prematurely after a total dose of 18–36 Gy because of progressive disease outside the irradiated volume, in five patients distant metastases, and in one patient ileus and peritoneal carcinosis. Twenty-two patients showed some acute/subacute treatment toxicity, mostly of grade I or II. The most frequent symptoms of toxicity were diarrhoea and perineal skin irritation (Table 1).

Resectability. Out of the 44 patients who started treatment, 17 (39%) underwent local resection and 15 (34%) locally curative resection. In six of the 17 patients in whom resection was performed, generalized disease was discovered at surgery. Among the 15 patients who underwent locally curative resection six had a tumour classified as Dukes' B and nine as Dukes' C, and the 15 patients represented 39% of the 38 patients who received 40 Gy or more. Based on all 56 patients seen during the time period in question, the resectability rate was 36% (20/56), with 18 locally curative resections (32%) and 13 patients possibly cured, i.e. with no detectable metastases (Table 3). Fifteen had an abdomino-perineal resection (APR) and five had an anterior resection (AR); in four of the 20 patients uterine or vaginal resection was also performed.

Postoperative complications. One of the 28 patients who underwent laparotomy after irradiation died postoperatively of pulmonary embolus. Two of the 15 patients who had an APR had postoperative perineal wound sepsis.

Survival (Figs. 2 and 3). Four (36%) of the 11 possibly cured patients are alive. In four of the seven patients who died, the cause of death was cancer. The median survival of the 47 patients who had any treatment but palliative surgery (44 started preoperative radiotherapy and 3 had surgery alone) was 12 months, and five of 17 patients are alive 3–7 years after diagnosis. Two of the 20 patients who underwent resection have had a local recurrence (6 and 12 months postoperatively); in neither of these two patients was resection performed with curative intent.

Preoperative irradiation and drug therapy—second series

Treatment and toxicity. Eighteen of the 21 patients who started treatment received irradiation to a total dose of 40 Gy in combination with drug therapy. One patient only had three treatment courses, as previous palliative radiotherapy had been given at another hospital. In two patients the treatment was interrupted after two and three courses, because of a Stevens–Johnson syndrome and ileus, respectively. The latter patient had a previous history of ileus and had to be operated upon again during the treatment, and was found to have a generalized disease. Two patients started without MTX because of a high serum-creatinine level. In three patients the MTX was discontinued after one, one and two courses, respectively, because of an elevation of serum creatinine (128, 143 and 156 μmol/l). In two patients MTX was discontinued because of allergic reactions. The 5-FU dose could be increased in three patients to maximally 45 mg/kg/day, but

Table 1. Symptoms of acute/subacute toxicity of preoperative irradiation alone; 44 patients

Organ		Grade				
		0	I	II	III	IV
Haematological	Leucopenia	44				
	Thrombocytopenia	44				
Gastrointestinal	Diarrhoea	33	3	8		
	Nausea	43	1			
Skin		35	2	5	2	
Micturition symptoms		41	3			
Weakness		41	3			
Abdominal pain		41	3			

Table 2. Symptoms of acute/subacute toxicity of irradiation + MFL treatment; 21 patients

Organ		Grade				
		0	I	II	III	IV
Haematological	Leucopenia	6	4	7	3	1
	Thrombocytopenia	21				
Gastrointestinal	Mucositis	6	4	7	3	1
	Nausea	15	6			
	Diarrhoea	11	2	7	1	
Kidney	S-Creatinine elevation	17	4			
Micturition symptoms		19	2			
Allergy		18	2			1
Skin		17	3			1
Alopecia		18	1	1	1	
Neurological		18	3			

Table 3. Resectability after preoperative irradiation (first series, January 1979–June 1985), and preoperative irradiation + MFL treatment (second series, July 1985–June 1987)

	1979–1985		1985–1987	
	Started treatment	Total	Started treatment	Total
No. of patients	44	56	21	26
Refused surgery	1	2	0	0
Underwent laparotomy	27 (61%)	32 (57%)	20 (95%)	23 (88%)
Underwent resection	17 (39%)	20 (36%)	16 (76%)	18 (69%)
Resection with locally curative intent	15 (34%)	18 (32%)	15 (71%)	17 (65%)
Possibly cured	11 (24%)	13 (23%)	12 (57%)	13 (50%)
No resection	10 (23%)	12 (21%)	4 (19%)	5 (19%)
Still locally inoperable	9 (20%)	9 (16%)	3 (16%)	3 (12%)
Metastases at laparotomy	1 (2%)	3 (9%)	1 (5%)	2 (8%)

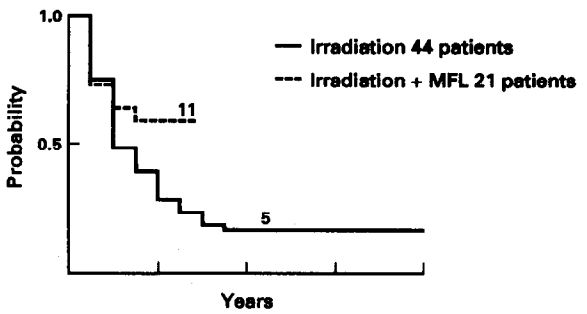

Fig. 2. Postoperative cancer-specific survival, patients who started the intended treatment.

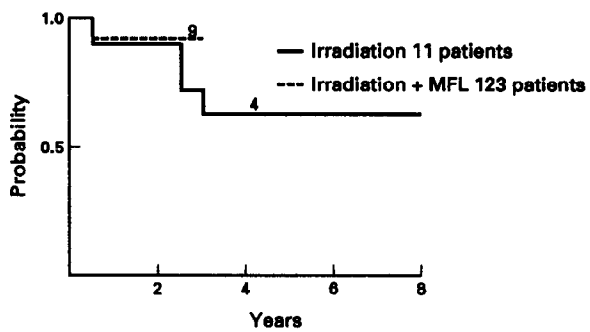

Fig. 3. Postoperative cancer-specific survival, possibly cured patients.

these patients had modifications in the MTX delivery because of the reasons previously described. In seven patients the 5-FU dose was reduced because of toxicity (any haematological/gastrointestinal grade 3–4 toxicity between the treatment courses, or grade 2 toxicity persisting at the time of the start of the next treatment course). Nine patients received the same 5-FU dose in all four courses. Some kind of dose modification was made in all patients. In two patients the third course was delayed for one week because of persistent grade 3 toxicity. The observed symptoms of acute and subacute toxicity are presented in Table 2. The most frequent symptoms were mucositis, diarrhoea and nausea. There was no symptomatic haematological toxicity except in the patient who developed the Stevens–Johnson

syndrome with grade 4 allergy and skin toxicity, who had a septic episode with a B-LPK value of $0.6 \times 10^3/mm^3$. No other patient had any serious (grade 4) toxicity.

Resectability. Three to four weeks after the end of the last treatment course, local tumour regression (almost total in one case, considerable in 14 and less extensive in five) was noted at digital examination in 20/21 patients. In the 12 patients who were examined with MRT, these estimations were confirmed. Among 20/21 patients who underwent laparotomy (in one patient liver metastases were discovered by ultrasound just before surgery and no laparotomy was performed), 16 (76%) underwent resection and in 15 (71% of the patients who received irradiation and drug treatment) the resection was potentially locally curative; five of these had an APR and 10 an AR. Among these 15 patients, nine had a tumour classified as Dukes' B and five as Dukes' C, and in one case no viable tumour cells could be found histopathologically. Three patients with liver metastases underwent local radical resection, leaving 12 patients treated for cure. In the four patients on whom no resection was undertaken, the reason in one was that extensive liver metastases were found at laparotomy and in three that the tumour was still non-resectable and fixated to the pelvic wall. In the total consecutive material of 26 patients, the resectability was 65% (17/26) (Table 3).

Postoperative complications. Thirteen of the 20 laparotomized patients had no complications of surgery. Two patients died in the early postoperative period, both from heart failure; they had a previous history of cardiac disease. These patients were 78 and 83 years old. Two of the five patients who underwent APR (with primarily closed perineal wounds), had perineal wound sepsis, which healed within 5 months. Two of nine patients in the AR group had an anastomotic dehiscence, necessitating a loop transversostomy. Five months after surgery, one patient in this group developed a recto-vaginal fistula.

Follow-up. One patient in whom radical surgery was not performed has had a local recurrence after 30 months. Eleven of the 23 patients who had any form of treatment (21 started preoperative MFL with irradiation, one had preoperative radiotherapy only and one surgery alone) are alive, with a median survival of 20 months, and nine patients have died of cancer. Four of 13 possibly cured patients have died: one early postoperative death, two of cancer and one of a cerebrovascular lesion (Figs. 2 and 3).

DISCUSSION

In the first study with preoperative radiotherapy alone, between 1979 and 1983, comprising 28 consecutive patients, the resectability was 39% [3]. This result appears less favourable than those reported from several other hospitals [1, 6–11]. Using the defined criteria for selection of patients and non-resectability, we considered the results unsatisfactory and the therapy was therefore changed in 1985. The present treatment programme was designed with the aim of delivering 'adequate' radiation therapy simultaneously with 'full-dose' chemotherapy, with the intention of achieving a locally at least additive effect [32]. Based upon the findings of Rich *et al.* [17], we also wanted to give the 5-FU as a continuous infusion during and for some time after the irradiation. In order to make this practical, i.e. to complete one treatment course including the required preparation (e.g. radiation simulation, control of kidney function) within 5 days (Monday to Friday), and to get a sufficiently high dose, the radiation was given twice daily in the first 2 days. The total treatment time should also be long in order to allow regression of the tumour, since regression of adenocarcinoma of the large bowel has been reported to be slow [33]. It must be pointed out that the rationale of giving the treatment as it was designed is weak and can be much discussed. The long duration could e.g. result in repopulation of tumour cells in the intervals between treatments. This doubt also refers to the simultaneous delivery of chemotherapy and radiotherapy [32, 34].

The present combination of irradiation and cytostatic drug therapy, with a resectability rate of 71%, seems to be superior to irradiation alone. It should be mentioned that the referral pattern and the selection criteria have been the same since 1979 and that all clinical evaluations were made by the same clinicians (B.G., L.P.), which allowed us to compare the two treatment series. The extent of patient selection in these materials is, due to the organization of hospital care in Sweden, probably less than in other hospital based series. This could be one of the major reasons for the apparently less favourable results in the radiotherapy alone group compared to other series [3].

The occurrence of any late complications of the treatment has not yet been evaluated, but the acute toxicity of the regime was acceptable for therapy with a curative intent. It was severe (grade 4; Stevens–Johnson syndrome) in one patient (5%). The toxicity seemed to be attributable mostly to the chemotherapy and less to the irradiation, or to chemotherapy-induced additive local toxicity on the normal tissue in the irradiated area (compare Tables 1 and 2). The local symptoms did not in general

appear to be either more serious or more frequent than would be caused by isolated irradiation to the same total dose and with the same target volume, although the present mode of fractionation has never been tested before. It is possible that the initial 5-FU dose was somewhat too high for most patients. However, the dose escalation and dose reduction schedules allowed appropriate adjustments of the dose in order to deliver as much drug as possible without a high risk of severe toxicity.

In conclusion, although a long-term survival evaluation is not yet possible, the relatively high resectability rate after combined treatment shows a positive trend, with an acute/subacute toxicity that can be accepted. To confirm these preliminary data of increased resectability and improved short-term survival, it is of interest to continue with the combined therapy in a larger patient material, and, if the preliminary positive results still hold and late toxicity does not appear, to perform a controlled study against radiation alone.

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